SiFA Azide: A New Building Block for PET Imaging Using Click Chemistry

Lutz F. Tietze,* Kianga Schmuck

Institute of Organic and Biomolecular Chemistry, Georg-August-University Göttingen, Tammannstr. 2, 37077 Göttingen, Germany
Fax +49(551)399476; E-mail: ltietze@gwdg.de

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Abstract: We present a new highly potent building block for PET imaging based on silicon fluoride acceptors (SiFA) which can easily be coupled to bioactive compounds by means of click chemistry. Owing to a remarkable chemoselectivity, short reaction times, and high yields the labeling reactions thoroughly meet the stringent demands for PET investigations.

Key words: azides, cancer, click chemistry, fluorine labeling, PET

Imaging technologies, which allow a noninvasive monitoring of biological processes in vivo are very important tools for the understanding of living systems and the development of new drugs. Several methods as optical imaging employing compounds labeled with fluorescence dyes,[1] magnetic resonance imaging (MRI),[2] single-photon emission tomography (SPECT),[3] and positron-emission tomography (PET)[4] are in use. The latter nuclear imaging technique, which is mainly employed in the field of clinical oncology, neurology, and cardiology has the advantage of high sensitivity and only minor structural changes of the molecules to be investigated are necessary. Thus, PET can give valuable information about the in vivo distribution of diagnostic as well as bioactive compounds and allows one to map the corresponding molecules. On the other hand, a major disadvantage of this procedure is that positron-emitting radioisotopes such as ^{18}F, ^{11}C, and ^{13}N with a short lifetime have to be used. Therefore, as a prerequisite, the introduction of the radioisotope must be fast.

In our work on the development of novel highly selective anticancer agents using the antibody-directed enzyme prodrug therapy (ADEPT)[5] and the prodrug mono therapy (PMT)[6] we have designed glycosidic derivatives of analogues of the natural antibiotic duocarmycin SA (**1**) with relatively low cytotoxicity which can be cleaved either by an antibody–enzyme conjugate or an enzyme overexpressed in the tumor tissue (Figure 1).[7] The cytotoxicity of the formed drugs is very high with an IC_{50} value of as low as 110 fM. On the other hand, the selectivity which corresponds to the therapeutic window in a treatment and which was defined by us by the QIC_{50} value ($QIC_{50} = IC_{50}$ of prodrug/IC_{50} of prodrug in the presence of cleaving enzyme)[5a] can reach the value of almost one million.[7b] For the determination of the in vivo distribution of our prodrugs and drugs the only suitable procedure is PET using

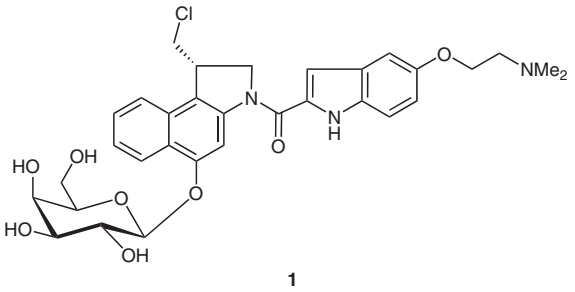

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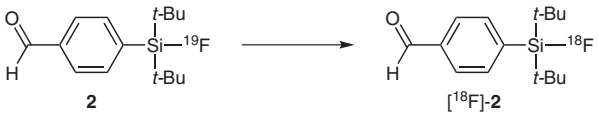
Figure 1 Glycosidic duocarmycin analogue prodrug **1** as anticancer agent for application in ADEPT

preferably ^{18}F as the most stable positron-emitting radioisotope with $t_{1/2}$ = 109.7 min.

Previously, Waengler and Schirrmacher et al. reported on silicon fluoride acceptors (SiFA) like *p*-(di-*tert*-butylfluorosilyl)benzaldehyde (**2**) as potent labeling reagents for PET (Scheme 1).[8] Using a fast and highly efficient isotopic ^{19}F–^{18}F exchange specific activities of up to 680 GBq/μmol for [^{18}F]-**2** can be obtained and thus only a small amount of the precursor is needed. Furthermore, [^{18}F]-**2** was proven to be stable under physiological conditions, and the group has shown that [^{18}F]-**2** can be efficiently coupled to aminooxy-derivatized peptides via oxime formation in a fast and high-yielding reaction.



2 [^{18}F]-**2**

Scheme 1 Radiosynthesis of SiFA aldehyde [^{18}F]-**2**. *Reagents and conditions*: $^{18}F^-/K_{222}/K^+$ (1–2.5 GBq), MeCN, r.t., 10 min, 80–95% radiochemical yield. K_{222} = Kryptofix® 222.

Unfortunately, we were not able to successfully employ aldehyde **2** for fluorine labeling of our anticancer agents containing a primary amino functionality probably due to the more complex and electronically different structure of our compounds compared to the given examples. Therefore we have developed SiFA azide **4**, which can be introduced to any compound containing a terminal alkyne moiety using click chemistry based on the work of Huisgen, Sharpless, and Meldal.[9]

For the synthesis of SiFA azide **4**, the alcohol **3**, being available from 4-bromobenzylic alcohol in three steps,[8a] was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diphenylphosphoryl azide (DPPA) in toluene for 13 hours at 50 °C to give the azide **4** in an excellent

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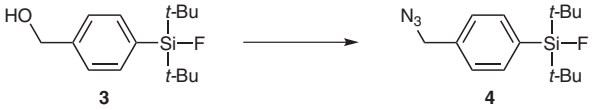
yield of 92% (Scheme 2). SiFA azide **4** was proven to be stable under labeling-like conditions with KF (1.0 equiv) and 18-crown-6 (1.3 equiv) in acetonitrile for 10 minutes at room temperature. The compound was recovered without any changes and especially with no loss of the azide group.



Scheme 2 Synthesis of SiFA azide **4**. *Reagents and conditions*: DPPA, DBU, toluene, 50 °C, 13 h, 92%.

The Cu(I)-catalyzed cycloaddition of azide **4** with different alkynes **5**–**8** consistently furnished high yields of the corresponding 1,4-substituted triazoles **9** in a reaction time of 60 minutes or less as shown in Table 1. All transformations were performed in aqueous *tert*-butyl alcohol and under convenient in situ generation of Cu(I) out of $CuSO_4$ and sodium ascorbate. With regard to our antitumor active duocarmycin analogues for application in ADEPT and PMT we were also able to rapidly connect our modified DNA binder **7** to the SiFA azide **4** to give the triazole **9c** in 88% yield within 20 minutes. In addition, we employed the corresponding acid **8**, which again gave high yields of the desired cycloadduct **9d**. However, the compound could not be separated completely from the used copper salt presumably due to the chelating properties of the COOH and NH functionalities in **8** resulting in broad signals in the NMR spectrum.

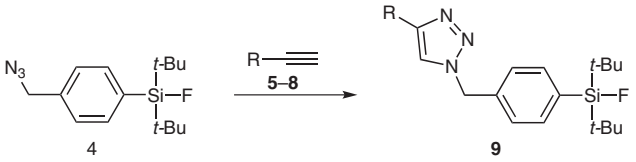
In summary, the new SiFA azide **4** comprises a highly efficient labeling reagent for PET imaging with remarkable chemoselectivity, short reaction times, and facile performance.

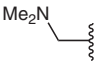
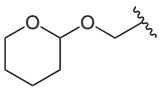
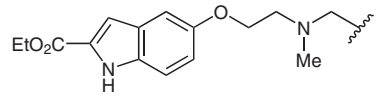
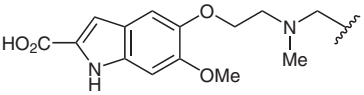
The reactions were carried out under argon. Solvents were used from commercial sources in p.a. grade and stored over molecular sieves. All reagents purchased from commercial sources were used without further purification. TLC was performed on silica gel 60 F_{254} plates from Merck and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. UV spectra were taken with a V-630 (Jasco), IR spectra with a FT/IR-4100 (Jasco). ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded with Mercury-300, Unity-300, and Inova-500 spectrometers. Spectra were taken at r.t. in deuterated solvents as indicated using the solvent peak as internal standard. ESI-HRMS was performed on a micrOTOF (Bruker) spectrometer and on an AccuTOF (Jeol) spectrometer for EI-HRMS.

4-(Di-*tert*-butylfluorosilyl)benzylazide (4)

A solution of alcohol **3** (1.00 g, 3.73 mmol, 1.0 equiv) in toluene (10 mL) was treated with DBU (835 µL, 5.59 mmol, 1.5 equiv) and DPPA (1.20 mL, 5.59 mmol, 1.5 equiv), and the mixture was stirred for 13 h at 50 °C. The reaction was quenched by addition of sat. NH_4Cl solution (20 mL) and MTBE (20 mL), and the aqueous layer was extracted with MTBE (3 × 40 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (PE–EtOAc = 50:1) to give **4** as a colorless oil (1.01 g, 3.43 mmol, 92%). R_f = 0.55 (PE–EtOAc = 10:1).

Table 1 Copper(I)-Catalyzed Coupling of Alkynes **5**–**8** with SiFA Azide **4** To Give the 1,4-Substituted Triazoles **9**



R	Time (min)	Product	Yield (%)
 **5**	20	**9a**	quant.
 *rac*-**6**	30	*rac*-**9b**	88
 **7**	20	**9c**	95
 **8**	60	**9d**	80[b]

[a] Reaction conditions: (a) $CuSO_4 \cdot 5H_2O$, Na ascorbate, *t*-BuOH–H_2O, r.t.

[b] Compound contains small amounts of copper ions.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 [d, $^4J_{H,F}$ = 1.1 Hz, 18 H, 2 × $C(CH_3)_3$], 4.37 (s, 2 H, CH_2), 7.33 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, 2-H, 6-H), 7.63 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.2 [d, $^2J_{C,F}$ = 12.4 Hz, 2 × $C(CH_3)_3$], 27.3 [d, $^3J_{C,F}$ = 1.1 Hz, 2 × $C(CH_3)_3$], 54.7 (CH_2), 127.2 (C-2, C-6), 133.8 (d, $^2J_{C,F}$ = 13.7 Hz, C-4), 134.4 (d, $^3J_{C,F}$ = 4.5 Hz, C-3,C-5), 136.7 (C-1) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –188.9 ($^1J_{Si,F}$ = 298 Hz) ppm. IR: ν = 2933, 2859, 2095, 1605, 1471, 1273, 1251, 1106, 824, 813 cm^{-1}. UV (MeCN): λ_{max} (lg ε) = 225 (4.1394), 267 (2.7330), 358 (2.2454) nm. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{15}H_{24}FN_3Si$: 293.1724; found: 293.1726.

General Procedure for the Cu(I)-Catalyzed Cycloaddition To Give the Triazoles 9

A mixture of the alkyne **5**–**8**, the azide **4**, $CuSO_4 \cdot 5H_2O$, and sodium L-ascorbate in *t*-BuOH–H_2O (3:1, degassed) was stirred for 20–60 min at r.t. Then, H_2O (5 mL) and CH_2Cl_2 (10 mL) were added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. In the case of *rac*-**9b** double the amount of solvents was used in workup.

{1-[4-(Di-*tert*-butylfluorosilanyl)benzyl]-1*H*-1,2,3-triazole-4-ylmethyl}dimethylamine (9a)

A suspension of 1-dimethylamino-2-propyne (**5**, 8.1 µL, 75 µmol, 1.1 equiv), **4** (20 mg, 68 µmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (3.4 mg, 14 µmol, 0.2 equiv), and Na ascorbate (8.1 mg, 41 µmol, 0.6 equiv) in *t*-BuOH–H_2O (3:1, 2.8 mL) was stirred for 20 min at r.t. After workup, the triazole **9a** was obtained as slightly yellow solid (26 mg, 68 µmol, quant.). R_f = 0.52 (CH_2Cl_2–MeOH = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 [s, 18 H, 2 × $C(CH_3)_3$], 2.26 (s, 6 H, NMe_2),

3.60 (s, 2 H, Me_2N-CH_2), 5.51 (s, 2 H, triazole-CH_2-Ar), 7.22 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, 2′-H, 6′-H), 7.45 (s, 1 H, 5-H), 7.57 (d, $^3J_{H,H}$ = 7.7 Hz, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.6 [d, $^2J_{C,F}$ = 12.5 Hz, 2 × *C*(CH_3)$_3$], 26.9 [2 × C(*C*H_3)$_3$], 43.1 (NMe_2), 52.1 (Me_2N-*C*H_2), 52.5 (triazole-*C*H_2-Ar), 125.4 (C-5), 126.9 (C-2′, C-6′), 132.4 (d, $^2J_{C,F}$ = 13.8 Hz, C-4′), 133.9 (d, $^3J_{C,F}$ = 4.4 Hz, C-3′, C-5′).137.6 (C-1′), 145.5 (C-4) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –188.8 ($^1J_{Si,F}$ = 304 Hz) ppm. IR: ν = 2941, 2857, 1605, 1466, 1433, 1223, 1107, 1057, 1012, 824 cm^{-1}. UV (MeCN): λ_{max} (lg ε) = 223 (4.2115), 261 (2.7447) nm. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{20}H_{33}FN_4Si$: 377.2531; found: 377.2526.

rac-1-[4-(Di-*tert*-butylfluorosilyl)benzyl]-4-(tetrahydro-2*H*-pyran-2-yl-oxymethyl)-1*H*-1,2,3-triazole (_rac_-9b)

A suspension of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (*rac*-**6**, 23.9 mg, 170 μmol, 1.0 equiv), **4** (50.0 mg, 170 μmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (8.50 mg, 34.1 μmol, 0.2 equiv) and Na ascorbate (20.2 mg, 102 μmol, 0.6 equiv) in *t*-BuOH–H_2O (3:1, 4 mL) was stirred for 30 min at r.t. After workup, the crude product was purified by column chromatography on silica gel (PE–EtOAc = 2:1, 1% Et_3N) to give the triazole *rac*-**9b** as white solid (64.7 mg, 149 μmol, 88%). R_f = 0.14 (PE–EtOAc = 2:1, 0.5% Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02, 1.03 [d, $^4J_{H,F}$ = 1.1 Hz, 18 H, 2 × C(CH_3)$_3$], 1.41–1.63 (m, 4 H, 3′-H_a, 4′-H_a, 5′-H_2), 1.64–1.86 (m, 2 H, 3′-H_b, 4′-H_b), 3.45–3.55 (m, 1 H, 6′-H_a), 3.78–3.92 (m, 1 H, 6′-H_b), 4.63 (d, $^2J_{H,H}$ = 12.4 Hz, 1 H, OCH_a-triazole), 4.71 (dd, $^3J_{H,H}$ = 4.2, 2.6 Hz, 1 H, 2′-H), 4.84 (d, $^2J_{H,H}$ = 12.4 Hz, 1 H, OCH_b-triazole), 5.51 (s, 2 H, triazole-CH_2-Ar), 7.24 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2″-H, 6″-H), 7.48 (s, 1 H, 5-H), 7.58 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 3″-H, 5″-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.4 (C-4′), 20.2 [d, $^2J_{C,F}$ = 12.4 Hz, 2 × *C*(CH_3)$_3$], 25.3 (C-5′), 27.2 [2 × C(*C*H_3)$_3$], 30.4 (C-3′), 54.0 (triazole-*C*H_2-Ar), 60.7 (O*C*H_2-triazole), 62.4 (C-6′), 98.4 (C-2′), 122.5 (C-5), 127.1 (C-2″, C-6″), 134.5 (d, *J* = 13.6 Hz, C-4″), 134.6 (d, *J* = 4.5 Hz, C-3″, C-5″), 135.9 (C-1″), 145.6 (C-4) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –188.8 ($^1J_{Si,F}$ = 304 Hz) ppm. IR: ν = 2945, 2931, 2857, 1469, 1367, 1213, 1201, 1103, 1037, 825, 807, 646 cm^{-1}. UV (MeCN): λ_{max} (lg ε) = 223 (4.1933), 262 (2.5451), 267 (2.5511), 272 (2.4169) nm. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{36}FN_3O_2Si$: 456.2453; found: 456.2453.

Ethyl 5-[2-({1-[4-(Di-*tert*-butylfluorosilyl)benzyl]-1*H*-1,2,3-triazole-4-ylmethyl}methylamino)ethoxy]-1*H*-indole-2-carboxylate (9c)

A suspension of indole **7** (22 mg, 68 μmol, 1.0 equiv), **4** (22 mg, 75 μmol, 1.1 equiv), $CuSO_4 \cdot 5H_2O$ (3.4 mg, 14 μmol, 0.2 equiv), and Na ascorbate (8.1 mg, 41 μmol, 0.6 equiv) in *t*-BuOH–H_2O (3:1, 2.8 mL) was stirred for 20 min at r.t. After workup, the crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH = 60:1, 0.5% Et_3N) to give the triazole **9c** as slightly brown solid (38 mg, 64 μmol, 95%). R_f = 0.15 (CH_2Cl_2–MeOH = 20:1, 0.5% Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 [d, $^2J_{H,F}$ = 1.0 Hz, 18 H, 2 × C(CH_3)$_3$], 1.38 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, OCH$_2$CH_3), 2.42 (s, 3 H, NMe), 2.91 (t, $^3J_{H,H}$ = 5.2 Hz, 2 H, OCH$_2$CH_2), 3.87 (s, 2 H, MeN-CH_2-triazole), 4.13 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, OCH_2CH$_2$), 4.37 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 5.48 (s, 2 H, triazole-CH_2-Ar), 6.94 (dd, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,H}$ = 2.4 Hz, 1 H, 6-H), 7.03 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 4-H), 7.10 (dd, $^4J_{H,H}$ = 2.1, 0.9 Hz, 1 H, 3-H), 7.20 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2″-H, 6″-H), 7.28 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, 7-H), 7.54 (s, 1 H, 5′-H), 7.56 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 3″-H, 5″-H), 8.92 (br s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 (OCH$_2$*C*H$_3$), 20.2 [d, $^2J_{C,F}$ = 12.4 Hz, 2 × *C*(CH_3)$_3$], 27.2 [d, $^3J_{C,F}$ = 1.0 Hz, C(*C*H$_3$)$_3$], 42.7 (NMe), 52.6 (MeN-*C*H_2-triazole), 54.0 (triazole-*C*H_2-Ar), 55.5 (OCH$_2$*C*H$_2$), 60.9 (O*C*H$_2$CH$_3$), 66.3 (O*C*H$_2$CH$_2$), 103.7 (C-4), 108.1 (C-3), 112.7 (C-7), 117.2 (C-6), 123.1 (C-5′), 126.9 (C-2″, C-6″), 127.8 (C-3a), 128.0 (C-2), 132.2 (C-7a), 134.4 (d, $^2J_{C,F}$ = 13.7 Hz, C-4″), 134.6 (d, $^3J_{C,F}$ = 4.5 Hz, C-3″, C-5″), 135.9 (C-1″), 144.8 (C-4′), 153.6 (C-5), 161.8 (C=O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –188.8 ($^1J_{Si,F}$ = 304 Hz) ppm. IR: ν = 3320, 2931, 2858, 1688, 1526, 1469, 1449, 1399, 1378, 1337, 1207, 1103, 1018, 803 cm^{-1}. UV (MeCN): λ_{max} (lg ε) = 194 (4.7546), 220 (4.5712), 294 (4.2371), 324 (3.626) nm. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{32}H_{44}FN_5O_3Si$: 594.3270; found: 594.3268.

5-[2-({1-[4-(Di-*tert*-butylfluorosilyl)benzyl]-1*H*-1,2,3-triazole-4-ylmethyl}methylamino)ethoxy]-1*H*-indole-2-carboxylic Acid (9d)

The compound was prepared as described for **9c** with a yield of about 80%, it contains small amounts of copper ions, which could not be removed, resulting in broad signals in the NMR spectra. Thus, an unambiguous spectroscopic identification was not possible. ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{31}H_{42}FN_5O_4Si$: 596.3063; found: 596.3064.

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