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# Click Linker: Efficient and High-Yielding Synthesis of a New Family of SPOS Resins by 1,3-Dipolar Cycloaddition

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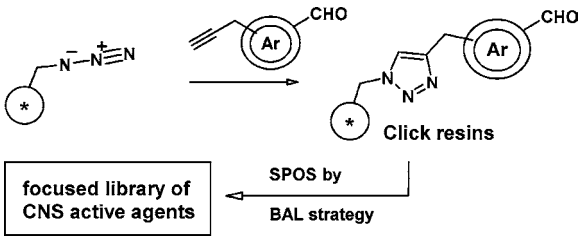
## ABSTRACT




**Highly efficient methodology for the construction of functionalized resins was presented involving 1,3-dipolar cycloaddition as the key reaction step. On the basis of this concept, the first series of click backbone amide linkers were synthesized and the application of the FIMT resin 3f to the parallel synthesis of putative dopaminergic agents was demonstrated leading to the selective receptor ligands 10i and 10s revealing high affinity to the D4 subtype.**

In a very recent paper, Sharpless et al. disclosed the concept of "click chemistry", designating powerful and selective reactions for an efficient synthesis of interesting compounds and combinatorial libraries through heteroatom links,[1] when the Huisgen 1,3-dipolar cycloaddition of azides and alkynes[2] is regarded as the "cream of the crop" of concerted reactions. The process is modular, wide in scope, high yielding, and requires only simple reaction and purification conditions. Taking advantage of the outstanding reaction profile, the chemical orthogonality of the formation conditions not requiring activating reagents and the stability toward strong bases, we started to develop a new family of "click resins" incorporating a 1,2,3-triazole moiety for the fusion of linker functionality and resin backbone. On the basis of this concept, we describe herein the first series of click linkers when an aldehyde functionality should be employed for the traceless attachment of the substrate through the BAL (*B*ackbone *A*mide *L*inker) strategy.[3] Furthermore, an application for a solid phase supported preparation of a focused library of biologically active compounds is demonstrated. Commercially available BAL resins are prepared by acylation of aminomethyl-substituted polystyrenes requiring activation of the carboxylic acid building block (Scheme 1). We aspired to replace this amide coupling by a click reaction permitting a convenient IR monitoring to prove the completeness of the linker loading. Thus, we planned to apply the highly efficient triazole formation employing an azide-substituted solid support and a suitable alkyne attached to an aryl aldehyde moiety.

The methodology should be based on Merrifield resin, which was treated with sodium azide to give the immobilized 1,3-dipole **4**[4] in 94% yield (calculated on the amount of N

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(2) (a) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613−628. (b) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494−2507. (c) Rostrovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (d) Tornoe, C. W.; Christensen, C.; Medal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(3) Alsina, J.; Jensen, K. J.; Albericio, F.; Barany, G. *Chem. Eur. J.* **1999**, *5*, 2787−2795 and references therein.

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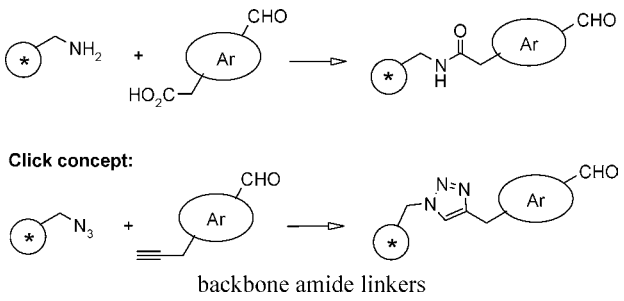
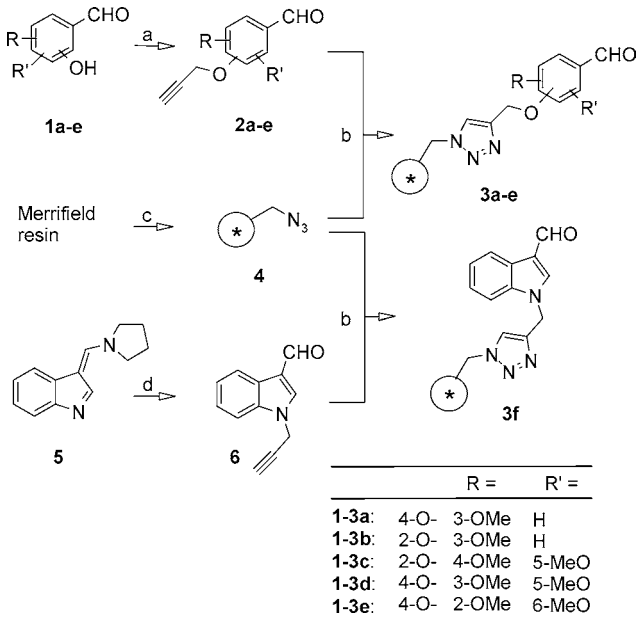
**Scheme 1.** Attachment Concepts for the Immobilization of Backbone Amide Linkers




determined by elementary analysis). Our initial investigations started from vanilline (**1a**) as a commercially available low-cost building block that was *O*-alkylated with propargyl bromide to obtain the aryloxypropyne **2a** (Scheme 2).

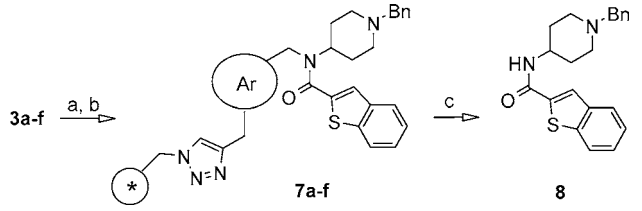
**Scheme 2.** Preparation of the Resins **3a**−**f**[a]




[a] Reagents and conditions: (a) propargyl bromide, DMF, $K_2CO_3$, 70 °C, 24 h; (b) THF, DIPEA, Cu(I)I, 35 °C, 16 h; (c) $NaN_3$, DMSO, 60 °C, 48 h; (d) (1) $BrCH_2CCH$, THF, rt to 60 °C, 1 h, (2) NaOH, $H_2O$, rt, 0.5 h.

Cu(I)-promoted loading onto the azidomethyl polystyrene **4** gave the formylaryloxymethyltriazole resin **3a**. The conversion was monitored by on-bead FTIR analysis when complete disappearance of the azide signal (2096 $cm^{-1}$) was observed after 16 h. To test the applicability of the vanilline derived linker **3a**, we chose a three-step reaction sequence including reductive amination, acylation, and acidic liberation of the produced carboxamide. FTIR reaction control indicated complete reductive coupling with 1-benzyl-4-aminopiperidine in the presence of $Na(OAc)_3BH$. Subsequent DIC/HOAt-induced reaction with benzopthiophene-2-carboxylic acid

**Scheme 3.** SPOS with BAL Resins **3a**−**f**[a]




[a] Reagents and conditions: (a) 4-amino-1-benzylpiperidine, $Na(OAc)_3BH$, $CH_2Cl_2$, rt, 16 h; (b) benzothiophene-2-carboxylic acid, DIC, HOAt, DIPEA, DMF, rt, 16 h; (c) TFA (2% in $CH_2Cl_2$), rt, 2 h.

resulted in formation of the resin-bound amide **7a** (Scheme 3). However, the cleavage product **8** was obtained only in 6% yield when the process was promoted by 2% TFA in $CH_2Cl_2$ (Table 1). Increasing the TFA concentration up to 70% caused an increase of the yield and decomposition of **8** at the same time.

**Table 1.** Yields ($^1$H NMR Derived Purities) of the SPOS Product **8** Synthesized on the BAL Resins **3a**−**f**

| resin | loading, mmol/g | theor. loading,[a] mmol/g | yield, % (purity, %), of **8**[b] |
|---|---|---|---|
| **3a** | 0.80 | 0.92 | 6 (>95) |
| **3b** | 0.89 | 0.92 | 9 (>95) |
| **3c** | 0.80 | 0.90 | 94 (>95) |
| **3d** | 0.81 | 0.90 | 9 (>95) |
| **3e** | 0.81 | 0.90 | 67 (>95) |
| **3f** | 0.83 | 0.92 | 94 (>95) |

[a] Calculated on the loading of the Merrifield resin (1.10 mmol/g). [b] Yields were calculated by weight.

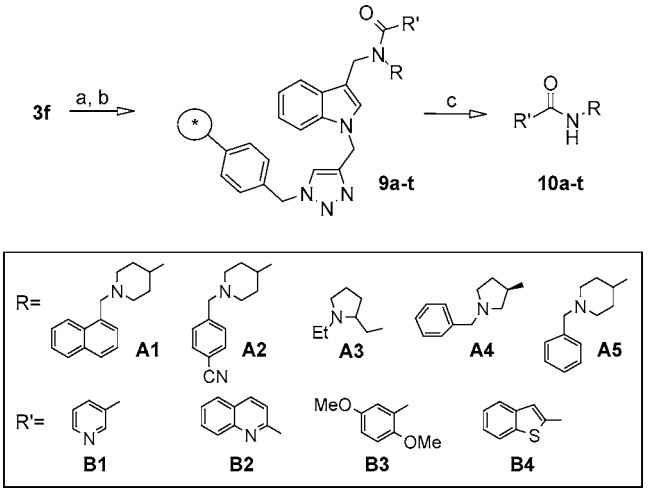
We aspired to optimize the vanilline-based unit by modifying the relative dispositions and the number of electron-donating substituents that are responsible for the stabilization of the cationic transition state during the cleavage. Thus, isovanilline **1b** and the dimethoxy-substituted hydroxybenzaldehydes **1c**, **1d**, and **1e** were transformed into the propargyl ether **2b**−**e** and, subsequently, immobilized by 1,3-dipolar cycloaddition with the azidomethyl resin **4**. When investigating the resulting FAMT (*F*ormyl*A*ryloxy-*M*ethyl*T*riazole) resins **3b**−**e** for the above-mentioned model reaction sequence, we found that both reductive amination and *N*-acylation worked very well. When a cleavage concentration of 2% TFA in $CH_2Cl_2$ was used the isovanilline derivative **3b** and 3,4,5-trialkoxy derivative **3d** displayed low cleavage yields. On the other hand, the 2,4,5- and 2,4,6-substituted regiosiomers **3c** and **3e** turned out to be very effective BAL linkers affording pure products in 94% and 67% yield, respectively.

As an extension, the electron-donating properties of the enamine functionality of indole-3-carbaldehyde should be exploited.[5] A highly practical synthetic pathway was elabo-

rated when condensation of indole-3-carbaldehyde with pyrrolidine gave the enamine **5**[6] that could be transformed into the *N*-substituted 3-formylindole **6**. Subsequent immobilization gave the formylindolylmethyltriazole (FIMT) resin **3f**. Applying **3f** for the model synthesis, the carboxamide **8** could be isolated analytically pure in 92% yield, after cleavage with 2% TFA.

To demonstrate the utility of the click linker strategy, we employed the FIMT resin **3f** for the parallel synthesis of a focused library of putatively dopaminergic arylcarbamides. Whereas we followed the above-mentioned conditions for the reductive amination, we avoided the use of the expensive reagent HOAt for the parallel synthesis employing a TFFH (tetramethylfluoroformamidinium hexafluorophosphate)[7] induced coupling, instead (Scheme 4). Thus, subsequent

**Scheme 4.** SPOS of **10a**−**t** on FIMT Resin **3a**[a]




[a] Reagents: (a) **A(1**−**5)**-$NH_2$, $Na(OAc)_3BH$, $CH_2Cl_2$, rt, 16 h; (b) **B(1**−**4)**-COOH, TFFH, DIPEA, DMF, rt, 24 h; (c) TFA (2% in $CH_2Cl_2$) rt, 16 h.

attachment of the primary amines **A1**−**A5** and the arylcarboxylic acids **B1**−**B4** furnished the resin-bound carboxamides **9a**−**t**, which could be liberated by 2% TFA in $CH_2Cl_2$ to afford the desired test compounds **10a**−**t** in 50−93% yield and 77−99% purity (Table 2).

The carboxamides **10a**−**t** were evaluated in vitro for their ability to displace the radioligand [$^3$H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$, D3, and D4. The test compounds of the focused library were not able to substantially displace the radioligand from the $D2_{long}$, $D2_{short}$, and D3 receptor subtype in $10^{-7}$ molar concentration indicating poor binding affinity. In contrast, highly interesting structure activity relationships could be observed for the D4 subtype when the 3-acylaminopyrrolidines **10i** and **10s** were detected to displace more than 67% of [$^3$H]spiperone. These hit compounds can serve as leads for the development of new dopamine D4 selective ligands, which are discussed as valuable tools for the therapy of schizophrenia an ADHD.[8]

**Table 2.** Yields, HPLC-Purities (in Parentheses), and Dopamine D4 Affinity of the SPOS Products **10a**−**t**[a]

| | B1 | B2 | B2 | B4 |
|---|---|---|---|---|
| A1 | **10a**, 55%, (85%) | **10f**, 92%, (94%) | **10k**, 90%, (94%) | **10p**, 73%, (85%) |
| A2 | **10b**, 50%, (77%) | **10g**, 91%, (98%) | **10l**, 88%, (97%) | **10q**, 74%, (91%) |
| A3 | **10c**, 58%, (90%) | **10h**, 93%, (93%) | **10m**, 93%, (93%) | **10r**, 78%, (94%) |
| A4 | **10d**, 53%, (90%) | **10i**, 90%, (96%) | **10n**, 88%, (96%) | **10s**, 72%, (95%) |
| A5 | **10e**, 60%, (97%) | **10j**, 90%, (99%) | **10o**, 86%, (95%) | **10t**, 74%, (99%) |

[a] HPLC-purities were determined at 240 nm. Dopamine D4 affinities were measured by the displacement of the radioligand [$^3$H]spiperone from the D4.4 receptor subtype at a concentration of the test compound of $10^{-7}$ mol/L. Color code: gray = 0−33% displacement, yellow = 34−66% displacement, red = 67−100% displacement.

In conclusion, the 1,3-dipolar cycloaddition proved to be an efficient and practical reaction for the linkage of SPOS handles. Employing the BAL methodology as an example, the *F*ormyl*A*ryloxy*M*ethyl*T*riazole (FAMT) handle **3c** and the *F*ormyl*I*ndolyl*M*ethyl*T*riazole linker (FIMT) **3f** were developed. Application for the parallel synthesis of pharmacological test compounds led to the selective dopamine D4 receptor ligands **10i** und **10s**.

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**Supporting Information Available:** Experimental details for the construction of the resins **3a**−**f**, for parallel synthesis of **10a**−**t**, and for receptor binding assays including affinities of the test compounds for the $D2_{short}$, $D2_{long}$, and D3 subtypes. This material is available free of charge via the Internet at http://pubs.acs.org.

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