Synthesis and Diversification of 1,2,3-Triazole-Fused 1,4-Benzodiazepine Scaffolds
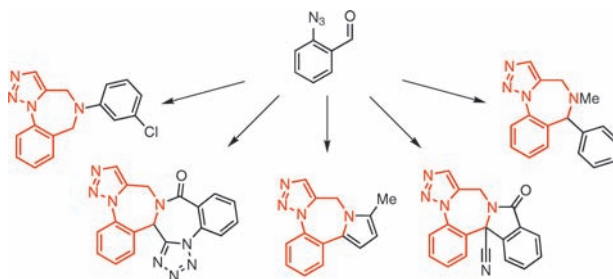
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ABSTRACT

A substituted heterocyclic scaffold comprising a 1,4-benzodiazepine fused with a 1,2,3-triazole ring has been synthesized and diversified via a variety of refunctionalizations. The strategy features the rapid assembly of the scaffold by combining 3−4 reactants in an efficient multicomponent assembly process, followed by an intramolecular Huisgen cycloaddition.

Privileged scaffolds are uniquely suited to the preparation of molecular libraries for lead development in medicinal chemistry.[1] Such frameworks are attractive for drug discovery because of the high hit rates and the pharmacological profiles of their derivatives relative to those of other ring systems. By varying substitutents on these privileged scaffolds, one can often identify potent and selective binders for multiple biological targets from a single library. Indeed, a retrospective analysis of all known drugs reveals that nearly 25% can be traced back to a mere 41 substructures that have since been catagorized as privileged.[2]

The 1,4-benzodiazepine ring system present in **1** is the archetypal privileged structure as defined by Evans more than 20 years ago.[3] Compounds derived from the 1,4-benzodiazepine ring system, which has been suggested to serve as a structural mimic of peptide β-turns[4] and α-helices,[5] bind to a multitude of targets, including G-protein coupled receptors, ligand-gated ion channels, and enzymes.[1a] Accordingly, it is hardly surprising that 1,4-benzodiazepines are found in a large number of pharmaceutical agents.[2] Biologically active natural products such

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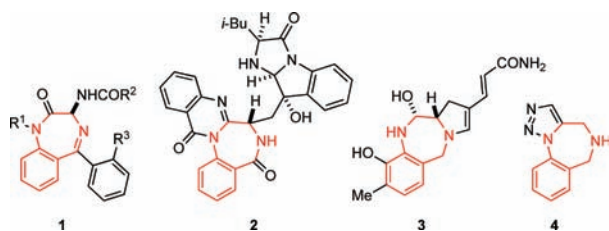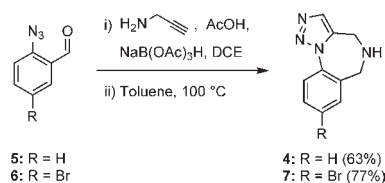(2) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887–2893.

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Figure 1. Derivatives of the 1,4-benzodiazepine ring system.

as asperlicin (**2**)[6] and anthramycin (**3**)[7] also possess a 1,4-benzodiazepine substructure (Figure 1).

We recently developed a general approach for preparing a variety of substituted scaffolds of possible medical relevance by a strategy that involves sequencing multicomponent assembly processes (MCAPs) with subsequent cyclizations.[8,9] During the course of these investigations, we developed an expedient route to a compound bearing the 1,2,3-triazolo-1,4-benzodiazepine scaffold **4**.[10] Although compounds derived from **4** are known to bind weakly to the benzodiazepine receptor[11] and also to inhibit serine proteases,[12] little else is known regarding the biological activity of compounds having this substructure. We now report some extensions of our initial discovery that have led to the facile synthesis of a number of novel members of this intriguing structural subclass of benzodiazepines, including more complex analogs possessing additional fused heterocyclic rings.

We first explored a simple variant of our original MCAP-cyclization approach in accord with the plan outlined in Scheme 1. The parent 1,2,3-triazolo-1,4-benzodiazepine scaffold **4** was prepared from known aldehyde **5**[13] employing a reductive amination, followed by a thermally induced, intramolecular Huisgen cycloaddition. This entry to **4** is both shorter and higher yielding than the reported method.[14] The brominated scaffold **7** was accessed in a similar fashion from the known aldehyde **6**.[15]

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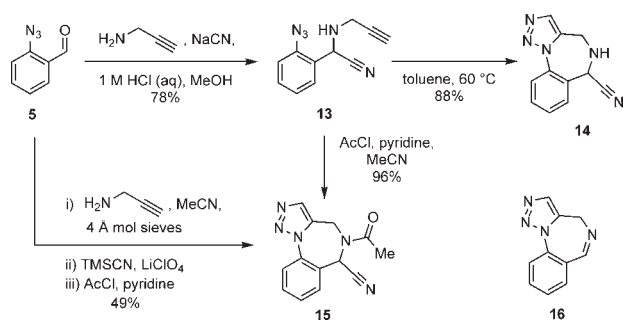
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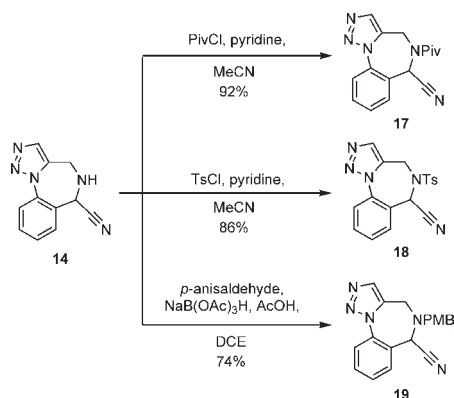(14) Alajarín, M.; Cabrera, J.; Pastor, A.; Villalgordo, J. M. *Tetrahedron Lett.* **2007**, *48*, 3495–3499.

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Scheme 1. Synthesis of Scaffolds **4** and **7**

Scheme 2. Diversification of Scaffolds **4** and **7**
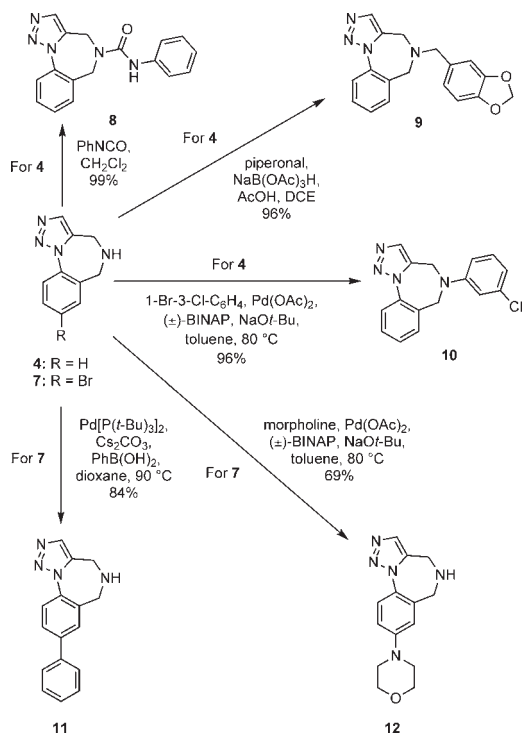
With an efficient route to amine **4** in hand, *N*-diversification was undertaken to afford various analogs. Representative examples of urea formation, reductive amination and cross-coupling using conditions developed by the Buchwald group are given in Scheme 2.[16] The aryl bromide **7** is also a useful intermediate that can be used in diverse cross-coupling reactions. For example, biphenyl substrates are found in many biologically active compounds.[1,2] It therefore occurred to us that hybrid biphenyl-benzodiazepine scaffolds might be of use in lead discovery. We found that **7** underwent a facile Suzuki cross-coupling to give the biaryl **11** in 84% yield. The bromide **7** could also be coupled with secondary amines under Buchwald conditions as exemplified by the use of morpholine to give the aniline derivative **12**.[16]

We envisioned that the triazolobenzodiazepine **14**, which bears an α-amino nitrile function, would be a useful point of embarkation for the preparation of a number of tricyclic and tetracyclic analogs. The benzodiazepine scaffold **14** was thus prepared in 69% overall yield from

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Scheme 3. Synthesis of Scaffold **14** and Direct Access to Amide **15**

Scheme 4. *N*-Diversification of Scaffold **14**

Scheme 5. Amide Derived Diversification of Scaffold **14**

and methyl iodide respectively (Scheme 5). The fused β-lactam **24** was prepared by sequential *N*-acylation of **14** with chloroacetyl chloride to give **20** and treatment of the intermediate amide with sodium hydride in DMF. The β-lactam motif is also a privileged substructure that is present in several pharmaceutical agents and numerous biologically active compounds.[2,17] Under the same conditions, the 2-fluorobenzamide derivative **21** afforded isoindolinone **25** in 76% yield. To the best of our knowledge, this is the first example wherein a nitrile α-anion participates in an intramolecular *ipso*-substitution; this sequence also represents a new entry to isoindolinones, compounds that have also been identified as privileged scaffolds.[18] For example, 1,4-benzodiazepine-fused isoindolinones are of interest as potassium channel antagonists in the treatment of cardiac arrhythmia[19] and Meniere's disease.[20]

1,2,5-Trisubstituted pyrroles can be synthesized from *N*-acyl-α-aminoacetonitriles.[21] Recognizing that pyrrole-fused 1,4-benzodiazepines have been reported as HIV-1 reverse transcriptase inhibitors,[22] we were attracted to the possible application of this underutilized methodology to the synthesis of such compounds. In the event, treatment of the anions generated upon deprotonation of **15** or **26** with NaH with vinyltriphenylphosphonium bromide (Schweizer's reagent) delivered the pyrroles **28** and **29** in 72 and 85% yields, respectively (Scheme 6). Notably, pyrrole formation was complete at ambient temperature within an hour, conditions significantly milder than the high temperatures
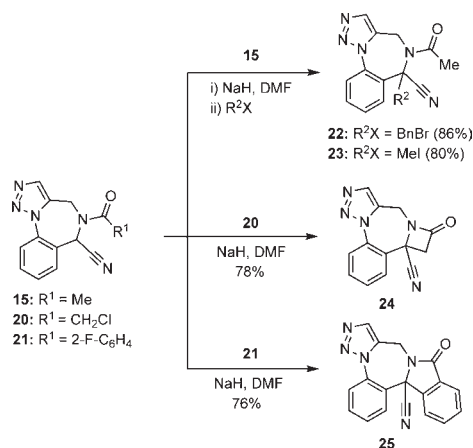
aldehyde **5** via a facile two-step sequence that involved a Strecker reaction as the MCAP, followed by a dipolar cycloaddition (Scheme 3). Careful control of temperature in this conversion is essential because elimination of hydrogen cyanide to produce the known imine **16**[14] is observed at temperatures above 60 °C. *N*-Acetylation of the α-aminonitrile **13** gives an amide that undergoes dipolar cycloaddition at room temperature to afford benzodiazepine **15** in 96% yield; the marked difference in the reactivities of the amine **13** and its derived amide is notable. A "one-pot", four-component reaction was also developed that furnished benzodiazepine **15** in 49% yield.

The *N*-diversification of **14** using a variety of different electrophiles was straightforward and generally proceeded in excellent yields (Scheme 4). Representative examples of *N*-diversification include *N*-acylation of **14** to give amide **17** and *N*-sulfonylation to provide sulfonamide **18**. Reductive amination of **14** led to a variety of tertiary amines of the general type **19**.

The nitrile function in **14** was incorporated at the outset to serve as a functional handle for introducing additional substituents and to facilitate the formation of other rings. We first exploited the acidic character of the proton adjacent to the nitrile to prepare benzodiazepine derivatives **22** and **23** through intermolecular alkylation of the anion generated by deprotonation of **15**, with benzyl bromide

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Scheme 6. Preparation of Pyrrole and Tetrazole-Fused 1,4-Benzodiazepines

Scheme 7. Diversification using the Bruylants Reaction
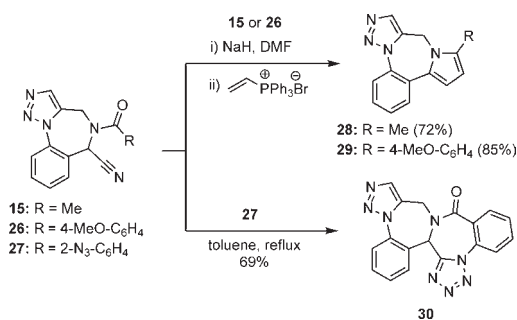
and extended reaction times previously reported in the literature for related cyclizations.[21]

Tetrazole-fused 1,4-benzodiazepines are known benzodiazepine receptor binders[23] and glycoprotein GPIIb/IIIb antagonists.[24] Toward preparing such compounds, we found that **27**, which was readily prepared from **14** by acylation with 2-azidobenzoyl chloride,[25] underwent an intramolecular dipolar cycloaddition upon heating to give the hexacylic fused-tetrazole **30**; a related approach to tetrazole-fused 1,4-benzodiazepines has been reported by Garanti.[26]

The capability of the nitrile function to serve as a leaving group was exploited to synthesize compounds via the Bruylants reaction (Scheme 7). Displacement of the nitrile from **19** under "Reformatsky-type" conditions afforded ester **32** in 75% yield.[27] Amines **33** and **34** were also prepared using a variant of the Bruylants reaction wherein organozinc reagents were used as nucleophiles. It was necessary to transmetallate the Grignard reagents to the

corresponding organozinc species in order to obviate competing deprotonation alpha to the cyano function.

In summary, we have demonstrated the synthesis of a number of diversely substituted 1,2,3-triazolo 1,4-benzodiazepines based upon scaffolds prepared using our approach to diversity oriented synthesis that features an MCAP involving imines followed by various cyclization reactions. A more efficient route to the parent scaffold **4** was developed, and representative derivatives of **4** were prepared. Brominated analogues of **4** are also readily available and may be used in a variety of cross-coupling reactions. Employing the Strecker reaction as the MCAP introduced an α-amino nitrile into the scaffold as a versatile functional handle. The nitrile functionality present in scaffold **14** can be exploited to enable the introduction of additional substituents by Bruylants reaction, α-alkylation or arylation reactions. The nitrile group was also used in ring-forming reactions to give pyrroles and tetrazoles. Extensions of these discoveries to the efficient syntheses of novel targeted libraries are the subject of current investigations.

Supporting Information Available. Experimental procedures, spectral data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds and an improved method for preparing **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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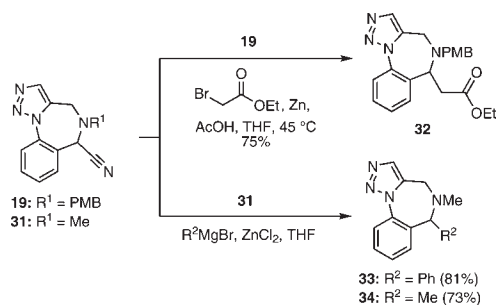
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