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A Combinatorial Scaffold Approach Based upon a Multicomponent Reaction

Fabio Bertozzi, Birgitte V. Gundersen, Magnus Gustafsson, and Roger Olsson*

Discovery Chemistry, ACADIA Pharmaceuticals A/S, Fabriksparken 58, DK-2600 Glostrup, Denmark

roger@acadia-pharm.com

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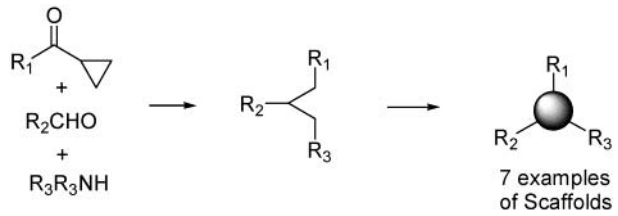
ABSTRACT



A combinatorial scaffolding procedure for the synthesis and spatial arrangement of tripartite structures was developed.

The design of drug-like chemical entities for nonbiased screening constitutes an enormous challenge.[1] Exploring the diversity represented by the amino acid side chains on nonpeptidic scaffolds has proven to be a powerful method for the design of ligands toward a wide range of targets.[2] Recently, ligand-based drug design techniques were utilized for identification of novel nonpeptidic ligands at the somatostatin (SST)[3] and urotensin II (UII)[4] receptors. Both strategies were based on the minimal peptidic motif required for the biological activity, Tyr-D-Trp-Lys and Trp-Lys-Tyr, respectively. Contemporaneously, Hacksell and co-workers published the first nonpeptide UII receptor agonist discovered by screening, using the functional assay technology R-SAT.[5] It is notable that the discovered agonist resembles the minimalized UII peptide motif. In addition to peptidomimetic design, the spatial arrangement of three amino acid side chains or analogues thereof has also been successful in proteomimetic design, mimicking the α-helix.[2b] Overall, these examples signify the importance of the subtle three-dimensional arrangement of the three amino acid side chains. This is especially evident in the case of SST and UII ligands, where the same triad of pharmacophore elements results in activity at different receptors.

Combinatorial scaffold approaches have mainly been based on the decoration of core structures, e.g. dichlorohetero-cycles,[6] or by formation of the skeleton during the addition of the diversity generating building blocks, i.e., diversity-oriented synthesis.[7] We herein report a conceptually distinct methodology of combinatorial scaffolding built upon first

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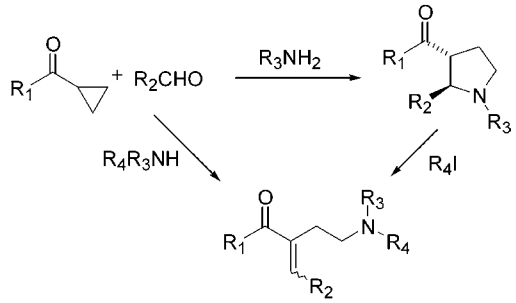
Scheme 1. Metal Iodide Promoted Three-Component Reaction



generating the three necessary pharmacophore elements followed by constructing the central core unit as a fourth diversity point. This fourth diversity point is mainly the diverse spatial arrangement of the pharmacophore elements.

α,*β*-Enones have been used as branching points for the creation of drug-like heterocyclic libraries[8] and were therefore regarded as useful intermediates to set the stage for the construction of the core structures. However, a drawback was that most of the published synthetic procedures of α,*β*-enones gave only products with two diversity points. With the combinatorial scaffolding objectives in mind, we recently developed a practical and efficient multicomponent reaction (MCR) by which substituted pyrrolidines and α,*β*-enones incorporating three diversity points could be synthesized (Scheme 1).[9] Furthermore, these reactions were applicable toward a diverse range of substrates and the products were easily purified by a scavenger resin/ion exchange chromatography procedure.

The chemistry described herein is exemplified by using the structural motif found in the UII[10] receptor agonist (**AC-7954**) previously discovered in our laboratories (Scheme 2).[5] Mixing cyclopropyl phenyl ketone, 4-chlorobenzaldehyde, and ethylamine in the presence of MgI_2 afforded pyrrolidine **1** in 69% yield with an excellent diastereomeric ratio (>99:1).

The central α,*β*-enone **2** was synthesized in a similar way as pyrrolidine **1**, with two exceptions. First, a secondary amine, diethylamine, was used instead of ethylamine and second, to complete a Hofmann elimination of the formed intermediate pyrrolidinium salt, KO^{t}Bu was added at room temperature 2 h prior to the aqueous workup. This procedure gave the α-substituted-α,*β*-enone **2** in 48% isolated yield with an *E*/*Z* ratio of 85:15. Using Et_2AlI instead of MgI_2 as the Lewis acid afforded **2** in 60% yield without any change in the *E*/*Z* ratio.

Although α,*β*-enones have been widely used for the creation of a range of heterocycles, only a few reported examples have incorporated α-substituents and to the best of our knowledge none with additional heteroatom functionalities such as basic amines. The synthesis of five drug-like core structures (**3**−**7**) was selected to exemplify the use of α-substituted-α,*β*-enones (e.g. **2**) as building blocks.

Reaction of *N*-methylurea with **2** at room temperature in the presence of NaOEt proceeded uneventfully and resulted in dihydropyrimidinone **3** in 48% yield as a single regioisomer. ^{1}H NMR experiments showed two singlets at 6.60 and 4.48 ppm assigned as N*H* and H_6, respectively, corroborating the previously assigned structure.[8a]

Reaction of excess dimethyloxosulfonium methylide with **2** resulted in the formation of cyclopropyl ketone **4** as the major product in 70% isolated yield.[11] Only one diastereoisomer was indicated by NMR experiments, and the relative stereochemistry was determined to be anti by NOE measurements. Oxirane byproducts were formed in minor amounts (<5%) according to LC/MS, probably due to the use of excess dimethyloxosulfonium methylide. When a stoichiometric amount of dimethyloxosulfonium methylide was used, a low conversion of the starting material was observed.

The next core structure based on the pyrazoline scaffold was prepared by the condensation of **2** with methylhydrazine in the presence of $InCl_3$. This reaction resulted in 72% yield of pyrazoline **5** as a 3:1 diasteromeric mixture. The stereochemistry of the major isomer was confirmed as having an anti configuration by the strong interaction between H_5 and the protons in the diethylamino chain and by the absence of any NOESY correlation between H_4 (3.56 ppm) and H_5 (3.98 ppm) (see Supporting Information). Furthermore, the minor diastereoisomer had a strong NOESY correlation between H_4 (3.58 ppm) and H_5 (4.17 ppm), clearly indicating a syn configuration of this compound. Additionally, the pyrazoline core was stable to oxidation by air during storage, which also has been noted by others.[8b,12]

Treatment of **2** with benzamidine in DMF under an air atmosphere at 100 °C provided pyrimidine **6** in 53% yield. When the reaction was performed under an argon atmosphere, the corresponding nonaromatized dihydropyrimidine was obtained. Attempts to oxidize it further by vigorously stirring the reaction mixture at 100 °C under an air atmosphere were unsuccessful. Use of the corresponding HCl salt of benzamidine mainly resulted in a poor conversion, and the starting material was recovered.[13]

Finally, the benzothiazepine scaffold **7** was synthesized in 45% yield by reacting **2** with 2-aminothiophenol in toluene

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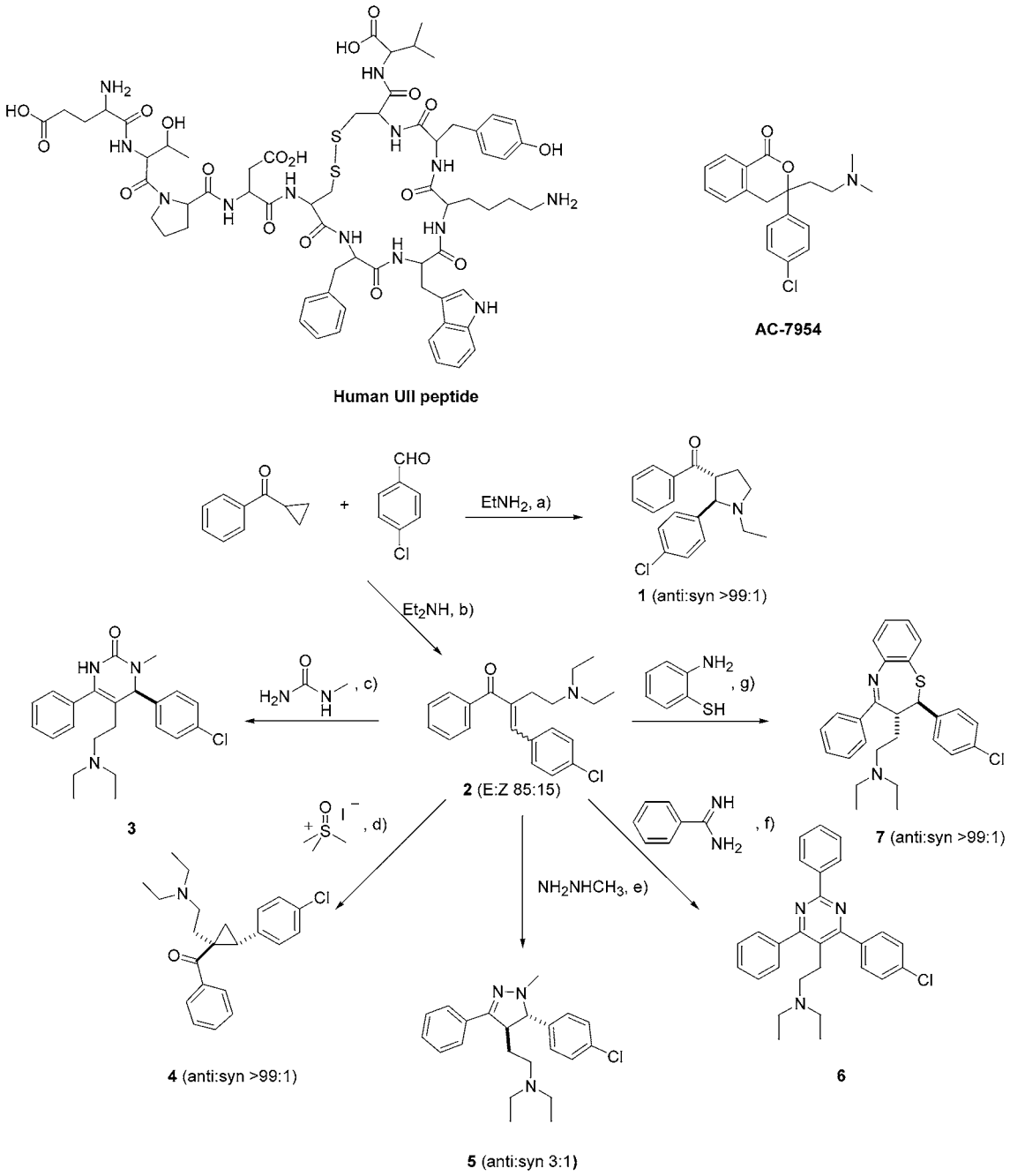
Scheme 2. Combinatorial Scaffolding[a]



[a] Reagents and conditions: (a) MgI_2, THF, 80 °C, 6 h, 69% yield. (b) (i) Et_2AlI, CH_3CN, rt, 15 h; (ii) KO^{t}Bu, rt, 2h, 60% yield. (c) NaOEt, DMF, rt, 12 h, 48% yield. (d) NaH, DMSO, 60 °C, 3.5 h, 76% yield. (e) $InCl_3$, EtOH, 80 °C, 10 h, 72% yield. (f) DMF, air, 100 °C, 12 h, 53% yield. (g) *p*-Toluenesulfonic acid, toluene, 4 Å MS, 110 °C, 24 h, 45% yield.

in the presence of a stoichiometric amount of *p*-toluenesulfonic acid.[14] Other reaction conditions tested, such as AcOH/MeOH or EtOH/reflux,[15] PPh_3/acetone−water/rt,[14] and $InCl_3$/EtOH/reflux or Et_3N/EtOH/reflux,[16] were unsuccessful, resulting in either uncyclized Michael addition adduct or poor conversion. The lack of reactivity in the synthesis of this scaffold might be a reflection of the additional steric crowding in the trisubstituted enone. LC/MS analysis and NMR experiments indicated the formation of one diastereoisomer, which was determined to be anti by NOESY measurements.

In conclusion, we have developed a strategy for the synthesis and spatial arrangement of tripartite structures. The

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one- or two-step synthetic procedure, which affords products having a central cyclic or α,β-enone core, has been achieved by using inexpensive and readily accessible starting materials. Furthermore, including the core structure, this protocol provides compounds with four diversity points, thus giving an average of two diversity points per step. A full account including library synthesis and biological evaluation will be presented in due course.

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Supporting Information Available: General experimental procedures and compound characterization (HRMS, ^{1}H NMR, ^{13}C NMR and stereochemical assignments). This material is available free of charge via the Internet at http://pubs.acs.org.

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