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MULTICOMPONENT REACTIONS IN ALKALOID-BASED DRUG DISCOVERY

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Abstract

Multicomponent reactions are emerging as a powerful tool in alkaloid-based drug discovery. This Highlight describes several recent (all published in 2011) examples of the employment of multicomponent reactions for the synthesis of biologically active alkaloids and their medicinally relevant analogues.

Keywords

alkaloid; cyanocycline A; luotonin; rigidin; tubulyisin; drug discovery; multicomponent reactions

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and a significant component of modern drug discovery. A powerful approach to addressing this challenge involves the utilization of multicomponent reactions (MCRs), which combine three or more reactants together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. In addition to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time and energy savings as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and industry [1, 2]. Although the first example of alkaloid synthesis using an MCR dates back to the classical 1917 synthesis of tropinone by Robinson [3], the utilization of MCRs in natural product chemistry, and specifically alkaloid-based drug discovery, has been rare due to the difficulty in accessing multiple stereogenic centers and/or intricate ring systems commonly associated with natural products [4].

However, a number of creative contributions to this area of research, all published in 2011, have signalled an important emerging paradigm shift. Thus, we believe this timely Highlight, describing these breakthroughs, will foster the "MCR way of thinking" for

synthetic and medicinal chemists involved in alkaloid-based or alkaloid-inspired drug discovery.

Microtubule modifiers tubulysins, alkaloidal tetrapeptides isolated from myxobacteria culture broths, are among the most potent antimitotic agents known to date (structure of tubulysin D in Figure 1). With antiproliferative potencies in picomolar region they represent remarkable leads for the development of new anticancer agents. Wessjohann and co-workers reported an elegant multiple MCR approach to the synthesis of tubugis, tubulysin analogues incorporating a retro-amide functionality in lieu of the acid- and base-labile *N,O*-acetal ester moiety (Figure 1) [5].

This multiple MCR approach involves the assembly of the left hand side dipeptide fragment consisting of D-*N*-methylpipecolic acid and L-isoleucine (Mep-Ile-OH) using the Ugi–Nenajdenko MCR. The right hand side of the molecule is put together through the Passerini–Dömling MCR strategy to give the protected thiazole-containing amino acid tubuvaline. After deprotection and functional group manipulation Mep-Ile-OH and tubuvaline are coupled in an Ugi-4CR process with HCHO or MeCHO as the aldehyde component and *n*-BuNC or Me₂CHNC as the isocyanide component. The addition of the right hand side terminal tubuphenylalanine amino acid then provides several tubugi analogues **1–3**.

The synthesized tetrapeptides were evaluated for cytotoxic activities and found to display subnanomolar potencies similar to the reference compound tubulysin A (Table). These potencies were superior to the gold standard microtubule-modifying agent Taxol. This work serves as an excellent illustration of the power of MCR strategies wherein structurally complex alkaloid-inspired tetrapeptides possessing picomolar antiproliferative activities are synthesized in the most straightforward fashion by an intelligent application of a multiple MCR sequence.

Compound	GI ₅₀ , nM	
	Prostate cancer PC-3	Colon cancer HT-29
Tubugi 1	0.23	0.14
Tubugi 2	0.29	0.34
Tubugi 3	0.22	0.56
Tubulysin A	0.21	0.32
Taxol	7.2	5.3

A cytotoxic alkaloid luotonin A (Figure 2) was isolated from the Chinese medicinal plant *Peganum nigellastrum* and found to display promising anti-topoisomerase I activity. In an attempt to explore its anticancer potential many syntheses of luotonin A have been developed, but because of its topologically challenging structure they involved lengthy sequences and low overall yields. In a groundbreaking contribution to this area of research, Chu and co-workers developed an MCR approach, which allowed to synthesize luotonin A and a number of its analogues **4**, **5** in one step from commercially available materials [6].

The MCR approach is based on reacting isatoic anhydride with propargylamine followed by the addition of aniline, Yb(OTf)₃ and glyoxal and refluxing this mixture in *o*-xylene to furnish luotonin A in 35% yield [6]. A plausible mechanism for this astounding transformation involves a Lewis acid-catalyzed inverse electron demand aza-Diels–Alder reaction of imine **8** to give fully assembled heterocycle **9** followed by its oxidation to the final product luotonin A.

To obtain luotonin A analogues using this MCR, substituted anilines (to obtain **4a–f**) or homopropargylamine (to obtain **5a–e**) were used with equal success [6]. The evaluation of the synthesized analogues in a topoisomerase I inhibition assay revealed that heterocycles **4c,d** and **5b** exhibited more potent activities than luotonin A or the well-known topoisomerase I poison camptothecin. Thus, this simple and effective MCR approach will undoubtedly allow for the generation of ample systematic SAR data and lead to novel anti-topoisomerase I agents potentially useful in the treatment of cancer.

With a focus on pyrrole-containing biologically active alkaloids, our group has developed a series of MCRs leading to the preparation of diversely substituted pyrroles. Thus, we showed that pentasubstituted pyrroles **11** can be prepared by reacting various sulfonamidoacetophenones **10** with aldehydes and active methylene compounds with the

subsequent oxidation of the intermediate pyrrolines with DDQ [7]. In addition, if the mixture of these three components is treated with ethanolic K_2CO_3 , the reaction proceeds *via* sulfonyl elimination and provides tetrasubstituted pyrroles **12**.

We utilized the latter MCR in the synthesis of marine alkaloids rigidins A, B, C, and D, isolated from tunicates obtained near Okinawa and New Guinea [7]. To this end, commercially available aminoacetophenones **13** are converted to the corresponding sulfonamides, which are then condensed with the requisite aldehydes and cyanoacetamide in the presence of K_2CO_3 to give tetrasubstituted pyrroles **14**. The pyrimidinedione ring closure with oxalyl chloride leads to compounds **15**, which are hydrogenolyzed to give rigidins A, B, C, and D in 61, 58, 60, and 53% overall yields, respectively.

Rigidins display antiproliferative and calmodulin antagonistic properties, but their detailed biological evaluation has been hampered by the extremely small quantities of material available from isolation. Several previous synthetic approaches to the rigidin skeleton allowed for the synthesis of rigidin A only and proceeded in 7–9 steps with 13–26% overall yields. Our approach, general for all natural rigidins and highly suitable for the preparation of rigidin analogues, involves only four steps and provides the target molecules in 50–60% overall yields [7]. Studies to utilize this synthetic discovery for the medicinal exploration of the rigidin skeleton are underway.

The naphthyridinomycin family of tetrahydroisoquinoline antibiotics have attracted a considerable attention due to their antimigratory properties and a potential usefulness in the treatment of cancer metastases. The limited availability of these structurally complex alkaloids has plagued their therapeutic development and resulted in a flurry of synthetic activity leading to many total syntheses, for the most part lacking efficiency and generality. Garner and co-workers offered a powerful solution to this problem by reporting a concise total synthesis of cyanocycline A, a representative of this group of alkaloids, based on an asymmetric [C + NC + CC] multicomponent coupling [8]. This MCR of glycyl sultam **21**, aldehyde **20** and methyl acrylate is based on an *in situ* generation of an azomethine ylide from **20** and **21** and its subsequent reaction with the dipolarophile to yield the

stereochemically complex pyrrolidine **19** in 73% yield as a 4:1 mixture with an unwanted stereoisomer.

This successful synthesis of cyanocycline A illustrates the power of an asymmetric MCR in a complex synthetic setting and demonstrates that such approaches can be successful even with highly stereochemically challenging targets. This research also led to the discovery that intermediate **16** inhibited cell migration in a different manner by binding to galectin-3, identifying a new therapeutic target previously not associated with cell migration. Clearly, further biological discoveries and a possible therapeutic development of compounds of this class of alkaloids are now facilitated through this efficient MCR approach.

We believe these examples demonstrating the power of the MCR-based approaches in the synthesis of alkaloids and their medicinally important analogues represent an important paradigm shift in alkaloid-based drug discovery. The "MCR way of thinking" is entering the natural product synthetic and medicinal programs by offering short and versatile synthetic approaches to complex structures. These feats are becoming increasingly more relevant due to the renewed interest in natural products by the pharmaceutical industry and to the failure of alternative methods to deliver many therapeutic lead compounds.

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Fig. 1.
Structures of tubulysin D and its retro-amide analogues – tubugis

Fig. 2.
Structures of luotonin A and several of its analogues prepared in one step by an MCR