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An Efficient Combinatorial Synthesis of Allocolchicine Analogues via a Triple Cascade Reaction and their Evaluation as Inhibitors of Insulin Aggregation

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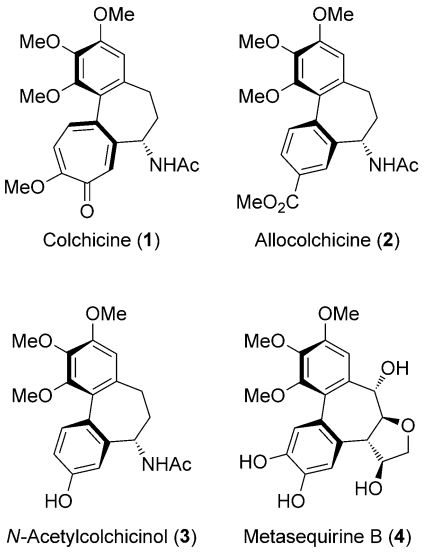
Colchicine (**1**), a known antimitotic alkaloid, exerts its biological action by inhibiting microtubule assemblies via tubulin binding thus acting as a spindle poison during mitosis.[1] Interestingly, colchicine (**1**) also interferes with systemic amyloidosis conditions, and it has been specially used for treatment of amyloidosis implicated for familial Mediterranean fever.[2] Formation of amyloid plaques and fibrils has been established as critically associated with various neurodegenerative conditions, such as Alzheimer's, Parkinson's, Huntington's, and prion diseases, as well as type II diabetes.[3] Triggered by aggregation of misfolded proteins, amyloid fibrillation interferes with several biochemical processes.[4] Thus, inhibition of protein aggregation or disruption of fibrillation might hold the key to understanding the disease pathology and designing small-molecule inhibitors that can interfere with the fibrillation process.[5] Recently, we successfully demonstrated that colchicine inhibits fiber formation in a synthetic peptide, derived from the prion octarepeat sequence, with a propensity to undergo aggregation.[6] Allocolchicine (**2**) and its analogues, such as compounds **3** and **4**, containing a bisbenzocycloheptane [6,7,6] ring system, are known to be efficient tubulin-interactive agents with less apparent toxicity as compared with colchicine.[7] With this in mind and as a continuation of our previous investigations, we designed a set of allocolchicinoids, accessible via a novel synthetic route, to investigate the disaggregation properties of this class of compounds, and this Communication discloses our efforts in this direction.



Allocolchicine (**2**) has been a prominent target in natural product synthesis, and several distinct synthetic approaches have been reported in the literature. These synthetic methodologies include the transformation of natural colchicines,[8] and the use of established chemistry, such as Diels–Alder reactions,[9] biaryl oxidative couplings,[10] direct arylations[11] and Nicholas reactions.[12] Elegant routes to several allocolchicine variants have also been reported.[13] However, the search for a general strategies that allow expeditious access to structural analogues of **2** remains a challenging goal.

Cascade processes, which result in the sequential formation of multiple new bonds in a single synthetic step, are attractive options in natural product synthesis.[14] Our own work has investigated the potential applications of Morita–Baylis–Hillman (MBH) adducts in the preparation of natural-product-like structures through cascade strategies.[15] In this context, we envisioned to develop a one-pot cascade approach to allocolchicine analogues using the allylbenzamides prepared from MBH adducts (Scheme 1). We reasoned that a Suzuki–Miyaura reaction between a 2-formylphenyl boronic acid (**IV**) and an allylbenzamide (**III**) synthesized from a MBH adduct of a 2-halobenzaldehyde in the presence of a base in alkanolic medium would not only result in the formation of the appropriate biaryl compound (**II**) but these conditions might also induce a successive Michael reaction between the alkoxyl group and

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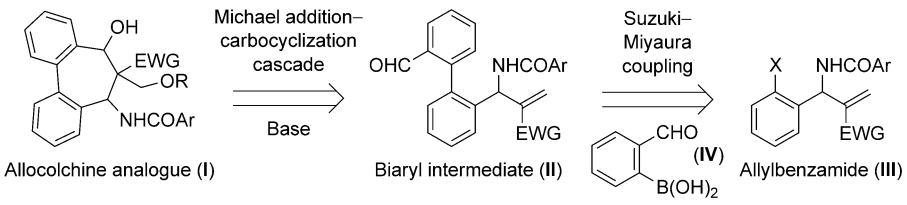
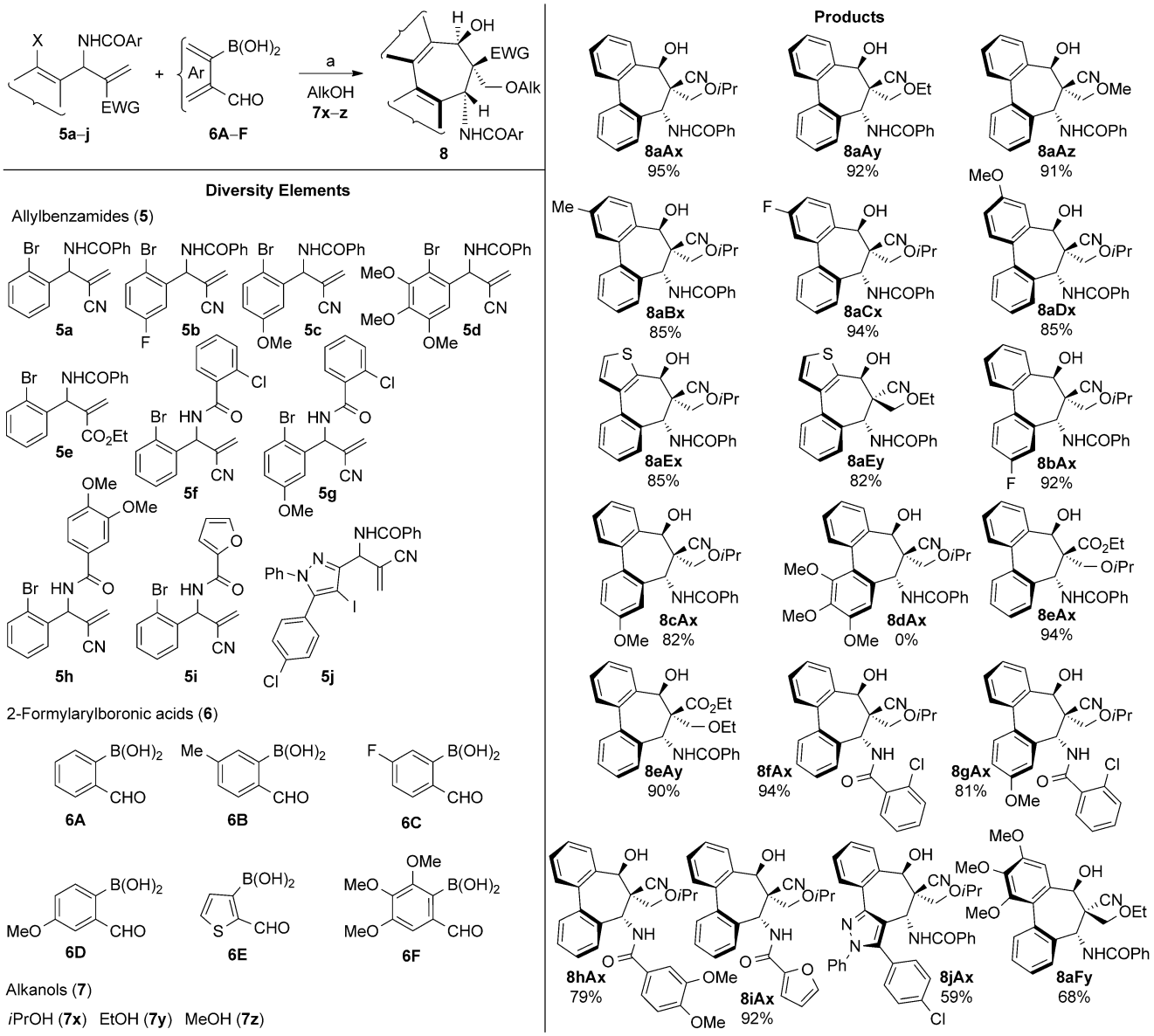


Scheme 1. Retrosynthesis for the preparation of bisbenzocycloheptane ring system (**I**) from allylbenzamide (**III**) and boronic acid (**IV**) via the biaryl intermediate (**II**).

the allylic double bond, with subsequent carbocyclization to afford the bisbenzocycloheptane core (**I**) in one-pot (Scheme 1). Such a strategy would be significantly more flexible than the previously described synthetic approaches to allocolchicinoids as it would allow the introduction of diversity elements at several sites in the allocolchicine structure, making it useful for a medicinal chemistry program.

We began our investigations by exploring the Suzuki–Miyaura reaction of allylbenzamide **5a** with 2-formylphenyl boronic acid **6A** in the presence of tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) and aqueous sodium carbonate in isopropanol (**7x**) at 80 °C under a nitrogen atmosphere. The reaction reached completion in five hours, giving a product in 95% yield, which was characterized to be the anticipated bisbenzocycloheptane derivative **8aAx** (Scheme 2). Importantly, while the product was racemic,



Scheme 2. Synthesis of allocolchicine analogues and scope of the strategy. *Reagents and conditions*: a) **5** (0.5 mmol), **6** (0.6 mmol), Na_2CO_3 (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), **7** (3 mL), 80 °C, 5 h. Isolated yields (%) are reported.

it was observed to be diasteroisomerically pure. The relative stereochemistry of the substitutions in the cycloheptane ring was assigned on the basis of X-ray analysis of the single crystal of **8aAx**. It was observed that the hydroxy group and the nitrile groups were oriented *syn* to each other, while the amide group was *anti* (Figure 1).

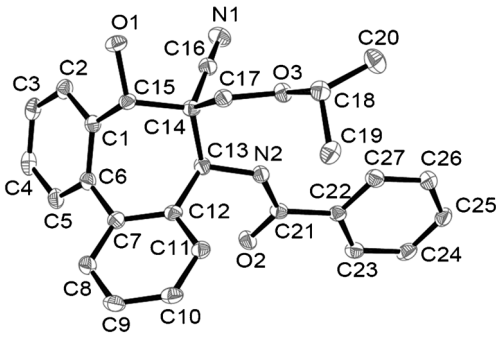


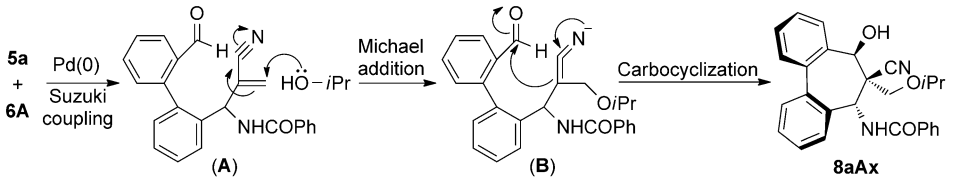
Figure 1. Ortep structure of **8aAx** at 35% probability level

Encouraged by this outcome, the scope of the Suzuki–Michael–carbocyclization cascade was investigated with random combinations of diverse allylamides (**5a**–**j**), substituted 2-formylphenyl boronic acids (**6A**–**F**), and various alkanols (**7x**–**z**), and the results are summarized in Scheme 2. Firstly, different allylbenzamides were investigated by introducing changes in the aryl ring, the electron-withdrawing group (EWG) and the halogen. With the exception of **5d**, all 2-bromophenyl-substituted allylbenzamides (**5a**–**c**,**e**–**i**) reacted with 2-formylphenyl boronic acid **6A** in isopropanol (**7x**) to give the anticipated products in excellent yields. In contrast, reaction with allylbenzamide **5d** invariably resulted in the debrominated allylbenzamide (see the Supporting Information). Replacing the nitrile group with a carboxyethyl as in **5e** or varying the aroyl moiety as in **5f**–**i** had no effect on the outcome. However, replacing the bromide with iodide as in allylbenzamide **5j** did give the desired product (**8jAx**), albeit in only moderate yield.

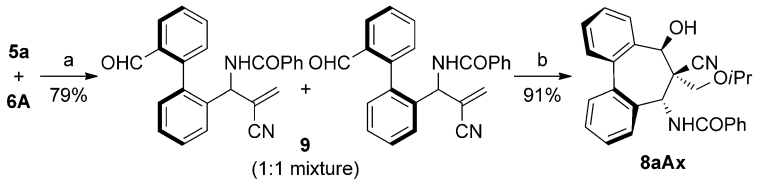
With the effectiveness of the methodology to afford a 6,7,5 tricyclic system confirmed, the versatility of the one-pot protocol was further investigated by employing different commercially available 2-formylphenyl boronic acids (**6A**–**E**), and encouragingly, all reactions afforded the corresponding products in excellent yields (Scheme 2). The successful formation of compounds **8aEx** and **8aEy** containing a 5,7,6 fused tricyclic core extended the scope of the methodology still further. The effect of alkanols was investigated by replacing the isopropanol (**7x**) with ethanol (**7y**) and methanol (**7z**). Fortunately, the reactions were successful in these additional alkanols, giving access to products **8aAy** and **8aAz**, respectively, in excellent yields. Finally, in order to obtain the product containing the trimethoxy phenyl unit as in allocolchicine, boronic acid **6F** was prepared (see the Supporting Information) and reacted with allylbenzamide **5a** in ethanol (**7y**) to give **8aFy** in 68% yield.

A plausible mechanism for the one-pot tandem synthesis of allocolchicine-like derivatives is outlined in Scheme 3. We propose that an initially Suzuki coupling between allylbenzamide (**5**) and 2-formylaryl boronic acid (**6**) affords a biaryl intermediate (**A**), which in the presence of a base undergoes a Michael addition of the alkoxyl group onto the double bond to afford intermediate **B**. Concomitant carbocyclization of intermediate **B** affords product **8**.

In order to ascertain the mechanism, in a controlled experiment, **5a** was reacted with **6A** in the presence of 5 mol% of $Pd(PPh_3)_4$ and aqueous sodium carbonate in dioxane at 80 °C. The reaction reached completion in two hours to afford the anticipated biaryl intermediate (**9**) in 79% yield as a 1:1 mixture of atropisomers (Scheme 4). Treating biaryl **9** further with aqueous sodium carbonate in isopropanol (**7x**) at 80 °C furnished the expected compound (**8aAx**) in 91% yield as a pure diastereomer. This result infers that the Michael-addition-induced carbocyclization controls the stereochemistry of the product.



Scheme 3. Plausible mechanism for the triple cascade reaction. The reaction of **5a**, **6A** and isopropanol (**7x**) to form **8aAx** is used here as an example.



Scheme 4. Synthesis of biaryl intermediate **9** and its transformation to the corresponding allocolchicine analogue. **8aAx** was used as representative compound to study the mechanism of formation. *Reagents and conditions*: a) **5a** (0.3 mmol), **6A** (0.4 mmol), Na_2CO_3 (0.6 mmol), $Pd(PPh_3)_4$ (5 mol%), dioxane (2 mL), 80 °C, 2 h; b) **9** (0.1 mmol), Na_2CO_3 (0.2 mmol), isopropanol (2 mL), 80 °C, 3 h.

With the allocolchicine-like compounds in hand, a structurally diverse subset including **8aAx**, **8aCx**, **8aAz**, **8eAx**, **8eAy** and **8hAx** was selected to probe their disaggregation potential in a general assay involving a self-aggregating pentapeptide conjugate. Microscopic experiments revealed that co-incubation of these compounds with the peptide conjugate prevented fibrillation, and furthermore, addition of these compounds to 10 days old mature aggregated peptide conjugate samples

gave rise to disaggregation of the fibers (see the Supporting Information). All of the synthesized compounds were evaluated for their cytotoxicity in Vero C1008 cells (monkey kidney fibroblasts). Compared with podophyllotoxin, none of the compounds show cytotoxicity. Despite the lack of cytotoxicity, compounds **8eAx** was selected as a representative compound (due to its superior solubility in aqueous medium) for evaluation of its tubulin polymerization inhibitory activity, and it was found to have no effect (see the Supporting Information). It is was previously reported that alteration of the trimethoxy substitutions in the A ring of allocolchicine (**2**) leads to loss of tubulin binding activity.[16]

Encouraged by the preliminary result concerning the potential of these compounds to inhibit fibrillation of a synthetic peptide, we were prompted to investigate their ability to interfere with protein aggregation taking bovine insulin (BI) as a model. Insulin, a zinc-containing peptide hormone, is an essential component of glucose metabolism, and it self-aggregates to form amyloidogenic fibers.[17] These fibers are formed through a series of sequential events that include monomer nucleation, elongation, and maturation. These stages require an intricate interplay of both hydrophobic and electrostatic interactions, along with the requirement of cross β-structures.[18] External factors such as temperature, pH, ionic strength, and solvent effects, are known to accelerate the process of fiber formation.[19]

As a preliminary screen, **8hAx** was selected for the insulin aggregation inhibition studies using circular dichroism (CD), thioflavin T (ThT) florescence, and atomic force microscopy (AFM). The inhibitory effect of **8hAx** was first monitored by far-ultraviolet (UV) CD spectroscopy. As a control, a fresh solution of BI was prepared in hydrochloric acid (pH 1.6) at 65 °C. CD bands characteristic of the native α-helix conformation were noted at 209 and 220 nm (Figure 2).[5e,20] However, after one hour of incubation, a new CD band at 218 nm corresponding to a β-sheet was observed, indicating involvement of a conformational change during insulin fibrillation. BI was then co-incubated with **8hAx** at three different concentrations (50 and 100 μM: Figure 2; and 200 μM: see the Supporting Information). Maximum inhibition up to 18 hours was seen with 100 and 200 μM solutions of **8hAx**. Interestingly, fibrillation was resumed upon longer incubation, as confirmed by the appearance of a peak at 218 nm (see the Supporting Information). This resumption of insulin fiber formation could be ascribed to a shift in the equilibrium of the fibrillation process.[17b]

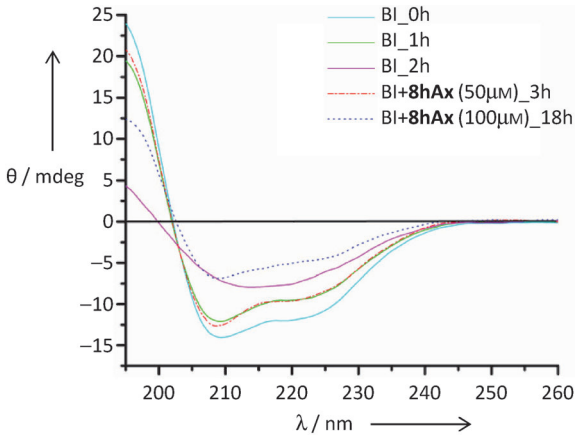


Figure 2. Far-UV circular dichroism (CD) spectra of bovine insulin (BI) and its inhibition by **8hAx** at 50 μM and 100 μM in HCl (pH 1.6) at 65 °C recorded at different time intervals.

A ThT florescence assay, typically used to observe amyloid fibrillation, was employed to further monitor the inhibition process. Upon interaction with amyloid fibers, ThT, a nonflorescent dye, exhibits an enhanced emission at 482 nm.[21] Incubation of insulin with ThT alone (20 μM) afforded a fluorescence maxima at ~485 nm after two hours, suggesting the amyloidogenic nature of the aggregated fibers. Next, fresh solutions of BI were co-incubated with five different concentrations of **8hAx** along with ThT (pH 1.6) at 65 °C. Compound **8hAx** exerted an inhibitory effect as evident by a loss of fluorescence intensity. Notably, a concentration as low as 50 nM was able to inhibit insulin fibrillation up to three hours (Figure 3). This is a remarkable observation as further optimization of pharmacophores present in the allocolchinoid skeleton might afford better and more potent inhibitors of insulin amyloidogenesis.

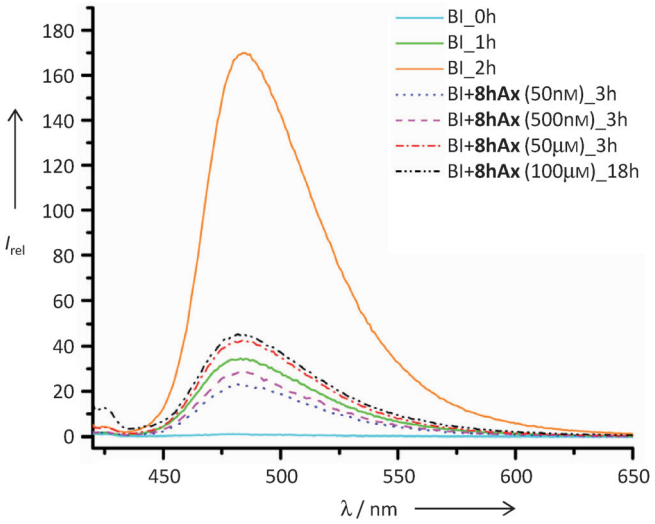


Figure 3. Results of a ThT fluorescence assay of bovine insulin (BI) and its inhibition by **8hAx** at varying concentrations in HCl (pH 1.6) at 65 °C recorded at different time intervals.

The native state of the insulin polypeptide can become compromised under particular solution conditions, characterized by a conformational switch from a predominantly helical structure to a cross β-structure, which is a hallmark of amyloidogenic fibrillar aggregates.[22] It is also recognized that insulin fibers impede long-term storage of hormone and may lead to formation of insulin fibers at the site of hormone injection.[17c] Thus, it was of interest to visualize aggregated fibers and possible changes in their morphology upon interaction with **8hAx**. Using AFM, mature bovine insulin fibers were characterized as having a diameter of 20 nm after incubation in HCl solution (pH 1.6) at 65 °C for 18 hours (Figure 4a). Notably, time-dependent microscopy of insulin solution, co-incubated with **8hAx**

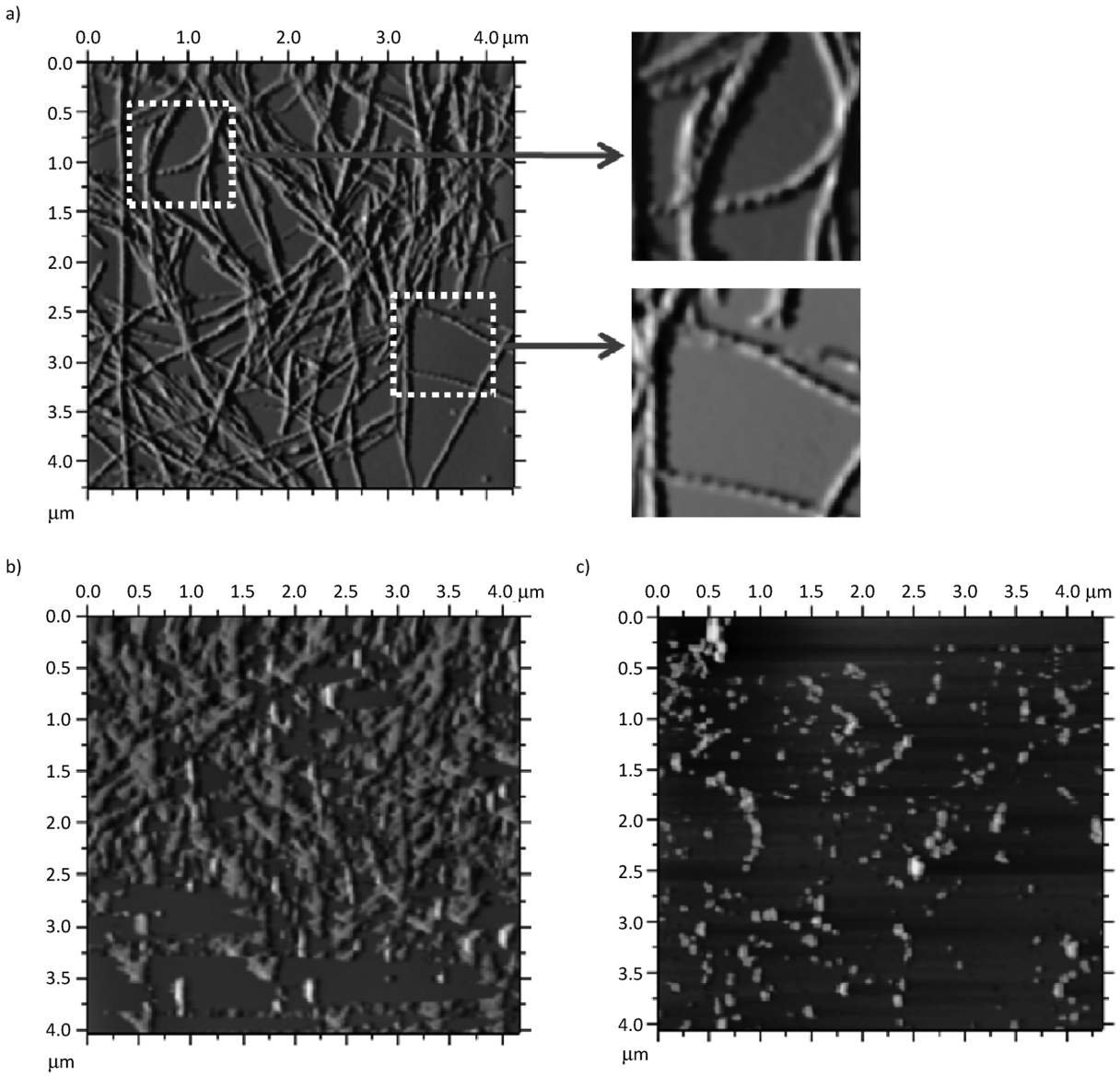


Figure 4. AFM micrographs of a) bovine insulin after 18 h; inset shows magnified view of the braided fibrillar structure. Time dependent co-incubation with **8 hAx** (100 μM) after b) 6 h and c) 18 h.

(100 μM), also showed effective inhibition of fibril formation (Figure 4 b,c). Hence, from the results of inhibition of BI aggregation, it can be inferred that **8 hAx** could serve as a potential peptide/protein aggregation inhibitor possibly by interfering with the early steps of insulin nucleation. The precise mechanism of this interference remains to be elucidated.

In conclusion, we have developed a one-pot diastereoselective preparation of allocolchicine analogues from allylbenzamides derived from MBH adducts. This protocol, which progresses via an unusual triple cascade reaction comprising of a Suzuki coupling, a Michael addition, and a carbocyclization, is highly versatile, working over a broad range of substrates, and affords structurally diverse allocolchinoids, which may become important when creating drug-like libraries of this class of compound. The preliminary results with **8 hAx**, one of the synthesized derivatives, reveal effective inhibition of fiber formation at 50 nM in ThT amyloidogenic fluorescence studies suggesting potential of these derivatives as inhibitors of insulin amyloid formation. These results show that allocolchicinoids warrant further exploration as inhibitors of peptide/protein amyloidogenesis, and it is proposed that further structural refinement will be able improve the activity of this class of compounds.

Experimental Section

An example procedure for the synthesis of compounds **8** is given below. Full experimental protocols and characterization data for all other compounds **8** are given in the Supporting Information, along with details of the biological assays used to evaluate these compounds.

***N*-(6-Cyano-7-hydroxy-6-(isopropoxymethyl)-6,7-dihydro-5*H*-dibenzo[*a*,*c*][7]annulen-5-yl)benzamide (8 aAx)**: A suspension of **5 a** (0.20 g, 0.59 mmol), 2-formylphenylboronic acid **6 A** (0.10 g, 0.65 mmol), 2 M aq Na_2CO_3 (0.13 g, 1.18 mmol) in 2-propanol (3 mL) was degassed with N_2 for 15 min and maintained under an N_2 atmosphere. $Pd(PPh_3)_4$ (0.034 g, 0.03 mmol) was added to the suspension, and the reaction mixture was transferred to an oil bath and heated with stirring at 80 °C until all starting materials were consumed (monitored by TLC). Excess 2-propanol was removed in vacuo, and the crude aqueous mixture was extracted with EtOAc (3×10 mL). The combined organic layer was washed with saturated aq NaCl, dried over anhyd Na_2SO_4, filtered and concentrated in vacuo to yield the crude product as a brown oil. Chromatographic purification using silica gel (EtOAc/hexane, 1:4) afforded **8 aAx** as a white solid (0.24 g, 95%): R_f = 0.21 (hexane/EtOAc, 70:30); mp > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3H, J = 6.0 Hz), 1.41 (d, 3H, J = 6.1 Hz), 2.66 (d, 1H, J = 5.8 Hz), 3.84–3.97 (m, 2H), 4.10–4.19 (m, 2H), 5.22 (d, 1H, J = 6.3 Hz), 7.39–7.47 (m, 4H), 7.53–7.56 (m, 4H), 7.76–7.84 (m, 3H), 9.00 ppm (d, 1H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 21.6, 22.1, 55.7, 57.1, 68.5, 69.2, 74.0, 118.4, 124.6, 124.7, 126.7, 127.7, 127.9, 128.0, 128.2, 128.3, 131.5, 133.7, 134.4, 136.4, 137.4, 137.7, 166.0 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1668, 2268, 3402 cm^{-1}; MS (ES+): *m/z* (%): 427.1 $[M+H]^+$ (100); HRMS-ES: *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_3$: 427.2022, found 427.2026.

CCDC 954008 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: alkaloids · antiaggregation agents · cascade reactions · natural products · one-pot syntheses

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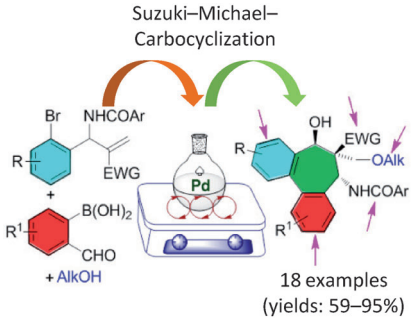
COMMUNICATIONS

A controlled cascade: A divergent, diastereoselective and efficient one-pot synthesis of allocolchicinoids via a cascade Suzuki–Michael addition–Carbocyclization sequence is described. The utility of the compounds as possible inhibitors of insulin aggregation is also presented.



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An Efficient Combinatorial Synthesis of Allocolchicine Analogues via a Triple Cascade Reaction and their Evaluation as Inhibitors of Insulin Aggregation