

Highlights in the Solid-Phase Organic Synthesis of Natural Products and Analogues

Vera Lucia Eifler-Lima,^{*,a} Cedric S. Graebin,^{#,a} Flavia De Toni Uchoa,^a
Patrícia D. Duarte^b and Arlene G. Corrêa^{*,b}

^aLaboratório de Síntese Orgânica Medicinal - LaSOM, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Avenida Ipiranga, 2752/705, 90610-000 Porto Alegre-RS, Brazil

^bLaboratório de Síntese de Produtos Naturais, Departamento de Química, Universidade Federal de São Carlos, Rodovia Washington Luis km 235, CP 676, 13565-905 São Carlos-SP, Brazil

Neste trabalho nós apresentamos uma revisão sobre a síntese em fase sólida de metabólitos secundários, tais como alcalóides, poliaminas, esteróides, terpenos e flavonóides, descritos na literatura a partir de 2000. Um número considerável de rotas sintéticas elegantes e desafiadoras, usando suportes sólidos, será discutido.

In this manuscript, we disclose solid-phase organic syntheses (SPOS) of small-molecules of some secondary metabolites, such as alkaloids, polyamines, steroids, terpenes, and flavonoids, described in the literature since 2000. A number of elegant, efficient and challenging syntheses on solid support will be presented.

Keywords: solid-phase organic synthesis, combinatorial chemistry, natural products, secondary metabolites

1. Introduction

Combinatorial Chemistry, which came to light in the early 90s, is the art and science of synthesizing and testing compounds for bioactivity *en masse*, instead of one by one, the aim being to discover drugs and materials more quickly and inexpensively than was formerly possible.¹ The combinatorial methodologies applying to the medicinal chemistry purposes try to incorporate elements capable to furnish a library with both diversity and drug likeness properties in order to shorten time and costs. Combinatorial chemistry has changed the paradigms of drug discovery because with the automatized and miniaturized synthesis, the research time consuming is shortened, rapidly leading to a library of analogues substances with different functional groups or conformational architectures.

The solid-phase organic synthesis (SPOS) has emerged as a powerful tool in the synthesis of small molecules intending to exploit combinatorial chemistry to discover new hits.² In SPOS,³ the solid support-bound substrates are

elaborated synthetically by using an excess of reagents to drive reactions to completion. Desired products can then be isolated easily by simple filtration and removed from the support material. In SPOS, the substrate is coupled to a chemically inert insoluble polymer (resin or lantern) by a covalent bond. This bond must remain stable during the whole chemical process (the orthogonally principle¹), allowing the cleavage of the product from the resin (*e.g.* by hydrolysis or nucleophilic attack) at the end of the synthetic pathway.

The solid-phase has a principal advantage upon the synthesis carried out in solution, the facility in the purification process which can allow the automation of the whole synthesis. Moreover, the SPOS presents additional advantages: the possibility of using excess of reagents to assure the completion of reactions and the “pseudo-dilution” effect.⁴

Despite of these advantages, SPOS also presents some important drawbacks: it can be difficult to adapt some conventional solution phase chemistry to a solid-phase format and the progress of solid-phase reactions can be difficult to monitor. An alternative is the use of polymer-support reagents, catalysts, and cleanup agents (scavengers), which facilitate reactions of substrates in solution.

*e-mail: eifler@farmacia.ufrgs.br; agcorrea@ufscar.br

[#] Present address: Departamento de Química, Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro - UFRRJ - BR 465, km 7, 23890-000 Seropédica-RJ, Brazil

The SPOS is an effective tool for organic synthesis of molecules with low molecular mass. Conceived by Bruce Merrifield for the peptide synthesis,² more than four decades ago, the SPOS have had its action field increased towards polyfunctionalized molecules synthesis and medicinal chemistry. Nowadays SPOS grows up with the development of new resins, linkers, synthesizers, methods to monitoring reactions and resins for scaling up. The SPOS saves time, one of the most important feature at the initial stage of a new drug discovery programs and, in fact, SPOS made combinatorial chemistry successfully and feasible.

Natural products (NPs) are very important for human therapy due to their ability to modulate many pharmacological events. The use of NP in medicine is as older as human civilization.⁵ The first NPs isolated from natural sources in the 19th century were the alkaloids, since then, hundreds of bioactive compounds have been isolated from plants, animal or microorganisms with different architectures, presenting high chemical diversity like: terpenes, coumarins, flavonoids, acetogenins and many others.

The true inventor of combinatorial chemistry is nature, with the generation of molecules with all possible structures: sophisticated or simple compounds.⁶ However, we have few examples of “natural drugs” (templates) which are formulated for ready availability as medicine.⁷ In the majority of cases the “natural drugs” must be chemically modified in order to improve their pharmacological profile.⁸ Sometimes the medicinal chemist synthesizes structural analogs because its pharmacological profile cannot be appropriate to the target, in function of several aspects from biological, chemical or even physic-chemical nature. Actually, the medicinal chemists employ natural products as a source of potentially bioactive compounds (hits) for drug discovery or even as scaffolds for chemical diversification employing numerous options for the synthesis of a wide array of structural variations, like solid-phase synthesis as well as combinatorial approaches. They can synthesize derivatives more potent than the template, with higher drug-like properties or with new pharmacological activities not detected before. Thus, new routes of solid-phase synthesis are drawn from three general strategies: *i*) employing natural products as scaffold, that is, anchoring on solid support for chemical changes, *ii*) use of building blocks linked to the solid support for synthesize natural products and analogs, and *iii*) the total synthesis of natural products.

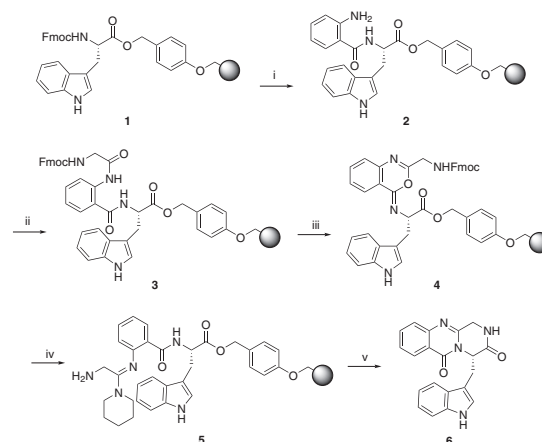
In this manuscript, we disclose SPOS of small-molecules of some secondary metabolites, in the literature since 2000, employing those strategies. A number of elegant, efficient and challenger synthesis on solid support will be described.

2. Alkaloids

Alkaloids are one of the most important classes of natural products due to their ability to modulate many pharmacological events. The earliest alkaloids isolated from natural sources in the 19th century are still used in therapy (*e.g.*, morphine, quinine, or atropine). After that, many alkaloids with different chemical structures were isolated, contributing to the discovery of new and important drugs. Because of this, the synthesis of alkaloids has become an important milestone for medicinal chemistry, as illustrated by the numerous synthetic routes and methods found in literature in order to facilitate their use in pharmaceutical production.

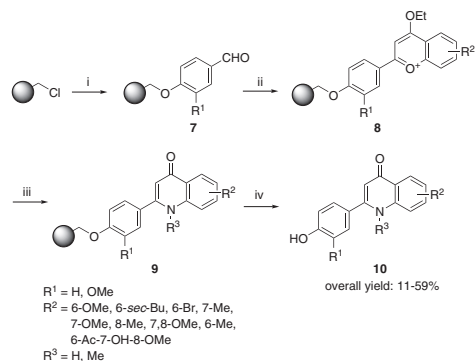
In 2000, Wang and Ganesan⁹ published the total solid-phase synthesis of the fumiquinazoline alkaloids. Commercially available Wang resin loaded with Fmoc-L-Trp **1** was deprotected and coupled with anthranilic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) as activating agent, followed by coupling with Fmoc-Gly in pyridine. Dehydrative cyclization of linear tripeptide **3** was carried out with 10 equiv. of triphenylphosphine. The final reaction was piperidine mediated deprotection of the Fmoc group and rearrangement of oxazine **4** to amidine carboxamide **5**. After washing, the resin was refluxed in a mixture of acetonitrile/dichloroethane to induce cyclization and cleavage furnishing (+)-glyantrypine **6** (Scheme 1).

Sato *et al.*¹⁰ synthesized fourteen 4-quinolinones by aqueous ammonia treatment of the flavylium salts **8** obtained by the three-component condensation reaction of acetophenones, aldehydes, and ethyl orthoformate on a solid support with excellent purity and in overall yields of 11-59% (Scheme 2).



Reagents and conditions: (i) (a) piperidine; (b) anthranilic acid (10 equiv.), EDC (12 equiv.); (ii) Fmoc-Gly-Cl (7 equiv.), pyridine (15 equiv.); (iii) $\text{Ph}_3\text{P}/\text{I}_2/\text{EtN}(i\text{-Pr})_2$ (11/11/22 equiv.); (iv) piperidine; (v) $\text{MeCN}/\text{ClCH}_2\text{CH}_2\text{Cl}$ (1:1), reflux overnight.

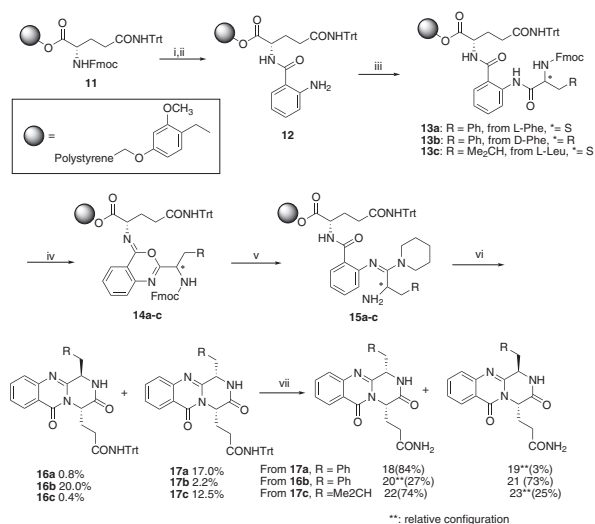
Scheme 1.



Reagents and conditions: i) *p*-hydroxybenzaldehydes, NaH, DMF, 80 °C; ii) acetophenones, HC(OEt)₃, CF₃SO₃H, CH₂Cl₂, rt; iii) NH₃, rt; iv) CF₃CO₂H, CH₂Cl₂.

Scheme 2.

Wang and Sim¹¹ reported the synthesis of the quinazoline alkaloids verrucine A (**18**) and B (**21**) (Scheme 3). Starting with Fmoc-L-Gln(Trt)-Sasrin-resin **11**, the Fmoc was removed using piperidine, and the resulting amino resin was coupled with anthranilic acid to give peptide **12**. The anthranilamide **12** was initially acylated with Fmoc-L-phenylalanine acid chloride. Due to the highly acid labile property of the Sasrin resin, the reaction solution was kept neutral to minimize the possible cleavage of the resin. The linear peptide **13a** was dehydrated to give benzoxazine **14a**, which was further deprotected and transformed to the amidine intermediate **15a**. Cyclization of **15a** in refluxing MeCN-Cl(CH₂)₂Cl provided *N*-trityl verrucine A **17a** as the



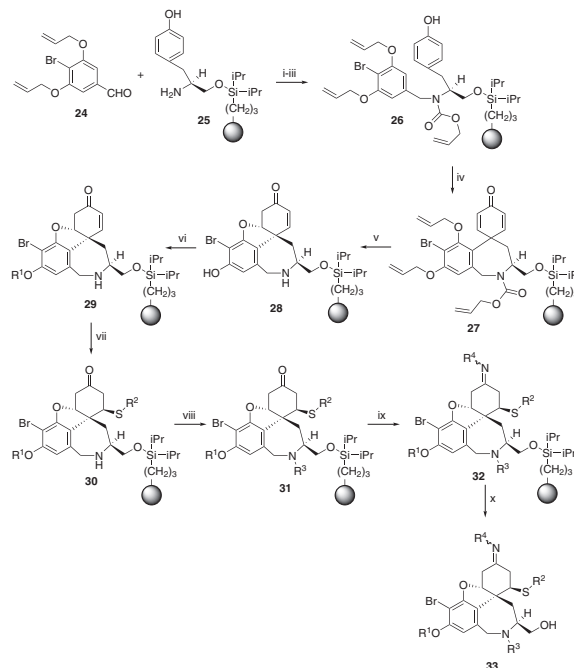
Reagents and conditions: i) 20% piperidine in DMF, 15 min (2×). ii) EDC (13.4 equiv.), anthranilic acid (12.1 equiv.), DMF (method A) or NMP (method B), r.t. 19 h. For **13a-17a**: iii) pyridine (7.9 equiv.), Fmoc-L-Phe-Cl (5.1 equiv.), CH₂Cl₂, r.t. 13 h, workup; repeat once in MF. iv) Ph₃P (12.0 equiv.), I₂ (11.1 equiv.), Et(*i*-Pr)₂N (25.0 equiv.), CH₂Cl₂, r.t., overnight (15 h). v) 20% piperidine in CH₂Cl₂, r.t. 30 min. (vi) MeCN/(CH₂Cl₂)₂ (1:1), reflux overnight. vii) TFA/Et₃SiH/CH₂Cl₂ (2:2:1), r.t., 15 min.

Scheme 3.

major product in 12% overall yield from **11**. Verrucine A (**18**) was obtained in 84% yield by deprotecting **17a** with 40% trifluoroacetic acid (TFA) in CH₂Cl₂.

Galanthamine is a tetracyclic alkaloid isolated from *Galanthus woronowii* and shows potent acetylcholinesterase inhibition. This alkaloid has several points for diversity-generating reactions. In order to explore the potentialities of galanthamine beyond those previously related to this natural product, Pelish and co-workers¹² employed the diversity oriented synthesis (DOS) approach to build a library based upon galanthamine core **33** (Scheme 4). The synthetic strategy chosen was the biomimetic solid-phase synthesis of 2527 galanthamine analogues, starting with the attachment of a tyrosine derivative to a resin through a Si-O bond. The diversity was accomplished by using several building blocks that reacted in > 80% yield. After six steps, including the cleavage stage, the presence of 2527 out of 2946 (86%) compounds was confirmed by mass spectrometry. Evaporation of the cleavage reaction solution and resuspension in dimethylsulfoxide (DMSO) afforded the stock solutions for biological screening.

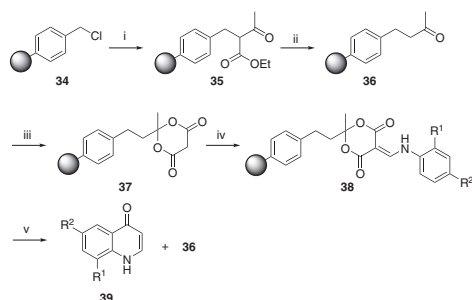
Huang and Liu described a solid-phase synthesis of a series of 4(*H*)quinolones.¹³ A resin-bound cyclic



Reagents and conditions: Reagents: i) CH(OCH₃)₃, CH₂Cl₂, wash, then NaBH₃CN, AcOH, MeOH, THF, 23 °C; ii) allylchloroformate, *i*-Pr₂EtN, CH₂Cl₂, 23 °C; iii) piperidine, THF, 23 °C; iv) Ph(OAc)₂, (CF₃)₂CHOH, CH₂Cl₂, 23 °C; v) Pd(PPh₃)₄, morpholine, THF, 23 °C; vi) R¹OH, PPh₃, diisopropyl azodicarboxylate (DIAD), THF, 0 °C, (2×); vii) R²SH, 2,6-lutidine, *n*-BuLi, THF, 0 to 40 °C; viii) R³CHO, AcOH, MeOH, THF, then NaBH₃CN in MeOH, 23 °C or R³COCl, 2,6-lutidine, CH₂Cl₂, 23 °C or R³NCO, CH₂Cl₂, 23 °C; ix) R⁴NH₂, AcOH, MeOH, CH₂Cl₂, 23 °C; x) HF, pyridine, THF, 23 °C, then trimethylsilyl methoxyde (TMSOMe).

Scheme 4.

malonic ester has been prepared on Merrifield resin (Scheme 5). Reaction of the cyclic malonic ester **37** with triethyl orthoformate and subsequent substitution by an arylamine afforded arylaminomethylene cyclic malonic ester preloaded resin **38**. A series of 4(1*H*)quinolones were prepared by thermal cyclization in moderate yields and high purity.

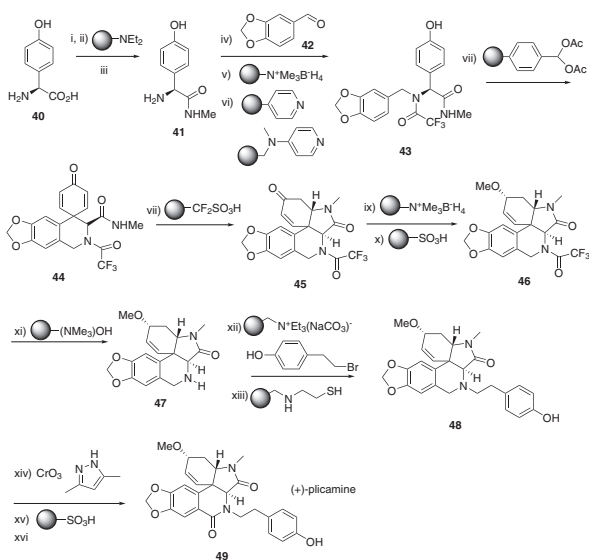


Reagents and conditions: i) sodium ethyl acetoacetate, DMF, 80 °C, 16 h; ii) DMSO, NaCl, 140 °C, 48 h; iii) malonic acid, acetic anhydride, conc. H₂SO₄; iv) a. HC(OEt)₃, reflux, 6 h; b. substituted anilines, reflux, 20 h; v) thermolysis, N₂, 240 °C, 30 min.

Scheme 5.

In 2002, Baxendale and co-workers¹⁴ described the total synthesis of the amaryllidaceae alkaloid (+)-plicamine (**49**) and its unnatural enantiomer by using solid-supported reagents and scavengers in a multistep sequence of reactions (Scheme 6).

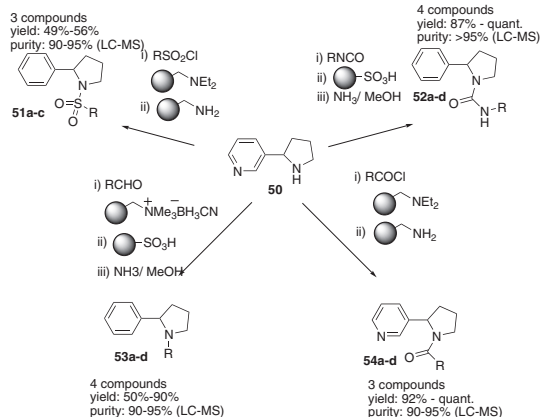
In the same year, Baxendale *et al.*¹⁵ demonstrated the rapid construction of a small collection of nicotine derivatives using a range of readily available monomers



Reagents and conditions: i) TMSCl/MeOH; iii) NH₂Me; vi) (CF₃CO)₂O, CH₂Cl₂; x) TMS-CHN₂; xvi) Clay scavenger.

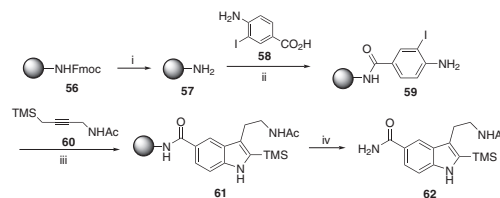
Scheme 6.

(Scheme 7). They synthesized normicotine (**50**) and other functionalized derivatives using solid-supported reagents and scavengers.



Scheme 7.

Finaru *et al.*¹⁶ reported the solid-phase synthesis of the indole core of melatonin analogues under microwave irradiation. The acid-labile Rink linker was chosen for connection of aromatic iodide **58** to polystyrene. Generation of various indole derivatives **62** was performed in four steps via a palladium-mediated reaction between 2-iodoaniline **59** derivatives and functionalized acetylenes **60** (Scheme 8).

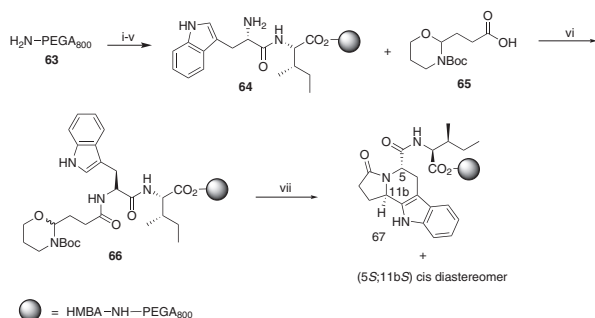


Reagents and conditions: (i) piperidine 20%, dimethylacetamide (DMA), r.t., 60 min; (ii) **61** (4.4 equiv.), O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoroborate (TBTU) (4.4 equiv.), HOBT (2 equiv.), NEt₃ (14.4 equiv.), DMAP (1 equiv.), dioxane, microwave (MW), 3 min; (iii) **63** (3-5 equiv.), Pd(OAc)₂ (0.2 equiv.), PPh₃ (0.4 equiv.), LiCl (2 equiv.), NaOAc (4 equiv.), DMA, MW, 13 min (2×); (iv) TFA, 20%, CH₂Cl₂, r.t.

Scheme 8.

In 2004, Nielsen and Meldal¹⁷ described a highly efficient approach for solid-phase generation of a range of pharmacologically interesting tri- and tetracyclic scaffolds from masked aldehyde building blocks protected as their *N*-Boc-1,3-oxazinanes **65**. Subsequently, a quantitative and highly stereoselective Pictet-Spengler reaction takes place by attack of the indole from a neighboring tryptophan, thus appending two new *N*-fused rings to the indole moiety **67**. (Scheme 9). Finally, the reaction products may conveniently be released from the solid support polyethylene glycol-dimethylacrylamide co-polymer (PEGA) by cleavage of

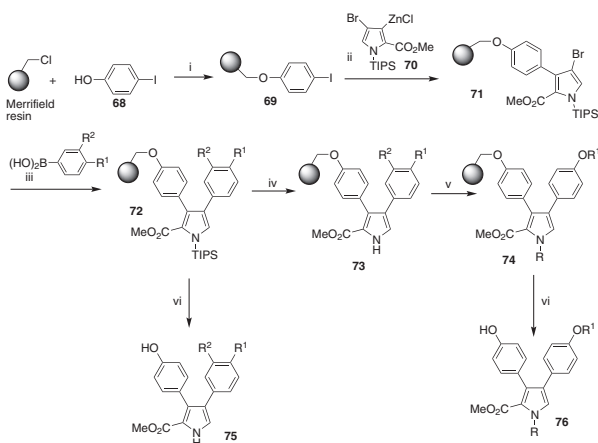
the base-labile linker *N,N'*-hexamethylene bis(acetamide) (HMBA).



Reagents and conditions: (i) HMBA, TBTU, *N*-ethylmorpholine (NEM), DMF; (ii) Fmoc-Ile-OH, 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT), MeIm, CH₂Cl₂; (iii) 20% piperidine (DMF); (iv) Fmoc-Trp-OH, TBTU, NEM, DMF; (v) 20% piperidine (DMF); (vi) **67a**, TBTU, NEM, DMF; (vii) H⁺ (aq) (*cis/trans* 1:10).

Scheme 9.

An efficient solid-phase synthesis of the pyrrole-based alkaloids lamellarins Q (**75**) and O (**76**) using Merrifield resin was published by Marfil *et al.*¹⁸ (Scheme 10). Compound **70** was obtained by selective orthodirected bromine/lithium interchange at position 3 by treatment of methyl 3,4-dibromopyrrole-2-carboxylate with *n*-BuLi at low temperature followed by metal-metal interchange using zinc chloride. The organometallic compound **70** was employed in a Pd(0)-catalysed Negishi cross-coupling reaction with the resinbound iodophenol **69**.

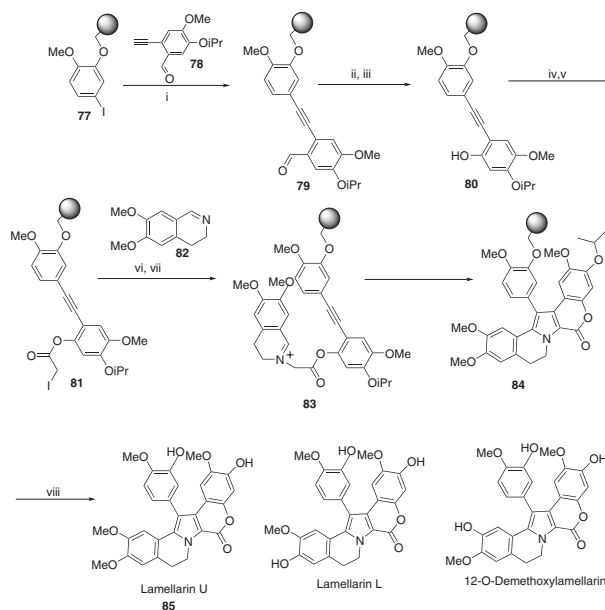


Reagents and conditions: (i) NaOMe, dry DMF, N₂, 80 °C, 24 h; (ii) Pd(PPh₃)₄, dry THF, N₂, r.t., 24 h; (iii) aq. 2 M Na₂CO₃, Pd(PPh₃)₄, dioxane, reflux, 21-48 h; (iv) NH₄F, CH₂Cl₂/MeOH (1:1), reflux, 6 h; (v) NaH (or LDA), dry THF, N₂, -78 °C, 24 h; or 18-crown-6 (2.5 M in DMF), microwave, 100 °C, 30-40 W, 2 min; (vi) AlCl₃, dry CH₂Cl₂, r.t., 3 h.

Scheme 10.

Cironi *et al.*¹⁹ have also published the solid-phase synthesis of lamellarins (Scheme 11). Three different

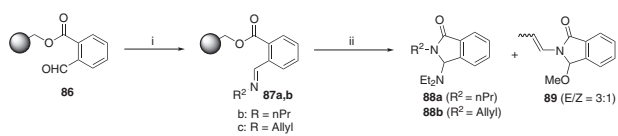
polystyrene resins, chloro and hydroxyl Merrifield and Wang resins were tested. At the final step resins were cleaved with a Lewis acid such as AlCl₃, ZnBr₂ or TFA in CH₂Cl₂, furnishing lamellarin U (**85**) and analogues.



Reagents and conditions: i) Pd(PPh₃)₂Cl₂, Cu THF.Et₃N; ii) *m*CPBA, NaHCO₃, CH₂Cl₂; iii) 2M KOH, THF, MeOH; iv) ICH₂COOH, DMAP; v) *N,N*-diisopropylcarbodiimide (DIPCDI), DMF; vi) CH₂ClCH₂Cl; vii) DIEA reflux; viii) AlCl₃, CH₂Cl₂.

Scheme 11.

Knepper *et al.*²⁰ described the reaction of immobilized *o*-carboxybenzaldehydes **86** with primary amines at room temperature furnishing imines **87** formation, which underwent 1,2-addition-cleavage reaction with various nucleophiles, yielding isoindolinones **89** (Scheme 12).

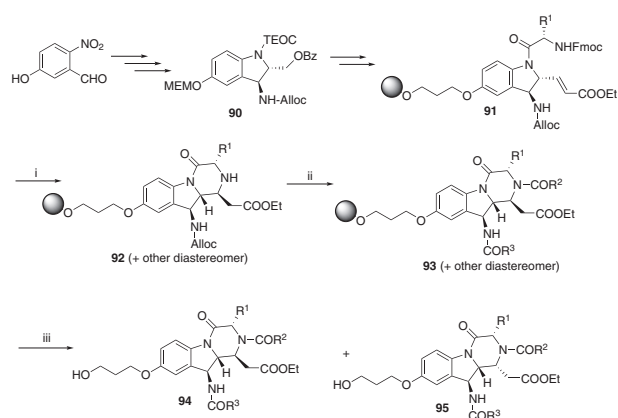


Reagents and conditions: i) H₂NR², THF, rt, 6h; ii) Nu¹, THF, reflux, 24 h (Nu = NEt₃, OMe).

Scheme 12.

The synthesis of a library of indoline-alkaloid-like polycycles from an enantioenriched aminoindoline was described (Scheme 13).²¹ The intermediate **91** was treated with piperidine to give the tricyclic derivative **92** during the removal of the Fmoc group. The *in situ* conjugate hetero-Michael reaction was efficient. The mild conditions for this cyclization reaction are highly appealing and attractive to explore its potential in the

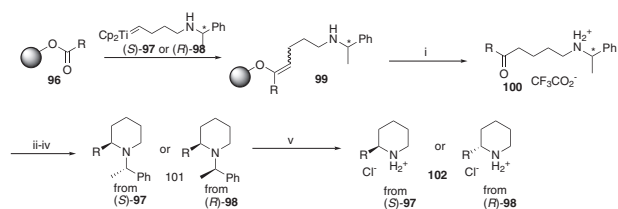
generation of a library. The stereochemical outcome of this reaction was found to be dependent upon the choice of the amino acid. To complete the test sequence in the solid phase, **92** was then subjected to *i*) an amide coupling reaction to introduce the second diversity, *ii*) removal of the Alloc protecting group to give the free amine, and *iii*) reaction with carboxylic acid chloride to introduce the third diversity and to give **93**. Finally, compounds **94** and **95** were obtained in a ratio varied from 5:1 to 1:1, upon cleavage of the substrates from the support under desilylation conditions.



Reagents and conditions: i) 20% piperidine; ii) 1. $R_2\text{COCl}$, pyridine; $2\text{Pd}(\text{PPh}_3)_4$; 3. $R_3\text{COCl}$, pyridine; iii) pyridine-HF; 80-85% yield of **94** and **95**.

Scheme 13.

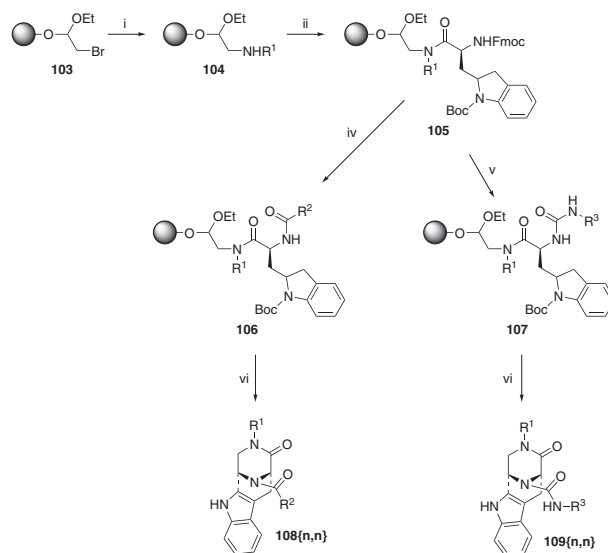
Adriaenssens *et al.*²² described that the use of alkylidenetitanium reagents enable to control the high throughput asymmetric synthesis of 2-substituted piperidines **102** and a rapid access to multiple cyclic imines using solid-phase synthesis (Scheme 14). The Schrock carbenes (**97** and **98**) generated by reduction of thioacetals, convert resin-bound esters into enol ethers **99**. Treatment with acid releases amino ketones to give iminium salts **100** that are cyclized in the presence of NaOH and TMSCl. Reduction introduces a chiral centre at C-2 of **101**, whose absolute stereochemistry is determined by a phenethylamine (PEA) chiral auxiliary.



Reagents and conditions: i) 4% $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 ; ii) NaOH(aq); iii) TMSCl; iv) $\text{NaBH}(\text{OAc})_3$; v) H_2 , Pd/C, HCl, EtOH, 65 °C.

Scheme 14.

Lee and Park²³ developed a multistep, practical solid-phase strategy for the synthesis of natural product-like diaza-bridged heterocycles **108** and **109** (Scheme 15). A key step in the library synthesis is the tandem acidolytic cleavage with subsequent *in situ* iminium formation followed by the Pictet-Spengler intramolecular cyclization. This cyclization was regio- and diastereoselective to give final products as single diastereomers in exceptional yields and purities, which was confirmed by NMR structural study and LC/MS analysis.

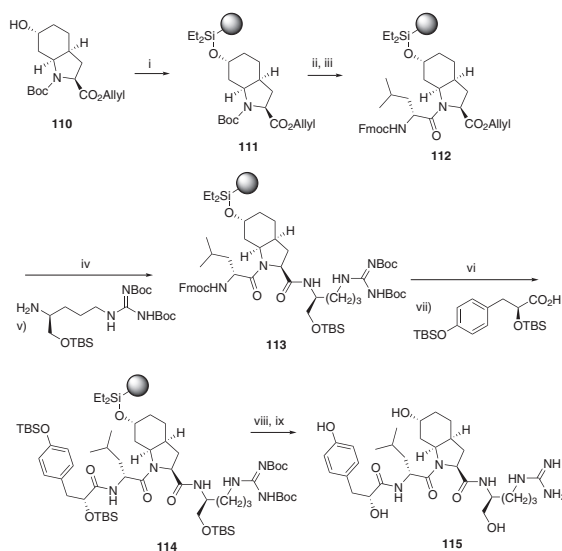


Reagents and conditions: (i) $R_1\text{NH}_2$, DMSO, 60 °C; (ii) Fmoc(*N*-Boc) TrpOH, O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate(HATU), DIPEA, DMF, r.t.; (iv) (a) 25% piperidine, r.t.; (b) $R_2\text{CO}_2\text{H}$, DIC, HOBt, DIPEA, r.t.; (v) $R_3\text{NCO}$, DIPEA, $\text{ClCH}_2\text{CH}_2\text{Cl}$, r.t.; (vi) neat HCO_2H , r.t.

Scheme 15.

A 24-member combinatorial library based on the structure of aeruginosin 298-A (**115**) was synthesized by Doi *et al.*²⁴ utilizing a silyl linker. Attachment of **110** to PS-DESCI provided polymer-supported **111**. Removal of the Boc group in **111**, followed by condensation with Fmoc-D-Leu-OH using *N*-hydroxybenzotriazole(DIC)-*N*-hydroxybenzotriazole(HOBt), repeated twice, afforded polymer-supported dipeptide **112** in 93% purity (Scheme 16). The *O*-allyl ester in **112** was removed with $\text{Pd}(\text{PPh}_3)_4$ /dimedone. Coupling of the free acid with (*S*)-*N*- ω '-(di-*tert*-butoxycarbonyl)argininol *tert*-butyldimethylsilyl ether afforded **113** in 94% purity. After Fmoc deprotection in **113**, a propionic acid derivative was coupled using DIC-HOBt in 14 h. Acid cleavage of the polymer-supported **114** and simultaneous removal of the TBS and Boc groups with TFA/ CH_2Cl_2 / H_2O provided a mixture of aeruginosin 298-A in 66% purity and its trifluoroacetate derivatives in 25%

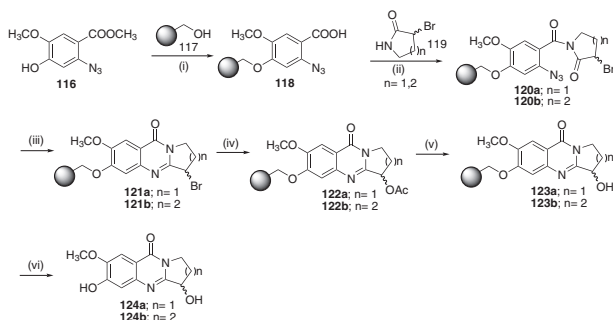
purity. Then, the crude mixture was treated with polymer-supported *N*-methylmorpholine (PS-NMM) to remove the trifluoroacetate providing **115** in 84% purity. After purification by ODS column chromatography, aeruginosin 298-A was isolated.



Reagents and conditions: i) PS-SiEt₂Cl, Imidazole, CH₂Cl₂; ii) TMSOTf, 2,6-lutidine, CH₂Cl₂; iii) Fmoc-D-Leu-OH, DIC, HOBT; iv) Pd(PPh₃)₄, dimedone, THF; v) DIC, HOBT; vi) piperidine, DMF; vii) DIC, HOBT; viii) TFA, CH₂Cl₂, H₂O; ix) PS-NMM, MeOH, CH₂Cl₂.

Scheme 16.

The solid-phase synthesis of fused [2,1-b]quinazolinone alkaloids has been developed for the preparation of vasicinone (**124a**) and deoxyvasicinone (**124b**) by two approaches illustrated in the Scheme 17.²⁵ Firstly, the resin-linked azido-benzoic acids were coupled with bromo-substituted lactams followed by cyclization in an aza-Wittig reductive cyclization process giving the bromo-

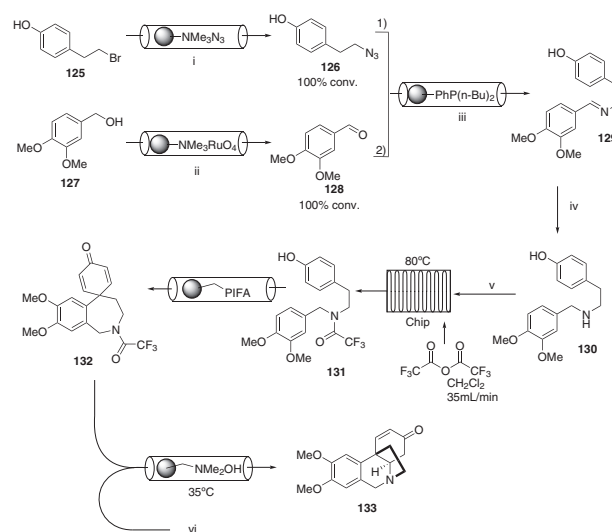


Reagents and conditions: (i) PPh₃, DIAD, NMP, 16 h, r.t.; (b) 1 mol L⁻¹ NaOH, 1,4-dioxane, 100 °C, 12 h; (ii) *N,N'*-dicyclohexylcarbodiimide (DCC), DMAP, CH₂Cl₂, 12 h, 0 °C-r.t.; (iii) PPh₃, toluene, 3 h, r.t.; (iv) KOAc, 18-crown-6-ether, CH₃CN, 80 °C, 6 h or DMF, 8 h, r.t.; (v) K₂CO₃, THF-MeOH (1:1), 6 h, rt; (vi) TFA, CH₂Cl₂, (1:1) 1 h, r.t.

Scheme 17.

substituted quinazolinone intermediates (**121a-b**) which, by subsequent acetylation, hydrolysis and resin cleavage, afford the fused [2,1-b]quinazolinones.

Baxendale *et al.*²⁶ described a flow process for the multi-step synthesis of the alkaloid natural product (±)-oxomaritidine (**133**). This synthesis was mediated through the use of microfluidic pumping systems that drive the material through various packed columns containing immobilized reagents, catalysts, scavengers or catch and release agents. The route involves seven synthetic steps, can generate gram quantities of oxomaritidine in 40% overall yield and 90% purity in only one day. Key steps include trapping previously prepared 4-(2-azidoethyl)phenol (**126**) with a polymer-supported phosphine on a column and subsequently coupling it with 3,4-dimethoxybenzaldehyde (**128**), which is prepared in a separate channel. The resulting imine intermediate is sequentially converted to an amide **131** in steps that include changing solvents and a palladium-mediated hydrogenation that takes place in a flow-through unit. In the final stages, the third ring of oxomaritidine is formed and the amide is cleaved, promoting a bridging 1,4-addition to give the end product **133** (Scheme 18).

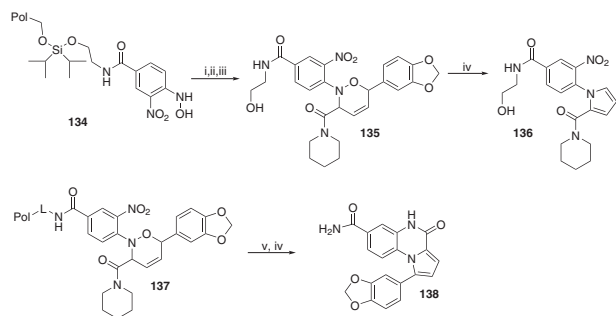


Reagents and conditions: i) 20 eq, 70 °C, CH₃CN: THF (1:1), 50 mL min⁻¹; ii) 10 eq., THF, r.t., 50 mL min⁻¹; iii) 20eq., 1 r.t., 2. 55 °C; iv) flow hydrogenation, 10% Pd/C, THF; v) CH₂Cl₂, 35 mL min⁻¹; vi) MeOH/H₂O, 4:1, 70 mL min⁻¹.

Scheme 18.

Krchnak and co-workers²⁷ described the synthesis of new pyrrole and quinoxalinone analogues. The strategy involved the cycloaddition of piperine, a natural conjugated diene, with polymer supported acyl- and aryl nitroso dienophiles **136** (Scheme 19). The aryl nitroso dienophiles were prepared immobilized by using ethanolamine to a silyloxy linker.

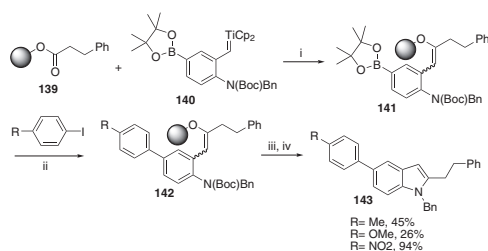
Treatment of the nitroaryl nitroso HDA adduct **135** with 50% TFA, trifluoroacetic acid, was accompanied by ring contraction and formation of pyrrole derivative **136**. Subjected HDA adducts **137** to reducing conditions. Treatment with 1 mol L⁻¹ SnCl₂·2H₂O, 1 mol L⁻¹ *N,N*-diisopropylethylamine (DIEA) in 1-methyl-2-pyrrolidinone (NMP) for 2 h afforded, after cleavage by 50% TFA, 5*H*-pyrrolo[1,2-*a*]quinoxalin-4-one derivative **138** as the major component.



Reagents and conditions: (i) 0.1 M *n*-Bu₄NIO₄, CH₂Cl₂, r.t., 1 h; (ii) piperine, CH₂Cl₂, overnight; (iii) 0.1 M tetra-*n*-butylammonium fluoride (TBAF), THF, r.t., 30 min; (iv) 50% TFA, CH₂Cl₂, 30 min, 33%; (v) SnCl₂·2 H₂O, DIEA, NMP, r.t., 2 h.

Scheme 19.

Calver *et al.*²⁸ reported a high throughput synthesis of diverse 2,5-disubstituted indoles **143** using titanium carbenoids bearing boronate functionality (Scheme 20). Suzuki cross-coupling with aryl iodides followed by cleavage with acid completed the solid-phase synthesis of 2,5-disubstituted indoles.

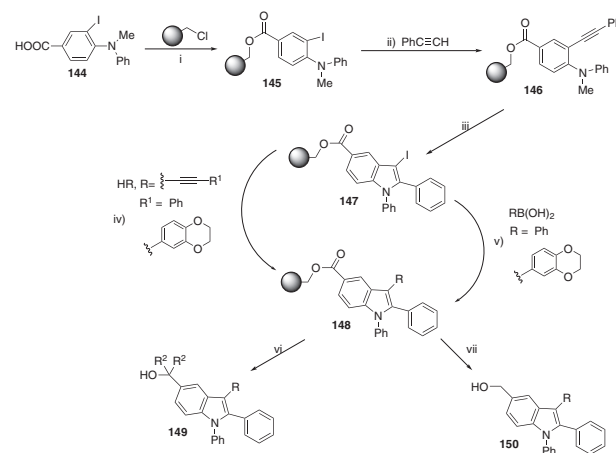


Reagents and conditions: i) THF; ii) 4 mol% Pd(PPh₃)₄, 1 eq. H₂O, DMF, 80 °C; iii) 1% TFA, CH₂Cl₂; iv) 10% TFA, CH₂Cl₂.

Scheme 20.

Recently, Larock *et al.*²⁹ report the construction of a 42-member library of highly substituted indoles **149** and **150** by the solid-phase synthesis of 4-iodoindoles **147** and subsequent palladium-catalyzed Sonogashira and Suzuki-Miyaura cross-coupling reactions with various commercially available terminal alkynes and boronic acids (Scheme 21). The chemistry has been successfully performed in a solid support using chlorinated Wang

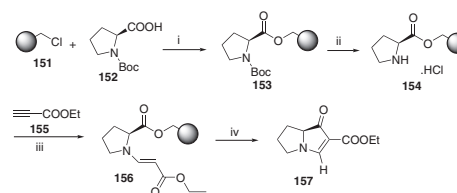
resin and diversity has been achieved at the 5-position by different cleavage reactions. The average yield of the library was 46% and the average purity after purification was 94%.



Reagents and conditions: i) Cs₂CO₃, KI, DMF, 80%; ii) 5 mol% PdCl₂(PPh₃)₂, 10 mol% CuI, HNEt₃, r.t.; iii) 3.0 I₂, CH₂Cl₂, 24 h; iv) 5 mol% PdCl₂(PPh₃)₂, 10 mol% CuI, HNEt₃, 48 h, 65 °C; v) cat. Pd(OAc)₂, PPh₃, CsF, DME, 40 h, 80%; vi) R₂MgBr, THF (R₂ = Me, Et); vii) LiAlH₄, THF.

Scheme 21.

Hyacinthacine is a new set of alkaloids isolated from *Hyacinthoides non-scripta* and *Scilla campanulata* immature fruits and bluebell stalks which inhibit several glycosidase enzymes. A new solid-phase synthesis of pyrrolizidine nucleus related to hyacinthacine core using *L*-Boc-proline (**152**) as the building block was reported (Scheme 22).³⁰ The synthesis with Merrifield resin **151** as solid support occurs only in four steps. The route includes an elegant cyclization cleavage strategy step, which releases product **157** from the resin in good yields under Baylis-Hillman conditions.



Reagents and conditions: i) K₂CO₃, KI, reflux, 24 h; ii) CH₂Cl₂/ Et₂O, HCl 3 mol L⁻¹; iii) DIPEA, DMF, 4 days, r.t.; iv) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), MW, 10 min.

Scheme 22.

3. Terpenes and Steroids

Terpenoids, also referred to as terpenes, are the largest group of natural compounds (over 55,000 members isolated

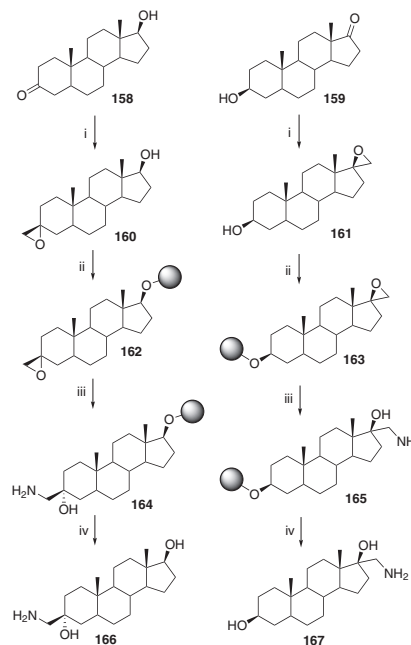
so far). From simple structures as menthol until complex ones as taxol, terpenes are a ubiquitous group of molecules that have long provided humans with flavours, fragrances, hormones, medicines and even commercial products such as rubber.³¹ They are often found in significant quantities, and a wide array isolated and characterized. Chemically, they are built from five-carbon isoprene units and so can also be called “isoprenoids”. Molecules with multiples of 5 carbons and particularly with single carbon side chains belong to this group, even if they are cyclic. Based on the number of the building blocks, terpenoids are commonly classified as monoterpenes (C₁₀), sesquiterpenes (C₁₅), diterpenes (C₂₀), and sesterterpenes (C₂₅). More complex terpenoids include the sterols. Many terpenes have biological activities and are used for the treatment of human diseases, been active against cancer, malaria, inflammation, and a variety of infectious diseases.³² There are several methods described in literature to obtain these compounds by synthesis, however, they are not easily synthesized by solid-phase synthesis. The current literature revealed a few examples.

To input molecular diversity in hydroxysteroids (primary alcohol, secondary alcohols, and phenol), Maltais and co-workers³³ utilized solid-phase reactions where hydroxysteroids were linked to solid support using the butyldiethylsilane polystyrene (PS-DES) resin. The synthesized compounds were made by running steroidal alcohols **158** and **159** through a model sequence of reactions: solid-phase coupling, aminolysis of oxirane or reduction of azide, amidation, and final cleavage, as seen in Schemes 23 and 24. The reaction led to good overall yields (> 45%) and high HPLC purities (> 90%) of hydroxysteroids derivatized as alkylamides (**174**) and alkylamines (**166**, **167**, **175**) without purification.

Another steroid considered in the solid-phase combinatorial synthesis is estradiol and its derivatives that contain a functionalized side chain at positions 16β or 7α.³⁴ Both types of derivatives have demonstrated inhibitory activity toward biosynthesis and action of estradiol. In 2000,³⁵ the same group enlarged the library of estradiol 16p-(azidopropyl) compounds (**177**)³⁴ with the synthesis of phenolic sterols derivatives. The authors used the same approach in which they generated two levels of diversity from two functional groups, where they introduced commercially available building blocks, such as amino acids, acyl chlorides, and anhydrides (Scheme 25).

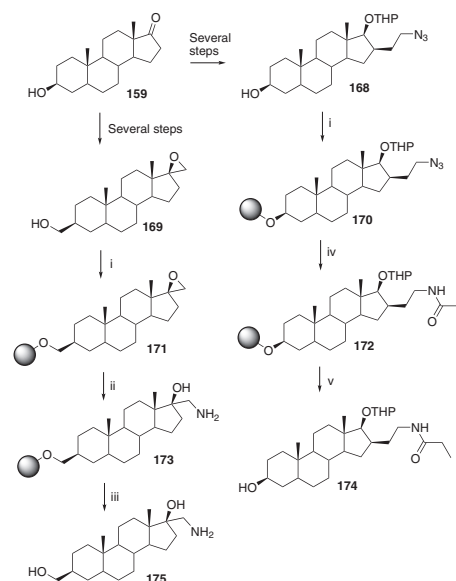
Taxol (paclitaxel) is an antimicrotubule agent clinically available to treat ovarian, breast, lung cancer and also Kaposi sarcoma.³⁶ Systematic SPOS and structure activity relationship (SAR) studies of taxol analogs were done

by Nicolaou *et al.*³⁷ They started with an appropriately functionalized taxol core (five steps from baccatin III, **181**) that was attached onto 2-chlorotriethylchloride polystyrene resin and the loaded resin is distributed into 400 Rf-tagged MicroKan reactors (Scheme 26). The reactors



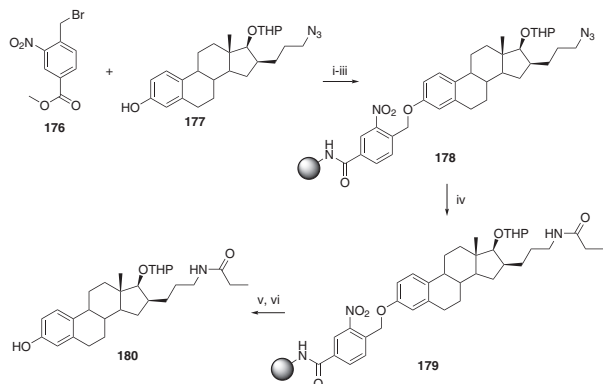
Reagents and conditions: i) NaH, (CH₃)₃SOI, DMSO, r.t.; ii) imidazole, polymer supported butyldiethylcholol (PS-DES-Cl) resin, CH₂Cl₂, r.t.; iii) Amine/EtOH (1:1), 60 °C; iv) HF-pyridine, THF, r.t.

Scheme 23.



Reagents and conditions: i) imidazole, PS-DES-Cl resin, CH₂Cl₂, r.t.; ii) Amine/EtOH (1:1), 60 °C; iii) HF-pyridine, THF, r.t.; iv) SnCl₂, Et₃N, PhSH, THF, r.t.; v) TBAF, THF, r.t.

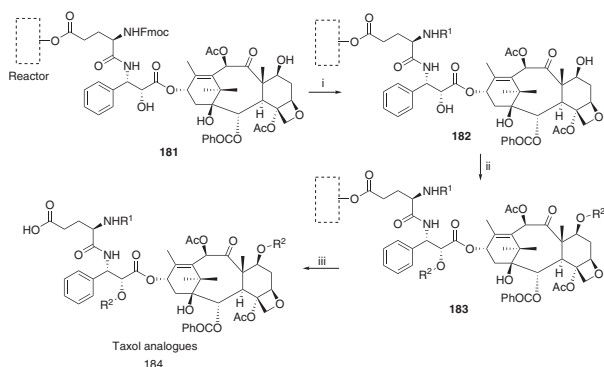
Scheme 24.



Reagents and conditions: i) Cs_2CO_3 , $\text{CH}_3\text{CN}/\text{DMF}$ (4:1), r.t. (67%); ii) LiOH aq, THF, r.t. (83%); iii) aminomethyl resin (1.0 mmol g^{-1}), DIPC, HOBT, DMF, r.t.; iv) propionic acid, EDC, HOBT, dioxane, then Bu_3P in toluene, r.t.; v) hv (350 nm), MeOH, r.t.; vi) 2% HCl, MeOH, r.t.

Scheme 25.

were treated as one single batch with 5% piperidine/*N,N*-dimethylformamide (DMF) (r.t., 30 min) to deprotect the Fmoc group and, after that, the reactors were sorted into 20 groups that were acylated with a carboxylic acid to yield the resin-bound amides (**182**). The amides were divided again and each new group was acylated with a second carboxylic acid 1,3-diisopropylcarbodiimide(DIC)/*N,N*-dimethylaminopyridine(DMAP)/ CH_2Cl_2) yielding the diesters (**183**) on resin. Finally the cleavage furnished a library of 400 (20 × 20) taxol analogues (**184**).

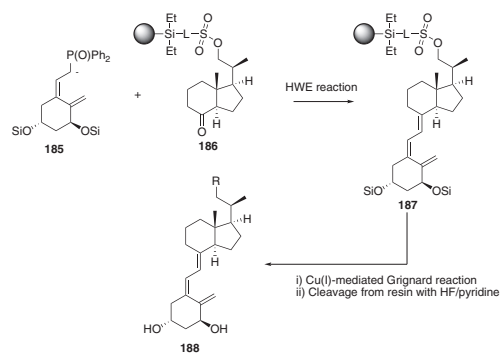


Reagents and conditions: i) 5% piperidine, DMF, then carboxylic acids (R^1), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate (PyBOP), DIEA, DMF; ii) carboxylic acids (R^2); iii) AcOH , $\text{CF}_3\text{CH}_2\text{OH}$, CH_2Cl_2 .

Scheme 26.

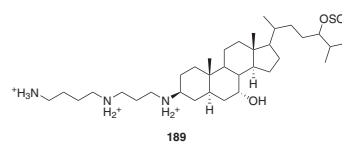
Secosteroids, as vitamin D, are steroids in which one of the bonds in the rings is broken. Vitamin D is obtained by SPOS through different approaches. In 2001, Hojikuro and Takahashi³⁸ proposed a route where synthetic analogs of vitamin D were prepared by using a solid-supported CD-ring **186** (Scheme 27). The vitamin D3 system (**188**)

was synthesized by Horner-Wadsworth-Emmons (HWE) reaction of the A-ring phosphine oxide **185** to resin **186**, followed by introduction of the side chain and cleavage from resin.



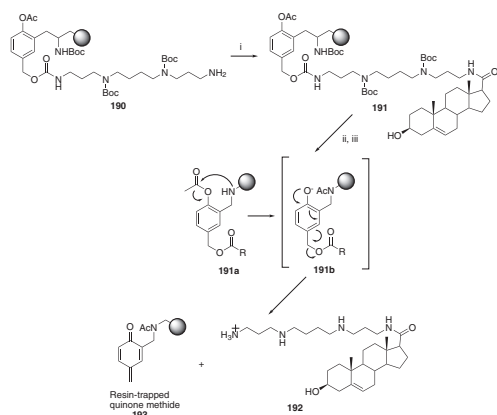
Scheme 27.

Squalamine **189** (Figure 1) is a water-soluble antibiotic, which exhibits potent bactericidal activity against both Gram-negative and Gram-positive bacteria, is fungicidal and induces osmotic lysis of protozoa.³⁹ Squalamine was used as template in solid-phase synthesis to produce analogues.⁴⁰ The chosen linker was suitable for cleaving directly within a biological assay. This approach was based on the 1,6-elimination process that uses an in-built amine 'activator' (N from NHBoc in **191**) to cleave a phenoxy ester (**191a** and **191b**) and hence to activate the linker without giving rise to free quinone methide by-products **193**, as seen in Scheme 28. The utilization of this linker could be useful to accelerate the screening processes of libraries prepared by SPOS.

Figure 1. Chemical structure of squalamine **189**.

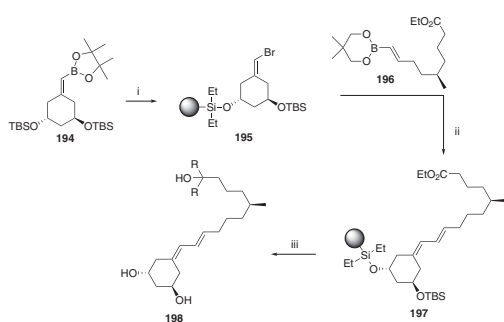
To produce a library of des-C,D derivatives of 19-nor-1 α ,25-dihydroxyvitamin D₃, Hanazawa and colleagues developed a general methodology disclosed in Scheme 29.⁴¹ After the A ring **195** been attached to the resin, the product was coupled with **196** to give **197** and then treated with an excess amount of MeMgCl or EtMgBr and then aqueous HF to produce the new des-C,D-19-nor-vitamin D₃ derivatives, such as **198**.

Jagtap⁴² and co-workers used as alternative solid-support a polystyrene-divinyl benzene resin functionalized with a PE-DES-Cl1 to obtain a series of 10-acyl (**203**) and 7,10-diacyl (**202**) paclitaxel analogues (Scheme 30). The starting material was 10-deacetylpaclitaxel **198** that



Reagents and conditions: i) β -acetoxybisnor-5-chlolenic acid/DIC/HOBt; ii) $\text{Py}\cdot\text{SO}_3$, CHCl_3 ; iii) 50% TFA in dichloromethane (DCM) 1 h, then phosphate buffer (pH 8.0), 24 h.

Scheme 28.



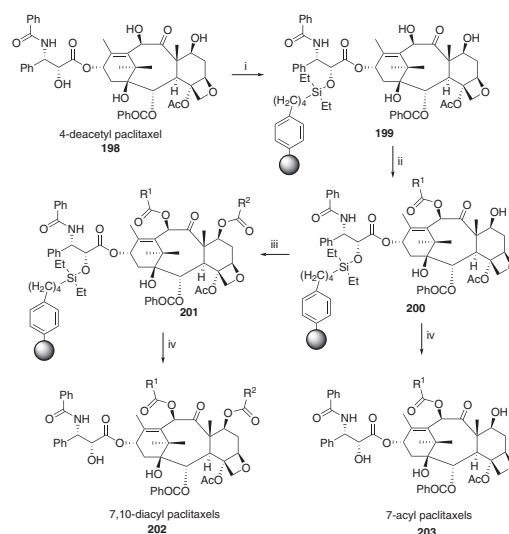
Reagents and conditions: i) PS-DES-Cl, imidazole, DCM; ii) PdCl_2 catalyst, KOH, THF, H_2O ; iii) MeMgCl or EtMgBr , THF, then aqueous HF, THF.

Scheme 29.

was bonded into resin **199** to give and then converted to the correspondent 10-acyl analogues **200** by Holton's method. Subsequent acylation at the C-7 position was performed using different carboxylic acid and the acyl and diacyl libraries were delivered from the resin under acidic condition.

The sesquiterpenoid dysidiolide (**204**) (Figure 2) is an inhibitor of the dual-specificity Cdc25 protein phosphatase family that acts in the regulation of the cell cycle, isolated from the Caribbean sponge *Dysidia etheria*, Laubenfels.⁴³ The solid-phase synthesis was employed to obtain dysidiolide analogues with overall yields ranging from 6% to 27%.⁴⁴ The eleven step transformation includes a variety of diverse reaction types widely used in organic synthesis like an asymmetric cycloaddition employing a removable chiral auxiliary, organometallic transformations, olefination reactions, oxidation reactions, acidic hydrolyses, and nucleophilic substitution.

Lupeol (**205**) is a triterpene found in fruits and vegetable and recently it was discovered that it is capable to inhibit



Reagents and conditions: i) resin, imidazole, CH_2Cl_2 ; ii) $\text{R}_1\text{COOCOR}_1$, CeCl_3 , THF; iii) R_2COOH , DIPC, Toluene; iv) Pyridine, HF, THF, then MeOSiMe_3 .

Scheme 30.

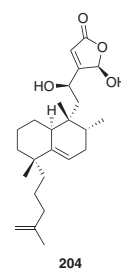
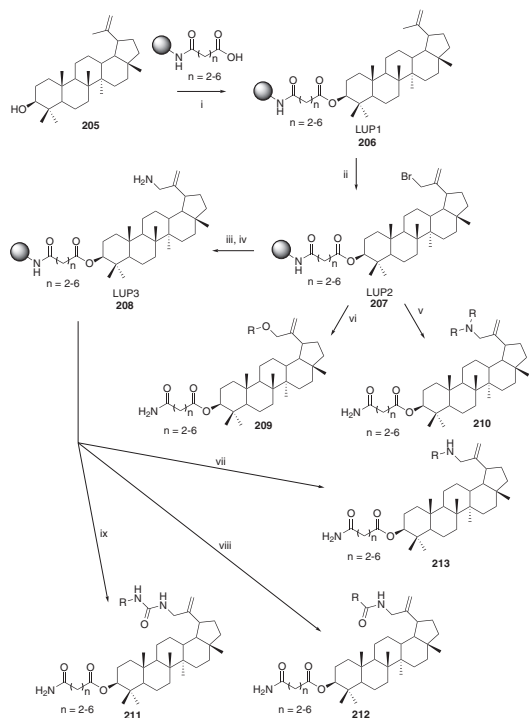


Figure 2. Chemical structure of dysidiolide.

tumors growth,⁴⁵ to act as anti-inflammatory,⁴⁶ urolithic and anticalciuric and also express antimalarial activity against chloroquine-resistant *Plasmodium falciparum*.⁴⁷ The use of lupeol as a scaffold for the synthesis of a library was described by Srinivasan (Scheme 31).⁴⁸ The synthesis starts with lupeol **205** been attached to a Rink amide and Sieber amide solid resin, through aliphatic dicarboxylic acid moieties. These sites also served as point to introduce chemical diversity. The resulting polymer linked 3β -O (resin-alkanoyl)-lup-20(29)-ene **206** was used to obtain intermediates 3β -O (resin-alkanoyl)-30-bromo-lup-20(29)-ene **207** and 3β -O (resin-alkanoyl)-30-amino-lup-20(29)-ene **208**. The intermediates were used to prepared several derivatives (**209-213**).

The triterpenoids betulinic acid (**214**) and ursolic acid (**217**) were investigated as scaffolds for the generation of combinatorial libraries in parallel format using solid-phase organic synthesis.⁴⁹ Both compounds have the potential for the synthesis and presenting two-point of structural diversity at C-3 and C-28 positions. The synthesis consisted in immobilization of **214** or **217** to pre-derivatized amino

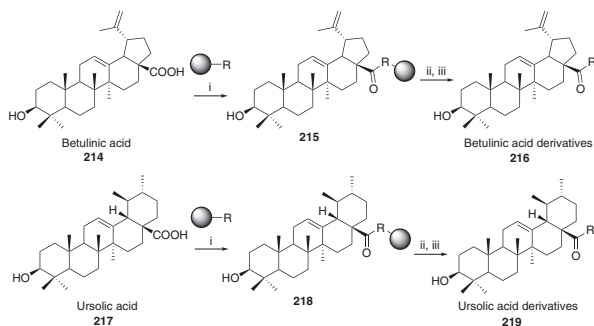


Reagents and conditions: i) DIC, DMAP, DMF/THF (1:1); ii) *N*-bromosuccinimide (NBS), CH_2Cl_2 : CCl_4 (1:1), 6 h; iii) NaN_3 , DMSO, 80 °C, 24 h; iv) SnCl_4 , PhSH, Et_3N , THF, 2 h; v) primary or secondary amine, DBU, 16 h / 1% TFA- CH_2Cl_2 , 10 min; vi) Benzyl alcohol derivatives, DBU, 16 h / 1% TFA- CH_2Cl_2 , 10 min; vii) R_3CHO , trimethyl orthoformate (TMOF)/DMF (2:1), 2 h then NaCNBH_3 , 1% AcOH in TMO, 1 h / 1% TFA- CH_2Cl_2 , 10 min; viii) R_3COOH , HOBT, DIC, DMF, 6 h / 1% TFA- CH_2Cl_2 , 10 min; ix) R_5NCO , CH_2Cl_2 , 24 h / 1% TFA- CH_2Cl_2 , 10 min.

Scheme 31.

acid 2-chlorotrityl or Sieber amide resins, and then treated with a variety of aliphatic, aromatic and amino acids (Scheme 32).

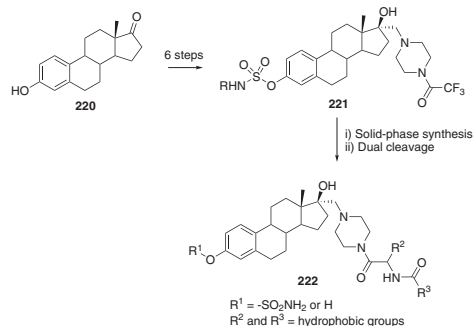
In 2003, Ciabanou and Poirier⁵⁰ reported an application of the detachable sulfamate linker in the synthesis of libraries of *N*-derivatized 17 α -piperazinomethyl estradiols (phenols and sulfamates) by solid-phase parallel



Reagents and conditions: i) pyridinium dichromate (PDC)/DMF; ii) RCOOH/DMA/DIC; iii) TFA/ CH_2Cl_2 .

Scheme 32.

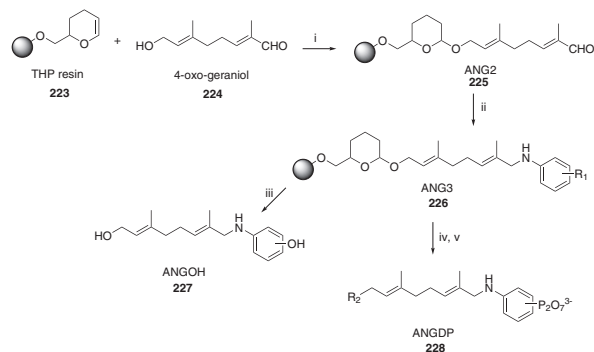
chemistry. The starting material was a 3-sulfamoyl-17 α -(*N*-trifluoroacetyl-piperazinomethyl) estradiol **221**, that was prepared in solution from estrone **220** and loaded efficiently onto trityl chloride resin (Scheme 33). After cleavage of the trifluoroacetyl protecting group, sequential acylation reactions with five Fmoc-protected amino acids and five carboxylic acids were performed to introduce two levels of molecular diversity. The final step with the resin split and the delivery of the products occurred using two protocols: under acidic conditions with 5% trifluoroacetic acid in dichloromethane, and by nucleophilic attack with piperazine in tetrahydrofuran.



Scheme 33.

Analogues of geraniol, a monoterpene found in essential oils of fruits and herbs, have been studied by Subramanian and co-workers.⁵¹ They published the solid-phase synthesis of a library of 80 anilino geranyl alcohols **227** and diphosphates **228** in three steps: reductive amination, bromination, and treatment with $((n\text{-Bu})_4\text{N})_3\text{HP}_2\text{O}_7$ [tris (tetra-*N*-butylammonium)hydrogendiphosphate]. The SPOS started with the attachment of synthetic intermediates to the tetrahydropyranyl (THP) resin **223** (prepared from the Merrifield resin), combining a five-fold excess of 8-oxo-geraniol **224** with the polymeric support in the presence of 0.2 equiv. of PPTS at 60 °C (Scheme 34). Anilino geraniols attached to the resin **226** were obtained by reductive amination of **225** with 10 equiv. of the anilines and 12 equiv. of acetic acid in 1:1 THF/*N,N'*-dicyclohexylcarbodiimide (DCE) and subsequent reduction with 10 equiv. of $\text{NaBH}(\text{OAc})_3$. The cleavage step of **227** was done by treatment of the solid support with DCE/MeOH/pyridinium *p*-toluenesulfonate (PPTS) at 60 °C. To obtain the diphosphates **228**, compound **226** reacted with 3 equiv. of Ph_3PBr_2 in CH_2Cl_2 for 4 h followed by addition of 10 equiv. of $[(n\text{-Bu})_4\text{N}]_3\text{HP}_2\text{O}_7$ in CH_3CN , furnishing the desired diphosphates in moderate yield.

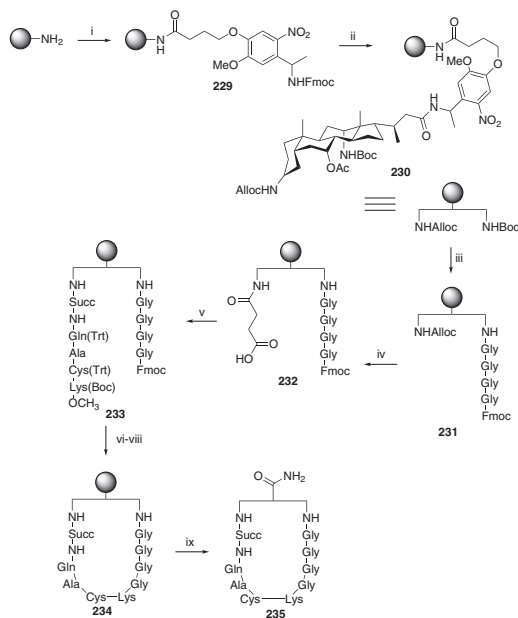
Another steroid synthesized by SPOS was a new type of cyclic peptidosteroid **235**, in which a bile-acid-based scaffold was used for the conformational restriction of



Reagents and conditions: i) PPTS, DCE, 60 °C, 78%; ii) Aniline, AcOH, NaBH(OAc)₃, THF/DCE (1:1), r.t.; iii) PPTS, CH₃OH/DCE (1:1), 60 °C, 24-90%; iv) ((*n*-Bu)₄N)₃HP₂O₇, CH₃CN, r.t. v) DCE/MeOH/PPTS at 60 °C.

Scheme 34.

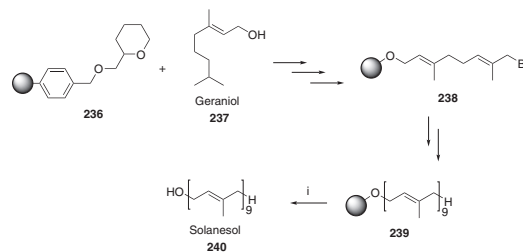
a loop-like peptide.⁵² The coupling of two tetrapeptides to the non-peptidic bili-acid scaffold **230** was carried out once in the classical C-to-N peptide synthesis and once in the non-classical N-to-C direction. Peptide backbone cyclization was then carried out, giving rise to a ring size equivalent to approximately 12 amino acids (Scheme 35).



Reagents and conditions: i) 4-[4-[1-(9-fluorenylmethoxycarbonylamino)ethyl]-2-methoxy-5-nitrophenoxy]butanoic acid, PyBOP, DIPEA, DMF, 2 h, r.t.; ii) 20% piperidine/DMF, 2 × 20 min, r.t., then, methyl 7- α -acetoxo-3 α -[*N*-(allyloxycarbonyl)amino]-12 α -[*N*-(*t*-butyloxycarbonyl)amino]-5 β -cholan-24-oate, PyBOP, DIPEA, DMF, 2 h, r.t. iii) 20% TFA, CH₂Cl₂, 20+90 min, r.t. then, Fmoc-Gly4-OH, HOAt, DIC, DMF, r.t.; iv) Pd(PPh₃)₄, Bu₃SnH, succinic anhydride, CH₂Cl₂, 2×17 h, r.t.; v) H-Gln(Trt)-Ala-Cys(Trt)-Lys(Boc)-OMe, HATU, TMP, DMF, r.t.; vi) LiOH 0.33M, MeOH/H₂O, 4 d, r.t.; vii) 1-hydroxy-7-azabenzotriazole (HOBt), TBTU, DIPEA, DMF, r.t.; viii) TFA/H₂O/ triisopropylsilane (TIS), 2 h, r.t.; ix) hv (365 nm), 1% DMSO/dioxane, 4×4 h, r.t.

Scheme 35.

Solanesol **240** is a terpene isolated from tobacco and it is an important intermediate of nutrients such as vitamin K2 and coenzyme Q10. Besides the efforts to obtain it by solution-phase synthesis, which require expensive chromatographic purification, Yu *et al.*⁵³ described a solid-phase synthetic strategy of solanesol. The SPOS route started from commercially available geraniol **237** and provided the facile isolation of product from the support-bounded intermediate in 50% of overall yield. In the proposed route, a dihydropyran-modified resin (**236**) is coupled to Merrifield resin and after some steps a polymer-supported bromide **238** is prepared (Scheme 36). This bromide reacted to give polymer-support nonamer **239**. Finally, treatment with PPTS was performed and completes the total solid-phase synthesis of solanesol **240**.

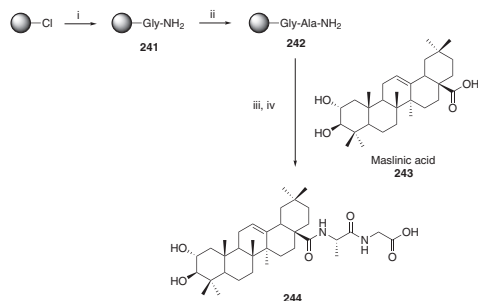


Reagents and conditions: (i) PPTS, 1:1 *n*-butanol/1,2 dichloroethane, 80 °C, 16 h.

Scheme 36.

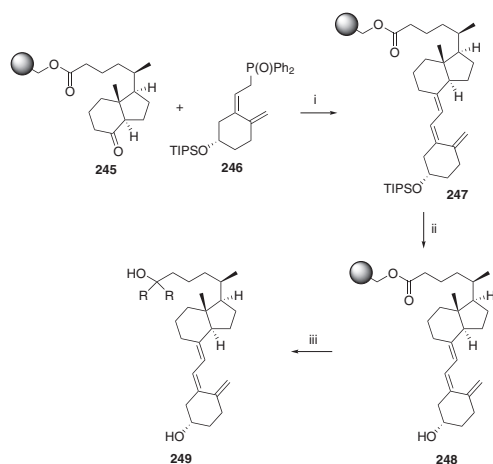
The triterpene maslinic acid **243** is an oleanane isolated from olive oil which has been identified as antiproliferative agent of colon cancer cells⁵⁴ and anti-HIV.⁵⁵ The construction of a library with the maslinic acid as a scaffold was presented in 2009,⁵⁵ where the acid was coupled at C-28 with several amino acids using solid-phase reactions to prepare a dipeptide, a tripeptide, and a series of conjugate dipeptides. Due to the high hydrophobicity of maslinic acid, it is very suitable to be utilized in solid-phase. The strategy consisted on the coupling of one, two, or three amino acid fragments with the carboxyl group at C-28 of maslinic acid. The pathway employed for the synthesis of one dipeptide derivative is described in Scheme 37.

Recently, Nicolletti *et al.*⁵⁶ described the synthesis of 25-hydroxylated vitamin D3 analogues by a five-step route using a (hydroxymethyl)polystyrene support (Scheme 38). The CD-side chain fragment was anchored to the solid support through an ester group at C25 (**245**) and coupled to the A ring of building block **246** to assemble the vitamin D triene system **247** by Wittig-Horner reaction. Prior to functionalization at C25 of **248**, the hydroxy group was deprotected and the cleavage was done by nucleophilic attack on the ester carbonyl group.



Reagents and conditions: i) Fmoc-Gly-OH, *N,N*-diisopropylethylamine (DIEA), CH_2Cl_2 /Piperidine-DMF; ii) Fmoc-Ala-OH, *N*-hydroxybenzotriazole (HOBt), *N,N*-diisopropylcarbodiimide (DIPCDI), CH_2Cl_2 /Piperidine-DMF; iii) Maslinic acid, 7-azabenzotriazol-1-yloxytris (pyrrolidino) phosphonium hexafluorophosphate (PyAOP), 1-hydroxy-7-azabenzotriazole (HOAt), DIEA, DMF; iv) TFA, CH_2Cl_2 .

Scheme 37.



Reagents and conditions: i) *n*-BuLi, THF; ii) HF, Py, CH_2Cl_2 , Acetonitrile; iii) MeLi, THF.

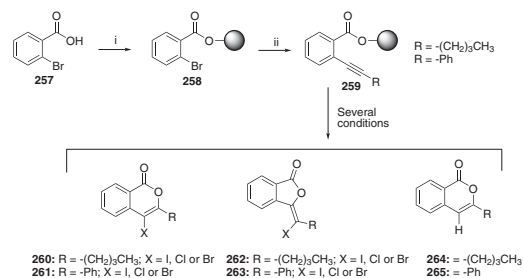
Scheme 38.

4. Coumarins

Coumarins are structurally related to lactones from *o*-cinamic acid, where the 1,2-benzopyrone is the simplest representative. The most investigated in medicinal chemistry is the use of furanocoumarins, which possesses some biological properties like vasodilator and bronchodilator. Because of this, the synthesis of coumarins by combinatorial chemistry has gained some interest including the synthesis of coumarins by SPOS or its use as scaffold to prepare combinatorial libraries of coumarins derivatives.

The design of a reliable synthetic route for the solid-phase method for parallel synthesis of 2,3-disubstituted 6H-pyrano[2,3-*f*]benzimidazole-6-ones (2,3-disubstituted imidazocoumarins) has been achieved.⁵⁷ This strategy, which is based on the mild imidazole ring closure reaction, provides a 2,3-disubstituted imidazocoumarin library **256**

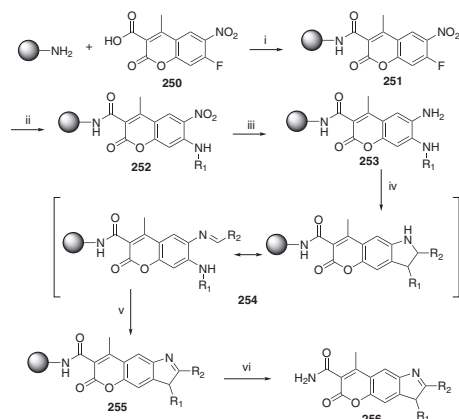
with two sites of chemical diversity for anticancer drug investigations (Scheme 40). The synthesis started with coupling of Rink amide resin MBHA with 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid **250**, after which furnished 26 tricyclic compounds in six steps with high purity and good yields. The synthesis employs available building blocks and the reactions were carried out under ambient conditions.



Reagents and conditions: i) 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid, DIC, HOBt, DMF, 16 h, r.t.; ii) $\text{R}'\text{NH}_2$ in 5% DIPEA/DMF, overnight, r.t.; iii) SnCl_2 1M in DMF, 24 h, r.t.; iv) R^2CHO , DMF, r.t. 2 h; v) 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), DMF, 5 h, r.t.; vi) TFA/ H_2O , 2 h, r.t.

Scheme 39.

In order to develop a synthetic approach to gain both efficiency and diversity around the isocoumarin scaffold, it was recently established a parallel solid-phase synthesis method for the production of 3-substituted 4-haloisocoumarins based on an electrophile-promoted halocyclization of supported 2-(alk-1-ynyl)benzoates (Scheme 39).⁵⁸ The authors employed two-step strategy involving (i) a Sonogashira cross-coupling reaction between polymer-bound 2-bromobenzoates **258** and terminal alkynes, followed by (ii) an electrophile-induced halocyclization of the resulting 2-(alk-1-ynyl)benzoates **259** through activation of the triple bond with the subsequent release of the isocoumarins. This synthesis allowed large variations at positions 3 and 4 of the isocoumarin scaffold and on the aromatic moiety. Using this strategy they built a library of 58 isocoumarins with high purities (82% of compounds with purity above 80%) and the yields for the key reactions (Sonogashira cross-coupling and electrocyclization) were moderate to excellent (30% to quantitative). In addition, the authors could recycle the resin and apply one of well-known advantage of the solid support, which is the temporary protection of one functional group (*i.e.*, the carboxylic group). In fact, the traceless cleavage would ensure that only the desired cyclized product is released from the polymer, with no cleavage of side products arising from an incomplete Sonogashira reaction.

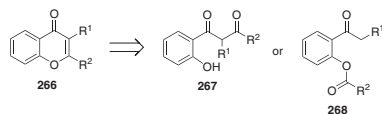


Reagents and conditions: i) Cs_2CO_3 , EtOH, 3 h, r.t., then bromo-Wang resin, DMF, 12 h, r.t.; ii) alkyne (hex-1-yne or phenylacetylene), $\text{PdCl}_2(\text{PPh}_3)_2$, CuI, $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, 65 °C, 12 h.

Scheme 40.

5. Flavonoids

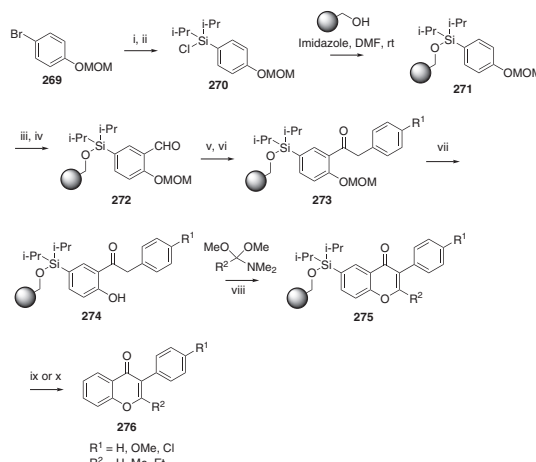
The benzopyranone-ring system found in flavonoids is a molecular scaffold of considerable interest. Medicinal chemistry efforts have focused on diversifying benzopyranones and utilizing combinatorial chemistry approaches to construct small libraries in order to be evaluated, for example as potential enzyme inhibitors.⁵⁹ Classically, 2,3-disubstituted benzopyranones **266** are synthesized by intramolecular condensation of compound **267**, which is usually obtained by Baker-Venkataraman rearrangement of compound **268** or via Claisen ester condensation (Scheme 41). Previous reviews have discussed the importance of combinatorial libraries of flavonoids prepared by solid-phase synthesis.⁶⁰



Scheme 41.

Harikrishnan and Showalter⁶¹ prepared a small library of isoflavone analogs employing a solid-supported diisopropylsilyloxy traceless linker. The key steps were the addition of Grignard reagents to salicyl aldehyde derivatives **272** and the cyclization employing amide acetals which introduced the R^2 substituents on the isoflavones **275** (Scheme 42).

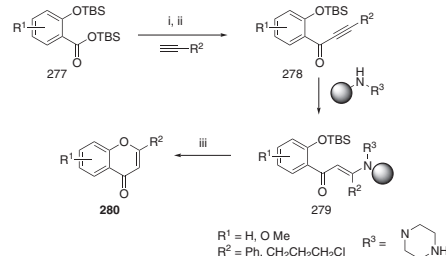
Bhat *et al.*⁶² employed a piperazinyl Merrifield resin in the synthesis of a library of flavones. The synthetic strategy involved the one pot conversion of bis-silylated salicylic acids **277** into alkynyl ketones **278** via an acid chlorination and subsequent Sonogashira coupling with



Conditions: i) *n*-BuLi, THF, -78 °C; ii) $(i\text{-Pr})_2\text{SiCl}_2$, THF, -78 °C to r.t.; iii) *n*-BuLi, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), Et_2O , 0 °C; iv) DMF, 0 °C; v) $4\text{-R}^1\text{-C}_6\text{H}_4\text{CH}_2\text{MgCl}$, THF, 4 h; vi) 2-iodoxybenzoic acid (IBX), DMSO/THF; vii) 4% THF, CH_2Cl_2 , 0 °C; viii) THF, 40 °C, 6 h; ix) sat. CsF, DMF, 60 °C, 16 h; x) 0.2 eq. TBAF, THF/DMF (1:4), 45 °C, 30 min.

Scheme 42.

terminal alkynes. The alkynyl ketones **278** were treated with the secondary amine to form enaminones **279**, which underwent a facile cyclization and elimination of secondary amine to provide the benzopyrone nucleus **280** (Scheme 43).

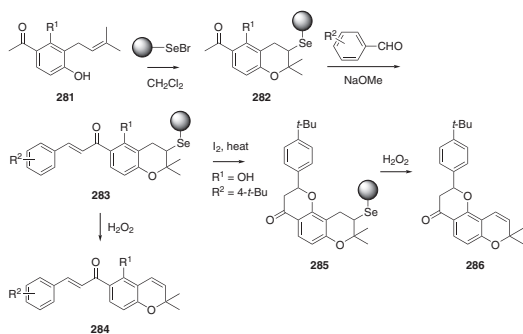


Reagents and conditions: i) $(\text{COCl})_2$, DMF; ii) CuI, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, Et_3N ; iii) MeOH, reflux.

Scheme 43.

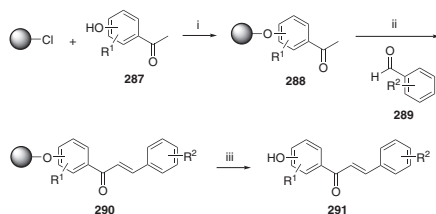
Nicolaou *et al.*⁶³ reported a solid-phase synthesis of a 2,2-dimethylbenzopyran motif employing a cycloloading strategy that relies on the use of a polystyrene-based selenenyl bromide resin. In one natural product based library, a chalcone family of compounds was synthesized in parallel approach by condensing a variety of 11 aldehydes to a set of three resin-bound benzopyrans **282** containing a methyl ketone substituent (Scheme 44). Spontaneous dehydration of the resulting β -hydroxy ketone led to the supported chalcone **283** which was cleaved from the resin by hydrogen peroxide promoted selenoxide elimination to give the final product **284**. On the other hand, treatment of supported chalcones **283**

with iodine, followed by oxidative elimination, furnished flavones **286**.



Scheme 44.

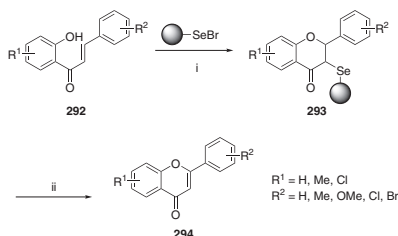
Cheng *et al.*⁶⁴ prepared a small library of 12 chalcones *via* parallel solid phase synthesis. The immobilized hydroxyacetophenones **288** were submitted to a Claisen-Schmidt condensation with a series of arylaldehydes resulting in the chalcones **290** which were then cleaved from the resin yielding chalcones **291** (Scheme 45).



Reagents and conditions: i) pyridine, CH_2Cl_2 ; ii) NaOH, MeOH, DMF; iii) TFA, CH_2Cl_2 .

Scheme 45.

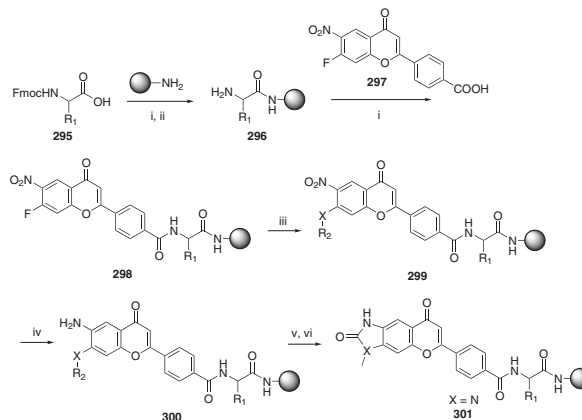
Huang *et al.*⁶⁵ described a solid-phase synthesis of flavones employing a Lewis acid-mediated polystyrene-supported selenium which induced intramolecular cyclization of chalcones **292**. After the oxidative cleavage of selenium resin, the flavones **294** were obtained in good overall yields and high purity (Scheme 46).



Reagents and conditions: i) ZnCl_2 , CH_2Cl_2 , r.t., 12h; ii) H_2O_2 , THF, 0 °C to r.t.

Scheme 46.

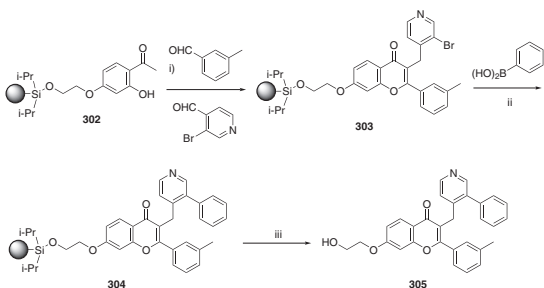
A different strategy was employed by Yao *et al.*⁶⁶ for the preparation of a flavone library. The functionalized flavone **297** was prepared in solution phase by classical Claisen condensation, mixed acid nitration and oxidative cyclization reaction with iodine-DMSO. Then, this flavone **297** was employed as scaffold for the synthesis of a combinatorial library in solid phase (Scheme 47). The linker **296** was constructed by coupling of Fmoc-glycine **295** onto Rink resin, followed by Fmoc deprotection. After that, the flavone **297** was readily attached to the resin **296** using 1,3-diisopropylcarbodiimide (DIC). The subsequent aromatic nucleophilic substitution was performed with 1 mol L^{-1} phenols, mercaptans, or secondary amines in 25% diisopropylethylamine (DIPEA)/*N,N*-dimethylformamide (DMF) furnishing **299**. The aryl nitro group was then reduced with tin(II) chloride to aryl amine **300**, which was employed for the construction of different heterocyclic rings. For example, treatment with 1,1'-carbonyldiimidazole (CDI), followed by cleavage from the resin with trifluoroacetic acid -TFA furnished a benzimidazolone flavonoid **301**.



Reagents and conditions: i) HOBt/DIC, DMF, r.t.; ii) 20% piperidine/DMF; iii) 1 mol L^{-1} phenol, mercaptan or amine, 25% DIPEA/DMF, r.t.; iv) 2 mol L^{-1} SnCl_2 , DMF, r.t.; v) CDI, CH_2Cl_2 , r.t.; vi) 95% TFA, r.t.

Scheme 47.

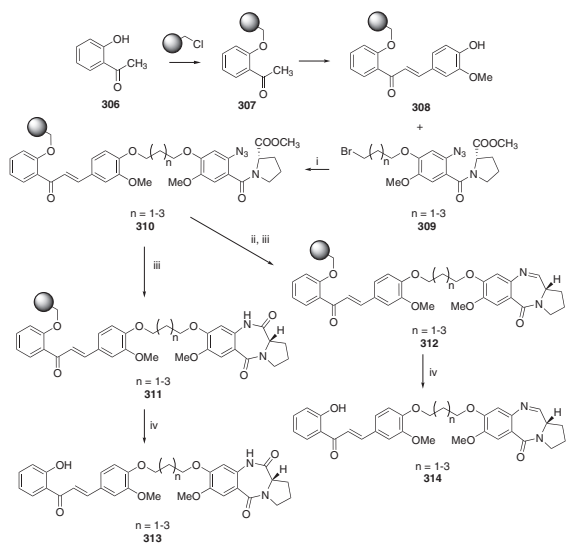
Arai *et al.*⁶⁷ developed an efficient one-pot synthesis of chromone and flavonoid derivatives bearing heterocyclic units by Michael aldol reaction. They have also examined the one-pot reactions in the solid phase by attaching an acetophenone derivative to (4-methoxyphenyl)diisopropylsilylpropyl polystyrene beads leading to resin **302**. The use of substituted benzaldehydes and subsequent addition of heterocyclic aldehydes gave 3-pyridyl-substituted flavones **303**. To introduce an additional point of diversity into the molecules, Suzuki-Miyaura coupling was performed, followed by cleavage from the resin, furnishing flavone **305** in good overall yields and high purity (Scheme 48).



Reagents and conditions: i) KOH, EtOH, 40 °C; ii) Pd₂(dba)₃, NaOMe, THF/H₂O, 60 °C, 24 h; iii) 2% HCl, dioxane, 3h, r.t.; 1N NaOH

Scheme 48.

Chalcones are known to possess some pharmacological activities, among them antitumor. The synthesis of new pyrrolobenzodiazepine-chalcones conjugates by SPOS has been achieved.⁶⁸ The authors used the molecular hybridization strategy, combining chalcone (which binds to tubulin, preventing the proliferation of microtubules) to pyrrolobenzodiazepine, a compound that targets the minor groove of DNA. The divergent synthetic pathway is depicted in Scheme 49 and the synthesis started with the coupling of 2-hydroxyacetophenone **306** with Merrifield resin (NaH, dry DMF, 50-60 °C, 48 h), followed of aldolisation with vanillin to afford the ketone-bound **308** (NaOMe/THF/MeOH, r.t., 4 days). The starting material **309** is prepared in solution and coupled with the resin intermediate **308** in the presence of K₂CO₃. Simple intramolecular aza-Wittig reductive cyclization process afforded compounds-bound **311** and **312**, which



Reagents and Conditions: (i) K₂CO₃, dry DMF, 50 °C, 48 h; (ii) diisobutylaluminium hydride (DIBAL)-H, dry CH₂Cl₂, -78 °C, 2 h; (iii) PPh₃, dry toluene, r.t., 16 h; (iv) TFA/CH₂Cl₂ (1:1), r.t., 2 h, 65-78%.

Scheme 49.

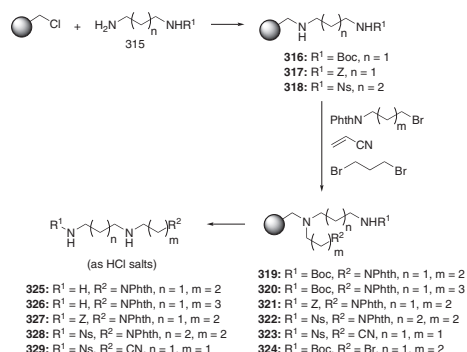
are released from the resin by employing TFA/CH₂Cl₂ at r.t., in 2 h.

6. Polyamines

Polyamines are organic polycations present in all cells and biologic liquids of live organisms that play an important role in control the general mechanism of the cellular proliferation. Putrescine is involved in many important biological processes such as embryogenesis and proliferation of normal or cancer cells while spermine, a putrescine metabolite, is known to inhibit cellular proliferation. In function of its considerable relation with the mechanisms involved in the proliferative process, the enzymes of the polyamines metabolism are potential targets for the design of new anticancer drugs and the knowledge of the mechanism implicated in the transport of polyamines can allow the development of polyamines analogues.⁶⁹ Furthermore, these pathways contain enzymes that can be harvested as powerful biocatalysts for the synthesis of both new drugs and existing blockbuster therapeutics. All of these considerations have led medicinal chemists to employ the polyamine core as building block to design several small libraries of compounds combining heterocycle natural products scaffolds and polyamines.

An interesting divergent approach to built polyamines and polyamines derivatives was published by Manov and Bienz⁷⁰ employing the Merrifield resin and protected amines. They synthesized a library of 28 polyamines in which Scheme 50 depicted part of the synthesis. The Merrifield resin was modified with primary amines **315** and rapidly dialkylated. After selective deprotection of either of the two terminal amines, the specific prolongation or derivatization of the resin-bound triamines was performed. The resulting polyamines **325-329** were easily released from the polymer by treatment with 1-chloroethyl chloroformate (ACE-Cl) and subsequent methanolysis.

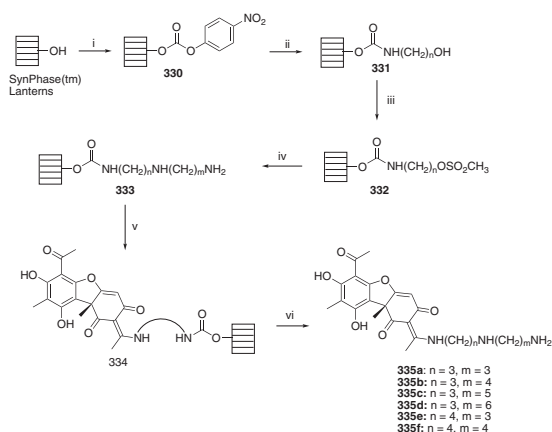
Uriac and co-workers⁷¹ have published the solid-phase synthesis of a small set based on a natural



Scheme 50.

lichen dibenzofurane derivative, usnic acid **335a-335f** (Scheme 51). The authors took advantage of the antibacterial activity of usnic acid amino derivatives and they functionalized this dibenzofuran with polyamines in order to improve the antibacterial activity and to overcome their poor hydrosolubility.

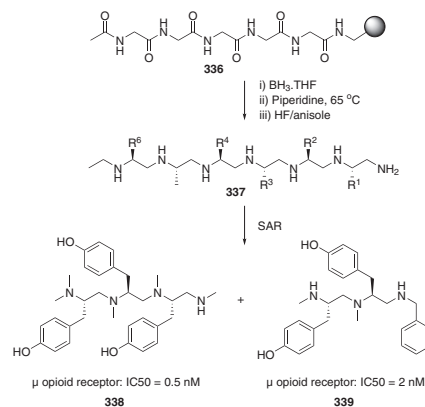
Two sets of usnic acid derivatives polyaminated were synthesized by a split-and-mix method using SynPhase supports. Scheme 51 depicts one set of usnic acid triamines derivatives. SynPhase Lanterns supports were activated under anhydrous conditions with 4-nitrophenylchloroformate in the presence of *N*-methylmorpholine, then reacted with commercial amino alcohols ($n = 3-5$), affording supports **331**. The supports **331** were pooled for the mesylation (**332**) then divided into four pools for the nucleophilic displacement by various diamines, and led to supported triamines **333**. The supports **333** were mixed in two batches for the condensation with usnic acid and then the products **335a-335f** were delivery from the supports in acid conditions. The products were obtained in good yield (30-40%) and purity (87%).



Scheme 51.

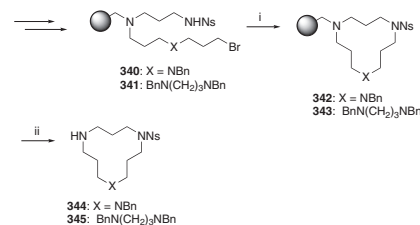
An elegant strategy to synthesize and test a mixture based chiral heptaamine library **338-339** (34,012,170 compounds) against μ opioid receptor, was recently developed by Houghten and co-workers.⁷² The authors prepared and screened the library using a Positional Scanning Synthetic Combinatorial Library (PS-SCLs) as strategy, which is composed by one sublibrary for each variable position. The solid-phase synthesis was performed starting with the polyamides reduction which consisting of a 72 h treatment of resin-bound peptides **336** with BH_3 -THF at 65 °C (Scheme 52).

A method for the synthesis of cyclic polyamines based on solid-phase chemistry has been reported.⁷³ The use of SPOS to obtain the cyclic polyamines was selected by the authors because the products and intermediates are very polar, which



Scheme 52.

makes it difficult to purification, and to avoid the dimerization and polymerization in the macrocyclization step, due to the high dilutions necessary for their enforcement. Scheme 53 illustrates the selected route. The linear polyamines **340** and **342** have been synthesized stepwise on solid support in a convergent manner using Merrifield resin as solid support. Cyclisations on the resins were effected conventionally by direct intramolecular $\text{S}_{\text{N}}2$ reactions between sulphonyl-protected terminal amino groups and primary alkyl bromides under basic conditions. The release of products from the resin was carried out by treatment with ACE-Cl followed by methanolysis.



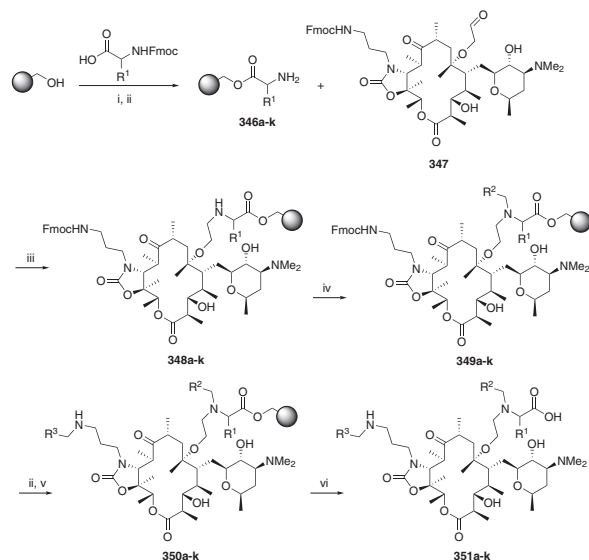
Reagents and conditions: i) Cs_2CO_3 , DMF, 50 °C; ii) ACE-Cl, DIEA, DCE, then MeOH, reflux.

Scheme 53.

7. Others

Lactones are important classes of organic compounds due to their high occurrence in nature, and also because they are versatile building blocks in the synthesis of a wide range of natural and synthetic products. Macrolides are a class of antibiotic compounds that contain a large lactone (macrolide) ring of 12 to 16 atoms and several sugars linked to the ring. Sowin and co-worker⁷⁴ published the first example of a library that employs the macrolide core as a template for combinatorial synthesis (Scheme 54). The synthesis was carried out using the aldehyde **347** as starting material, this core is accessible in large quantities

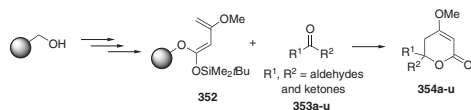
from 6-*O*-allyl-erythromycin A. For the library synthesis they used aminonomethylpolystyrene resin containing a fluorine tag and an extended modified Wang type linker. The library introduces three sites of diversity to macrolide scaffold via reductive aminations.



Reagents and conditions: i) DIC, DMAP, $\text{CH}_2\text{Cl}_2/\text{THF}$; ii) 20% piperidine/DMF (2 x); iii) 10% AcOH/DMF, wash, NaCNBH_3 , 10% AcOH/DMF; iv) R^2CHO , 10% AcOH/DMF, NaCNBH_3 ; v) R^3CHO , 10% AcOH/DMF, wash, NaCNBH_3 , 10% AcOH/DMF; vi) 90% TFA/ CH_2Cl_2 .

Scheme 54.

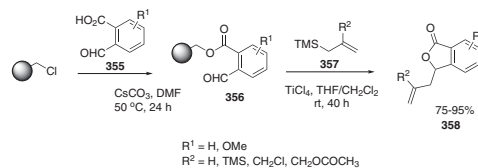
Pierres and co-workers⁷⁵ related the SPOS of pyrones employing a hetero Diels-Alder approach (Scheme 55). In this work, the authors prepared a set of 5,6-dihydropyrones **354** grafting the Brassard diene **352** analogue on a modified Merrifield resin and reacted it with aldehydes or ketones. The diene **352** grafted on Wang resin proved to be more stable than the corresponding diene in solution which may offer significant short-cuts for the preparation of libraries of 5,6-dihydropyrones, with yields ranging from 20 to 55%.



Scheme 55.

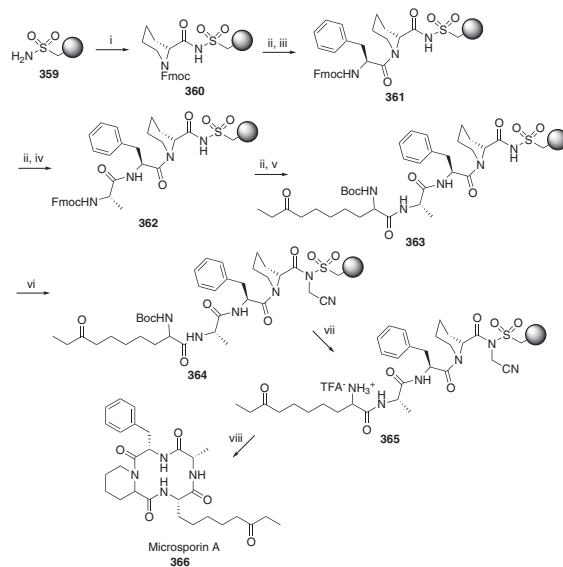
Benzoannulated butyrolactones (phthalides) are present in various natural products. Knepper and coworkers⁷⁶ employed the Sakurai reaction for the solid-phase synthesis of phthalides (Scheme 56). For example, 2-formyl benzoic acids were immobilized on Merrifield resin using standard conditions. Treatment of resin **356** with allyltrimethyl silanes in the presence of five equivalents of titanium

tetrachloride furnished the phthalides **358** in good yields and excellent purity. They have also demonstrated that asymmetric induction could be achieved by using chiral ligands.



Scheme 56.

Gu *et al.*⁷⁷ reported the isolation, characterization and the solid-phase synthesis of microsporin A, a cyclic peptide with cytotoxic activity. The total solid-phase synthesis (Scheme 57) starts with the safety-catch sulfonamide linker resin **359**. After several steps where amino acids were selectively added and unprotected, the intermediate *N*-Boc **363** was obtained. Activation of **363** by treatment with ICH_2CN under basic conditions afforded the activated resin **364**. Boc deprotection of **364** followed by cyclization and cleavage furnished the microsporin A **366**.

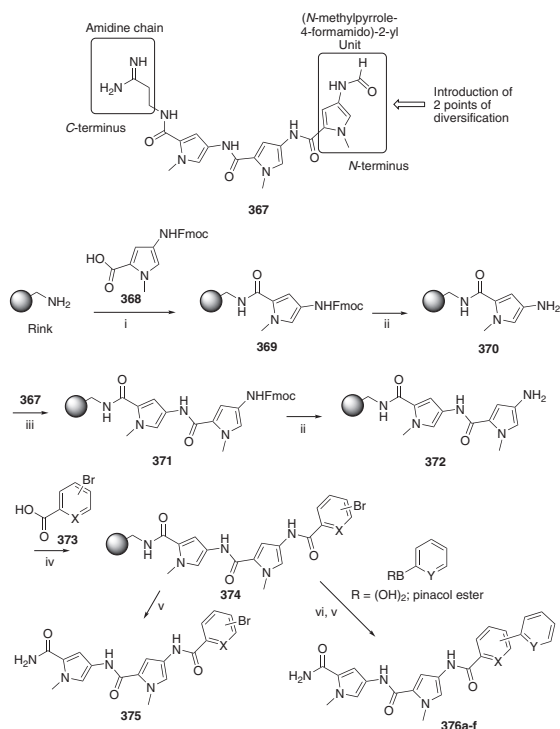


Reagents and conditions: i) Fmoc-D-Pip-OH, PyBOP, DIEA, CH_2Cl_2 ; ii) Piperidine, DMF; iii) Fmoc-Phe-OH, PyBOP, DIEA, NMP; iv) Fmoc-Ala-OH, PyBOP, DIEA, NMP; v) Boc-Aode-OH, PyBOP, DIEA, NMP; vi) ICH_2CN , DIEA, NMP; vii) TFA/ CH_2Cl_2 ; viii) 20% DIPEA, THF, reflux.

Scheme 57.

Distamycin **367** (Scheme 58) is a natural compound present in *Streptomyces* species which have an ability of recognize AT-rich sequences through noncovalently binding in the minor groove of B-form DNA. A combinatorial approach based on radiofrequency tagget split-and-mix methodology was exploited to prepare a 72 member library

of distamycin analogs in two points of diversification at the template.⁷⁸ One of the diversity was at *N*-methylpyrrole-4-formamido-2-yl unit, where it was replaced by novel biaryl motifs. The other one occurred when the amidine portion was changed by primary carboxamides after cleavage step from solid support by acid hydrolysis. The solid support employed was the easily available Fmoc-protected Rink Amide SynPhase Lanterns. The authors have developed an efficient coupling-cycle protocol on solid-phase based on standard methods for both assembly of the heteroaromatic polyamide chain and for the Suzuki-Miyaura cross-coupling reaction.



Reagents and conditions: i) **368** (0.2 mol L⁻¹), HOBT (0.2 M), DIC (0.2 mol L⁻¹), dry DMF/CH₂Cl₂ (50/50), 12 h; ii) 80% Piperidine/DMF, 30 min (× 2); iii) 10 (0.2 mol L⁻¹), HOBT (0.2 mol L⁻¹), DIC (0.2 mol L⁻¹), dry DMF/CH₂Cl₂ (50/50), 1.5 h (× 2); iv) **373** (carboxylic acids) (0.2 mol L⁻¹), HOBT (0.2 mol L⁻¹), DIC (0.2 mol L⁻¹), dry DMF/CH₂Cl₂ (50/50), 1.5 h, r.t. (× 2); v) 50% TFA/CH₂Cl₂, 1 h; vi) boronic acid/esters (0.5 M), Pd(PPh₃)₄ (0.02 mol L⁻¹), Na₂CO₃ (0.25 mol L⁻¹), DMF/H₂O (90/10), 80 °C, 16 h.

Scheme 58.

8. Conclusions

The application of combinatorial chemistry science has revolutionized the medicinal chemistry paradigms, as well as high-throughput screening, chemical lead optimization, library purification and post purification sample handling, at the same time as *in vitro* and *in vivo* drug metabolism and pharmacokinetic assays.⁷⁹ While there are several

ways to conduct high-throughput synthesis, combinatorial chemistry is by far the dominant activity leading to new diversity in compound libraries.⁸⁰ In a recent review, Dolle *et al.*⁸¹ described 505 libraries and 30 molecular probes extracted from 490 literature citations in 2008. Several technologies alongside the solid-phase organic synthesis (SPOS) has emerged in recent years aiming to facilitate the rapid generation of compound libraries, as for example microwave-assisted organic synthesis (MAOS) and continuous-flow organic synthesis.⁸²

Though SPOS is now considered an established tool for synthetic chemists, the challenge of handle it as well as the traditional solution chemistry still remains so demanding as at the beginning of the 1990's. New solid supports and solid-phase techniques also continue to emerge as well hundreds of reactions have been adapted to SPOS. Moreover, the reactions on solid support may be staggered, with several reports in the literature of large-scale synthesis.⁸³ For instance, the industrial peptide synthesis is carry out on solid-phase and can be adapted to synthesis of small compounds. Also, this technology can be extended to solution phase synthesis with the employment of polymer-support reagents, catalysts, and cleanup agents (scavengers), which facilitate reactions of substrates in solution. Employing SPOS to build compounds with multiple stereocenters with natural building blocks or to prepare complex natural product libraries is also a very elegant approach to find new hits and have a great impact on drug development.⁸⁴



Vera Lucia Eifler-Lima has graduated in Pharmacy and received her Master Degree in Pharmaceutical Sciences (Federal University of Rio Grande do Sul - UFRGS). She has received her PhD in Organic Chemistry from the Faculty of Pharmacy (University of Rennes I, France, Professor Jean Huet). She is

currently an Associate Professor in the Faculty of Pharmacy at UFRGS. She has experience in medicinal chemistry, with emphasis on organic synthesis. Her research interests include new strategies of synthesis for use in combinatorial chemistry, and development and obtaining antiparasitic and antitumor hits. She is the head of the CNPq Research Group on Medicinal Organic Synthesis and has been a long-time member of the Brazilian Chemical Society.

Cedric Stephan Graebin has received his PhD Degree from the Federal University of Rio Grande do Sul (UFRGS - 2008), and completed his postdoctoral training with Professor Dr. Jorge A. Guimaraes (UFRGS - 2009).



He is an Adjunct Professor at the Department of Chemistry, Rio de Janeiro Federal Rural University. His research interest is the synthesis of new pharmacologically active compounds from both solution and solid-phase synthesis.



Flavia De Toni Uchoa graduated in Pharmacy from the Federal University of Rio Grande do Sul (1997). She received her Master Degree in Bioactive Products of Biotechnology from the Federal University of Pernambuco (2004) and a PhD Degree in Medicinal Chemistry and Pharmacology from the same

institution. She completed her Postdoctoral training at UFRGS in 2009 and works mainly with the synthesis and preclinical studies of candidate drugs.



Arlene G. Corrêa received her PhD from the Federal University of São Carlos (1991) and completed her Postdoctoral training with Professor Paul A. Wender (Stanford University, CA, 1997). She is an Associate Professor in the Department of Chemistry at the University Federal of São Carlos. Her research interests

are isolation, identification and synthesis of insect pheromones; synthesis of bioactive natural products and analogs employing combinatorial chemistry technologies and green chemistry. She is a member of the Brazilian Chemical Society and the American Chemical Society.



Patricia Domingos Duarte, graduated in Chemistry from the Federal University of São Carlos (2007). She is currently a PhD student in Organic Chemistry at the same institution, working on the asymmetric synthesis of alkaloids under the supervision of Professor Arlene G. Corrêa.

References

- Fenniri, H.; ed. In *Combinatorial Chemistry: Practical Approach*. Oxford University Press: Oxford, 2000; Dias, R. L. A.; Correa, A. G.; *Quim. Nova* **2001**, *24*, 236.
- Merrifield, R. B.; *J. Am. Chem. Soc.* **1963**, *85*, 2149; Früchtel, J. S.; Jung, G.; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17; Thompson, L. A.; Elmann, J. A.; *Chem. Rev.* **1996**, *96*, 555; Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C.; *Tetrahedron* **1998**, *54*, 15385.
- Marquardt, M.; Eifler-Lima, V. L.; *Quim. Nova*, **2001**, *24*, 846.
- Delgado, M.; Janda, K. D.; *Curr. Org. Chem.* **2002**, *6*, 1031.
- Rates, S. M. K. *Toxicon* **2001**, *39*, 603-613.
- Verdine, G. L.; *Nature* **1996**, *384*, 11.
- Newman, D. J.; Cragg, G.M.; *J. Nat. Prod.* **2007**, *70*, 461.
- Rouhi, M. A.; *Chem. Eng. News* **2003**, *81*, 77.
- Wang, H.; Ganesan, A.; *J. Comb. Chem.* **2000**, *2*, 186.
- Sato, S.; Kubota, Y.; Kumagai, H.; Kumazawa, T.; Matsuba, S.; Onodera, J.; Suzuki, M.; *Heterocycles* **2000**, *53*, 1523.
- Wang, H.; Sim, M. M.; *J. Nat. Prod.* **2001**, *64*, 1497.
- Pelish, H.; Westwood, N.; Feng, Y.; Kirchhausen, T.; Shair, M.; *J. Am. Chem. Soc.* **2001**, *123*, 6740.
- Huang, X.; Liu, Z.; *J. Org. Chem.* **2002**, *67*, 6731.
- Baxendale, I. R.; Ley, S. V.; Piutti, C.; *Angew. Chem. Int. Ed.* **2002**, *41*, 2194.
- Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V.; *J. Chem. Soc., Perkin Trans. I* **2002**, 143.
- Finaru, A.; Berthault, A.; Besson, T.; Guillaumet, G.; Berteina-Raboin, S.; *Org. Lett.* **2002**, *4*, 2613.
- Nielsen, T. E.; Meldal, M.; *J. Org. Chem.* **2004**, *69*, 3765.
- Marfil, M.; Albericio, F.; Álvarez M.; *Tetrahedron* **2004**, *60*, 8659.
- Cironi, P.; Cuevas, C.; Albericio, F.; Álvarez, M.; *Tetrahedron* **2004**, *60*, 8669.
- Knepper, K.; Ziegert, R. E.; Brase, S.; *Tetrahedron* **2004**, *60*, 8591.
- Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P.; *Angew. Chem. Int. Ed.* **2005**, *44*, 1366.
- Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C.; *Eur. J. Org. Chem.* **2006**, 4998.
- Lee, S.; Park, S. B.; *J. Comb. Chem.* **2006**, *8*, 50.
- Doi, T.; Hoshina, Y.; Mogi, H.; Yamada, Y.; Takahashi, T.; *J. Comb. Chem.* **2006**, *8*, 571.
- Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L.; *Tetrahedron Lett.* **2006**, *47*, 9025.
- Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby, S.; Tranmer, G. K.; *Chem. Commun.* **2006**, 2566.
- Krchnak, V.; Waring, K. R.; Noll, B. C.; Moellmann, U.; Dahse, H.; Miller, M. J.; *J. Org. Chem.* **2008**, *73*, 4559.
- Calver, A.; Main, C. A.; Petersson, H. M.; Rahman, S. S.; Hartley, R. C.; *Tetrahedron* **2008**, *64*, 901.
- Worlikar, S. A.; Neuenswander, B.; Lushington, G. H.; Larock, R. C.; *J. Comb. Chem.* **2009**, *11*, 875.
- Duarte, M.; Stedile, G.; Pazinato, M.; Oliveira, E. R.; Eifler-Lima, V. L.; *Lett. Org. Chem.* **2009**, *6*, 90.
- Chen, K.; Phil, S.; *Nature* **2009**, *459*, 824.

32. Wang, G.; Tang, W.; Bidigare, R. R. In *Natural Products – Drug Discovery and Therapeutic Medicine*; Zhang, L.; Demain, A. L., eds.; Humana Press: Totowa, 2005, ch. 9.
33. Maltais, R.; Tremblay, M. R.; Poirier, D.; *J. Comb. Chem.* **2000**, *2*, 604.
34. Tremblay, M. R.; Poirier, D.; *Tetrahedron Lett.* **1999**, *40*, 1277.
35. Tremblay, M. R.; Poirier, D.; *J. Comb. Chem.*, **2000**, *2*, 48.
36. Kufe, D. W.; Pollock, R. E.; Weichselbaum, R. R.; Bast, R. C., Jr.; Gansler, T. S.; Holland, J. F.; Frei III, E., eds. In *Cancer Medicine Hamilton*, BC Decker: Canada, 2003.
37. Xiao, X. Y.; Li, R.; Zhuang, H.; Ewing, B.; Karunaratne, K.; Lillig, J.; Brown, R.; Nicolaou, K. C.; *Biotechnol. Bioeng.* **2000**, *71*, 44.
38. Hijikuro, T. D.; Takahashi, T.; *J. Am. Chem. Soc.* **2001**, *123*, 3716.
39. Moore, K. S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J. N.; McCrimmon, D.; Zasloff, M.; *Proc. Natl. Acad. Soc.* **1993**, *90*, 1354.
40. Chitkul, B.; Atrash, B.; Bradley, M.; *Tetrahedron Lett.* **2001**, *42*, 6211.
41. Hanazawa, T.; Wada, T.; Matsuda, S.; Okamoto, S.; Sato, F.; *Org. Lett.* **2001**, *3*, 3975.
42. Jagtap, P. G.; Baloglu, E.; Barron, D. M.; Bane, S.; Kingston, D. G.; *J. Nat. Prod.* **2002**, *65*, 1136.
43. Miyaoka, H.; Kajiwara, Y.; Yamada, Y.; *Tetrahedron Lett.* **2000**, *41*, 911.
44. Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Müller, O.; Lieb, F.; Waldmann, H.; *J. Am. Chem. Soc.*, **2002**, *124*, 13171.
45. Saleem, M.; Murtaza, I.; Witkowsky, O.; Kohla, A. M.; Maddodi, N.; *Biochem. Biophys. Res. Comm.* **2009**, *388*, 576.
46. Geetha, T.; Varalakshmi, P.; *J. Ethnopharmacol.* **2001**, *76*, 77.
47. Ziegler, H. L.; Stärk, D.; Christensen, J.; Hviid, L.; Hägerstrand, H.; Jaroszewski, J. W.; *Antimicrob. Ag. Chemother.* **2002**, *46*, 1441.
48. Srinivasan, T.; Srivastava, G.K.; Pathak, A.; Batra, S.; Raj, K.; Singh, K.; Puri, S.K.; Kundu, B.; *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2803.
49. Pathak, A.; Singh, S. K.; Biabani, M. A. Farooq; Kulshreshtha, D. K.; Puri, S. K.; Srivastava, S.; Kundu, B.; *Comb. Chem. High Through. Screen.* **2002**, *5*, 241.
50. Ciobanu, L. C.; Poirier, D.; *J. Comb. Chem.*, **2003**, *5*, 429.
51. Subramanian, T.; Wang, Z.; Troutman, J. M.; Andres, D. A.; Spielmann, H.P.; *Org. Lett.* **2005**, *7*, 2109.
52. Bod'E, C. A.; Muller, C. P.; Madder, A.; *J. Pept. Sci.* **2007**, *13*, 702.
53. Yu, X.; Wang, S.; Chen, F.; *J. Comb. Chem.* **2008**, *10*, 605.
54. Juan, M. E.; Planas, J. M.; Ruiz-Gutierrez, V.; Daniel, H.; Wenzel, U.; *Br. J. Nutr.* **2008**, *100*, 36.
55. Parra, A.; Rivas, F.; Lopez, P. E.; Garcia-Granados, E.; Martinez, A.; Albericio, F.; Marquez, N.; Muñoz, E.; *Bioorg. Med. Chem.* **2009**, *17*, 1139.
56. Nicoletti, D.; Mouriño, A.; Torneiro, M.; *J. Org. Chem.* **2009**, *74*, 4782.
57. Song, A.; Lam, K. S.; *Tetrahedron* **2004**, *60*, 8605; Song, A.; Zhang, J.; Lebrilla, C. B.; Lam, K. S.; *J. Comb. Chem.* **2004**, *6*, 604.
58. Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J-F.; *J. Org. Chem.* **2009**, *74*, 4158.
59. Brueggemeier, R. W.; Gu, X. J.; Mobley, J. A.; Joomprabutra, S.; Bhat, A. S.; Whetstone, J. L.; *Ann. New York Acad. Sci.* **2001**, *948*, 51.
60. Hall, D. G.; Manku, S.; Wang, F.; *J. Comb. Chem.* **2001**, *3*, 125; Horton, D. A.; Bourne, G. T.; Smythe, M. L.; *Chem. Rev.* **2003**, *103*, 893; Ziegert, R. E.; Toräng, J.; Knepper, K.; Bräse, S.; *J. Comb. Chem.* **2005**, *7*, 148.
61. Harikrishnan, L. S.; Showalter, H. D. H.; *Tetrahedron* **2000**, *56*, 515.
62. Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W.; *J. Comb. Chem.* **2000**, *2*, 597.
63. Nicolau, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H.; *J. Am. Chem. Soc.* **2000**, *122*, 9939.
64. Cheng, M. S.; Li, R. S.; Kenyon, G.; *Chin. Chem. Lett.* **2000**, *11*, 851.
65. Huang, X.; Tang, E.; Xu, W.; Cao, J.; *J. Comb. Chem.* **2005**, *7*, 802.
66. Yao, N.; Song, A.; Wang, X.; Dixon, S.; Lam, K. S.; *J. Comb. Chem.* **2007**, *9*, 668.
67. Arai, M. A.; Sato, M.; Sawada, K.; Hosoya, T.; Ishibashi, M.; *Chem. Asian J.* **2008**, *3*, 2056.
68. Kamal, A.; Shakaraiah, N.; Prabhakar, S.; Reddy, C. R.; Markandeya, N.; Reddy, K. L.; Devaiah, V.; *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2434.
69. Delcros, J. G.; Tomasi, S.; Duhieu, S.; Foucault, M.; Martin, B.; Le Roch, M.; Eifler-Lima, V. L.; Renault, J.; Uriac, P.; *J. Med. Chem.* **2006**, *49*, 232; Casero, R. A.; Woster, P. M.; *J. Med. Chem.* **2009**, *52*, 4551.
70. Manov, N.; Bienz, S.; *Tetrahedron* **2001**, *37*, 7893.
71. Tomasi, S.; Picard, S.; Lainé, C.; Babonneau, V.; Goujeon, A.; Boustie, J.; Uriac, P.; *J. Comb. Chem.* **2006**, *8*, 11.
72. Nefzi, A.; Ostresh, J. M.; Appel, J. R.; Bidlack, J.; Dooley, C. T.; Houghten, R. A.; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4331.
73. Bisegger, P.; Manov, N.; Bienz, S.; *Tetrahedron.* **2008**, *64*, 7531.
74. Akritopoulou-Zanze, I.; Sowin, T. J.; *J. Comb. Chem.* **2001**, *3*, 301.
75. Pierres, C.; George, P.; Hijfte, L.; Ducep, J. B.; Hibert, M.; Mann, A.; *Tetrahedron Lett.* **2003**, *44*, 3645.
76. Knepper, K.; Zieger, R. E.; Bräse, S.; *Tetrahedron* **2004**, *60*, 8591.
77. Gu, W.; Cueto, M.; Jensen, P. J.; Fenical, W.; Silverman, R. B.; *Tetrahedron* **2007**, *63*, 6535.
78. Brucoli, F.; Howard, P.; Thurston, D.; *J. Comb. Chem.* **2009**, *11*, 576.

79. Kennedy, J. P.; Williams, L.; Bridges, T. M. R.; Daniels, N.; Weaver, D.; Lindsley, C. W. *J. Comb. Chem.* **2008**, *10*, 345.
80. Czarnik, A. W.; *J. Comb. Chem.*, **2008**, *10*, 1.
81. Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W.; *J. Comb. Chem.* **2009**, *11*, 739.
82. Boldt, G. E.; Dickerson, T. J.; Janda, K. D.; *Drug Discov. Today* **2006**, *11*, 143; Baxendale, I. R.; Hayward, J. J.; Ley, S. V.; *Comb. Chem. High Throughput Screening* **2007**, *10*, 802.
83. Ryba, T. D.; Depew, K. M.; Marcaurette, L. A.; *J. Comb. Chem.* **2009**, *11*, 110 ; He, U.; Chan, T. H.; *Org. Lett.* **2007**, *9*, 2681; Verlander, M.; *Intl. J. Pept. Res. Therapeut.* **2007**, *13*, 75; Prühs, S.; Dienter, C.; Blume, T.; Schültz, A.; Harre, M.; Neh, H.; *Org. Proc. Res. Dev.* **2006**, *10*, 441.
84. Moss, W.H.; Hurt, C.R.; Morales, G.A.; *Mol. Divers.* **2009**, *13*, 241.

Received: January 8, 2010

Web Release Date: May 27, 2010

FAPESP has sponsored the publication of this article.