Review

Solid-Phase Parallel Synthesis of Drug-Like Artificial 2H-Benzopyran Libraries

Taeho Lee 1 and Young-Dae Gong 2,*

1 Research Institute of Pharmaceutical Sciences, College of Pharmacy, Kyungpook National University, 1370, Sangyuk-dong, Buk-gu, Daegu 702-701, Korea; E-Mail: tlee@knu.ac.kr
2 Center for Innovative Drug Library Research, Department of Chemistry, College of Natural Science, Dongguk University-Seoul, 26 Pildong 3-ga, Jung-gu, Seoul 100-715, Korea
* Author to whom correspondence should be addressed; E-Mail: ydgong@dongguk.edu; Tel.: +82-2-2260-3206; Fax: +82-2-2268-8204.

Received: 10 April 2012; in revised form: 25 April 2012 / Accepted: 7 May 2012 / Published: 9 May 2012

Abstract: This review covers the construction of drug-like 2H-benzopyrans and related libraries using solid-phase parallel synthesis. In this context, the preparation of substituted benzopyrans such as mono-, di- and trisubstituted benzopyran derivatives and additional ring-fused benzopyrans such as benzopyranoisoxazoles, benzopyranopyrazoles, six-membered ring-fused benzopyrans, and polycyclic benzopyrans are highlighted.

Keywords: combinatorial chemistry; solid-phase synthesis; chemical library; drug-like molecules; 2H-benzopyran

1. Introduction

Combinatorial chemistry has become an extremely powerful technique for the generation of drug-like and biologically active small organic molecule libraries in either the solution-phase or on solid supports [1–5]. In combinatorial synthesis, solid-phase organic synthesis (SPOS) is now routinely used to prepare a large number of small heterocyclic molecules and is especially useful in creating massive numbers of hit and lead compounds as part of high-throughput screening (HTS) technologies [6–10]. This is especially true for the privileged structures, which are core components of a large number of substances that possess a wide range of interesting biological activities and have been developed on solid-phase strategies [11–15].
Among biologically active heterocyclic scaffolds, the well-known privileged benzopyran structure frequently appears in many natural products and artificial bioactive molecules, that exhibit a wide range of biological activities [16–49]. Representative examples of benzopyran-containing natural products and artificial bioactive molecules are illustrated in Figure 1.

Figure 1. The representative examples of benzopyran-containing natural products and artificial bioactive molecules.

Hydroxylonchocarpin, lonchocarpin, and lonchocarpane exhibit anticancer activities [16–18], whereas moracin D exhibits antifungal activities [19,20]. Cromakalim [21–24] with its benzopyran moiety produces anti-hypertensive effects via potassium channel modulation, and SD8381 [25,26] with a 2H-benzopyran scaffold represents anti-inflammatory effects as a novel cyclooxygenase (COX)-2 inhibitor. Catechin and epigallocatechin gallate (EGCG) show both an antiallergic effects and anticancer action [27–29], whereas KRH-102140 with a 2H-benzopyran moiety is identified as a 5-lipoxygenase (5-LO) inhibitor [30,31]. Also, seselin and xanthylein with tricyclic benzopyrans exhibit anticancer activities [32–34].

(−)-Δ9-Tetrahydrocannabinol (−)-Δ9-THC, dronabinol) and other cannabinoids have been used to treat the symptoms of cancer, pain relief, and spasticity in multiple sclerosis, or as appetite stimulants for acquired immunodeficiency syndrome (AIDS) patients [35–39]. Suksdorfin (khellactone ester) inhibits human immunodeficiency virus (HIV)-1 replication in H9 lymphocytes [40,41], whereas daleformis shows inhibitory activities against endothelin-converting enzyme [42]. Rotenone has been used as an antianaphylactic agent for the treatment of asthma [43–49].

This paper reviews the use of solid-phase parallel synthesis in the construction of 2H-benzopyran libraries that contain substituted 2H-benzopyrans (A, B, and C) and additional cycle-fused
benzopyrans (D and E), except the derivatives of 1H-benzopyran, coumarin, and chromone moieties (Figure 2). In addition, the solid-phase synthesis of modified benzopyran derivatives using the 2H-benzopyran moiety as an intermediate is also discussed. The sections have been divided according to the number of substituents in the benzopyran core and the kinds of fused-benzopyran cores. Publications cited herein are mostly refereed journals and not patents.

**Figure 2.** The core structures of benzopyran.

2. Solid-Phase Synthesis of Substituted Benzopyran Compounds

2.1. Solid-Phase Synthesis of Monosubstituted Benzopyran Compounds

2.1.1. Solid-Phase Synthesis of 3-Substituted Benzopyran Compounds

Park and co-workers reported the solid-phase synthesis of 3-substituted 2H-benzopyran 1 (Scheme 1) and the fluorous-tag-based solution-phase synthesis of benzopyran derivatives with discrete core scaffolds to construct a 284-member library [50].

**Scheme 1.** Solid-phase synthesis of 3-substituted 2H-benzopyrans 1 by Park et al. [50].
The library construction was started from four different chromanones 2 (2a–d, see Figure 3), which were subjected to α-bromination and subsequent silyl protection at the phenolic hydroxyl group. α-Bromoketones 3 were reduced to α-bromoalcohols 4 by NaBH₄, followed by acid-catalyzed dehydration and subsequent silyl deprotection, to yield four vinyl bromides containing 2H-benzopyran moiety 5. After the activation of (4-methoxyphenyl)-diisopropylsilylpropyl polystyrene resin 6 with TfOH, vinyl bromide intermediates 5 were immobilized on the activated resin 7 in the presence of 2,6-lutidine to afford polymer-bound intermediates 8.

**Figure 3.** Various structures of 2H-benzopyran precursor (chromanone) moieties 2.

The 3-substituted 2H-benzopyran resins 9 were introduced to various aryl and heteroaryl moieties via Suzuki coupling of boronic acids (24 commercially available aryl- and heteroaryl-boronic acids) with Pd(PPh₃)₄ and Na₂CO₃ in aqueous 1,4-dioxane with high yields and purity. After the standard cleavage protocol of silyl linkers using HF/pyridine and subsequent quenching with TMSOEt, the desired 3-substituted 2H-benzopyrans 1 (96 examples) were successfully prepared on a scale of 5–10 mg with an average purity of 86%.

2.1.2. Solid-Phase Synthesis of 4-Substituted Benzopyran Compounds

Park and co-workers also reported the solid-phase synthesis of 4-substituted 2H-benzopyran 10 using similar methods for the solid-phase synthesis of 3-substituted 2H-benzopyran 1 (see Scheme 1) except 3-triflated moiety in 11 as starting materials instead of 3-bromo-benzopyrans 5 (Scheme 2) [51].

**Scheme 2.** Solid-phase synthesis of 4-substituted 2H-benzopyrans 10 by Park et al. [51].
The synthetic route for 4-substituted 2\(H\)-benzopyran 10 was initiated from triflate resins 12, which were derived from eight different 2\(H\)-benzopyran moieties 2 (2a–h, see Figure 3), and the activated solid support 7. 4-Triflate-benzopyrans 11 were synthesized from four different hydroxyacetophenones through cyclization with acetone [\(R^2 = \text{methyl}\)] or cyclopentanone [\(R^2 = -(\text{CH}_2)_4-\)] in the presence of pyrrolidine catalyst, and triflation of the resulting chromanones 2 using triflic anhydride in the presence of the proton sponge 2,6-di-tert-butyl-4-methylpyridine (DTBMP). After activation of resin 6 by treating TfOH, eight different vinyl triflated intermediates 2 were immobilized on these activated resins 7 in the presence of 2,6-lutidine to afford intermediates 12 on solid supports (average loading level: ~0.9 mmol/g).

The various substituted aryl rings (\(R^3\)) were introduced via palladium-mediated Suzuki coupling of aryl boronic acids. Among the many conditions tested in the solid-phase, the reaction condition with Pd(PPh\(_3\))\(_4\) and Na\(_2\)CO\(_3\) in aqueous 1,4-dioxane displayed a robust chemical transformation of 3 with various substituted aryl boronic acids (18 different aryl boronic acids), resulting in high yields of the desired 3-substituted 2\(H\)-benzopyran resins 13. Finally, the privileged benzopyrans 10 were produced by cleavage of resins 13 by using HF/pyridine in tetrahydrofuran (THF) and subsequent quenching with TMSOEt, and the resulting 144-member small-molecule collection was synthesized on a scale of 10–20 mg and their average purity was 87% without any purification steps.

Additionally, the solid-phase synthesis of the mono-substituted 2\(H\)-benzopyran-attaching 1,2,3-triazole ring at position 4 was described by Park and co-workers [51]. For the solid-phase synthesis of 1,2,3-triazole-substituted 2\(H\)-benzopyrans 14, terminal alkyne resins 15 were introduced to the vinyl triflate intermediates 12 on the solid support through a palladium-mediated Negishi-type cross-coupling reaction (Scheme 3) [51]. After Negishi-type alkynylation with ethynylmagnesium bromide, Pd(PPh\(_3\))\(_4\) and ZnCl\(_2\), the resulting terminal alkynyl moiety on the benzopyran core skeletons with azides 16 was subjected to regioselective Huisgen 1,3-dipolar [3 + 2] cycloaddition, namely, Click chemistry, in the presence of BrCu(PPh\(_3\))\(_3\) [52–54], a Cu-catalyst soluble in organic solvent, and \(N,N\)-diisopropylethylamine (DIPEA) to yield a new 1,2,3-triazole-substituted 2\(H\)-benzopyran resins 17 using solid-phase parallel synthesis. The eight different azides 16 were utilized for the Click chemistry and produced the novel 1,2,3-triazole-substituted 2\(H\)-benzopyrans 14 (64 examples) after HF/pyridine cleavage from the solid support and subsequent quenching with TMSOEt. The average purity, measured by liquid chromatography-mass spectrometry (LC-MS) analysis of the crude products, was 85%.

Scheme 3. Solid-phase synthesis of 1,2,3-triazole-substituted 2\(H\)-benzopyrans 14 by Park et al. [51].
Gong and Yoo reported the solid-phase synthesis of 3-hydroxy-4-amino-substituted benzopyrans 18 via epoxide opening in a two-phase solvent system [55]. The reaction of 4-nitrophenyl carbonate resin 19, which was formed by the reaction of Wang resin 20 and p-nitrophenyl chloroformate in CH$_2$Cl$_2$, with 6-amino-2,2-dimethyl chromene (21) and DIPEA in N,N-dimethylacetamide (DMA) afforded the carbamate resin 22 (Scheme 4).

**Scheme 4.** Solid-phase synthesis of 3-hydroxy-4-amino-substituted benzopyrans 18 by Gong and Yoo [55].

After various solvent systems and oxidizing agents were examined to avoid the formation of m-chlorobenzoic acid-added adduct resin in the case of oxidation of resin 22 with m-chloroperbenzoic acid (mCPBA), the two-phase solvent system comprised of chloroform and saturated aqueous NaHCO$_3$ with mCPBA afforded the epoxide resin 23. The regioselective ring opening of the polymer-bounded epoxide 23 with nine amines produced the 3-hydroxy-4-amino-substituted benzopyran resins 24 in good overall yields without significant contamination of the by-products. The desired benzopyran derivatives 18 (9 examples) were finally liberated from the resin 24 using trifluoroacetic acid (TFA).

2.1.3. Solid-Phase Synthesis of 6-Substituted Benzopyran Compounds

Solid-phase synthesis of 6-amino-substituted 2H-benzopyrans 25 was reported for the enlargement of diverse points in the benzopyran moiety by Gong et al. [56]. The N-alkylation [57,58] of the carbamate resin 22 [55] with alkyl halides and lithium t-butoxide in dimethyl sulfoxide (DMSO) introduced subsequently to various alkyl substituents in the 6-amino moiety of resins 26. The desired 6-amino-substituted 2H-benzopyran products 25 (16 examples, 87–71% yields) were liberated from the resins 26 with TFA (Scheme 5).

**Scheme 5.** Solid-phase synthesis of 6-amino-substituted 2H-benzopyrans 25 by Gong et al. [56].
2.1.4. Solid-Phase Synthesis of 8-Substituted Benzopyran Compounds

The new lead SD-8381 (see Figure 1) with 2H-benzopyran was identified as a novel COX-2 inhibitor from in-house HTS [25,26]. The synthesis of SD-8381 derivatives 27 (8-substituted 2H-benzopyrans) was carried out on solid-phase parallel synthetic approach to find more potent COX-2 inhibitors by Liao et al. (Scheme 6) [59].

**Scheme 6.** Solid-phase synthesis of 8-substituted 2H-benzopyrans 27 by Liao et al. [59].

![Scheme 6](image)

As a starting material, 3-bromo-5-chloro-2-hydroxybenzaldehyde (28) was reacted with ethyl trifluoro-methylcrotonate (29) in the presence of K₂CO₃ and N,N-dimethylformamide (DMF) under nitrogen at 70 °C (Scheme 6). The resulting 2H-benzopyran intermediate 30 was produced in 90% yield. After hydrolysis of ester 30 with aqueous lithium hydroxide in THF, acid 31 with an attached point was obtained in 80% yield. The benzopyran acid 31 was then loaded on bromo Wang resin 32 [4-(bromomethyl)phenoxyethyl-polystyrene] in the presence of cesium carbonate/DMA at 60 °C. Subsequently the bromo group on benzopyran 33 was converted into various aromatic substituents via palladium-mediated Suzuki coupling catalyzed by Pd(PPh₃)₄ with a diverse set of aromatic boronic acids [60]. The desired 8-substituted 2H-benzopyrans 27 (17 examples) were cleaved from resin 34 with 95% TFA in CH₂Cl₂ using triisopropylsilane as scavenger. A few analogs of 8-substituted 2H-benzopyran 27 (Ar = 4-Et-Ph and 3-Me-4-MeO-Ph) were used for further investigation in vivo.

2.2. Solid-Phase Synthesis of Disubstituted Benzopyran Compounds

2.2.1. Solid-phase Synthesis of 2,3-Disubstituted Benzopyran Compounds

Takahashi and co-workers described the efficient solid-phase synthesis of EGCG (see Figure 1) and the combinatorial synthesis of protected methylated epicatechin derivatives 35 (2,3-disubstituted benzopyran derivatives) (Scheme 7) [61,62].
Scheme 7. Solid-phase synthesis of 2,3-disubstituted benzopyrans 35 by Takahashi et al. [61,62].

The solid-phase synthetic strategy of 2,3-disubstituted benzopyrans 35 began with the treatment of the aldehyde 36 with bromo Wang resin 32 (1.6 mmol/g) to provide the aldehyde resins 37 [63]. The treatment of the aldehyde resins 37 with the methyl ketones 38 under NaOMe basic conditions provided the solid-supported enone 39, which underwent epoxidation with tBuOOH to give the solid-supported epoxide 40. The regioselective epoxide-ring opening [64] of 40 with 1-dodecanethiol in the presence of Zn(OTf)2 proceeded without cleavage of the Wang linker to afford the solid-supported α-hydroxyketone 41, the acylation of which with benzoic acids (42) then gave the precursor 43 for reductive cyclization. The exposure of 15%TFA in CH2Cl2 in the presence of a PS–benzaldehyde resin followed by the addition of triethylsilane promoted the cleavage of the Wang linker, reduction of the sulfide and the bromide, and reductive etherification to provide the protected 2,3-disubstituted benzopyrans 44. Finally, the 2,3-disubstituted benzopyran derivatives 44 were deprotected by conventional hydrogenolysis in the solution-phase by using a palladium catalyst to provide EGCG derivatives 35 (64 examples).

The two aldehydes 36, six ketones 38, and five carboxylic acids 42 were used as building blocks for the synthesis of 60 members of 2,3-disubstituted benzopyran library. The purity of the library was estimated by LC-MS analysis (58–15% purities). The growth-inhibitory effects of the resulting library compounds were examined [62]. Most of the 7-OME derivatives exhibited biological activity comparable to that of the naturally occurring EGCG.

2.2.2. Solid-Phase Synthesis of 2,6-Disubstituted Benzopyran Compounds

Gong and co-workers reported the construction of a 2,6-difunctionalized 2H-benzopyran library of 1,200 analogues by using the solid-phase protocols [65]. An alternative linker-based synthetic strategy
was developed because of a restriction that a carbamate linker based solid-phase synthetic pathway to generate a substituted benzopyran library (18 and 25) could not be introduced at the 2-position of the benzopyran system by using strong bases. In the strategy, acid sensitive methoxy benzaldehyde (AMEBA) resin 45 [2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene from Merrifield resin] [66] was selected as the polymer support since the secondary amino group, resulting from reductive amination, should be highly reactive towards various alkyl halides, acid halides, isocyanates, and sulfonyl chlorides (Scheme 8). Moreover, the final products should be readily cleaved from the support by using dilute TFA solutions [67,68]. In the first step of the sequence, 6-aminobenzopyran resin 46 was prepared by reaction of AMEBA resin 45 with 6-aminobenzopyran 47 [69] under reductive amination conditions [70] [NaBH(OAc)₃ in DMF containing 1% acetic acid].

**Scheme 8. Solid-phase synthesis of 2,6-difunctionalized benzopyrans 49, 53, and 547 by Gong et al. [65].**

![Scheme 8](image-url)

In the first-generation diversification step, the secondary amine group in 46 was transformed into the amide, sulfonamide, or urea groups in resin 48 by respective reactions with acid chlorides, sulfonyl chlorides, and isocyanates in the presence of triethylamine in DMF. To confirm the product formation, resin 48 was treated with 20% TFA in CH₂Cl₂ to give 6-amino-substituted 2H-benzopyran 49 (25 examples, 85–65% yields, and 99–72% purities).
For the purpose of second-generation diversity, resins 50 containing a free primary hydroxyl group were prepared by reaction of resins 48 with NaOMe in MeOH/THF at room temperature [71]. Functionalization of the hydroxyl groups in resins 50 was promoted by reactions with alkyl halides and acid chlorides to generate respective 2,6-difunctionalized 2H-benzopyran resins 51 with an ether-substituent and 52 with an ester-substituent at position 2 in the 2H-benzopyran moiety. Alkylation reactions of 50 were carried out in the presence of lithium tert-butoxide in DMF and took place smoothly to yield the corresponding ethers. Subsequent treatment of the resins 51 with 20% TFA in CH2Cl2 produced the desired 2,6-difunctionalized 2H-benzopyran derivatives 53 with an ether-substituent (the representative 22 examples, 73–26% yields, and 99–83% purities) in high four-step overall yields from resin 46. The ester-containing resins 52 were prepared by treatment of resins 50 with various acid chlorides in the presence of DBU and 4-dimethylaminopyridine (DMAP) in DMF. To confirm product formation, the resins 52 were treated with 20% TFA in CH2Cl2 to yield the desired 2,6-difunctionalized 2H-benzopyrans 54 with an ester-substituent (the representative 21 examples, 73–29% yields, and 99–81% purities).

Also, Gong and co-workers developed the solid-phase parallel synthesis of the additional 2,6-difunctionalized 2H-benzopyrans 55 and 56, which provided a 2,000-member library of novel 6-alkylamino-2-(functionalized-aminomethyl)-2H-benzopyrans [72]. The overall synthetic strategy used to prepare the target 2H-benzopyran analogues 55 and 56 is outlined in Scheme 9. The Fmoc-protected 2H-benzopyran amine 57 was prepared from 2-dimethoxymethyl-2-methyl-2H-1-benzopyran 58 [31] using the reaction sequences by acetal deprotection, reductive amination with methylamine, secondary amine protection with Fmoc-Cl, and reduction of nitro-group.

In the parallel solid-phase protocol (Scheme 9), 6-aminobenzopyran resin 59 was prepared from the backbone amide linker (BAL) resin 60 [73–75] by reaction with 6-aminobenzopyran 57 under reductive amination conditions with NaBH(OAc)3 [70].

In the first-generation diversification step, resin 61, containing a secondary amine group, was reacted with alkyl halides in the presence of diisopropylethylamine (DIEA) in CH2Cl2. For second-generation diversification, resins 61 containing a secondary amino group were prepared by removal of Fmoc on resins 61 with 20% piperidine in DMF. Functionalization of the secondary amine groups on resins 62 is promoted by reaction with various electrophiles, including acid chlorides, sulfonyl chlorides, isocyanates, and isothiocyanates. This leads to the generation of the respective amide, sulfonamide, urea and thiourea derivatives. Further confirmation of product formation was accomplished by treatment of resins 63 and 64 with 20% TFA in CH2Cl2 and by characterization of the liberated 2,6-difunctionalized 2H-benzopyrans 11 and 12 with 2-functionalized-aminomethyl group.

Lipinski’s rule [76] and similar formulations [77,78] serve as guidelines to estimate the physicochemical properties of the 2,000-member library of 6-alkylamino-2-(functionalized-aminomethyl)-2H-1-benzopyran derivatives 55 and 56. Most of the key parameters for members of the library fall within the range of those predicted for reasonable oral bioavailable drugs by using the commonly known guidelines.

The drug-like small molecule library with variously substituted benzopyrans was constructed by Gong and co-workers [79,80]. An orally active 5-LO [81–87] inhibitor KRH-102140 [30,31] with the benzopyran moiety (see Figure 1) was discovered as a lead compound on the drug discovery program.
via HTS of in-house small molecule library by Gong et al. [88]. Also, KRH-102140 showed hypoxia-inducible factor (HIF)-1α [89–93] inhibitory activities [94].

**Scheme 9.** Solid-phase synthesis of 6-alkylamino-2-(functionalized-aminomethyl)-2H-benzopyrans 55 and 56 by Gong et al. [72].

On the basis of the biological activities of the benzopyran moiety with KRH-102140, Gong and co-workers demonstrated the solid-phase synthesis of a 222-number library of 2,6-difunctionalized 2H-benzopyran 65 and 66 for the lead optimization as a 5-LO inhibitor [80].

As shown in Scheme 10, resin-bounded spirobenzopyran 67 was prepared by reaction of BAL resin 60 with N-[ethylcarbamate-spiro(2H-1-benzopyran-2,4-piperidine)-6-yl]amine 68, which was synthesized by general manipulations, under reductive amination conditions. In the first generation diversification step, the secondary amine group on resin 67 was transformed into the tertiary amine and amide on benzopyran resins 68 and 69 at position 6 by the reactions with various acid chlorides and alkyl halides in the presence of bases, respectively.

After the carbamate deprotection in a spiro-ring of benzopyran resins 68 and 69 by hydrolysis reactions, the secondary piperidine amines on the 6-amino- or 6-amido-substituted 2H-benzopyran resins 70 and 71 were converted by reactions with various sulfonyl chlorides to generate respective
6-amino-substituted amide resins 72 and 6-amino-substituted resins 73 for the introduction of second generation diversity.

**Scheme 10.** Solid-phase synthesis of 6-amido- and 6-amino-substituted-2-functionalized benzopyrans 65 and 66 by Gong et al. [80].

Finally, the liberation of solid support on the resins 72 and 73 with 20% TFA in CH$_2$Cl$_2$ gave the desired drug-like 2-functionalized-6-amido-substituted 2$H$-benzopyran derivatives 65 (the representative 25 examples) and 2-functionalized-6-amino-substituted 2$H$-benzopyran derivatives 66 (the representative 25 examples), respectively.

In general, the goal of a drug discovery process is to synthesize chemical entities which are orally bioavailable; *i.e.* they possess physiological properties that allow them to be absorbed into the gastrointestinal system. Lipinski’s Rule [76] and similar formulations [77,78] served as guidelines to estimate the physicochemical properties of the synthesized 222-member library of 6-amido- and 6-amino-substituted-2-functionalized benzopyrans 65 and 66, respectively [80].

2.3. Solid-Phase Synthesis of Trisubstituted Benzopyran Compounds

2.3.1. Solid-Phase Synthesis of 2,4,6-Trisubstituted Benzopyran Compounds

Breitenbucher and Hui developed the titanium-mediated reductive amination procedure for the practical solid-phase synthesis of 2,4,6-trisubstituted benzopyran derivatives 74 (2,4,6-trisubstituted chromane) [95]. The three different 6-carboxybenzopyran-4-one scaffolds 75 [96] was attached to Merrifield/hydroxythiophenol resin 76 via diisopropylcarbodiimide (DIC) coupling, to provide benzopyranone resins 77 (Scheme 11). Treatment of resin 77 with Ti(OiPr)$_4$ and a primary amine
(eight $R_1NH_2$) in toluene provided a tetrahedral intermediate resin 78. Na(OAc)$_3$BH was then added to the reaction to effect reduction to the amine on resin, followed by washings to afford 4-amino-benzopyran resins 79.

Scheme 11. Solid-phase synthesis of 2,4,6-trisubstituted benzopyrans 74 by Breitenbucher and Hui [95].

Acylation (16 acylating agents) of the 24 different resins 79 was then performed by addition of either an isocyanate, or acid chlode to afford 4-disubstituted benzopyran resins 80. Cleavage from support was accomplished by treatment with 4 equivalents of an amine (22 amines) in pyridine at room temperature. The resulting library products 74 (8,448 spatially separated benzopyrans) were then concentrated and subjected to supported liquid extraction (SLE) [97,98] to remove the excess cleaving amines from the products. Their average purity of samples measured by LC-MS analysis of the crude products was around 73%.

2.3.2. Solid-Phase Synthesis of 3,4,6-Trisubstituted Benzopyran Compounds

Gong and co-workers described the construction of a 3,4,6-trisubstituted benzopyran library of 2,000 analogues using consecutive nucleophilic addition via m-CPBA epoxidation on solid support [99,100]. Various reaction conditions were examined to find a condition of the nucleophilic alcohol addition at an epoxide on resin and completion of 3-hydroxy-4-alkoxy-6-amino-substituted benzopyrans 81 on solid support. The desired 3-hydroxy-4-alkoxy-benzopyran resins 82 were obtained by the consecutive nucleophilic alcohol addition reactions of resins 26 with nucleophiles, immediately followed by m-CPBA epoxidation. Finally, the cleavage of resins 82 with 25% TFA in CH$_2$Cl$_2$ produced the target 3-hydroxy-4-alkoxy-6-amino-substituted benzopyrans 81 (26 examples) without significant contamination of by-products (Scheme 12).
After confirmation of the consecutive regioselective nucleophilic addition via m-CPBA epoxidation on solid support, the 3-hydroxyl benzopyran resins 82 were scrutinized for enlargement of diverse points in the benzopyran moiety. The reactions with alkyl halides and acid chloride were examined to generate ethers and esters in 3-hydroxyl benzopyran resins 82. To prepare the ether-type at position 4 in resins 83, the resins 82 were treated with various alkyl and benzyl halides in the presence of lithium t-butoxide in DMF. The reaction proceeded nicely to provide polymer-bounded benzopyrans 83 with an ether-substituent, and subsequent treatment of the resins 83 with 25% TFA in CH2Cl2 produced the desired 3,4,6-trisubstituted benzopyrans 84 with an ether-substituent (the representative 26 examples) in good four-step overall yields.

For the preparation of esters at position 4 in the benzopyran moiety, the resins 82 were treated with various acid chlorides with pyridine and DMAP as bases in CH2Cl2 to produce the benzopyran resins 85 with an ester-substituent, which were again treated with 25% TFA in CH2Cl2 to give the desired 3,4,6-trisubstituted benzopyrans 86 with ester-substituent (26 representative examples) in good four-step overall yields. The obtained 3,4,6-trisubstituted benzopyrans 84 with an ether-substituent were identified as prolyl 4-hydroxylase inhibitors via a screening process using HSC-T6 and LI 90 cells that express an immortalized rat hepatic stellate cell line and as part of a test of the type I collagen contents employing the ELISA method [100].

3. Solid-Phase Synthesis of Additional Cycle-Fused Benzopyran Compounds

3.1. Solid-Phase Synthesis of Tricyclic Benzopyran Compounds

Collins and co-workers developed the solid-phase synthesis of isoxazole-fused benzopyrans (benzopyranisoazoxoles) 87 as potential steroid mimetic templates using intramolecular 1,3-dipolar cycloaddition with a tethered alkyne [101].

The reductive amination reaction of the commercially available AMEBA [66] resin 45 (2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene) and butylamine with sodium triacetoxyborohydride gave
polymer-bounded secondary amine 88 (Scheme 13). 3-Formyl-4-hydroxybenzoyl moiety loaded resin 89 was introduced by amide formation of amine resin 88 and 3-formyl-4-hydroxybenzoyl chloride (90) in the presence of 2,6-lutidine. The various Mitsunobu reactions [102–106] were explored for a polymer-bounded aldoxime containing a phenol-tethered alkyne 94. A Mitsunobu reaction between polymer-bounded phenol 89 and propargyl alcohol 91 with R² and R³ using sulfonamide betaine 92 gave disubstituted resins 93. The isoxazole precursor resins 94 with aldoxime and alkyne were obtained upon treatment of aldehyde resins 93 with hydroxylamine hydrochloride and triethylamine.

Scheme 13. Solid-phase synthesis of isoxazole-fused benzopyrans 87 by Collins and co-workers [101].

An intramolecular 1,3-dipolar cycloaddition of 94 with NBS and Et₃N in DMF generated polymer-bounded benzopyranoisoxazoles 95. After cleavage with 15% TFA in CH₂Cl₂, the target benzopyranoisoxazoles 87 (9 examples) were obtained.

3.1.2. Solid-Phase Synthesis of Pyrazole-Fused Benzopyran Compounds

Park and co-workers developed the solid-phase construction of a pyrazole-fused benzopyran (benzopyranopyrazole) library with the recombination of privileged benzopyran and pyrazole structures [107]. The solid-phase synthesis was started from the functionalized benzopyranopyrazoles 96 (Scheme 14). A 7-fluoro-2,2-dimethyl-2,3-dihydrochromen-4-one 97 underwent nitration with potassium nitrate to introduce the aniline moiety in a masked form, followed by nucleophilic aromatic substitution of monoprotected Cbz-piperazine at the fluoride position because of its rich body of biological effects. The resulting chromenone 98 was converted to s-cis enone 99 by the sequent reactions of acetal formation [108–110] with triethyl orthoformate in high yield (93%) and I₂-catalyzed acetal deprotection [111–117] (84% yield). In the case of an electron-deficient chromenone 98, the acidic proton at the C-3 position was readily removed by treatment with sodium methoxide (the reaction condition for hydroxysubstituted s-cis enone 99), which led to the decomposition of benzopyran itself.
Scheme 14. Solid-phase synthesis of pyrazole-fused benzopyrans 104 by Park et al. [107].

The regioselective synthesis of benzopyranopyrazole derivatives 100 was achieved by the condensation of a β-keto aldehyde with mono-substituted hydrazine (R₁BocNNH₂) in AcOH [108,109]. The Cbz protection group on the piperazine moiety was removed from benzopyranopyrazole 96 by 40% KOH or dimethyl sulfate and BF₃·OEt₂ [118] for the immobilization of the piperazinyl secondary amine 96 on a solid support.

As shown in Scheme 14, Wang resin was activated with p-nitrophenylchloroformate in the presence of DIPEA, followed by the loading of the piperazinyl secondary amine 96 on the solid support. The nitro group on polymer-bounded intermediates 101 was reduced with tin chloride dihydrate in DMF. The resulting aniline resins 102 were subsequently diversified with a set of 12 building blocks (six carboxylic acids, one isothiocyanate, two isocyanates, and three sulfonyl chlorides) identical to that used for the modification at the R² position. The final cleavage step with resins 103 was performed under 50% TFA in dichloromethane to liberate various benzopyranopyrazoles 104 (96 examples). Overall, the average purity of the final 96 benzopyranopyrazoles 104 with R¹ and R² diversification was 84%.
3.1.3. Solid-Phase Synthesis of Six-Membered Ring-Fused Benzopyran Compounds

A novel solid-phase synthetic approach toward tricyclic benzopyrans 105–109 (cannabinoid derivatives) is described by Bräse and Kapeller [119]. The synthetic approach for the solid-phase synthesis of tricyclic benzopyrans 105–109 was to immobilize the commercially available 4-hydroxysalicylaldehyde (4-HSA) with Ellman’s acid-labile DHP-linker 110 [120,121], which was prepared by etherification of a 3,4-dihydro-2H-pyran-2-methanol (111) and Merrifield resin 112 [122] (0.99 mmol/g). At first, polymer 110 was treated with 4-HSA/PPTS (pyridinium p-toluenesulfonate) to give polymer-bounded aldehyde 113 (Scheme 15).

Scheme 15. Solid-phase synthesis of tricyclic benzopyrans 105–109 by Bräse and Kapeller [119].

To generate the benzopyran core structure, the domino oxa-Michael-aldol (DOMA) condensation [123–125] for the resin 113 and α,β-unsaturated carbonyl moieties 114 as Michael acceptors gave polymer-bounded benzopyrans 115 by employing K₂CO₃ in 1,4-dioxane at 80 °C. The next step for a diene moiety was either Wittig reaction with CH₃PPh₃Br to 116 or TBS-enol ether formation yielding 117. For the Diels-Alder reaction, a thermal condition at 80 °C was chosen, as Lewis or Brønsted acid catalysis would lead to concomitant cleavage from the resin. The Diels-Alder reaction of diene resins 116 and various dienophiles (see Figure 4) gave tricyclic benzopyran resins 118 and 119 in this thermal condition. After cleavage of resins 118 and 119 with PPTS in DCE/EtOH, the desired tricyclic benzopyran derivatives 105 and 106 (14 examples, 95–11% yields) were obtained.
Also, enol ether resin 117 was subjected to the Diels-Alder reaction. The resulting tricyclic benzopyran resins 120 with enol ether were at first cleaved with PPTS in DCE/EtOH giving ketones 107 directly under concomitant loss of the TBS-group. When switching the solvent to THF/water, but the TBS group was only partially cleaved-off, mainly giving enol-ethers 121. Further treatment with TBAF in acetonitrile finally liberated tricycles 107 (4 examples, 51–10% yields) in all cases except for 108 (R5 = CO2iPr), where side-product 109 was formed exclusively.

**Figure 4.** Diverse dienophile reagents for the Diels-Alder reaction.

Lee and co-workers described the asymmetric solid-phase parallel synthesis of (3'R,4'R)-di-O-cis-acyl 3-carboxyl khellactones (tricyclic benzopyrans) as potent anti-HIV agents [126,127]. The strategy was begun with ethyl malonate bound resin 122, which was introduced by a reaction of Wang resin 20 and ethyl potassium malonate (Scheme 16). The resin-bound tricyclic benzopyran 123 was prepared by a Knoevenagel condensation [128–131] between ethyl malonate resin 122 and o-hydroxyarylaldehyde 124 in pyridine and piperidine. The o-hydroxyarylaldehyde 124 was prepared from an acetyl acetaldehyde dimethyl acetal using the reaction sequences by Grignard addition, nucleophilic substitution of 2,4-dihydroxybenzoylaldehyde, and regiospecific aromatic cyclization.

**Scheme 16.** Asymmetric solid-phase synthesis of tricyclic benzopyrans 127 by Lee et al. [126,127].

The polymer-bounded 3,4-diacyl-substituted tricyclic benzopyrans 125 were obtained by acylation with various carboxylic acids and an optically active cis-diol resin 126 from the Sharpless asymmetric dihydroxylation (AD) reaction of resin 123. The treatment of diacyl resins 125 with TFA in CH2Cl2 gave the desired tricyclic benzopyran derivatives 127 (6 examples, 44–24% yields, and >90% purities).
3.2. Solid-Phase Synthesis of Polycyclic Benzopyran Compounds

Novel polycyclic scaffolds 128–130 containing the benzopyran moiety with variable substituents were described by Park et al. [51]. The excellent endo-selective Diels-Alder reaction with dienophiles 131 (17 substituted maleimides) and solid-supported dienes 132 (8 resins from 2, see Scheme 2 and Figure 3), which were derived from palladium-mediated Stille-type vinylation on vinyl triflate intermediate 12, gave benzopyran-containing polycycloheterocyclic resins 133 (Scheme 17). After HF/pyridine cleavage of resins 133 and subsequent quenching with TMSOEt, diastereomerically enriched novel tricyclic benzopyran derivatives 128 were obtained on a scale of 10 mg each (136 examples). Their average purity measured by LC-MS analysis of the crude products, was around 85%.

**Scheme 17.** Solid-phase synthesis of polycyclic benzopyrans 128–130 by Park et al. [51].

To expand the molecular diversity of the small-molecule library, novel polycyclic benzopyran derivatives 128 were transformed to discrete core skeletons 129 and 130, using chemical transformations such as Pd/C-based diastereoselective hydrogenation of 128 by the library-to-library approach and the sequence reaction of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated aromatization of resins 133 and liberation of resins 134, respectively. The average purity of 129 (54 examples), which obtained from 12 without further purification, was about 81%, and that of 130 (36 examples) measured by LC-MS analysis of the crude products, was 84%.

The shape of the resulting core skeleton 129 is structurally discrete and more concave than that of its precursor 128 because of the conversion at the monoene site of sp² carbon to sp³ carbon. Compared to heterogeneous hydrogenation, which introduces the sp³ carbon center in an asymmetric fashion, the aromatization using DDQ can remove the existing stereogenic carbon centers of the monoene precursor 128 and provide a new flatter core skeleton 130.
4. Solid-Phase Synthesis of Miscellaneous Benzopyran Compounds

The selenium-mediated solid-phase syntheses of various 2,2-dimethylbenzopyran derivatives 131 were published by Nicolau et al. [132–138]. The solid-phase synthetic strategy started from the treatment of selenyl bromide resin 132 [139,140] with a three-fold excess of various ortho-prenylated phenols 133 in CH₂Cl₂. The dihydrobenzopyran resins 135 were produced via a 5-endo-trig cycloaddition of 134. The desired 2H-benzopyrans 131 (45 examples) were obtained in high yields with high purities by oxidation to selenium oxide with H₂O₂ and syn-elimination of intermediate resin 136 in a traceless manner (Scheme 18).

Scheme 18. Solid-phase synthesis of benzopyrans 131 by Nicolau et al. [132–138].

After preliminary studies, their utility was demonstrated for the syntheses of the benzopyran-based privileged structures 137a–l (natural benzopyrans, multi-substituted and polycyclic benzopyrans, and so on) from polymer-bounded 2-selenodihydrobenzopyrans 135 (Scheme 19).

Scheme 19. Benzopyran-based privileged structures from 2-selenodihydrobenzopyran resins 135 by Nicolau et al. [132–138].
The acquired polymer-bounded benzopyrans 135 were subsequently used as scaffolds in the synthesis of several benzopyran-based combinatorial libraries (for example, a 52-member library [137] aimed at the development of new NADH/ubiquinone oxidoreductase inhibitors, and a 10,000-member library[135] constructed by directed split-and-pool chemistry).

5. Summary

The combinatorial synthesis of drug-like small organic molecules plays a significant role in the area of drug discovery. Especially, the various natural and artificial benzopyran compounds as bioactive molecules have proven to be broadly useful as therapeutic agents because of their high degree of structural diversity. In this respect, many synthetic methods have been developed for fabricating the privileged benzopyran structures with drug-like properties by using solid-phase synthetic strategies. In this article, we have introduced the preparation of diverse and drug-like benzopyrans as substituted benzopyrans, additional cycle-fused benzopyrans, and their related compounds. Further studies in this area are underway and the various strategies for syntheses of benzopyran derivatives on solid support will be reported for medicinal chemistry and drug discovery.

Acknowledgments

This research was supported by the National Research Foundation of Korea (NRF) grants (NRF-2010-0004128 and NRF-2011-0014063) from the Basic Science Research Program, the Ministry of Education, Science and Technology, Korea; and funded by the Ministry of Knowledge Economy, Korea.

References and Notes

1. Dolle, R.E.; le Bourdonnec, B.; Worm, K.; Morales, G.A.; Thomas, C.J.; Zhang, W. Comprehensive survey of chemical libraries for drug discovery and chemical biology: 2009. J. Comb. Chem. 2010, 12, 765–806.
2. Dolle, R.E.; le Bourdonnec, B.; Goodman, A.J.; Morales, G.A.; Thomas, C.J.; Zhang, W. Comprehensive survey of chemical libraries for drug discovery and chemical biology: 2008. J. Comb. Chem. 2009, 11, 739–790.
3. Dolle, R.E.; le Bourdonnec, B.; Goodman, A.J.; Morales, G.A.; Thomas, C.J.; Zhang, W. Comprehensive survey of chemical libraries for drug discovery and chemical biology: 2007. J. Comb. Chem. 2008, 10, 753–800.
4. Kennedy, J.P.; Williams, L.; Bridges, T.M.; Daniels, R.N.; Weaver, D.; Lindsley, C.W. Application of combinatorial chemistry science on modern drug discovery. J. Comb. Chem. 2008, 10, 345–354.
5. Nicolaou, K.C., Hanko, R., Hartwig, W., Eds.; Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials; Wiley-VCH: Weinheim, Germany, 2002.
6. Dandapani, S.; Marcaurelle, L.A. Accessing new chemical space for “undruggable” targets. Nat. Chem. Biol. 2010, 6, 861–863.
7. Drewry, D.H.; Macarron, R. Enhancements of screening collections to address areas of unmet medical need: an industry perspective. *Curr. Opin. Chem. Biol.* **2010**, *14*, 289–298.

8. Bleicher, K.H.; Böhm, H.-J.; Müller, K.; Alanine, A.I. Hit and lead generation: Beyond high-throughput screening. *Nat. Rev. Drug Discov.* **2003**, *2*, 369–378.

9. Horton, D.A.; Bourne, G.T.; Smyth, M.L. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.* **2003**, *103*, 893–930.

10. Krchnáč, V.; Holladay, M.W. Solid phase heterocyclic chemistry. *Chem. Rev.* **2002**, *102*, 61–91.

11. Welsch, M.E.; Snyder, S.A.; Stockwell, B.R. Privileged scaffolds for library design and drug discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

12. Bannwarth, W., Hinzen, B., Eds.; *Combinatorial Chemistry: From Theory to Application*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2006.

13. Gil, C.; Bräse, S. Solid-phase synthesis of biologically active benzoannelated nitrogen heterocycles: An update. *J. Comb. Chem.* **2009**, *9*, 175–197.

14. Ziegert, R.E.; Toräng, J.; Knepper, K.; Bräse, S. The recent impact of solid-phase synthesis on medicinally relevant benzoannelated oxygen heterocycles. *J. Comb. Chem.* **2005**, *7*, 147–169.

15. Franzén, R.G. Recent advances in the preparation of heterocycles on solid support: A review of the literature. *J. Comb. Chem.* **2000**, *2*, 195–214.

16. Fang, N.; Casida, J.E. Anticancer action of cubé insecticide: Correlation for rotenoid constituents between inhibition of NADH: Ubiquinone oxidoreductase and induced ornithine decarboxylase activities. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3380–3384.

17. Fang, N.; Casida, J.E. New Bioactive Flavonoids and Stilbenes in Cubé Resin Insecticide. *J. Nat. Prod.* **1999**, *62*, 205–210.

18. Kaouadjji, M.; Agban, A.; Mariotte, A.M.; Tissut, M. Lonchocarpene, a Stilbene, and Lonchocarpusone, an Isoflavone: Two new pyranopolyphenols from lonchocarpus nicou roots. *J. Nat. Prod.* **1986**, *49*, 281–285.

19. Takasugi, M.; Nagao, S.; Ueno, S.; Masamune, T.; Shirata, A.; Takahashi, K. Studies on phytoalexins of the Moraceae. 2. Moracin C and D, new phytoalexins from diseased mulberry. *Chem. Lett.* **1978**, 1239–1240.

20. Shirata, A.; Takahashi, K.; Takasugi, M.; Nagao, S.; Ishikawa, S.; Ueno, S.; Munoz, L.; Masamune, T. Antimicrobrial spectra of the compounds from mulberry. *Sanshi Shikenjo Hokoku* **1983**, 28, 793–806.

21. Tyrrell, E.; Tesfa, K.H.; Greenwood, I.; Mann, A. The synthesis and biological evaluation of a range of novel functionalised benzopyrans as potential potassium channel activators. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1237–1240.

22. Drizin, I.; Holladay, M.W.; Lin, Y.; Zhang, H.Q.; Gopalakrishnan, S.; Gopalakrishnan, M.; Whiteaker, K.L.; Buckner, S.A.; Sullivan, J.P.; Carroll, W.A. Structure-activity studies for a novel series of tricyclic dihydropyrimidines as K<sub>ATP</sub> channel openers (KCOs). *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1481–1484.

23. Chiu, H.-I.; Lin, Y.-C.; Cheng, C.-Y.; Tsai, M.-C.; Yu, H.-C. N-Acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano-[3,4-b][1,4]oxazine-9-carbonitriles as bladder-selective potassium channel openers. *Bioorg. Med. Chem.* **2001**, *9*, 383–393.
24. Andersson, K.-E. Clinical pharmacology of potassium channel openers. *Pharmacol. Toxicol.* 1992, 70, 244–254.

25. Simmons, D.L.; Botting, R.M.; Hla, T. Cyclooxygenase isozymes: The biology of prostaglandin synthesis and inhibition. *Pharmacol. Rev.* 2004, 56, 387–437.

26. Carter, J.S.; Obukowicz, M.G.; Devedas, B.; Talley, J.J.; Brown, D.L.; Graneto, M.J.; Bertenshaw, S.R.; Rogier, D.J.; Srinivasan, R.; Hanau, C.E.; et al. Substituted Benzopyran Derivatives for the Treatment of Inflammation. WO 9847890 A1, 1998.

27. Stuart, E.C.; Scandlyn, M.J.; Rosengren, R.J. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. *Life Sci.* 2006, 79, 2329–2336.

28. Fujimura, Y.; Yamada, K.; Tachibana, H. A lipid raft-associated 67kDa laminin receptor mediates suppressive effect of epigallocatechin-3-O-gallate on FcεRI expression. *Biochem. Biophys. Res. Commun.* 2005, 336, 674–681.

29. Tachibana, H.; Koga, K.; Fujimura, Y.; Yamada, K. A receptor for green tea polyphenol EGCG. *Nat. Struct. Mol. Biol.* 2004, 11, 380–381.

30. Gong, Y.-D.; Yoo, S.-E.; Cheon, H.G.; Cho, Y.S.; Seo, J.-S.; Hwang, J.Y.; Park, J.Y. 2,2'-Disubstituted-3,4-dehydro-7,8-disubstituted-6-alkylamino benzopyran derivatives as 5-lipoxgenase inhibitor. Korea Patent 10–0602191, 2006.

31. Gong, Y.-D.; Yoo, S.-E.; Cheon, H.G.; Cho, Y.S.; Seo, J.-S.; Hwang, J.Y.; Park, J.Y. Preparation of 6-Alkylamino-2,2'-disubstituted-7,8-disubstituted-2H-1-benzopyran Derivatives as 5-Lipoxgenase Inhibitor. US 7368575, 2005.

32. Gunatilaka, A.A.L.; Kingston, D.G.I.; Wijeratne, E.M.K.; Bandara, B.M.R.; Hofmann, G.A.; Johnson, R.K. Biological activity of some coumarins from sri lankan rutaceae. *J. Nat. Prod.* 1994, 57, 518–520.

33. Bandara, B.M.R.; Gunatilaka, A.A.L.; Wijeratne, E.M.K.; MacLeod, J.K. Acridone alkaloids and coumarins from *Pleiospermium alatum*. *Phytochemistry* 1990, 29, 297–301.

34. Magiatis, P.; Melliou, E.; Skaltsounis, A.-L.; Mitaku, S.; Leonce, S.; Renard, P.; Pierre, A.; Atassi, G. Synthesis and cytotoxic activity of pyranocoumarins of the seselin and xanthyletin series. *J. Nat. Prod.* 1998, 61, 982–986.

35. Sarfaraz, S.; Adhami, V.M.; Syed, D.N.; Afaq, F.; Mukhtar, H. Cannabinoids for cancer treatment: Progress and promise. *Cancer Res.* 2008, 68, 339–342.

36. Ware, M.A.; Daeninck, P.; Maida, V. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. *Ther. Clin. Risk Manag.* 2008, 4, 99–107.

37. Pertwee, R.G. Cannabinoids and multiple sclerosis. *Mol. Neurobiol.* 2007, 36, 45–49.

38. Mackie, K. Cannabinoid receptors as therapeutic targets. *Annu. Rev. Pharmacol. Toxicol.* 2006, 46, 101–122.

39. Romero, J.; Lastres-Becker, L.; de Miguel, R.; Berrendero, F.; Ramos, J.A.; Fernandez-Ruiz, J. The endogenous cannabinoid system and the basal ganglia: biochemical, pharmacological, and therapeutic aspects. *Pharmacol. Ther.* 2002, 95, 137–152.

40. Lee, T.T.-Y.; Kashiwada, Y.; Huang, L.; Snider, J.; Cosentino, L.M.; Lee, K.H. Suksdorfin: An anti-HIV principle from Lomatium suksdorfii, its structure-activity correlation with related coumarins, and synergistic effects with anti-AIDS nucleosides. *Bioorg. Med. Chem.* 1994, 2, 1051–1056.
41. Willette, R.E.; Soine, T.O. Isolation, purification, and structure determination of pteryxin and suksdorfin. *J. Pharm. Sci.* **1962**, *51*, 149–156.

42. Patil, A.D.; Freyer, A.J.; Eggleston, D.S.; Haltiwanger, R.C.; Tomcowicz, B.; Breen, A.; Johnson, R.K. Rigidone, a sesquiterpene o-quinone from the gorgonian *Pseudopterogorgia rigida*. *J. Nat. Prod.* **1997**, *60*, 306–308.

43. Zhou, Z.-Z.; Yang, G.-F. Insecticidal lead identification by screening benzopyrano[4,3-c]-pyrazol-3(2H)-ones library constructed from multiple-parallel synthesis under microwave irradiation. *Bioorg. Med. Chem.*** **2006**, *14*, 8666–8674.

44. Yenesew, A.; Derese, S.; Midiw, J.O.; Heydenreich, M.; Peter, M.G. Effect of rotenoids from the seeds of *Millettia dura* on larvae of *Aedes aegypti*. *Pest. Manag. Sci.* **2003**, *59*, 1159–1161.

45. Cabizza, M.; Angioni, A.; Melis, M.; Cabras, M.; Tuberoso, C.V.; Cabras, P. Rotenone and rotenoids in cubè resins, formulations, and residues on olives. *J. Agric. Food Chem.* **2004**, *52*, 288–293.

46. Nussbaumer, P.; Lehr, P.; Billich, A. 2-Substituted 4-(Thio)chromenone 6-O-Sulfamates: Potent inhibitors of human steroid sulfatase. *J. Med. Chem.* **2002**, *45*, 4310–4320.

47. Joo, Y.H.; Kim, J.K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J.K.; Lim, K.M.; Lee, C.H.; Chung, S. 2,3-Diarylbenzopyran derivatives as a novel class of selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413–417.

48. Pal, M.; Subramanian, V.; Parasaruman, K.; Yeleswarapu, K.R. Palladium catalyzed reaction in aqueous DMF: Synthesis of 3-alkynyl substituted flavones in the presence of prolinol. *Tetrahedron*** **2003**, *59*, 9563–9570.

49. Maliar, T.; Jedinak, A.; Kadrabova, J.; Sturdik, E. Structural aspects of flavonoids as trypsin inhibitors. *Eur. J. Med. Chem.* **2004**, *39*, 241–248.

50. Zhu, M.; Lim, B.J.; Koh, M.; Park, S.B. Construction of polyheterocyclic benzopyran library with diverse core skeletons through diversity-oriented synthesis pathway: Part II. *ACS Comb. Sci.* **2012**, *14*, 124–134.

51. Oh, S.; Jang, H.J.; Ko, S.K.; Ko, Y.; Park, S.B. Construction of a polyheterocyclic benzopyran library with diverse core skeletons through diversity-oriented synthesis pathway. *J. Comb. Chem.* **2010**, *12*, 548–558.

52. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. Click chemistry: Diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2004–2021.

53. Bock, V.D.; Hiemstra, H.; van Maarseveen, J.H. Cu¹-Catalyzed Alkyne-Azide “Click” Cycloaditions from a mechanistic and synthetic perspective. *Eur. J. Org. Chem.* **2006**, *51*, 61–68.

54. Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F.G.; Calvo-Asín, J.A.; Isac-García, J.; Santoyo-González, F. Multivalent neoglycoconjugates by regiospecific cycloaddition of alkynes and azides using organic-soluble copper catalysts. *Org. Lett.* **2003**, *5*, 1951–1954.

55. Gong, Y.-D.; Yoo, S.-E. Solid-phase synthesis of benzopyran derivatives via highly efficient epoxidation using two-phase solvents. *Bull. Korean Chem. Soc.* **2001**, *22*, 941–942.

56. Gong, Y.-D.; Seo, J.-S.; Chon, Y.S.; Hwang, J.Y.; Park, J.Y.; Yoo, S.-E. Construction of 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2h-1-benzopyran library by solid phase synthesis. *J. Comb. Chem.* **2003**, *5*, 577–589.
57. Alvarez-Gutierrez, J.M.; Nefzi, A.; Houghten, R.A. Solid phase synthesis of 1-substituted pyroglutamates. *Tetrahedron Lett.* **2000**, *41*, 851–854.

58. Huang, W.; Scaborough, R.M. A new “Traceless” solid-phase synthesis strategy: Synthesis of a benzimidazole library. *Tetrahedron Lett.* **1999**, *40*, 2665–2668.

59. Xing, L.; Hamper, B.C.; Fletcher, T.R.; Wendling, J.M.; Carter, J.; Gierse, J.M.; Liao, S. Structure-based parallel medicinal chemistry approach to improve metabolic stability of benzopyran COX-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 993–996.

60. Miyaura, N.; Yamada, K.; Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenyloboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

61. Tanaka, H.; Miyoshi, H.; Chuang, Y.-C.; Ando, Y.; Takahashi, T. Solid-phase synthesis of epigallocatechin gallate derivatives. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 5934–5937.

62. Tanaka, H.; Yamanouchi, M.; Miyoshi, H.; Hirotsu, K.; Tachibana, H.; Takahashi, T. Solid-phase synthesis of a combinatorial methylated (−)-epigallocatechin gallate library and the growth-inhibitory effects of these compounds on melanoma B16 cells. *Chem. Asian J.* **2010**, *5*, 2231–2248.

63. Micheli, F.; Degiorgis, F.; Feriani, A.; Paio, A.; Pozzan, A.; Zarantonello, P.; Seneci, P. A combinatorial approach to [1,5]benzothiazepine derivatives as potential antibacterial agents. *J. Comb. Chem.* **2001**, *3*, 224–228.

64. Tosaki, S.; Tsuji, R.; Ohshima, T.; Shibasaki, M. Dynamic ligand exchange of the lanthanide complex leading to structural and functional transformation: One-pot sequential catalytic asymmetric epoxidation-regioselective epoxide-opening process. *J. Am. Chem. Soc.* **2005**, *127*, 2147–2155.

65. Hwang, J.Y.; Choi, H.-S.; Seo, J.-S.; La, H.J.; Kim, D.-S.; Jeon, H.S.; Jeon, M.-K.; Lee, D.-H.; Gong, Y.-D. Construction of a 2,6-difunctionalized 2-methyl-2H-1-benzopyran library by using a solid-phase synthesis protocol. *J. Org. Chem.* **2005**, *70*, 10151–10154.

66. Fivush, A.M.; Wilson, T.M. AMEBA: An acid sensitive aldehyde resin for solid phase synthesis. *Tetrahedron Lett.* **1997**, *38*, 7151–7154.

67. Ouyang, X.; Tamayo, N.; Kiselyov, A.S. Solid support synthesis of 2-substituted dibenz[b,f]oxazepin-11(10H)-ones via S_NAr methodology on AMEBA resin. *Tetrahedron* **1999**, *55*, 2827–2834.

68. Katritzky, A.R.; Toader, D.; Watson, K.; Kiely, J.S. New synthesis of SASRIN™ resin. *Tetrahedron Lett.* **1997**, *38*, 7849–7850.

69. Katritzky, A.R.; Toader, D.; Watson, K.; Kiely, J.S. New synthesis of SASRIN™ resin. *Tetrahedron Lett.* **1997**, *38*, 7849–7850.

70. Boojamra, C.G.; Burow, K.M.; Thompson, L.A.; Ellman, J.A. Solid-phase synthesis of 1,4-benzodiazepine-2,5-diones. Library preparation and demonstration of synthesis generality. *J. Org. Chem.* **1997**, *62*, 1240–1256.
71. Arya, P.; Wei, C.-Q.; Barnes, M.L.; Daroszewska, M. A solid phase library synthesis of hydroxyindoline-derived tricyclic derivatives by mitsunobu approach. *J. Comb. Chem.* **2004**, *6*, 65–72.

72. Hwang, J.Y.; Choi, H.-S.; Seo, J.-S.; La, H.-J.; Yoo, S.-E.; Gong, Y.-D. Method for the solid-phase parallel synthesis of a 6-alkylamino-2-(functionalized-aminomethyl)-2H-1-benzopyran library. *J. Comb. Chem.* **2006**, *8*, 897–906.

73. Fernandez-Forner, D.; Huerta, J.M.; Ferrer, M.; Casals, G.; Ryder, H.; Giralt, E.; Albericio, F. Solid-phase syntheses of N-substituted carbamates. Reaction monitoring by gel-phase \(^{13}\)C-NMR using a \(^{13}\)C enriched BAL-linker. *Tetrahedron Lett.* **2002**, *43*, 3543–3546.

74. Alsina, J.; Yokum, T.S.; Albericio, F.; Barany, G. A modified Backbone Amide Linker (BAL) solid-phase peptide synthesis strategy accommodating prolyl, N-alkylamino acyl, or histidyl derivatives at C-terminus. *Tetrahedron Lett.* **2000**, *41*, 7277–7280.

75. Jensen, K.J.; Alsina, J.; Songster, M.F.; Vagner, J.; Albericio, F.; Barany, G. Backbone amide linker (BAL) strategy for solid-phase synthesis of C-terminal-modified and cyclic peptides. *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452.

76. Lipinski, C.A.; Lombardo, F.; Doming, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.

77. Oprea, T.I. Property distribution of drug-related chemical databases. *J. Comput. Aided Mol. Des.* **2000**, *14*, 251–264.

78. Veber, D.F.; Johnson, S.R.; Cheng, H.-J.; Smith, B.R.; Ward, K.W.; Kopple, K.D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623.

79. Gong, Y.-D.; Cheon, H.-G.; Lee, T.; Bae, M.-S.; Kang, N.S. A novel 6-(2-methyl-2-alkylsubstituted-2H-chromen-6-yl)-amine derivatives and pharmacophore model as 5-lipoxygenase inhibitors. *Bull. Korean Chem. Soc.* **2011**, *32*, 3752–3755.

80. Kim, J.-H.; Gong, Y.-D.; Lee, G.-H.; Seo, J.-S. Solid-phase parallel synthesis of a novel N-[Alkylsulfonylamido-spiro(2H-1-benzopyran-2,4-piperidine)-6-yl] substituted amide and amine drug-like libraries. *Bull. Korean Chem. Soc.* **2012**, *33*, 128–136.

81. Radmark, O. 5-Lipoxygenase-derived leukotrienes: Mediators also of atherosclerotic inflammation. *Arterioscler Thromb. Vasc. Biol.* **2003**, *23*, 1140–1142.

82. van Deventer, S.J.H. Small therapeutic molecules for the treatment of inflammatory bowel disease. *Gut* **2002**, *50*, iii47–iii53.

83. Sampson, A.P. The leukotrienes: Mediators of chronic inflammation in asthma. *Clin. Exp. Allergy* **1996**, *26*, 995–1004.

84. Brooks, C.D.W.; Summers, J.B. Modulators of leukotriene biosynthesis and receptor activation. *J. Med. Chem.* **1996**, *39*, 2629–2654.

85. Israel, E.; Rubin, P.; Kemp, J.P.; Grossman, J.; Pierson, W.; Siegel, S.C.; Tinkelman, D.; Murray, J.J.; Busse, W.; Segal, A.T.; et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann. Intern. Med.* **1993**, *119*, 1059–1066.

86. Falgueyret, J.P.; Hutchinson, J.H.; Rienteau, D. Criteria for the identification of non-redox inhibitors of 5-lipoxygenase. *Biochem. Pharmacol.* **1993**, *45*, 978–981.
87. Lau, C.K.; Bélanger, P.C.; Dufresne, C.; Scheigetz, J.; Therieu, M.; Fitzsimmons, B.; Young, R.N.; Ford-Hutchinson, A.W.; Riendeau, D.; Denis, D.; et al. Development of 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (L-670,630) as a potent and orally active inhibitor of 5-lipoxygenase. *J. Med. Chem.* 1992, 35, 1299–1318.

88. Cho, Y.S.; Song, J.S.; Huh, J.Y.; Kim, C.H.; Gong, Y.-D.; Cheon, H.G. Discovery of (2-fluoro-benzyl)-(2-methyl-2-phenethyl-2H-chromen-6-yl)-amine (KRH-102140) as an orally active 5-lipoxygenase inhibitor with activity in murine inflammation models. *Pharmacology* 2011, 87, 49–55.

89. Semenza, G.L. Evaluation of HIF-1 inhibitors as anticancer agents. *Drug Discov. Today* 2007, 20, 853–859.

90. Berra, E.; Ginouvès, A.; Pouysségur, J. The hypoxia-inducible-factor hydroxylases bring fresh air into hypoxia signaling. *EMBO Rep.* 2006, 7, 41–45.

91. Kaelin, W.G. Proline hydroxylation and gene expression. *Ann. Rev. Biochem.* 2005, 74, 115–128.

92. Hirsila, M.; Koivunen, P.; Gunzler, V.; Kivirikko, K.I.; Myllyharju, J. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. *J. Biol. Chem.* 2003, 278, 30772–30780.

93. Wang, G.L.; Jiang, B.H.; Semenza, G.L. Effect of protein kinase and phosphatase inhibitors on expression of hypoxia-inducible factor 1. *Biochem. Biophys. Res. Commun.* 1995, 216, 669–675.

94. Nepal, M.; Gong, Y.-D.; Park, Y.R.; Soh, Y. An activator of PHD2, KRH102140, decreases angiogenesis via inhibition of HIF-1α. *Cell Biochem. Funct.* 2011, 28, 1–9.

95. Breitenbucher, J.G.; Hui, H.C. Titanium mediated reductive amination on solid support: Extending the utility of the 4-hydroxy-thiophenol linker. *Tetrahedron Lett.* 1998, 39, 8207–8210.

96. Cho, H.; Katoh, S.; Sayama, S.; Murakami, K.; Nakanishi, H.; Kajimoto, Y.; Ueno, H.; Kawasaki, H.; Aisaka, K.; Uchida, I. Synthesis and selective coronary vasodilatory activity of 3,4-dihydro-2,2-bis(methoxymethyl)-2H-1-benzopyran-3-ol derivatives: Novel potassium channel openers. *J. Med. Chem.* 1996, 39, 3797–3805.

97. Johnson, C.R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K.M. Libraries of N-alkylaminoheterocycles from nucleophilic aromatic substitution with purification by solid supported liquid extraction. *Tetrahedron* 1998, 54, 4097–4106.

98. Braitenbucher, J.G.; Johnson, C.R.; Haight, M.; Phelan, J.C. Generation of a piperazine-2-carboxamide library: A practical application of the phenol-sulfide react and release linker. *Tetrahedron Lett.* 1998, 39, 1295–1298.

99. Gong, Y.-D.; Hwang, J.Y.; Chon, Y.S.; Seo, J.-S.; Yoo, S.-E. Solid-phase synthesis of benzopyran building blocks via highly efficient hydroxy-alkoxylation. *Bull. Korean Chem. Soc.* 2002, 23, 1658–1660.

100. Seo, J.-S.; Joo, Y.-H.; Yi, J.B.; Lee, E.J.; Lee, N.; Cho, Y.-B.; Kwak, W.J.; Hwang, J.Y.; Jeon, Y.S.; Jeon, H.S.; et al. Novel inhibitors of prolyl 4-hydroxylase; Solid-phase synthesis of 2,2-dimethyl-3,4-dialkoxy-substituted 6-aminobenzopyran derivatives. *Bull. Korean Chem. Soc.* 2006, 27, 909–917.

101. Chao, E.Y.; Minick, D.J.; Sternbach, D.D.; Shearer, B.G.; Collins, J.L. A novel method for the generation of nitrile oxides on solid phase: Application to the synthesis of substituted benzopyranoisoxazoles. *Org. Lett.* 2002, 4, 323–326.
102. Brummond, K.M.; Lu, J. Solid-phase synthesis of BRL 49653. *J. Org. Chem.* **1999**, *65*, 1723–1726.

103. Swayze, E.E. Secondary amide-based linkers for solid phase organic synthesis. *Tetrahedron Lett.* **1997**, *38*, 8465–8468.

104. Devraj, R.; Cushman, M. A versatile solid phase synthesis of lavendustin a and certain biologically active analogs. *J. Org. Chem.* **1996**, *61*, 9368–9373.

105. Hamper, B.C.; Dukesherer, D.R.; South, M.S. Solid-phase synthesis of proline analogs via a three component 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **1996**, *37*, 3671–3674.

106. Castro, J.L.; Matassa, V.G.; Ball, R.G. Mitsunobu-like processes with a novel triphenylphosphine-cyclic sulfamide betaine. *J. Org. Chem.* **1994**, *59*, 2289–2291.

107. Park, S.O.; Kim, J.; Koh, M.; Park, S.B. Efficient parallel synthesis of privileged benzopyrylpyrazoles via regioselective condensation of β-keto aldehydes with hydrazines. *J. Comb. Chem.* **2009**, *11*, 315–326.

108. Mock, W.L.; Tsou, H.R. A procedure for diethoxymethylation of ketones. *J. Org. Chem.* **1981**, *46*, 2557–2561.

109. Dasgupta, R.; Gharak, U.R. A simple synthesis of α,β-unsaturated aldehydes by 1,3-carbonyl transposition through one carbon homologation. *Tetrahedron Lett.* **1985**, *26*, 1581–1584.

110. Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. High efficiency chemoselective deprotection of o,o-acetals and o,o-ketals catalyzed by molecular iodine in acetone. *J. Org. Chem.* **2004**, *69*, 8932–8934.

111. Sagar, R.; Kim, M.-J.; Park, S.B. An improved synthesis of pyrimidine- and pyrazole-based acyclo-C-nucleosides as carbohybrids. *Tetrahedron Lett.* **2008**, *49*, 5080–5083.

112. Sagar, R.; Park, S.B. Facile and efficient synthesis of carbohybrids as stereodivergent druglike small molecules. *J. Org. Chem.* **2008**, *73*, 3270–3273.

113. Lee, S.-C.; Park, S.B. Novel application of Leuckart-Wallach reaction for synthesis of tetrahydro-1,4-benzodiazepin-5-ones library *Chem. Commun.* **2007**, *3714–3716*.

114. Lee, S.-C.; Park, S.B. Practical solid-phase parallel synthesis of Δ²-2-oxopiperazines via N-acyliminium ion cyclization. *J. Comb. Chem.* **2007**, *9*, 828–835.

115. Lee, S.-C.; Choi, S.Y.; Chung, Y.K.; Park, S.B. Preparation of pilot library with tetrahydro-β-carboline alkaid core skeleton using tandem intramolecular Pictet-Spengler cyclization. *Tetrahedron Lett.* **2006**, *47*, 6843–6847.

116. Ko, S.K.; Jang, H.J.; Kim, E.; Park, S.B. Concise and diversity-oriented synthesis of novel scaffolds embedded with privileged benzopyran motif. *Chem. Commun.* **2006**, *2962–2964*.

117. Lee, S.-C.; Park, S.B. Solid-phase parallel synthesis of natural product-like diaza-bridged heterocycles through pitet-spengler intramolecular cyclization. *J. Comb. Chem.* **2006**, *8*, 50–57.

118. Sanchez, I.H.; Lopez, F.J.; Soria, J.J.; Larraza, M.I.; Flores, H.J. Total synthesis of (±)-elwesine, (±)-epipelwesine, and (±)-oxocrinine. *J. Am. Chem. Soc.* **1983**, *105*, 7640–7643.

119. Kapeller, D.C.; Bräse, S. Versatile solid-phase synthesis of chromenes resembling classical cannabinoids. *ACS Comb. Sci.* **2011**, *13*, 554–561.

120. Thompson, L.A.; Ellman, J.A. Straightforward and general method for coupling alcohols to solid supports. *Tetrahedron Lett.* **1994**, *35*, 9333–9336.

121. Yu, X.; Wang, S.; Chen, F. Solid-phase synthesis of solanesol. *J. Comb. Chem.* **2008**, *10*, 605–610.
122. Merrifield, R.B. Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* 1963, 85, 2149–2154.

123. Kapeller, D.C.; Bräse, S. Towards a library of chromene cannabinoids: A combinatorial approach on solid supports. *Synlett* 2011, 161–164.

124. Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S. The Diels-Alder approach towards cannabinoids. *Synthesis* 2005, 1888–1900.

125. Lesch, B.; Toräng, J.; Vanderheiden, S.; Bräse, S. Base-catalyzed condensation of 2-hydroxybenzaldehyes with α,β-unsaturated aldehydes: Scope and limitations. *Adv. Synth. Catal.* 2005, 347, 555–562.

126. Xia, Y.; Yang, Z.-Y.; Brossi, A.; Lee, K.-H. Asymmetric solid-phase synthesis of (3'R,4'R)-di-O-cis-acyl 3-carboxyl khellactones. *Org. Lett.* 1999, 1, 2113–2115.

127. Xie, L.; Takeuchi, Y.; Cosentino, L.M.; Lee, K.-H. Anti-AIDS Agents. 37. Synthesis and structure-activity relationships of (3'R,4'R)-(+-)cis-khellactone derivatives as novel potent anti-HIV agents. *J. Med. Chem.* 1999, 42, 2662–2672.

128. Watson, B.T.; Christiansen, G.E. Solid phase synthesis of substituted coumarin-3-carboxylic acids via the knoevenagel condensation. *Tetrahedron Lett.* 1998, 39, 6087–6090.

129. Hamper, B.C.; Kolodziej, S.A.; Scates, A.M. Knoevenagel condensation of unsymmetrical malonamic esters and malonates on a solid support. *Tetrahedron Lett.* 1998, 39, 2047–2050.

130. Gordeev, M.F.; Patel, D.V.; Wu, J.; Gordon, E.M. Approaches to combinatorial synthesis of heterocycles: Solid phase synthesis of pyridines and pyrido[2,3-d]pyrimidines. *Tetrahedron Lett.* 1996, 37, 4643–4646.

131. Zaragoza, F. Carbon-carbon bond formation on solid support: Synthesis of monoacyl piperazines by knoevenagel-type condensation reactions. *Tetrahedron Lett.* 1995, 36, 8677–8678.

132. Nicolaou, K.C.; Pfefferkorn, J.A.; Cao, G.-Q. Selenium-based solid-phase synthesis of benzopyrans I: Applications to combinatorial synthesis of natural products. *Angew. Chem. Int. Ed. Engl.* 2000, 39, 734–739.

133. Nicolaou, K.C.; Cao, G.-Q.; Pfefferkorn, J.A. Selenium-based solid-phase synthesis of benzopyrans ii: Applications to combinatorial synthesis of medicinally relevant small organic molecules. *Angew. Chem. Int. Ed. Engl.* 2000, 39, 739–743.

134. Nicolaou, K.C.; Pfefferkorn, J.A.; Roecker, A.J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H.J. Natural product-like combinatorial libraries based on privileged structures. 1. General principles and solid-phase synthesis of benzopyrans. *J. Am. Chem. Soc.* 2000, 122, 9939–9953.

135. Nicolaou, K.C.; Pfefferkorn, J.A.; Mitchell, H.J.; Roecker, A.J.; Barluenga, S.; Cao, G.-Q.; Affleck, R.L.; Lillig, J.E. Natural product-like combinatorial libraries based on privileged structures. 2. construction of a 10 000-membered benzopyran library by directed split-and-pool chemistry using NanoKans and optical encoding. *J. Am. Chem. Soc.* 2000, 122, 9954–9967.

136. Nicolaou, K.C.; Pfefferkorn, J.A.; Barluenga, S.; Mitchell, H.J.; Roecker, A.J.; Cao, G.-Q. Natural product-like combinatorial libraries based on privileged structures. 3. The “Libraries from Libraries” principle for diversity enhancement of benzopyran libraries. *J. Am. Chem. Soc.* 2000, 122, 9968–9976.
137. Nicolaou, K.C.; Pfefferkorn, J.A.; Schuler, F.; Roecker, A.J.; Cao, G.Q.; Casida, J.E. Combinatorial synthesis of novel and potent inhibitors of NADH:ubiquinone oxidoreductase. *Chem. Biol.* **2000**, *7*, 979–992.

138. Nicolaou, K.C.; Roecker, A.J.; Barluenga, S.; Pfefferkorn, J.A.; Cao, G.Q. Discovery of novel antibacterial agents active against methicillin-resistant staphylococcus aureus from combinatorial benzopyran libraries. *ChemBioChem* **2001**, *4*, 460–465.

139. Ruhland, T.; Anderson, K.; Pedersen, H. Selenium-linking strategy for traceless solid-phase synthesis: Direct loading, aliphatic C–H bond formation upon cleavage and reaction monitoring by gradient MAS NMR spectroscopy. *J. Org. Chem.* **1998**, *63*, 9204–9211.

140. Nicolaou, K.C.; Pastor, J.; Barluenga, S.; Winssinger, N. Polymer-supported selenium reagents for organic synthesis. *Chem. Commun.* **1998**, *1947–1948.

© 2012 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).