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Synthesis of Azaphilone-Based Chemical Libraries

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Introduction

Preparation of chemical libraries based on the elaboration of scaffolds resembling natural products is a viable strategy for discovery of small molecules which perturb biological pathways.[1] As part of our interest in the synthesis of complex natural products, we have reported syntheses of a number of azaphilone natural products and derivatives.[2] The azaphilones are a structurally diverse family of natural products containing a highly oxygenated bicyclic core and quaternary center (**1**, Figure 1).[3] This class of molecules also has numerous biosynthetic modifications of the fused ring system including oxidation (**2** and **3**), annulation (**4**), and halogenation (**4, 5** and **6**).

We have reported the preparation of the azaphilone core by oxidation of a benzopyrylium salt employing IBX[2a] or using buffer-mediated cycloisomerization of a vinylogous acid[2d] prepared from oxidative dearomatization of the corresponding *o*-alkynylbenzaldehyde derivative. Utilizing these methodologies, we considered the azaphilone core as a scaffold for chemical library synthesis. Specifically, we sought to develop a strategy which would ultimately yield a collection of azaphilones and derived chemoptypes containing orthogonal diversification points.

Our overall approach is outlined in Figure 2 and begins with Sonogashira coupling of bromo-benzaldehyde (**7**)[2a] to afford alkynyl benzaldehydes (**8**) to install R_1 diversity. Oxidative dearomatization followed by cycloisomerization affords azaphilone core structures **9** which may also be diversified at R_2 (C5) by bromination and Stille coupling to afford compounds **10**. Scaffolds **9** and **10** (chemset 1) may be acylated to afford a collection of esters (**11**, chemset 2). Select members of chemset 2 may also be utilized in condensations[2a,d] to afford vinylogous 4-pyridones (**12**, chemset 3). Overall, the library plan leading to vinylogous pyridone chemset 3 leads to projection of R_1-R_4 diversity elements in four sectors of the azaphilone core structure.

Results and Discussion

Synthesis of chemset 1 was initiated with Sonogashira coupling of bromobenzaldehyde **7** utilizing nine terminal alkynes (**13{1-9}**) to afford alkynyl benzaldehydes **8** (Scheme 1).[4] Cycloisomerization mediated by $Au(OAc)_3$[2a,5] in the presence of TFA afforded an intermediate 2-benzopyrylium salt.[6] *In situ* oxidation of the salt with SIBX[7] (a stabilized form of IBX) or IBX and tetrabutylammonium iodide as phase transfer catalyst[2a] afforded azaphilones **9**. Overall, Sonogashira coupling proceeded in excellent yield for all alkynes evaluated (Figure 3). The two step cycloizomerization/oxidation sequence proceeded in good to moderate yields (Table 1). Generally, electron poor alkynes required higher reaction

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temperatures and alkynes bearing a NHBoc group only proceeded when IBX was utilized as oxidant.

In order to further diversify chemset 1, we considered further functionalization through cross coupling processes at C5 (Scheme 2). Preparation of the requisite vinyl bromide was readily facilitated by reaction of azaphilone core structures with NBS in acetonitrile. However, attempts at Pd-mediated coupling of aryl and vinylstannanes were unsuccessful utilizing azaphilones bearing a free tertiary alcohol. Further investigation revealed that cross-couplings with scaffolds bearing tertiary esters proceeded cleanly. Upon further reaction optimization, we found that Stille cross-coupling of **15-17** with a variety of tributylstannanes afforded coupled products **18-20** in moderate to good yields.

Interestingly, we found that reaction of azaphilone **9{1}** with acetic acid/acetic anhydride (1:1) in the presence of phenyliodine diacetate (PIDA) (μW 90 °C, 10 minutes) led to both acylation of the tertiary alcohol and acetoxylation[8] of the C5 position. However, *O*-acetylation could be avoided if the oxidation was performed at room temperature to afford exclusively tertiary alcohol **21** in 65% yield (Scheme 3).

We next sought to further elaborate chemset 1 utilizing acid chlorides (**25**) to afford azaphilone esters (**11**) (Scheme 4). Acylation proceeded in the presence of DMAP but with significant formation of side products.[9] However, utilization of solid supported DMAP (PS-DMAP)[10] minimized formation of side products. Accordingly, acylation of tertiary alcohol **9{1}** with propionyl chloride in the presence of PS-DMAP (1.3 equiv.) afforded **11{1,1}** in good yield (90%) and a crude HPLC purity of >90% after filtration.

Utilizing the optimized protocol for preparation of azaphilone esters, we carried out the synthesis of chemset 2 employing eleven scaffolds from chemset 1 (Figure 3) and eight acid chlorides (Figure 4). The reaction mixtures were filtered, evaporated, and the crude material purified by mass-directed preparative HPLC. Overall, the reactions proceeded smoothly although aryl substituted scaffolds (**9{2}, 9{3}, 9{5}**, and **22**) required additional amounts of acid chloride (0.5 equiv) and longer reaction times. Notably, compounds **9{8}** and **9{9}** were successfully acylated with no detectable loss of the NHBoc protecting group. Representative products from chemset 2 are illustrated in Figure 5.[9]

We next set out to optimize conditions for condensation of azaphilones with primary amines to afford vinylogous 4-pyridones.[2a,b,d] Initial reaction conditions entailed treatment of azaphilone **9{1}** in the presence of 1.2 equiv. of benzylamine at room temperature in CH_2Cl_2 (1 h) which afforded vinylogous 4-pyridone **24** in excellent yield (Scheme 5, a). However, reaction with ester **11{1,1}** afforded only enamine **25** (Scheme 5, b).[2a,b] Based on these results, we considered that the azaphilone alcohol may activate of the carbonyl through hydrogen bonding, thereby facilitating a faster rate of cyclization relative to elimination. In an effort to enhance the cyclization rate, we examined use of the polymer-supported carboxylic acid resin (IRC-76) which may function as both a Bronsted acid catalyst and amine scavenger. Compound **11{1,1}** was treated with benzylamine (1.3 equiv.) in acetonitrile/water (10:1) at room temperature for 8 h followed by microwave irradiation for 15 minutes (120 °C). Addition of Amberlite IRC-76 and further microwave irradiation (15 minutes, 120 °C) afforded the desired vinylogous 4-pyridone **26** in good yield and purity after filtration of the resin.

We consequently selected ten azaphilone scaffolds from chemset 2 to be converted to vinylogous 4-pyridones (Figure 6). Utilizing the optimized reaction conditions (Scheme 6) and a selection of twenty amines (Figure 7), we conducted parallel synthesis of chemset 3. Overall, reactions proceeded well with good isolated yields and generally high crude purities by HPLC/ELSD. However, bulky or less nucleophilic amines required longer reaction times

(24 h) to afford complete conversion. Representative chemset-3 library members are shown in Figure 8.

We also wished to take advantage of the NHBoc-containing members of chemset 1 and considered that cyclization of the corresponding deprotected amines may afford tricyclic azaphilone pyridone derivatives.[2d] Treatment of **9{8}** with aqueous HCl (3 N) at 40 °C afforded the cyclized product **32** in moderate yield (55%) (Scheme 7, a). Reaction of **9{9}** under the same conditions afforded tricyclic product **33** in a lower but synthetically useful yield (40%) (Scheme 7, b). Due to difficulties in scaleup and purification of the tricyclic products, compounds were immediately acylated to afford esters **34** and **35**.

During exploratory investigations, we attempted the condensation of NH_4OAc with azaphilone scaffold **11{1,1}** with NH_4OAc (Scheme 9). Interestingly, reaction of this scaffold under standard conditions for condensation with primary amines afforded a mixture of tautomers **36** and **37** (4:1 by ^1H NMR analysis). Acylation of the tautomeric mixture (**36**/**37**) with 2-furan carbonyl chloride as a representative acid chloride afforded derivative **38**. It is noteworthy that scaffolds **38** contain the isoquinolin-6(*7H*) core structure found in natural product **6**.[2f]

Conclusion

We have achieved the synthesis of azaphilone scaffolds which have further diversified by cross coupling (chemset 1). A selection of chemset 1 was further acylated to afford a collection of azaphilone esters (chemset 2). Select members of chemset 2 were utilized in condensations to afford vinylogous 4-pyridones (chemset 3). Methodology development also led to the novel modifications including C5 acetoxylation and condensations producing isoquinolin-6(*7H*) structures. Overall, the library synthesis led to three azaphilone sub-libraries including vinylogous pyridones which project diversity elements in four sectors of the azaphilone core. Calculation of key physiochemical and structural properties revealed that chemsets 1 -3 have values are within range of generally acceptable values (Table 2).

Compounds produced in this study have been submitted for biological screening including to the Molecular Libraries Screening Center Network (MLSCN). In this regard, initial results from the MLSCN indicate interesting activity of select compounds against *P. falciparum* HSP90[11,12] and inhibition of the parasite plastid.[13] Further studies on the synthesis of chemical libraries based on natural product scaffolds are in progress and will be reported in future publications.

Experimental

General Information: General Information

All nuclear magnetic resonance spectra were recorded on either a Varian or Bruker spectrometer. ^1H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 100 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^1H, δ 7.27; ^{13}C, δ 77.0) and acetone-d_6 (^1H, δ 2.05; ^{13}C, δ 30.8). Data for ^1H NMR are reported as follows: chemical shift, integration, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet) and coupling constants are reported as values in hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Analytical LC was performed on a 2.1 × 50 mm 1.7 μM C18 column. Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60-F plates. Otherwise, flash chromatography was performed using 200-400 mesh silica gel. Yields refer to chromatographically and

spectroscopically pure materials unless otherwise stated. Acetonitrile, CH_2Cl_2, THF, and toluene were purified by passing through two packed columns of neutral alumina. All reactions were performed under an argon atmosphere in oven-dried or flame-dried glassware.

6-(Hex-1-ynyl)-2,4-dihydroxy-3-methylbenzaldehyde 8{1}

To a mixture of 2-bromo-4,6-dihydroxybenzaldehyde[1] (2.00 g, 8.65 mmol), $PdCl_2(PPh_3)_2$ (607 mg, 0.86 mmol) and CuI (164 mg, 0.86 mmol) in anhydrous DMF (40 mL), were successively added 1-hexyne (1.60 mL, 13.9 mmol) and triethylamine (4 mL, 30 mmol). The resulting mixture was heated at 65 °C for 16 h. After cooling the resulting black mixture to room temperature, water (20 mL) and a solution of HCl 1 N (20 mL) were successively added and the resulting mixture was extracted three times with EtOAc (75×3 mL). The combined organic layers were washed with water and brine, dried over Na_2SO4, filtered and concentrated *in vacuo*. Purification of the crude solid by flash chromatography (SiO_2, EtOAc/hexanes, 20:1 to 10:1) afforded 1.840 g (91 %) of 6-(hex-1-ynyl)-2,4-dihydroxy-3-methylbenzaldehyde **8{1}** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ12.33 (1H, s), 10.20 (1H, s), 6.48 (1H, s), 5.48 (1H, s), 2.44 (2H, t, J = 7.0 Hz), 2.10 (3H, s), 1.63-1.56 (2H, m), 1.51-1.42 (2H, m), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR (75.0 MHz, DMSO-*d6*) δ 194.1, 162.8, 162.1, 126.2, 112.8, 112.0, 111.0, 97.1, 75.7, 29.9, 21.4, 18.3, 13.3, 7.2; IR (thin film) 3412, 3005, 2925, 1631, 1421, 1362, 1092; HRMS calculated for $C_{14}H_{17}O_3$: 233.1178, found: 233.1176 [M+H].

4-((2-Formyl-3,5-dihydroxy-4-methylphenyl)ethynyl)benzonitrile 8{3}

2-Bromo-4,6-dihydroxy-5-methylbenzaldehyde[2a] (1.00 g, 4.3 mmol), $PdCl_2$(COD) (50 mg, 0.17 mmol), CuI (17 mg, 0.09 mmol), 4-ethynylbenzonitrile (687 mg, 5.4 mmol) and $P(^tBu)_3HBF_4$ (101 mg, 0.34 mmol) were weighed and transferred into a flame-dried Schlenk tube. The system was evacuated and purged with argon. Dioxane and diisopropylamine were successively added and the resulting mixture was stirred under argon for 18 h and the reaction was filtered through a silica pad eluting with EtOAc. The combined solutions were concentrated *in vacuo* and purified by flash chromatography (SiO_2, EtOAc/hexanes, 10:1 to 4:6) to afford 1.15 g (96%) of 4-((2-formyl-3,5-dihydroxy-4-methylphenyl)ethynyl)benzonitrile **8{3}** as a yellow solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 12.45 (1H, s), 10.32 (1H, s), 9.76 (1H, s), 7.85 (m, 4H), 6.83 (1H, s), 2.10 (3H, s); ^{13}C NMR (75.0 MHz, DMSO-*d6*) δ 194.1, 162.6, 162.2, 132.4, 132.3, 126.2, 123.9, 118.2, 112.7, 112.6, 112.5, 111.3, 92.9, 88.3, 7.4; IR (thin film) 3352, 3000, 2218, 1622, 1105; HRMS calculated for $C_{17}H_{13}NO_3$: 279.0895, found: 279.0905 [M+H]

3-Butyl-7-hydroxy-7-methylisochroman-6,8-dione 9{1}

Trifluoroacetic acid (6.5 mL) was quickly added to a mixture of 6-(hex-1-ynyl)-2,4-dihydroxy-3-methylbenzaldehyde **8{1}** (1.206 g, 5.2 mmol) and $Au(OAc)_3$ (116 mg, 0.31 mmol) in 1,2-dichloroethane (20 mL) and the resulting solution was stirred at room temperature for ten minutes. IBX (1.673 g, 5.97 mmol) or SIBX (3.970 g) and tetrabutylammonium iodide (95 mg, 0.25 mmol) were successively added to the solution and the resulting mixture was stirred at room temperature for 90 minutes. The reaction mixture was quenched with a minimum of saturated $Na_2S_2O_3$ (5 mL) and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography (SiO_2: EtOAc/ hexanes,10:1 to 4:6) gave 1.08 g (84%) using IBX and 980 mg (76%) using SIBX of 3-butyl-7-hydroxy-7-methylisochroman-6,8-dione **9{1}** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, s), 6.10 (1H, s), 5.50 (1H, s), 3.92 (1H, brs), 2.42 (2H, t, J = 7.0 Hz), 1.64-1.57 (2H, m), 1.54 (3H, s), 1.43-1.34 (2H, m), 0.94 (3H, t, J = 7.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 196.2, 195.7, 163.0, 152.9, 144.0, 115.7, 108.2, 104.8, 83.3, 32.7, 28.41,

28.40, 21.9, 13.5; IR (thin film) 3460, 2997, 2919, 1723, 1658, 1537, 1443; HRMS calculated for $C_{14}H_{17}O_4$: 249.1127, found: 249.1118 [M+H].

5-Bromo-7-hydroxy-3-(4-methoxyphenyl)-7-methyl-6H-isochromene-6,8(7H)-dione 22

To a solution of 3-butyl-7-hydroxy-7-methylisochroman-6,8-dione **9{2}** (1.01 g, 4.06 mmol) in acetonitrile (30 mL) was added *N*-bromosuccinimide in one portion and the resulting mixture was stirred for one hour at room temperature. Concentration *in vacuo* and purification by flash chromatography (SiO_2, EtOAc/hexanes, 70:30) afforded 1.21 g (91%) of 5-bromo-3-butyl-7-hydroxy-7-methylisochroman-6,8-dione **22** as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.78 (2H, d, *J*= 9.0 Hz), 7.15 (1H, s), 7.02 (2H, d), 3.92 (1H, s), 3.90 (3H, s), 1.61 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 194.0, 189.9,162.8, 159.4, 151.7, 142.2, 127.8, 122.1, 116.1, 114.7, 104.6, 100.4, 83.9, 55.6, 28.6; IR (thin film) 3445, 3002, 1721, 1650, 1553, 1206; HRMS calculated for $C_{17}H_{14}O_5Br$: 377.0025, found: 377.0022 [M+H].

Azaphilone 18

Tributylstannylfuran (944 μL, 2.99 mmol) was added under argon to a solution of palladium acetate (49 mg, 0.21 mmol) tri-*o*-tolyl phosphine (163 mg, 0.53 mmol), and 5-bromo-3-butyl-7-methyl-6,8-dioxoisochroman-7-yl 4-methoxybenzoate **15** (988 mg, 2.14 mmol) in anhydrous degassed DMF (15 mL). The resulting solution was heated at 60 °C for 12 h. After cooling to room temperature, HCl 1N (5 mL) was added to the resulting black mixture and the solution was extracted three times with EtOAc. The organic layers were washed with brine and dried over sodium sulfate. Purification by flash chromatography (SiO_2, EtOAc/hexanes, 90:10 to 70:30) afforded 778 mg (81%) of azaphilone **18** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 9.3 Hz), 8.02 (1H, s), 7.46 (1H, brs), 6.99 (1H, s), 6.90 (2H, d), 6.82 (1H, d, *J* = 3.1 Hz), 6.47 (1H, dd, *J* = 1.5 Hz), 3.85 (3H, s), 2.45 (2H, t, *J* = 7.8 Hz), 1.72 (3H, s), 1.66-1.59 (2H, m), 1.46-1.37 (2H, m), 0.96 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 192.7, 190.1, 165.3, 163.8, 162.6, 154.3, 148.2, 140.8, 138.0, 132.4, 121.1, 115.3, 113.6, 111.8, 111.3, 108.4, 107.5, 84.4, 55.4, 32.3, 28.8, 22.4, 22.0, 13.7; IR (thin film) 2985, 2972, 2865, 1736, 1722, 1643, 1554; HRMS calculated for $C_{26}H_{24}O_7Na$: 471.1420, found: 471.1440 [M+Na].

General Procedure A for the Synthesis of Chemset 2

To a solution of azaphilone (1 equiv.) was added acid chloride (2 equiv.) and the mixture was stirred for 3 minutes. PS-DMAP (2 equiv. (0.35 mmol/g)) was added to the reaction mixture and the solution was stirred at room temperature for 24-48h. Filtration over Celite® eluting with CH_2Cl_2 afforded **Chemset 2**.

11{1,5}

1H NMR (400 MHz, $CDCl_3$) δ 9.53 (1H, s), 8.31 (1H, dd, *J* = 1.5, 8.6 Hz), 8.17 (1H, dd), 7.94 (1H, s), 7.92-7.83 (2H, m), 6.15 (1H, s), 5.60 (1H, s), 2.43 (2H, t, *J* = 7.8 Hz), 1.81 (3H, s), 1.66-1.59 (2H, m), 1.45-1.36 (2H, m), 0.96 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75.0 MHz, CDCl3) δ 192.5, 191.6, 163.0, 162.7, 154.2, 145.2, 143.7, 143.0, 141.7, 141.5, 132.5, 131.0, 130.8, 129.2, 115.2, 108.6, 106.7, 86.2, 32.8, 28.5, 22.5, 22.0, 13.66.

General Procedure B for the Synthesis of Chemset 2

To a solution of azaphilone (1 equiv.) was added acid chloride (2 equiv.) and the mixture was stirred for 3 minutes. PS-DMAP (2 equiv. (0.35 mmol/g)) was added to the reaction mixture and the solution was heated under microwave conditions (80°C, 15 mins, 300W, stirring on, cooling on). Filtration over Celite® eluting with CH_2Cl_2 afforded Chemset 2.

11{1,4}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.35-7.31 (3H, m), 7.27-7.23 (2H, m), 6.14 (1H, s), 5.58 (1H, s), 3.01 (2H, t, *J* = 7.8 Hz), 2.78-2.74 (2H, 2dt, *J* = 10 Hz), 2.45 (2H, t, *J* = 7.4 Hz), 1.69-1.61 (2H, m), 1.59 (3H, s), 1.48-1.39 (2H, m), 1.00 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.3, 192.7, 172.0, 162.4, 154.0, 142.8, 140.2, 128.4, 128.2, 126.2, 115.1, 108.6, 106.7, 84.4, 34.8, 32.7, 30.5, 28.5, 22.2, 22.0, 13.6; IR (thin film) 2985, 1734, 1716, 1619, 1543, 1456; HRMS calculated for $C_{23}H_{25}O_5$: 381.1702, found: 381.1728 (M +H).

General Procedure for the Synthesis of Chemset 3

To a solution of azaphilone (1 equiv.) in acetonitrile/water (10:1, 2 mL) was added amine (1.3 equiv.) and the mixture was stirred at room temperature for 8 h. The red reaction mixture was heated under microwave conditions (120°C, 15 mins, Powermax on, stirring on, cooling on). After cooling the reaction to room temperature, 10 to 15 mg of dry Amberlite IRC76 resin was added and the mixture was heated under microwave conditions (120 °C, 15 mins, Powermax on, stirring on, cooling on). After cooling the reaction to room temperature, the mixture was filtered through a pad of Celite® using ethyl acetate as elution solvent. After concentration, library members were purified by mass-directed HPLC to afford Chemset 3.

33{1,1,4}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, s), 7.17 (2H, d, *J* = 9.4 Hz), 6.99 (2H, d), 6.29 (1H, s), 5.37 (1H, s), 3.87 (3H, s), 2.52-2.45 (2H, m), 2.17 (2H, t, *J* = 7.8 Hz), 1.54 (3H, s), 1.37 (2H, q, *J*= 7.8 Hz), 1.25-1.16 (2H, m), 1.13 (3H, t, *J* = 7.8 Hz), 0.79 (3H, t, *J* = 7.8 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 195.1, 192.0, 173.8, 160.4, 149.2, 148.6, 142.7, 133.2, 119.2, 115.3, 115.1, 114.3, 100.0, 84.2, 55.7, 32.0, 30.1, 26.7, 22.9, 22.0, 13.5, 8.7; IR (thin film) 2965, 2927, 2853, 1725, 1695, 1637, 1603, 1525; HRMS calculated for $C_{24}H_{28}NO_5$: 410.1967, found: 410.1995 [M+H].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. See Supporting Information for further details.
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11. For azaphilone inhibitors of Hsp90, see: Musso L, Dallavalle S, Merlini L, Bava A, Nasini G, Penco S, Giannini G, Giommarelli C, De Cesare A, Zuco V, Vesci L, Pisano C, Castorina M, Milazzo F, Cervoni ML, Dal Piaz F, De Tommasi N, Zunino F. Natural and semisynthetic azaphilones as a new scaffold for Hsp90 inhibitors. Bioorg Med Chem. 2010; 18:8687.
12. Pubchem AID#540270: http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=540270
13. PubChem AID# 504832: http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=504832

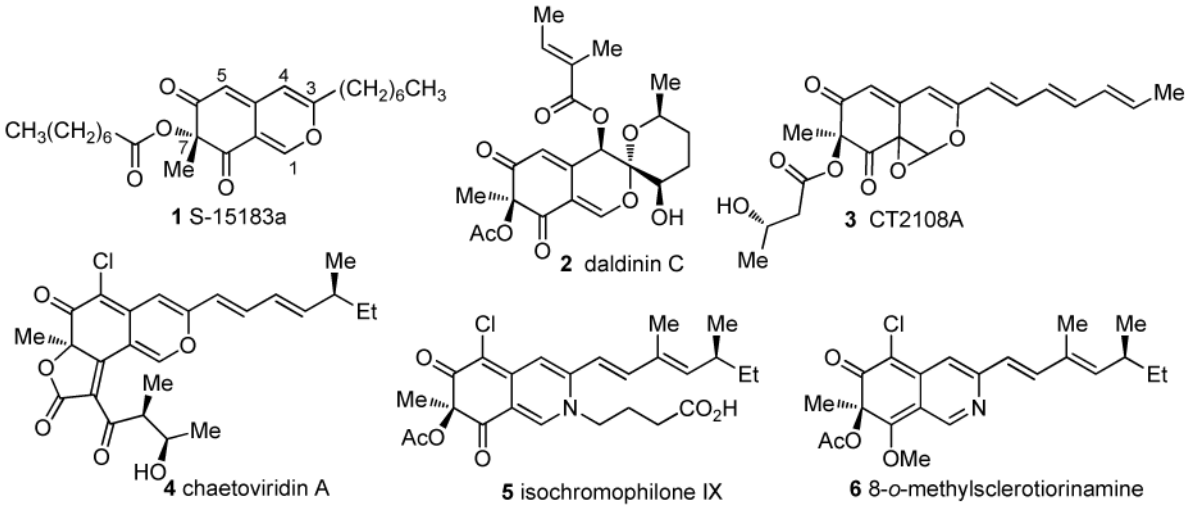


Figure 1.
Representative azaphilone natural products.

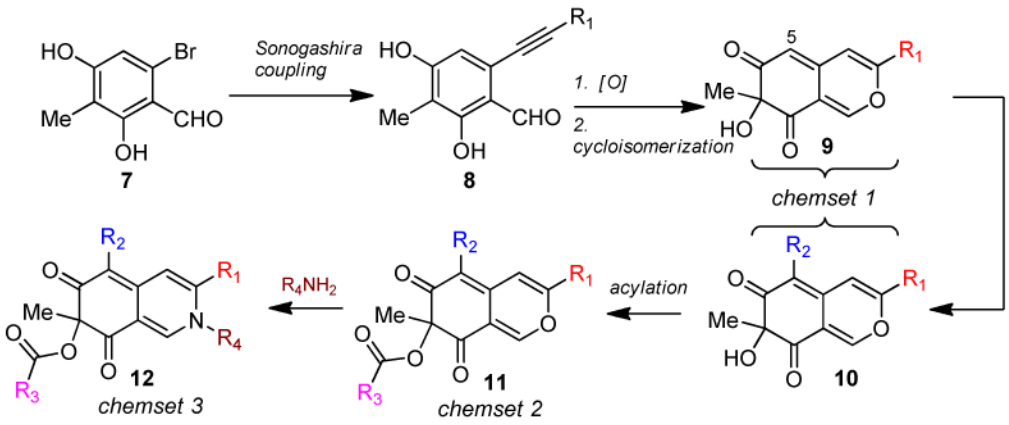


Figure 2.
Azaphilone library synthesis plan.

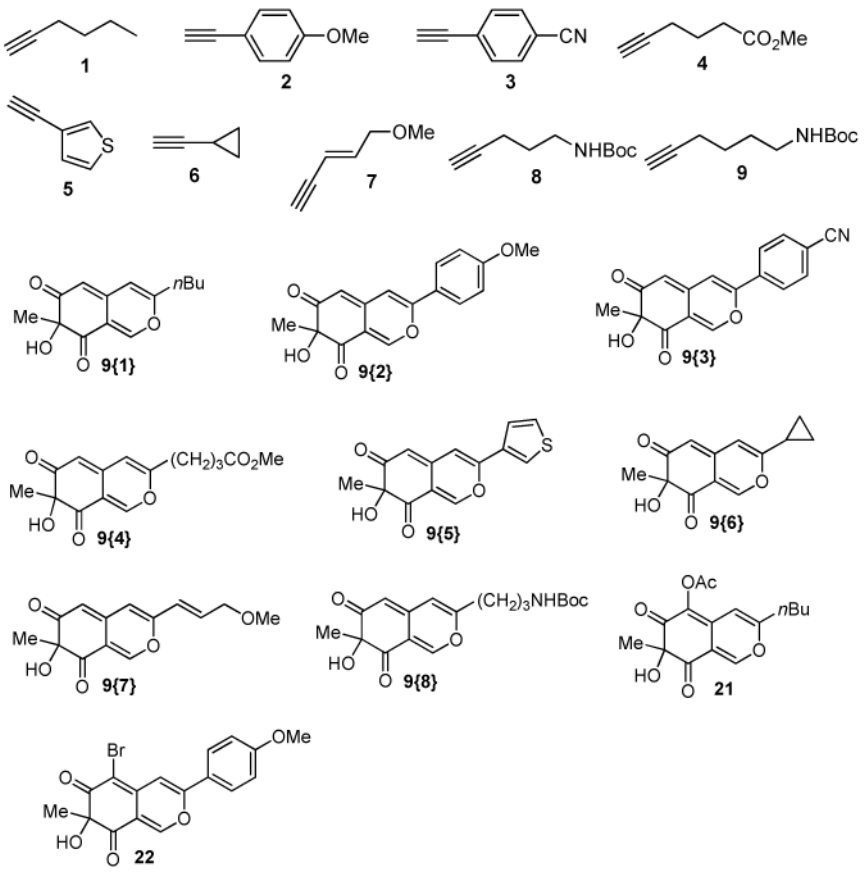


Figure 3.
Diversity reagents 13{1-9}.
Azaphilone scaffolds derived from chemset 1.

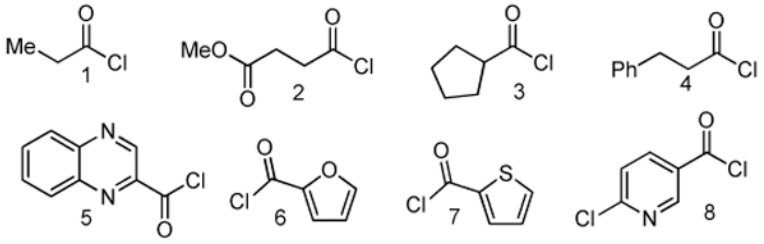


Figure 4.
Diversity reagents **23{1-8}**.

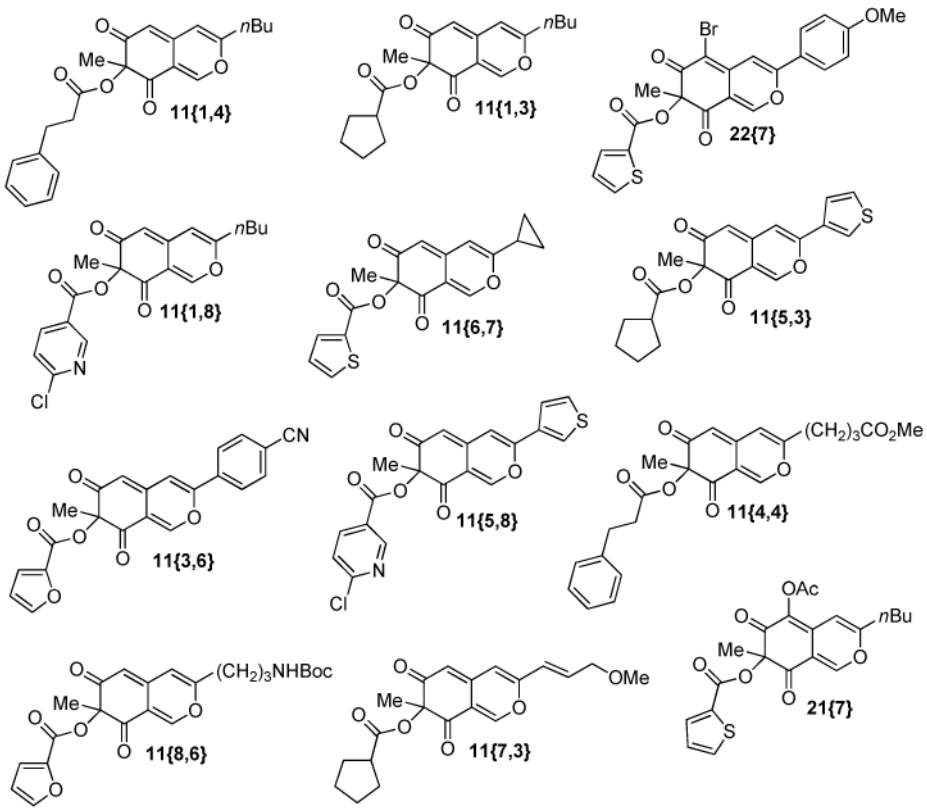


Figure 5.
Representative compounds from chemset 2.

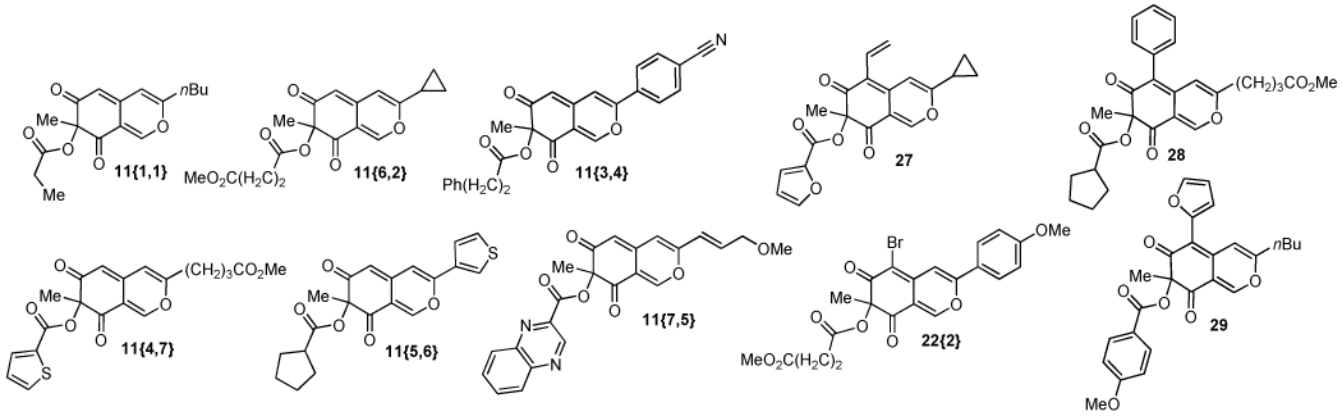


Figure 6.
Scaffolds from chemset 2 utilized in the synthesis of chemset 3.

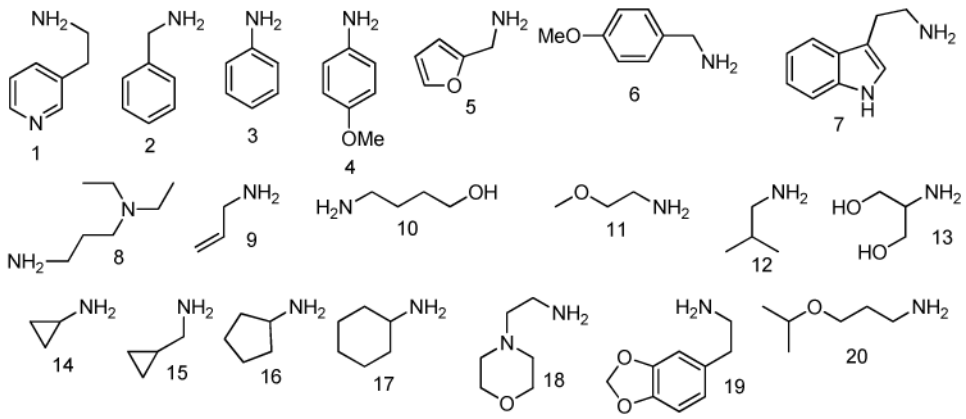


Figure 7. Diversity reagents 30{1-20}

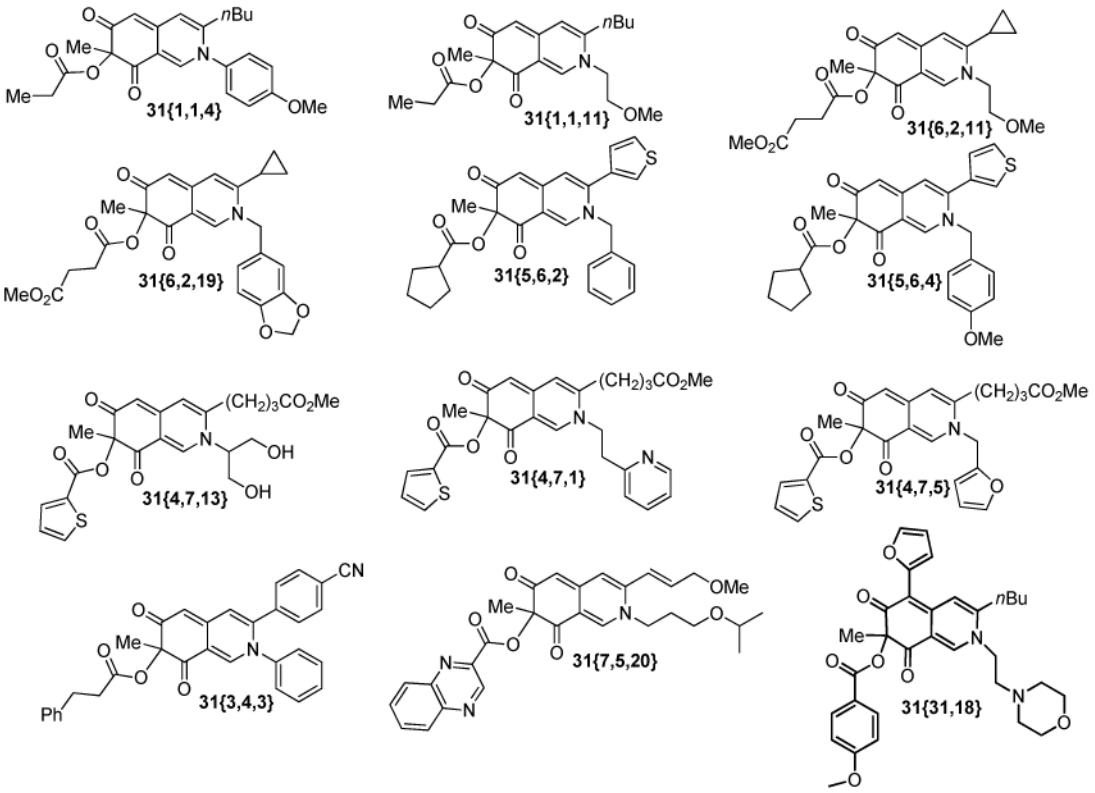
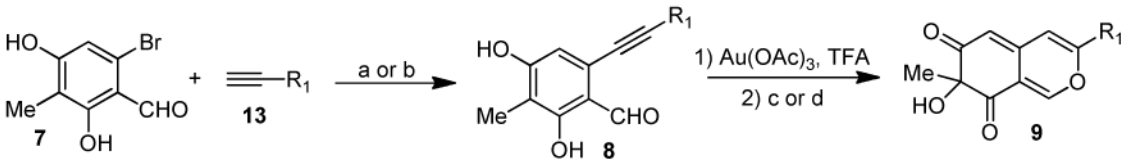
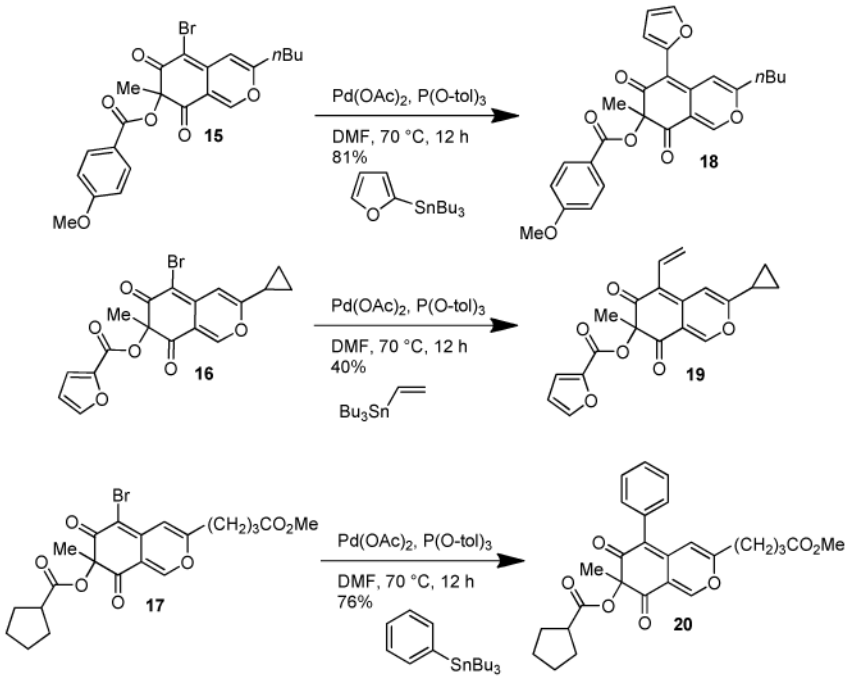


Figure 8.
Representative Chemset 3 library members.

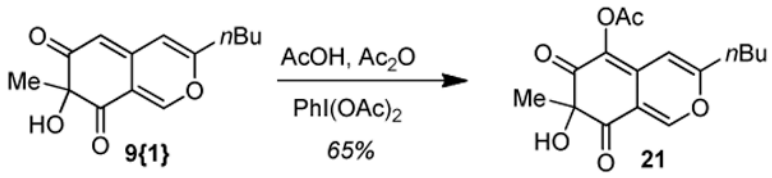


Scheme 1. Synthesis of chemset 1

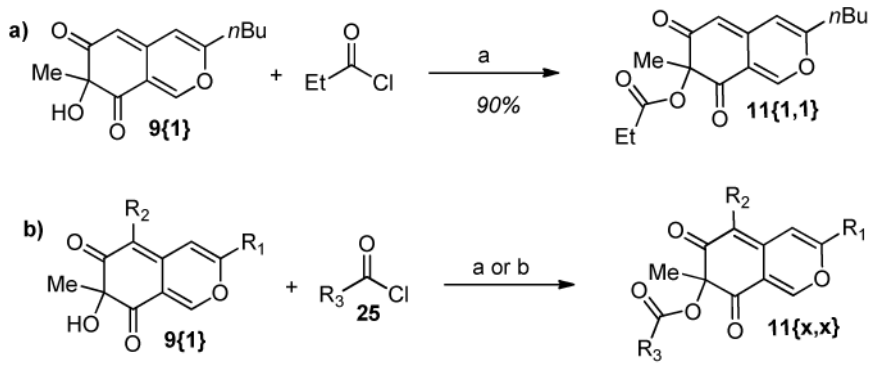
a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 65 °C, 16 h. *b)* $PdCl_2$(COD), *t*$Bu_3PH;BF_4$, CuI, *i*Pr_2NH, dioxane, rt, 18 h. *c)* SIBX. *d)* IBX.



Scheme 2.
Functionalization of the azaphilone core *via* Stille cross-coupling.

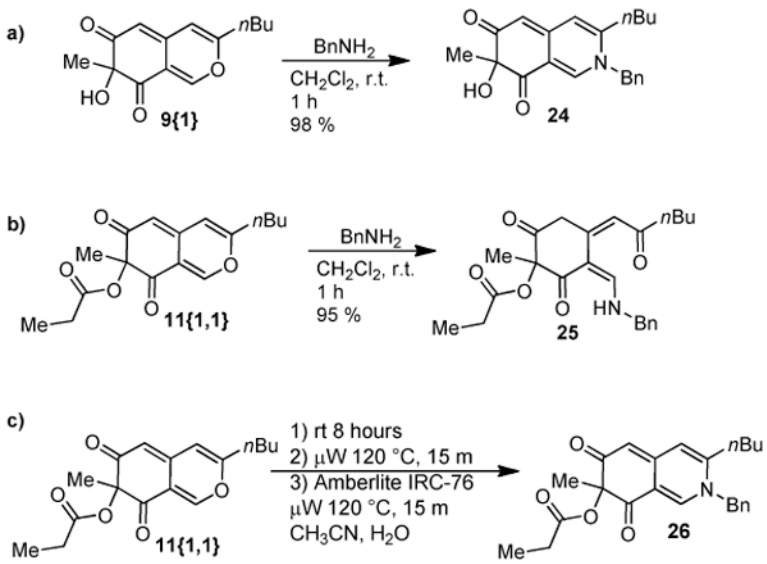


Scheme 3. C5-Acetoxylation of the azaphilone scaffold

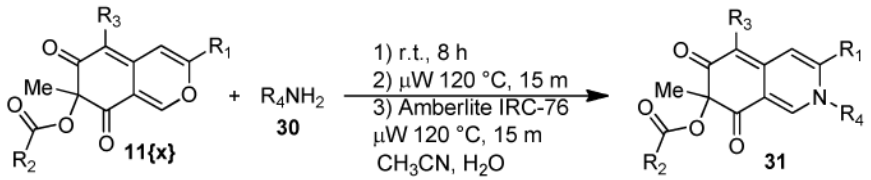


Scheme 4. Acetylation of chemset 1

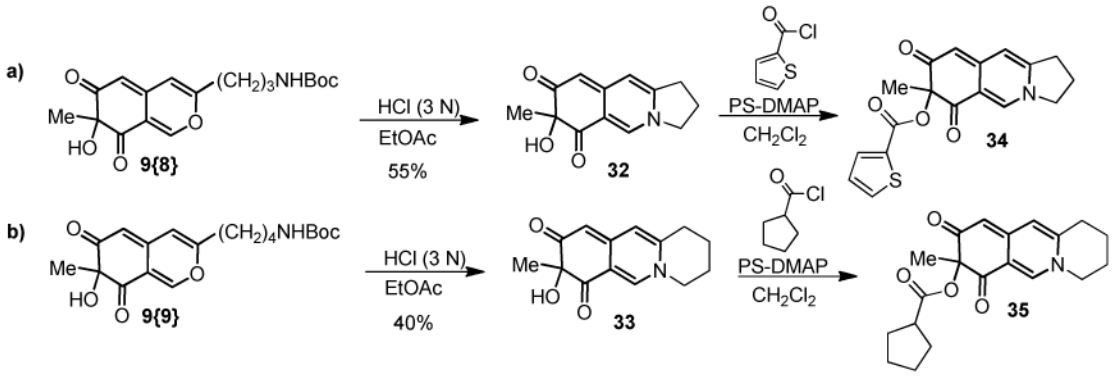
a) PS-DMAP (2.0 equiv), CH_2Cl_2, μW 80 °C, 15 mins, 90-98%. b) PS-DMAP (1.3 equiv), CH_2Cl_2, r.t. 24-48 h, 70-89%



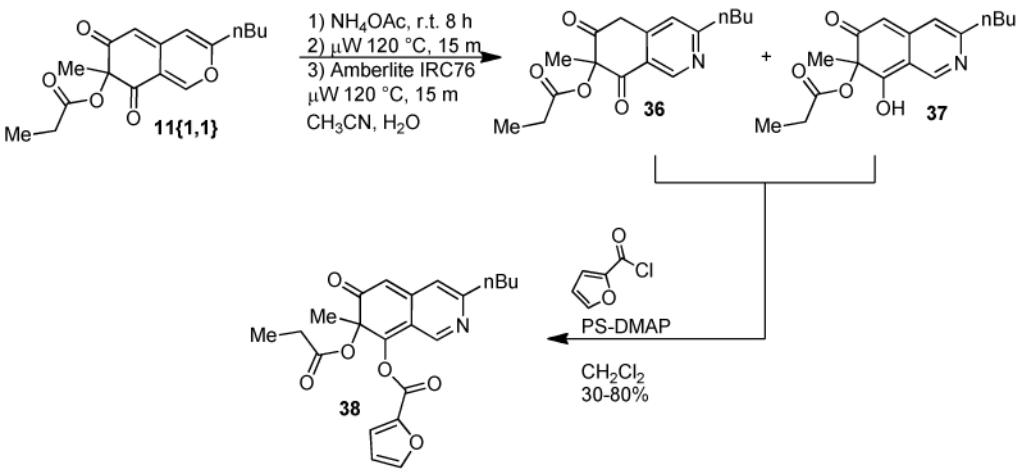
Scheme 5. Reactions of azaphilones with primary amines



Scheme 6. Conditions for synthesis of chemset 3



Scheme 7.
Formation of tricyclic vinylogous 4-pyridone scaffolds.



Scheme 9.
Isoquinolin-6(*7H*) structures.

Table 1

Isolated yields for compounds in chemset 1[a]

product	condition	yield (%)	product	product	product
8{1}	a	91%	**9{1}**	c	76%
8{2}	b	96%	**9{2}**	c	76%
8{3}	b	96%	**9{3}**	c	40%
8{4}	a	87%	**9{4}**	c	70%
8{5}	a	84%	**9{5}**	c	51%
8{6}	a	82%	**9{6}**	c	43%
8{7}	b	85%	**9{7}**	c	65%
8{8}	a	88%	**9{8}**	d	55%
8{9}	a	86%	**9{9}**	d	44%

[a]See Scheme 1 for conditions a-d

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Table 2

Physiochemical and structural properties of azaphilone libraries.

library	MW (median, range)	LogD(median, range)	PSA (median, range)	H-Acceptor (median, range)	H-donor (median, range)	rotatable bond (median, range)
Chemset 1	293, 232 - 377	1.1, 0 - 1.6	87, 63 -101	5, 1 - 2	1, 1 - 2	2.5, 1 - 7
Chemset 2	338, 248 - 428	2, 1.4 - 2.7	86, 64 - 109	5.5, 4 - 7	0.5, 0 - 1	6.5, 3 - 10
Chemset 3	426, 383 - 469	3.5, 3.3 - 3.6	89, 76 - 101	5.5, 5 - 6	0, 0 -0	8.5, 8 - 9