Palladium- and Copper-Catalyzed Solution Phase Synthesis of a Diverse Library of Isoquinolines

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The solution-phase synthesis of a 111 member isoquinoline library is described. The isoquinoline scaffold has been accessed through the palladium- and copper-catalyzed cyclization of iminoalkynes and the palladium-catalyzed iminoannulation of internal alkynes, followed by diversification of hydroxyl functionality where it is present.

Introduction

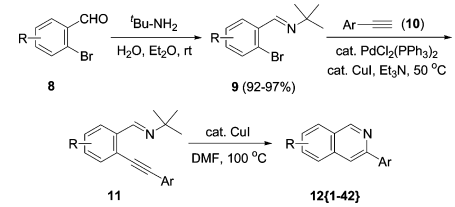
The isoquinoline nucleus is one of the most abundant structural motifs found in natural products and biologically active molecules.[1] Isoquinoline derivatives exhibit a broad range of pharmacological activity, including antitumor, antifungal, antimalarial, antihypertensive and antihistaminic activity.[2,3] Some simple biologically active isoquinoline derivatives are shown in Figure 1. The opium alkaloid papaverine (**1**) has been found to be useful as a vasodilator.[4] Decumbenine B (**2**) has been found to inhibit spontaneous contraction of the intestine.[5] Simple isoquinolines, such as **3a** and **3b**, have been shown to be useful for the treatment and prevention of cardiovascular diseases.[6] Similarly, isoquinolines **4a** and **4b** are potent anti-inflammatory agents.[7] The isoquinoline backbone is also found in nitidine (**5**), pseudopalmitine (**6**), and related biologically active plant alkaloids.[8] The tetrahydroisoquinoline **7**, known as quinapril, is an angiotensin-converting enzyme (ACE) inhibitor and its hydrochloride salt is marketed under the brand name Accupril for the treatment of hypertension and congestive heart failure.[9]

The immense biological importance of isoquinolines has led to extensive studies toward the synthesis of this ring system. Most of the classical methods, such as the Pomeranz−Fritsch,[10] Bischler−Napieralski,[11] and Pictet−Spengler reactions,[12] generally require either harsh conditions and/or tedious reaction procedures,[13] which are not desirable for library synthesis. Several metal-mediated methods have been reported for the synthesis of the isoquinoline scaffold in recent years.[14] Contrary to the classical methods, the mild metal-catalyzed methods developed earlier in our laboratory[14a−e] are well suited for library generation. These methods readily accommodate a wide variety of functionality, allowing one to dramatically increase molecular complexity in just a few synthetic steps starting from commercially available materials. In a continuation of our research efforts to adapt heterocyclization chemistry to a high-throughput synthesis format,[15] we herein report the first solution-phase synthesis of three combinatorial libraries **I**−**III** of isoquinolines using our Pd- and Cu-catalyzed alkyne annulations as the key step.[16] The presence of the isoquinoline scaffold in numerous biologically active compounds justifies the generation of this discovery library of isoquinolines.[17] Indeed, preliminary biological results from this library, which will be reported elsewhere, have proven quite interesting.

Results and Discussion

For generation of the first isoquinoline library, we have utilized the copper-catalyzed cyclization of iminoalkynes (Scheme 1).[14d] For this purpose, seven commercially available alkynes (**10**) and seven differentially substituted 2-bromobenzaldehydes (**8**) were chosen. These electron-rich and -deficient aldehydes and the variety of alkyne building blocks contribute substantially to the diversity of library **I**. Toward this goal, aldehydes **8** were first converted to their imine derivatives **9** (Figure 2), which were subsequently subjected to a Sonogashira reaction with the various alkynes **10** (Figure 3) to furnish the key *N-tert*-butyl-2-(1-alkynyl)benzaldimines **11**. Gratifyingly, the final copper-catalyzed cyclization readily accommodated a wide variety of iminoalkynes and thus furnished the targeted 42 library **I** members. Because of the increasing importance of fluorine in pharmacologically active

Scheme 1. Isoquinoline Library **I**



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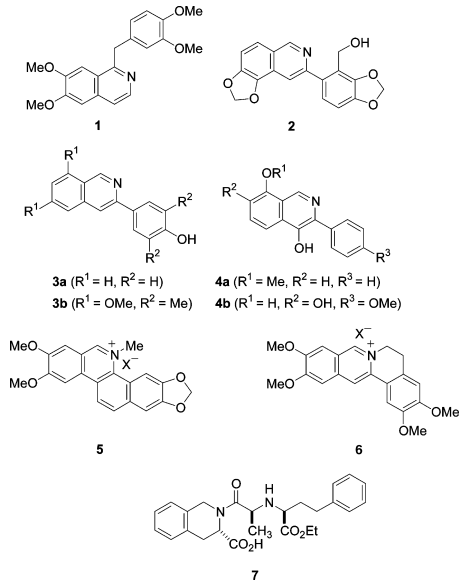


Figure 1. Selected biologically active isoquinoline derivatives.

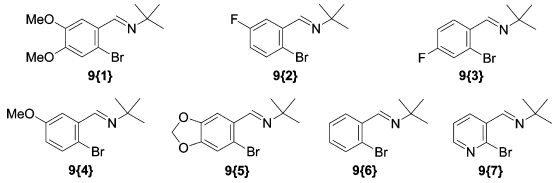
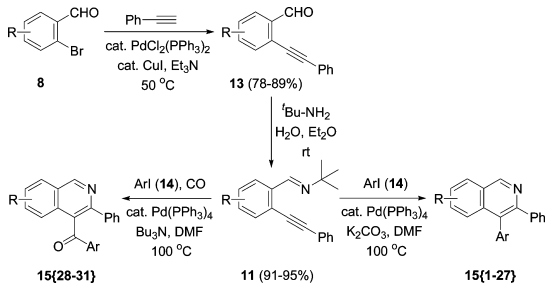


Figure 2. Imine intermediates **9**{*1*−*7*}.

Scheme 2. Isoquinoline Library **II**



molecules,[18] we have utilized several fluorinated building blocks to incorporate a fluorine atom in our library members. All of the isoquinolines **12** were isolated in >90% purity. As summarized in Table 1, modest yields (17−75%) of isoquinoline derivatives were obtained over the two steps from the 2-bromobenzaldimines **9**.

For the second isoquinoline library, we have used the palladium-catalyzed cyclization of the iminoalkynes **11** in the presence of aryl iodides (Scheme 2).[14a,b] These functionally substituted aryl groups provide an additional element of diversity in library **II** members. For this purpose, three commercially available 2-bromobenzaldehydes were subjected to a Sonogashira reaction with phenylacetylene to synthesize the corresponding 2-(phenylethynyl)benzaldehydes **13**, which were subsequently converted to the key *o*-(1-alkynyl)benzaldimine intermediates **11**. The palladium-catalyzed cyclization of these iminoalkynes **11** in the presence of various commercially available aryl iodides furnished the targeted isoquinoline library **II**. On the basis of our previous results with this cyclization,[14a] aryl iodides

Table 1. Library Data for Compounds **12**{*1*−*42*}

compound	imine	alkyne	yield[a] (%)	purity[c] (%)
12{*1*}	**9**{*1*}	**10**{*1*}	75[b]	98
12{*2*}	**9**{*1*}	**10**{*2*}	40[b]	>99
12{*3*}	**9**{*1*}	**10**{*3*}	43[b]	96
12{*4*}	**9**{*1*}	**10**{*4*}	38	>99
12{*5*}	**9**{*1*}	**10**{*5*}	22	98
12{*6*}	**9**{*1*}	**10**{*6*}	56	99
12{*7*}	**9**{*1*}	**10**{*7*}	43	>99
12{*8*}	**9**{*2*}	**10**{*1*}	58	97
12{*9*}	**9**{*2*}	**10**{*2*}	23	>99
12{*10*}	**9**{*2*}	**10**{*3*}	56	>99
12{*11*}	**9**{*2*}	**10**{*4*}	40	>99
12{*12*}	**9**{*2*}	**10**{*5*}	38	>99
12{*13*}	**9**{*2*}	**10**{*6*}	26	94
12{*14*}	**9**{*3*}	**10**{*1*}	37	90
12{*15*}	**9**{*3*}	**10**{*2*}	38	97
12{*16*}	**9**{*3*}	**10**{*3*}	56	98
12{*17*}	**9**{*3*}	**10**{*4*}	36	>99
12{*18*}	**9**{*3*}	**10**{*5*}	51	97
12{*19*}	**9**{*3*}	**10**{*6*}	34	>99
12{*20*}	**9**{*3*}	**10**{*7*}	53	>99
12{*21*}	**9**{*4*}	**10**{*1*}	17	99
12{*22*}	**9**{*4*}	**10**{*2*}	18	90
12{*23*}	**9**{*4*}	**10**{*3*}	51	93
12{*24*}	**9**{*4*}	**10**{*4*}	20	89
12{*25*}	**9**{*4*}	**10**{*5*}	21	90
12{*26*}	**9**{*4*}	**10**{*6*}	40	92
12{*27*}	**9**{*4*}	**10**{*7*}	40	95
12{*28*}	**9**{*5*}	**10**{*1*}	30	>99
12{*29*}	**9**{*5*}	**10**{*2*}	44	97
12{*30*}	**9**{*5*}	**10**{*3*}	43	98
12{*31*}	**9**{*5*}	**10**{*5*}	33	>99
12{*32*}	**9**{*5*}	**10**{*6*}	31	>99
12{*33*}	**9**{*6*}	**10**{*1*}	22	>99
12{*34*}	**9**{*6*}	**10**{*2*}	62	>99
12{*35*}	**9**{*6*}	**10**{*3*}	64	93
12{*36*}	**9**{*6*}	**10**{*5*}	37	>99
12{*37*}	**9**{*6*}	**10**{*6*}	38	>99
12{*38*}	**9**{*6*}	**10**{*7*}	41	>99
12{*39*}	**9**{*7*}	**10**{*1*}	38	>99
12{*40*}	**9**{*7*}	**10**{*2*}	19	91
12{*41*}	**9**{*7*}	**10**{*3*}	23	92
12{*42*}	**9**{*7*}	**10**{*5*}	27	99

[a] Isolated yield (over two steps from **9**) after preparative HPLC. [b] Isolated yield (over two steps from **9**) after column chromatography. [c] UV purity determined at 214 nm after preparative HPLC.

bearing an electron-withdrawing group or groups were mostly chosen for this reaction. The carbonylative version of this reaction with selected iodides also gave the targeted isoquinoline derivatives.[14b] However, lower compound purities were obtained using this carbonylative process. The results for the synthesis of library **II** members obtained in 11−72% yields are summarized in Table 2.

It is worth mentioning that the attempted cyclization of **16** with the aryl iodides **14**{*2*, *3*, *4*, *6*, *7*, *11*} gave complex mixtures containing the *bis*-arylated product **18** (as determined by LC-MS) as one of the major byproduct (Scheme 3). Similar C−H arylation chemistry for thiophene derivatives has been previously reported.[19] Only in one case (**14**{***3***}) have we been able to isolate the desired monoarylated product **17** (R = 4-F) in good purity (92%) and 18% yield.

Our strategy for the construction of a third library of isoquinolines is outlined in Scheme 4. We planned to exploit the palladium-catalyzed iminoannulation[14e] of suitably functionalized internal alkynes to provide diversification. We speculated that the presence of alcohol functionality in the key intermediates **22** would be an ideal point for further

Table 2. Library Data for Compounds **15**{*1*−*31*}

compound	iminoalkyne	iodide	yield[a] (%)	purity[b] (%)
15{*1*}	**11**{*1*}	**14**{*1*}	41	94
15{*2*}	**11**{*1*}	**14**{*2*}	39	93
15{*3*}	**11**{*1*}	**14**{*3*}	45	86
15{*4*}	**11**{*1*}	**14**{*4*}	60	92
15{*5*}	**11**{*1*}	**14**{*5*}	36	92
15{*6*}	**11**{*1*}	**14**{*6*}	87	99
15{*7*}	**11**{*1*}	**14**{*7*}	51	91
15{*8*}	**11**{*1*}	**14**{*8*}	47	93
15{*9*}	**11**{*1*}	**14**{*9*}	28	93
15{*10*}	**11**{*1*}	**14**{*10*}	40	90
15{*11*}	**11**{*1*}	**14**{*11*}	48	91
15{*12*}	**11**{*2*}	**14**{*2*}	24	91
15{*13*}	**11**{*2*}	**14**{*3*}	24	88
15{*14*}	**11**{*2*}	**14**{*4*}	18	90
15{*15*}	**11**{*2*}	**14**{*6*}	14	98
15{*16*}	**11**{*2*}	**14**{*10*}	23	95
15{*17*}	**11**{*2*}	**14**{*12*}	27	90
15{*18*}	**11**{*2*}	**14**{*13*}	11	94
15{*19*}	**11**{*3*}	**14**{*1*}	72	96
15{*20*}	**11**{*3*}	**14**{*3*}	30	88
15{*21*}	**11**{*3*}	**14**{*4*}	50	86
15{*22*}	**11**{*3*}	**14**{*6*}	43	91
15{*23*}	**11**{*3*}	**14**{*7*}	44	95
15{*24*}	**11**{*3*}	**14**{*8*}	27	94
15{*25*}	**11**{*3*}	**14**{*10*}	30	93
15{*26*}	**11**{*3*}	**14**{*12*}	50	90
15{*27*}	**11**{*3*}	**14**{*13*}	32	87
15{*28*}	**11**{*1*}	**14**{*3*}	71	93
15{*29*}	**11**{*1*}	**14**{*11*}	55	77
15{*30*}	**11**{*1*}	**14**{*14*}	57	75
15{*31*}	**11**{*1*}	**14**{*15*}	26	87

[a] Isolated yield after preparative HPLC. [b] UV purity determined at 214 nm after preparative HPLC.

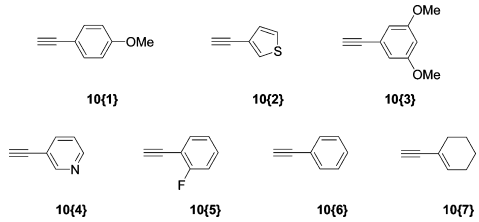
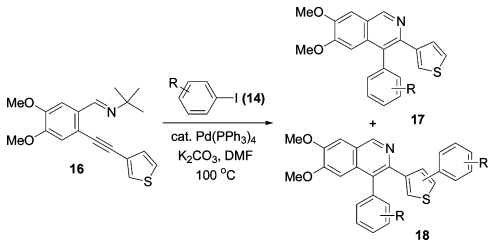


Figure 3. Terminal alkynes **10**{*1*−*7*}.

Scheme 3. Attempted Synthesis of 3-(3-Thienyl)isoquinolines



diversification, because such alcohols could be readily elaborated to more complex isoquinolines using a wide variety of commercially available carboxylic acid derivatives. Toward this goal, *N-tert*-butyl-2-iodobenzaldimine (**20**), prepared in two steps from commercially available 2-iodobenzyl alcohol (**19**), was treated with the appropriate internal alkynes **21** to furnish the targeted isoquinoline intermediates. These hydroxyl-bearing isoquinolines **22** were subsequently treated with a variety of acid chlorides, acid anhydrides and carbamoyl chlorides to furnish a diverse 38 member library of isoquinolines. The cyclic anhydrides **24**{*1*−*3*} were chosen to have a polar carboxylic acid functionality in the final molecules. The acylation reaction with acid chlorides and acid anhydrides proceeded smoothly. However, the reactions with carbamoyl chlorides were less efficient. For the reactions with acyl chlorides and anhydrides, the yields were 18−82% and 31−67%, respectively, while the yields

Scheme 4. Isoquinoline Library **III**

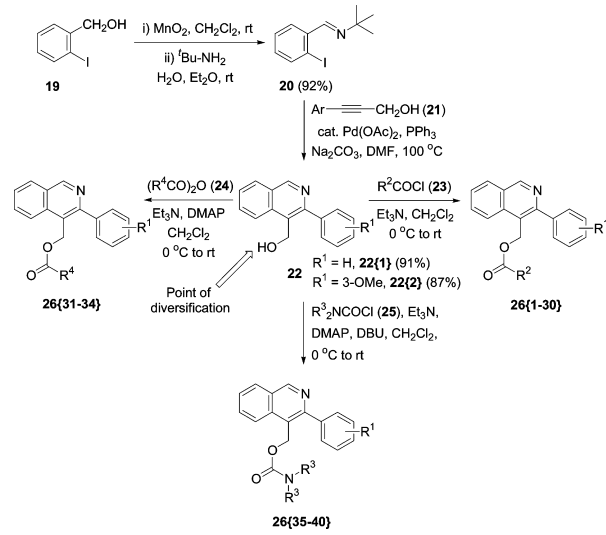


Table 3. Library Data for Compounds **26**{*1*−*38*}

compound	alcohol	acid derivative	yield[a] (%)	purity[c] (%)
26{*1*}	**22**{*1*}	**23**{*1*}	71[b]	>99
26{*2*}	**22**{*1*}	**23**{*2*}	82[b]	97
26{*3*}	**22**{*1*}	**23**{*3*}	69[b]	96
26{*4*}	**22**{*1*}	**23**{*4*}	44[b]	96
26{*5*}	**22**{*1*}	**23**{*6*}	55[b]	>99
26{*6*}	**22**{*1*}	**23**{*8*}	50	>99
26{*7*}	**22**{*1*}	**23**{*9*}	27	>99
26{*8*}	**22**{*1*}	**23**{*10*}	21	>99
26{*9*}	**22**{*1*}	**23**{*11*}	38	>99
26{*10*}	**22**{*1*}	**23**{*12*}	35	91
26{*11*}	**22**{*1*}	**23**{*13*}	66	>99
26{*12*}	**22**{*2*}	**23**{*1*}	55	97
26{*13*}	**22**{*2*}	**23**{*2*}	76	97
26{*14*}	**22**{*2*}	**23**{*3*}	67	>99
26{*15*}	**22**{*2*}	**23**{*4*}	49	97
26{*16*}	**22**{*2*}	**23**{*5*}	35	94
26{*17*}	**22**{*2*}	**23**{*6*}	48	>99
26{*18*}	**22**{*2*}	**23**{*7*}	23	>99
26{*19*}	**22**{*2*}	**23**{*8*}	51	>99
26{*20*}	**22**{*2*}	**23**{*11*}	66	>99
26{*21*}	**22**{*2*}	**23**{*12*}	18	>99
26{*22*}	**22**{*2*}	**23**{*13*}	69	>99
26{*23*}	**22**{*2*}	**23**{*14*}	49	>99
26{*24*}	**22**{*2*}	**23**{*15*}	47	>99
26{*25*}	**22**{*1*}	**24**{*1*}	31	>99
26{*26*}	**22**{*1*}	**24**{*2*}	34	>99
26{*27*}	**22**{*1*}	**24**{*3*}	59	>99
26{*28*}	**22**{*1*}	**24**{*4*}	43	99
26{*29*}	**22**{*2*}	**24**{*1*}	50	>99
26{*30*}	**22**{*2*}	**24**{*2*}	61	>99
26{*31*}	**22**{*2*}	**24**{*3*}	67	>99
26{*32*}	**22**{*1*}	**25**{*1*}	39	>99
26{*33*}	**22**{*1*}	**25**{*2*}	13	98
26{*34*}	**22**{*1*}	**25**{*4*}	22	>99
26{*35*}	**22**{*2*}	**25**{*1*}	34	>99
26{*36*}	**22**{*2*}	**25**{*2*}	35	97
26{*37*}	**22**{*2*}	**25**{*3*}	42	99
26{*38*}	**22**{*2*}	**25**{*4*}	42	96

[a] Isolated yield after preparative HPLC. [b] Isolated yield after column chromatography. [c] UV purity determined at 214 nm after preparative HPLC.

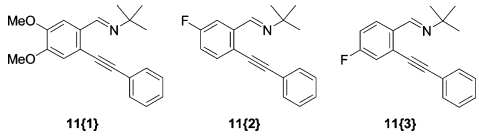


Figure 4. Iminoalkyne intermediates **11**{*1*−*3*}.

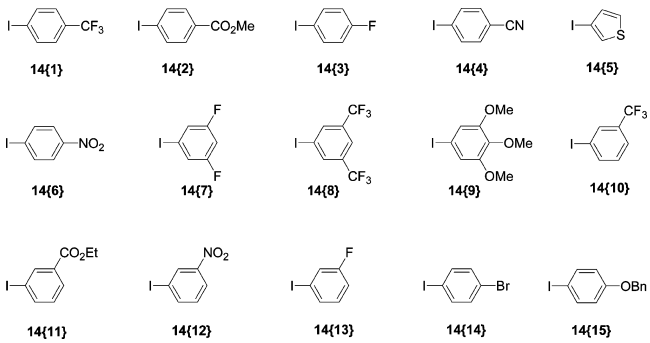


Figure 5. Aryl iodides **14**{*1*−*15*}.

for the carbamoyl chloride reactions were in the range of 13−42%. Among the 38 library members, 36 compounds have greater than 95% purity. The results for the library **III** members are summarized in Table 3.

Most of the desired isoquinoline library members were highly Lipinski compliant.[20] Overall, 55% of the library members are entirely compliant with Lipinski's rules and 45% had one violation. The most common violation was c log P (calculated by EPI Suite)[21] for which the average value for the entire library was 4.95. The molecular weight distribution, shown in Figure 6, indicates that all members of the library reside in the desirable molecular weight range (<500).[20]

In conclusion, a 111-member isoquinoline library has rapidly been constructed utilizing palladium- and copper-catalyzed reactions. Variation of the substituents on the isoquinoline scaffold has been achieved by the choice of the commercially available building blocks. These isoquinoline library members will be evaluated against various biological

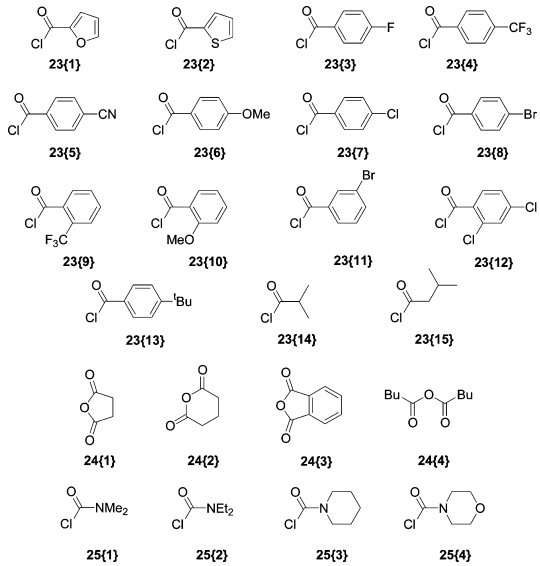


Figure 6. Acid chlorides, acid anhydrides, and carbamoyl chlorides.

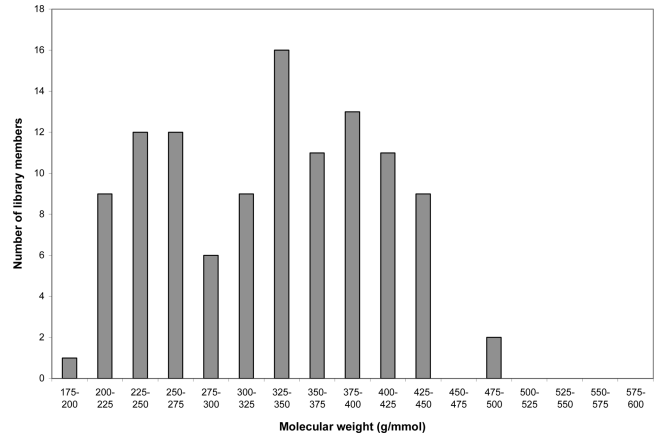


Figure 7. Molecular weight distribution for members of libraries **I**−**III**.

screens by the National Institutes of Health Molecular Library Screening Center Network.

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Supporting Information Available. Experimental details and characterization of a representative 20 library members, including full ^{1}H and ^{13}C NMR spectra and conditions for the high throughput liquid chromatography purification.This material is available free of charge via the Internet at http://pubs.acs.org.

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