Solution-Phase Synthesis of a Diverse Isocoumarin Library

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The solution-phase synthesis of a 167-member library of isocoumarins is described. The key intermediates for library generation, 4-iodoisocoumarins, are easily prepared by iodocyclization of the corresponding 2-(1-alkynyl)arenecarboxylate esters. The 4-iodoisocoumarins undergo palladium-catalyzed Sonogashira, Suzuki−Miyura, and Heck reactions to yield a diverse set of isocoumarins. Alternatively, isocoumarins, bearing hydroxyl or bromine functionalities, have been prepared by $ZnCl_2$- and $Pd(PPh_3)_4$-mediated cyclization of the corresponding *o*-iodobenzoic acid and appropriate terminal alkynes. The resulting isocoumarins were further diversified by derivatization of the hydroxyl or bromine groups. A small set of isoquinolinones were also prepared from the corresponding isocoumarins.

Introduction

Isocoumarins are an important class of naturally occurring lactones.[1] They exhibit a wide range of pharmacological properties, including antifungal, antitumor, antiallergic, antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and immunomodulatory activities.[2] Selected simple biologically active isocoumarins are shown in Figure 1. Among these, capillarin (**1a**), artemidin (**1b**) and cercophorin A (**5**) have been shown to possess antifungal activity.[3] Capillarin (**1a**) also acts as an insect antifeedant.[4] Oosponol (**2a**) and oospolactone (**2b**) exhibit antifungal as well as antibiotic activities.[5] Thunberginol A and B (**3a** and **3b**) are known for their antiallergic, antimicrobial, and immunomodulatory activities.[6] Cytogenin (**4a**) is known as an immunomodulator, antitumor and antiarthritic agent.[7] Reticulol (**4b**) also exhibits antitumor activity.[8] Diaporthin (**4c**) is a phytotoxin.[9] The synthetic isocoumarin NM-3 (**6**) has been found to be highly effective in the treatment of solid tumors and has entered clinical trials.[10] Due to substantial biological activity, our group has long been interested in the synthesis of isocoumarins and several new methodologies have been developed in our laboratories.[11] Many other useful methods have also been reported for the synthesis of the isocoumarin scaffold.[12−14]

High-throughput screening of selected chemical libraries, having a heterocyclic or carbocyclic ring at their core, is one of the most expeditious ways to search for useful medicinal activity. The heteroatoms improve binding and the rigid cyclic framework imparts rigidity, enhancing the selectivity and further improving the binding. In a continuation of our efforts to adapt heterocyclization chemistry to a high-throughput format,[15] we herein report the first solution phase library synthesis of isocoumarins using alkyne cyclization chemistry as the key step. As shown in Schemes 1−5, we have constructed a diverse 167 membered library of isocoumarins. The presence of the isocoumarin scaffold in both synthetic and natural biologically active compounds justifies the preparation of this discovery library of isocoumarins.[16] These compounds will be subjected to various high throughput screening (HTS) assays for their potential medicinal activity.

Result and Discussion

Our initial strategy for the library generation is outlined in Schemes 1 and 2. We planned to utilize the 4-iodoisocoumarins as key intermediates that can be efficiently prepared using our alkyne iodocyclization chemistry.[11a] Subsequent diversification by various palladium-catalyzed cross-coupling reactions should afford a diverse set of isocoumarins.

Initially, the 3,4-dimethoxybenzoic acid ester **8** was chosen as the starting material because it was envisioned that the methoxy groups would provide desired polarity in the resulting library members. Compound **8** was prepared from the corresponding commercially available 2-iodo-4,5-dimethoxybenzoic acid (**7**). Sonogashira coupling of **8** with appropriate terminal alkynes **12**{*1*−*4*} afforded the prerequisite starting materials **9**{*1*−*4*} for the iodocyclization chemistry (Scheme 1). Accordingly, a set of four 4-iodoisocoumarins **10**{*1*−*4*} (Figure 2) were efficiently prepared on a gram scale by electrophilic cyclization of the *o*-(1-alkynyl)benzoates **9**{*1*−*4*} using iodine monochloride.

According to the plan, the 4-iodoisocoumarins **10**{*1*−*4*} were used as key components for library generation and subsequently elaborated to produce a wide variety of isocoumarins. Thus, the palladium-catalyzed Sonogashira cross-coupling of the 4-iodoisocoumarins with various terminal acetylenes afforded isocoumarins **11**{*1*−*25*}. The

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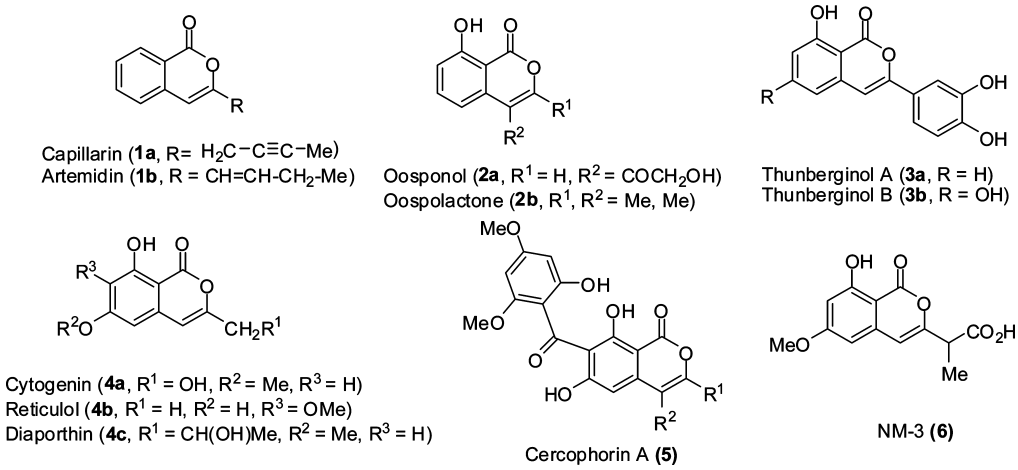
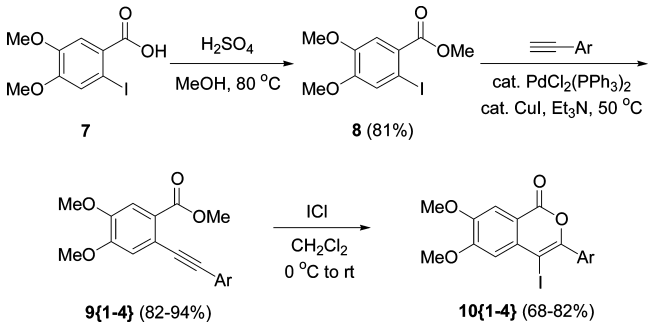
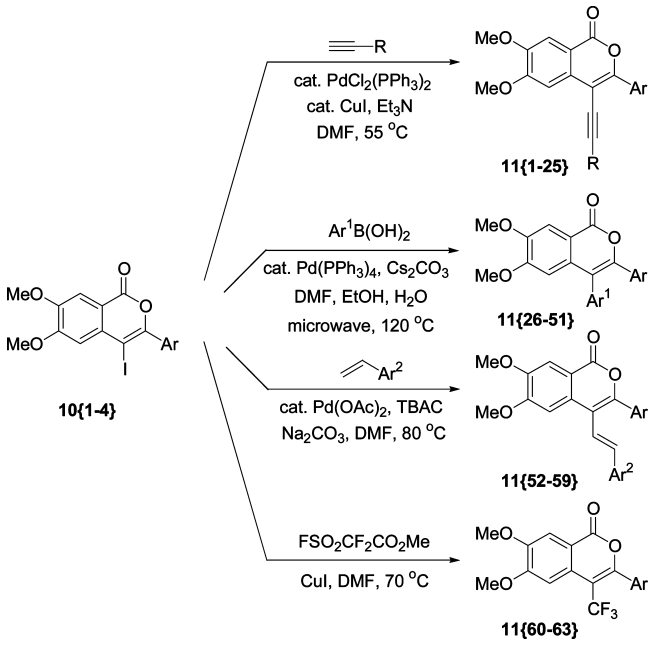


Figure 1. Selected biologically active isocoumarins.

Scheme 1. Synthesis of 4-Iodoisocoumarins



Scheme 2. Library Generation from the 4-Iodoisocoumarins



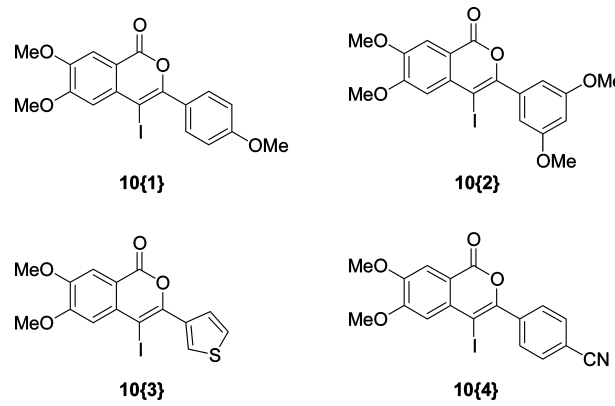


Figure 2. Key 4-Iodoisocoumarin Intermediates **10**{*1*−*4*}.

alkyne sublibrary (Figure 3) was chosen to include commercially available heteroatom- and heterocycle-containing (such as pyridine, thiophene and imidazole) alkynes that could provide hydrogen bond donors and/or acceptors. Mestranol was chosen as a representative steroid with the ability to diffuse readily across cell membranes.

Similarly, we obtained isocoumarins **11**{*26*−*51*} by the palladium-catalyzed Suzuki−Miyaura reaction of the iodoisocoumarin intermediates **10{1−4}** with various boronic acids (Figure 3). Commercially available boronic acids were chosen to include diverse functionality. Thus, boronic acids containing an indole scaffold, fluorine atoms, and polar functional groups were chosen in order to incorporate drug-like moieties into the resulting cross-coupling products. A brief examination of the reaction conditions suggested that microwave heating in these Suzuki−Miyaura cross-couplings is more effective than conventional heating and affords the desired isocoumarins in better yields. Microwave heating also allowed much shorter reaction times, which is desirable for library synthesis. However, the overall low yields in the Suzuki−Miyaura reactions are partially attributed to the instability of the lactone ring in the basic reaction medium used for cross-coupling, due to possible ring-opening of the lactone starting materials.[12n]

The isocoumarins **11**{*52*−*59*} have also been prepared by the Heck reaction of the 4-iodoisocoumarins. A small styrene sublibrary (Figure 3) for the Heck reaction was chosen to demonstrate vinylic functionalization as only a few functionally diverse styrenes were available from commercial sources. We avoided using well-known Michael acceptors, such as acrylates or acrylonitriles, in this Heck chemistry, since the resulting Heck products would also be good Michael acceptors and therefore undesirable for pharmaceutical applications. Because of the increasing importance of fluorine in pharmacologically active molecules because of its ability to enhance binding interactions and metabolic stability or to alter the physical or biological properties,[17] we have prepared a small set of (4-trifluo-

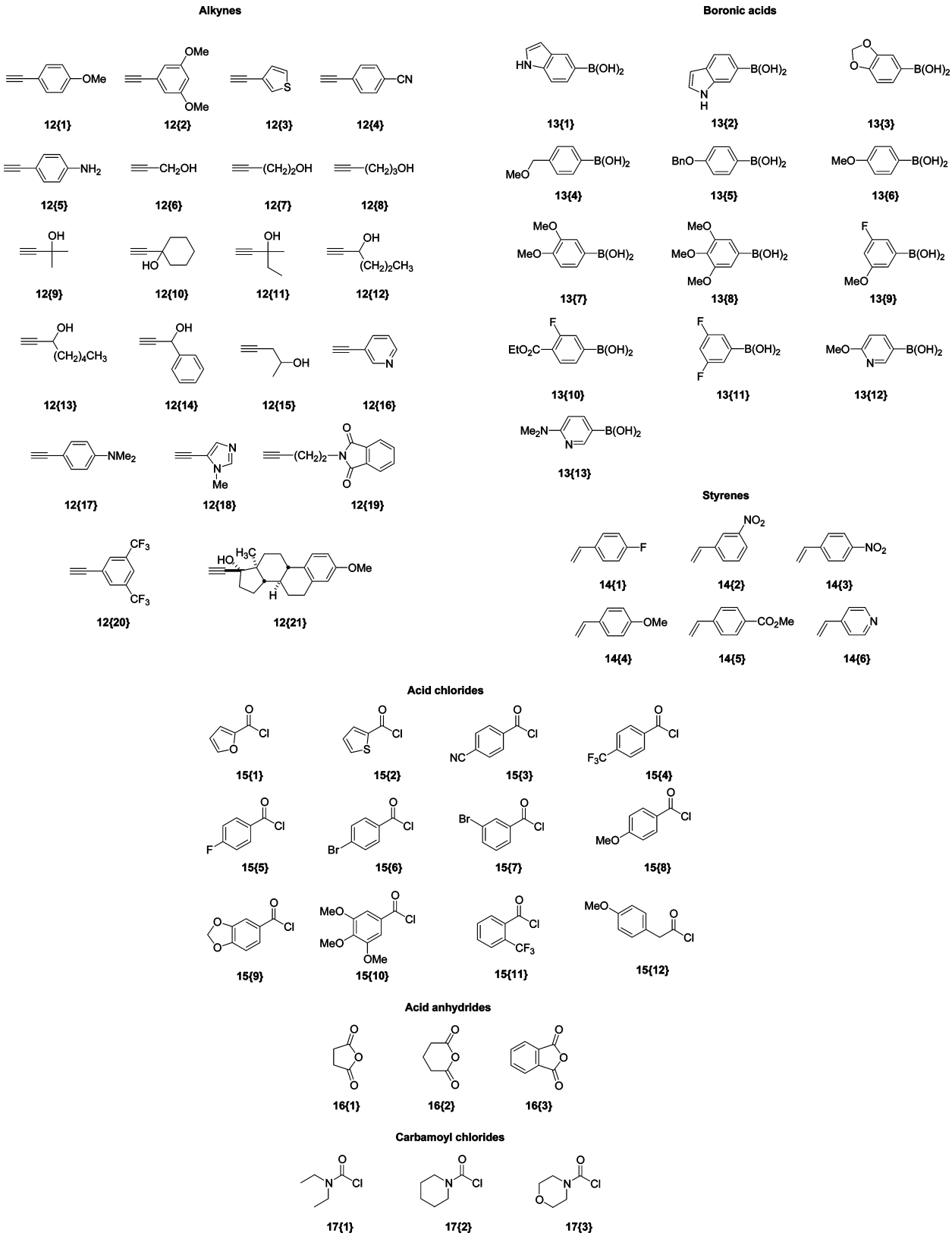


Figure 3. Diverse terminal alkynes **12**{*1*−*21*}, boronic acids **13**{*1*−*13*}, styrenes **14**{*1*−*6*}, acid chlorides **15**{*1*−*12*}, acid anhydrides **16**{*1*−*3*}, and carbamoyl chlorides **17**{*1*−*3*} used for library synthesis.

romethyl)isocoumarins **11**{*60*−*63*} from the 4-iodoisocoumarins. Generally, the strongly electron-withdrawing nature of the trifluoromethyl group significantly increases the binding interactions, thus improving oral bioavailability, as well as enhancing CNS penetration in certain cases.[18] We have also utilized several fluorinated building blocks, such as **12**{*20*}, **13**{*9*−*11*}, and **14**{*1*}, to incorporate fluorine atoms in our final library members. For synthesis of the trifluoromethyl analogs, the 4-iodoisocoumarins were treated with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate,[19] which generates the trifluoromethyl species in situ to provide compounds **11**{*60*−*63*}.

Table 1. Library Data for Compounds **11**{*1*−*63*}

compound	isocoumarin	reactant	method[a]	yield[b] (%)	purity[d] (%)	compound	isocoumarin	reactant	method[a]	yield[b] (%)	purity[d] (%)
11{*1*}	**10**{*1*}	**12**{*1*}	A	57[c]	>99	**11**{*33*}	**10**{*1*}	**13**{*12*}	B	17	93
11{*2*}	**10**{*1*}	**12**{*3*}	A	33	99	**11**{*34*}	**10**{*2*}	**13**{*3*}	B	32	98
11{*3*}	**10**{*1*}	**12**{*6*}	A	8	>99	**11**{*35*}	**10**{*2*}	**13**{*4*}	B	37	>99
11{*4*}	**10**{*1*}	**12**{*7*}	A	56	98	**11**{*36*}	**10**{*2*}	**13**{*5*}	B	20	98
11{*5*}	**10**{*1*}	**12**{*8*}	A	79	99	**11**{*37*}	**10**{*2*}	**13**{*9*}	B	30	96
11{*6*}	**10**{*1*}	**12**{*10*}	A	52	92	**11**{*38*}	**10**{*3*}	**13**{*2*}	B	31	99
11{*7*}	**10**{*1*}	**12**{*16*}	A	39	99	**11**{*39*}	**10**{*3*}	**13**{*3*}	B	47	95
11{*8*}	**10**{*1*}	**12**{*17*}	A	37	95	**11**{*40*}	**10**{*3*}	**13**{*4*}	B	20	99
11{*9*}	**10**{*1*}	**12**{*21*}	A	50	92	**11**{*41*}	**10**{*3*}	**13**{*5*}	B	46	98
11{*10*}	**10**{*2*}	**12**{*3*}	A	10	99	**11**{*42*}	**10**{*3*}	**13**{*6*}	B	85	>99
11{*11*}	**10**{*2*}	**12**{*7*}	A	42	>99	**11**{*43*}	**10**{*3*}	**13**{*7*}	B	15	96
11{*12*}	**10**{*2*}	**12**{*8*}	A	57	>99	**11**{*44*}	**10**{*3*}	**13**{*8*}	B	5	>99
11{*13*}	**10**{*2*}	**12**{*16*}	A	41	99	**11**{*45*}	**10**{*3*}	**13**{*10*}	B	38	98
11{*14*}	**10**{*2*}	**12**{*17*}	A	38	93	**11**{*46*}	**10**{*3*}	**13**{*11*}	B	24	96
11{*15*}	**10**{*3*}	**12**{*1*}	A	41	98	**11**{*47*}	**10**{*3*}	**13**{*12*}	B	13[c]	92
11{*16*}	**10**{*3*}	**12**{*7*}	A	67	96	**11**{*48*}	**10**{*3*}	**13**{*13*}	B	10	96
11{*17*}	**10**{*3*}	**12**{*8*}	A	61	96	**11**{*49*}	**10**{*4*}	**13**{*1*}	B	41	99
11{*18*}	**10**{*3*}	**12**{*16*}	A	51	>99	**11**{*50*}	**10**{*4*}	**13**{*2*}	B	43	97
11{*19*}	**10**{*3*}	**12**{*18*}	A	68	95	**11**{*51*}	**10**{*4*}	**13**{*6*}	B	21	98
11{*20*}	**10**{*3*}	**12**{*20*}	A	46	98	**11**{*52*}	**10**{*1*}	**14**{*1*}	C	58	93
11{*21*}	**10**{*4*}	**12**{*3*}	A	7	97	**11**{*53*}	**10**{*1*}	**14**{*2*}	C	25	96
11{*22*}	**10**{*4*}	**12**{*7*}	A	34	90	**11**{*54*}	**10**{*1*}	**14**{*3*}	C	21	98
11{*23*}	**10**{*4*}	**12**{*8*}	A	43	95	**11**{*55*}	**10**{*1*}	**14**{*4*}	C	46[c]	>99
11{*24*}	**10**{*4*}	**12**{*16*}	A	6	>99	**11**{*56*}	**10**{*1*}	**14**{*5*}	C	62	99
11{*25*}	**10**{*4*}	**12**{*19*}	A	36	99	**11**{*57*}	**10**{*1*}	**14**{*6*}	C	15	>99
11{*26*}	**10**{*1*}	**13**{*1*}	B	6	96	**11**{*58*}	**10**{*2*}	**14**{*1*}	C	50	>99
11{*27*}	**10**{*1*}	**13**{*2*}	B	32	99	**11**{*59*}	**10**{*3*}	**14**{*3*}	C	23	99
11{*28*}	**10**{*1*}	**13**{*3*}	B	39	>99	**11**{*60*}	**10**{*1*}		D	80[c]	98
11{*29*}	**10**{*1*}	**13**{*4*}	B	25	97	**11**{*61*}	**10**{*2*}		D	84[c]	97
11{*30*}	**10**{*1*}	**13**{*5*}	B	60	98	**11**{*62*}	**10**{*3*}		D	80[c]	>99
11{*31*}	**10**{*1*}	**13**{*9*}	B	42	96	**11**{*63*}	**10**{*4*}		D	65[c]	92
11{*32*}	**10**{*1*}	**13**{*10*}	B	29	95						

[a] Method A: alkyne (1.5 equiv), $PdCl_2(PPh_3)_2$ (3 mol %), CuI (2 mol %), 2:1 DMF/Et_3N, 55 °C. Method B: boronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), Cs_2CO_3 (2 equiv), 1.5:0.3:0.2 DMF/EtOH/H_2O, microwave irradiation, 120 °C. Method C: styrene (2 equiv), $Pd(OAc)_2$ (15 mol %), Na_2CO_3 (2.5 equiv), TBAC (1.1 equiv), DMF, 80 °C. Method D: $FSO_2CF_2CO_2Me$ (5 equiv), CuI (1 equiv), DMF, 70 °C. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. [d] UV purity determined at 214 nm after preparative HPLC.

Thus, a total of 63 compounds have been prepared in unoptimized yields from the 4-iodoisocoumarin scaffold.

Next, we utilized the reaction of 2-iodobenzoic acids with terminal alkynes in the presence of a $Pd(PPh_3)_4$-$ZnCl_2$-Et_3N system[12a] in DMF to produce another set of diverse isocoumarins **11**{*64*−*86*} (Scheme 3). We considered this reaction to be an attractive option for library synthesis, because it not only affords the final library members quite directly, but it also permits easy access to the isocoumarin scaffold containing handles that could be very useful for further modifications. Thus, the reaction of 2-iodobenzoic acid with appropriate terminal alkynes readily afforded the desired isocoumarins. The results are summarized in Table 2. We also briefly examined a similar method of isocoumarin synthesis from 2-iodobenzoic acid and terminal alkynes using 10% Pd/C, CuI, PPh_3, and Et_3N in ethanol.[12b] However, we found that the reaction employing the palladium−zinc chloride system afforded much cleaner reactions, yielding the desired products in better yield and purity. Benzoic acids **7**, **18**{*1*−*2*} and alkynes **12**{*7*−*10*} were chosen to maximize the utility of the resulting isocoumarin scaffold and allow for further derivatization of the embedded bromo or hydroxyl functionalities.

We have speculated previously that the presence of alcohol functionality in the isocoumarins would be an ideal point for further diversification, because such alcohols could be readily elaborated to more complex isocoumarins using a wide variety of commercially available carboxylic acid derivatives. Thus, isocoumarins **11**{*68*−*71*, *78*, *79*, *83*−*86*}, prepared in gram quantities for further derivatization, were subjected to an additional diversity step. Consequently, these hydroxyl-bearing isocoumarins were subjected to acylation reaction using various acid chlorides **15**{*1*−*12*}, acid anhydrides **16**{*1*−*3*}, and carbamoyl chlorides **17**{*1*−*3*} to generate a wide variety of isocoumarins **11**{*87*−*145*}. The

Table 2. Library Data for Compounds **11**{*64*−*86*}

compound	2-iodobenzoic acid	alkyne	yield[a] (%)	purity[c] (%)
11{*64*}	**18**{*1*}	**12**{*1*}	64[b]	92
11{*65*}	**18**{*1*}	**12**{*2*}	43	>99
11{*66*}	**18**{*1*}	**12**{*3*}	42	>99
11{*67*}	**18**{*1*}	**12**{*5*}	33[b]	>99
11{*68*}	**18**{*1*}	**12**{*7*}	68[b]	97
11{*69*}	**18**{*1*}	**12**{*8*}	67[b]	>99
11{*70*}	**18**{*1*}	**12**{*9*}	64[b]	>99
11{*71*}	**18**{*1*}	**12**{*10*}	51[b]	>99
11{*72*}	**18**{*1*}	**12**{*11*}	33	>99
11{*73*}	**18**{*1*}	**12**{*12*}	28	>99
11{*74*}	**18**{*1*}	**12**{*13*}	27	92
11{*75*}	**18**{*1*}	**12**{*14*}	31	92
11{*76*}	**18**{*1*}	**12**{*15*}	54[b]	>99
11{*77*}	**18**{*1*}	**12**{*17*}	23	95
11{*78*}	**7**	**12**{*7*}	52[b]	>99
11{*79*}	**7**	**12**{*8*}	56[b]	>99
11{*80*}	**7**	**12**{*9*}	51	98
11{*81*}	**7**	**12**{*12*}	35	97
11{*82*}	**7**	**12**{*15*}	39	>99
11{*83*}	**18**{*2*}	**12**{*7*}	42[b]	99
11{*84*}	**18**{*2*}	**12**{*8*}	41[b]	>99
11{*85*}	**18**{*2*}	**12**{*9*}	61[b]	90
11{*86*}	**18**{*2*}	**12**{*10*}	46[b]	>99

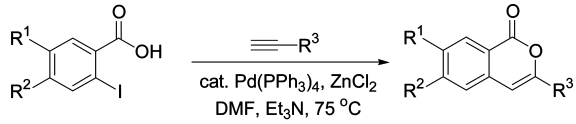
[a] Isolated yield after preparative HPLC. [b] Isolated yield after column chromatography. [c] UV purity determined at 214 nm after preparative HPLC.

Table 3. Library Data for Compounds **11**{*87*−*145*}

compound	isocoumarin	reactant	method[a]	yield[b] (%)	purity[d] (%)	compound	isocoumarin	reactant	method[a]	yield[b] (%)	purity[d] (%)
11{*87*}	**11**{*68*}	**15**{*1*}	A	70	>99	**11**{*117*}	**11**{*71*}	**15**{*6*}	A	21	>99
11{*88*}	**11**{*68*}	**15**{*2*}	A	66[c]	>99	**11**{*118*}	**11**{*78*}	**15**{*1*}	A	90[c]	>99
11{*89*}	**11**{*68*}	**15**{*3*}	A	59	>99	**11**{*119*}	**11**{*78*}	**15**{*2*}	A	21	>99
11{*90*}	**11**{*68*}	**15**{*4*}	A	59	>99	**11**{*120*}	**11**{*78*}	**15**{*3*}	A	65	>99
11{*91*}	**11**{*68*}	**15**{*5*}	A	49	>99	**11**{*121*}	**11**{*78*}	**15**{*4*}	A	45	>99
11{*92*}	**11**{*68*}	**15**{*6*}	A	74	>99	**11**{*122*}	**11**{*78*}	**15**{*5*}	A	60	>99
11{*93*}	**11**{*68*}	**15**{*7*}	A	74	>99	**11**{*123*}	**11**{*78*}	**15**{*7*}	A	40	>99
11{*94*}	**11**{*68*}	**15**{*8*}	A	75	99	**11**{*124*}	**11**{*78*}	**15**{*12*}	A	14	95
11{*95*}	**11**{*68*}	**15**{*9*}	A	76	>99	**11**{*125*}	**11**{*79*}	**15**{*1*}	A	58[c]	99
11{*96*}	**11**{*68*}	**15**{*10*}	A	55	>99	**11**{*126*}	**11**{*79*}	**15**{*2*}	A	80	>99
11{*97*}	**11**{*68*}	**15**{*11*}	A	77	>99	**11**{*127*}	**11**{*79*}	**15**{*3*}	A	58	>99
11{*98*}	**11**{*69*}	**15**{*1*}	A	64[c]	>99	**11**{*128*}	**11**{*79*}	**15**{*4*}	A	79	>99
11{*99*}	**11**{*69*}	**15**{*3*}	A	88	>99	**11**{*129*}	**11**{*79*}	**15**{*5*}	A	72	>99
11{*100*}	**11**{*69*}	**15**{*4*}	A	89	>99	**11**{*130*}	**11**{*79*}	**15**{*6*}	A	67	99
11{*101*}	**11**{*69*}	**15**{*5*}	A	45	>99	**11**{*131*}	**11**{*79*}	**15**{*7*}	A	82	>99
11{*102*}	**11**{*69*}	**15**{*8*}	A	52	>99	**11**{*132*}	**11**{*79*}	**15**{*9*}	A	20	97
11{*103*}	**11**{*69*}	**15**{*9*}	A	76	>99	**11**{*133*}	**11**{*79*}	**15**{*10*}	A	8	99
11{*104*}	**11**{*69*}	**15**{*10*}	A	45	>99	**11**{*134*}	**11**{*68*}	**16**{*1*}	B	86[c]	>99
11{*105*}	**11**{*69*}	**15**{*11*}	A	62	>99	**11**{*135*}	**11**{*68*}	**16**{*2*}	B	42	99
11{*106*}	**11**{*70*}	**15**{*1*}	A	37	94	**11**{*136*}	**11**{*68*}	**16**{*3*}	B	68	98
11{*107*}	**11**{*70*}	**15**{*2*}	A	37	97	**11**{*137*}	**11**{*69*}	**16**{*1*}	B	39	>99
11{*108*}	**11**{*70*}	**15**{*3*}	A	35	97	**11**{*138*}	**11**{*69*}	**16**{*2*}	B	17	>99
11{*109*}	**11**{*70*}	**15**{*4*}	A	38	99	**11**{*139*}	**11**{*78*}	**16**{*2*}	B	61	>99
11{*110*}	**11**{*70*}	**15**{*5*}	A	33	>99	**11**{*140*}	**11**{*79*}	**16**{*1*}	B	68	>99
11{*111*}	**11**{*70*}	**15**{*6*}	A	38	>99	**11**{*141*}	**11**{*79*}	**16**{*2*}	B	67	>99
11{*112*}	**11**{*71*}	**15**{*1*}	A	36	>99	**11**{*142*}	**11**{*68*}	**17**{*1*}	C	17	>99
11{*113*}	**11**{*71*}	**15**{*2*}	A	23	98	**11**{*143*}	**11**{*68*}	**17**{*3*}	C	12	>99
11{*114*}	**11**{*71*}	**15**{*3*}	A	29	>99	**11**{*144*}	**11**{*69*}	**17**{*3*}	C	13	>99
11{*115*}	**11**{*71*}	**15**{*4*}	A	14	>99	**11**{*145*}	**11**{*78*}	**17**{*2*}	C	37	95
11{*116*}	**11**{*71*}	**15**{*5*}	A	20	>99						

[a] Method A: RCOCl (1.3 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to rt. Method B: $(RCO_2)_2O$ (4 equiv), toluene, 110 °C. Method C: R_2NCOCl (2 equiv), cat. DMAP, Et_3N (3 equiv), CH_2Cl_2, 0 °C to 50 °C. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. [d] UV purity determined at 214 nm after preparative HPLC.

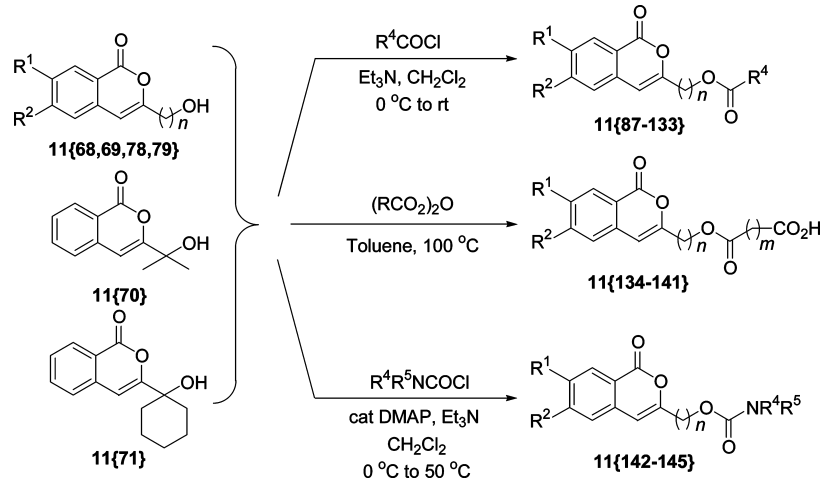
Scheme 3. Synthesis of 3-Substituted Isocoumarins



cyclic anhydrides **16**{*1*−*3*} were chosen to have a polar carboxylic acid functionality present in the final molecule. In general, the reactions with carbamoyl chlorides were less efficient than those with acid chlorides and acid anhydrides. Although triethylamine was found to be sufficient in most acylation reactions with acid chlorides, DMAP was used in combination with triethylamine in some instances, especially for the more sluggish reactions. However, as shown in Table 3, the products were obtained in excellent purity (>99%) in most cases for this diversification of the hydroxyl functionality.

To further expand the diversity present in the aromatic core of the isocoumarin ring, 7-bromoisocoumarins **11**{*83*−*86*} were subsequently modified using palladium-catalyzed cross-coupling reactions to generate the more complex isocoumarins **11**{*146*−*167*} (Scheme 5). The new isocoumarins, prepared by further diversification through Sonogashira, Suzuki−Miyaura and Heck reactions, are summarized in Table 4.

Scheme 4. Diversification of the 3-Substituted Isocoumarins



Scheme 5. Synthesis of 7-Substituted Isocoumarins by Further Diversification

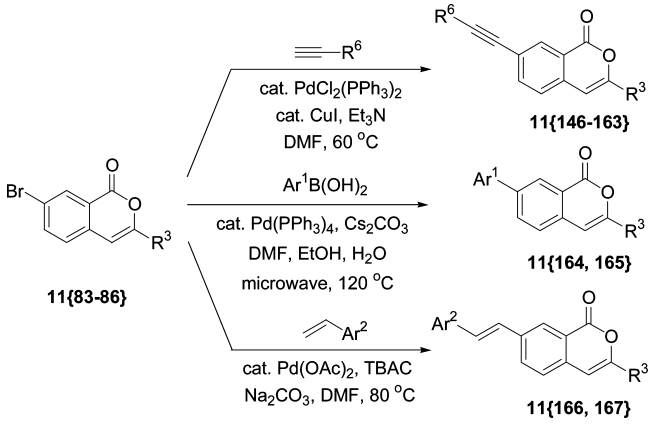
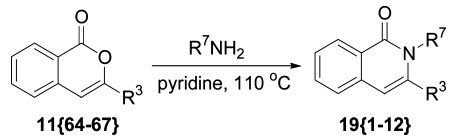


Table 4. Library Data for Compound **11**{*146*−*167*}

compound	isocoumarin	reactant	method[a]	yield[b] (%)	purity[c] (%)
11{*146*}	**11**{*83*}	**12**{*2*}	A	80	>99
11{*147*}	**11**{*83*}	**12**{*3*}	A	79	>99
11{*148*}	**11**{*83*}	**12**{*17*}	A	69	95
11{*149*}	**11**{*83*}	**12**{*18*}	A	45	92
11{*150*}	**11**{*83*}	**12**{*19*}	A	62	99
11{*151*}	**11**{*84*}	**12**{*2*}	A	77	>99
11{*152*}	**11**{*84*}	**12**{*3*}	A	58	91
11{*153*}	**11**{*84*}	**12**{*10*}	A	70	>99
11{*154*}	**11**{*84*}	**12**{*16*}	A	14	92
11{*155*}	**11**{*84*}	**12**{*17*}	A	54	>99
11{*156*}	**11**{*84*}	**12**{*18*}	A	59	96
11{*157*}	**11**{*84*}	**12**{*19*}	A	21	>99
11{*158*}	**11**{*85*}	**12**{*2*}	A	58	>99
11{*159*}	**11**{*85*}	**12**{*3*}	A	53	>99
11{*160*}	**11**{*85*}	**12**{*18*}	A	58	94
11{*161*}	**11**{*85*}	**12**{*19*}	A	58	>99
11{*162*}	**11**{*86*}	**12**{*18*}	A	45	99
11{*163*}	**11**{*86*}	**12**{*19*}	A	58	99
11{*164*}	**11**{*83*}	**13**{*1*}	B	47	>99
11{*165*}	**11**{*86*}	**13**{*1*}	B	10	>99
11{*166*}	**11**{*84*}	**14**{*2*}	C	26	>99
11{*167*}	**11**{*86*}	**14**{*1*}	C	69	>99

[a] Method A: alkyne (1.5 equiv), $PdCl_2(PPh_3)_2$ (3 mol %), CuI (2 mol %), 3:1 DMF/Et_3N, 60 °C. Method B: boronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), Cs_2CO_3 (2 equiv), 1.5:0.3:0.2 DMF/EtOH/H_2O, microwave irradiation, 120 °C. Method C: styrene (2 equiv), $Pd(OAc)_2$ (15 mol %), Na_2CO_3 (2.5 equiv), TBAC (1 equiv), DMF, 80 °C. [b] Isolated yield after preparative HPLC. [c] UV purity determined at 214 nm after preparative HPLC.

Scheme 6. Conversion of Isocoumarins to Isoquinolin-1-ones



3-Aryl-substituted isocoumarins **11**{*64*−*67*}, prepared previously from 2-iodobenzoic acid **7**, were used to generate a small set of isoquinolinones by reaction with various amines (Scheme 6).[20] The isoquinolinone subunit is present in a large number of natural products (e.g., narciclasine, pancratistatin, lycoricidine, etc.) and its derivatives possess a broad spectrum of biological activities, including NK3 antagonists and inhibitors of potassium channels, Rho-kinase, NR5A1 and PARP-2.[21] For the generation of the isoquinolinone library, commercially available amines (Figure 4) were chosen that contain polar functionality or heterocycles that would provide compounds with potentially attractive drug-like features. Cleaner reactions were achieved with amines containing hydroxyl functionality (i.e., for amines **20**{*1*−*4*}). The resulting alcohols are attractive intermediates for expanding the isoquinolinone library via subsequent chemical modification. As summarized in Table 5, we have obtained the desired isoquinolinone products in high purity (>90%) in unoptimized yields in the range of 16−70%.

Table 5. Library Data for Compounds **19**{*1*−*12*}

compound	isocoumarin	amine	yield[a](%)	purity[c] (%)
19{*1*}	**11**{*64*}	**20**{*1*}	46[b]	>99
19{*2*}	**11**{*64*}	**20**{*2*}	50[b]	>99
19{*3*}	**11**{*64*}	**20**{*5*}	57	>99
19{*4*}	**11**{*64*}	**20**{*6*}	54	>99
19{*5*}	**11**{*64*}	**20**{*7*}	70	95
19{*6*}	**11**{*64*}	**20**{*8*}	29	97
19{*7*}	**11**{*65*}	**20**{*1*}	63	>99
19{*8*}	**11**{*65*}	**20**{*2*}	64	96
19{*9*}	**11**{*66*}	**20**{*1*}	16	92
19{*10*}	**11**{*66*}	**20**{*3*}	24	96
19{*11*}	**11**{*67*}	**20**{*3*}	25	>99
19{*12*}	**11**{*67*}	**20**{*4*}	26	90

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

Most of the desired isocoumarin library members were highly Lipinski compliant.[22] Overall, 80% of the library members are entirely compliant with Lipinski's rules, 18% had one violation and 2% had two or more violations. The most common violation was c log P (calculated by EPI Suite)[23] for which the average value for the entire library was around 4.0. The molecular weight distribution, shown in Figure 5, indicates that almost all of the members of the library reside in the desirable molecular weight range (<500).[22]

In conclusion, we have efficiently constructed a 167-member library of isocoumarins with high purity (>90%). Our emphasis on high compound purity partially contributed to the lower yields in some instances. A couple of isocoumarins have also been converted to the corresponding isoquinolin-1-ones. These library members will be evaluated against various biological screens by the

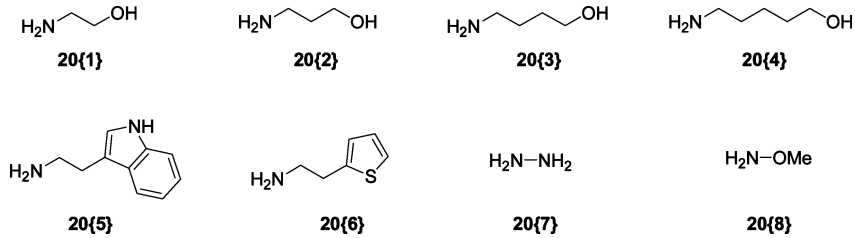


Figure 4. Diverse amines **20**{*1*−*8*} used for isoquinolin-1-one library synthesis.

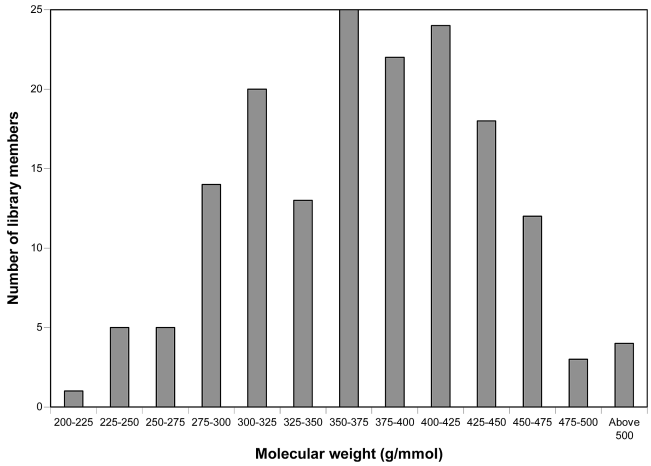


Figure 5. Molecular weight distribution of library members.

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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