Parallel Liquid-Phase Synthesis of Benzopyrano[2,3-*d*]pyrimidine Libraries

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Introduction. Many derivatives of 2-iminocoumarin are applied as luminescence indicators[1] or laser dyes;[2−4] they are also known as biologically active compounds.[5−7] Furthermore, structural features of the 2-iminopyrane cycle cause unusual reactivity of these compounds.[8,9] Most the reported transformations affect directly the iminopyrane cycle, and the imino group is the main target for nucleophilic and electrophilic attacks in many cases. Furthermore, the imino group of these compounds can contain other functional groups, which can participate in such interactions. Thus, vicinal arrangement of the imino and amide nucleophilic groups in 2-iminocoumarin-3-(thio)carboxoamides **4**, **5** produces a great opportunity to utilize these compounds as building blocks to construct different heterocyclic systems. In the course of this work, we apply the reactivity of 2-iminocoumarin-3-(thio)carboxoamides **4**, **5** for a facile liquid-phase parallel synthesis of diverse benzopyrano[2,3-*d*]pyrimidine libraries.

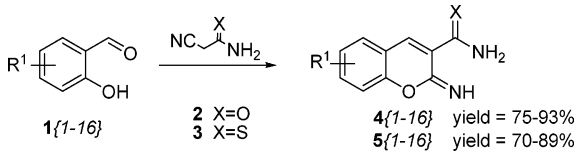
Initially, 2-aryl-3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-ones were synthesized by O'Callahan,[9,10] and some of them were recognized to exhibit in vivo antitumor activity in mice with P388 lymphocytic leukemia. More recently,[7] a series of substituted benzopyrano[2,3-*d*]pyrimidines were tested for cytotoxic activity against a panel of cancer cell lines, and a number of them were shown to cause a significant perturbation in cell cycle kinetics. Thus, in this work, we present application of improved conditions for the reaction of 2-iminocoumarin-3-(thio)carboxoamides **4**, **5** with aromatic aldehydes, leading to different substituted benzopyrano[2,3-*d*]pyrimidines. To increase the diversity of such derivatives, we propose also facile protocols for S- and O-alkylation of this scaffold.

Results and Discussion. All starting 2-imino-R[1]-coumarin-3-carboxamides **4**{*1*−*16*} and 2-imino-R[1]-coumarin-3-thioamides **5**{*1*−*16*} were obtained by interaction of salicylic aldehydes **1**{*1*−*16*} (Table 1) with cyanoacetamide **2** and its thio analogue **3** (Scheme 1) following the known procedure[10−12] using isopropyl alcohol as the solvent. It is known that the obtained compounds **4**, **5** in DMSO-d_6 are in equilibrium with their isomeric forms that result from the opening of the 2-iminobenzopyran ring.[10] However, in solutions of $CDCl_3$, they exist exclusively in the cyclic form (Scheme 1); therefore, they could be characterized by NMR spectroscopy as individual compounds. In ^{1}H NMR spectra of solutions 4, 5 in $CDCl_3$, a singlet of the imino group proton is observed at 7.79−7.89 ppm, and broad signals of the amide (thioamide) group magnetically nonequivalent protons are shown in the range of 8.05−8.27 and 12.66−12.80 ppm. This fact may be caused by inter- or intramolecular hydrogen bond formation between the amide proton and the imino group of the obtained compounds.

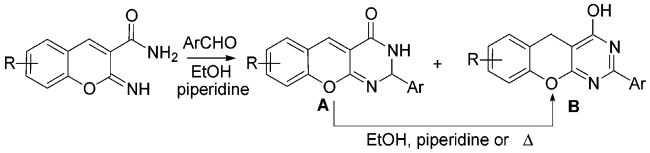
Table 1. Salicylic Aldehydes, **1**{*1*−*16*}

entry	R^1	entry	R^1
1{*1*}	H	**1**{*9*}	5-F
1{*2*}	3-OMe	**1**{*10*}	5-Br
1{*3*}	4-OMe	**1**{*11*}	4-OH
1{*4*}	5-OMe	**1**{*12*}	3-OEt
1{*5*}	3-Me	**1**{*13*}	3-OMe-5-Br
1{*6*}	5-Me	**1**{*14*}	5-COOMe
1{*7*}	5-Et	**1**{*15*}	5,6-benzo
1{*8*}	5-Cl	**1**{*16*}	3-OH-5-*t*-Bu

Scheme 1. Synthesis of 2-Iminocoumarin-3-(thio)carboxamides **4** and **5**



Scheme 2. Interaction of 2-Iminocoumarin-3-carboxamides with Aldehydes[9,10]



Previously, O'Callaghan[9,10] described the interaction of 2-iminocoumarin-3-carboxamides with aldehydes that resulted in a mixture of isomers **A** and **B** (Scheme 2). They were separated due to their different solubility in boiling ethanol. At the same time, the yields of each compound were very low. The ratio of isomers depended on the structure of the starting aldehyde and the reflux time in the ethanol. Thus, this protocol for the synthesis of benzopyrano[2,3-*d*]pyrimidine-4-ones is unsuitable for designing combinatorial libraries.

To improve the method of preparation of these fused heterocycles for application in automated parallel synthesis, instead of ethanol we used high-boiling solvents as the reaction media (*n*-butanol, *n*-pentanol). Under high reaction temperature, we expected to obtain **B** as the only product of the thermodynamic reaction . Indeed, carrying out the condensation in these solvents led to formation of isomers

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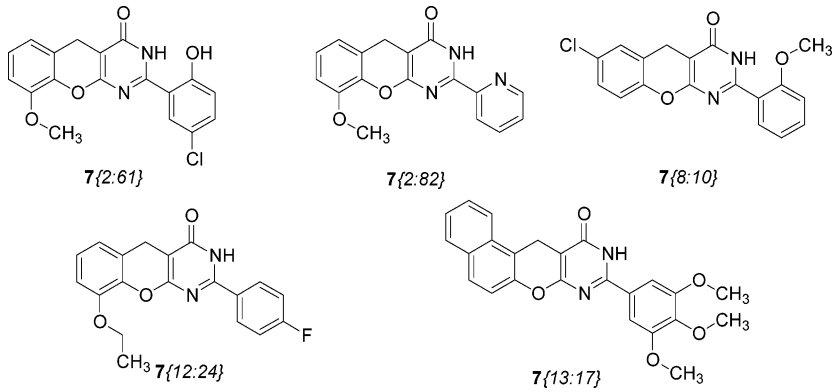
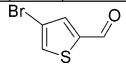
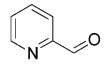


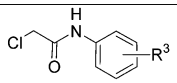
Figure 1. Examples of synthesized 2-aryl-3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-ones **7**.

Table 2. Aldehydes, **6**{*1*−*82*}

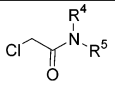
Aromatic aldehydes, **6***{1-78}*			
entry	R^2	entry	R^2
6*{1}*	H	**6***{40}*	2,4-diMe
6*{2}*	3-OH	**6***{41}*	3,5-diOMe-4-OH
6*{3}*	4-OH	**6***{42}*	4-Et
6*{4}*	2-Me	**6***{43}*	4-*i*-Pr
6*{5}*	3-Me	**6***{44}*	3-Br
6*{6}*	4-Me	**6***{45}*	4-Br
6*{7}*	2-Cl	**6***{46}*	2,4-diCl
6*{8}*	3-Cl	**6***{47}*	4-CF_3
6*{9}*	4-Cl	**6***{48}*	4-COOH
6*{10}*	2-OMe	**6***{49}*	4-COOMe
6*{11}*	3-OMe	**6***{50}*	4-CN
6*{12}*	4-OMe	**6***{51}*	4-SMe
6*{13}*	2,3-diOMe	**6***{52}*	4-NMe_2
6*{14}*	3,4-diOMe	**6***{53}*	2-OH
6*{15}*	2,4-diOMe	**6***{54}*	2-OH-3-OMe
6*{16}*	2,5-diOMe	**6***{55}*	2-OH-4-OMe
6*{17}*	3,4,5-triOMe	**6***{56}*	2-OH-5-OMe
6*{18}*	2,3,4-triOMe	**6***{57}*	2-OH-3-Me
6*{19}*	2,4,5-triOMe	**6***{58}*	2-OH-5-Me
6*{20}*	3-OMe-4-OH	**6***{59}*	2-OH-5-Et
6*{21}*	2-OMe-5,6-	**6***{60}*	2-OH-3-Cl
6*{22}*	2-F	**6***{61}*	2-OH-5-Cl
6*{23}*	3-F	**6***{62}*	2-OH-3,5-diCl
6*{24}*	4-F	**6***{63}*	2-OH-5-F
6*{25}*	3,4-diF	**6***{64}*	2-OH-3,5-diF
6*{26}*	3-Br-4-F	**6***{65}*	2-OH-4-O-benzyl
6*{27}*	3-O-*n*-Pr	**6***{66}*	2-OH-3-OMe-5-
6*{28}*	4-O-*n*-Pr	**6***{67}*	2-OH-5-Br
6*{29}*	3-O-*i*-Pr	**6***{68}*	2-OH-3,5-diBr
6*{30}*	4-O-*i*-Pr	**6***{69}*	2-OH-3-allyl
6*{31}*	4-$OCHF_2$	**6***{70}*	2-OH-3-OEt
6*{32}*	3-O-allyl	**6***{71}*	2-OH-5-COOMe
6*{33}*	4-O-allyl	**6***{72}*	2-OH-5-COOEt
6*{34}*	4-OEt	**6***{73}*	2-OH-3,5-di(*t*-
6*{35}*	3-OEt-4-OH	**6***{74}*	2-OH-5,6-benzo
6*{36}*	3-OH-4-OMe	**6***{75}*	2-OH-3-OH
6*{37}*	2-OMe-5-Br	**6***{76}*	2-OH-4-OH
6*{38}*	3-OMe-4-OEt	**6***{77}*	2-OH-3-Me-4-OH
6*{39}*	3-Br-4-OMe	**6***{78}*	2-OH-3-OH-5-*t*-
Heteroaromatic aldehydes, **6***{79-82}*			
6*{79}*		**6***{81}*	
6*{80}*		**6***{82}*	

B almost exclusively (monitored by HPLC). In the final protocol, we chose to apply *n*-pentanol for 2-iminocoumarin-3-carboxamides **4**{*1*−*16*} for solubility reasons and *n*-butanol for 2-iminocoumarin-3-thioamides **5**{*1*−*16*}. In this manner, the products **7**{*1*−*936*} and **8**{*1*−*724*} (Tables 1, 2 and Scheme 3) were obtained as crystalline precipitates without impurities of isomers **A**. In ^{1}H NMR spectra, a singlet of the methylene group protons in the fifth position is observed

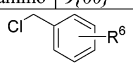
Table 3. Diversity of *N*-Arylchloroacetamides, **9**{*1*−*56*}, *N*-Alkylchloroacetamides, **9**{*56*−*60*}, Benzyl Chlorides, **9**{*61*−*80*}, and Alkyl Iodides, **9**{*81*−*84*}



entry	R^3	entry	R^3
9*{1}*	H	**9***{29}*	3,5-diMeO
9*{2}*	2-Me	**9***{30}*	2,4-diMe
9*{3}*	3-Me	**9***{31}*	3,5-diMe
9*{4}*	4-Me	**9***{32}*	3,4-diMe
9*{5}*	2-Cl	**9***{33}*	2,6-diMe
9*{6}*	3- Cl	**9***{34}*	2,5-diMe
9*{7}*	4- Cl	**9***{35}*	2,3,4-triMeO
9*{8}*	2-F	**9***{36}*	2-F,4-Br
9*{9}*	3-F	**9***{37}*	3-Me,4-F
9*{10}*	4-F	**9***{38}*	2-Me, 5-Cl
9*{11}*	2-CF3	**9***{39}*	2-Me, 4-Et2N
9*{12}*	3-CF3	**9***{40}*	2-Me, 5-F
9*{13}*	2,4-diF	**9***{41}*	3-Me,4-Br
9*{14}*	2,5-diF	**9***{42}*	2-MeO,5-Cl
9*{15}*	3,4-diF	**9***{43}*	2-MeO,5-Me
9*{16}*	2-Et	**9***{44}*	2,4-diMeO, 5-Cl
9*{17}*	3-Et	**9***{45}*	3-Cl, 4-MeO
9*{18}*	4-Et	**9***{46}*	2-Cl,4-F
9*{19}*	3-Ac	**9***{47}*	3-Cl,4-F
9*{20}*	4-Ac	**9***{48}*	4-Br
9*{21}*	2-MeO	**9***{49}*	3-MeS
9*{22}*	3-MeO	**9***{50}*	2-CF3, 4-Cl
9*{23}*	4-MeO	**9***{51}*	4-i-Pr
9*{24}*	2-EtO	**9***{52}*	4-COOMe
9*{25}*	4-EtO	**9***{53}*	3,4-Methylenedioxy
9*{26}*	2,4-diMeO	**9***{54}*	1,4-Benzodioxane
9*{27}*	2,5-diMeO	**9***{55}*	4-COOH
9*{28}*	3,4-diMeO	**9***{56}*	3-COOH



entry	R^4-N-R^5	entry	R^4-N-R^5
9*{57}*	H	**9***{59}*	morpholine-1-yl
9*{58}*	N,N-diethylamino	**9***{60}*	piperidin-1-yl



entry	R^6	entry	R^6
9{6}*{1}*	H	**9{7}***{1}*	3-CF3
9{6}*{2}*	2-Me	**9{7}***{2}*	3-MeO
9{6}*{3}*	3-Me	**9{7}***{3}*	4-Et
9{6}*{4}*	4-Me	**9{7}***{4}*	2-F-6-Cl
9{6}*{5}*	2-Cl	**9{7}***{5}*	4-F-2-Cl
9{6}*{6}*	3- Cl	**9{7}***{6}*	2,4-diMe
9{6}*{7}*	4- Cl	**9{7}***{7}*	2,5-diMe
9{6}*{8}*	2-F	**9{7}***{8}*	4-Br
9{6}*{9}*	3-F	**9{7}***{9}*	3-Br
9{7}*{0}*	4-F	**9{8}***{0}*	2,4,6-diMe
Alkyl iodides			
entry	Alk	entry	Alk
9*{81}*	Me	**9***{83}*	n-Pr
9*{82}*	Et	**9***{84}*	n-Bu

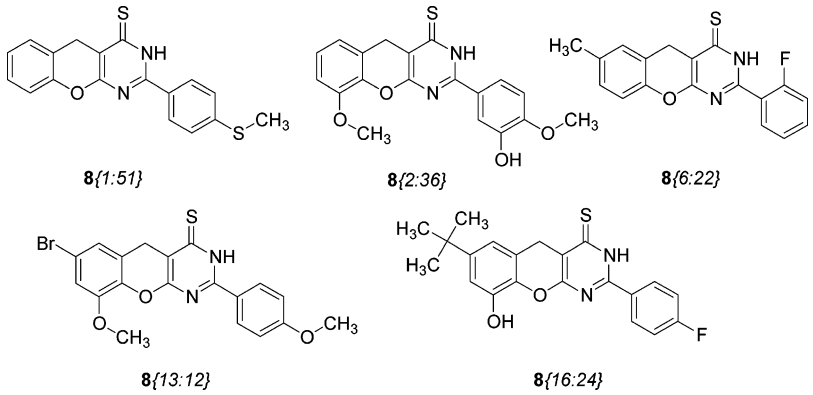


Figure 2. Examples of synthesized 2-aryl-3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-thiones **8**.

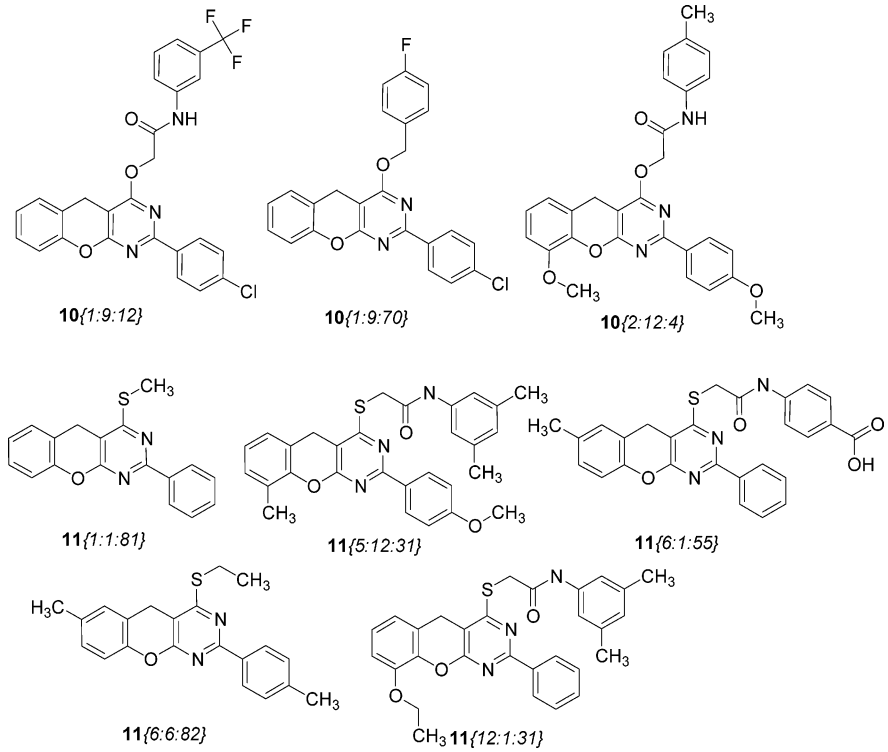
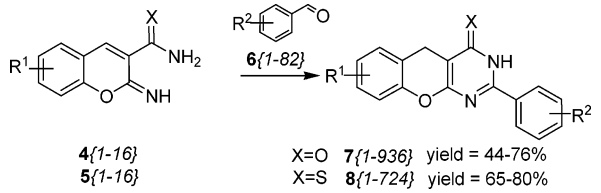
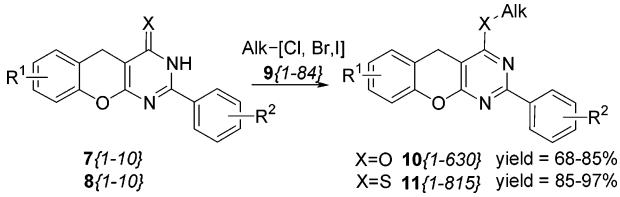


Figure 3. Examples of synthesized 2-aryl-3-alkyl-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-ones **10** and 4-S-substituted 2-aryl-5*H*-benzopyrano-[2,3-*d*]pyrimidines **11**.

Scheme 3. Preparation of 2-Aryl-3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-one **7**{*1*−*936*} and **8**{*1*−*724*} Combinatorial Libraries



Scheme 4. Preparation of Combinatorial Libraries of 4-Alkyloxy-2-aryl-5*H*-benzopyrano[2,3-*d*]pyrimidines **10**{*1*−*630*} and 4-S-Substituted 2-Aryl-5*H*-benzopyrano[2,3-*d*]pyrimidines **11**{*1*−*815*}



at 3.70−3.80 ppm and a broad singlet of a pyrimidine NH group is at 12.30−12.95 ppm.

Several representative structures of the 936-member library of 2-aryl-substitued 3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-ones **7** are shown in Figure 1.

Corresponding 2-aryl-3,5-dihydro-4*H*-benzopyrano[2,3-*d*]pyrimidine-4-thiones **8**{*1*−*724*} (Figure 2) were synthesized by the condensation of substituted coumarin-3-thioamides **5**{*1*−*16*} with aromatic aldehydes **6**{*1*−*86*}. Carrying out of this reaction in boiling *n*-butanol in the presence of a catalytic amount of piperidine for 15−20 min excluded the possibility of formation of another isomeric product and guaranteed high yields of the desired products **8** (Figure 2). This general method was previously described by Satzinger and co-workers.[11,12]

To increase diversity of the benzopyrano[2,3-*d*]pyrimidine scaffold, we involved the synthesized derivatives **7**{*1*−*10*} and **8** {*1*−*10*} in alkylation with several types of alkylation agents **9**{*1*−*84*} (Table 3) (N-substituted chloroacetamides,

benzyl chlorides, alkyl iodides; see Scheme 4). Alkylation of pyrimidin-4-one derivatives was carried out in DMF at 80 °C in the presence of 3 equiv of potassium carbonate. In all cases, O-alkylated products **10**{*1*−*630*} were isolated in high yields, except **9**{*55* and *56*} as a result of side reactions. (Scheme 4, Figure 3). Alkylation of thio analogous **8** was carried under the same conditions, but by using a small excess of triethylamine as catalyst (Scheme 4, Figure 3).

Conclusion. An efficient synthetic route for solution-phase parallel synthesis of diverse benzopyrano[2,3-*d*]-pyrimidine libraries was developed. All the reactions proposed allowed us to obtain products with low levels of impurities using a simple isolation. The reaction products were obtained in high average yield, even when starting materials with bulky side chain substituents or various functional groups were used. Biological evaluation of these benzopyrano[2,3-*d*]pyrimidines is currently in progress with respect to a number of GPCR and protein kinase biotargets and may lead to the design and synthesis of analogues possessing interesting physiological activity. Finally, the results provide further confirmation of the scope and generality of the applied approach to fused pyrimidines: >6000 analogues of these molecules have been made in our laboratories in the past 2 years by parallel synthesis methods.

Acknowledgment. We thank Dr. Alexandre V. Ivachtchenko (Chemical Diversity Labs, Inc.) for discussion and help in preparation of the manuscript.

Supporting Information Available. Experimental procedures, spectroscopic data, and references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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