ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

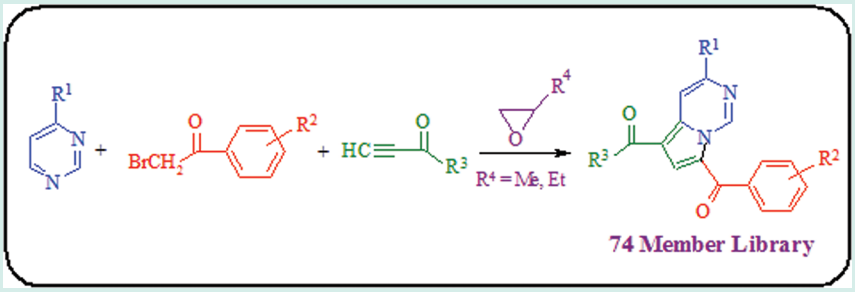
Efficient One-Pot, Three-Component Synthesis of a Library of Pyrrolo[1,2-*c*]pyrimidine Derivatives

Emilian Georgescu,[†] Florentina Georgescu,[†] Marcel M. Popa,[‡] Constantin Draghici,[‡] Laszlo Tarko,[‡] and Florea Dumitrascu*[,‡]

[†]Research Center Oltchim, 1 Uzinei str., 240050 Ramnicu Valcea, Romania

[‡]Center for Organic Chemistry "C.D. Nenitzescu", Romanian Academy, 202 B, Spl. Independentei, 060023, Bucharest, Romania

Supporting Information



ABSTRACT: Herein is reported a simple and efficient one-pot three-component synthesis of pyrrolo[1,2-*c*]pyrimidine derivatives starting from various substituted pyrimidines, 2-bromoacetophenones, and electron deficient alkynes in epoxides acting both as reaction medium and HBr scavanger. This method proved to be very lucrative and avoids formation of ylide inactivation products. The synthesis represents an environmentally benign alternative to classical methods. The new library of compounds was briefly characterized regarding the improved Lipinski rule to asses the potential drug-likeness of the compounds. The majority of compounds are statisfing the Lipinski rule.

KEYWORDS: *one-pot synthesis, three-component reaction, pyrrolo[1,2-c]pyrimidine derivatives*

INTRODUCTION

Multicomponent reactions in which several reactions are combined into one synthetic operation have been used extensively to form carbon−carbon or carbon−nitrogen bonds in the synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single step, thus avoiding complicated purification operations and saving materials. When combined with the one-pot procedure, multicomponent reactions provide an efficient synthetic strategy for a wide range of highly complex molecules.

Pyrrolo[1,2-*c*]pyrimidine is an N-bridgehead heterocyclic ring system of significant interest because of several biological activities associated with this scaffold. Pyrrolo[1,2-*c*]pyrimidine is the heterocyclic skeleton of the variolin family of marine alkaloids.[2] Some pyrrolo[1,2-*c*]pyrimidine derivatives have been found to exhibit therapeutic antioxidant, tissue- or neuroprotective effects in any disorders which may be associated with the oxidative stress;[3a] others are useful for the treatment or prevention of cancer, inflammatory disorders, and autoimmune diseases[3b] or present antifungal and antimicrobial properties.[3c]

Several methods have been reported for the synthesis of pyrrolo[1,2-*c*]pyrimidine derivatives, starting from pyrrole[4] or pyrimidine[5] derivatives. One of the most versatile synthetic methods is the 1,3-dipolar cycloaddition of the corresponding pyrimidinium-*N*-ylides with both acetylenic and olefinic dipolarophiles.[6] Usually, this synthetic pathway involves two distinct steps: the preparation, in the first step, of the pyrimidinium salts which, in the second step, react with acetylenic or olefinic dipolarophiles in the presence of a base whose role is to generate the *N*-ylide in situ. By using organic or inorganic bases, inactivation products of pyrimidinium-*N*-ylides are obtained along with the target products.[7] To avoid the formation of the inactivation products, we have developed an alternative procedure which involves the direct reaction of the pyrimidinium salts with dipolarophiles in the presence of epoxides, such as propylene oxide or 1,2-epoxybutane, which plays both the role of the reaction medium and proton scavenger.

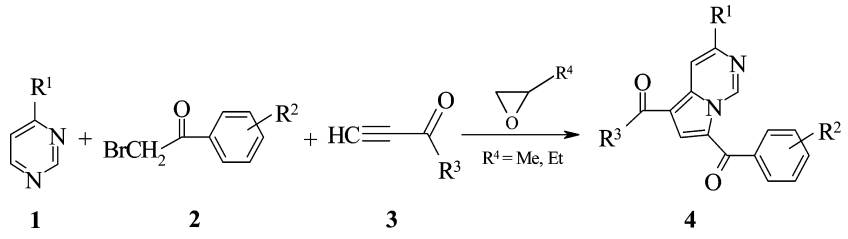
Therefore, the development of an efficient, rapid, and clean synthetic route toward focused libraries of such compounds is of great importance to both medicinal and synthetic chemists.

As a continuation of our research devoted to the development of multicomponent reactions,[8] in this paper we report an efficient synthesis of a library of pyrrolo[1,2-*c*]pyrimidine via the one-pot, three component reaction starting from the readily available materials.

Received: August 17, 2011
Revised: January 17, 2012
Published: January 23, 2012

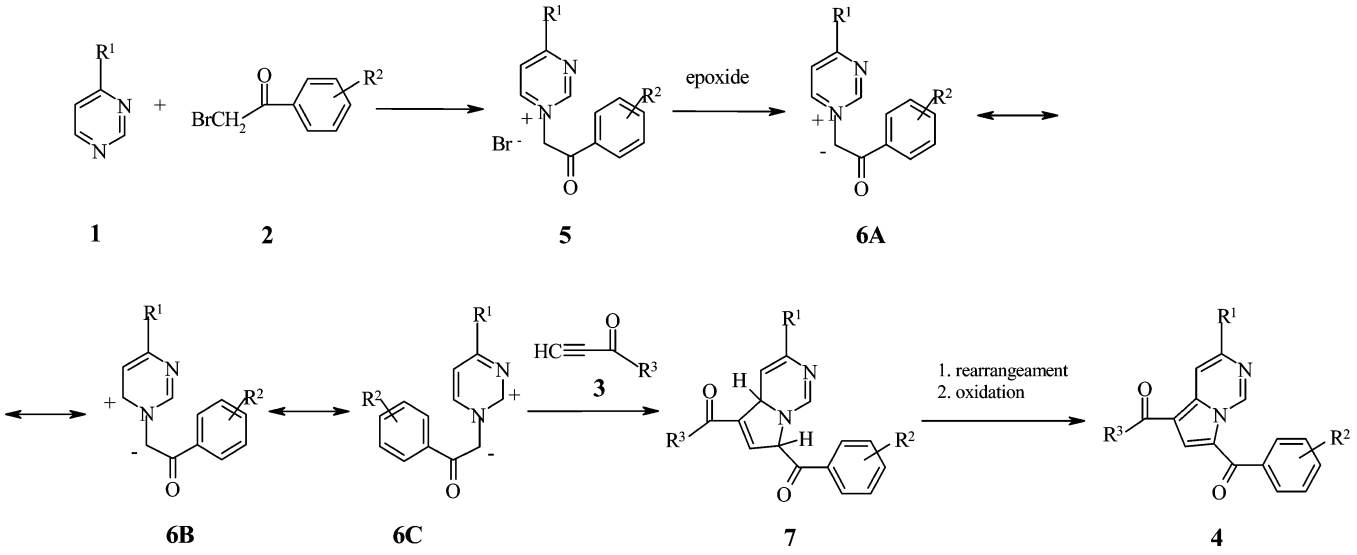
   dx.doi.org/10.1021/co2002125 | *ACS Comb. Sci.* 2012, 14, 101−107

Scheme 1. Synthesis of Pyrrolo[1,2-*c*]pyrimidines 4 via One-Pot Three-Component Reaction



1 2 3 4

Scheme 2. Proposed Mechanism of Novel Three Component Synthesis of Pyrrolo[1,2-c]pyrimidines



1 2 5 6A 6B 6C 7 4

RESULTS AND DISCUSSION

The key components for the synthesis of a library of pyrrolo-[1,2-*c*]pyrimidines **4** by the one-pot three-component procedure are 4-substituted pyrimidines **1**{*1*−*10*}, substituted 2-bromoacetophenones **2**{*1*−*14*} and nonsymmetrical electron deficient alkynes **3**{*1*−*3*} in propylene oxide or 1,2-epoxybutane, which acts both as solvent and proton scavenger (Scheme 1). The reaction conditions are mild, involving only mixing the components at room temperature for 40 h when using propylene oxide or at reflux temperature for 24 h in the case of 1,2-epoxybutane, followed by solvent evaporation and subsequent crystallization.

The reaction mechanism (Scheme 2) implies the intermediate formation of the pyrimidinium salts **5** from the corresponding 4-substituted pyrimidines **1** and 2-bromoacetophenones **2**. In the next step, the bromine ion of the salt attacks the oxirane ring from propeneoxide or 1,2-epoxybutane, resulting in ring-opening of the epoxide and generation of the *N*-ylide **6** by action of the alkoxide. The *N*-ylide reacts with the activated alkyne **3** to give the corresponding dihydro pyrrolo[1,2-*c*]pyrimidine **7** as the primary cycloadduct. Finally, the pyrrolo[1,2-*c*]pyrimidines **4** are obtained by rearrangement and spontaneous in situ dehydrogenation of the primary cycloadduct **7**. The NMR data indicated that the 1,3-dipolar cycloaddition reaction occurs regioselectively with formation of 3-substituted products and no product from mesomeric form **6C** were obtained, namely, pyrrolo[1,2-*a*]-pyrimidine. Also, no traces of dimers resulting from 3 + 3-cycloaddition reaction of two molecules of *N*-ylide **6** were obtained as reported in literature.[7]

In this method, unsubstituted or 4- and 5-substituted pyrimidines bearing different substituent can be used as starting compounds. 2-Substituted pyrimidines bearing a large substituent or 4,6-disubstituted pyrimidines are not appropriate as starting compounds because the quaternization reaction is sterically hindered. Instead of substituted 2-bromoacetophenone, bromoacetic esters, bromoacetyl derivatives of different heterocyclic compounds, or other quaternizing agents that could stabilize the intermediate *N*-ylides can be used in this synthetic method. Activated alkynes with different substituents can be used as dipolarophiles. Poor yields are obtained when dimethyl acetylenedicarboxylate or diethyl acetylenedicarboxylate are used as dipolarohiles. Because of their high reactivity, these alkynes react also with the nitrogen atom from the starting pyrimidine leading to mixtures of compounds.

To compare the yields, the pyrrolo[1,2-*c*]pyrimidines **4** (Table 1, entry 1−4) generated from 4-(2-methylphenyl)-pyrimidine **1**{*1*} were obtained both by the one-pot, three component procedure (A) and by the alternative procedure starting from the corresponding pyrimidinium salts **5** and electron deficient alkynes **3** in an epoxide (B). Corresponding pyrimidinium salts **5** were obtained separately from 4-(2-methylphenyl)pyrimidine **1**{*1*} and 2-bromoacetophenones **2** in acetone.

To verify if the synthesized molecules present a potential drug likeness regardless of biochemical activity, we verified if the molecules fulfill the "improved Lipinski rule of five".[9] The Lipinski's rule of five focuses mainly on oral absorption and distribution of drugs and is of importance in the generation and optimization of drug like libraries of compounds. According to this empirical rule the value of five molecular descriptors of possible bioactive molecules should be within a suitable range.[9] The considered molecular descriptors are the number of the

dx.doi.org/10.1021/co2002125 | *ACS Comb. Sci.* 2012, 14, 101−107

Table 1. Synthesis of Pyrrolo[1,2-*c*]pyrimidine Derivatives 4

entry	products	mp (°C)	isolated yield, A/B (%)	entry	products	mp (°C)	isolated yield, A/B (%)
1	4{*1,3,2*}	201−203	52/55	38	4{*5,2,1*}	137−139	46
2	4{*1,5,1*}	131−133	40/41	39	4{*5,5,1*}	183−185	45
3	4{*1,11,1*}	147−148	42/44	40	4{*5,8,1*}	152−153	44
4	4{*1,14,2*}	172−174	51/50	41	4{*5,9,1*}	161−163	45
5	4{*2,1,3*}	187−189	42	42	4{*5,13,2*}	196−198	52
6	4{*2,3,1*}	132−134	44	43	4{*5,14,1*}	153−155	46
7	4{*2,4,1*}	140−142	52	44	4{*6,3,1*}	150−152	54
8	4{*2,5,3*}	159−161	42	45	4{*6,5,1*}	154−156	52
9	4{*2,8,1*}	160−162	41	46	4{*6,6,1*}	140−142	45
10	4{*2,9,1*}	224−226	49	47	4{*6,8,1*}	150−152	43
11	4{*2,10,1*}	175−177	47	48	4{*6,10,1*}	189−191	59
12	4{*2,11,1*}	199−201	50	49	4{*6,11,1*}	196−197	62
13	4{*2,12,1*}	151−153	40	50	4{*7,1,1*}	203−204	53
14	4{*2,13,2*}	203−205	41	51	4{*7,3,1*}	214−215	50
15	4{*2,14,2*}	198−200	52	52	4{*7,5,1*}	212−214	49
16	4{*3,1,1*}	205−206	41	53	4{*7,8,1*}	255−257	54
17	4{*3,2,1*}	206−207	43	54	4{*7,11,1*}	250−251	61
18	4{*3,3,1*}	189−190	44	55	4{*7,12,1*}	234−236	52
19	4{*3,4,1*}	172−173	41	56	4{*7,13,1*}	223−225	50
20	4{*3,5,1*}	175−176	47	57	4{*8,1,1*}	160−162	46
21	4{*3,6,1*}	188−190	42	58	4{*8,3,1*}	195−197	41
22	4{*3,8,1*}	198−200	42	59	4{*8,4,1*}	187−188	47
23	4{*3,9,1*}	224−225	40	60	4{*8,6,1*}	186−187	46
24	4{*3,10,1*}	229−231	51	61	4{*8,7,1*}	177−178	49
25	4{*3,11,1*}	238−240	46	62	4{*8,12,1*}	198−200	50
26	4{*3,11,3*}	236−238	71	63	4{*8,14,1*}	163−164	48
27	4{*3,12,1*}	239−241	52	64	4{*9,2,1*}	193−195	46
28	4{*3,13,2*}	213−215	53	65	4{*9,3,1*}	186−187	47
29	4{*4,1,1*}	148−150	45	66	4{*9,6,1*}	197−199	53
30	4{*4,3,1*}	158−160	47	67	4{*9,7,1*}	178−179	45
31	4{*4,5,1*}	139−141	51	68	4{*9,8,1*}	190−192	51
32	4{*4,6,1*}	162−164	47	69	4{*9,9,1*}	180−181	42
33	4{*4,8,1*}	163−165	52	70	4{*9,13,1*}	210−212	42
34	4{*4,10,1*}	231−233	49	71	4{*9,14,1*}	197−199	45
35	4{*4,11,1*}	205−207	43	72	4{*10,1,1*}	200−201	53
36	4{*4,13,1*}	202−204	42	73	4{*10,3,1*}	175−176	44
37	4{*4,14,1*}	155−157	53	74	4{*10,6,1*}	162−163	39

atoms in molecule (N), molecular mass (MW), molar refractivity (MR), the logarithm of the partition coefficient in octanol−water (logP), and polar surface area (PSA). A molecule is considered that is violating the Lipinski rule if two or more descriptors are outside the accepted range.

According to the results of descriptor computation, all but 13 members of the 74-member library passed the Lipinski rule (see the table in Supporting Information). Many of the molecules that are not fulfilling the Lipinski rule or do not satisfy at least one of the rules are "too lipophilic" (see the LogP values). Also from the calculated data could be observed that all the values of the descriptors are not covering the entire allowable interval imposed by Lipinski rule of five the values of the descriptors being estimated in the upper part of this interval. Figure 1 presents a graphical summary of the physicochemical property space distribution which characterizes the obtained library of pyrrolo[1,2-*c*]pyrimidines including the thirteen compounds which are violating two or more criteria of the improved Lipinski rule.

We could also observe from Figure 1 how the property-distributions ared fitted to a normal distribution (see also the Supporting Information), knowing that there is interest in statistical interpretation of drug-likeness or to create more accurate filters before further QSAR studies.[10]

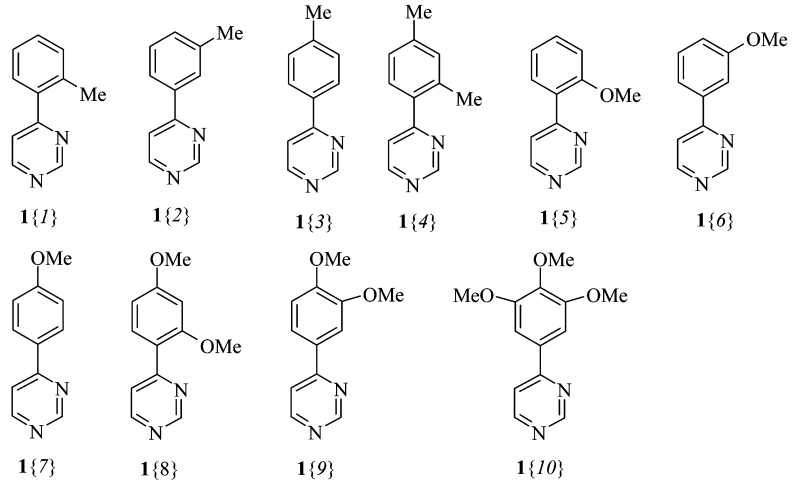
CONCLUSIONS

We have developed an efficient one-pot, three-component reaction of pyrimidine, 2-bromoacetophenone, and electron-deficient alkyne in the presence of an epoxide such as propylene oxide or 1,2-epoxybutane for the synthesis of pyrrolo[1,2-*c*]pyrimidine compounds. On the basis of this method, we have prepared a 74-member library of pyrrolo[1,2-*c*]pyrimidines. The process is wide in scope and requires simple reaction conditions in which all final products are removed by simple, nonchromatographic methods, such as crystallization. Of significance are the regioselectivity of the procedure, and the absence of secondary 3 + 3-cycloaddition products. According to the "Improved Lipinski Rule of Five", the majority of the members of this novel library of pyrrolo[1,2-*c*]pyrimidine present a potential oral drug-likeliness, which opens the path for further studies regarding their biochemical activity. The present method is applicable to synthesis of libraries of N-bridgehead heterocyclic systems with high diversity.

dx.doi.org/10.1021/co2002125 | *ACS Comb. Sci.* 2012, 14, 101−107

Chart 1. Diversity of Reagents

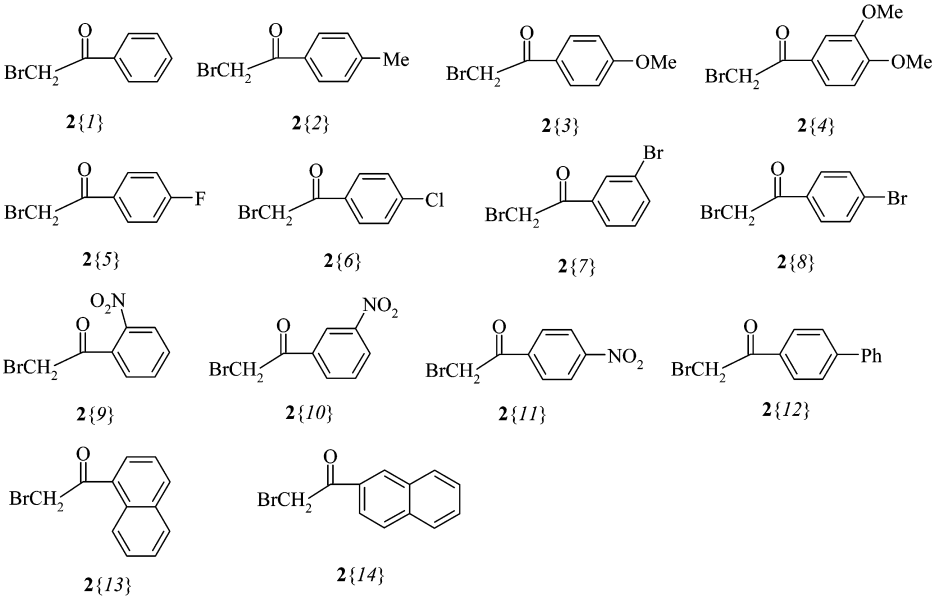
Pyrimidines 1:



1{1} 1{2} 1{3} 1{4} 1{5} 1{6}

1{7} 1{8} 1{9} 1{10}

2-Bromoacetophenones 2:



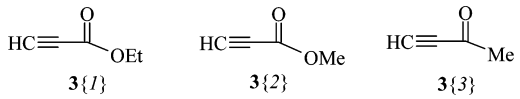
2{1} 2{2} 2{3} 2{4}

2{5} 2{6} 2{7} 2{8}

2{9} 2{10} 2{11} 2{12}

2{13} 2{14}

Electron-deficient alkynes 3:



3{1} 3{2} 3{3}

EXPERIMENTAL PROCEDURES

General. Melting points were determined on a Boëtius hot plate microscope. The elemental analysis was carried out on a COSTECH Instruments EAS32 apparatus. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets with absorptions in cm^{-1}. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard. Supplementary evidence was given by COSY and HETCOR experiments.

2-Bromoacetophenones, 3-butyn-2-one, methyl propiolate, ethyl propiolate, and 1,2-epoxybutane were purchased from Aldrich, propylene oxide was obtained from Oltchim SA. All commercial reagents and solvents were used without further purification.

4-Substituted pyrimidines **1** were obtained by the condensation of the triformylaminomethane with 2-substituted acetophenone in the presence of a catalytic amount of *p*-toluensulfonic acid.[11] The intermediate triformylaminomethane was obtained from formamide and dimethylsulfate.[12] Properties and spectral data of 4-(4-methylphenyl)pyrimidine,[13] 4-(4-methoxyphenyl)-pyrimidine,[13] 4-(2-methoxyphenyl)-pyrimidine,[14] 4-(3-methoxyphenyl)pyrimidine,[14] and 4-(2,4-dimethoxyphenyl)pyrimidine[14] were reported in literature.

General Procedure for Synthesis of 4-Substituted Pyrimidinium Salts 5. A solution of 1.7 g of 4-(2-methylphenyl)pyrimidine **1**{*1*} (10 mmol) and 2-bromoacetophenone **2** (10 mmol) in 50 mL of acetone was heated at reflux temperature for 8 h and left overnight at room temperature. The precipitated solid was filtered off and washed on the filter with a small quantity of acetone.

dx.doi.org/10.1021/co2002125 | ACS Comb. Sci. 2012, 14, 101−107

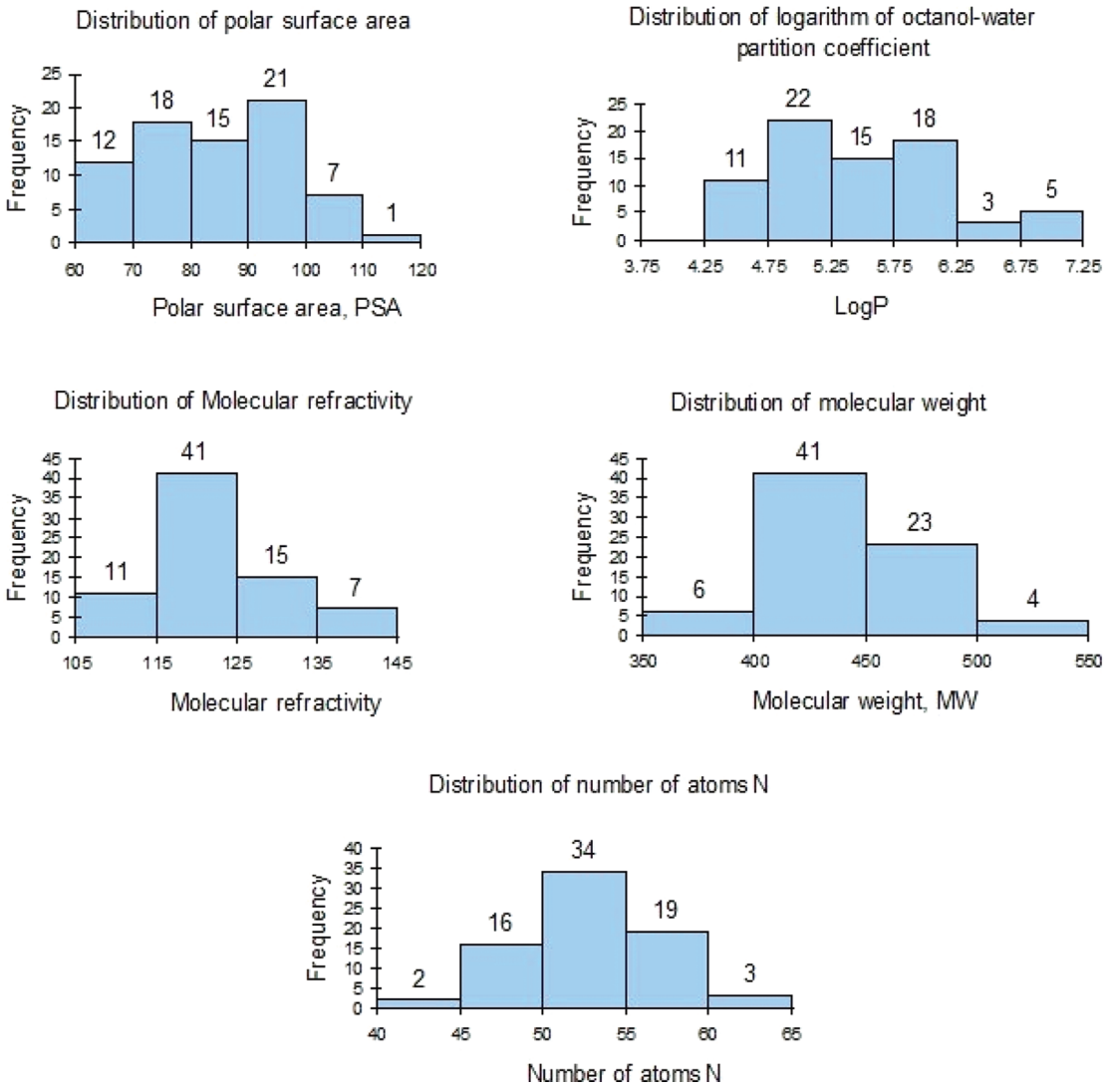


Figure 1. Property distributions as resulted from the estimated descriptors.

*1-[2-(4-Methoxyphenyl)-2-oxoethyl]-4-(2-methylphenyl)-pyrimidinium Bromide **5**{1,3}:* Yellow crystals, mp 208–210 °C; yield 91%; IR (cm^{-1}) 1670, 1632, 1601, 1453, 1347, 1249, 1181; ^1H NMR (300 MHz, $CDCl_3$ + TFA) δ 2.61 (s, 3H, Me), 3.92 (s, 3H, OMe), 6.43 (s, 2H, CH_2), 7.04 (d, 2H, J = 9.0 Hz, ArH), 7.42–7.46 (m, 2H, ArH), 7.56–7.59 (m, 1H, ArH), 7.76–7.79 (m, 1H, ArH), 8.07 (d, 2H, J = 9.0 Hz, ArH), 8.24 (dd, 1H, J = 0.8, 6.7 Hz, H-5), 9.14 (dd, 1H, J = 1.9, 6.7 Hz, H-6), 9.38 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ 20.9 (Me), 55.7 (OMe), 62.8 (CH_2), 114.8, 122.2, 125.1, 127.2, 131.5, 132.7, 133.3, 133.8, 139.2, 151.9, 152.8, 165.9, 174.7, 188.1 (CO); Anal. Calcd $C_{20}H_{19}BrN_2O_2$ C 60.16, H 4.8, N 7.02; Found C 60.39, H 4.67, N 7.21.

General Procedure for Synthesis of Pyrrolo[1,2-*c*]-pyrimidine Derivatives 4. A solution of 4-substituted pyrimidine **1** (2.5 mmol), 2-bromoacetophenone **2** (2.5 mmol), and alkyne **3** (3.5 mmol) in 40 mL of 1,2-epoxybutane was heated at reflux temperature for 24 h. The solvent was partly removed under vacuum; 10 mL of MeOH was added under a gentle stirring, and the mixture was left overnight at room temperature. The solid formed was filtered off, washed on the filter with a mixture of MeOH/diethyl ether 1:1, and crystallized from $CHCl_3$/MeOH.

When propylene oxide was used instead of 1,2-epoxybutane, the reaction was carried out at room temperature, under stirring for 40 h, and the crude solid was worked out in the same way.

Comparative General Procedure for Synthesis of Pyrrolo[1,2-*c*]pyrimidine Derivatives 4. To a suspension of 4-substituted pyrimidinium bromide **5** (2.5 mmol) in 40 mL of 1,2-epoxybutane was added alkyne **3** (3.5 mmol), and the solution was heated at reflux temperature for 24 h. The solvent was partly removed under vacuum; 10 mL of MeOH was added under a gentle stirring, and the mixture was left overnight at room temperature. The solid formed was filtered off, washed on the filter with a mixture of MeOH/diethyl ether 1:1, and crystallized from $CHCl_3$/MeOH.

*Methyl 3-(2-Methylphenyl)-7-(4-methoxybenzoyl)pyrrolo-[1,2-c]pyrimidine-5-carboxylate **4**{1,3,2}:* Yellow crystals; IR (cm^{-1}) 1705, 1622, 1480, 1324, 1260, 1207, 1168; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H, 2′-Me), 3.98 (s, 6H, 2MeO), 7.04 (d, 2H, J = 8.9 Hz, H-3″, H-5″), 7.32–7.36 (m, 3H, H-3′, H-4′, H-5′), 7.56–7.59 (m, 1H, H-6′), 7.88 (s, 1H, H-6), 7.90 (d, 2H, J = 8.9 Hz, H-2″, H-6″), 8.31 (d, 1H, J = 1.5 Hz, H-4), 10.58 (d, 1H, J = 1.5 Hz, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (2′-Me), 51.4, 55.5 (2MeO), 106.3 (C-4), 113.0 (C-5), 113.9 (C-3″, C-5″), 122.4 (C-7), 126.1, 129.0, 129.1, 131.1

dx.doi.org/10.1021/co2002125 | *ACS Comb. Sci.* 2012, 14, 101–107

(C-3′, C-4′, C-5′, C-6′), 129.8 (C-6), 131.3 (C-2″, C-6″), 131.5, 136.4, 137.9, 140.0 (C-4a, C-1′, C-2′, C-1″), 140.3 (C-1), 152.4 (C-3), 163.1 (COO), 164.0 (C-4″), 184.2 (COAr); Anal. Calcd $C_{24}H_{20}N_2O_4$ C 71.99, H 5.03, N 7.0; Found C 72.35, H 5.22, N 6.89.

Ethyl 3-(2-Methylphenyl)-7-(4-fluorobenzoyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate ***4****{1,5,1}:* Pale yellow crystals; IR (cm^{-1}) 1696, 1622, 1600, 1523, 1476, 1327, 1222, 1203; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.1 Hz, Me), 2.52 (s, 3H, 2′-Me), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 7.24 (t, 2H, J = 8.6 Hz, H-3″, H-5″), 7.33−7.36 (m, 3H, H-3′, H-4′, H-5′), 7.58−7.61 (m, 1H, H-6′), 7.86 (s, 1H, H-6), 7.90 (dd, 2H, J = 5.4, 8.6 Hz, H-2″, H-6″), 8.34 (d, 1H, J = 1.5 Hz, H-4), 10.60 (d, 1H, J = 1.5 Hz, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (Me), 20.7 (2′-Me), 60.5 (CH_2), 107.0 (C-4), 113.0 (C-5), 115.7 (d, J = 22.0 Hz, C-3″, C-5″), 122.0 (C-7), 126.2, 129.2, 129.6, 131.2 (C-3′, C-4′, C-5′, C-6′), 129.8 (C-6), 131.4 (d, J = 8.9 Hz, C-2″, C-6″), 135.1 136.3, 137.7, 140.2 (C-4a, C-1′, C-2′, C-1″), 140.3 (C-1), 152.6 (C-3), 163.5 (COO), 165.1 (d, J = 250 Hz, C-4″), 183.8 (COAr); Anal. Calcd $C_{24}H_{19}FN_2O_3$ C 71.63, H 4.76, N 6.96; Found C 71.42, H 4.92, N 7.12.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic characterization are presented for compounds **1**{*1*}, **1**{*2*}, **1**{*4*}, **1**{*9*}, **1**{*10*}, compounds **4** and **5** and tabulated improved Lipinski's rule parameters and property distributions. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fdumitra@yahoo.com.

Author Contributions

EG., F.G., and F.D. conceived and designed experiments, E.G., F.G., M.M.P., and F.D. performed the experiments, analysis, and cowrote the manuscript and Supporting Information, C.D. performed all NMR spectra and cowrote the Supporting Information, and L.T. calculated and evaluated the Lipinski's rule parameters.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Orru, R. W. A.; De Greef, M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, 1471−1499. (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing synthetic efficiency: multi-component transformations lead the way. *Chem.—Eur. J.* **2000**, *6*, 3321−3329. (c) Ramon, D. J.; Yus, M. Asymmetric multicomponent reactions (AMCRs): The new frontier. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602−1634. (d) Li, D.; Duan, S.; Hu, Y. Three-component one-pot approach to synthesize benzopyrano[4,3-*d*]pyrimidines. *J. Comb. Chem.* **2010**, *12*, 895−899. (e) Huang, Z.; Hu, Y.; Zhou, Y.; Shi, D. Efficient one-pot three-component synthesis of fused pyridine derivatives in ionic liquid. *ACS Comb. Sci.* **2011**, *13*, 45−49. (f) Zhuang, Q.-Y.; Wang, X.; Gao, Y.; Shi, F.; Jiang, B.; Tu, S.-J. Diversity-oriented synthesis of spiro-substituted 1,3-thiazine library via a one-pot, two-step, three-component reaction. *ACS Comb. Sci.* **2011**, *13*, 84−88.

(2) (a) Alvarez, M.; Fernandez, D.; Joule, J. A. Synthesis of deoxyvariolin B. *Tetrahedron Lett.* **2001**, *42*, 315−317. (b) Ahaidar, A.; Fernandez, D.; Danelon, G.; Quevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Alvarez, M. Total syntheses of variolin B and deoxyvariolin B. *J. Org. Chem.* **2003**, *68*, 10020−10029. (c) Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. J. Reaction of bromomethylazoles and tosylmethyl isocyanide. A novel heterocyclization method for the synthesis of the core of marine alkaloids variolins and related azolopyrimidines. *J. Org. Chem.* **2004**, *69*, 4974−4983.

(3) (a) Rise, F.; Wikstroem, H.; Ugland, S.; Dijkstra, D.; Gundersen, L. L.; De Boer, P.; Bast, A.; Haenen, G.; Antonsen, O. G . The use of heterocyclic compounds as antioxidants, radical scavengers, Fe^{2+} complexing agents tissue- and/or neuroprotectants. Intl. Pat. WO 9621662 A1, 1996. (b) Ono, M.; Sun, L.; Xia, Z. Q.; Kostik, E.; Koya, K.; Wu, Y.; Nagai, M. Preparation of fused pyrrolo compounds as TNF_α and/or PDE 4 inhibitors for treatment of cancer, inflamatory disorders and autoimmune diseases. Intl. Pat. WO 2004082606 A2, 2004. (c) Mangalagiu, G.; Ungureanu, M.; Grosu, G.; Mangalagiu, I. I.; Petrovanu, M. New pyrrolo-pyrimidine derivatives with antifugal or antibacterial properties in vitro. *Ann. Pharm. Fr.* **2001**, *59*, 139−140.

(4) (a) Minguez, J. M.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J. Improved synthesis of pyrrolo[1,2-*c*]pyrimidine and derivatives. *Tetrahedron Lett.* **1996**, *37*, 4263−4266. (b) Alvarez, M.; Fernandez, D.; Joule, J. A. Synthesis of 1,2-dihydropyrrolo[1,2-*c*]pyrimidin-1-one. *J. Chem. Soc. Perkin Trans. 1* **1999**, 249−256.

(5) (a) Ivanov, V. B.; Reznik, V. S.; Ivanov, B. E.; Musina, A. A.; Efremov, Yu. Ya. Preparation of 6-substituted 1-oxopyrrolo[1,2-*c*]-pyrimidines. *Izv. Akad. Nauk. SSSR, Seriya Khim.* **1980**, 2428−2436. (b) Weidner, C. H.; Michaels, F.-M.; Beltman, D. J.; Montgomery, C. J.; Wadsworth, D. H.; Briggs, B. T.; Picone, L. M. Indolizine. 5. Preparation and structural assignments of azaindolizinols. *J. Org. Chem.* **1991**, *56*, 5594−5598. (c) Copar, A.; Stanovnik, B.; Tisler, M. A new approach for the synthesis of fused pyrroles. The synthesis of acyl substituted pyrrolo[1,2-*x*]azines. *J. Heterocycl. Chem.* **1993**, *30*, 1577−1579. (d) Romashin, Y. N.; Liu, M. T. H.; Nijjar, S. S.; Attanasi, O. A. Arylchlorocarbenes in the synthesis of heterocycles containing two nitrogen atoms. *Chem. Commun.* **2000**, 1147−1148.

(6) (a) De la Hoz, A.; De Paz, J. L. G.; Diez-Barra, E.; Elguero, J.; Pardo, C. Pyrimidinium *N*-dicyanmethylide. Synthesis and reactivity towards dimethyl acetylenedicarboxylate. *Heterocycles* **1986**, *24*, 3473−3476. (b) Iuhas, P. C.; Georgescu, F.; Georgescu, E.; Draghici, C.; Caproiu, M. T. Regiochemistry of the 1,3-dipolar cycloaddition of some N-heterocyclic cycloimmonium ylides to unsymmetrical alkynes. *Rev. Roum. Chim.* **2002**, *47*, 333−338.

(7) (a) Mangalagiu, G. C.; Mangalagiu, I. I.; Olariu, R. I.; Petrovanu, M. G. 4-Methylpyrimidinium ylides. II. Selective reactions of pyrimidinium ylides with activated alkynes. *Synthesis* **2000**, 2047−2050. (b) Moldoveanu, C. C.; Mangalagiu, I. I. 4-Methyl- and 4-(halophenyl)pyrimidinium (4-halobenzoyl)methylides. correlation of structure, stability, reactivity and biological activity. *Helv. Chim. Acta* **2005**, *88*, 2747−2756.

(8) (a) Georgescu, E.; Caira, M. R.; Georgescu, F.; Draghici, B.; Popa, M. M.; Dumitrascu, F. One-pot three-component synthesis of a library of new pyrrolo[1,2-*a*]quinoline derivatives. *Synlett* **2009**, 1795−1799. (b) Dumitrascu, F.; Caproiu, M. T.; Georgescu, F.; Draghici, B.; Popa, M. M.; Georgescu, E. New pyrrolo[1,2-*a*]phthalazine derivatives by one-pot three component synthesis. *Synlett* **2010**, 2407−2410. (c) Caira, M. R.; Georgescu, E.; Georgescu, F.; Albota, F.; Dumitrascu, F. Contributions to syntheses of pyrrolo[2,1-*a*]phthalazines. *Monatsh. Chem.* **2011**, *142*, 743−748.

(9) (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *J. Comb. Chem.* **1999**, *1*, 55−68. (b) Ertl, P.; Rohde, B.; Selzer, P. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. *J. Med. Chem.* **2000**, *43*, 3714−3717.

(10) (a) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; 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. (b) Viswanadhan, V. N.; Rajesh, H.; Balaji, V. N. Atom type preferences, structural diversity, and property profiles of known drugs,

leads, and nondrugs: A comparative assessment. *ACS Comb. Sci.* **2011**, *13*, 327−336.
(11) Bredereck, H.; Gompper, R.; Geiger, B. Synthese von pyrimidinen mittels tris-formylamino-methan. *Chem. Ber.* **1960**, *93*, 1402−1406.
(12) Bredereck, H.; Gompper, R.; Rempfer, H.; Klemm, K.; Keck, H. Alkylierungs und acylierungs reaktionen an formamid: tris-formylamino-methan. *Chem. Ber.* **1959**, *92*, 329−343.
(13) (a) Bredereck, H.; Gompper, R.; Herlinger, H. Darstellung, eigenschaften und umsetzungen des pyrimidins. *Chem. Ber.* **1958**, *91*, 2832−2849. (b) Balasubrahmanyam, N. S.; Jeyashri, B.; Namboothiri, N. N. I. Selectivities in the formation of pyridines and pyrimidines by ammonia-induced cyclocondensations of vinamidiniums. *Tetrahedron* **1994**, *50*, 8127−8142.
(14) Nishiwaki, N.; Yamashita, K.; Azuma, M.; Adachi, T.; Tamura, M.; Ariga, M. Novel synthesis of bihetaryl compounds. *Synthesis* **2004**, 1996−2000.