ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

High Throughput Synthesis of Extended Pyrazolo[3,4-*d*]dihydropyrimidines

Sergey V. Ryabukhin,*[,†,‡] Dmitry S. Granat,[‡] Andrey S. Plaskon,[‡] Alexander N. Shivanyuk,*[,†,§] Andrey A. Tolmachev,[∥] and Yulian M. Volovenko[‡]

[†]The Institute of High Technologies, Kyiv National Taras Shevchenko University, 4 Glushkov str., Building 5, Kyiv, 03187, Ukraine

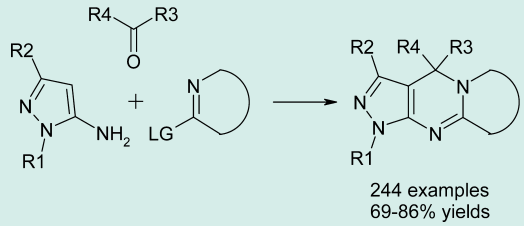
[‡]Department of Chemistry, Kyiv National Taras Shevchenko University, 64 Volodymyrska str., Kyiv, 01601, Ukraine

[§]The Institute of Pharmacology and Toxicology, The National Academy of Medical Sciences, 14 Ejen Pottier str, Kyiv, 03680, Ukraine

[∥]Enamine Ltd., 23 A. Matrosov str., Kyiv, 01103, Ukraine

Supporting Information

ABSTRACT: Thirteen 5-hetarylaminopyrazoles were synthesized in 62−93% yield through the arylation of 1-isopropyl- and 1-phenyl-5-aminopyrazoles with electrophilic hetarylhalides under optimized conditions. Condensation of 5-hetarylaminopyrazoles with carbonyl compounds facilitated by AcOH or Me_3SiCl furnished 23 pyrazolo[3,4-*d*]dihydropyrimidines in 69−86% yield. The target compounds were isolated through simple crystallization. The scope and limitation of the method are discussed.



KEYWORDS: *aldehydes, aminopyrazoles, dihydropyrimidines, chlorotrimethylsilane, high throughput synthesis*

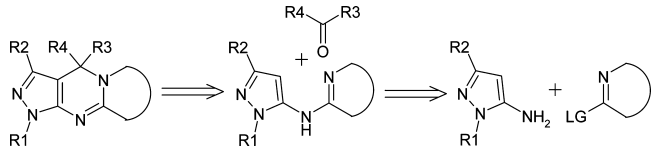
INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidine is an isomer of imidazolo[3,4-d]-pyrimidine (purine), the central core of adenine, cytosine, xanthine alkaloids, and other important biomolecules.[1] Various pyrazolo-[3,4-*d*]pyrimidine derivatives have been shown to possess remarkable biological activities. For example, 1*H*-pyrazolo[3,4-*d*] pyrimidin-4(2*H*)-one (allopurinol), a drug used for treatment of hyperurecemia and gout,[1] was synthesized through acid catalyzed condensation of 4-carboxamido-5-aminopyrazole with formamide.[2] The methylation of allopurinol with methyliodide followed by the reaction with $POCl_3$ resulted in 4-chloro-1-methyl-pyrazolo[3,4-*d*] pyrimidine which reacted with 5-substituted oxindoles to give the inhibitors of glycogen synthase, kinase 3 and cyclin dependent kinase 5.[3] The reaction of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine with amines gave a library of inducible nitric oxide synthase inhibitors.[4] A one pot procedure afforded pyrazolo[3,4-*d*]pyrimidine derivatives possessing potent and selective inhibitory activity against p38α, EphB4 receptors and VEGFR2 kinase.[5] The reaction of 1-methyl-3-cyano-5-aminopyrazole with formamide resulted in 4-aminopyrazolo[3,4-*d*]-pyrimidine whose oxidation with H_2O_2 gave the corresponding 5-oxide possessing antitumor activity.[6]

The extension of pyrazolo[3,4-*d*]pyrimidine system through annulation of an additional aromatic ring is a potentially promising approach to new molecular scaffolds for rational drug discovery. Herein we report a facile synthesis of extended pyrazolo[3,4-*d*]dihydropyrimidines which to the best of our knowledge have not been described in the literature.[7]

The reaction of 5-aminopyrazoles with reactive 2-halogenazines or azoles followed by [1 + 5]cyclization with carbonyl compounds was chosen as the synthetic approach for the extension of the pyrazolo[3,4-*d*]pyrimidine ring system (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

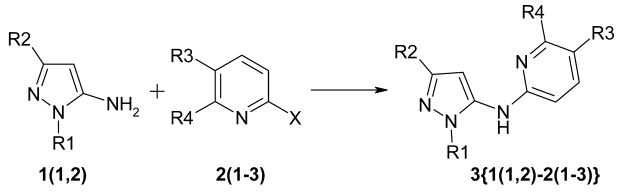
In the process optimization study aminopyrazoles **1**(**1**−**2**) were reacted with halopyridines **2**(**1**−**3**) under several sets of conditions (Table 1).

Under conditions A (Cs_2CO_3/LiF/DMF) the reactions of **1**(**1**−**2**) and **2** (**1**−**3**) resulted in formation of mixtures of **3** and **3a** or exclusively in compounds **3a** (Figure 1). Surprisingly under conditions B (NaH/DMF/100 °C) 5-aminopyrazoles **1**(**1**) and **1**(**2**) reacted with DMF to give amidines **3b** rather than reacting with 2-halopyridine **2**(**1**), whereas the more reactive compounds **2**(**2**) and **2**(**3**) were converted to mixtures of **3** and **3b**. In the later case, the minor amounts of **3b** could be removed from the target products **3** through simple recrystallization.

Received: January 19, 2012
Revised: July 9, 2012
Published: July 9, 2012

   dx.doi.org/10.1021/co300063x | *ACS Comb. Sci.* 2012, 14, 465−470

Table 1. Optimization of Reaction Conditions



R1 = i-Pr, R2= H **1(1)**
R1 = Ph, R2= Me **1(2)**

X= Cl, R3 = R4 = H **2(1)**
X= Cl, R3 = CF_3, R4 = H **2(2)**
X= Cl, R3,R4 = C_4H_4 **2(3)**

entry	1[a]	2[a]	conditions[b]	yield of 3 (%)[c]	yield of 3a[d] (%)[c]	yield of 3b[d] (%)[c]
1	1(1)	2(1)	A		17	
2			B			84
3			C	71		
4			D	60	5	
5		2(2)	A	11	63	
6			B	58		27
7			C	74		
8			D	63	23	
9		2(3)	A	14	67	
10			B	84		6
11			C	88		
12			D	58	12	
13	1(2)	2(1)	A		47	
14			B			69
15			C	87		
16			D	64	13	
17		2(2)	A	25	26	
18			B	68		22
19			C	83		
20			D	49	26	
21		2(3)	A	28	20	
22			B	82		11
23			C	79		
24			D	57	12	

[a]The pyrazole/pyridine ratio was 1:1 in all experiments. [b]Conditions: (A) Cs_2CO_3/LiF/DMF, 100 °C, 12 h; (B) NaH/DMF, 100 °C, 12 h; (C) NaH/THF, 60 °C, 12 h; (D) *t*-BuOK/*t*-BuOH, 60 °C, 12 h. [c]According to HPLC APCI MS of the reaction mixture [d]Structures of compounds **3a** and **3b** are shown in Figure 1

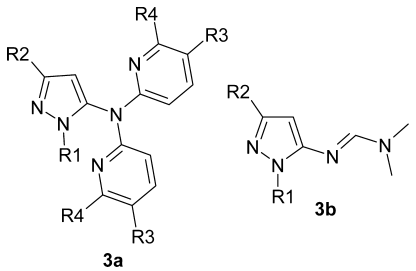


Figure 1.

The reactions of compounds **1(1,2)** and **2(1−10)** under optimal conditions C or B gave 13 compounds **3** in 62−93% yield (Table 2) which were purified by simple crystallization.

The pyrimidine ring closing reaction of aminopyrazoles **3** and carbonyl compounds **4** were carried out under two sets of conditions using Me_3SiCl[8] or AcOH as activators of carbonyl groups and water scavengers (Table 3). As a result, 36 parallel syntheses afforded 23 compounds **5** (39−85% yield) which were purified through simple crystallizations. The reactions of carbonyl compound **4(5)** gave noncyclic products **6** (Scheme 2, Table 3) and the reaction of **4(6−8)** failed to give compounds **5** under both sets of conditions most probably due to some side reactions.[7b−d] Me_3SiCl showed somewhat better condensing activity (entries 1, 6, 7, 12, 29) and therefore was used as water scavenger in majority of the parallel syntheses.

The structure and composition of compounds **3** and **5** were established through ^1H, ^{13}C and NOE, NMR spectroscopy, LC-MS and elemental analysis. For example, methine protons of the dihydropyrimidine ring (H1) in **5{1(1)−2(4)−4(1)}** gave NOE and in **5{1(2)−2(2)−4(1)}** gave NOESY correlations to the closest protons both in the pyrazole and in pyridine rings appropriately (Figure 1). These effects unambiguously prove the proposed structure of expended pyrazolo[3,4-*d*]pyrimidines.

More than 500 pyrazolo[3,4-*d*]dihydropyrimidines were synthesized through the optimized synthetic procedures. Physico chemical properties of 250 of them (see Experimental Procedures and Supporting Information) were calculated[9] to evaluate their "drug likeness" (Table 4, Figures 3−8).

Molecular weight and cLogP are the most important parameters determining the number of "drug-" and "lead-like" compounds in the library. Molecular weight varies between 282 and 554 Da with mean value of 422 Da, whereas the range of cLogP is 0.27−7.35 with mean value of 4.18. Figure 9 shows the distribution of number of pyrazolo[3,4-*d*]dihydropyrimidines in M_w cLog P plot. 162 (65%) compounds strictly obey the Lipinsky rule of 5[10a] and are drug-like: 106, 45, and 6 compounds pass through finer filters of physicochemical properties suggested by Oprea,[10b] Gleeson,[10c] and Churcher,[10d] respectively (Figure 9).

CONCLUSION

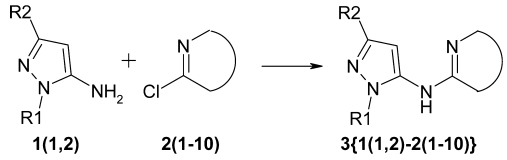
In conclusion, the reaction of 5-hetarylaminopyrazoles with carbonyl compounds furnish annulated pyrazolo[3,4-*d*]-dihydropyrimidines in preparative yields. The optimized synthetic and purification procedures allow high throughput synthesis of extended pyrazolo[3,4-*d*]dihydropyrimidines bearing various functional groups. The new scaffolds have four variation points which allow synthesis of large and diverse combinatorial arrays for high throughput screening of biological activity. More than 500 compounds of such type have been synthesized in our laboratories (some examples (221 additional compounds) are shown in the Supporting Information).

EXPERIMENTAL PROCEDURES

General. All chemicals were obtained from commercially available sources and used without further purification (Aldrich, Fluka, Enamine Ltd.). All solvents for the reactions (DMF, THF, *t*-BuOH) were freshly distilled and dried by standard methods, monitoring of the water concentration in solvents (all solvents had <0.05%, usually 0.02% of water) was performed using Mettler Toledo DL31 KF Titrator. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. Melting points were measured on a Buchi melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker Avance DRX 500 using DMSO-d_6 as a solvent and TMS as an internal standard. LC/MS spectra were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. Column, Zorbax SB-C18, 1.8 μm, 4.6 mm ×15 mm. Eluent, A, MeCN−water with

dx.doi.org/10.1021/co300063x | *ACS Comb. Sci.* 2012, 14, 465−470

Table 2. Synthesis of Compounds 3



Entry	1	2	Product	Conditions	Yield (%)
1	1(1)	2(1)	3{1(1)-2(1)}	C	62
2	1(1)	2(2)	3{1(1)-2(2)}	C	69
3	1(1)	2(3)	3{1(1)-2(3)}	C	84
4	1(1)	2(4)	3{1(1)-2(4)}	C	79
5	1(2)	2(1)	3{1(2)-2(1)}	C	78
6	1(2)	2(2)	3{1(2)-2(2)}	C	78
7	1(2)	2(3)	3{1(2)-2(3)}	C	81
8	1(2)	2(5)	3{1(2)-2(5)}	C	83
9	1(2)	2(6)	3{1(2)-2(6)}	C	64
10	1(2)	2(7)	3{1(2)-2(7)}	B	91
11	1(2)	2(8)	3{1(2)-2(8)}	B	87
12	1(2)	2(9)	3{1(2)-2(9)}	B	72
13	1(2)	2(10)	3{1(2)-2(10)}	B	93

0.1% of TFA (95:5); B, water with 0.1% of TFA. Flow rate: 1.8 mL/min. The volume of the injected sample was 1 μL. UV-detectors operate at 215, 254, and 265 nm. Ionization method: chemical ionization under atmospheric pressure (APCI). Ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80−1000 m/z. According to HPLC/MS data all the synthesized compounds have purity over 95%.

General Procedures for Arylation of Aminopyrazoles 1. *Method A.* Arylating agent **2** (0.01 mol) was added in one portion to the vigorously stirred solution of pyrazole **1** (0.01 mol), Cs_2CO_3(0.015 mol), and LiF (0.015 mol) in DMF (30 mL) in a round-bottom flask. The reaction mixture was heated at 100 °C for 12 h. After it was cooled to r.t., the reaction mixture was poured into water (300 mL) and was sonicated at r.t. in ultrasonic bath for 1 h. The precipitate formed was filtered off and washed with *i*-PrOH−water (1:1) and recrystallized from EtOH. In the cases where an oil formed, these were purified by HPLC on silica (hexane−EtOAc 9:1).

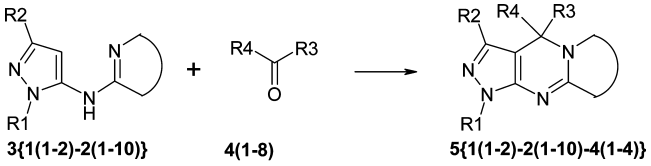
Method B. NaH (0.015 mol, 60% suspension in oil) was added by four equal portions during 10 min to the vigorously stirred solution of pyrazole **1** (0.01 mol) in DMF (30 mL) in a round-bottom flask. The reaction mixture was maintained at r.t. for 30 min, than arylating agent **2** (0.01 mol) was added in one portion, and the reaction mixture was heated at 100 °C over 12 h. Isolation/purification was achieved as described in method A.

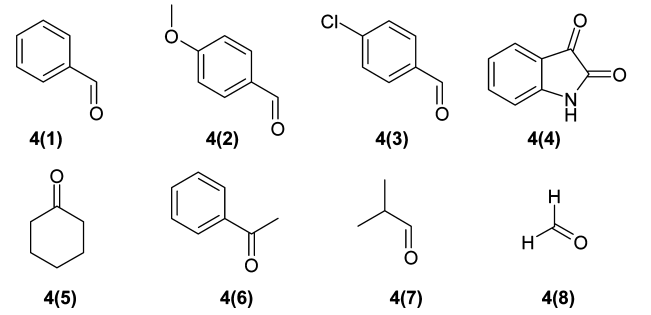
Method C. NaH (0.015 mol, 60% suspension in oil) was added in four equal portions during 10 min to the vigorously stirred solution of pyrazole **1** (0.01 mol) in THF (50 mL) in a round-bottom flask. The reaction mixture was maintained at r.t. for 30 min, than arylating agent **2** (0.01 mol) was added in one portion, and the reaction mixture was stirred at 60 °C over 12 h. Isolation/purification was achieved as described in method A.

Method D. *t*-BuOK (0.012 mol) was added in one equal portion to the vigorously stirred solution of pyrazole **1** (0.01 mol)

dx.doi.org/10.1021/co300063x | ACS Comb. Sci. 2012, 14, 465−470

Table 3. [5 + 1] Cyclocondensation of 3 and 4

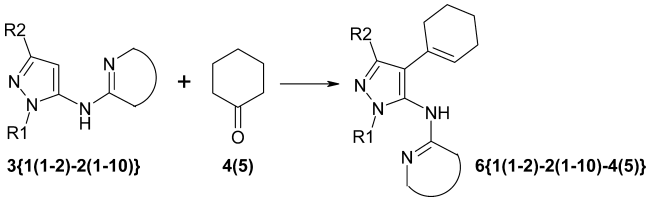




	3	4	product	conditions[a]	yield (%)
1	3{1(1)−2(1)}	4(1)	5{1(1)−2(1)−4(1)}	A/B	69/42
2	3{1(1)−2(2)}	4(1)	5{1(1)−2(2)−4(1)}	A	82
3	3{1(1)−2(3)}	4(1)	5{1(1)−2(3)-4(1)}	A	84
4	3{1(1)−2(4)}	4(1)	5{1(1)−2(4)−4(1)}	A	79
5	3{1(2)−2(1)}	4(1)	5{1(2)−2(1)−4(1)}	A	81
6	3{1(2)−2(2)}	4(1)	5{1(2)−2(2)−4(1)}	A/B	86/57
7	3{1(2)−2(5)}	4(1)	5{1(2)−2(5)−4(1)}	A/B	78/49
8	3{1(2)−2(3)}	4(2)	5{1(2)−2(3)−4(2)}	A	84
9	3{1(2)−2(7)}	4(2)	5{1(2)−2(7)−4(2)}	A	76
10	3{1(2)−2(8)}	4(2)	5{1(2)−2(8)−4(2)}	A	77
11	3{1(2)−2(9)}	4(2)	5{1(2)−2(9)−4(2)}	A	85
12	3{1(2)−2(10)}	4(2)	5{1(2)−2(10)−4(2)}	A/B	81/58
13	3{1(2)−2(3)}	4(3)	5{1(2)−2(3)−4(3)}	A	78
14	3{1(2)−2(6)}	4(3)	5{1(2)−2(6)−4(3)}	A	73
15	3{1(2)−2(7)}	4(3)	5{1(2)−2(7)−4(3)}	A	81
16	3{1(2)−2(8)}	4(3)	5{1(2)−2(8)−4(3)}	A	83
17	3{1(2)−2(10)}	4(3)	5{1(2)−2(10)−4(3)}	A	85
18	3{1(2)−2(5)}	4(4)	5{1(2)−2(5)−4(4)}	A/B	84/58
19	3{1(2)−2(6)}	4(4)	5{1(2)−2(6)−4(4)}	A	82
20	3{1(2)−2(7)}	4(4)	5{1(2)−2(7)−4(4)}	A	80
21	3{1(2)−2(8)}	4(4)	5{1(2)−2(8)−4(4)}	A	83
22	3{1(2)−2(9)}	4(4)	5{1(2)−2(9)−4(4)}	A	82
23	3{1(2)−2(10)}	4(4)	5{1(2)−2(10)−4(4)}	A	85
24	3{1(1)−2(1)}	4(5)	6{1(1)−2(1)−4(5)}	A	64
25	3{1(1)−2(2)}	4(5)	6{1(1)−2(2)−4(5)}	A	67
26	3{1(1)−2(3)}	4(5)	6{1(1)−2(3)−4(5)}	A	68
27	3{1(1)−2(4)}	4(5)	6{1(1)−2(4)−4(5)}	A	64
28	3{1(2)−2(2)}	4(5)	6{1(2)−2(2)−4(5)}	A	68
29	3{1(2)−2(5)}	4(5)	6{1(2)−2(5)−4(5)}	A/B	62/32

[a]Conditions: (A) Me_3SiCl, DMF, 100 °C; (B) AcOH, reflux.

Scheme 2



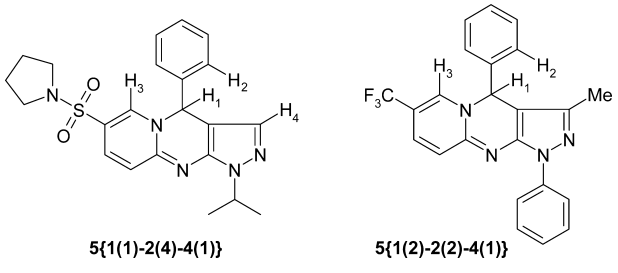


Figure 2. Important NOE and NOESY correlations in representative compounds **5**. H1(H2) = 17%, H1(H3) =17%, H1(H4) = 3%.

Table 4. Physicochemical Properties of Compounds Synthesized

property	range	mean value
M_w	282−554	422
cLogP	0.27−7.35	4.18
HBA	3−10	5.86
HBD	0−3	0.32
RB	1−6	2.94
TPCA	33.4−136.8	67.76

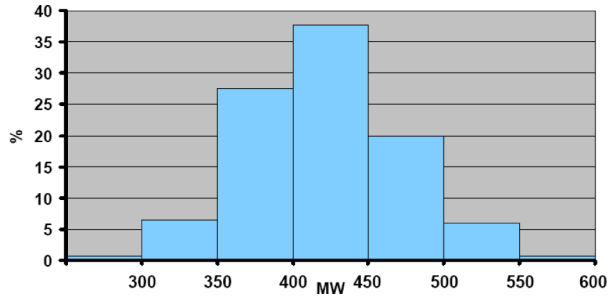


Figure 3. Molecular weight distribution.

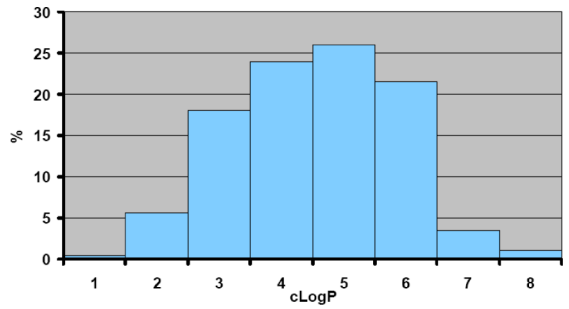


Figure 4. cLog P distribution.

in *t*-BuOH (40 mL) in a round-bottom flask. The reaction mixture was maintained at r.t. for 30 min, than arylating agent **2** (0.01 mol) was added in one portion, and the reaction mixture was stirred at 60 °C over 12 h. Isolation/purification was achieved as described in method A.

General Procedures for Synthesis of Pyrazolodihydropyrimidines 5. *Method A.* A solution of compound **3**

dx.doi.org/10.1021/co300063x | *ACS Comb. Sci.* 2012, 14, 465−470

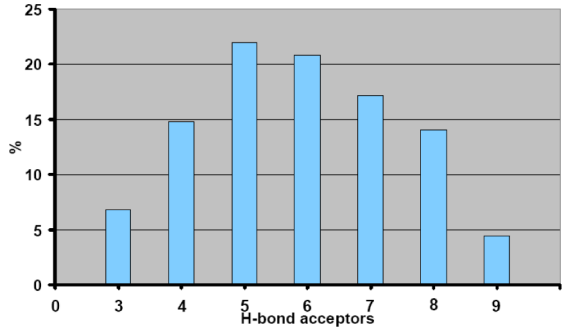


Figure 5. H-bond acceptors distribution.

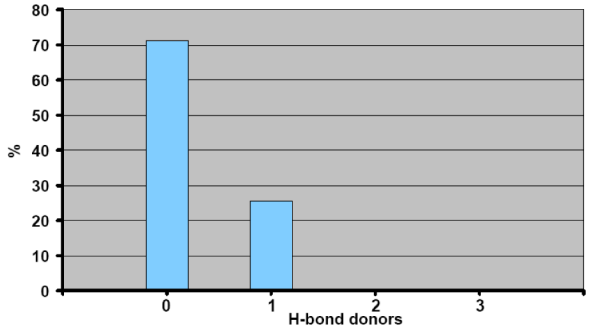


Figure 6. H-bond donors distribution.

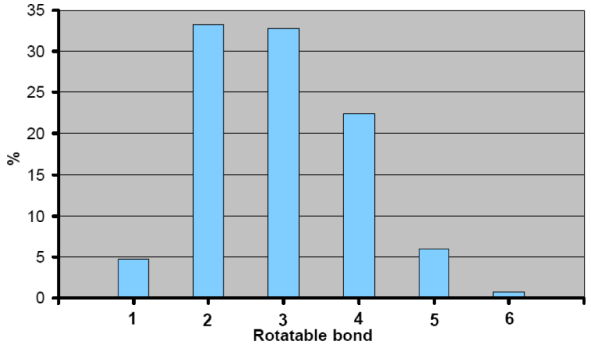


Figure 7. Rotatable bonds distribution.

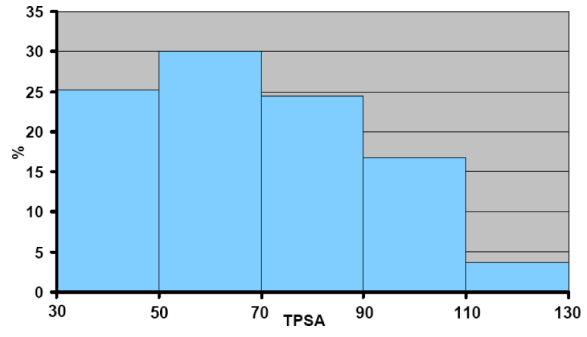


Figure 8. TPSA distribution.

(1 mmol), **4** (1.1 mmol), and Me_3SiCl (3 mmol) in DMF (1 mL) was heated at 100 °C for 16 h in a sealed tube (10 mL). Then the reaction mixture was cooled down to room temperature and diluted with water (8 mL). The suspension formed was sonicated at r.t. for 1−2 h, the precipitate was

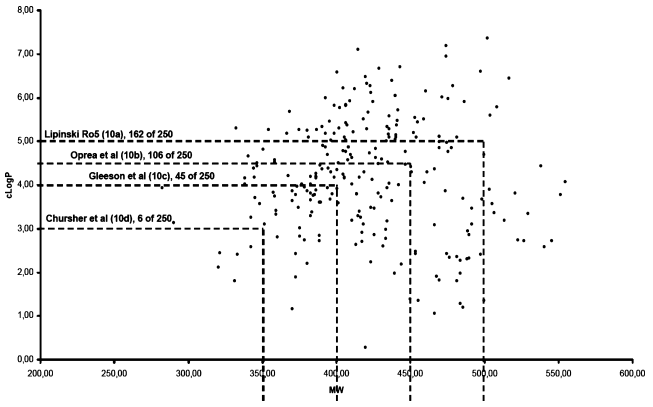


Figure 9. cLogP−MW plot for 250 pyrazolo[3,4-*d*]dihydropyrimidines.

filtered off and washed with aq. $NaHCO_3$, (8 mL of 5% aq. solution), *i*-PrOH (1 mL), and MeCN (1 mL).

Method B. A solution of compound **3** (1 mmol) and **4** (1.1 mmol) in glacial AcOH (1 mL) was heated at 120 °C for 16 h in sealed tube (10 mL). Isolation/purification was achieved as described in method A.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Compound data for representative set of compounds synthesized and ^{1}H NMR, ^{13}C NMR, NOE, and NOESY spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: s.v.ryabukhin@gmail.com, a.shivanyuk@univ.kiev.ua.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Mr. Vitaliy V. Polovinko (Enamine Ltd) for NMR measurements.

■ REFERENCES

(1) Pacher, P.; Nivorozhkin, A.; Szabó, C. Therapeutic effects of xanthine oxidase inhibitors: Renaissance half a century after the discovery of allopurinol. *Pharm. Rev.* **2006**, *58*, 87−114.

(2) Ovcharova, I. M.; Zasosova, I. M.; Gerchikov, L. N.; Shuvalova, M. E.; Golovchinskaya, E. S.; Liberman, S. S. Allopurinol, its synthesis and pharmacological activity. *Pharm. Chem. J.* **1973**, *7*, 735−737.

(3) Bacon E. R.; Bailey, T.; Becknell, N. C. ; Gingrich, D. E.; Hostetler, G.; Hudkins, R. L.; Learn K. S.; Wagner J. C. Preparation of substituted pyrazolopyrimidines as inhibitors of glycogen synthase kinase 3 and cyclin dependent kinase 5. U.S. Patent 20070281949, 2007.

(4) Smith, N. D.; Bonnefous, C.; Zhuang H.; Chen, X.; Duron, S.; Lindstrom, A. Preparation of diarylaminoquinolone derivatives for use as inducible nitric oxide synthase inhibitors. U.S. Patent 2009029617, 2009.

(5) (a) Das, J.; et al. Pyrazolo-pyrimidines: A novel heterocyclic scaffold for potent and selective p38α inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2652−2657. (b) Holzer, P.; Imbach, P.; Furet, P.; Schmideberg, N. Preparation of 3-(substituted amino)-pyrazolo[3,4-d]pyrimidines as EphB4 receptors and VEGFR2 kinase inhibitors. WO2007062805, 2007.

(6) (a) Hayashi, E.; et al. Antitumor activity of eighty-four synthesized N-heteroaromatic compounds. *Yakugaku Zasshi (Jap.)*

1977, *97*, 1022−1033. (b) Higashino, T.; Iwai, Y.; Hayashi, E. Studies on pyrazolo[3,4-d]pyrimidine derivatives. IV. On 1-methyl- and 1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine 5-oxide. *Chem. Pharm. Bull.* **1976**, *24*, 3120−3134.

(7) For other methods for the synthesis of this kind of compounds see: (a) Higashino, T.; Sato, S.; Miyashita, A.; Katori, T. Studies on pyrazolo[3,4-d]pyrimidine derivatives. XVI. Preparation of Reissert compounds from condensed pyrimidine systems catalyzed by Lewis acids. *Chem. Pharm. Bull.* **1987**, *35*, 4803−4812. (b) Higashino, T.; Sato, S.; Miyashita, A.; Katori, T. Studies on pyrazolo[3,4-d]pyrimidine derivatives. XIV. Preparation and reactions of 1-phenyl-1*H*-pyrazolo-[3,4-d]pyrimidine Reissert compound. *Chem. Pharm. Bull.* **1986**, *34*, 4569−4576. (c) Ishikawa, F.; Yamaguchi, H. Cyclic guanidines. XIII. Synthesis of 2-amino-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine derivatives. *Chem. Pharm. Bull.* **1980**, *28*, 3172−3177.

(8) (a) Volochnyuk, D. M.; Ryabukhin, S. V.; Plaskon, A. S.; Grygorenko, O. O. Organosilicon compounds as water scavengers in reactions of carbonyl compounds. *Synthesis* **2009**, *22*, 3719−3743. (b) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. Synthesis of fused imidazoles and benzothiazoles from (hetero)aromatic *ortho*-diamines or *ortho*-aminothiophenole and aldehydes promoted by chlorotrimethylsilane. *Synthesis* **2006**, *21*, 3715−3726. (c) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Tolmachev, A. A. *N*-Substituted ureas and thioureas in Biginelli reaction promoted by chlorotrimethyl-silane: Convenient synthesis of *N*1-alkyl, *N*1-aryl-, and *N*1,*N*3-dialkyl-3,4-dihydropyrimidin-2(1*H*)-(thio)ones. *Synthesis* **2007**, *3*, 417−427. (d) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Shivanyuk, A. N.; Tolmachev, A. A. Combinatorial Knoevenagel reactions. *J. Comb. Chem.* **2007**, *9*, 1073−1078. (e) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Shishkin, O. V.; Shivanyuk, A. N.; Tolmachev, A. A. A one step fusion of 1,3-thiazine and pyrimidine cycles. *Org. Lett.* **2007**, *9*, 4215−4218. (f) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Shishkin, O. V.; Tolmachev, A. A. A CF_3-substituted 1,3-dicarbonyl compounds in the Biginelli reaction promoted by chlorotrimethylsilane. *J. Fluor. Chem.* **2008**, *129*, 625−631. (g) Ryabukhin, S. V.; Plaskon, A. S.; Bondarenko, S. S.; Ostapchuk, E. N.; Grygorenko, O. O.; Shishkin, O. V.; Tolmachev, A. A. Acyl pyruvates as synthons in the Biginelli reaction. *Tet. Lett.* **2010**, *51*, 4229−4232. (h) Ryabukhin, S. V.; Plaskon, A. S.; Boron, S. Y.; Volochnyuk, D. M.; Tolmachev, A. A. Aminoheterocycles as synthons for combinatorial Biginelli reactions. *Mol. Div.* **2011**, *15*, 189−195.

(9) Instant JChem was used for prediction of the physicochemical properties of the library members, Instant JChem 3.0, 2009, ChemAxon (http://www.chemaxon.com).

(10) (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug. Deliv. Rev.* **1997**, *23*, 3−25. (b) Oprea, T. I.; Davis, A. M.; Teague, S. J.; Leeson, P. D. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1308−1315. (c) Gleeson, M. P. *J. Med. Chem.* **2008**, *51*, 817−834. (d) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114−1122.