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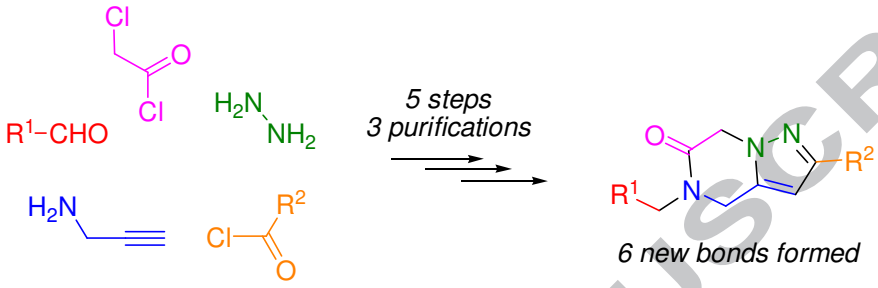

An expeditious and atom-economic synthesis of lead-like, medicinally important 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones

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Abstract: We have developed an expeditious and atom-economic synthesis of lead-like, privileged 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones, which is based on Sonogashira coupling and a two-step condensation with hydrazine hydrate leading to two ring-forming events, with full control over the two elements of diversity present.

Keywords: propargylamine, Sonogashira coupling, ynone, pyrazole, intramolecular alkylation, atom efficiency, lead-likeness, privileged structure

The choice of a synthetic target may not only be dictated by the current practical needs of a specific research program, but may be a result of a chemist's conscious effort to undertake a creativity exercise in synthetic planning and identifying particularly simple ways to construct structurally complex scaffolds with an underlying potential to exert biological activities. Undertaking such an exercise regularly, besides its scholastic value, may very well be the principal, if not the only driving force behind various scaffold-oriented efforts aimed at increasing the volume and improving the quality of the chemical matter currently available for biological screening.

Numerous ideas generated in the course of such an activity require some level of prioritization before taking a decision to realize them in a laboratory setting. A scaffold idea will be more likely to progress through the 'paper exercise' stage if it scores highly on such basic criteria as novelty, medicinal relevance (i.e., availability of biological activity data for related structural motifs) and, very importantly, the low number and practical simplicity of synthetic manipulations required to translate the scaffold idea into a set of tangible compounds.

Ample use of ring-forming transformations engaging multiple reactive centers within synthetic precursors is a proven strategy to achieve convergent, atom-economic synthetic planning, and thus shorten the sequence of synthetic operations.[1] In the course of one of our group's brain-storming sessions, the idea of assembling ynone **1** was raised. It was recognized as a versatile, triply electrophilic synthon and was expected to give rise to 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2** on reaction with hydrazine, in which case, the latter would act as an "N^{2-}–N^{-}" equivalent (Figure 1). A quick analysis of the literature available on the pyrazolo[1,5-*a*]pyrazine scaffold revealed it to be relatively novel with the vast majority of reports published in the last 3-5 years. At the same time, the scaffold appeared highly relevant in terms of possible medicinal chemistry applications. In fact, based on the number of diverse biological activities displayed by the compounds containing the pyrazolo[1,5-*a*]pyrazine motif, it could be considered privileged, as defined by Evans.[2] To support this view, the following selected examples can be mentioned (Figure 2):

i. the core was central to the design of Janssen's BACE-1 inhibitors (exemplified by **3**) for treatment of Alzheimer's disease;[3]
ii. positive allosteric modulators of metabolic glutamate receptor 5 (mGluR5), such as **4**, have recently been disclosed by Janssen and Vanderbilt University;[4]
iii. a team from Millennium Pharmaceuticals developed selective HDAC6 inhibitors (e.g., **5**)[5] that are essentially the pyrazolo[1,5-*a*]pyrazine scaffold decorated with a pharmacophoric hydroxamic acid functionality;
iv. a large team of researchers from Shandong University discovered potent cytotoxic agents such as **6**[6] that have subsequently been found to act as apoptosis inducers;[7]
v. Merck and Co. incorporated the pyrazolo[1,5-*a*]pyrazine scaffold in the design of their selective MK2 inhibitors (e.g., **7**);[8]
vi. the bicyclic heterocycle has appeared as part of a bioactive molecule's unique periphery in Genentech's BTK inhibitors,[9] in the selective TrkA inhibitors from Dr. Reddy's

Laboratories,[10] in Janssen's SCD-1 inhibitors which are potentially useful as anti-obesity drugs,[11] in GSK's inhibitors of NADPH oxidase II[12] and Zalizus Pharmaceuticals' calcium channel blockers for pain management.[13]

In addition to these considerations, the development of screening libraries based on the 4,5-dihydropyrazolo[1,5-*a*]pyrazine scaffold would fill an important void in the currently available screening collections – namely, the scarcity of so-called lead-like compounds. According to a recent seminal account from GSK's computational chemistry team,[14] the synthetic methods reported in the literature over recent decades appear to be unintentionally biased toward producing more lipophilic (high logP) compounds of higher molecular weight (Mw), whereas the chemistry space defined by Mw <350 and logP <3.0 and thus most relevant to screening-based drug discovery efforts, remains alarmingly underpopulated (Figure 3). The 4,5-dihydropyrazolo[1,5-*a*]pyrazine core itself resides very well within this range (Mw = 137, clogP = -1.87),[15] which leaves ample room (both in terms of lipophilicity and heavy atom count) for growing the periphery of a compound during library development.

To access the key synthons (such as **1**), two possibilities were considered (Figure 4). One of them was described by Wipf[16] and implied the generation, from an appropriately decorated propargylamine synthon, of a lithium acetylide species and its addition to an aldehyde followed by oxidation of the intermediate alcohol to the corresponding carbonyl compound. The other possibility would be to invoke Sonogashira-type coupling of the same synthon with an acyl chloride. The latter approach, being very well described by Cox,[17] was chosen by us due to its practical simplicity.

The overall synthetic scheme toward 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2a-m** developed based on this approach is presented in Scheme 1. Terminal alkyne synthon **8** was prepared in three simple chemical operations (imine formation, imine reduction and capping of the secondary amine with chloroacetyl chloride in the presence of a polymer-supported piperidine base as an HCl scavenger) and purified chromatographically in good to excellent yields. Sonogashira coupling with a set of acyl chlorides (aliphatic and aromatic) proved to work very well under the conditions reported by Cox.[17] Finally, condensation with hydrazine hydrate was very quick under reflux conditions in ethanol, however, it did not lead, even over prolonged reaction times and on using excess hydrazine hydrate, to the concomitant piperazinone ring closure as we had hoped. We discovered, however, that once the initial formation of the pyrazole nucleus was complete (according to TLC analysis), the desired

intramolecular alkylation could be relatively quickly brought about by the addition of an equivalent amount of sodium ethoxide and continued heating at reflux (similarly to the conditions for intramolecular pyrazole alkylation described by Janssen earlier).[3] As can be seen from Table 1, a set of diversely substituted 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2a-m** was prepared in good to excellent overall yields.[18] The synthesis is remarkably atom-efficient (all the synthons used were almost entirely incorporated into the product structure with the loss of condensation water and two equivalents of HCl), involves formation of five chemical bonds and requires only three purifications. The resulting compounds are distinctly lead-like as can be seen from their Mw/clogP profile (Figure 5).[15]

In summary, we have developed an expeditious and atom-economic synthesis of lead-like, privileged 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones with full control over the two elements of diversity present. The biological activity of these compounds will be studied extensively, via a panel biological annotation approach, and any promising bioactivity leads identified will be reported in due course.

Acknowledgements

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References and notes

1. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259-281.
2. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235-2246.
3. Trabanco-Suarez, A. A.; Tresadern, G. J.; Delgado-Jimenez, F. PCT Int. Appl. WO2012038438, **2012**; *Chem. Abstr.* **2012**, *156*, 477738.
4. (a) Conn, P. J.; Lindsley, C. W.; Stauffer, S. R.; Jones, C. K.; Conde-Ceide, S.; Tong, H. M.; Bartolome-Nebreda, J. M.; Macdonald, G. J. PCT Int. Appl. WO2012078817, **2012**; *Chem. Abstr.* **2012**, *157*, 76803; (b) Conn, P. J.; Lindsley, C. W.; Stauffer, S. R.; Bartolome-Nebreda, J. M.; Conde-Ceide, S.; Macdonald, G. J.; Tong, H. M.; Jones, C.

K.; Alcazar-Vaca, M. J.; Andres-Gil, J. I.; Malosh, C. PCT Int. Appl. WO2012083224, **2012**.; *Chem. Abstr.* **2012**, *157*, 133822.

5. Blackburn, C.; Chin, J.; Gigstad, K. M.; Xu, H. US Patent Appl. US20110251184, **2011**; *Chem. Abstr.* **2011**, *155*, 536170.
6. Liu, N.; Zhang, J.-H.; Zhao, B.-X.; Zhao, J.; Su, L.; Dong, W.-L.; Zhang, S.-L.; Miao, J.-Y. *Eur. J. Med. Chem.* **2011**, *46*, 2359-2367.
7. Lv, H.-S.; Kong, X.-Q.; Ming, Q.-Q.; Jin, X.; Miao, J.-Y.; Zhao, B.-X. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 844-849.
8. Barf, T.; Kaptein, A.; de Wilde, S.; van der Heijden, R.; van Someren, R.; Demont, D.; Schultz-Fademrecht, C.; Versteegh, J.; van Zeeland, M.; Seegers, N.; Kazemier, B.; van de Kar, B.; van Hoek, M.; de Roos, J.; Klop, H.; Smeets, R.; Hofstra, C.; Hornberg, J.; Oubrie, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3818-3821.
9. (a) Crawford, J. J.; Ortwine, D. F.; Wei, B.; Young, W. B. PCT Int. Appl. WO2013067274, **2013**; *Chem. Abstr.* **2013**, *158*, 695455; (b) Crawford, J. J.; Ortwine, D. F.; Wei, B.; Young, W. B. PCT Int. Appl. WO2013067264, **2013**; *Chem. Abstr.* **2013**, *158*, 679309.
10. Sasmal, P. K.; Ahmed, S.; Prabhu, G.; Tehim, A.; Paradkar, V.; Dattatreya, M. P.; Mavinahalli, N. J. PCT Int. Appl. WO2013088257, 272 pp.; *Chem. Abstr.* **2013**, *159*, 133927.
11. Yang, S.-M.; Tang, Y.; Zhang, R.; Lu, H.; Kuo, G.-H.; Gaul, M. D.; Li, Y.; Ho, G.; Conway, J. G.; Liang, Y.; Lenhard, J. M.; Demarest, K. T.; Murray, W. V. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6773-6776.
12. Chen, D. W.; Duncan, S.; King, N. P.; Lee, K. C.; Mak, S. Y.; Rivers, D. A. PCT Int. Appl. 2012170752, **2012**; *Chem. Abstr.* **2012**, *158*, 77237.
13. Pajouhesh, H.; Holland, R.; Zhou, Y.; Zhu, Y.; Grimwood, M. E.; Chahal, N. PCT Int. Appl. WO2012061926, **2012**; *Chem. Abstr.* **2012**, *156*, 666176.
14. Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114-1122.
15. Calculations were performed using ACD/Labs 6.00 software.
16. Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593-3595.
17. Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Commun.* **2005**, 1037-1039.
18. Characterization data for representative compounds: **2b –** sticky white solid, mp = 116-123 °C (broad); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.78 (m, 2H), 7.12-7.21 (m, 2H), 6.31 (s, 1H), 5.11 (s, 2H), 4.12 (s, 2H), 2.83 (d, *J* = 7.1 Hz, 2H), 1.62 (m, 1H), 0.57 (d, *J*

= 7.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.5, (d, J_{C-F} = 254.0 Hz), 150.2, 140.2, 127.5 (d, J_{C-F} = 9.8 Hz), 126.9 (d, J_{C-F} = 2.7 Hz), 115.6 (d, J_{C-F} = 27.6 Hz), 101.6, 49.2, 48.3, 44.6, 28.0, 19.6; LC MS (EI) *m/z* $[M+H]^+$ 288.3; anal. calcd for $C_{16}H_{18}FN_3O$: C, 66.88; H, 6.31; N 14.62; found: C, 67.02; H, 6.42; N, 14.68; **2h –**white solid, mp = 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.72 (m, 2H), 7.33 – 7.46 (m, 2H), 7.19 – 7.23 (m, 2H), 6.23 (m, 1H), 6.11 (s, 1H), 5.82 (d, *J* = 4.6 Hz, 1H), 5.08 (s, 2H), 4.63 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 150.3, 149.3, 142.4, 138.7, 130.8, 129.1, 127.5, 124.5, 111.8, 106.3, 100.4, 46.9, 45.8, 37.3; LC MS (EI) *m/z* $[M+H]^+$ 294.3; anal. calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N 14.33; found: C, 69.53; H, 5.07; N, 14.44; **2l –**white solid, mp = 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.26 – 7.32 (m, 3H), 7.08 – 7.16 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.23 (s, 1H), 4.98 (s, 2H), 4.18 (s, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 154.5, 141.5, 139.6, 138.4, 129.6, 128.9, 128.7, 128.0, 126.7, 126.3, 100.9, 50.3, 49.1, 43.9, 33.8, 21.7; LC MS (EI) *m/z* $[M+H]^+$ 332.4; anal. calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N 12.68; found: C, 76.03; H, 6.33; N, 12.74;

Figure 1. The idea for possible synthetic access to 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2** developed in this work.

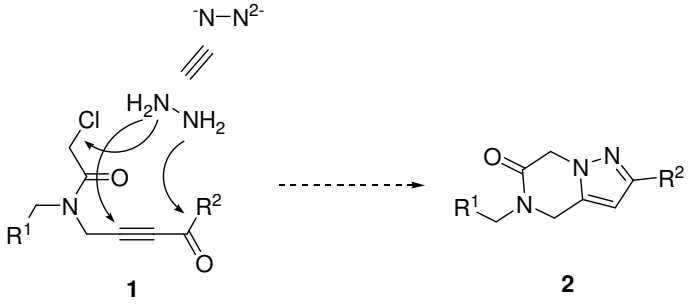


Figure 2. Examples of bioactive pyrazolo[1,5-*a*]pyrazines reported in the literature.

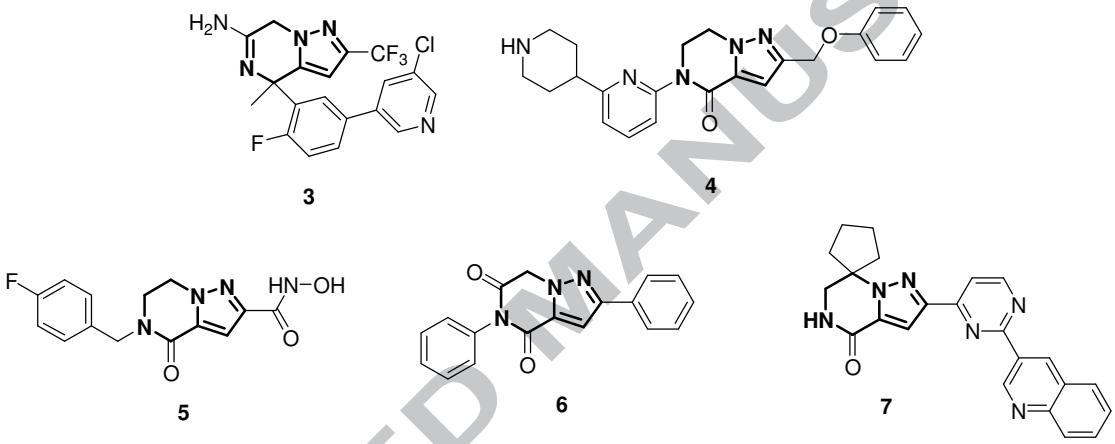


Figure 3. Distribution of Mw and clogP values for two sets of ~30,000 compounds selected from two major screening library vendors – Enamine and ChemDiv (MK's personal account).

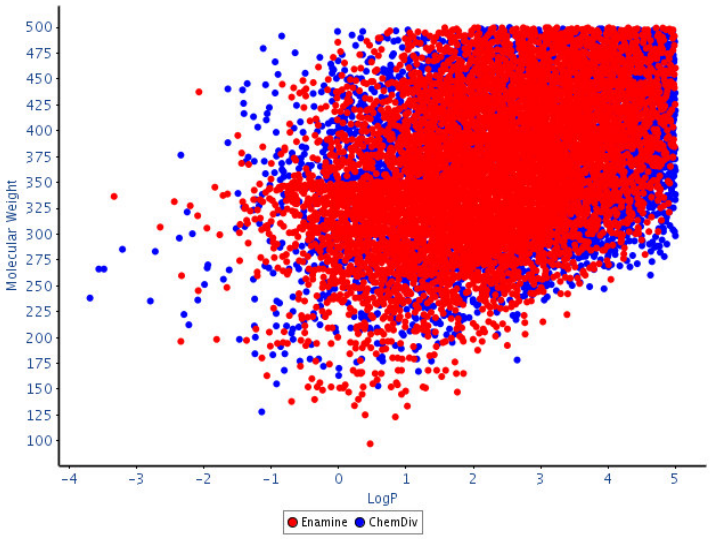


Figure 4. Possible retrosynthetic considerations of synthon **1**.

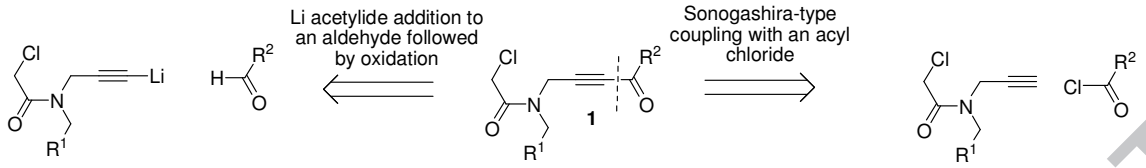
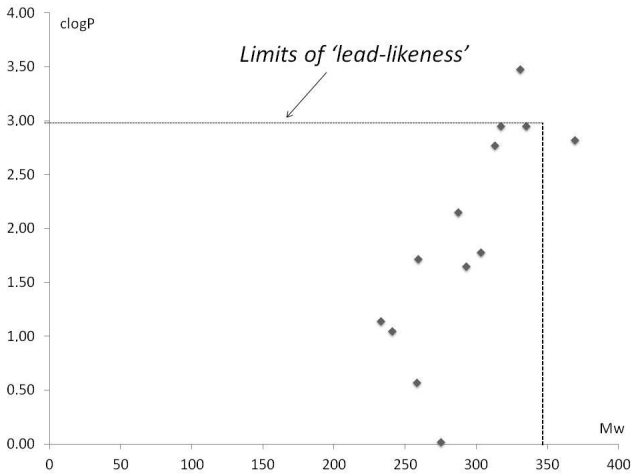


Figure 5. Mw/clogP profile[15] of 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2a-m** synthesized in this work.



Scheme 1. Synthesis of 4,5-dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2** developed in this work.

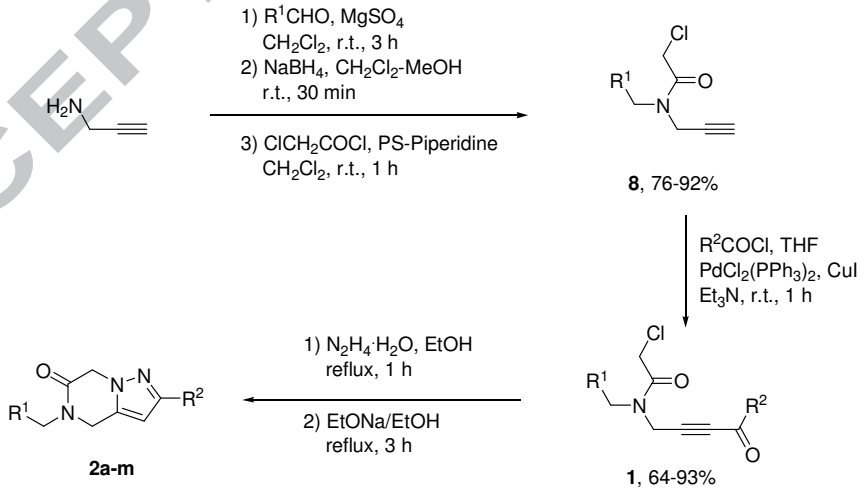
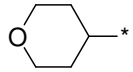
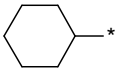
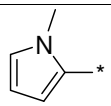
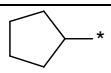


Table 1. 4,5-Dihydropyrazolo[1,5-*a*]pyrazin-6-ones **2** prepared in this work.

Entry	R^1	R^2	Yield of **8** (%)	Yield of **1** (%)	Yield of **2** (%)
a	Ph	4-MeC_6H_4	73	89	59
b	*i*-Pr	4-FC_6H_4	84	77	63
c	*n*-Pr	2-furyl	86	66	78
d			77	65	67
e	Ph	Me	92	64	75
f	3,5-$F_2C_6H_3$		77	71	57
g	2,4-$(MeO)_2C_6H_3$		81	70	75
h	2-furyl	Ph	81	93	73
i		Et	90	68	64
j		4-FC_6H_4	92	91	78
k	Bn	4-FC_6H_4	77	90	81
l	Bn	4-MeC_6H_4	83	83	63
m		*i*-Pr	90	71	48