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# Synthesis of two 'heteroaromatic rings of the future' for applications in medicinal chemistry

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**In a computational study, the 1H-pyrazolo[3,4-c]pyridin-5-ol and 2,6-naphthyridin-3-ol heterocycles were identified unknown heteroaromatic ring systems of potential value for medicinal chemistry. Here we report robust and concise synthetic protocols that provide access to these two scaffolds on a multigram scale.**

Heterocycles are an indispensable component of life occurring in a vast array of natural small molecules as well as biopolymers such as proteins and nucleic acids. Consequently, it is not surprising that medicinal chemists are heavily dependent on heterocycles for drug discovery. In addition to mimicking natural motifs, heterocycles serve important functions as bioisosteres and their inclusion can profoundly influence a drug's physicochemical properties. Their prevalence can be appreciated by examining the top 200 pharmaceutical products by US retail sales in 2012.[1] Among the 147 small molecule entries, 97 (66%) incorporate at least one heterocycle.

A recent publication by Taylor *et al*. has identified the heterocycles that are most frequently present in drug molecules.[2] The adoption of a given heterocycle by the medicinal chemistry community has largely relied on synthetic tractability and historical precedents with known scaffolds. While this conservative strategy may be a valid choice given the high rate of attrition in drug discovery, it is not clear if popular heterocycles are inherently superior or if less explored alternatives could be equally profitable for the discovery of drug-like compounds. In other words, in addition to 'privileged scaffolds', are there 'underprivileged scaffolds' that could enable access to unexploited areas of chemical space and have the added advantage of avoiding overlap with the patent coverage of competitors? In order to access such rare heterocycles, it is first necessary to design reliable synthetic routes for their preparation. For example, we have recently reported the solution- and solid-phase synthesis of 2,4,5-trisubstituted-1,2,4-triazine-3,6-diones.[3] This heterocyclic ring system can be considered an aza-analogue and bioisostere of diketopiperazines, but has far fewer reports than the latter in the literature.

**Figure 1.** Structures of two scaffolds **1** and **2** identified as 'Heteroaromatic Rings of the Future' and of bioisosteric scaffolds **3**-**6**.

Here we describe our efforts in the synthesis of two scaffolds that belong to the underprivileged category. Our starting point was the computational study conducted by UCB Celltech, which sought to identify 'Heteroaromatic Rings of the Future'.[4] A virtual library of all the 24847 possible small heteroaromatic ring systems was generated. Of these heterocycles, only 1701 were described in the literature and over 3000 synthetically tractable unpublished heteroaromatic ring systems were identified using a machine learning approach. These were further filtered down to 22 heterocycles containing four or fewer heteroatoms that were described as a 'challenge to creative organic chemists to either make or explain why they cannot be made!' We have risen to the challenge and targeted two of these heterocycles, 1,6 -dihydro-5*H*-pyrazolo[3,4-*c*]pyridin-5-one **1a** and 2,6-naphthyridine-3(2*H*)-one **2a**, as depicted in the UCB Celltech publication and shown here with their alternative tautomeric forms **1** and **2** (Fig. 1).

These heterocycles represent a complementary pair containing a pyridine-2-ol unit fused to either a π-excessive or a π-deficient heterocycle. While neither of the parent heterocycles, **1** and **2**, have previously appeared in the medicinal chemistry literature, they are isosteres of more familiar fused-ring heteroaromatic systems such as **3**-**6**.

**1*H*-Pyrazolo[3,4-*c*]pyridin-5-ol (1)**

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Chapman and Hurst's investigations on pyrazolopyridines inspired our synthesis of scaffold **1**. As part of this work, a 1980 publication reported the acetylation of pyridine **7** to **8** and its conversion to **12.** It is proposed that this conversion proceeds via the fragmentation of intermediate *N*-nitroso pyridine **9** to diazonium salt **10**, followed by cyclization and acetylation to **12**.[5] Hydrolysis then afforded **11**, which is the methoxy derivative of scaffold **1** (Scheme 1). We repeated this procedure by replacing nitrosyl chloride with the safer and more easily handled sodium nitrite for nitrosation, as in Zhu's analogous cyclization.[6] Although Chapman and Hurst do not report the scale of the final reactions, we were able to prepare **11** in multigram quantities using this method. In a similar fashion, we synthesized the chloride derivative **15**. In this case, the acetylation, nitrosation, and cyclization of **13** to **14** and acetate hydrolysis to **15** were accomplished by one-pot simplification of the original procedure. However, we were unable to reach the parent heterocycle **1**, either by demethylation of **11** or by displacement of the chloride in **15**, under a variety of reaction conditions. Although the demethylation of **11** with TMSCl was recently reported as part of an NMR study by Tsikouris *et al*.,[7] we were unsuccessful in similar attempts. Additionally, demethylation methods with boron tribromide,[8] $CH_3SNa$,[9] and $AlCl_3$[10] were also fruitless. For chloride replacement in **14** we used several aromatic substitutions described for 2-chloropyridines using both acidic[11-13] and basic catalysis;[14] however, none of these methods were successful.

Faced with the above-mentioned difficulties, we turned to an alternative starting material lacking the methoxy substitution present in **7**. Raney nickel reduction of nitropyridine **16** (Scheme 1), which is coincidentally less expensive than **7**, afforded pyridone **17**, which was subjected to one-pot acetylation and nitrosation. This step yielded a complex mixture of products, from which the acetylated pyrazolopyridine **18** (32%) was isolated, alongside traces of **1** and monoacylated derivatives.

This three-step sequence from an inexpensive starting material can also be conveniently carried out using the one-pot methodology. This one-pot procedure proved to be more effective, yielding 82% of **1** as its hydrochloride salt without requiring any chromatographic purification of the intermediates, even on scales larger than 1 g. In solution, IR and NMR spectroscopy reveal that **1** is present in the hydroxy pyridine tautomer with a characteristic O-H stretch at 3154 $cm^{-1}$.

**Scheme 1.** Synthetic strategies to develop **1**.

**2,6-Naphthyridin-3-ol** (**2**)

Our retrosynthetic approach to the unknown heterocycle **2** was based on oxidation of dihydro derivative **19**. We assumed that **19** would be formed via spontaneous intramolecular lactamization upon reduction of nitrile **20**, a recently described intermediate in a Novartis patent.[15] In practice, the ethyl ester **21** (Scheme 2) of homonicotinic acid was converted to *N*-oxide **22** and alkylated to give **23** in 87% overall yield. As reported by Novartis, nucleophilic addition of cyanide and concomitant rearomatization[16] provided the desired 4-cyano derivative **20** of the homonicotinate. Catalytic hydrogenation of the nitrile proceeded as envisioned, with the intermediate amine undergoing cyclization to lactam **19**.

**Scheme 2**. Synthesis of a 'Heteroaromatic Ring of the Future' **2** from **21**.

The dehydrogenation of **19** to heteroaromatic ring system **2** proved to be challenging. A number of investigated methods, such as Pd/C,[17] DDQ,[18] and $MnO_2$,[19] did not lead to the desired product. Success was finally achieved with Hayashi's method using activated charcoal in an oxygen-rich atmosphere.[20] Overall, this five step route is amenable to the preparation of **2** in good yield, and this experimental procedure is carried out on multigram scale. As was the case for **1**, the spectroscopic evidence indicated that the hydroxy tautomer **2** was present in solution with an O-H stretching band at 3261 $cm^{-1}$ in the IR spectrum and a broad singlet for the OH proton at δ 11.25 in the $^1$H NMR spectrum in DMSO-$d_6$.

**Physicochemical properties**

In addition to serving as a template for further functionalization, heterocycles **1** and **2** should be of interest for researchers involved in fragment-based drug discovery. The physicochemical properties of both heterocycles fit with the Rule of Three[21] proposed for fragments (Table 1), and the values are more compliant than those for the isosteric heterocycles indazole (**3**), 3-hydroxyisoquinoline (**5**), and isoquinoline (**6**). This comparison is particularly evident with respect to lipophilicity and ionization at physiological pH (7.4).

We employed a spectrophotometric procedure to detect the protonation/deprotonation processes of these heterocycles. Based on the spectral changes observed in aqueous solutions at different pH, we could detect two $pK_a$ values for **1**, at 4.5 and 11.5. For heterocycle **2**, we observed one $pK_a$ above 12.

**Table 1.** Predicted physicochemical properties for the synthesized compounds

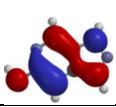
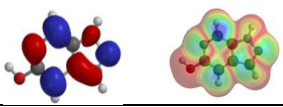
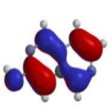
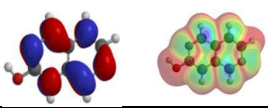
| Property | 1 | 2 | 3 | 5 | 6 |
|---|---|---|---|---|---|
| MW[a] | 135 | 146 | 118 | 145 | 129 |
| HBA[a] | 4 | 3 | 2 | 2 | 1 |
| HBD[a] | 2 | 1 | 1 | 1 | 0 |
| TPSA[a] | 61.8 | 46 | 28.7 | 33.1 | 12.9 |
| HAC[a] | 10 | 11 | 9 | 11 | 10 |
| aLogP[a] | 0.05 | 0.85 | 1.61 | 2.5 | 2.14 |
| logP[b] | 0.57 | 0.84 | 1.47 | 2.15 | 1.74 |
| $LogD_{5.5}$[b] | 0.57 | 0.84 | 1.47 | 2.15 | 1.57 |
| $LogD_{7.4}$[b] | 0.57 | 0.84 | 1.30 | 2.15 | 1.73 |
| aLogS[a] | -1.3 | -1.6 | -0.75 | -1.79 | -1.66 |

**properties calculated with VORTEX ® (DOTMATICS, UK): MW (molecular weight), HBA (hydrogen bond acceptor), HBD (Hydrogen bond donor), TPSA (topological polar surface area), HAC (heavy atoms count) and aLogP (calculated logarithm of partition-coefficient), and aLogS (logarithm of solubility-coefficient); b properties calculated with Marvin Sketch 15.7.20.0 (CHEMAXON Ltd): LogP (calculated lipophilicity), LogD5.5-7.4 (logarithm of distribution-coefficient).*

For drug discovery applications, the aqueous solubility of the heterocycles is of paramount importance. The experimentally determined aqueous solubilities of the heterocycles **1** and **2** were 301 g/L and 2.1 g/L, respectively, which are higher than those of the common isosteres (Supplementary Table 1).

Molecular orbital calculations (Table 2) indicate that both heterocycles have similar electronic distributions and energies for their HOMO and LUMO. The density maps suggest that both **1** and **2** can react with electrophiles and nucleophiles at carbon sites as well as with nitrogen and oxygen moieties; this feature permits further functionalization of the heterocycle towards elaborate fragments.

**Table 2.** Calculated highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) for heterocycles **1** and **2** with maps indicating the electron density of the LUMO. (color range: 0 = red to 0.026 = blue) using Spartan'10 software (B3LYP/6-31g*).

| | HOMO | HOMO map | LUMO | LUMO map |
|---|---|---|---|---|
| 1 | $E_{HOMO}$ (eV) -5.85 |  | $E_{LUMO}$ (eV) -1.31 |  |
| 2 | $E_{HOMO}$ (eV) -6.11 |  | $E_{LUMO}$ (eV) -1.90 |  |

## Conclusions

In summary, we report a short and inexpensive route to heterocycle **1** and to the previously unknown heterocycle **2**, both of which were considered synthetic challenges and were identified as promising scaffolds for medicinal chemistry. These heterocycles have high aqueous solubility and are not significantly ionized at physiological pH. Therefore, we recommend that medicinal chemists consider them for diverse applications and carry out further study. Currently, we are exploring the incorporation of the parent heterocycles into drug-like molecules and the results will be reported in due course.

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## Notes and references

1 N.A. McGrath, M. Brichacheck, J.T. Njardarson, *J. Chem. Educ.,* 2010, **87**, 1348.
2 R.D. Taylor, M. McCoss, A.D.G. Lawson, *J. Med. Chem*., 2014, **57**, 5845.
3 D. Bonnet, J.F. Margathe, S. Radford, E. Pflimlin, S. Riché, P. Doman, M. Hibert, A. Ganesan, *ACS Comb. Sci*., 2012, **14**, 323.
4 W.R. Pitt, D.M. Parry, B.G. Perry, C.R. Groom, *J. Med. Chem*., 2009, **52**, 2952.
5 D. Chapman, J. Hurst, *J. Chem. Soc., Perkin Trans.,* 1980, **1**, 2398.
6 G.D. Zhu, J. Gong, V.B. Gandhi, K. Woods, Y. Luo, X. Liu, R. Guan, V. Klinghofer, E.F. Johnson, V.S. Stoll, M. Mamo, Q. Li, S.H. Rosenberg, V.L. Giranda, *Bioorg. Med. Chem.,* 2007, **15**, 2441.
7 O. Tsikouris, T. Bartl, J. Tousek, N. Lougiakis, T. Tite, P. Marakos, N. Pouli, E. Mikros, M. Radek, *Magn. Reson. Chem*., 2008, **46**, 643.
8 J.F.W. McOmie, M.L. Watts, D.E. West, *Tetrahedron,* 1968, **24**, 2289.
9 G.I. Feutrill, R.N. Mirrington, *Tetrahedron Lett.,* 1970, **11**, 1327.
10 C. Hartmann, L. Gatterman, *Chem. Ber*., 1892, **25**, 3531.
11 Y. Hirata, S. Ito, H. Kawamoto, T. Kimura, Y. Nagatomi, H. Ohta, A. Sato,A. Satoh, G. Suzuki, Diaryl-substituted five-membered heterocycle derivative. World patent 85214, 2005.
12 S.D. Taylor, F. Mirzaei, A. Sharifi, S.L. Bearne, *J. Org. Chem*., 2006, **71**, 9420.
13 E. Fukuda, Y. Takahashi, N. Hirasawa, O. Sugimoto, K. Tanji, *Heterocycles*., 2009, **77**, 1163.
14 G. Lavecchia, S. Berteina-Raboin, G. Guillaumet, *Tetrahedron Lett*., 2004, **45**, 6633.
15 M.G. Bock, C. Gaul, V.R. Gummadi, H. Moebitz, S. Sengupta, 17 alpha-Hydroxylase/C17,20-lyase inhibitors. World patent 35078, 2012.
16 W. E. Feely, E.M. Beavers, *J. Am. Chem. Soc*., 1959, **81**, 4004.
17 E.C. Horning, *J. Org. Chem*., 1945, **10**, 263.
18 E.A. Braude, A.G. Brook, R.P. Linstead, *J. Chem. Soc*., 1954, 3569-3574.

19 A.B.A. Jansen, J.M. Johnson, J.R. Surtees, *J. Chem. Soc.,* 1964, 5573.
20 T. Tanaka, K. Okunaga, M. Hayashi, *Tetrahedron Lett*., 2010, **51**, 4633.
21 M. Congreve, R. Carr, C. Murray, H. Jhoti, *Drug Discov. Today*, 2003, **8**, 876.

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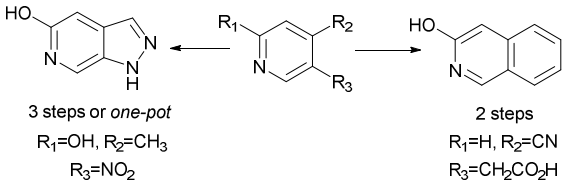


Synthetic protocols that provide access on multigram scale to unknown heteroaromatic ring systems of potential value for medicinal chemistry.