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Keeping it small, polar, and non-flat: diversely functionalized building blocks containing the privileged 5,6,7,8-tetrahydro [1,2,4]triazolo[4,3-*a*]- and [1,5-*a*]pyridine cores

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ABSTRACT

Six sets of functionalized building blocks based on 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine as well as 5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine cores have been prepared. These compounds are non-flat, bicyclic heterocycles that are likely to find utility as privileged motifs for lead-like compound design. One set of building blocks, (5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-6-ylmethyl)amines, proved useful as a scaffold for developing compounds that stimulate glucagon-like peptide-1 (GLP-1) secretion and are novel anti-diabetes drug leads.

The modern design of small molecules for bioactivity screening appears to be significantly be influenced by two major concepts, namely, those of lead-likeness and 'non-flatness'. Lead-like compounds[1] conform to more stringent criteria of lipophilicity (log*P*) and molecular weight (MW) compared to the Lipinski 'rule-of-five' chemical space.[2] Lead-likeness offers ample room for medicinal chemistry optimization, which normally results in increasing a molecule's size and lipophilicity. Noticeably, compounds in current screening collections (proprietary or commercially available) fill the higher-end space of the Lipinski boundaries while the lead-like space is scarcely populated.[3] In response to this obvious void, the term 'lead-oriented synthesis' (LOS) was coined by a GlaxoSmithKline team[4] to signify the synthetic organic chemistry methodologies capable of primarily delivering lead-like compounds. While being a technically more challenging concept to implement,[5] LOS has become a necessary challenge for organic chemists to face, as the current productivity crisis in pharmaceutical industry[6] is frequently linked to the lack of quality drug leads emerging from screening.[7] The concept of 'non-flatness', that is, increasing a molecule's three-dimensional character by reducing the number of flat aromatic rings (or increasing the fraction of sp^3-hybridized heavy atoms, F_{sp3}) has also gained a particular importance after it was noted that, on a statistical level, compounds become more saturated as they progress through the drug development cycle.[8] Besides this pure statistical significance, more 'shapeliness' for a compound means being more complimentary to its protein target, more selective against off-targets, less toxic, and, ultimately, more successful in the drug development cycle.

The 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine core (**1**) as well as its bioisosteric 5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine counterpart (**2**) clearly incorporate the aforementioned features, considering their low molecular weight (123), high hydrophilicity ($c\mathrm{Log}P \sim -0.17$[9]), and the saturation of the pyridine ring, while preserving the essential 1,2,4-triazole moiety (Fig. 1). While preparation of these cores by partial reduction of their fully aromatic congeners was well established several decades ago,[10,11] only recently have we seen their advent (of **1** in particular) in various drug leads. Notable examples include modulators of γ-secretase (an important target in Alzheimer's disease) from Janssen Pharmaceutica (**3**)[12] and Takeda (**4**),[13] multi-target anti-inflammatory compound **5**[14] from Pharmacia & Upjohn, as well as inhibitors of dipeptidyl peptidase IV (DPPIV) from Merck (**6**)[15] and The

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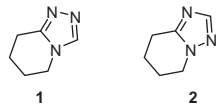


Figure 1. Lead-like, non-flat cores **1**–**2** that are the subjects of the present study.

University of Nottingham (**7**),[16] both of which are related to the FDA-approved anti-diabetic drug sitagliptin (Fig. 2).[17]

In light of these latest developments, it is particularly desirable to gain convenient access to a series of building blocks based on core motifs **1** and **2**. On first viewing, the task may seem simple, considering the usual way to access these by the reduction of the triazolopyridine precursors (vide supra). However, core **1** appears to be a lot more challenging, in light of its known propensity for a Dimroth rearrangement.[18] In this Letter, we describe a convenient, scalable synthesis of a series of diversely functionalized cores **1** and **2** and demonstrate the application of one of them for anti-diabetic drug lead generation.

A series of (5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-6-ylmethyl)amine building blocks **8a**–**e** was synthesized starting from commercially available 2-chloro-5-cyanopyridine (Scheme 1). Elaboration of the fully aromatic precursor **9** presented no issues. However, simultaneous reduction of the pyrido ring and the cyano group could only be achieved by high-pressure (100 atm) hydrogenation over Raney nickel in 7 M methanolic ammonia. On the contrary, reduction under the reported literature conditions (which normally involve Pd/C),[12,14] produced a complex mixture of products mostly consisting of the de-amination product **10**. Notably, the 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine core of building blocks **8a**–**e** remained intact over the course of the reduction and did not undergo the Dimroth rearrangement, as was confirmed by ^{1}H–^{15}N HMBC spectroscopy (vide infra).

In the preparation of a set of carboxylic acids **11a**–**d**, $Pd(OH)_2$ rather than Pd/C was identified as the optimal catalyst for the hydrogenation step, which allowed the reduction of the pyrido ring in **12** without decarboxylation, which was the case when Pd/C was used. Remarkably, the efficient three-step synthesis from readily available 6-chloronicotinic acid did not require protecting the carboxylic acid functionality (Scheme 2).

Building blocks **8a**–**e** and **11a**–**d** are noteworthy as in the course of their synthesis, the formation of the [1,2,4]triazolo[4,3-*a*]pyridine cycle was not accompanied by Dimroth rearrangement. This was despite the fact that in both cases, the pyridine ring was substituted with an electron-withdrawing substituent, which has been shown to increase the tendency for the Dimroth rearrangement.[18,19] The latter, however, was the sole course of the reaction during the 1,2,4-triazole ring formation step involving 3- and 5-nitro-substituted 2-hydrazinopyridines. In both cases, only the

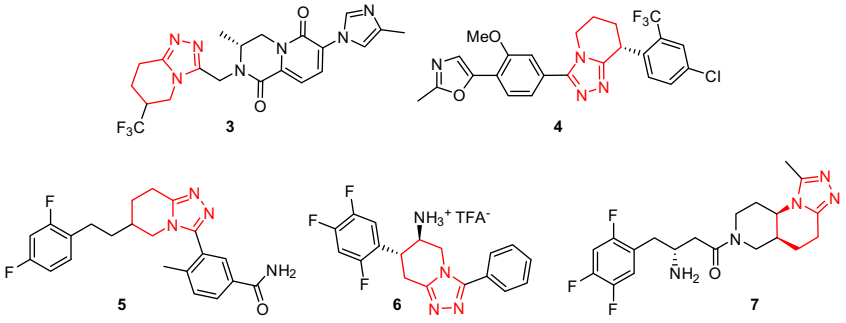
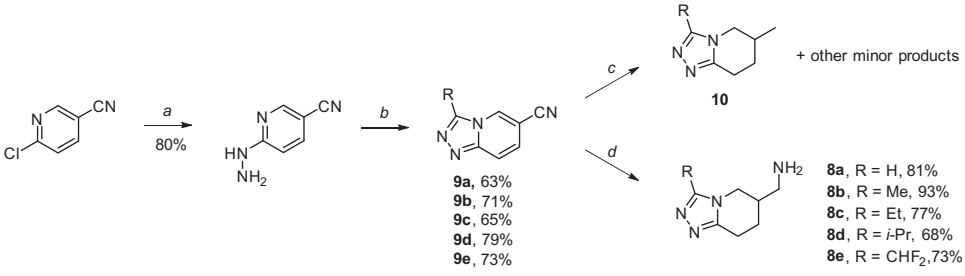
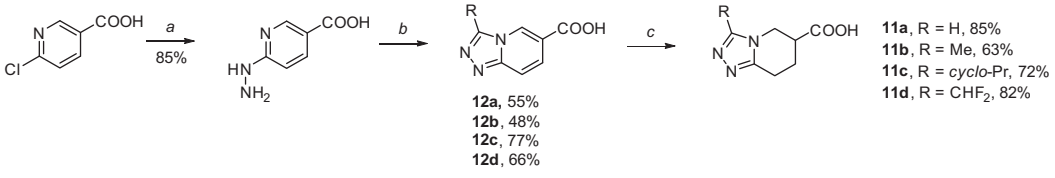


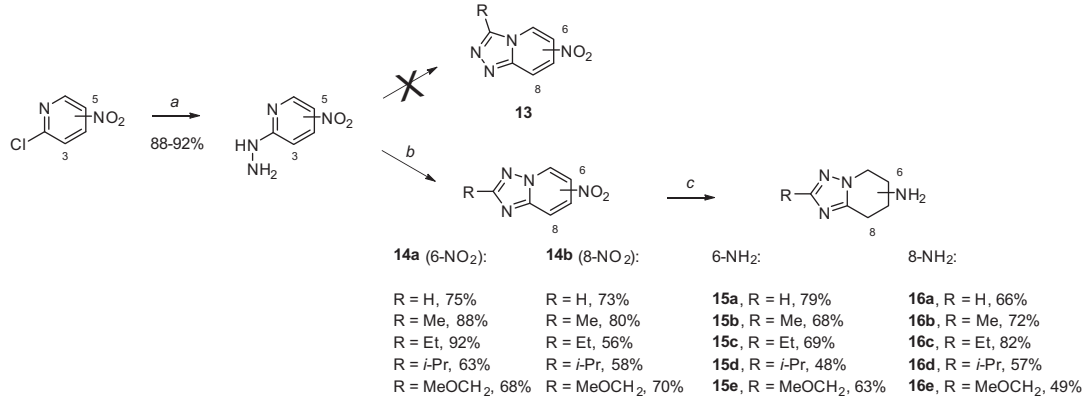
Figure 2. Examples of biologically active compounds based on scaffold **1**.



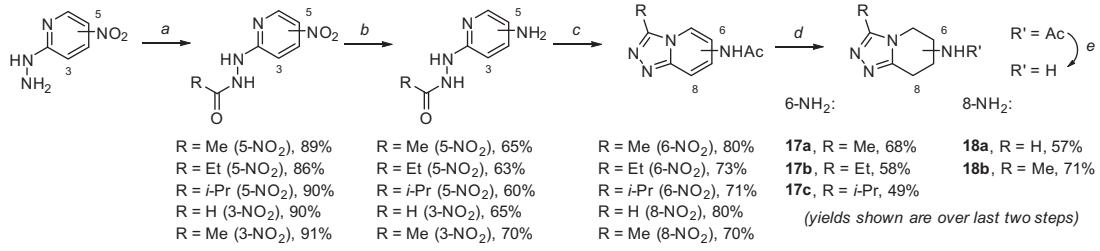
Scheme 1. Synthesis of (5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-6-ylmethyl)amines **8a**–**e**. Reagents and conditions: (a) hydrazine hydrate (5 equiv), *i*-PrOH, reflux, 24 h; (b) RCO_2H, 110 °C, 48 h; (c) H_2, Pd/C, 100 atm, 60 °C; (d) H_2, Raney Ni, 7 M NH_3 in MeOH, 100 atm, 60 °C.



Scheme 2. Synthesis of 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylic acids **11a**–**d**. Reagents and conditions: (a) hydrazine hydrate (10 equiv), EtOH, reflux, 72 h, then AcOH; (b) RCO_2H, 110 °C, 48 h; (c) H_2, $Pd(OH)_2$, 100 atm, 100 °C.



Scheme 3. Dimroth rearrangement observed on attempted preparation of 6- and 8-nitro-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridines **13**. Reagents and conditions: (a) hydrazine hydrate (5 equiv), *i*-PrOH, rt; (b) RCO_2H, 110 °C, 48 h; (c) H_2, 10% Pd/C, 7 M NH_3 in MeOH, 100 atm, 100 °C, 48 h.



Scheme 4. Preparation of 6- and 8-amino-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridines **17a–c** and **18a–b** via sequential reduction of the nitro group and the pyridine ring. Reagents and conditions: (a) RCOCl (1.1 equiv), pyridine (2 equiv), DMF, 0 °C → rt; (b) H_2, Pd/C, MeOH, 1 atm, rt; (c) AcOH, reflux, 48 h; (d) H_2, Pd/C, MeOH, 100 atm, 70 °C; (e) aq HCl (10 M), reflux, 24 h.

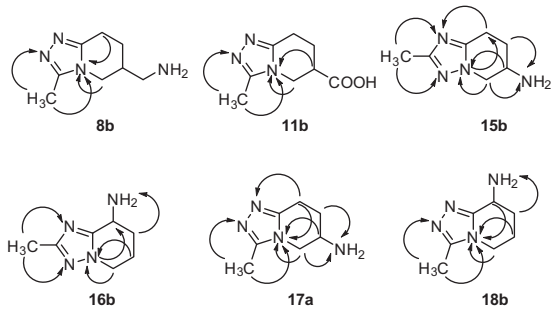


Figure 3. $^1H–^{15}N$ HMBC correlations observed for compounds **8b**, **11b**, **15b**, **16b**, **17a**, and **18b**.

respective sets of compounds **14a–b** were obtained (incorporating various substituents at position 3 of the 1,2,4-triazole ring). Hydrogenation over Pd/C using 100 atm of hydrogen gas in methanolic ammonia yielded the products of concomitant reduction of the pyrido ring and the nitro group (Scheme 3).

Clearly, the preparation of the targeted 6- and 8-nitro precursors **13** for subsequent reduction would require a substantial change in synthetic strategy. We reasoned that the tendency of the 2-hydrazinopyridine precursors to undergo the Dimroth rearrangement would be suppressed if the nitro functional group was converted to an electron-donating amino group prior to the formation of the 1,2,4-tiazolo ring. As presented in Scheme 4, this reasoning proved correct. The synthetic route included the protection of the amino group and delivered two isomeric sets of 6- and 8-amino-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridines **17a–c** and **18a–b**.

The identity of the heterocyclic cores in **8**, **11**, **17**, and **18** ('non-rearranged') as well as in **15** and **16** ('Dimroth rearranged') was unequivocally established by the correlations observed in the $^1H–^{15}N$ HMBC spectra of representative compounds in each series (Fig. 3).

The utility of the 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine core which were developed as building blocks in this work for application in antidiabetic drug design is clearly exemplified by compounds **6** and **7** which are DPPIV inhibitors (vide supra). Inhibition of DPPIV leads to an increase in the levels of glucagon-

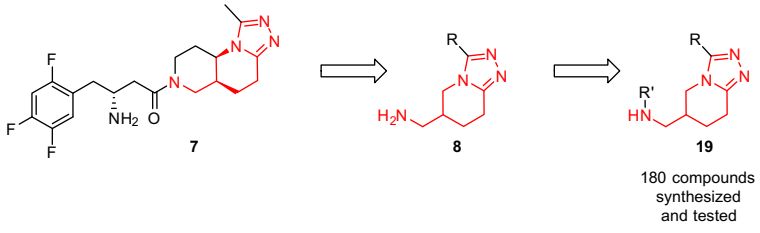
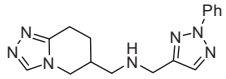
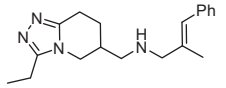
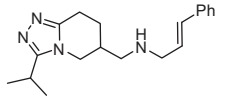


Figure 4. Library of GLP-1 secretion stimulators inspired by compound **7**.

Table 1
GLP-1 release stimulation in mSTC-1 and NCI-H716 cell lines by compounds **19a–c**

Compound	Structure	EC_{50} (mSTC-1) (μM)	EC_{50} (NCI-H716) (μM)
19a		4.19	>40
19b		12.6	>40
19c		12.2	>40

like peptide-1 (GLP-1) and results in the lowering of the blood glucose levels.[20] The structure of the aminomethyl-substituted core **8** is clearly recognizable in compound **7** (Fig. 4) and this led to the design of a focused library of 180 compounds **19** (see ESI for exact structures)[21] which was synthesized and tested as part of the Eli Lilly Open Innovation Drug Discovery program.[22] To our delight, three compounds tested (**19a–c**) selectively stimulated GLP-1 secretion in mouse enteroendocrine-like STC-1 cells (relevant cellular model)[23] but not in NCI-H716 cells (Table 1).[24]

In conclusion, we have described a facile synthesis of six types of functionalized building blocks based on 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine and 5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine cores. Both of these non-flat bicyclic heterocycles are attractive from the standpoint of lead-likeness and represent emerging privileged motifs for drug design. We have exemplified the latter aspect by designing new GLP-1 secretion stimulators based on a set of (5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridin-6-ylmethyl)amines **8**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.094.

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