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Luise, Nicola; Wyatt, Paul G.

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Diversity-oriented synthesis of bicyclic fragments containing privileged azines

Nicola Luise, Paul G. Wyatt

Drug Discovery Unit, School of Life Sciences, University of Dundee, Dow Street, Dundee DD1 5EH, Scotland, UK

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ABSTRACT

An innovative and efficient reagent- and scaffold-based diversity oriented synthesis (DOS) of a fragment set was developed for fragment-based drug discovery (FBDD) programs. Twelve diverse, functionalized and bicyclic scaffolds were rapidly accessed by adopting a convenient synthetic toolkit around three privileged azine cores in order to effectively modulate biomolecules. These structures are characterized by both key motifs for interacting with diverse biological targets *via* hydrogen bonds and useful points of growth for subsequent fragment optimization.

Since the seminal paper in 2000 by Shreiber, diversity-oriented synthesis (DOS) has gained considerable popularity within the field of chemical biology, medicinal chemistry and drug discovery due to its ability to deliver reliable solutions to the complexity and diversity issues encountered by combinatorial chemistry.[1]

More recently, attention has been focused on the ability to produce relevant biological active molecules *via* incorporation of essential privileged structures (privileged-substructure-based DOS (pDOS)). Indeed, as stated by Kim et al., privileged structures (e.g. indole, pyridine, purine, etc.) are recurring motifs within bioactive molecules that can be exploited as "chemical navigators" to access novel chemical and biological space.[2]

Despite the tangible benefit of this approach to furnish complex drug-like molecules able to modulate biological targets,[3] its application to fragment-based drug-discovery (FBDD)[4] has been infrequent and only a few publications highlight the preparation of low-molecular weight ($\leq$250 Da) fragments.[5]

In view of this, we describe both optimized and new convenient synthetic routes (one- or two-step reactions) to access bicyclic fragments with an embedded privileged motif that are either novel or have limited commercial availability. In particular, both reagent- and scaffold-based DOS was applied to three privileged structures that are commonly present in drugs and bioactive natural products: pyridine, pyrimidine and pyrazine (Fig. 1).[6]

The application of such synthetic approach delivered twelve scaffolds with optimal fragment properties for subsequent optimization and for binding to biomolecules, for example by exploiting the ability of the pyridine, pyrazine and pyrimidine motifs to not only accept hydrogen bonds but to act as hydrogen bond donators through aromatic C–H (C–H HBD) adjacent to the ring nitrogens (Scheme 1).[7] This ability is particularly highlighted in the field of kinase inhibitors where diverse heteroaromatic scaffolds interact with the amides of the backbone of the kinase hinge region, through this hydrogen bonding pattern.[8] Although the strength of binding delivered by C–H HBDs is possibly not as strong as that provided by an amide N–H or hydroxyl O–H, these interactions are important because of their ability to modulate ADME properties, especially at the late lead optimization stage within drug discovery programs.[9] An increased number of heteroatom-H bond donor functionalities in a compound has been shown to be detrimental for multiple ADME parameters, including solubility (intermolecular H-bonding), membrane penetration, and CNS penetration (ability to cross membrane and PgP substrate susceptibility). Therefore replacing amides and ureas with heteroaromatics can alleviate these issues. These bicyclic fragments were synthesized based on their compliance with the Drug Discovery Unit, University of Dundee, UK's (DDU) fragment criteria (MW $\leq$ 300; log P = -2 to 2; log D = -2 to 2; tPSA = $\leq$90; HBA $\leq$ 6; HBD $\leq$ 3; NROT $\leq$ 3), which conforms to the "rule-of-three" (Ro3).[10] The rules were adopted to control complexity to increase hit rates and physicochemical properties to ensure compounds were soluble at the high concentration needed for fragment screening, and minimize aggregation in solution and non-specific interactions with proteins.

The described chemistry emphasizes how medicinal chemists can readily access interesting small molecules, from readily available starting material, in order to enrich fragment libraries. Moreover, this approach can be widely applied to diverse privileged scaffolds to construct unprecedented heterocyclic systems.

Our strategy for the construction of bicyclic fragments (**6–14** and **17–30**) (Scheme 1) was based on the presence of two adjacent

E-mail address: p.g.wyatt@dundee.ac.uk (P.G. Wyatt).

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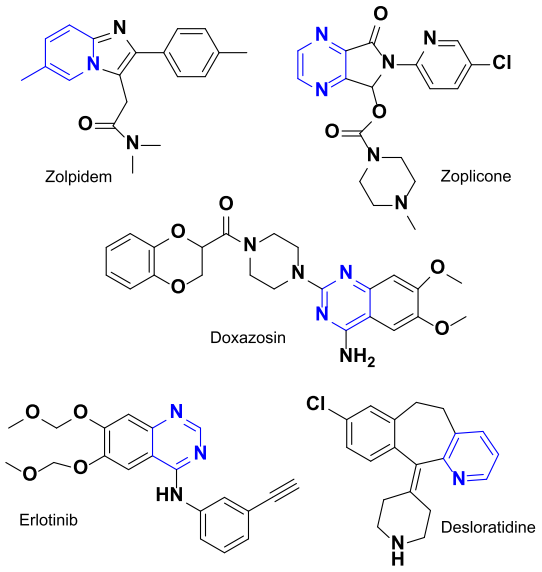
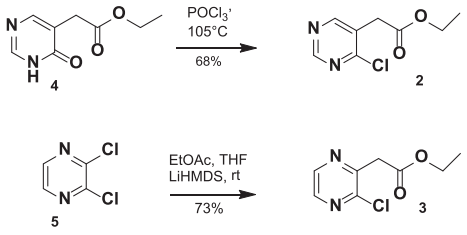


Fig. 1. Bioactive molecules containing privileged structures.

functionalities on the azine cores to develop key reactions. In this regard, compounds **1–3** were initially chosen, bearing a methylene-ester and a halide as exploitable functional groups. Because of the high cost of **2** and **3**, it was decided to synthesize them by following literature methods. Pyrimidinone **4** was treated with $POCl_3$ at high temperature to access **2**,[11] whereas dichloropyrazine **5** yielded **3** after treatment with the enolate of EtOAc (Scheme 2).[12]

The first set of fragments were the bicyclic thienoazines **6–8** (Scheme1(A)), bearing two handles (ester and amine) either for further functionalization and elaboration or to make interesting interactions (e.g. hydrogen bonds) (Scheme 1(A)). The idea was to exploit the nucleophilicity of an activated methylene and the high electrophilicity of methyl isothiocyanate, inspired by Bremner et al.'s strategy.[13] The synthetic route was rapidly tested on **1** (Table 1), considering its lower propensity for SnAr compared to **2** and **3**. In this regard, higher temperature and shorter reaction time, under microwave irradiation (entry 3), led to a better yield compared to conventional heating (entry 1 and 2), whereas no substantial increase in yield was observed when DMSO and NMP were used instead of DMF (entries 4 and 5). Then, the

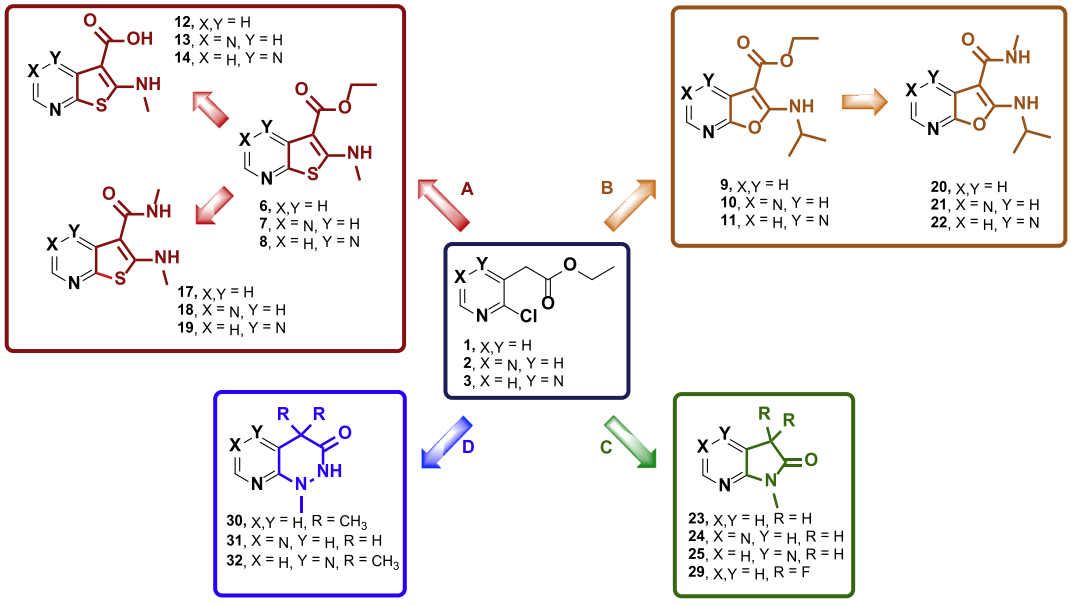


Scheme 2. Synthetic approach for **2** and **3**.

optimized reaction conditions were successfully applied to **2** and **3** to afford the novel thieno-pyrimidine **7** and -pyrazine **8**, respectively (entries 6 and 7).

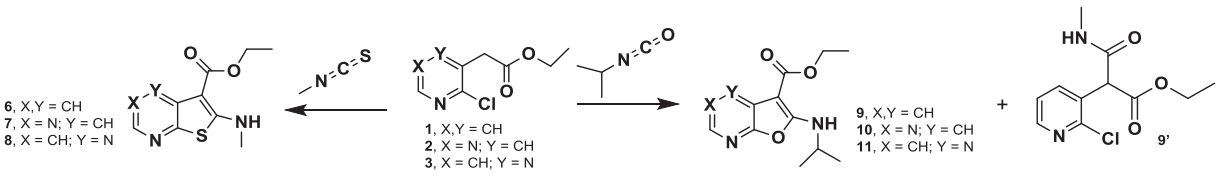
Similarly, the synthesis of the unprecedented functionalized furoazines **9**, **10** and **11** was attempted (Scheme 1(B)) (Table 1). The electrophilic species was in this case an isocyanate, which is rarely used in organic synthesis. Gratifyingly, the abovementioned reaction conditions gave similar results when employed for the pyrimidine and pyrazine core (**10** and **11**) (entries 8 and 9). However, a decrease in yield was observed for the synthesis of **9** (entry 10), probably due to a combination of the lower reactivity of both oxygen and pyridine compared to sulfur and diazines, respectively. After chromatographic purification, intermediate **9′** was recovered along with the desired final fragment **9**. Unfortunately, neither an enhanced reaction time nor a higher temperature were beneficial for improving the reaction outcome (entry 13). An extra 0.5 equivalent of base, potentially due to deprotonation of the alpha carbon next to the carbonyls of the forming **9′**, augmented the final yield (entry 11). In contrast, an increase in the isocyanate amount or a change of base did not enable any significant improvements (entries 12 and 14). With these six bicyclic systems in hand (**6–11**), the conversion of the ester group into more polar functionalities was attempted. NaOH promoted the hydrolysis of **6–8** to afford **12–14** in excellent yield, conversely **9–11** were not stable under the same reaction conditions and the side products **15** (trace) and **16** were mainly obtained (Scheme 3).

Concurrently, generation of secondary amides was attempted. Reaction of **12–14** with diverse coupling reagents did not deliver the required results, so the Weinreb's procedure was tried to access **17–22** *via* ester aminolysis of **6–11**. Pleasingly, the use of $AlMe_3$ and methylamine, in a sealed microwave vial under conventional heating, led to **17–22** in > 50% yields (Table 2).[14]

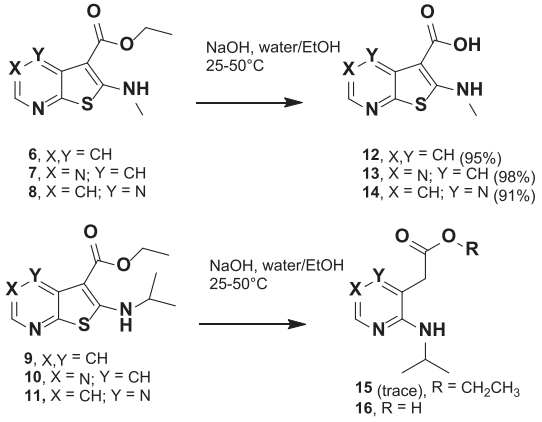


Scheme 1. Reagent- and scaffold-based diversity-oriented synthesis of pyrido-, pyrimido- and -pyrazo-containing heterobicyclic fragments.

Table 1
Optimization of reaction conditions for the synthesis of thieno- and furo-azines.

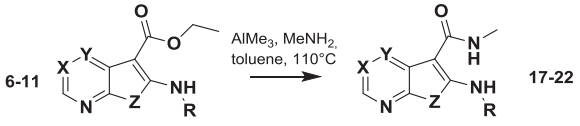


Entry (substrate)	Reagent	Solvent	Base	Temperature/heating conditions	Time (h)	Product	Yield %
1 (1)	Isothiocyanate (1.1 equiv.)	DMF	NaH (1.2 equiv.)	70 °C (conventional)	24	**6**	59
2 (1)	”	”	”	120 °C (conventional)	2	**6**	67
3 (1)	”	“	”	120 °C (microwave, 250 W)	2	**6**	72
4 (1)	”	DMSO	”	”	2	**6**	69
5 (1)	”	NMP	”	”	2	**6**	68
6 (2)	”	DMF	”	”	2	**7**	75
7 (3)	”	”	”	”	2	**8**	73
8 (2)	Isocyanate (1.1 equiv.)	”	”	”	2	**10**	68
9 (3)	”	”	”	”	2	**11**	71
10 (1)	”	”	”	”	2	**9**	28
11 (1)	”	”	NaH (1.7 equiv.)	”	2	**9**	40
12 (1)	Isocyanate (1.5 equiv.)	”	NaH (1.2 equiv.)	”	2	**9**	29
13 (1)	Isocyanate (1.1 equiv.)	”	”	120–150 °C (microwave, 250 W)	5	**9**	29
14 (1)	”	”	KHMDS/LiHMDS/*t*-BuOK (1.2 equiv.)	”	2	**9**	22–26

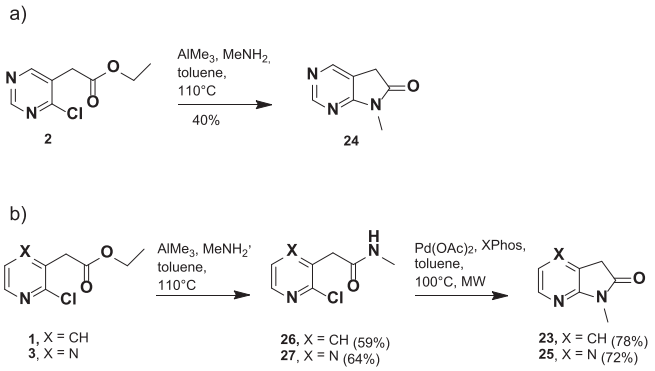


Scheme 3. Ester hydrolysis of fragments **6–11**.

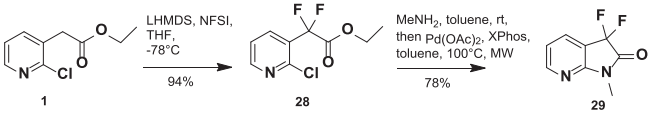
Table 2
Ester aminolysis of **6–11**.



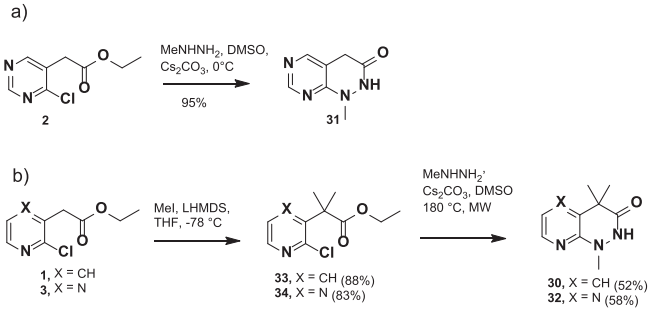
Entry (substrate)	Product	Yield %
1 (1)	**17** (X, Y = CH; Z = S; R = CH_3)	57
2 (2)	**18** (X = N; Y = CH; Z = S; R = CH_3)	60
3 (3)	**19** (X = CH; Y = N; Z = S; R = CH_3)	59
4 (1)	**20** (X, Y = CH; Z = O; R = $CH(CH_3)_2$)	51
5 (2)	**21** (X = N; Y = CH; Z = O; R = $CH(CH_3)_2$)	53
6 (3)	**22** (X = CH; Y = N; Z = O; R = $CH(CH_3)_2$)	55



Scheme 4. Synthesis of aza-oxo-indoles fragments.



Scheme 5. Synthesis of fluorinated fragment **29**.



Scheme 6. Synthesis of dihydropyridazinone-containing fragments.

Generation of the bicyclic aza-oxo-indole moieties was then investigated (Scheme 1(C)). 2-Chloropyridines and 2/4-chlorodiazines readily undergo SnAr reactions and the preparation of **23–25** was based around the concept of promoting nucleophilic aromatic displacement and amide formation, preferably, in a single step. However, **1–3** showed low reactivity towards amines. This result was in line with a recent work published by Simig et al.,[15] which described a two-step synthesis of pyrimido-pyrrolidinones, starting from **2** and other derivatives, by employing harsh conditions (T = 260 °C). In order to identify a shorter and milder route, it was decided to try an $AlMe_3$-mediated amide

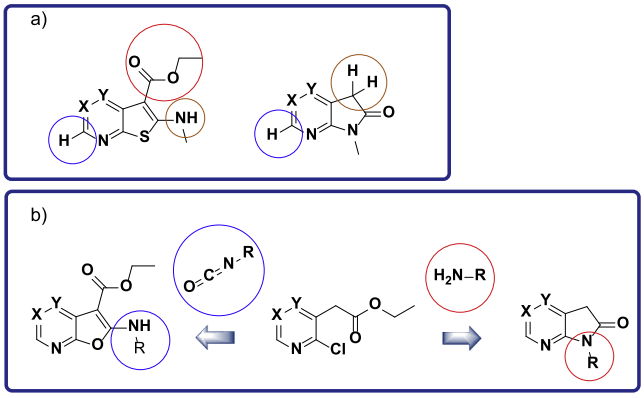


Fig. 2. (a) Examples of exploitable vectors for fragment optimization. (b) Potential fragment elaboration upon acquisition of ligand-target binding knowledge, by varying the commercial available reactants.

formation and cyclisation in one step. Pleasingly, when **2** was reacted at 110 °C for 2 h with a mixture of $AlMe_3$ and $MeNH_2$, ester aminolysis and successive intramolecular lactam generation was achieved in one step to give **24** (Scheme 4a). By contrast, no cyclisation took place on the pyridine and pyrazine scaffold probably due to their lower reactivity towards SnAr. However, the desired fragments **23** and **24** were successfully accessed when intermediate **26** and **27** were irradiated in microwave under Buchwald-Hartwig's conditions (Scheme 4b).[16]

The fluorinated version can be considered as an interesting variation of the latter small set of fragments, especially from a medicinal chemistry standpoint, although a vector (an activated methylene) for potential elaboration is removed from the final fragments. Indeed, fluorine functionalities can provide significant beneficial properties such as increased membrane penetration, enhanced metabolic stability, modulation of the pKa values, etc.[17] In this respect, electrophilic fluorination of the activated methylene was attempted with *N*-fluorobenzenesulfonimide (NFSI).[18] Substitution of **1** with a *gem*-difluoro group was afforded in excellent yield to give **28**. In contrast, difluorination next to the carbonyl did not occur on **2** and **3**, leading to complex mixtures. The increased electrophilicity of **28** allowed a room temperature ester aminolysis to yield **29**, which was successively cyclized in a microwave-assisted Buchwald-Hartwig reaction (Scheme 5).

The synthesis of dihydropyridazinone-containing bicyclic derivatives have not been extensively described in the literature, therefore attention was turned to those compounds presenting this pattern (Scheme 1(D)). Reaction of **2** with methylhydrazine in DMSO at 0 °C generated the novel fragment **31** after 10 min, conversely **1** and **3** did not give similar results when treated under the same reaction conditions (Scheme 6). Higher temperature and longer reaction time were not found beneficial, leading to the respective hydrazide intermediates along with diverse not identified side products. Diminishing the angle between the aromatic ring and the carboxylic functionality was considered to be a plausible solution to obviate the encountered issues, considering that also Cu and Pd-catalyzed intramolecular cyclization were not effective. In light of this, the introduction of a *gem*-dimethyl functionality (different reagents can be used for the methylene functionalization based on the optimization need) would promote the cyclisation because of the Thorpe-Ingold effect.[19] Hence, **1** and **3** were treated with MeI at low temperature to afford intermediate **33** and **34**. Under optimized conditions, the latter were successfully cyclized in a one-pot microwave-assisted reaction to yield **30** and **32** (Scheme 6).

As mentioned above and outlined in Fig. 2a, the described fragments in this work are characterized by different vectors for successive optimization. Moreover, the fragment elaboration process, considering the rapid and facile access to the final compounds, can also be performed by reacting a wide variety of commercially available reagents (e.g. isocyanates, isothiocyanates, alkylating agents, amines, etc.) with either the selected building blocks (**1–3**) or their subsequent intermediates (e.g. **28** and **33**/**34**), once binding information is acquired (Fig. 2b). In summary, structurally diverse fragments (**6–14** and **17–30**), compliant with the DDU fragment library's rules that conform to the Ro3, were rapidly generated by harnessing the concept of reagent- and scaffold-based DOS. A limited set of optimized reaction conditions was applied to three privileged azines (**1–3**), sharing two functionalities to build aromatic and non-aromatic counterparts. This approach permitted the access of twelve diverse and functionalized scaffolds that were either novel or had limited commercial availability, providing potential ligands for diverse biological targets during FBDD campaigns. Moreover, these small molecules are characterized by distinct point of growths that can be exploited for further optimization during a hit-to-lead phase.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2018.11.046.

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