Generation of Polar Semi-Saturated Bicyclic Pyrazoles for Fragment-Based Drug Discovery Campaigns

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Generation of Polar Semi-Saturated Bicyclic Pyrazoles for Fragment-Based Drug Discovery Campaigns.

Nicola Luise, and Paul G. Wyatt*

Abstract: *Synthesising polar semi-saturated bicyclic heterocycles can lead to better starting points for fragment-based drug discovery (FBDD) programs. We report the application of diverse chemistry to construct bicyclic systems from a common intermediate, where pyrazole, a privileged heteroaromatic able to bind effectively to biological targets, is fused to diverse saturated counterparts. The generated fragments can be further developed either after confirmation of their binding pose or early in the process, as their synthetic intermediates. Essential quality control (QC) for selection of small molecules to add to a fragment library is discussed.*

Introduction

Over the past two decades, fragment-based drug discovery (FBDD) has played a major role in the drug discovery arena as either an alternative or complementary method to high-throughput screening (HTS).[1] Starting points in FBDD projects are ligand efficient small molecules, usually identified by biophysical techniques, and subsequently optimised to deliver leads and drug candidates by optimising potency and pharmacokinetic properties, while controlling molecular weight and physicochemical properties.[2]

More than 30 drug candidates in clinical development and three registered drugs derived from FBDD prove the unequivocal success of the methodology.[3]

Although, many commercially available fragments can identify optimal binders for many biological targets (e.g. kinases),[4] they cover limited biochemical space and are in the main sp^2-rich leading to less than ideal developability properties.[5] Decreasing aromaticity and increasing the sp^3 content of compounds are established approaches within drug discovery programmes to enhance the clinical success of candidates.[6] However there is debate over the benefit of 3-dimentionality within fragments, due to increased complexity and reduced probability of binding.[7] We therefore decided to explore semi-saturated bicyclic heterocycles as a compromise, where an unsaturated heterocycle delivered the key binding to protein targets through H-bonding and a fused saturated ring delivered some shape to improve physicochemical properties and a range of optimisation vectors.

Semi-saturated bicyclic heterocycles are embedded in diverse drug candidates and approved drugs (Figure 1),[8] supporting the notion of building sp^3-rich and polar fragment libraries, containing compounds with good physicochemical properties. Further, these substructures are common amongst natural products (Figure 1),[9] which are biological validated ligands that target macromolecules and can deliver several advantages e.g. higher solubility, chemical diversity, polar-specific interactions.

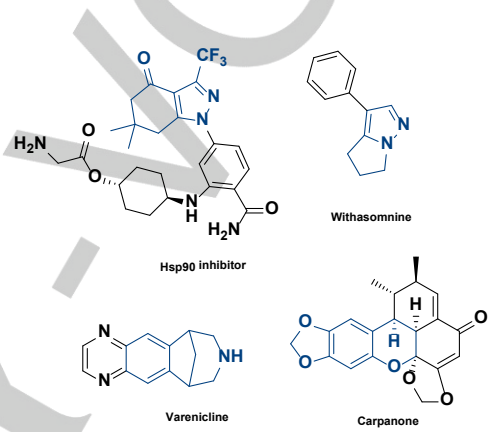

Figure 1. Bioactive molecules containing semi-saturated bicyclic heterocycles.

Recently, a collection of partially saturated bicyclic heterocycles with enhanced sp^3-content was described by Twigg *et al.* and, to the best of our knowledge, it remains one of the few published examples of how a fragment collection can be constructed from a purely synthetic chemistry standpoint.[10]

Concurrently with the aforementioned work, we had commenced the design and synthesis of high quality, semi-saturated bicyclic heterocycles as fragments. This type of compounds is neither extensively described in the literature nor readily provided by chemical suppliers. Thus, we sought to synthesise diverse compounds to explore this chemical space.

We commenced our study by selecting pyrazole as the unsaturated ring of our bicyclic systems, because of its ability to create a bifurcated, H-bond donor-acceptor network with multiple biological targets (Figure 2), with the H-bond donor proton able to be located on either nitrogens due to tautomerism. This 5-membered azole ring is a rare chemical structure in natural products, probably because of the difficulty in making N-N bonds by living organisms.[9c] However, it is one of the most common ring in approved drugs, covering a wide spectrum of biological activities (e.g. anti-fungal, anticancer, antiviral, neuroprotectants, antimicrobals).[11] Moreover, pyrazole appears in five drug candidates derived from a FBDD approach, emphasising its current importance in the FBDD field.[12] We then devised and developed a range of chemistry to create semi-saturated bicyclic *1H*-pyrazoles. In these systems, pyrazole is fused to various heteroaliphatic rings, which can provide better developability parameters compared to carboaliphatic rings, as highlighted by Ritchie *et al*.[6]

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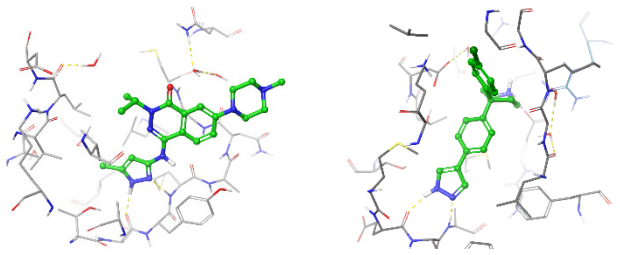


Figure 2. Examples of pyrazole-containing bioactive molecules binding (a) Bruton's tyrosine kinase (PDB code: 3PIX) and (b) protein kinase B (PDB code: 2UW9) via H-bond donor-acceptor network

Table 1. Fragment criteria of DDU fragments.[a]

Fragment criteria	DDU range
LogP	-2 to 2
LogD	-2 to 2
Heavy atom count	5 to 18
Hydrogen bond acceptor	≤ 6
Hydrogen bond donor	≤ 3
Total polar surface area	≤ 90
Rotable bonds	≤ 3
Solubility	Sample concentration > 1 mM based on comparison to residual DMSO-d_6 peak.
Stability	< 1% increase in impurities after 48 hours
Aggregation	No evidence in the waterLOGSY of aggregation of the compound in buffer.
Purity	≥ 95%

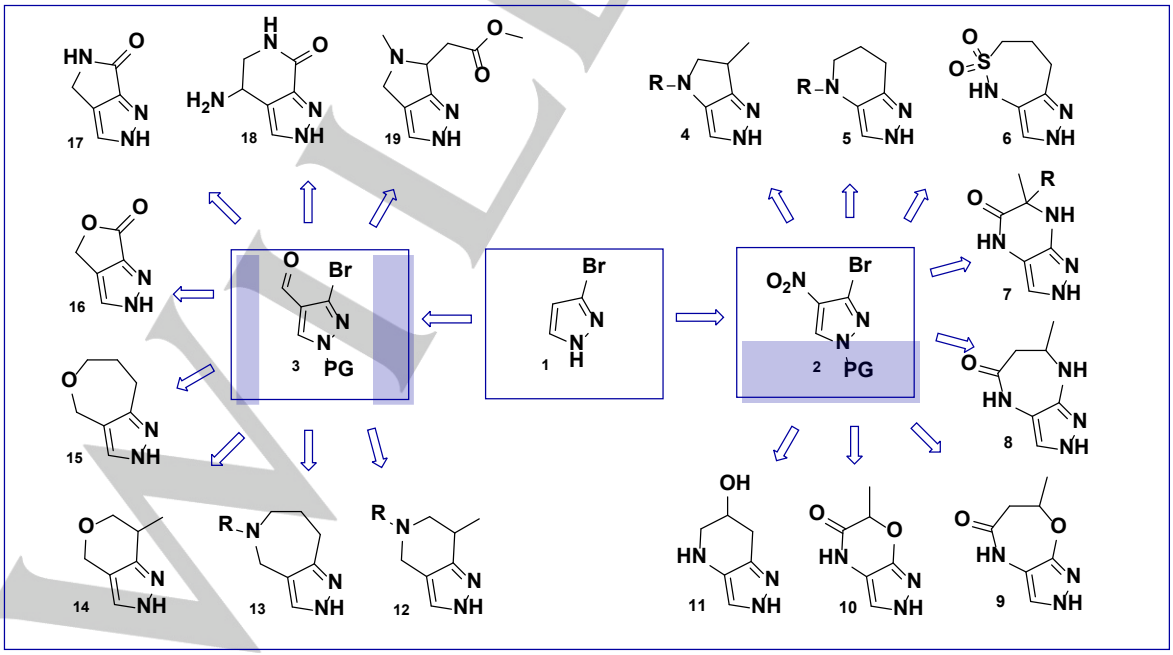
[a] Physicochemical and quality control parameters employed by the DDU.

Results and Discussion

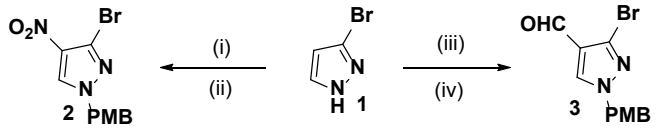
The compounds were designed using a set of criteria employed by the Drug Discovery Unit (DDU) to compile our fragment libraries, see Table 1. The parameters conform to the rule of three conceived by Congreve,[13] but also include quality control parameters including solubility, stability, aggregation and purity standards required for compounds to be added to the DDU's fragment library.

Synthesis of semi-saturated fused pyrazoles have been recently described,[10] albeit N1 was generally involved in the formation of the saturated portion, impeding possible and interesting key interactions with drug target proteins, as discussed above. This paper describes a complimentary approach to access fragments without substitution at N1 (Scheme 1).

3-Bromopyrazole (**1**), was selected as the starting material as it was cheap and commercially available in bulk (Scheme 2). Initially, we exploited the nucleophilicity of position 4 to insert a nitro or formyl group.[14] Typical electrophilic nitration conditions were applied on the unprotected pyrazole, followed by PMB-protection to yield separable regioisomers through column flash chromatography. High temperature and a long reaction time afforded an 80% yield of the more stable thermodynamic product **2**. Conversely, protection of **1** was necessary before Vilsmeier-Haak formylation to afford **3**. In this case, the protection step yielded a mixture (4:1) of inseparable regioisomers, which was used as such in the next step. Surprisingly, the Vilsmeier-Haak reaction gave a single regioisomer **3** after purification, due to the



Scheme 1. Synthetic approach for the synthesis of pyrazole-containing semi-saturated bicyclic heterocycles from a common intermediate.



Scheme 2. Synthesis of intermediate **2** and **3** (i) H_2SO_4, HNO_3, 50 °C, 95%; (ii) K_2CO_3, MeCN, PMB-Cl, 65 °C, 79%; (iii) K_2CO_3, MeCN, PMB-Cl, 65 °C, 95%; (iv) DMF, $POCl_3$, 95 °C, 65%.

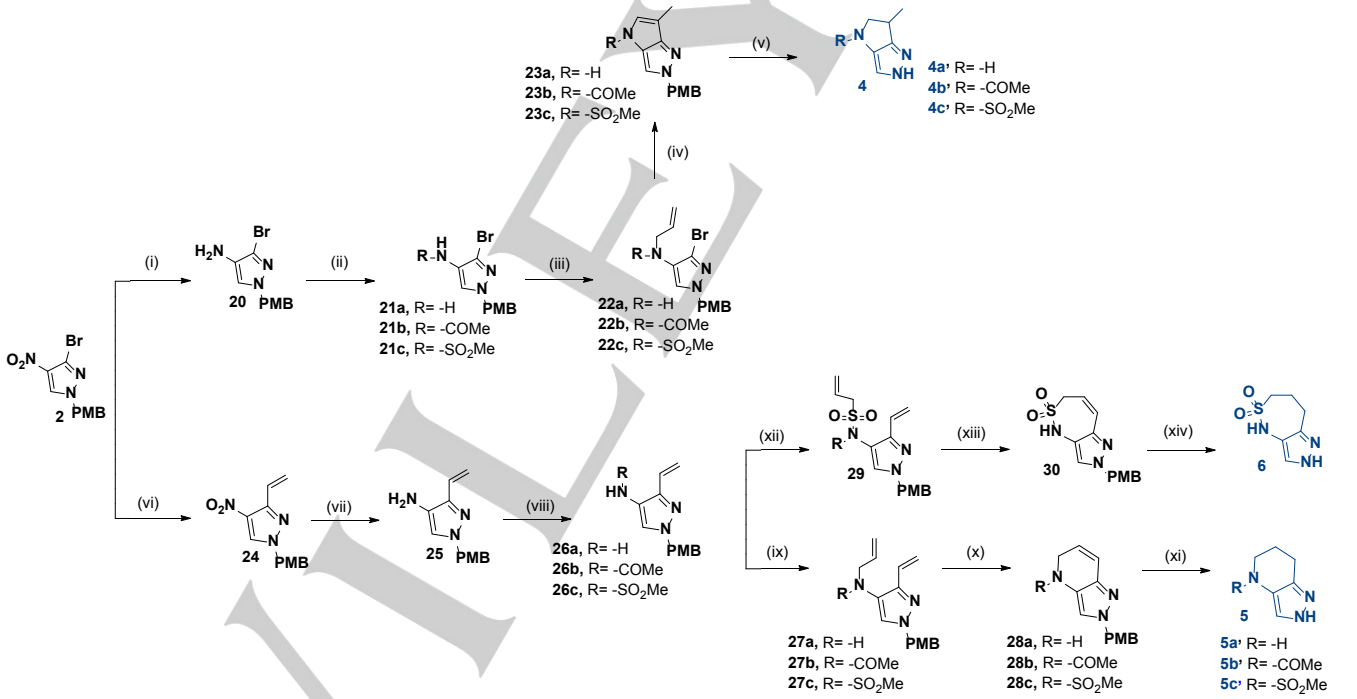
selective removal of the PMB from the minor regioisomer due to the acidic reaction conditions, resulting in the partial recovery of **1**. The PMB protecting group was selected because of its stability towards a variety of reaction conditions, however its cleavage proved to be problematic for some fragments proving resistant to both reductive and oxidative methods.[15] However, in these cases anisole in TFA provided conditions suitable for delivery of the fragments described here.[16]

The versatile intermediates **2** and **3** allowed a broad range of chemistry to be developed to provide diverse semi-saturated heterocycles.

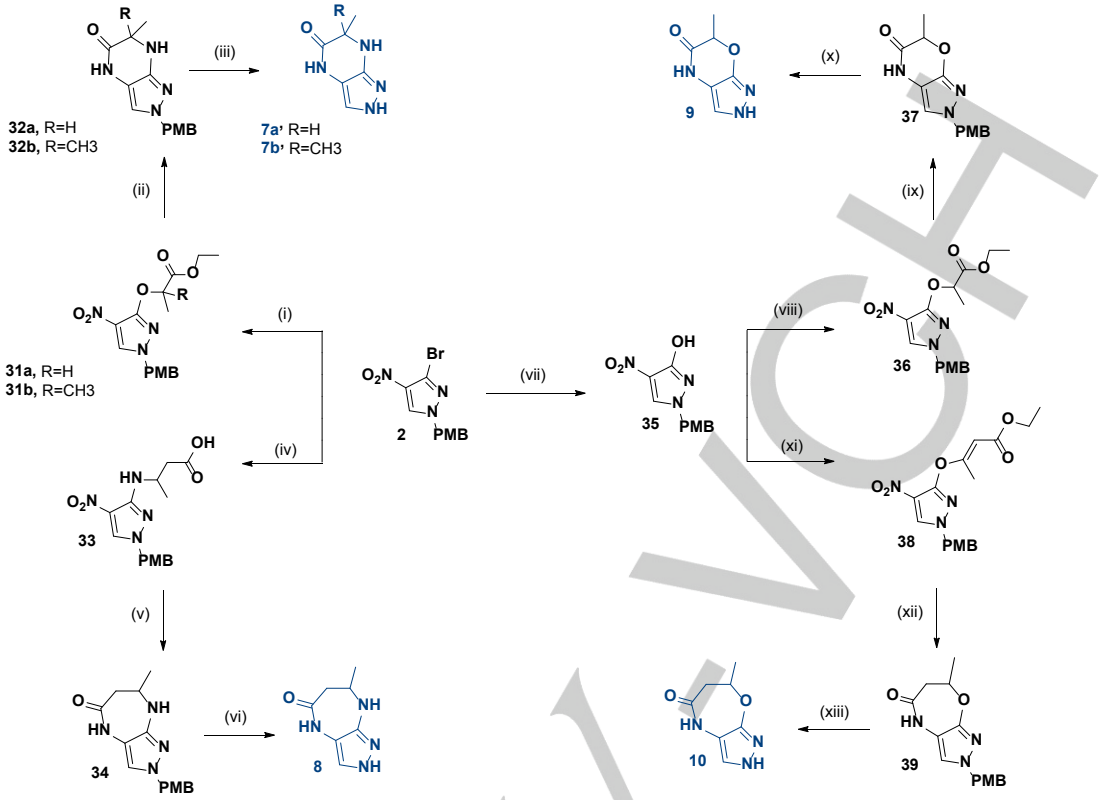
Iron-mediated nitro reduction of **2** yielded **20**,[17] which in turn was capped with methanesulfonyl chloride, acetyl chloride or Boc anhydride to afford respectively **21a**-**c** (Scheme 3). Subsequent allylation gave three key intermediates (**22a**-**c**) for an intramolecular Heck-Mizoroki reaction. $Pd(dppf)Cl_2$, Cs_2CO_3 in DMF were found to be the most effective reagents for such cross-coupling and microwave irradiation afforded the bicyclic systems (**23a**-**c**) in excellent yields.[18] Hydrogenation of the double bond of **23a-c** was successfully performed in an H-cube Pro using 10% Pd/C CartCar,[19] followed by deprotection to afford **4a**-**c** as racemic mixtures. A recent poll in the *Practical fragments blog* shows a clear preference for using racemates rather than pure enantiomers for fragment screening and this result is consistent with the DDU fragment library generation.[20] The most active enantiomer can be identified from a protein-ligand X-ray structure derived from the racemic mixture.[21]

The Stille reaction between **2** and tributyl(vinyl)stannane to generate **24** was effectively catalysed by $Pd/P(t\text{-}Bu)_3$ and CsF (Scheme 3).[22] Nitro-reduction, amine-capping and allylation gave access to **27a**-**c**, presenting two olefin groups for further functionalization. Compounds **27a-c** were reacted *via* intramolecular Ring Closing Metathesis (RCM) using second generation Grubbs' catalyst to provide the unsaturated rings of **28a-c**,[23] which were subsequently hydrogenated in an H-cube Pro to yield **5a**-**c**. A similar approach using ethenesulfonyl chloride gave the sultam **6**, a system with proven biological activity.[24]

To exploit the versatility of amino acids as building blocks to generate chiral heterocycles, we coupled **2** with alanine or 3-aminobutanoic acid *via* a copper-catalysed Ullmann reaction in a DMF-water mixture (Scheme 4).[25] Excellent yields were obtained when 30 equivalents of water were used. The desired cyclic 6- and 7-membered ring products **7a** and **8** were afforded after treatment of **31** and **33** with iron and NH_4Cl. However, compound



Scheme 3. Synthesis of semi-saturated heterocycles *via* Heck-Mizoroki and RCM reaction. (i) Fe, NH_4Cl, EtOH, 80 °C, 94%; (ii) a) Et_3N, Boc anhydride, THF, rt, 99%; b) pyridine, acetyl chloride, DCM, 0 °C, 92%; c) pyridine, methanesulfonylchloride, DCM, 0 °C, 96%; (iii) a) allyl bromide, NaH, THF, reflux, 82%; b) allyl bromide, NaH, DMF, rt, 87%; c) allyl bromide, K_2CO_3, MeCN, reflux, 89%; (iv) a/b/c) Cs_2CO_3, $Pd(dppf)Cl_2$, DMF, 140 °C, MW, 62%/69%/79%; (v) a/b/c) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole, 80 °C, 52%/60%56%; (vi) CsF, $Pd(t\text{-}Bu_3P)_2$, THF, tributyl(vinyl)stannane, rt, 85%; (vii) Fe, NH_4Cl, EtOH, 80 °C, 84%; (viii) a) Et_3N, Boc anhydride, THF, rt, 99%; b) pyridine, acetyl chloride, DCM, 0 °C, 85%; c) pyridine, methanesulfonylchloride, DCM, 0 °C, 91%; (ix) a) allyl bromide, NaH, THF, reflux, 87%; b) allyl bromide, NaH, DMF, rt, 90%; c) allyl bromide, K_2CO_3, MeCN, reflux, 93%; (x) a/b/c) Grubbs II, DCM, 40 °C, 73% 70%, 79%; (xi) a/b/c) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole, 80 °C, 53%/65%71%; (xii) pyridine, prop-2-ene-1-sulfonyl chloride, DCM, 0 °C, 89%; (xiii) Grubbs II, DCM, 40 °C, 83%; (xiv) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole 80 °C, 56%.



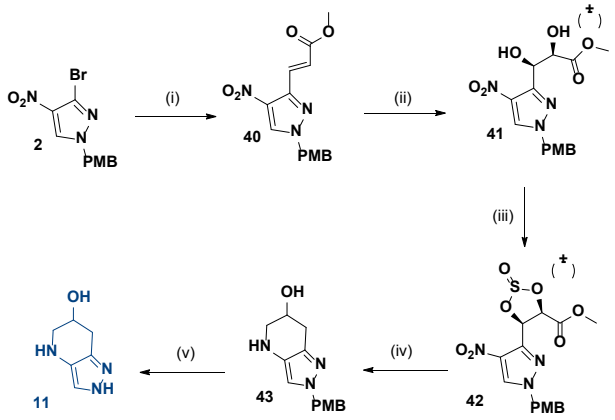
Scheme 4. Synthesis of bicyclic heterocycles from hydroxy and amino acid building blocks. (i) a/b) CuI, Cs_2CO_3, water, DMF, alanine/2-amino-2-methyl-propanoic acid, 50 °C, MW, 69%/68%; (ii) a/b) Fe, NH_4Cl, EtOH, 80 °C, 87%/89%; (iii) TFA, anisole, 80 °C, 57%/55%; (iv) CuI, Cs_2CO_3, water, DMF, 3-amino-2- methyl-propanoic acid, 50 °C, MW, 70%; v) Fe, NH_4Cl, EtOH, 80 °C, 67%; (vi) TFA, anisole, 80 °C, 52%; (vii) Cs_2CO_3, $Pd_2(dba)_3$, tBuBrettPhos, water, DMF, 130 °C, MW, 52%; (viii) K_2CO_3, ethyl 2-bromopropanoate, DMF, 0 °C, 93%; (ix) Fe, NH_4Cl, EtOH, 80 °C, 82%; (x) TFA, anisole, 80 °C, 66%; (xi) DABCO, ethyl but-2-yonate, MeCN, 70 °C, 92%; (xii) 10% Pd/C, EtOH, 1,4-dioxane, H-cube Pro, then Fe, NH_4Cl, EtOH, 80 °C, 64%; (xiii) TFA, anisole, 80 °C, 55%.

7a failed quality control (QC), due to oxidation to the cyclic imine. Conversely, the gem-dimethyl derivative **7b**, upon successful synthesis, passed QC.

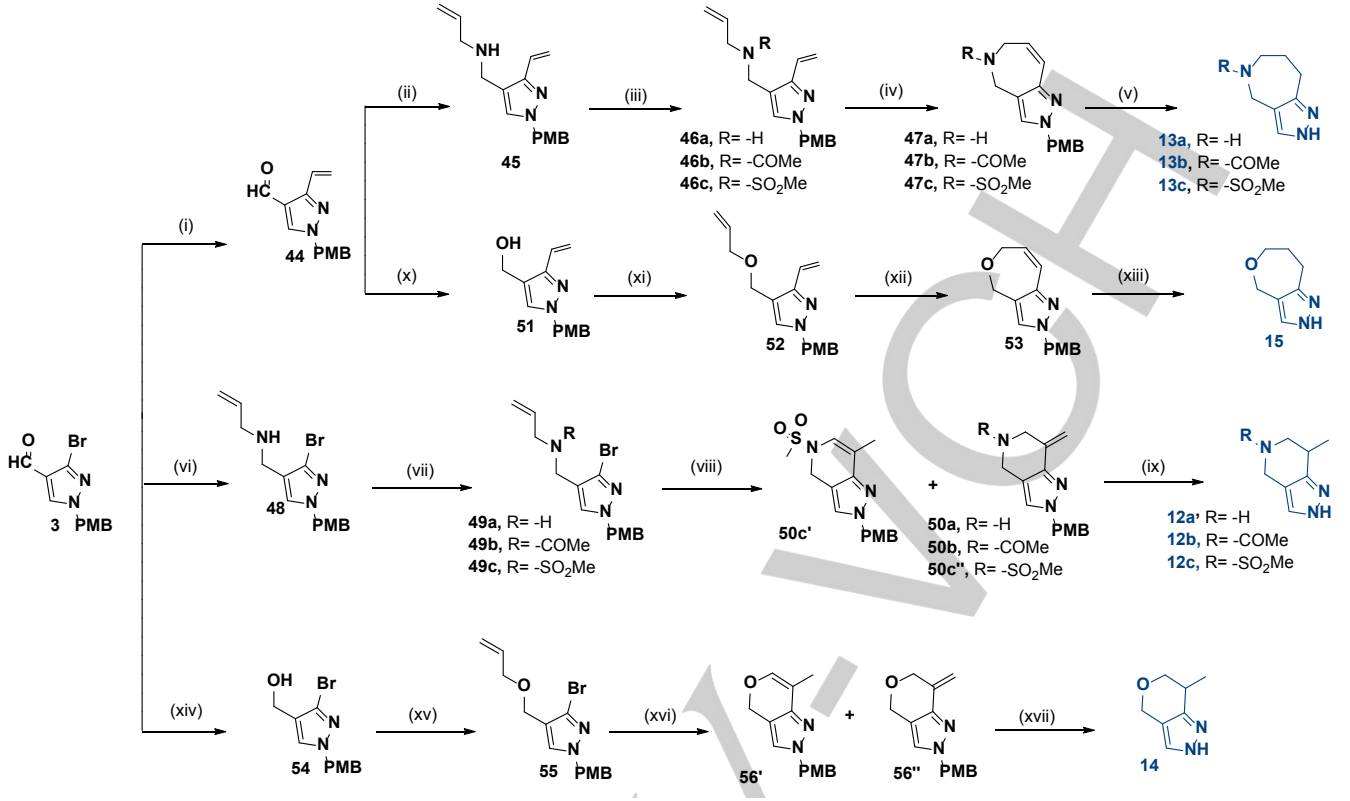
The same reaction conditions failed to access analogous intermediates, after reacting **2** with lactic acid and 3-hydroxybutanoic acid. To the best of our knowledge, only Xiao *et al*.[26] has reported a valid procedure for performing a Cu/Pd-catalysed cross-coupling between an aryl bromide/iodide and an alpha-hydroxy acid. However, these conditions were not effective in delivering the desired products. Thus, it was decided to reverse the chemistry by exploiting a hydroxyl group in position 3 of the pyrazole ring (**35**). Replacement of the bromine of **2** with hydroxyl was achieved using $Pd_2(dba)_3$/tBuBrettPhos.[27] Alkylation of **35** with ethyl 2-chloropropanionate or an oxa-Michael addition to methyl but-2-ynoate afforded **36** and **38** respectively, the latter using DABCO as an organocatalyst.[28] Hydrogenation of the double bond of **38** and Bechamp conditions, as described above, were used to promote cyclisation of **37** and **38** to afford **9** and **10**, respectively, after deprotection (Scheme 4).

An interesting synthesis of functionalized tetrahydroisoquinolines was reported by Jagdale *et al*.,[29] where $NaBH_4$ and catalytic amount of $CoCl_2$ were able to reduce a nitro group, open a cyclic sulphite and carry out the subsequent reduction of an intermediate lactam after cyclisation. Inspired by this efficient chemistry, we tried a similar approach to synthesise **11** (Scheme 5). Initially, **2** was coupled with ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate in a microwave-assisted Suzuki cross-coupling reaction.[18] Upjohn dihydroxylation catalysed by OsO_4 generated **41**, which was readily reacted with thionyl chloride to provide **42** as a diastereomeric mixture. The Jagdale conditions were then applied to **42** to afford the novel semi-saturated bicyclic **11**.

In a parallel approach to using **2** as the common starting material, we used the formyl group of **3** to create related new



Scheme 5. Synthesis of an hydroxy piperidine bicyclic derivative. (i) Cs_2CO_3, $Pd(dppf)Cl_2$, ethyl (2E)-3-(4,4,5,5-tetramethyl,3,3-dioxaborolan-2-yl)acrylate, DMF, 145 °C, MW, 71%; (ii) acetone, water, OsO_4, NMO, rt, 94%; (iii) pyridine, thionyl chloride, 0 °C, 95%; (iv) $CoCl_2 \bullet 6H_2O$, $NaBH_4$, EtOH, rt, 25%; (v) TFA, anisole, 80 °C, 53%.



Scheme 6. Synthesis of 6- and 7-membered N- and O-containing rings. (i) CsF, Pd(t-$Bu_3P)_2$, THF, tributyl(vinyl)stannane, rt, 78%; (ii) $MgSO_4$, propylamine, $NaBH_4$, DCM, rt, 89%; (iii) a) Et_3N, Boc anhydride, THF, rt, 92%; b) pyridine, acetyl chloride, DCM, 0 °C, 85%; c) pyridine, methanesulfonylchloride, DCM, 0 °C, 93%; (iv) a/b/c) Grubbs II, DCM, 40 °C, 77% 75%, 79%; (v) a/b/c) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole, 80 °C, 49%/53%55%; (vi) $MgSO_4$, propylamine, $NaBH_4$, DCM, rt, 94%; (vii)) a) Et_3N, Boc anhydride, THF, rt, 92%; b) pyridine, acetyl chloride, DCM, 0 °C, 89%; c) pyridine, methanesulfonylchloride, DCM, 0 °C, 92%; (viii) a/b/c) Cs_2CO_3, Pd(dppf)Cl_2, DMF, 140 °C, MW, 55%/68%/61%;(ix) a/b/c) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole, 80 °C, 47%/55%56%; (x) $NaBH_4$, MeOH, 0 °C, 95%; (xi) NaH, allyl bromide, THF, 50 °C, 94%; (xii) Grubbs II, DCM, 40 °C, 78%; (xiii) TFA, anisole, 80 °C, 49%; (xiv) $NaBH_4$, MeOH, 0 °C, 96%; (xv) NaH, allyl bromide, THF, 50 °C, 93%; (xvi) Cs_2CO_3, Pd(dppf)Cl_2, DMF, 150 °C, MW 65%; (xvii) TFA, anisole, 80 °C, 51%.

pyrazole-containing bicyclic fragments. Six and seven-membered rings containing both oxygen and nitrogen were accessed by using analogous chemistry to that previously described (Scheme 6). Stille conditions gave the alkene intermediate **44** after treating **3** with tributyl(vinyl)stannane, which underwent reductive amination using allylamine to afford **45**. Capping **45** with acetyl chloride, methanesulfonyl chloride and Boc-anhydride gave **46a-c** respectively as ideal substrates for Ru-catalysed cyclisation *via* RCM using the second generation Grubbs' catalyst, affording the cyclic olefins(**47a-c**), which were efficiently hydrogenated in an H-cube Pro to provide **13a-c**.

Reductive amination of **3** and subsequent capping of the secondary amine (**48**) afforded the allyl-derivatives (**49a-c**). A microwave-assisted Heck-Mizaroki reaction using Pd(dppf)Cl_2 was successfully employed on **49a-c** to generate the chiral systems **12a-c**, after reduction and following deprotection.

Reduction of the aldehyde moiety of **44** and **3** with $NaBH_4$ gave primary alcohols **51** and **54**, respectively. Compounds **51** and **54** were alkylated with allylbromide, using NaH as the base, to provide allyl-ethers (**52** and **55**), which were intramolecularly cyclised and then simultaneously reduced and deprotected to give tetrahydropyrane (**14**) and oxepane (**15**).

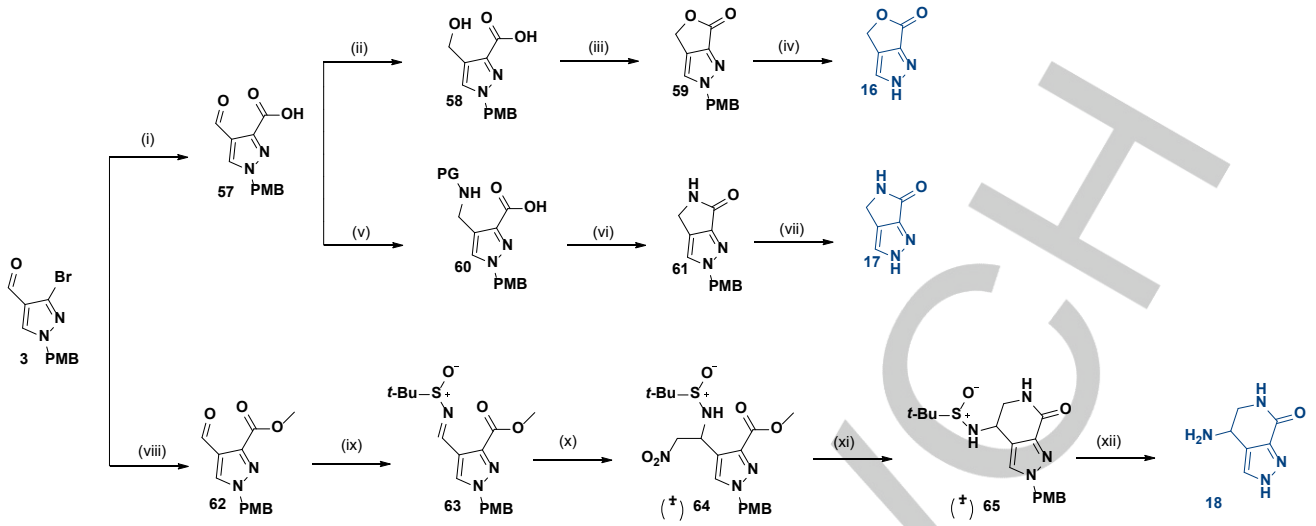
Although, the cyclisation of **49c and 55** gave a mixture of isomers, due to isomerisation (*exo-endo* migration), the last step was an olefin reduction, so this was not an issue. However, control of the chemistry could deliver useful intermediates for further functionalisation of the tetrahydropyridine and tetrahydropyrane ring of **12c** and **14**, respectively.[30]

We then investigated generating lactone (**16**) and lactam (**17**) (Scheme 7). Despite their simple structure, these scaffolds, without any further functionality on the two rings, are not synthetically described and commercially limited. We started their synthesis by carbonylation of **3** in a Pd-catalysed fluorocarbonylation where N-formyl saccharin was employed as the CO surrogate.[31] Treatment of the acyl fluoride intermediate with water gave the desired carboxylic acid (**57**) in good yield.

Reduction of **57** gave the alcohol (**58**) and reductive amination gave the amine (**60**). Subsequent reaction of **58** and **60** with HATU and Hunig's base in DMF successfully promoted alcohol and amine acylation to provide lactone **16** and lactam **17** after deprotection.

Quenching the fluorocarbonylation of **3** with methanol afforded ester (**62**). The versatile β-nitroamine (**64**) was generated by aza-Henry addition of nitromethane to the *N-tert*-butanesulfinyl aldimine (**63**) catalysed by TBAF.[32] Next, nitro reduction under acidic conditions and subsequent basification of the reaction mixture led to the protected 6-membered lactam **65**, which was deprotected to afford the novel fragment **18** (Scheme 7).

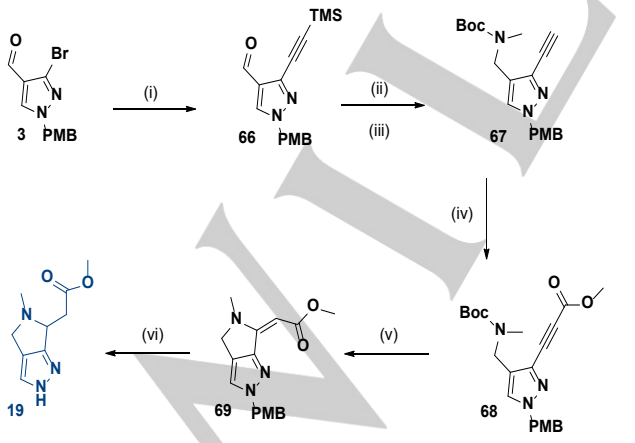
We next turned our attention to the synthesis of a pyrazole fused to a functionalised tetrahydropyrrole motif (Scheme 8). Initially, we tried diverse aza-Michael conditions on an acrylate derivative.[33] This unprecedented approach on a pyrazole was unsuccessful, possibly because of the limited electrophilicity of the electron rich carbon beta to the carbonyl. We attempted to circumvent this synthetic problem by an intramolecular Heck



Scheme 7. Synthesis of lactone **16** and lactam **17** and 18. (i) KF, N-formylsaccarin, Xantphos, $Pd(OAc)_2$, water, Et_3N, 90 °C, 48%; (ii) $NaBH_4$, MeOH, 0 °C, 83%; (iii) HATU, DIPEA, DMF, rt, 68%; (iv) TFA, anisole, 80 °C, 41%; (v) $MgSO_4$, (2,4-dimethoxyphenyl)methanamine, $NaBH_4$, DCM, rt, 92%; (vi) HATU, DIPEA, DMF, rt, 82%; (vii) TFA, anisole, 80 °C, 40%; (viii) KF, N-formylsaccarin, Xantphos, $Pd(OAc)_2$, MeOH, Et_3N, 90 °C, 50%; (ix) $Ti(OEt)_4$, 2-methylpropane-2-sulfinamide, DCM, rt, 92%; (x) NO_2Me, 1,4-dioxane, TBAF, rt, 90%; (xi) Zn, AcOH, EtOH, 70 °C then Et_3N, 1,4-dioxane, rt, 85%; (xii) TFA, anisole, 80 °C, 60%.

reaction or a radical cyclisation,[34,35] however, both approaches failed to deliver the desired product after exploring a range of reaction conditions. We then re-examined the Michael addition approach using an activated alkyne to effect the intramolecular cyclisation. The key intermediate (**68**) could not be made by cross-coupling **3** with a propynoic ester under Sonogoshira conditions,[36] thus we opted for a four step route to give the desired propynolate intermediate (**68**) in 55% overall yield. The synthetic route was commenced by coupling **3** with trimethyl(2-tributylstannylethynyl)silane, followed by simultaneous reductive amination with methylamine and alkyne deprotection, and protection of the resulting secondary amine gave **67**. Then, the alkyne **67** was deprotonated with *n*BuLi in THF at -78°C and reacted with methyl chloroformate to provide **68**. Treatment of **68** with HCl in dioxane and subsequent basification of the reaction mixture led to the cyclic adduct (**69**) by spontaneous intramolecular aza-Michael addition. Finally, reduction of the double bond provided the bicyclic system (**19**) after deprotection.

Due to the low binding affinity of fragments to the majority of target proteins, high compound concentrations are required to detect fragment binding. Therefore, the synthesised fragments required rigorous QC before addition to the DDU's fragment library. Fragments must be soluble in a 2mM phosphate buffer solution, with purity greater than 95%, in order to avoid impurities that could lead to false-positives/negatives.[37] The latter could be generated even for pure compounds through self-aggregation,



Scheme 8. Synthesis of a functionalised tetrahydropyrrolidine derivative *via* aza-Michael adduct. (i) CsF, $Pd(t\text{-}Bu_3P)_2$, trimethyl(2-tributylstannylethynyl)-silane, 1,4-dioxane, rt, 84%; (ii) $MgSO_4$, methylamine, DCM, $NaBH_4$, rt, 79%; (iii) Et_3N, Boc anhydride, THF, rt, 96%; (iv) *n*-Buli, methyl chloroformate, THF, -78 °C, 86%; (v) HCl, 1,4-dioxane, DCM, rt, then Et_3N, 40%; (vi) 10% Pd/C, EtOH, H-cube Pro, then TFA, anisole, 80 °C, 51%.

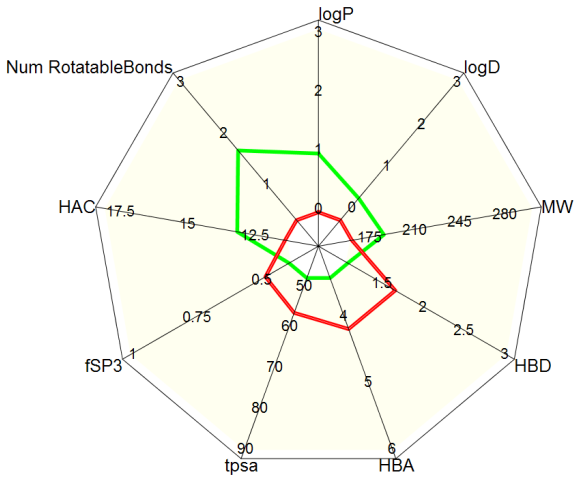


Figure 3. Radar chart showing the physicochemical properties of fragments described here (red) against those of the DDU fragments (green).

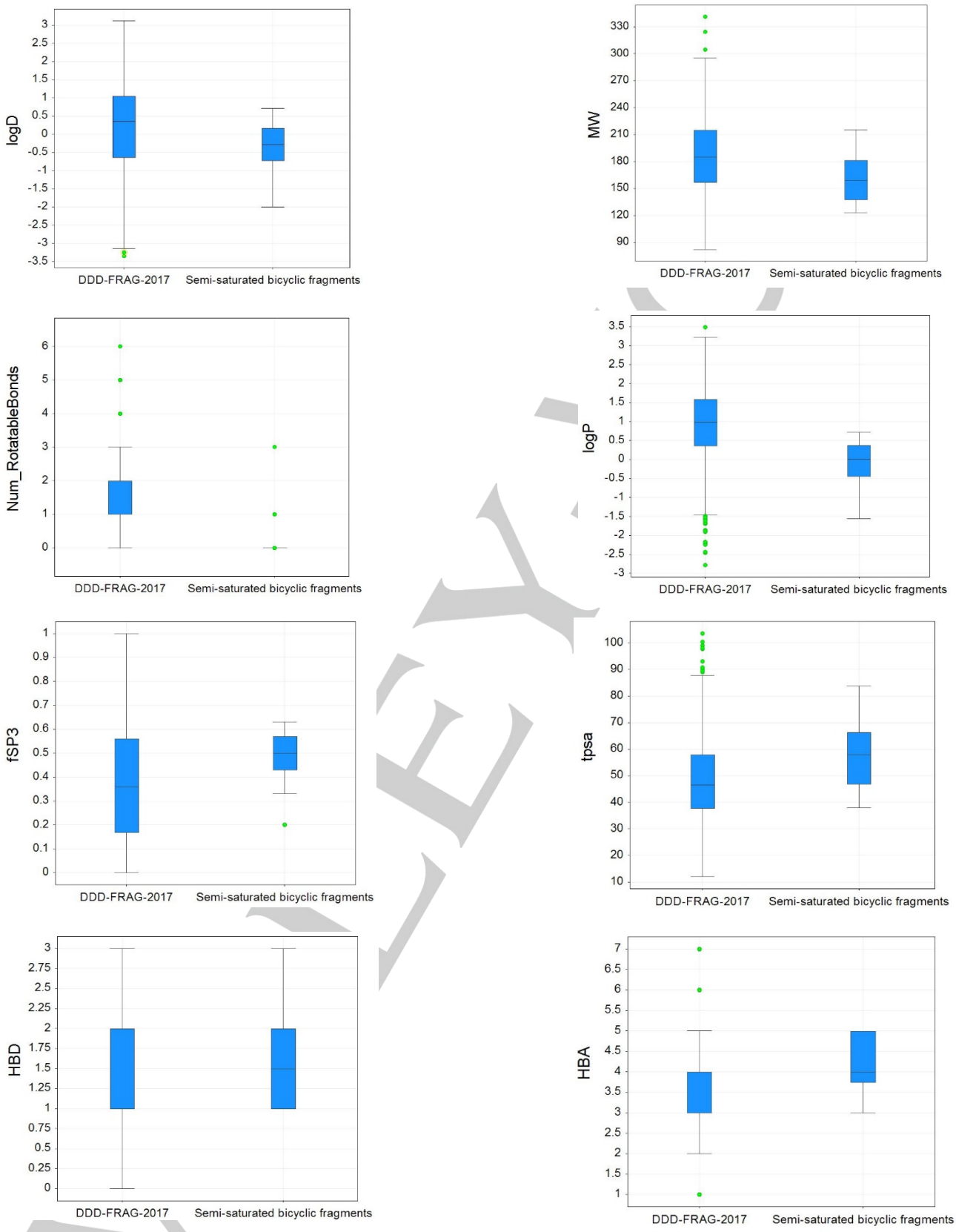


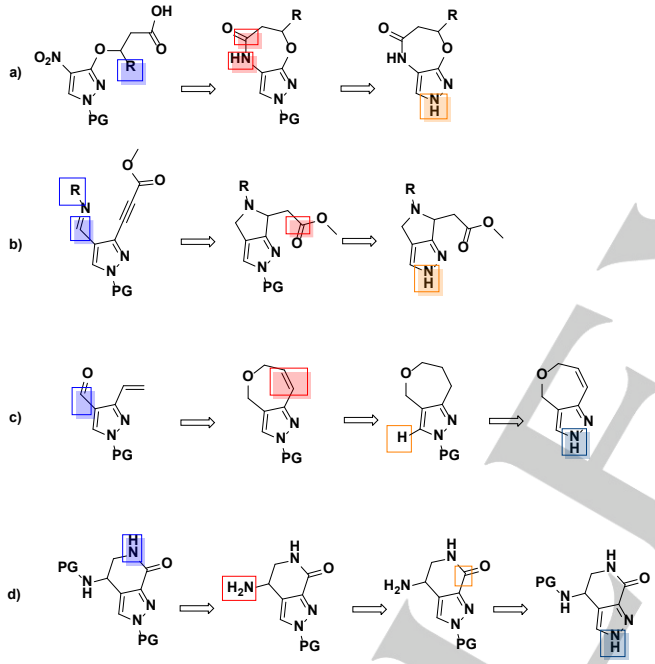
Figure 4. Blox plots showing the physicochemical properties of fragments described here (semi-saturated bicyclic fragments) against those of the DDU fragments (DDD-FRAG-2017).

thus a WaterLOGSY experiment was crucial to assess whether a fragment tended to aggregate or not.[38] Finally, comparison of 1D NMR profiles acquired 48 hours apart were used to evaluate compound stability.

For a more extensive description of the DDU fragment library's QC process, see the publication by Ray *et al.*[39]
All the fragments except **7a** passed the QC and were added to the DDU fragment library, expanding the available chemical space. To provide a better understanding of the physicochemical properties of these fragments, calculated properties were plotted against those of the existing DDU fragments. (Figure 3 and 4).

This approach can be efficiently used to deliver additional diverse compounds by elaborating the fragment templates described with novel vectors and/or elaborating substituents. Their functionalisation/ elaboration could be carried out either on the final fragments or their synthetic intermediates.

The use of diverse building blocks (e.g. amino acids), functionalisation of amines, nucleophilic addition to imines/ aldehydes, olefin derivatisation, exploitation of the position 5 of the pyrazole are only few examples. An illustration of this concept is depicted in Scheme 9.



Scheme 9. Examples showing were possible functionalisation/elaboration can be effectively developed.

Conclusions

In summary, we describe the synthesis of multiple semi-saturated bicyclic fragments starting from a common starting material 3-bromopyrazole (**1**). Pyrazole was selected as the aromatic core of these fragments because its H-bond donor-acceptor motif makes high efficiency interactions with a range of drug targets. Compound **1** was initially functionalised in position 4 to give the highly versatile intermediates **2** and **3**, and then a variety of chemistry was applied to provide either novel fragments or fragments with limited commercial availability and lacking published synthetic route. These structures fit the DDU fragment library's criteria for optimal physicochemical properties, which conform to those commonly used and accepted as guidelines in the FBDD field, particularly high aqueous solubility, a very desirable characteristic in FBDD programs.

Fragments described in this paper are also characterised by suitable vectors and functionality for further elaboration/ optimisation. The conceived synthetic routes are flexible and allow the introduction of diverse chemical functionality at multiple steps. Moreover, this chemistry can be widely applied to a broad range of 5- and 6-membered aromatic heterocycles to construct further novel semi-saturated bicyclic systems.

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Keywords: Fragment-based drug discovery · synthetic methods · polar small molecules · pyrazole · fused-ring systems

[1] a) G. M. Keseru, D. A. Erlanson, G. G. Ferenczy, M. M. Hann, C. W. Murray, S. D. Pickett, *J. Med. Chem.* **2016**, *59*, 8189–8206; b) D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke, H. Jhoti, *Nat. Rev. Drug Discov.* **2016**, *15*, 605–619; c)M. Baker, *Nat. Rev. Drug Discov.* **2012**, *12*, 5–7; d) D. Joseph-McCarthy, A. J. Campbell, G. Kern, D. Moustakas, *J. Chem. Inf. Model.* **2014**, *54*, 693–704.

[2] J. P. Renaud, C. W. Chung, U. H. Danielson, U. Egner, M. Hennig, R. E. Hubbard, H. Nar, *Nat. Rev. Drug Discov.* **2016**, *15*, 679–698.

[3] B. C. Doak, R. S. Norton, M. J. Scanlon, *Pharmacol. Ther.* **2016**, *167*, 28–37.

[4] a) J. Y. Mérour, F. Buron, K. Plé, P. Bonnet, S. Routier, *Molecules* **2014**, *19*, 19935–19979; b) J. A. Erickson, *Methdos Mol. Biol.* **2015,** 1289, 157-183.

[5] a) C. W. Murray, D. C. Rees, *Angew. Chemie - Int. Ed.* **2016**, *55*, 488–492.

[6] T. J. Ritchie, S. J. F. MacDonald, R. J. Young, S. D. Pickett, *Drug Discov. Today* **2011**, *16*, 164–171; b) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, 52, 6752-6756.

[7] M. M. Hann, A. R. Leach, G. Harper, *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856–864.

[8] a) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442–495; b) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319.

[9] a) M. G. Sankar, L. Mantilli, J. Bull, F. Giordanetto, J. O. Bauer, C. Strohmann, H. Waldmann, K. Kumar, *Bioorganic Med. Chem.* **2015**, *23*, 2614–2620; b) K. Kumar, H. Waldmann, *Angew. Chemie - Int. Ed.* **2009**, *48*, 3224–3242; c) V. Kumar, K. Kaur, G. K. Gupta, A. K. Sharma, *Eur. J. Med. Chem.* **2013**, *69*, 735–753.

[10] D. G. Twigg, N. Kondo, S. L. Mitchell, W. R. J. D. Galloway, H. F. Sore, A. Madin, D. R. Spring, *Angew. Chemie - Int. Ed.* **2016**, *55*, 12479–12483.

[11] a) J. V. Faria, P. F. Vegi, A. G. C. Miguita, M. S. dos Santos, N. Boechat, A. M. R. Bernardino, *Bioorganic Med. Chem.* **2017**, *25*, 5891–5903; b) G. Küçükgüzel, S. Şenkardeş, *Eur. J. Med. Chem.* **2015**, *97*, 786–815.

[12] Fragments in the clinic: 2016 edition, Practical Frgaments, Dan Erlanson. 15 Jul **2016**. http://practicalfragments.blogspot.co.uk/2016/07/fragments-in-clinic-2016-edition.html

[13] M. Congreve, R. Carr, C. Murray, H. Jhoti, *Drug Discov. Today* **2003**, *8*, 876–877.

[14] J. A. Joule, K. Mills, G. F. Smith, *Heterocyclic Chemistry,* Chapman& Hall, London, **1995**, p. 396.

[15] M. Lukáč, E. Smoláriková, *Acta Pharm.* **2005,** 52, 31-45.

[16] C. Subramanyam, *Synth. Commun.* **1995**, *25*, 761–774.

[17] Z. Zhan, J. Ai, Q. Liu, Y. Ji, T. Chen, Y. Xu, M. Geng, W. Duan, *ACS Med. Chem. Lett.* **2014**, *5*, 673–678.

[18] a) V. P. Mehta, E. V. Van der Eycken, *Chem. Soc. Rev.* **2011**, *40*, 4925; b) A. de la Hoz, Á. Díaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164–178; c) C. O. Kappe, *Angew. Chemie-International Ed.* **2004**, *43*, 6250–6284.

[19] P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey, C. P. Gordon, *Org. Biomol. Chem.* **2015**, *13*, 7119–7130.

[20] a) Chiral fragments-and poll!, Practical Fragments, Dan Erlanson. 11 Sep **2017**. http://practicalfragments.blogspot.co.uk/2017/09/chiral-fragments-and-poll.html; b) A. Ballard, H. O. Ahmad, S. Narduolo, L. Rosa, N. Chand, D. A. Cosgrove, P. Varkonyi, N. Asaad, S. Tomasi, N. J. Buurma, A. G. Leach, *Angew. Chemie-International Ed.* **2017**, *57*, 982–985.

[21] a) A. M. Taylor, A. Côté, M. C. Hewitt, R. Pastor, Y. Leblanc, C. G. Nasveschuk, F. A. Romero, T. D. Crawford, N. Cantone, H. Jayaram, et al., *ACS Med. Chem. Lett.* **2016**, *7*, 531–536; b) C. N. Johnson, D. A. Erlanson, C. W. Murray, D. C. Rees, *J. Med. Chem.* **2017**, *60*, 89–99.

[22] A. F. Littke, L. Schwarz, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

[23] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

[24] a) R. Bihovsky, M. Tao, J. P. Mallamo, G. J. Wells, *Bioorganic Med. Chem. Lett.* **2004**, *14*, 1035–1038; b) G. J. Wells, M. Tao, K. A. Josef, R. Bihovsky, *J. Med. Chem.* **2001**, *44*, 3488–3503.

[25] a) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525–3550; b) D. Ma, C. Xia, *Org. Lett.* **2001**, *3*, 2583–2586; c) N. Narendar, S. Velmathi, *Tetrahedron Lett.* **2009**, *50*, 5159–5161.

[26] Y. Xiao, Y. Xu, H. S. Cheon, J. Chae, *J. Org. Chem.* **2013**, *78*, 5804–5809.

[27] a) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695; b) C. W. Cheung, S. L. Buchwald, *J. Org. Chem.* **2014**, *79*, 5351–5358; c) C. W. Yu, G. S. Chen, C. W. Huang, J. W. Chern, *Org. Lett.* **2012**, *14*, 3688–3691.

[28] W. Zhou, Y. Zhang, P. Li, L. Wang, *Org. Biomol. Chem.* **2012**, *10*, 7184.

[29] A. R. Jagdale, R. S. Reddy, A. Sudalai, *Org. Lett.* **2009**, *11*, 803–806.

[30] D. Bankston, F. Fang, E. Huie, S. Xie, *J. Org. Chem.* **1999**, *64*, 3461–3466.

[31] T. Ueda, H. Konishi, K. Manabe, *Org. Lett.* **2013**, *15*, 5370–5373.

[32] J. L. García Ruano, M. Topp, J. López-Cantarero, J. Alemán, M. J. Remuiñán, M. B. Cid, *Org. Lett.* **2005**, *7*, 4407–4410.

[33] a) S. Fustero, J. Moscardó, M. Sánchez-Roselló, E. Rodríguez, P. Barrio, *Org. Lett.* **2010**, *12*, 5494–5497; b) A. Farwick, G. Heimchen, *Adv. Synth. Catal.* **2010**, *352*, 1023–1032; c) R.T. Backer, *PCT Int. Appl.*, WO2003061660, **2003;** d) K. Muñiz, A. Lishchynskyi, J. Streuff, M. Nieger, E. C. Escudero-Adán, M. M. Belmonte, *Chem. Commun.* **2011**, *47*, 4911; e) S. Kim, S. Kang, G. Kim, Y. Lee, *J. Org. Chem.* **2016**, *81*, 4048–4057.

[34] Y. C. Fan, O. Kwon, *Org. Lett.* **2012**, *14*, 3264–3267.

[35] A. Navarro-Vázquez, A. García, D. Domínguez, *J. Org. Chem.* **2002**, *67*, 3213–3220.

[36] a) H. Huang, H. Liu, H. Jiang, K. Chen, *J. Org. Chem.* **2008**, *73*, 6037–6040; b) B. Panda, T. Sarkar, *Synth.* **2013**, *45*, 817–829; c) F. Zhou, X. Han, X. Lu, *J. Org. Chem.* **2011**, *76*, 1491–4.

[37] T. L. Hwang, A. J. Shaka, *J. Magn. Reson. - Ser. A* **1995**, *112*, 275–279.

[38] C. Dalvit, *Drug Discov. Today* **2009**, *14*, 1051–1057.

[39] P. C. Ray, M. Kiczun, M. Huggett, A. Lim, F. Prati, I. H. Gilbert, P. G. Wyatt, *Drug Discov. Today* **2017**, *22*, 43–56.

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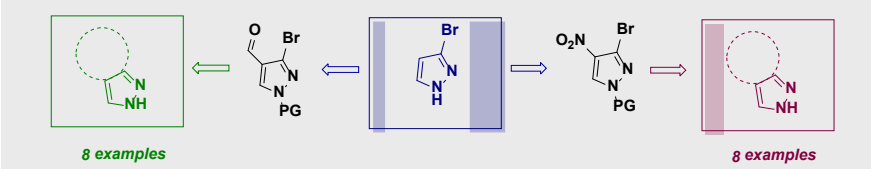

Synthesis of multiple polar semi-saturated bicyclic fragments starting from a common starting material for fragment libraries is reported. Pyrazole was selected as the aromatic core of these fragments because its H-bond donor-acceptor motif makes high efficiency interactions with a range of drug targets. These structures fit criteria for optimal physicochemical properties commonly used and accepted as guidelines in the FBDD field. Quality tested fragments can be further developed either after confirmation of their binding pose or early in the process, as their synthetic intermediates.

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Generation of Polar Semi-Saturated Bicyclic Pyrazoles for Fragment-Based Drug Discovery Campaigns.