feature

Increased building block access through collaboration

Christopher J. Helal[1], chris.j.helal@pfizer.com, **Alessandra Bartolozzi**[2], abartolozzi@bartolozzi-consulting.com, **Steven D. Goble**[3], **Neelakanda S. Mani**[4], **Angel Guzman-Perez**[5], **Ajay K. Ohri**[6], **Zhi-Cai Shi**[3] and **Chakrapani Subramanyam**[1]

Introduction

The commercial availability of chemical reagents that support the synthesis of molecules with desirable structural attributes and physical properties for drug discovery accelerates the testing of medicinal chemistry hypotheses and ultimately the identification of clinical candidates to treat human disease. Of particular interest, is a class of reagents known as building blocks (BB). BB are used to introduce chemical diversity into a fixed-core lead structure and are essential in modulating the overall ADME, pharmacological and safety properties of drug candidates. An example of this is shown for the phosphodiesterase 9A (PDE9A) inhibitor project at Pfizer (Fig. 1) [1,2]. Lead molecule **1** contained a central pyrazolopyrimidinone core (blue) that was crucial for making multiple direct PDE9A protein interactions and was deemed invariant, whereas the benzyl and cyclopentyl appendages (black) made hydrophobic interactions that it was felt could be varied to obtain an optimal profile. Optimization of **1** led to the clinical candidate **2** by replacing the benzyl group with a substituted pyrrolidine that was derived from ester BB **3** and substituting the cyclopentyl with 4-tetrahydropyran that originated from the corresponding hydrazine BB **4**. Importantly, the availability of BB **3** and **4** played a highly influential part in the rapid identification of **2**.

As a result of beneficial physicochemical properties being associated with many BB, it is common for the same BB to be incorporated into diverse lead structures across different projects. Key features of desirable BB have been recently disclosed in an article from AstraZeneca, such as the presence of a chemical functional group that facilitates their incorporation into core structures (e.g., amines, carboxylic acids or esters, aldehydes, halides, etc.) as well as conformance to the 'Rule of 2' for the BB fragment that is ultimately incorporated into the target molecule: molecular weight $<$200, clogP $<$2, H-bond donors $\leq$2, H-bond acceptors $\leq$4 [3].

To provide access to BB, many pharmaceutical companies have made significant investments in purchasing bulk quantities of commercially available molecules or synthesizing custom reagents based upon the expertise of their medicinal chemistry teams, as well as efficiently distributing BB to chemists as needed. Execution of parallel or library synthesis has particularly benefited because this mode of compound preparation is dependent upon accurate weighing and timely delivery of all BB to execute the synthesis; delays in BB access lead to delays in library synthesis or exclusion of compounds from preparation.

In medicinal chemistry, fluorination of lead molecules has been a strategy to optimize potency and control conformation [4–6], improve ADME properties [7–9], identify potential positron emission tomography (PET) ligands to establish biological target engagement [10] and enable fragment-based screening methods [11]. Incorporation of fluorine, however, can be a significant synthetic challenge that limits the widespread utilization of this approach [12]. At Pfizer, we have sought to address this issue by increasing the number of fluorinated BB in our compound collection. In this way, the carbon–fluorine bonds are formed in advance and in the presence of established BB functional groups, which enables the synthesis of fluorinated project analogs.

Challenges to Pfizer efforts to increase fluorinated BB access

Initial efforts to increase fluorinated BB access on a small scale focused on purchasing commercially available compounds from an established vendor who would supply them in high quality and also have the capabilities to support larger scale synthesis should the need arise. Navin Fluorine was identified as a vendor who had the desired capabilities with a fine chemicals arm in the UK (Manchester Organics), a large-scale production facility in India and previous experience working with Pfizer.

We identified a set of 20 fluorinated BB listed in the vendor catalog and submitted a purchase

1359-6446/
https://doi.org/10.1016/j.drudis.2018.03.001

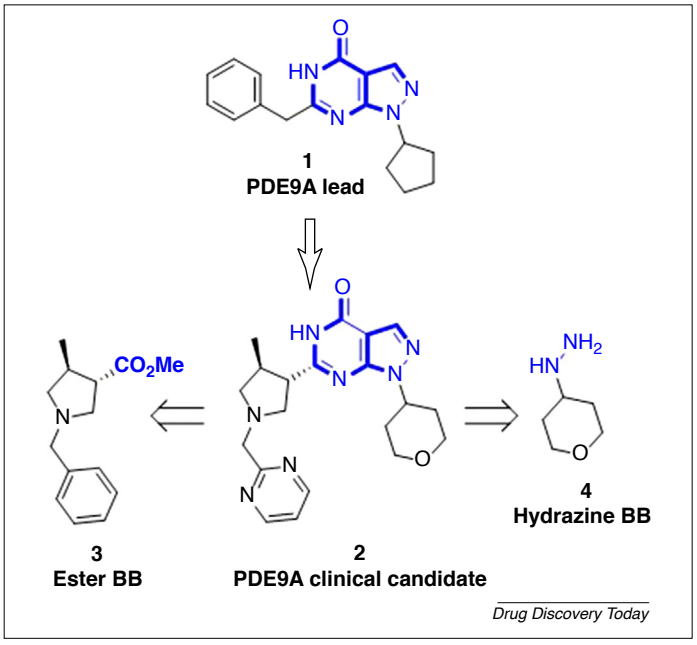

FIGURE 1

Optimization of a phosphodiesterase 9A (PDE9A) lead (**1**) to clinical candidate (**2**) with critical BB highlighted.

order for 5 g quantities to get a quote on the set for the purchase. Our previous experience was that orders of this type would be in the <US$1K range for each compound. Many of the compounds, however, came back with prices in the US$3–5K range, well above our budget for compounds that were being purchased without a specifically defined project need. A second quote on these compounds was requested, this time for a 1 g quantity, assuming that this would reduce the cost for these compounds by at least fivefold and bring the price back into our target range. Interestingly, the quotes came back with essentially no change in price. In following up with the vendor, these compounds listed in the catalog had not been synthesized but confidence to do so was high. Nevertheless, there was a significant chemistry development cost that would be part of the compound price, no matter the quantity delivered. We ultimately declined to purchase the compounds and our effort to increase fluorinated BB, and preparation of fluorinated project analogs, was put on hold.

An idea: multiple companies share chemistry development costs

Although we were mildly surprised at the outcome of our above experience, in reality this is a very common scenario experienced by medicinal chemists seeking access to small quantities of BB – prices are high and quoted time cycles are often long, the demand for the BB is soft because no actual compound has been made with it and ultimately the chemist decides to forgo the purchase of the BB and the synthesis of a specific compound. This cycle repeats itself time and time again with the BB remaining a picture in an online catalog and the potential value untapped.

If multiple companies placed orders for a BB at the same time, however, we wondered whether the interested parties would be able to share the development costs equally. This would produce a win–win scenario wherein the BB is produced at a considerably reduced cost for each purchaser, whereas the vendor generates a sale and the technology to synthesize the compound, ultimately leading to future purchases and a reduction in price because the technology to deliver the BB has been established. Importantly, the more purchasers that are part of this the more the BB price drops, as shown in Table 1. These changes in cost not only save money but also allow existing funds to be used more efficiently, as in the comparison of the number of BB that can be purchased with US$150K by a single company (30) versus five companies (150). This is important because chemical space is vast and gaining access to large numbers of desirable BB that can probe this space is essential to derive maximum value [13]. We saw potential challenges to this proposal such as:

- identification of capable and interested vendors;
- identification of interested pharmaceutical companies;
- coordination of the process and ensuring confidentiality;
- agreement on pricing and quantity delivered;
- generation of BB for purchase consideration;
- choosing BB for synthesis and purchase;
- other potential benefits to be negotiated in addition to cost reduction.

Development of formal cross-pharma–vendor Buying Group proposal

We made a decision to explore the creation of a pilot proposal that would align pharmaceutical company BB purchases with a single vendor, seeking to systematically address the challenges mentioned above.

Identification of capable and interested vendors

We met with Navin Fluorine (referred to as 'the vendor') following our quoting process above and shared the concept in Table 1. There was high interest from the vendor to participate in a unique business deal because many vendors are open to novel approaches to meet customer needs better.

Identification of interested pharmaceutical companies

The next step required contacting different pharmaceutical companies and gauging interest. In some cases, there was great enthusiasm for participating, whereas in other cases there were concerns about working across companies and providing a competitor with knowledge of internal BB. Ultimately, we identified five pharmaceutical companies (Amgen, Boehringer Ingelheim, Janssen, MSD and Pfizer) who were eager to engage in discussions about how to best enable the business model. The openness to consider such a proposal suggests that companies have a significant interest in acquiring BB and that this space is not seen as a competitive arena but as one where collaboration can lead to increased value for all. There was no financial obligation to participate at this point.

Coordination of the process and ensuring confidentiality

It was decided that the vendor should be the coordinator of this effort, termed a Buying Group, not a single pharmaceutical company. This would ensure confidentiality by all compound orders going through the vendor and operating in a more traditional vendor–purchaser model as opposed to a precompetitive consortium. The vendor prepared a formal proposal that was reviewed internally by each

TABLE 1

Modeled cost savings by sharing costs of custom, expensive building blocks (BB)

No. purchasing pharma	Purchase order	Purchase price	BB available at US$150K
1	30 BB × US$5K	US$150K	30
5	30 BB × US$5K/5	US$30K	150

participating company. In the following paragraphs, some of the details of the proposal will be disclosed.

Agreement on pricing and quantity delivered

The price for each compound that was synthesized and purchased was agreed to be equal to US$5500 per company choosing the compound. For each compound chosen, the participating company would receive 1 g.

Generation of BB for purchase consideration

Because the vendor was coordinating the Buying Group, it was agreed that they would provide an initial set of unsynthesized BB from their catalog that had not been publicized. The Buying Group members would evaluate these BB for purchase. A discussion between Pfizer chemists and Navin scientists allowed the selection of a set of BB with a range of chemical and physical properties because we were interested in seeing whether there were trends in properties of the BB selected by each company. Specific examples of some BB included are shown in Fig. 2. The properties of the full set under consideration plotted by molecular weight (MW) on the y-axis and topological polar surface area (TPSA, Å^2) on the x-axis with each compound colored by the reactive functional group and shaped by the number of fluorine atoms (≤3 and ≥4) is shown in Fig. 3. Key points are that a range of commonly reactive functional groups were included with the majority of compounds having three or fewer fluorine atoms. Because the reactive functional group is present for calculated properties, the actual MW and TPSA of the BB fragment incorporated into the final molecule could be significantly lower than what is shown.

Choosing BB for synthesis and purchase

The minimum number of compounds that a company would agree to purchase would be 25 to ensure that the vendor would generate a reasonable profit from the effort. A company could choose more if desired. The vendor would collate the final selections and agree to synthesize all compounds that were chosen by four or more companies as long as at least 25 total compounds were chosen. If a compound was chosen by fewer than four companies, the vendor would share this information with the interested companies with the price equal to US$5500 per number of companies purchasing. All companies were able to review the final cost of compounds that they chose before agreeing to the purchase. A company purchase order was the official and only agreement to purchase.

Other potential benefits

It was agreed that Buying Group members would have exclusivity on the ordered BB set for 6 months before they were publicized for purchase. Buying Group members would also receive improved pricing for repeat orders from the BB set and any scale-up chemistry that was to be determined on a case-by-case basis. The exact cost structure was not determined in advance owing to the specificity of chemistry for each BB.

Compounds chosen for synthesis, delivered and selected usage data

After following the above process, 49 total compounds out of the 100 proposed by the vendor were actually synthesized and distributed to the participants. The success rate for synthesis was >97% and all compounds were delivered within 5 months of purchase orders being submitted which shows the importance of working with a highly skilled vendor. Although the data were blinded as to which actual compounds were ordered by each company, 20 BBs were selected by the majority of companies according to the vendor. This shows a significant alignment of interests in the BB chosen because only 25 compounds were required to be chosen for synthesis by each company.

To assess usage of these compounds across individual companies as a measure of value added, four of the participants provided blinded data on the number of BB received and how many were ordered from their internal compound stores at least once over a 2-year period (Table 2). For companies A, B and C there was significant utilization of BB (~50–70%). This shows that making previously inaccessible BB available can serve as a stimulus to synthesize molecules that incorporate the new BB. Interestingly, company D had no reported orders, which could be a result of how this effort was communicated within the company or specific design practices.

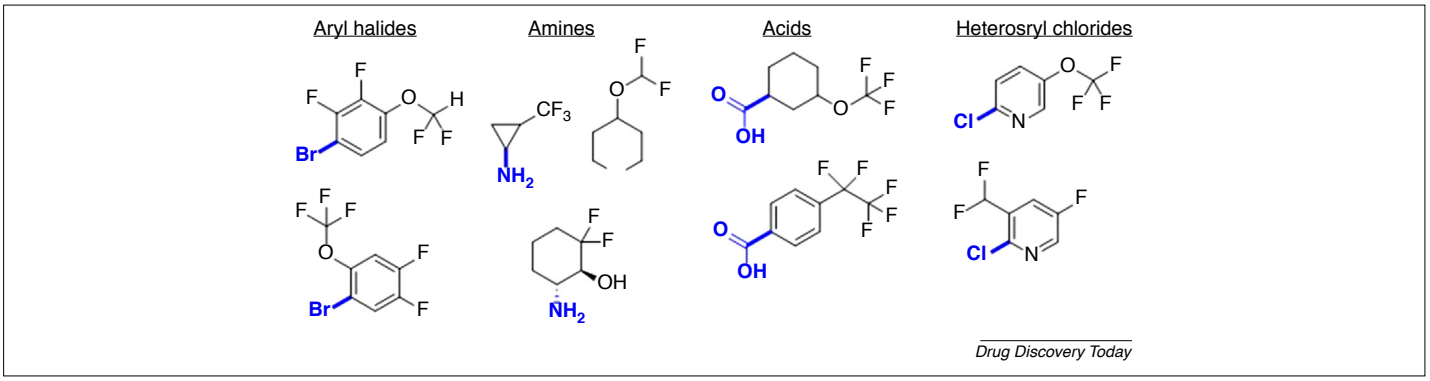

FIGURE 2

Representative fluorinated building blocks (BB) from 100 proposed for synthesis by Navin Fluorine for the Buying Group.

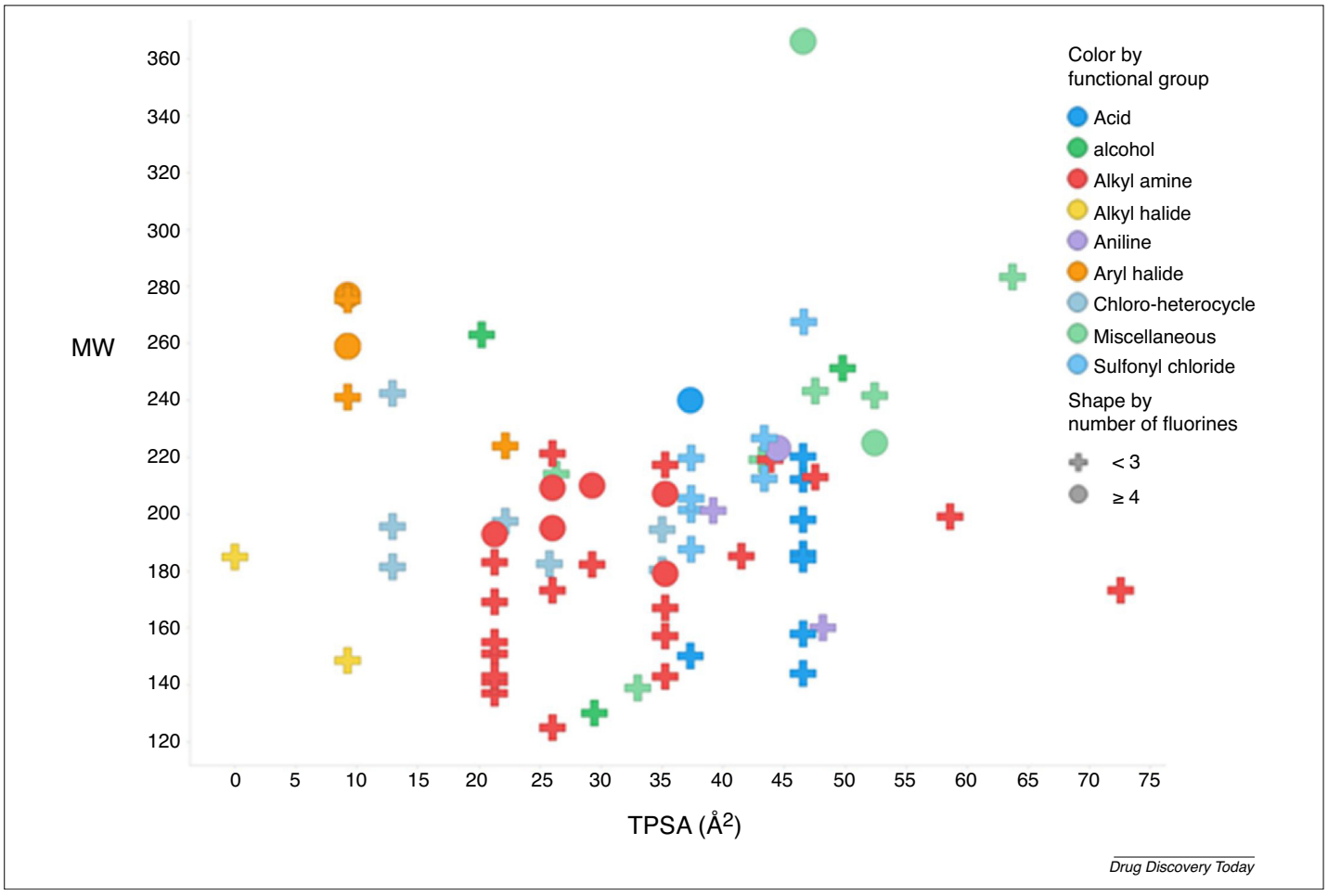

FIGURE 3

Plot of molecular weight (MW) vs topological polar surface area (TPSA) for fluorinated building blocks (BB). Colored by reactive functional group and shaped by number of fluorines.

TABLE 2

Usage of fluorinated building blocks (BB) across different companies (blinded) over 2 years

Company	A	B	C	D
No. BB purchased in Buying Group	30	29	28	30
No. of BB ordered ≥1 time internally (%)	22 (73)	15 (52)	17 (61)	0

One of the benefits of the Buying Group was the 6-month BB exclusivity and reduced rates for repeat orders and larger scale synthesis (see above). Significant value was not derived in either case because exclusive access did not ensure complete BB utilization across any company in 2 years (Table 2), much less in 6 months, and no repeat orders or large-scale synthesis requests for any BB were submitted to the vendor. It is possible, however, that the small scale of the effort was less likely to result in identifying a high-value BB requiring bulk preparation and that incorporating a larger number of BB (hundreds or thousands) could increase the likelihood of uncovering a critical project fragment.

Concluding remarks

Multiple pharmaceutical companies and the chemical vendor Navin Fluorine successfully formed a Buying Group that aligned timing of fluorinated BB purchase to synthesize and deliver at significantly reduced cost. There was considerable overlap in BB of interest by the participants from the compound set under consideration, suggesting there are shared interests in general classes of BB and that most, if not all, pharmaceutical companies would benefit from increased availability of BB. Analysis shows considerable use of these BB over a 2-year period by several of the participating companies. The lack of complete BB usage by any company, and a case of no usage by one, indicates that proactive acquisition of BB without a defined project need presents some financial risk. Indeed, there were other companies that participated in initial Buying Group discussions that ultimately were not able to access the funds to participate. In discussions regarding developing a second, expanded Buying Group, several companies declined to participate owing to a lack of funds for proactive BB purchase on a scale that would be highly impactful. As such, a second Buying Group has not been established. We believe that the development of additional business models to facilitate access of existing BB and influence the design and synthesis of BB that reduce upfront financial investment would be of high interest and have significant impact on me-

dicinal chemistry efforts to identify next-generation therapeutics.

Acknowledgments

Amgen: Erin DiMauro, David Bauer; Bristol-Meyers Squibb: Percy Carter; Janssen: Nicholas I. Carruthers, Michael A. Letavic and James P. Edwards; Merck: Petr Vachal; Navin Fluorine: Rob Grant, David Tovell; Pfizer: James Tornos and Anabella Villalobos.

References

1 Verhoest, P.R. *et al.* (2009) Identification of a brain penetrant PDE9A inhibitor utilizing prospective design and chemical enablement as a rapid lead optimization strategy. *J. Med. Chem.* 52, 7946–7949

2 Verhoest, P.R. *et al.* (2012) Design and discovery of 6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (PF-04447943), a selective brain penetrant PDE9A inhibitor for the treatment of cognitive disorders. *J. Med. Chem.* 5, 9045–9054

3 Goldberg, F.W. *et al.* (2015) Designing novel building blocks is an overlooked strategy to improve compound quality. *Drug Discov. Today* 20, 11–17

4 Shah, P. and Westwell, A.D. (2007) The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. Med. Chem.* 22, 527–540

5 Gillis, E.P. *et al.* (2015) Applications of fluorine in medicinal chemistry. *J. Med. Chem.* 58, 8315–8359

6 Wang, J. *et al.* (2014) Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* 114, 2432–2506

7 Pettersson, M. *et al.* (2016) Quantitative assessment of the impact of fluorine substitution on P-glycoprotein (P-gp) mediated efflux, permeability, lipophilicity, and metabolic stability. *J. Med. Chem.* 59, 5284–5296

8 Murphy, C.D. and Sandford, G. (2015) Recent advances in fluorination techniques and their anticipated impact on drug metabolism and toxicity. *Expert Opin. Drug Metab. Toxicol.* 11, 589–599

9 Walker, M.A. (2017) Improvement in aqueous solubility achieved via small molecular changes. *Bioorg. Med. Chem. Lett.* 27, 5100–5108

10 Bernard-Gauthier, V. *et al.* (2017) Discovery of PET radiopharmaceuticals at the academia–industry interface. *Drug Discov. Today Technol.* 25, 19–26

11 Norton, R.S. *et al.* (2016) Applications of 19F-NMR in fragment-based drug discovery. *Molecules* 21 860/1–860/13

12 Richardson, P. (2016) Fluorination methods for drug discovery and development. *Expert Opin. Drug Discov.* 11, 983–999

13 Visini, R. *et al.* (2017) Fragment database FDB-17. *J. Chem. Inf. Model.* 57, 700–709

Christopher J. Helal[1,*]
Alessandra Bartolozzi[2]
Steven D. Goble[3]
Neelakanda S. Mani[4]
Angel Guzman-Perez[5]
Ajay K. Ohri[6]
Zhi-Cai Shi[3]
Chakrapani Subramanyam[1]

[1]Pfizer, Eastern Point Rd, Groton, CT 06340, USA
[2]Boehringer-Ingelheim, 900 Ridgebury Road, Ridgefield, CT 06877, USA
[3]Merck&Co., 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[4]Janssen Pharmaceuticals, 3210 Merryfield Row, San Diego, CA 92121, USA
[5]Amgen, 360 Binney Street, Cambridge, MA 02142, USA
[6]Navin Fluorine International Limited, 2nd Floor, Sunteck Centre, 37/40, Subhash Road, Vile Parle (E), Mumbai 400057, India

**Corresponding author.*