Reviews • FOUNDATION REVIEW

Teaser Modern medicinal chemistry impacts drug discovery in many ways beyond just optimization of clinical candidates. Here we describe the formation and work of a small team dedicated to hit and lead generation with novel methods inside Janssen.

Industrial medicinal chemistry insights: neuroscience hit generation at Janssen

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The role of medicinal chemistry has changed over the past 10 years. Chemistry had become one step in a process; funneling the output of high-throughput screening (HTS) on to the next stage. The goal to identify the ideal clinical compound remains, but the means to achieve this have changed. Modern medicinal chemistry is responsible for integrating innovation throughout early drug discovery, including new screening paradigms, computational approaches, novel synthetic chemistry, gene-family screening, investigating routes of delivery, and so on. In this Foundation Review, we show how a successful medicinal chemistry team has a broad impact and requires multidisciplinary expertise in these areas.

Introduction

Since the early 2000s, drug discovery has faced a productivity challenge. The cost of a new drug is increasing, now estimated to be US$2.6 billion [1–5], while returns are falling [6]. Although most costs are incurred during clinical development, early discovery must identify molecules with the best chance of success. By the turn of the millennium, drug discovery had shifted away from a pharmacology focus towards molecular biology with genetic validation [7]. New technologies arose, such as combinatorial chemistry and HTS, beckoning in a new era of high-throughput drug discovery [8] and meaning that medicinal chemistry was no longer center stage [9]. The workhorse of iterative drug design, the 'design–make–test' cycle, slipped to later stages of an industrialized process. Thousands of HTS hits prompted doubts about which were best; the molecular beauty versus obesity contest began [10–14]. Often, chemistry would only start after significant biology and screening was complete. The high-throughput focus reduced innovative and iterative thinking and made data analysis and hypothesis testing more difficult [15]. Although many projects have been launched from successful HTS, a plan 'B' was often lacking in the event of not finding hits. By the mid-2000s, progress was slowing [16] and the technological advances did not appear to enable drug discovery within new target classes [17]. At the same time, reorganizations, outsourcing, and downsizing increased disruption.

Frederik Rombouts is a principal scientist in the Neuroscience Medicinal Chemistry Department of Janssen Research and Development. He joined Janssen Pharmaceutica (Belgium) in 2003, initially working on macrocycle chemistry. In 2007, he became team leader of the Hit Generation Team. In this role, he was responsible for generating high-quality chemical starting points across the neuroscience portfolio, and fueling synthetic and technology innovation in medicinal chemistry. In 2015, he assumed the role of project team leader and is now responsible for the preclinical development of imaging agents and therapeutics for Alzheimer's disease. He has co-authored 38 publications and features as co-inventor on more than ten patents.
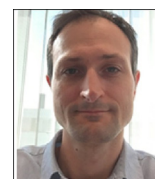
Daniel Oehlrich was awarded his MChem in Chemistry from Exeter University, UK, in 2001. Subsequently, in 2004, he was awarded his PhD from Warwick University, UK, under the supervision of Michael Shipman, where he was successful in the total synthesis of luminacin D. He did postdoctoral studies at the University of Manchester, UK, working with E.J. Thomas investigating 'The Target Synthesis of Novel Anti-Alzheimer Compounds'. He subsequently joined the department of medicinal chemistry at Janssen in 2005, initially in Toledo, Spain, before transferring to Beerse, Belgium, in 2009. He is a principal scientist in medicinal chemistry, currently leading the Beerse Hit Generation Team.

Andrēs A. Trabanco was awarded his PhD from the Universidad de Oviedo-Spain in 1999. He then moved to Imperial College of Science Technology and Medicine, London, UK for postdoctoral studies. Andrēs joined the Neuroscience MedChem Team at Janssen in 2000 and, since 2008, has led the Neuroscience Hit Generation Team in the search for novel hits/leads within the neuroscience therapeutic area. Andrēs has been a chemistry leader and active team member for several programs in the areas of schizophrenia, depression, anxiety, and cognition/Alzheimer's disease, which have delivered various clinical candidates. He is an inventor on 48 patent applications and an author of over 60 scientific publications.

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Today, improvements can be seen. Failure because of poor pharmacokinetics (PK) has been reduced [18] although not eradicated [19] thanks to the front-loading of *in vitro* ADMET and *in vivo* PK screening [20]. Lead quality is improving: fragment screening emphasizes optimal ligand–target interactions, and the impact of molecular physicochemical properties on success is better appreciated. Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) metrics help balance potency versus optimal properties, in short the 'bang-per-buck' of activity [21]. Phenotypic approaches are resurging and research suggests that they are more successful in identifying first-in-class drugs compared with single-target approaches [22]. It is hoped that compounds identified from the outset to act on the relevant disease phenotype will translate to more favorable clinical outcomes, thus improving efficacy-based failure in Phase II/III trials. In the meantime, better understanding of the role of single targets in disease is needed at the earliest discovery stage [20]. Hence, it is challenging to choose the right time to commit significant chemistry resources to a project, that is, knowing when the degree of target validation is optimal. Chemical biology is impacting these early stages [23] and medicinal chemistry overall is adapting to the changing environment.

Since 2005, multiple industrial groups have either withdrawn or substantially changed their strategy in neuroscience (NS) research [24]. GlaxoSmithKline restructured and Bristol Myers Squibb exited NS research; Novartis focused on deeper genetic understanding; and AstraZeneca shifted towards an external virtual model [25] (www.fiercebiotech.com/story/gsk-cuts-neuroscience-rd-staff-rtp/2011-02-17; www.fiercebiotech.com/story/bristol-myers-ax-75-rd-staffers-focus-late-stage-efforts/2013-11-07). Janssen has remained in NS research but partly shifted focus from psychiatry to neurodegeneration. This has brought a change to enzyme targets that are either increasingly competitive [26] or entirely unexplored. Tractability is often lower than for traditional NS target classes, such as G-protein-coupled receptors (GPCRs). Nevertheless, NS is well suited to small-molecule medicinal chemistry because, although biologics have a role, brain exposure is not straightforward.

Amid this backdrop, reports have suggested new roles for chemistry varying from assembling chemical probe libraries to interface with biology [27], or in regenerative medicine, epigenetics, and peptide therapeutics [28], or in pursuing modern synthetic strategies, novel structural motifs, and computational methods to capture data and intelligence [29]. Janssen has responded by expanding the role of chemistry to impact NS projects from multiple angles. Here, we describe efforts within the European Janssen NS Hit Generation (HG) chemistry team. We see this as reflective of many, but not all, industry medicinal chemistry groups. This report provides an insight into modern-day medicinal chemistry, describing our response to the changing scenario and highlighting the diversity of applications and impact of chemistry in the current drug discovery environment.

Accessing novel chemistry both internally and externally

HTS hits often originate from commercial libraries synthesized using a few robust synthetic transformations. The lack of synthetic diversity promotes increased aromatic planarity and poor drug-like properties [30,31]. The best leads often emerge from costly synthetic efforts; consider, for example, the evolution of beta secretase 1 (BACE1) inhibitors [32]. Stepping beyond tried and tested isosteric replacements can improve drug-like properties or move to uncluttered intellectual property (IP) space. Therefore, medicinal chemists should continually expand their synthetic expertise [33], exploring more exotic transformations and embracing technologies such as synthesis workstations, microwave reactors, photochemistry devices, and flow technology. We dedicate substantial efforts to these areas, often with external collaborators. In almost all fields of scientific endeavor, most innovation occurs outside of any one institution. Successfully harnessing this external innovation is paramount. Similar to other disciplines, a successful medicinal chemistry team needs to collaborate and partner if it is to bring truly transformational innovation to drug discovery. However, the challenge is to seek out innovation that will enhance, complement, and diversify the internal expertise, allowing partnerships to deliver more than the sum of the parts. Contrasting with collaborations of the past [34], we ensure common goals and a direct link to our internal projects. Our collaborations with leading academic groups have explored novel chemical transformations, bioisosteres, and access to advanced scaffolds of interest. Many of these collaborations allow the academic researcher (normally a PhD or postdoctoral student) to work in our own laboratories. This has several benefits, including the effective transfer of new science to the internal team and allowing the researcher access to world-class infrastructure. We have collaborated with the group of Professor Molander (University of Pennsylvania, USA) in developing and implementing synthetic coupling approaches for novel tetrafluoroborates that simplify introducing alkoxy substituents into lead molecules. Two representative investigations were the generation of alkoxyethyl tetrafluoroborates and dioxolanylethyl tetrafluoroborates, which incorporate homologated alkoxy substituents in one synthetic transformation. We developed methodology that enabled the introduction of alcohol substituents with an appropriate protecting group, permitting further diversification [35,36].

Additionally, we have investigated the formation of fluorinated heteroaromatic and heteroalkylic ring systems in collaboration with the group of Professor De Kimpe (Ghent University, Belgium). The focus was the generation of useful building blocks to be applied to ongoing projects or library enrichment. We also focused on understanding the methodology and its tolerance for future implementation in medicinal chemistry programs [37,38]. We are also interested in novel isosteric replacements, such as the use of azaborinines as naphthalene bioisosteres, with a focus on druggability for application in future projects [39,40]. Similarly, we worked with the group of Professor Fustero (University of Valencia, Spain) on the synthesis of novel fluorinated amino-alcohol intermediates aimed at the efficient synthesis of BACE1 inhibitors. These intricate substitutions permit subtle modulation of the physical chemical properties of the compounds [41–43]. Identifying enantioselective synthetic routes addressed problems associated with chiral separation and or resolution of the intermediates in our ongoing projects [44]. We also collaborate within the Synthesis for Biology and Medicine (SBM) Consortium at the University of Oxford (for information about SBM visit, see www.oxfordsynthesiscdt.ox.ac.uk). This offers opportunities to advance the methodology of medicinal chemistry, performed

within a precompetitive environment. The consortium has the added advantage that research is not limited solely to the expertise of one group, but connects multiple investigators.

Janssen has embarked on creative ways to enrich its internal compound screening collection [45]. This has been one objective of the HG team. As mentioned above, novel chemistry or scaffolds arising from collaborations or internal projects are passed to library enrichment. We typically enumerate small libraries around new scaffolds biased towards central nervous system (CNS) chemical space, while including 15–20% of compounds with looser property cut-offs. Libraries are kept deliberately small and designed to include substituents providing diverse interaction types at specific distances from their attachment point [46]. This permits a wide interaction space to be explored with relatively few (dozens rather than hundreds) of reagents. A recent example of a *de novo* scaffold originating from novel synthetic chemistry was a fused bicyclic pyridone providing attractive gamma secretase modulators with inherent lower lipophilicity compared with known scaffolds [47]. Additionally, the team has also been one of the main drivers in establishing Janssen as an important founding partner in the European Lead Factory (for more information on the European Lead Factory, see www.europeanleadfactory.eu).

Through membership of this consortium, we have the opportunity to regularly screen a large and diverse compound library that is complementary to the in-house screening collection. This library, assembled through contributions of member companies and expanded with novel chemistries provided by academic, biotech, and contract research organisations (CROs), provides an important new resource for matching emerging biology and chemical space [48,49] (Fig. 1).

Macrocyclization

Our first efforts at HG by macrocyclization were for an internal EGFR kinase inhibitor program some years before the NS HG team was established. The chain, or linker, provided several benefits, in particular the modulation of selectivity versus other kinases, modulation of physicochemical properties, and the creation of IP. Interestingly, only the 22nd macrocycle that was synthesized progressed into Phase I clinical trials. It displayed improved brain penetration compared with erlotinib and gefitinib, which was considered beneficial for the treatment of brain tumors (Table 1). A dedicated team was then formed with macrocycle chemistry expertise, generating linker diversity, parallelizing chemistry, and scale-up. As well as targeting project leads, this
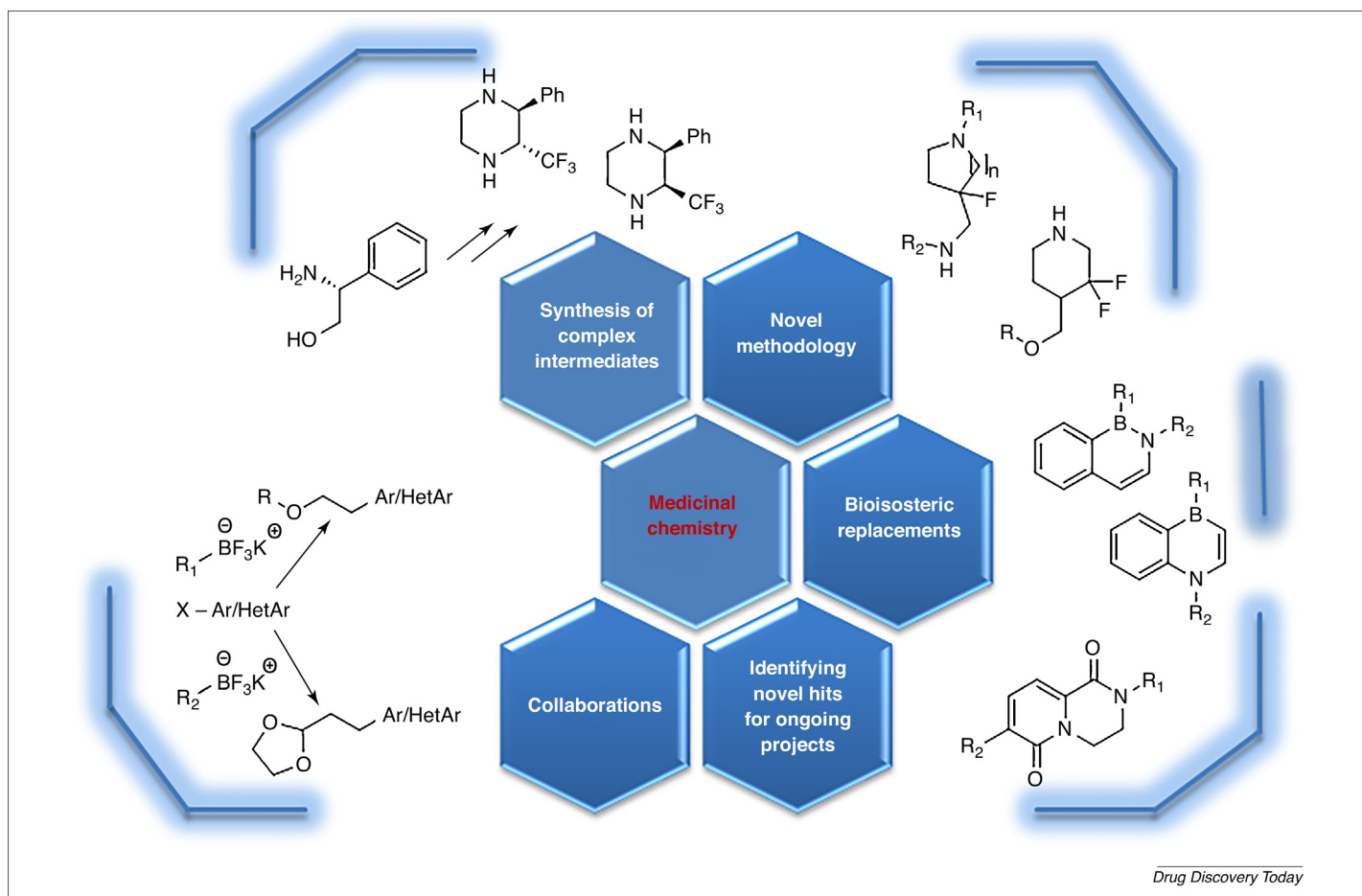

FIGURE 1

Accessing novel chemistry transformations and their impact in project chemistry. A schematic of our approach to using areas of synthetic innovation to support core medicinal chemistry. Illustrated are examples of trifluoroborates useful for the introduction of complex functional groups in a single transformation; new amino alcohol transformations to introduction aliphatic fluorinated substituents, benzazaborinines as aromatic isosteres, and a bicyclic pyridone scaffold active for gamma secretase modulation.
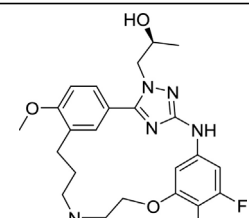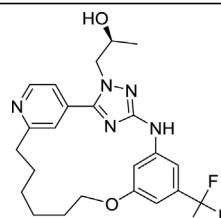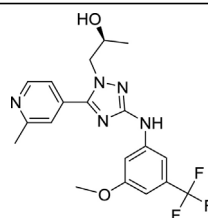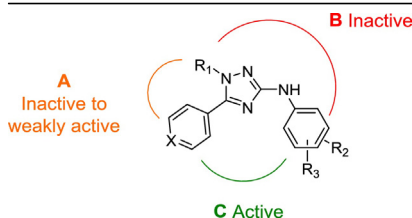
TABLE 1

Examples of the macrocyclization of ligands of EGFR and α7 nicotinic receptor[a]

EGFR example
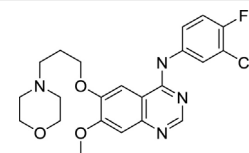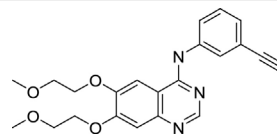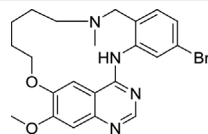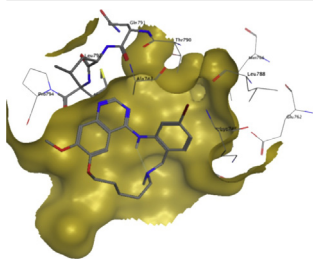
Compound	1	Erlotinib	Gefitinib
EGFR pIC$_{50}$ (Millipore)	7.74	8.67	8.33
ClogP, TPSA, MW	6.45, 59, 457	4.19, 75, 393	5.25, 69, 447
AUC$_{0-inf}$ (ng.h/g) (rat 10 mg/kg PO)	2347	7458	3334
B:P ratio (rat 10 mg/kg PO)	1.6	0.11	0.35

α7 nicotinic receptor

Compound	2	3	4
α7 PAM pEC$_{50}$	6.1	6.4	6.5
ClogP, TPSA, MW	3.62, 85, 407	5.46, 85, 461	4.45, 85, 474
HLM, %met. at 15 min	17	11	36
Thermodynamic solubility (mg/mL at pH 4)	0.006	N/A	0.084
Concentration in brain at 90 min (ng/g) (mouse, 10 mg/kg SC)	855	1750	283
B:P ratio at 90 min (mouse, 10 mg/kg SC)	1.7	2.1	1.2

[a] Abbreviations: B:P, brain over plasma; EGFR, epidermal growth factor receptor; HLM, human liver microsomes; PAM, positive allosteric modulator; PO, personal observation.

group also synthesized a 'linker-diverse' kinase inhibitor library of over 5000 compounds that was partly spun out to Oncodesign (www.oncodesign.com/).

More recently, macrocyclization has been applied as a HG strategy in NS. In a project targeting positive allosteric modulators of the α7 nicotinic receptor, the lead series suffered from poor solubility, and no position in the molecule tolerated an aliphatic basic center, such as a pendant morpholine or piperazine. Hence, three carbon-chain macrocyclizations (A, B, and C) were synthesized with the aim of later introducing a basic nitrogen more remotely from the core pharmacophore. Only macrocyclization C gave equipotent compounds and **3** was one of the early examples, with a simple linker showing brain penetration. Interestingly, it was found that the linker tolerated aliphatic amines, with **4** being a promising lead with improved solubility and brain penetration. Macrocyclization is a powerful strategy to create new lead compounds [50,51], especially in a crowded IP space, but the medicinal chemistry optimization remains challenging. We believe that this strategy is best considered for advanced compounds that have already shown an attractive profile.

Hits off-the-shelf: gene family screening

One of the challenges for kinase drug discovery is optimizing inhibitor selectivity across the human kinome. To study this, kinase family-wide *in vitro* profiling of inhibitors has been developed. Broad screening is used not only to characterize selectivity, but also for lead generation. The approach capitalizes on either purchased or in-house synthesized kinase libraries that, according to chemogenomic similarity principles, can provide starting hits for related kinases [52]. Within Janssen, we have invested in screening thousands of kinase inhibitors in panels of hundreds of kinases [53]. These data have provided selective in-house kinase inhibitors 'off-the-shelf', helping our efforts for HG and target validation when kinases might be relevant [54]. Beyond kinases, we have championed the same gene family screening for phosphodiesterases (PDEs) and metabotropic glutamate (mGlu) receptors. Our approach was to compile PDE-focused libraries, identifying substructures similar to cyclic nucleotide heterocycles and other known PDE inhibitors. The approach paid dividends, delivering hits for internal PDE2 and PDE10 inhibition projects [55,56].

We have a longstanding interest in allosteric modulation of mGlu receptors dating back to the late 1990s, with mGlu$_1$ [57,58] and, more recently, mGlu$_2$ and mGlu$_5$. Group III mGlu receptors (4, 6, 7, and 8) are less explored than groups I (1 and 5) and II (2 and 3); hence, to speed up the hit-finding approach, we compiled an mGlu-focused library and routinely began screening against a full panel of mGlu$_{1-8}$ functional assays. We built a data set of approximately 2500 compounds tested in all assays. The molecules were chosen from mGlu receptor allosteric modulator projects, and using computational analogue methods. The data set permitted computational proteochemometric modeling developed in collaboration with the University of Leiden [59]. The approach (Fig. 2) compares the bioactivity data for a protein family based on their binding-site amino acids. The resultant models can discriminate active and inactive compounds for multiple targets, and have improved performance compared with models built for a single protein. These approaches led to the identification of new hits for less-explored group III mGlu receptors.

Fragment screening

Fragment-based screening (FBS) is now an integrated part of drug discovery, and has been pursued as a hit-finding strategy by the HG team in multiple NS projects [61,62]. The principle is that structurally smaller hits [molecular weight (MW) <250 D or number of heavy atoms <21] form a few but optimal interactions, such that resultant leads are superior to those from HTS. Fragment hits typically have low affinity (μM–mM range); hence, sensitive biophysical detection techniques are required, such as surface plasmon resonance (SPR), ThermoFluor® (TF), ligand-observed NMR, and sometimes X-ray screening. Although normally lower throughput than biochemical HTS assays, the fragment space is exponentially smaller, requiring only thousands of fragments to
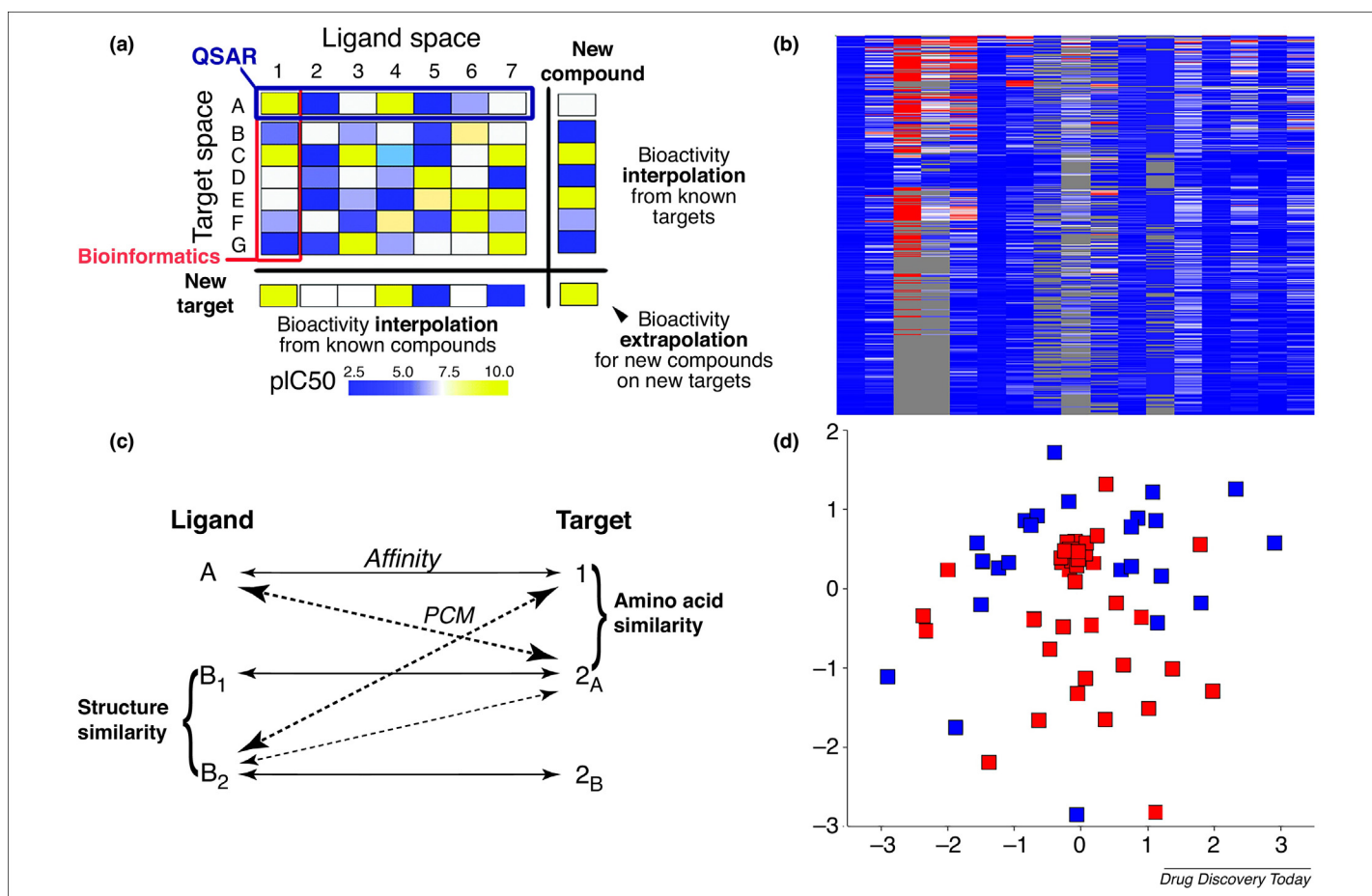
FIGURE 2

Proteochemometric modeling and metabotropic glutamate (mGlu) receptor broad screening. (a) The concept of proteochemometrics [60]: conventional quantitative structure–activity relations (QSAR) is represented by the top row of the matrix (one target multiple compounds), whereas conventional bioinformatics typically tackles the first column (multiple targets with one or few compounds). By contrast, proteochemometrics uses multiple targets and multiple compounds, enabling one to predict the activity of a new compound against the full set of targets (final column), or identify compounds that might be suitable for a new target (final row). (b) Heatmap showing the percentage effect activity for a random selection of 800 molecules (rows) screened in mGlu$_{1-8}$ functional assays (columns sorted from left to right as mGlu$_1$ agonism, mGlu$_1$ antagonism, mGlu$_2$ PAM, mGlu$_2$ agonism, mGlu$_2$ antagonism, mGlu$_3$ agonism and antagonism, etc., through to the final two columns, mGlu$_8$ agonism and antagonism). (c) Computational models are then built comparing targets based on the similarity of binding-site amino acids and comparing ligands using properties such as substructural fingerprints. (d) Virtual screening was performed to identify hits for a relatively unexplored group III mGlu receptor. The plot shows the chemical structure clustering of the hits that were identified. Those from proteochemometrics (red) covered more chemical space than those from fingerprint analog searches (blue). Hence, the contribution of additional target activities enables proteochemometrics to find hits that simple analog searching cannot identify.
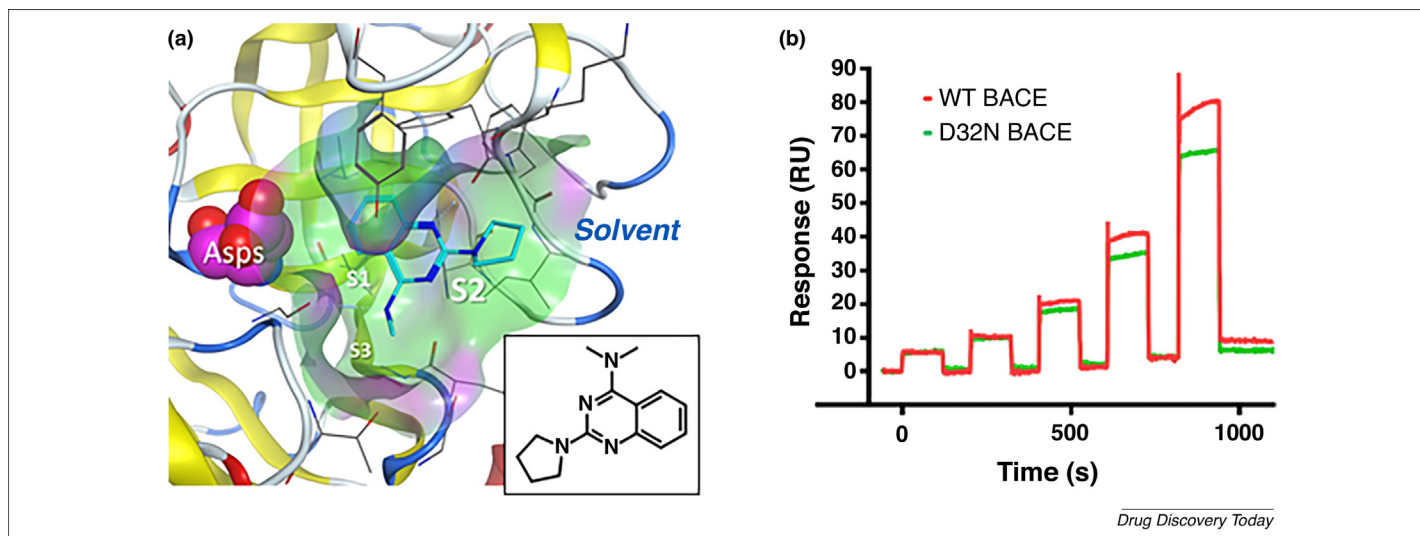
FIGURE 3

The co-crystal structure of a fragment found to bind the S2 pocket of beta secretase 1 (BACE1) without catalytic aspartate interactions (a). This was identified via orthogonal screening methods with BACE1 and an aspartate (D32N) mutant. (b) The sensorgram shows comparable binding to both wild-type and D32N BACE1.

cover a similar chemistry space as hundreds of thousands of HTS compounds [63].

High-concentration screens often render assays sensitive to false positives resulting from minor impurities in the screening samples [64]. The HG team contributed greatly to establishing a high-quality global Janssen fragment collection. The fragment library contains approximately 2600 fragments with 8–21 heavy atoms that have been analyzed by LCMS and NMR to ensure >95% purity. As a result of the high concentration, solubility was an important criterion for fragment selection, and kinetic solubility at pH 7.4 measured up to 1 mM was a requirement. Fragments were chosen based on 2D-shape, 2D-fingerprint, and scaffold diversity. Similarity to known drugs and number of sp^3 centers were also promoted. Of note is that approximately 50% of fragments in the library originate from Janssen proprietary chemistry and new internal molecules continue to be added (Fig. 3).

BACE1 inhibition benefited from fragment screening [65,66] and many groups, including ourselves [67], have explored similar amidine and/or guanidine motifs. Hence, we performed a fragment screen to specifically identify non-Asp-binding fragments in new IP space. An SPR screen was performed in parallel with TF and enzymatic FRET assays. This combination of assays helped discard false positives. Additional information on the binding site and mode was derived by two more SPR screens, first in the presence of a potent substrate-like inhibitor then with a BACE1 catalytic Asp mutant. Further hit confirmation with NMR approaches and/or X-ray crystallography led to a fragment with a unique binding mode in the S2 pocket of BACE1 (Fig. 3) [68]. Hit confirmation with orthogonal techniques maximizes the chances of obtaining an X-ray co-crystal structure. Including mutants and competition experiments in the screening cascade can be a general approach for finding novel ligands for targets with crowded IP space. We have also identified fragments with unusual allosteric binding modes at the α7 nicotinic acetylcholine receptor by a similar approach performing parallel SPR screens [69]. Furthermore, we have performed fragment screens on NS targets that have proven difficult for CNS drug discovery, such as serine racemase or inositol monophosphatase, where a parallel computational study shed light on the nature of the active site [70].

Computational approaches

Since the creation of the HG team, computational approaches have had a useful role, such as for scaffold hopping. In this regard, methods that compare shape, features, and electrostatics are ideal because similarity is assessed using the properties of biological recognition and not the underlying atom connectivity. Databases of fragments are searched to identify those that replicate the shape and electrostatics of a scaffold but have different underlying covalent connectivity and, hence, possibly different properties or new IP [71]. We applied this to mGlu$_2$ receptor-positive allosteric modulators (PAMs) with the aim of identifying a replacement for a pyridone scaffold exhaustively explored in the program [72]. The searches identified an imidazopyridine fragment as an ideal replacement, active compounds were synthesized [73] and the series quickly evolved to the attractive triazopyridine scaffold (Fig. 4), which delivered multiple key leads [74] Confirming the overlapping binding mode permitted quantitative structure–activity relation (QSAR) approaches to identify new R$_{1–3}$ groups [75].

Computational methods contribute to a variety of initiatives in HG. As mentioned above, amidine and/or guanidine chemistry is characteristic of BACE1 inhibition, but not widely represented in HTS decks; hence, novel exploratory chemistry assisted with computational prioritization provided multiple lead series that could not be identified from high-throughput methods [76]. We routinely use ligand-based virtual screening methods to identify analogs that otherwise would not be included in HTS [77]; this has delivered important hits for several programs. More recently, we have moved into exploring molecular dynamics methods for drug discovery applications [78]. This includes free energy perturbation, a method for accurately ranking relative binding affinities of close analogs. Joint computational and experimental evaluations have been performed in the HG team [55,79,80]. Central to our efforts
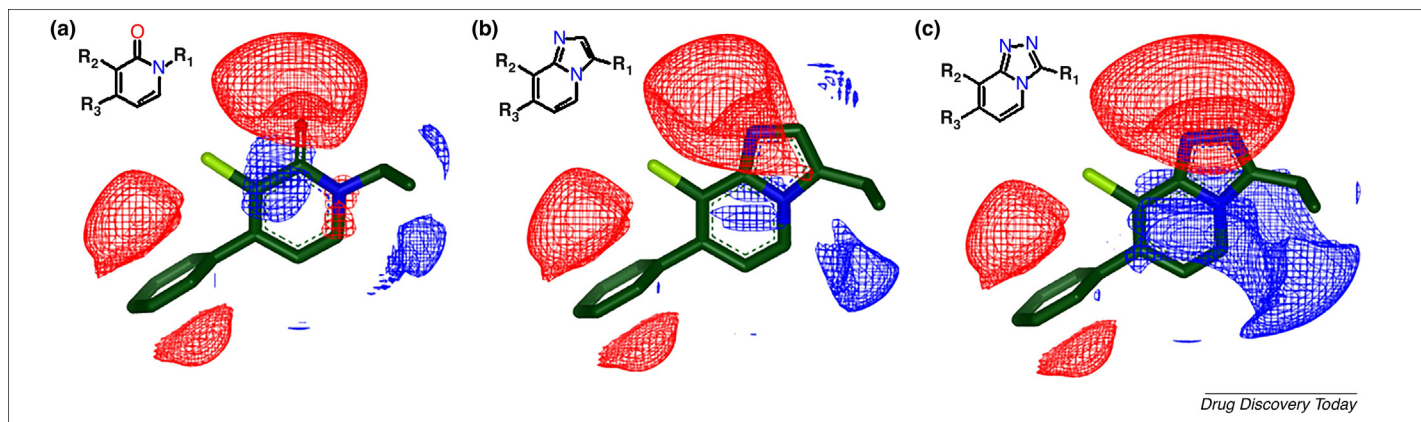
FIGURE 4

Metabotropic glutamate 2 (mGlu$_2$) receptor-positive allosteric modulator scaffold-hopping example. The pyridone scaffold (a) was the first lead series and computational shape and electrostatic field similarity analysis identified imidazopyridines (b) as an ideal replacement. Subsequently triazopyridines (c) became a crucial back-up series scaffold. Red and blue surfaces represent regions of negative and positive electrostatic charge, respectively.

on early targets is to access linked data sources and, in this regard, Janssen experience with OpenPHACTS is often leveraged [81].

Alternative routes for drug delivery

Developing a strategy for alternative brain delivery was an attractive HG project to complement the focus on oral dosing within drug discovery teams. The blood–brain barrier (BBB) regulates brain homeostasis and only permits molecules essential for brain function to enter [82]. Most approved small-molecule drugs and almost all biologics do not readily cross the BBB [83]. Parameters such as lipophilicity, Topological polar surface area (TPSA), and membrane permeability impact brain penetration; however, designing for CNS penetration remains challenging [84]. Various strategies have been attempted to target the brain, such as liposomal [85] or exosomal [86] formulations, nanoparticles [87], prodrugs [88], receptor-mediated transport [89], focused ultrasound [90], and intranasal (IN) delivery [91]. We were interested in the nose-to-brain delivery (NTB) of small molecules because of its non-invasiveness. We aimed to identify the critical parameters for efficient delivery, in particular the deposition area, formulation, applied volume, and the optimal physicochemical properties of the drug. We wanted to verify whether the BBB could be bypassed via NTB delivery, providing access to a broader drug space [92].

The exact mechanisms of IN delivery are not understood. Two main transport routes have been suggested: (i) systemic absorption from the nasal respiratory epithelium followed by transport across the BBB; and (ii) direct transport via perineuronal and perivascular channels associated with olfactory and trigeminal nerves. Drug deposition on the olfactory nerves in the roof of the nasal is thought to be critical for NTB delivery [90]. Alternatively, the trigeminal nerve could transport to the brainstem [93]. Regarding drug properties, IN delivery is advantageous for potent water-soluble biomolecules (proteins, peptides, steroids, vaccines, and oligonucleotides) but that have poor permeability and low brain bioavailability [94]. Nonetheless, some studies claimed that IN administration can allow drugs to enter the brain preferentially via direct pathways [95,96]. Interestingly, morphine is the low-MW drug that is most studied for NTB delivery [97–99].

We developed a reproducible NTB rat model with a correct olfactory epithelium deposition and performed IN administration of small molecules with claimed NTB delivery, including morphine, lidocaine, and also a chemically diverse set of compounds with varying brain permeability. To our surprise, we did not observe improved brain:plasma ratios with IN administration compared with subcutaneous (SC) or intravenous (IV) delivery. However, we did observe uptake in the olfactory bulb (OB); hence, there is a possibility of nose-to-OB transport after which molecules clear rapidly to the blood and lymphatic system before reaching the brain. Although we did not find evidence for the direct uptake of permeable small molecules via the NTB pathway in rats, and consider this unlikely in humans, there could be opportunities for poorly permeable compounds that could be the subject of follow-up work.

Use of optimization metrics

Within the HG team, we have explored optimization metrics, such as LE and LLE, by analyzing their performance within NS projects. The logP for approved oral drugs between 1983 and 2007 was essentially constant in a range of 2–4, whereas other properties, such as MW, increased [100]. This suggests that an ideal logP is an inherent property of a good drug. Despite this, most patented molecules are outside of the preferred range, whereas the optimized leads return to the better property space [101]. The concept of minimal hydrophobicity in drug design is not new [102], but a simple LLE metric (pIC$_{50}$–logP) has been defined to assess molecules in lead optimization programs. We were interested in this because of its potential benefits for efficiency and finding better leads. Synthesizing more molecules with optimal LLE >5 would reduce wastage associated with molecules having an inherent low probability of being drugs. We analyzed multiple historic projects from our NS portfolio. The two examples (Fig. 5) are from projects with different underlying chemistry targeting mGlu$_2$ receptor PAMs and PDE10 inhibitors. In retrospect, we see that preferred clinical compounds were among the mid-range of MW but in the highest range of LLE, confirming the value of this metric. These results were consistent for other programs and suggest that, where possible, synthesis to reach compounds with preferred balance between potency and lipophilicity should increase the chances to find better clinical candidates.

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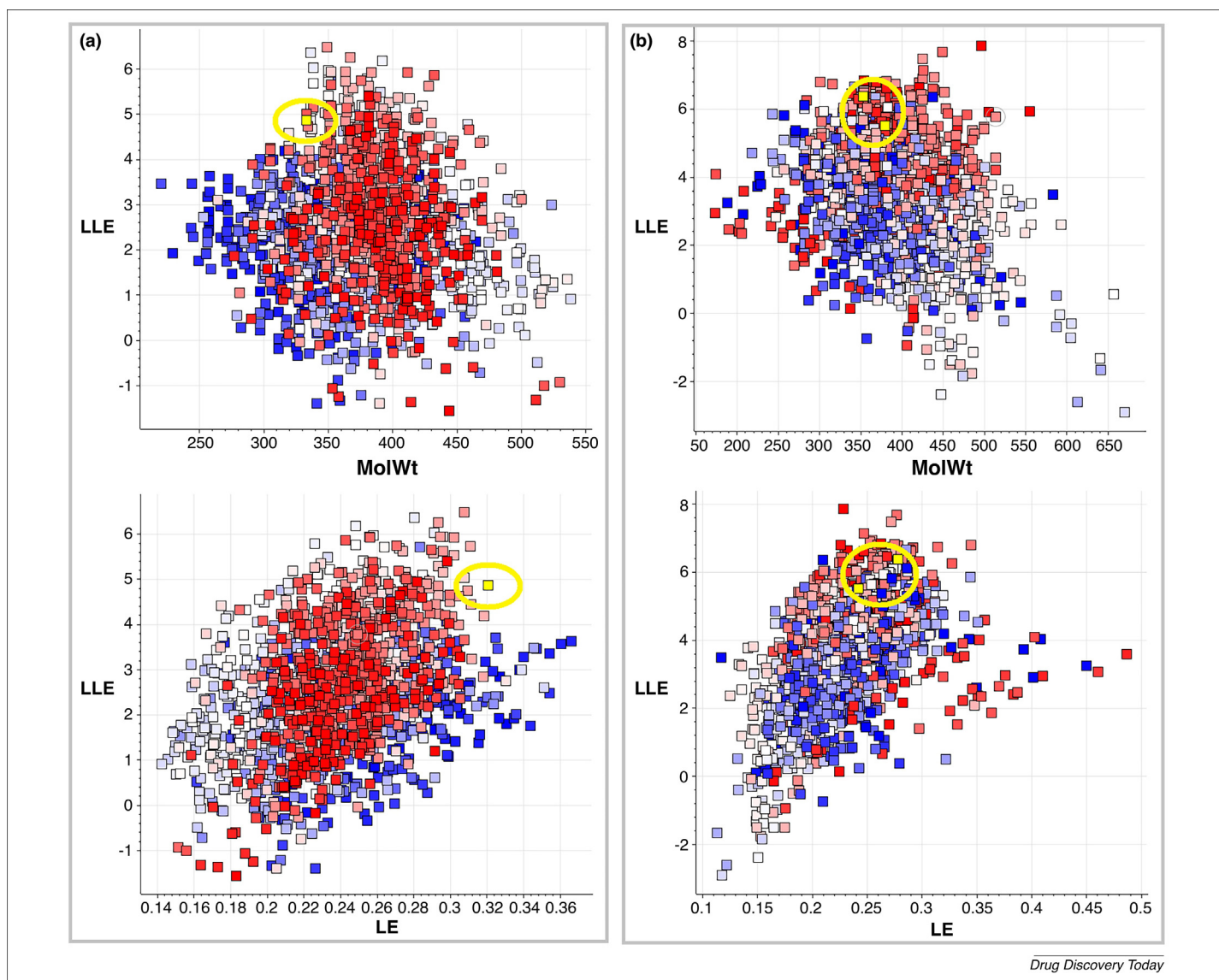
FIGURE 5

Application of lipophilic ligand efficiency (LLE) and ligand efficiency (LE) analysis to neuroscience (NS) projects. The plots in (a) show molecules synthesized for our metabotropic glutamate 2 (mGlu$_2$) positive allosteric modulator (PAM) program, whereas those in (b) show molecules from our phosphodiesterases 10 (PDE10) inhibition program. In both cases, the top plot shows molecular weight (MW) and LLE, whereas the bottom plot shows LE. Coloring represents date of compound registration, with blue being the oldest and red the latest. Clinical candidate molecules for both projects are highlighted in yellow (and circled) showing how the optimal compounds lie in the mid-range of MW, but in the highest range of LLE.

Discussion and concluding remarks

Over several years, we have suffered from unproductive HTS for targets such as peptidic GPCRs or allosteric binding sites. Given the interest and investment up to that point, not being able to identify tractable hit series was problematic. Singleton hits, which traditionally would have been discarded, were often the best that were found. It is in this scenario where medicinal chemistry should return to make an impact. New screening paradigms (such as fragment screening or DNA-encoded libraries [103]) or creative *de novo* chemistry ideas require dedicated focus to ensure they succeed. Hence, a small internal group supported with appropriate external chemistry resources could follow-up singleton hits from different HTS in parallel and rescue some projects. This became one of the founding goals of our HG team. Success soon came because chemistry exploration of a chromanone ester, an undesirable

singleton, quickly delivered more drug-like mGlu$_5$ receptor PAMs that inspired confidence for deeper exploration [104].

Since its inception, the role of the HG team has expanded greatly. We have outlined applications in diverse areas from synthetic organic chemistry, applied computational chemistry, to alternative routes of delivery. This group has also delved into the follow-up of phenotypic screens, using selective probe compounds from literature or internal sources to assist target deconvolution. In addition, the group collaborates with other expert teams within Janssen in areas of chemical biology and positron emission tomography (PET) chemistry. Of course, this team does not monopolize innovation and major contributions come from across the NS medicinal chemistry team. However, this team has contributed to an increased focus on new science, and has been a major source of evaluating and applying new methods in projects,

often leading to valuable hits or new scaffolds in the process. From the various topics we have described, azaborinine chemistry is in its infancy and yet to make a substantial impact, and efforts to reach macrocyclic leads need to be carefully assessed. Meanwhile, the European Lead Factory screening has delivered hits for projects as well as computational approaches; novel chemistry methodology has enabled challenging synthetic chemistry in projects such as BACE inhibition. For modern synthetic techniques to have a wider impact, uptake within internal chemistry teams should be more actively encouraged by leadership and culture. Overall, this dedicated team works in parallel with lead optimization groups and pursues alternative ideas and synthesis of different chemical scaffolds and hits, often originating from the chemists themselves. This has led to a flow of viable chemical series for key programs, as illustrated by the mGlu$_2$ receptor example.

Charles Darwin famously said: 'In the long history of humankind, those who learned to collaborate and improvise most effectively have prevailed'. Combining the best external and internal innovation has brought significant impact to the Janssen NS HG team. External partners have challenged the way we prosecute science internally and helped develop new methodologies and technologies. The strong collaborative mindset along with the strategic objectives of the Janssen research and development (R&D) organization, have driven a broader partnering strategy within NS. At times, almost 50% of portfolio projects are prosecuted in an external partnership model, a testament to the opportunities that external innovation can bring [105,106].

Chemistry is an archetypal multidisciplinary science, and we expect that most modern-day medicinal chemistry groups invest in novel areas similar to ourselves. However, reports are scarce and we have recounted our approach, initially to overcome practical problems with low hit-rate HTS on challenging targets, to what is today a lean group investing in multiple areas to support projects. It should also be noted that this focus has happened amid various pressures: increased outsourcing, downsizing and/or mergers, external innovation, harder and/or more-novel drug discovery targets, and fiercer competition in key disease areas. We partly consider the NS HG team a response to the words of Hann and Oprea: 'There is a risk that high-throughput experiments reduce the opportunity for innovative and iterative thinking, as millions of molecules are screened simultaneously without the possibility of interpretation *and analysis between the* traditional rounds of experiments for this number of datapoints' [15]. We formed a team with responsibilities to perform this essential iterative and innovative thinking, often on small numbers of molecules and low quantity of data, as early as possible. In this regard, we consider the work of our team a success.

Conflict of interest
All authors are employees of Janssen.

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