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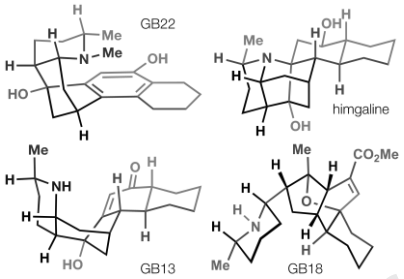

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Synthesis of psychotropic alkaloids from *Galbulimima*

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ABSTRACT

Efficient syntheses of valuable natural products open gateways from kind learning environments to wicked worlds, where long-term, interdisciplinary research questions can be asked and answered. In this Perspective, we discuss the *Galbulimima* (GB) alkaloids, metabolites of a rainforest canopy tree that exhibit potent but poorly understood effects in humans, including accounts of hallucination. Recent syntheses from our group have opened up GB alkaloid chemical space for investigation by way of new cross-coupling reactions and gram-scale target production. Although natural product synthesis can be challenging, its objective is obvious. Realization of long-term, enabling goals will be a circuitous journey at the interface of chemistry, pharmacology and neuroscience—a potent mix to foster discovery in the coming century.

1. Introduction

In his 2019 book Range,[1] David Epstein classifies diverse styles of art, music, sport and science according to learning environments described[2] by psychologist Robin Hogarth: a "kind" environment like performance of a Bach sinfonia provides quick assessments and requires knowledge of limited patterns, whereas a "wicked" environment like improvisation on a Horace Silver chart by a jazz quartet proves dynamic, with unclear patterns and delayed feedback. Research projects can adopt these dissimilar paths—linear (kind) vs. tortuous (wicked)—depending on the type and quality of question that is posed, as well as the metrics applied to measure success. In academic total synthesis, simple metrics provide "kind" paths: if yield, step count and elegance are target metrics, then evaluation of success is clear and quantifiable. A downside of kind metrics is that they exemplify Goodhart's law, paraphrased as "every measure which becomes a target becomes a bad measure,"[3] i.e. if a metric like step count or yield becomes the target instead of the gateway, then a more valuable target is lost. The more valuable target—what the synthesis enables—often is reached in a wicked environment where questions change over time, analogous studies are few or absent, and answers arrive over years or decades. The dilemma faced by every practitioner of total synthesis is when to leave the linear, kind environment of mere target acquisition and venture into the warren of discovery: what will our total synthesis allow us to accomplish? The wicked environment is now within reach of the *Galbulimima* alkaloids due to a series of syntheses reported earlier this year.[4,5] Here we describe the rich history of these psychoactive plant metabolites, summarize our routes to access members on large scale and gaze into the wicked future to evaluate prospects for discovery.

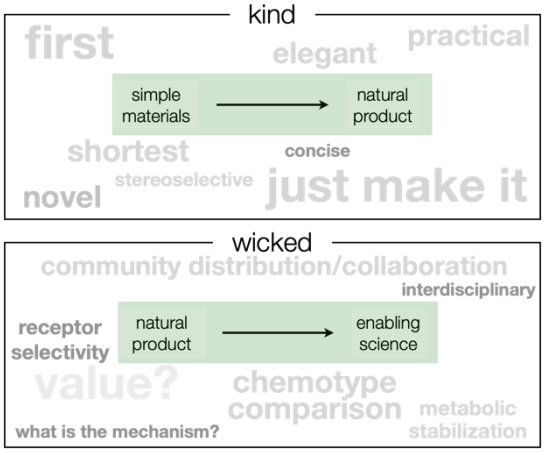

Figure 1. Different types of research questions embody different learning environments.

2. Effects of the *Galbulimima* bark ingestion in humans

The direct relevance of most plant metabolites to human health can be unclear, but some privileged classes find their way into a society's pharmacopoeia by reproducible and useful effects in humans, already clearing hurdles in drug development like aqueous solubility,[6] oral bioavailability, sufficient metabolic stability and, in the case of psychotropic substances, blood-brain barrier penetrance.[7] The ethnopharmacology of *Galbulimima belgraveana* ingestion in Papua New Guinea falls into this

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translational category but is complicated by the diverse and inconsistent descriptions of effects in humans.[8]

In 1887, Mueller described large trees (35 m tall with a 60 cm trunk diameter) found in the rainforests of Papua New Guinea, named over the years as *Eupomatia belgraveana, Himantandra belgraveana, Himantandra nitida*, and *Galbulimima nitida*; the broadly accepted scientific name is currently *Galbulimima belgraveana*. The number of distinct species within the genus has been the subject of confusion and has ranged from four (*G. belgraveana, G. baccata, G. nitida and G. parvifolia*)[9] to only one (*Galbulimima belgraveana*).[9] Today two species are recognized: *G. belgraveana* in Papua New Guinea, and *G. baccata*, in North Queensland, Australia.[50] Within English vernacular, both trees may be referred to as Northern pigeonberry ash[51,52] although *G. belgraveana* has also been dubbed white magnolia,[52] a confusing moniker that can also refer to taxonomically unrelated plants such as *Magnolia denudata*.[53] The section below highlights the most striking accounts gathered by Benjamin Thomas, who has written several ethnobotanical reviews centered on *Galbulimima.*[10,11,12]

Peoples of Indonesia and Australia have used *Galbulimima sp.* in medicine and ritual, but most reports center on its use in Papua New Guinea. The Gimi people of the New Guinea Highlands reportedly chewed the bark of *G. belgraveana* to induce a 'trance-like state' and attain a temporary spiritual connection with their *iuna* ("souls").[13] Within the Okapa region of New Guinea, the *kuru* disease ("laughing death") was believed to be a type of magic strongly associated with hallucinogenic plants such as *G. belgraveana.*[14] Chewing the bark of *G. belgraveana* (known within the region as agara) along with dry leaves from a plant *Homalomena ereriba*, induced visions that were thought to diagnose disease or prepare for hunting or war. Effects presented as tremors, sudden violence accompanied by pupil miosis, then a euphoric phase followed by drowsiness along with stomach aches.[14]

Inhabitants of the Aseki Valley in the Morobe province of Papua New Guinea referred to *G. belgraveana* as *waga*, which was chewed and spat into a bamboo container, mixed with "traditional salt" (essentially evaporated aqueous extract of plant ashes; high in potassium and carbonate ions) and the sputum swallowed to relieve abdominal and body pains.[15] In other instances, the bark and leaves have been boiled and made into a tea to induce hallucination.[4] Of particular note is its use by the Bimin-Kuskusmin in the West Sepik Province of Papua New Guinea in the final stage of initiation of a male to the highest rank of "senior-grade ritual elder," preceded by ritual abstention which enhances the dissociative states of these ceremonies. Men "who have denied themselves sleep for three nights, water for two days and food for three days" (except for cassowary faeces, a substance associated with Afek, see below) would ingest one or two mushrooms (*Boletus sp.* and/or *Psilocybe kumaenorum*, the latter of which may be better known today as a member of the family of "magic mushrooms"), along with at least ten other substances associated with "heart palpitations". Two of these included the bark (*maasiik*) and leaves (*muuraap*) of *G. belgraveana*, associated in this context with self-control/dream-like states and "complex forms of 'trance' marked by various synesthesias" respectively. Poole reports, writing with an unknown degree of poetic license, that "the revered ritual elders who use powerful 'twelfth-stage mushrooms' and related 'heart palpitations' substances represent the pinnacle of entitlement, ritual strength, knowledge and power. Standing alone near karst holes in the wind, rain, thunder and lightning, with tiny fires flickering and frail drums answering the echoes of thunder and flashes of lightning, they identify with Afek, the ancestral source of all ritual knowledge."[16]

Although reports also describe ingestion of *G. belgraveana* bark combined with various other plant materials,[14-16] the behavioral effects of the GB bark alone cannot be extrapolated from these data. Attempts to extract meaning from scattered, anecdotal stories presents a problem: effects of GB plant mixtures may stem from polypharma*cology* (one substance, multiple biochemical targets), polypharma*cy* (one person, multiple substances), or both. These problems have motivated Western scientists, chemists in particular, to procure pure metabolites of *Galbulimima* and study their effects in animals and animal tissue.

3. Overview of the *Galbulimima* alkaloids

The diversity of psychotropic effects of *Galbulimima* plant material captured the attention of chemists as early as 1909 and led to the identification of alkaloids in the bark.[17] Then, as now, the low abundance of alkaloids was notable. Nearly 60 years later, a seminal review by Ritchie and Taylor underscored the "striking variability" in both total alkaloid content (trace to 0.5%) and ratio between individual alkaloids: "of the eleven bark samples from North Queensland and the seven from New Guinea that have been worked up for alkaloids no two have been alike. Even samples collected in the same area and at approximately the same season have been quite dissimilar."[9] This variability required ad hoc procedures for isolation of alkaloids. Simple physical handling of plant specimens is not trivial either; Mander noted that "it is not an easy plant to deal with, the trunks being 30–40 m high to the first branch in mature specimens".[18]

To date at least 40 alkaloids unique to *Galbulimima* have been identified despite these practical isolation difficulties (see Figure 2). Adequate amounts of purified alkaloids for animal pharmacology were isolated from 6 bark samples, some weighing 1500 lbs,[19] and subjected to a battery of assays in a collaboration of CSIRO and Smith, Kline & French (SKF) between 1950–1970. While the original laboratory result sheets are not available, a summary of pharmacological screening data for 12 alkaloids was published in 1990.[7]

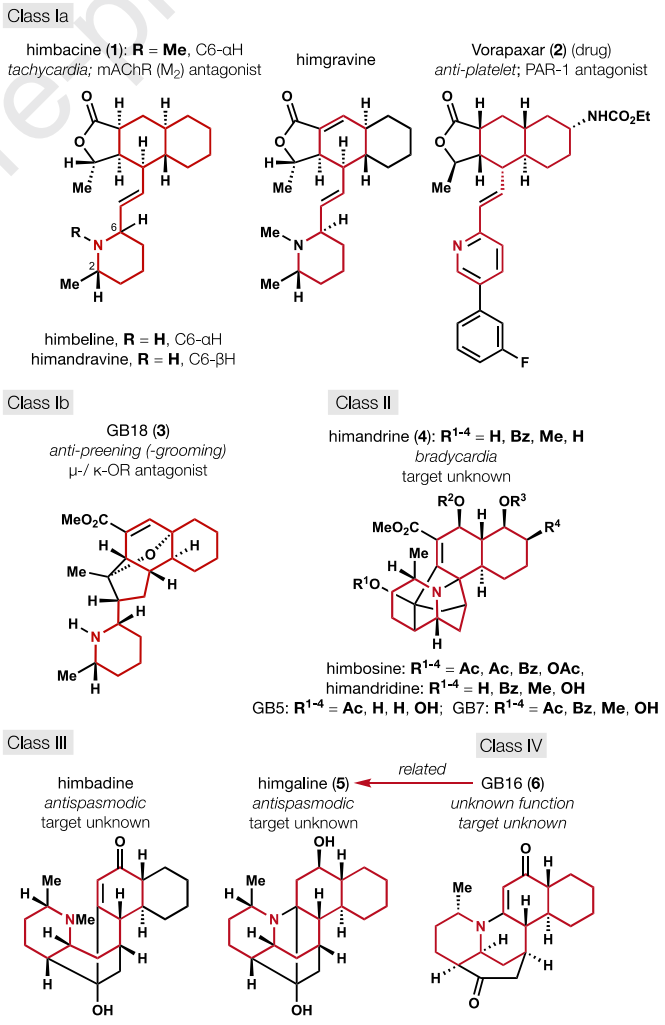

Figure 2. Structural and functional overview of *Galbulimima* (GB) alkaloids that were found to exhibit activity in animals or animal tissue, including the FDA approved drug, Vorapaxar, derived from himbacine. Conserved decalin, piperidine and two-carbon bridge are highlighted in red.

Each alkaloid elicited effects in mammals or mammalian tissue using standard procedures at the time, which were viewed as "inadequately informative" and in need of further inquiry.[40] Himbacine (**1**, Class Ia, Figure 2) garnered the most interest as a candidate for treatment of bradycardia

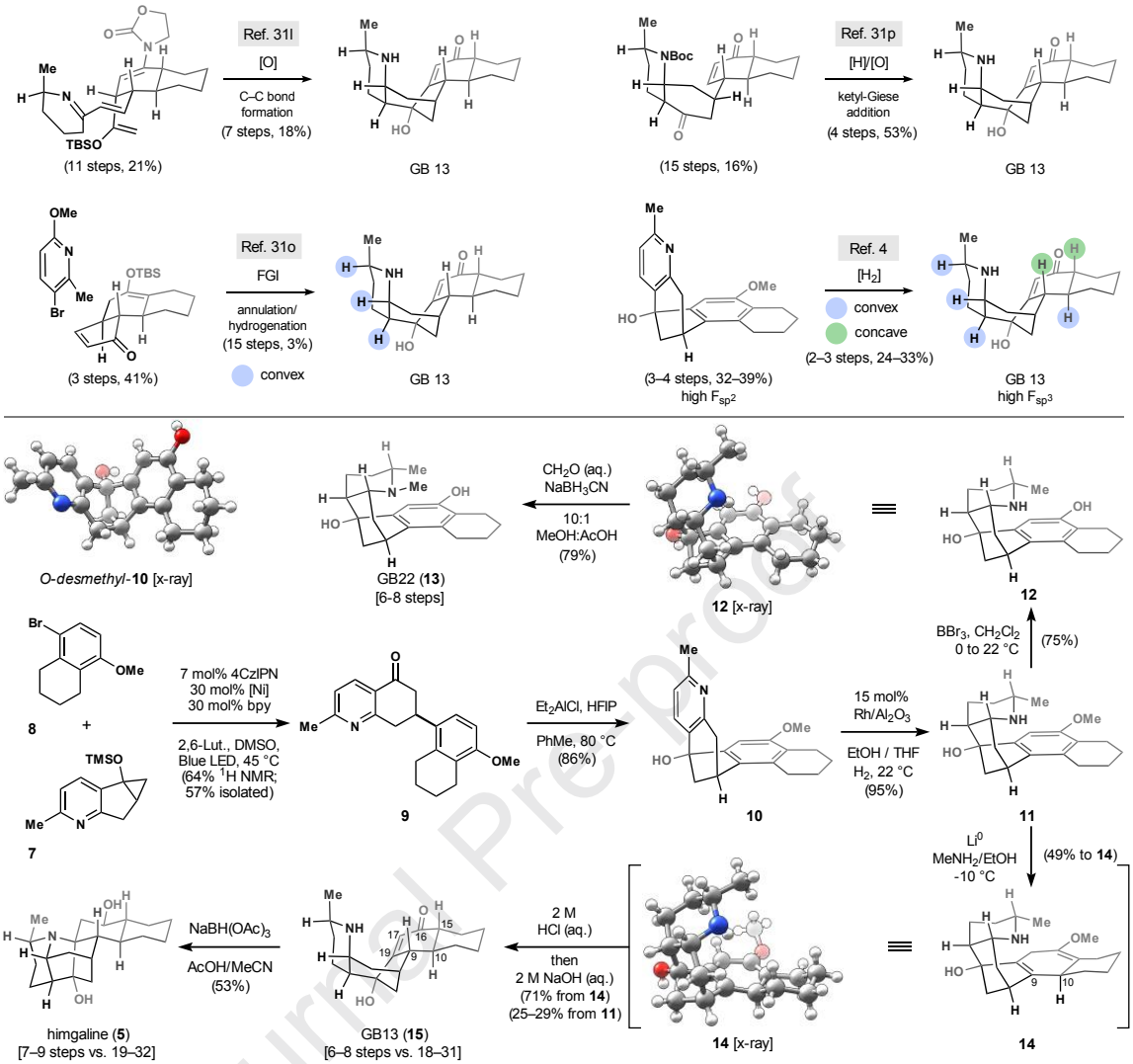

Figure 3. A short synthesis of Class III GB alkaloids GB22, GB13 and himgaline enable investigation of the origin of potent (0.1 mg/mL) antispasmodic effects in rabbit intestine.

(abnormally slow heart beat),[20] Alzheimer's disease[21] and intraocular pressure[22] due to its potent antagonism of muscarinic acetylcholine receptor (mAChR) M_2 (K_d = 4 nM).[20,23] Himandrine (**4**, Class II) induced marked and sustained hypotension in cats at 2.5 mg/kg (i.v. administration) and, opposite to himbacine, reduced heart rate (induced bradycardia).[24] SKF suggested himandrine may suppress sympathetic centers of the hypothalamus region of the brain.[7] Himgravine and himbosine (Class I, not shown) induced modest hypotension in cats between 2.5 to 10 mg/kg; himbadine and himgaline (**5**) (both Class III) effected significant antispasmodic activity at 10 and 0.1 mg/L, respectively, in rabbit intestine (furmethide-induced spasm); himbeline (Class Ia, not shown) was weakly depressant and hypotensive (no dose listed); 2.5 mg/kg of himandridine (Class II, not shown) produced moderate to marked hypotensive activity with no indication of peripheral autonomic nervous system effects; himandravine (Class Ia) induced strong CNS depression and anticonvulsant activity against electroshock seizure; GB7 led to rapid breathing and somnolence, albeit at the high dose of 50 mg/kg; GB5 produced hypotension (no dose listed); and finally GB18 (**3**) inhibited mouse preening with no influence on pain threshold at 5 mg/kg.[7]

Whereas isolation provided structural assignment and preliminary animal pharmacology, the practical difficulties of repeated, large-scale isolation hindered follow-up assays and optimization. In contrast, Schering-Plough's 1996 himbacine synthesis[25] enabled systematic medicinal chemistry exploration of the scaffold and led to the development of Vorapaxar (**2**, Figure 2), a PAR-1 antagonist and himbacine analog of the non-natural enantiomeric series, culminating in its FDA approval (2014) for patients with a history of myocardial infarction and or peripheral arterial disease.[26]

Himbacine is the least complex of all GB alkaloid congeners (375.9 mcbits, 15.04 mcbits/atom according to Böttcher's complexity analysis[27,28]) and occurs in 1000x greater abundance than any other member, spurring work in biological characterization and functional optimization. The therapeutic promise of the remaining 39 congeners, therefore, remains unexplored due to their lower abundance and higher complexity (e.g. GB18: 448.39 mcbits, 17.25 mcbits/atom; himgaline: 477.83 mcbits, 20.78 mcbits/atom). This dilemma has attracted interest from across the synthetic community,[29,30] with 17 reported syntheses of GB alkaloids apart from Schering-Plough's work.[31] None of these syntheses, however, resulted in characterization of biomolecular targets or pharmacology of the targeted GB alkaloids—a leap from the kind environment of synthesis to the wicked environment of interdisciplinary research. Below we detail recent work from our lab that has begun to deliver on these goals, aided by the awesome advances made in receptor discovery and assay development over the past four decades.[32,33]

4. Synthesis of Class III alkaloids via attached-ring coupling

Among the compelling reasons to synthesize GB alkaloids—mechanism of action assignment, target identification, optimization of physicochemical properties—their unique scaffolds represent an opportunity to probe terra incognita and to deliver novel composition of matter even among well-explored receptors. By the same token, new chemistry would be required to arrive at enabling chemical syntheses.

Class III alkaloids stood out because representative members himgaline and himbadine elicited antispasmodic effects in assays for anti-muscarinic activity (10 and 0.1 mg/mL or 30 μM and 300 nM, respectively),[7] but did not share the tachycardia of himbacine, a potent anti-muscarinic. Also unlike

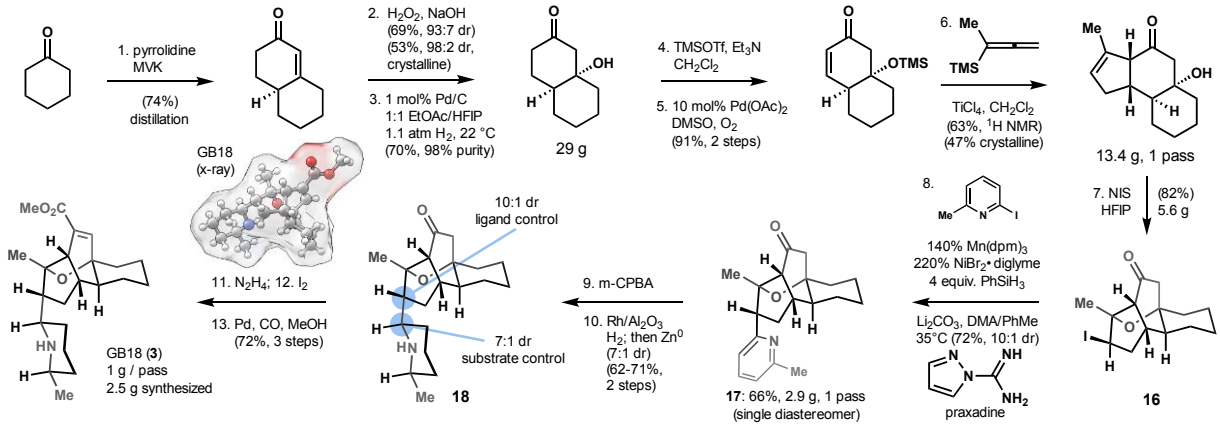

Figure 4. A short synthesis of Class Ib alkaloid GB18, which exhibits a potent anti-preening (-grooming) phenotype in mice. Large scale synthesis enabled its assignment as a mixed KOR/MOR antagonist, as well as ongoing pharmacological characterization.

himbacine, prior routes[31j-q] had not enabled large material throughput necessary for pharmacology follow-up, and thus practical access to Class III might prove fruitful. The shortest routes obtained GB13 in 18–19 steps as: either enantiomer by resolution (Movassaghi),[31l] both enantiomers by racemic synthesis (Sarpong),[31o] or either enantiomer by chiral pool synthesis (Ma, (–)-GB13).[31p]

We recently published a route to class III GB alkaloids GB22, GB13, and himgaline[4] that allowed easy access to large amounts of a common intermediate. Each synthesis generated racemates, but only required 6-8 steps (Figure 3). Prior syntheses addressed the methine stereocenters of himgaline iteratively, outlined briefly in Figure 3, via intermediates that already contained saturated scaffolds. Inspired by Sarpong's pyridine reduction, our route aimed at increased efficiency by simultaneous methine installations. This design cross-coupled two high fraction sp^2 (F_{sp2}) fragments and stereoselectively reduced prochiral carbons to the 100% fraction sp^3 (F_{sp3}) natural product, himgaline. In order to enact this strategy, we developed a novel metallaphotoredox cross-coupling of siloxycyclopropanes (e.g. **7**) with aryl bromides (e.g. **8**), which circumvented a two-electron arene conjugate addition where the required enone would favor the phenol tautomer. The bridging bicycle of Class III required an intramolecular Friedel-Crafts reaction under weakly Brønsted acidic conditions because strong Brønsted acid tended to split tetracycle **9** in two! Instead, we discovered a combination of HFIP and aluminum Lewis acids that enabled clean cyclization to pentacycle **10**. The pyridine hydrogenation protocol employed by the Sarpong group in their synthesis of GB13 proved highly diastereoselective for piperidine **11**. This despite the lower steric encumbrance associated with the phenyl ring of **10** compared to the saturated decalin intermediate employed in Sarpong's seminal example.[31o] Intermediate **11** could be used to access GB22 (**13**) via BBr_3 demethylation and reductive amination with formalin. This same intermediate (**11**) could also be subjected to Benkeser or Koide reduction conditions[34] to access GB13 (**15**) after hydrolysis of the resulting enol ether. Himgaline was reduced under acidic conditions to GB13 as established in its synthesis by Chacklamannil *et al*.[31m] The brevity and scalability of this route to himgaline and its Class III congeners are now allowing us to evaluate their targets, mechanisms of action and therapeutic potential.

5. Synthesis of GB18 and assignment of high-affinity biomolecular targets

Among biologically annotated alkaloids, GB18 stood out as a compelling target due to its potent anti-preening effects[7,11] at 5 mg/kg and its structural relationship to himbacine.[18] Anti-preening behavior seemed unlikely to derive from anti-muscarinic activity like himbacine and the piperidine differed in its

connection to the decalin core as an attached-ring motif. While himbacine and GB18 are both classified as Class I alkaloids, we considered the structures different enough to group himbacine and its close congeners as Class Ia, and separate GB18 and its congeners into Class Ib.[5]

The complex oxacyclic core and challenging attached-ring motif of GB18

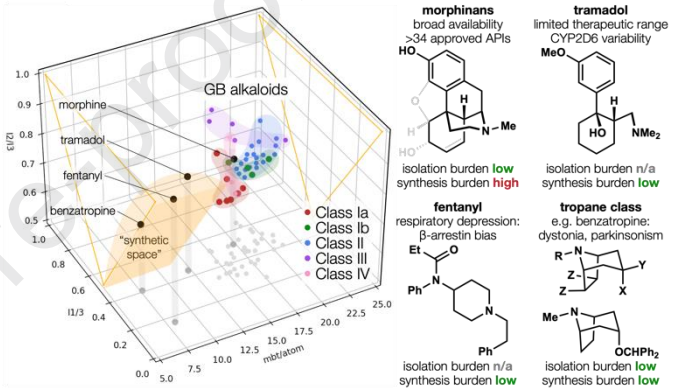

Figure 5. Tramadol, fentanyl and benzatropine are easy to access, but lack shape diversity (PMI, x-, y-axis) and complexity (C_m/atom, z-axis)—associated with specificity and lower rates of attrition in clinical trials—whereas natural products like morphine and the GB alkaloids embody high complexity. Recent syntheses allow facile access, diversification and navigation of GB alkaloid space.

required fundamental discoveries in organometallic reactions before an efficient route emerged. The resulting synthesis, however, scaled readily in all steps to deliver 2.5 grams of racemic GB18 and multi-decagram quantities of advanced intermediates for analog synthesis. A major, enabling step in this synthesis involved ligand-controlled cross-electrophile coupling (**16** to **17**) using a putative Mn–H reductant (Zn^0, Mn^0 and TDAE were ineffective or fragmented the oxacycle). The most effective ligand happened to be a commercial, inexpensive amidine called praxadine, which also serves as an anti-inflammatory. Its use in this cross-electrophile coupling positions the pyridyl coupling partner on the more-hindered *endo*-face of the ring system, possibly due to hydrogen-bonding between the ligand and ethereal oxygen. To establish the next attached-ring stereocenter, we reduced the pyridine *N*-oxide with high stereoselectivity to piperidine **18**, whereas the corresponding pyridine (**17**) reduced with low selectivity. Finally, Barton iodination and Pd-catalyzed carbonylation completed the synthesis.

With quick access to multigram amounts of racemic GB18, we separated its two enantiomers to identify high-affinity targets potentially involved in its anti-preening behavioral effects. The NIH Psychoactive Drug Screening Program PDSP maintains a battery of assays to probe ligation of 45 common receptors of the human nervous system.[32,33] Whereas GB18 failed to displace radioligands from 43 receptors, it reproducibly displaced ^{3}H-U69,593 and ^{3}H-DAMGO from μ- and κ-opioid receptors, respectively, and antagonized salvinorin A- and DAMGO-induced β-arrestin recruitment at ca. pIC_{50} 8 (IC_{50} ~ 10 nM). The connection between these high-affinity targets and anti-preening behavior is now being pursued in collaboration with animal pharmacologists, made possible by synthesis of large amounts of GB18 and its analogs. We

anticipate that ligand-controlled cross-electrophile coupling can be used to perturb selectivity of this chemotype among GPCRs. This chemical space walk through the GPCRome is exemplified by Schering-Plough's repurposing of himbacine (a mAChR GPCR antagonist) to Vorapaxar (a PAR-1 GPCR antagonist). Whether similar GPCR perturbations occurs among the other naturally occurring GB alkaloids remains an open question.

5. Conclusion

The GB alkaloids represent new lead scaffolds/chemotypes to advance towards therapeutic endpoints, analogous to existing useful chemotypes. For example, there are at least 34 approved morphinan drugs and critical tool compounds because morphine has been widely available via isolation for 150 years. Its synthesis burden is high, however, so scaffold hops to simpler substances derived from chemical feedstocks (e.g. tramadol[35]) enable more extensive diversification. Whereas scaffold hops may maintain important receptor contacts, morphine, tramadol and fentanyl have different pharmacodynamics and pharmacokinetics: tramadol requires demethylation in the liver to potently agonize MOR and it also binds mAChRs, $5HT_{2c}$ and SERT;[35] fentanyl biases MOR signaling towards β-arrestin recruitment and strongly depresses respiratory function.[36] Simpler compounds are not necessarily better. Complexity can confer advantages[37,38,39,40,41] and is mainly limited by the constraints of synthesis, which we aim to overcome.

That is our goal for the GB alkaloids, archetypal natural products (NPs) that differ significantly from small molecule occupants of "synthetic" space.[38,42,43] On average, drugs comprise high fraction aromatic (F_{Ar}), low fraction sp^3 (F_{sp3}), low chirality-content small molecules that derive often from amide bond formation, sulfonylation, biaryl formation and other workhorse reactions.[44] In this area of chemical space, hit-to-lead development is not rate-limited by chemistry. These simple chemotypes, however, have been correlated with local, as opposed to global, functional minima that can confine exploration within the limits of project timelines.[45] In contrast, the GB alkaloids contain cores of F_{sp3} > 85% and >8 stereocenters, a single nitrogen and multiple oxygen atoms. Informatics studies suggest these attributes differentiate NPs from other compound collections and may confer advantages for protein selectivity, metabolism and toxicity compared to simpler, unsaturated small molecules.[37–45] Indeed, simplification of the himbacine core (movement away from NP space) significantly reduces potency[46] and/or selectivity[47] for the M_2 muscarinic receptor.[48]

Mapping the affinity and selectivity of GB alkaloids across human neuron receptors will identify uses as potential therapeutic leads, applications currently frustrated by inadequate animal pharmacology, unknown targets, and variable alkaloid content in bark samples. The recent advances in GB alkaloid synthesis discussed above have the potential to enable these applications. The future looks bright for taking the GB alkaloids from bush to bedside.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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