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Privileged scaffolds for library design and drug discovery

Matthew E Welsch[1], Scott A Snyder[1] and Brent R Stockwell[1,2]

This review explores the concept of using privileged scaffolds to identify biologically active compounds through building chemical libraries. We hope to accomplish three main objectives: to provide one of the most comprehensive listings of privileged scaffolds; to reveal through four selected examples the present state of the art in privileged scaffold library synthesis (in hopes of inspiring new and even more creative approaches); and also to offer some thoughts on how new privileged scaffolds might be identified and exploited.

Addresses
[1] Columbia University, Department of Chemistry, Havemeyer Hall, MC 3129, 3000 Broadway, New York, NY 10027, United States
[2] Howard Hughes Medical Institute, Columbia University, Department of Biological Sciences, Sherman Fairchild Center for the Life Sciences 614A, 1212 Amsterdam Avenue, MC 2406, New York, NY 10027, United States

Corresponding author: Snyder, Scott A (sas2197@columbia.edu) and Stockwell, Brent R (bstockwell@columbia.edu)

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Introduction

Small organic molecules can be powerful tools for impacting biology and medicine, functioning as both therapeutics and as probes that help to illuminate the macromolecules regulating biological processes [1•]. Yet, despite advances on many fronts, including the ability of synthetic chemists to prepare libraries containing thousands of compounds efficiently, the ability to make critical discoveries pertinent to disease remains a slow and, arguably, serendipitous one [2•]. For instance, high-throughput synthesis and screening of compound collections through phenotypic or biochemical assays often yields disappointing results in terms of a paucity of specific, useful compounds discovered, relative to the high cost in time and resources expended [3•].

In large part, this state of affairs reflects the fact that we simply do not understand all the factors necessary to create compound collections that have potent and specific biochemical activity. Commercial compound libraries, for example, while readily available, suffer from low hit rates; this result is in part because their members typically possess low structural diversity and poor physicochemical properties (often combined with reactive and undesirable functional groups) since they are produced with an eye towards overall quantity, rather than quality [3•]. Collections based on bioactive natural products, to some degree, overcome the issue of low hit rates since the parent structure has evolved over millennia for a specific biochemical purpose [3•]; however, these natural product collections less frequently lead to the discovery of activity distinct from the parent compound, since they are typically the product of simple analog generation by modulating functional handles, rather than rationally altered with an eye towards generating novel specificity [1•]. Consequently, solving the challenge of creating collections of unique, highly potent bioactive small molecules, could dramatically accelerate the rate at which critical biochemical discoveries are made, and ultimately, potentially enable a number of diseases not only to be managed, but also to be eradicated.

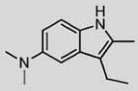
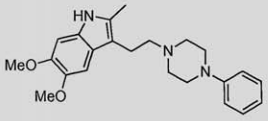
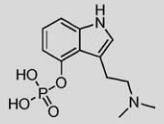
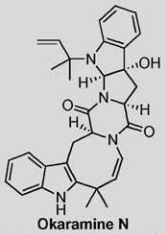
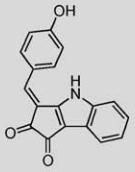
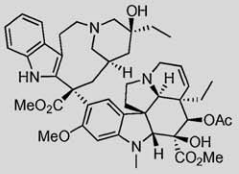
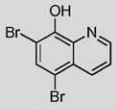
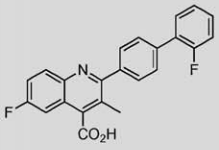
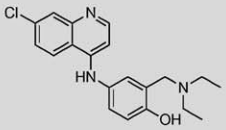
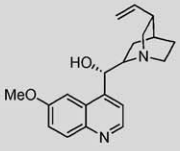
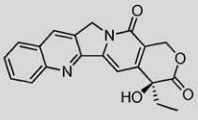
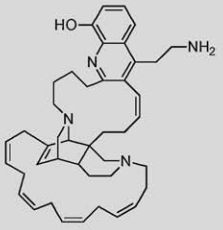
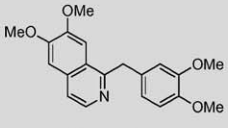
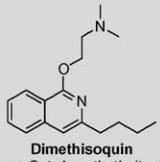
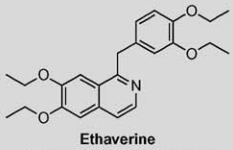
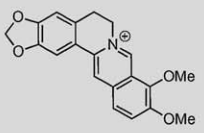
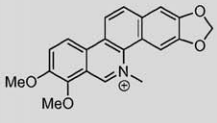
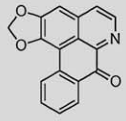
Here, we focus on one approach to this problem: creating compound collections based on 'privileged scaffolds,' molecular frameworks, as first coined by Evans in the late 1980s, are seemingly capable of serving as ligands for a diverse array of receptors [4]. Though he was originally referring to the benzodiazepine nucleus, which is thought to be privileged because of its ability to structurally mimic beta peptide turns [5], work over the past several decades from both academic and industrial groups has revealed that there are additional such scaffolds; a major challenge is in accessing large number of a given privileged framework [6••]. In this review, we hope to accomplish three main objectives: to provide one of the most comprehensive listings of privileged scaffolds; to reveal through four selected examples the present state of the art in privileged scaffold library synthesis (in hopes of inspiring new and even more creative approaches); and also to offer some thoughts on how new privileged scaffolds might be identified and exploited.

Privileged scaffolds

As revealed by a thorough search of the literature, the term 'privileged scaffold' has been used fairly liberally versus Evans' original conception of the term, in that the ability to bind multiple targets is less thoroughly employed as a strict criterion for membership versus the notion of multiple molecules of the same scaffold having bioactivity. Such an expansion, in our opinion, is reasonable since it allows for a more thorough evaluation of the idea. We note, however, that because work with such scaffolds has derived from multiple environments

Table 1

Examples of privileged scaffolds in drugs and natural products

Privileged Scaffold	Structures		
Indole	*Drugs*		
	 **Medmain** Therap Cat: Serotonin inhibitor	 **Oxypertine** Therap Cat: Antidepressant	 **Psilocybin** Therap Cat: Psychomimetic
	Natural Products		
	 **Okaramine N** Source: Penicillium simplicissium Biological Activity: Insecticidal activity	 **Nostodione A** Source: The terrestrial blue-green algae Nostoccommune Biological Activity: Mitotic spindle posion	 **Vinblastine** Source: Leaves of Madagascar periwinkle plant (Cantharanthus roseus) Biological Activity: Anticancer agent; causes apoptosis by stopping spindle formation during mitosis
Quinoline	*Drugs*		
	 **Broxyquinoline** Therap Cat: Antiseptic; disinfectant	 **Brequinar** Therap Cat: Immunosuppressant	 **Amodiaquin** Therap Cat: Antimalarial
	Natural Products		
	 **Quinine** Source: Quina Bark Biological Activity: Anti-malarial	 **Camptothecin** Source: The Chinese tree Camptotheca acuminata Decne Biological Activity: Anti-cancer activity	 **Njaoamine F** Source: Neopetrosia Biological Activity: Cytotoxic
Isoquinoline	*Drugs*		
	 **Papaverine** Therap Cat: Vasodilator (cerebral)	 **Dimethisoquin** Therap Cat: Anesthetic (topical)	 **Ethaverine** Therap Cat: Antispasmodic
	Natural Products		
	 **Berberine** Source: Berberis and Mahonia Biological Activity: Causes Respiratory stimulation, transient hypotension, and convulsion. Cholinesterase and tyrosine decarboxylase inhibitor.	 **Chelerythrine** Source: The plant Greater celandine, Chelidonium majus Biological Activity: Potent protein kinase C inhibitor.	 **Liriodenine** Source: The tulip tree Liriodendron tulipifera Biological Activity: Leishmanicidal activity.