



Digest Paper

Recent advances in metal catalyzed intramolecular aryl additions—accessing bioactive molecules



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ABSTRACT

1-Aminotetraline, 1-aminoindane, and benzocycloalkanol structures are privileged scaffolds demonstrating broad ranging pharmacological properties. In this review recent advances in the synthesis of molecules containing these scaffolds via metal catalyzed intramolecular aryl additions to activated groups like: imines, ketones, and aldehydes are discussed.

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Introduction

At the current time, 1-aminotetraline, 1-aminoindane, and benzocycloalkanol structures are considered privileged scaffolds demonstrating broad ranging pharmacological properties. Some important molecules containing these cores are shown in Figures 1 and 2. Molecules like the Parkinson disease treatment drug Rasagiline, the anti-depressant drug Sertraline, the Amgen BACE-1 lead candidate for treating Alzheimer's disease,¹ and others shown in Figure 1 contain either a 1-aminoindane or a 1-aminotetraline scaffold.

In the case of those bioactive molecules containing a benzocycloalkanol structure, there is for instance the dihydrobenzofuranol core unit, which is present in, PH46A, which has shown promise for the treatment of inflammatory bowel disease² and Avenicenol A for the treatment of cancer, then there are those compounds containing a 3-hydroxyoxindole unit which show broad spectrum biologically activity, for example, ECi8 is a potent antimicrobial lead drug³ (Fig. 2).

Accessing these molecules by traditional methods can be both time consuming, expensive, and hazardous on the industrial scale. From the industrial angle, most of these key cores are accessed via asymmetric hydrogenation^{4,5} or by non-asymmetric hydrogenation

followed by a chiral resolution (see below). For example, for the synthesis of Sertraline hydrochloride, Pfizer used Pd/CaCO₃ as the catalyst, and the product enantiomers were separated via chiral resolution with D-(–)-mandelate.⁶ The method is wasteful in that unwanted isomeric products are obtained. Expensive Raney nickel has also been used for this hydrogenation.⁷ Sepracor reported a stereoselective reduction of a sulfinamide intermediate with 9-BBN for the large-scale production of (1*R*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine, the process was non-catalytic and large quantities of 9-BBN needed to be used.⁸ In the case of chromanol 293B (a I_{Ks}-Channel blocker) an entirely different approach was used.⁹ This involved an epoxide ring opening reaction of a key precursor with deprotonated *N*-methylmethanesulfonamide. For the potent psychoactive compound indatraline (Lu 19-005)¹⁰ (Fig. 1) a multi-step synthesis involving an enantioselective carbenoid C–H insertion, cyclization to a key benzocyclopentanone intermediate, followed by a *K*-Selectride reduction to the alcohol and substitution of the activated OH group with methylamine was used.¹¹ Although organocatalysts can now be used to access chiral amine units, generally via asymmetric catalytic ketamine reduction,¹² as far as we are aware there have been no reports on their application to afford 1-aminotetraline or 1-aminoindane type products.

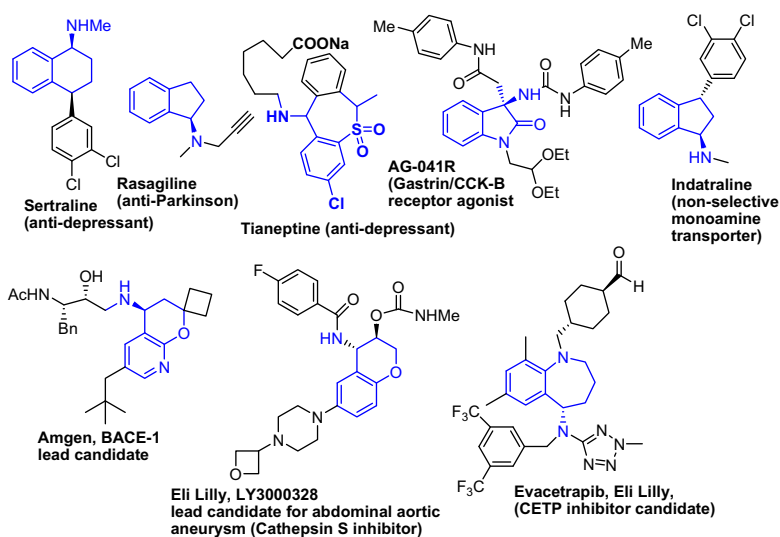


Figure 1. A selection of pharmaceuticals containing the 1-aminotetraline core unit (CETP = Cholesteryl Ester Transfer Protein).

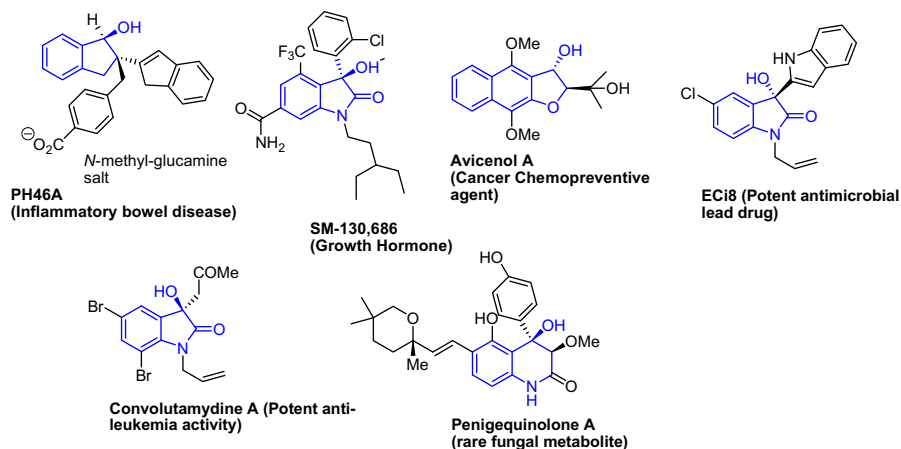


Figure 2. Selection of pharmaceuticals and bioactive compounds containing a benzocycloalkanol core unit.

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