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Pharmaceuticals that contain polycyclic hydrocarbon scaffolds

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Numerous variations on structural motifs exist within pharmaceutical compounds that have entered the clinic. These variations have amounted over many decades based on years of drug development associated with screening natural products and *de novo* synthetic systems. Caged (or bridged) bicyclic structural elements offer a variety of diverse features, encompassing three-dimensional shape, and assorted pharmacokinetic properties. This review highlights approximately 20 all carbon cage containing pharmaceuticals, ranging in structure from bicyclo[2.2.1] through to adamantane, including some in the top-selling pharmaceutical bracket. Although, a wide variety of human diseases, illnesses and conditions are treated with drugs containing the bicyclic motif, a common feature is that many of these lipophilic systems display CNS and/or neurological activity. In addition, to an extensive overview of the history and biology associated with each drug, a survey of synthetic methods used to construct these entities is presented. An analysis section compares natural products to synthetics in drug discovery, and entertains the classical caged hydrocarbon systems potentially missing from the clinic. Lastly, this unprecedented review is highly pertinent at a time when big pharma is desperately trying to escape flatland drugs.

1. Introduction

Many different structural motifs exist within pharmaceutical compounds, which arise from decades of screening and evaluating natural products[1] and synthetic entities.[2,3] A structure may be as simple as the antibacterial agent acetic acid or as complex as a chemotherapeutic natural product, such as paclitaxel (**1**) (Fig. 1). That considered, the structure and functional groups incorporated into a drug determine not only molecular recognition at the target site, but also broader pharmacological properties, such as membrane permeability, selectivity and susceptibility to metabolic processes [*i.e.* absorption, distribution, metabolism, and excretion (ADME)]. This premise alone has been the topic of many wide ranging review articles in drug discovery.[4–8] Reviews targeting specific functional groups and structural motifs within drugs and drug discovery have also appeared;[9,10] however, a survey covering approved pharmaceutical compounds incorporating polycyclic hydrocarbon scaffolds seems not to have been undertaken. Polycyclic hydrocarbon, caged bicyclic (or bridged bicyclic) scaffolds or motifs are simply defined as an atomic bridge appended across an underlying ring of atoms connected at bridgeheads (see extracted systems **2** and **4** in Fig. 1). Such systems offer a variety of diverse structures, encompassing three-dimensional shape and assorted pharmacokinetic properties, often attributed to their hydrocarbon nature.

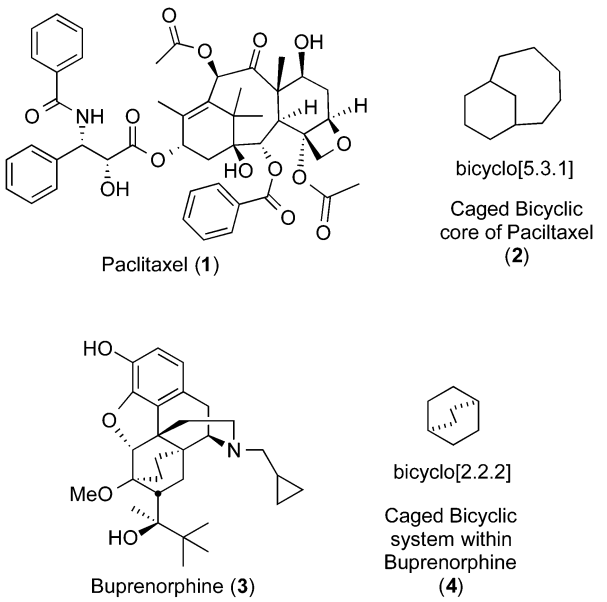

Fig. 1 Paclitaxel (**1**) and buprenorphine (**3**) and their corresponding polycyclic hydrocarbon core structural elements **2** and **4**.

They can differ substantially in size, and the identity of the atoms that compose the cage skeleton, which is a substantial sideways shift away from planar systems.[11] These features have facilitated a wide spectrum of approved pharmaceutical applications

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ranging from smoking cessation to antitumour agents, some of which are in the top-selling pharmaceutical bracket, *e.g.* buprenorphine (**3**) (Fig. 1).

Given the importance, and future inspiration, members of this class offer, a review of the literature up to January 2014 was performed. Selected databases were systematically searched to identify pharmaceutical compounds incorporating polycyclic hydrocarbon structures (all carbon atoms only) and to gather information regarding their approval status and current applications: ''Drugs@FDA'' (Approved Drug Products) and the ''DrugBank''. Further searching, using PubMed and SciFinder, was conducted for each identified compound in order to compile comprehensive information regarding discovery, synthesis, indications, pharmacology, mechanism of action and areas of continuing research.

Approximately 20 all carbon systems were identified and these are discussed below according to their polycyclic classification. Lastly, some drugs discussed herein have been removed from the market place, but are still under investigation for the treatment of new conditions so they have been included herein.

2. Bicyclo[2.2.1]

2.1. Biperiden

Biperiden (**5**) is a weak peripheral anticholinergic agent used to reduce symptoms of Parkinson's disease (PD).[12] Traditionally, natural product anticholinergic agents, such as atropine (**6**) and hyoscine (**7**), were used in PD symptom relief.[13] However, synthetic drugs were later developed in an attempt to lessen side effects. Klavehn developed racemic biperiden in 1953 and studied the activity of the molecule with Hass.[14] The molecule received patent protection in 1957,[15] and was approved by the FDA in 1959. It was marketed as Akineton™ (Knoll and Abbvie) (Fig. 2).

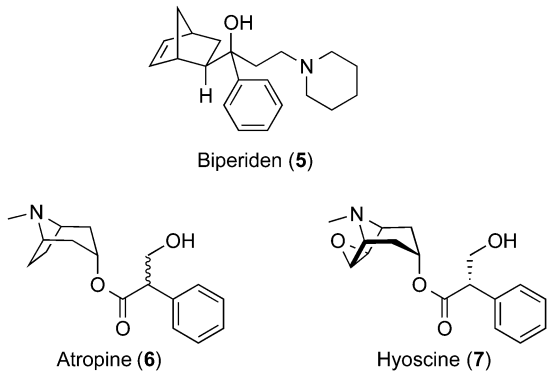

Fig. 2 Anticholinergic agents biperiden (**5**), atropine (**6**) and hyoscine (**7**) used for treatment of Parkinson's symptoms.

PD symptoms are thought to be at least partly attributable to an imbalance in the corpus striatum caused by excessive excitatory cholinergic activity over lesser inhibitory dopaminergic system activity.[16] Biperiden acts as a competitive antagonist of cholinergic muscarinic receptor M1 in the central and peripheral nervous systems and confers antisecretory, antispasmodic and mydriatic effects.[13,16,17] Blocking acetylcholine, and thereby reducing cholinergic receptor activation, is thought to address the dopaminergic–cholinergic imbalance. Due to commonality in mechanism of action, all cholinergic drugs, including biperiden, have similar adverse effects, including excitation, defective near

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Craig M. Williams was born in Adelaide, Australia. He received his BSc(Hons) degree in chemistry in 1994 and in 1997 was awarded his PhD in organic chemistry from Flinders University under the supervision of Prof. Rolf H. Prager. He worked as an Alexander von Humboldt Postdoctoral Fellow with Prof. Armin de Meijere at the Georg-August-Universität, Göttingen, Germany until 1999 and then took up a postdoctoral fellowship at the Australian National University with Prof. Lewis N. Mander. He has held an academic position, currently Assoc. Professor, at The University of Queensland since 2000 and during this time has won a number of awards including a Thieme Chemistry Journals Award in 2007. The primary research focus of the Williams group is the construction and isolation of biologically active complex natural products, and designing methodology to assist in this endeavour. The group also enjoys dabbling in medicinal, physical organic and computational chemistry.

vision, drowsiness and confusion, as well as effects such as constipation and dry mouth associated with reduced secretion.[12,13,16]

Numerous PD drugs are now available, including amantadine (**100**) (discussed below, Scheme 17);[16] the strongest and most widely used of these is levodopa.[13] Biperiden may also be used in moderate PD as a synergistic adjunct to levodopa and in cases where levodopa is ineffective or not recommended.[18]

Biperiden is also used to relieve extrapyramidal disorders secondary to neuroleptic drug administration.[13,19,20] However, in light of a recent study showing improved cognitive function and quality of life following careful discontinuation of biperiden in schizophrenic patients receiving second generation antipsychotics, cessation of routine biperiden co-administration with second generation antipsychotics was recommended.[21] Recent research has also indicated that biperiden affects appetitive behaviour and pre-attentive auditory processing.[22,23] It was suggested that biperiden may have a role in addressing cocaine dependence; however, further studies are required. Although levodopa is now the PD symptom relief drug of choice, biperiden retains a role in mild and moderate cases. Research on the neurological effects of this drug still continues.[24]

Synthesis of biperiden (**5**) is relatively simple and a number of different procedures exist.[15,25,26] A more recent method described by Kastner,[27] starts with a Diels–Alder reaction involving methyl vinyl ketone (**8**) and cyclopentadiene, which affords the norbornene adduct (**9**), as a mixture of *exo*- and *endo*-isomers. Isomerisation of **9** with methoxide gives predominantly the *exo*-isomer (**10**), which is subjected to a Mannich reaction with paraformaldehyde and piperidine to give ketone **11**. Biperiden was then obtained as a racemate from exposure of ketone **11** to phenyl magnesium bromide (Scheme 1).

2.2. Cyclothiazide

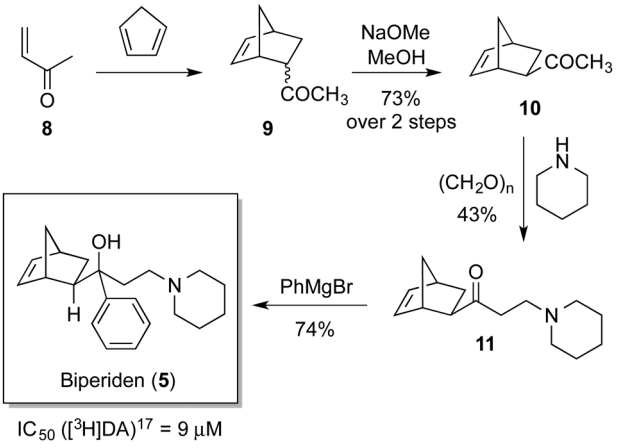
Cyclothiazide (**12**) is a member of the pharmaceutically active benzothiazides, which are reasonably potent, orally effective, diuretics.[28] This class of drug, used to treat heart failure and hypertension, was developed following a report by Schwartz in 1949, that sulfanilamide (**13**) produced a natriuretic effect in congestive heart failure patients.[28] Cyclothiazide was approved, as a new diuretic antihypertensive in 1963, and marketed as Anhydron™ by Lilly.

Thiazide diuretics act by interfering with the sodium and chloride ion reabsorption in the distal cortical diluting region of the renal tubule.[29] Consequently, cyclothiazide decreases the glomerular filtration rate.[30] Unfortunately, however, this mechanism of action also gives rise to side effects, such as hyperglycaemia, hypokalaemia and hyperuricaemia.[31] Lower potency, relative to other diuretics, and a flattened dose–response relationship render thiazides inappropriate for cases of severe renal insufficiency.[32] Although also used in Europe and Japan, cyclothiazide has now been discontinued in the United States. Despite this, further studies into the activity of cyclothiazide have shown that it is a positive allosteric modulator of ionotropic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA, **14**) glutamate receptors, blocking the desensitisation of these receptors.[33–36] It is no surprise then that this drug acts as a negative allosteric modulator of the $GABA_A$ receptor.[37,38] For these reasons, cyclothiazide may have relevance in the treatment of depression.[39]

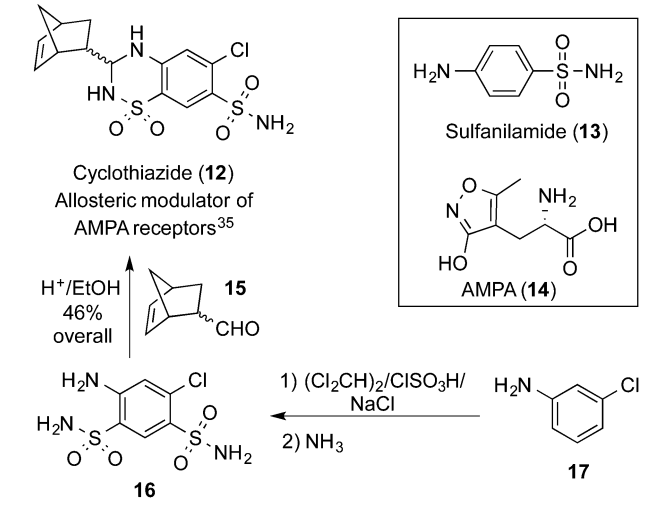
Cyclothiazide (**12**) was first synthesised in 1961 from the condensation of norbornenal (**15**) and 6-amino-4-chlorobenzene-l,3-disulfonamide (**16**), which is obtained from *m*-chloroaniline (**17**), in 46% overall yield (Scheme 2).[40–44] Information about the stereochemical consistency of this drug is very limited. A report by Gal[45] determined, using a range of modern analytical techniques, that, of the eight possible stereochemical isomers (*i.e.* four racemates), all are present in the marketed drug. It was also found that the norbornene *endo* configuration predominates over the *exo* racemates, in addition to small but significant differences in isomer distribution between different batches of produced material.

2.3. Fencamfamine

Fencamfamine (**18**) is an anorectic psychostimulant developed by Merck in the late 1950s.[46,47] It was released as an appetite suppressant, in countries such as Brazil, in the early 1960s.[48]



Scheme 1 Synthesis of biperiden (**5**).

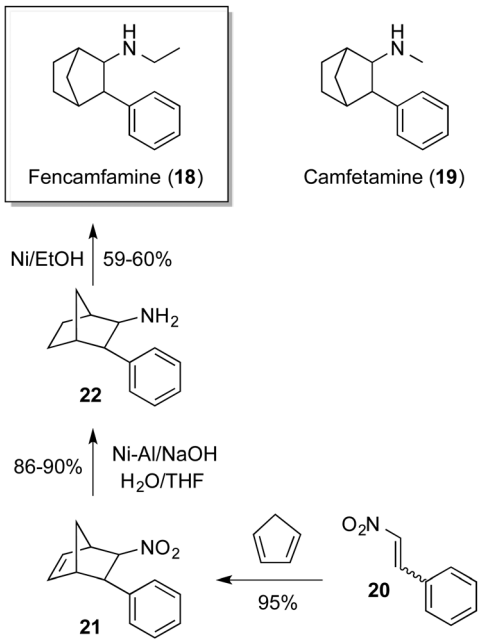


Scheme 2 Synthesis of cyclothiazide (**12**).

However, the amphetamine-like stimulant properties of this drug also led to recreational use.[48–50] In the United States, fencamfamine has been used illicitly as a cocaine substitute and is now listed as a Schedule IV controlled substance.[51,52]

Pharmacologically, fencamfamine is a CNS stimulant that increases locomotion and enhances alertness and mood.[48,53–55] It acts by inhibiting the dopamine and norepinephrine reuptake by the presynaptic neuron.[53,55–57] Although fencamfamine displays amphetamine-like effects,[57,58] it is viewed as a safer entity than amphetamine, because it does not inhibit monoamine oxidases.[56] The addictive nature of fencamfamine has been evidenced by conditioning place preference studies in rats, where repeat administration was shown to have a reinforcing effect.[59,60] The stimulant properties of fencamfamine were later optimised to create the designer drug camfetamine (**19**). Although **19** is a more potent stimulant than fencamfamine, it has a less favourable safety profile with more adverse side-effects.[61]

The synthesis of fencamfamine (**18**) is relatively straightforward. A Diels–Alder reaction between cyclopentadiene and β-nitrostyrene (**20**), first reported in 1939,[62–64] gives rise to the core structure (*i.e.* **21**). The nitro group and carbon–carbon double bond can be reduced separately, with iron filings in acid, and hydrogen with catalytic platinum respectively, or in a single step with hydrogen and a RANEY®-nickel catalyst (see **22**). Subsequent *N*-ethylation gives fencamfamine in an overall yield of 13–29%.[62–64] The original synthetic procedure, however, was recently optimised by Novakov *et al.* to increase product yield in the hydrogenation and alkylation stages, while maintaining product purity.[65] Following the Diels–Alder reaction, the core (*i.e.* **21**) was directly reduced, with a nickel–aluminium alloy, in the presence aqueous sodium hydroxide in tetrahydrofuran to give **22**. The hydrogenation was accelerated using this protocol because nickel–aluminium and aqueous alkali react to give molecular hydrogen. *N*-Alkylation was achieved by boiling the amine in excess absolute alcohol with catalytic nickel metal, giving fencamfamine (**18**) in an overall yield of 51–54% (Scheme 3). Fencamfamine is administered as a dual racemic mixture consisting of *endo*-*N*-ethyl/*exo*-phenyl and *exo*-*N*-ethyl/*endo*-phenyl enantiomeric pairs in an approximate ratio of 9 : 1.[65]



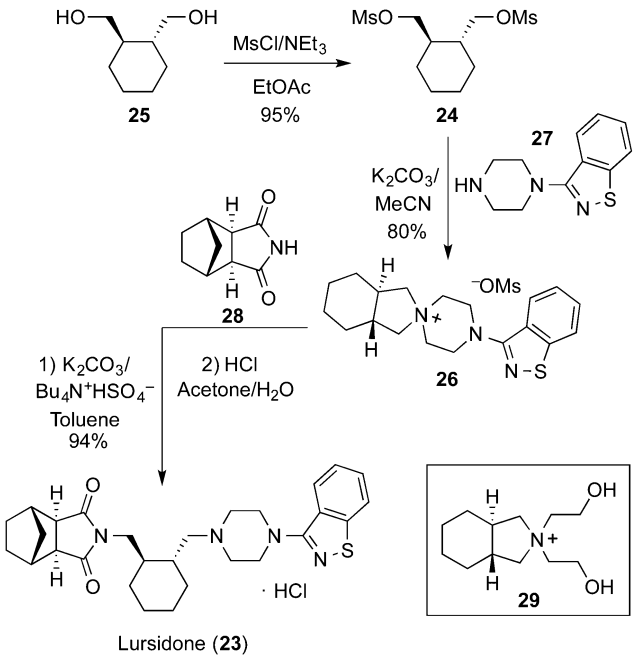
Scheme 3 Synthesis of fencamfamine (**18**).

2.4. Lurasidone

Lurasidone (**23**) is an atypical antipsychotic drug (APD) used to treat schizophrenia and, more recently, bipolar I depression.[66–69] It was designed and developed by Dainippon Sumitomo in Japan. Lurasidone is marketed as Latuda™ (Sunovion Pharms Inc.) and was approved by the FDA as a new molecular entity for schizophrenia treatment in 2010 and approved for treatment of bipolar I depression in June 2013. It differs from traditional APDs, and other related APDs, having a more favourable safety and tolerability profile while maintaining similar efficacy.[70] The disadvantages of other related APDs, include weight gain, hyperlipidemia, and glucose impairment. In contrast, lurasidone is neutral or minimally adverse in these areas.[67,71] It acts as a full antagonist at the dopamine 2 (D_2) and serotonin 2A (5-HT_{2A}) receptor sites,[72–74] with the highest binding affinity to the 5-HT_7 receptor,[72] and partial agonist activity at the 5-HT_{1A} receptor. The therapeutic and safety differences are thought to be attributable to receptor affinity differences, especially at the 5-HT_7 receptor interaction.[66,75–77] Weak affinity for norepinephrine α_{2C} and 5-HT_{2C} receptors, and negligible affinity for muscarinic receptors and the histamine H_1 receptor, has been suggested to be responsible for minimal hypotension, sedation, weight gain, hyperlipidemia and glucose metabolism impairment during treatment.[67,71]

In bipolar I depression treatment, lurasidone has been shown to be effective as a monotherapy,[78] and is also an adjunctive therapy with mood stabilisers.[67,79] Bipolar depression has been linked with high rates of metabolic syndrome and a significant increase in the risk of cardiovascular disease,[72,80,81] and therefore, the favourable metabolic profile of lurasidone will allow treatment, while minimising cardiometabolic risk.

This drug can be described as a benzoisothiazole or an azaspirone derivative.[82–84] Originally, commercial synthesis proceeded with construction of a disulfonate (**24**), by bismesylation of 1,4-diol (**25**),[79] which gave spirocyclic tetralkylammonium salt (**26**) when reacted with the piperazine benzothiazole (**27**). The lurasidone (**23**) synthesis was completed *via* reaction of the [2.2.1]-bicyclosuccinimide (**28**) with the spirocyclic tetralkylammonium salt **26** (Scheme 4).[82–84] An issue with this approach is that the benzoisothiazole, and its intermediates are strong dermal, ocular, and nasal irritants, requiring particular containment and cautious handling. Furthermore, the synthesis utilises other hazardous compounds/reagents, and requires expensive separation processes to be undertaken. Therefore, a number of newer asymmetric, scalable and more commercially viable processes were explored, for example, adding the *trans*-1,2-disubstituted cyclohexane (**29**) to the [2.2.1]-bicyclo-succinimide (**28**), followed by sequential piperazine formation (Scheme 4).[85]

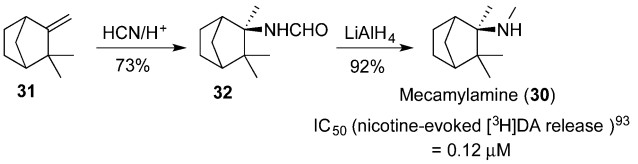


Scheme 4 Synthesis of lurasidone (**23**).

2.5. Mecamylamine

Mecamylamine (**30**) is a nicotinic acetylcholine receptor (nAChR) antagonist that was originally introduced to treat hypertension.[86] It was marketed as Inversine™ (Targacept™) and approved by the FDA, as a new molecular entity in 1956. It is rapidly, and almost quantitatively, absorbed through the gastrointestinal tract and is, therefore, orally available,[87] which was considered an advantage over existing poorly orally available tertiary amines at the time.[86] Furthermore, it had an extended duration of action as a non-specific ganglionic blocker.[88] At therapeutic levels, this lack of specificity affected the sympathetic and parasympathetic nervous system, giving rise to a number of adverse side effects, including dry mouth and constipation.[88–90] Consequently, therapeutic use has been discontinued, except in cases of severe hypertension, in favour of more specific antihypertensives affecting only the sympathetic nervous system.[90] However, it has been shown that the central effects of mecamylamine are observable at a dose three times lower than that used to treat hypertension.[91] This lower dosage avoids or minimises the severity of side effects, allowing for mecamylamine to potentially be used to treat conditions, such as addiction and depression (*e.g.* smoking cessation[91]), in which the nAChRs have been indicated to play a key role.[92] Although promising use avenues have recently opened, at this stage, no other therapeutic usage has been approved for mecamylamine.[93]

The synthesis of mecamylamine (**30**) was described by Merck researchers in 1956.[94] The racemic synthesis commenced by reacting racemic camphene (**31**) with hydrogen cyanide, under



Scheme 5 Resolution of mecamylamine (**30**).

strongly acidic conditions to form 3-formylamido-2,2,3-trimethylnorcamphane (**32**). Reduction with lithium aluminium hydride gave mecamylamine (**30**). Enantiomerically pure mecamylamine can be obtained by resolving racemic mecamylamine, using D-camphorsulfonic acid in acetone (Scheme 5), or can be synthesized directly from D-camphene.[95]

Structure–activity relationship (SAR) studies indicated that alkylating the amine increased activity, but activity decreased as the size of the alkyl substituent was increased.[87] Thus, a methyl group was optimal. Critical steric hindrance of the amine group is essential for biological activity. In addition, the *exo* form is also optimal as it was shown that maximal hindrance in the *endo* form, with the amine resting within the cage, decreases activity.[87]

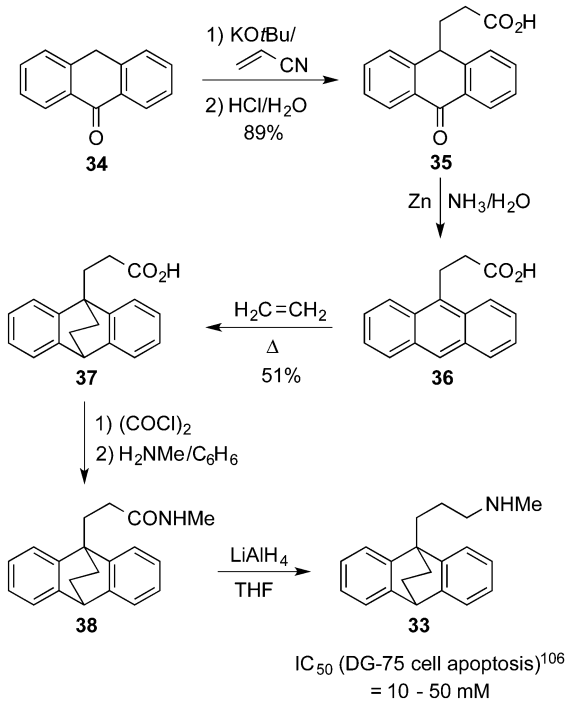
3. Bicyclo[2.2.2]

3.1. Maprotiline

The tetracyclic second generation antidepressant maprotiline (**33**), is used to treat major depressive disorders and alleviate associated anxiety.[96] It was first synthesised in the 1960s and was marketed in a number of countries, including England, in the 1970s.[97] However, it was not until 1980 that maprotiline was approved by the FDA as a new molecular entity for the US, marketed as Ludiomil™ (Novartis).

Maprotiline is classified as a noradrenaline reuptake inhibitor.[98] It is a strong inhibitor of noradrenaline reuptake in both neuronal and peripheral tissues and a strong neuronal norepinephrine reuptake inhibitor.[99] This activity is thought to be attributable to the secondary amine functionality.[100] The sedative properties of maprotiline are thought to be ascribable to strong antihistaminic action. The absence of monoamine oxidase inhibition and weak anticholinergic activity improves the safety profile of maprotiline compared to some other antidepressants.[101,102] The ethylene bridge is the distinguishing feature from standard tricyclic antidepressant molecules, which could be the reason for the above feature.[98]

Overall, maprotiline appears to have a similar, or even greater, incidence rate of adverse events compared to standard tricyclic antidepressants.[103] Given that tricyclic antidepressants have the highest potential overdose toxicity[101,102] and that, despite structural and biochemical differences, maprotiline has a similar pharmacological profile to tricyclic antidepressants, it is unsurprising that selective serotonin reuptake inhibitors are the antidepressants of choice.[104,105] However, a recent study focussing on the potent selective antiproliferative effects of maprotiline against Burkitt's lymphoma, and the mechanisms of maprotiline induced apoptosis, suggests that maprotiline may have a continued use in cancer treatment.[106,107]



Scheme 6 Synthesis of maprotiline (**33**) (not all yields reported[97]).

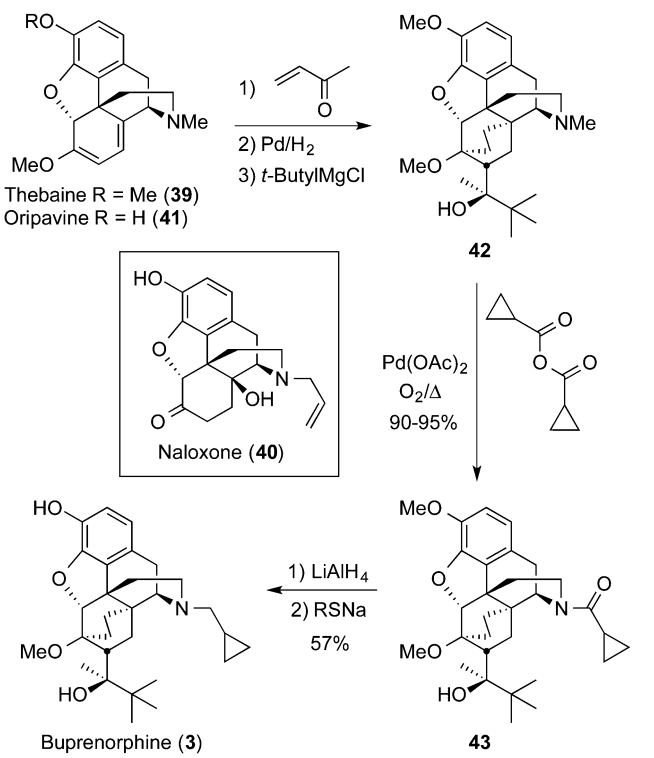
The synthesis of this drug commences with the installation of the eventual bridgehead substitution. This was achieved by deprotonation of anthrone (**34**), and subsequent reaction with acrylonitrile followed by hydrolysis with aqueous hydrochloric acid, affording acid **35**. Reduction of the keto function with zinc gave the anthracene **36**, which was poised to undergo reaction with ethylene giving the bicyclo[2.2.2]octane system (*i.e.* **37**). Acid chloride formation, and direct conversion to amide **38**, facilitated access to maprotiline (**33**) after treatment with lithium aluminium hydride (Scheme 6).[97]

3.2. Buprenorphine

Buprenorphine (**3**) is a semi-synthetic derivative of the opioid alkaloid thebaine (**39**) and is used for moderate to severe pain, pre-operative analgesia and treatment of opioid dependence.[108,109] In light of the dependence issues with opium together with dependence and adverse side effects of morphine, a detailed campaign was undertaken in order to identify the factors responsible for analgesic activity and those responsible for addiction liability.[109] In 1966, buprenorphine was identified, as a more potent and longer lasting analgesic than morphine, with lower dependence potential and favourable tolerability profile.[109,110] It was initially developed as a non-addictive analgesic. It was marketed as Buprenex™ (Reckitt Benckskiser), receiving FDA approval as a new molecular entity in 1981.

Relatively low level doses are needed to achieve analgesia, however, at higher doses buprenorphine, commonly in combination with naloxone (**40**), can be used as an addiction therapeutic.[108] The potential of buprenorphine as an addiction therapeutic was first announced in 1978.[111,112] It is most popularly marketed as Suboxone™ (Reckitt Benckskiser), a buprenorphine hydrochloride and naloxone hydrochloride mix, which is used as an opioid agonist/antagonist to treat opioid dependence. Suboxone™ placed within the top 200 brand name drugs by US retail sales from 2006–2012, within the top 200 worldwide sales in 2008 and 2009, and in the top 200 drugs by US prescriptions in 2010 to 2012. Further applications include intravenous, sublingual, implants and transdermal patches.[108,109,113] Buprenorphine was identified as a full agonist at the ORL-1 receptor with an IC_{50} value of 8.4 nM.[114]

Buprenorphine can actually be classified as a thevinol and an orvinol, as it can be derived from both thebaine and orvipavine (**41**). Buprenorphine (**3**) was first synthesised by Bentley, in an eight-step process from thebaine (**39**).[115] However, this synthetic process required high temperature and pressure conditions and involved *N*-demethylation with cyanogen bromide and phenolic *O*-demethylation with potassium hydroxide in digol, both of which were difficult steps. When orvipavine (**41**) was used as the starting material by Hudlicky *et al.*, in a six-step process, no *O*-demethylation was necessary and a thiolate could be used for the *N*-demethylation of the quaternary salt, thereby avoiding the use of cyanogen bromide.[116] Whereas, starting with thebaine Hudlicky reduced the process to six steps, with an improved yield of 66% for the final three steps.[117] The shortened approach employs an advanced Diels–Alder intermediate (**42**), which undergoes a demethylation/acetylation sequence with cyclopropanecarboxylic acid anhydride mediated by palladium acetate in air to give the *N*-acetamide (**43**). Reduction and *O*-aryl demethylation afforded buprenorphine (**3**) as the final product (Scheme 7).



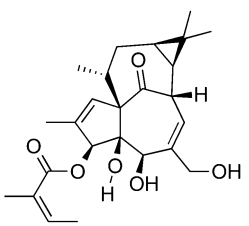
Scheme 7 Synthesis of buprenorphine (**3**).

4. Bicyclo[4.4.1]

4.1. Ingenol mebutate

Ingenol mebutate (**44**) (ingenol 3-angelate) (Fig. 3), was approved by the FDA in January 2012, as a new molecular entity, marketed under the name Picato™ (LEO Pharma) as a topical application for treatment of actinic keratosis (premalignant condition of thick, scaly, or crusty patches of skin). It is a natural product metabolite found in a number of members of the *Eurphorbia* family,[118] first described in 1980 as a component of *E. paralias*.[119] Additional isolation sources have been reported from *E. antiquorum*, *E. helioscopia* and *E. virgate*,[120,121] but is most well-known as a component of *E. peplus*.[122,123]

Originally used in traditional medicine to treat the precancerous skin condition actinic keratosis and basal cell carcinomas,[124,125] evaluation to determine whether there was a realistic pharmacological basis for traditional treatments, began in Australia in 2004.[126] Tumouricidal activity was demonstrated against a number of cell lines, including resistant cell lines. A 100% cure rate was shown for three day topical application in mouse models of mouse and human skin cancer lines.[127] Further phase II and III human trials evidenced the efficacy and safety for topical treatment of actinic ketatosis.[128] Preclinical and clinical study data were employed to elucidate the mechanism of action of ingenol mebutate.[124,125] The initial cell line studies indicated that, upon application cancerous cells were much more sensitive to rapid mitochondrial disruption and cell death by primary necrosis than normal cells.[126] Ingenol mebutate inhibits protein kinase C (PKC) α and activates PKCδ in cancerous cells, thereby inducing apoptosis with considerable potency.[129–132] However, in T cells, PKCθ is activated creating a strong survival signal.[133] A differentiating feature between cancerous and noncancerous cells is that, while PKCδ is expressed widely, PKCθ is only highly expressed in T cells and myocytes.[134] Thus, in contrast to other chemotherapeutic agents, which decrease immune function, ingenol mebutate may in fact stimulate the immune system while inducing cancerous cell death. In 2011, Rosen *et al.* concluded that ingenol mebutate acts through a dual mechanism of action causing both rapid lesion necrosis and specific neutrophil-mediated, antibody-dependent cellular cytotoxicity, which is crucial in precluding relapse.[125] In human studies, a three day, 0.015% gel treatment course for facial areas and a two day, 0.05% gel treatment course for trunk and extremities proved to be most safe and efficacious.[135] Although the majority of participants had mild-moderate skin reactions,[136] this is to be expected, given that cell death is being induced in cancerous cells. Generally adverse events were only of mild-moderate severity and included pain, pruritus and irritation.[136]



Ingenol Mebutate (**44**)

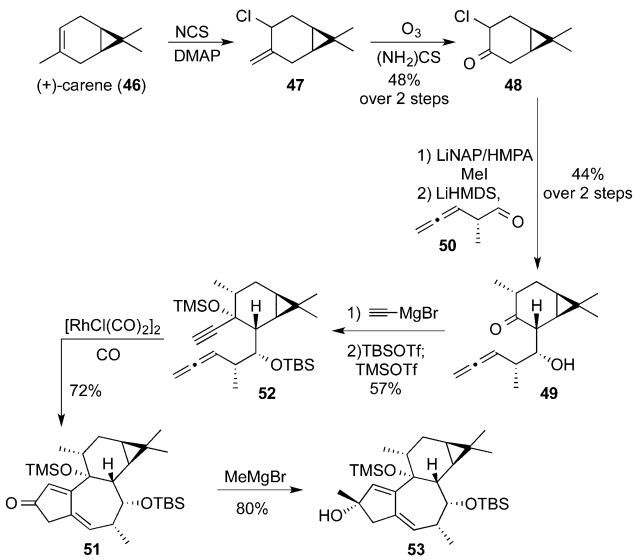
IC_{50} (HCC2998)[132] = 30 μM
IC_{50} (MDA-MB- 435)[132] = 3 μM
IC_{50} (Colo205-S)[132] = 0.01 μM

Fig. 3 The structure of ingenol mebutate (**44**).

The drug has also completed phase II clinical trials for basal cell carcinoma treatment.[128] Unfortunately, rapid degradation through ester migration and hydrolysis result in poor pharmacodynamics properties that would not be easily addressed by available synthetic modifications.[122] Thus, the broader application of ingenol mebutate in treatment of cancerous conditions is currently limited.

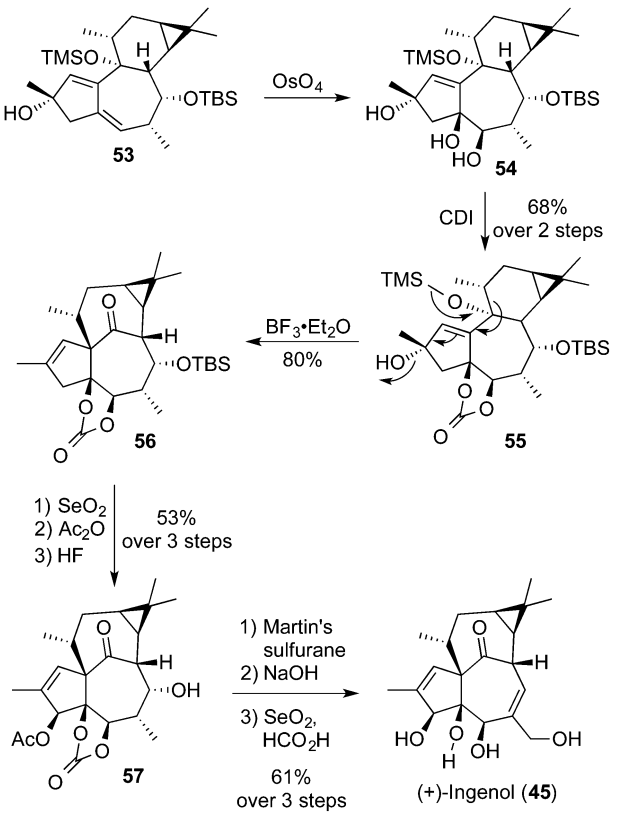
Semi-synthesis from the commercially available natural product ingenol (**45**), extracted from *E. lathyris* seeds,[137] has been explored as an avenue to obtain commercially relevant amounts of ingenol mebutate.[138] However, only 275 mg of ingenol (**45**) could be extracted per kg of seeds and further synthesis was still required.[137] In 2013, a new extraction process was patented claiming an extraction of 750 mg of ingenol (**45**) per kg of seeds.[139] Still, the process was costly and possibly not environmentally sustainable. Attempts to develop a total synthesis for this diterpene class commenced in the 1980s and it was recognised that development of a synthetic approach for ingenol (**45**)[140] would allow synthesis of multiple analogues, including ingenol mebutate. However, it has only been recently, with the publication by Baran *et al.* of a 14 step synthesis of (+)-ingenol (**45**) from (+)-3-carene (**46**), that fully synthetic commercial production has become a potentially viable option.[141,142] Although three total syntheses, and one formal synthesis, of ingenol (**45**) have been published, these approaches involved 35–47 steps, rendering them commercially non-viable, especially as ingenol (**45**) is not the desired final product.[143–145] Baran *et al.*[141,142] applied a retrosynthetic approach employing two main phases: a cyclase phase, to form the tigliane carbon skeleton and an oxidase phase, to achieve rearrangement to the ingenane skeleton, and thus create the necessary hydroxyl functionalities. In determining the best method to obtain the in-out bridged core of the molecule, inspiration was sought from the biosynthetic pathway of ingenane terpenoids.[146] A 1,2-pinacol rearrangement was necessary to obtain ingenane from tigliane.[147] Despite the thermodynamic challenge of a favourable reverse reaction, the vinylogous pinacol rearrangement was considered to be a crucial simplifying synthetic step.

The cyclase phase (Scheme 8) to obtain the tigliane core was seen as an endpoint from which analogues such as ingenol mebutate (**44**) may be obtained. The alkene functionality on carene (**46**) was exploited to install chlorine as a leaving group (*i.e.* **47**), and ozonolysis was used to create chloroketone **48**. This facilitated alpha methylation followed by an aldol reaction to install C-11 (*i.e.* **49**) using allenal **50**. An ethynyl unit was installed to drive a Pauson–Khand cyclisation (*i.e.* **51**),[148] which would create fused rings A and B, after the hydroxyl functionalities were protected (*i.e.* **52**). Methyl magnesium bromide was then utilised to install the C-2 methyl group (**53**), providing the cyclase phase endpoint.



Scheme 8 Cyclase phase to obtain the tigliane core in the synthesis of ingenol mebutate (**44**).

The oxidase phase (Scheme 9) began with the dihydroxylation of the B ring alkene with osmium tetroxide (*i.e.* **54**). The hydroxyl functionalities were then protected as carbonate **55**, before the key vinylogous pinacol reaction was undertaken providing the ingenol framework (**56**). Careful manipulation of reaction temperature was needed as it had previously been reported that thermodynamic factors favour the reverse reaction.[149] Allylic oxidation was used to install the C-3 hydroxyl (*i.e.* **57**). Addition of Martin's sulfurane[150] and base hydrolysis caused elimination of C-6 and global deprotection. Creation of hydroxyl functionality was challenging due to steric hindrance. However, Shibuya's conditions[151] were successfully employed to undertake allylic oxidation of the crowded bicyclic olefin and obtain the final product (**45**) in 1.2% overall yield. Although this is a low yield, it is favourably comparable to the 0.028% w/w and more recent 0.075% w/w obtained by extraction from *E. lathyris* seeds[137,139] and the 0.0011% w/w of ingenol mebutate (**44**) obtained from isolation from *E. peplus*.[123]



Scheme 9 Key stages in the final synthesis of ingenol (**45**).

5. Bicyclo[5.3.1]

5.1. Paclitaxel

The taxanes have become the major treatment choice in a broad range of solid cancers, including breast, prostate, ovary, lung, head and neck tumours.[152–154] The class of chemotherapeutic taxanes is composed of paclitaxel (**1**) (Taxol™, Bristol-Meyer Squibb), docetaxel (**58**) (Taxotere™, Sanofi-Aventis) and cabazitaxel (**59**) (Jevtana™, Sanofi-Aventis) (Fig. 4). These drugs all act *via* the same broad mechanism of action to induce cell death through binding to β tubulin and promotion of microtubulin polymer assembly.[155] However, the binding also stabilises microtubules, preventing the lengthening and shortening of the microtubules that normally allows chromosome movement during cell division. Therefore, the taxanes act by preventing cell division, effectively arresting the cell cycle and leading to cell apoptosis. Issues with resistance have arisen with both paclitaxel and docetaxel, especially in the realm of treating metastatic castration-resistant prostate cancer (mCRPC). However, these drugs continue to improve the life expectancy in a range of cancerous conditions, while exhibiting an acceptable therapeutic safety profile. Docetaxel based chemotherapy remains a cornerstone in the treatment of mCRPC and cabazitaxel has become the standard second-line chemotherapy. Cabazitaxel based treatments have also emerged as follow-on treatments to docetaxel based treatment.[156,157]

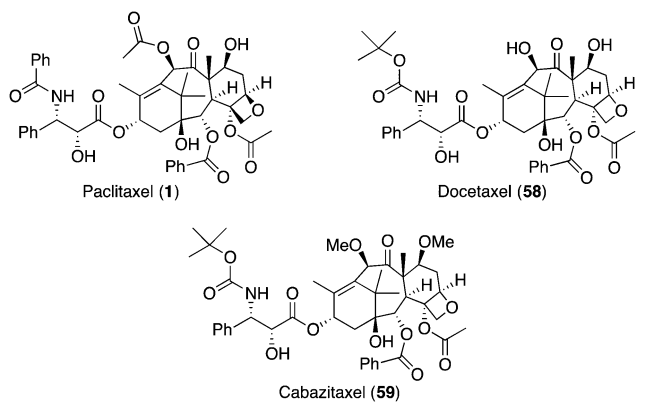


Fig. 4 Chemotherapeutic taxanes: paclitaxel (**1**), docetaxel (**58**) and cabazitaxel (**59**).

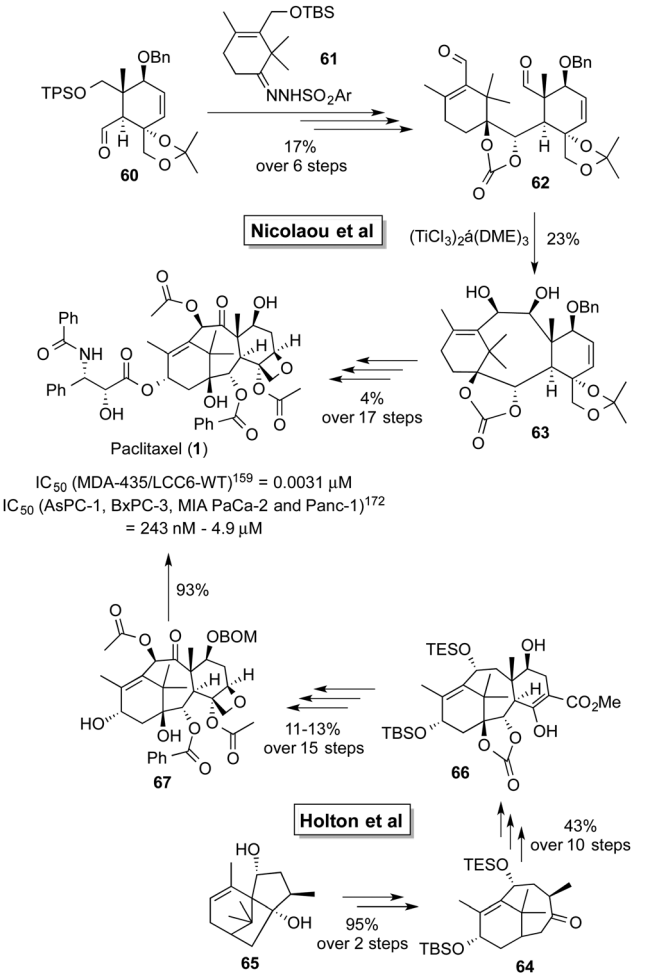
Paclitaxel is the original pharmaceutical taxane. It is a highly complex natural product that was isolated from Pacific yew (*Taxus brevifolia*) bark in 1967.[158–162] In 1992, the FDA approved paclitaxel as a new molecular entity. Paclitaxel has been found to be effective in a number of different cancers, including breast cancer,[163–166] non-small cell lung cancer (NSCLC),[167,168] ovarian cancer,[169] prostate cancer,[170] AIDS-associated Kaposi's sarcoma[171] and, possibly, pancreatic cancer.[172,173] Paclitaxel ranked in the top 200 US brand name drugs in 2011 and 2012, when marketed as Abraxone™ (Celgene™), for treatment of breast cancer, NSCLC and pancreatic cancer. The nanoparticle formulation of this drug promotes binding with albumin, decreasing hypersensitivity and increasing cellular uptake.[172,173]

Paclitaxel directly affects mitotic spindle function during G2 and M phases, causing cell cycle arrest and cell death.[174] It also induces bcl-2 phosphorylation, leading to apoptotic cell death.[175] The major limitation, reducing paclitaxel efficacy, is the emergence of multidrug resistance transporters.[153,174] These transporters, particularly P-glycoprotein (P-gp; ABCB1), act as efflux pumps, expelling the drug from cancerous cells, preventing it from reaching pharmaceutically relevant concentrations within cells.[174] There are also adverse reactions associated with paclitaxel treatment, namely haematological events (neutropenia, thrombocytopenia, anaemia), nausea and diarrhoea.

Although the structure was published in 1971,[158–162] due to the size and complexity of the molecule, it was over 20 years later, in 1994, that two total syntheses were reported basically at the same time by Nicolaou *et al.*[176,177] and Holton *et al.*[178,179] Even though paclitaxel had been approved as an anticancer agent at this stage, the low yield and detrimental environmental consequences of natural harvesting acted as a strong incentive to develop a synthetic, semisynthetic or bioengineering route to obtain relevant quantities of paclitaxel. In the view that taxane synthesis has been previously reviewed on a number of occasions[159–161] only the Nicolaou and Holton syntheses are presented below in brief.

The Nicolaou group took a retrosynthetic approach involving a Shapiro reaction,[180,181] which joined the two fragments **60** and **61** to create the precursors for rings A and C. McMurry coupling was then employed to cyclise the system and obtain the ABC ring skeleton (*i.e.* transformation **62** to **63**). The subsequent installation of the oxetane ring was to be followed by creation of the B and C ring peripheral functionalities and C-13 oxygenation, before final attachment of the side chain by esterification with Ojima's β-lactam[182] gave the side chain, which was then deprotected to give the final paclitaxel product. Despite employing a convergent synthesis approach, commencing from two previously reported intermediates,[183–185] the sequence required 27 steps (Scheme 10).

The Holton group synthesis constructed the core of paclitaxel (*i.e.* **64**) from the epoxidation, and subsequent fragmentation, of the alkene **65** derived from β-patchoulene. This Grob type fragmentation was developed over a nine year period by the Holton group and was put to good effect. The C and D rings were then laboriously installed (*i.e.* traversing intermediates **66** and **67**), with final deprotection and sidechain installation providing the target (Scheme 10).



Scheme 10 Key steps in the synthesis of paclitaxel: Nicolaou route top and Holton route bottom.

Both syntheses were milestone accomplishments, which were long and intensive synthetic campaigns, yielding limited amounts of material. Thus, neither route was feasible for the production of paclitaxel on a commercial scale. However, semi-synthesis reality emerged when it was discovered that the English yew (*T. baccata*) contained significant amounts of the natural products 10-deacetylbaccatin III (**68**) and baccatin III (**69**) (Fig. 5).[158–162] In later years problems in commercially viable isolation of paclitaxel itself have been overcome by plant cell culture technology.[162]

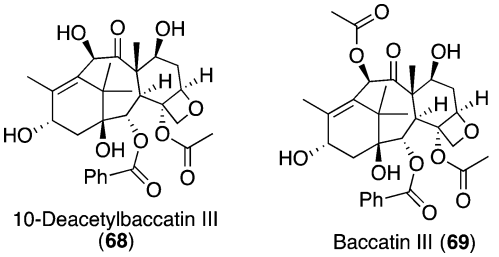


Fig. 5 Baccatin natural products **68** and **69** used in semi-synthesis of paclitaxel (**1**).

5.2. Docetaxel

Like other taxane drugs, docetaxel (**58**) is a semi-synthetic taxane analogue that was derived from the parent structure, paclitaxel (**1**), through examination of structure–activity relationships.[186] It was first approved by the FDA in 1996 as a new molecular entity for use in locally advanced or metastatic breast cancer.[163,164] It has also been approved for use, after initial paclitaxel treatment, in ovarian cancer and NSCLC.[187,188] Since the TAX 327 trial[189] and subsequent FDA approval, in 2004, docetaxel has been the standard-of-care first-line-treatment for mCRPC.[190]

Docetaxel is structurally different from paclitaxel in that C10 has a hydroxyl rather than an acetate ester, which increases the hydrophilicity and solubility of the molecule. Also the phenylpropionate side chain has a *t*-butyl carbamate ester in place of benzyl amide. As a result of these structural changes, docetaxel has almost twice the binding affinity for β-tubulin.[154] Consequently, docetaxel affects a broader range of the cell cycle, including S, G2 and M phases. It may be this broader range span of activity that allows docetaxel to be active in paclitaxel resistant cells. The disruption of centrosome organisation, during S phase, results in incomplete mitosis. Furthermore, docetaxel need only be present at a hundredth of the concentration of paclitaxel to exert the same extent of bcl-2 phosphorylation.[175] In the specific case of mCRPC, studies indicate that docetaxel impairs androgen receptor nuclear translocation and activity to suppress tumour growth.[191]

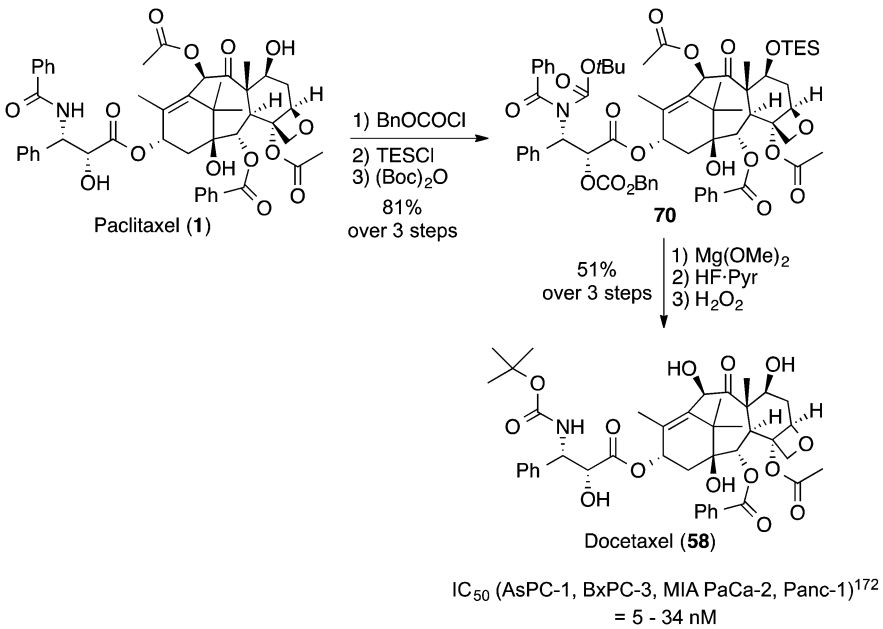
Comparison studies between the two drugs (*i.e.* paclitaxel and docetaxel) indicate that docetaxel experiences greater cellular uptake and reduced efflux, resulting in longer retention time in cells.[153] Although docetaxel treatment does cause higher dermatologic responses, fluid retention and pulmonary toxicity,[192] it results in less neuropathy, myalgias and hypersensitity, without reducing efficacy, when compared with paclitaxel.[187,193] A major cause for low activity and resistance to both these drugs (*i.e.* **1** and **58**) is that both act as substrates for the multidrug resistant efflux pumps, particularly P-gp.[194,195]

The synthesis of docetaxel (**58**) is achieved by further modifying paclitaxel, for example, as demonstrated by Kingston.[196] First the sidechain and C7 hydroxyls were protected as a benzylcarbonate and TES groups respectively, and then reaction with di-*tert*-butyl dicarbonate gave **70**. Reaction with magnesium methoxide and deprotection gave docetaxel (Scheme 11).

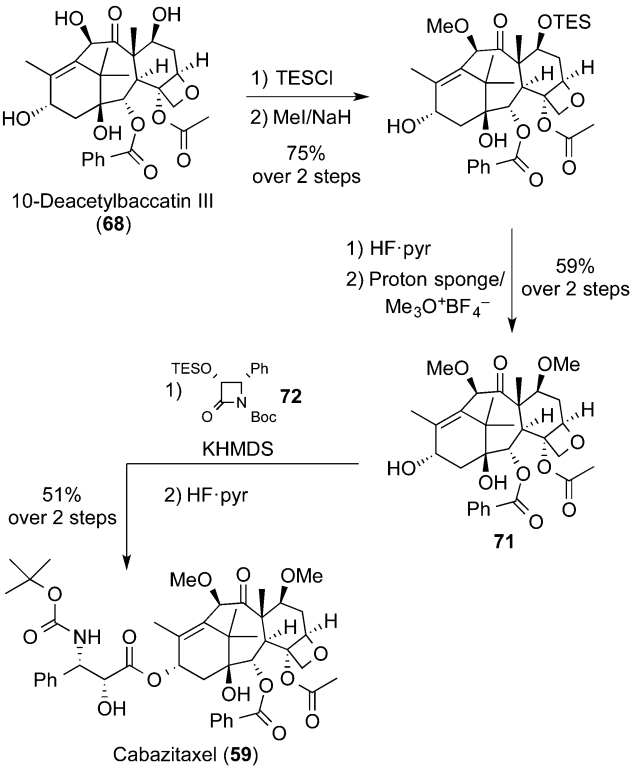
5.3. Cabazitaxel

Cabazitaxel (**59**) is a semi-synthetic chemotherapeutic that makes up the last member of the pharmaceutical taxane family. It was designed to be a poor P-gp substrate, such that it was less susceptible to resistance attributable to multidrug efflux pumps.[197,198] The nature of cabazitaxel as a poor P-gp substrate is thought to be the key explanation for the effect of this drug in cases of docetaxel (**58**) resistance.[197,198] Such a drug was particularly desirable in light of the fact that there was previously no second-line chemotherapy treatment available for docetaxel resistant cancer.[199] After the successful phase III TROPIC trial,[156] cabaxitaxel was approved by the FDA in 2010 as a new molecular entity, and has become the standard-of-care second-line mCRPC treatment drug.[200–202]

This drug differs from docetaxel in that two of the hydroxyl groups are replaced with methoxy groups. It is this change that is thought to account for the increased ability of cabazitaxel to permeate the blood brain barrier.[203] Like paclitaxel (**1**) and docetaxel, cabazitaxel binds to β-tubulin.[204] It acts in the G2 and M phases to arrest cell cycle, leading to cell death. Although cabazitaxel increases survival time in docetaxel-resistant patients, the incidence of adverse events, such as



Scheme 11 Synthesis of docetaxel (**58**) from paclitaxel (**1**).



Scheme 12 Synthesis of cabazitaxel (**59**) from 10-deacetylbaccatin III (**68**).

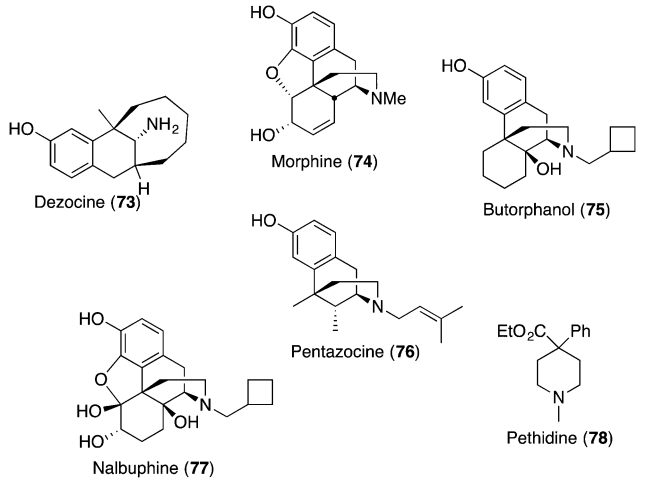


Fig. 6 Mixed agonist–antagonist analgesics: dezocine (**73**), morphine (**74**), butorphanol (**75**), pentazocine (**76**), nalbuphine (**77**) and pethidine (**78**).

allergic responses, neutropenia, diarrhoea and treatment-related mortality, is increased.[205] Currently a number of clinical trials involving cabazitaxel are being undertaken to determine optimal dosage, combinations and sequencing.[200–202] Many cell lines have been exposed to this drug with considerable potency being observed.[206]

Zhang and Fang[207] recently reported an optimized synthesis of cabazitaxel starting from 10-deacetylbaccatin III (**68**) (Scheme 12). Protection of the C-7 hydroxyl as a triethylsilyl (TES) ether allowed selective methylation with sodium hydride giving the TES intermediate, which was methylated with trimethyloxonium tetrafluoroborate (*i.e.* **71**). Attachment of the sidechain using the known protected β-lactam (**72**) followed by deprotection afforded cabazitaxel (**59**) (Scheme 12).

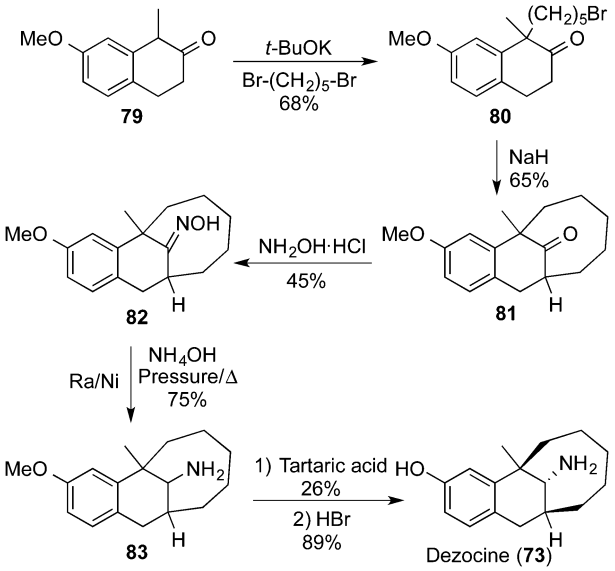
5.4. Dezocine

Dezocine (**73**) (Dalgan™, AstraZeneca) was approved by the FDA, as a new molecular entity, in 1986. It has been used as an analgesic for moderate-severe post-operative pain,[208,209] renal colic[210] and severe cancer pain.[211,212] A 2011 study concluded that preoperative administration of low dosage dezocine improved post-laparoscopic surgery pain and reduced requests for pain relief. However, despite the generally favourable pharmaceutical profile of dezocine, the drug was discontinued by the FDA in 2011.

It was identified, through SAR studies, as a compound having analgesic properties comparable with morphine (**74**),[213,214] but also shares broad structural similarities with a number of other mixed agonist–antagonist pharmaceutical compounds, including butorphanol (**75**) and pentazocine (**76**) (Fig. 6). Unlike traditional analgesic opioid receptor agonists, dezocine is a synthetic mixed agonist–antagonist.[215] Significant limitations of pure opioid receptor agonists, such as morphine (**74**), include associated respiratory depression, tolerance and dependence liability. In contrast, mixed agonist–antagonists display a ceiling of respiratory depression. The issue with mixed agonist–antagonists, such as butorphanol (**75**) and pentazocine (**76**), is that they display other serious adverse reactions, including nausea, significant sedation and psychomimetic effects.[216,217] Thus, there appeared to be a gap for an effective mixed agonist–antagonist analgesic with a desirable safety profile.

Animal and human clinical studies found dezocine to be at least as effective as morphine,[211,218–222] nalbuphine,[218] pethidine[223,224] and butorphanol,[216,225–227] in therapeutically comparable dosages, as an analgesic for moderate to severe pain.[227] Dezocine displays the ceiling effect for respiratory depression at a comparably high level of analgesia and was found to work well in combination with morphine.[215] Perhaps most importantly, adverse effects, such as sedation and nausea, were found to be mild, dose-dependent and transient. Studies concluded that dezocine is generally tolerated at least as well as morphine, pethidine, butorphanol and nalbuphine, and was consistently preferred by patients' and physcians'.[215,218] Due to the agonist–antagonist nature of dezocine the risk of dependence was reduced.[228] Like morphine, the effects of dezocine are fully reversible through naloxone administration.[221] Furthermore, whereas tolerance and toxicity upon extended administration of other agonist–antagonists, such as butorphanol, led to discontinuation of treatment, extended dezocine administration did not cause similar tolerance or toxicity.[216]

Dezocine (**73**) is synthesised from 1-methyl-7-methoxy-2-tetralone (**79**),[213,214] *via* alkylation with 1,5-dibromopentane in the presence of potassium *t*-butoxide (*i.e.* **80**). Subsequent treatment with sodium hydride (NaH) drives cyclisation, completing the bridge junction (*i.e.* **81**). Reaction with hydroxylamine affords oxime **82**, which is then reduced, over a RANEY®



Scheme 13 Synthesis of dezocine (**73**).

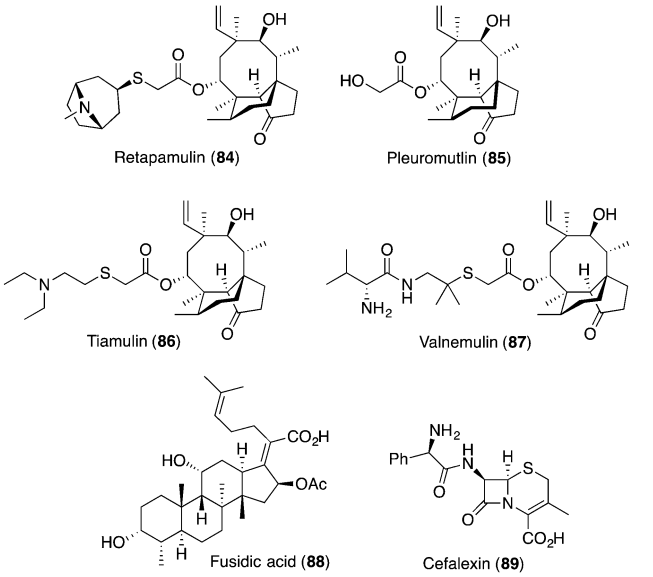


Fig. 7 Tricyclic diterpenoids derived from the natural product pleuromutilin (**85**) [retapamulin (**84**), tiamulin (**86**), valnemulin (**87**)], the topical antibiotic fusidic acid (**88**), and cephalexin (**89**).

nickel catalyst, to give the aminotetralin (**83**). Resolution of the α and β amine epimers was achieved by fractional crystallisation or chromatography. This was found to be improved by treatment with D- and L-tartaric acid, and fractional crystallisation.[229] Treatment with HBr converts the phenyl methoxy functionality to the desired hydroxyl functionality (Scheme 13).

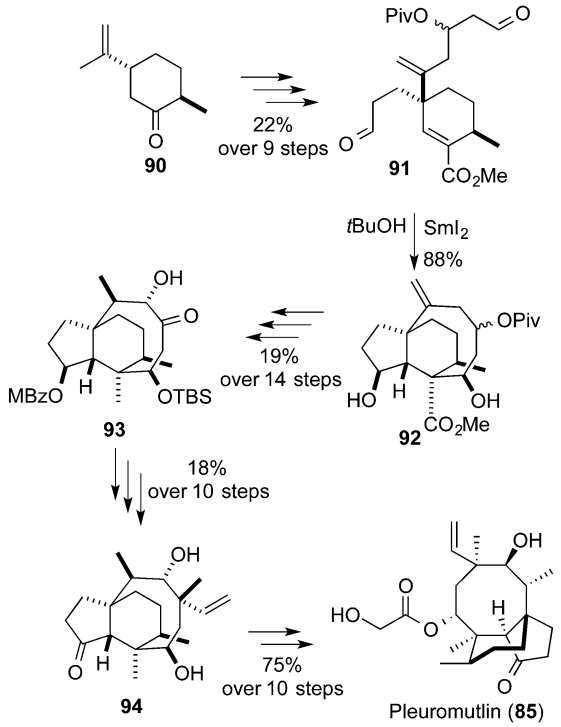
5.5. Retapamulin

Retapamulin (**84**) is an antibiotic, used in ointment form (1% **84**) to treat skin infections, such as impetigo, largely caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.[230–233] It is a tricyclic diterpenoid derived from the natural product pleuromutilin (**85**). The discovery of pleuromutilin (**85**), isolated from the basidiomycete bacterial species *Pleurotus mutilis* (now known as *Clitopilus scyphoides*) and *Pleurotus passeckeranius*, was reported in 1951.[234,235] Pleuromutilin was found to have modest antibacterial activity against Gram-positive bacteria.[234] However, due to poor pharmacodynamic properties and toxicity, was unsuitable for systematic use.[236] SAR studies revealed that suphanyl-acetate modifications at C-14 increased activity against Gram-positive bacteria and mycoplasms.[237] Indeed such modifications gave rise to the veterinary compounds tiamulin (**86**) and valnemulin (**87**).[238] Interestingly, retapamulin showed higher antimicrobial activity than pleuromutilin,[237,239] but it too had poor oral absorption and rapid metabolism, leading to a short half-life, and rapid excretion.[238] Nevertheless, having been shown to have comparably efficacious to fusidic acid (**88**) and oral cephalexin (**89**),[240–242] retapamulin became the first new topical application antibiotic within the last 20 years (Fig. 7).[240]

This drug has been shown to be well tolerated, with few adverse side effects.[240–242] This may be largely due to the fact that it is topically, rather than systematically administered, and has low systematic absorption. After successful clinical trials, retapamulin ointment for treatment of impetigo (marketed as Altabax™ by GlaxoSmithKline), was approved in 2007 by the FDA as a new molecular entity. In the EU, where it is also marketed as Altargo™ (GlaxoSmithKline) retapamulin was also approved, for the short-term treatment of the following superficial skin infections: impetigo and infected small lacerations, abrasions, and sutured wounds.

Retamapulin, like other antibiotics, such as β-lactams and quinolones, exerts its antibiotic activity by inhibiting protein synthesis.[243] However, the unique mechanism of action by which this occurs avoids the occurrence of cross resistance, experienced by antibiotics that have the same target as existing antibiotics.[230–233] Mutilins, such as retapamulin, inhibit the initiation of protein synthesis by binding to a specific site on the 50S subunit of the bacterial ribosome.[243] By selective binding, pleuromutilins inhibit peptidyl transfer, block P-site interactions, and prevent the normal formation of active 50S ribosomal subunits.[243] Schild analysis indicates that the binding of retapamulin is not competitive with P-site tRNA, suggesting that there is an allosteric component to the inhibition of tRNA binding.[230–233] In addition to a different mechanism of action than existing antibiotics, retapamulin has a low propensity to resistance development.[244] This is because retapamulin exhibits a multistep resistance pathway for ribosomal protein L3, in which the most resistant third-step mutants are also affected by growth defects and frequently revert to more swiftly growing retapamulin sensitive strain. As resistance to existing treatments, such as topical fusidic acid, increases, retapamulin will become a more attractive treatment option.[244,245]

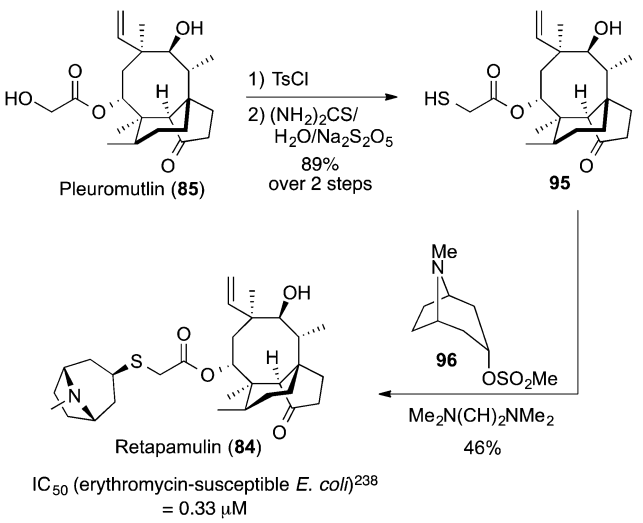
It is no surprise that the complex structural features of retapamulin are naturally-derived. This tricyclic diterpene contains two caged bicyclic structures: a [5.3.1]bicyclo and a [3.2.1]azabicyclo motif, which has been synthesised previously, most recently by Procter *et al.*[246] A brief overview of their synthesis is presented below in Scheme 14. The synthesis began



Scheme 14 Synthesis of pleuromutilin (**85**) by Procter *et al.*

with the chiral pool terpene, (+)-*trans*-carvone (**90**), which was elaborated into the key intermediate dial (**91**) poised for a samarian diiodide-mediated pinacol reaction affording the bicyclic framework (**92**). Further manipulation of the peripheral functionality and alcohol oxidation states, *via* intermediates **93** and **94**, delivered the target [pleuromutilin (**85**)] with expediency and efficiency (Scheme 14).

Retapamulin, however, is produced by a semi-synthetic route using naturally occurring pleuromutlin, which is itself biosynthesised.[247] This commences with tosylation of pleuromutilin with tosyl chloride, followed by reaction with thiourea to give a thiourea ester. The thiourea ester is hydrolysed to the thiol (**95**) and then used to substitute tropine mesylate (**96**) to give retapamulin (**84**) (Scheme 15).



Scheme 15 Synthesis of retapamulin (**84**).

6. Tricyclo[3.3.1.1^{3,7}]

The adamantane class is composed solely of synthetic drugs, covering seven drugs approved for a wide range of clinical conditions. Current approved uses for pharmaceuticals within the adamantane class of compounds range from *Influenza A*, *Herpes simplex* and *Acne vulgaris* treatments, to Parkinsonism, Alzheimer's disease and type II diabetes mellitus. The common feature of the adamantane class of compounds is a substituted adamantyl system, tricyclo[3.3.1.1^{3,7}]decane (**97**) (Fig. 8).

Adamantane (**97**, $R_1 = R_2 = R_3 = H$), was first isolated from crude oil in 1933,[248] and first synthesised in 1941.[249] However, it was not until the development of Schleyer's adamantane synthesis in 1957 that adamantane synthesis and derivative research markedly increased.[250] Schleyer's synthesis proceeds *via* Lewis-acid induced rearrangement of tetrahydodicyclopentadiene (**98**). Once the cage is formed, the tertiary position can then be brominated (*i.e.* **99**)[251] and substituted with the desired functionality (Scheme 16). For the more structurally complex members of the adamantane subgroup, syntheses diverging from this general scheme have been developed.

Drugs in the adamantane class have desirable pharmacodynamic properties attributable to the presence of the adamantyl functionality. The hydrocarbon nature of the adamantane group increases lipophilicity, allowing such molecules to move more easily across biological membranes, as elegantly summarized by Wanka and Schreiner.[252] This is of crucial importance in the area of central nervous system (CNS) drugs that need to travel across the blood brain barrier to reach their target sites.[253,254] Furthermore, this lipophilic moiety can be added to pharmaceutically active compounds and known pharmacophors to improve pharmacokinetic properties or to exploit a lipophilic pocket in the target in order to increase selectivity.[252,255–257] These favourable properties have prompted studies investigating the potential for use of adamantyl containing compounds in cancer and CNS diseases, such as those involving the AMPA and KATP channels

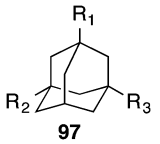
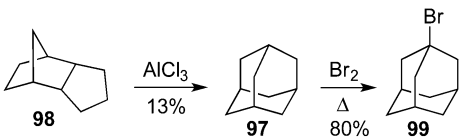


Fig. 8 The adamantyl system, tricyclo[3.3.1.1^{3,7}]decane (**97**).



Scheme 16 Formation and functionalisation of adamantane (**97**).

and the GABAergic system.[252] That being said, for a number of members of the adamantane family the mechanism of action and mode of binding of the drug molecule to its biological target has yet to be fully elucidated. For other members of the class, the major issue is resistance. Overall, however, it appears that the adamantane class of compounds is a valuable and developing class of drugs.

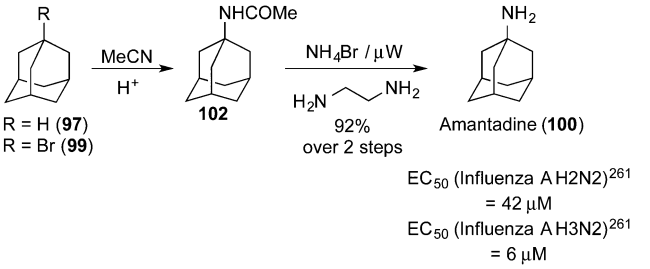
6.1. Amantadine and rimantadine

Amantadine (**100**) is the first pharmaceutical derived from the adamantane scaffold. Rimantadine (**101**), a derivative of amantadine, also forms part of the adamantane family of compounds. Amantadine and rimantadine are both antiviral compounds that have been used to treat *Influenza A*.[258] The antiviral activity of amantadine was reported in 1963,[259] with *Influenza A* antiviral activity confirmed in tissue culture, chick and mouse models.[260,261] The FDA approved amantadine, as a new molecular entity, for use in Asian flu, in 1966 and for *Influenza A* in 1976. The drug has been marketed as Symmetrel™ (Endo Pharm) and Symadine™ (Solvay).

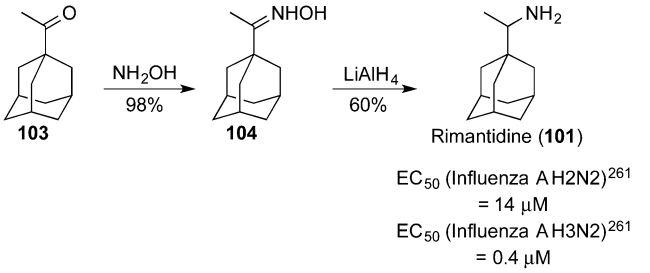
It should be noted that amantadine was not a drug developed for a disease with a known mechanism, but rather was identified as a hit in a random screen. Similarly, rimantadine was a hit in further SAR screening, completed without prior knowledge of the target.[262,263] It is a racemic mixture, with equipotent enantiomers, which is more potent than amantadine.[262] Rimantadine was approved by the FDA, as a new molecular entity, for treatment of *Influenza A*, in 1993 and is marketed as Flumadine™ (Caracao).

Both these drugs are M_2 ion channel blockers.[264] This conclusion was reached only after extensive and wide-ranging mechanistic studies.[264–267] These studies commenced from sequence comparison between wild type and resistant *Influenza A* strains, showing that differences existed in the M_2 protein transmembrane sequence.[268,269] More recent NMR and X-ray crystallography studies indicate that, although there may be allosteric interaction sites, amantadine and rimantadine bind inside the M_2 ion channel, blocking proton movement.[270] This affects important pH balances and pathways that control the uncoating of the viral particle, thereby affecting the infectiveness of the virus.[271] The consensus from the most current structural studies strongly indicates that binding consists of hydrophobic interactions between the adamantyl group and the N-terminal channel gate, and water mediated interactions with key residues.[264] Studies of the mechanism of action of amantadine and rimantadine have led to further elucidation of the *Influenza A* viral replication process and also allowed for the design of derived pharmaceutically active compounds that avoid interactions that give rise to building resistance against amantadine and rimantadine.[264]

The synthesis of amantadine is trivial, as derived from a number of different strategies. Bromoadamantane (**99**) can be lithiated and then reacted with chloroamine.[272] Alternatively adamantane (**97**) [or bromoadamantane (**99**)] can undergo a Ritter reaction, and then be hydrolysed (Scheme 17).[255–257] More recently, microwave-assisted deacylation of unactivated amides using ammonium-salt-accelerated transamidation has been used to transform *N*-acetylamantadine (**102**) to amantadine (**100**) (Scheme 17).[273]



Scheme 17 Microwave-assisted synthesis of amantadine (**100**).



Scheme 18 Synthesis of rimantidine (**101**).

Rimantadine can be produced by a series of 1,2-anisotropic rearrangements from 1-boraadamantane[274] or by titanium(IV) catalysed reductive amination of acetyladamantane (**103**).[275] However, the initial synthesis by Stetter,[276,277] which was utilised by Aldrich[262] to develop this drug, was conversion of acetyladamantane (**103**) to the oxime (**104**) followed by reduction with lithium aluminium hydride to rimantadine (**101**) (Scheme 18).

A patient taking amantadine, who also suffered from Parkinson's disease (PD), reported experiencing relief in PD symptoms.[278] This led to successful clinical trials[279] and confirmatory studies.[280] In 1973, the FDA approved an additional indication for use in treatment of PD symptoms. It is thought that amantadine lessens PD symptoms, such as tremors and dyskinesia, by increasing presynaptic terminal dopamine release.[281,282] In this way a further indication for amantadine was serendipitously added.

6.2. Memantine

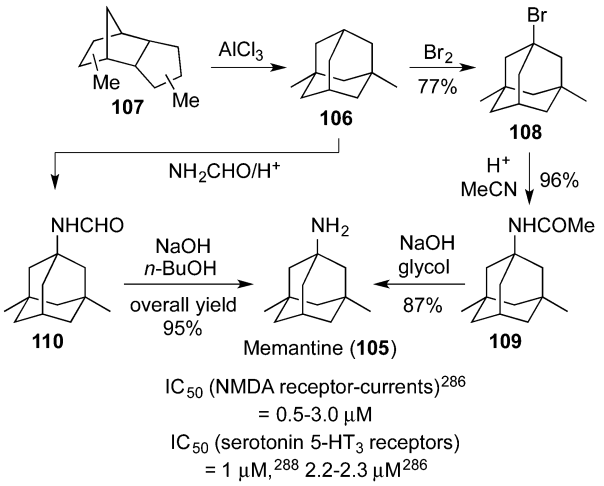
Memantine (**105**) was first patented by Merz, in 1973, as a PD treatment.[283] However, numerous studies, mentioned above, indicated that amantadine was a much more effective PD treatment. In a summary of early studies, Maj emphasised that the major CNS effect of memantine was its influence on the dopaminergic system.[284] Yet, a clinical trial, in 1986, showed no significant difference between memantine and placebo in treatment of dementia.[285] Further studies showed that memantine is a non-competitive, voltage-dependent *N*-methyl-D-aspartate (NMDA) receptor antagonist, with low-moderate affinity and fast on/off kinetics.[286]

Memantine binds to the NMDA receptor only when the receptor is opened by NMDA or an endogenous agonist, such as glycine or glutamate.[287] Although, not yet completely

resolved, evidence elucidating the mechanism of action of memantine is accumulating.[288] The consensus emerging from numerous studies is that memantine acts as a neuroprotective compound by acting as a channel blocker, preventing over-activation of NMDA receptors by high glutamate levels. This avoids excessive Ca^{2+} influx into neurons and resultant excito-toxicity.[289] Overall, memantine appears to promote or preserve synaptic plasticity and protect against cholinergic neuronal degradation.

Due to these neuroprotective features of memantine, it is used to treat the neurodegenerative symptoms of Alzheimer's disease (AD).[290,291] In 2002, the European Medicines Agency (EMA) approved memantine as an AD treatment. This was followed by FDA approval of memantine as a new molecular entity for treatment of AD in 2003. Memantine hydrochloride is marketed as Namenda™ (Forest Labs) and quickly became a top selling drug. From 2006 to 2012, in surveyed years, Namenda™ was ranked in the top 200 US brand name drugs. It also ranked in the top 200 drugs for worldwide sales, in 2008–2009, and US prescriptions, in 2010–2012. Furthermore, memantine is the only approved drug for treatment of moderate to severe AD and has been shown to act synergistically with existing acetylcholinesterase inhibitors.[292] A number of mono- and combination-therapy clinical trials have been undertaken, and the results of key trials were recently evaluated.[292] The comparative meta-analysis paper found that memantine recipients displayed a significant and consistent benefit in cognition, ability to undertake daily living activities and overall assessment, compared with placebo recipients. The authors concluded that memantine appears to be a valuable pharmaceutical compound for treatment of the neurodegenerative symptoms of AD.

The original synthesis of memantine (**105**), required as a hypoglycaemic sulfonylurea intermediate, was reported by Gerzon *et al.*,[255–257] who applied Stetter's procedure for the synthesis of adamantylamine (**100**, amantadine) to 1,3-dimethyl-adamantane (**106**).[293] Gerzon reacted 1,3-dimethyladamantane (**106**), obtained from methylcyclopentadiene dimer (**107**),[293] with excess bromine to give the bromide (**108**). Subsequent treatment of the bromide (**108**) with acetonitrile and sulphuric afforded the acetamide (**109**), which was hydrolysed with sodium hydroxide to the primary amine (Scheme 19). More recently, however, memantine has been prepared with excellent conversion from 1-formylamido-3,5-dimethyladamantane (**110**) in the presence of sodium hydroxide in *n*-butanol (Scheme 19).[294]



Scheme 19 Synthesis of memantine (**105**).

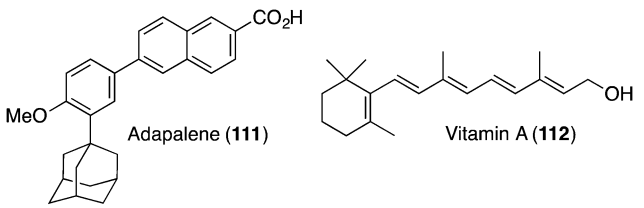


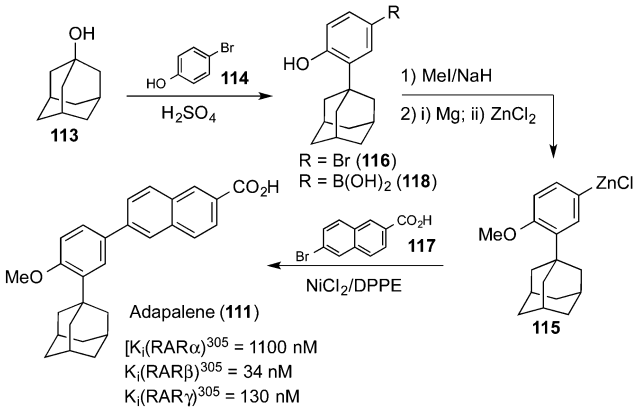
Fig. 9 Adapalene (**111**) a mimic of vitamin A (**112**).

6.3. Adapalene

Adapalene (**111**) (Fig. 9) is an anti-acne topical application marketed as Differin™ (Galderma), and was approved by the FDA in 1996 as a new molecular entity. It has enjoyed high sales, ranking in the top 200 brand name drugs in US retail sales in 2006, 2007, 2008 and in the top 200 brand names and prescription sales in 2010. Adapalene is also marked in combination with benzoyl peroxide as Epiduo™ (Galderma). A number of studies indicate that adapalene may be effective in other cutaneous disorders, such as rosacea.[295–297]

It was identified in SAR studies as a mimic of vitamin A (**112**), with the adamantyl group delivering the bulky hydrocarbon unit and the aryl component providing the π component.[298,299] Vitamin A (**112**) is the original retinoid and binds to retinoic acid receptor (RAR), retinoid X receptor (RXR) and cytosolic retinoic acid binding protein (CRABP).[300] Adapalene binds selectively to RAR-β and RAR-γ as an agonist. RAR-γ is thought to mediate the efficacy and irritation levels of retinoids.[301] The selectivity of adapalene decreases skin irritation suffered with previous retinoids and is a more effective acne treatment.[302,303] Additionally, increased stability, which is likely due to the adamantyl functionality, overcomes previous light degradation issues and allows adapalene to be used in combination formulations.[298,299,304]

The synthesis of adapalene was first described by Shroot in a 1986 patent[298,299] and a later report by Charpentier.[305] In the original description adamantanol (**113**) was reacted with 4-bromophenol (**114**) giving the aromatic substitution product **116**. The key step consisted of generating the organozinc reagent (**115**) from the Grignard of 2-(1-adamantyl)-4-bromoanisole (**116**) and reacting that with methyl-6-bromo-2-napthenoate (**117**), mediated by nickel catalysis (Scheme 20). The main issue with this approach was that the yield of 2-(1-adamantyl)-4-bromoanisole (**116**) was low, and the majority appeared to undergo formal reduction before engaging with the electrophile (**117**), resulting in an overall yield of 32%. Furthermore, the extraction and purification was highly laborious. A recent paper reported successfully pursuing an optimised



Scheme 20 Synthesis of adapalene (**111**).

Suzuki–Miyaura method,[306] using boronic acid **118**,[307] which gave an increased overall yield of 57%. Altered extraction and purification conditions also improved production (Scheme 20).

6.4. Tromantadine

Tromantadine (**119**), like amantadine (**100**) and rimantadine (**101**), was identified during SAR studies when screening for antiviral activity.[308] The drug displays antiviral activity against *Herpes simplex* (HSV) and *Herpes zoster*.[308] It has been approved in South America, and some European and Asian countries, for use in treating cold sores. It is marketed as Viru-Merz™ (Merz & Co.), as a topical application hydrogel. However, tromantadine is not a first-line HSV treatment. The reason is that comparative clinical trials did not show significant efficacy differences,[309,310] contact dermatitis has been reported to arise in a small number of patients, with some studies reporting incidences of less than one percent, while others suggest as high as six percent occurrence.[311,312]

A detailed explanation of the mechanism of action of tromantadine has yet to be established. However, numerous studies indicate that tromantadine inhibits both an early and a late stage of viral replication.[314] In early stages, it appears that it inhibits the viral uncoating process. In later stages, it appears to inhibit membrane fusion by changing host surface glycoproteins, thereby interfering with absorption of the virus.[313–315] This is quite different from the mechanism of action of acyclovir (**120**), which interferes with viral replication by inserting a nucleobase analogue.[316] Although tromantadine is not a first line treatment, the different mechanisms of action mean that it may be appropriate in cases of acyclovir resistant HSV infections (Fig. 10).

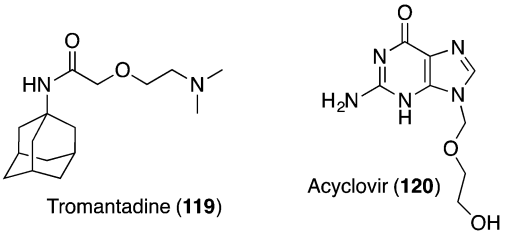
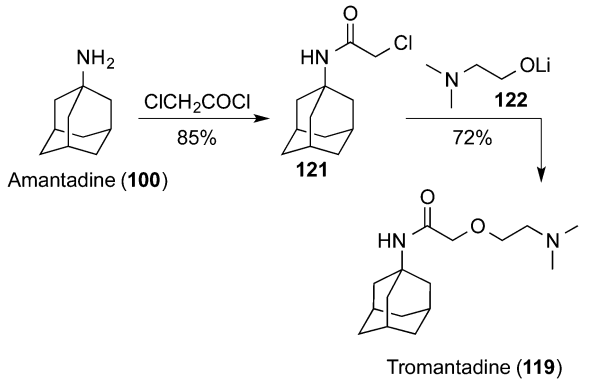


Fig. 10 *Herpes simplex* treatments tromantadine (**119**) and acyclovir (**120**).



Scheme 21 Synthesis of tromantadine (**119**).

Tromantadine was first synthesised by May and Peteri.[308] However, Rosenthal improved the practical ease of this process and increased the overall yield (Scheme 21).[313] This involved reacting amantadine (**100**) with chloroacetyl chloride, to give *N*-(1-adamantyl)-2-chloroacetamide (**121**), which was then reacted with the lithium anion of *N*,*N*-dimethylethanolamine (**122**) to give tromantadine (**119**) in 72% yield (Scheme 21).

6.5. Vildagliptin and saxagliptin

Vildagliptin (**123**) and saxagliptin (**124**) are both orally active antihyperglycemic agents used in the treatment of type II diabetes.[317–321] Saxagliptin was approved by the FDA, in 2009, as a new molecular entity and marketed as Onglyza™ (Bristol-Meyer-Squibbs, AstraZeneca). It is approved for use in the EU and Australia, where it is also used in combination with metformin (**125**), sulfonylureas (**126**), thiazolidediones (**127**) or insulin.[322] It has been quite successful, ranking in the top 200 brand name US drugs in 2011 and 2012. In contrast, vildagliptin has not been approved by the FDA, but has been approved in the EU and Australia, where it is marketed as

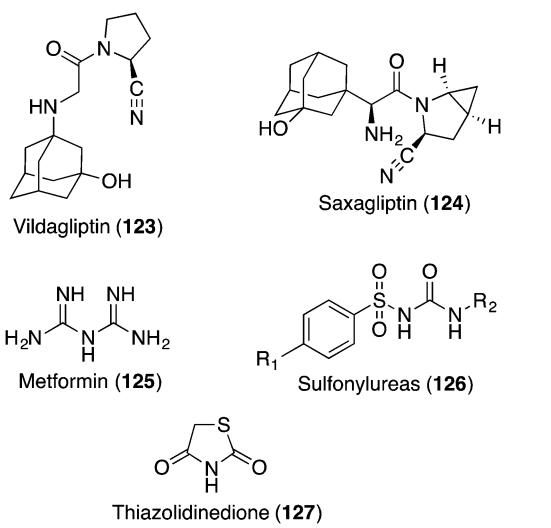


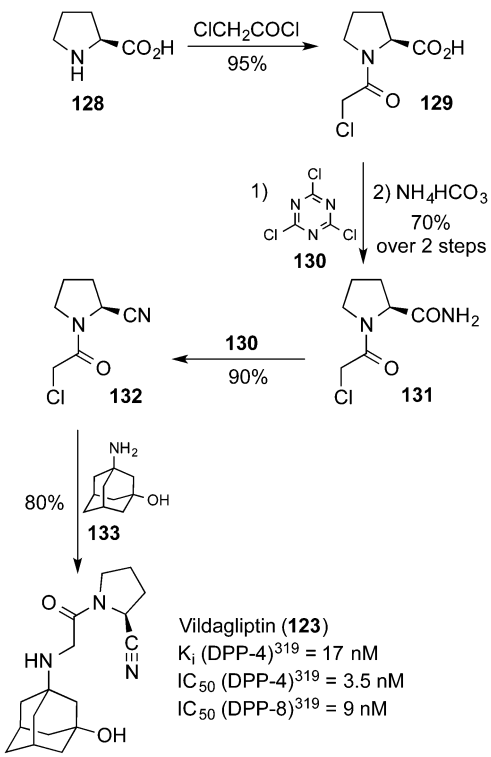
Fig. 11 Pharmaceuticals used in the treatment of type II diabetes: vildagliptin (**123**), saxagliptin (**124**), metformin (**125**), sulfonylureas (**126**) and thiazolidinedione (**127**).

Galvus™ (Novartis) and may be used in combination with metformin, sulfonylureas or thiazolidediones (Fig. 11).[323,324]

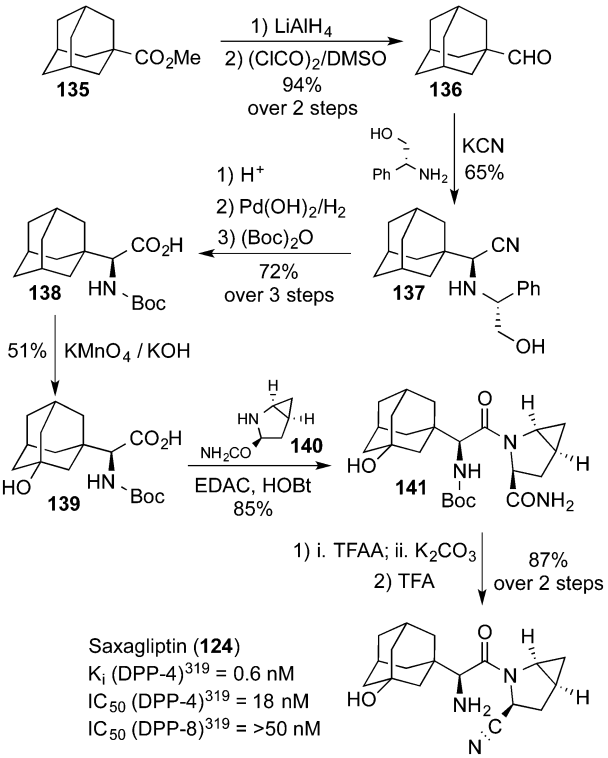
Both drugs (*i.e.* **123** and **124**) are potent and selective dipeptidyl peptidase IV (DPP-IV) inhibitors. DPP-IV is a serine protease that cleaves the N-terminal dipeptide from glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP), preventing their agonist activities at their GCPRs.[325] GLP-1 stimulates insulin production when blood glucose is high, suppresses glucagon and lowers release of glucose by the liver.[326] The rate of food absorption is reduced, promoting satiety and lessening appetite. Thus, GLP-1 is crucial to blood glucose homeostatsis and inhibition of DPP-IV is an effective way to ensure that GLP-1 degradation is lessened.[327]

Vildagliptin and saxagliptin were both identified through structure activity studies commencing from peptide derived structures mimicking the DPP-IV substrate.[317–321] Due to the fact that they act as anti-hyperglycemics, the safety profiles of both drugs are improved compared to hypoglycemics.[327] Furthermore, they have been shown to be non-inferior to a range of other treatments, and to be weight neutral.[328–331] Animal studies suggest that vildagliptin may have relevance for Alzheimer's disease treatment.[332,333]

Hu *et al.* have reported the most efficient synthesis of vildagliptin.[334] L-Proline (**128**) was firstly reacted with chloroacetyl chloride to form 1-(2-chloroacetyl)-pyrrolidine-2-carboxylic acid (**129**) (Scheme 22). This was reacted with 2,4,6-trichloro-1,3,5-triazine (TCT) (**130**) affording 1-(2-chloroacetyl)-pyrrolidine-2-carboxamide (**131**), which is then further dehydrated by TCT producing 1-(2-chloroacetyl)-pyrrolidine-2-carbonitrile (**132**).



Scheme 22 Synthesis of vildagliptin (**123**).



Scheme 23 Synthesis of saxagliptin (**124**).

Reaction with 3-aminoadamantanol (**133**) yields vildagliptin (**123**) (Scheme 22).

The saxagliptin synthesis was originally an approximate ten step process.[317] However, enzymatic syntheses utilising lipase B from *Candida antactica* and dehydrogenase from *Thermoactinomyces intermedius*, which provide better access to advanced intermediates, have now been reported.[335–337] Furthermore, an optimised commercial scale synthesis, emphasising environmental and workplace safety considerations, with five transformations, three isolations and an overall yield of 65%, has been disclosed.[338] Nevertheless, the most illustrative synthesis is that initially described by Augeri and Hamann.[317] The synthesis firstly proceeded with conversion of methyl adamantan-1-carboxylate (**135**) to the corresponding aldehyde (**136**). An asymmetric Strecker was then deployed, using (*R*)-(−)-2-phenylglycinol with addition of potassium cyanide, which delivered the advanced intermediate **137** that was subjected to functional group manipulation giving the protected amino acid **138**. Oxidation of the adamantane core with potassium permanganate introduced the hydroxyl function (*i.e.* **139**). Subsequent peptide coupling with the commercially available *cis*-4,5-methanoprolinamide (**140**) gave **141**, which was finally followed by deprotection of the Boc protected amine, and dehydration of the primary amide, to afford saxagliptin (**124**) (Scheme 23).

7. Polycyclic hydrocarbon analysis and structural significance

In the DrugBank database alone over 1500 approved pharmaceutical compounds are listed. It is, therefore, perhaps somewhat

surprising that less than one percent of these compounds incorporate all carbon polycyclic hydrocarbon scaffolds. A cursory glance at the DrugBank database reveals the fact that many drugs have relatively simple chemical structures, and although many pharmaceuticals incorporate cyclic structures, these motifs are often largely planar.[11] It is our view that the limited frequency of caged hydrocarbon scaffolds seen in the clinic (Fig. 12) is largely attributable to aspects concerned with (1) chemical synthesis, (2) the third dimension and complexity, (3) natural products, and (4) target selection, ligand efficiency and physicochemical properties.

7.1. Chemical synthesis encompassing polycyclic ring systems

In general, polycyclic hydrocarbon scaffolds usually command significantly more synthetic challenges, due to difficulties in functionalization. In addition, they often lack reaction and functional group diversity as compared to aryl systems, and have historically been of limited commercial supply as initial building blocks. These factors have without doubt had a negative impact on overall polycyclic structural diversity as evidenced by the fact that only five polycyclic systems have reached the clinic so far, *i.e.* bicyclo[2.2.1], [2.2.2], [4.4.1], [5.3.1] and tricyclo[3.3.1.1^{3,7}] (adamantane) (Fig. 12).

That being said, the survey presented in Fig. 12 highlights those structure classes that have maintained a high level of popularity, such that viable synthesis have enabled their drug discovery. Two examples that reinforce this notion is the bicyclo[2.2.1] and adamantane systems. Utilising the bicyclo[2.2.1] series (*e.g.* **5**, **12**, **16**, **23**, **30**) (Fig. 12), as an initial example, reveals a clear synthetic trend in the use of the robust Diels–Alder reaction involving cyclopentadiene, which is readily available and cheap. Of special note, however, is that all the examples in this class that made it to the clinic (*e.g.* **5**, **12**, **16**, **23**, **30**) have no substitution on two of the three bridges. This lack of functionalisation is easily understood, because substituted cyclopentadienes invariably create regioisomers, *via* the Diels–Alder reaction, which affect yield and thus cost (*i.e.* potential requirement for chromatography). The adamantane class (*e.g.* **100**, **101**, **111**, **119**, **124**) highlights a similar situation, in that, it is a popular structure class, but most are mono-substituted, with only two examples being di-substituted (*i.e.* **123–124**) (Fig. 12). This is a result of historical difficulties associated with multi-functionalisation of the adamantane system as compared to other motifs, although recent successful efforts to overcome this issue (*i.e.* C–H functionalization) have been reported.[339]

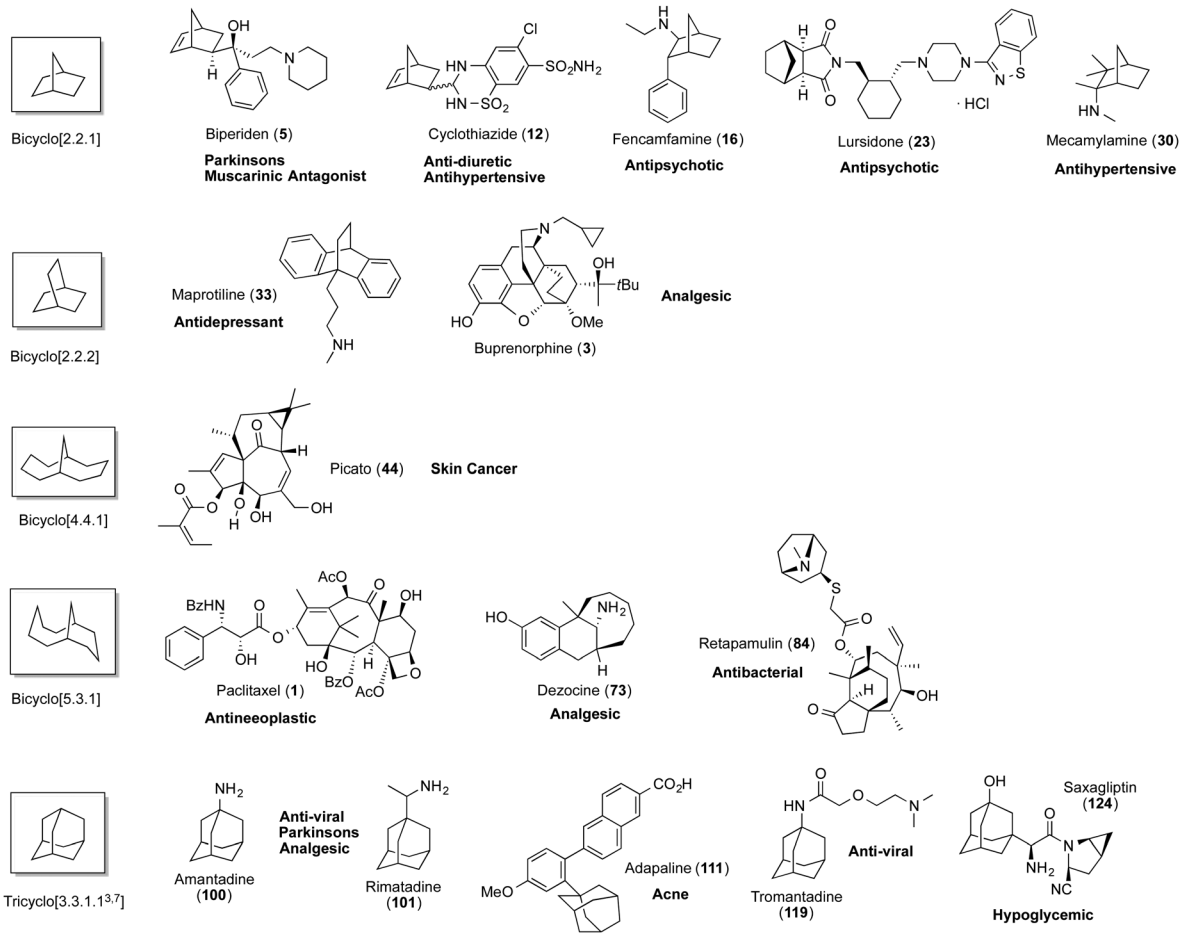
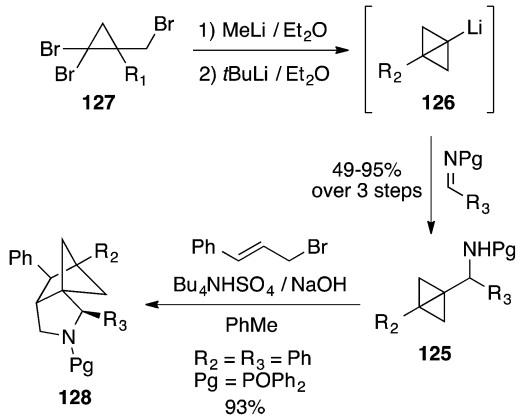


Fig. 12 A structural collection of the all-carbon polycyclic hydrocarbon scaffolds covered in this review.



Scheme 24 Synthesis of the bicyclo[1.1.0] and bicyclo[2.1.1] systems for utilisation in bio-assay screening.

What about the many other bicyclo[1.*x*.*x*], [2.*x*.*x*], [3.*x*.*x*], and so on, series of polycyclic systems missing from the clinic? In fact, apart from natural products, only a few of the synthetic systems (*e.g.* bicyclo[1.1.1],[340] [3.2.1],[341,342] [3.3.1][343,344]) are accompanied with any reasonable supporting synthetic literature. These structure voids, however, have opened up many opportunities for medicinal and synthetic chemists to develop new systems and supporting reactions for functionalisation.

Wipf *et al.* have demonstrated that various amines (**125**) containing the bicyclo[1.1.0] system can be prepared from suitably protected imines and substituted bicyclo[1.1.0]lithium anions (**126**) derived from tribrominated cyclopropanes (**127**) (Scheme 24).[345,346] Later, it was discovered that the bicyclo-[1.1.0]amines (**125**) will undergo base promoted rearrangement in the presence of various electrophiles to give fused bicyclo-[2.1.1]pyrrolidines (**128**) (Scheme 24).[345] An extensive biological screening program evaluating the bicyclo[2.1.1]pyrrolidines (**128**) unearthed a wide range of biological activities, including for example, inhibition of the enzymes TGF-β and fatty acid synthase, in addition to hepatitis C activity.[345]

A team at Pfizer lead by Stepan[347] recently demonstrated that bicyclo[1.1.1]pentane could act as a benzene function replacement for the γ-secretase inhibitor of BMS-708,163 (**129**) with the synthesis and biological evaluation of **130**, which demonstrated greater activity and drugability (Fig. 13). This, however, was not the first example of benzene ring replacement using the bicyclo[1.1.1]pentane system. In 1996 Pellicciari reported[348] that (*S*)-(+)-2-(3′-carboxybicyclo[1.1.1]pentyl)glycine (**131**) was a structurally novel, potent and selective, mGluR1 antagonist modeled off (+)-methyl(4-carboxyphenyl)glycine (**132**), which was known to exhibit mGluR1 antagonist properties (Fig. 13). Lastly on this front, both these pieces of work inspired Adsool *et al.*[349] to prepare a benzene isostere of 4-phenylaniline (**133**) using the bicyclo[1.1.1]pentane scaffold (*i.e.* **134**) for an in-house drug discovery program.

Eaton, in the 1990s, suggested that the classical hydrocarbon cubane (**135**) might also act as a benzene surrogate, and went on to say this offers exciting prospects for pharmaceutical development.[350] Although the known chemistry of cubane

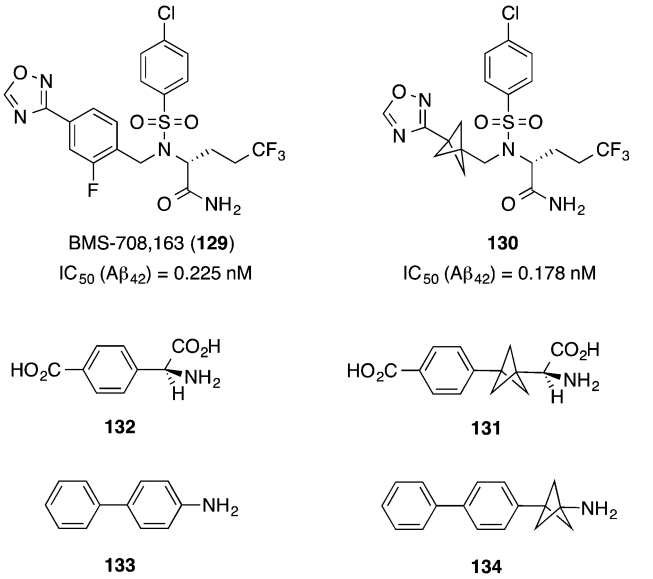


Fig. 13 Investigating the concept of bicyclo[1.1.1]pentane as a benzene bioisostere.

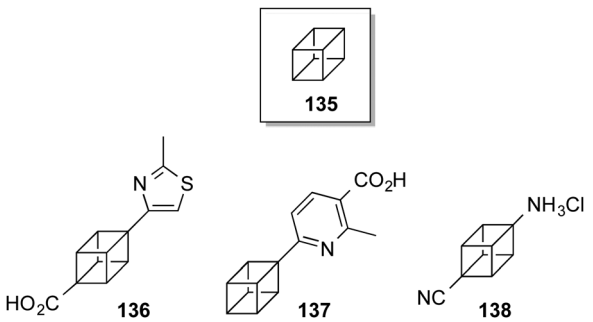


Fig. 14 Cubane (**135**) and pharmaceutically relevant cubane derived molecules (**136–138**).

is substantial,[350,351] it is not at the same level of benzene substitution chemistry. Nevertheless, Wlochal and Davies[352] have recently demonstrated that incorporation of cubane into pharmaceutically relevant containing molecules is possible (*e.g.* **136–138**) (Fig. 14).

Furthermore, Schreiner recently synthesised aminocubane (**139**) in addition to homo (**140**), bishomo (**141**) and trishomo (**142**) cubane derivatives, and subsequently investigated their bioactivity potential against NMDA receptors (Fig. 15). The driving force for this study was the carbocyclic similarity of the cubanes to memantine (**105**, see Section 6.2). Evaluation of cubanes **139–142** in the hydrochloride form showed pronounced affinity suggesting these systems would act as efficient voltage-dependent NMDA receptor antagonists.[353]

7.2. The third dimension and complexity

Initiated by the advent of Lipinski's rules[354] the medicinal chemistry community embarked on the adoption of substantial computational analysis of screening libraries, hits, leads and clinical drugs, to better understand attrition rates based on physical properties (*e.g.* molecular weight, topological polar

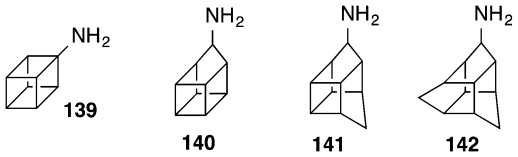


Fig. 15 Aminocubane (**139**), homo (**140**), bishomo (**141**) and trishomo (**142**) cubane derivatives investigated for bioactivity potential against NMDA receptors.

surface area, rotatable bonds, and hydrogen bond donors and acceptors).[355] However, the legacy of both combinatorial chemistry and the expansion of sp^2 coupling and functionalization methodologies, gave rise to a high proportion of aromatic molecules within screening libraries, which therefore influenced computational analyses towards the selection of planar sp^2 rich molecules eventuating in a "flatland" drug domination scenario.[11] Flatland drugs,[356] or perhaps more importantly flatland drug candidate development programs, are raising real constraint concerns in some quarters of the pharmaceutical drug design and development community.[357] Although total flatland withdrawal would be counterproductive,[358] avenues to sidestep potential flat scaffold problems by the introduction of sp^3 carbons has been proposed.[11,356,359] Furthermore, increasing overall saturation and thus "complexity",[360] as indicated by various measures (*e.g.* Fsp^3),[11,356,360] seems a viable path to escape flatland. It also makes sense that deployment of chirality and non-planar architecture construction will provide greater access to new chemical space.[361] Furthermore, chirality has recently been proposed to address low-druggability recognition sites,[362] and complexity shown to potentially reduce toxicity,[356] and increase target specificity.[363] *Surely, all these desirable features could be justifiably addressed via the incorporation of a polycyclic hydrocarbon system, which by their very nature are sp^3 complex, often chiral and can potentially act as direct benzene bioisosteres.*

7.3. Natural products

There has been considerable debate in recent years about the value and contribution of natural products to drug discovery as evaluated by molecule types that reach the clinic.[1–3,5] Evaluation of the 20 candidates discussed herein reveals a conservative estimate that more than 50% are natural products, or derivatives thereof. This is perhaps unsurprising when one considers that adamantane is a natural product,[248] and thus the entire tricyclo[3.3.1.$1^{3,7}$] class, can then be considered as naturally derived. Furthermore, the predominance of natural products or derivative representatives is partially explained by taking into account the fact that Mother Nature is able to bypass many of the issues faced in attempting to synthesise such bicyclic compounds. Thus, in the portion of drugs that are natural products a high density of more structurally complex compounds is not unexpected. *Even in the extreme complexity cases this did not impact on their development.* For example, in the case of both the taxanes (*e.g.* **1**) and retapamulin (*e.g.* **84**) (see Section 5), not to mention buprenorphine (**3**) (see Section 3.2), chemical synthesis was supplemented in part with readily available bio-engineered advanced intermediates.[364] Whereas, very recently microbial synthesis potentially offers much promise to simplify production of natural products from glucose.[365]

7.4. Target selection, ligand efficiency and physicochemical properties

The 20 pharmaceuticals discussed in this review cover treatment of a wide range of disorder types, conditions, and diseases (see Fig. 12 overview). These include, (1) Parkinson's treatments; (2) antidiuretics to treat heart failure and hypertension; (3) antihypertensives for hypertension and smoking cessation; (4) antipsychotics for appetite suppression, schizophrenia, and bipolar I depression; (5) antidepressants; (6) analgesics for pain; (7) treatment of actinic keratosis for skin cancer; (8) antineoplastic agents for treating solid tumours; (9) antivirals, (10) antibacterials, (11) acne treatments; and (12) hypoglycemics for the treatment of diabetes.

So what is the key to understanding broad target diversity and potency of polycyclic hydrocarbon drugs? Although the aforementioned disorder types, conditions, and diseases are wide-ranging, a common feature of the polycyclic hydrocarbon class thus far is that many of these clinical agents engage central nervous system (CNS) and/or neurological targets. When the polycyclic cage is more exposed or predominates, the majority of the molecule is inherently more lipophilic in character (*e.g.* **5**, **16**, **30**, **33**, **73**, **100**) (Fig. 12). This confers on such systems further attributes more suited to crossing the blood brain barrier (BBB)[366,367] and entering the CNS.[368] That being said, lipophilicity, which is not necessarily target dependent, has a narrow window for optimal drug design (*i.e.* $\log D$ 1–3), but enviably correlates well with increased potency.[369] *Therefore, is lipophilicity the key desirably feature polycyclic hydrocarbon scaffolds can provide?* For those systems that have the polycyclic hydrocarbon scaffold buried deep within the drug (*e.g.* **1**, **3**, **44**, **84**) (Fig. 12), not only is a shift away from CNS activity observed, but it is hard not to conceive that the scaffold is key to rigid functional group placement. That is, the attached functional groups are in high probability at the perfect three-dimensional distances with in the binding pocket, which impact substantially on ligand efficiency. Interestingly, ligand efficiency metrics concentrate on both lipophilic ligand efficiency and ligand binding thermodynamics and kinetics[370] (*i.e.* entropy/enthalpy and Michaelis–Menten kinetics[371]). This suggests that polycyclic hydrocarbon scaffolds could better satisfy both criteria of lipophilicity and functional group placement control, and thus limit undesirable polypharmacology[372,373] or metabolic profiles.[252]

8. Conclusion

It is clear that polycyclic hydrocarbon systems have played an important role in the clinic thus far, however the meagre impact of no greater than one percent compared to all other clinical agents, is fuelling a welcomed renaissance in both

traditional polycyclic hydrocarbon scaffolds and the development of new medicinally relevant polycyclic hydrocarbon systems. Furthermore, new developments in benzene bioisostere discovery, anti-flatland complexity factors, and ligand efficiency measures will drive research in this underdeveloped area. Lastly, it is our view that the identification that limited classes of chemical reactions are being deployed in the pharmaceutical sector[374,375] together with the current search for new scaffolds[376] will ultimately reinforce caged polycyclic systems as a reliable medicinal chemistry scaffold having increased clinical impact well into the future.

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