

# **GENERAL INTRODUCTION**

## **Natural Products – an introduction**

Plants and other natural products have been in use for the human sufferings from time immemorial. The search for new chemical entities obtained by screening natural sources such as plant extracts and microbial fermentations has led to the discovery of many clinically useful drugs that play a major role in the treatment of human significance as important sources of novel compounds useful directly as medicinal agents, as lead compounds for synthetic or semi-synthetic structure modifications and optimization as biochemical or pharmacological probes.

During the course of evolution, plants have acquired effective defense mechanisms, which secure their survival amidst hostile environment and enemies. Thick cuticular waxes, thorns, prickles, sticky hairs are some of the familiar protective features. Though less obvious, more important subtle defense mechanisms are based on chemicals (secondary metabolites), which protect the plants from the attack of insects, microbes and other predators. Many plants produce a stratagem of chemicals, which make them unsuitable for utilization by insects and other predators by imparting repellency, toxicity, unpalatability or biochemical incompatibility. An understanding of these, which may be called ‘natural defense technologies’, might therefore provide clues for the development of new biotechnological procedures based on ecologically acceptable biocides.<sup>1</sup>

Plants contribute a great deal too wide range of industries such as pharmaceuticals; fine chemicals, agrochemicals, cosmetics, industrial raw chemical etc. and substantial portion of all the currently prescribed drugs are directly or indirectly derived from plant sources. A recent investigation revealed that approximately 60% of the antitumor and antiinfective agents that are commercially available are in various stages of clinical development originate from natural sources.<sup>2</sup> The development cost of synthetic drugs has increased tremendously hence the drug discovery taken an economical path utilizing natural products. Research in natural product area continues now because of presence of the diversified structural features of the secondary metabolites, which may act as therapeutic agents. It is important to note that some of the remarkable drugs have been isolated from common plants, which are not known to have any medicinal reputation in the folklore or indigenous system of medicines. For example, the most potent antiluekemic

drugs, vincristine and vinblastin were discovered by chance from *Catharanthus roseus* but this plant was reported earlier to have only hypoglycemic activity.<sup>1</sup>

The plants not only continue to retain their historical significance as important sources for development of new drugs, but also are extremely useful as sources of ‘lead’ compounds for structural modification and optimization that can be employed as specific probes in biochemical studies. More recently, as the lead compound generation and drug discovery processes have been significantly influenced by emerging approaches such as advanced genomics, combinatorial chemistry and computer assisted drug design. However, occurrence of an array of organic structures in nature has directed natural product research towards newer frontiers dealing biotechnology, physiology and ecology.

Despite of many important past contributions from the plant kingdom, a great many folklore medicinal plant species have remained unknown to science and relatively few have been surveyed systematically for biologically active constituents. In spite of numerous past successes in the development of plant derived drug products, it has been estimated that only 10-15% of the existing plant species have been systematically studied for the presence of biologically active compounds, which is a challenge to the chemists specializing in natural products and to pharmacologists. The powerful new chemical and biological technologies now permit receptor isolation and characterization so that drug design principles can be applied rapidly to fast track natural product leads as never before.

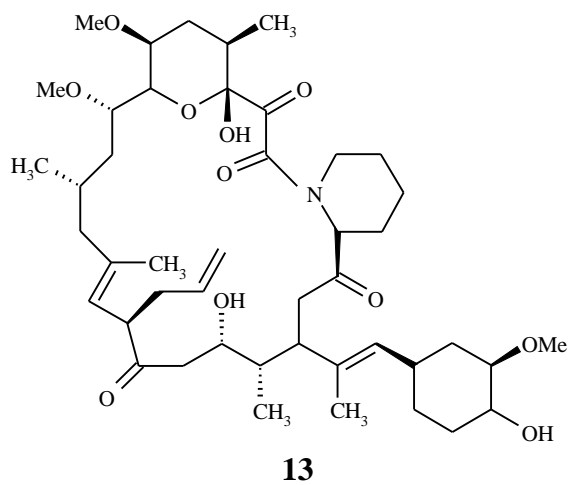
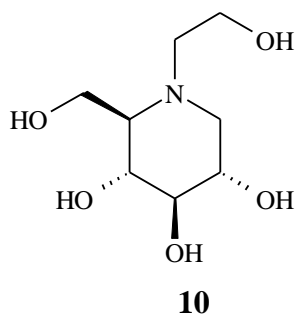
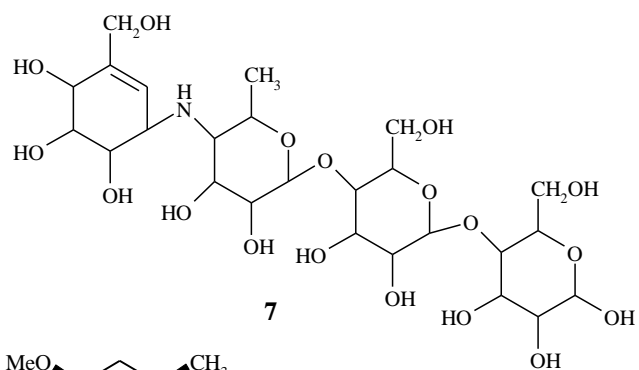
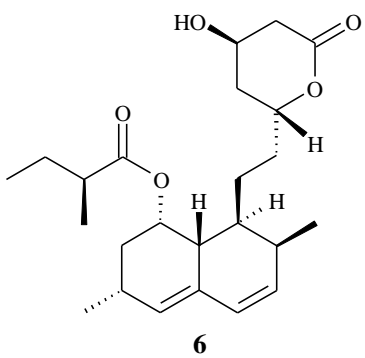
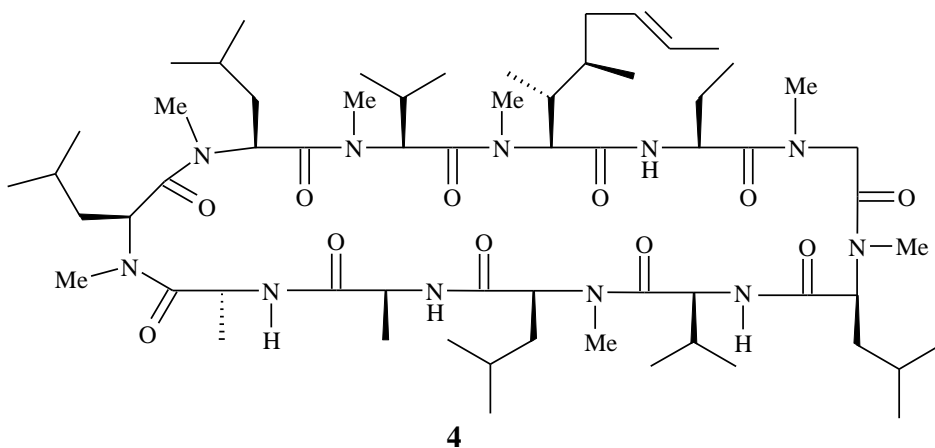
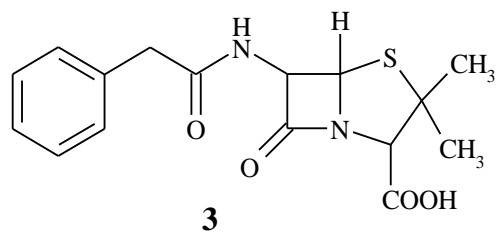
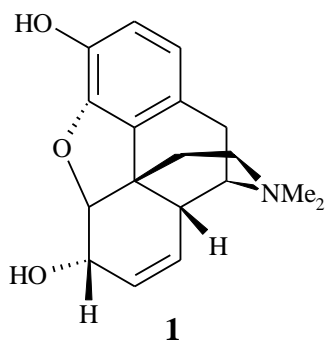
### **Breakthroughs in the research of natural products:**

Natural products have long been and will continue to be extremely important as sources of medicinal agents and models for the design of synthetic and semi synthetic novel substances for treating human diseases. The commercialization of some modern drugs derived from plants or microbes<sup>3</sup> is given in below (**Table 1**).

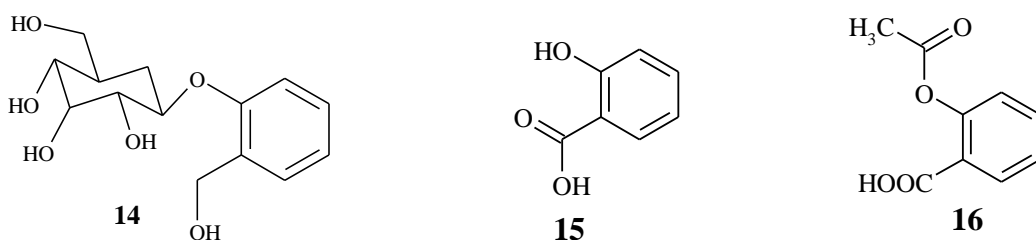
**Table-1**  
**Commercialization of some modern drugs derived from nature**

<b>S.No.</b>	<b>Drug</b>	<b>Commercialized as</b>	<b>Indication</b>
1	Manufacturing of Morphine (1)	Natural compound (p)	Analgesic
2	Acetylsalicylic acid (Aspirin) (2)	Synthetic analog (p)	Analgesic, antiphlogistic etc.,
3	Penicillin (3)	Natural compound (m)	Antibacterial
4	Cyclosporin A (4)	Natural compound (m)	Immunosuppressant
5	Artemisinin (5)	Natural compound (p)	Antimalarial
6	Lovastatin (6)	Natural compound	Antihyperlipidemic
7	Acarbose (7)	Natural compound (m)	Antidiabetic
8	Paclitaxel (8)	Natural compound (p) as a semi-synthetic derivative	Anticancer
9	FK 506 (10)	Natural compound (m)	Immunosuppressant
10	Docetaxel (9)	Semi-synthetic derivative (p)	Anticancer
11	Irinotecan (11) Topotecan (12)	Semi-synthetic derivative (p)	Anticancer
12	Miglitol (13)	Synthetic analog (m,p)	Antidiabetic

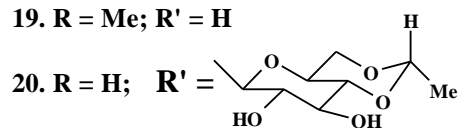
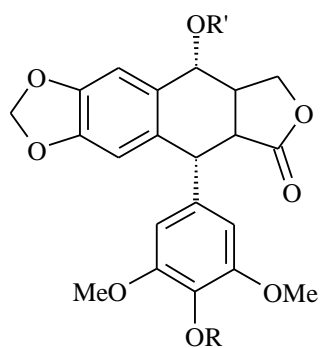
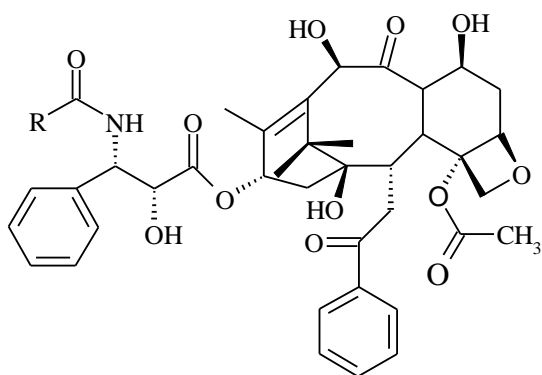
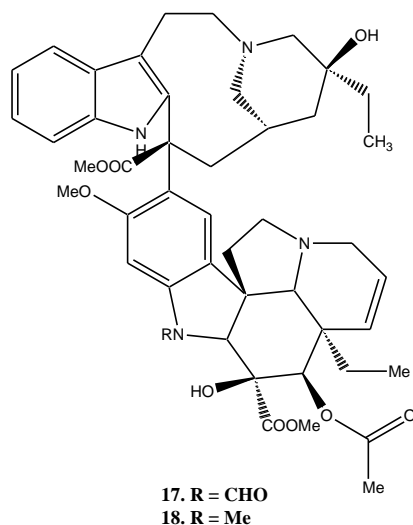
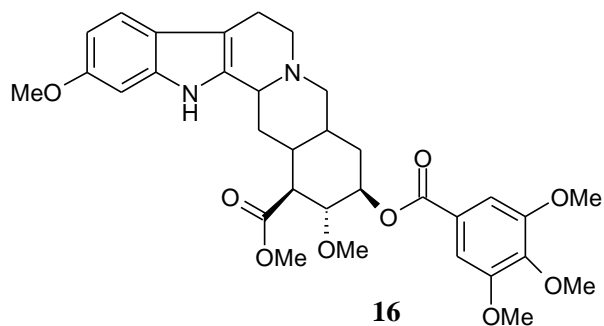
M = microbial metabolite; P = plant metabolite



Classically plants have played a dominant role in the introduction of new therapeutic agents and continue to occupy important niche in the modern medicine. At least 130 drugs, either single chemical entity extracted from higher plants or synthetically modified, are currently in use. Some of these are now being made synthetically for economic reasons. For example, antipyretic and analgesic properties of the bark willow-tree (*Cortex salicis*) were already known around 400 BC by the Greeks and Romans. It was used for more than two thousand years, until the middle of the last century its main bioactive principle salicin (**14**), the  $\beta$ -glucoside of salicylic alcohol was identified. Degradation reactions of salicin yielded salicylic acid (**15**) featuring improved analgesic, antipyretic, antiphlogistic and antirheumatic properties. Nearly 100 years later, the synthesis of aspirin (acetyl salicylic acid) was guided by natural salicylic acid featured as most successful drug worldwide.<sup>3</sup>



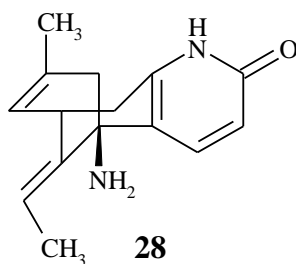
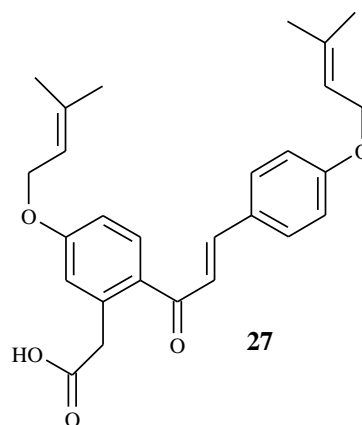
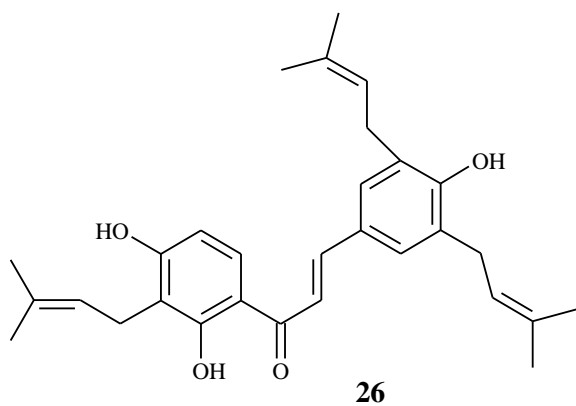
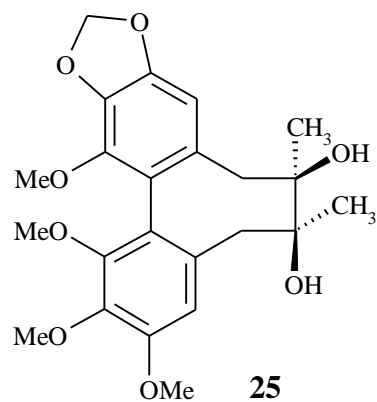
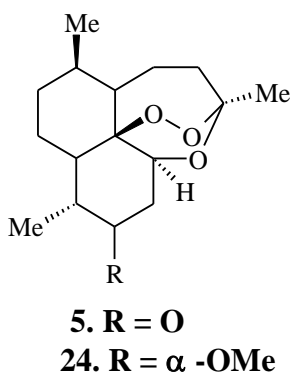
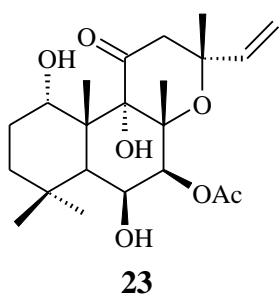
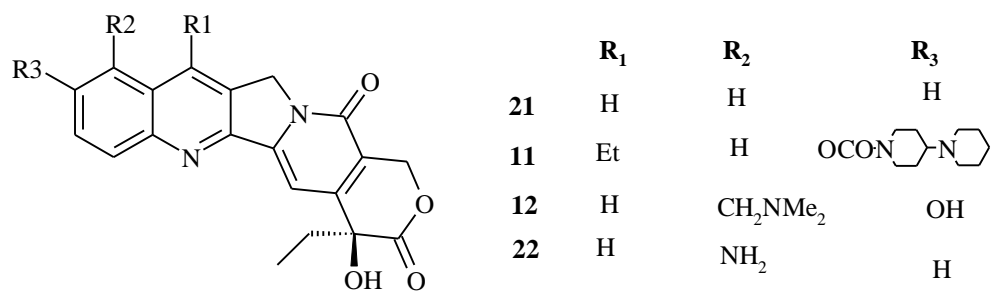
Reserpine (**16**), isolated from the roots of the India plant *Rauwolfia serpentine* by M/s. CIBA, India was heralded as a revolutionary event in the treatment of hypertension and CNS activity.<sup>4-6</sup> Some of the most important chemotherapeutic agents, currently in use, for the treatment of certain types of cancers viz., Hodgkin's disease, lymphosarcoma, and leukemia in children, are vincristine (**17**) and vinblastine (**18**), both isolated from *Catharanthus roseus*.<sup>7,8</sup> Etoposide (**20**), developed from the antineoplastic lignan podophyllotoxin (**19**), a constituent of Himalayan tree *Podophyllum hexandrum*, is currently being used against testicular cancer, small cell lung cancer and lymphomas.<sup>9-12</sup> Paclitaxel (**8**), previously known in the scientific literature as taxol, a diterpenoid constituent of several *Taxus* sp. is effective in the treatment of metastatic ovarian cancer and has potential uses in the treatment of lung cancer, metastatic breast cancer and malignant melanoma.<sup>13-15</sup>



Irenotecan (**11**), an analogue of quinoline alkaloid camptothecin (**21**), first isolated from the Chinese tree *Camptothca acuminata*, but now obtained mostly from the Indian tree, *Mappia foetida*<sup>16,17</sup> is being used in Japan for the treatment of lung, ovarian, and cervical cancers.<sup>18,19</sup> As a matter of fact, development of new antineoplastic therapeutic agents based on natural product leads is proving to be a fertile area of activity.<sup>20,21</sup> Several derivatives of camptothecin, besides irenotecan (**11**) already referred to above, are now in clinical phase, and mention may be made of topotecan (**12**) and 9-aminocamptothecin (**22**), both of them have shown promising activity<sup>22</sup>. Camptothecin (**21**) itself has potent antineoplastic activity, but has serious side effects, which includes bleeding.

Some of the biologically active natural products have proved useful as tools in drug discovery. A good example is forskolin (**23**), a diterpene from the roots of the Indian plant

*Coleus forskohlii*, which is being used in the activation of adenylate cyclase, in receptor binding assays and as an antihypertensive.<sup>23</sup>





The herb *Artemisia annua* L. has been used traditionally in China for treatment of fevers. It has yielded an effective antimalarial, a sesquiterpene peroxide, artemisinin (**5**). The compound is active against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falsiparum* and *P.vivax*, and is equally effective against cerebral malaria.<sup>24</sup> Artemether, a simple derivative of artemisinin, has a better clinical profile, and is under clinical development.<sup>25-27</sup> Gomishin (**25**), a lignan from the fruits of Chinese medicinal plant *Schizandra chinensis*, has hepatoprotective activity as revealed from studies carried out in China and Japan, and is now under clinical trials for the treatment of chronic hepatitis.<sup>28</sup> The Chinese plant *Sophora substrata* has been used in China for the treatment of stomach troubles and sophoradin (**26**), a chalcone, isolated from this has shown significant anti-gastric ulcer activity; a synthetic compound, sofalcone (**27**) developed after this lead is now in clinical use.<sup>29</sup> An alkaloid, named huperzine A (**28**), has been isolated from the plant *Huperzia serrata* used in some parts of the China to alleviate memory disorders has been demonstrated to be a powerful acetylcholine esterase (AChE) inhibitor, and is being clinically evaluated for the treatment of Alzheimer's disease.<sup>25</sup>

### **Ayurveda (Indian System of Medicine): Potential and opportunity**

The origin of Ayurveda is lost in prehistoric antiquity, but its characteristic concepts appear to have matured between 2500 and 500 BC in India. The word Ayurveda is derived from 'Ayus', meaning life, and 'Veda', meaning knowledge, thus, Ayurveda literally means science of life.

Disease, according to Ayurveda<sup>30</sup>, can arise from body and/or mind due to external factors or intrinsic causes. Ayurvedic treatment is aimed at the patient as an organic whole, and treatment consists of salubrious use of drugs, diets and certain practices. Ayurveda has vast literature in Sanskrit and various Indian languages, covering all aspects of diseases, therapeutics and their methodical preparations. It has evolved its own theoretical base, which is difficult to comprehend in terms of modern scientific concepts.

In Ayurveda, Medicinal preparations are invariably complex mixtures, being derived from plant and animal products as also minerals and metals. Earliest references to

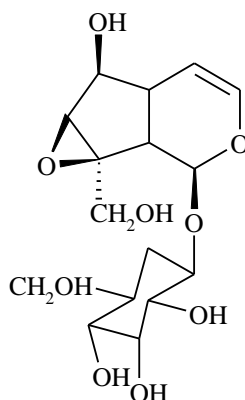
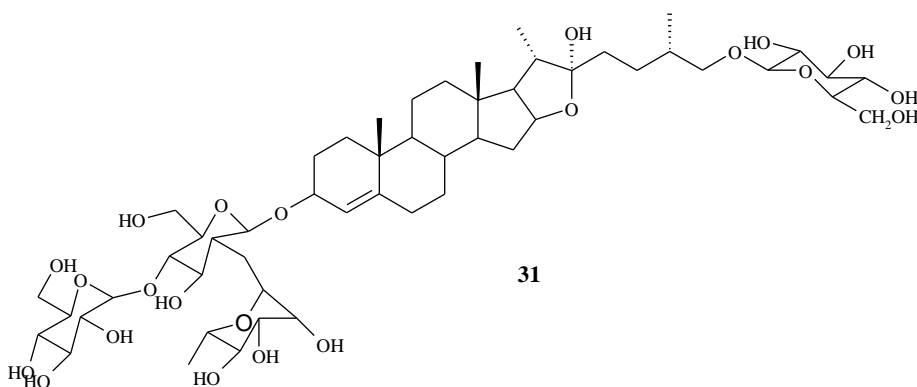
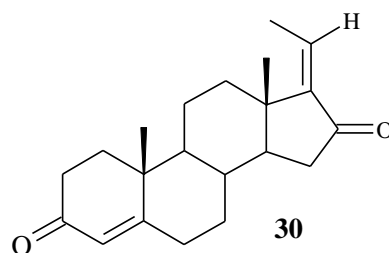
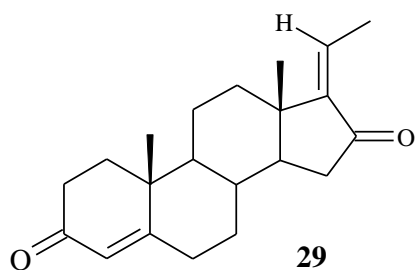
such plants are to be found in the Rig-Veda and Atharva Veda, dating back to second millennium BC. Charaka Samhita (~900 BC), which has special emphasis on surgery. After Charaka and Sushruta, was Vagbhata of Sind, who practiced in 7<sup>th</sup> Century AD. Charaka, Sushruta and Vagbhata are the Vriohat Traya (Powerful Triad) of Ayurveda.<sup>28</sup>

The earliest contribution of Ayurveda to modern drug development is reserpine (**16**), the anti-hypertensive drug, which is a minor alkaloid of the Ayurvedic drug plant Sarpagandha (*Rauwolfia serpentine*). It has received international attention and in a way rekindled interest of researchers in identifying possible leads from the natural products. The next landmark is the isolation of antihyperlipoproteinemic (hypolipidemic) steroids, Z-guggulsterone (**29**) and E-guggulsterone (**30**) from the gum resin of *Commiphora wightii*.<sup>31,32</sup>

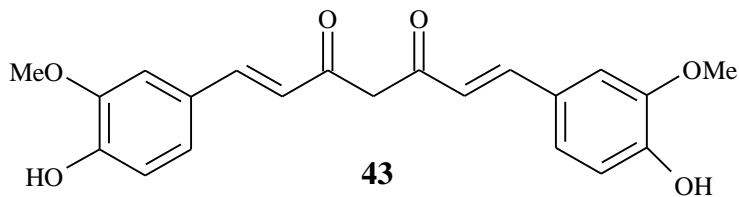
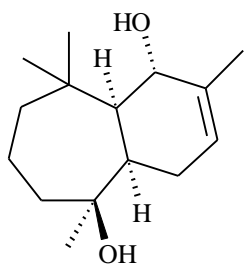
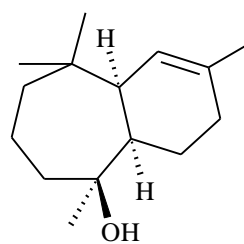
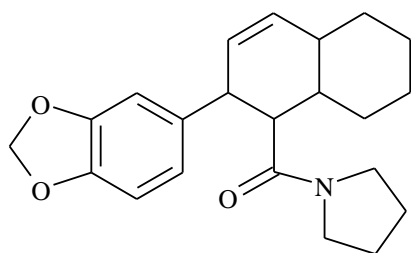
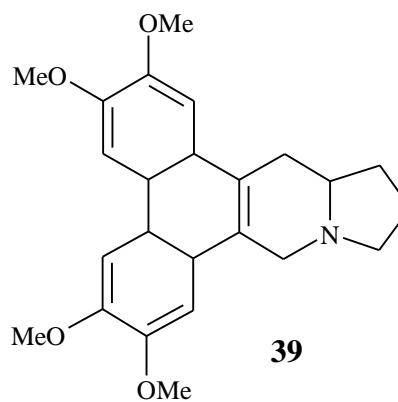
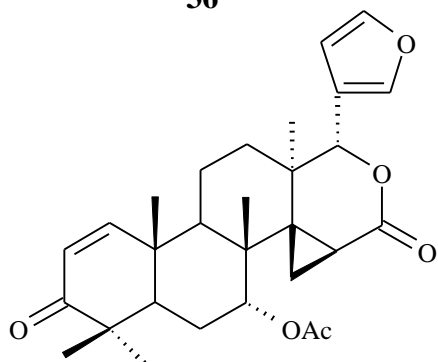
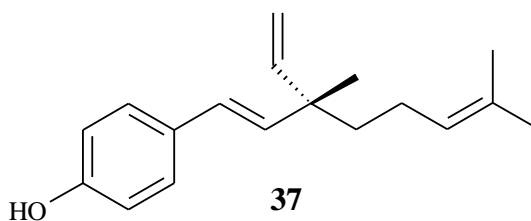
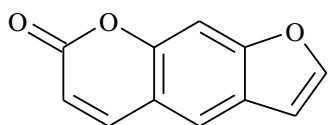
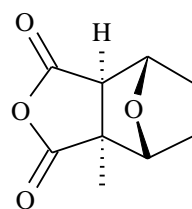
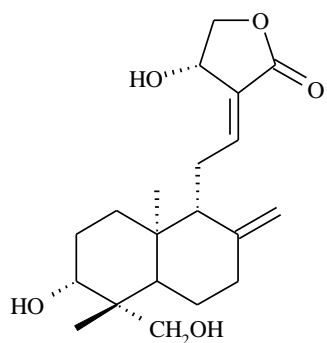
Roots of *Asparagus recemosus* are well known in Ayurveda as galactagogue, and preparations based on these are used in cases of threatened abortion. Shatavarin-I (**31**), a component of this plant material has been shown to produce a specific and competitive block of oxytocin induced contraction of rat, guinea pig and rabbit uteri *in situ*<sup>33</sup>. The active compounds of *Andrographis paniculata* and *Picrorrhiza kurroa* has been identified as andrographolide (**32**), and picrosides (picroside-I (**33**), picroside – II (**34**)) respectively.<sup>34</sup>

Seeds of *Butea frondosa* constitute an important component of Ayurvedic anthelmintic preparations. Palasonin (**35**) has been identified as the active principle from *B. frondosa*.<sup>28</sup> *Psoralea corylifolia* seed powder is having much value in Ayurveda for the treatment of vitiligo and other skin diseases. Psoralen (**36**), the active principle from this plant stimulates formation of melanin.<sup>34</sup> Bakuchiol (**37**), another active component has been shown to possess potent antibacterial activity, and is effective against psoriasis, a skin disease.<sup>35,36</sup> The use of neem (*Azadirachta indica*) in the treatment of fevers is available in folklore literature and researchers have isolated gedunin (**38**), an antimalarial agent. This tetranor-triterpene showed good *in-vitro* activity against certain clones of the causative organism *Plasmodium falsiparum*.<sup>37</sup>

Among the alkaloids isolated from *Tylophora indica*, tylophorine<sup>38,39</sup> (**39**) has a paralyzing action on the heart muscle, but a stimulating action on the muscles of the blood vessels and was found to show significant anticancer activity.<sup>40,41</sup> Cyclostachine A (**40**) was isolated from *Piper trichostachyon* and was found to have anticonvulsant, antifungal, antibacterial and anti-TB activities.<sup>42,43</sup> Himachalol (**41**) and centdarol (**42**) isolated from *Cedrus deodara* exhibited pronounced spasmolytic activity.<sup>44</sup> Curcumine (**43**) is a major constituent of *Curcuma longa*, which was reported to possess local as well as systemic anti-inflammatory property.<sup>44</sup>



**33. R = Cinnamoyl**  
**34. R = Vaniloyl**



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