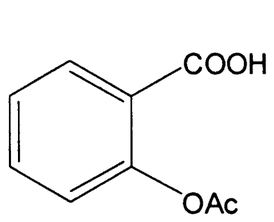
GENERAL INTRODUCTION AND OBJECTIVE

Plants have been used as medicines for thousands of years.[1] These medicines initially took the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations.[1,2] The specific plants to be used and the methods of application for particular ailments were passed down through oral history. Eventually information regarding medicinal plants was recorded. In more recent history, the use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century.[1,3] Drug discovery from medicinal plants led to the isolation of early drugs such as aspirin (**1**), cocaine **(2),** codeine **(3),** digitoxin **(4),** and quinine **(5),** in addition to morphine **(6)**, of which some are still in use.[1,4,5]



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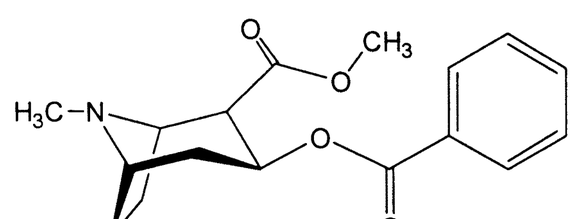

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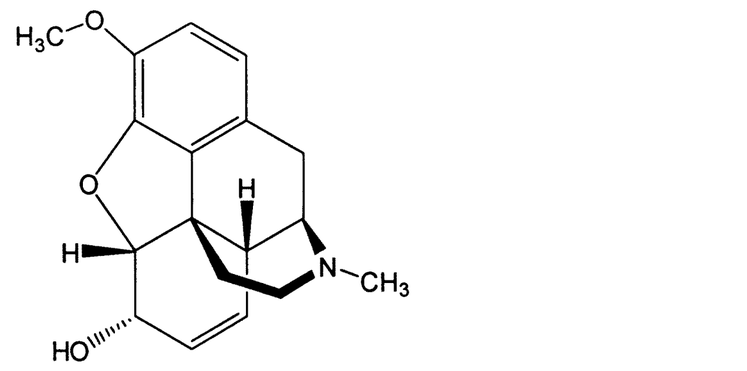

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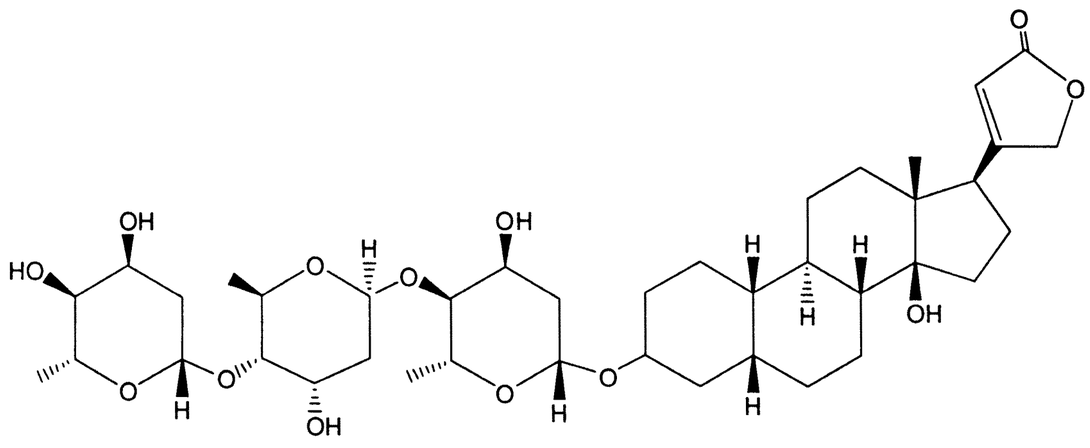

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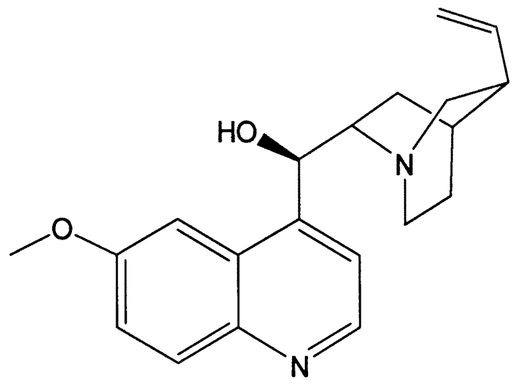
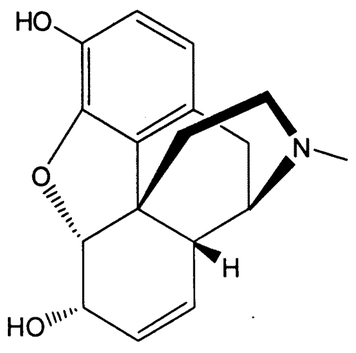
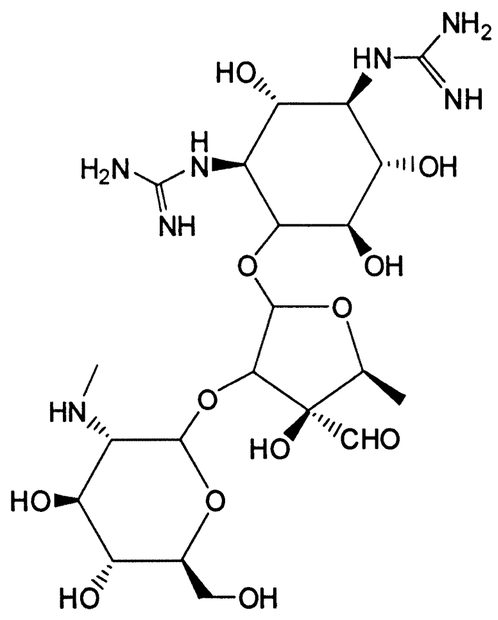




The discovery of antibacterial filtrate "penicillin" by Fleming in 1928, re-isolation and clinical studies by Chain, Florey, and co-workers in the early 1940s, and commercialization of synthetic penicillins revolutionized drug discovery research.[6-9] Following the success of penicillin, drug companies and research groups soon assembled large microorganism culture collections in order to discover new antibiotics. The output from the early years of this antibiotic research was prolific and included examples such as streptomycin (**7**), chloramphenicol (**8**), chlortetracycline (**9**), cephalosporin C (**10**) and erythromycin (**11**).[1,4,8,9] All of these compounds, or derivatives thereof, are still in use as drugs today.



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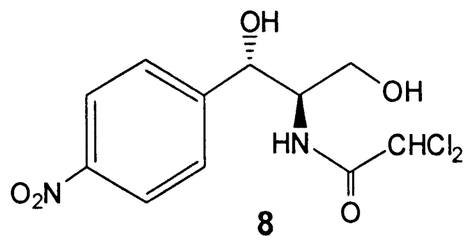

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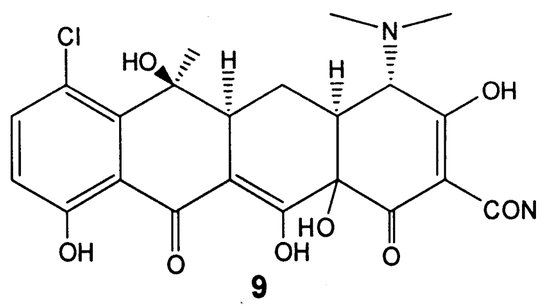

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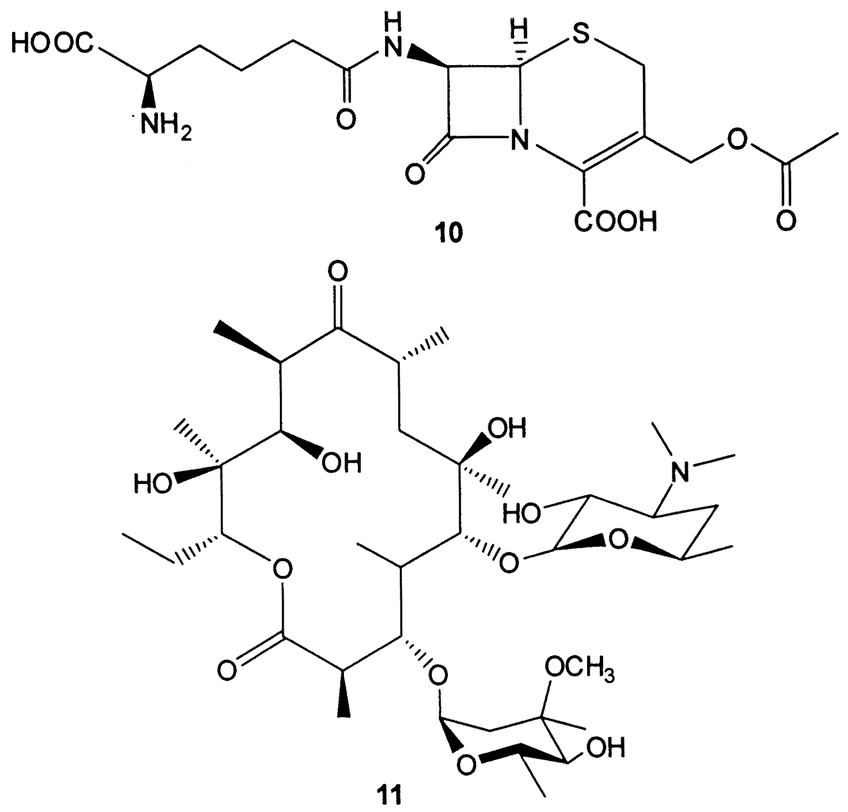

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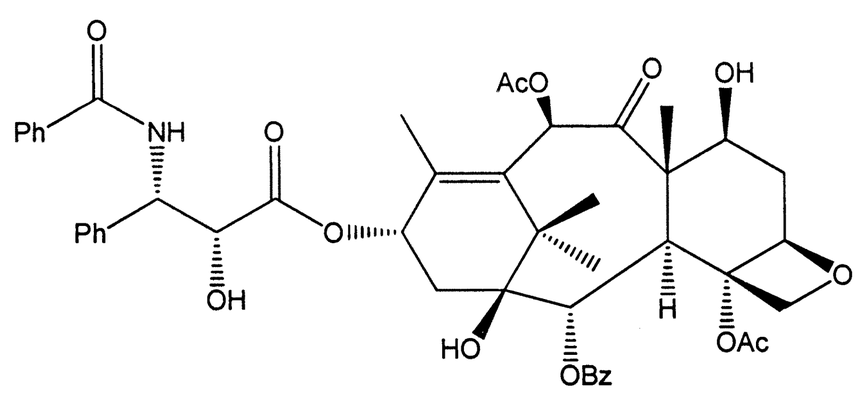
The subject of plant chemistry was revolutionized after the Second World War through the development of a range of sophisticated instruments and techniques for isolation and characterization of plant secondary metabolites. These analytical and spectroscopic methods have resulted into rapid identification of several kinds of natural product from plants which have led to the discovery of new drug candidates. Isolation and characterization of pharmacologically active compounds from medicinal plants continue today. Some possible sources of natural products include plants, marine organisms, microbes and fungi. Of the approximately 250,000 higher species of plants it is estimated that only 5-15% has been investigated for natural products.[6] Marine organisms are abundant in the oceans, which cover more than 70% of the Earth's surface.[6] Also, research suggests that less than 1% of bacterial species and less than 5% of fungal species are currently known.[7] Therefore, it is important that natural product chemistry continues to explore natural resources in search of new natural products.

Despite competition from other drug discovery methods, natural products are still providing their fair share of new clinical candidates and drugs. It is interesting to note that 6 out of the top 20 pharmaceutical prescription drugs dispensed in 1996 were natural products and that over 50% of the top 20 drugs could be linked to natural product research.[10] The isolation and use of natural products such as

digoxin, morphine and quinine has resulted in replacing the plant extracts used with single chemical entities. In order to expand the range of natural compounds, alternative methods such as biotechnology, biotransformation, fungal cultures and chemical synthesis are used for the production of natural products. Chemical modification of phytochemicals into biologically active and commercially exploited natural compounds is considered as one of the easier and cheaper alternative to fulfill the world demands. Interest in natural product research is strong and can be attributed to several factors. First, unmet therapeutic needs, second, remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites, third, utility of bioactive natural products as biochemical and molecular probes, fourth, development of novel and sensitive techniques to isolate, purify and structurally characterize the active constituents and sixth, advance in solving the demand for supply of complex natural products.

At present, about 80% of the world's population relies predominantly on plants and plant extracts for health care.[8] About 25 % of the more important prescriptions are based on plant derived drugs.[8] The clinical applications of isolated secondary metabolites such as taxol (**12**), etoposide (**13**) and artemisinin (**14**) have helped to revive an interest in higher plants as sources of new drugs.[9] Among these medicinal plants, *Taxus wallichiana*, *Lonicera japonica*, *Rosa damascena* and *Holarrhena antidydenterica* are well reputed due to their use in tradition system of medicines and source of modern drugs.



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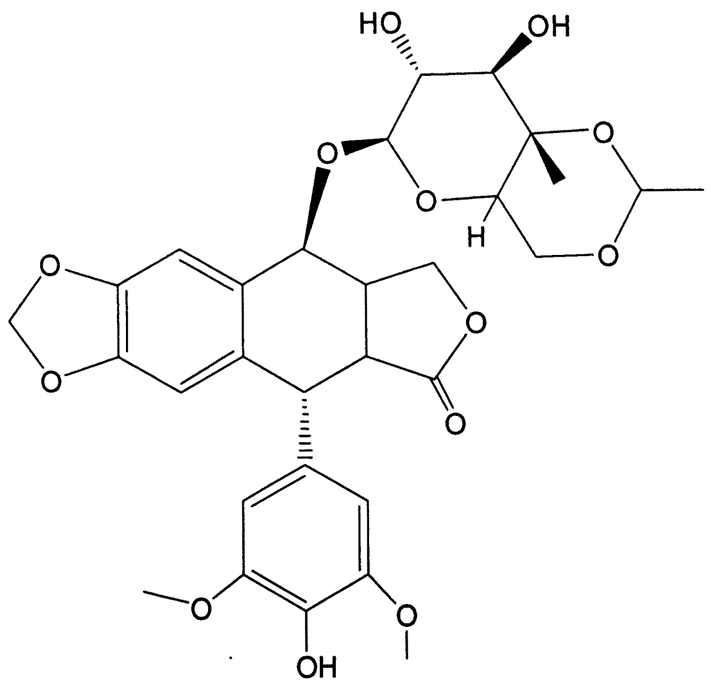

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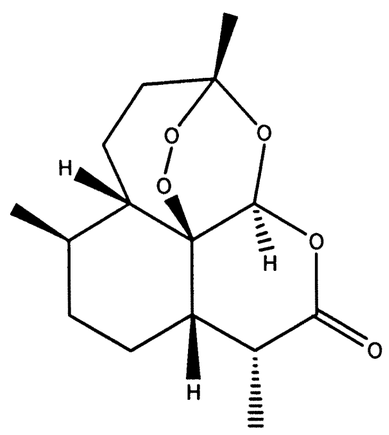

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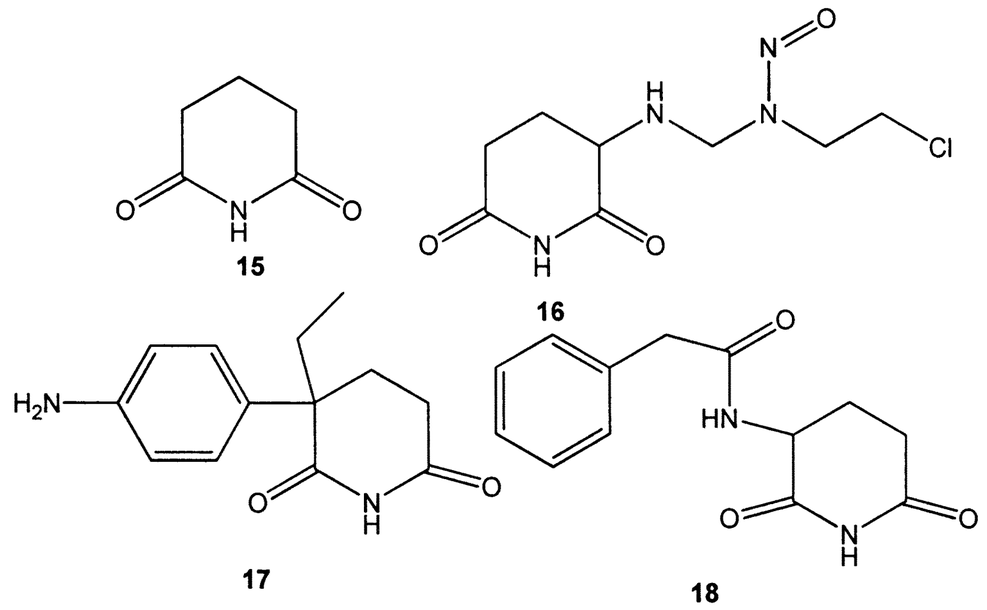
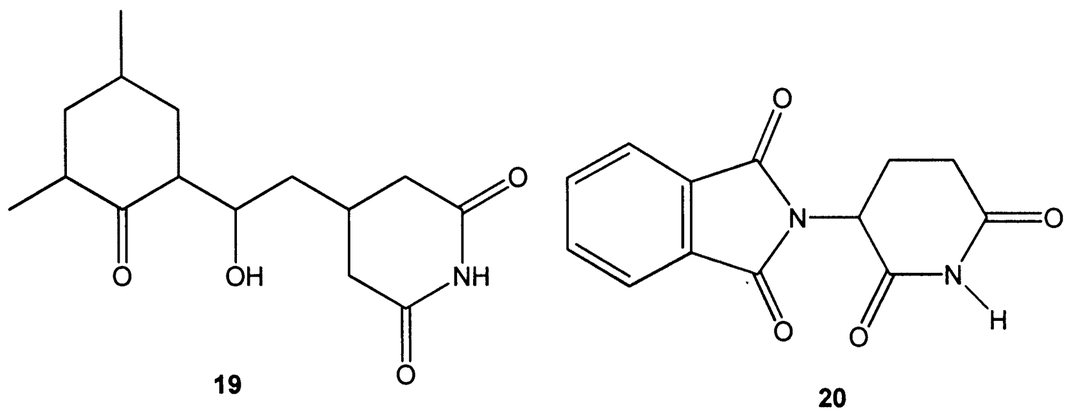
Modern approaches to understand the action of plant constituents all the time rely on careful structural characterization that is predominantly done by UV, IR, NMR and mass spectroscopy. Therefore, without any question natural products chemistry, especially phytochemistry, has proven to be the single most successful approach in finding new medicines.

The number of cyclic imides have been reported from plant sources and synthetically prepared due to their wide biological activities. Cyclic imide is an important functionality which has been found to maintain significant biological activity. Among these imides, glutarimide (2,6-piperidinedione, **15**) is a structural part of a number of natural product molecules with interesting biochemical activity such as antibacterial, antiviral or cytotoxic activity.[11] A general synthetic procedure for the preparation of glutarimide derivatives therefore is of interest to many natural products chemists. It is suggested that glutarimide moiety with the intact imide group (OC-NH-CO) and substituted at α or β position in the ring, is acting as the carrier molecule (vector), which transports biologically active substituents (functional groups) through cell membranes. Several glutarimide derivatives have been reported to possess significant anticancer activity. For example, PCNU [λ-(chloroethyl)-3-(2,6-piperidinedione)-1-nitrosourea, **16**] can easily cross the blood-brain barrier, and it shows activity against brain tumors;[11]

aminoglutethimide (**17**) is a strong inhibitor of steroid biogenesis and is used in the treatment of metastatic breast cancer;[12] and antineoplaston A10 (*N*-phenylacetyl-*R*-aminoglutarimide, **18**), which has recently been introduced into experimental chemotherapy, has a remarkable anticancer activity, particularly against brain tumors, and it shows very low toxicity.[13,14]



Glutarimide is also a component of newly synthesized antibiotics which exert antiviral and antifungal activity.[15,16] Cycloheximide (**19**), the best known member of glutarimide antibiotics, is a very strong inhibitor of protein synthesis.[17] Among different glutarimide analogues thalidomide (**20**) is mostly studied due to its prominent therapeutic effect on leprosy and cancers.[18] This indicates that the biological activity of these drugs is determined by the specific hydrogen bonding between glutarimide and other molecules in biological systems. Thus, it amply justifies the need to do further study on the synthesis glutarimide analogues for their biological activities.



Keeping in view the importance of bioactive molecules as mentioned above, the research work was envisaged to carry out in two parts as given hereunder-

Part A: This deals with the phytochemical investigations of some important medicinal plants and constitutes the four chapters (Chapters 1-4) of the dissertation. The plants selected for these studies are-

1. *Taxus wallichiana* Zucc.
2. *Lonicera japonica* Thunb.
3. *Holarrhena antidysenterica* (L.) Wall.
4. *Rosa damascena* Mill.

Part B: This deals with the synthetic studies towards biologically active glutarimide analogues and constitutes Chapter-5 of the dissertation.

Each chapter describes introduction and review of literature followed by results and discussion, and experimental section. References are given at the end of the chapter.

Chapter-1 deals with the phytochemical investigation of *Taxus wallichiana* which involves isolation and characterization of compounds, screening of endophytic fungi of plant for production of active principles i.e. paclitaxel, baccatin III and 10-DAB III, development of HPTLC and UPLC-ESI-QTOF-MS/MS methods for determination of taxanes and phenolics in the plant.

Chapter-2 deals with the phytochemical investigation of *Lonicera japonica* which includes isolation and characterization of new and known compounds, assessment of antioxidant and immunomodulatory activities, GC-MS determination of volatile constituents of flowers, development of HPTLC and UPLC-ESI-QTOF-MS/MS methods for determination of phenolics, iridoids and saponins in the plant.

Chapter-3 deals with the phytochemical investigation of *Rosa damascena* which includes GC-MS determination of essential oil constituents of flowers, isolation and characterization of new and known compounds from spent (marc) flowers, assessment of antioxidant activity, and development of HPTLC, HPLC

and UPLC-ESI-QTOF-MS/MS methods for determination of phenolics in the plant.

Chapter-4 deals with the phytochemical investigation of *Holarrhena antidysenterica* which includes isolation and characterization of new and known compounds, assessment of antioxidant activity, and development of HPTLC method for determination of conessine and ESI-QTOF-MS/MS methods for determination of steroidal alkaloids in the plant.

Chapter-5 deals with the synthetic studies on glutarimide analogues which includes synthesis of glutarimide, 3-aminoglutarimide and thalidomide, assessment of immunomodulatory activities.

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