Chapter 1

Introduction

1.1 Introduction

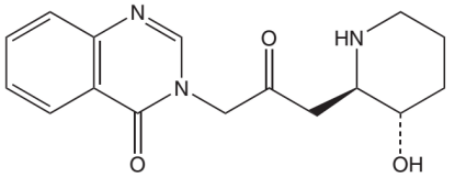
Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound.[1]

Heterocyclic compounds are classified into aromatic and aliphatic. The aromatic heterocyclic compounds are those which have a heteroatom in the ring and behave similar to benzene in some of their properties. The aliphatic heterocycles in contrast, are the cyclic analogues of amines, ethers, thio ethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring.

Heterocyclic compounds constitute major portion of the currently approved FDA drug. Over 80% of top small molecule drugs by US retail sales in 2010 contain at least one heterocyclic fragment in their structures.[2] One of the reasons is high occurrence of sulfur, oxygen, and especially nitrogen-containing rings in drug molecules. An identification of an effective therapeutic treatment in the field of drug research is largely based on mimicking nature by "fooling" it in a very subtle way. Heterocyclic compounds are the key motifs in wide range of natural products such as vitamins, carbohydrates, nucleic and amino acids and medicinal chemistry often engage in stimulating such natural motifs.[3]

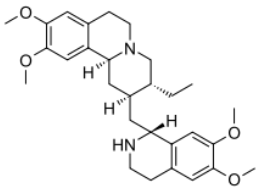
History of heterocyclic compounds and their use as therapeutics.

Heterocycles have been used in medicines since the beginning of written records. A Chinese scholar-emperor Shen Nung, in 2735 B.C., wrote of the herb Ch'ang Shan as beneficial in treating fevers.[4] It was later found to contain dichroins, for example, beta–dichroine **Figure 1.1**



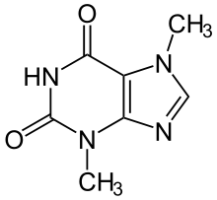
beta-dichroine

Figure 1.1Beta–dichroine



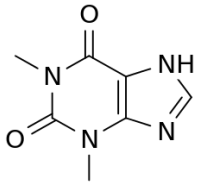
Emetine

anti-protozoal



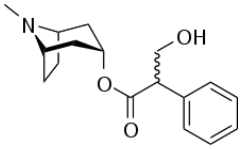
Theobromine

vasodilator, diuretic, heart stimulant



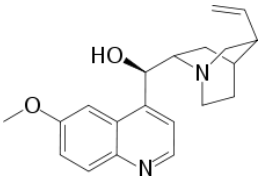
Theophyline

asthma, chronic obstructive pulmonary disease (COPD)



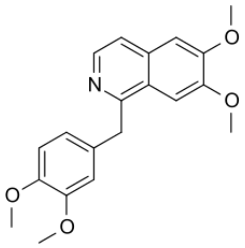
Atropine

bradycardia, hyperhidrosis



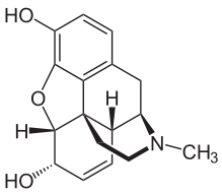
Quinine

anti-pyretic, antiarrhythmic



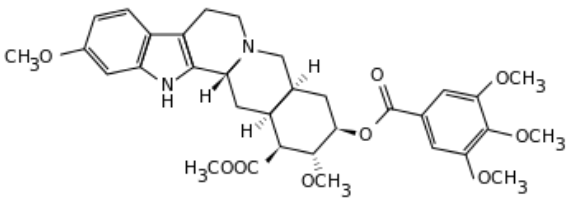
Papaverine

antispasmodic, coronary vasodilator, e rectile dysfunction



Morphine

analgesic drug,



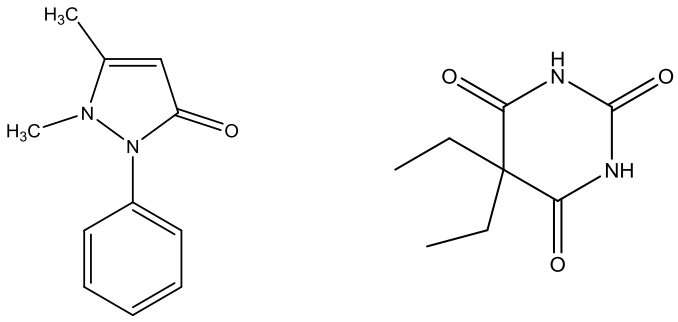
Reserpine

anti-psychotic , anti-hypertensive

Figure 1.2 heterocyclic drugs isolated from natural products

Another example of ancient usage of a heterocyclic compound is opium. Opium was imported from Greece by the Egyptians before the war of Troy, which was waged in approximately 1200 B.C [5] Many natural drugs such as emetine, the obromine, theophyline, atropine, quinine, papaverine, reserpine, morphine **(Figure 1.2**).[6,7,8,9]

The first synthetic heterocyclic compound is believed to be Antipyrine. In the year 1885 Knorr was granted a patent for the synthesis of antipyrine.[10]



Antipyrine Diethylbarbituric acid

Figure. 1.3 Antipyrine & Diethylbarbituric acid – early synthesised heterocyclic compounds.

Another class of early synthetic drugs is derivatives of barbituric acid. Diethylbarbituric acid was among the first to be marketed as a barbituric acid. Diethylbarbituric acid was also known as barbital, gardenal & malonal.[11] In early nineteen century Phenobarbital introduced by Bayer pharmaceutical is important till date as it is used in the treatment of epilepsy.[12] Synthetic heterocycles have widespread therapeutic uses such as anti-bacterial, anti-fungal, anti-mycobacterial, trypanocidal, anti-HIV activity, anti-leishmanial agents, genotoxic, anti-tubercular, anti-malarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, anti-depressant, anti-tumoral, anthelmintic andinsecticidal agents.[13,14,15,16,17,18,19]

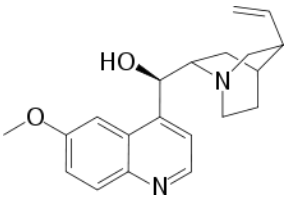
1.2 History of quinine, discovery and use.

Peruvian Indians used to chew on cinchona bark, but they barely knew its constituents. Later Alphonse Laveran, Ronald Ross, Battista Grassi, and others were able to identify the malaria parasite and link the transmission of malaria to mosquitoes in the year 1880s and 1890s.[20] It was really surprising that Cinchona bark was used for the treatment of malaria prior to the understanding of the mosquito cycle. In Europe Cinchona bark was introduced as a treatment for the ague in the early 17th century by Jesuit priests returning from Peru.

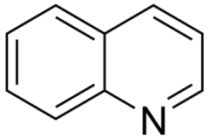
Young French chemists, Pierre Pelletier and Joseph Caventou, isolated the alkaloids quinine and cinchonine from cinchona bark.[20] Indeed, what is remarkable about malarial fevers is that two herbal treatments, cinchona bark and qinghao, were used to treat malaria effectively for hundreds of years prior to the understanding of the mosquito cycle.

1.3 Quinuclidine

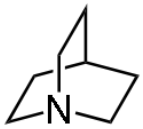
Quinuclidine is a bicyclic heterocyclic compound; it is found in bark of cinchona tree and isolated by alkaloid extraction.[21] Quinine contains two major ring systems: 1) aromatic ring system quinoline and 2) bicyclic quinuclidine (**Figure 1.4**).



Quinine



Quinoline



Bicyclic quinuclidine

Figure 1.4 Structure of quinine and its constituents quinoline and quinuclidine

Quinine is a white crystalline alkaloid with bitter taste. It is useful because of anti-pyretic, anti-malarial, analgesic, anti-flamatory properties. Quinine occurs naturally in

the bark of cinchona trees and can also be synthesised in the laboratory. Quinine was the first effective western treatment of malaria caused by *Plasmodium falciparum*.[22] Quinine is also known to arthritis, and cramps in legs. Quinine is also useful in preparation of beverages. In Canada and Italy quinine is used in the preparation of carbonated chinotto beverages. In Scotland United Kingdom, Australia, New Zealand, South Africa and Egypt it is used as an ingredient in Schweppes and other tonic water mixed drink called 'dry lemon'. In Uruguay and Argentina, quinine is used as an ingredient of Pepsico Inc. Toic water named Paso de los Toros.

1.4 Quinuclidine based drug

1.4.1 Palonosetron

Palonosetron **(Figure 1.5**) is a 5-HT_3 antagonist used in the prevention and treatment of Chemotherapy-Induced Nausea and Vomiting (CINV).[23] It is the only drug of its class approved by the U.S. Food and Drug Administration (US-FDA) which can control nausea and vomiting which appears for 24h after the first dose of chemotherapy.

It is an anti-nauseant and anti-emetic agent. It is highly selective serotonin 5-HT_3 receptor antagonist. The serotonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery, and centrally in the chemoreceptor trigger zone of the area postrema. Intake of chemotherapeutics will release the serotonin from enterochromaffin cells which are situated in small intestine. Serotonin secretion causes the degenerative changes in GI (gastrointestinal) tract. The serotonin then stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.

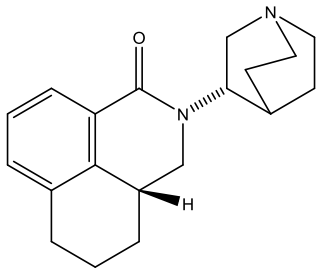


Figure 1.5 Palonosetron5-HT$_3$ antagonist

Table1.1 List of company manufacturing Palonosetron and brand name

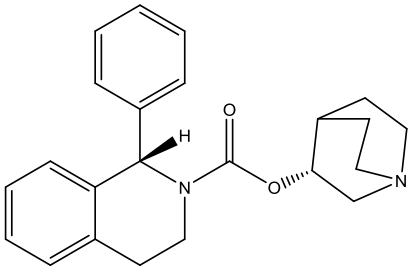
Name	Company
Jiouting	Jiuyuan gene engineering
Onicit	Pfizer
Palnox	Glenmark
Paloxi	Kalbe
Palzen	Dr. Reddy's
Themiset	Themis medicare
Zhirou	Chia tai tianqing

Probable mechanism of Palonosetron

Palonosetron inhibits 5-HT$_3$receptor which is present in the periphery of GI tract and centrally in medullary chemoreceptor zone. It inhibits visceral afferent stimulation of the vomiting centre, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone. It has been hypothesized that palonosetron's potency and long plasma half-life may contribute to its observed efficacy in preventing delayed nausea and vomiting caused by moderately emetogenic cancer chemotherapy.

1.4.2 Solifenacin

Solifenacin **(Figure 1.6)** is competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion.



Solifenacin

Figure 1.6 Solifenacin muscarinic acetylcholine receptor antagonist

Table1.2 List of company manufacturing Solifenacin and brand name

Name	Company
Vesicare	Astellas Pharma Technologies, Inc
Vesicare	Cardinal Health
Vesicare	Astellas Pharma Canada Inc
Vesicare	Physicians Total Care, Inc

Probable mechanism of Solifenacin

Solifenacin is muscarinic acetylcholine receptor antagonist. Acetylcholine binds with M_3 receptor which plays an important role in contraction of smooth muscle. Restricting the binding of Solifenacin to Acetylcholine, the drug reduces the smooth muscle tone in bladder and as a result of that large volume of urine can be held by bladder.

1.4.3 Cevimeline

Cevimeline (Figure 1.7) is a cholinergic agonist and it binds to muscarinic receptors. Insufficient dosage of muscarinic agonists can increase secretion of exocrine glands (salivary and sweat glands) and increase tone of the smooth muscle in the gastrointestinal and urinary tracts

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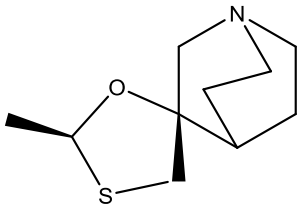


Figure: 1.7 Cevimeline M1 & M3 receptor agonist

Table 1.3 List of company manufacturing Cevimeline and brand name

Name	Company
Cevimeline	Ranbaxy Pharmaceuticals Inc
Evoxac	STAT Rx USA LLC
Evoxac	Daiichi Sankyo Pharma Development

Probable mechanism of Cevimeline

Cevimeline binds with M1 and M3 receptor. M1 receptor commonly present in exocrine glands such as salivary glands and sweat. Activation of Muscarinic receptor such as M1 will results increase in secretion form salivary glands which smooth's muscle contraction and increase glandular secretion.

Table 1.4 Quinuclidine based drugs their route of administration and strength

Name of Drug	Form	Route of drug administration	Strength
Palonosetron	Capsule	Oral	0.5mg
	Gelatine Capsule	Oral	0.5mg
	Injection	Intravenous	0.075mg/ 1.5ml
	Injection	Intravenous	0.25mg/5ml
	Solution	Intravenous	0.25mg
Solifenacin	Tablet (film coated)	Oral	5mg
	Tablet (film coated)	Oral	10mg
	Tablet	Oral	5mg
	Tablet	Oral	10mg
Cevimeline	Capsule	Oral	30 mg

1.5 Quinuclidinone and its use in different disease.

1.5.1 Use of quinuclidinone derivatives in muscarinic receptor activity

Muscarinic receptors are the receptor sites for the neurotransmitter of the parasympathetic autonomic nervous system. Their primary location is on the post-synaptic cell membranes of smooth muscle, cardiac muscle and glandular tissue at the ends of parasympathetic nerve pathways. It is responsible for mediating the physiological effect of parasympathetic nerve activity such as cardiac slowing, vasodilatation. It also helps in secretion from exocrine glands such as salivary glands, mucosal glands present in airways, lachrymal and gastric acid secretion. It is also

involved in contraction of a broad range of smooth muscles urethra, detrusor muscle of the bladder, gastro-intestinal tract bronchioles, gall bladder and ducts, seminal vesicles, circular muscle and vas deferens.[24]

Quinuclidinone derivatives are reported as a potent muscarinic agonist. They act as centrally active muscarinic agonists and are a potential remedy for Alzheimer's disease (AD)**.**[25,26] Attempts have also been made to develop novel subtype selective muscarinic antagonists; M_2 receptor-selectivedrugs might be beneficial in the treatment of heart disorders[27] and possibly also in the therapy of AD by acting as antagonists at auto receptors in the central nervous system (CNS).[28] Furthermore, the use of antagonists with selectivity for M_1 and M_3 receptors in the trachea has been suggested in the treatment of lung disorders,[29] and antagonists with selectivity for muscarinic receptors in the bladder would be useful in the treatment of incontinence.[30,31] Nordvall et al found 3-(2-benzofuranyl)quinuclidin-2-ene as most active derivative as shown in (**Figure 1.8)**

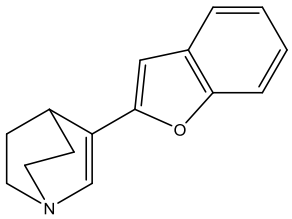


Figure 1.8 3-(2-Benzofuranyl)quinuclidin-2-ene active derivative for the treatment of incontinence

Authors further extended their study and observed that affinity might be obtained by making the ring system more electron rich and binding molecule to the receptor region which is lipophilic and sterically constrained. [32]

Researcher Gunilla et al form Kabi pharmacia had filed a patent. They had prepared quinuclidinone based derivatives which are active CNS and PNS agents.[33] They had evaluated the affinity of these compounds for muscarinic receptor sub type in the

cerebral cortex, parotid gland. Quinuclidinylbenzilate (well known muscarinic receptor agonist) was used as reference. They found these derivatives can be used for the diseases or disorder such as bradycardia, peptic ulcer, schizophrenia, insomnia and glaucoma dementia and incontinence.[33]

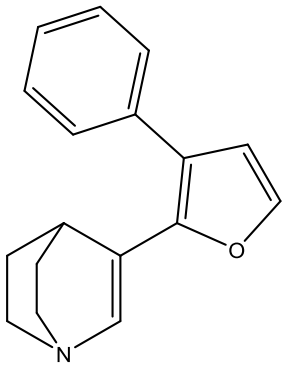


Figure 1.9 3-(Phenylfuran-2-yl)-1-azabicyclo[2.2.2]oct-2-one potent CNS agent

1.5.2 Use of quinuclidinone Irritable Bowel Syndrome (IBS)

Muscarinic agents also possess analgesic activity, hence these derivatives can also be used in irritable bowel syndrome. Irritable bowel syndrome is patho physiological condition of the gastrointestinal tract, defined by a characteristic symptomatology of altered bowel habits, such as diarrhea, constipation, or alternating episodes of both, frequently accompanied by abdominal pain. [34] Mitch et al had synthesised quinuclidinone based compounds which were possess potent excellent candidate for evaluation as a potential treatment of IBS.[35]

O-alkynyloxime moiety linked with quinuclidine is a potentially useful muscarinic pharmacophore that can be exploited for the design of muscarinic agonists.[36]

1.5.3 Use of quinuclidinone as diuretic agents

Some [(2-Substituted and 2,2-disubstituted vinyl) aryloxy]acetic acids derivatives which observed to be saluretic and diuretic agents. Among them quinuclidinone based derivatives exhibited significant activity.[37]

1.5.4 Use of quinuclidinone in potent anti-histaminic and anti-depressant.

Frank et al synthesised tricyclic quinuclidylidenes compounds. Which showed potent anti-histaminic, anti-depressant, and anti-cholinergic as well as anti-serotonin properties in laboratory animals and in human.[38]

1.5.5 Use of quinuclidinone in potent α7 nicotinic receptor

Neuronal nicotinic acetylcholine receptors are members of the ligand-gated ion channel receptor super family and may play vital roles such as modulating neurotransmission, cognition, sensory gating, and anxiety because of its distribution and abundance in the CNS, the α7 nicotinic receptor is strongly believed to be involved in some of these conditions. Several derivatives of quinuclidinone were reported as potent α7 agonists for the treatment of schizophrenia.[39]

Methylquinuclidine (MQN) showed lower potency of α-7 agonists and its α3β4 activity was lost whereas quinuclidinone (QN-O) or quinuclidinol (QN-OH) also resulted in a loss of activity at α3β4 receptors and reduced efficacy at α7receptors as compared to quinuclidine **Figure: 1.10**.[40, 41]

Quinuclidine (QN) is a full agonist of α7 receptors and a partial agonist of α3β4 receptors with an efficacy of 46% as compared to that of ACh (1) at α7 receptors and is a key motif seen in numerous selective agonists.[42]

The spiro-oxazolidinone are unique and it can be useful for the understanding the function of the α7 nicotinic agonists for treating neurodegenerative diseases.[43, 44, 45] Novel spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one] were prepared which serve as a potent full agonist at the rat α7 nicotinic receptor.[46]

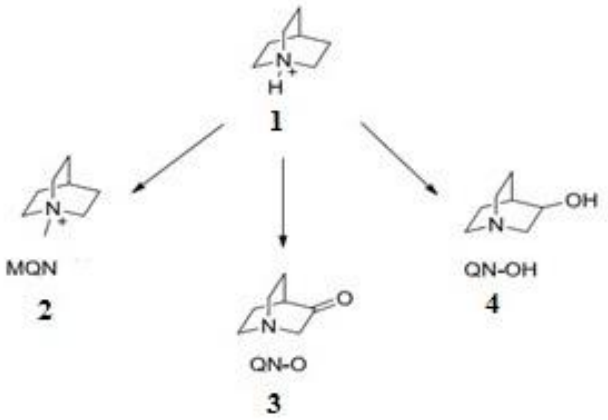


Figure 1.10 Methylquinuclidine, quinuclidinone, quinuclidinol, quinuclidine as α7 agonist

A US patent reported use of novel spiro-quinuclidinyl derivatives as shown in **Figure 1.11** were used for the treatment of diseases associated with central nervous system.[47] These synthesised compounds can be used for the Alzheimer's disease, mild cognitive impairment, senility, dementia, Down's syndrome and Parkinson's disease.

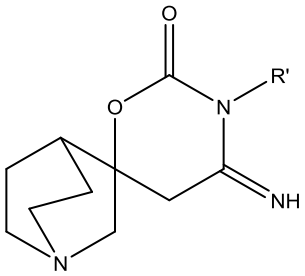


Figure 1.11 Spiro-quinuclidinyl derivatives used for the treatment CNS diseases

Spiro-imidazoline quinuclidines were synthesised and used for pharmacophore elucidation. Molecular docking study was performed and the interactions of benzylidene anabaseine congeners with AChBPs were studied.[47] They found that binding affinity is primarily mediated via electrostatic interactions (hydrogen-bond, π-cation and π-π) and hydrophobic interactions as well. Some of the compounds were observed to bind with a high affinity to α7nAChR receptor.[48]

Novel quinuclidine, quinazoline and tropane based spiro amide ligands were synthesised.[49] Quinuclidineamide derivatives were found to have good affinity in nM concentration for α7nAChR.

Aquinuclidine-based nicotinic acetylcholine receptor-nAChR ligand, designated as AR-R17779 26 [(-)-spiro(1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one)]**(Figure 1.12)** were reported in US Patent.[50]

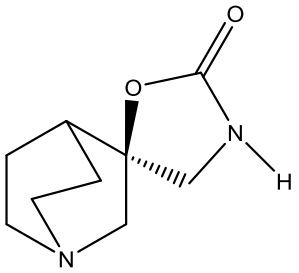
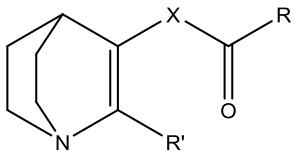


Figure 1.12 ((-)-Spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one]) potent α7 agonist

The derivative AR-R17779, is a potent full agonist (efficacy =96%) at the rat α7 nicotinic receptor subtype and exhibits remarkable selectivity for α7 (Ki= 92 nM) receptor over α4β2 (Ki = 16,000 nM). AR-R17779 26 has been reported to enhance learning and memory function in rats.[51]

In another patent 2-(arylalkyl)-1-azabicycloalkanes were substituted with amide, urea, carbamate, thioamide, thiourea derivatives of quinuclidinone.[52] The compounds were active against nAChRs specifically α-7 subtype. These derivatives (**Figure 1.13)** can be used for modulating neurotransmission and hence for the treatment of inflammation and auto immune disorders.



Where X= O or N

R'=H or substituted ethyl benzene derivatives.

Figure 1.13 3-Subsitituted-2-(arylalkyl)-1-azabicycloalkanes neurotransmission modulator

These compounds are useful in modulating neurotransmission and for the treatment of disorder which is associated with dysfunction of central and autonomic nervous system.

1.5.6 Use of quinuclidinone as anti-inflammatory agent

Quinuclidinone derivatives are important anti-inflammatory agent. 2-Substituted benzhydryl-3-quinuclidinols have considerable anti-inflammatory property. [53] Substituted fused and bridged bicyclic compounds were patented as therapeutic agents.[54] It was observed that quinuclidinone derivatives can inhibit the Protein Kinase C isozymes (PKC) which plays an important role in inflammatory and reperfusion injury. It is believed that PKC blocks platelet aggregation and activates platelet activating factor which is basically a neutrophil activating agent. PKC inhibitor shows inhibition of neutrophil activation and chemotactic migration and also neutrophil degranulation and release of proteolytic enzyme release of proteloytic enzyme and reactive oxygen intermediates. Thus PKC inhibitors block most significant mechanism of pathogenesis which is associated with reperfusion injury and inflammation.[54]

1.5.7 Use of quinuclidinone as anti-arrhythmic agent

To increase the oral bioavailability of anti-arrhythmic agents quaternary ammonium derivatives 2- and 3-substituted l-azoniabicyclo[2.2.2]octanes (quinuclidinium salts)were synthesised.[54] It was also observed that 2-substituted quinuclidines can

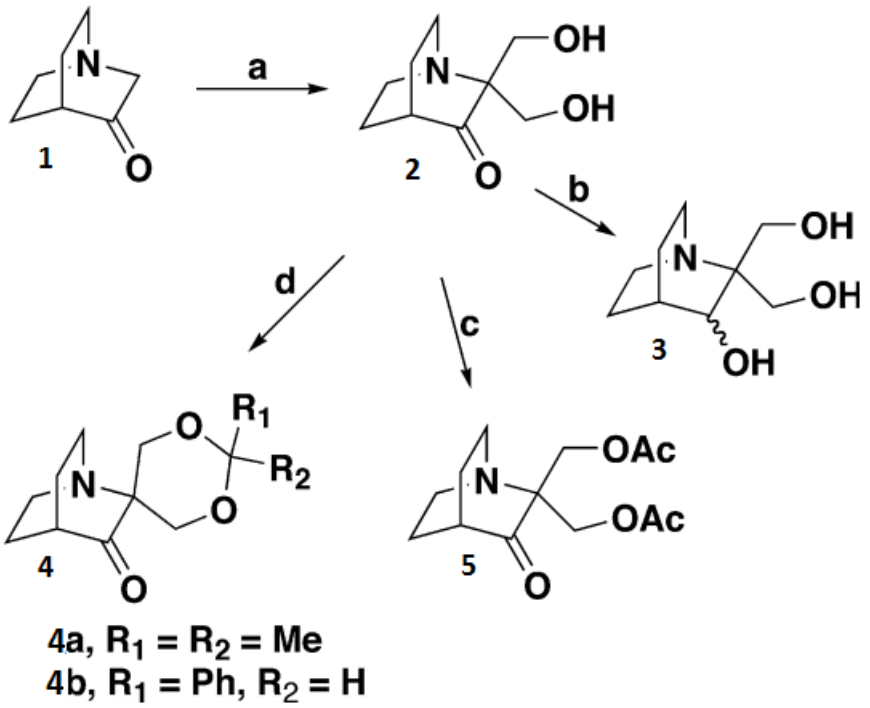
accommodate the sites responsible for class I and class III activity where as 3-substituted quinuclidine shows selective class III activity [55] N-[3R-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide (ABBF) were identified as selective agonist for the α-7 receptor (Ki = 62 nM).[55] that did not show agonist activity at the other nAChR subtypes. It acts as a 5-HT_3 antagonist (Ki= 60 nM) at higher concentrations at the α3β4, α4β2 and muscle type nAChRs.[56]

1.5.8 Use of quinuclidinone as anticancer agents

Cancer remains a major cause of mortality worldwide. The *in vitro* cell migration assay of synthesised quinuclidine based analogues showed that eight analogues were found to potent angiogenesis inhibitors at 10μM concentration. It was determined to be nontoxic by colony formation assay. Compound which showed potent anti-angiogenic ENOX1inhibitor were also identified.[57]

Survival rates of five year for some cancers have significantly improved in the past two decades while those of other cancers, such as lung cancer and pancreatic remain low.[58] The major form of cancer treatment is chemotherapy, it alone or combined with radiation is the usual treatment of choice for lung cancer. Different theories have been proposed for the cause of cancer and several strategies have been formulated and examined for combating the disease. According to Malki et al. analogue of quinuclidinone can provide an excellent scaffold for novel anti-cancer agents with improved safety profile.[59] It was observed that quinuclidinone derivatives induce apoptosis in human breast cancer cells via reduced expression level of Bcl-2, Bcl-XL and increased mitochondrial apoptotic pathways by activating the release of cytochrome C.[59] Cancer is treated by cytotoxic agents by inducing apoptosis.[60] The derivatives of this molecule may have a selective mode of action as they are

structurally unique, and yet have a great deal of known chemistry upon which to prepare analogs. These analogs are (2, 2-bis (hydroxymethyl)-1-azabicyclo [2,2,2] octan-3-one**2**) and its derivatives. These derivatives belong to class of small heterocyclic compounds which restore function of mutant p53 (p53 is a tumour suppressor gene, which is found frequently mutated in a wide variety of cancers).

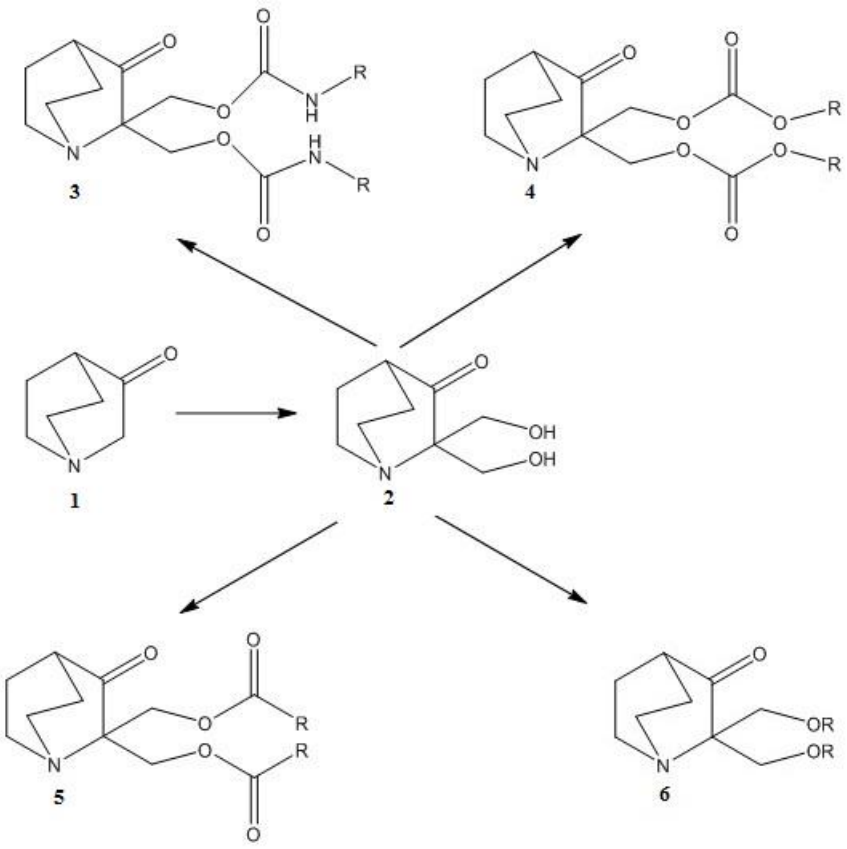


Scheme: 1.1 Synthetic scheme for quinuclidione based acetals and diacetals.

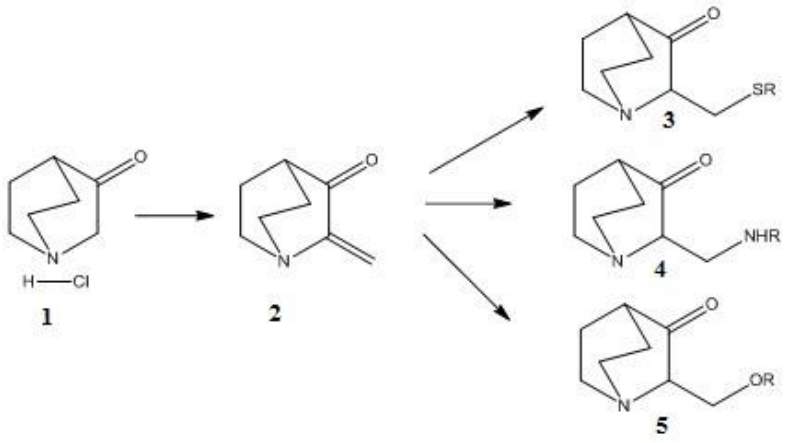
According to literature **2** is reported to induce conformational change in the structure of p53, leading to apoptosis.[61,62] Malki et. al. synthesised acetals and di-acetates derivatives which were found to be potent in decreasing cancer cell viability. While parent compound showed no activity in MTT assay. In the first step quinuclidinone **1** was converted to **2** by two successive aldol condensation. Derivative **2** showed tremendous activity, interesting result found in MTT assay less than 10% cells remains viable. Triol **3** is formed when ketone is reduced in presence of $LiAlH_4$. Complete loss of activity was observed. Diacetate **5** is formed from diol **2**. This derivative **5** showed similar activity as **1**. Compounds **4a** and **4b** both showed

comparable activity as lead compound **2**, this observation indicates free hydroxyl group is not required for the activity. Among all derivatives, the acetal derivatives having benzylidine and acetonide were selected for the further study. 20 to 1000 µM concentration were prepared and screened for MTT assay using H1299 cell line. Both compounds showed % of cell survival in dose dependent manner. Growth Inhibition of 50% (GI_{50}) of compound **4a** was found to be 17.2 µM and 19.2 µM for compound **4b**. γ- Irradiation is local treatment which focuses only specific area of body. On the other hand chemotherapy makes systemic attack on whole body to treat cancer. In presence of γ- irradiation decrease in GI_{50} was observed, for compound **4a** it was found 4.49 µM where as for **4b** it was found as 4.74 µM. This synthesis of quinuclidinone derivative leads to highly potent and selective newer anticancer agents.

In agreement with Malki et. al.'s observations, Westman et. al. claimed that quinuclidinone derivative can be used for disease related to p53 malfunctioning. These compounds are believed to have very favourable ADME properties due to their higher ClogP value which allow a high cellular uptake. Thus these derivatives can be used in hyper-proliferative disease such as cancer and auto immune disease and heart disease. They had used human- His175 lung carcinoma cell line that carries tetracycline-regulated mutant p53 was used for study of anti-proliferative and apoptosis inducing effect of synthesised derivative.[63]



Scheme 1.2 General scheme for the derivative derived from 2, 2-bis (hydroxymethyl)-1-azabicyclo [2,2,2] octan-3-one



Scheme: 1.3 General scheme synthesis of derivative derived from 2-methylenequinuclidin-3-one.

Substituted fused and bridged bicyclic derivatives of quinuclidinone can inhibit the Protein Kinase C isozymes (PKC).[63] PKC activation has been implicated in several human diseases. PKC also plays important role in neoplasm. Cells transforms along with oncogenes (Ras, Sis, Ereb, Abl) elevate levels of Diacylglycerol (DAG) which thought to activate PKC. Several research articles showed that in certain tumours like breast and lung & colon carcinoma increased expression of PKC found. Various chemotherapeutics drugs such as cisplatin and doxorubicin are found as found as PKC inhibitor.

PKC also plays important role in inflammatory and reperfusion injury. It is believed that PKC blocks platelet aggregation and activates platelet activating factor which is basically a neutrophil activating agent. PKC inhibitor shows inhibition of neutrophil activation and chemotactic migration and also neutrophil degranulation and release of proteolyticenzyme and reactive oxygen intermediates.

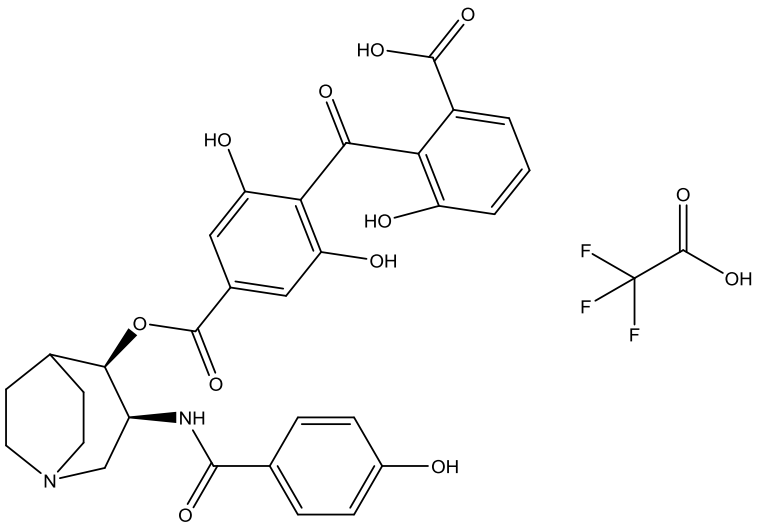
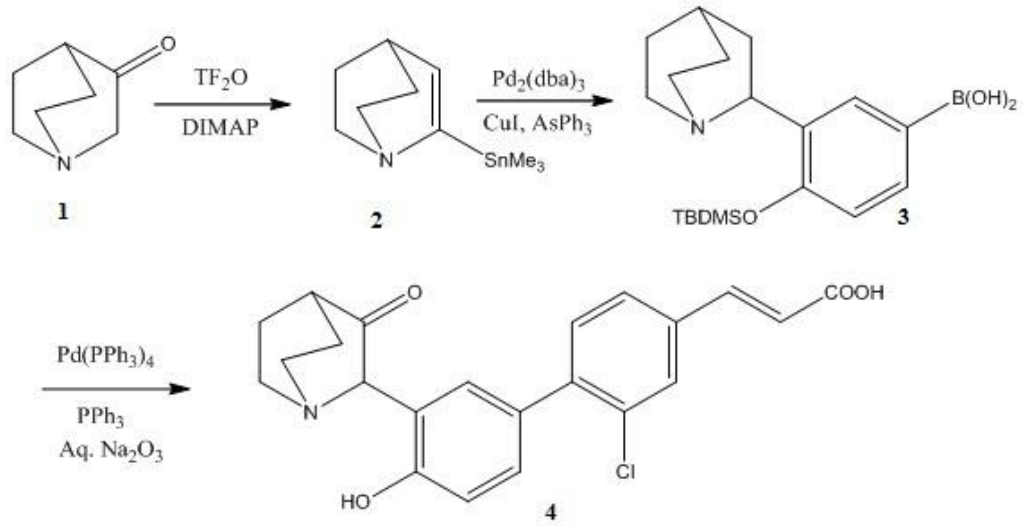


Figure 1.14 Fused and bridged bicyclic compounds as therapeutic as potent PKC inhibitor.

Thus PKC is thought to believe to block most significant mechanism of pathogenesis which is associated with reperfusion injury and inflammation.[64]

Quinuclidine derivatives can be used for leukaemia or other forms of cancer as they were inhibitors of apoptosis or apoptosis by cell arrest (Scheme 1.4). [65]



Scheme: 1.4 Synthesis cyclic derivatives as inhibitors of apoptosis.

1.5.9 Use of Quinuclidinone as 5-HT inhibitor

A US patent was filed for discovery of quinuclidinone derivatives that can be used for effective treatment of disorder associated with imbalance of 5-HT (serotonin), by inhibition or modulation of selective 5-HT activities. These derivatives can be useful for the treatment of migraine, disorder of memory and learning.[66]

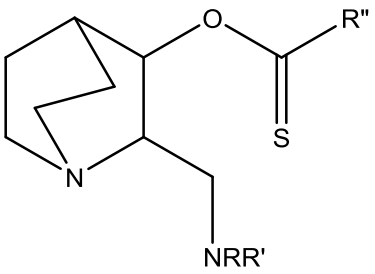


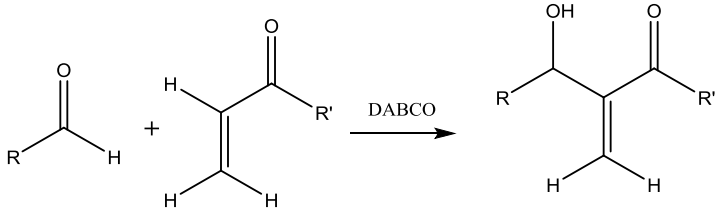
Figure: 1.15 General structure of 5-HT (serotonin) inhibitor

1.6 Quinuclidinone based catalysis

The first cinchona based asymmetric reaction was published by Bredig and Fiske as early in 1912.[67,68] These two German chemists reported the addition of HCN to benzaldehyde is accelerated by the pseudo-enantiomeric alkaloids, quinine and quinidine and the resulting cyanohydrins are optically active and having opposite chirality. However, the optical yields achieved were in therange of < 10% ee. Pracejus was first to obtain useful levels of enantioselectivity (74% ee) by using O-acetylquinine as a catalyst (1 mol%)in the addition of methanol to phenylmethylketene, affording (-)-α-phenyl methylpropionate.[69 , 70] Since their pioneering studies, the popularity of cinchona derivatives in asymmetric catalysis has increased considerably. During the late 1980s and early 1990s, quite successful examples in terms of the catalytic activity and enantioselectivity have been reported, where the symmetry was induced by cinchona alkaloids. Thus, now a days, cinchona alkaloids and their derivatives are classified as the most privileged organic chirality inducers.

1.6.1 Baylis-Hillman reaction

Baylis-Hillman reaction is coupling of an activated alkene derivative with an aldehyde. This reaction is catalyzed by a tertiary amine. In other words it is an exquisite reaction as simple starting materials are converted into densely functionalized products in a catalytic process without generating waste or by products .[71,72,73,74]



Scheme 1.5 Baylis-Hillman reaction

Baylis and Hillman, three amine catalysts were tested, DABCO **1**, quinuclidine **2**, and pyrrocoline **3**, but their relative efficiencies were not clearly stated (Figure1.16).[75]

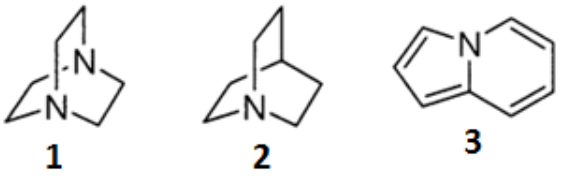


Figure 1.16 Catalyst used for Baylis-Hillman reaction

Correlation between the basicity of the base and its reactivity was examined and following order of reactivity was established with pKa's of the conjugate acids: Quinuclidine (11.3), 3-hydroxyquinuclidine (9.9), DABCO (8.7), 3-acetoxyquinuclidine (9.3), 3-chloroquinuclidine (8.9), andquinuclidinone (7.2).[76]

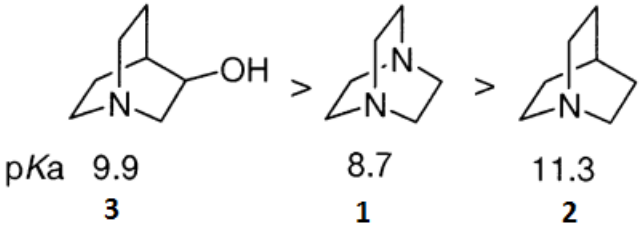


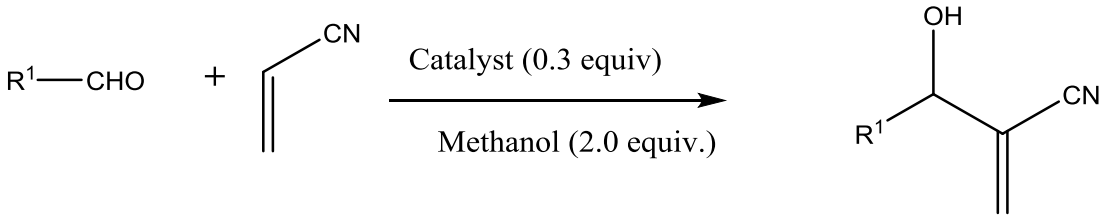
Figure 1.17 Basicity of the base used in Baylis-Hillman reaction

quinuclidine-based catalysts were used in the Baylis−Hillman reaction 3-hydroxyquinuclidine **3** have considerably faster rates[77,78] compare DABCO **1** and quinuclidine **2**.[79,80] Indeed, 3-hydroxyquinuclidine was regarded as the optimum catalyst for the Baylis-Hillman reaction.[75]

1.6.2 Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillman reaction is one of the most versatile carbon-carbon bond-forming reactions. As the reaction has advantages like non-metal catalysis,

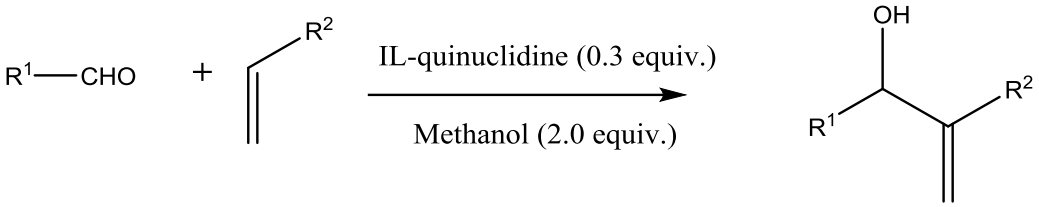
compatibility of multiple functional groups, mild conditions, it has drawn much attention in the field of modern organic chemistry. [70, 81,82,83,84,85]



Scheme: 1.8 Morita-Baylis-Hillman reaction

Various catalyst used in Morita-Baylis-Hillman reaction. Some of them are DABCO[86,87,88] DMAP[89,90] DBU[91,92] PPh_3[93], PBu_3[94,95,96] PPh2Me[97,98].

Xueling et al found application of Ionic Liquid (IL) supported quinuclidinone catalyst for catalysis of Morita-Baylis-Hillman reactions.[99] Protic solvent were found more suitable as compare to aprotic solvents.



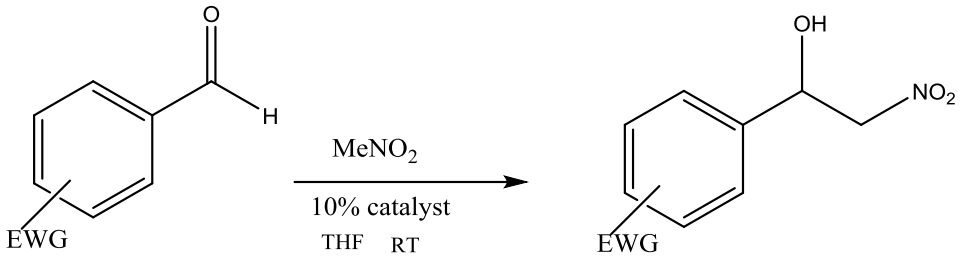
Scheme: 1.9 Use of IL-supported quinuclidinone in Morita-Baylis-Hillman reactions

In the same reaction condition Xueling et al found that Ionic Liquid IL-supported quinuclidinone showed more activity compare to DABCO and 3-quinuclidinone. Synthesised catalyst offers easy product separation and could be recycled for at least six times without too much loss of activity providing a highly efficient alternative for the reaction.

1.6.3 Use of quinuclidinone in asymmetric Henry reaction

The reaction between a carbonyl compound and a nitroalkane, known as the Henry (or nitroaldol) reaction.[100,101] This reaction was used for the construction of complex molecule.

Use of Cinchona derivatives as asymmetric catalysts for the reaction between activated aromatic aldehydes and nitromethane were also reported.[102]



Scheme: 1.7 Cinchona derivatives as asymmetric catalysts for activated aromatic aldehydes and nitromethane

Authors also carried out the following reaction in which benzaldehyde[103] was reacted with nitromethane in the presence of 20% catalyst in DMF or THF to yield nitroalcohol in 62-67% ee. Use of other solvent such as MDC and toluene will result in racemic mixture.

1.7 Conclusion

Quinuclidinone ring system is found in many natural products. It has also been used in synthesis of some catalysts which are useful in asymmetric reactions such as aldol reaction, Henry and Aza Henry reaction, Diels-Alder reaction etc. It is used to prepare various therapeutically potent derivatives. Several FDA approved drugs like Azasetron, Benzoclidine, Palonosetron, Solifenacin, Quinupramine contains Quinuclidinone as main component. In view of these facts we thought of designing relatively simple and safer route for the synthesis of 3-quinuclidinone hydrochloride and pharmaceutically important derivatives of quinuclidinones.

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