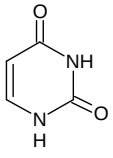
Chapter-I

Heterocyclic Compounds: General Introduction

Heterocyclic compounds are the major class of organic substrates that contain at least two different types of atoms in the ring. The mixed rings without any carbon atoms are inorganic heterocyclics and ring with one or more carbon atoms and heteroatoms (N, O & S) are organic heterocyclics. Over half of all known chemical compounds incorporate at least one heterocyclic moiety which makes them the largest class of compounds in organic chemistry. The presence of heteroatom gives heterocyclic compounds many significant physical and chemical properties. Heterocycles are abundant in nature[1] and are of great importance to human life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and pigments.[2,3] Thus these derivatives have attracted considerable attentions in the design of biologically active molecules.[4] The nitrogen containing heterocyclics are synthetically challenging models for a number of physiologically active natural products.[5-7] Modern society is dependent on synthetic heterocycles for many purposes such as drugs, pesticides, dyes, plastics, cosmetics, information storage, solvents, antioxidants and vulcanization accerlators.[8-11] Besides the vast distribution of heterocyclics in natural products, these substrates are also the major components of biological molecules which are without a doubt the most important macromolecules of life and nucleotides.

Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV, antileishmanial, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer, lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, antihelmintic and insecticidal activities.[12-18]

Heterocyclic substrates play an immense role in many biochemical processes[19] and numerous heterocyclic compounds are biosynthesized by plants and animals which are also associated to significant biological properties. *N*-Heterocycles were involved at the very beginning of life in the genesis of DNA and play an essential role in many living systems. The nucleic acid bases are the derivatives of pyrimidine and purine[20] which are found in RNA and DNA in the form of uracil **1.1**, thymine **1.2**, cytosine **1.3**, adenine **1.4** and guanine **1.5**.



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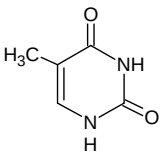

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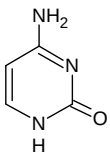

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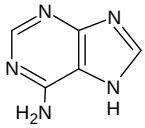

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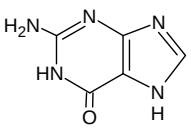
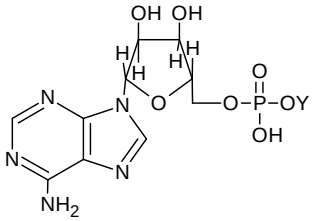


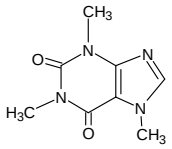
1.5

Adenosine monophosphate (AMP), diphosphate (ADP) and triphosphate[21] (ATP) **1.6** are important participants in energy processes in the living cell. Each of the compounds is composed of the nucleotide base adenine linked to sugar ribose, which is in turn is linked to a linear tail of the one, two or three phosphate group respectively.



1.6

The naturally occurring purines[22] include the alkaloids caffeine **1.7** (found in tea & coffee), theobromine **1.8** and uric acid **1.9**. Caffeine is a bitter white crystalline xanthine derivative that acts as a stimulant drug and a reversible acetylcholinesterase inhibitor.



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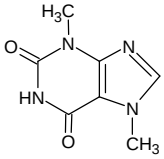

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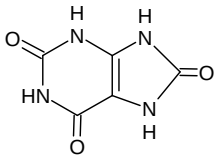
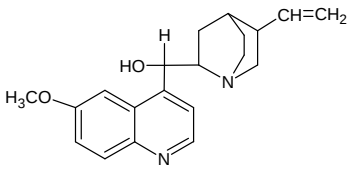


1.9

Quinine **1.10** which is the active component of cinchona bark has been used for several hundred years for the treatment of malaria. Many quinolines like plasmoquine **1.11**, pentaquine **1.12** and chloroquine **1.13**[23,24] have been synthesized to investigate the better antimalarial drug.



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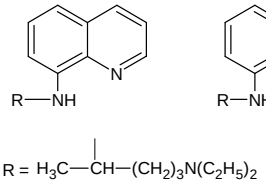

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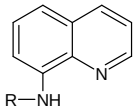

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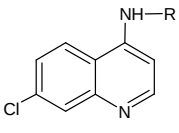
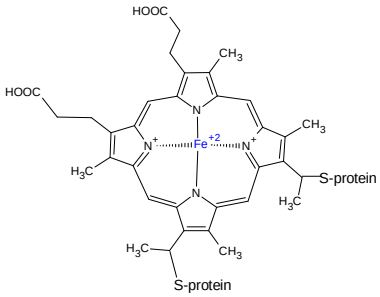


1.13

Heme **1.14** and chlorophyll **1.15** are the derivatives of large porphyrin ring[25-27] which act as the oxygen carriers in plants and animals respectively. These derivatives are also used in the photodynamic therapy for the dermatological diseases such as psoriasis and subcutaneous cancer.[28-30]



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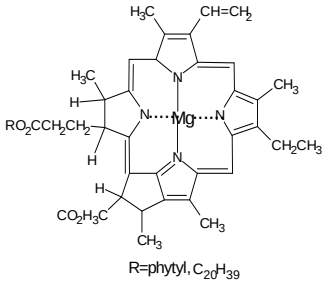
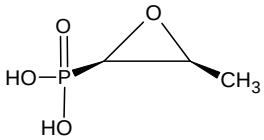


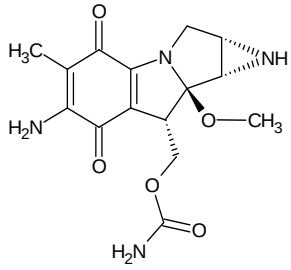
1.15

The naturally occurring compound containing one or more oxirane rings are abundant which include insect juvenile hormones[31-35] that are associated with the promising pharmacological applications. An important synthetic oxirane is fosformycin **1.16** which is used as an antibacterial drug[36] particularly in the treatment of urinary tract infections.



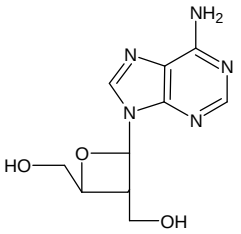
1.16

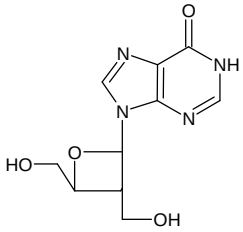
The aziridine derivatives are also employed in plastics, coating and as a curing agent.[37-40] The mitomycin[41] **1.17** is the most well known class of natural product which acts as a antitumor and antibacterial agent.

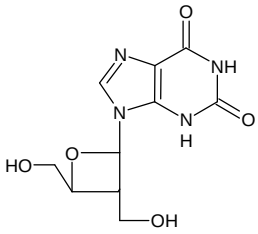


1.17

The synthetic analogs of the antiviral natural product oxetanocin[42] are under investigations for antifungal, anti-inflammatory, anticancer and antiviral activities. Oxetanocines like **1.18**, **1.19**, **1.20**, **1.21** and **1.22** are reported as inhibitor of the human cytomegavirus.[43] Oxetane derivatives are also widely used in polymer manufacturing and in agriculture as herbicides, fungicides and bactericides.

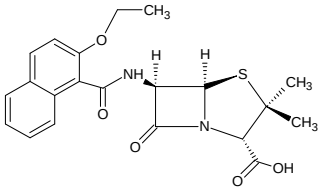


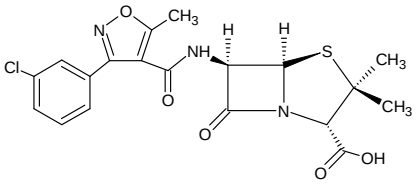




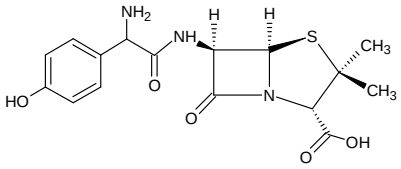
1.18 (R=H) &**1.19** (R=NH_2) **1.20** (R=H) **&1.21** (R=NH_2) **1.22**

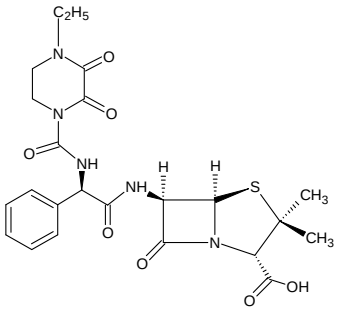
The four membered heterocyclics such as lactum are present in some important antibiotics such as penicillin **1.23**, nafcillin **1.24**, oxacilline **1.25** and amoxicillin **1.26** which are found to be highly significant antibiotics for medicinal purposes.[44-47]





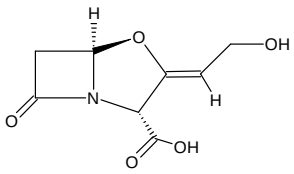
1.23 **1.24**





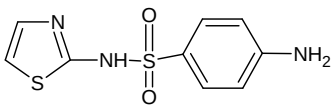
1.25 **1.26**

Clavulanic acid **1.27** produced by *Streptomycin clavuligenus* also contains lactum ring in its chemical structure. It has little or no intrinsic antibacterial activity but it is used to enhance the activity of antibiotics by blocking bacterial beta-lactamases.[48,49]



1.27

Thiazole ring system occurs in thiamine and numerous synthetic drugs, dyes and industrial chemicals. The sulfathiazole **1.28**, thiamine **1.29**, acinitrazole **1.30**, pramipexole **1.31** and cinalukast **1.32** are used as important antimicrobial drugs.



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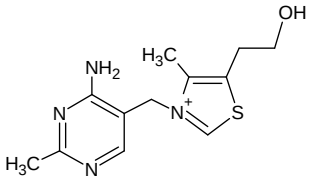

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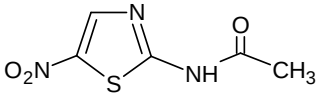

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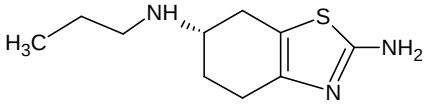

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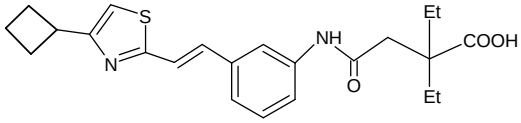
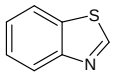


1.32

Benzothiazole **1.33** are known to have many biological behavior such as antimicrobial,[50-54] anticancer,[55-58] anthelmintic[59], antidiabetic[60] activities. Luciferin **1.34** is a compound found in fireflies as a light emitting component. 2-Mercapto-benzothiazoles **1.35** are also used in polymer chemistry, dyes, drugs and accelerators of rubber vulcanization.



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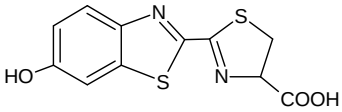

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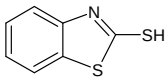
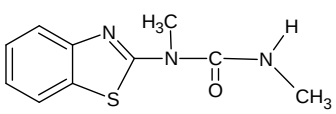


1.35

Methabenzthiazuron **1.36** is used as a herbicide in winter corn crops and also used to control a spectrum of broad leaved weeds and grasses in cereals, legumes, maize, garlic and onions. Thioflavin **1.37** is a dye which is used to visualize and quantify the presence of misfolded protein aggregates called amyloid.[61] Riluzole **1.38** has been utilized to treat amyotrophic lateral sclerosis, it delays the onset of ventilator dependence or tracheostomy in selected patients[62].



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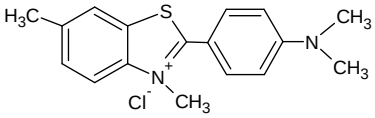

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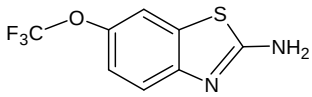
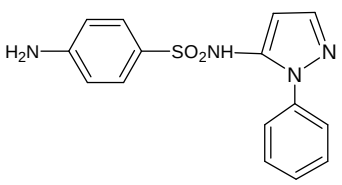


1.38

Pyrazole is an important member of 1,2-azole family in which the direct linking of the two hetero atoms has a very marked effect upon its basicity, making it less basic than imidazole and these are extensively used as useful synthon in organic synthesis.[63-67] It is interesting to note that fused bispyrazole are reported as known pharmacophores.[68] The sulfonamide based pyrazoles like orisul **1.39**, antipyrine[69] **1.40**, butazolidine **1.41** and novalgin[70] **1.42** show significant activities.[71] Many derivatives of pyrazole are

utilized as photosensitizers[72] and tetrazine[73] **1.43** is used as a yellow dye for wool in the textile industry.



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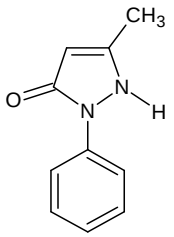

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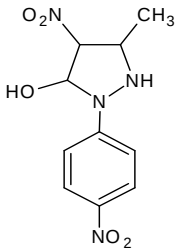

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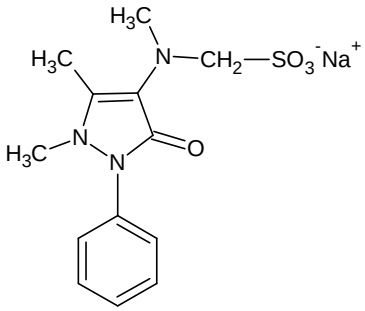

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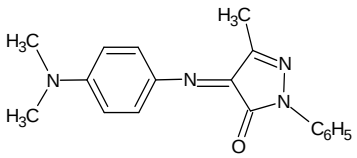
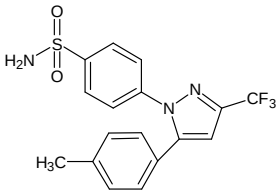


1.43

Celecoxib **1.44**, a pyrazole derivatives and veledecoxib **1.45**, an isoxazole derivatives are widely used as the anti-inflammatory drugs.[74] In addition, a number of pyrazoles exhibit fluorescence characteristics and also act as agrochemical herbicides, fungicides, pesticides and insecticides.[75]



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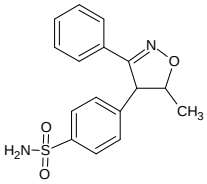
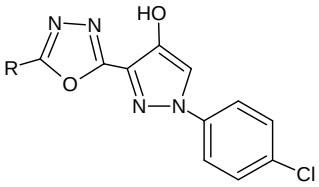


1.45

1,3,4-Oxadiazole and thiadiazole derivatives containg three heteroatoms in the five membered ring are found to exhibit diverse biological activities such as anti-HIV (**1.46)**, anticancer (**1.47)**, insecticidal (**1.48)**, antibacterial (**1.49)**, anti-inflammatory (**1.50)**, antimycotic, analgesic, antipyretic, anticonvulsant (**1.51)**, antifungal (**1.52)** and antituber properties (**1.53)**.



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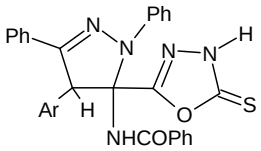

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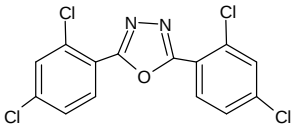

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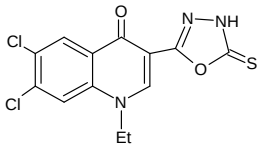

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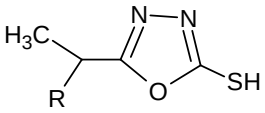

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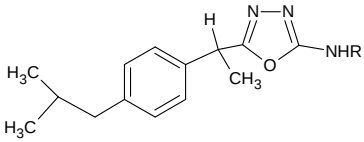

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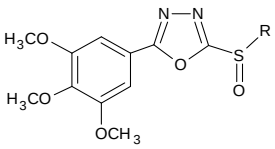

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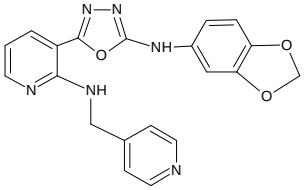
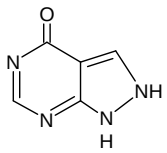


1.53

Imidazoles are essential components of biologically active compounds, including natural products and display a broad range of biological activities,[76] i.e. antibacterial,[77] anticancer,[78] and anti-inflammatory.[79] Allopurinol **1.54** is a synthetic drug which is used primarily to treat hyperuricemia and its complications including chronic gout.[80] Mebendazole **1.55**, thiabendazole **1.56**, albendazole **1.57**, and fenbendazole **1.58** are the broad spectrum antihelmintics agents.[81-83]



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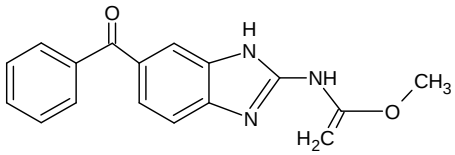

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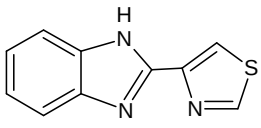

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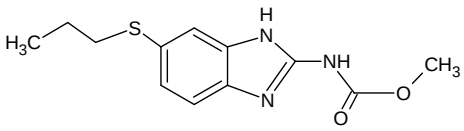

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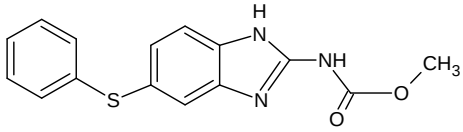
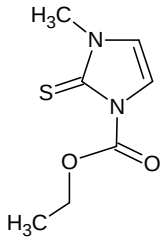


1.58

Carbimazole **1.59** is an important imidazole derivatives which is used to treat hyperthyroidism whereas clotrimazole **1.60**, econazole nitrate **1.61** and ketoconazole **1.62** act as antifungal agents.



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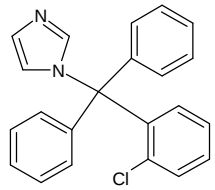

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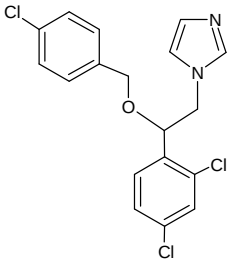

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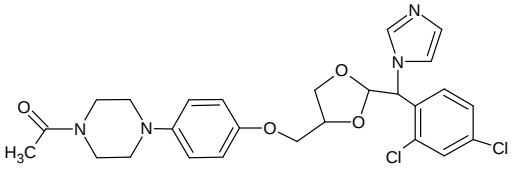
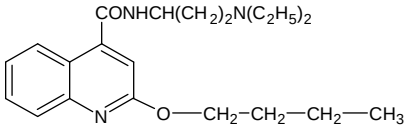


1.62

The pyridine derivatives are also found to exhibit many biological applications. Nupercaine **1.63** is a powerful, but rather toxic, local anesthetic agent and bioform **1.64** has been used for the treatment of gastrointestinal infections. Camptothecin **1.65** an alkanoid from *Camptotheca acuminate* has attracted much interest due to its anticancer properties.



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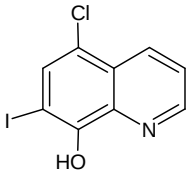
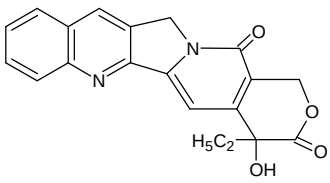
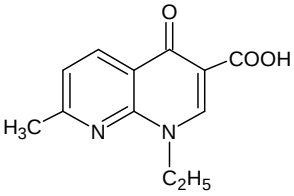


1.64

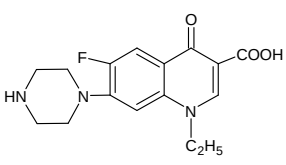


1.65

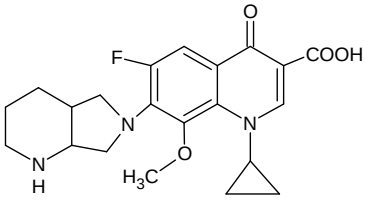
The broad spectrum antibiotics such as nalidixic acid **1.66**,[84] ciprofloxacin **1.67**, moxifloxacin **1.68**, prulifloxacin **1.69**, ofloxacin **1.70** and gemifloxacin **1.71** belongs to the quinolone family.



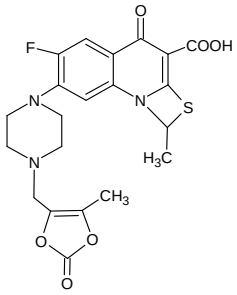
1.66



1.67



1.68



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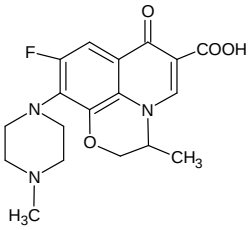
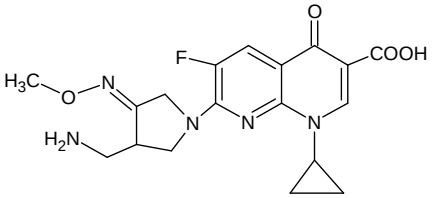
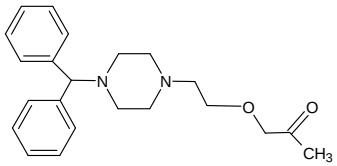


1.70

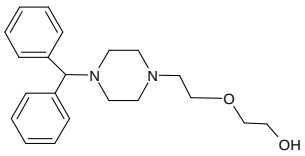


1 .71

Piperazine derivatives such as levocetrizine **1.72**, hydroxyzine **1.73** and niaprazine **1.74** act as the sedative antihistamines.[85, 86]



1.72



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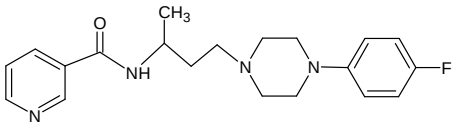
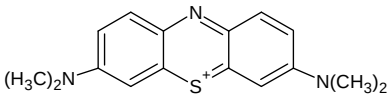


1.74

Phenothiazine **1.75** has been used as the worming and insecticidal agent. Chloropromazine[87] **1.76**, thioridazine **1.77**, promethazine[88] **1.78** and ethopropazine[89] **1.79** are the medicinally useful derivatives.



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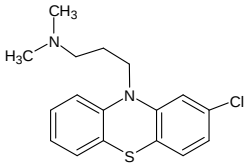

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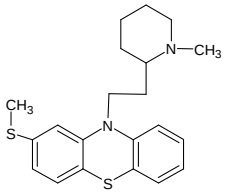

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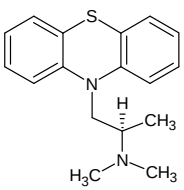
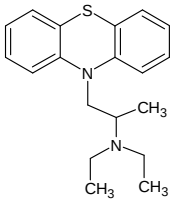
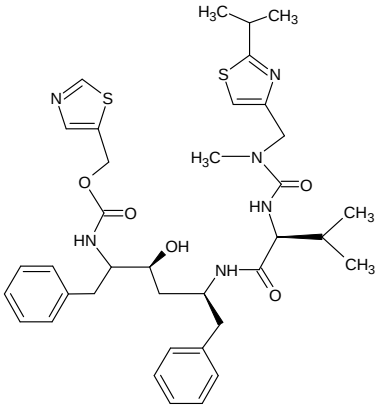


1.78

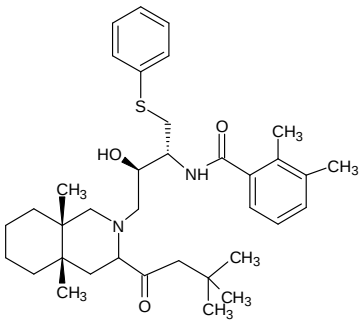


1.79

Ritonavir **1.80** and nelfinavir **1.81** are the antiretroviral drugs which are used to treat HIV and AIDS infections.[90-91]

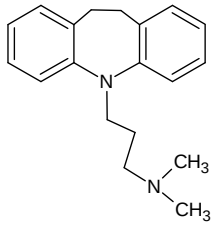


1.80

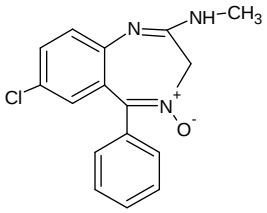


1.81

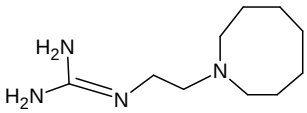
The seven membered heterocyclic compound imipramine **1.82** act as as an antidepressant[92,93] while the compound chlordiazepoxide **1.83**[94,95] has sedative, ammestic, anxiolytic, hypnotic and skeletal muscle relaxant properties. Guanethidine **1.84** is an antihypertensive drug that reduces the release of catecholamines such as norpinephrine.



1.82

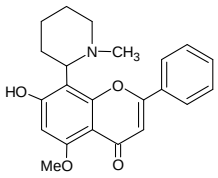


1.83

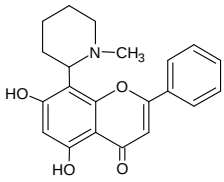


1.84

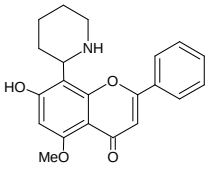
Pyrone are the six membered oxygen heterocyclics which are found in many natural products. Buchenavianine **1.85** is the major alkaloid from the leaves of *B. macrophylla* and *B. capitata*[96]. *O*-Demethylbuchenavianine **1.86**, which is present in both species, showed anti-HIV activity.[97] *N*-Demethylbuchenavianine **1.87** has been obtained from the leaves and fruits of *B. macrophylla*.



1.85



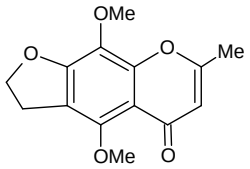
1.86



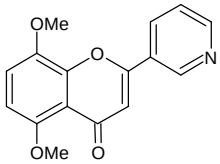
1.87

Khellin **1.88** has been isolated from the fruit of Mediterranean plant, *Ammi visnaga*, possesses a direct relaxing action on muscle and has been used frequently in the treatment of coronary related disease.[98] 5,8-Dimethoxy-2-(3'-pyridyl)-chromone **1.89** was found to be a very active agent as a central nervous system depressant. The

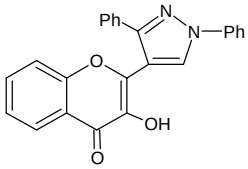
3-hydroxychromone **1.90** bearing a pyrazolyl moiety at C-2 has been tested *in vitro* for its antifungal activity.[99,100]



1.88

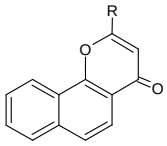


1.89

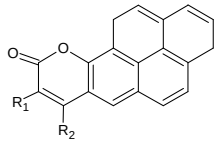


1.90

Some of the biological activities attributed to chromone derivatives include cytotoxic anticancer,[101-103] neuroprotective,[104] HIV-inhibitory,[105] antimicrobial,[106,107] antifungal[108] and antioxidant activities.[109] The 5,6-benzoflavone **1.91** and coumarin **1.92** have been known to exhibit significant activity as the inhibitors of tumor induction by carcinogenic polycyclic aromatic hydrocarbons.[110,111]

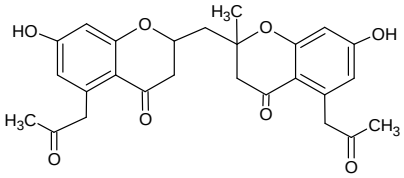


1.91



1.92

The chrobisiamone A **1.93** having antiplasmodial activity has been isolated from the leaves of *Casia siamea*[112] and disodium cromoglycate (DSCG) **1.94** is used in the treatment of bronchial asthma.[113]



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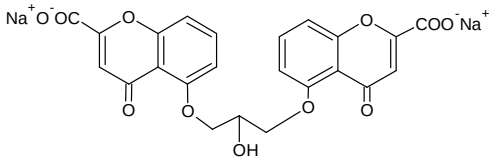
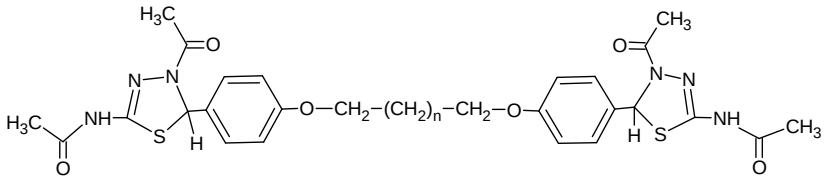


1.94

It is evident from the above literature studies that five membered heterocyclics particularly thiadiazolines, pyrazolines, chromones and related compounds have been the subject of major attraction for the researchers in the area of synthetic organic chemistry. Here, major emphasis has been laid down upon the antibacterial, antifungal, antitubercular, anticancer, antidepressant and anti-inflammatory behaviors of these heterocyclic compounds. It is also clear that very little attention has been paid upon the studies of bisheterocyclic compounds. By considering this aspect in view, the researches have been directed upon the detailed syntheses of new symmetrical bisheterocyclic derivatives.

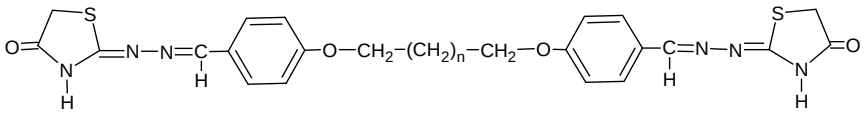
Thus, in the coming chapters we have presented the result of our investigations upon the synthesis and antimicrobial studies of new bisthiadiazolines, bisthiazolidinones, bispyrazolines and bischromones built around the carbon chain of varying lengths.

Chapter-IIa: Synthesis of new 1,3,4-bisthiadiazolines.



n = 0, 1, 2, 3, 4, 6, 8, 10

Chapter-IIb: Synthesis of new 1,3-bisthiazolidinones.



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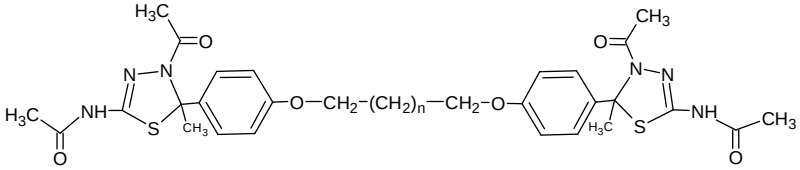
Chapter-IIc: Synthesis of new acetophenone based 1,3,4-bisthiadiazolines.



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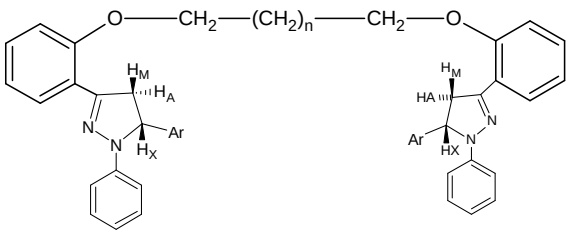
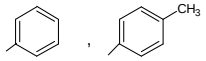
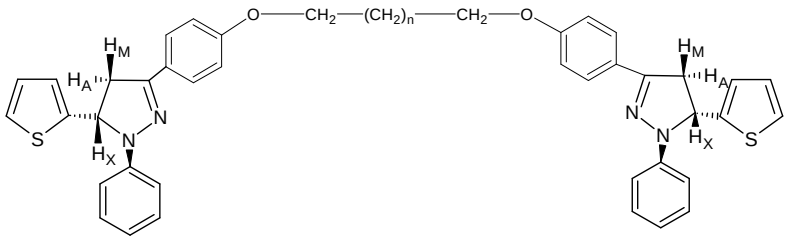
Chapter-IIIa: Synthesis of new 1,3,5-triphenyl-bispyrazolines linked *via* the 3-aryl ring.



Ar = 

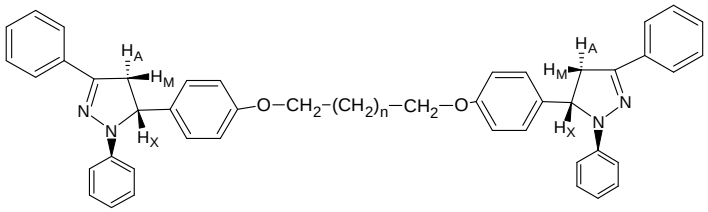
n = 2, 3, 4, 6, 8, 10

Chapter-IIIb: Synthesis of new 1,3-diphenyl-5-thienyl-bispyrazolines linked *via* the 3-aryl ring.



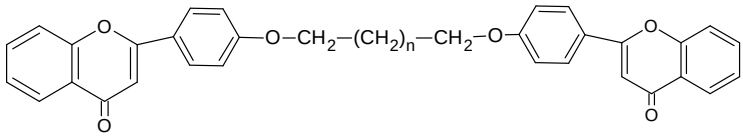
n = 1, 2, 3, 4, 6, 8, 10

Chapter-IIIc: Synthesis of new 1,3,5-triphenyl-bispyrazolines linked *via* the 5-aryl ring.



n = 0, 1, 2, 3, 4, 6, 8, 10

Chapter-IV: Synthesis of new bischromones linked *via* the 2-aryl ring.



n = 0, 1, 2, 3, 4, 6, 8, 10

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