Chapter-1

Introduction

Cyclic organic compounds with at least one hetero atom in the ring structure are known as heterocycles. An excessive number of natural as well as synthetic heterocyclic compounds having a wide range of applications constitute heterocyclic chemistry as one of the largest classes of organic chemistry. Major parts of the living cells are composed of heterocycles that play vital roles in various biochemical processes such as cell metabolism and cell replication. The genetic material DNA and RNA consist of heterocycles; purines and pyrimidines, as the bases. Vitamins, enzymes, chlorophyll and haemoglobin possess heterocyclic core as the active site[1]. Heterocyclic compounds are the major constituent of various drugs including antimalarial, antimicrobial, antidiabetic, antidepressant, antibiotic and anti-HIV agents. Heterocyclic compounds exhibiting bio and chemiluminescent properties are used as fluorescent sensors. They find applications in organic light emitting diodes (OLEDs), optical data carriers and organic conductors. In organic synthesis heterocyclic compounds have been employed as synthetic intermediates, protecting groups and organic catalysts[2].

Heterocycles are the compounds of synthetic interest due to their wide range of applications in biological and medical fields. Nitrogen based heterocyclic compounds are emerging scaffolds in medicinal chemistry due to their diverse pharmacological applications. Industries such as cosmetics, plastics and reprography employ heterocycles as additives or modifiers. Various natural as well as synthetic weed killers, pesticides and rodenticides are found to be heterocyles[3]. For example, (**Fig. 1**) heterocyclic compound 1,3,4-oxadiazolo-(3,2-a)-s-triazin-7-thione **1** is found to be antifungal. Substituted triazolo-pyrimidine derivatives **2** possess significant antibacterial activity. 2-(Hydroxymethyl)-5-phenyl-1,3,4-oxadiazoles **3** exhibited anti-inflammatory properties. Oxadiazole functionalized benzoic acid derivatives **4** are useful as herbicides. 2,4-Dichloro-6-dialkylamino-1,2,5-triazenes **5** are proven to be effective anticonvulsant. 1-Methyl-2[1,3,4-oxadiazol-2(3H)-one-5yl]benzimidazole **6**

is an example for antiallergic drug. Phthalimides containing benzothiazole ring **7** have applications in medicinal chemistry as anticancer agents[4].

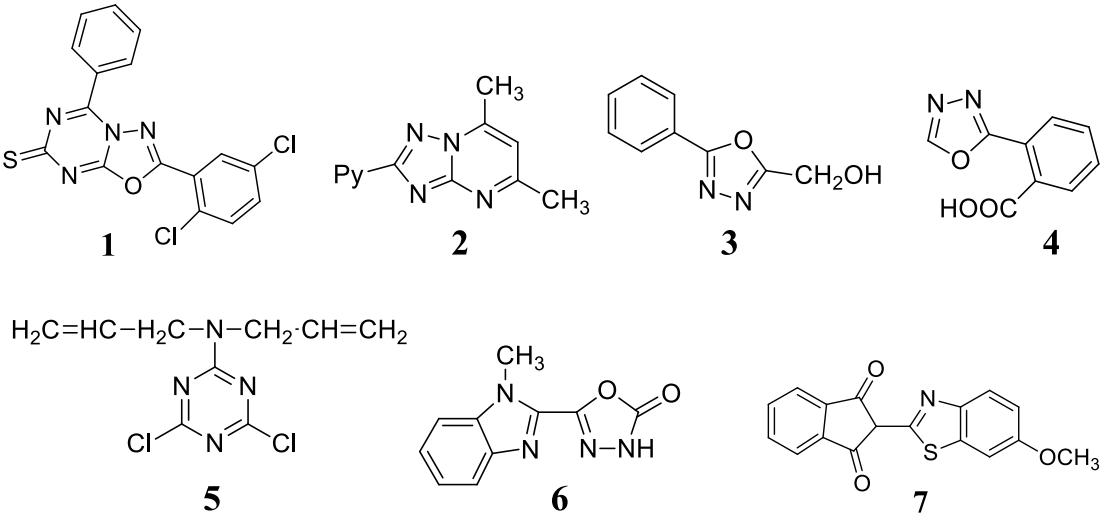
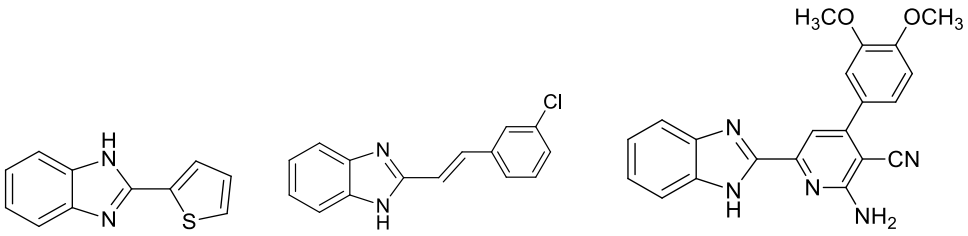


Fig. 1

A vast number of heterocyclic compounds have been synthesised that can mimic the role of naturally occurring heterocycles. The increasing demand for heterocyclic compounds in pharmaceutical and industrial fields made biochemists enthusiastic to develop new synthetic strategies for the synthesis of heterocycles. A large number of heterocyclic compounds having varying combinations of heteroatoms with carbon and hydrogen have been designed. Its synthetic strategies utilise reactions such as substitution, addition, elimination, cyclocondensation and enzyme catalysed reactions. These methods have the disadvantage of longer reaction times, lesser yield and production of waste byproducts[5]. Later, the development of green chemistry resulted in the designing of new efficient, cost effective, green synthetic protocols for the synthesis of heterocyclic compounds. Solvent-free microwave irradiation method has been widely used due to its improved atom economy and higher yields of selective products accompanied by lesser reaction time and decreased formation of waste products[6].

Benzimidazole derivatives (**Fig. 2**) are well-known antibacterial agents. Many synthetic strategies including microwave irradiation method have been introduced for the synthesis of antibacterial agents with benzimidazole scaffold[7]. Benzimidazole **8** is an antibacterial for *Pseudomonas aeruginosa*, **9** is active against the bacteria *Bacillus subtilis* and **10** against *Escherichia coli*.



8 **9** **10**

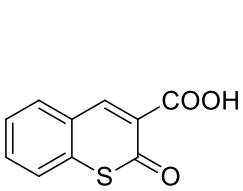
Fig. 2

Chalcone functionalized compounds showed promising anticancer properties. Indolyl chalcones are highly selective anticancer drugs. Chalcone functionalized imidazolones are potential anticancer drugs against cancer cell lines of humans. Coumarin chalcones were found to be potent against cervical carcinoma cell lines in human[8].

Indolocarbazoles are emerging scaffolds that are active against cancerous cells of the central nervous system. Indolocarbazole moiety is a vital part of antitumor agents such as topoisomerase inhibitors, protein platelet-derived growth factor (PDGF) signal transduction inhibitors, protein kinase C (PKC) inhibitors, tyrosine kinase (Trk) inhibitors etc. An indolocarbazole named BE-13793C, produced from the bacteria *Streptomyces mobaraensis,* is an inhibitor for topoisomerase I and II. A well-known PDGF signal transduction inhibitor K-252a isolated from *Nocardiopsis species* is an indolocarbazole derivative[9].

N-heterocyclic compounds are capable of forming strong coordinate bonds with metal ions. This property makes them applicable as corrosion inhibitors. Derivatives of pyridine containing electron donating groups or electron withdrawing groups act as inhibitors of metallic corrosion. Pyridine-2-carbaldehyde (4AAPA), 2-cyanopyridine (2-PCN) and 2-amino-3-methyl pyridine (AMP) are examples of corrosion inhibitors[10].

Thiocoumarins are heterocyclic compounds containing oxygen and sulphur as hetero atoms. Thiocoumarins exhibit anticancer, antibacterial, antifungal, carbonic anhydrase (CA)[11] and TNF-α inhibitory properties[12] (**Fig. 3**).



CA inhibitor

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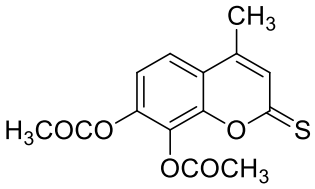

TNF-α inhibitor

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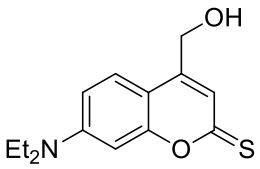
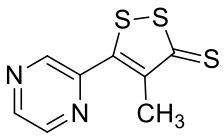


Thio-DEACM

13

Fig. 3

1,2-Dithiole-3-thiones (**Fig. 4**) are sulphur containing heterocyclic compounds. These compounds showed chemoprotective and antioxidant properties and are widely used as drugs in medicinal chemistry. They are also used as insecticides, fungicides and anticorrosion agents. The wide range of applications led to the development of various synthetic methods that involve sulphonation of the substrate followed by cyclisation to get 1,2-dithiole-3-thiones. Oltipraz **14** is a 1,2-dithiole-3-thione derivative that shows antischistosomal properties and inhibits HIV-1 replication[13]. Anethole dithiolethione **15** was proved to be an efficient corrosion inhibitor for copper[14]. The chemopreventive agent 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT-OH) **16** was found to be specific for the prevention of bladder cancer[15].



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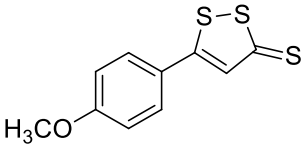

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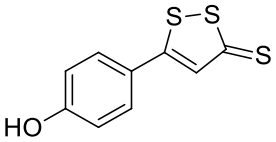

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Fig. 4

Pyridine-2-thiones are heterocyclic compounds exhibiting anticancer and antibacterial properties. These compounds possess good chelating properties that enable them to form complexes with various metals. Harringer *et al.* synthesised some piano-stool complexes of pyridine-2-thiones with Ru^{II}, Rh^{III} or Ir^{III} as metal centre that exhibited cytotoxic activity against human cancer cell lines[16]. Pyridin-2-thione and 5-(trifluoromethyl)pyridine-2-thione act as an antithyroid drug[17]. N-benzoyloxy-2-

thiopyridones **17** (**Fig. 5**) are nucleic acid cleaving agents of high selectivity. DNA photocleavage was found to be time and concentration dependent which can be effectively tuned by structural modifications of thiopyridone core[18].

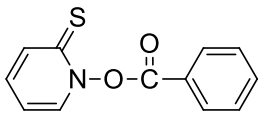


Fig. 5 **17**

Thiophenes (**Fig. 6**) are aromatic heterocyclic compound exhibiting diverse biological and pharmacological properties. Thiophene ring when fused with other ring systems gives rise to fused heterocyclic compounds with advanced biological activities. Thiophene core is present in many biologically important natural products having antifungal, antibacterial, anti-inflammatory, anticonvulsant and anticancer properties [19]. Several synthetic approaches such as metal-catalysed, metal-free, multi-component, iodine catalysed etc. reactions have been developed for thiophenes[20]. Rasool *et al.* synthesised 2-chloro-5-phenylthiophenes **18** and 2,5-bisaryl thiophenes **19** from 2-bromo-5-chlorothiophenes via Suzuki cross-coupling reaction[21]. The 2-chloro-5-phenylthiophenes **18** are found to be antibacterial agents whereas 2,5-bisaryl thiophenes **19** are antioxidants. Deng *et al*. synthesised thieno[3,2-b]thiophene-2-carboxylic acid derivatives **20** having anticancer properties[22].

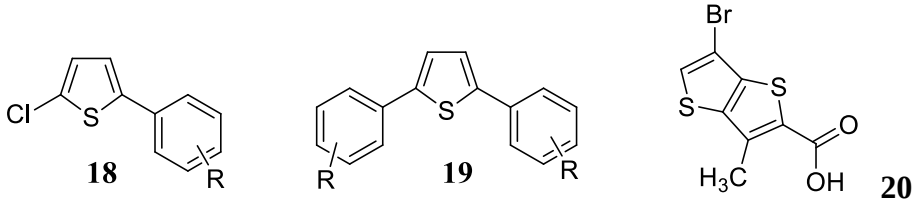
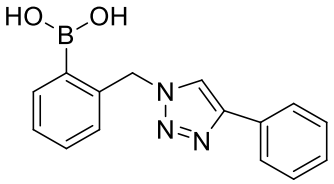


Fig. 6

Compounds such as triazoles, imidazoles, thiazoles, thiadiazoles, indoles, pyrazoles, pyridines, pyrimidines and nucleosides showed antiviral activity depending on the substituents on the ring[23]. Triazoles are used as chemosensors for the detection of ions and molecules[24]. A number of synthetic routes for triazoles have been reported in the literature that involve simple click reaction between alkyne, dihaloalkane and

azide in the presence of a suitable catalyst[25]. Open chain **21** as well as macrocyclic **22** chemosensors having triazole moiety as a binding unit (**Fig. 7**) have been developed. 1,2,3-Triazoles having hydroxyphenyl group as substituent exhibit fluorescence due to intramolecular charge transfer transitions[26].



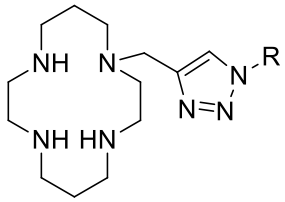
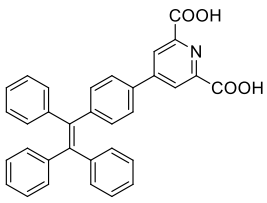
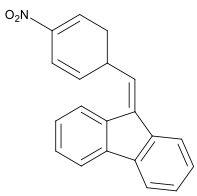
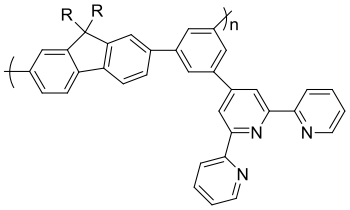


Fig. 7 **21** **22**

Heterocyclic compounds have been widely used for the detection of metal ions (**Fig. 8**). 2,6-Pyridinedicarboxylic acid substituted tetraphenylethene (TPE-PDA) **23** is an aggregation-induced emission (AIE) sensor for the detection of thorium in aqueous solution[27]. Fluorene functionalized derivatives **24** are used as chemical sensors and also in organic optoelectronic[28]. Highly soluble turn off fluorescence sensor **25** consisting of π-conjugated copolymer with pendant terpyridyl groups, has been synthesised by Suzuki coupling reaction using Pd(0) as the catalyst. The fluorescent chemosensor was found to exhibit high sensitivity and selectivity for on-site detection of Cu^{2+} by quenching of fluorescence[29].







23 **24** **25**

Fig. 8

Objectives of the present study

The work presented in this dissertation consists of developing efficient synthetic strategies for some heterocyclic compounds and studying their applications. The compounds of our interest were thicoumarins, 1,2-dithiole-3-thiones, dihydropyridine-2-thione, 3,4-diphenyl thiophene, triazoles, triazole functionalized coumarin and fluorine derivatives. These are the compounds of synthetic interest due to their varied applications in biological and medical fields. Techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and single crystal XRD analysis were used for the characterisation of the synthesised compounds. The applications of the synthesised compounds have been studied for their cytotoxicity and antibacterial activity: *in vitro* and *in silico* methods. In addition to these, fluorescence properties of triazoles, triazole functionalized coumarin and fluorine derivatives in the uncomplexed and complexed form with thorium (IV) ion have been studied quantitatively for the selective detection of the metal ion.

We describe the whole work in **7 chapters**. Since majority of the synthetic transformations presented in this dissertation utilises β-oxodithioesters, a review of its synthetic utility has been described in **chapter 2**.

The synthesis, characterisation and applications of thiocoumarins have been explained in **chapter 3**. Thiocoumarins have been synthesised from β-oxodithioesters. The protocol involves the synthesis of β-oxodithioesters followed by their conversion to thiocoumarins. For the conversion of β-oxodithioesters to thiocoumarins, we have developed two methods: conventional heating and microwave irradiation. Characterisation of the thiocoumarins has been carried out using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and single crystal XRD. *In vitro* cytotoxic activity of the compounds has been studied in cancer cell lines as well as in normal cell lines. The *in silico* molecular docking studies provided theoretical support for the anticancer activity.

Chapter 4 depicts the synthesis, characterisation and applications of 1,2-dithiole-3-thiones. Here, β-oxodithioesters were converted to 1,2-dithiole-3-thiones via

microwave heating method. Microwave irradiation provided the product with high yields within a few minutes. The techniques such as FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy were used for the characterisation of the synthesised compounds. The *in vitro* cytotoxic activity of the compounds has been studied in cancer cell lines as well as in normal cell lines. *In silico* molecular docking studies provided theoretical support for the anticancer activity.

Chapter 5 describes the synthesis, characterisation and applications of dihydropyridine-2-thione and 3,4-diphenyl thiophene. The reaction between thioamide derived from β-oxodithioester was treated with chalcone to furnish dihydropyridine-2-thione. On the other hand, the reaction between β-oxodithioester and phenacyl bromide afforded 3,4-diphenyl thiophene. The characterisation and biological applications of the synthesised compounds are discussed in this chapter. Characterisation of the synthesised compounds has been carried out using FT-IR, ^{1}H NMR, ^{13}C NMR and single crystal XRD. The anticancer and antibacterial properties of the compounds were theoretically studied using *in silico* molecular docking method.

Chapter 6 gives a description of the synthesis, characterisation and applications of triazoles, triazole functionalized coumarin and fluorene derivatives. The reaction between alkyne, sodium azide and excess of dihaloethane in the presence of copper supported polymer catalyst CuPVPNNMBA yielded 1,2,3-triazole. CuPVPNNMBA catalysed reaction between phenylacetylene, sodium azide and chloromethyl coumarin afforded highly fluorescent triazole functionalized coumarin. Triazole functionalized fluorene, a thorium ion detector, has been synthesised by the reaction between 2-acetylfluorene, phenylacetylene and sodium azide in the presence of catalyst CuPVPNNMBA. 2-Acetylfluorene on reaction with phenylisothiocyanate afforded fluorescent thioamide functionalized fluorene. The techniques such as FT-IR, ^{1}H NMR and ^{13}C NMR and mass spectroscopy were used for the characterisation of the synthesised compounds. The applications of the compounds as antibacterial agents and fluorescence detectors of metal ions have been studied. **Chapter 7** includes a summary and conclusion of the present work

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