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I would like to confess that even though I try my level best, it is not possible for me to acknowledge and thank all those known and unknown individuals' for their direct and indirect contribution for the successful completion of this work.

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Namitha R

Contents

General Remarks

Chemicals used are of Analar grade purchased from Aldrich, Alfa Aesar, Merck, Loba, SRL and Sd-Fine (India) and used directly without further purification. Solvents were purified by appropriate methods and dried using standard procedures. Visualization on TLC was done by iodine and eluted with petroleum ether, ethyl acetate and chloroform. Melting points were taken in CINTEK melting point apparatus.

IR spectra were recorded in ATR-IR Affinity instrument and the absorption frequencies quoted in reciprocal centimeters.

^{1}H NMR and ^{13}C NMR spectra were recorded in AMX-400(400MHz) spectrometer recorded in $CDCl_3$ and DMSO-d_6 as solvent with TMS as internal standard. The chemical shift were expressed in parts per million (ppm).

High resolution mass spectra were recorded on Bruker micro TOF and Agilent 1100/LC MSD Trap SL version QII instrument. Column chromatography was performed on silica gel (100–200 mesh, SRL. India).

The DFT employing the closed-shell Becke-Lee–Yang–Parr hybrid exchange-correlation three parameter functional (B3LYP) was adopted. All the calculations were performed using Gaussian 09 program (G09W) package. The 6-31G (d, p) basis set augmented by d polarization functions on heavy atoms and p polarization functions on hydrogen atoms as well as diffuse functions for both hydrogen and heavy atoms were used.

The single beam Z-scan technique was used to measure the nonlinear susceptibility of the samples.

Invitro antibacterial, antifungal activity were studied by the agar well diffusion method (Perez *et al.*,1990) is used to determine the growth inhibition and MICs of the synthesized compounds are compared with existing drugs.

Antioxidant activity was determined by DPPH radical scavenging activity.

Invitro cytotoxicity of the selected triazino quinolines were studied using Dalton's Lymphoma Ascites (DLA) cells.

Invivo toxicity, anti-inflammatory and analgesic activities of the compounds were done using Balb/c mice (20–25 g).

The following abbreviations are used in the thesis:

MP: melting point; mL: milli liter; Con.: Concentrated; Lit: Literature; g: gram; ℃: degree celsius; IR: infra red; ^{1}H NMR: proton NMR; ^{13}C NMR: carbon NMR; Fig: figure; TLC: thin layer chromatography; mmoles: millimoles; cm: centimeter; ppm: parts per million; NBO: natural bond orbital; DFT: density functional theory; ED: electron density; min: minutes; LUMO: lowest unoccupied molecular orbital; HOMO: highest occupied molecular orbital; ps: picoseconds; fs: femto second; MIC: minimum inhibitory concentration; DLA: Dalton's Lymphoma Ascites; h: hours; DMSO: dimethyl sulphoxide;$CDCl_3$: chloroform(deuteriated);SHG: simple harmonic generation; Com. : compound; *S. aureus: Staphylococcus aureus; S. Pyogens: Streptococcus pyogens; P. aeruginosa; Pseudomonas aeruginosa; E. coli: Escherichia coli; K. pneumonia : klebsiella pneumoniae;* b.wt: body weight;

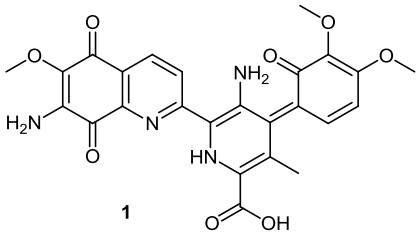
Objective and Scope

Heterocyclic chemistry is the most explored area of organic chemistry and an important building blocks for new materials which hold electronic, mechanical and biological properties.

The compounds bearing quinoline moiety are well known for their broad spectrum of biological importance[5]. The usage of quinoline derivatives in medicine[1] food catalyst[2-4] dye materials, refineries and electronics are well known. Quinoline derivatives being non-centro-symmetric are recently explored for non linear optics[6-9] and have been extensively studied due to their potential application in the field of organic light emitting diodes (**OLED**) [10-17].

Since the identification of antimalarial drug Quinine, the quinoline derivatives[18, 19] have been extensively utilized in the treatment of various diseases.

Antitumor drugs like Streptonigrin (**1)**, Luotonin A **(2)**, Camptothecin (**3)** and Dynemicin A (**4)** were found to possess quinoline moiety in their structure.



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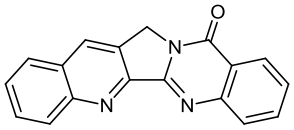

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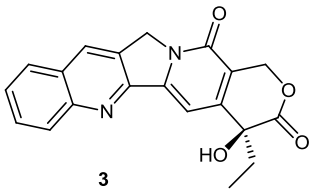

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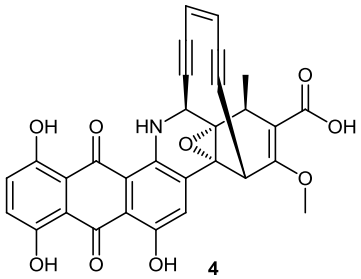

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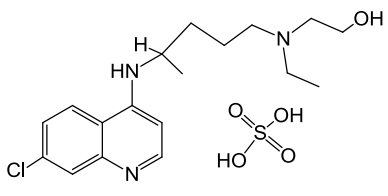
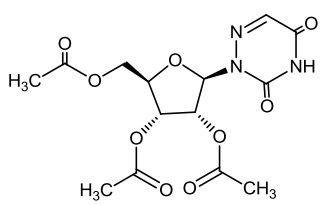
Literature survey revealed that synthetic quinolines are well associated with a wide range of biological properties in treating a number of diseases such as antiinflammatory, analgesic, anticancer, antimalarial (plaquenil) **5**.[20,21]



5

The 1,2,4-triazine derivatives, obtained from synthetic and natural sources, have different biological activity [22]. 1,2,4-triazine compound and its condensed derivatives with the heterocyclic ring, showed the application in various fields as pharmaceuticals, agriculture, dyes, pesticides, and herbicides [23].

Azaribine [24] (**6**), ceftriaxone [25] **(7),** lamotrigine [26] (**8),** tirapazamine [27] (**9**), apazone[28] (**10**), are 1,2,4-triazine moiety containing drugs showing different pharmacological activities.



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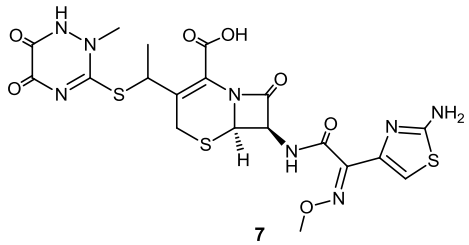

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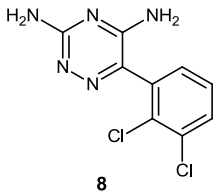

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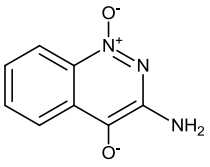

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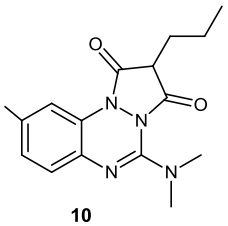
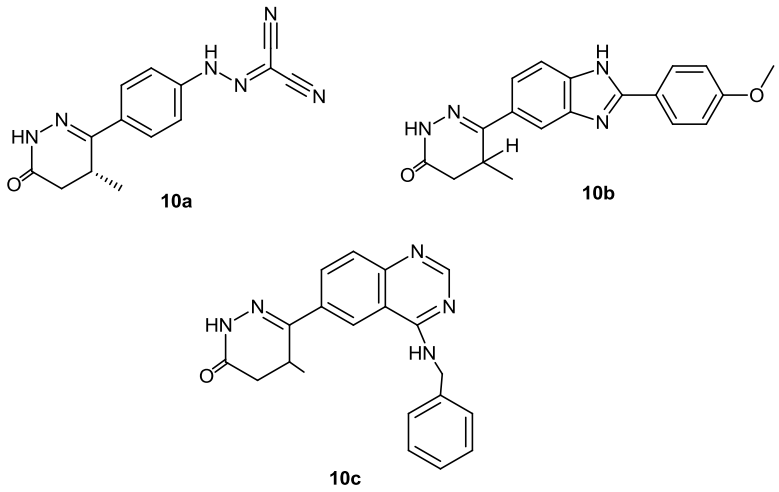


10

Pyridazines and pyridazinones belong to an important category of heterocycles, which have been reported to show wide range of biological activities, such as analgesic and anti-inflammatory [29-32], antihypertensive [33,34], anticancer [35], antiplatelet [36,37], antidiabetic [38], anticonvulsant [39,40] and anti-microbial activities [41].

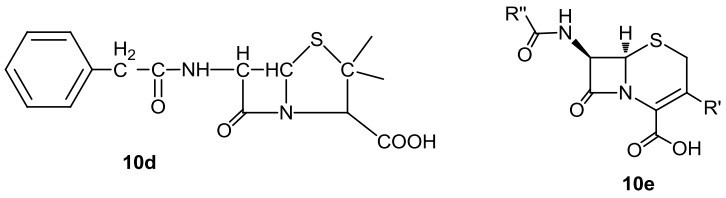
Literature has highlighted the importance of pyridazinone nucleus as an excellent template for the synthesis of anti-inflammatory agents [42] particularly in the light of the platelet aggregation inhibitory and vasodilatory properties associated with this core structure.

A variety of compounds containing pyridazinone ring found to possess potent pharmacological activity for the treatment of heart failure such as Levosimendan (**10a)**, Pemobendan (**10b)**, and KF15232 [43] (**10c).**



10a **10b** **10c**

Azetidinones are of great importance because of the utility of its derivatives as antibacterial agents [44]. The well known miracle drugs such as penicillins (**10d)** and cephalosporins (**10e)** which have significantly improved human health and life expectancy contain *β*-lactam ring. Developments in the field of azetidinone, during the last decades indicate that the only essential feature for the antibacterial activity is the presence of *β*-lactam ring. In addition, the azetidinone derivatives have also been recognized as TNF-alpha converting enzyme (TACE) inhibitors, antiinflammatory [45], anticonvulsant [46], anticoccidial [47], anticancer [48], cardiovascular [49] and mutagenic [50].



10d **10e**

Imidazolidines are biologically active nitrogen containing heterocyclic moiety, that have been reported to show wide array of significant pharmacological activities such as anti-inflammatory, analgesic, antimicrobial, antiparasitic, oral hypoglycemic and anticonvulsant activities [51-54].

Several substituted-imidazolidine derivatives have been shown to be potential anti-edema agents in animal models of inflammation. Khan and Chawla, reported them to be promising group of NSAIDs with potential anti-inflammatory activities [55].

Imidazolidine, a versatile moiety, could be a possible pharmacophore in designing safer anti-inflammatory medicinal agents [56-58].

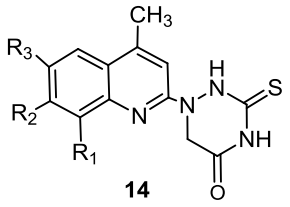
Among the family of heterocyclic compounds, nitrogen containing heterocycles with a sulphur atom is an important class of compound in medicinal chemistry.

4-thiazolidinone motifs possess many interesting active profiles namely EOX-1 inhibitors [59], inhibitors of the bacterial enzyme Mur-B[60], non- nucleosides inhibitors of HfV-RT [61] and antihistamine agents [62] apart from analgesic, local and spiral anesthetic, CNS stimulant, hypnotics, anticancer and anti HIV [63-64] properties.

The challenge of discovering new biologically important heterocyclic system and to study their potential towards the goal of marketable synthetic drugs, insist us to focus our research towards the synthesis of new heterocyclics.

The pharmaceutical importance of quinoline compounds intended us to choose our precursors (**11, 15, 19)** to achieve our targeted triazinones **(14,18,22),** pyridazinones **(24,26),** azetidinones **(28,32,36)**, imidazolidinones **(29,33,37)** and thiazolidinones **(30,34,38).**

Based on the above said facts, various substituted triazino quinoline-5-one derivatives (**14, 18, 22)** were developed and it is described in **Chapter 1.**



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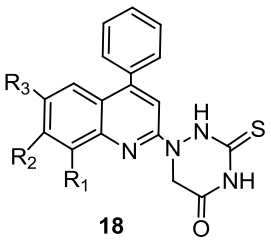

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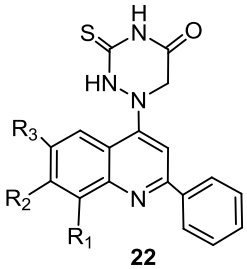

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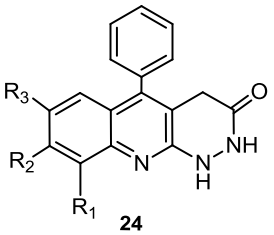
Chapter II describes the synthesis of various substituted linear and angular pyridazino quinoline (**24, 26)** derivatives.



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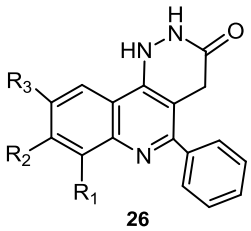

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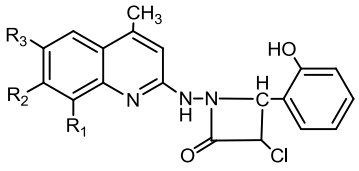
On the basis of pharmacological importance, it was felt worthwhile to develop various substituted azetidinones (**28,32,36)** imidazolidinones (**29,33,37)** and thiazolidinones (**30,34,38)** through the intermediate Schiff bases (27, 31, 35). The synthesis of the above said compounds have been discussed in **Chapter III.**



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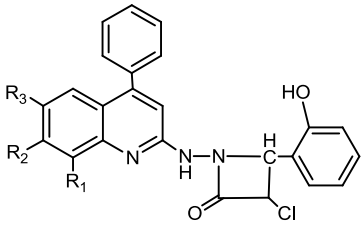

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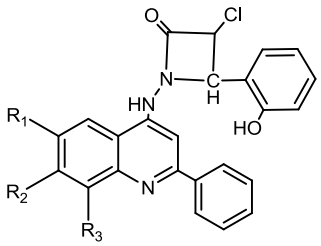

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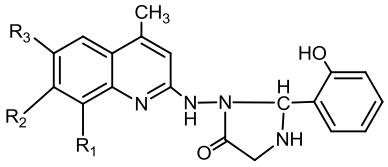

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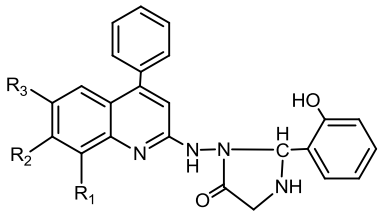

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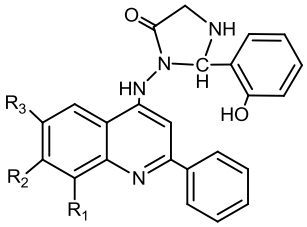

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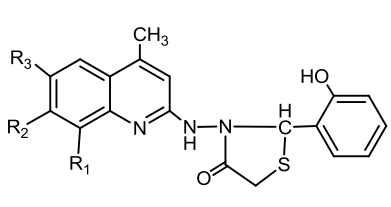

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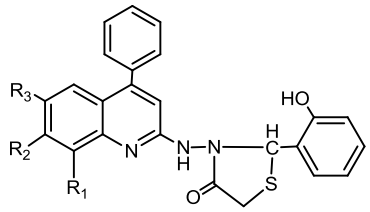

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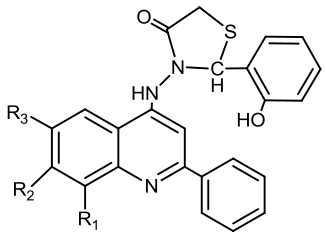

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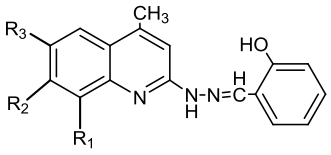

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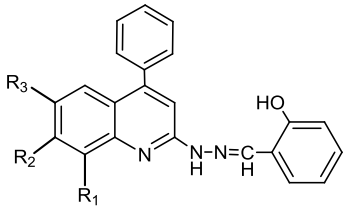

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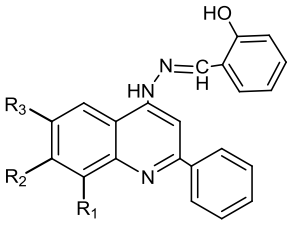

35

Though the origin of organic chemistry lie in the study of natural products, numerous pharmaceuticals and other heterocyclic compounds with practical application are not extracted from natural compounds but are synthesised.

Hence the rationale behind the synthetic compounds directed our research towards their pharmaceutical and industrial applications.

With this view we have performed the theoretical studies of our compounds using G09W/DFT method.

Non linear optical properties are the major criteria for any molecule to act as a sensor for both industrial as well as for medicinal applications. Prior to fabrication of **OLED** it is inevitable to evaluate the material for the nonlinear optical property since the **NLO** property is a necessary condition for a material to act as an **OLED**. Hence we are interested to analyse the non-linear optical character for our selected compounds both by *insilico* and instrumental method. In *insilico* method we have

calculated the hyperpolarisability of all the compounds and compared the values with the standard urea and were found to exhibit good nonlinear optical character. **Z scan** technique was performed and nonlinear optical coefficient was calculated. The results are discussed in **chapter IV.**

As per the literature, the quinoline compounds also assured their pharmacological potential. Hence **Chapter V** explains the antimicrobial, antioxidant, cytotoxicity, antiinflammatory, analgesic activities both by *invitro* and *invivo* methods selectively.

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