Summary

of the thesis entitled

Synthesis and Characterization of Some New Oxazole Containing Heterocyclic Compounds and Study of Their Biological Activities.

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By

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Introduction

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Synthesis and study of antidiabetic and anticancer activities of 1-Aryl-3-(2-aryl-1,3-oxazol-4-yl)- 3-hydroxy-propanones and (E)-1-aryl-3-(2-aryl-1,3-oxazol-4-yl)propenones.

Chapter-3

Synthesis and study of anti-inflammatory activity of 3-Aryl-5-(2-aryl-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazoles.

Chapter-4

Synthesis and study of antimicrobial and anticancer activities of (E)-1-Aryl-3-(2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-propenones and [5-Aryl-3-{(2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl)}-4,5-dihydro-1H-pyrazol-1-yl)](pyridin-4-yl) methanones.

Chapter-5

Synthesis and study of anti-tubercular activity of (E)-N'-((2-Aryl-5-methyl-1,3-oxazol-4-yl) methylene)isonicotino-/nicotino-hydrazides and their docking study.

Chapter-6(A)

Synthesis and study of antimicrobial, anti-tubercular and anticancer activities of (E)-2-Aryl-4-[{N'-(6-bromo-/6-chloro-2-methylquinolin-4-yl)hydrazono}methyl]-5-methyl-1,3-oxazole and their docking study.

Chapter-6(B)

Synthesis and study of antimicrobial and anticancer activities of (E)-4-{N'-Arylidene-hydrazinyl}-6-bromo-/6-chloro-2-methylquinoline and their docking study.

Chapter-1

Introduction

Medicinal Chemistry and Drug Design

Medicinal chemistry involves design, development and synthesis of therapeutic agents useful for the treatment and cure of various diseases affecting the human health. Medicinal chemistry is an interdisciplinary science with intersection between chemistry, biology and pharmacy.

Drug design includes computational aspect of the targeted molecules with the targeted enzymes and understanding of structure activity relationship. Synthesis of the designed new molecules involves methodology and functional group alteration to make them more effective and therapeutically more viable compounds.

Chemistry and Heterocyclic Chemistry

Organic chemistry is the chemistry of carbon and carbon compounds. Organic chemistry is an important branch of chemistry as it is closely associated with life on this planet. Organic compounds are broadly classified into acyclic organic compounds and cyclic organic compounds. Cyclic organic compounds are those in which three or more atoms bind together via covalent bonding to form a closed structure which can be compared to a ring.

When the atoms which are essential part of cyclic structures are only carbon atoms the resulting compounds are known as carbocyclic compounds. When at least one of the carbon atoms in a ring structure is replaced with any other atom (called heteroatom) with capability of covalent bonding, the resulting compounds are classified as **heterocyclic compounds**. The most commonly found heteroatoms are nitrogen, oxygen and sulphur.

Heteroatoms are essential part of biomolecules due to which the secondary bonding, also known as supramolecular interactions, becomes possible. These secondary interactions are essential for enzymatic processes in living organisms. Among heterocyclic compounds the nitrogen heterocycles are much more common and

important due to several reasons. Nitrogen heterocycles are widely prevalent in nature and play very important role in biological processes.

Azoles are five membered heterocyclic compounds with two or more heteroatoms, out of which at least one has to be nitrogen. 1,3-Oxazole heterocycles has attracted much attention of scientists due to various reasons. Oxazole compounds with oxygen and nitrogen occupying the specific positions in the five membered aromatic heterocycle has binding capability with a range of enzymes and receptors in biological systems via noncovalent interactions and shows various biological activities.[1]

The compounds with different heterocycles possess different bioactivities or different efficacy for a particular bioactivity, it is a topic of current interest to synthesis new molecules with two or more heterocycles connected via covalent bonds or separated by a spacer and to study their bioactivity prompted by the reported activity of individual heterocycles.

Incorporation of two molecular entities existing in a large number of scaffolds with a varied biological profiles display unusual enhanced biological properties.[2,3] It is assumed that the combination of two or more bioactive heterocycles in a single molecule may not only synergize their biological potency but may also improve their ability to act upon more than one biological target.[4]

Chapter-2

Synthesis and study of antidiabetic and anticancer activities of 1-Aryl-3-(2-aryl-1,3-oxazol-4-yl)- 3-hydroxy-propanones and (E)-1-aryl-3-(2-aryl-1,3-oxazol-4-yl)propenones.

Oxazole is associated with a number of biological activities due to a number of non-bonding interactions it can undergo. 1,3-Oxazole may undergo weak intermolecular interactions such as π–π stacking, co-ordination bonding, ion-dipole interactions, van der Waals interactions or may exhibit hydrophobic effects depending on its exposure to different types of donor/acceptor atoms or group of atoms or molecules.

Having the biological importance of oxazole in mind several new oxazole containing 3-hydroxy-1-propanones and aryl-oxazolyl-propenones with the inclusion of an important heterocycle 1,3-oxazole and with the two types of linkers connecting the substituted aromatic and heteroaromatic parts have been synthesized from the corresponding 2-aryl-1,3-oxazole-4-carbaldehydes and 4-substituted acetophenones.[5]

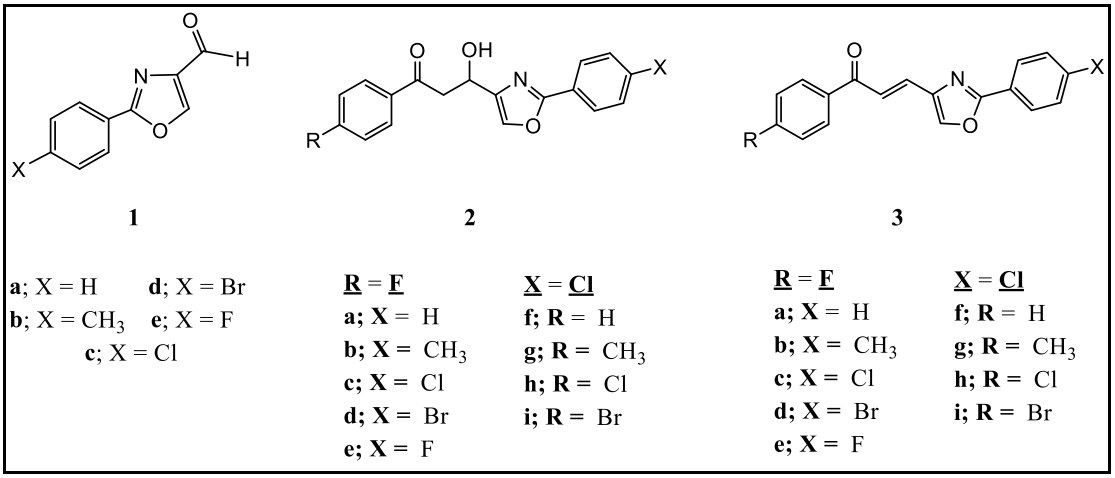


Figure 1.1

All the new compounds were fully characterized by using various spectro analytical techniques. The final new compounds' NMR characteristics are studied in detail with the emphasis on ^{19}F NMR and signal assignments are made using 2D NMR techniques. The X–ray crystal diffraction study of one of one of the β-hydroxy ketones and one α,β-unsaturated compound were carried out.

Biological Evaluation

Anticancer Activity Study

The final new 3-hydroxy-1-propanone and aryl-oxazolyl-propenone entities were screened for *in vitro* anticancer activity (60 cancer cell line screening at the Development Therapeutic Program (DTP), National Cancer Institute (NCI), Chemotherapeutic Research division, USA).

Antidiabetic Activity Study

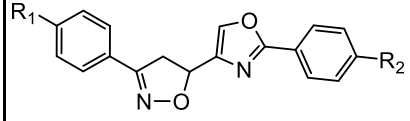
All the newly synthesized compounds were subjected to *in vivo* oral glucose tolerance test on male C57 mice with the testing facility available at the Zydus Research Centre, Ahmedabad. Molecular docking studies were performed to find out the binding interactions of the synthesized compounds with the active site of PPAR-α and PPAR-γ.

Chapter-3

Synthesis and study of anti-inflammatory activity of 3-Aryl-5-(2-aryl-1,3-oxazol-4-yl)-4,5-dihydro-1,2-oxazoles.

Isoxazoline is a 4,5-dihydro isoxazole. Isoxazolines or 4,5-dihydro-1,2-oxazoles have marked their individual existence because of the diverse biological activities. Isoxazolines show a broad range of biological activities including antifungal,[6] anti-inflammatory,[7–9] antibacterial,[10] antioxidant,[11] anticonvulsant,[12] anti-HIV,[13] antidiabetic,[14] anticancer,[15–18] anti-tubercular activity.[19,20]

The existence of α-β unsaturated keto function in chalcones makes them prone to undergo reactions with bidentate nucleophiles to give various biologically potent heterocyclic compounds. This property of chalcones was explored in the present work to generate isoxazolines incorporated derivatives of biological interest. In this chapter five membered heterocycle, isoxazoline was built on the molecules already possessing 1,3-oxazole in the form of aryl-heteroaryl chalcones as described in the preceding chapter.



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R_1 = F	**R_2** = Cl
a; **R_2** = H	**f**; **R_1** = H
b; **R_2** = CH_3	**g**; **R_1** = CH_3
c; **R_2** = Cl	**h**; **R_1** = Cl
d; **R_2** = Br	**i**; **R_1** = Br
e; **R_2** = F	

Figure 3.1

All the newly synthesized aryl-oxazolyl-4,5-dihydroisoxazoles were characterized by various spectro-analytical techniques. Structure of one of the compounds was studied using single crystal X-ray diffractometer.

Biological Evaluation

Anti-inflammatory Activity Study

All the newly synthesized compounds were screened for their *in vivo* anti-inflammatory activity in terms of measuring TNFα inhibitory activity. All the compounds showed moderate TNFα inhibitory activity.

Chapter-4

Synthesis and study of antimicrobial and anticancer activities of (E)-1-Aryl-3-(2-(4-chlorophenyl)-5-methyl-1,3-oxazol-4-yl)-propenones and [5-Aryl- 3-{(2-(4-chloro- phenyl)-5-methyl-1,3-oxazol-4-yl)}-4,5-dihydro-1H-pyrazol-1-yl)](pyridin-4-yl) methanones.

The chalcone family has attracted much interest not only from the synthetic and biosynthetic perspectives but also due to its wide range of biological activities. With a large number of papers on synthesis and study of chalcones bioactivity many mini reviews published are published in past few years .[21–27]

The privileged scaffold chalcone has been an attraction among chemists and biologist due to ease of synthesis, diversity of substituents, wide range of biological activities such as anticancer,[28,29] anti-diabetic,[30] anti-hypertensive,[31] anti-inflammatory,[32] anti-parasitic,[33] anti-malarial,[34] antioxidant,[35] anti-fungal,[36] anti-bacterial,[37] anti-platelet,[38] anti-retroviral,[39] anti-tubercular,[40] hypnotic,[41] anti-protozoal[42] activities.

Pyrazoline is the 4,5-dihydro derivatives of pyrazole. Considerable attention has been focused on the pyrazolines and substituted pyrazolines due to their interesting biological activities. A wide array of synthetic compounds containing pyrazoline moiety have been reported so far exhibiting diverse biological activities such as antimicrobial,[43] antiamoebic,[44] antitubercular,[45] anti-HIV,[46] anticancer,[47] antidepressant,[48] anticonvulsant,[49] anti-inflammatory,[50] and antimalarial[51] activities.

Looking at the biological importance of the chalcones, pyrazolines and pyridine possessing compounds, some new compounds having α,β-unsaturated linkage were synthesized. Employing these α,β-unsaturated compounds, several new pyrazoline hybrid compounds containing oxazole and pyridine heterocycles were prepared.

To overcome the difficulty in the preparation and handling of aromatic acyl halides and fluctuation in the yields of the formyl oxazoles, another synthesis route was explored. The alternate synthesis was leading to 5-methyl derivatives of 2-aryl-4-formyl-1,3-oxazoles. [52–54]

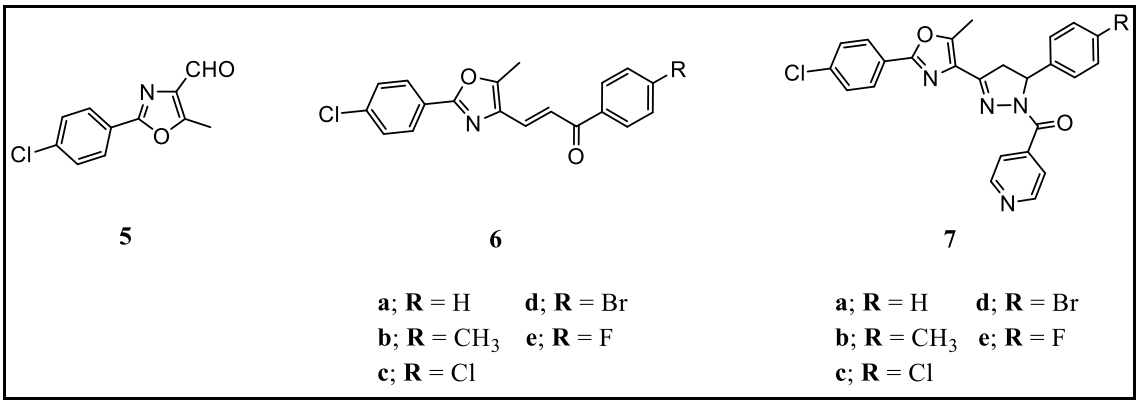


Figure 4.1

All the synthesized compounds 1-aryl-3-(aryloxazolyl)-propenones and (oxazolyl-pyrazolyl)-(pyridinyl)-methanones were characterized by various spectro analytical technoques. The single crystal X-ray diffraction study of compounds give further insight on the conformation and crystal packing of these compounds.

Biological Evaluation

Antimicrobial Activity Study

All the newly synthesized compounds were screened for antibacterial activity against (*Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 619) as a Gram positive bacteria and *Escherichia coli* (MTCC 739) and *Pseudomonas aeruginosa* (MTCC 741) as Gram negative bacteria. The study antifungal activity was carried out against *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 183). Both the studies were carried out at Microcare Laboratory, Surat, Gujarat.

Anticancer Activity Study

The newly synthesized compounds were also studied for their anticancer activities with the support from project of Development Therapeutic Program (DTP), at National Cancer Institute (NCI), Chemotherapeutic Research division, United States of America (USA) against 60 cancerous cell line panels as per their protocol.

Chapter-5

Synthesis and study of anti-tubercular activity of (E)-N'-((2-Aryl-5-methyl-1,3-oxazol-4-yl) methylene)isonicotino-/nicotino-hydrazides and their docking study.

This chapter deals with the synthesis of some new nicotino/isonicotino hydrazones prepared by condensation of 1,3-oxazole carbonyl compounds to produce dual heterocyclic entities. The newly synthesized compounds are studied for their anti-tubercular activity and docking studies are carried out to understand the interactions of the active compounds with the enzyme inhA.

Tuberculosis (TB) is one of the deadly diseases and remains a foremost global health problem.[55] Tuberculosis was declared a global health emergency by the World Health Organization (WHO) in 1993.[55] With billions of people being infected, TB is still a leading killer in the world.[55,56] The development of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB) and totally drug resistance (TDR) increase the challenges in elimination TB globally.[56] According to the recently released statistics, 52 crore (520 million) people in India are suffering from tuberculosis with 20% growth in one decade.[57]

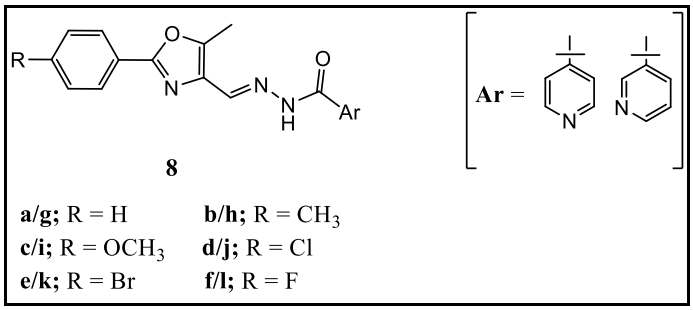
Nitrogen containing heterocycles constitute a major part of natural products[58] and possess a wide range of applications as drug molecules.[59–61] **Isoniazid** or **INH** is isonicotinic acid hydrazide, which is a widely employed first-line drug used for the treatment of tuberculosis.[62,63] Within last few years syntheses of a number of derivatives of isoniazid (INH) were reported and some of them exhibited good *in vitro* antimycobacterial activity.[64–67] Isoniazid (**INH**) and its derivatives, the N-containing heterocyclic hydrazone and derivatives, have added importance in medicinal chemistry due to their variety of biological activities such as anti-mycobacterial,[65–67] anti-bacterial,[68] anti-virus,[69] anti-fungal,[70] anti-tumor,[71,72] analgesic[73] activities. Amongst the numerous activities, the anti-TB activity is remarkable and due to that it is currently used in the treatment of tuberculosis.

In this chapter some new oxazolyl hydrazones have been prepared by employing 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes and two different isomeric heteroaryl hydrazides namely isonicotinic acid hydrazide and nicotinic acid hydrazide. All the

new oxazole containing hydrazones were well characterized and evaluated for their *in vitro* anti-tubercular activity.

To start with the synthesis of six 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes was undertaken following the procedure discussed in the previous chapter.

N'-((2-Aryl-5-methyl-1,3-oxazolyl)methylene)isonicotino/nicotino-hydrazides were synthesized following reported procedure by condensation[74] of 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes with the corresponding hydrazides in ethanol using acetic acid as a catalyst to afford the final new nicotinoyl/isonicotinoyl hydrazones.



8

a/g; R = H **b/h;** R = CH_3
c/i; R = OCH_3 **d/j;** R = Cl
e/k; R = Br **f/l;** R = F

Figure 5.1

All the synthesized aryl oxazolyl carbaldehydes and oxazolyl hydrazones were characterized by various spectro-analytical techniques.

Biological Evaluation

Antitubercular Activity Study

All the new (aryl-oxazolyl)-isonicotino/nicotino-hydrazide derivatives **25(a–l)** were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain in collaboration with NIRT (National Institute for Research in TB), Chennai. Isoniazid was used as the positive standard. Further, the molecular docking study of all new compounds with InhA enzyme were carried out to understand the favourable interactions of the active molecules with amino acid residues of the enzyme.

Chapter-6

This chapter is presented into two following parts.

Chapter-6(A)

Synthesis and study of antimicrobial, anti-tubercular and anticancer activities of (E)-2-Aryl-4-[{N'-(6-bromo-/6-chloro-2-methylquinolin-4-yl) hydrazono}methyl]-5-methyl-1,3-oxazole and their docking study.

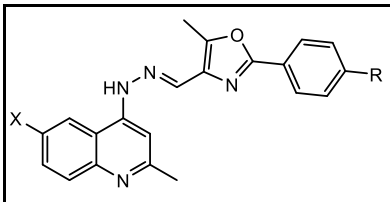
In continuation with our interest in the synthesis of new heterocyclic compounds including 1,3-oxazole unit, in this part of the chapter, several new compounds containing 1,3-oxazole heterocycle linked with quinoline moiety via hydrazine linkage have been prepared. All the newly synthesized compounds were screened for their biological activities including antimicrobial, anti-tubercular and anticancer activities.

It is well known that heterocyclic entities play an important role in designing a new class of structurally diverse molecules for medicinal applications.[75] Because of the broad spectrum of biological activities among all the heterocyclic compounds, quinoline and its derivatives are pharmacologically important.[76–80] Quinoline derivatives are important key building blocks for many naturally occurring bioactive compounds,[81] specially quinoline alkaloids which are found in many different plants[82–84] and hence quinoline derivatives have attracted attention from chemists as well as biologists.

Quinoline containing compounds display a wide range of biological activities including insecticidal,[85] antimicrobial,[86] antimalarial,[87] anti-amoebic,[88] antiasthmatic,[89] analgesic,[90] vasorelaxing,[91] antidiabetic,[92] antimicobcterial,[93,94] anticancer,[95,96] anti-inflammatory,[97] antihypertensive,[98] antiulcer[99] and anti-HIV[100] activities.

Keeping in mind the medicinal importance of the quinoline compounds and hydrazone linked heterocycles in the field of medicinal chemistry, it is worth to synthesize and study some new target hybrid molecules possessing two pharmacophores with enhanced biological activities.

In this part of the chapter some oxazolyl quinoline hydrazones are prepared from 6-bromo/6-chloro-2-methyl-quinolin-4-yl-hydrazines and 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes and are evaluated for their biological activities.



9

X = **Br**	**X** = **Cl**
a; **R** = H	**b**; **R**= H
c; **R** = CH_3	**d**; **R** = CH_3
e; **R** = OCH_3	**3**; **R** = OCH_3
g; **R** = Cl	**h**; **R** = Cl
i; **R** = Br	**j**; **R** = Br
k; R = F	**l**; **R** = F

Figure 6.1

All the newly synthesized aryl-6-bromo/6-chloro-methylquinolinyl-hydrazono-1,3-oxazoles are characterized using various spectroanalytical techniques and the results are in full agreement with their proposed structures.

Biological Evaluation

Antitubercular Activity Study

Anti-tubercular activity of all the newly synthesized 6-bromo/6-chloro-methylquinolinyl-hydrazono-aryl-1,3-oxazoles was studied against *Mycobacterium tuberculosis* H37Rv. Molecular modelling studies of synthesized compounds were performed in order to recognize the feasible binding mode of the compounds on enoyl-ACP reductase as the target receptor.

Antimicrobial Activity Study

To extend the study of biological activity of these compounds**,** antimicrobial activity was carried out against two Gram positive bacteria, two Gram negative bacteria and antifungal activity against two fungal strains using paper disc diffusion technique.

Anticancer Activity Study

Anticancer activity of all the new 6-bromo/6-chloro-methylquinolinyl-hydrazono-aryl-1,3-oxazoles were carried under the screening project at the National Cancer Institute (NCI), USA. Primary *in vitro* single dose anticancer assay was performed at a single dose (10 μM).

The compounds which fulfilled pre-determined criteria at a single dose of (10 μM) were selected for NCI full panel five dose assays. Nine of the ten compounds are further screened at five different concentrations (0.01, 0.1, 1, 10 & 100 μM) of the test compounds against all the NCI 60 tested cell lines.

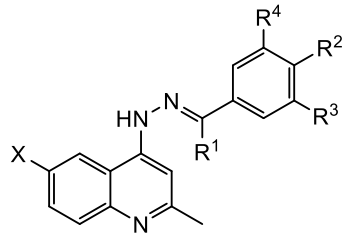
Chapter-6(B)

Synthesis and study of antimicrobial and anticancer activities of (E)-4-{N'-Arylidene-hydrazinyl}-6-bromo-/6-chloro-2-methylquinoline and their docking study.

Keeping diverse biological activities of quinoline derivatives in mind, hydrazine compounds in form of hydrazones, using quinoline-4-hydrazine derivatives, several new hydrazones have been prepared in this part of the chapter dealing with quinoline hydrazones and their bioactivity study.

For the synthesis of new hydrazones, several new alkoxy substituted aromatic aldehydes were prepared from corresponding hydroxy aldehydes. 4-alkoxy acetophenones were also prepared from 4-hydroxy acetophenone and was condensed with the quinoline hydrazines to yield the corresponding hydrazones.

Synthesis of alkoxy substituted aromatic aldehydes or ketones were carried out with varying alkyl chain lengths to have different hypophilicity of the final compounds. These alkoxy substituted aromatic aldehydes and 4-alkoxy acetophenones were condensed with 6-bromo/6-chloro-2-methyl-quinolin-4-yl-hydrazine to get the final targeted new hydrazones.



44

X = Br/Cl
R_1 = H, CH3
R_2 = H, NO_2, OC_2H_5, OC_3H_7, OC_4H_9, OC_6H_{13}, OC_8H17, $OC_{10}H_{21}$
R_3/R_4 = H, OC_8H_{17}

All the newly synthesized quinolyl hydrazones were characterized using various spectroanalytical techniques and spectral characteristics of the new compounds well in agreement with the proposed structures.

Biological Evaluation

Antimicrobial Activity Study

To extend the study of biological activity of these compounds**,** antimicrobial activity was carried out against two Gram positive bacteria, two Gram negative bacteria and antifungal activity against two fungal strains using paper disc diffusion technique.

Anticancer Activity Study

Anticancer activity of all the new 6-bromo/6-chloro-methylquinolinyl-hydrazono-aryl-1,3-oxazoles were carried under the screening project at the National Cancer Institute (NCI), USA. Primary *in vitro* single dose anticancer assay was performed at a single dose (10 μM).

The compounds which fulfilled pre-determined criteria at a single dose of (10 μM) were selected for NCI full panel five dose assays. Nine of the ten compounds are further screened at five different concentrations (0.01, 0.1, 1, 10 & 100 μM) of the test compounds against all the NCI 60 tested cell lines.

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