Synopsis
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A comprehensive summary of the work to be incorporated in the thesis entitled “STUDIES ON MEDICINALLY IMPORTANT PYRAZINE DERIVATIVES” has been described as under.

PART-A: STUDIES ON PYRAZINE 2-CARBOXYLIC ACID DERIVATIVES

PART-B: STUDIES ON IMIDAZO [1,2-a]PYRAZINE DERIVATIVES

Over the years, synthetic heterocyclic chemistry is providing momentum to the development of new drug scaffolds through interactive manipulation of functional groups around the basic skeleton. Among these, heterocyclic compounds have been given special importance because of a wide variety of biological properties associated with them. The importance of heterocycles in biological systems encouraged chemists to design and modify new heterocyclic compounds

PART-A: STUDIES ON PYRAZINE 2-CARBOXYLIC ACID DERIVATIVES

Pyrazine play an important role in pharmaceuticals, perfumery industries, and agricultural chemicals. Various pyrazine derivatives exhibit important biological activity such as analgesic, anti-inflammatory etc. Pyrazine and its derivatives are commonly used in combination with other drugs as a treatment of tuberculosis. As pharmacological profile pyrazine derivatives possess antioxidant activity the activity of compounds was detected by comparing induction periods of soybean oil substrates each compound. Pyrazine and its derivatives showed pro-oxidant activity.

Pyrazine 2-carboxylic acid and their derivatives constitute an important class of organic compounds with diverse agriculture, industrial and biological activities. The synthesis of this moiety has received considerable attention in recent years. It is a key starting material for the preparation of various active biological scaffolds. Pyrazinamide used as antitubercular agent is also synthesized from pyrazine 2-carboxylic acid.

This part is divided into following three chapters.

CHAPTER-1: STUDIES ON 1,2,4 TRIAZOLE DERIVATIVES

CHAPTER-2: STUDIES ON HYDRAZIDE-HYDRAZONE DERIVATIVES

CHAPTER-3: STUDIES ON OXADIAZOLE DERIVATIVES
CHAPTER-1: STUDIES ON 1,2,4 TRIAZOLE DERIVATIVES

1,2,4-Triazoles have proved to be most useful framework for biological activities among nitrogen containing five membered heterocycles. In five membered heterocyclic ring system 4-aryl triazole (I) have three nitrogen atoms at 1,2 and 4 positions, an aryl group at 4-position and free mercapto group at 3-position.

Synthesis of nitrogen bridged heterocyclic systems has attracted many scientists over the past decade because of their high efficacy. 1,2,4-Triazoles coupled to another heterocyclic ring like Schiff base, thiadiazole and thiadiazine shows wide applications as antibacterial, antiviral, antihypertensive, antidepressant, anti-inflammatory, anticonvulsant, antitumor agents, pesticides, herbicides, lubricants, dyes and analytical reagents. Among these, the most common systems are triazoles condensed to thiadiazines, incorporated into a wide variety of therapeutically important compounds possessing wide verity of biological activities such as antiviral, antifungal, antihelminthic, antitumor, antibacterial, anti-inflammatory, antitubercular, analgesic, antiviral, diuretics, CNS-stimulant, PDE4 inhibitors and hypoglycemic agents. Looking to the good potentiality it is worthwhile to study of 1,2,4 triazole which are described in following sections.

SECTION-I: Synthesis and antitubercular evaluation of (E)-4-(substitutedbenzylideneamino)-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiols.

SECTION-II: UV studies of some (E)-4-(substitutedbenzylideneamino)-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiols.

SECTION-III: Synthesis and antimicrobial evaluation of 6-(Substitutedphenyl)-3-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles.

SECTION-IV: Synthesis and antimicrobial evaluation of 6-(substitutedphenyl)-3-(pyrazin-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines.

SECTION-I: Synthesis and antitubercular evaluation of (E)-4-(substitutedbenzylideneamino)-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiols.
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Synthesis of (E)-4-(substituted benzylideneamino)-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiols were carried out by the reaction of 4-amino-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiol and various aryl aldehydes in the presence of catalytic amount of conc. HCl

SECTION-II: UV studies of some (E)-4-(substituted benzylideneamino)-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiols.

SECTION-III: Synthesis and antimicrobial evaluation of 6-(Substituted phenyl)-3-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles.

Synthesis of 6-(Substituted phenyl)-3-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles were carried out by the reaction of 4-amino-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiol and various aryl acids in the presence of POCl3 at 95-100°C temperature.

SECTION-IV: Synthesis of 6-(substituted phenyl)-3-(pyrazin-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives

Where R= 4-Cl, 4-F, 2-Cl, 3-Br, 4-NO2 etc.

Where R= 4-Cl, 4-F, 2-Cl, 3-Br, 4-NO2 etc.

Where R= 4-OMe, 4-Cl, 2-Br, 3-OMe, 2,4-Di Cl etc...

Where R= H, 4-Cl, 4-Br, 4-OMe, 4-Me etc.
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Synthesis of 6-(substitutedphenyl)-3-(pyrazin-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines were carried out by the reaction of 4-amino-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3-thiol and various phenacyl bromide in the presence of DABCO as catalyst.

CHAPTER-2: STUDIES ON HYDRAZIDE-HYDRAZONE DERIVATIVES

Pyrazinamide is one of the frontline agents that played a significant role in shortening the duration of treatment of MDR-TB. It is considered to be a prodrug that requires activation by pyrazinamidase to pyrazinoic acid, which is believed to be the active form. The SAR of pyrazinamide derivatives is still very limited because the drug is active only under acidic conditions and more efficacious in vitro than would be predicted by its in vitro potency with vaguely defined mechanism of action. On the other hand, the hydrazine-hydrazide derivatives as well as the N4-alkyl thiosemicarbazides of the anti-mycobacterial drug isoniazid were reported to improve its activity. Therefore, guided by the above mentioned data as well as the high activity of pyrazinamide against MDR-TB, we would like to report the synthesis, antimycobacterial screening of a new series of pyrazine-2-carboxylic acid hydrazide derivatives which have been further described in following sections.

SECTION-I: Synthesis and biological evaluation of (E)-N'-((E)-3-(4-chlorophenyl)-1-(substitutedphenyl)allylidene)pyrazine-2-carboxyhydrazides.

SECTION-II: Crystallographic study of (E)-N'-(E)-1-(4-bromophenyl)-3-(4-chlorophenyl)allylidene)pyrazine-2-carboxyhydrazide

SECTION-I: Synthesis and biological evaluation of (E)-N'-(E)-3-(4-chlorophenyl)-1-(substitutedphenyl)allylidene)pyrazine-2-carboxyhydrazides.

Where R = 4-Br, 4-F, 4-Me, 3,4-DICl, 4-NO₂
(E)-N’-((E)-3-(4-chlorophenyl)-1-(substitutedphenyl)allylidene)pyrazine-2-carbohydrazides were synthesized by the reaction of pyrazine 2-carbohydrazide and different chalcone in acetic acid as a solvent at reflux temperature.

SECTION-II: Crystallographic study of (E)-N’-((E)-1-(4-bromophenyl)-3-(4-chlorophenyl)allylidene)pyrazine-2-carbohydrazide

In the present study, methanol was selected as solvent; however, methanol yielded good quality single crystals. Good quality crystals were picked for X-RAY analysis.

CHAPTER-3: STUDIES ON OXADIAZOLEDERIVATIVES

Oxadiazoles belong to an important group of heterocyclic compounds having –N=C-O- linkage. 1,3,4-Oxadiazoles are of significant interest in material science, because of their chemical/thermal stabilities and their high photoluminescence quantum yields. Since oxadiazoles groups are known as one of the most extensively investigated class of electron-accepting species, Oxadiazoles based compounds have been used as electron transport materials in organic light emitting diodes.

1,3,4-Oxadiazoles are imported class of compounds have long attracted attention owing to their remarkable biological and pharmacological properties such as antitubercular, antibacterial, antiviral, antiinflammatory, antifungal and insecticidal activity. In our research we found that oxadiazole and substituted oxadiazole itself possessed antibacterial and antifungal activities.

The purpose of the synthesis is to crossbreed molecule possessing two active parts in one molecular scaffold. It is a deep rooted approach to synthesize more potent compounds with twin activity such hybridization was designed in order to investigate the effects of structural variation on the anticipated antimicrobial and antitubercular activities.

These studies are described in following section.

SECTION-I: Synthesis and biological evaluation of 2-(5-(4-(substituted phenyl)-1,3,4-oxadiazol-2-yl) pyrazines.
SECTION-II: Synthesis and biological evaluation of N-(substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)thio)acetamides.

SECTION-III: Thermal studies of some N-(substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)thio)acetamide derivatives.

SECTION-I: Synthesis and biological evaluation of 2-(5-(4-(substituted phenyl)-1,3,4-oxadiazol-2-yl) pyrazines.

2-(5-(4-(Substitutedphenyl)-1,3,4-oxadiazol-2-yl) pyrazines of type(I) were synthesized by the reaction of pyrazine 2-carbohydrazide and various aryl acids in the presence of POCl$_3$ at 90-100°C temperature.

SECTION-II: Synthesis and biological evaluation of N-(substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol 2yl)thio)acetamides.

N-(Substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)thio) acetamides of type(II) were synthesized by the reaction of 4-amino-5-(pyrazin-2-yl)-4H-1,2,4-triazole-3 thiol, 2-chloro-N-(substituted-phenyl)acetamide in presence of potassium carbonate as base.

SECTION-III: Thermal studies of some N-(substitutedphenyl)-2-((5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)thio)acetamides.

In this section, the thermal properties of some selected compounds were studied by TGA and DSC techniques. From this data, different kinetic parameters like energy of activation, order of degradation, frequency factor and entropy change were evaluated. The stability of various compounds was also determined from these data.
PART-B: STUDIES ON IMIDAZO [1,2-a]PYRAZINE DERIVATIVES

The imidazo[1,2-a]pyrazine is an interesting skeleton to design inhibitors with variable substitutions because of its planar shape. While C3, C5 and C6 form one edge of the plane, and the N7, C8 and N1 form the other. The C2 is positioned at the middle where these two edges meet. Note that N1 and N7 are hydrogen bond acceptors. Larger substitutions on C8 may be deleterious on the activity due probably to affecting the hydrogen bonding capacity of N1 and N7.

Imidazo[1,2-a]pyridines, -pyrazines, and -pyrimidines, nitrogen- bridgehead fused heterocycles containing an imidazole ring, are a common structural motif in pharmacologically important molecules, with activities spanning a diverse range of targets. Imidazo[1,2-a]pyrazines have been gaining attention in drug discovery realm especially as structural analogues of purines. Derivatives of imidazo[1,2-a]pyrazines exhibit various pharmacological activities such as antibiotic, anti-inflammatory, uterine relaxing activity, antibronchospastic, antiulcer, cardiac stimulating, antidepressant, hypoglycemic activity, antiproliferative activity, controlling allergic reactions, smooth muscle relaxant properties and phosphodiesterase inhibitory activity. They have also been shown to inhibit the receptor tyrosine kinase EphB4 recently.

CHAPTER-1 Synthesis and antimicrobial evaluation of 6-bromo-2-(substitutedphenyl)imidazo[1,2-a]pyrazines.

6-Bromo-(2-substitutedphenyl)imidazo[1,2-a]pyrazines have been synthesized by the condensation of 2-amino 5- bromo pyrazine and different phenacyl bromides in the presence of DABCO as a catalyst.

The constitution of all the synthesized compounds have been characterized by FT-IR and $^{1}$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all these synthesized compounds has been checked on thin layer chromatography.

Many of the synthesized compounds were subsequently screened for their in vitro antitubercular activity against Mycobacterium tuberculosis H$_{37}$Ra using Isoniazid as reference standard.