DESIGN, SYNTHESIS AND EVALUATION OF PHARMACOLOGICALLY ACTIVE COMPOUNDS

A

SYNOPSIS SUBMITTED

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INTRODUCTION

The lack of the wide spectrum of biological data is an important obstacle preventing the efficient molecular design. Quinoline derivatives are known to exhibit a variety of biological effects.[1] Quinolines have wide varieties of activities including antimalerial, antimicrobial, anti HIV, etc. Newer approaches of quinolines are also established as immunosuppressive agents, dual antagonists for NK2 and NK3 Receptors, as antimycobacterial agents, antifungal agents, useful in cardiovascular therapy, as local anesthetic agents etc.

A novel and highly convergent synthesis leading to 2-phenyl-quinolines has already been developed.[2] The newer quinoline carboxylic acids are active against a broad spectrum of bacteria. Preliminary results of pharmacokinetic studies indicate that plasma and tissue concentrations of these compounds may be within the therapeutic range, even after oral administration.[3]

Immunosuppressive drugs, immunosuppressive agents, or immunosuppressants are drugs that inhibit or prevent activity of the immune system. They are used in immunosuppressive therapy to[4-12]:

- Prevent the rejection of transplanted organs and tissues (e.g., bone marrow, heart, kidney, liver, etc)
- Treat autoimmune diseases or diseases that are most likely of autoimmune origin (e.g., rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, pemphigus, and ulcerative colitis).
- Treat some other non-autoimmune inflammatory diseases (e.g., long term allergic asthma control).

Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions. Deliberately induced immunosuppression is generally done to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease. [4-12]

A person who is undergoing immunosuppression, or whose immune system is weak for other reasons (e.g. chemotherapy, and HIV patients) is said to be immuno-compromised. When an organ is transplanted, the immune system of the recipient will most likely recognize it as foreign tissue and attack it. The destruction of the organ will, if untreated, end in the death of the recipient. [4-12]

In the past, radiation therapy was used to decrease the strength of the immune system, but now immunosuppressant drugs are used to inhibit the reaction of the immune system. The downside is that with such a deactivated immune system, the body is very vulnerable to opportunistic infections, even those usually considered harmless. Also, prolonged use of immunosuppressants increases the risk of cancer. [4-12]

Varieties of drugs are used as immunosuppressive agents like glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins, etc. Current recommended therapy for the prevention of organ transplantation rejection and related disorders, including graft versus host disease, traditionally involves patient treatment with cyclosporin A (CSA) and adjunctive therapy with corticosteroids and other immunosuppressive agents.[4-12]

The synthesized series of compounds in present investigation will be useful to permit the administration of reduced doses of other immunosuppressive agents like CSA and analogs thereof, FK506, corticosteroids including Prednisolon, azathioprine (AZA),

mycophenolic acid or the morpholine ethyl ester, mycophenolate mofetil, rapamycin, 15-deoxyspergualin, mizoribine, leflunomide, OKT3, anti-interleukin-2 receptor antibodies, misoprostol, methotrexate, cyclophosphamide, and anti-lymphocyte/thymocyte serums, therewith, thereby reducing the adverse effects of these agents.[4-12]

2-carbocyclic and 2-heterocyclic quinoline-4-carboxylic acids and their salts are newly developed series of compounds which are useful as immunosuppressive agents. This invention relates to 2-carbocyclic and 2-heterocyclic quinoline-4-carboxylic acid compounds, pharmaceutical compositions comprising such compounds, and to methods of using such compounds for the treatment and/or prevention of organ transplantation rejection, graft versus host disease, autoimmune diseases, and chronic inflammatory diseases, including but not limited to psoriasis and rheumatoid arthritis, in a mammal.[13]

The 2-carbocyclic and 2-heterocyclic quinolinecarboxylic acids are potent inhibitors of dihydroorotate dehydrogenase, the fourth enzyme in the de novo pyrimidine nucleotide biosynthesis pathway, and therefore have a unique mechanism of action (inhibition of dihydroorotate dehydrogenase) which is distinct from other available immunosuppressive agents. The compounds of this series could be useful as single therapy agents as well as agents to be used in combination with other compounds currently used in these clinical regimens such as CSA (Cyclosporine A), prednisolone, etc.[13]

A diuretic is any drug that elevates the rate of urination (diuresis). The mammalian kidney generates its excretory product, the urine, in a two-step process where filtration of a large volume of plasma-like fluid across the glomerular blood capillaries is followed by the absorption and secretion of solutes and water across the tubular epithelial cell wall. Transcellular absorption of filtered Na is achieved by apical Na uptake along a favorable electrochemical gradient, and by basolateral Na extrusion through the energy consuming action of Na/K ATPase.

The renal tubule is cytologically and functionally heterogeneous along its longitudinal axis. One expression of the functional heterogeneity is the type of transport protein responsible for apical Na uptake. As a general rule, currently available diuretics inhibit a specific apical Na transporter, and their action therefore displays tubule segment-specificity. Na uptake in the proximal tubule, a segment in which about 2/3 of the filtered Na is reabsorbed, is mediated by a Na/H exchanger (NHE3) and a number of other transporters that typically carry a second solute in a Na-dependent co-transport mode. Along the thick ascending limb of the loop of Henle Na uptake occurs mostly through the electro-neutral Na/K/2Cl – cotransporter (NKCC2) in a process that accounts for roughly 25% of total renal Na absorption. Na uptake in the distal convoluted tubule is mediated by a NaCl cotransporter (NCC), and this segment accounts for about 5% of Na absorption. Finally, electrogenic Na absorption through the epithelial Na channel (ENaC) is the uptake mode across the cortical collecting duct, a process that may be responsible for 2–3% of Na absorption. Na transport through ENaC is regulated by the adrenal gland steroid aldosterone.[4-12]

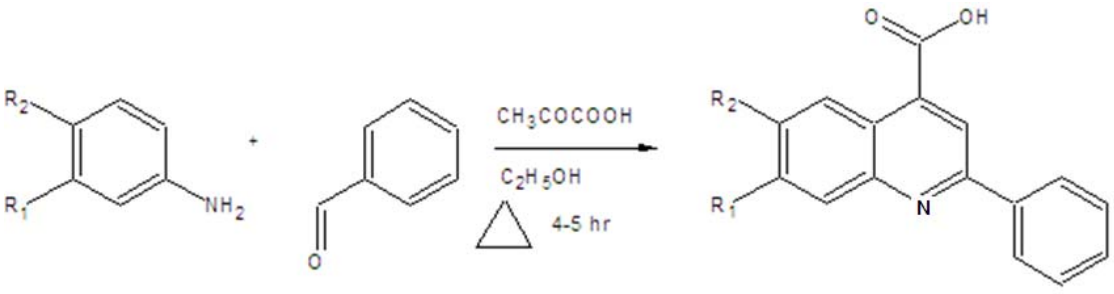
There are several categories of diuretics. All diuretics increase the excretion of water from the body, although each class of diuretic does so in a distinct way. These types of drugs are also involved in excretion of sodium, potassium, and chloride ions from body in different proportion. Diuretic drugs are useful with drugs used in hypertension to avoid edema and hypernetremia. They are classify as High ceiling loop diuretics, Thiazides, Potassium-sparing diuretics, Osmotic diuretics and Low ceiling diuretics.[4-12] No such activity of these derivatives is reported yet.

Quinolines are broad spectrum antibiotics. They are increasingly used because of their relative safety, their availability, both orally and parenterally and their favorable pharmacokinetics. There is increasing concern about the emergence of resistance to these agents. Quinolines as well as quinolones are bactericidal. They inhibit bacterial DNA synthesis in several ways causing rapid cell death. Quinolones bind the DNA-DNA gyrase (topoisomerase II) complex blocking further DNA replication. Quinolines have wide verities of activities including antimalarial, antimicrobial, anti

HIV, etc. Fluoro-quinolones are widely used drugs as antimicrobial agents. Good and comparative results were already reported for substituted quinoline-4-carboxylic acid derivatives against gram positive and gram negative organisms.[14-16]

AIM AND SCOPE

2-carbocyclic and 2-heterocyclic quinoline-4-carboxylic acids and their salts are newly developed series of compounds and useful in various diseases. Various different methods were used for the synthesis of quinoline derivatives [17-24] and for the synthesis of quinoline-4-carboxylic acid derivatives.[13, 25-32] A review of the literature reveals that a little work has been carried out on 2-phenyl-6,7-substitutedquinoline-4-carboxylic acid derivatives. Thus it was thought to synthesize novel derivatives of 2-phenyl-6,7-substituted-quinoline-4-carboxylic acid by short and efficient method. All the compounds are synthesized by conventional as well as microwave assisted route. The well known name reaction methods were used for the synthesis of substituted quinoline-4-carboxylic acid derivatives.[33,34]



The synthesized compounds are evaluated for their immunosuppressive activity, diuretic activity and for their antimicrobial activity by well known models.

PRESENT INVESTIGATION

The present investigation describes synthesis of 2-phenyl-6,7-substitutedquinoline-4-carboxylic acid derivatives by conventional and microwave irradiated route by short and efficient method. These synthesized novel derivatives are evaluated for their immuno-modulatory activity by estimating White Blood Cell counts in rat blood.[35-41]

Diuretic activity is estimated by measuring volume of urine, by estimating sodium, potassium and chloride ion concentration in urine and also their ratio. Ratio is also used for evaluation of synthesized compounds for their natriuretic, saluretic or carbonic anhydrase inhibition activity.[42-49] Finally, antimicrobial activity was evaluated for gram positive and gram negative organisms by cup well method on nutrient agar plat by measuring zone of inhibition.[50-55]

Thesis contains EIGHT chapters:

Chapter I: Introduction

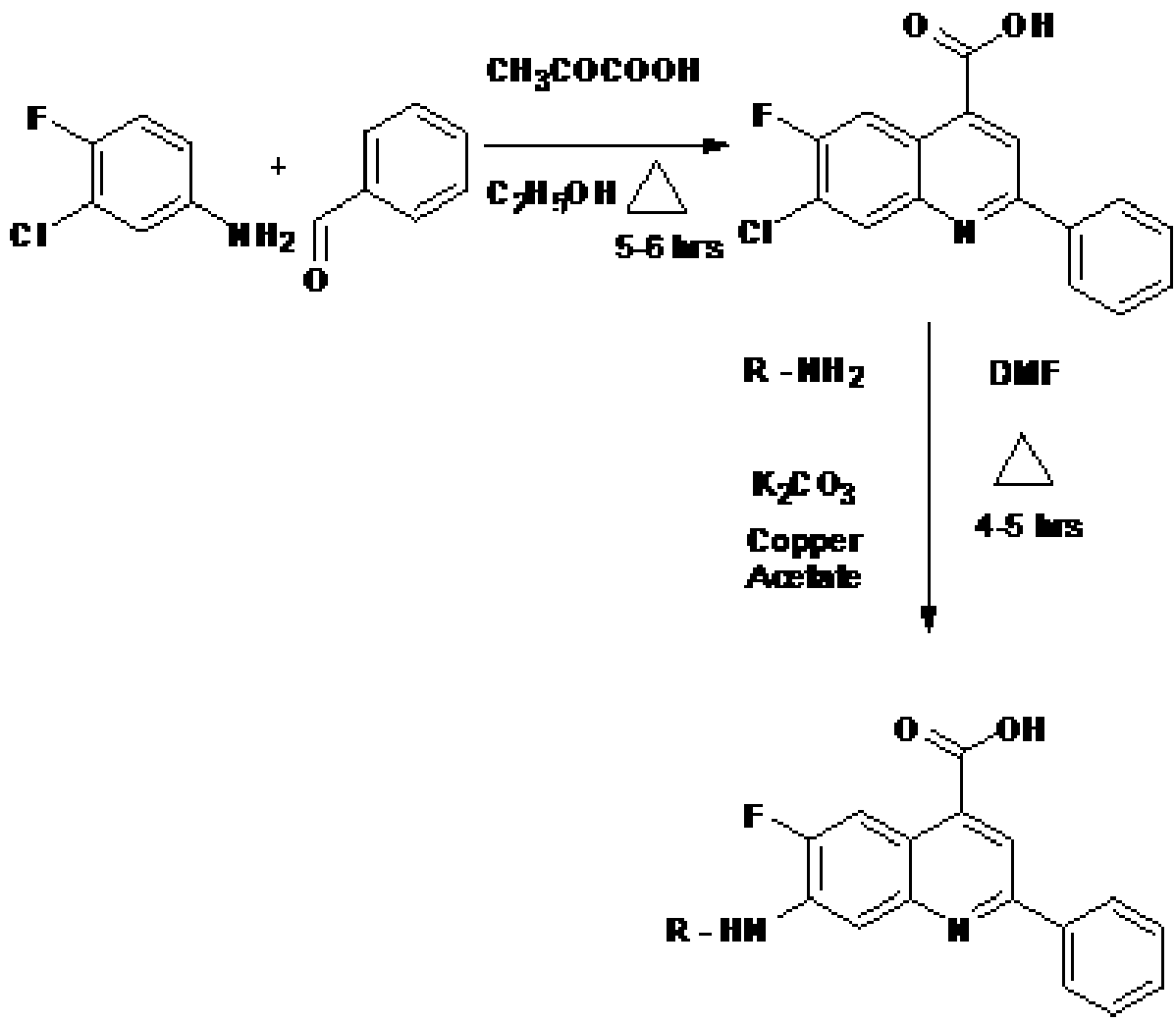
An introduction is given regarding quinoline derivatives, current treatment and drugs used as immunosuppressive agents, diuretic agents, and as antimicrobial agents. An extensive review of the literature work related with various newly developed quinoline-4-carboxylic acid derivatives and their application is discussed in given chapter. Aim and scope of the present work is discussed.

Chapter II: Experimental

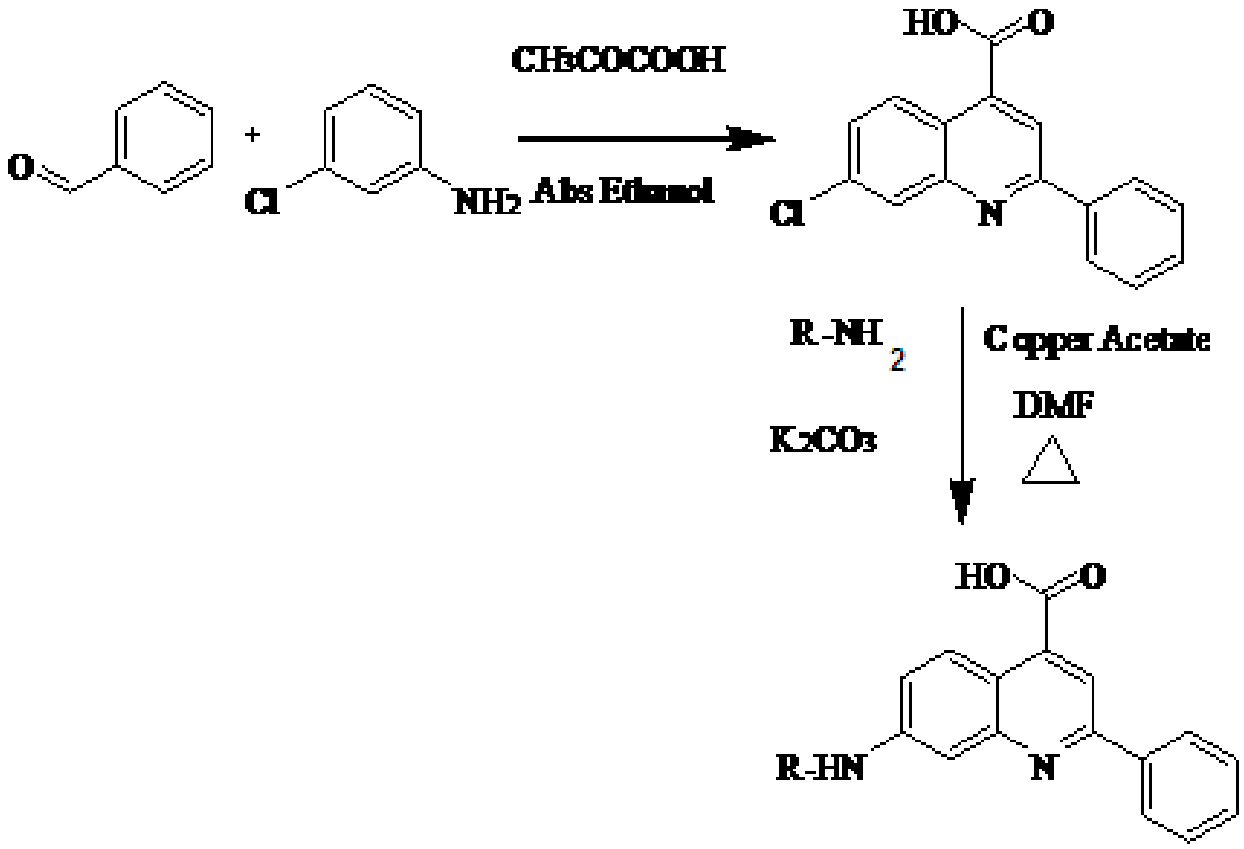
Compounds of the present invention are synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry. Equimolar quantity of starting materials are taken and reacted. Aldehyde, pyruvic acid and substituted aromatic amine were dissolved in absolute ethanol and refluxed. Keep the solution overnight at room temperature. Filter off the solid precipitates from the solution. Wash the solid with little quantity of ether and dry. Recrystallize the intermediate quinoline-4-carboxylic acid molecules and report their melting point.

The intermediate quinoline-4-carboxylic acid molecules were substituted with different amines. After completion of refluxing, add the solution to crushed ice, stir well. Solid separates out, filter it and dry. Recrystallize the solid and report their melting point.

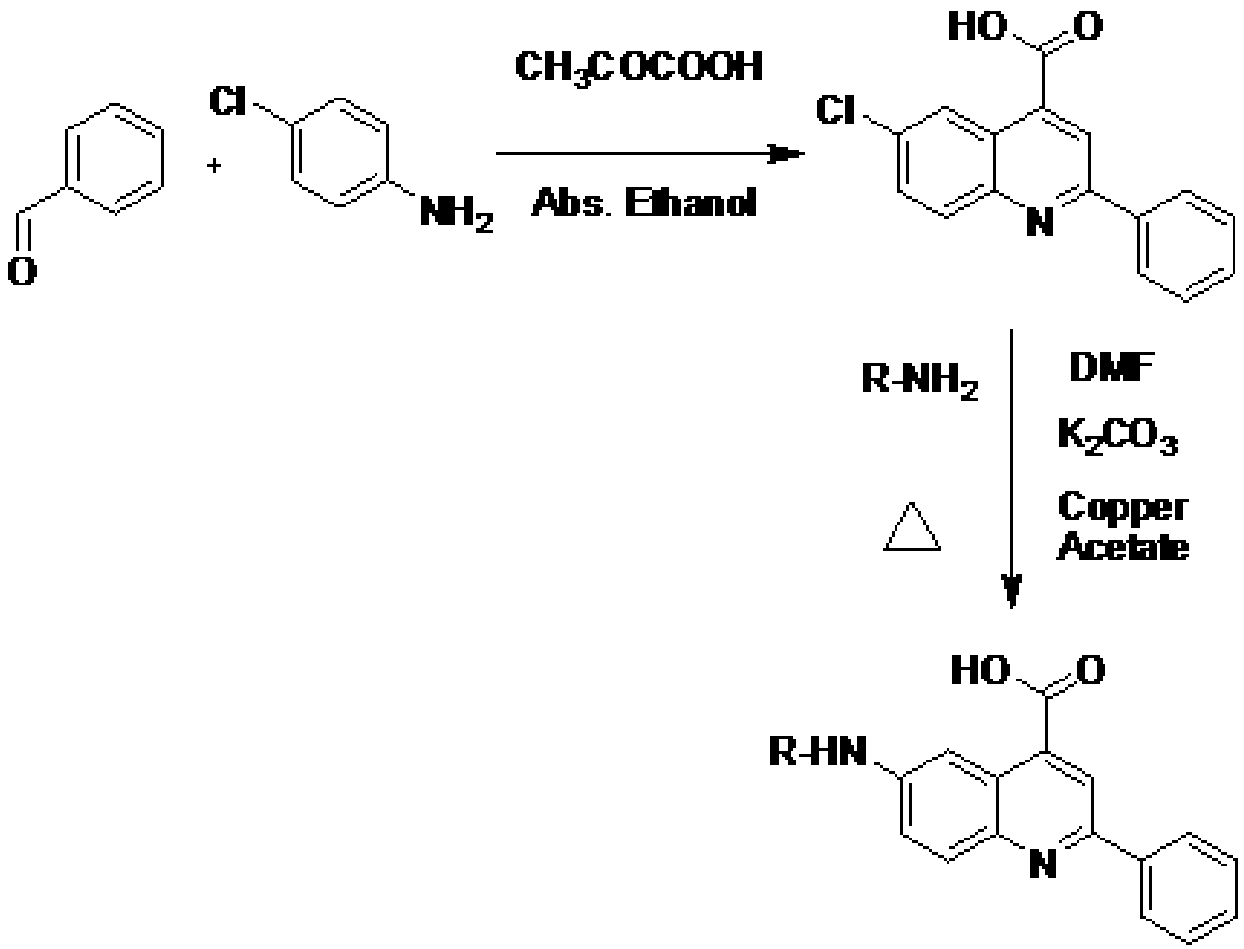
Scheme 1.


F
Cl
NH2
O
+
CH3COCOOH
C2H5OH
5-6 hrs
O
OH
F
Cl
N
R - NH2
DMF
K2CO3
Copper
Acetate
4-5 hrs
O
OH
F
R - HN
N

Scheme 2.


CH3COCOOH
Abs Ethanol
HO
O
Cl
N
R-NH2
K2CO3
Copper Acetate
DMF
R-HN

Scheme 3.



Mainly two different routes for the synthesis are used:

1. Conventional route
2. Microwave assisted route

Microwave assisted route has many advantages over conventional methods which include:

1. Shorter duration time for reaction
2. High purity
3. High yield of compound
4. Solvent free synthesis

Chapter III: Results and Discussion

Finally, in all, we have synthesized more than 35 compounds, by both routes-conventional and microwave irradiated method, which were also compared. Melting points of compounds were taken, all were uncorrected. Purity of the compounds was also checked by TLC analysis. The composition and the structure of synthesized quinoline-4-carboxylic acid derivatives had been confirmed by elemental analysis, FT-IR, ^{1}H NMR and Mass spectroscopy.

Chapter IV: Immunosuppressive Activity of Synthesized Compounds

The synthesized compounds were screened for their immunosuppressive activity by estimating white blood cell counts in rat blood. Rats were divided in the group of six animals each for control, standard, and treated groups. Dose of drugs were given orally. Prednisolon, 50mg/kg was taken as a standard drug. Blood samples were collected from the retro-orbital plexus into EDTA tubes and WBC counts were measured by cell counter. Satisfactory results of treated groups were found as compare to standard drug.

Chapter V: Diuretic Activity of Synthesized Compounds

The synthesized compounds were screened for their diuretic activity by estimating urine output volume, concentration of sodium ion, potassium ion, chloride ion and their ratio. Rats were divided in the group of six animals each for control, standard, and treated groups. Dose of drugs were given orally. Furosemide, 10mg/kg was taken as a standard drug. Kept rats in metabolic cage (Three rat in each cage) and they were deprived of food and water. After 24hr, collect urine, measure volume, and find out concentration of Na, K, Cl by known reported methods, and their ratio. Satisfactory results of treated groups were found as compare to standard drug Furosemide.

Chapter VI: Anti-Microbial Screening of Synthesized Compounds

The synthesized compounds were screened for antimicrobial activity by taking ofloxacin and Gentamycin (10, 100 and 200 μg) as standard drugs by cup well method

using nutrient agar. Nutrient agar was solidified in petri-dish; gram positive and gram negative organisms were spread over solidified agar with the use of glass spreader. Well was made with the help of borer and specific concentration of drug is filled in the well. Three different concentrations of drugs were used and zone of inhibition was measured. Comparative and satisfactory results were obtained.

Chapter VII: Conclusion

The present invention relates to the synthesis of series of novel substituted Quinoline-4-carboxylic acids and their derivatives. All the compounds were synthesized by both, conventional and microwave irradiated methods for the first time and methods of using such compounds as immunosuppressive agents for the treatment and/or prevention of organ transplantation rejection, graft versus host disease, autoimmune diseases, and chronic inflammatory diseases. Few of the synthesized compounds show good results as compare to standard drug. The synthesized compounds were also screened as diuretic agents and few compounds show comparative result with standard. Some of the synthesized compounds also showed good to moderate natriuretic activity. Synthesized compounds were also evaluated as antimicrobial agents. Satisfactory results were obtained. The synthesized quinoline-4-carboxylic acid series can be further exploited in future.

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(Hardik G. Bhatt)

Signature of the Research Guide
(Prof. Y. K. Agrawal)