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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED PIPERAZINE COMPOUNDS & NEW SUBSTITUTED BIOLOGICAL ACTIVE DERIVATIVE OF QUINOLINE

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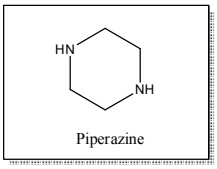
ABSTRACT:

Pharmaceutical chemistry related with the discovery, development & identification of mechanism of action of biologically active compounds. Further various biologically active synthetic compounds have six membered two nitrogen containing heterocyclic ring in their structures. The high therapeutic properties of the piperazine related drugs have encouraged the medicinal chemists to synthesize a large number of novel antihypertensive, antibacterial and antifungal agents.



Piperazine

Piperazine ring has been found to exhibit wide spectrum of biological activities and it is used in many drugs against different diseases.

Moreover, Quinoline and its fused heterocyclic derivatives tested with diverse pharmacological activity functional groups constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities.

make up an important class of drugs , match up to several types of pharmacological agents possessing antibacterial , antiviral and ant carbonic anhydrase , diuretic , protease inhibitor, cyclo-oxygenase and anticancer activities among other. In the present study we have synthesized new analogs of piperazine and quinoline. The structure of these synthesized compounds was confirmed by NMR, IR, Mass and CHN analysis. According to the result of this spectra and analysis were found that in the normal range. These compounds were evaluated for the antibacterial and antifungal.

KEYWORDS: *Pharmaceutical chemistry , possessing antibacterial , antiviral and ant carbonic anhydrase.*

INTRODUCTION :-

Drug development has been one of important research areas in the field of pharmaceutical industry, as a result the development the new molecules with the help of heterocyclic compound continuous drag toward academic and industrial level. Here attempted trial for prepared newer class of the safer

antibacterial and antifungal agent as per necessitate according to time and cost.

Piperazine is a heterocyclic compound containing four carbon atoms and two nitrogen at 1 & 4 postion (as called 1,4 –hexahydropyrazine) Moreover here Nitrogen atom is play major role in piperazine derivative as a biological research and drug manufacturing industry. Moreover , the piperazines are a wide class of chemical compound, many with important pharmacolgical properties which contain a centre piperazine functional group.

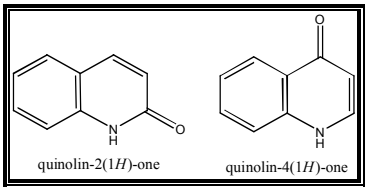
IMPORTANT OF PIPERAZINE MOIETY:

1. Piperazine moieties are promising as a primary gallows to enhance the drug –like properties of the molecules in the based on reason drug design process.
2. Piperazine skeleton have been originate in a multiplicity of marketed drugs if the various therapeutic categories.
3. Piperazines can be good substitute to other nucleophilic in order to influence the overall pharamacogical side view of the parent molecules positively.
4. Replacement functional group present on the piperazine ring system may be the factor responsible for the unpredictable drug action of the molecules.
5. Molecules possessing piperazine entities can be useful to aim multiple pharamacogical activities.

QUINOLINE DERIVATIVES:

Quinoline was discovering by Runge IN 1834. It is a colourless hygroscopic liquid; additionally, the application of the quinoline is varied, this quinoline found from the natural product like alkaloids. It is mainly used in the pharmaceutical, agrochemical, dye stuff and as a chelate metallic ion as N-donor ligands also. Subsequent, quinoline has been found wide range in the pharamacogical activities. It was well known for malaria but it's also play role in the antitumor and anti-inflammatory.

Quinoline is a collection of compounds synthesis from the bicyclic aromatic compounds with fused six membered heterocyclic nucleuses containing the one nitrogen atom in the moiety. While the carbonyl group contain with any position of the quinoline ring that it is known as the 2-oxo-quinolone / quinolines. At this moment oxo quinoline moiety also take part in the therapeutic drug. Moreover the quinoline derivative was research carried out past many decades due to its good therapeutic potential.



Quinoline derivative are variety of human disease like the HIV- treatment, antiviral, antibacterial, antimalarial and anti-immflamatory, anti-ischemia and anticancer, antifungal also. Malaria is one of the world serious public health problems. Quinoline is one of the best effective medicines for the malaria disease. Additionally, these moieties also very important play the role in the covid-19 which is very serious matter for our all world in March 2020. As per result this moiety is very good biological result the cure the covid-19.

The exchange of the quinoline ring with another heterocyclic substitution is also take part in to the new drug preparation in research. As per literature of the quinoline moiety is shown the new drug for malaria treatment was proceed with help of the pyrimidines and triazole derivatives resultant it was give the less toxic drug and more selective for the biological activity.

RESEARCH METHODOLOGY

My Research approaches include the plan and the procedure for research than duration the steps from broad assumptions to detailed methods of data collection, analysis and interpretation using

NMR, IR and mainly thin layer chromatography. The overall decision involves which approach should be used to study a topic.

A research design is the arrangement of conditions for collections and analysis of data in a manner that aims to combined relevance to the research purpose with economy in procedure.

OBJECTIVE

Thesis work based on "Evaluation, synthesis and characterization of novel heterocyclic compounds contain biological activity.

Taking a view, the applicability of heterocyclic compounds, I have undertaken the preparation of heterocycles bearing piperazine and quinoline nucleus. The placements of a wide variety of substituent's of nuclei have been a design in order to evaluate the synthesized products for their pharmacological profile against several of antibacterial, antifungal, and antibiotic. The objective of the proposed research work is as follow:

To study on biological active derivative of piperazine& new substituted quinoline compounds.

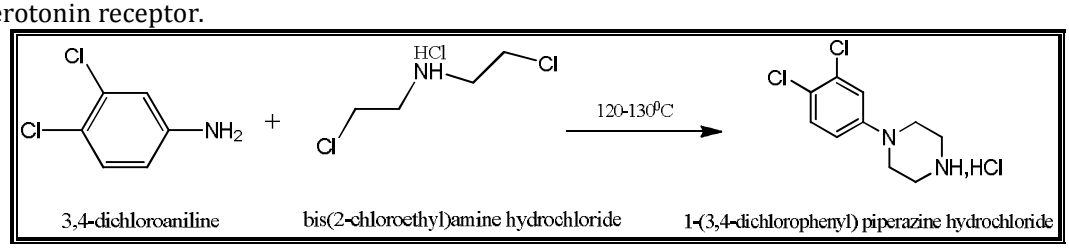
Scope of Study

Research statement of the study is to develop an efficient synthesis route and salt derivatives to isolated class of Antibacterial, antipsychotic, antifungal and therapeutic compounds the unique chemical structure of this series of compound contain Nitrogen, Oxygen and sulpher atom skeleton and their significant activity. The novel structure of the compound makes it a desirable synthetic target, as a successful synthetic route to allow the investigation of related heterocyclic compounds which may show improve research study. Heterocyclic compounds play important role towards the development of drug discovery. The study of biological properties of newly synthesized heterocyclic compounds is the main significance of the proposed research work. The rich activity of heterocyclic compounds in biological systems is important for pharmaceuticals, agricultural, and natural products. Heterocyclic compounds have provided a platform for the rapid exchange of research in the areas of organic, pharmaceutical, analytical, and medicinal chemistry.

RESULT AND DISCUSSION

Novel piperazine intermediate prepared as per following route of synthesis for 1-(3,4-dichlorophenyl) piperazine. Further conduct reaction with different functional group moiety resultant formation of new compound with biological activity.

This intermediate is a potential precursor in synthesizing important drugs that target dopamine and serotonin receptor.

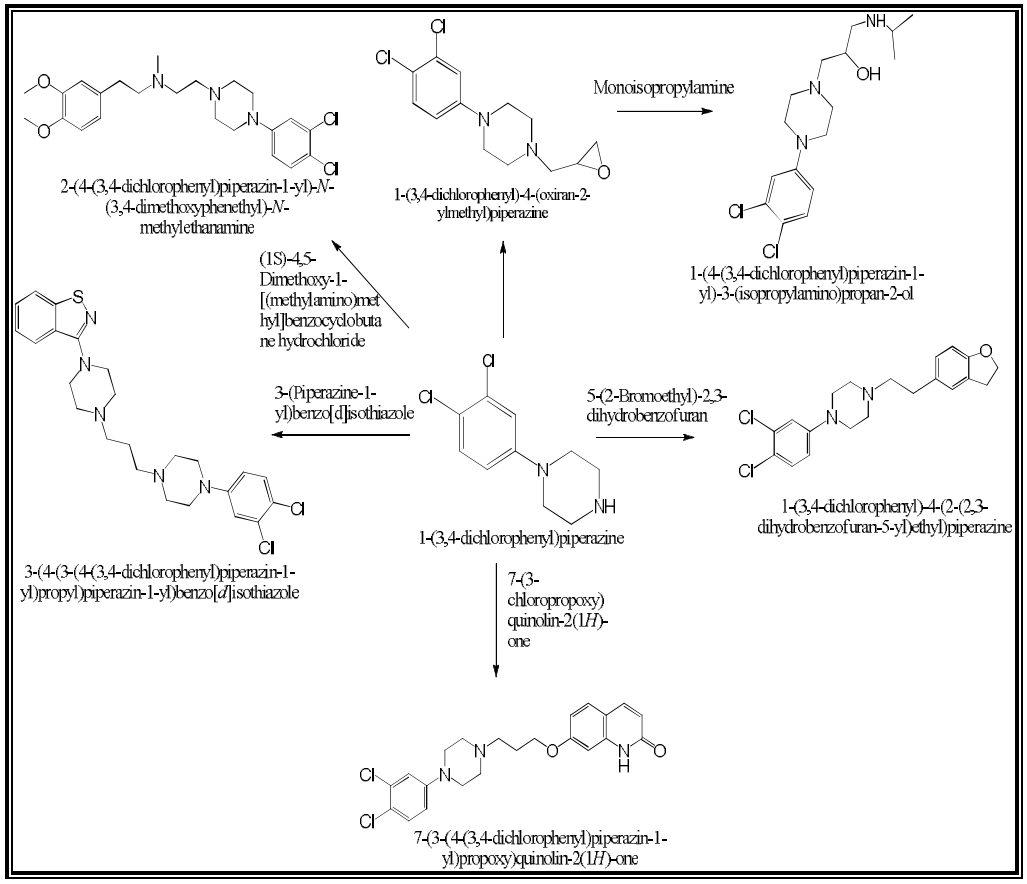


Process

3,4-Dichloroaniline react with bis(2-chloroethyl)amine hydrochloride at 120-130^{0}C resultant the cyclization occur during the reaction progress; further this reaction monitored on TLC (Dichloromethane : Methanol: Ammonia :8 :1:1). If the reaction complies; cool the reaction mass and added the water into the reaction mass and extract in the dichloromethane (3 volumes) solvent. Took organic layer and wash with saturated sodium bicarbonate solution still neutral pH . Finally, water and brine washed to organic layer and distilled it completed & isolated in methanol at 10-15^{0}C. Additional worked as this intermediate react with other heterocyclic compound follow on formation of novel

intermediates which shown the good biological activity as the antibacterial and antifungal, antihypertensive.

a).1-(3,4-dichlorophenyl)-4-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)piperazine.
b).7-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propoxy)quinolin-2(1H)-one.
c).3-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propyl)piperazin-1-yl)benzo[d]Isothiazole.
d).2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-N-(3,4-dimethoxyphenethyl)-N-methylethanamine.
e).1-(3,4-dichlorophenyl)-4-(oxiran-2-ylmethyl)piperazine.
f).1-(4-(3,4-dichlorophenyl) piperazin-1-yl)-3-(isopropylamino)propan-2-ol.



Note: prepared different derivative using the piperazine moiety with condense the heterocyclic compounds (R: Alkyl group, aromatic ring derivatives, Heterocyclic compounds).

Process

a) 1-(3,4-dichlorophenyl)-4-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)piperazine.

This intermediate is prepared using the 1-(3,4-dichlorophenyl)piperazine react with 5-(2-Bromoethyl)-2,3-dihydrobenzofuran in the presence of the potassium carbonate as a inorganic base in dimethylactamide solvent; further maintain the reaction mass at 40-45^{0}C for 12 hours. Reaction progress was monitored on TLC. After intermediate complied on TLC; follow on cooled reaction mass 10-15^{0}C & charge the process water (10 volume) in to reaction mass with maintain temperature. Extract reaction mass in ethyl acetate. Distilled the organic layer and isolated in disopropyl ether. Further, isolated material 89%.

b) 7-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propoxy)quinolin-2(1H)-one.

Prepared this intermediate compound in the presence of the inorganic base in N, N-Dimethylformamide resultant formation of the desired compound with good yield and quality. Isolated yield: 95 %.

c) 3-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propyl)piperazin-1-yl)benzo[d]Isothiazole.

1-(3,4-dichlorophenyl)piperazine is reacted with 3-(Piperazine-1-yl)benzo[d]Isothiazole in the presence of the organic base like triethylamine at 45-50^{0}C; resultant reaction did not complies after prolong stirring ; yield low. Further in this direction; performed this condensation reaction using the sodium bicarbonate, sodium carbonate and potassium carbonate; according to optimized condition sodium carbonate is better base for complete conversion of intermediate. Follow on the yield and purity was good. Yield of isolated material shown 88 % w/w.

d).2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-N-(3,4-dimethoxyphenethyl)-N-methylethanamine.

(S)-2,2-diphenyl-2-(pyrrolidin-3-yl)acetamide(2R,3R)-2,3-dihydroxysuccinate heterocyclic compound is conducted reaction with 7, 8-diethoxy-4, 5-dihydro-1H-benzo[d]azepin-2(3H)-one in the presence of the Dimethyl acetamide solvent and inorganic base at 40-45^{0}C. Monitor the reaction complies on the thin layer chromatography; further isolation conduct with addition of the water and extract in the dichloromethane solvent. Yield of isolated material: 89 %.

e) (S)-3-(4-(((3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl)(methyl)amino)butyl)-7,8-diethoxy-1H-benzo[d]azepin-2(3H)-one

1-(3,4-dichlorophenyl)piperazine is reacted with(1S)-4,5-Dimethoxy-1-[(methylamino) methyl]benzocyclobutane hydrochloride in the presence of potassium carbonate in N,N-Dimethylformamide resultant reaction was complies. Further, cool the reaction mass 0-10^{0}C.add slowly the process water into the reaction mass follow on the solid was precipitate. Cool the reaction mass and maintain for 1 hr. filter the reaction mass and wash the process water at 20-25 ^{0}C.yield of isolated material 91%.

f) 1-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-(isopropylamino)propan-2-ol

1-(3,4-dichlorophenyl)piperazine is reacted oxirane intermediate in the presence of the Triethylamine as a base follow on ; further the react this intermediate monoisopropylamine resultant 1-(4-(3,4-dichlorophenyl)piperazin-1-yl)-3-(isopropylamino)propan-2-ol. Yield of isolated material 85 %.

RESULT

The physical data as well as UV-vis, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral data confirmed formation of the desired products. All synthesized compounds showed the very good biological activity.

a) 1-(3,4-dichlorophenyl)-4-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)piperazine (I):

Yield; 78%, RF: 0.56, IR (KBR cm-1); 3010, 2950 (Aromatic group); 1320-1000 (-C-O); 1400-1500 (methylene group).^{1}H-NMR (dmso-d_6, δ ppm); 6.88 (d,2H,Ar-H), 7.37 (d,2H,Ar-H), 3.44 (triplet,2H piperazine),2.67 (2H,methylene chain benzofuran and piperazine), 2.97-4.27 ppm (2H, methylene compound benzofuran). ^{13}C-NMR (dmso-d6, δ ppm) 112.9-129.2 (Ar-C), 51.3-56.3 (-CH_2), 29.8-79.8 (-CH_2 benzofuran), 33.7-60.4 (-CH_2 chain of benzofuran and piperazine).

b) 7-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propoxy)quinolin-2(1H)-one.

Isolated material yield 88 % (w/w) ; , IR (KBR cm-1); 1660 (Amide group of quinoline ring) ;3000-3100 (Aromatic –C=C) ; 1145 (-C-O); 1570 (-N-H); 735-770 (Halogen group ortho substitute). ^{1}H-NMR (dmso-d_6, δ ppm); (7.73-6.66 : d,2H Aromatic proton) ; 3.47 (Methylene group of piperazine) ; 8.0(s) -NH-C=O , 1,82-4.06 (Alkyl chain of methylene group between piperazine and quinoline ring) .

^{13}C-NMR (dmso-d6, δ ppm): 112.9,113.8, 129.2 and 131.9 (Aromatic –C) ; 51.3-56.3(carbon of piperazine ring); 27.7,58.3 ,73.4 (methylene carbon of alkyl chain) ; 162.5 (-C=O of quinoline ring).

c) 3-(4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propyl)piperazin-1-yl)benzo[d]Isothiazole.

Yield of this intermediate: 88 %; 3000-3050 (Aromatic -C-H stretching) ; 2480 (-S-H, weak peak) ; 3000-2850 (-CH peak) ; 1550-1630 (-NH peak); 690-530 (halogen ortho substitute); 880-920 (meta substitute). ^{1}H-NMR (dmso-d_6, δ ppm); 6.88-7.37 (-d, 2H, Aromatic); 3.44-3.65 (Methylene proton of piperazine ring); 1.54-2.46 (methylene proton of alkyl chain between alkyl chain both piperazine derivative). ^{13}C-NMR (dmso-d6, δ ppm): 25.3,52.2 (Methylene carbon of piperazine ring) ; 123.3-127.3(-CH aromatic carbon) ; 165.2, 158.2(-C, aromatic ring) ; 48.5-51.7 (methylene carbon of piperazine ring).

d)2-(4-(3,4-dichlorophenyl)piperazin-1-yl)-N-(3,4-dimethoxyphenethyl)-N-methylethanamine.

Yield: 77 % (w/w); IR (KBR cm-1); 1570-1630 (-NH); 100-1130 (-C-O); 3030-3110 (-Aromatic –CH); 745-765 (ortho substitute); 3087-3130 (Aromatic –CH). ^{1}H-NMR (dmso-d_6, δ ppm); 3.44 (- CH_2 of piperazine); 6.88-7.37 (Aromatic ring proton –CH); 2.24(-N-CH_3); 3.83 (-OCH_3). ^{13}C-NMR (dmso-d6, δ ppm): 112.9-129.2 (Aromatic carbon –CH); 131.9-147.1 (Aromatic carbon –C); 51.2-56.7 (methylene carbon of piperazine ring); 56.1 (-O-CH_3); 46.9 (-N-CH_3).

e) 1-(4-(3,4-dichlorophenyl) piperazin-1-yl)-3-(isopropylamino)propan-2-ol.

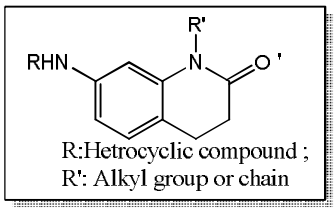
Isolated product yield: 88 %; IR (KBR cm-1); 3500-3200 (-OH , Broad peak) ; 1510-1620 (-NH peak) ; 3100-3030(-CH aromatic) ; 1610-1630 (Aromatic –C=C); 1000-1230(-C-O , alkoxy); 850-550(ortho substitute). ^{1}H-NMR (dmso-d_6, δ ppm); 6.58-7.37 (Aromatic ,d,2H); 2.84-3.44 (Methylene proton of piperazine ring); 3.58 (-OH group) ; 1.07 (-Methyl proton of amine group) ; 2.63-2.83 (Methylene group of alkyl chain) . ^{13}C-NMR (dmso-d6, δ ppm): 69.7 (-CH-OH) ; 112.6-129.8 (Aromatic –CH) ; 146.5 , 131.9 ,122.8 (Aromatic –C) ; 56.2-56.6 (Methylene carbon of Piperazine ring) ; 23.7 (methyl group of amine group).

RESULT AND DISCUSSION QUINOLINE DERIVATIVES:

According to literature of quinoline shown the variety of human disease like the HIV- treatment, antiviral, antibacterial, antimalarial and anti-immflamatory, anti-ischemia and anticancer, antifungal also. Malaria is one of the world serious public health problems. Quinoline is one of the best effective medicines for the malaria disease. Additionally, these moieties also very important play the role in the covid-19 which is very serious matter for our all world in March 2020. As per result this moiety is very good biological result the cure the covid-19.

The exchange of the quinoline ring with another heterocyclic substitution is also take part in to the new drug preparation in research.

Using this quinoline intermediate and conduct the reaction with different heterocyclic compound in the presence of the base and solvent, as per literature know that the quinoline is very important functional group in the therapeutic activity.



Here quinoline intermediate react with substitute alkyl halide chain (butyl chain , propyl chain and other alkyl chain) ; further this intermediate perform the reaction with bicyclic compound , benzofuran , Isothiazole and quinoline derivative resultant isolated the novel intermediate in terms of

good yield and quality of material. Moreover above reaction was performed with help of simple chemistry in presence of various base and solvents. Follow on this intermediates shown biological activity.

g).4-bromo-N-(1-methyl-2-oxo-1, 2, 3, 4-tetrahydroquinolin-7-yl)benzo[b]thiophene-2-carboxamide.
h) 7-((2-(2,3-dihydrobenzofuran-6-yl)ethyl)amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
i). 1-methyl-7-((oxiran-2-ylmethyl) amino)-3,4-dihydroquinolin-2(1H)-one.
j).7-((2-hydroxy-3-(isopropylamino) propyl) amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
k).(R)-7-((3-(((3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)methyl)(methyl)amino)propyl)amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
l) 7-(3-(4-(benzo[d]isothiazol-3-yl) piperazin-1-yl)propoxy)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
m)1-methyl-7-(3-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1H)-one.

g).4-bromo-N-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-yl)benzo[b]thiophene-2-carboxamide.

Quinoline intermediate is react with 4-Bromobenzo[b]thiophene-2-carboxylic acid in the presence of potassium carbonate in N,N-Dimethylformamide resultant formation of the desired product. Here the reaction monitored using the TLC. Moreover the after complies reaction. Cooled the reaction mass added the process water into the reaction mass at 10-15^{0}C. Stir the reaction mass for 1 hr; filter the reaction mass and wash with process water and Recrystalisation in ethyl acetate solvent.

h).7-((2-(2,3-dihydrobenzofuran-6-yl)ethyl)amino)1-methyl-3,4dihydroquinolin- 2(1H)-one.

5-(2-bromoethyl)-2,3-dihydrobenzofuran is conducted reaction with 7-amino-1-methyl-3,4-dihydroquinolin-2(1H)-one using the potassium hydroxide as a strong base with maintained the reaction mass at 0-5^{0}C ; reaction was monitored on TLC ; after reaction complies; add process water into the reaction mass and charged the dichloromethane into the reaction mass for extract product in organic layer ; after wash with 1N hydrochloric acid solution still neutral PH. After distilled organic layer completed and recrystalised material in diisoprpyl ether.

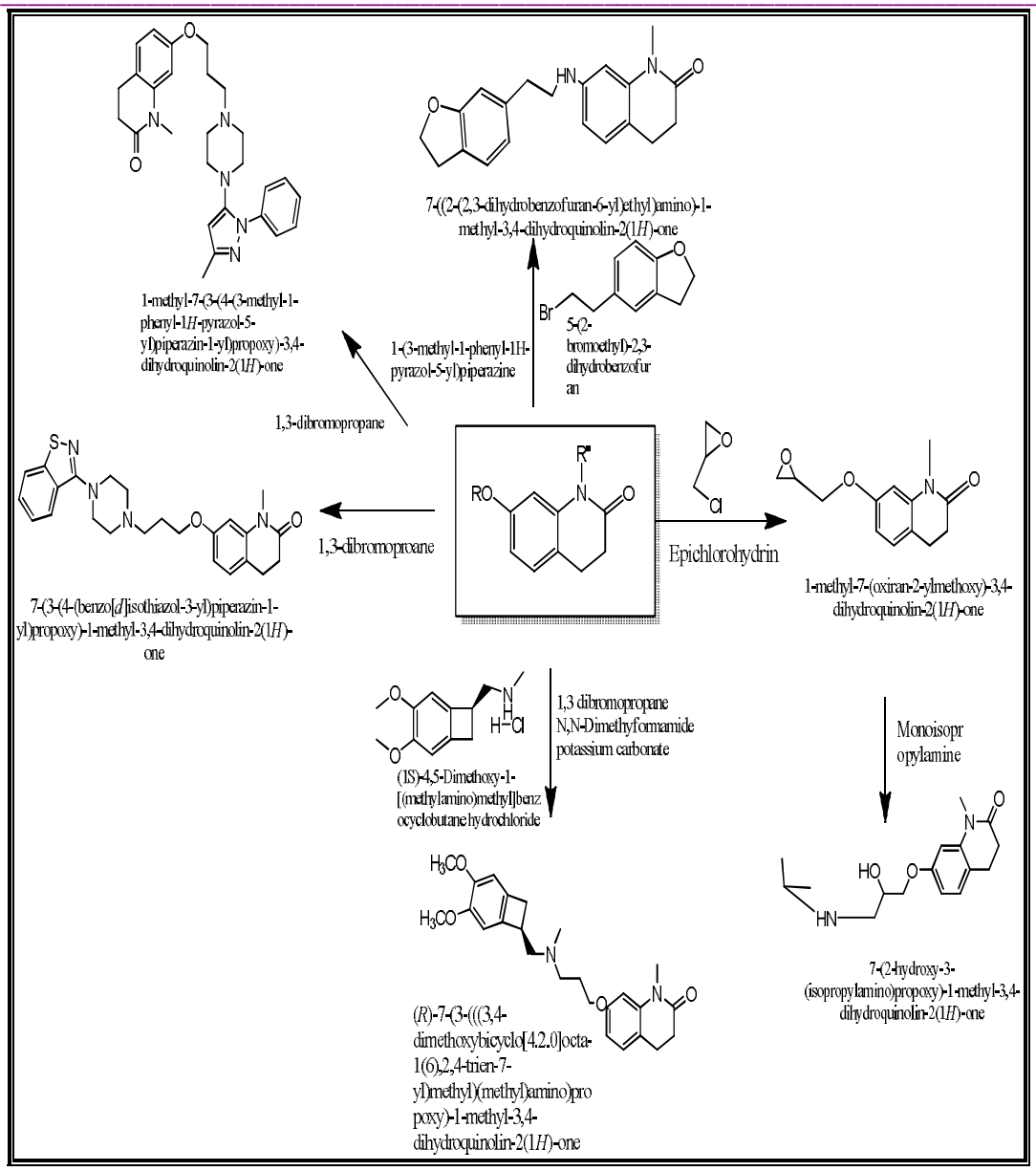
Reaction schemes for different intermediate prepared using the quinoline intermediate.

i). 1-methyl-7-((oxiran-2-ylmethyl) amino)-3,4-dihydroquinolin-2(1H)-one.

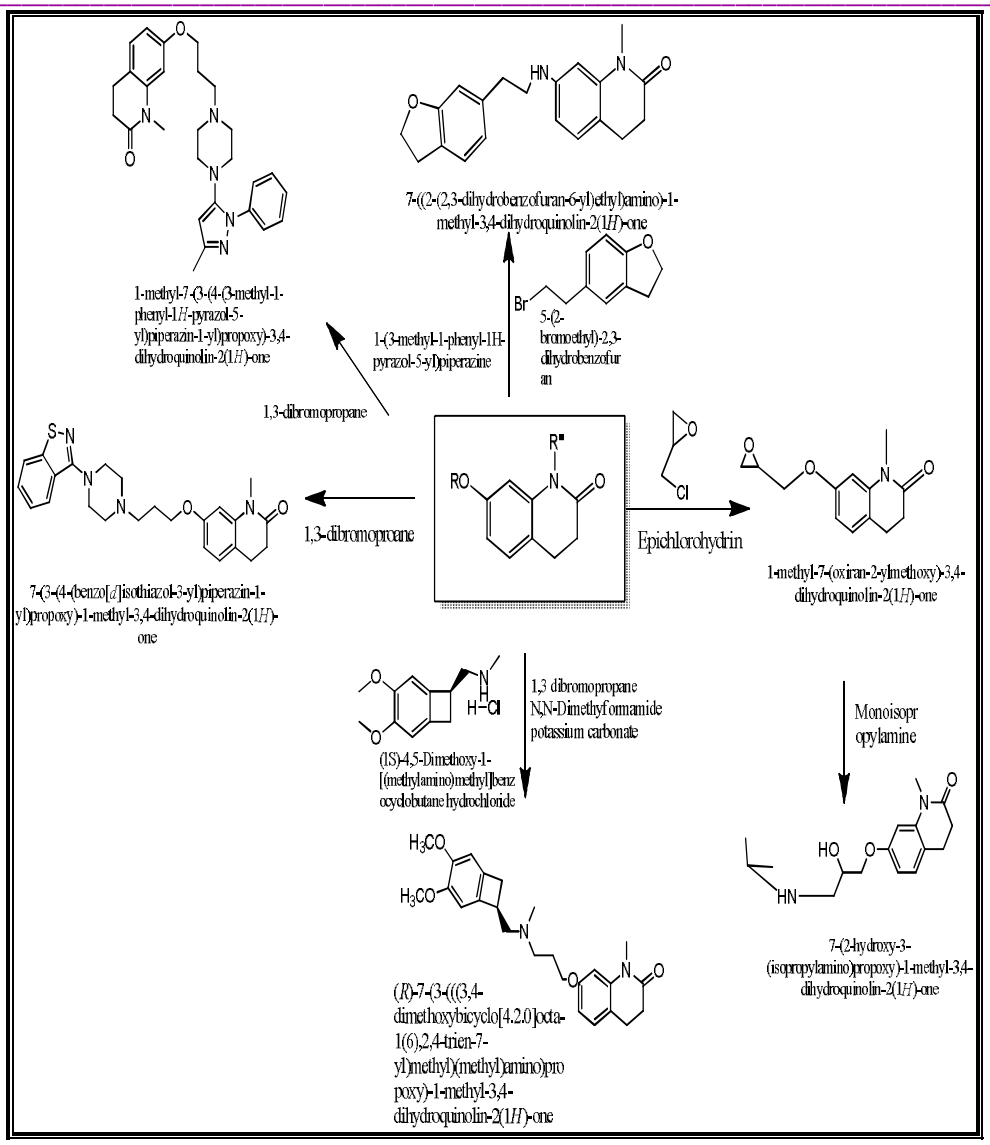
Epichlorohydrin reacted with 7-amino-1-methyl-3,4-dihydroquinolin-2(1H)-one using the potassium carbonate in the presence of the dimethyl acetamide solvent at 40-45^{0}C for 7-8 hrs. Further, reaction monitored on TLC; charged process water into the reaction mass at 5-10^{0}C. Charged the dichloromethane into the reaction mass and extract product in dichloromethane; distilled organic layer and striping with Cyclohexane; follow on leaching with methyl tert butyl ether resultant isolated solid.

k).(R)-7-((3-(((3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)methyl)(methyl)amino)propyl)amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.

(1S)-4,5-Dimethoxy-1-[(methylamino)methyl]benzocyclobutane hydrochloride is conducted reaction with quinoline intermediate and 1,3-dibromopropane in the presence of the potassium carbonate in N,N-Dimethylformamide at 40-45^{0}C for 10-11 hrs ; follow on the reaction complies ; add process water into the reaction mass to quenched N,N-Dimethyl formamide , further the isolated product through filtration and wash with N,N-Dimethylformamide & Process water mixture.



Further, attempted 3,4 dihydroquinoline-2(1H)-one derivative reaction with different heterocyclic compounds resultant formation new compounds with shown the biological activity antibacterial, antihypertensive, anticancer and anticonvulsant activity . Some compounds mentioned in following reaction scheme diagram. Moreover, it was confirmed by NMR, Mass and IR analysis.



RESULT

g)4-bromo-N-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-yl)benzo[b]thiophene-2-carboxamide. Isolated solid material yield: 80 %; **IR (KBR cm-1);** 2850-3000 (Aromatic CH stretching); 1000-1220 (-C-O); 1620-1640 (Amide –CO-NH) ; 2570 (-S-H) ; 740-760 (Ortho substitution); 1600-1490 (weak peak of aromatic –C=C). **^{1}H-NMR ($CDCl_3$ ppm);** 6.39-7.32 (Aromatic ring proton ,d(2H)); 3.44 (s, -N-CH_3) ; 8.45 (-NH-C=O) , 8.28 ,7.47 ,7.93 (Aromatic proton of Isothiazole ring).3.02-3.72 (Methylene group of quinoline ring). **^{13}C-NMR ($CDCl_3$, δ ppm);** 116.9-124.8, 126.1 (Aromatic –CH); 137.3,130.9 (Aromatic –C); 36.1(-N-CH_3); 171.2, 161.3 (-CO-NH_2) ; 138.4,141.9 (Aromatic –CH Isothiazole ring).

h) 7-((2-(2,3-dihydrobenzofuran-6-yl)ethyl)amino)1-methyl-3,4dihydroquinolin- 2(1H)-one. Isolated yield of product: 85 %, **IR (KBR cm-1);** 1670 (Amide peak of quinoline ring) ; 1540 (-N-CH_3); 1120 (-C-O); 2988-3100 (Aromatic ring C-C) ; ^{1}H-NMR ($CDCl_3$ ppm) : 3.44 (-N-CH_3 group of quinoline) ; 2.49,2.89 (methylene group of quinoline ring) ; 6.61-7.13 (Aromatic ring proton) ; 2.97, 4.27 (methylene group of benzofuran). **^{13}C-NMR ($CDCl_3$, δ ppm):** 170.1(-CO-NH_2) ; 26.6,26.8 (Methylene group of quinoline ring) ; 105.1,109.0,128.7 (Aromatic ring carbon –CH) ; 138.1,119.3 (Aromatic carbon –C); 29.5,79.8 (Methylene group of the benzofuran).

j)7-((2-hydroxy-3-(isopropylamino) propyl) amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
Isolated product yield: 92%; **IR (KBR cm-1);** 1620-1670 (-$CONH_2$); 1100-1230 (-C-O); 3600-3480 (broad peak –OH); 1530-1620 (-N-H); 2850-3000(-C-H). **^{1}H-NMR ($CDCl_3$ ppm);** 3.44 (-N-CH3); 6.33-7.12 (Aromatic proton value); 3.58 (-OH); 2.50-2.86 (Methylene group of quinoline ring); 1.01(Isopropyl methyl group); 3.09-3.34 (Methylene group of alkyl chain). **^{13}C-NMR ($CDCl_3$, δ ppm):** 170.4 (-$CONH_2$) ; 36.1(-N-CH_3); 26.6,26.8(Methylene group of quinoline ring); 105.1,109.2,128.7 (Aromatic carbon –CH); 119.3,138.1 (Aromatic –C); 23.7 (Isopropyl group of methyl); 71.3(-CH-OH).

k).(R)-7-((3-(((3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)methyl)(methyl)amino)propyl)amino)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
Isolation yield of the product: 89 %; **IR (KBR cm-1);** 1670 (-$CONH_2$); 2860-2980 (-CH); 1020-1190(-C-O); 1550-1630 (-N-H). **^{1}H-NMR ($CDCl_3$ ppm);** 3.44 (-N-CH_3); 6.33-7.12 (Aromatic proton of quinoline ring); 2.86-2.49 (Methylene group of quinoline); 3.88 (O-CH_3); 2.71, 2.96 (Methylene group of bicyclic ring), 4.2(-NH). **^{13}C-NMR ($CDCl_3$, δ ppm):** 170.3 (-$CONH_2$); 109.1, 105.6, 128.7 (Aromatic -CH); 119.3, 138.1 (Aromatic –C); 37.6, 40.0 (Methylene group of the bicyclic ring); 56.1 (-OCH_3); 26.8, 41.1, 57.1 (Methylene group of alkyl chain).

l) 7-(3-(4-(benzo[d]isothiazol-3-yl) piperazin-1-yl) propoxy)-1-methyl-3,4-dihydroquinolin-2(1H)-one.
Isolation yield of the product: 85 %; **IR (KBR cm^{-1});** 1695 (-$CONH_2$); 3000-3100 (-CH); 1320-1100(-C-O); 1250-1000 (-C-N). **^{1}H-NMR ($CDCl_3$ ppm);** 3.44 (-N-CH_3); 6.77-7.23 (Aromatic proton of quinoline ring); 1.82-4.06 (Methylene group of quinoline).

m) 1-methyl-7-(3-(4-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl) propoxy)-3,4-dihydroquinolin-2(1H)-one.
Yield of isolated material: 90 %; **IR (KBR cm-1)**; 1250-1010(-C-N); 1320-1000(-C-O); 1695 (-$CONH_2$). **^{1}H-NMR ($CDCl_3$ ppm); 7.58**-7.62 (Aromatic proton); 3.44-3.62 (Methylene proton of piperazine ring); 6.92-7.23 (Aromatic proton of quinoline ring).

BIOLOGICAL ACTIVITY

The synthesized Substituted piperazine compound and quinoline derivatives were screened for their antibacterial and antifungal activity against five gram –negative bacteria (Escherichia coli, aeruginosa, gram positive bacteria (Staphylococcus aures, moreover, three fungal strains (Aspergillus Niger and aspergillus flavus).

All the synthesized compounds **(a-l)** were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pyogenes* or *Bacillus megaterium*, two Gram-negative bacteria *E. coli* and *Pseudomonas aeruginosa* and two fungal strain *Aspergillus niger* and *Aspergillus clavatus* taking streptomycin, ampicillin,nystatin as standard drugs.

The minimal inhibitory concentration (MIC) values for all the synthesized compounds **(a-l)**, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards

Minimal Inhibition Concentration [MIC]

The main advantage of the broth dilution method for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary as well as secondary screening.
2. The control tube including no antibiotic is immediately subculture (before inoculation) by spreading a loopful evenly over a quarter of a plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.

The lowest concentration controlling growth of the organism is recorded as the MIC.

4. The amount of growth the control tube before incubation (which represents the original inoculums) is compared.

Methods used for primary and secondary screening

Each sample was diluted obtaining 2000 µg mL^{-1} concentration, as a stock solution. Inoculum size for test strain was adjusted to 10^8 CFU (colony forming unit) per millilitre by comparing the turbidity.

Primary screen: In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of the synthesized compounds were taken. The active samples found in this primary screening were further tested in the second set of dilution against all microorganisms.

Secondary screen: The samples found active in primary screening were similarly diluted to obtain 200 µg mL^{-1}, 100 µg mL^{-1}, 62.5 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12.5 µg mL^{-1} and 6.250 µg mL^{-1} concentrations.

Reading Result: The highest dilution showing at least 99% inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10^8organisms/mL.

Antibacterial and antifungal activity data of compounds

Compound Number	Antibacterial activity (Zone of inhibition in mm)				Antifungal activity	
	Gram positive		Gram negative			
	Bacillus sub tilts	Staphylococcus aureus	Escherichia coli	Pseudomonas aeruginosa	Aspergillus niger	Aspergillus flavus
	1000	1000	500	500	500	250
	250	500	1000	1000	500	500
	250	1000	500	1000	1000	250
	1000	1000	500	250	500	1000
	250	250	500	500	1000	1000
	500	250	500	500	1000	500
	500	250	250	500	500	1000
	1000	500	1000	1000	1000	500
	1000	1000	500	1000	500	250
	500	1000	1000	500	500	500
	500	500	500	250	500	1000
	1000	1000	500	1000	250	500
Streptomycin			50	50		
Ampicillin	100	100	--			
Nystain					100	100

Here the compound a), d), h), i), l) shown the greater degree activity for bacillus subtiits. Moreover, the compound a), c), d), i), j), l) shown the fruitful activity for staphylococcus aureus. Further, compound h), j), b) shown the positive activity against the Escherichia coli and compound. Here the antifungal activity compound c),e) f) & k) against shown Aspergillus niger & Aspergillus flavus.

CONCLUSION

We have successfully synthesized a series of novel piperazine and quinoline derivatives in higher yields with adopting simple and straight forward process. The advantage is shorter reaction times with low cost of the staring material and scale activity also feasible. All compounds exhibited antibacterial and antifungal activities.

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