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Synthesis and biological screening of some novel Quinoline derivatives

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Abstract

A new series of quinoline derivatives 2-chloro 3-formyl quinoline, 3-chloro-4(2-chloroquinolin-3-yl)1-phenyl amine azetidin 2-one, 3-chloro-4(2-chloroquinolin-3-yl)2,4-dinitro phenyl amine azetidin 2-one, 3-chloro-4(2-chloroquinolin-3-yl) 4-initro phenyl amine azetidin 2-one, 3-amino 1H-pyrazoloquinoline, 3-diazo-1H-pyrazoloquinoline, 6-methoxy-1-phenyl pyrazolo quinoline were synthesized by 4 scheme methods, containing various steps. The structures of the synthesized compounds have been established on the basis of physical and spectral data and are screened for diuretic and antimicrobial activities, some of the exhibited significant activity.

Keywords : Quinoline, pyrazoloquinoline, Diuretic

Introduction

Quinoline, also known as L-azanaphthalene, 1-benzaine or benzo(b) pyridine is an aromatic nitrogen compound characterized by a double ring structure contains a benzene fused to pyridine at two adjacent carbon. The chemical formula for quinoline C_9H_7N, and it has a molecular weight of 129.15g/mol.quinoline family compounds are widely used as a parent compound to make drugs (especially antimalarial medicine), fungicides, biocides, alkaloids, dyes, rubber, chemicals, flavoring agents, antisepic and antipyretic. Quinaldine, 2-methylqunoline is used as animalaria and preparing other antimalarial drugs. Quinaldic acid is carbolic acid substituted quinoline at 2-position a catabolite of tryptophan (aromatic side

chain aminoacid. It is a fundamental structure in some antihypertensive agents such as prazosin and doxazosin which are peripheral vasodilator.

Quinoline derivatives have been reported for anti-inflammatory [1], anti bacterial [2,3,4], antifungal [5,6], antiallergy [7], antidepressant [8], antiasthmatic[9], antimalarial[10-12],antiviral[13,14],antitumour[15],neurolepticactivity[16],antihypertensive[17,18],cytotoxic [19-21], antihistamine[22], CVS[23], antiseptic[24], analgesic[24], antihelmintic[24], hypnotic [25], sedativeand CNS[25], Bronchodilator[26] activities. It was found that when one biodynamic heterocyclic system was coupled with another heterocyclic system, enhanced biological activity was produced.

The present investigation was aimed at synthesizing the 3-diazo-1H-pyrzolo quinoline derivatives. Various reports describing the synthesis and activities of quinoline coupled to 1, 2, 4-triazolo, 1, 3, 4-thiadiazepino and cyano at C-3 position have been reported.

A survey of existing literature revealed that there were no reports describing the synthesis and activity of heterocyclic system in which pyrazolo moiety has been linked with substituted quinoline nucleus. Hence it is thought worthwhile to synthesize and explore the activity of these compounds.

Results and Discussion

Diuretics relive pulmonary congestion and peripheral edema. These agents are useful in reducing the syndrome of volume overload, including orthopnea and paroxysmal nocturnal dyspnoea. They decrease plasma volume and subsequently venous return to the heart (preload). This decreases cardiac workload, oxygen demand and plasma volume, thus decreasing blood pressure [27]. Thus, diuretics play an important role in hypertensive patients. In present study, we can demonstrate that ethanol, aqueous and chloroform extract may produce diuretic effect by increasing the excretion of Sodium, Potassium and Chloride. The control of plasma sodium is important in the regulation of blood volume and pressure; the control of plasma potassium is required to maintain proper function of cardiac and skeletal muscles [28]. The regulation of Sodium, Potassium balance is also intimately related to renal control of acid-base balance. The Potassium loss that occurs with many diuretics may lead to hypokalemia. For this reason, generally potassium-sparing diuretics are recommended [29]. In present study the compounds showed elevated levels of Potassium in urine, which may increase risk of hypokalemia and hence its potassium sparing capacity has to be investigated.

Disc diffusion methods are used extensively to investigate the antibacterial activity. These assays are based on the use of discs as reservoirs containing solutions of the substances to be examined. In the case of solutions with a low activity, however, a large concentration or volume is needed. Due to limited capacity of discs, holes or cylinders are preferably used.

It allowed with the conclusion that the aqueous extract most effect in increasing urinary electrolyte concentration of all ions Sodium, Potassium and Chloride.

As evident from the results antibacterial action of the compounds are more pronounced on Gram positive than on Gram negative bacteria and these findings correlate with the observation of the various screenings of medicinal plants for antibacterial activity where the most of the active plants showed activity against Gram positive strains only .

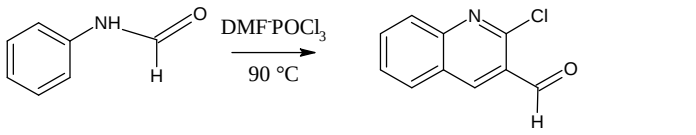
The present study was aimed at synthesis and characterization of some novel substituted Quinoline derivatives, 2-chloro 3-formyl quinoline, 3-chloro-4(2-chloroquinolin-3-yl)1-phenyl amine azetidin 2-one, 3-chloro-4(2-chloroquinolin-3-yl)2,4-dinitro phenyl amine azetidin 2-one, 3-chloro-4(2-chloroquinolin-3-yl) 4-initro phenyl amine azetidin 2-one, 3-amino 1H-pyrazoloquinoline, 3-diazo-1H-pyrazoloquinoline, 6-methoxy-1-phenyl pyrazolo quinoline compounds. The compounds were screened for anti diuretic, anti bacterial and anti fungal activities and were found to possess considerable activity.

Materials and Methods

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Perkin –Elmer FTIR using KBr discs. PMR on Bruker spectrospeir 200MHz NMR instrument using $CDCl_3$ as solvent and TMS as internal reference (Chemical shifts in δ, ppm) Elemental analysis of all the synthesized compounds were performed on a Perkin Elmer 2400. Series – II Elemental CHNS analyzer.

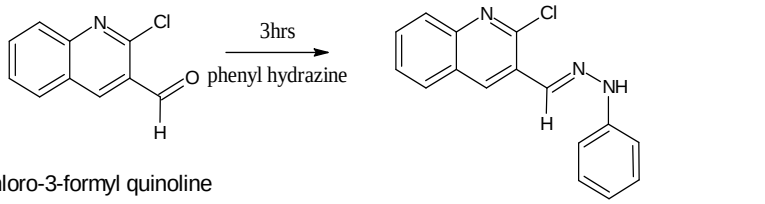
General methods of synthesis

Scheme-I: Step-I [30,31]
Synthesis of 2-chloro -3-formyl quinoline:(CFQ)
To a solution of acetanilide (5m moles) in dry DMF (15mmoles)at 0-5^{0}C, $POCl_3$(60mmoles) was added drop wise with stirring and the mixture was then stirred at 80-90^{0}C for time ranging between 4-16 hours. The mixture was poured on to crushed ice, stirred for 5 minutes and resulting solid filtered, washed well with water and dried. The compounds were recrystallized from ethyl acetate.



Acetnilide 2-Chloro-3-formyl quinoline

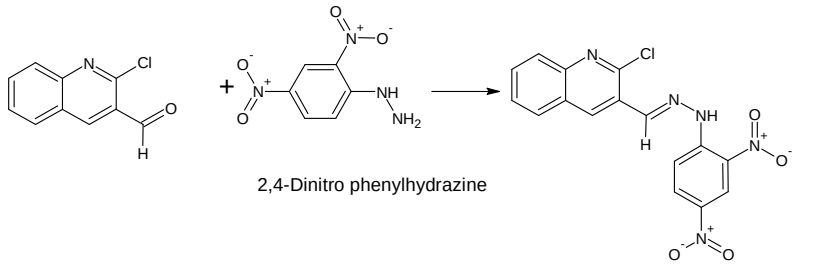
Step-II-A:
Synthesis of N-(2-chloro quinoline-3-yl methylene)-N-Phenyl hydrazone
To a solution Synthesis of 2-chloro-3-formyl quinoline 6mmoles were added aryl hydrazine (phenyl hydrazine11mmoles) and refluxed for three hours, and then left to cool to room temperature or the solvent was removed and the separated solid was poured in to the water. The precipitated product was filtered, washed well with water and dried.



2-Chloro-3-formyl quinoline N(2-chloroquinoline-3-ylmethylene)-n-phenyl hydrazone

Step –II-B:
Synthesis of N-(2-chloro quinoline-3-yl methylene)-N-(2,4-dinitroPhenyl) hydrazone:
To a solution Synthesis of 2-chloro-3-formyl quinoline 6mmoles were added aryl hydrazine (2,4- dinitrophenyl hydrazine11mmoles) and refluxed for three hours, and then left to cool to

room temperature or the solvent was removed and the separated solid was poured in to the water. The precipitated product was filtered, washed well with water and dried**.**

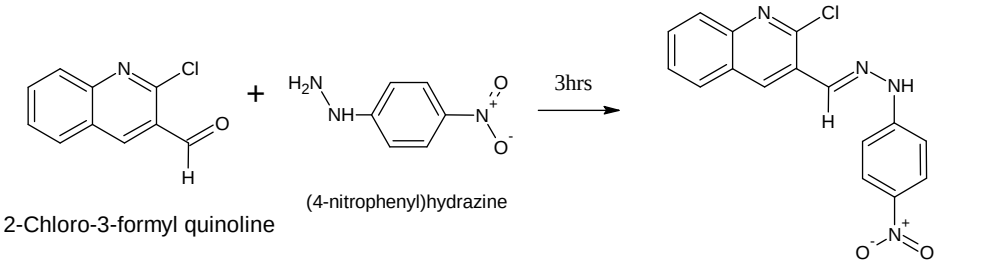


N(2-chloroquinolin-3ylmethylene-N-(2,4-dinitrophenyl) hydrazine

Step-II-C

Synthesis of N-(2-chloro quinoline-3-yl methylene)-N-(4-nitroPhenyl) hydrazone:

To a solution Synthesis of 2-chloro-3-formyl quinoline 6mmoles were added aryl hydrazine (4- nitrophenyl hydrazine11mmoles) and refluxed for three hours, and then left to cool to room temperature or the solvent was removed and the separated solid was poured in to the water. The precipitated product was filtered, washed well with water and dried.



2-Chloro-3-formyl quinoline

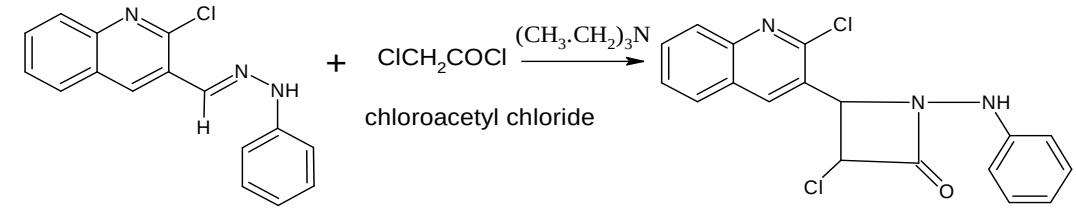
(4-nitrophenyl)hydrazine

N-(2-chloro-quinoline-3-yl methylene)-N-(4-nitrophenyl)hydrazone

Step-III –A [32]

Synthesis of 3-chloro-4 (2-chloro- quinolin-3-yl)1-phenylamine-azetidine-2-one(PH-I)

The compound N-(2 chloro-quinolin-3-yl methylene)-N-phenyl hydrazone (0.01mol) was dissolved in DMF (40ml) and triethyl amine (0.02mol) was added to it. Chloroacetyl chloride (0.02mol) was added drop wise a period of 30 minutes. The reaction mixture was refluxed for 5 hr, and filtered t separate the solid formed. The filtrate was poured on to crushed ice, the product was filtered and recrystallized from ethylacetate.



N-(2-Chloro-quinolin-3yl-methylene)-N-phenylhydrazone

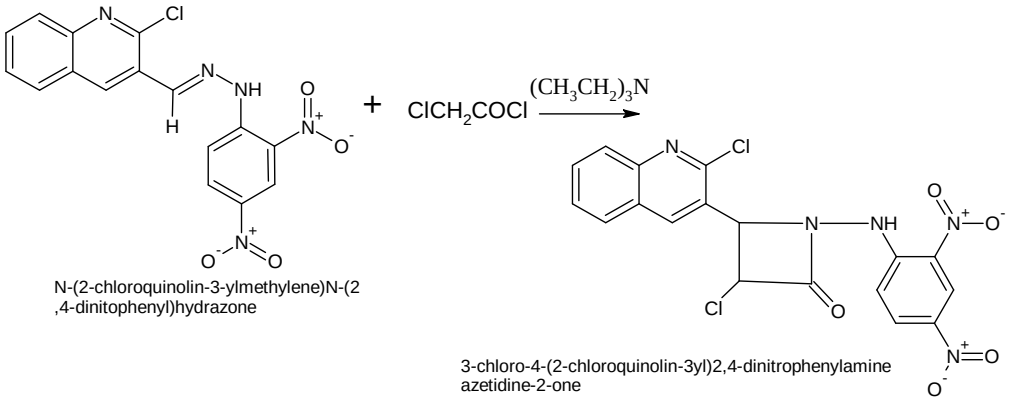
3-chloro-4-(2-chloroquinolin-3yl)1-phenylamineazetidine-2-one

Step –III –B

Synthesis of 3-chloro-4 (2-chloro- quinolin-3-yl)2,4-dinitrophenylamine-azetidine-2-one (PH-II)

The compound N-(2 chloro-quinolin-3-yl methylene)-N-(2,4-dinitrophenyl hydrazone (0.01mol) was dissolved in DMF (40ml) and triethyl amine (0.02mol) was added to it. Chloroacetyl chloride (0.02mol) was added drop wise a period of 30 minutes. The reaction

mixture was refluxed for 5 hr, and filtered t separate the solid formed. The filtrate was poured on to crushed ice, the product was filtered and recrystallized from ethylacetate.



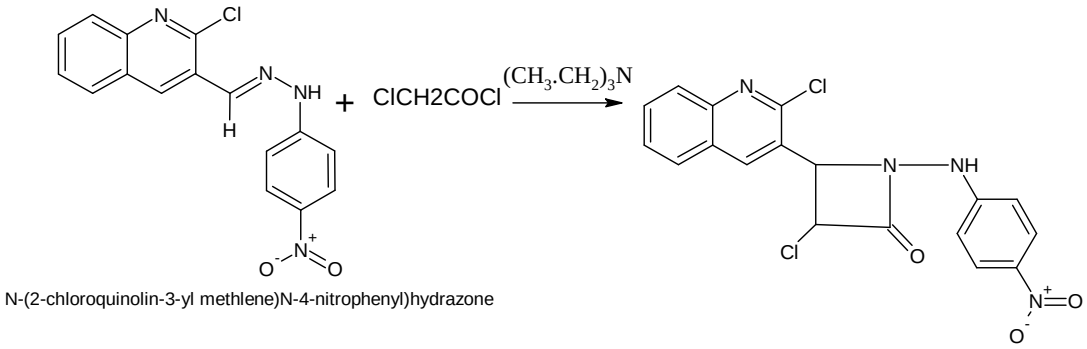
N-(2-chloroquinolin-3-ylmethylene)N-(2 ,4-dinitophenyl)hydrazone

3-chloro-4-(2-chloroquinolin-3yl)2,4-dinitrophenylamine azetidine-2-one

STEP – III-C

Synthesis of 3-chloro-4 (2-chloro- quinolin-3-yl) -4-nitrophenylamine-azetidine-2-one (PH-III)

The compound N-(2 chloro-quinolin-3-yl methylene)-N-(4-nitrophenyl hydrazone (0.01mol) was dissolved in DMF (40ml) and triethyl amine (0.02mol) was added to it. Chloroacetyl chloride (0.02mol) was added drop wise a period of 30 minutes. The reaction mixture was refluxed for 5 hr, and filtered t separate the solid formed. The filtrate was poured on to crushed ice, the product was filtered and recrystallized from ethylacetate.



N-(2-chloroquinolin-3-yl methlene)N-4-nitrophenyl)hydrazone

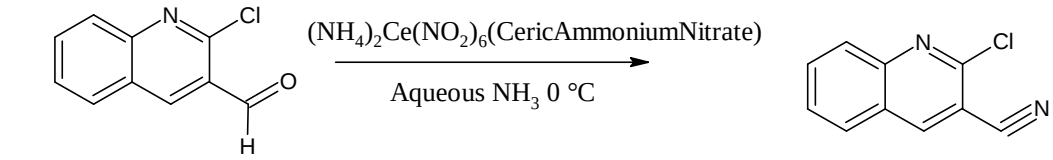
3-chloro-4-(2-chloroquinolin-3-yl)4-nitro phenylamine azetidin-2-one

Scheme II: Synthesis of 3-amino-1H-pyrazolo quinoline

Step – I

Synthesis of 2-chloro-3-cyano quinoline from 2-chloro-3-formylquinoline,

a suspension of 2-chloro-3-formylquinoline (1mmole) in 30% aqueous ammonia (3ml) was stirred for 5 minutes at room temperature, resulting in the formation of a turbid solution. To the ceric ammonium nitrate (1mmole) was added with constant stirring at 0^0C. After completion of the reaction (monitored by TLC, disappearance of reddish brown colour of reaction mixture in (10-15 minutes) the reaction mixture was extracted with chloroform-ethyl acetate(5:3) dried (Na_2SO_4) and evaporated under vacuum to obtain the solid product which was recrystallized from ethanol.



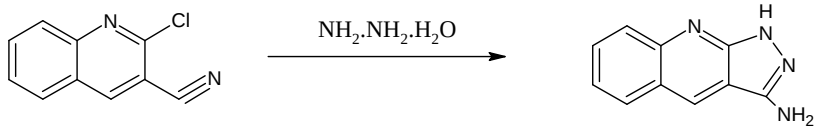
2-Chloro-3-formyl quinoline

2-Chloro-3-cyano quinoline

Step – II

Synthesis of 3-amino 1H-pyrazoloquinoline (PH-IV)

A mixture of 2-chloro-3-cyano quinoline(1mmole) and hydrazine hydrate (3ml) was refluxed for 15 minute, and then left to cool to room temperature, where upon the product crystallized out whch was filtered and washed well with water and needed no further purification.



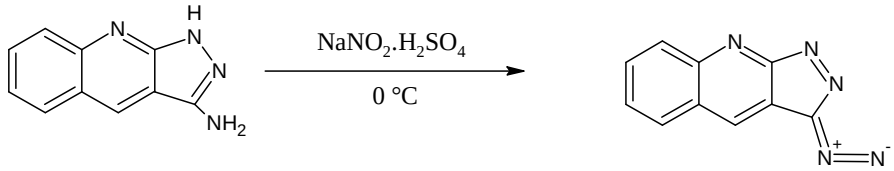
2-Chloro-3-cyano quinoline

3-amino-1H pyrazoloquinoline

Scheme – III

Synthesis of 3-diazo-1H pyrazolo quinoline (PH-V)

To a solution of 3-amino-1H pyrazoloquinoline (1mmole) in 70% H2SO4 (3-4ml) cooled in ice salt to -50 C was added , drop wise a solution of sodium nitrite(3mmole) in water(1ml) and the reaction mixture was maintained at -50C for 1 hr and then was poured into ice water. The precipitated product was filtered, washed well with water and dried.



3-amino-1H pyrazoloquinoline

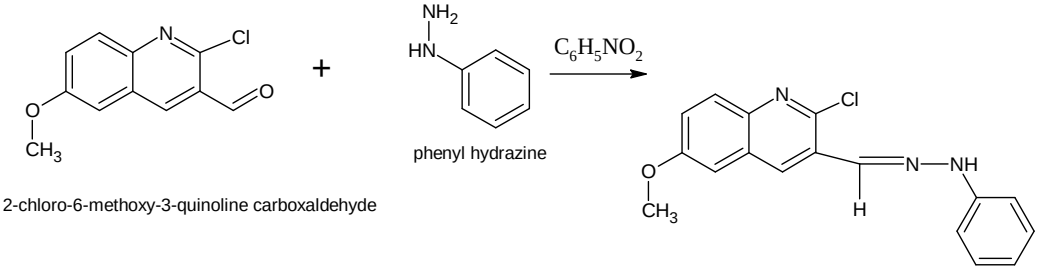
3-diazo-1H-pyrazoloquinoline

Scheme – IV synthesis of 6-methoxy-1-phenyl-pyrazoloquinoline (PH-VI)

Step – I [33]

Synthesis of 2-chloro-6-meythoxy-3-phenyl hydrazine quinoline

Mixture of 2-chloro-6-methoxy-3-quinoline carboxaldehyde (0.005mol) and phenyl hydrazine (0.005mol) in 50 ml (0.005mol) methanol was refluxed on a water bath for 3-4hr. the reaction mixture was allowed to cool and separated solid was filtered, washed with water, dried and recrystallized from ethanol to give the product.



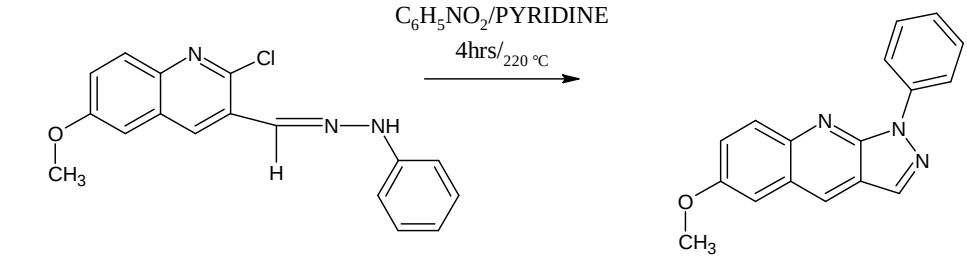
2-chloro-6-methoxy-3-quinoline carboxaldehyde

phenyl hydrazine

2-chloro-6-methoxy-3-[(2-phenylhydrazinylidene)methyl]quinoline

Step – II

A mixture of step I (0.011mol), nitrobenzene (35ml) and few drops of pyridine was refluxed in an oil bath at 2200Cfor 4 hr. it was then cooled and stem distilled to remove nitrobenzene. The product separated in the distillation flask was filtered washed with petroleum ether, dried and recrystalized from DMF-ethanol to get the product.

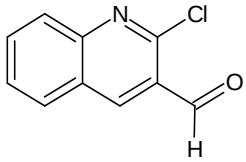


2-chloro-6-methoxy3-(phenyl hydrazino)quinoline

6-methoxy-1-phenyl pyrazolo quinoline

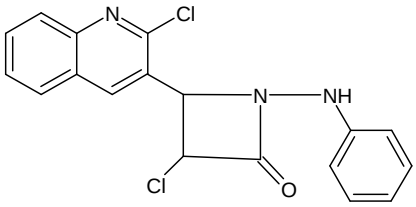
Spectral data of synthesized compounds [31, 32, 33]

2-chloro-3-formyl quinoline **– (CFQ)**



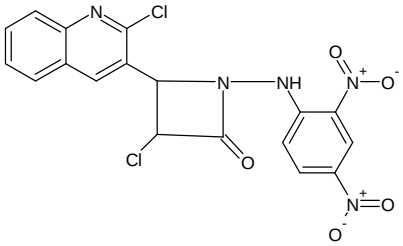
IR (KBr) - 2927 (C-H aromatic stretching), 1686 (C=O stretching), 1576 (C=N stretching), 1458 (C=C stretching), 1374 (C-N ar-stretching), 759 (C-Cl stretching); ^{H}NMR ($CDCl_3$) - 7.3-8 (ar- hydrogen), 8.8 (Heteroaromatic proton), 10.5 (-CHO)

3-chloro-4-(2-chloroquinolin-3yl)1-phenylamineazetidine-2-one **–(PH-I)**



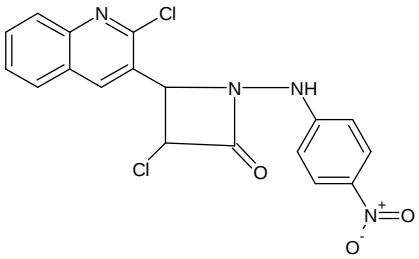
IR (KBr) - 2925 (C-H aromatic stretching), 1654 (C=O stretching), 1500 (C=N stretching), 1122 (C-N Ali-stretching), 751 (C-Cl stretching), 3448 (N-H stretching); ^{H}NMR ($CDCl_3$) - 8.7 (Heteroaromatic proton), 7.3-8 (aromatic proton)

3-chloro-4-(2-chloroquinolin-3yl) 2, 4-dinitrophenylamine azetidine-2-one-**(PH-II)**



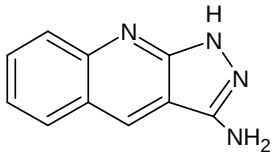
IR (KBr) - 2928 (C-H aromatic stretching), 1654 (C=O stretching), 1460 (C=N stretching), 1100 (C-N Ali-stretching), 1340 (C-N ar stretching), 735 (C-Cl stretching), 3445 (N-H stretching); ^{H}NMR ($CDCl_3$) - 8.7 (Heteroaromatic proton), 7.3-8 (aromatic proton), 3.5 (CH-Cl), 2.2 (CH-N aromatic)

3-chloro-4-(2-chloroquinolin-3-yl)4-nitro phenylamine azetidin-2-one-**(PH-III)**



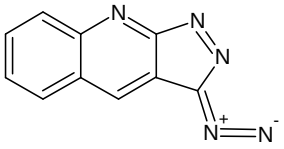
IR (KBr) - 2929 (C-H aromatic stretching), 1654 (C=O stretching), 1463 (C=N stretching), 1096 (C-N Ali-stretching), 1561 (C=C ar stretching), 761 (C-Cl stretching), 3441 (N-H stretching), 673 (C-H bending); ^{H}NMR ($CDCl_3$) - 8.7 (Heteroaromatic proton), 7.3-8 (aromatic proton)

3-amino-1H pyrazoloquinoline-**(PH-IV)**



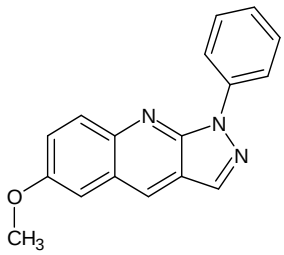
IR (KBr) - 1047 (C-N stretching), 3397 (N-H stretching), 1321 (N-H Bending), 1581 (C-N) stretching, 751 (C-H bending out of plane); ^{H}NMR ($CDCl_3$) - 7.3-8 (aromatic proton).

3-diazo-1H-pyrazoloquinoline-**(PH-V)**



IR (KBr) - 3042 (C-H aromatic stretching), 1654 (C=O stretching), 1687 (C=N stretching), 1613 (C=N ar stretching), 1045 (C-N stretching), 3445 (N-H stretching);

PH-VI- 6-methoxy-1-phenyl pyrazolo quinoline-**(PH-VI)**



IR (KBr) - 2925 (C-H aromatic stretching), 1684 (C=O stretching), 1554 (C=N stretching), 1143 (C-N Ali-stretching), 1105 (C-N ar stretching), 763(C-H stretching out of plane)

Diuretic activity [34,35,36]

Normal healthy male albino wistar rats, weighing between 150 – 200 gms were used for this study. The animals were divided into 8 groups consisting of six animals in each group. These animals were placed in metabolic cages provided with a wire mesh bottom and a funnel to collect the 24 hrs urine sample. Stainless steel sieves are placed in the funnel to retain faeces and to allow the urine to pass. The rats were fed with standard diet and water fifteen hours prior to the experiment food and water were withdrawn. The dosages of the drug administered to different groups were as follows. Group 1 control group received orally 2.5ml/gm body weight of dimethyl formamide solution. Group II standard group received orally 60mg/kg body weight of furosemide loop diuretics Lasix. Group III – VIII consists of synthesized compounds PH – I, PH – II, PH – III, PH – IV, PH – V, PH – VI respectively.

The above synthesized compounds were dissolved in 0.5ml of DMF at the dose 25mg/kg. The urine samples were measured at 24hrs. after collection of urine, the urine was analysed by flame photometer for evaluation of various electrolytes like Na^+, K^+ and Cl^- concentration was evaluated by titration with silver nitrate solution (N/50) using 3 drops of 5% potassium chromate as an indicator. The role of above said electrolytes as tabulated.

Antimicrobial activity [37- 40]

Assay was carried out by diffusion plate method. The method followed was spread plate technique. The plates free from contamination were spread with 50µl of 48h old culture of bacterial test organism using sterile buds. The standard disc of Amikacin (sterile) of 5 mm diameter was in the Petri plates. Then the filter paper discs (sterile) of 5mm were soaked in 1ml (1µg/ml) of the test solution and in solvent control DMF. After evaporating the solvent in a sterile atmosphere the drug impregnated discs were placed in Petri plates. The plates were refrignated for 1h to arrest the growth and for easier diffusion of test compounds. Then the plates were removing from refrigerator and incubated at 37^0C over night is an inverted position. The clear zones of inhibition were measured using Hi media zone reader scale. The values are tabulated. The zones of test solutions were compared with standard Amikacin.

Antifungal activity

Glucose, peptone and agar were taken in the above proportions and dissolved upto 1000 ml of distilled water. The constituents were heated gently at 100° C with agitation. The pH of the medium was adjusted to 5.4. Then it was transferred to boiling tubes in hot condition and sealed with non-absorbent cotton and sterilized by autoclaving at 121° C (15 lbs pressure) for 15 mts. Then poured aseptically into sterile Petri dishes. The temperature of the medium should not exceed above 50° C when the organisms were inoculated. The standard drug ketoconazole (10µg/disc) was placed on the media. The sterile whatmann no.2 filter disc (5mm diameter) was soaked in synthesized compounds (200µg/disc) separately and evaporated to dryness and then kept on the media. One more disc immersed in dimethyl formamide and kept on the media as control. The Petri dishes were incubated at 37° C for 24hrs, after placing them in the refrigerator for one hr to facilitate uniform diffusion. Observations were made for the zone of inhibition around the synthesized compounds with that of standard.

Diuretic activity

Increase in urine output a sufficient index for assessing the diuretic effect through estimating the urinary concentration of Ions like Na^+, K^+ and Cl^- etc may reveal in specific the Ion responsible for the diuretic effect. Tables values reveals that electrolyte excretion and diuretic activity of various synthesized compounds like PH - I, PH – II, PH – III, PH – IV, PH – V,

PH – VI. Among these compounds significant diuretic activity was observed with compound PH – II(3-chloro-4-(2-chloro-quinolin-3-yl)-2,4 -dinitro phenylamine-azetidin-2-one), PH – III(3-chloro-4-(2-chloro-quinolin-3-yl)-4 - nitrophenylamine azetidin-2-one and PH – V(3-diazo-1*H*-pyrazolo quinoline). Also above mentioned potent diuretic compound produced significant fall in K^+ excretion compound to control (P<0.001).

Antibacterial activity

Antibacterial activity of the test compounds in DMF was determined by filter paper disc method at a concentration of 200µg/ml. All the compounds showed comparable activity as that of the standard Amikacin against *Staphylococcus aureus* (MTCC 96). None of the test compounds could exhibit comparable activity to that of the standard amikacin against *Escherichia Coli* (MTCC 722). The test compounds showed better activity at 200µg/ml concentration against *S. Aureus*. Further test can be done using higher concentration is diffusion is not the barrier. The compounds PH – III and PH – VI are promising ones against *Staphylococcus aureus*. The further, some more test organisms of gram positive and gram negative types can be used.

Anti fungal activity

The anti fungal activities of the compounds were evaluated against *Candida albicans* using ketaconazole as the standard compound. The activity of the compounds measured in terms of zone of inhibition (in mm) ranged between 9 to 10 mm where the upper limit is lower than that of Ketaconazole (13 mm). The compound PH – IV showed high degree of anti fungal activity.

Table 1 Physical data of Synthesized compounds

Sl. No.	Code	Molecular formula	Molecular weight	Melting point	% yield	R_f- value
1	PH - I	$C_{18}H_{13}Cl_2N_3O$	476.150	279°C	57	0.63
2	PH - II	$C_{18}H_{11}ClN_5O_4$	448.221	281°C	59	0.61
3	PH - II	$C_{18}H_{12}Cl_2N_4O_3$	403.223	191°C	74	0.60
4	PH - IV	$C_{10}H_8N_4$	184.20	290°C	63	0.62
5	PH - V	$C_{10}H_5N_5$	195.183	164°C	62	0.63
6	PH - VI	$C_{17}H_{13}N_3O$	275.307	143°C	61	0.59
7	CFQ	$C_{10}H_6NOCl$	191.616	144°C	79	0.67

Table 2 Electrolyte excretion and diuretic activity of Various Synthesis compounds

S.No.	Compound	Dose mL/Kg/mg/Kg	Urine volume (ml) 24 hrs	Electrolyte excretion (ME q/lit)			
				Na^+	K^+	Cl^-	Na^+/K^+
1	Control(DMF	2.5ml/kgDMF	6.5±1.48	106.0±4.56	208.1±8.40	68.43±4.18	0.51
2	Standard (Lasix loop diuretic)	25mg/kg	13.8±1.97	138.6±1.76	87.6±7.17	976±3.96	1.55
3	PH - I	25mg/Kg	7.8±0.97	122.0±0.96	196.0±6.17	64.3±0.96	0.62
4	PH – II	25mg/Kg	8.5±1.02*	130.6±2.08**	97.7±1.18**	84.6±4.78*	1.33
5	PH – III	25mg/Kg	9.6±1.58**	128.3±3.06**	101.18±5.08**	82.4±3.68*	1.26
6	PH - IV	25mg/Kg	5.0±0.95	108.6±3.96	190.4±4.08	69.7±6.08	0.57
7	PH – V	25mg/Kg	10.4±1.21**	132.6±1.97**	92.0±2.48**	93.6±4.96**	1.44
8	PH - VI	25mg/Kg	5.4±0.78	104.2±2.08	176.2±6.08	72.46±2.08	0.59

Standard – Lasix (loop diuretic) ** P < 0.05 Significant
SEM – Standard Error Mean * P < 0.01 Significant

Table 3 Antimicrobial activity of various synthesized compounds

S. No.	Compound	Antibacterial activity (Zone of inhibition in mm)	
		S.aureus	E.coli
1	PH - I	12	10
2	PH – II	13	11
3	PH – III	15	13
4	PH - IV	12	12
5	PH – V	11	9
6	PH - VI	14	8
7	Standard	18	18
8	Control	0	0

Standard – Amikacin Control – Dimethyl formamide

Table 4 Antifungal activity of various synthesized compounds

S. No.	Compound	Antifungal activity(Zone of inhibition in mm)
		C.albicans
1	PH - I	9
2	PH – II	8
3	PH – III	8
4	PH - IV	10
5	PH – V	9
6	PH - VI	9
7	Standard	13
8	Control	0

Standard – ketoconazole Control – Dimethyl formamide

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