INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

Research Article

Analgesics, Antibacterial and Locomotor activity of synthesised Mannich bases of Quinazoline 2-one derivatives.

K. Byju[1]*, B. Jayalakshmi[2].

[1]Department of Pharmaceutical Chemistry, Devaki Amma Memorial College of Pharmacy, Chelembra, Pulliparambu(PO.), Malappuram-673634

[2]Department of Pharmaceutical Chemistry, J.K.K. Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam, Erode, Tamil Nadu.

ABSTRACT

Objectives: To synthesise some new N-mannich bases of hexahydroquinazoline-2-one derivatives and evaluate these compounds from their pharmacological activities like analgesics, antibacterial and locomotor activities.

Methods: In this study the final derivative is synthesised by three step process in the first step 2-benzylidene cyclohexanone were synthesised from cyclohexanone and benzaldehyde. In the next step 3-amino,4-phenyl,3,4,5,6,7,8-hexahydroquinazoline-2-one were synthesised from first step product (2-benzylidene cyclohexanone) and semi carbazide hydrochloride. Final derivatives were synthesised by mannich reaction. Pharmacological activities like analgesics, antibacterial and locomotor activity also performed.

Results: N-Manich bases of 2-amino-4-phenyl-3,4,5,6,7,8 hexahydroquinazoline-2-one were synthesised derivatives has been characterised by FTIR Spectroscopy, H1 NMR and other physicochemical properties. Pharmacological activity like analgesic were carried out by Eddy's hot plate method, antibacterial is carried out by Cup Plate method and locomotor activity is performed by Actophotometer, all the synthesised derivatives showed good analgesic, anti bacterial activity and locomotor activity.

Keywords: - Quiazoline 2-one, Chalcone, Mannich bases, Acute toxicity, Analgesics, Anti bacterial, Locomotor activity.

INTRODUCTION

Quinazoline and Quinazolinones:

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Quinazolin-2-ones, quinazoline-4-ones and related quinazolines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties[1]. Methaqualone was synthesized for the first time in 1951 and it is the most well-known synthetic quinazoline drug, famous for its sedative–hypnotic effects[2]. Quinazoline is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. Its chemical formula is $C_8H_6N_2$[3].

Moreover, the quinazoline skeleton is very common in several naturally occurring alkaloids displaying a wide range of biological activities useful in developing chemotherapeutic agents against many diseases and hence the exploration of this skeleton as privileged new chemical entities (NCE's) in drug discovery research is of paramount importance[4]. The quinazoline skeleton is of great importance to chemists as well as biologists as it is available in a large variety of naturally occurring compounds[5].

Quinazolines, Quinazolin-2-one and quinazoline-4-one can possess hypnotic[3] and diverse biological activities such as antiviral, antimalarial, anticonvulsant, antibacterial, diuretic, hypnotic, hypoglycaemic, antitumoral and antihypertensive[2,5]. The derivatives of quinazolin-2-ones are potential drugs which can possess hypnotic, analgesic, antiallergic, anticonvulsant, antimalarial, and other effects[4,6].

The sedative and hypnotic (neurotoxicity) properties of quinazolinone are well documented.The possibility that appropriate derivatives of quinazolinone as CNS-active compounds, which obviously cross the blood brain barrier, might find use as anticonvulsant or CNS depressant if the parent ring system could be appropriately functionalized. Among the few reports in the literature of tentative separation of anticonvulsant and sedative properties of quinazolinones[5,6,7].

Chalcones:

Many biological activities have been attributed to this group, such as anticancer anti-inflammatory, antipyretic and analgesic cytotoxic in vitro bactericidal, insecticidal, anti-fungal, antioxidant and phytoestrogenic activities[8]. Chalcone is a generic term given to compounds bearing the 1,3-diphenylprop-2-en-1-one framework. They are the first isolable compounds from flavonoid biosynthesis in plants[9]. Chalcones (1,3-diaryl-2-propen-1-one) are natural or synthetic flavonoids displaying an impressive array of biological properties. Their antimicrobial activity and particularly the antifungal action have been largely attributed to the reactive enone moiety[6,7,8].

Chalcones are prepared by condensing Aryl ketones with aromatic aldehydes in presence of suitable condensing agents. They undergo a variety of chemical reactions and are found useful in synthesis of variety of heterocyclic compounds. Chalcones have been used as intermediate for the preparations of compounds having therapeutic value[8,9,10].

Mannich Bases:

Mannich reaction is widely used for the synthesis of many kinds of compounds[11]. Mannich reaction is a three-component condensation reaction consisting of active hydrogen containing compound, formaldehyde and a secondary amine[12]. Mannich base is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde (or an aldehyde) and a carbon acid. The Mannich base is an end product in the Mannich reaction, which is nucleophilic addition reaction of a non-enolizable aldehyde and any primary or secondary amine to produce resonance stabilized imine (iminium ion or imine salt). The addition of a carbanion from a acidic compound (any enolizable carbonyl compound, amide, carbamate, hydantoin or urea) to the imine gives the Mannich base [12,13].

When considering N-Mannich bases as prodrug forms for primary and secondary amines the amide-type component would act as a transport group. By N-Mannich base formation the pKa, of the amines is lowered by about 3 units. Therefore, by transforming amino compounds into N-Mannich base transport forms it would be possible to increase the lipophilicity of the parent amines at physiological pH values by depressing their protonation, resulting in enhanced biomembrane passage properties. This expectation of increased lipophilicity has been confirmed [13] Mannich bases possess comprehensive bioactivities like anticancer, analgesic, antibacterial and antifungal activities [14,15].

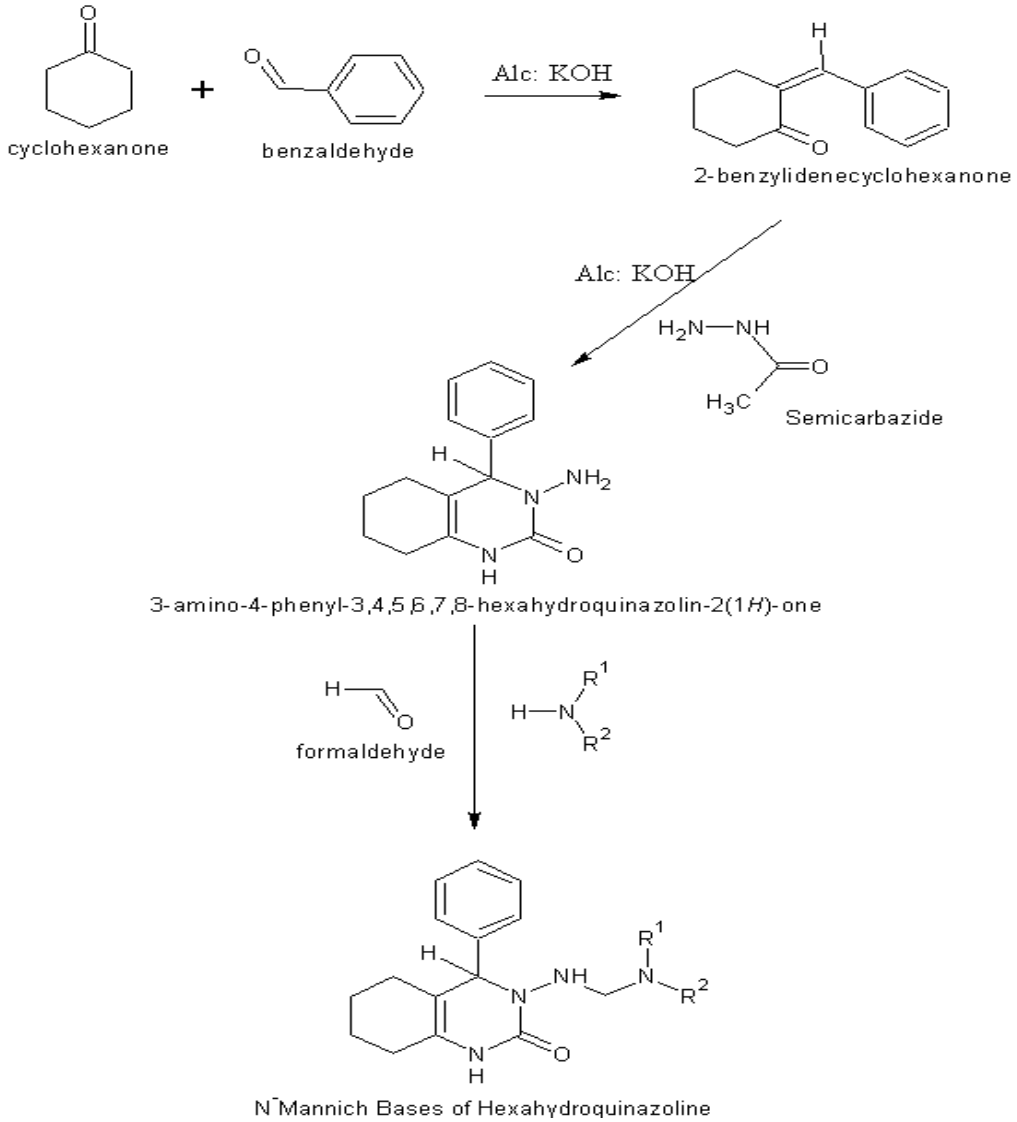
Mannich bases have been reported as potential biological agents. They find application as antitubercular, antimalarial, vasorelaxing, anticancer, and analgesic drugs. They are also used in polymer industry as paints and surface active agents[15]. The various drugs obtained from Mannich reaction are proved to be more effective and less toxic than the parent ncleus[14,15,16].

MATERIALS AND METHODS

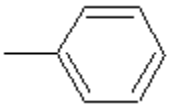
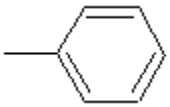
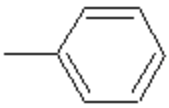
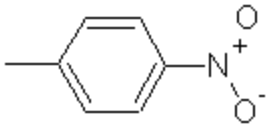
Cyclohexanone, benzaldehyde, potassium hydroxide, semicarbazide, formaidehyde, diphenyl amine, diethanolamine, aniline, ethanolamine, p-nitro aniline, ethanol were purchased from Merck India, Penicillin(used as control drug in antibacterial study) pure drug was donated thankfully by Maxheal Pharmaceuticals (India) Ltd, Mumbai and the quality of all these chemicals together with the other ones used through out the study were of analytical grade and used without further purification. The melting points were determined by the open capillary method using Macro Scientific Works Pvt. Ltd, Delhi, India. Infra-red spectra were recorded in KBr disc on Shimadzu FTIR 8400 spectrophotometer (Japan), at JKKMMRF College of Pharmacy, The Tami Nadu Dr. MGR Medical University, Chennai. H1 NMR recorded with the help of Ultra-High Field AVANCE III 850 MHz NMR system- Bruker at Sastra University, Thanjavur, Tiruchirapalli, Tamil Nadu. Chromatograms were eluted using Chloroform: Benzene: Ethylacetate (1:1:0.2) solvent system. The bacterial strains Staphylococcus aureus (ATCC 25923) and Escherichia coli (TCC 25922) were collected from microbiology lab of J.K.K. Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam, Erode, Tamil Nadu.

The animals were obtained from Government Agricultural University, Mannuthy, Thrissur, Kerala, India. All animals were housed in polypropylene cages in the standard environmental conditions (20-25°C), 12:12 light: dark cycle, fed with standard rodent diet and water ad libitum. The experiments on animals were conducted in accordance with the international accepted principle for laboratory animal use and the experimental protocols duly approved by the institutional animal ethical committee (IAEC) of J.K.K. Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam, Erode, Tamil Nadu, (Approval order no. 1158/PO/ac/07/CPCSEA). Statistical methods used to identify statistical significance by Anova test followed by Students T-test.

Chemical synthesis:



Scheme 1: synthetic pathway

Compound code	R1	R2
A11		
A12	$-CH_2CH_2OH$	$-CH_2CH_2OH$
A13	H	
A14	H	$-CH_2CH_3$
A15	H	

Step I

Synthesis of 2-benzylidene cyclohexanone (Chalcone):

Chalcone were synthesised according to the synthetic pathway depicted in scheme 1 and in accordance to the previously reported procedure in reference[6,17]. The procedure is as follows Cyclohexanone (0.01 mole) and benzaldehyde (0.01 mole) were taken into a clean and dry reaction vessel and dissolved in methanol (50ml). To this solution alcoholic KOH (2% 40ml) was added slowly drop wise while shaking the contents thoroughly. Then the reaction mixture was allowed to stand at room temperature for an hour while shaking periodically. An yellow crystalline solid that resulted was filtered and washed with small quantities of methanol and dried. The product was purified by recrystallisation from methanol to get an yellow crystalline solid.

Step II

Synthesis of 3-amino 4-phenyl hexahydroquinazoline 2(1H)-one:

Quinazoline 2-one derivative were synthesised according to the synthetic pathway depicted in scheme 1 and in accordance to the previously reported procedure in reference[4,18,19]. The reaction procedure as follows a mixture of step I product (0.01 mole), semi carbazide hydrochloride (0.01mole) and an alcoholic solution of KOH(6g in 150ml alcohol) were taken in a reaction flask and heated under reflux for 3hr on a hot water bath. The volume of the mixture was reduced to half by distilling off alcohol .The concentrated solution was then diluted with cold water and cooled further. The clear solution was then neutralised carefully with dilute acetic acid and kept in an ice chest. The solid mass thus resulted was filtered, washed with small portions of cold water and dried. It was purified by recrystallisation from alcohol to get a colourless crystalline solid.

Step III

Synthesis of N-Mannich bases of 3-amino 4-phenyl hexahydroquinazoline 2(1H)-one:

N-Mannich bases were synthesised according to the synthetic pathway depicted in scheme 1 and in accordance to the previously reported procedure in reference [20,21] the reaction procedure as follows, a mixture of A1 (0.01mole), formaldehyde(0.02mole) and amines(five defferent amines were taken)(0.02mole) in DMSO was warmed on a water bath with stirring for 30mts and there after it was allowed to stand over night at room temperature. Then added to cold water, the solid mass thus resulted was filtered, washed with small portions of cold water and dried. It was purified by recrystallisation from alcohol:chloroform (1:1) to get a crystalline solid.

RESULT AND DISCUSSION

The chalcone derivative[22] was prepared as intermediate compound for the synthesis of quinazoline 2-one nucleus by Aldol condensation, reaction between an aldehyde and ketone is usually feasible especially when the aldehyde has no α-hydrogen. 3-amino, 4-phenyl, 3,4,5,6,7,8-hexahydro quinazoline 2-one was synthesised by the reflux reaction of 2-Benzylidinecyclohexanone (chalcone)

with semi carbazide in the presence of alcoholic potassium hydroxide. The final derivatives (N-Mannich bases) were synthesised by the reaction on the 3-amino group present in the quinazoline 2-one nucleus and five defferent amines in presence of formaldehyde.

The structures of the synthesised compounds were confirmed by FTIR Spectroscopy, H1 NMR and other physicochemical properties (Table 1). The synthesised quinazoline 2-one derivatives (A11-A15) showed several characteristic sharp bands in the IR region, where the bands in range between 1266-1344cm^{-1} indicated the appearance of N-C-N bond, which gives the confirmation of formation of formation of Mannich bases, the bands in range between 1602-1649cm^{-1} indicated the appearance of C=O group, that is present in quinazoline 2-one nucleus(Table 2). The 1H NMR showed several characteristic peaks, indicated the presence of alicyclic, aliphatic, aromatic and amino group protons.(Table 3).

All the synthesised compounds showed analgesic((Table 4), antibacterial((Table 5) and loco motor(Table 6) activities . Among the synthesised compounds A15 showed very good analgesic activity, the derivative A13 showed good zone of inhibition against Gram positive strains and A12 has good zone of inhibition against Gram negative strains. Regarding loco motor activity the derivative A13 showed more activity.

CONCLUSSION

The result obtained in the study strongly suggests that quinazoline 2-one derivatives are pharmacologicaly more active than quinazoline derivatives[23]. All the synthesised compounds showed analgesic, antibacterial and loco motor activities[24]. Among the synthesised compounds A15 showed very good analgesic activity is due to the presence of highly electron withdrawing group(-NO_2)[25], the derivative A13 showed good zone of inhibition against Gram positive strains is due to the presence of nucleopholic group[26] and A12 has good zone of inhibition against Gram negative strains is due to the presence of aliphatic group[27]. Regarding loco motor activity the derivative A13 showed more activity is due to the presence of nucleopholic group[28]. In this study the intermediate compound 2-Benzylidinecyclohexanone (chalcone), formed is also have predominant role in activity of final derivative[29]. Thus quinazoline 2-one is not only synthetically important but also possesses a wide range of promising biological activities[30]. Future investigations of this study could give some more encouraging results. This study is self explanatory about the clinical therapeutic potential of quinazoline 2-one and its derivatives.

ACKNOWLEDGEMENTS

We are thankful to Department of Pharmaceutical Chemistry, Devaki Amma Memorial College of Pharmacy, Chelembra, Pulliparambu(PO.), Malappuram-673634 and Department of Pharmaceutical Chemistry, J.K.K. Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam, Erode, Tamil Nadu, for providing all assistance to carry out the research work successfully.

Table 1
Physicochemical characterization data for synthesised compounds

Compound code	Molecular formula	Molecular weight (gm)	Percentage yield (%)	Melting range (° C)	R_f value
A	$C_{13}H_{14}O$	188.26	73.42	87-90	0.629
A1	$C_{14}H_{17}N_3O$	243.30	52.40	159-163	0.315
A11	$C_{27}H_{28}N_4O$	424.53	80.20	50-54	0.545
A12	$C_{19}H_{28}N_4O_3$	359.46	75.60	77-81	0.735
A13	$C_{21}H_{24}N_4O$	347.45	78.65	90-94	0.625
A14	$C_{17}H_{24}N_4O$	300.39	70.68	90-93	0.844
A15	$C_{21}H_{23}N_5O_3$	393.43	75.68	94-98	0.596

Table 2
IR spectral data of synthesised compounds

Compound code	Chemical name	Characteristics IR spectral Bands (KBr)v cm^{-1} with its interpretation
A	2-Benzylidinecyclohexanone	693(C-H, alkanes), 1492(C-C, aromatic), 1649(C=O),2365 (C-O, bond), 2854(CH_2,alkanes),2924(=CH, alkenes).
A1	3-amino-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	693(C-H,alkanes),1170(CN),1310(NCN),1492(C-C,aromatic), 1594(C=N,Quinazoline),1649(C=O),2365(C-O bond),2924(=CH,alkenes),3447(-NH, group)
A11	4-phenyl-3[(1,1'diphenylamino)methyl]amino-3,4,5,6,7,8 hexahydroquinazoline-2(1H)-one	693(C-H,alkanes),1170(CN),1310(NCN),1492(C-C,aromatic), 1594(C=N,Quinazoline),1649(C=O),2365(C-Obond), 2854(CH_2,alkanes),2924(=CH,alkenes),3447(-NH, group)
A12	4-phenyl-3-[(1,1'-diethanolamino)methyl]amino-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-one	699(C-H,alkanes),1029(C-O,alcohols),1179,(C-N),1340(N-C-N), 1445(C-N),1493(Ar-C=C),1538(C=C,aromatic),1624(C=O), 2365(C-Obond),2857(C-H_2,alkanes),2927(=CH,alkens),3453(-NH, group)
A13	4-phenyl-3-[(phenylamino)methyl]amino-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	698(C-H,alkanes),1027(C-O,alcohols),1185(C-N),1342(N-C-N),1449(ArC=C),1491(NH,),1543(C=C),1601,(C=N), 1627(C=O),2367(COobond),2858(CH_2,alkanes), 2927(=CH,alkenes),3446(-NH, group)
A14	4-phenyl-3-[(ethylamino)methyl]amino-3,4,5,6,7,8-hexahydroquinazolin- 2(1H)-one	699(C-H,alkanes),1088(C-O,alcohols),1191(C-N),1344(N-C-N), 1447(Ar-C=C),1491(N-H,bending),1544(C=C),1622(C=O), 2367(C-Obond),2855(CH_2,alkanes),2928(=CH,alkenes), 3445(-NH, group)
A15	4-phenyl-3-[(4'-nitrophenylamino)methyl]amino-3,4,5,6,7,8 hexahydroquinazolin-2(1H)-one	697(C-H,alkanes),1040(C-O,alcohols),1187(C-N),1266(N-C-N), 1470(Ar-C=C),1494(NH),1529(C=C),1602(C=O),2363(C-Obond), 2855(CH_2,alkanes),2926(=CH,alkenes),3369(-NH, group)

Table 3
1HNMR data of synthesised compounds

Compound code	Chemical name	Characteristics H1 NMR peaks with its interpretation
A	2-Benzylidinecyclohexanone	1.33-2.94[m 4H, 3,4,5,6H of CH_2(cyclo hexane)],7.15 [s 1H of CH(aliphatic)], 7.21-7.3[m 5H, 2'(2, 3, 4, 5 6H) of CH(aromatic)].
A1	3-amino-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2,6[s H of 1,3(1') NH].
A11	4-phenyl-3[(1,1'diphenylamino)methyl]amino-3,4,5,6,7,8 hexahydroquinazoline-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2,6[s H of 1,3(1') NH], 6.43-7.08{m 2x5H, 3[3'(2,3,4,5,6),aromatic]}.
A12	4-phenyl-3-[(1,1'-diethanolamino)methyl]amino-3,4,5,6,7,8- hexahydroquinazoline-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2,6[s H of 1,3(1') NH], 2.52-3.63{m 2x2H, 3[3'(1,2,aliphatic]}.
A13	4-phenyl-3-[(phenylamino)methyl]amino-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2,4,6[s H of 1,3(1',3') NH], 6.43-7.04{m 5H,3[3'(2,3,4,5,6),aromatic]}.
A14	4-phenyl-3-[(ethylamino)methyl]amino-3,4,5,6,7,8-hexahydroquinazolin- 2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2 [s H of 1,3(1') NH], 6[s H of 3(3') NH], 1-2.59[m H of 3(4',5'H) of aliphatic hydrogen].
A15	4-phenyl-3-[(4'-nitrophenylamino)methyl]amino-3,4,5,6,7,8 hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclo hexane)], 5.56 [s 1H, 4 of CH(aliphatic)], 7.06-7.14[m 5H, 4(2', 3', 4', 5' 6'H) of CH(aromatic)], 2,4,6[s H of 1,3(1',3') NH], 6.69-7.97{m 4H,3[3'(2,3,5,6),aromatic]}.

Table 4
Analgesic activity data for prepared compounds

Compoud code	Before admn (paw licking)	After administration (paw licking response)					
		30mts	60mts	90mts	120mts	150mts	180mts
A11	7.16±1.33	10.3±0.88**	10.33±1.4**	10.33±2.4 1**	8.33±1.20	7±0.58	5.66±0.88
A12	5.5±1.00	11±2.0 0***	12±2.08***	15.3±2.41***	10.33±2.41**	6.66±1.72	5.33±1.33
A13	4.66±0.17	8.33±0.33**	8.66±0.67**	9.3±0.34***	7.6±0.67**	5.3±0.34	4.3±0.34
A14	4.83±0.55	8.33±0.33**	10.66±1.6 7***	9.3±0.33***	8.66±0.67**	6±0.58*	4±0.00
A15	6.16±1.20	10±0.5 8**	12±1.53***	12.33±2.9 7***	8.6±1.77*	7±1.01	5.66±1.20

* = p < 0.05, ** = p<0.01, *** = p<0.001

Table 5
Data for antibacterial screening

Compound code	Bacteria	1.(1000µg)	2.(500µg)	3.(250µg)	4.(125µg)	5.(62.5µg)	C(1000µg)
A11	Staphylococcus aureus	18mm	14mm	10mm	7mm	4mm	26mm
A12	Staphylococcus aureus	16mm	10mm	5mm	3mm	2mm	21mm
A13	Staphylococcus aureus	22mm	18mm	14mm	8mm	3mm	28mm
A14	Staphylococcus aureus	20mm	16mm	9mm	4mm	2mm	22mm
A15	Staphylococcus aureus	15mm	9mm	4mm	2mm	0mm	18mm
A11	Escherichia coli	18mm	15mm	13mm	8mm	2mm	22mm
A12	Escherichia coli	22mm	18mm	12mm	10mm	5mm	24mm
A13	Escherichia coli	16mm	14mm	9mm	3mm	0mm	20mm
A14	Escherichia coli	15mm	8mm	6mm	0mm	0mm	22mm
A15	Escherichia coli	18mm	12mm	10mm	9mm	1mm	23mm

Table 6
Data for locomotor activity

Compound code	Before admn	After administration					
		30mts	60mts	90mts	120mts	150mts	180mts
A11	234 ± 4.0	217.67 ± 4.34	193.33 ± 3.76***	183.67 ± 4.98***	207.6 ± 4. 3*	216.33 ± 3.17	232.33 ± 4.33
A12	266 ± 3.06	184 ± 4.1 6***	153.67 ± 4.48***	78 ± 4.1 6***	139 ± 3.2 1***	207.33 ± 71**	254.33 ± 3.84
A13	198.67 ± 4.67	109.6 ± 5.4 4***	90 ± 4.6***	100 ± 4.60***	143.33 ±4.42**	170 ± 3.47*	184.67 ± 4.06
A14	185 ± 2.89	162.33 ± 1.67	126 ± 4.9***	103.67 ± 3.48***	127 ± 3.6***	155.33 ± 2.91*	195 ± 2.89
A15	166.33 ± 3.48	144 ± 3.22*	135 ± 2.8 9**	99 ± 2.0 8***	139.33 ± 4.81*	150.33 ± 4.63	160 ± 3.47

*= p<0.05, **= p<0.01, ***= p<0.001

REFERENCES

1. David J.Connolly, Declan Cusack, Timothy PO.Sullivan and Patrick J.Guiry. Synthesis of quinazolinones and quinazolines. Tetrahedron Letters, 2005; 61(2): 10153-10202.
2. Santosh B.Mhaske and Narshinha P.Argade. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. Tetrahedron Letters 2006; 62(1): 9787–9826.
3. Palle VR.Acharyulu, Dubey PK, Prasada Reddy PVV, Thatipally Suresh. Synthesis of new 4(3H)-quinazolinone derivatives under solvent free conditions using PEG-400. Arkivoc, 2008; 11(3): 104-111.
4. Vinod K.Tiwari, Raju R.Kale, Bhuwan B.Mishra, and Archana Singh. A facile one-pot MW approach for 3-heteroaryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one, Arkivoc. 2008; 14(11): 27-36.
5. Balbir Kaur and Ramandeep Kaur. Synthesis of fused quinazoline thiones and their S-alkyl/aryl derivatives. Arkinov, 2007; 15(12): 315-323.
6. Lahtchev KL, Batovska DI, St.Parushev P, Ubiyvovk VM, Sibirnyet AA. Antifungal activity of chalcones: A mechanistic study using various yeast strains. European Journal of Medicinal Chemistry, 2008; 43(9): 2220-2228.
7. Varsha Jatva, Pradeep Mishra, Sushil Kashaw, Stables JP. CNS Depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline- 4(3H)-ones. European journal of medicinal chemistry, 2008; 43(10): 1945-1954.
8. Ohad Nerya, Ramadan Musa, Soliman Khatib, Snait Tamir, Jacob Vaya. Chalcones as potent tyrosinase inhibitors : the effect of hydroxyl positions and numbers. Phytochemistry Letters, 2004; 65(1): 1389-1395.
9. Nielson SF, Kharazmi A, Christensen SB. Examination of growth inhibitory properties of synthetic chalcones for which antibacterial activity was predicted. Bioorganic and Medicinal Chemistry, 1998; 12(2): 937-939.
10. Jovan Y.Alston, Albert J.Fry. Substituent effects on the reduction potentials of benzalacetophenones (chalcones) Improved substituent constants for such correlation. Electrochimica Acta, 2004; 49(9): 455-459.
11. Li Yuan MOU, Zi Yun Lin, Li Y ZHU, Xiao Tian Liang. A New Investigation of Mannich Reaction. Chinese Chemical Letter, 2001; 12(8): 471-474.
12. Raman N and Esthar SA. New Mannich base and its transition metal (II) complexes-Synthesis, structural characterization and electrochemical study. Journal of Chemical Sciences, 2004; 116: 209-213.
13. March-Jerry. Advanced Organic Chemistry: Reactions, Mechanisms and Structure. III Edition. Wiley. New York. 2006; 920-922.
14. Pandeyaa SN, Srirama D, Nathb G, De Clercqcet E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and *N*-[4-(49-chlorophenyl)thiazol-2-yl] thiosemicarbazide. European Journal of Pharmaceutical Sciences, 1999; 9(1): 25-31.
15. Mithun Ashok, Bantwal Shivarama Holla, Boja Poojaryet. Convenient one pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. European Journal of Medicinal Chemistry, 2007; 42(7): 1095-1101.
16. Sheela Joshi, Navita Khosla, Deepak Khare and Rakesh Sharda. Synthesis and in vitro study of novel Mannich bases as antibacterial agents. Bioorganic & Medicinal Chemistry Letters, 2005; 15(11): 221-226.
17. Sarojini BK and Narayana B. Synthesis and studies on non-linear optical property of new chalcones. Journal of Medicinal and Pharmaceutical Chemistry, 1991; 108(16): 688-695.
18. Pachaippan Shanmugam, Cruz Sabstein, Paramasivan T.Perumal, Synthesis of fused dihydro pyrimdiones from cyclic-1,3-dicarbonyl compounds: Modified Biginelli synthesis of 1,2,3,4,5,6,7,8-octahydroquinazolinediones and 3,4-dihydro-1H-indino[1,2-*d*]pyrimidine-2,5-diones. Indian journal of chemistry, 2004; 43(2): 135-140.
19. Gamal A El-hiti and Mohamed Fabdol-megeed. Synthesis and reactions of some 3-aryl-2-thioquinazolin-4(3H)-ones. Indian Journal of Chemistry, 2002; 41(2): 1519-1522.
20. Alagarsamy V, Pathak US, Goyal RK. Synthesis and Evaluation of some novel 2-Mercapto-3-(substituted methyl amino) quinazolin-4(3H)-ones as Analgesic, anti-inflammatory and antibacterial agents. Indian Journal of Pharmaceutical Sciences, 2000; 43(15): 63-66.
21. Seshaiah Krishnan Sridhara, Muniyandy Saravanana, Atmakuru Ramesh. Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives. European Journal of Medicinal Chemistry, 2001; 36: 615-625.
22. Samer A.Hasan and Amer N.Elias. Synthesis of new diclofenac derivatives by coupling with

chalcone derivatives as possible mutual prodrugs. International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(1): 239-245.

23. Mohammed F.Zayed, Memy H.Hassan. Synthesis and biological evaluation studies of novel quinazolinone derivatives as antibacterial and anti inflammatory agents. Saudi Pharm. J., 2014; 22(2): 157-162.
24. Dan Wang and Feng Gao. Quinazoline derivatives: synthesisand bioactivities. Chemistry Central Journal, 2013, 7(1): 95-110.
25. Abbas Ahmadi, Mohsen Khalili, Ramin Hajikhani, Leila Barghi *a*nd Farnaz Mihandoust. Synthesis and Determination of Chronic and Acute Thermal and Chemical Pain Activities of a New Derivative of Phencyclidine in Rats. Iranian Journal of Pharmaceutical Research, 2010; 9(4): 379-385.
26. Samija Muratovic, Kemal Duric, Elma Veljovic, Amar Osmanovic, Dženita Softic, Davorka Zavrsnik. Synthesis of Biscoumarin Derivatives as Antimicrobial Agents. Asian J. Pharm. Clin. Res., 2013; 6(3): 132-134.
27. Sethukkarasi M, Asha Devi NK, Vasuki B, Nishanthini A, Falaq Naz and Thirumurugan R. Antagonistic Activity of Marine Bacteria from Cochin Backwater of Arabian Sea. International Journal of Microbiological Research, 2012; 3(1): 16-23.
28. Veerachamy Alagarsamy, Rajani Giridhar B and Mangae Ram Yadav. Synthesis and H1-Antihistaminic Activity of some Novel 1-Substituted-4-(3-Methylphenyl)-1,2,4-Triazolo[4,3-α]Quinazolin-5(4H)-Ones. Biol. Pharm. Bull., 2005; 28(8): 1531-1534.
29. Kulathooran S, Selvakumar B and Dhamodaran M. Synthesis and biological activities of novel heterocyclic chalcone derivatives by two different methods using anhydrous potassium carbonate as an efficient catalyst. Der. Pharma. Chemica, 2014; 6(3): 240-249
30. Theivendren Panneer Selvam, Palanirajan Vijayaraj Kumar. Quinazoline Marketed drugs – A Review Research in Pharmacy, 2011; 1(1): 1-21.