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Research Article

Synthesis and Biological evaluation (Analgesics, Antibacterial and Locomotor activity) of N-Mannich bases of-3-amino 4-(4-ethylphenyl)-3,4,5,6,7,8-exahydroquinazoline-2-one derivatives.

Byju K, Biju CR, Arunlal VB, Vimal KR, Anilasree BP, Babu G

1Department of Pharmaceutical Chemistry, Devaki Amma Memorial College of Pharmacy. Pulliparambu(po), Chelembra, Malappuram-673634, Kerala, India.

Address for Correspondence
Byju K
E-mail : byjukadav@gmail.com

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ABSTRACT

In this research work synthesized some new N-mannich bases of hexahydroquinazoline-2-one derivatives and evaluate these compounds from their pharmacological activities like analgesics, antibacterial and locomotor activities. Here the final derivative is synthesized by three step process in the first step 2-(4-methyl benzylidene) cyclohexanone were synthesized from cyclohexanone and 4-methyl benzaldehyde. In the next step 3-amino-4-(4-methylphenyl),3,4,5,6,7,8-hexahydroquinazoline-2-one were synthesized from first step product 2-(4-methyl benzylidene) cyclohexanone and semi carbazide hydrochloride. Final derivatives were synthesized by mannich reaction. Pharmacological activities like analgesics, antibacterial and locomotor activity also performed. N-Manich bases of 3-amino-4-(4-methylphenyl)-3,4,5,6,7,8 hexahydroquinazoline-2-one were synthesized derivatives has been characterized by FTIR Spectroscopy, H1 NMR and other physicochemical properties. Pharmacological activity like analgesic activity 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 synthesized derivatives showed good analgesic ,anti bacterial and locomotor activity. Quinazolin-2-one derivatives synthesized in this study got in very good practical yield, all derivatives is not only synthetically important but also possesses a wide range of promising biological activities. Future investigations of this study could give some more encouraging results. This study is self explanatory about the clinical therapeutic potential of quinazolinone and its derivatives.

Key words: Quinazoline 2-one, 4-Methyl benzaldehyde, Chalcone, Mannich bases.

INTRODUCTION

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.

Quinazoline and Quinazolinones:

Quinazolin-2-ones, quinazoline-4-ones and related quinazolines are classes of fused heterocyclics 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 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[5,7].

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[6,8]. 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 compound. 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, 4-methyl 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 and C13 NMR were 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 pharmacologiacal activities of synthesized compounds carried out are anti bacterial, analgesic and locomotor. 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^{o}C), 12:12 light: dark cycle, fed with standard rodent diet and water ad libitum. The experimental protocol was approved by Institutional Animal Ethical Committee (IAEC) of J.K.K. Munirajah Medical Research Foundation, College of Pharmacy, Komarapalayam, Erode, Tamil Nadu. (Letter No: MU/UCMS/IAEC/4109) with CPCSEA Registration No: 1158/PO/ ac /12/CPCSEA.

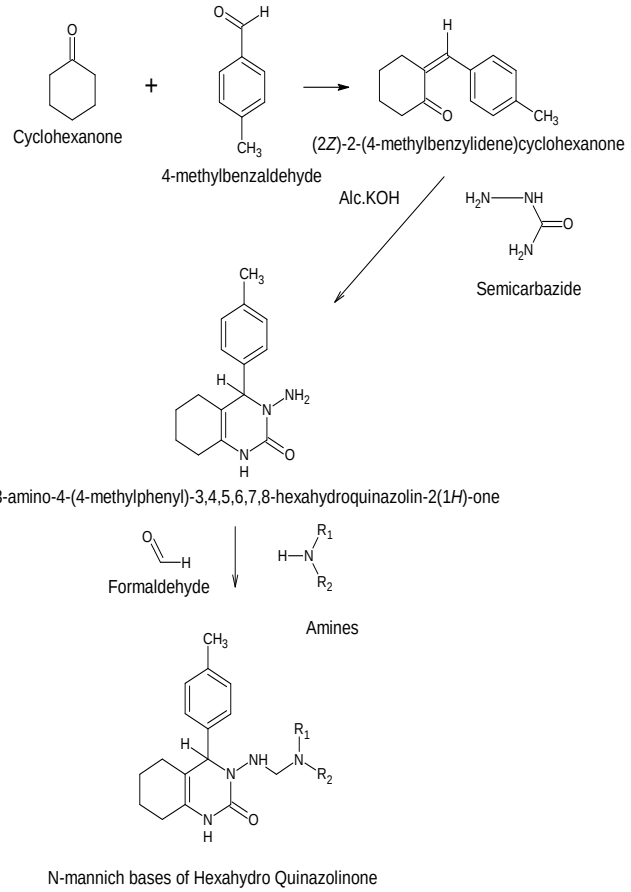
STEP I

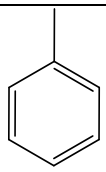
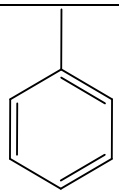
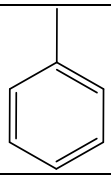
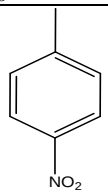
Synthesis of 2-(4-methyl benzylidene) cyclohexanone (chalcone) , (code-a):

Chalcone were synthesized 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 4-methyl 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.

Chemical synthesis (scheme 1):



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

STEP II

Synthesis of 3-amino 4-(4-methyl phenyl) hexahydroquinazoline 2(1h)-one, (code-a1):

Quinazoline 2-one derivative were synthesized 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 neutralized 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 recrystallization from alcohol to get a colourless crystalline solid.

STEP III

Synthesis of N-Mannich bases of 3-amino 4-(4-methyl phenyl) hexahydroquinazoline 2(1h)-one, (code-a11 to a15):

N-Mannich bases were synthesized 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 different 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 overnight 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 recrystallization from alcohol: chloroform (1:1) to get a crystalline solid.

RESULTS AND DISSCUSSION

TABLE 1: Physicochemical characterization data for synthesized compounds

Compound code	Molecular formula	Molecular weight (gm)	Percentage yield (%)	Melting range (° C)	R_f value
A	$C_{14}H_{16}O$	200.27	78.42	88-91	0.678
A1	$C_{15}H_{19}N_3O$	**257.33**	75.42	159-163	0.415
A11	$C_{28}H_{30}N_4O$	438.56	80.20	60-64	0.645
A12	$C_{20}H_{28}N_2O_3$	344.44	75.60	67-71	0.635
A13	$C_{22}H_{24}N_2O$	347.44	78.65	90-94	0.635
A14	$C_{18}H_{24}N_2O$	284.39	70.68	90-93	0.844
A15	$C_{22}H_{23}N_3O_3$	377.43	75.68	94-98	0.596

Table 2: IR spectral data of synthesized compounds

Compound code	Chemical name	Characteristics IR spectral Bands (KBr)v cm^{-1} with its interpretation
A	2-(4-methylbenzylidene) cyclohexanone	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-(4-methylphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-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	3-[(diphenylamino)methyl]4-(4-methylphenyl),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	3-[(diethanolamino)methyl]4-(4-methylphenyl),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	3-[(phenylamino)methyl] 4-(4-methylphenyl),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(CObond),2858(CH_2,alkanes), 2927(=CH,alkenes),3446(-NH, group)
A14	3-[(ethylamino)methyl]4-(4-methylphenyl),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	3-[(4'-nitrophenyl amino) methyl] 4-(4-methylphenyl),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: H1NMR Data of Synthesized Compounds

Compound code	Chemical name	Characteristics H1 NMR peaks with its interpretation
A	2-(4-methylbenzylidene) cyclohexanone	1.33-2.94[m 4H, 3,4,5,6H of CH_2(cyclohexane)],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-(4-methylphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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	3-[(diphenylamino)methyl]4-(4-methylphenyl),3,4,5,6,7,8 hexahydroquinazoline-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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	3-[(diethanolamino)methyl]4-(4-methylphenyl),3,4,5,6,7,8-hexahydroquinazoline-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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	3-[(phenylamino)methyl] 4-(4-methylphenyl),3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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	3-[(ethylamino)methyl]4-(4-methylphenyl),3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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	3-[(4'-nitrophenyl amino) methyl] 4-(4-methylphenyl),3,4,5,6,7,8 hexahydroquinazolin-2(1H)-one	1.65-1.96[m 4H, 5,6,7,8H of CH_2(cyclohexane)], 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

Compound code	Before administration (paw licking)	After administration (paw licking response)					
		30 min	60 min	90 min	120 min	150 min	180 min
A11	8.26±1.33	11.4±0.88**	11.43±1.4**	11.43±2.4 1**	9.33±1.20	8±0.58	6.66±0.88
A12	6.5±1.00	12±2.0 0***	13±2.08***	16.3±2.41***	11.33±2.41**	7.66±1.72	6.33±1.33
A13	5.66±0.17	9.33±0.33**	9.66±0.67**	10.3±0.34***	8.6±0.67**	6.3±0.34	5.3±0.34
A14	5.83±0.55	9.33±0.33**	11.66±1.6 7***	10.3±0.33***	9.66±0.67**	7±0.58*	5±0.00
A15	7.16±1.20	11±0.5 8**	13±1.53***	13.33±2.9 7***	9.6±1.77*	8±1.01	6.66±1.20

** = p < 0.05, ** = p<0.01, *** = p<0.001, Statistical methods used to identify statistical significance by Anova test followed by Students T-test.*

Table 5: Data for Antibacterial screening

Compound code	Bacteria	1 (1000µg)	2 (500µg)	3 (250µg)	4 (125µg)	5 (62.5µg)	C (1000µg)
		Zone of Inhibition (mm)					
A11	*Staphylococcus aureus*	19	15	11	8	5	22
A12	*Staphylococcus aureus*	17	11	6	4	3	21
A13	*Staphylococcus aureus*	23	19	15	10	5	23
A14	*Staphylococcus aureus*	21	17	10	5	3	22
A15	*Staphylococcus aureus*	16	10	4	3	2	21
A11	*Escherichia coli*	19	16	14	9	3	24
A12	*Escherichia coli*	23	19	13	11	6	23
A13	*Escherichia coli*	17	15	10	4	1	23
A14	*Escherichia coli*	16	9	7	2	1	25
A15	*Escherichia coli*	19	13	11	10	2	22

Table 6: Data for locomotor activity

Compound code	Before admn.	After administration					
		30 min	60 min	90 min	120 min	150 min	180 min
A11	244±4.0	227.67±4.34	203.33±3.76**	193.67±4.98***	217.6±4. 3*	226.33±3.17	242.33±4.33
A12	276±3.06	194±4.1 6***	163.67±4.48**	88±4.1 6***	149±3.2 1***	217.33±71**	264.33±3.84
A13	208.67±4.67	119.6±5.4 4***	100±4.6***	110±4.60***	153.33±4.42**	180±3.47*	194.67±4.06
A14	195±2.89	172.33±1.67	136±4.9***	113.67±3.48***	137±3.6***	165.33±2.91*	205±2.89
A15	176.33±3.48	154±3.22*	145±2.8 9**	100±2.0 8***	149.33±4.81*	160.33±4.63	170±3.47

**= p<0.05, **= p<0.01, ***= p<0.001, Statistical methods used to identify statistical significance by Anova test followed by Students T-test.*

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-(4-methylphenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one was synthesized by the reflux reaction of 2-(4-methylbenzylidene) cyclohexanone (chalcone) with semi carbazide in the presence of alcoholic potassium hydroxide. The final derivatives (N-Mannich bases) were synthesized 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 synthesized compounds were confirmed by FTIR Spectroscopy, H1 NMR(Table 3) and other physicochemical properties (Table 1). The synthesized quinazoline 2-one derivatives (A11-A15) showed several characteristic sharp bands in the IR region(Table 2), 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 synthesized compounds showed analgesic((Table 4), antibacterial((Table 5) and loco motor(Table 6) activities . Among the synthesized 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

In conclusion the result obtained in the study strongly suggests that quinazoline 2-one derivatives are pharmacologicaly more active than quinazoline derivatives. All the synthesized compounds showed good analgesic, antibacterial and loco motor activity. In this study the intermediate compound 2-(4-methylbenzylidene)

cyclohexanone (chalcone), formed is also have predominant role in activity of final derivative. Thus quinazoline 2-one is not only synthetically important but also possesses a wide range of promising biological activities. 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.

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