NEW SYNTHETIC METHODOLOGY, CHARACTERIZATION, DOCKING STUDIES, AND PHARMACOLOGICAL EVALUATION OF NOVEL SUBSTITUTED 3-ALKYL AMINO QUINAZOLINE 4- (3H)-ONE DERIVATIVE

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Abstract

A novel series of 3-alkyl Amino Quinazoline 4-(3H) one derivative was prepared by a methodical and facile method. Substitution of phenyl group at 2nd position in the novel quinazoline derivative ring system for exceeding Analgesic activity and Anti-anxiety activity. Synthesis of novel Substituted 3-alkyl Amino Quinazoline 4-(3H)-one derivatives were synthesized where Intermediate I (2-amino-N-(2 aminoethyl benzamide) and intermediate II {3-(2-aminoethyl)-2-(chloromethyl) quinazoline-4(3H)-one)} were the two intermediates formed during the synthesis of novel molecules and total twelve compounds (I_1- I_4 & I_{17} - I_{24}) were derived and was evaluated for Analgesic activity and Anti-anxiety activity. Analytical and statistical verification was performed on each molecule that was synthesized. Binding energy and RMSD value were calculated with respect to ligand-receptor interaction with the aid of various docking software. Two intermediates were formed during the synthetic scheme. Anti-anxiety and analgesic activity were evaluated with the help of the tale flick method and elevated plus maize test. Estimated six compounds were more potent (**I_1, I_2, I_3, I_{17}, $I_{19}$and I_{24}**) and estimated eight compounds (**I_1-I_4)** & **(I_{17}, I_{19}, I_{21} and I_{24}**) showed moderate analgesic activity out of twelve compounds (**I_1-I_4) & (I_{17}-I_{24}**). Estimated ten compounds **(I_1,I_3,I_4,I_{17},I_{18},I_{20}-I_{24})** showed moderate anti-anxiety activity and six compounds (**I_{17},I_{18}, I_{20}, I_{21}, I_{22} and I_{23}**) were more potent out of twelve compounds (**I_1-I_4) & (I_{17}-I_{24}**). These compounds (I_1-I_4) as well as (I_{17} - I_{24}) could be useful as a template for further design, optimization and investigation to produce a more active analogue. The absence of toxic symptoms or fatality rates in compounds assessed for acute toxicity 24 hours after ingestion suggests their high safety margin.

Keywords: Quinazoline derivatives, molecular docking, analgesic activity, anxiolytic activity.

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1. INTRODUCTION

Due to their extensive and unique biological activity, quinazoline derivatives—which are heterocyclic molecules with a N-atom—have raised concerns throughout the world [1]. These compounds provide the basis for numerous pharmacological applications [2]. Quinazoline derivatives, which are N-containing heterocyclic compounds, exhibit wide-ranging and distinctive biological actions, including diuretic, antihypertensive, antihistaminic, analgesic and anti-inflammatory, anticancer and anti-HIV effects[3, 24]. By adding various active groups to the quinazoline moiety using advanced synthetic techniques, medicinal chemists were able to create a number of quinazoline molecules with various biological activity. Moreover, research has been done on the possible uses of quinazoline derivatives in the realms of biology, insecticides, and medicine[4]. Quinazolinone groups are found in a number of natural alkaloids with important pharmacophores. For instance, the plants, animals, and microbes included febrifugine, isofebrifugine, thiabutazide, benzomalvin A, 2-(4-hydroxybutyl) quinazolin-4-one, and luotonin F[5]. Life depends on a number of heterocyclic compounds, including the haemoglobin derivatives in blood and the chlorophyll needed by plants for photosynthesis. The DNA and RNA both include heterocycles. The teal blue used to tint jeans is one of the dyes having plant origins. The main structural component of compounds like nicotine, pyridoxine, cocaine, morphine, etc. is a large number of N-containing rings[6]. Many quinazoline and quinazolinone derivatives are created when isatoic anhydrides interact with certain nitrogen nucleophiles, followed by electrophile cyclocondensation [7]. 2-[4-(2-furoyl) piperazin -1-yl] 6,7 dimethoxyquinazolin-4-amine is the chemical name for the drug prazosin. It lowers blood pressure by acting as a sympathomimetic drug. It is a member of the class of drugs called alpha-adrenergic blockers, which lower blood pressure by relaxing veins and arteries. [8]. Several enzymes involved in the production of analgesic effects have already been reported to be inhibited by derivatives of quinozolinone[9]. A pyrimidine and benzene rings fuse at two nearby carbon atoms to create quinazolines. A diverse set of compounds known as quinolines have a variety of pharmacological activities[10]. Due to their numerous biological actions, including anticancer, antimalarial, and antitumor properties, heterocyclic nitrogen compounds—particularly 4(3H)-quinazolinone (also known as quinazolinone) and its derivatives—are extensively employed in medicinal chemistry[11]. A medication with a range of therapeutic potential is produced by the optimization of various functional groups around the quinazoline scaffold. [12]. The six-membered heterocyclic ring system quinazoline is known for its various pharmacological activities and is often used in the development of compounds with multiple pharmacophores. These compounds combine a comprehension of a target with knowledge of the various types of molecules that can possibly interact with the target family[13]. The quinazoline ring is a highly advantageous substructure in organic synthesis, commonly used to prepare a wide range of biologically active molecules[14].Quinazolinones, which are the saturated form of quinazolines, can be classified based on the position of the carbonyl group as either 2(1H), 4(3H), or 2,4(1H,3H) quinazolinone[15]. Since the 1888 discovery of peganine, a quinazoline alkaloid, the two nitrogen atoms in quinazoline have captivated scientists due to their unusual features[16]. he synthesis of 4-azapapaverine analogues, which incorporate a quinazoline ring system through a key catalytic aroylation reaction, was found to be interesting and incorporating many medicinal values[17].

2-substituted-3,1-benzoxazin-4-ones and their corresponding quinazoline derivatives have been found to exhibit diverse biological activities, including antipyretic, anti-inflammatory, antimitotic, and anticancer properties, as well as good storage stability in detergents[18]. The process of triple helix formation involves binding a short oligonucleotide to homopurine-homopyrimidine, Hoogsteen or reverse Hoogsteen hydrogen bonding, which offers a tailored method for DNA binding, can bind to specific sequences in double-stranded DNA. Although there had been only scattered reports on the medicinal properties of quinazoline compounds, their chemistry has generated significant interest among researcher[19,20,26]. Some quinazoline derivatives have been found to possess remarkable medicinal properties, which have the potential to benefit human health[21]. The antifolate substances investigated in this work are derivatives of the quinazoline with structures resembling those of the tomudex/ZD1694 class of antifolates. A pyrimidine ring, a benzene ring, and two fused six-membered simple aromatic rings make up quinazoline[22]. Many pharmaceutical, agricultural, and veterinary products are based on heterocyclic nuclei since these structures are known to have a wide variety of pharmacological actions. Among them, quinazolin-4[3H]-ones are a significant class of

heterocycles that have drawn a great deal of interest because of their wide variety of biological activities, including their impact on infection, cancer, convulsions, tuberculosis, and inflammation [23].

Several series of quinazolinone derivatives have been reported to exhibit notable antimicrobial and antifungal properties. Moreover, molecules containing the quinazolinone scaffold can act as modulators of calcium and sodium ion transport across cellular membranes by inhibiting the sodium/calcium exchange process[24, 25]. A method for estimating the affinities between two molecules is called molecular docking. To enhance and assess ligand-receptor interactions, it entails locating the ligand's optimal position within the receptor's active region[27]. The use of docking to do virtual screening on large libraries of compounds, evaluate the results, and provide structural suggestions for how the ligands inhibit the target has a significant positive impact on lead optimization. [28,29]. Quinazolines have recently been identified as adaptable template molecules for the inhibition of a variety of tyrosine kinases[30].

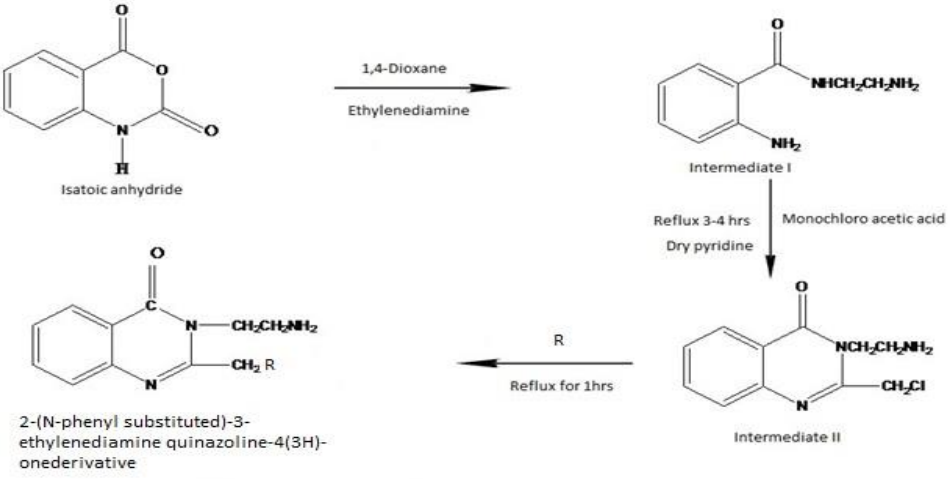
The ligands were made using Chemoffice 7.0 from Cambridge Software Company in the United States. The research into the docking was done using the PyRx application.

2. EXPERIMENTAL

2.1 Chemistry

Scheme 1 describes the synthesis of chemicals (I1-I4) and (I17-I24). All of the chemicals were of synthetic grade, and the solvents were all distilled and desiccated prior to application. One approach was used to produce derivatives of quinazoline. Derivatives of 3-alkyl amino quinazolin-4(3H)-1 were synthesized using a three-step process.

The scheme is provided as follows:



SCHEME 1

Isotoic anhydride was used as the commenced material for this research endeavour. Dioxane is an appropriate solvent for the synthesis of intermediate novel quinazoline derivatives. Amine was used in the synthesis of the intermediate. The mentioned reaction took place in an anhydrous environment. The reflux method was used for two to three hours while monochloroacetic acid is present. In the constant presence of dry alcohol and a drying agent, the reflux method was utilised to induce group attachment.

Utilizing silica gel for chromatography and distillation, solvents were purified. Thin-layer chromatography was used to monitor each reaction. The dots were made visible using UV light (254nm). Prior to use, all of the solvents were freshly distilled and dried in accordance with standard practise. The melting point was measured using the LABINDA melting point equipment (MEPA).

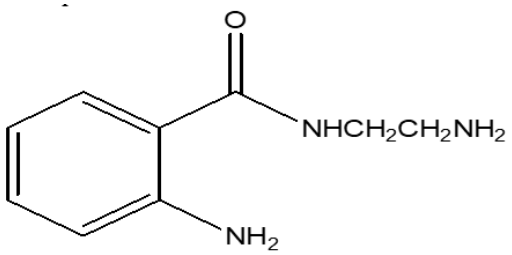
Novel quinazoline derivatives that have been synthesised were optimised using a variety of molecular modelling techniques, including Auto Dock, Avogadro, Swiss model, R-Dock, Ochem database, Schrodinger programme, and others. The SAIF, Chandigarh, used spectral methods for spectroscopy, including NMR, UV, IR, and mass , FTIR, and others on the final products.

Six animals in group were used to test the analgesic and anti-anxiety effects of all synthesized derivatives. A number of models, including the

Elevated plus maize test and Tale Flick was used to assess the pharmacological evaluation .

2.1.1 Preparation of 2-(N-phenyl substituted)-3-alkylamino quinazoline-4- (3H)-one derivatives

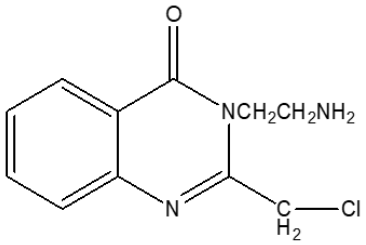
Isotoic anhydride (1), 3.26gm in 1,4-Dioxane (30 ml), and ethylene diamine (3 ml) were prepend dropwise while the temperature was kept between 0 and 6°C for an hour. When there were no lumps left, the reaction mixture was then constantly agitated on a magnetic stirrer for the following two hours at the temperature of room. For the whole night, the reaction mixture was kept at a temperature of 4°C. In the presence of crushed ice, the reaction mixture was neutralised with glacial acetic acid, and the neutral colour can be seen on the blue litmus paper. The neutralized reaction mixture was kept in the petri dish at 25°C. Dry pyridine was prepared through fractional distillation in the presence of KOH (5gm) in liquid pyridine (50ml). Intermediate (I) was weighed (1.79gm) and added to the round bottom flask of the prepared reflux assembly in the presence of dry pyridine (15ml) and few pieces of porcelain was added to the round bottom flask to absorb the moisture at 30°C, monochloroacetic acid (2gm) was added very rapidly in to the above reaction and the round bottom flask neck was closed immediately with the help of anhydrous gauze to maintain the anhydrous condition. The reflux process went on for one to two hours. The mixture for the reaction was left overnight at 4°C in the anhydrous condition with the help of anhydrous gauze. The reaction mixture was transferred into the petri dish from the round bottom flask into the beaker in the presence of crushed ice and dry pyridine was removed with the help of the light brownish solid and the saturated sodium bicarbonate solution of intermediate (II) was separated, filtered and cleansed with water and re-crystallized from ethyl aceto acetate (30ml). Intermediate (II) was kept for drying at 25^{0}C temperature.



2-amino-*N*-(2-aminoethyl)benzamide

Intermediate I

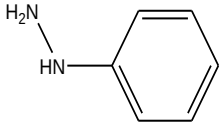
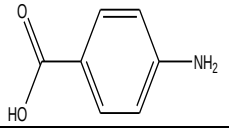
Dried Intermediate (II) (2.34 gm) was taken in the round bottom flask , dry ethyl alcohol (25ml) was prepared through fractional distillation in the presence of liquid ethyl alcohol (30 ml) and was added into the round bottom flask with intermediate(II). K_2CO_3 (1gm) and porcelain pieces were added as a drying agent. Substituted group was weighed and added into the round bottom flask and reflux was carried out for 2.5 hrs. The reaction mixture was cooled overnight at 3°C. After being filtered, the finished product was held at 25°C for drying, and the yield was measured.

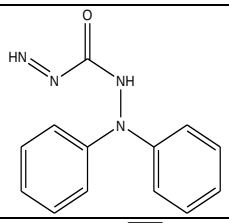
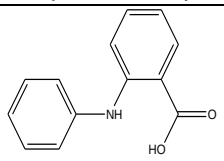
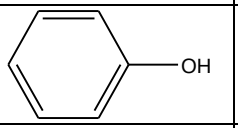
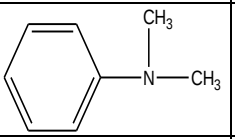
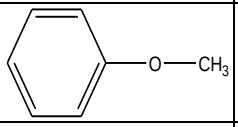
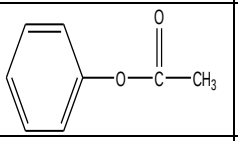
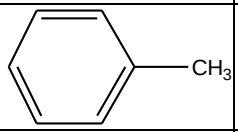
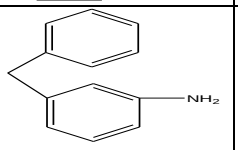
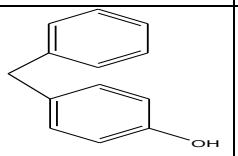
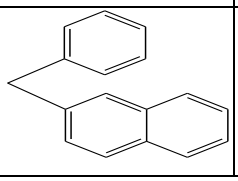


3-(2-aminoethyl)-2-(chloromethyl)quinazolin-4(3*H*)-one

Intermediate II

Table 1: Representing the R1 and R2 groups with the physico-chemical properties of the synthesized derivatives.

COMPOUND CODE	MOLECULAR FORMULA	R_1	R_2	MOL. WEIGHT	% YIELD	M.P.	R_f Value
I_1	$-C_6H_5NHNH-$	$NH_2CH_2CH_2NH_2$		310	87%	235^{0}C	0.51
I_2	$-C_7H_7NO_2$	$NH_2CH_2CH_2NH_2$		340	55%	240^{0}C	0.45

I_3	$-C_{13}H_{12}N_4O$	$NH_2CH_2CH_2NH_2$		442	80%	238^0C	0.67
I_4	$-C_{13}H_{11}NO_2$	$NH_2CH_2CH_2NH_2$		415	61.2%	235^0C	0.71
I_{17}	$-C_{17}H_{18}O_2N_3$	$NH_2CH_2CH_2NH_2$		296	83%	240^0C	0.53
I_{18}	$-C_{19}H_{23}N_5O$	$NH_2CH_2CH_2NH_2$		337	82%	242^0C	0.48
I_{19}	$-C_{18}H_{20}N_4O_2$	$NH_2CH_2CH_2NH_2$		324	79%	238^0C	0.29
I_{20}	-C19H20N $_4O_2$	$NH_2CH_2CH_2NH_2$		352	85%	250^0C	0.52
I_{21}	$-C_{18}H_{20}N_4O$	$NH_2CH_2CH_2NH_2$		308	86%	229^0C	0.62
I_{22}	$-C_{24}H_{23}N_5O$	$NH_2CH_2CH_2NH_2$		397	81%	243^0C	0.38
I_{23}	$-C_{24}H_{22}N_4O_2$	$NH_2CH_2CH_2NH_2$		398	88%	238^0C	0.25
I_{24}	$-C_{17}H_{24}N_4O$	$NH_2CH_2CH_2NH_2$		420	79%	257^0C	0.49

2.1.2 ***2-(N-phenylhydrazine)-3-ethylamin-4(3H)-one quinazoline (I1).*** **Yield:87%, M.P. : 235^0C, UV (λ_{max}):** 284 nm , **IR Spectrum (v,cm^{-1}):** 3550-3474(N-H stretching),3414 (N-H stretching , symmetrical) , 2030(N-C) , 1636(C=O-NH), 1618(-C=O) ,1383 (C-N stretching) , 619(C_6H_6), 480(C_6H_6), **^{1}HNMR(DMSO)d_6)δ;*ppm*:** 9.1-8.9(1S,1H,-CHO),7.9-7.2(M,aro,12H,-NH),3.4-3.3(S,-CH=CH),2.4-2.5(S,6H,CH_3)$_2$,**^{13}CNMR (δ;400MHz,DMSOd6):**38.5(S),52.0(d),113.2(2C, D),119(S),120.9,122.4,127.4,128.8,129.3(2c,S),133.5,147.1,151.0,161.5,164,**MS(m/z):**309(m+), 279,172,130,**CHNOcalcdfor$C_{17}H_{19}N_5O$**,309,C, 66%;H,6.19%;N,22.64%;O,5.17%**Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is is -9.3 and RMSD value is 32.75., Binding with Kappa receptor the binding affinity is -8.4 and RMSD value is 26.53.

2.1.3 ***2-(N-4-amino benzoic acid)-3-ethylamine-4-(3H)-one quinazoline(I_2).*** **Yield: 55%, M.P.:240^0C, UV (λ_{max}):** 398 nm **, IR spectrum**

(cm^{-1}): 3550.69-3474.86 anti-symmetry (-NH stretching), 3414 symmetry (-NH stretching), 2032 (-NC stretching), 1637 (-CONH amide group), 1618.28 (-C=O ketone), 1382.12 (-CN group stretching), 618-480 (Aromaric)**, Mass spectrum (m/z):** 338 (M^+), 337, 204, 162,121**, ^{1}H NMR (500 MHz, DMSO-d6) δ;*ppm*:** 9.2-8.9(s, 1H, -CHO),7.72 -7.12(m, aro. 9H), 3.52-3.13(s, -CH_3N), 2.4-2.5 (s, 6H, -N(CH_3)$_2$)**, ^{13}CNMR (500 MHz, DMSO-d6):** 38.5(s), 52 (d), 52.9 (2C d), 113.2(2C, d), 120.2, 120.7, 122.4, 127.4, 128.8, 130.8 (2C, s), 133.5, 147.1, 156.2, 164, 169.4**,CHN calculated for ($C_{18}H_{18}N_4O_3$) (338.36):** C = 63.8%, H = 5.36%, N = 16.56%, O = 14.19%**, Binding affinity and RMSD value**: Binding with GABA receptor the bindig affinity is - 8 and RMSD value is 23.352.Binding with Kappa receptor the binding affinity is - 8.3 and RMSD value is 25.432

2.1.4 2-*(N-1-anilino-3phenylaminourea)-3-ethylamineine-4(3H)-one quinazoline (I_3).* Yield:80%, **M.P.:**238^{0}C , **UV(λ_{max})** : 312 nm, **IR Spectrum** (v, cm^{-1}):3548, 3473 (anti-symmetrical, N-H stretching), 3414(Symmetrical , N-H Stretching), 2032 (N-C), 1636(CONH), 1618(-C=O), 1382(C-N Stretching), 620(C_6H_6), 430 (C_6H_6), **^{1}H NMR(DMSO)d6)δ; ppm** :9.89-9.62 (d,2H,CHO), 8.17.2 (M,14H,aro), 6.29-6.12 (M,CH=CH),3.27-2.9(S,CH_3-N), **^{13}CNMR;DMSOd6)**:**δ;*ppm:*** 38.5,52,113.2(2C),119.2,120.9,122.4,127.4,128.8(sc),129.5(2C),133.5,147.1,161.5,164, **MS m/z:** 441,411(CH_2NH_2) ,319 (NHC_6H_6),214(=O-N=N-C_6H_6), 200 (-),**CHN** calcd for $C_{24}H_{23}N_7O_2$, 441, C,65.29%; H,5.25; N,22.21%,O,7.25%, **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is is -9.9 and RMSD value is 33.11.Binding with Kappa receptor the binding affinity is - 8 and RMSD value is 29.30

2.1.5 *2-(N,N-Phenyl anthranillic acid)-3-ethylamine-4(3H)-one quinazoline(I_4).* Yield: 61.20, **M.P**.: 235^{0}C, **UV (λmax):** 326nm, **IR Spectrum**(v,cm^{-1}):3548 , 3474 (anti-symmetrical , N-H, stretching),3414 (Symmetrical , N-H , stretching) , 2031 (N-C, stretching), 2031(N-C stretching),1636(O=C-NH), 1618(-C=O) , 1382(C-N Stretching) ,1236(-OH bend)620, 479, 408(C_6H_6),**^{1}H NMR(DMSO)d6)δppm;**10(S,1H,COOH),8.87-7.49(M,13H,aro), 7.14 -7.11(m,CH_2=CH_2),2.51-2.50(S,CH_3N),**^{13}C NMR δ *ppm*;** 38.9, 52,60.3,113.1,118.2,118.3,119,119.1(2C),120.9,122.4 , 127.4 , 128.8,129.7 (2C) , 131.2, 133.5 , 144.5,MS m/z : 414(M^+), 384, 307, 262, 171, **CHN** calcd for $C_{24}H_{22}N_4O_3$, 414, C,69.55%; H,5.35%, N,13.52 %, O,11.58%, **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is is -7.9 and RMSD value is 28.12.Binding with Kappa receptor the binding affinity is -7.6 and RMSD value is 27.17.

2.1.6 2-((4hydroxyphenylamino)methyl)-3-(2-aminoethyl)quinazolin-4(3H)-one *(I_{17}):* Yield: 83% , M.P.: 240^{0}C, UV (λ_{max}): 319nm, IR spectrum (cm^{-1}): 3570.19 anti-symmetry (-NH stretching), 3415.92 symmetry (-NH stretching), 2030 (-NC stretching), 1634.19 (-CONH amide group), 1619.17 (-C=O ketone), 620-500 (Aromatic)**,Mass spectrum (m/z):** 296 (M^+), 252, 108, 44,**^{1}H NMR (500 MHz, DMSO-d6):** 7.9-7.4 (s, 1H, CHO) 6.51- 5.0 (m, aro. 8H), 4.0 (m, CH=CH), 3.46-2.95 (s, CH_3N), 2.0(amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5(s), 47.5, 52 (aliphatic), 114.9(d), 116.7(s), 120.9, 122.4, 127, 128.8 (C), 133.5, 140.2, 146.9, 147.1, 161.5, 164,**CHN calculated for (**$C_{17}H_{18}N_4O_2N_3$**) (296):** C = 68.91%, H = 6.08%, N = 10.81%, O = 14.18% **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -7.3 and RMSD value is 20.97.Binding with Kappa receptor the binding affinity is -7.4 and RMSD value is 23.89.

2.1.7 *2((4(dimethylamino)phenylamino) methyl)-3-(2-aminoethyl)quinazolin-4(3H)-one (I_{18}):* Yield: 82% , M.P.: 242^{0}C, UV (λ_{max}): 312 nm, IR spectrum (cm^{-1}): 3563.76 anti-symmetry (-NH stretching), 3410.96 symmetry (-NH stretching), 2029 (-NC stretching), 1632 (-CONH amide group), 1617.77(-C=O ketone), 1380 (-CN group stretching), 680-550 (Aromatic)**,Mass spectrum (m/z): 337** (M^+), 293, 44**,^{1}H NMR (500 MHz, DMSO-d6):** 8.0-7.9 (s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 6.20- 6.03 (m, CH=CH), 4.0 (aro. C-NH) 3.46-2.95 (s, CH_3N), 2.85(d, CH_3), 2.0 (amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5(s), 40.5, 47.5, 52, 114.4(2C, d), 115.1, 120.9(s), 121.9, 122.4, 127.4, 128.8, 133.3, ,137.1, 138, 147.1, 161.5, 164**,CHN calculated for (**$C_{19}H_{23}N_5O$**) (337):** C = 67.65%, H = 6.82%, N = 20.77%, O = 4.74%, **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -7.4 and RMSD value is 24.9, .Binding with Kappa receptor the binding affinity is -6.3 and RMSD value is 24.332.

2.1.8 *2-((4-methoxyphenylamino)methyl)-3-(2-aminoethyl)quinazolin-4(3H)-one (I_{19}):* Yield: 79% , M.P.: 238^{0}C, UV (λ_{max}): 298 nm, IR spectrum (cm^{-1}): 3533 anti-symmetry (-NH stretching), 3411.00 symmetry (-NH stretching),

2030 (-NC stretching), 1635 (-CONH amide group), 1612.87 (-C=O ketone), 1380 (-CN group stretching), 650-569 (Aromatic)**,Mass spectrum (m/z):** 324 (M^+), 280, 216, 108, 44**,^{1}H NMR (500 MHz, DMSO-d6):** 7.9 -6.55(aro. 8H),6.32(D), 4.0 (aro. C-NH),3.75(CH_3) 3.46-2.95(methylene), 2.0 (amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5(s), 47.5 , 55.9, 114.5(2C, d), 115.1 (D) 120.9(s), 122.4, 127.4, 128.8, 133.5, 139.9, 147.1, 149.1, 161.5, 164,**CHN calculated for (**$C_{18}H_{20}N_4O_2$**) (**324**):** C = 66.67 %, H = 6.17%, N = 9.87 %, O = 17.28% , **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is is -7.7 and RMSD value is 24.38.Binding with Kappa receptor the binding affinity is -6.7 and RMSD value is 35.34.

2.1.9 2((4(methylperoxy)benzeneamine)-3-(2-aminoethyl)quinazolin-4(3H)-one *(I_{20}):* Yield: 85% , M.P.: 250^{0}C, UV (λ_{max}): 323 nm, IR spectrum (cm^{-1}): 3562.65 anti-symmetry (-NH stretching), 3413.32 symmetry (-NH stretching), 2031.54 (-NC stretching), 1638 (-CONH amide group), 161.83 (-C=O ketone), 1383 (-CN group stretching), 620-535 (Aromatic)**,Mass spectrum (m/z):** 352 (M^+), 308,189,44,**^{1}H NMR (500 MHz, DMSO-d6):** 8.4-8.2 (s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 7.29- 6.40 (m, CH=CH), 4.0, 3.46 -2.95 (s, methylene), 2.08(CH3), 2.0 (amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 20, 38.5(s), 47.5 , 52, 113.9(D), 120.9, 122.4, 127.4, 128.8, 133.5,139.8, 144.4, 147.1, 161.5, 164,**CHN calculated for (**$C_{19}H_{20}N_4O_3$**) (352):** C = 64.77%, H = 5.68 %, N = 15.90 %, O = 13.60%, **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is is -6.4 and RMSD value is 19.49.Binding with Kappa receptor the binding affinity is -6.6 and RMSD value is 21.83.

2.1.10 2-((p-toluidino)methyl)-3-(2-aminoethyl) quinazolin-4(3H)-one(I_{21}): Yield: 86% , M.P. 229^{0}C, UV (λ_{max}): 321 nm, IR spectrum (cm^{-1}): 3565.80 anti-symmetry (-NH stretching), 3415.38 symmetry (-NH stretching), 2029 (-NC stretching), 1635 (-CONH amide group), 1618.87 (-C=O ketone), 1380 (-CN group stretching), 690-450 (Aromatic)**,Mass spectrum (m/z):** 308 (M^+), 264 ,120, 44,**^{1}H NMR (500 MHz, DMSO-d6):** 8.6-8.5(s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 4.0 (m, aro CNH), 3.46-2.95 (s, methylene), 2.35 (methyl), 2.0(amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 24.3, 38.5(s), 47.5, 52, 113.4(d), 120.9, 122.4, 126, 127.4, 128.8, 129.9(d), 133.5,144.6, 147.1, 161.5, 164, **CHN calculated for (**$C_{18}H_{20}N_4O$**) (**308**):** C = 70.12%, H = 6.49 %, N = 5.19 %, O = 18.18% , **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -7.1 and RMSD value is 22.01.Binding with Kappa receptor the binding affinity is -7.5 and RMSD value is 26.87.

2.1.11 2-((4-phenylbenzene1,4diamine) phenyl)-3-(2-aminoethyl)quinazolin-4(3H)-one *(I_{22})*: Yield : 81%, M.P.: 243^{0}C, UV (λ_{max}): 354 nm, IR spectrum (cm^{-1}): 3569.99 anti-symmetry (-NH stretching), 3419.59 symmetry (-NH stretching), 2028 (-NC stretching), 1639 (-CONH amide group), 1618.23 (-C=O ketone), 1379 (-CN group stretching), 688-470 (Aromatic)**,Mass spectrum (m/z):** 397 (M^+), 253, 44,**^{1}H NMR (500 MHz, DMSO-d6):** 8.5-8.2 (s, 1H, CHO) 7.9 -6.43(m, aro. 8H), 4.0 (m, CHN), 3.46- 2.95 (s, methylene), 3.1, 2.0 (amine)**,^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5(s), 47.5, 52, 117.2, 118.3, 119, 120, 122.4, 127.4, 128.8, 129.7(2C, d), 133.5,139.1, 147.1, 149.1, 161.5, 164,**CHN calculated for (**$C_{24}H_{23}N_5O$**) (**397**):** C = 72.54%, H = 5.79%, N = 4.03%, O = 17.63% , **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -6.9 and RMSD value is 20.73.Binding with Kappa receptor the binding affinity is -7.8 and RMSD value is 28.11.

2.1.12 2-((4-phenylamino)phenyl)-3-(2-aminoethyl)quinazolin-4(3H)-one *I_{23}:* Yield: 88%, M.P.: 238^{0}C, UV (λ_{max}): 290 nm, IR spectrum (cm^{-1}): 3560.60 anti-symmetry (-NH stretching), 3414.15 FDsymmetry (-NH stretching), 2031 (-NC stretching), 1634 (-CONH amide group), 1618.80 (-C=O ketone), 1375 (-CN group stretching), 680-520 (Aromatic)**,Mass spectrum (m/z):** 398 (M^+), 354 , 44 ,**^{1}H NMR (500 MHz, DMSO-d6):** 7.9-7.4(Aro), 6.51(d) ,6.26(d),6.43(d) , 7.04 (benzene N-C) ,5.0(Ar, -OH), 3.46-2.95(methylene), 2.0(amine), **^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5(s), 52.0, 60.3(aliphatic CH_2), 116.8(d-CH),118.3,119.1(d), 120.5(d), 120.9, 122.4 ,127.4 ,128.8 , 129.7(d), 123.5, 141.70 ,148.0 , 149.1 , 161.5 , 164, **CHN calculated for (**C24H22N4O2) **(**398**):** C = 72.36%, H = 5.52%, N = 8.04%, O = 14.07% , **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -6.1 and RMSD value is 17.84.Binding with Kappa receptor it's binding affinity is -8.5 and RMSD value is 27.36.

2.1.13 2-(((naphthalen-3-yl)(phenyl) methylamino)methyl)-3-(2-aminoethyl) quinazolin-4(3H)-one *(I_{24})*:Yield: 79%, M.P.:257^{0}C, UV (λ_{max}): 305 nm, IR spectrum (cm^{-1}): 3565.19 anti-symmetry (-NH stretching), 3417.46 symmetry (-NH stretching), 2040 (-NC stretching), 1634 (-

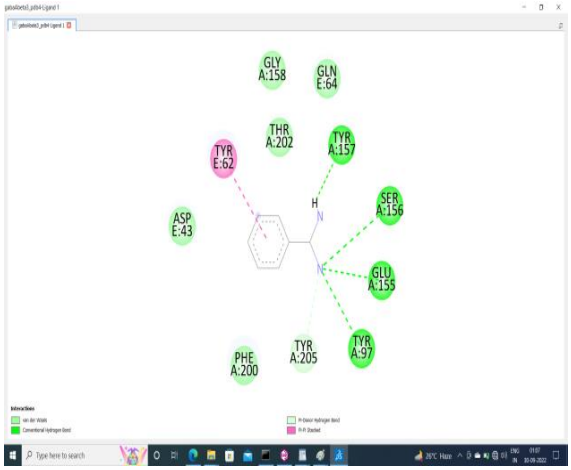
CONH amide group), 1624.82 (-C=O ketone), 1375 (-CN group stretching), 650-565(Aromatic)**,Mass spectrum (m/z): 420** (M^+), 376 , 44**, ^{1}H NMR (500 MHz, DMSO-d6):** 7.9-7.4(benzene) , 6.76 , 7.51 , 7.44, 7.23, 7.09, 7.04, 6.79, 6.55, 6.43 (d) (benzene) , 3.46-2.45(methylene) , 2.0(amine) **, ^{13}CNMR (500 MHz, DMSO-d6) δ;*ppm*:** 38.5 , 52, 108 , 118.1,118.3 ,119.1(d), 120.9, 121.4 ,122.4 , 124.6 , 125.3 , 126.5, 126.8, 127.4 , 127.9**, CHN calculated for (**$C_{27}H_{24}N_4O$**) (420):** C = 77.20 %, H = 5.71%, N = 3.80 %, O = 13.33 % , **Binding affinity and RMSD value:** Binding with GABA receptor the binding affinity is -6.8 and RMSD value is 21.67.Binding with Kappa receptor the binding affinity is -7.1 and RMSD value is 22.96.

2.2 MOLECULAR DOCKING

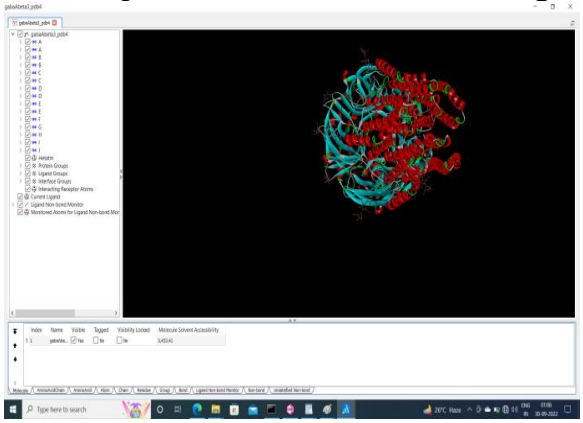
Two-dimensional (2D) structures were converted into three-dimensional (3D) structures using the chem3D Ultra mode. For 3D structures, the molecular mechanics (MM2) approach was employed to reduce energy.

PyRx is a graphical user interface for auto dock 4.2 and autodock Vina that is used for virtual screening. Autodock Vina is a revolutionary technology that offers multicore capability, high performance, greater accuracy, and ease of use for drug discovery, molecular docking, and virtual screening. Hydrogen bonds, interplay, and the assessment of the ligand binding site were looked at in the finest configurations after docking. Discovery Studio 4.5 was used to visualise all of the structure files in order to identify the amino acid residue's target binding location and the hydrogen bonding interaction.

Docking studies revealed that all the deigned ligands of **Synthesis of 2-(N-phenyl substituted)-3-ethylenediamine quinazoline-4(3H)-one derivatives** have binding free energy with GABA receptor between -6.1 to – 9.9 Kcal/mol and RMSD value ranging between 17.846 to 33.118Å. Docking studies revealed that all the deigned ligands of **Synthesis of 2-(N-phenyl substituted)-3-ethylenediamine quinazoline-4(3H)-one derivatives** have binding free energy with Kappa receptor between -6.3 to – 8.8 Kcal/mol and RMSD value ranging between 21.833 to 35.345Å.



2D–Representation of molecular docking



3D-Representation of molecular docking

2.3 ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD) GUIDELINES

The OECD Guidelines were followed for all of the pharmacological evaluations.

The Wistar rats were randomly selected for each derivative and were sequentially dosed at an interval of 48 hours. The cage observation was carried out daily to detect different changes in the animal viz. General changes in the skin, eyes, movement, fur, urinary inconsistence, and vice versa.

2.4 PHARMACOLOGICAL EVALUATION:

2.4.1 ANTI-ANXIETY SCREENING

An institutional animal facility provided Wistar rats (110–130 g, either sex). Under the typical laboratory conditions (25 °C, 50–60% relative humidity, and a 12:12 h light–dark cycle), they were housed in groups of three, with a constant supply of water and a regular pellet diet. Experiments were only performed on the animals after they had been acclimated to the lab setting for at least seven days. The protocol for the study received clearance from the institutional animal ethics committee (IAEC).

The rats were randomly divided into five groups of six animals each for the two distinct experimental paradigms. The first group was given normal saline (10 ml/kg) as a vehicle. The second group received diazepam at a normal dose of 1.2 mg/kg for each of the common drugs. The oral mode of administration was used to administer 0.14 mg/kg of the synthetic derivatives to the third, fourth, and fifth groups.

ELEVATED PLUS MAZE TEST

Freshly made suspensions of 10 mg/kg of each compound's concentration were employed. Every solution was administered orally on test days at an amount of 0.14 mg/kg the size of rats. The test animals were administered with diazepam (2mg/Kg, n=6) and the Test substances (10 mg/Kg) 60 minutes before maze evaluation. A saline solution was given orally to the group in control. Additionally, there were two open, with two closed facing arms towards each other while having an open roof (a maze of 50*40*10 cm). The maze is elevated to a maximum height of 50 cm all throughout. Rats were tested individually in this equipment for five minutes at a time during the trial. With one arm towards it, each rat was positioned on the platform in the centre. The number of admissions into open and closed arms, as well as the length of time spent in each arm, were counted over a five-minute period and duration in percentage. It was determined how much time each rat spent the open arms [open/open+closed] 100].

2.4.2 ANALGESIC ACTIVITY

Wistar rats (110-130 g), of either sex, were obtained from an institutional animal facility. They were kept in groups of three under the usual laboratory conditions (Temp 25 °C, relative humidity 50-65%, and 12:12 h Dark-light cycle), with standard edibles pellets and water available at all times. Only after the animals had been accustomed to the laboratory environment for at least seven days prior to experiments conducted on them. The institutional animal ethics committee (IAEC) gave its approval for the study's protocol.

For the two independent experimental paradigms, the rats were randomised into five groups of six animals each. As a vehicle, the first group received normal saline (10 ml/kg). As a standard, the second group received the medications diclofenac, each at a dose of 6 mg/kg. The third, fourth and fifth group received a 0.72 mg/kg dosage of the synthesized derivatives through the oral route administration.

TAIL FLICK RESPONSE

The tail flick method was used to assess the anti-nociceptive (analgesic) activity the distal end of each rat's tail was submerged in warm water that was kept at constant temperature of 50^0 C. The Rat's reaction time was measured by how long it took to flick its tail in response to discomfort (in seconds). The average of three readings was used to determine the reaction time. Prior to (0 min), 30, 60, and 90 min following the administration of the medications, the reaction time was measured to sustain the tail tissue, a 15 sec max. reaction time. The highest level of analgesia (MPA) was calculated by:

MPA = (Reaction time for treatment – reaction time of saline) / (15 sec – reaction time for saline) * 100

Tail flick response

3. RESULT AND DISCUSSION

3.1 CHEMISTRY:

Isatoic anhydride was used as the starting material to synthesize the distinct 2-(N-phenyl substituted)-3- alkyl amino quinazoline-4(3H)-one derivatives (I_1-I_4) & (I_{17}-I_{24}) of the desired product. Two intermediates were synthesized for each phase. During the last phase, the desired quinazoline derivatives were synthesized. It was observed that the reaction technique was more facile, and efficient. The synthesis of quinazoline derivatives was substantiated by physical and spectroscopic studies. With the aid of laboratory results and literature reviews, physical data were confirmed.

Based on data from IR, LC-MS, NMR, and elemental studies, the target molecule was assessed. The final synthesised compound had a strong peak between 3549 and 3470 cm^{-1}, confirming the moiety's inclusion of an amine group. Stretching of the C-H axis was seen in a range of 2945 to 2830 cm^{-1}. Between 1600 and 1720 cm^{-1}, cyclic amide was detected; around 1620 cm^{1}, it was discovered that the molecule had a ketone group. ^{1}HNMR validates the position and quantity of hydrogen in the molecule. Aromatic

ring present at 800-450 cm^{-1}. The range of aromatic proton is 7.9 to 6.69 *ppm*. At 4.0 *ppm*, an aromatic amine proton is produced. The number of carbon atoms in the compound is confirmed by ^{13}CNMR at 2.0, where the proton of the amine occurs. There is carbon present in the range of 38.5-164 *ppm*. The actual proportion of various elements present in the synthesized molecules is confirmed by elemental analysis.

Table 2. Data representing molecular docking of synthesized compounds

Ligand code	Binding Affinity(kcal/mol)		RMSD Value	
	GABA	KAPPA	GABA	KAPPA
I_1	-9.3	-8.4	32.750	26.537
I_2	-8	-8.3	23.352	25.430
I_3	-9.9	-8.8	33.118	29.306
I_4	-7.9	-7.6	28.122	27.175
I_{17}	-7.3	-7.4	20.974	23.895
I_{18}	-7.4	-6.3	24.920	24.332
I_{19}	-7.7	-6.7	24.382	35.345
I_{20}	-6.4	-6.6	19.497	21.833
I_{21}	-7.1	-7.5	22.012	26.871
I_{22}	-6.9	-7.8	20.738	28.115
I_{23}	-6.1	-8.5	17.846	27.365
I_{24}	-6.8	-7.1	21.671	22.961

Analysis of the ligand's RMSD values and free energy of binding to the GABA and KAPPA receptor using 2-N phenyl substituted 3-ethylenediamine quinazolin-4(3H)-one.

3.2MOLECULAR DOCKING:

Utilizing AutoDock vina, the linkages and interactions between proteins and ligands were evaluated. The GABA and KAPPA receptor crystal structures were obtained from the Protein Data Bank (PDB) and converted into pdbqt files. Ligand was also converted into pdbqt format. Calculations were made using the auto dock vina, auto dock MGL, and pymol visualization tools, as well as RMSD value and binding affinity.

3.3 ANTI-ANXIETY ACTIVITY

Wistar rats (110-130 g), of either sex, were obtained from an institutional animal facility. They were kept in groups of five under the usual laboratory conditions (Temp 25 °C, relative humidity 50-60%, and 12:12 h Dark-light cycle), with a standard edible pellet and water available at all times. Only after the animals had been accustomed to the lab environs for about minimum of seven days and experiments were conducted on them. The institutional animal ethics committee (IAEC) gave its approval for the study's protocol.

As the two independent experimental paradigms, the rats were randomized into five groups of six animals each. As a vehicle, the first group received normal saline (10 ml/kg). As a standard, the second group received the usual medication diazepam, each at a dose of 1.2 mg/kg. The third, fourth and fifth group received a 0.14 mg/kg dosage of the synthesized derivatives through the oral route administration. Statistical data is given below:

3.4ANALGESIC ACTIVITY:

Wistar rats (110-130 g), of either sex, were obtained from an institutional animal facility. They were kept in groups of three under the usual laboratory conditions (Temp 25 °C, relative humidity 50-60%, and 12:12 h light-dark cycle), with standard pellet diet and water available at all times. Only after the animals had been accustomed to lab environs for about minimum of seven days and experiments were conducted on them The institutional animal ethics committee (IAEC) gave its approval to the study's protocol. For the two independent experimental paradigms, the rats were randomised into five groups of six animals each. As a vehicle, the first group received normal saline (10 ml/kg). As a standard, the second diclofenac, each at a dose of 30 mg/kg. The third, fourth and fifth groups received a 0.72 mg/kg dosage of the synthesized derivatives through the oral route administration. Statistical data is given below**:**

CONCLUSION

Total of twelve (12) derivatives of **2-(N-phenyl substituted)-3-ethylenediamine quinazoline-4(3H)-one (I_1-I_4) derivatives** were synthesized as well as **(I_{17}- I_{24})** derivatives were characterized and evaluated for the anti-anxiety and analgesic activity.

All the derivatives (I_1- I_4) and (I_{17} - I_{24}) were undergone through the various physicochemical properties like sharp melting point, solubility, TLC

and column chromatography for the purity verification and a single and clear spot was obtained on the TLC plate which indicated the purity of the compound. All of the synthetic derivatives underwent a molecular docking investigation to see how well they bind to the groups.

Anti-anxiety and analgesic activity was evaluated with the help of the tale flick method and elevated plus maize test. Estimated six compounds were more potent (**I_1, I_2, I_3, I_{17}, $I_{19}$and I_{24}**) and estimated eight compounds (**I_1-I_4)** & **(I_{17},I_{19},I_{21} and I_{24}**) showed moderate analgesic activity out of twelve compounds (**I_1-I_4) & (I_{17}-I_{24}**). Estimated ten compounds **(I_1,I_3,I_4,I_{17},I_{18},I_{20}-I_{24})** showed moderate anti-anxiety activity and six compounds (**I_{17},I_{18}, I_{20}, I_{21}, I_{22} and I_{23}**) were more potent out of twelve compounds (**I_1-I_4) & (I_{17}-I_{24}**).

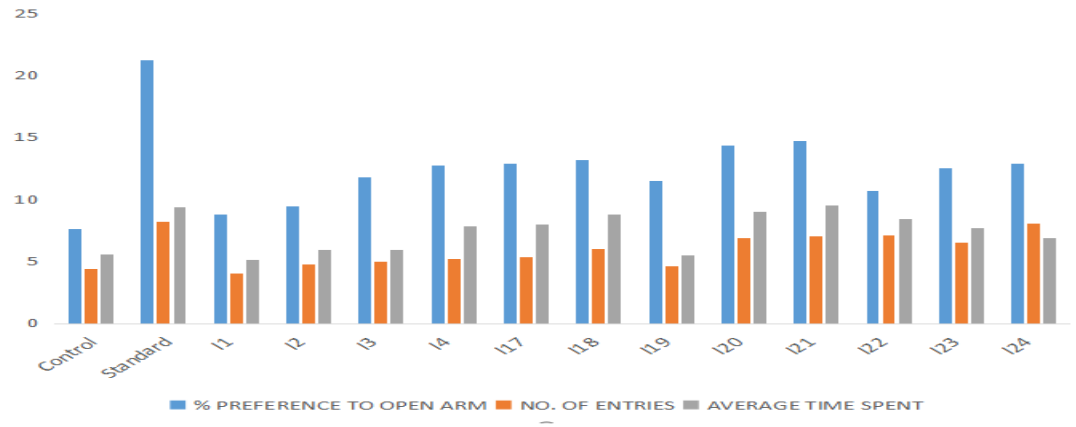
These compounds (I_1-I_4) as well as (I_{17} - I_{24}) could be useful as a template for further design, optimization, and investigation to produce a more active analogue.

Thus, the study infers from this that the recently synthesized quinazolinone derivatives do, in fact, have a notable anti-anxiety and analgesic impact.

Table 3. Statistical data of Anti-anxiety activity of synthesized compounds.

COMPOUND	% PREFERENCE TO OPEN ARM	NO. OF ENTRIES	AVERAGE TIME SPENT
Control	7.6	4.4±0.18	5.53±0.6
Standard	21.2	8.21 ±0.52	9.34±0.4***
I_1	8.8	4.0±0.2	5.1±0.68*
I_2	9.4	4.78±0.6	5.89±0.4**
I_3	11.8	4.98±0.18	5.92±0.21*
I_4	12.7	5.21±0.54	7.8±3.7**
I_{17}	12.9	5.35±0.60	8.0±4.1**
I_{18}	13.2	6.01±0.69	8.8±4.9*
I_{19}	11.5	4.6±0.11	5.50±0.17*
I_{20}	14.3	6.9± 0.70	9.0±0.1**
I_{21}	14.7	7.0±0.81	9.5±1.5*
I_{22}	10.7	7.08±0.23	8.4±0.32**
I_{23}	12.5	6.5±0.14	7.7±0.21**
I_{24}	12.9	8.02±0.68	6.9±3.2*

*Where *indicates the value which represents the Mean± S.E.M. of six rats significantly different from the control at p < 0.05.*



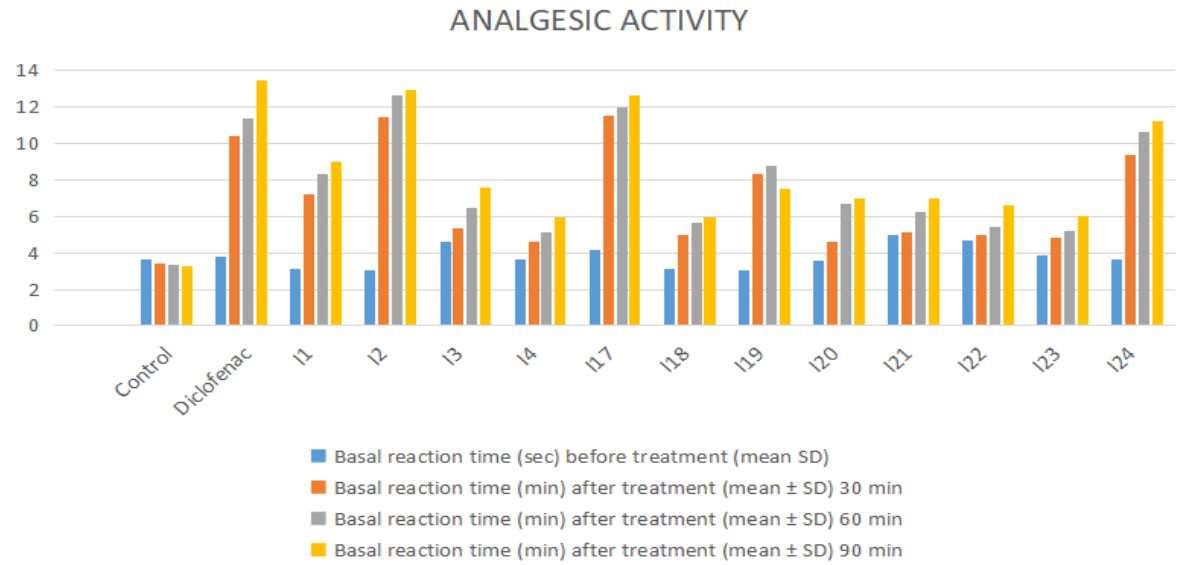
Graph 1. Graphical representation of anti-anxiety effect of synthesised derivatives.

Table 4. Statistical data of Analgesic activity of synthesized compounds.

Compound	Basal reaction time before treatment (mean ±SD) in seconds	Basal reaction time after treatment (mean±SD) in minutes		
		30 Minutes	60 Minutes	90 Minutes
Control	4.62± 0.672	4.43± 0.525	4.37± 0.5263	4.24± 0.415
Diclofenac sodium	4.81± 0.563	11.44± 0.641**	12.35± 0.69**	14.46±0.732**
I_1	4.14±0.542	8.25±0.213*	9.32± 0.342**	9.99± 0.341**
I_2	3.02±0.513	11.44±0.761**	12.64±0.86**	12.93±0.898**
I_3	4.64±0.6767	5.34±0.764	6.51±0.664	7.61±0.768
I_4	3.66±0.542	4.63±0.763	5.14±0.461	5.95±0.617
I_{17}	4.14±0.562	11.54±0.785**	11.95±0.794**	12.67±0.814**
I_{18}	3.15±0.563	4.97±0.763	5.67±0.761	5.93±0.615

I_{19}	3.04±0.262	8.36±0.413**	8.81±0.467**	7.51±0.326**
I_{20}	3.54±0.761	4.65±0.625	6.726±0.436	6.96±0.472
I_{21}	4.96±0.831	5.11±0.691*	6.271±0.401*	6.984±0.487*
I_{22}	4.71±0.652	4.98±0.735	5.41±0.852	6.65±0.935
I_{23}	3.84±0.784	4.86±0.831	5.23±0.901	5.99±0.986
I_{24}	3.61±0.613	9.35±0.490**	10.65±0.682**	11.26±0.697**

*Each value reflects the mean plus standard deviation (n=6), and * denotes a significant difference from the control group (p 0.05) and ** a highly significant difference (p 0.001)*



Graph 2: Graphical representation of analgesic effect of synthesised derivatives

HUMAN AND ANIMAL RIGHTS

The Ethics Committee of the Institute authorised the animal experiment protocol, and experiments were carried out in accordance with the CPCSEA, Reg No. 1884/GO/Re/S/16/(CPCSEA) India (CPCSEA) recommendations for the use and care of experimental animals.

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

No financial or other conflicts of interest are disclosed by the authors.

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