SYNTHESIS, MOLECULAR DOCKING AND EVALUATION STUDIES OF NOVEL 2-(N-PHENYL SUBSTITUTED)-3-ALKYL AMINO-QUINAZOLINE-4(3H)-ONE DERIVATIVES FOR ANTI-INFLAMMATORY & ANTICONVULSANT ACTIVITIES

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Abstract:

However, the novel quinazoline derivatives were designed to retain anti-inflammatory and anticonvulsant activities. The derivatives of novel 2-(N-phenyl substituted)-3-alkyl amino-quinazoline-4(3H)-one were synthesized by condensation of Isatoic anhydride with alkyl amine. Total 12 compounds (I_5- I_{16}) of the series of derivatives were synthesized by novel drug design approach. Two intermediates were formed during the process. 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. Chemical structure of the novel synthesized compound was confirmed by FT-IR (functional groups), ^{1}HNMR (position of hydrogen), ^{13}CNMR (position of Carbon), LC-MS (mass determination), UV (Purity of compound) and elemental analysis. Molecular docking was done by using Autodocking software, autodock MGL tools and PyMol visualization graphic software. Excellent binding affinity was obtained I_7 (-9 kcal/mol) with COX receptor and I_{13} (-9.3 kcal/mol) with GABA receptor. Excellent Root Mean Square Deviation (RMSD) value was obtained I_7 (33.64) with COX receptor and I_8 (40.90l) with GABA receptor. These novel synthesized derivatives were evaluated for anti-inflammatory activity with COX receptor. Paw oedema model used for this screening. Compound **I_8, I_{10} and I_{14}** shows highest anti-inflammatory activity and **I_5, I_9 and I_{15}** moderate anti-inflammatory activity among all the novel synthesized derivatives due to presence of electron withdrawing groups. Further, these synthesized novel quinazoline derivatives were evaluated for anticonvulsant activities by using of MES method. Compound**I_5, I_6 and I_{14}**showed maximum anti-inflammatory activity and compound **I_8, I_{10} and I_{12}**have moderate anticonvulsant activities.

Keywords: Quinazoline, docking, anti-inflammatory, anticonvulsant.

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1. INTRODUCTION

Quinazoline is Nitrogen containing heterocyclic compound made up with two fused ring, benzene and pyrimidine [1]. Other names for Quinazoline is also known as 1-aryl-1,3-diazadiene, 1,3diaza-naphthalene, benzopyrimidine, phenmiazene, benzo-1,3-diazene [2,11]. There are two nitrogens present in the quinazoline ring system and its derivatives are reported for various biological activities like analgesic [22], anti-inflammatory [5,13,14, 21], anti histaminic[7,8,9], anti hypertensive [3,28], diuretics [3], antimicrobial [9], anticonvulsant [13], antioxidant [5] anticancer [45]. Various qunazoline derivatives as marketed drugs are Prazocine, Gefitinib, Erlotinib, Tetrodotoxin, Alfuzocine, Trimetexate, Bunazocine, Vandetinibe, Anagrelide, Evodiamin, Proquazone, Albaconazole, Febrifuzine, Afloqualone, Linagliptin, Quazione, Quazodine, Raltitrexade, Ketancerin, Benzouracil, etc [6].

Molecular hybridization is a new technique in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to synthesize a new hybrid compounds with improved biological activity and selectivity [40,41]. In drug design and development of new molecules with antioxidant properties is a very active domain of research so that free radical can't affect the human body. Antioxidant property of drug is defend against radical mediated damage and toxicity to the body [38]. Electron donating groups (-OH, -OCH_3 etc.) have good antioxidant property and electron withdrawing groups (-Cl, -NO_2etc) have excellent anti-inflammatory activity [40].

The development of new anti-inflammatory and anticonvulsant drugs is the need of present time because inflammation and cerebral behavior of body altering due to life style and biological reactions in response to various diseases. The vast majority of present day drugs utilized for the management of these diseases target the nervous and central nervous system. Thus, produce various systemic irreversible side effects [5,13,14, 21].

Based on literature review, the synthesis, docking study and *In-Vivo* studies of novel quinazoline analogues were carried out. In this experiment, various quinazoline derivatives were synthesized and by substituting different phenyl groups at 2nd position and evaluated for more potent anti-inflammatory and anticonvulsant activities [4,10]. Docking studies are conducted to establish the structure of the derivatives. *In-Vitro* study was performed on mast cells. *In-Vivo* study was carried out on rats and evaluated for H1 antihistaminic activity by *CPCSEA* guidelines [7,8,9].

The chemicals and solvents used in this research project were of analytical grade and commercially available. All the experimental glass wares were borosilicate grade.

Isatoic anhydride, ethylene diamine, monochloro acetic acid, other chemical and solvents were procured (E-Merck, Mumbai, sigma Aldrich, Germany. Prior to the experiment, each solvent was newly distilled and dried.

Silica gel was used in column chromatography to purify the chemicals (100-200 mesh). Using precoated silica gel 60 F254 (mesh), thin layer chromatography (TLC) was employed to detect and track the chemical reactions, and spots were seen under UV light at (254nm). With a melting point device (LABINDIA), the melting points of all the synthesised derivatives were recorded (MEPA).

Using the KBr pellet approach, IR spectra were captured using an FT-IR spectrophotometer (Perkin Elmer's Spectrum RX-II). With a UV- 1800 model spectrophotometer, UV spectra were captured (Shimadzu). Using CDCl3/DMSO d6 and TMS as an internal standard, 1H and 13C NMR spectra were captured on a 500 MHz spectrophotometer (500 MHz and 100 MHz) (Advance NEO) (Bruker) and reported in parts per million (ppm). The mass spectrometer (Micromass Q-TOF Micro) was used to record the entire electrospray ionisation mass spectrum (Waters).The elemental analysis of all the synthesis derivatives were performed on elemental analyzer (Thermo EA 2110 series). Docking study was carried out on AutoDockvina software. *In vivo* study was performed on healthy wistar rats.

In this research Isatoic anhydride was taken as a starting material. 1,4dioxane is a suitable solvent for the synthesis of intermediate novel quinazoline derivative. Amine was used for formation of intermediate. Dry pyridine was prepared by the fractional distillation method. The above reaction was carried out in the anhydrous environment. Reflux method, in the presence of mono chloro acetic acid was carried out for about 2-3 hours. Group attachment was carried out by the reflux method in the presence of distilled ethyl alcohol and drying agent. Characterization was carried out for intermediates as well as final compound by the thin layer chromatography (TLC) method, melting point apparatus and solubility.

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

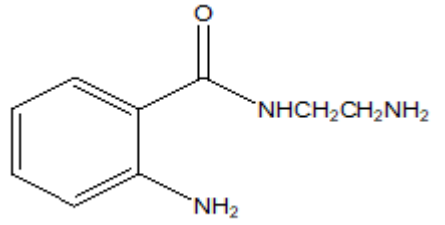
Step 1:

Isatoic anhydride used as starting reagent for the synthesis of 2-(N-phenyl substituted)-3-alkylamine quinazoline-4-(3H) - one derivatives. Isatoic

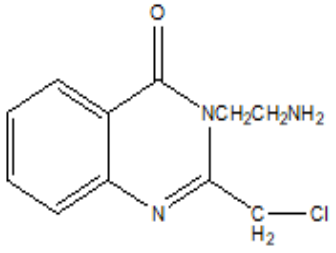
anhydride 1.63 g (0.01M) was transferred in round bottom flask. 15 ml of 1, 4-dioxane was added in that RBF. Appropriate amount of amine was added drop wise in the above solution with continuous stirring at low temperature to facilitate the reaction. The above solution was kept overnight in ice bath. Solvent 1, 4- dioxane was distilled off using rotary evaporator. Then, crushed ice was putted into the RBF and neutralized with glacial acetic acid (the excess of amine) and poured the entire reaction mixture into a petri dish. This was rubbed with ice cubes and filtered properly. 25-30 ml of ethyl acetoacetate was added in that filtrate and again filtered properly. The filtrate was dried at room temperature. (***Intermediate I***)

Step 2:
1.79 g of intermediate 1 (0.01 M) was weighed accurately and transferred into RBF. 15 ml of dry pyridine was added in it. 0.94 g of monochloroacetic acid was added immediately (within few seconds) and refluxed for 3-4 hours at appropriate temperature. After refluxed the sample was taken in Petri Dish and rub with ice cubes (to remove the pyridine). The mixture was filtered and filtrate was kept for dry at room temperature. (***Intermediate II***)

Step 3:
After that 2.34 g of intermediate 2 (0.01 M) was taken into RBF and 20 ml of dry alcohol added into above sample. Fused K_2CO_3 (1g) was added as drying agent as well as catalyst. Appropriate amount of substituent compound was weighed accurately and refluxed for 1 hour at mild temperature. It was filtered and kept for dry into a Petri Dish.



2-amino-*N*-(2-aminoethyl)benzamide
Figure No. 1: Intermediate I



3-(2-aminoethyl)-2-(chloromethyl)quinazolin-4(3*H*)-one
Figure No. 2: Intermediate II

FTIR, ^{1}HNMR, ^{13}CNMR, LCMS, UV and Elemental analysis were consistent with the assigned structures.

Compound I_5: *2-(N- phenylamine)-3-ethyleneamino quinazoline-4-(3H)-one*
Yield: 58% (faint yellow); M.P.: 247-249 ^{0}C; R_f: 0.62 (chloroform : methanol 4.7:0.3); UV (λ_{max}): 348 nm; IR spectrum (cm^{-1}): 3568.79 anti-symmetry (-NH stretching), 3416.38 symmetry (-NH stretching), 2031 (-NC stretching), 1637 (-CONH), 1619.87 (-C=O), 1381 (-CN stretching), 620-479 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.7-8.3 (s, 1H, CHO) 7.4 -7.2(m, Aro. 8H), 6.15-6.0 (m, CH=CH), 3.28-2.80 (s, CH_3N); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 52 (d), 53.5, 113.2(2C, d), 117.2(s), 120.9, 122.4, 127.4, 128.8, 129.6(2C, d), 133.5, 147.1, 147.7, 161.5, 164; Mass spectrum (m/z): 294 (M^+), 264, 172; CHN calculated for ($C_{17}H_{18}N_4O$) (294.35): C : 69.37%, H : 6.11%, N : 19.03%, O : 5.44%; Found: C: 69.30, H:6.18, N:19.10, O: 5.37.

Compound I_6: *2-(N-diphenylamine)-3-ethyleneamino quinazoline-4-(3H)-one*
Yield: 63% (yellowish brown); M.P.: 249 ^{0}C; R_f: 0.53 (chloroform : methanol 4.6:0.4); UV (λ_{max}): 390 nm; IR spectrum (cm^{-1}): 3473.78 symmetry (-NH stretching), 3416.24- 3292 symmetry (-NH bending), 2036 (-NC stretching), 1632.78 (-CONH),1583 -1452 (m), 1382.66 (-CN stretching), 687-500.69 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.7-8.3 (s, 1H, CHO) 8.3 -7.2(m, aro. 13H), 6.8 – 6.30 (m, CH=CH), 3.28-3.02 (s, CH_3N), 2.3-2.1 (CH_3-CH_3); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 52 (d), 60.3, 113.2(2C, d), 119.1(4C, s), 120.9, 122.4, 127.4, 128.8, 129.7(4C, s), 133.5, 147.1, 149.1(2C), 161.5, 164; Mass spectrum (m/z): 371(M^+), 340, 263,172; CHN calculated for ($C_{23}H_{22}N_4O$) (370.45): C : 74.57%, H : 5.90%, N = 15.12%, O : 4.32%; Found: C: 74.50, H: 65.97, N:15.17, O: 4.27

Compound I_7: *2-(N- 2, 4-dinitrophenylhydrazine)-3-ethyleneamino quinazoline-4-(3H)-one*
Yield: 48% (light yellowish crystals); M.P.: 245-247 ^{0}C; R_f:0.65 (chloroform : methanol 4.5:0.5); UV (λ_{max}): 413 nm; IR spectrum (cm^{-1}): 3472.81 symmetry (-NH stretching), 3428.57- 3296.70 symmetry (-NH bending), 2046 (-NC stretching), 1630.31(-CONH),1583-1449 (m), 1382.51 (-CN stretching), 749-506 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 9.3-9.1 (s, 1H, CHO) 8.5-7.1(m, aro. 7H), 7.2- 6.9 (m, CH=CH), 3.28-2.9 (s, CH_3N); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 52,

52.5(d), 115.3, 119.5(s), 120.9, 122.4, 127.4, 128.00, 128.8, 133.5, 137, 144.7, 147.1, 151, 161.5, 164; Mass spectrum (m/z): 384(M^+), 354, 185, 172; CHN calculated for ($C_{17}H_{16}N_6O_5$) (384.35): C : 53.12%, H : 4.80%, N = 18.87%, O : 20.8%; Found: C: 53.10, H: 4.82, N:18.80, O: 4.89.

Compound I_8: ***2-(N-morpholine)-3-ethylene-amino quinazoline-4-(3H)-one***

Yield: 42 % (brownish yellow solid); M.P.: 240-243 ^{0}C; R_f:0.48 (chloroform : methanol 4.4:0.6); UV (λ_{max}): 362 nm; IR spectrum (cm^{-1}): 3547.51anti-symmetry (-NH stretching), 3474.69-3284.81 symmetry (-NH bending), 2054 (-NC stretching), 1629.32 (-CONH), 1581-1290 (m), 1383.58 (-CN stretching), 1264.38 (C-O-C) 750-663 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 9.6-9.3 (s, 1H, CHO) 8.6 -7.2(m, aro. 4H), 7.15- 7.00 (m, CH=CH), 3.28-2.80 (s, CH_3N); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 52.0(s) 53.5(2C, d), 55.8(s), 56.5(2C, d), 120.9(s), 122.4, 127.4, 128.8, 133.5, 147.1, 151.5, 164; Mass spectrum (m/z):288(M^+), 258, 172, 130; CHN calculated for ($C_{15}H_{20}N_4O_2$) (288.34): C : 62.48%, H : 6.70%, N : 19.13%, O : 11.10%; Found: C: 62.58, H: 6.80, N:19.12, O: 11.11.

Compound I_9: ***2-(N-4chlorophenylamine)-3-ethyleneamino quinazoline-4-(3H)-one***

Yield: 52% (faint yellow solid); M.P.: 245-247 ^{0}C; R_f: 0.55 (chloroform : methanol 4.3:0.7); 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), 1619.17 (-C=O), 620-500 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 7.9-7.4 (s, 1H, CHO) 7.05-6.5 (m, aro. 8H), 4.0 (m, CH=CH), 3.46-2.95 (s, CH_3N), 2.0(NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 52 (aliphatic), 53.5, 114.9(1C, d), 117.2(s), 120.8, 122.4, 122.7, 127.4, 128.8 (C), 145.5, 147.1, 147.7, 161.5, 164; Mass spectrum (m/z): 329 (M^+), 264, 172; CHN calculated for ($C_{17}H_{18}N_4OCl$) (329.5): C : 62.00%, H : 5.4%, N : 17.03%, O : 4.86%, Cl : 10.77%; Found: C: 62.05, H: 5.35, N:17.00, O: 5.32, Cl : 10.76.

Compound I_{10}: ***2-(N-2chloro-4-iodophenylamine)-3-ethyleneamino quinazoline-4-(3H)-one***

Yield:47% (yellowish brown solid); M.P.: 241-243 ^{0}C; R_f: 0.27 (chloroform : methanol 4.2:0.8); UV (λ_{max}): 348 nm; IR spectrum (cm^{-1}): 3568.74 anti-symmetry (-NH stretching), 3415.38 symmetry (-NH stretching), 2031 (-NC stretching), 1637 (-CONH), 1619.87 (-C=O), 1381 (-CN stretching), 620-479 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.4-8.1 (s, 1H, CHO) 7.9 -7.2(m, aro. 8H), 6.25- 6.0 (m, CH=CH), 4.0 (aro. C-NH) 3.1-2.95 (s, CH_3N), 2.0 (NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5, 52 (d), 114.4(2C, d), 120.9(s), 121.9, 122.4, 127.4, 128.8, 133.3(2C, d), 133.5, 147.1, 153.7, 161.5, 164; Mass spectrum (m/z): 294 (M^+), 264, 172; CHN calculated for ($C_{17}H_{17}N_4OClI$) (455): C : 44.83%, H : 3.73%, N : 12.03%, O : 5.44%; Found: C: 44.87, H: 3.69, N:12.07, O: 5.40

Compound I_{11}: ***2-(N-4nitrophenylamine)-3-ethyleneamino quinazoline-4-(3H)-one***

Yield: 59% (faint yellowish crystalline solid); M.P.: 240-242 ^{0}C; R_f:0.65 (chloroform : methanol 4.9:0.1); UV (λ_{max}): 340; IR spectrum (cm^{-1}): 3568.79 anti-symmetry (-NH stretching), 3416.38 symmetry (-NH stretching), 2031 (-NC stretching), 1637 (-CONH), 1619.87 (-C=O), 1381 (-CN stretching), 620-479 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.7-8.3 (s, 1H, CHO) 7.9 -6.69(aro. 8H), 4.0 (aro. C-NH) 3.46-2.95(-CH_2), 2.0 (NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5 , 52, 114.2(2C, d), 120.9(s), 121,121.9(d), 127.4, 128.8, 133.5, 136.8, 147.1, 153.7, 161.5, 164; Mass spectrum (m/z): 340 (M^+), 303, 296; CHN calculated for ($C_{17}H_{18}N_5O_3$) (340): C : 60 %, H : 5.29%, N : 20.58 %, O : 14.11%; Found: C: 59.90, H: 5.19, N:20.55, O: 14.14.

Compound I_{12}: ***2-(N-4cynophenylamine)-3-ethyleneamino quinazoline-4-(3H)-***

Yield: 64% (light yellow solid); M.P.: 246-248 ^{0}C; R_f:0.43 (chloroform : methanol 4.8:0.2); UV (λ_{max}): 325 nm; IR spectrum (cm^{-1}): 3567.88 anti-symmetry (-NH stretching), 3417.32 symmetry (-NH stretching), 2031.88 (-NC stretching), 1636 (-CONH), 1619.83 (-C=O), 1383 (-CN stretching), 620-535 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.5-8.4 (s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 7.29-6.61 (m, CH=CH), 4.0, 3.46 -2.96 (s, CH_2), 2.0 (NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5 , 52, 101, 114..2 , 115 (s), 120.9, 122.4, 127.4, 128.8, 133(s), 133.5, 147.1, 151, 161.5, 164; Mass spectrum (m/z): 320 (M^+), 276,189; CHN calculated for ($C_{18}H_{18}N_5O$) (): C : 67.5%, H : 5.62 %, N : 21.87%, O : 5.00%; Found: C: 67.70, H: 5.52, N:21.80, O: 5.07

Compound I_{13}: ***2-(N-4aminobenzaldehyde)-3-ethyleneamino quinazoline-4-(3H)-one***

Yield: 64% (faint yellow crystal); M.P.: 242-245 ^{0}C; R_f:0.52 (chloroform : methanol 4.7:0.3); UV (λ_{max}): 352 nm; IR spectrum (cm^{-1}): 3565.70 anti-symmetry (-NH stretching), 3416.38 symmetry (-NH stretching), 2031 (-NC stretching), 1637 (-

CONH), 1619.87 (-C=O), 1383 (-CN stretching), 680-476 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.8-8.35(s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 4.0 (m, aro CNH), 3.46-2.95 (s, CH_2), 2.0(NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5, 52, 114, 120.9, 122.4,125.3, 127.4, 128.8, 130.7(d), 133.5, 147.1,153.4, 161.5, 164,191; Mass spectrum (m/z): 323 (M^+), 279, 203,120, 44; CHN calculated for ($C_{18}H_{19}N_4O_2$) (323): C : 66.87%, H : 5.88 %, N : 17.33 %, O : 9.90%; Found: C: 66.80, H: 5.95, N:17.38, O: 9.85

Compound I_{14}: *2-(N-4ethanonephenylamine)-3-ethyleneamino quinazoline-4-(3H)-one*

Yield: 56% (brownish yellow solid); M.P.: 240-243 ^{0}C; R_f: 0.67 (chloroform : methanol 4.6:0.4); UV (λ_{max}): 344 nm; IR spectrum (cm^{-1}): 3568.09 anti-symmetry (-NH stretching), 3416.54 symmetry (-NH stretching), 2029 (-NC stretching), 1638 (-CONH), 1619.90 (-C=O), 1378 (-CN stretching), 698-490 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.6-8.2 (s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 4.0 (m, CHN), 3.46- 2.95 (s, CH_2), 2.0 (NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 29.3, 38.5(s), 47.5, 52, 113.4(2C, d), 120.9(s), 122.4, 125.2, 127.4, 128.8, 129.6(2C, d), 133.5, 147.1, 152, 161.5, 164,199(carbonyl); CHN calculated for ($C_{19}H_{21}N_4O_2$) (329): C = 66.86%, H = 6.38%, N = 17.03%, O = 9.72%; Found: C: 66.81, H: 6.43, N:16.95, O: 9.80

Compound I_{15}: *2-(N-phenyl-1, 4-diamine)-3-ethyleneamino quinazoline-4-(3H)-on*

Yield:59% (yellowish brownish solid); M.P.: 242-244 ^{0}C; R_f:0.55 (chloroform : methanol 4.5:0.5); UV (λ_{max}): 336 nm; IR spectrum (cm^{-1}): 3561.60 anti-symmetry (-NH stretching), 3416.18 symmetry (-NH stretching), 2032 (-NC stretching), 1636 (-CONH amide group), 1619.97 (-C=O ketone), 1380 (-CN group stretching), 690-439 (Aromatic); ^{1}H NMR (500 MHz, DMSO-d6): 8.5-8.3 (s, 1H, CHO) 7.9 -7.4(m, aro. 8H), 4.0 (m, C-NH), 3.88 (CH_3), 3, 46-2.95 (CH_2), 2.0(NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5, 51.5, 52, 113.2(2C, d), 118.6(s), 120.9, 122.4, 127.4, 128.8, 130.7, 133.5, 147.1, 151.9, 161.5, 164, 166; Mass spectrum (m/z): 345 (M^+), 301, 195,44; CHN calculated for ($C_{19}H_{21}N_4O_3$) (345): C : 63.76%, H : 6.00%, N : 16.23%, O : 13.91%; Found: C: 63.70, H: 6.07, N:16.20, O: 13.94

Compound I_{16}: *2-(N-4-acetatephenylamine)-3-ethyleneamino quinazoline-4-(3H)-one*

Yield: 61% (pale yellowish brown solid); M.P.: 243-246 ^{0}C; R_f:0.39 (chloroform : methanol 4.4:0.6); UV (λ_{max}): 332 nm; IR spectrum (cm^{-1}): 3568.00 anti-symmetry (-NH stretching), 3415.38 symmetry (-NH stretching), 2032 (-NC stretching), 1637 (-CONH), 1619.87 (-C=O), 1380 (-CN stretching), 620-400 (Aro.); ^{1}H NMR (500 MHz, DMSO-d6): 8.6-8.2 (s, 1H, CHO) 7.9 -7.4 (m, aro. 8H), 4.0 (aro, NH, d) 3.46-2.95 (CH_2) 2.0 (NH_2); ^{13}CNMR (500 MHz, DMSO-d6): 38.5(s), 47.5, 52, 114.3(d), 117.2(d), 120.9, 122.4, 127.4, 128.8, 133.5, 136,137.6, 147.1, 161.5, 164; Mass spectrum (m/z): 310 (M^+), 266, 203, 107, 44; CHN calculated for ($C_{17}H_{20}N_5O$) (310): C : 65.80%, H : 6.45%, N : 22.58%, O : 5.16%; Found: C: 65.90, H: 6.35, N: 22.50, O: 5.24.

2.2 Molecular Docking:

Molecular modeling is an in-silico method in which scientist use computer to visualize molecules to predict their molecular structure numerically and simulate their behavior with the equation of quantum and classical physics, to discover new lead compound for drugs or to refine existing drugs [21, 26, 28].

The molecular docking plays a key role to predict the predominant binding mode of a ligand with a protein. It is basic part of structural molecular biology and computer aided drug design. In the structure based drug design process, we study binding site of receptor and calculation of binding affinity of ligand-protein complex. Docking pose (geometries of binding molecules) visualize by using PyMol software. Binding site analysis and virtual screening are core points of molecular docking study. Molecular docking is start with ligand and protein selection. After that binding site prediction process occurs. The size and location of the binding site are visualized by using of PyMol software. The results of multiple docking obtain automatically and give the values rank wise with respect to samples [39, 44, 46, 51, 56],

Figure No. 3: Drug –Receptor interaction

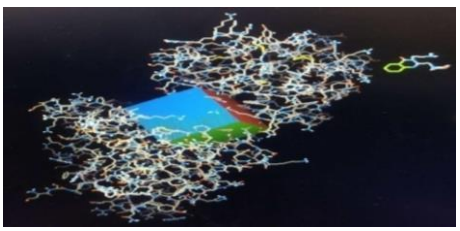


Figure No. 4: Molecular docking 3D representation

2.3 PHARMACOLOGICAL EVALUATION

2.3.1: *In-Vitro* Study for Anti-Inflammatory Activity:

Mast Cell Degranulation Studies:

Cervical dislocation method was used for sacrificing the male wistar rat. Buffer salt solution (NaCl 137 mM; KCl 2.7 Mm; $MgCl_2$ 1 mM, $CaCl_2$ 0.5 mM; NaH_2PO_4 0.4 mM, Glucose 5.6 mM HEPES 10Mm) were prepared. 15ml of pre warmed of these buffered salt solution were injected to the peritoneal cavity of animal. 90 second rubbed on peritoneal cavity to promote cell recovery. Peritonium was revealed by midline incision. Using a blunt Pasteur pipette made of plastic, pale fluid was collected. Five minutes of centrifugation at 1000 rpm were completed. Pale cell pellet produced by discarding supernatant. It was then centrifuged again after fresh buffer was introduced. The pellet was gathered and placed in buffer for suspension. Disodium chromogylcate was incubated with the cell suspension. On glass slides, it was spread out. Slides were infected with test chemicals. 1% toluidine blue was used to stain the mast cell, and 0.1% toluidine light green was used as a counterstain. Mast cells were counted by high resolution power after the slide had been air dried (X450). Egg albumin 10 g/ml was used for the remainder of the experiment for 10 minutes. Mast cells were then grown across glass slides after that. Mast cell percentages of protection and degranulation were evaluated. [9].

2.3.2 In-Vivo Study:

For the performance of oral toxicity the oral administration of single dose administered within 24 hours. In this experiment the acute oral toxicity of novel synthesized quinazoline derivatives were executed by acute toxicity method. The animals were weighed and synthesized novel quinazoline derivatives were administered as per OECD guideline (420). The body weight and starting dose of 2000 mg/kg were followed according to OECD guideline (423).

2.3.2.1 Anti-Inflammatory Activity:

Paw Oedema model

In this study Paw Oedema model was utilized. This is a simplest and very useful model for detecting the anti-inflammatory of new compounds. Paw oedema can be induced by carrageenan. The study was carried out on animal groups standard (normal saline solution), controlled (carrageenin administered), test (newly synthesized derivatives treated). Four treatment groups were taken. Each group contains 6 animals. 0.1 ml of carrageenan in saline was injected into the sub plantar tissue of the rat`s hind foot these animals were considered as controlled group. In the treatment group first oedema induced in all animal using carrageenan. Once oedema observed in all animas they were treated with newly synthesized derivatives as test drug. The recovery from oedema was observed visually and calculated. Paw volume of standard, controlled and treatment rats were calculated by Plethysmometer. The determination of ED50 of the test drug was obtained by comparing paw volume of treatment group with controlled and standard groups [15,16,17,18,19,20,21, 25,].

2.3.2.2 Anticonvulsant Activity:

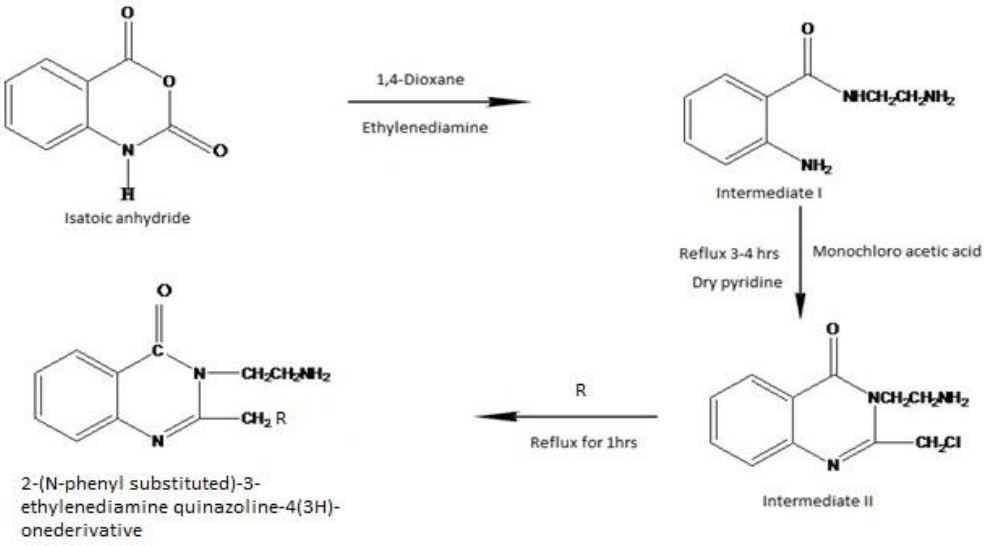
Maximal electro-shock (MES) method

In this experiment healthy wistar rats (100-150 gm) were randomly selected for the anticonvulsant activity. Four were prepared negative controlled, positive controlled, standard group, treatment group. First group (negative control) was received 5% w/v suspension of CMC and not received electrical stimulus. Second group (positive control) was received 5% w/v suspension of CMC and received electrical stimulus generated from Electro-convulsiometer (150 mA) current was used for 0.2 sec via auricular electrode. In the 3rdgroup (standard group) diazepam dissolve into 5% w/v CMC suspension was given before 30 min. Seizure arise. The test compound was dissolved into 5% w/v CMC and given to rest of group of rats. The phase and duration of convulsion were noted for 2 min. MES induced convulsion eradication of the hind leg .statistical analysis, One way ANOVA was used to analyzed the data. Graph Pad Prism software was used in this method to plot the graph. P value was calculated [13, 25, 54].

3. RESULTS AND DISCUSSION

3.1 CHEMISTRY

The designed molecule novel 2-(N-phenyl substituted)-3- alkyl amino quinazoline-4(3H)-one derivatives (**I_5-I_{16}**) were synthesized with the starting material Isatoic anhydride. Two intermediates were formed in each step, respectively. In the final step desired quinazoline derivatives were synthesized. The reaction procedure was found to be more practical, economical, and time-saving. Physical and spectroscopic data verified the synthesis of quinazoline derivatives. Physical data was verified by laboratory results and a literature review.



Based on results from IR, LC-MS, NMR, and elemental studies, the target compounds were assessed. The final synthesised compound had a strong peak between 3549 and 3470 cm^{-1}, confirming the presence of an amine group in the moiety. Stretching of the C-H shown between 2945 and 2830 cm^{-1}.Cyclic amide present in the range 1600-1720 cm^{-1}. 1620 cm^{-1} showed ketone group present in the compound. Aromatic ring present at the range between 800- 450 cm^{-1}. 1HNMR confirms the position and number of hydrogen in the compound. Aromatic proton occurs between 7.9- 6.69 ppm. Proton of aromatic amine occurs at 4.0 ppm. Proton of amine occurs at 2.0. 13CNMR confirms the number of carbon present in the compound. Carbon occurs at the range between 38.5-164 ppm. Elemental analysis confirms the actual percentage of different elements present in the synthesized molecules.

3.2 Molecular Docking:

AutoDockvina software was used to determine the protein-legand contacts and interactions strength. Crystal structure of COX and GABA receptor downloaded from protein Data Bank (PDB) and converted into pdbqt file. Ligand also converted into pdbqt format. RMSD value and binding affinity were calculated with the help of Autodockvina, autodock MGL tools and pymol visualization tool. Binding affinity (kcal/mole) and root mean square deviation (RMSD) Values were calculated automatically by using docking software. Binding affinity shows strength of interaction between ligand and protein interaction. Excellent binding affinity ocurred with COX were I5, I6, I7, I10, I11, I13, I16 and with GABA were I5, I6, I7, I12, I13. RMSD value describes the docked conformer with reference or another docked conformer. Lower the value of RMSD indicates higher the accuracy of ligand-protein interaction. Excellent RMSD values occurred with COX were I5, I6, I7, I8, I9, I12, I15, I16 and with GABA were I5, I6, I7, I8, I10, I11, I13, I14, I15, I16.

3.3 Pharmacological Evaluation:

In Vitro study:

Mast Cell Degranulation Studies:

This study is performed for anti-inflammatory activity of synthesized novel quinazoline derivatives. Mast cell mediators are responsible for inflammatory response so that chromolyn sodium and nedocromil are used to inhibit the inflammatory response. Disodium chromoglycate (DSCG) taken as reference drug (20µg/ml).

The ability of the newly created novel quinazoline derivatives to prevent mast cell degranulation caused by egg albumin was examined. Disodium chromoglycate (DSCG) (20 g/ml) dramatically prevents 76% of mast cell degranulation caused by egg albumin. Moreover, compounds I7, I8, I10, and I14 demonstrated notable anti-inflammatory action.

Anti-Inflammatory Activity:

Carrageenan-induced rat paw edema model were used to *In-vivo* anti-inflammatory screening of synthesized novel compounds and showed percentage inhibition of edema at the right hind paw in compare to control group. Carrageenan-induced rat paw edema model is very sensitive to NSAIDs but nonspecific to inflammation. Idomethacin was taken as a reference drug. It was bound with COX recepetor and inhibits the pain and inflammation. Wistar rats were obtained from

animal house MJP Rohilkhand university Bareilly, India and weighed between 150-200 g. all the wistar rats had free to access to food and water and maintained environmental condition, light-dark cycle. General and Normal behavior were found during the experimental periods. All the experimental protocols were approved by Institutional animal ethical committee (IAEC) and the works were followed as per guidelines of CPCSEA (committee for the purpose of control and supervision of experiments on animals) New Delhi India.

Compound **I_8, I_{10} and I_{14}** shows highest anti-inflammatory activity and **I_5, I_9 and I_{15}** moderate anti-inflammatory activity among all the novel synthesized derivatives due to presence of electron withdrawing groups.

Anticonvulsant Activity:

Maximum electro-shock (MES) model were used to anticonvulsant screening of synthesized compound. Synthesized novel quinazoline derivatives were evaluated for anticonvulsant activities by using of MES method. Compound**I_5, I_6 and I_{14}**showed maximum anti-inflammatory activity and compound **I_8, I_{10} and I_{12}**have moderate anticonvulsant activities.

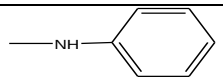
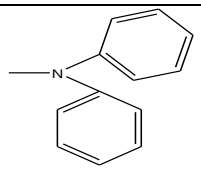
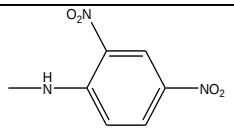
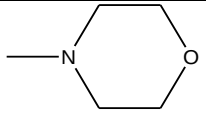
CONCLUSION

In the conclusion, the finding of this research was show that the compound **I_8, I_{10} and I_{14}** display the maximum inflammation inhibitory activity towards COX enzyme and compound **I_5, I_6 and I_{14}**showed the convulsion inhibition towards GABA receptor. With the help of molecular docking study the outcome suggest that the N-containing phenyl substitution at 2nd position of active compound could relate better binding and make adjacent to the reference drug. Molecular docking was done by using Autodockvina software, autodock MGL tools and PyMol visualization graphic software. Excellent binding affinity was obtained I_7 (-9 kcal/mol) with COX receptor and I_{13} (-9.3 kcal/mol) with GABA receptor. Excellent Root Mean Square Deviation (RMSD) value was obtained I_7 (33.64) with COX receptor and I_8 (40.90l) with GABA receptor.

Moreover, molecular modeling and pharmacological activity confirm these observations that COX and GABA receptor still an essential target for anti- inflammatory and anticonvulsant activity. Finding new, strong COX and GABA inhibitors is still necessary in light of the current anti-inflammatory and anticonvulsant situation.

This study's findings provide a new layer of justification for further investigating practical ideas for designing and creating increasingly strong and active quinazoline derivatives to block COX and GABA receptors.

Table No. 1: Formula and Physical Constants of Synthesized Compounds I_5-I_{16}

Comp.	R_1	R_2	Mol. Formula	Mol. Weight	m.p (^{0}C)	Yield%	R_fValue
I_5	NH_2CH_2-CH_2NH_2		$C_{17}H_{18}N_4O$	294.35	247-249 ºC	58 %	0.62
I_6	NH_2CH_2-CH_2NH_2		$C_{23}H_{22}N_4O$	370.45	249ºC	63 %	0.53
I_7	NH_2CH_2-CH_2NH_2		$C_{17}H_{16}N_6O_5$	384.35	245-247ºC	48%	0.67
I_8	NH_2CH_2-CH_2NH_2		$C_{15}H_{20}N_4O_2$	288.34	240-243ºC	42%	0.48

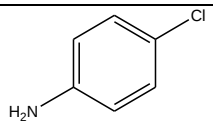
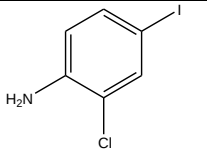
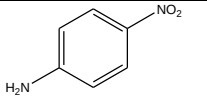
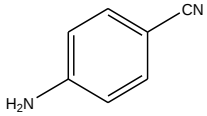
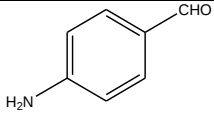
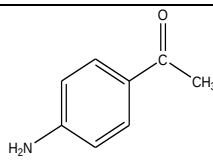
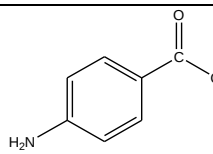
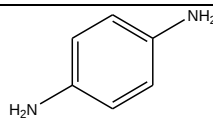
I_9	NH_2CH_2-CH_2NH_2		$C_{17}H_{18}N_4OCl$	329	245-247ºC	52%	0.55
I_{10}	NH_2CH_2-CH_2NH_2		$C_{17}H_{17}N_4OClI$	455	241-243ºC	47%	0.27
I_{11}	NH_2CH_2-CH_2NH_2		$C_{17}H_{18}N_5O_3$	340	240-242ºC	59%	0.38
I_{12}	NH_2CH_2-CH_2NH_2		$C_{18}H_{18}N_5O$	320	246-248ºC	63%	0.43
I_{13}	NH_2CH_2-CH_2NH_2		$C_{18}H_{19}N_4O_2$	323	242-245ºC	64%	0.52
I_{14}	NH_2CH_2-CH_2NH_2		$C_{19}H_{21}N_4O_2$	329	240-243ºC	56%	0.67
I_{15}	NH_2CH_2-CH_2NH_2		$C_{19}H_{21}N_4O_3$	345	242-244ºC	59%	0.55
I_{16}	NH_2CH_2-CH_2NH_2		$C_{17}H_{20}N_5O$	310	243-246ºC	61%	0.39

Table 2: Estimation of free energy of binding and RMSD values of ligands with COX and GABA receptor.

Ligand code	Binding Affinity(kcal/mol)		RMSD Value	
	COX	**GABA**	**COX**	**GABA**
I_5	-8.2	-9.1	22.908	20.314
I_6	-8.2	-8	22.319	23.532
I_7	-9	-8.7	33.644	22.924
I_8	-7.6	-7.2	29.173	40.908
I_9	-7.6	-7.2	27.668	19.750
I_{10}	-8.0	-7.4	6.366	24.920
I_{11}	-8.3	-7.7	8.591	28.392
I_{12}	-7.8	-8.4	21.65	19.463
I_{13}	-8.5	-9.3	19.92	22.947
I_{14}	-7.3	-7.8	14.73	30.854
I_{15}	-7.2	-6.4	21.00	25.375
I_{16}	-8.8	-6.9	27.80	22.673

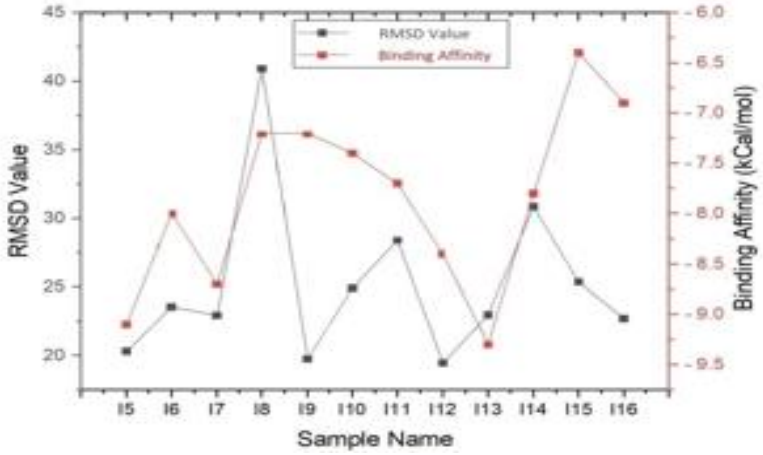


Figure No. 6: Relation between RMSD value and binding affinity

Table No. 3: **Mast Cell Degranulation Studies**

Groups	Treatment	Degranulation after treatment in Vehicle	%Egg albumin (10 µg/ml)
Control	1% Tween	32.3±1.98	87±3.32
Disodium Cromoglycate	20µg/ml	12.2±0.89	24±2.92
I5	20µg/ml	14.4±1.22	28±2.40
I6	20µg/ml	16.2±2.10	30±2.10
I7	20µg/ml	25.9±0.98	57±3.39
I8	20µg/ml	32.1±0.95	61±2.18
I9	20µg/ml	16.4±1.96	38±2.29
I10	20µg/ml	28.1±1.82	54±2.32
I11	20µg/ml	15.1±1.71	37±2.23
I12	20µg/ml	23.6±1.36	52±2.51
I13	20µg/ml	20.6±1.72	43±2.29
I14	20µg/ml	33.1±0.92	64±3.10
I15	20µg/ml	21.1±1.56	35±2.15
I16	20µg/ml	23.6±1.82	42±2.39

Each Value shows the mean ±SEM value of five observations.

Table No. 4: **Anti-inflammatory activity screening of synthesized Quinazoline derivative by Paw Oedema model**

Compound	Vol. of oedema (ml) 0 h	Vol. of oedema (ml) 1 h	Vol. of oedema (ml) 3 h	Vol. of oedema (ml) 4 h	ED_{50} (mg/kg)
Control	0.25±0.01	0.41±0.02*	0.52±0.01*	0.64±0.02*	-
I_5	0.28±0.01	0.39±0.01*(68)	0.50±0.02*(62)	0.63±0.01*(54)	8.20
I_6	0.30±0.02	0.34±0.02*(0)	0.42±0.01*(25)	0.49±0.03*(5)	-
I_7	0.26±0.01	0.35±0.03*(6)	0.39±0.03*(11)	0.58±0.02*(9)	-
I_8	0.29±0.01	0.37±0.01*(51)	0.41±0.01*(55)	0.49±0.01*(58)	8.94
I_9	0.24±0.02	0.37±0.02*(54)	0.39±0.02*(56)	0.48±0.01*(49)	8.43
I_{10}	0.27±0.01	0.36±0.03*(34)	0.44±0.01*(38)	0.53±0.02*(44)	8.91
I_{11}	0.30±0.02	0.38±0.01*(19)	0.48±0.03*(36)	0.54±0.01*(11)	-
I_{12}	0.26±0.01	0.35±0.02*(33)	0.46±0.01*(24)	0.49±0.03*(21)	-
I_{13}	0.25±0.01	0.36±0.02*(13)	0.44±0.01*(24)	0.48±0.03*(19)	-
I_{14}	0.29±0.01	0.37±0.02*(43)	0.45±0.01*(44)	0.50±0.03*(57)	9.21
I_{15}	0.24±0.01	0.35±0.02*(63)	0.48±0.01*(54)	0.48±0.03*(63)	8.57
I_{16}	0.26±0.01	0.36±0.02*(13)	0.43±0.01*(29)	0.47±0.03*(33)	-
Standard	0.28±0.03	0.38±0.01*(62)	0.48±0.01*(53)	0.58±0.01*(58)	11.23

**Values are expressed as mean± SEM; n=6 in each group. Values in parenthesis are percentage inhibition in wistar rat compared to control group statistical significance (P≤0.05). One way ANOVA followed by Dunnett'spost test. Between parentheses (percentage anti-inflammatory activity)*

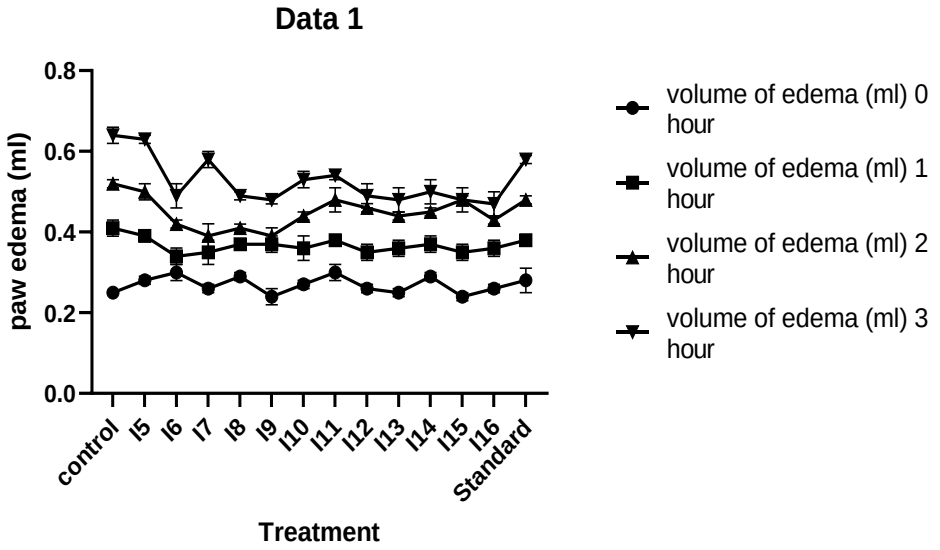


Figure No. 7: Paw edema control vs treatment for Anti-inflammatory activity

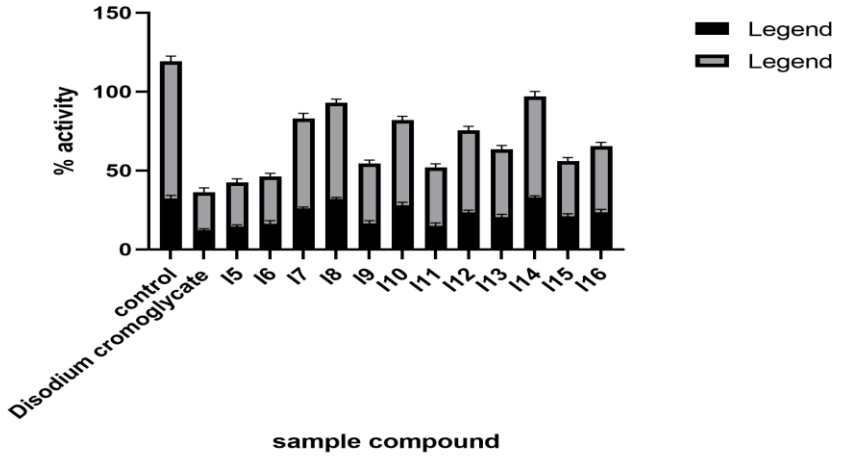


Figure No. 8: Bar diagram of % activity vs sample for Anti-inflammatory activity

Table No. 5: **Anticonvulsant activity screening of synthesized quinazoline derivative by MES model**

S.N	Group	Treatment	Mean duration of tonic hindleg extension ± SEM (sec.)
1.	I	Control (negative)	-
2.	II	Control (positive)	16.02 ± 0.62
3.	III	Standard (Diazepam)	NIL*
4.	IV	**I_5**	14.69 ± 0.52
5.	V	**I_6**	15.22 ± 0.43
6.	VI	**I_7**	8.23 ± 0.54
7.	VII	**I_8**	13.69 ± 0.52
8.	VIII	**I_9**	7.81 ± 0.82
9.	IX	**I_{10}**	11.02 ± 0.56
10.	X	**I_{11}**	10.32 ± 0.55
11.	XI	**I_{12}**	12.51 ± 0.44
12.	XII	**I_{13}**	9.42 ± 0.95
13.	XIII	**I_{14}**	14.71 ± 0.87
14.	XIV	**I_{15}**	8.11 ± 0.32
15.	XV	**I_{16}**	12.51 ± 0.89

*Values with *are statistically significant (P<0.05) from the control group by using one way ANOVA followed by Dunnett'spost test; NIL* indicate no tonic hind leg extension has been seen.*

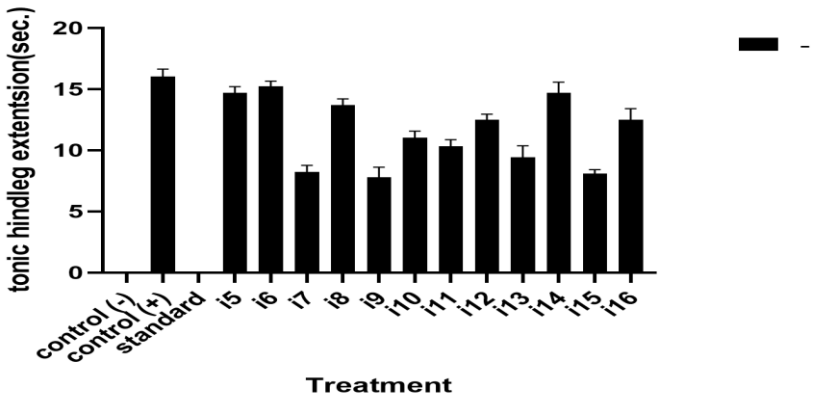


Figure No. 9: Bar diagram of % activity vs sample for Anticonvulsant activity

HUMAN AND ANIMAL RIGHTS

The Ethics Committee of the Institute authorized 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.

CONFLICT OF INTEREST: There is no conflict of interest for authors.

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