Synthesis and biological evaluation of substituted quinazoline derivatives

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Abstract---A new series of Quinazoline-oxadiazole analogues was designed, synthesized, and evaluated for anticonvulsant action against chemically induced seizures and compared with the reference drugs valproate., compounds Q4, Q8, Q10, and Q11 provided 70-100% protection against PTZ-induced seizure. FTIR, 1H- nuclear magnetic resonance, and mass spectrometry (MS) spectra analyses were used to determine the structure of the produced molecules. For all newly synthesised drugs, molecular docking was used to test their binding affinities towards the GABA-A receptor in effort to qualitatively justify their anticonvulsant actions. The results of molecular modelling were correlated with the results of biological screening. As GABAA receptor agonists,Compounds Q4, Q8, Q10, and Q11 have the highest binding affinities to the GABA-A receptor as well as the strongest anticonvulsant activity in mice. The results demonstrated that the majority of active compounds might be used as a template for future creation, adaption, and exploration to create more active analogues

Keywords---1,3,4-oxadiazole, quinazoline, anti convulsant activity, CHN analysis, NMR**.**

Introduction

Medicinal organic chemistry has emerged research field with increasing importance as heterocycle-based chemical entities and most prevalently benzofused five/six membered nitrogen containing heterocyclic systems provide framework for development of drug molecules with diverse biological activities.[1-2] Among the benzofused five/six membered nitrogen containing heterocycles, quinazoline has emerged as important heterocyclic system due to its presence in wide range of biological/pharmacological activity like antimicrobial [3],

anticonvulsant [4], antitumor [5], antihypertensive [6], antidiabetic [7], anti-inflammatory [8], anti-HIV [9], antioxidant [10], analgesic [11], etc. Optimisation of different functional groups around Quinazoline scaffold has resulted in drugs with diversified therapeutic potential like Prazosine as antihypertensive; Gefitinib as EGFR inhibitor; Alfuzosin as α1 receptor antagonist in treatment of benign prostatic hyperplasia(BPH); Bunazosin in treatment of glaucoma; Vandetanib as anticancer agent in treatment of thyroid cancer; Proquazone as non-steroidal anti-infalmmatory drug; Albaconazole as antibacterial agent and many other lead molecules in variety of other therapeutic areas. [12]

Owing to the diverse pharmacological activities possessed by this scaffold, active research has been sparked across the globe in order to design and develop quinazoline based drug molecules. In the present review, we have attempted to explore the insights of applications of quinazoline nucleus in different therapeutic fields. Quinazoline is a class of heterocyclic aromatic organic compound which share a fundamental structural features of six membered benzene fused to pyrimidine ring system. Quinazoline was first prepared in laboratory by Gabriel in 1903. [13] The name quinazoline was first proposed by Weddige as it is isomeric with compounds cinnoline and quinoxaline. Numbering of quinazoline ring was suggested by Paal and Bush. [14] The presence of fused benzene ring alters the properties of pyrimidine ring considerably. Quinazoline offer prodigious therapeutic potential and synthetic flexibility, thus efforts have been made from time to time to generate libraries of these compounds. In past decade, efforts have been made by many researchers for development of efficient and environment friendly synthetic routes for synthesis of quinazoline and its analogues.
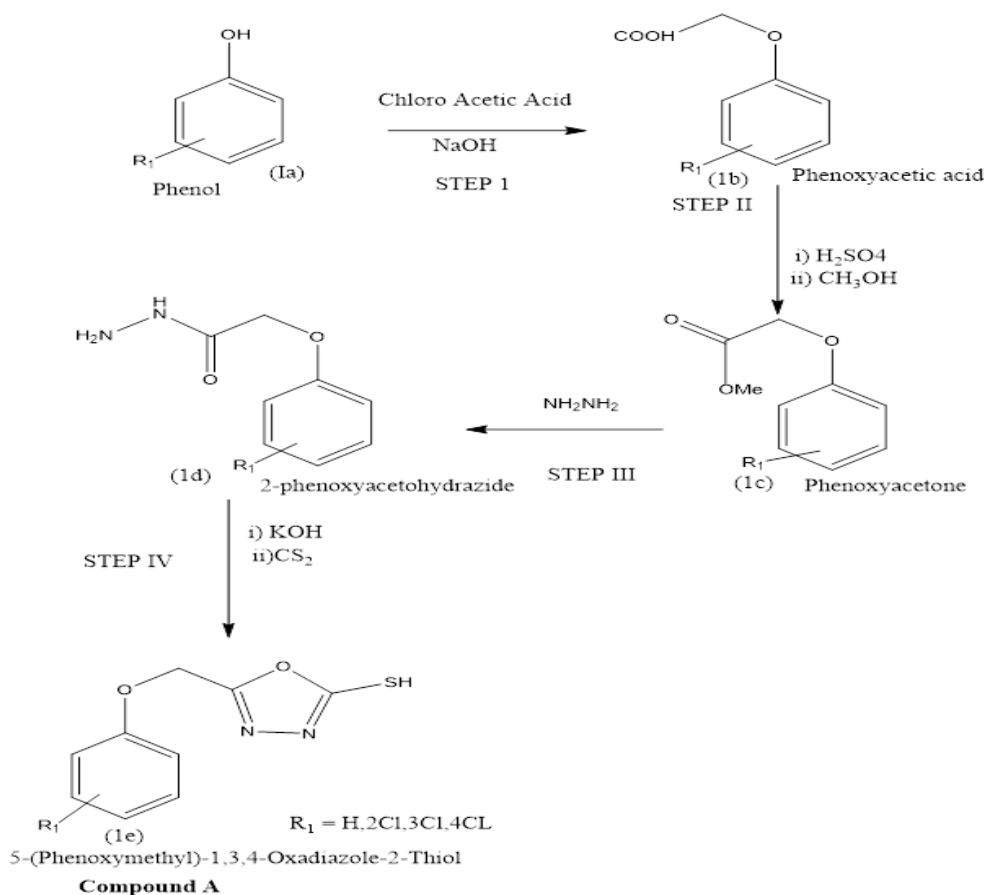
Materials and Methods

Materials

The required chemicals are purchased from local chemical suppliers of Nashik, MS, India

Methods

The synthesis of the target compound has been achieved by adopting following synthetic procedure

R₁ = H,2Cl,3Cl,4CL

5-(Phenoxymethyl)-1,3,4-Oxadıazole-2-Thiol
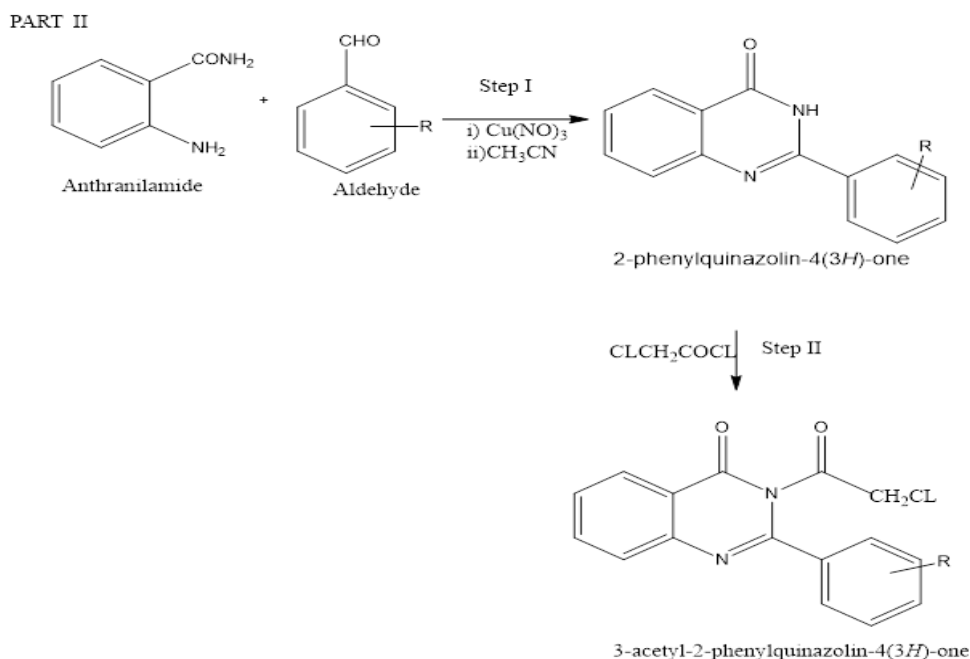
Compound A

Part I

Step-I: To a mixture of 2 g of phenol and 7ml of water in a 50 ml flask were added 3 g of NaOH pellets .3 gm of Chloro Acetic acid were added ,it was heated for 15mins in a boiling water bath .it was cooled slightly. Acidified with 6N hydrochloric acid (10-15 ml) .the mixture was cooled and extracted with 50 ml ether .the ether layer was washed with 15 ml water and extracted with solution of 2 gm of anhydrous sodium carbonate in 15 ml water. The carbonate solution was acidified to congo red in a beaker .Cooling yield flaky crystals. Yield is 50-65% and M.P is 98℃ - 99 ℃

.Step-II& III : Preparation of Aryloxy acyl hydrazide: Appropriate quantities of Acid (0.1mole) and Ethanol (50ml) was introduced into a clean and dry round bottomed flask and stirred well for 10 min. To the above mixture few drops of concentrated sulphuric acid were added and refluxed for 6hrs.The reaction mixture was concentrated by distilling the excess ethanol under the reduced pressure and treated with saturated solution of sodium bicarbonate. The ester formed in the reaction was used for the Preparation of Hydrazides directly. The appropriate Ester (0.1mole) was dissolved in 50ml of ethanol in a clean and dry RBF and to this Hydrazine Hydrate (0.1mole) was added. The reaction mixture was refluxed for period of 12 hrs. The excess ethanol was distilled off under

reduced pressure. The resultant mixture was then poured into ice cold water and obtained solid was filtered and recrystallized from ethanol.
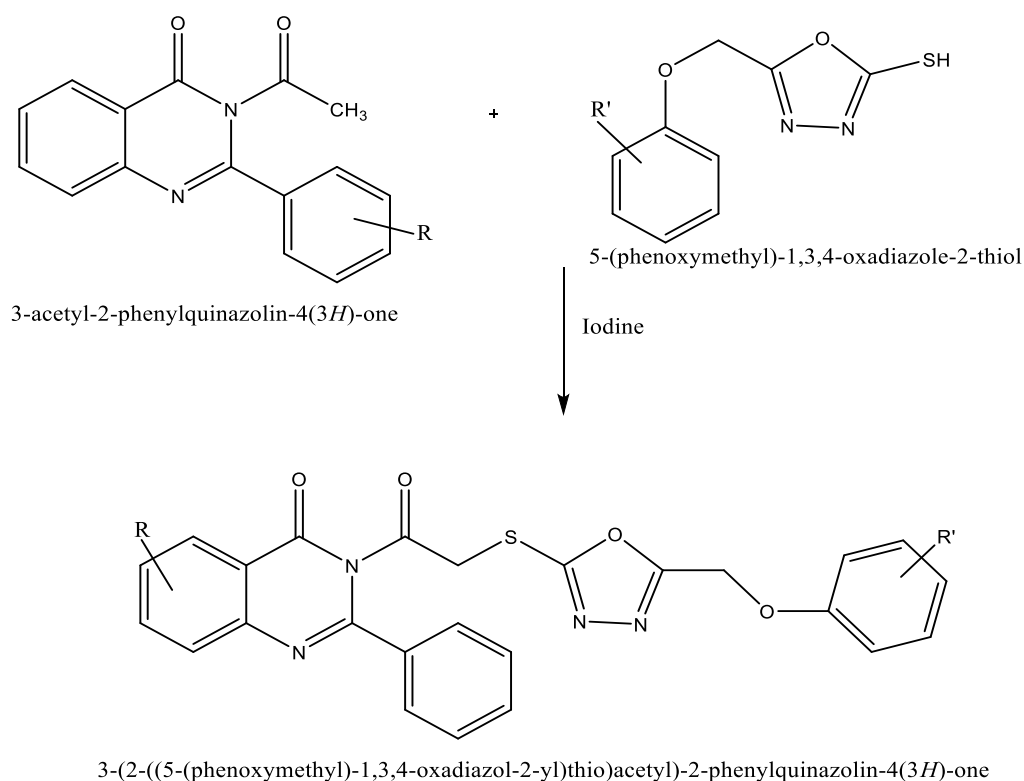
Step-IV: A mixture of Aryloxy acyl hydrazide, Potassium hydroxide (0.01mole), ethanol (50ml) and Carbon disulphide (3ml) was refluxed until the evolution of hydrogen sulphide ceased. The reaction mixture was concentrated, dissolved in water and acidified with HCl. The precipitate was filtered and recrystallized from ethanol to give 5-(Substituted Phenoxymethyl)-1,3,4-Oxadiazole-2-Thiol

Part II

PART II

Anthranilamide + Aldehyde → 2-phenylquinazolin-4(3H)-one

Step I
i) Cu(NO)₃
ii)CH₃CN

CLCH₂COCL | Step II

3-acetyl-2-phenylquinazolin-4(3H)-one

Step I: A mixture of anthranilamide (1 mmol), Copper nitrate (20 mmol) and appropriate aldehydes (1.3 mmol) in methyl nitril (10 ml) was heated at 80°C for 9 hrs. The product was washed with and extracted with ethyl acetate

Step II: Acetylation on Nitrogen atom of Quinazoline derivative: To mixture of quinazoline derivative (0.1 mol) is taken in a beaker and pyridine and acetyl chloride (0.2 mol) was added. The reaction mixture is stirred at 60 – 90°C for the follow by 5% of NaHCO3.The solid is obtained was washed with water and dried.

3-acetyl-2-phenylquinazolin-4(3*H*)-one

5-(phenoxymethyl)-1,3,4-oxadiazole-2-thiol

Iodine

3-(2-((5-(phenoxymethyl)-1,3,4-oxadiazol-2-yl)thio)acetyl)-2-phenylquinazolin-4(3*H*)-one

A mixture of mercapto linked triazole derivatives (2.0 mole), quinazoline derivative (2.0 mole) and iodine (0.28 mole) moist with 7 drops of ethanol was ground in a mortar by a pestle at RT for 10 min. The reaction mixture was left at Rt for 15 min until the completion of the reaction which was checked by TLC. The reaction mixture was diluted with ice cold water and iodine present was neutralized with sodium thiosulphate solution (10%).The solid thus separated out was filtered under vacuum, washed with water and purified from DMF-E to H (3:2) to give final compound.

PTZ induced anti-convulsant activity [15-16]

Animals will be divided into twelve groups as given above. Each group having 5 animals weighing about 200-220 g and the animals were allowed free access to standard laboratory diet and drinking water. Drug treatment in different animal group will be as mentioned in methods Pentylenetetrazol (dose 80 mg/kg ,ip; Prepare Stock solution containing 8mg/ml, Inject 1ml/100 g of body weight of mouse) . Weigh and number the animals.Divide the animals as per the group. Inject Pentylenetetrazol to control group and note the onset of action (indicated by straub's tail, Jerky movement of whole body and convulsions) and severity of convulsions due to drug. Administer the drug samples (proposed anticonvulsant drug) to the animal per orally. After 30 min inject pentylenetetrazol to these animals. Note onset and severity of convulsions. Note either delay or complete abolition of convulsions in mice treated with proposed anticonvulsant drug.

Molecular docking

The Glide (version 10.0, Schrödinger, LLC, New York, NY, 2005) software was used to dock potential inhibitors (Ligand) in the binding pocket of the human gamma-aminobutyric acid receptor structure. Glide is most commonly used and validated software designed to assist in high-throughput screening of potential ligands based on binding mode and affinity for a given receptor molecule. Docking studies were carried out using human gamma-aminobutyric acid receptor structure (GABA(A)R-beta3 HOMOPENTAMER) complexed with a inhibitor, BEN 500 (Benzamidine). It was solved by X-ray diffraction techniques with a resolution of 2.97 Å. We retrieved it from the Brookhaven protein database (code 4COF).

Ligand preparation

Ligand preparation was carried out using LigPrep panel in the software. The use of LigPrep produces a single low-energy 3D structure with correct chiralities for each successfully processed input structure. All the structures in .mae format were imported in the project file and subjected to ligand preparation using OPLS 2005 force field. Possible ionization states for each structure at the pH 7.0 ± 2.0 were generated using the ionizer option and only one low energy ring conformer per ligand was allowed to generate.

Ligand Docking

Docking was carried out using XP (Extra precision) mode. Flexible docking with flips of 5- and 6-member rings was allowed. Docking and scoring of potential three sets of ligands was carried out without calculating or using similarity scores. Additional filters were also used. Settings were done so that ligands with more than 120 atoms and 20 rotatable bonds will not be docked and one pose for each ligand was collected and written to the pose viewer file. A Van der Waals radius scaling for ligand atoms is set to the default values: Scale by 0.80 atoms with partial atomic charge less than 0.15.

Results and Disussion

The number of Quinazoline derivatives has been synthesized as per the procedure mentioned in the experimental section. The structure of the synthesized compounds was established by using NMR, IR, MS and CHN analysis.

Table no. 01: Physicochemical data of the synthesized compounds

COMPOUND CODE	R	R'	MOLECULAR FORMULA (M.W)	MP (°C)	YIELD (%)	Rf values
A1	2-Cl	H	$C_{25}H_{17}N_4O4SCl$ (504.5)	201-203	52.12	0.21
A2	3-Cl	H	$C_{25}H_{17}N_4O4SCl$ (504.5)	210-212	61.17	0.23
A3	4-Cl	H	$C_{25}H_{17}N_4O4SCl$ (504.5)	215-217	57.21	0.22
A4	H	2-Cl	$C_{25}H_{17}N_4O4SCl$	199-	50.12	0.24

				202		
A5	H	3-Cl	$C_{25}H_{17}N_4O_4SCl$ (504.5)	212-214	62.17	0.25
A6	H	4-Cl	$C_{25}H_{17}N_4O_4SCl$ (504.5)	218-219	58.21	0.26
A7	2-NO2	H	$C_{25}H_{17}N_5O_6S$ (509.0)	235-237	59.35	0.26
A8	4-NO2	H	$C_{29}H_{28}N_5O_6S$ (509.0)	235-237	60.12	0.28
A9	H	H	$C_{25}H_{18}N_4O_4S$ (470.0)	212-214	54.44	0.33
A10	2-OH	H	$C_{25}H_{18}N_4O_5S$ (486)	220-222	61.10	0.17
A11	4-OH	H	$C_{25}H_{18}N_4O_5S$ (486)	224-225	60.0	0.19
A12	4-CH3	H	$C_{26}H_{20}N_4O_4S$ (484.0)	218-219	55.1	0.25
A13	3-CH3	H	$C_{26}H_{20}N_4O_4S$ (484.0)	201-203	56.2	0.27
A14	2-CH3	H	$C_{26}H_{20}N_4O_4S$ (484.0)	207-209	59.3	0.29
A15	2-OCH3	H	$C_{26}H_{20}N_4O_5S$ (500.0)	197-198	61.1	0.15

Table no. 02: PTZ induced anti-convulsant activity of the synthesized compounds (A1-A15)

Comp. Code	Dose (mg/kg)	% Protection (PTZ)
A1	100	50.45
A2	100	45.40
A3	100	67.78
A4	100	78.65
A5	100	76.45
A6	100	49.76
A7	100	58.76
A8	100	80.34
A9	100	75.45
A10	100	82.45
A11	100	80.35
A12	100	70.15
A13	100	65.45
A14	100	70.35
A15	100	70.45
STD PHENOBARBITAL SODIUM	80	100

On the basis of results obtained from the anti convulsant activity of the synthesized compounds A4, A8, A10 and A11 shows significant anti convulsant activity.

Molecular docking

The combination of position and orientation of a ligand relative to the receptor, along with its conformation in flexible docking, is referred to as a *ligand pose*. The ligand poses that Glide generates pass through a series of hierarchical filters that evaluate the ligand's interaction with the receptor. The initial filters test the spatial fit of the ligand to the defined active site, and examine the complementarity of ligand-receptor interactions using a grid-based method Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA nonbonded ligand-receptor interaction energy. Final scoring is then carried out on the energy-minimized poses.
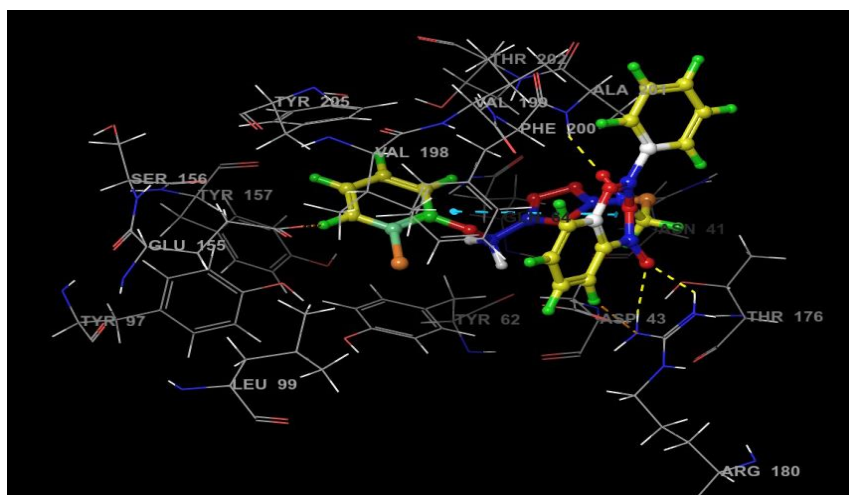

Figure no. 01: Binding of compound into the active site of 4COF receptor protein

The lower interaction energy observed for 4 rationalizes the tighter binding of 2-(substituted phenyl) quinazolin-4(3H)-one analogue. The compound 4 found to be involved in the hydrogen bonding with a residue ARG 180 (02 Hydrogen Bonds) and ALA 201 (01 Hydrogen Bond). The hydrogen bonding distance between C=O group of quinazolin-4(3H)-one ring in Compound 4 with NH of ARG 180 was found to be 2.01 A° and 2.11 A° (O-----H) while hydrogen bonding distance between acetyl C=O group and NH hydrogen of ALA 201 was found to be 1.90 A°. The -(substituted phenyl) quinazolin-4(3H)-one ring was surrounded by active site amino acid residues ARG 180, LEU 99, VAL 199, and ALA 201. The 3-(2-(5-(phenoxymethyl)-1,3,4-oxadiazol-2-ylthio)acetyl)- portion of molecule found to interact with residues PHE 200, THR 202, TYR 157, SER 156, TYR 205, GLU 155 and TYR 97.

Spectral data

A1: m/e: 504.5 ; FTIR(cm⁻¹): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (13H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2)

A2: m/e: 504.5; FTIR(cm⁻¹): 3035.46 (Ar-CH str.); 2845.38 (-CH str.); 1684.68 (-CONH str.); 1578.98 (-C=N str.); 1025.68 (-C-O-C str.); 987.45 (-C-Cl str.); 866.45 (C-S-C str.); 1H-NMR (ppm): 7.00-7.68 (13H of phenyl); 1.25-1.35 (2H of –CH2); 1.15-1.25 (2H of –CH2)

A3: m/e: 504.5 ; FTIR(cm⁻¹): 3032.12 (Ar-CH str.); 2835.67 (-CH str.); 1689.65 (-CONH str.); 1588.75 (-C=N str.); 1045.56 (-C-O-C str.); 986.78 (-C-Cl str.); 868.64 (C-S-C str.); 1H-NMR (ppm): 6.95-7.86 (13H of phenyl); 1.10-1.40 (2H of –CH2); 1.00-1.25 (2H of –CH2)

A4: m/e: 504.5 ; FTIR(cm⁻¹): 3056.75 (Ar-CH str.); 2876.56 (-CH str.); 1687.98 (-CONH str.); 1586.79 (-C=N str.); 1024.56 (-C-O-C str.); 879.85 (-C-Cl str.); 789.65 (C-S-C str.); 1H-NMR (ppm): 7.00-7.45 (13H of phenyl); 1.45-1.60 (2H of –CH2); 1.10-1.25 (2H of –CH2)

A5: m/e: 504.5 ; FTIR(cm⁻¹): 3045.65 (Ar-CH str.); 2889.55 (-CH str.); 1678.75 (-CONH str.); 1590.65 (-C=N str.); 1040.35 (-C-O-C str.); 965.45 (-C-Cl str.); 867.54 (C-S-C str.); 1H-NMR (ppm): 6.90-7.55 (13H of phenyl); 1.25-1.40 (2H of –CH2); 1.10-1.25 (2H of –CH2)

A6: m/e: 504.5 ; FTIR(cm⁻¹): 3024.66 (Ar-CH str.); 2866.75 (-CH str.); 1687.86 (-CONH str.); 1589.86 (-C=N str.); 1025.78 (-C-O-C str.); 986.75 (-C-Cl str.); 866.98 (C-S-C str.); 1H-NMR (ppm): 6.79-7.65 (13H of phenyl); 1.20-1.45 (2H of –CH2); 1.00-1.35 (2H of –CH2)

A7: m/e: 509; FTIR(cm⁻¹): 3045.65 (Ar-CH str.); 2860.85 (-CH str.); 1687.75 (-CONH str.); 1589.95 (-C=N str.); 1550.65 (-NO2); 1025.79 (-C-O-C str.); 966.55 (-C-Cl str.); 867.78 (C-S-C str.); 1H-NMR (ppm): 6.85-7.56 (13H of phenyl); 1.11-1.25 (2H of –CH2); 1.00-1.25 (2H of –CH2)

A8: m/e: 509; FTIR(cm⁻¹): 3035.66 (Ar-CH str.); 2860.61 (-CH str.); 1688.75 (-CONH str.); 1586.77 (-C=N str.); 1578.85 (-NO2); 1035.66 (-C-O-C str.); 984.35 (-C-Cl str.); 854.65 (C-S-C str.); 1H-NMR (ppm): 6.90-7.55 (13H of phenyl); 1.35-1.50 (2H of –CH2); 1.00-1.26 (2H of –CH2)

A9: m/e: 470; FTIR(cm⁻¹): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (15H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2)

A10: m/e: 486; FTIR(cm⁻¹): 3245.68 (-OH str.); 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (14H of phenyl); 5.0 (1H of –OH); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2)

A11: m/e: 486; FTIR(cm⁻¹): 3266.78 (-OH str.); 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (14H of phenyl); 5.0 1H of –OH; 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2)

A12: m/e: 484; FTIR(cm⁻¹): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (13H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2);1.0-1.10 (3H of –CH3)

A13: m/e: 484; FTIR(cm^{-1}): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (13H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2); 1.0-1.10 (3H of –CH3)

A14: m/e: 484; FTIR(cm^{-1}): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (13H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2); 1.0-1.10 (3H of –CH3)

A15: m/e: 500; FTIR(cm^{-1}): 3025.46 (Ar-CH str.); 2865.45 (-CH str.); 1686.57 (-CONH str.); 1585.75 (-C=N str.); 1030.59 (-C-O-C str.); 985.45 (-C-Cl str.); 865.75 (C-S-C str.); 1H-NMR (ppm): 6.80-7.65 (13H of phenyl); 1.30-1.45 (2H of –CH2); 1.10-1.35 (2H of –CH2); 1.0-1.10 (3H of –CH3)

Conclusion

The results revealed that most of the compounds displayed 50–100% anticonvulsant activity in the PTZ screen at a dose range of 100 mg/kg. Compounds A4, A8, A10 and A11 appeared the most potent in this series at doses of 100mg /kg, respectively. They were compared with standard drug Phenobarbital sodium at a dose of 80 mg/kg. The methyl substitution plays a significant role in the anticonvulsant activity and the seizure spreading.

- It is well known that Quinazoline and Pyrrolidine moiety play an important role in CNS activity and anticonvulsant activity. Synthesis of derivatives of Quinazoline and Pyrrolidine would be done which are not reported till date. Examples of drugs containing above moiety are Seletracetam, Brivaracetam ,Selurampanel and Pirampanel which are available in market for treatment of CNS Disorders.
- Derivatization of Basic Moiety Quinazoline and Pyrrolidone with substitution with, Alkyl Aryl, Halogen, Heterocyclic rings with nitrogen Etc. At least 20 derivatives for each moiety would be prepared.
- Screening of the Moiety using seizure model- maximal electroshock seizures (MES) and Subcutaneous Pentylenetetrazol (scPTZ) for anticonvulsant Activity and Anxiolytic activity.Hence synthesized compounds may show desired pharmacological effect better than existing compounds.

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