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Microwave Assisted Synthesis and Molecular Docking Studies of 3-Aryl-2-Alkyl-Quinazolin-4-one Derivatives

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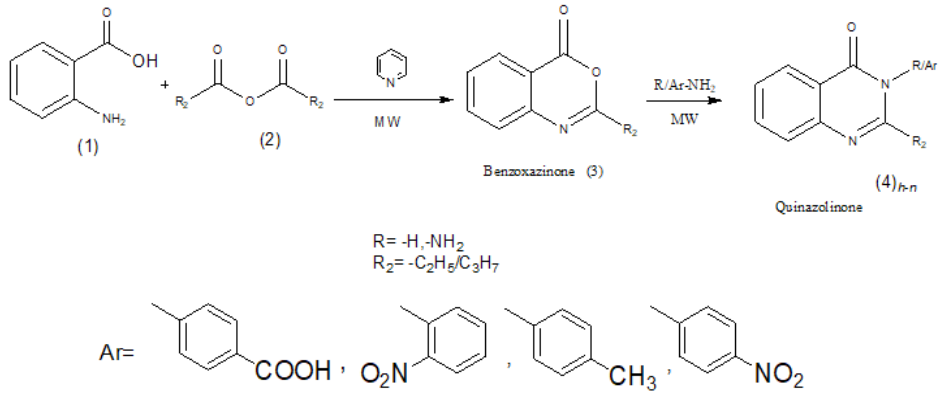
ABSTRACT

*A novel series of several **2, 3 DISUBSTITUTED-QUINAZOLIN-4-ONE** has been synthesized by the interaction of benzoxazinone with various amines yields quinazolin-4-one derivatives. In this study, fast flexible docking simulations were performed on GABA (A) R-beta3 homopentamer receptor. The results designate that the quinazoline ring forms hydrophobic and hydrogen bond contacts with TYR A: 157, TYR A: 205, PHE A: 200 amino acid residue.*

***Graphical abstract**:*



Keywords: Quinazolin-4-one, GABA (A) R-beta3 homopentamer, Molecular docking

INTRODUCTION

The Quinazoline appears in numerous alkaloids, most commonly in the form of 4-quinazolinone moieties [1]. A few of these alkaloids have been synthesized by Bergman et al., amongst them rutaecarpine [2,3], quinazolinocarboline are isolated from various plants belonging to the rutacea family. Chrysogine which is isolated from molds [4,5] and some of the derivative of auranthine which is benzodiazepine alkaloid [6-8] also been synthesized by members of this group. The quinazolinone moiety is an important hetrocycle showing many types of biological actions as revealed in recent comprehensive review on the chemistry of 2-heteroaryl & heteroalkyl-4-quinazolinones [9] 4-quinazolinones are the formal condensation products of anthranilic acid and amides, and they can also be prepared in this fashion through the Niementowski quinazolinone synthesis, which is discovered by Stefan Niementowski. Quinazoline and condensed Quinazoline exhibit potent central nervous system (CNS) activities like anti-anxiety, analgesic, anti-inflammatory [10] and anticonvulsant [11]. Quinazolin-4-ones with 2, 3-disubstitution is reported to possess significant analgesic, anti-inflammatory and anticonvulsant activities [12-15]. To expand these views and

application profiles, efforts have been developed for the synthesis of a new class of quinazolinone by incorporating different amines into synthesized benzoxazinone ring by replacing O atom in the ring. Up to now, a great number of various procedures have been proposed for the synthesis of quinazolin-4-ones in the past few years [16]. Using microwave radiation, this reaction could be easily and rapidly performed in very good yields, providing a large quantity of yields. We report a facile and efficient method for the synthesis of 3-substituted-2- alkyl-quinazolin-4-one by the condensation reaction of anthranilic acid or methyl anthranilate, propionic anhydride or butanoic anhydride with various amines. We have also attempted synthesis of 2-methylquinazoline-4-one and 2-phenylquinazolin-4-one using acetic anhydride and Benzoyl chloride respectively [17-35]. Drug/ligand or receptor/protein interactions can be studied by molecular docking. It works by identifying suitable active sites in protein. Once the active site is identified the best geometry of ligand receptor complex is obtained and to design more effective ligand, energy of interaction is calculated for different ligands. Dock score denotes the calculated interaction energy *i.e.* the strength of non covalent interaction between two molecules after docking. Docking can be done in either three ways as rigid docking, flexible docking and full flexible docking. In rigid docking a suitable position for the ligand in receptor environment is obtained, flexible docking favors a geometry for receptor-ligand interactions and in full flexible docking ligand is flexed *via* its torsion angles as well as the side chain of active site residues [36,37].

MATERIALS AND METHODS

All required analytical or laboratory grade chemicals were procured from commercial sources. Microwave reactions were carried in power range of 140W to 900W on 'Catalyst systems Scientific microwave System' with automatic power setting. Glass capillary method was used for determination of Melting points. IR spectras were recorded on FTIR-8400S SHIMADZU spectrophotometer. GC-MS spectras & chromatograms were recorded on GCMS-QP 2010 SHIMADZU instrument. Proton NMR spectras were recorded on Mercury Plus 300 MHz model with TMS as an internal standard. Chemical shifts (δ) were expressed in parts per million (δ ppm).

Synthesis

3-aryl-2-alkyl-quinazolin-4-one (4h-4n)

Solution of anthranilic acid/methyl anthranilate (1) (0.01 mol) in 10 ml pyridine and propionic anhydride/ butanoic anhydride (2) (0.01 mol) was refluxed in 100 ml RBF under microwave at 350W for 5-10 min. Thin layer chromatography was performed by using n-Hexane: Ethyl acetate as a solvent system on precoated silica gel 60 F254 (Merck) aluminum plates and Silica Gel G (Merck Index) coated on glass plates. Spots were visualized under ultra-violet light for precoated silica gel 60 F254 (Merck) aluminum plates and by exposure to iodine vapors for Silica Gel G (Merck Index) coated on glass plates. **2-alkyl-benzoxazin-4-one (3) (BZZN)** yielded as intermediate product. This intermediate is irradiated with the solution of desired amines under microwave at 350 W for 25-60 min with continuously monitoring a reaction using TLC. The reaction mixture was cooled & poured over a mixture of crushed ice & concentrated HCl with constant stirring for 30 min. The resulting solid precipitate is then filtered and washed with chilled water. The dry crude product so obtained is recrystallised by using aq. ethanol yielding to ***3-aryl-2-alkyl-quinazolin-4-one (4h-4n).***

Docking studies

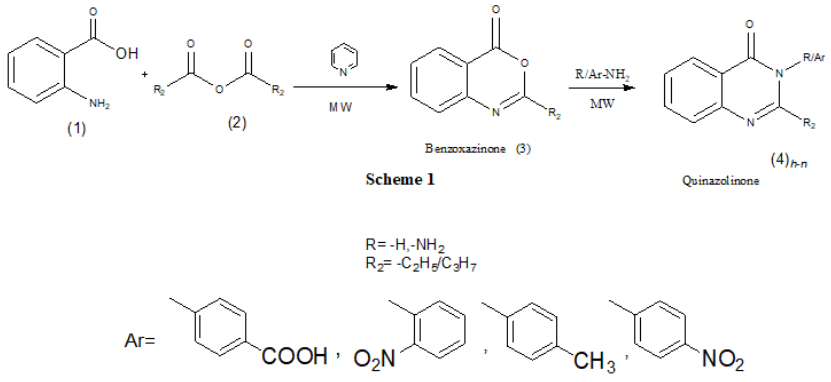
The synthesized molecules will affect their target in terms of structural and chemical complementation was explored using the Glide V 7.4 module of the Schrodinger molecular modeling interface [38]. Glide searches for favorable interactions between one or more ligand molecules and a receptor molecule using a grid-based method. For the present study the X-ray crystal structure of 4COF (Crystal structure of a GABA (A)R-beta3 homopentamer) was taken from PDB (www.rscb.org). Before docking, the proteins were prepared digitally using the protein preparation wizard (Maestro-v11.1, Schrodinger LLC, 2017) [39] by the removal of water molecule and cofactors from the proteins, optimizing hydrogen bonding and deleting the ligand present in the crystal structure. The solvent molecules were deleted and the bond order of the crystal ligand and protein was adjusted. The structures were minimized up to </= 20 Å. The ligands were built using the build panel of Maestro 8.0 (LigPrep 2.1 Schrodinger LLC, 2017) [40] and prepared using LigPrep2.1 [41] and the OPLS3 force field using the extra precision (XP) [42] mode of Glide v7.4. The title compounds were docked into the active site of a target molecule and final scoring was carried out in terms of the Glide multi-ligand scoring function.

RESULTS AND DISCUSSION

Chemistry

Present work is initiated with the reaction between anthranilic acid and propionic anhydride. For Investigation of irradiation power and reaction time the reaction conditions are optimized.

The reaction provided of 3-aryl-2-alkyl-quinazolin-4-one gives good yield as well as good quality of product by using Microwave. The first step in this reaction involves formation of benzoxazinone as an intermediate by reaction of the anthranilic acid with the carbonyl group of the propionic anhydride or butanoic anhydride, followed by the displacement reaction *i.e.* loan pair electrons on the nitrogen atom from anthranilic acid attack at the carboxylic carbonyl group, which forms the cationic compound which act as cationic base, then reaction undergoes cyclisation and formation of benzoxazinone. Reaction of various aromatic amines with benzoxazinone having recognized the advantages of the microwave irradiation approach for the construction of the Quinazolinone, we decided to utilize use of microwave for the synthesis of quinazolinone derivatives. From IR spectral studies, disappearance of peak of cyclic ester functional group and appearance of characteristic peaks of substituted amino group confirmed the quinazolinone derivatives. All Physical characteristics of quinazolinone derivatives were given in Table 2. We have thus developed a simplistic, speedy and environmentally benign microwave-assisted synthesis of quinazolinone moieties. Virtually chemical reactions under microwave irradiation have given better results than conventional heating. Therefore, it has been demonstrated that the synthesis of a variety of heterocyclic compounds can be carried out safely in microwave reactors with remarkable rate enhancements with the reduction of time, improved yields and purity of the products (Scheme 1 and 2).



Scheme 1

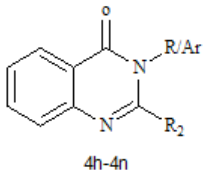
Scheme 1. Synthesis of 3-aryl-2- -4- alkyl-quinazolin one (4h-4n).

The structures of the synthesized compounds were confirmed by IR, GC-MS and H^1 NMR. (Table 1) Structures, yields, melting points and R_F values of the synthesized compounds are reported (Table 2).

Code	Spectral data
4h	3-(4'Carboxylphenyl)- 2-ethylquinazolin-4-one IR (KBr) cm^{-1}: 2500-3000 (Broad O-H band in acid) 3120.93(γ C-H in benzene) 1739.95 (γ C=O in acid) 1680.05(γCONH)1641.48(γ C=C) 1163.11(C=N bending) 850.64(P-Substituted ring) ^{1}H NMR (ppm) δ 7.10-8.77 (Ar-H) 7.60 (1H, d, at 5), 7.63 (1H, t, at 6), 7.60 (1H, t, at 7), 8.12 (1H, d, at 8), 7.26 and 8.15 (2H, d, C2'-C6' & C3',C5'of Phenyl at 3), 2.55 (2H, q, CH_2 at 2), 1.30 (3H, t, CH_3 at 2) 11.06 (1H,s,OH at 4') Mass spectrum (*m/z*) 294 (M^+), 264,250,224,146, 125, 77. Anal. Calculation for $C_{17}H_{14}N_2O_3$; C, 69.38; H, 4.79; N, 9.52; O, 16.31.
4i	3-(2'Nitrophenyl)- 2-ethylquinazolin-4-one IR (KBr) cm^{-1}: 3090.98 (γ C-H in benzene) 1668.45 (γCONH) 1595.16 (γ C=C) 1535.36 (γ NO_2 symmetric) 1345.37 (γ NO_2 asymmetric) 1158.27 (C=N bending). ^{1}H NMR (ppm) δ 7.50-7.81 (Ar-H) 7.73 (1H, d, at 5), 7.28 (3H, t, at 6, and C4',C5' of Phenyl at3), 7.01 (1H, t, at 7), 7.60 (1H, d, at 8), 7.68 (2H, m, C3'-C6' of Phenyl at3) 1.26 (2H, t, CH_2 at 2), 1.11 (3H, t, CH_3 at 2) Mass spectrum (*m/z*) 296(M^+), 275,121,116. Anal. Calculation for $C_{16}H_{13}N_3O_3$; C, 65.08; H, 4.44; N, 14.23; O, 16.25.
4j	3-amino- 2-ethylquinazolin-4-one IR (KBr) cm^{-1}: 3170.97 (γ N-H), 1681.93 (γ CONH) 1527.62 (γ C=C) 1597.06 (γ C=N), 1234.44 (γ C-N) Anal. Calculation for $C_{10}H_{11}N_3O$; C, 63.48; H, 5.86; N, 22.21; O, 08.46.

4k	3-(4'Nitrophenyl)- 2-Propylquinazolin-4-one IR (KBr) cm^{-1}: 3267.47 (γ C-H in benzene) 1656.88 (γCONH) 1409.99 (γ NO_2 symmetric) 1371.41 (γ NO_2 asymmetric) 1199.74 (C=N bending). ^1H NMR (ppm) δ 7.46-7.74 (Ar-H) 7.74 (1H, d, at 5), 7.12 (3H, t, at 6) , 7.49 (1H, t, at 7), 7.66 (1H, d1.12(3H, t, CH_3 at 2)., at 8), 7.68 (2H, m, C2'-C6' of Phenyl at3) 7.09 (2H, m, C3'-C5' of Phenyl at3) 1.29 (2H, t, CH_2 at 2), 1.04(3H, t, CH_3 at 2).2.46 (3H,s, CH_3 at C4')
4l	3-(4'Nitrophenyl)- 2-Propylquinazolin-4-one Mass spectrum (*m/z*) 307, 266, 148, 121, 117, 44 Anal. Calculation for $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.89; N, 13.58; O, 15.52.
4m	3-(4'Carboxylphenyl) - 2-propylquinazolin-4-one IR (KBr) cm^{-1}: 1674.21 (γ CONH) 1597.06 (γ C=N), 1303.88 (γ C-N) Anal. Calculation for $C_{18}H_{16}N_2O_3$; C, 70.12; H, 5.23; N, 9.09; O, 15.57. ^1H NMR (ppm) δ 7.19-8.85 (Ar-H) 7.69 (1H, d, at 5), 7.63 (1H, t, at 6), 7.67 (1H, t, at 7), 7.67 (1H, d, at 8), 7.22 and 8.85 (2H, d, C2'-C6' & C3',C5'of Phenyl at 3), 2.51 (2H, q, CH_2 at 2), 1.53 (3H, t, CH_3 at 2) 9.85 (1H,s,OH at 4')
4n	3-(2'Nitrophenyl)- 2-propylquinazolin-4-one IR (KBr) cm^{-1}: 3098.70 (γ C-H in benzene) 1626.98 (γCONH) 1555.62 (γ C=C) 1439.89 (γ NO_2 symmetric) 1328.01 (γ NO_2 asymmetric) 1183.35 (C=N bending). ^1H NMR (ppm) δ 7.93 (1H, d, at 5), 7.72 (1H, m, at 6 and 8), 7.66 (1H, m, at 7), 7.83 (3H, m, C4'-C6' & C5'of Phenyl at 3), 8.19 (1H, d, at C3'), 2.31 (2H, t, CH_2 at 2), 1.66 (2H, q, CH_2 at 2) 1.28 (3H, t, CH_3 at 2). Anal. Calculation for $C_{17}H_{15}N_3O_3$; C, 66.01; H, 4.89; N, 13.58; O, 15.52.

Table 1: Spectral Data of Representative Compounds from the Synthesized Series.



4h-4n

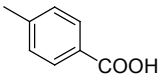
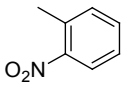
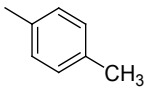
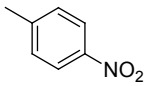
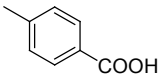
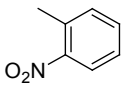
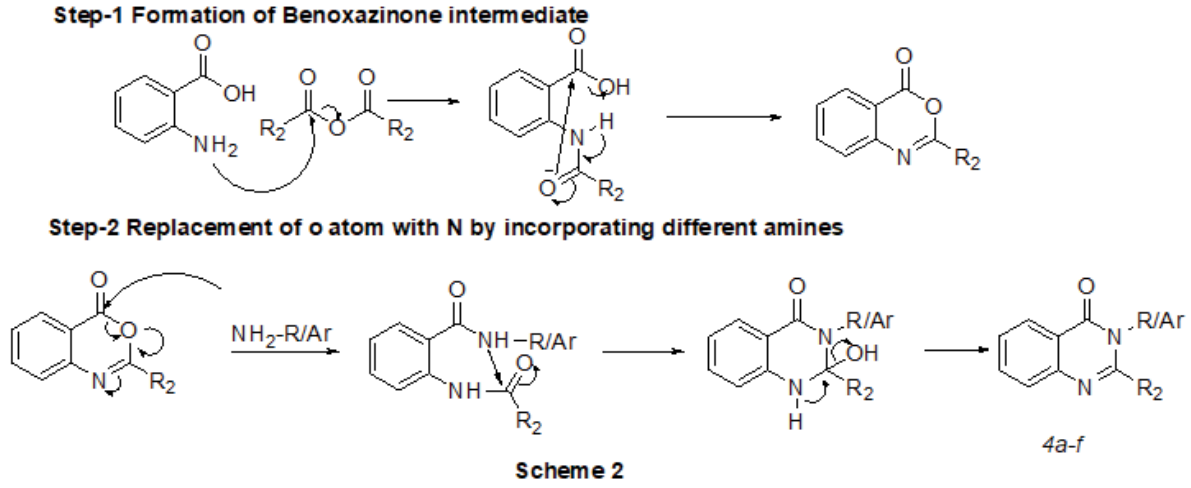
Compound No.	Code	R_2	R/Ar	IUPAC name	mp (^{0}C)	% Yield	R_F	Time (min.)
1	4h	C_2H_5		3-(4'Carboxylphenyl)-2-ethylquinazolin-4-one	170-173	63.45	0.66	40
2	4i	C_2H_5		3-(2'Nitrophenyl)-2-ethylquinazolin-4-one	185-187	79.34	0.73	55
3	4j	C_2H_5	$-NH_2$	3-amino- 2-ethylquinazolin-4-one	98-101	87.67	0.81	25
4	4k	C_3H_7		3-(4'methylphenyl)-2-propylquinazolin-4-one	92-94	68.44	0.66	35
5	4l	C_3H_7		3-(4'Nitrophenyl)-2-Propylquinazolin-4-one	211-214	88.93	0.74	60
6	4m	C_3H_7		3-(4'Carboxylphenyl)-2-propylquinazolin-4-one	75-78	66.39	0.66	45
7	4n	C_3H_7		3-(2'Nitrophenyl)-2-propylquinazolin-4-one	89-92	77.56	0.79	55

Table 2: Physical characteristics of synthesized quinazolinone derivatives.



Scheme 2. Plausible cyclization mechanism of 3-aryl-2- -4- alkyl-quinazolin one (4h-4n).

Docking Studies

The synthesized new chemical entities were subjected to grid-based molecular docking studies. The results shows that compound 4j have good affinity to the active site residue of Protein by interaction of hydrogen bond with protein residue TYR A 157 while compounds 4i, 4m and 4n not showing any kind of hydrogen bonding interaction, may be the probable reason for its lowest activity (Figures 1-6). The observations are given in Table 3.

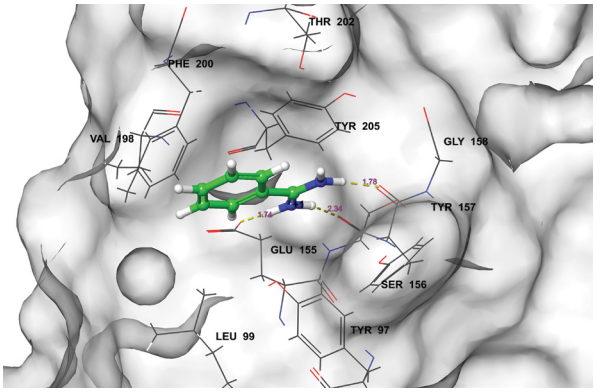


Figure 1: Binding mode of 4COF_ligand (Benzamidine) in the active site.

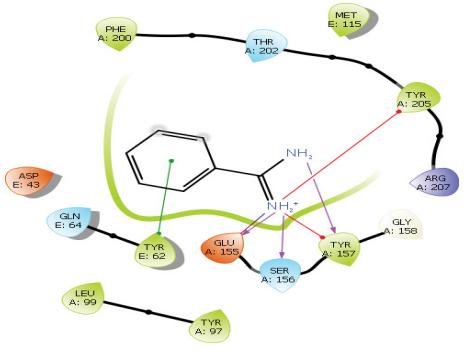


Figure 2: 2D interaction diagram of 4COF_ligand (Benzamidine) in the active site.

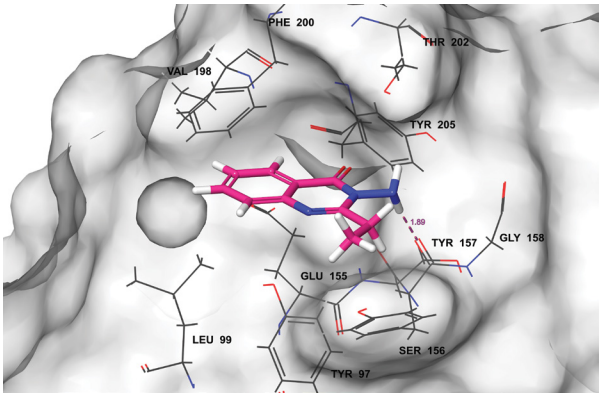


Figure 3: Binding mode of compound 4j in the active site.

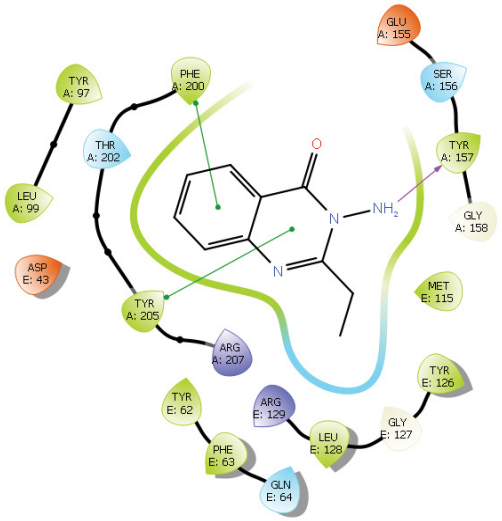


Figure 4: 2D interaction diagram of compound 4j in the active site.

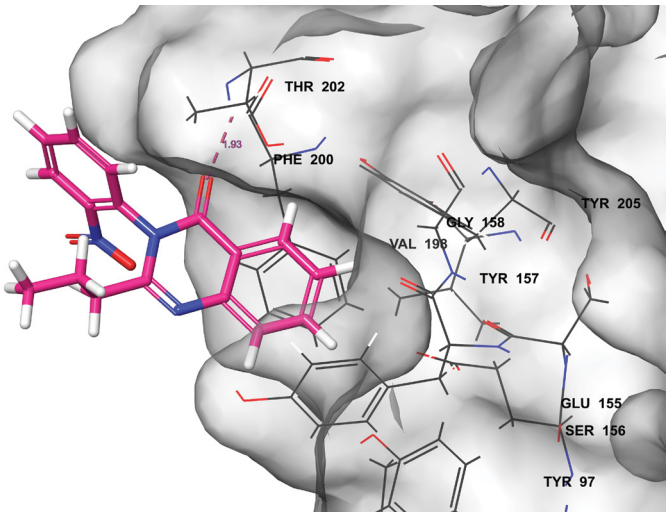


Figure 5: Binding mode of compound 4n in the active site.

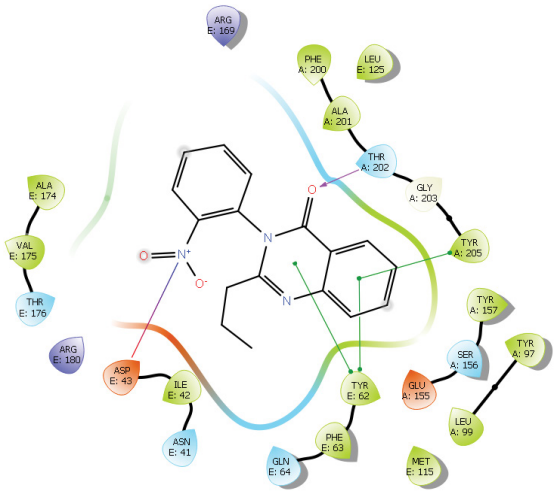


Figure 6: 2D interaction diagram of compound 4n in the active site.

Compound No.	Code	Docking score	MMGBSA dG Bind
4COF_ligand(Benzamidine)		-6.676	-37.498
1	4j	-5.426	-31.031
2	4m	-5.093	-36.68
3	4n	-5.083	-49.674
4	4i	-4.865	-58.602
5	4h	-4.06	-46.438
6	4l	-3.544	-50.011

Table 3: Docking results of the title compounds.

CONCLUSION

In conclusion, a series of 2, 3-disubstituted quinazolinone was synthesized by using microwave irradiation with reduction in reaction time, procedure simplicity, cleaner reaction, easy work up and improved yields. The title compounds were confirmed by IR, GC-MS and H^1 NMR. In our study, a molecular modeling based on hydrogen bond interaction was reported using docking studies. The docking studies revealed that the orientation and hydrogen bonding interactions of Quinazolinone moiety inside the active site of receptor site. Drug discovery is a challenging process due to complexity of biological systems, our study provides a structural hypothesis for the binding modes of new synthesized chemical entities the investigation of these binding models suggests that amino acid residues TYR A: 157, TYR A: 205, PHE A: 200 of the target GABA-A receptor play a key role in the binding of 2, 3-disubstituted quinazolinone. The results obtained will be helpful in designing of new series of drugs especially for the epilepsy or CNS related disorders.

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CONFLICT OF INTEREST

The authors have declared that this article content has no conflicts of interest.

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