



## Study, Docking, *In Silico* ADME and Bio-Evaluation of Novel Heter Aromatic Amino Acid Derivatives as Potential Anti-Epileptic Agents



Faez F. Alshehri<sup>1</sup>, Zafer S. Alshehri<sup>1</sup>, S. Alhajlah<sup>1</sup>, Nagwan M. Salama<sup>2</sup>,  
Zahra M. Alamshany<sup>3</sup>, Mohammed F. Arshad<sup>4</sup>, Ahmed F. Elkirdasy<sup>5</sup>, Allam A. Hassan<sup>6\*</sup>

<sup>1</sup>Department of Medical Laboratories, College of Applied Medical Sciences, Shaqra University, Shaqra 11961, Saudi Arabia

<sup>2</sup>Department of Medical Pharmacology, Faculty of Medicine, Cairo University, Egypt.

<sup>3</sup>Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah 21551, Saudi Arabia.

<sup>4</sup>Department of Research and Scientific Communications, Isthmus Research and Publishing House, U-13, Near Badi Masjid, Pulpehlah Pur, New Delhi 110044, India

<sup>5</sup>Department of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine, University of Sadat City, Sadat City, 32897, Egypt.

<sup>6</sup>Department of Chemistry, Faculty of Science, Suez University, Suez 43221, Egypt

### Abstract

A series of 1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid analogues (**Va-j**) were prepared, then tested for anticonvulsant efficacy. The analogues were tested using "gold standard procedures," which showed notable activity, particularly in chemically induced seizures. In the maximal electroshock seizure (MES) and the subcutaneous pentylenetetrazol (scPTZ) models, compounds **Vf**, **Ve**, **Vg**, and **Vc** were identified to be the most potent of the series. In order to assess motor damage, all synthetic analogues were also tested for acute neurotoxicity using the rotarod method. For the most part, all synthetic counterparts passed the test. The research also offers absorption, distribution, metabolism, and excretion (ADME) predictions for all 10 congeners produced and carefully analysed each parameter. Additionally, the  $\gamma$ -Aminobutyric acid-A (GABA-A) target protein was used in research on molecular docking. The results of molecular docking revealed significant interactions at the active site of GABA-A with Val B: 199, Arg A: 180, Phen B: 200, Ala B: 201 and Lys A: 173, and the outcomes were good and in agreement with *in vivo* findings. The compounds with electron donating group (EDG) at position 6 or unsubstituted analogues were found to be most active where as those with electron donating group have less activity. New anticonvulsant medications may be created as a result of more research on these substances.

**Keywords:** Anticonvulsant activity; GABA-A; Indole; *In-silico*; Molecular Docking; Quinoline

### 1. Introduction

There are almost 50 million people living with epilepsy all over the world. Generalized onset (motor or absent), focal onset (which may involve anomalous behaviours, responsiveness, feelings, or movements), and unknown onset are the three main categories used in the current classification of seizure types, as outlined by the International League Against Epilepsy [1,2]. Seizures are defined as disruptions in neurologic function resulting from

anomalous neuronal signalling in the brain. Despite the availability of numerous antiepileptic drugs (AEDs), it is widely acknowledged that approximately one-third of people with epilepsy do not attain satisfactory seizure control with existing medications [3-5]. Moreover, in cases of status epilepticus, which is characterized by abnormally prolonged seizures, neuronal mortality, neuronal injury, and alterations to neuronal networks can be

\*Corresponding author e-mail: Allam.hassan@sci.suezuni.edu.eg

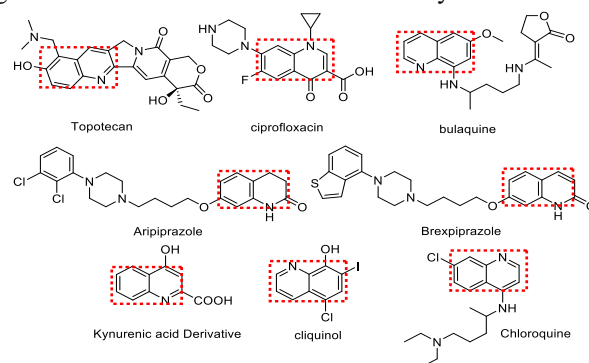
Receive Date: 03 September 2023, Revise Date: 22 September 2023, Accept Date: 04 October 2023

DOI: 10.21608/EJCHEM.2023.232868.8534

©2024 National Information and Documentation Center (NIDOC)

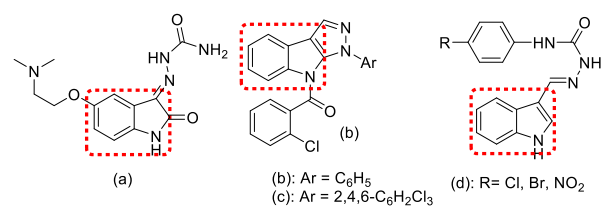
fatal, depending on the type and duration of the seizures. Recent estimates by the World Health Organization (WHO) suggest that the global epilepsy population is around 50 million, with nearly 80% of those affected living in low or middle-income countries. If appropriately diagnosed and treated, studies show that as many as 70 % of people with epilepsy can have seizure-free lives [6]. Thus, there is a significant unmet clinical need to find adequate and effective treatment of especially pharmaco-resistant epilepsy. There is still a concern with selectivity and toxicity among the currently available AEDs medications. Therefore, there is always a demand for improved anticonvulsant drugs that have fewer risks. The development of new anticonvulsant medicines is impeded by our limited understanding of the complex mechanisms underlying epilepsy (e.g., the modification of voltage-dependent Na<sup>+</sup> and/or Ca<sup>2+</sup> channels, the augmentation of inhibition mediated by  $\gamma$ -aminobutyric acid, which is popularly known as GABA or the other impact on the GABA system, the reduction of synaptic excitement mediated by ionotropic glutamate receptors, and the modification of synaptic release). Many synthetic nitrogen heterocycles have been shown to have useful pharmacological effects, making this class of molecules very important. Nitrogen-containing heterocycles include quinoline, pyrrole, indole, pyridine, pyrrolidine, triazole, oxadiazole, thiadiazole, triazines, pyrimidines, and quinazolines. It used to be widely believed that the structure of many anticonvulsant medications was composed of nitrogen-containing heterocycles, mainly lactam or imides joined by phenyl or alkyl groups [7,8]. The derivatives of quinolines have shown excellent results and have tremendous biological properties such as anticancer, antibacterial, antifungal, anthelmintic, antiprotozoal, cardiotoxic, anticonvulsant, antitubercular, antiinflammatory, analgesic or antimalarials [9]. Quinoline has main role in anticonvulsant drug development lead in the field of pharmaceutical prospective. Some novel quinoline derivatives have shown good anticonvulsant activity which are Food and Drug Administration (FDA) approved and some natural molecules have quinoline ring with hypnotic action. These drugs are used clinically for their anxiolytic, hypnotic,

muscle-relaxant and anticonvulsant actions. They act allosterically to influence central  $\gamma$ -aminobutyric acid (GABA)-mediated neurotransmission. Kynurenic acid derivatives analogue 4-urea-5,7-dichlorokynurenic acid has also been screened in mice for anticonvulsant activity. It stimulates the ion exchange channels to activate the discharge of neurotransmitters including serotonin (5-HT) and  $\gamma$ -aminobutyric acid (GABA) into the mesolimbic area, the corpus striatum, and the frontal cortex which contains quinoline scaffold [10-12]. Some drugs having quinoline moiety available in market are Aripiprazole and Brexpiprazole (Fig 1) which shows the importance of quinoline nucleus as maximum of them are used in central nervous system CNS related disorders. Many fused and other derivatives of quinoline also show anticonvulsant activity. Other derivative shown in figure have excellent anticonvulsant activity.



**Fig.1.** Drugs containing Quinoline moiety

The importance of indole nucleus as anticonvulsant and in epilepsy is also reported by many authors. Swathi et al (2017) synthesized a series of indole semicarbazole derivatives and evaluated for anticonvulsant activity by MES method and they reported compound **a**, to be active (Fig. 2). Also, compound **b**, **c** and **d** are indole derivatives reported to have anticonvulsant activity [13-16]. **Fig.2.** Compounds containing Indole nucleus.



**Fig.2.** Compounds containing Indole nucleus

Based on previous findings, the current study seeks to identify chemicals that are active in the standard MES or scPTZ assays. We have attempted to develop a series of 10 compounds with indole and quinoline system as a key scaffold. In order to qualitatively assess their anticonvulsant capabilities, all synthesized substances were submitted to a molecular docking analysis to ascertain their affinity to bind with ligand-gated ion channel (GABA-A) receptors. The data obtained from molecular docking were correlated with those obtained from biological screening.

## 2. Materials and methods

### 2.1 Experimental section

#### 2.1.1 Synthesis methods

All the reagents/chemicals used in the study were taken from Merck Chemicals (Bangaluru, India). Melting points of compounds were obtained using Hicon melting point apparatus were noted as having exposed capillary tubes and being incorrect. To determine how pure the copies were, silica gel G thin-layer chromatography (TLC) plates were employed. Iodine fumes and UV light were used as detecting reagents. In order to get the FTIR Spectra, a Shimadzu FTIR spectrophotometer was used. NMR study of compounds was done with Bruker DRX-300 and 400 MHz ( $^1\text{H}$  at 300 and 400 MHz and  $^{13}\text{C}$  at 100 MHz). Tetramethylsilane (TMS) is used as a comparative internal standard, and chemical changes ( $\delta$ ) are expressed in parts per million (ppm), while  $J$  values (coupling constants) are expressed in hertz (Hz). The mass of the developed chemical was measured using a mass spectrometer (Applied Biosystems; API-3000), and the result is given in daltons. C, H, and N elemental analysis of synthetic derivatives was performed using a Perkin-Elmer (240C analyzer).

#### 2.1.2. Synthesis of 3-(1H-indol-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one derivatives (IIa-IIj)

Equimolar amount of (0.1 M) 1H-indole-3-carbaldehyde and 1-(naphthalen-2-yl)ethan-1-one derivatives (Ia-Ij) was dissolved in ethanol, and added 1 ml of 40 % NaOH solution to the mixture. The mixture was stirred at room temperature for 12 hours. The resultant reaction mixture was placed onto a bed of crushed ice, and the pH was adjusted using diluted HCl to 7. The resulting solid was

filtered, rinsed, and dried. Pure chalcones were obtained by crystallizing the crude product in ethanol. The purity and rate of the reaction were analyzed by thin-layer chromatography (TLC) employing toluene: ethyl acetate: formic acid (5:4:1) v/v.

#### 2.1.3. Synthesis of 3-(1H-indol-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-ol derivatives (IIIa-IIIj) from (IIa-IIj)

To a solution of (IIa-IIj) derivatives product (0.01 mol) in absolute methanol, 0.46 g (0.012 mol) of solid sodium borohydride was added over 30 minutes while stirring constantly at ambient temperature. The residue has been triturated with water after the solvent was evaporated under reduced pressure, and the crystalline product had been filtered, washed, and dried. Methanol was used to recrystallize the object. To assess the rate of reaction and compound purity, TLC was used with a mobile phase made of benzene: acetone (8:2) v/v.

#### 2.1.4. Synthesis of 3-(3-chloro-3-(naphthalen-2-yl)prop-1-en-1-yl)-1H-indole derivatives (IVa-IVj) from (IIIa-IIIj)

1.54 g (0.013 mol) of  $\text{SOCl}_2$  were added to a compound (IIIa-IIIj) solution in dry toluene that contained 0.01 mol, and the combination was then refluxed for four hours. The solvent was evaporated at a decreased pressure, and the leftover material was dissolved in ether before being twice washed with water and 10%  $\text{NaHCO}_3$ . A methanol-crystallized residue was produced when it was dried over  $\text{Na}_2\text{SO}_4$  and concentrated under a vacuum. TLC was used to purity of the compounds using acetone: benzene (2:8) v/v mobile phase.

#### 2.1.5. Synthesis of target derivatives of 1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Va-Vj) (Quinoline derivatives)

To a mixture of compound (IVa-IVj) of 0.003 mol and 1,4-dihydroquinoline-4-carboxylic acid (0.003 mol) in 20 ml of absolute ethanol, 1 ml of triethylamine (TEA) was added and refluxed for 12–15 h. After completion of the reaction, content of the flask reduced to half and left overnight. The crystalline mass obtained was filtered off, washed with water, dried, and recrystallized from ethanol to give final compound.

**(E)-1-(1-(6-chloronaphthalen-2-yl)-3-(1H-indol-3-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Va)**

Yield: 52%; mp 142 °C; IR (KBr) (cm<sup>-1</sup>): 3376 (NH), 1720 (C=O acid), 1239 (C-N), 860 (C-Cl); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.12 (s, 1H, COOH), 11.96 (s, 1H, NH indole), 7.08-7.80 (m, 11H, CH aromatic), 6.66 (dd, 1H, CH), 5.83 (d, 1H, CH), 4.42 (d, 1H, CH), 6.36-6.60 (m, 8H, CH quinoline) <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 183.8, 136.3, 131.6, 130.7, 128.9, 126.1, 110.6, 102.7, 71.5, 42.3; ESI MS (m/z): 491 [M+H]; Anal. Calculated for C<sub>31</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 75.84; H, 4.72; Cl, 7.22; N, 5.71; O, 6.52; Found: C, 73.48; H, 4.81; Cl, 8.00; N, 6.37; O, 6.28%.

**(E)-1-(1-(6-bromonaphthalen-2-yl)-3-(1H-indol-3-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vb)**

Yield: 59%; mp 101 °C; IR (KBr) (cm<sup>-1</sup>): 3384 (NH), 1729 (C=O acid), 1233 (C-N), 746 (C-Br); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.70 (s, 1H, COOH), 11.92 (s, 1H, NH indole), 7.80-8.79 (m, 11H, CH aromatic), 6.5 (dd, 1H, CH), 5.91 (d, 1H, CH), 4.45 (d, 1H, CH), 6.59-7.23 (m, 8H, CH quinoline) <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 183.6, 135.3, 130.7, 129.5, 128.2, 125.0, 118.8, 110.1, 102.9, 71.2, 42.3; ESI MS (m/z): 536 [M+H]; Anal. Calculated for C<sub>31</sub>H<sub>23</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 69.54; H, 4.33; Br, 14.92; N, 5.23; O, 5.98; Found: C, 70.50; H, 4.78; Br, 13.10; N, 5.17; O, 6.22%.

**(E)-1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vc)**

Yield: 59%; mp 126 °C; IR (KBr) (cm<sup>-1</sup>): 3250 (NH), 1724 (C=O acid), 1241 (C-N); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 11.76 (s, 1H, COOH), 11.96 (s, 1H, NH indole), 7.22-7.92 (m, 20H, CH aromatic), 6.62 (dd, 1H, CH), 5.87 (d, 1H, CH), 4.38 (d, 1H, CH); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 183.6, 135.3, 130.6, 129.5, 128.2, 125.0, 119.7, 110.1, 102.9, 71.2, 42.3; ESI MS (m/z): 457 [M+H]; Anal. Calculated for C<sub>31</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.56; H, 5.30; N, 6.14; O, 7.01; Found: C, 80.33.78; H, 4.96; N, 6.72; O, 6.92%.

**(E)-1-(1-(6-fluoronaphthalen-2-yl)-3-(1H-indol-3-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vd)**

Yield: 45%; mp 102 °C; IR (KBr) (cm<sup>-1</sup>): 3284 (NH), 1722 (C=O acid), 1244 (C-N), 1020 (C-F);

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.32 (s, 1H, COOH), 11.98 (s, 1H, NH indole), 7.76-8.65 (m, 11H, CH aromatic), 6.59 (dd, 1H, CH), 5.91 (d, 1H, CH), 4.38 (d, 1H, CH), 6.10-6.50 (m, 8H, CH quinoline) <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 181.6, 135.1, 130.4, 129.1, 128.2, 124.7, 119.5, 108.1, 103.2, 72.4, 43.3; ESI MS (m/z): 475 [M+H]; Anal. Calculated for C<sub>31</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>2</sub>: C, 78.46; H, 4.89; F, 4.00; N, 5.90; O, 6.74; Found: C, 76.84; H, 4.42; F, 3.42; N, 5.79; O, 6.54%.

**(E)-1-(3-(1H-indol-3-yl)-1-(6-methylnaphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Ve)**

Yield: 48%; mp 107 °C; IR (KBr) (cm<sup>-1</sup>): 3278 (NH), 2990 (CH stretch), 1726 (C=O acid), 1241 (C-N); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.64 (s, 1H, COOH), 11.96 (s, 1H, NH indole), 7.20-7.99 (m, 19H, CH aromatic), 6.66 (dd, 1H, CH), 5.83 (d, 1H, CH), 4.42 (d, 1H, CH), 3.81 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 183.8, 145, 137.11, 134.2, 132, 129.3, 127.4, 117.8, 110.6, 71.5, 42.3; ESI MS (m/z): 471 [M+H]; Anal. Calculated for C<sub>32</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.68; H, 5.57; N, 5.95; O, 6.80; Found: C, 81.95; H, 5.64; N, 5.39; O, 5.28%.

**(E)-1-(1-(6-ethylnaphthalen-2-yl)-3-(1H-indol-3-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vf)**

Yield: 55%; mp 110 °C; IR (KBr) (cm<sup>-1</sup>): 3264 (NH), 2860 (CH stretch), 1730 (C=O acid), 1482 (CH<sub>2</sub> bends), 1244 (C-N); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.2 (s, 1H, COOH), 11.94 (s, 1H, NH indole), 7.06-7.80 (m, 19H, CH aromatic), 6.98 (dd, 1H, CH), 5.89 (d, 1H, CH), 4.56 (d, 1H, CH), 3.90 (q, 2H, CH<sub>2</sub>), 2.90 (t, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 183.5, 144.2, 136.5, 134.0, 129.1, 127.5, 118.0, 110.2, 70.3, 41.1; ESI MS (m/z): 485 [M+H]; Anal. Calculated for C<sub>33</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.79; H, 5.82; N, 5.78; O, 6.60; Found: C, 80.87; H, 5.73; N, 5.33; O, 5.43%.

**(E)-1-(3-(1H-indol-3-yl)-1-(6-propylnaphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vg)**

Yield: 53%; mp 112 °C; IR (KBr) (cm<sup>-1</sup>): 3362 (NH), 2890 (CH stretch), 1724 (C=O acid), 1470 (CH<sub>2</sub> bend), 1239 (C-N); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.42 (s, 1H, COOH), 11.53 (s, 1H, NH indole), 7.12-7.93 (m, 19H, CH aromatic), 6.34 (dd, 1H, CH), 5.82 (d, 1H, CH), 4.39 (d, 1H, CH), 3.78 (t, 2H, CH<sub>2</sub>), 2.90 (m, 2H, CH<sub>2</sub>), 2.18 (t,

3H, CH<sub>3</sub>) <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 173.0, 157.1, 135.7, 132.0, 129.1, 127.5, 72.7, 55.8, 43.7; ESI MS (m/z): 499 [M+H]; Anal. Calculated for C<sub>34</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>: C, 81.90; H, 6.06; N, 5.92; O, 6.42; Found: C, 80.23.48; H, 5.32; N, 5.37; O, 5.28%.

**(E)-1-(3-(1H-indol-3-yl)-1-(6-nitronaphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vh)**

Yield: 61%; mp 143 °C; IR (KBr) (cm<sup>-1</sup>): 3370 (NH), 1719 (C=O acid), 1243 (C-N), 1480, 1312 (NO stretching asymmetric and symmetric); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.38 (s, 1H, COOH), 11.49 (s, 1H, NH indole), 7.32-8.00 (m, 11H, CH aromatic), 6.18 (dd, 1H, CH), 5.62 (d, 1H, CH), 4.44 (d, 1H, CH), 6.25-6.90 (m, 8H, CH quinoline); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 173.2, 157.2, 135.9, 132.2, 129.5, 128.1, 72.5, 55.3, 43.5; ESI MS (m/z): 502 [M+H]; Anal. Calculated for C<sub>31</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: C, 74.24; H, 4.62; N, 8.38; O, 12.76; Found: C, 73.01; H, 3.61; N, 7.47; O, 11.08%.

**(E)-1-(3-(1H-indol-3-yl)-1-(6-methoxynaphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vi)**

Yield: 47%; mp 107 °C; IR (KBr) (cm<sup>-1</sup>): 3376 (NH), 3062 (CH stretch), 1720 (C=O acid), 1239 (C-N), 1210 (C-O); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.32 (s, 1H, COOH), 11.89 (s, 1H, NH indole), 7.72-8.20 (m, 11H, CH aromatic), 6.18 (dd, 1H, CH), 5.72 (d, 1H, CH), 4.52 (d, 1H, CH), 6.21-7.10 (m, 8H, CH quinoline), 3.66 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 172.9, 142.0, 134.8, 132.3, 126.8, 121.7, 118.6, 112.0, 72.8, 44.5, 21.3; ESI MS (m/z): 487 [M+H]; Anal. Calculated for C<sub>32</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>: C, 78.99; H, 5.39; N, 5.76; O, 9.86; Found: C, 77.48; H, 4.81; N, 4.62; O, 8.64%.

**(E)-1-(1-(6-ethoxynaphthalen-2-yl)-3-(1H-indol-3-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid (Vj)**

Yield: 49%; mp 109 °C; IR (KBr) (cm<sup>-1</sup>): 3369 (NH), 3111 (CH stretch), 1718 (C=O acid), 1450 (CH<sub>2</sub> bend), 1242 (C-N), 1205 (C-O); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 12.39 (s, 1H, COOH), 11.72 (s, 1H, NH indole), 7.82-8.11 (m, 11H, CH aromatic), 6.13 (dd, 1H, CH), 5.71 (d, 1H, CH), 4.49 (d, 1H, CH), 6.82-7.30 (m, 8H, CH quinoline), 3.98 (q, 2H, CH<sub>2</sub>), 3.10 (t, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ(ppm): 171.7, 142.1, 133.3, 126.9, 121.5, 118.8, 112.1, 72.6, 44.3, 21.5; ESI MS

(m/z): 501 [M+H]; Anal. Calculated for C<sub>33</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>: C, 79.18; H, 5.64; N, 5.60; O, 9.59; Found: C, 77.91; H, 4.72; N, 4.72; O, 7.73%.

## 2.2. Pharmacology

### 2.2.1. Anticonvulsant action assessment

Every step of the animal handling process, including sample administration and disposal, was followed as per Institutional Animal Care and Use Committee (IACUC) regulations, Faculty of veterinary medicine, University of Sadat City, with approval number VUSC-050-1-2023.

The experimental animals used were male albino mouse weighing 25-30g. For MES and scPTZ screening, test compounds were suspended in PEG 200. In a typical laboratory setting, six animals per cage were kept at room temperature with unfettered access to food and water.

#### 2.2.1.1. Maximal Electroshock Seizure (MES) Test

Test compounds at a dose level of 30, 100 and 300 mg/kg were administered as an intraperitoneal (i.p.) injection to measure the anticonvulsant effect at a different time interval (0.5 h and 4h). The most severe electroshock seizures in mice were induced utilising ear clip electrodes and 0.2 seconds of 60Hz, 50 mA electrical shocks. Protection is defined as the absence of the tonic extensor component of seizures in 50% or more of the animals [14].

#### 2.2.1.2. Subcutaneous Pentylentetrazole (scPTZ) Seizure Test

To determine which chemicals raise the threshold for seizures, the scPTZ is utilized. Pentylentetrazole is used in the scPTZ test at a dose of 85 mg/kg. In 97% (CD97) of the tested animals, this results in clonic convulsions lasting at least five seconds. Each animal received intraperitoneal doses of 30, 100, and 300 mg/kg of the test chemicals. PTZ was given subcutaneously at 0.5 h and 4.0 h, and the animals were watched for 30 minutes. The lack of clonic seizures in 50% or more of the animals over the specified time period served as a measure of the ability of synthesized analogues to counteract pentylentetrazole's influence on the seizure threshold [15].

## 2.2.2. Neurotoxicity study

### 2.2.2.1 Rotarod test

The rotarod test was used to assess the motor function of rodents. During the experiment, mice were taught to stay on a revolving rod with a diameter of 3.2 cm and a rotational speed of 10 revolutions per minute (RPM). The animal's failure to stay balanced on the rotating rod for at least one minute is used in all three trials to determine the level of neurotoxicity. The dosage at which fifty percent of the animals lost their ability to balance on the rotating rod was identified [15,16].

### 2.2.2.2 Ethanol Potentiation Test

Test compounds were given to mice. One hour later, the dose of 2.5 g kg<sup>-1</sup> of ethanol was administered to test animals except for control animals. In control animals, there won't be any lateral positioning brought on by ethanol. After being given ethanol, the number of animals in each group that were in the lateral posture was counted [16].

## 2.3. Molecular docking studies and ADME prediction

In order to assess the ADME characteristics of synthesized compounds, pre-ADMET software was employed. A number of characteristics were examined, including Human Intestinal Absorption (HIA), Log P, Plasma Protein Binding (PPB), Blood-Brain Barrier Penetration (BBB), and Skin Permeability (SP).

Molecular docking was performed using the AutoDock Vina software to determine the probable orientation and confirmation of the ligand at the binding site. Chem draw software (Cambridge Soft) was used to depict the structures of pyrrolidine analogues (5a-j) that were synthesized. The 2D structures were converted to 3D using Chem3D Ultra 8.0 software.

The GABA(A)R-beta3 homopentamer (code 4COF), the X-ray crystal structure of the GABA-A receptor, was found in the Protein Data Bank (PDB). With the help of the protein preparation wizard, UCSF Chimera 1.15 was used to prepare the protein. The protein was entered into the PyRx program, which produced a PDBQT file with the

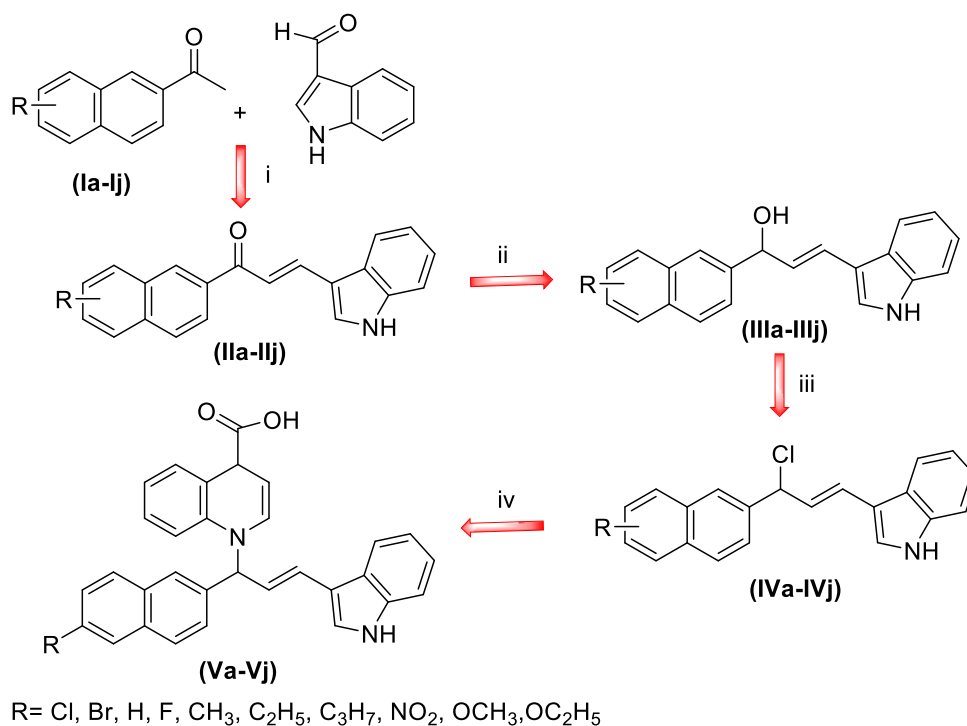
protein's structure and hydrogen atoms in each of its polar residues. For calculation, the Lamarckian Genetic Algorithm (LGA) approach was utilized.

After the completion docking search, the best conformation with the lowest docked energy was chosen. For each ligand structure, ten AutoDock Vina runs were performed and the best pose was captured and saved for each run. Discovery studio 3.5 investigated protein-ligand conformation interactions. The affinities of the molecule at the receptor's active site were determined using the docking score, pi-pi interactions and hydrogen bonds.

## 3. Results and Discussion

### 3.1. Chemistry

The work reported here explains the synthesis and characterization of substituted 1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid analogues. Simultaneously, these newly synthesized compounds were evaluated for anticonvulsant activities and molecular docking studies were also performed. A total 10 number of substrates were synthesized according to the synthetic procedure described in **Scheme 1**. **Table 1** presents the results of an investigation into various physicochemical properties. Utilizing compounds that had been crystallized and isolated with an appropriate solvent, these novel analogues were characterized with the use of NMR and IR spectroscopical data. New product elemental analyses were also carried out. N-H, C=O, and C-N stretching bands were visible in the region of 3376-3270 cm<sup>-1</sup>, 1730-1720 cm<sup>-1</sup>, and 1243-1239 cm<sup>-1</sup>, respectively, in IR measurements. Using TMS as an internal standard, the <sup>1</sup>H NMR spectrum data of the compounds were collected in CDCl<sub>3</sub>/DMSO-d<sub>6</sub> solvent. These newly developed products revealed Ar-H in the range of 7.08–8.65 ppm with various EDG and EWG replacements, a singlet for COOH in the range of 11.76–12.64 ppm, and a singlet for N-H in the range of 11.49–11.98. The region between 171.7 and 183.8 ppm was where the carbonyl carbon at pyridine reached its highest. In elemental analysis, observed data for C, H, N were within the limits of theoretical values.



**SCHEME 1-** Synthesis of analogs of 1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid. Reagents and parameters include (i) Methanol, agitation; (ii) NaOH, EtOH; reflux; (iii) neutralizing processes by diluted HCl; and (iv) EDC-HCl, HOBT, DMF, triethylamine, stirring for about 12–15h, water, brine, sodium sulfate, ethyl acetate used for recrystallization.

**Table 1.** Physicochemical properties of prepared analogs (Va-Vj)

Analog	-R	Formulae	Mol. Wt.	Yield %	M.P. (°C)	R <sub>f</sub> <sup>*</sup>	Physical state
Va	6-Cl	C <sub>31</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>2</sub>	490.98	52	142	0.53	Off white (Solid)
Vb	6-Br	C <sub>31</sub> H <sub>23</sub> BrN <sub>2</sub> O <sub>2</sub>	535.44	59	101	0.41	White (Powder)
Vc	6-H	C <sub>31</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub>	456.18	59	126	0.65	Yellowish-white(Solid)
Vd	6-F	C <sub>31</sub> H <sub>23</sub> FN <sub>2</sub> O <sub>2</sub>	474.53	45	102	0.40	Yellow (Powder)
Ve	6-CH <sub>3</sub>	C <sub>32</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	470.57	48	107	0.72	Cream (Solid)
Vf	6-C <sub>2</sub> H <sub>5</sub>	C <sub>33</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	484.59	55	110	0.79	Cream (Solid)
Vg	6-C <sub>3</sub> H <sub>7</sub>	C <sub>34</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub>	498.62	53	112	0.83	White (Solid)
Vh	6-NO <sub>2</sub>	C <sub>31</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub>	501.54	61	143	0.56	Off white (Powder)
Vi	6-OCH <sub>3</sub>	C <sub>32</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	486.19	47	107	0.59	White (Solid)
Vj	6-OC <sub>2</sub> H <sub>5</sub>	C <sub>33</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	500.59	49	109	0.61	Off white (Crystal)

\* Formic acid: ethyl acetate: toluene (1:4:5)-solvent system used

### 3.2. Pharmacological Assessment

Numerous pharmacological studies were carried out in line with the Anticonvulsant Drug Development (ADD) program's standard operating procedure. Studies on the compound's neurotoxicity were also carried out. The analysis techniques comprised scPTZ, MES, and neurotoxicity (Tox).

The anticonvulsant activity of the synthesized analogues was calculated at intervals of 0.5 and 4 hours after injections given intraperitoneally (i.p.) at doses of 30, 100, and 300 mg/kg. Neurotoxicity was evaluated using the rotarod test and ethanol potentiation.

**Table 2** contains the findings of the anticonvulsant and neurotoxicity data.

All molecules in the Maximal Electroshock (MES) model showed electroshock protection after 0.5 hours with **Vf** at a dose of 30 mg/kg, indicating a rapid beginning of action. At 100 mg/kg for 0.5 hours, molecules **Vc**, **Vd**, **Ve**, **Vg**, and **Vi** produced favorable outcomes. Molecules **Ve**, **Vf** and **Vg** demonstrated good activity at a dose of 100 mg/kg at the interval of 4.0 h, indicating that the analogues have a prolonged half-life at a moderate dose. Phenytoin and carbamazepine were the usual medications utilized.

Compounds **Vc**, **Ve**, **Vf**, **Vg**, **Vi** and **Vj** were found to exhibit action at 100 mg/kg at 0.5 h in the scPTZ model. At 100 mg/kg after 4.0 hours, compounds **Ve** and **Vf** were protective. When the neurotoxicity of the compounds was tested, the majority produced negative results. Only compound

**Vh** and **5j** were discovered to be neurotoxic at 0.5 and 4 hours, respectively.

Of all the synthetic compounds, compounds **Vf**, **Ve** and **Vg** were shown to be the most powerful and to function as specific GABA mediators. The compounds in the MES and scPTZ studies either showed no action or had no distinguishing characteristics.

According to the SAR investigations, molecules having electron-donating group substitutions (EWG) at position 6 of aryl ring appeared most potent compounds amongst the series. The compound **Vf** was discovered most potent in scPTZ screening and MES, has a EDG (-C<sub>2</sub>H<sub>5</sub>) at the 6<sup>th</sup> position. **Ve** and **Vg** has EDG (-CH<sub>3</sub> and C<sub>2</sub>H<sub>5</sub>) at 6<sup>th</sup> position. Compounds with EWG at 6<sup>th</sup> position were found to be less active. Even the unsubstituted compound (**Vc**) was found to be potent.

**Table 2.** Data on analogues (**Va-j**)'s neurotoxicity and anticonvulsant screening

Compound Number	Mice receiving an intraperitoneal/subcutaneous injection <sup>a</sup>						
	MES assessment		scPTZ assessment		Neurotoxicity assessment		Ethanol
	0.5 hr	4.0 hr	0.5 hr	4.0 hr	0.5 hr	4.0 hr	Potentiation
<b>Va</b>	300	300	300	300	X	X	X
<b>Vb</b>	300	300	300	300	-	-	-
<b>Vc</b>	100	300	100	300	X	X	X
<b>Vd</b>	100	300	300	300	-	-	-
<b>Ve</b>	100	100	100	100	-	-	-
<b>Vf</b>	30	100	100	100	-	-	-
<b>Vg</b>	100	100	100	300	-	-	X
<b>Vh</b>	300	300	300	300	+	+	-
<b>Vi</b>	100	300	100	300	-	-	X
<b>Vj</b>	300	300	100	300	+	+	-
Phenytoin	30	30	-	-	100	100	-
Carbamazepine	30	100	100	300	100	300	-

<sup>a</sup>A dose of 30, 100, and 300 mg/kg body weight of the newly synthesized molecules were administered to mice. After 0.5 and 4 hours, the protective effect and neurotoxicity were studied. The results showed how much of a minimum dose of new molecule was needed to protect 50% or more of the animals or cause neurotoxicity in at least 50% of them. The dash (—) meant that neither neurotoxicity nor anticonvulsant action was present in these compounds. X— means that it was not analyzed. <sup>b</sup>Ethanol potentiation test: (+) means that at least more than half of the animals had positive results; (–) means that at least half or more of the animals had negative results. X— stands for "not tested."



### 3.2.1. ADME Prediction

On the designed compounds, ADME prediction was performed, and the outcomes are presented shown in Table 3. It was feasible to determine whether a certain substance might pass through the BBB by examining BBB penetration. The values that were found also helped to reduce side effects and toxins, and they may have made drugs that had a psychological effect on the brain work better. Almost all of the targets that were looked at had positive values, which shows that they could easily cross the BBB. **Vg** and **Vf** has the highest value, 12.711 and 11.2171, that implies it is the most active. The process through which oral medications entered the circulation from the GIT is known as HIA. The results for the synthesized compounds were above 95%, which shows that they are well-absorbed compounds that can also be taken by the human intestine. PPB can alter a drug's effectiveness as well as how long a substance stays in the body. The amount of binding to plasma proteins has a big effect on how a drug works and how it moves through the body. As previously indicated, a percent bound value below 90 was regarded as low, and a value above 90 was seen as high.

As demonstrated, every synthetic chemical exhibited strong affinity for a plasmatic protein with a value greater than 90%, and compounds **Va**, **Vb**, **Vc**, **Vd**, **Vf** and **Vg** all had a value of 100%. Also, the way the drug is spread out depends a lot on how well it binds to proteins in plasma. For drugs that

are given through the skin, the SP rate is one of the most important factors. It is known that the way the drug moves into the lipid tissue between cells is an important part of how the skin absorbs the drug. All the compounds that were tested failed the SP check, showing that they can't be directed through the skin. The Log P numbers show how likely it is that the compound will be able to get to the target tissue in the body. Because  $\text{Log P} > 0$  (or  $P > 1$ ), the analogues that were tried were lipophilic. With a Log P of 8.536850 and 8.082880, **Vg** and **Vf** were the most lipophilic.

### 3.2.2. Molecular docking

Molecular docking studies were done to find out how the synthesized analogues (**Va–j**) might bind and how much energy they would need to do so. This helped to find the potential leads. The docking scores of the possible chemicals that were tested against the GABA-A receptor ranged from -9.3 to -9. **Figure 3** shows the docking images of all the compounds **Va–Vj** that were synthesized. **Table 4** shows the results of docking in form of scores of derivatives (**Va–j**) with GABA-A (4 COF).

From the docking studies, **Vf** was found to be most active with a score of -10.7. The residue Val B:199 was found to be involved in conventional hydrogen bonding with carboxyl group of compound at a distance of 4.96 Å respectively. Pi-cation interaction of aromatic ring of quinoline was observed with Arg A:180 at a distance of 6.91 Å.

**Table 3.** ADME prediction of synthesized derivatives

Compd	(R)	LogP	<sup>a</sup> BBB	<sup>b</sup> BS (mg/l)	CYP-inhibition	<sup>c</sup> HIA	<sup>d</sup> PPB	<sup>e</sup> SP
<b>Va</b>	6-Cl	7.876550	10.3584	0.305352	2D6 non inhibitor	95.350194	100	-2.17252
<b>Vb</b>	6-Br	7.993950	10.6343	0.137946	2D6 non inhibitor	95.372014	100	-2.23638*
<b>Vc</b>	6-H	7.166250	8.05691	0.875551	2D6 non inhibitor	95.287569	100	-2.19377
<b>Vd</b>	6-F	7.342130	8.77874	0.979054	2D6 non inhibitor	95.290578	100	-2.22794
<b>Ve</b>	6-CH <sub>3</sub>	7.691460	9.7629	0.368141	2D6 non inhibitor	95.309496	99.793323	-2.01181
<b>Vf</b>	6-C <sub>2</sub> H <sub>5</sub>	8.082880	11.2171	0.205679	2D6 non inhibitor	95.328636	100	-1.91147
<b>Vg</b>	6-C <sub>3</sub> H <sub>7</sub>	8.536850	12.711	0.104156	2D6 non inhibitor	95.345237	100	-1.82958
<b>Vh</b>	6-NO <sub>2</sub>	7.212270	0.451481	0.0999139	2D6 non inhibitor	96.478717	99.948210	-2.52391*
<b>Vi</b>	6-OCH <sub>3</sub>	7.161350	5.46832	0.483865	2D6 non inhibitor	95.690591	97.014309	-2.14717
<b>Vj</b>	6-OC <sub>2</sub> H <sub>5</sub>	7.532690	6.59262	0.238126	2D6 non inhibitor	95.709855	94.827492	-2.03888

<sup>a</sup>Blood brain barrier, <sup>b</sup>Buffer solubility, <sup>c</sup>Human Intestinal Absorption, <sup>d</sup>Plasma Protein Binding, <sup>e</sup>Skin Permeability

Pi-Pi stacked interactions were seen with aromatic ring system of naphthalene with Phe B:200 at a distance of 4.07 and 4.50 Å. Also, Pi-alkyl interactions of indole moiety of compound were observed with Ala B:201 and Lys A:173 at a distance of 4.95 and 6.01 Å. Vander Waal's interaction were seen with Gly A: 177, Thr A: 176, Val B: 198, Tyr B:97 and Glu B: 155.

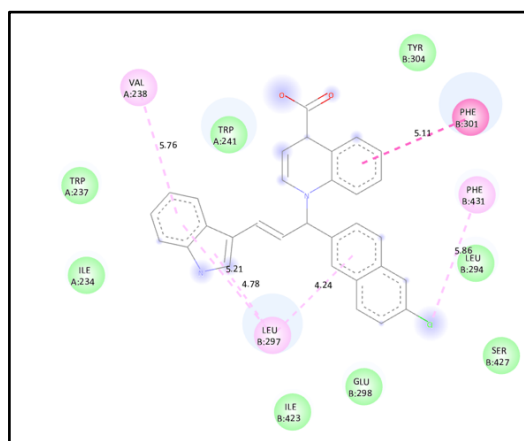
Hydrogen bonding was also seen for carboxyl group with Val B:199 at a distance of 4.49 Å for compound **Ve**, that is the second most active compound as predicted from docking score. Pi-cation interactions of the compound were observed with Arg A:180 with a distance of 7.21 Å. Also, Pi-alkyl interactions with Ala B:201 and Lys A: 173 were observed at a distance of 4.85 and 5.90 Å respectively which are similar as for compound **Vf**. Similarly, Pi-stacked interactions were observed with Phe B:200 at a distance of 4.02 and 4.57 Å respectively. The compound **Vg** and compound **Vc**, both with same docking score of -10 were also found to have some common interactions like Pi-Pi stacked interaction of aromatic quinoline ring with Phe B:301 at a distance of 5.02 Å for compound **Vg** and at distance of 4.5 and 4.08 Å for **Vc**.

Pi-alkyl interactions were found in both compounds, for **Vc** it was found to interact with Val B:430 and Phe B:431, for **Vg** it was found to interact with Val B:430, Phe B:431 and Leu B:297.

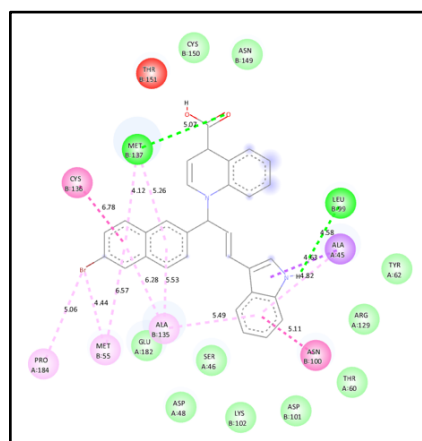
The study of pattern of docking in synthesized molecules **Va-j** represented that Pi-alkyl, Pi-cation and hydrogen bonding is the major binding source for the synthesized compound the receptor. The most active compounds **Vf**, **Ve** and **Vg** have methyl, ethyl and propyl group at position 6, thus signifying that if position 6 has ethyl as substituent, then it is most active.

The important amino acid residues involved are found to be Val B:199, Arg A:180, Phe B:200, Ala B:201 and Lys A:173 which served as a conduit for the ligand's access to the GABA-A receptor.

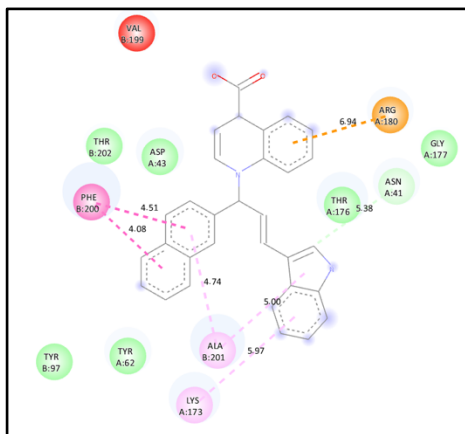
According to evidence from *in-silico* experiments, adding an electron-donating substituent to an aryl ring at position 6 can considerably boost GABA levels and, consequently, anticonvulsant action. The results correspond to those from the animal model. Thus *in silico* and biological activity result demonstrated activity in the following order:  $C_2H_5 > CH_3 > C_3H_7$ .



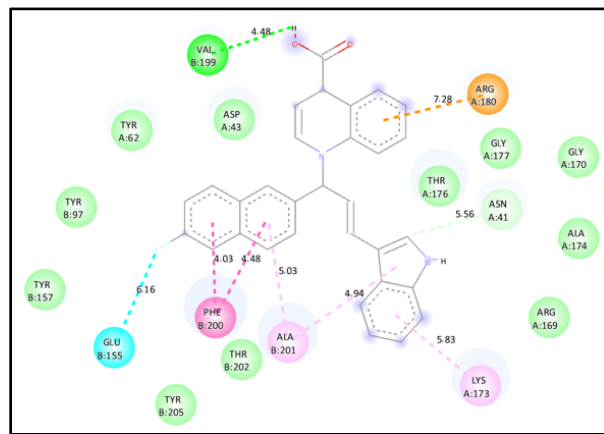
(Va)



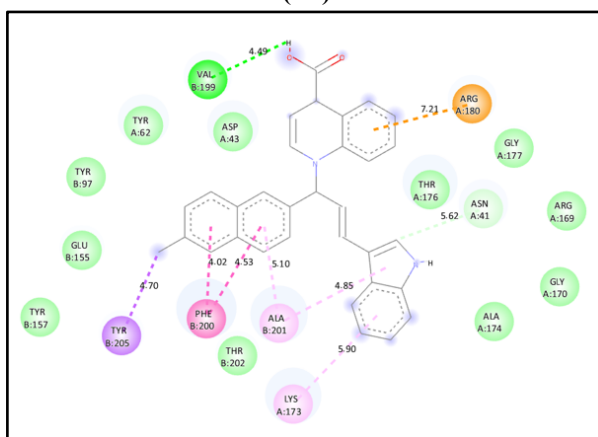
(Vb)



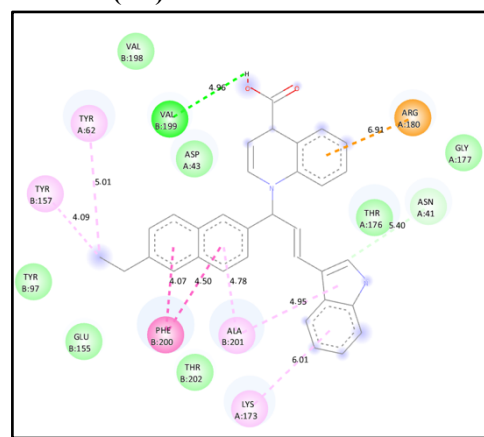
(Vc)



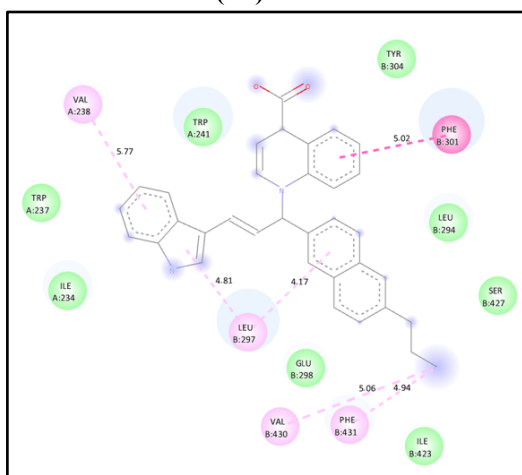
(Vd)



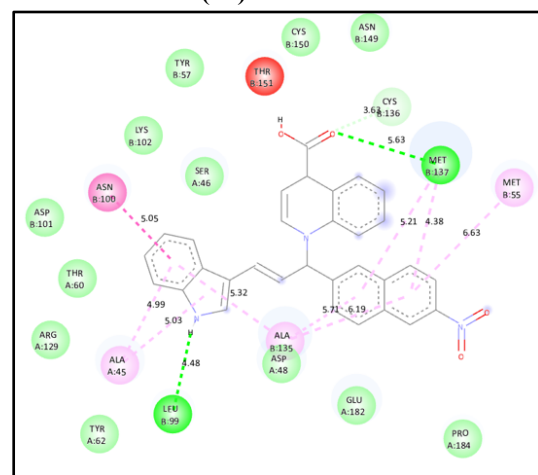
(Ve)



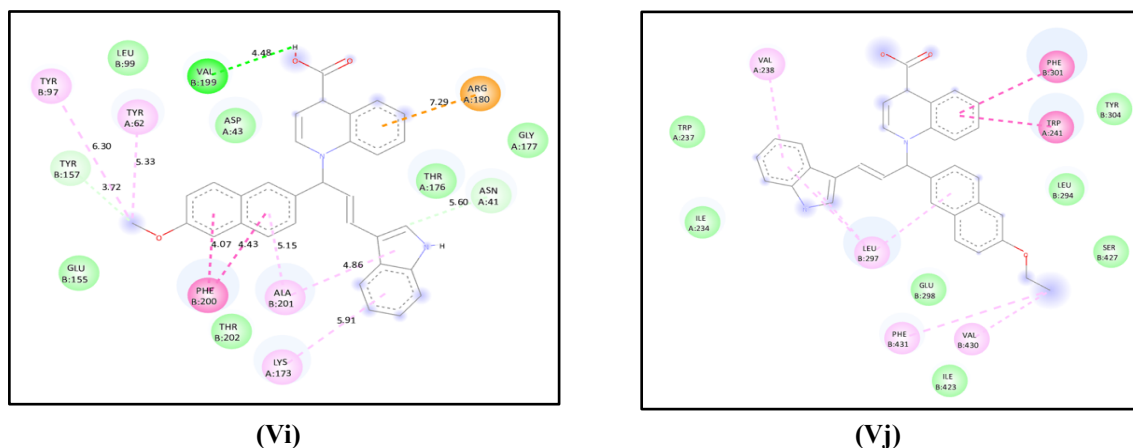
(Vf)



(Vg)



(Vh)



**Fig. 3.** 2D Ligand interaction of compound Va-Vj

**Table 4.** Results of Docking of final analogues (Va-Vj) with the GABA-A receptor, 4COF

S.No.	Derivative	Ligand	Binding Affinity
1	Va	4cof_uff_E=529.60	-9.7
2	Vb	4cof_uff_E=529.22	-9.5
3	Vc	4cof_uff_E=530.38	-10.2
4	Vd	4cof_uff_E=529.31	-9.8
5	Ve	4cof_uff_E=551.38	-10.3
6	Vf	<b>4cof_uff_E=534.31</b>	<b>-10.7</b>
7	Vg	4cof_uff_E=539.93	-10.2
8	Vh	4cof_uff_E=545.94	-9.4
9	Vi	4cof_uff_E=558.77	-10
10	Vj	4cof_uff_E=583.04	-9.3

#### 4. Conclusion

In the current study, 1-(3-(1H-indol-3-yl)-1-(naphthalen-2-yl)allyl)-1,4-dihydroquinoline-4-carboxylic acid analogues (Va-j) were synthesized and evaluated for their anticonvulsant activity using MES and scPTZ model. The series of fused derivatives were found to be active for anticonvulsant activity. Compounds **Vf**, **Ve**, **Vg** and **Vc** were revealed to be extremely effective throughout the series against both types, with a rapid start to the attack. As a result, it is hypothesized that these four compounds are those GABA facilitators who are most active and selective. The neurotoxicity test was passed successfully by every compound in the series except for compound **Vh** and **Vj**, that was discovered to be neurotoxic. In addition, the article includes

molecular interactions and ADME predictions for all analogues. In the manuscript, every ADME parameter is covered in depth. In order to carry out molecular docking, Autodock Vina was utilized, and the protein GABA-A served as the target. At the active site of GABA-A, Val B:199, Arg A:180, Phen B:200, Ala B:201 and Lys A:173 are involved in significant interactions. Vander Waals interactions, pi-cation, pi-alkyl, and significant hydrogen bonding are thoroughly examined. The docking results are similar to those of the animal model.

According to *in-silico* and biological activity studies, substituting the EDG at the aryl ring's sixth position can significantly raise GABA concentration and, have an anticonvulsant effect as

a result. The group of created analogues can be viewed as intriguing potential research subjects.

### Funding

This project was funded by the Deanship of Scientific Research at Shaqra university for funding this research work through the project number (SU-ANN-202223).

**Acknowledgments:** The authors extend their appreciation to the Deanship of Scientific Research at Shaqra university for funding this research work through the project number (SU-ANN-202223).

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Author Contributions Section

All authors participated in the experimental work, analysis the data, writing and revised the article.

### Sample Availability

Samples are available from the authors

### References

1. Fisher, R.S.; Cross, J.H.; French, J.A.; Higurashi, N.; Hirsch, E.; Jansen, F.E.; Lagae, L.; Moshé, S.L.; Peltola, J.; Roulet Perez, E.; et al. Operational Classification of Seizure Types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017, 58, 522–530.
2. Stevens, C.E.; Stafstrom, C. Pharmacotherapy for Focal Seizures in Children and Adolescents. *Drugs* 2018, 78, 1321–1337.
3. Chen, Z.; Brodie, M.J.; Liew, D.; Kwan, P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol.* 2018, 75, 279–286.
4. Wilcox, K. S.; West, P. J.; Metcalf, C. S. The Current Approach of the Epilepsy Therapy Screening Program Contract Site for Identifying Improved Therapies for the Treatment of Pharmacoresistant Seizures in Epilepsy. *Neuropharmacology* 2020, 166, 107811.
5. Góra M, Czopek A, Rapacz A, Gębska A, Wójcik-Pszczola K, Pękala E, Kamiński K. Synthesis, Anticonvulsant, and Antinociceptive Activity of New 3-(2-Chlorophenyl)-and 3-(3-Chlorophenyl)-2, 5-dioxo-pyrrolidin-1-yl-acetamides. *Molecules.* 2021, 12;26(6):1564.
6. Kwon, C. S., Wagner, R. G., Carpio, A., Jetté, N., Newton, C. R., & Thurman, D. J. (2022). The worldwide epilepsy treatment gap: A systematic review and recommendations for revised definitions—A report from the ILAE Epidemiology Commission. *Epilepsia*, 63(3), 551-564, doi: 10.1111/epi.17112.
7. Kaushik, D., Khan, S. A., Chawla, G., & Kumar, S. (2010). N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene] 2/4-substituted hydrazides: Synthesis and anticonvulsant activity. *European Journal of Medicinal Chemistry*, 45(9), 3943-3949.
8. Siddiqui, N., & Ahsan, W. (2010). Triazole incorporated thiazoles as a new class of anticonvulsants: Design, synthesis and in vivo screening. *European Journal of Medicinal Chemistry*, 45(4), 1536-1543.
9. Yadav P, Shah K. Quinolines, a perpetual, multipurpose scaffold in medicinal chemistry. *Bioorganic Chemistry.* 2021 Apr 1;109:104639.
10. Tigliani D, Salahuddin S, Mazumder A, Kumar R, Mishra S. Synthetic approaches and biological activities of quinoline derivatives: A Review. *International Journal of Pharmaceutical Research.* 2021 Jan 1;13(1).
11. Kumar S, Kaushik D, Bawa S, Khan SA. Design, Synthesis and Screening of Quinoline-Incorporated Thiadiazole as a Potential Anticonvulsant. *Chemical Biology & Drug Design.* 2012 Jan;79(1):104-11.
12. Shabana K, Salahuddin, Mazumder A, Singh H, Kumar R, Tyagi S, Datt V, Shankar Sharma A, Shahar Yar M, Jawed Ahsan M, Kumar Yadav R. Synthesis, Characterization, In Silico and In Vivo Evaluation of Benzimidazole-Bearing Quinoline Schiff Bases as New

- Anticonvulsant Agents. *ChemistrySelect*. 2023 Jun 5;8(21):e202300209.
13. Swathi K, Sarangapani M. Evaluation of anti-epileptic effect of new indole derivatives by estimation of biogenic amines concentrations in rat brain. *InGeNeDis 2016: Computational Biology and Bioinformatics 2017* (pp. 39-48). Springer International Publishing.
  14. Mandour A, El-Sawy E, Shaker K, Mustafa M (2010) Synthesis, antiinflammatory, analgesic and anticonvulsant activities of 1, 8-dihydro-1-aryl-8-alkyl pyrazolo (3, 4-b) indoles. *Acta Pharmaceutica* 60(1):73–88
  15. Kumar S. A brief review of the biological potential of indole derivatives. *Future Journal of Pharmaceutical Sciences*. 2020 Dec;6(1):1-9.
  16. Srivastava A, Pandeya SN, Khan AA. Anticonvulsant and Convulsant effects of Indole derivatives against Chemical Models of Epilepsy. *Int. J. Chem. Tech. Res.* 2011;3:2029-37.