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RESEARCH ARTICLE

Synthesis, in vivo and in silico evaluation of novel 2,3-dihydroquinazolin-4(1H)-one derivatives as potential anticonvulsant agents

Hend Kothayer[1] | Samy M. Ibrahim[1] | Moustafa K. Soltan[1,2] | Samar Rezq[3] | Shireen S. Mahmoud[4]

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[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

[2]Oman Pharmacy Institute, Ministry of Health, Muscat, Sultanate of Oman

[3]Department of Pharmacology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

[4]Department of Pharmacology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Correspondence
Hend Kothayer, Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, 44511 Zagazig, Egypt.
Email: hendo1311@hotmail.com or
Email: hkelhamalawy@pharmacy.zu.edu.eg

Abstract

In light of the pharmacophoric structural requirements for achieving anticonvulsant activity, a series of *N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)benzamide* **(4a-g)** *and N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)-2-phenylacetamide* **(4h-n)** derivatives were synthesized in two steps starting from the reaction of N-methyl isatoic anhydride with the appropriate hydrazide and followed by condensation with the appropriate aldehyde. The anticonvulsant activities of the synthesized compounds were evaluated according to the anticonvulsant drug development (ADD) programme protocol. Among the synthesized compounds, **4n** showed promising activity in both the maximal electroshock (MES) and pentylenetetrazole (PTZ) tests with median effective dose (ED_{50}) values of 40.7 and 6 mg/kg, respectively. The six most promising derivatives, **4b**, **4a**, **4c**, **4f**, **4j**, and **4i**, showed very low ED_{50} values in the PTZ test (3.1, 4.96, 8.68, 9.89, 12, and 13.53 mg/kg, respectively). All the tested compounds showed no to low neurotoxicity in the rotarod test with a wide therapeutic index. Docking studies of compound **4n** suggested that $GABA_A$ binding could be the mechanism of action of these derivatives. The in silico drug likeliness parameters indicated that none of the designed compounds violate Lipinski's rule of five and that they are able to cross the blood–brain barrier.

KEYWORDS

anticonvulsant, docking, $GABA_A$, hydrazide, quinazolin-4[3H]-ones

1 | INTRODUCTION

Epilepsy is a common and chronic brain disorder characterized by unpredictable recurrent seizures (Abd-Allah, Aboutabl, Aboul-Enein, & El-Azzouny, 2017). Despite the presence of many antiepileptic drugs (AEDs), approximately 30% of patients still suffer from uncontrolled episodes (Abd-Allah et al., 2017; Abram et al., 2017; Siddiqui et al., 2017; Waszkielewicz et al., 2017). Moreover, AEDs have numerous undesirable side effects including neurotoxicity, which is very common and dose-dependent (Edayadulla & Ramesh, 2015; Sangh Partap, Akhtar, Yar, Hassan, & Siddiqui, 2018; Rybka et al., 2017; St Louis, 2009). As AEDs are usually used as long-term treatments, there is an ongoing need for more effective and safer AEDs that have fewer side effects (Edayadulla & Ramesh, 2015; Partap et al., 2018; Rybka, Obniska, Rapacz, Filipek, & Żmudzki, 2016). The design of new AEDs is challenging because the exact etiology of epilepsy is still unknown. Moreover, many of the existing AEDs have multiple and complex mechanisms (Sahu, Siddiqui, Iqbal, Sharma, & Wakode, 2017; Ugale & Bari, 2016).

Thus, ligand-based drug design is the best choice for developing new AEDs. Many studies to identify pharmacophores responsible for antiepileptic activity have been carried out. The common structural

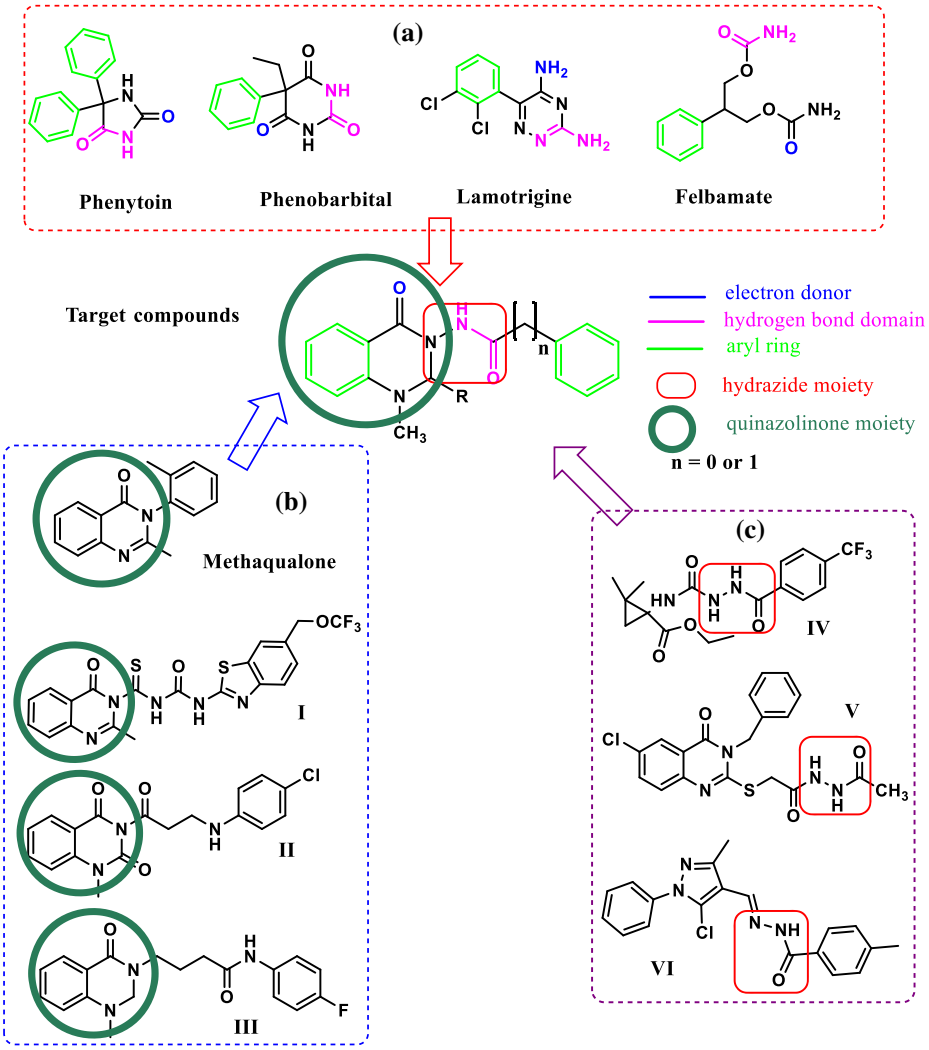


FIGURE 1 Rational design of the synthesized compounds (a) pharmacophoric structural features for antiepileptic activity (hydrogen bond domain, electron donor and one or two aryl rings). (b) Methaqualone and reported quinazolinones as anticonvulsants. (c) Reported anticonvulsants with hydrazide moiety

features are the presence of a hydrogen bonding domain (usually an amide), an electron donor and one or two aryl rings (He et al., 2012; Malawska, 2003; Obniska et al., 2015; Rybka, Obniska, Rapacz, Filipek, & Żmudzki, 2017; Siddiqui et al., 2017; Figure 1a).

The quinazoline moiety has attracted great interest in the field of anticonvulsant drug development (ADD). As the discovery of methaqualone (an anticonvulsant drug bearing a quinazolin-4(3H)-one scaffold) and the presence of the common anticonvulsant activity structural features (such as an amide group and a phenyl ring) in quinazoline derivatives many studies targeted the potential of quinazoline derivatives as anticonvulsants (compounds I-II; El-Azab & ElTahir, 2012; Malik, Bahare, & Khan, 2013; Prashanth, Madaiah, Revanasiddappa, & Veeresh, 2013; Ugale & Bari, 2014, 2016; Figure 1b).

The previous structure–activity relationship (SAR) studies on quinazolines concluded that (a) the presence of an aryl ring linked to Position 3 via a hydrogen bond domain is beneficial and (b) methyl or phenyl substitution at Position 2 can potentiate the anticonvulsant activity (El-Azab & ElTahir, 2012; Malik et al., 2013; Prashanth et al., 2013; Ugale & Bari, 2014).

In our previous work, we studied the effect of the length of the hydrogen bonding substituent at the 3-position on the anticonvulsant activity of quinazolin-4(3H)-one-derived compounds, and we found that the optimum activity was obtained when quinazoline and the phenyl ring were linked by an unbranched 3–5 atom linker (compound III); however, in that study, we did not test linkers shorter than three atoms (Noureldin et al., 2017).

The hydrazide scaffold is a promising linker in designing novel AEDs because it mimics the ureide moiety characteristic of classical AEDs (compounds IV, V, and VI; Al-Salem et al., 2015; Angelova, Karabeliov, Andreeva-Gateva, & Tchekalarova, 2016; He et al., 2012; Kaushik, Khan, Chawla, & Kumar, 2010; Figure 1c)).

In view of the aforementioned pharmacophoric features and as an extension of our research, we aim in this study to achieve synergistic improvement in the anticonvulsant potential in quinazoline derivatives by synthesizing a series of *N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)benzamide* **(4a-g)** *and N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)-2-phenylacetamide* **(4h-n)** derivatives where the quinazolinone scaffold was linked to a substituted

phenyl ring through a hydrazide linker (unbranched 2–3 atom distance). (Figure 1).

To expand the SAR study, we introduced different substituents at 3-position on the phenyl ring. Additionally, we added different substituents at Position 2.

An effective antiepileptic agent must cross the blood–brain barrier (BBB); thus, a balance between hydrophilicity and lipophilicity (Log *P*) is important in the design of novel AEDs (Palaty & Abbott, 1995; Rybka, Obniska, Żmudzki, et al., 2017; Ugale & Bari, 2016). Thus, the log *P* values for most of the synthesized compounds were between 2.60 and 4.42, which are consistent with those of most AEDs.

2 | MATERIALS AND METHODS

2.1 | Chemistry

Melting points (°C) were measured using a Gallenkamp melting point apparatus (London, UK) and are uncorrected.

Mass spectra were collected using a GC/MS Shimadzu Qp-2010 plus instrument (Shimadzu Corporation, Tokyo, Japan). Elemental analyses were performed using a Vario EL-III (Elementar) CHNS analyzer (Hanau, Germany). NMR spectra were recorded on a Bruker high-performance Digital FT-NMR spectrometer Avance III 400 MHz using dimethyl sulfoxide (DMSO)-d_6 or chloroform ($CDCl_3$)-*d* as solvents and tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 GF245 (E-Merck, Germany) and were visualized by a UV-lamp at a wavelength (λ) of 254 nm.

Benzohydrazide **(2a)** and *2-phenylacetohydrazide* **(2b)** were synthesized according to previously reported procedures (Al-Sabti, Al-Amiery, Al-Majedy, & Hameed, 2009).

General method for the synthesis of N′-benzoyl-2-(methylamino) benzohydrazide **(3a)** and *2-(methylamino)-N′-(2-phenylacetyl) benzohydrazide* **(3b)**:

A mixture of N-methyl isatoic anhydride (**1**, 0.025 mol) and *hydrazide* (**2a or 2b,** 0.025 mol) in ethanol (90 mL) containing a catalytic amount of glacial acetic acid (10 drops) was refluxed for 12 h. After cooling, the formed precipitate was isolated by filtration provide required intermediates **3a and b** in 81–88% yield and sufficient purity to be used in the next step without further purification.

N′-benzoyl-2-(methylamino) benzohydrazide **(3a):** (88% yield). M.p. 188–192°C as reported (Ibrahim, Abo-Kul, Soltan, Barkat, & Helal, 2014; Reddy, Reddy, & Ratnam, 1988; Reddy & Reddy, 1988). ^{1}H NMR (DMSO, d_6) δ 2.80 (3H, d, *J* = 4.9, NCH_3), 6.61 (1H, t, *J* = 7.4, ph H), 6.69 (1H, d, *J* = 8.4, ph H), 7.36 (1H, t, *J* = 7.7, ph H), 7.51–7.60 (4H, m, ph H + NH), 7.68 (1H, d, *J* = 6.9, ph H), 7.93 (2H, d, *J* = 7.2, ph H), 10.24 (1H, s, NHCO), 10.39 (1H, s, NHCO).

2-(methylamino)-N′-(2-phenylacetyl) benzohydrazide **(3b):** (81% yield). M.p. 176–178°C as reported (Reddy et al., 1988; Reddy & Reddy, 1988). ^{1}H NMR (DMSO, d_6) δ 2.78 (3H, d, *J* = 5, NCH_3), 3.53 (2H, s, CH_2CO), 6.56 (1H, t, *J* = 7.5, ph H), 6.66 (1H, d, *J* = 8.3, ph H), 7.24–7.34 (6H, m, ph H + NH), 7.48 (1H, d, *J* = 4.7, ph H), 7.58 (1H, d, *J* = 6.8, ph H), 10.05 (1H, s, NHCO), 10.08 (1H, s, NHCO).

General methods for the synthesis of N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)benzamide ***(4a-g)*** *and N-(1-methyl-4-oxo-2-un/substituted-1,2-dihydroquinazolin-3[4H]-yl)-2-phenylacetamide* **(4h-n)**:

a. *Method for compounds* **(4a, b, h, and i)**

To a suspension of *benzohydrazide* **(3a** or **3b**, 0.01 mol) in ethanol (50 mL), 40% formalin or acetaldehyde (0.015 mol) and a few drops of glacial acetic acid were added. The reaction mixture was heated at reflux for 12 h and then concentrated to half the initial volume. The mixture was cooled, and a precipitate was allowed to form. The obtained product was isolated by filtration and crystallized from ethanol to give title compounds **4a, b, h and i** in yields of 74–93%.

b. Method for compounds **4c-g** and **4j-n**

A mixture of *benzohydrazide* **(3a** or **3b**, 0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in glacial acetic acid (20 mL) was heated under reflux for 12 h. The reaction mixture was concentrated to half volume and then poured into cold water (100 mL). The separated solid was isolated by filtration, dried and crystallized from ethanol to give title compounds **4c-g** and **4j-n** in 73–88% yields.

N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3[4H]-yl)benzamide **(4a)**: (93% yield). M.p. 168–170°C as reported (Ibrahim, Abo-Kul, Soltan, & Helal, 2013). ^{1}H NMR (DMSO, d_6) δ 2.91 (3H, s, NCH_3), 4.77(2H, s, NCH_2N), 6.88–6.93 (2H, m, ph H), 7.46–7.51 (1H, m, ph H), 7.54 (2H, t, *J* = 7.5, ph H), 7.60–7.66 (1H, m, ph H), 7.79 (1H, dd, *J* = 7.7, 1.5, ph H), 7.93 (2H, d, *J* = 7.1, ph H), 10.97 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.83 ($N\underline{C}H_3$), 69.22 ($N\underline{C}H_2N$), 113.32, 116.36, 118.96, 128.05, 128.84, 129.05, 132.35, 132.68, 134.60, 150.16, 163.07, 166.08. MS, m/z: 281 (M^+), 282 (M^++1). Analysis calcd. For $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.50; H, 5.55; N, 15.16.

N-(1,2-dimethyl-4-oxo-1,2-dihydroquinazolin-3[4H]-yl)benzamide **(4b):** (76% yield). M.p. 187–189°C. ^{1}H NMR (DMSO, d_6) δ 1.30 (3H, d, *J* = 5.9, $NCH\underline{C}H_3$), 2.91 (3H, s, NCH_3), 4.97 (1H, q, *J* = 5.9, $NC\underline{H}CH_3$), 6.79 (1H, d, *J* = 8.3, ph H), 6.85 (1H, t, *J* = 7.4, ph H), 7.46 (1H, t, *J* = 7.8, ph H), 7.54 (2H, t, *J* = 7.5, ph H), 7.60–7.62 (1H, m, ph H), 7.76 (1H, dd, *J* = 7.7, 1.5, ph H), 7.95 (2H, d, *J* = 7.1, ph H), 10.86 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 15.08 ($NCH\underline{C}H_3$), 35.20 ($N\underline{C}H_3$), 75.73 ($N\underline{C}HCH_3$), 113.37, 115.77, 118.15, 128.11, 128.39, 129.00, 132.57, 132.68, 134.70, 147.24, 160.85, 165.80. MS, m/z: 295 (M^+), 296 (M^++1). Analysis calcd. For $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.91; H, 6.09; N, 14.50.

N-(1-methyl-4-oxo-2-phenyl-1,2-dihydroquinazolin-3[4H]-yl)benzamide **(4c):** (81% yield). M.p. 173–174°C. ^{1}H NMR (DMSO, d_6) δ 2.80 (3H, s, NCH_3), 5.94 (1H, s, NCHN), 6.76 (1H, d, *J* = 8.3, ph H), 6.88 (1H, t, *J* = 7.5, ph H), 7.34 (5H, bs, ph H), 7.44–7.50 (3H, m, ph H), 7.58 (1H, t, *J* = 7.4, ph H), 7.82 (3H, d, *J* = 7.5, ph H), 10.82 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.62 ($N\underline{C}H_3$), 80.38 ($N\underline{C}HN$), 112.49, 115.48, 118.39, 127.40, 128.17, 128.51, 128.88, 128.96, 129.51, 132.54, 132.59, 135.04, 137.60, 147.58, 161.07, 165.95. MS, m/z: 357 (M^+), 358 (M^++1). Analysis calcd. For $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.12; H, 5.74; N, 12.00.

N-(2-(4-chlorophenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3[4H]-yl) benzamide **(4d):** (73% yield). M.p. 183–185°C. ^{1}H NMR (DMSO, d_6) δ 2.81 (3H, s, NCH_3), 5.96 (1H, s, NCHN), 6.76 (1H, d, J = 8.3, ph H), 6.88 (1H, t, J = 7.4, ph H), 7.35 (2H, d, J = 8.4, ph H), 7.42 (2H, d, J = 8.4, ph H), 7.45–7.51 (3H, m, ph H), 7.59 (1H, t, J = 7.4, ph H), 7.81 (3H, t, J = 6.5, ph H), 10.79 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.54 ($N\underline{C}H_3$), 79.60 ($N\underline{C}HN$), 113.04, 115.31, 118.57, 128.12, 128.52, 128.93, 128.97, 129.26, 132.46, 132.62, 134.13,135.15, 136.58, 147.30, 160.87, 165.94. MS, m/z: 391 (M^+), 392 (M^++1), 393 (M^++2). Analysis calcd. For $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.25; H, 4.83; N, 10.98.

N-(2-(4-fluorophenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3[4H]-yl) benzamide **(4e):** (79% yield). M.p. 179–181°C. ^{1}H NMR (DMSO, d_6) δ 2.80 (3H, s, NCH_3), 5.97 (1H, s, NCHN), 6.77 (1H, d, J = 8.3, ph H), 6.88 (1H, t, J = 7.2, ph H), 7.16–7.21 (2H, m, ph H), 7.37–7.40 (2H, m, ph H), 7.45–7.51 (3H, m, ph H), 7.57–7.62 (1H, m, ph H), 7.81 (3H, d, J = 7, ph H), 10.79 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.50 ($N\underline{C}H_3$), 79.61 ($N\underline{C}HN$), 113.00, 115.38, 115.89, 118.49, 128.13, 128.52, 128.90, 129.59 (d, J = 8.5), 132.55, 133.99, 134.02, 135.08, 147.41, 160.92, 161.70, 165.89. MS, m/z: 375 (M^+), 376 (M^++1), 377 (M^++2). Analysis calcd. For $C_{22}H_{18}FN_3O_2$: C, 70.39; H, 4.83; N, 11.19. Found: C, 70.51; H, 5.10; N, 11.52.

N-(2-(4-methoxyphenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)benzamide **(4f):** (83% yield). M.p. 162–164°C. ^{1}H NMR (DMSO, d_6) δ 2.77 (3H, s, NCH_3), 3.72 (3H, s, OCH_3), 5.87 (1H, s, NCHN), 6.75 (1H, d, J = 8.3, ph H), 6.85–6.90 (3H, m, ph H), 7.26 (2H, d, J = 8.7, ph H), 7.44–7.50 (3H, m, ph H), 7.58 (1H, t, J = 7.4, ph H), 7.79–7.83 (3H, m, ph H), 10.77 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.44 ($N\underline{C}H_3$), 55.56 (OCH_3), 80.03 ($N\underline{C}HN$), 112.87, 114.01, 114.24, 115.44, 118.27, 128.16, 128.48, 128.87, 129.67, 132.64, 134.97, 147.60, 160.21, 161.08, 165.87, 172.55. MS, m/z: 387 (M^+), 388 (M^++1). Analysis calcd. For $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.30; H, 5.46; N, 10.85.

N-(1-methyl-2-(4-nitrophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl) benzamide **(4g):** (88% yield). M.p. 177–179°C. ^{1}H NMR (DMSO, d_6) δ 2.87 (3H, s, NCH_3), 6.16 (1H, s, NCHN), 6.78 (1H, d, J = 8.3, ph H), 6.91 (1H, t, J = 7.4, ph H), 7.47–7.51 (3H, m, ph H), 7.57–7.64 (3H, m, ph H), 7.82–7.84 (3H, m, ph H), 8.23 (2H, d, J = 8.7, ph H), 10.86 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.74 ($N\underline{C}H_3$), 79.27 ($N\underline{C}HN$), 113.27, 115.44, 118.85, 124.18, 128.16, 128.63, 128.77, 128.95, 132.40, 132.65, 135.21, 144.81, 147.07, 148.37, 160.70, 165.98. MS, m/z: 402 (M^+), 403 (M^++1). Analysis calcd. For $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.52; H, 4.67; N, 14.08.

N-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4h):** (87% yield). M.p. 157–159°C. ^{1}H NMR (DMSO, d_6) δ 2.85 (3H, s, NCH_3), 3.54 (2H, s, CH_2CO), 4.62 (2H, s, NCH_2N), 6.82–6.89 (2H, m, ph H), 7.25–7.33 (5H, m, ph H), 7.44 (1H, t, J = 7.2, ph H), 7.74 (1H, d, J = 7.6, ph H), 10.60 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.75 ($N\underline{C}H_3$), 40.26 ($\underline{C}H_2CO$), 69.03 ($N\underline{C}H_2N$), 113.25, 116.22, 118.89, 127.05, 128.77, 128.80, 129.57, 134.54, 135.76, 150.08, 162.84, 170.00. MS, m/z: 295 (M^+), 296 (M^++1). Analysis calcd. For $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.30; H, 5.97; N, 14.20.

N-(1,2-dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2 phenylacetamide **(4i):** (74% yield). M.p. 165–167°C. ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, J = 5.9, $NCH\underline{C}H_3$), 2.92 (3H, s, NCH_3), 3.69 (2H, q, J = 15, CH_2CO), 4.96 (1H, q, J = 5.7, $NC\underline{H}CH_3$), 6.65 (1H, d, J = 8.3, ph H), 6.84 (1H, t, J = 7.4, ph H), 7.28–7.38 (6H, m, ph H), 7.89 (1H, d, J = 7.5, ph H), 9.28 (1H, s, NHCO, exch.). ^{13}C NMR ($CDCl_3$) δ 14.23 ($NCH\underline{C}H_3$), 35.56 ($N\underline{C}H_3$), 41.27 ($\underline{C}H_2CO$), 75.26 ($N\underline{C}HCH_3$), 112.87, 114.89, 118.16, 127.12, 128.73, 129.32, 134.34, 134.63, 146.78, 162.36, 170.00, 176.65. MS, m/z: 309 (M^+), 310 (M^++1). Analysis calcd. For $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.04; H, 6.29; N, 13.60.

N-(1-methyl-4-oxo-2-phenyl-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4j):** (75% yield). M.p. 140–142°C. ^{1}H NMR (DMSO, d6) δ 2.76 (3H, s, NCH_3), 3.48 (2H, s, CH_2CO), 5.74 (2H, s, NCHN), 6.69 (1H, d, J = 8.4, ph H), 6.84 (1H, t, J = 7.2, ph H), 7.20–7.45 (10H, m, ph H), 7.78 (1H, d, J = 7.6, ph H), 10.44 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d6) δ 35.53 (NCH_3), 40.73 (CH_2CO), 80.02 (NCHN), 112.68, 114.44, 115.08, 118.25, 126.99, 127.09, 128.46, 128.70, 129.54, 135.04, 135.87, 137.55, 147.28, 150.68, 160.92, 169.47. MS, m/z: 371 (M^+). Analysis calcd. For $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.07; H, 6.02; N, 11.22.

N-(2-(4-chlorophenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4k):** (77% yield). M.p. 164–166°C. ^{1}H NMR ($CDCl_3$) δ 2.77 (3H, s, NCH_3), 3.58 (2H, q, J = 14.6, CH_2CO), 5.82 (1H, s, NCHN), 6.62 (1H, d, J = 8.3, ph H), 6.88 (1H, t, J = 7.5, ph H), 6.96 (2H, d, J = 8.4, ph H), 7.13 (2H, d, J = 8.3, ph H), 7.26–7.33 (5H, m, ph H), 7.43 (1H, t, J = 7.8, ph H), 7.75 (1H, d, J = 7.7, ph H), 8.86 (1H, s, NHCO, exch.). ^{13}C NMR ($CDCl_3$) δ 35.62 ($N\underline{C}H_3$), 41.41(CH_2CO), 79.46 ($N\underline{C}HN$), 111.96, 113.79, 118.44, 127.16, 128.11, 128.70, 129.02, 129.08, 129.29, 134.34, 135.13, 135.24, 135.25, 147.09, 162.30, 169.59. MS, m/z: 405 (M^+), 406 (M^++1), 407 (M^++2). Analysis calcd. For $C_{23}H_{20}ClN_3O_2$: C, 68.06; H, 4.97; N, 10.35. Found: C, 68.17; H, 5.29; N, 10.64.

N-(2-(4-fluorophenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4l):** (77% yield). M.p. 147–149°C. ^{1}H NMR (DMSO, *d6*) δ 2.75 (3H, s, NCH_3), 3.47 (2H, s, CH_2CO), 5.78 (1H, s, NCHN), 6.71 (1H, d, J = 8.4, ph H), 6.85 (1H, t, J = 7.6, ph H), 7.14–7.32 (9H, m, ph H), 7.44 (1H, t, J = 8.4, ph H), 7.78 (1H, d, J = 7.6, ph H), 10.43 (1H, s, NHCO, exch.). ^{13}C NMR ($CDCl_3$) δ 35.61 ($N\underline{C}H_3$), 41.58 ($\underline{C}H_2CO$), 79.55 ($N\underline{C}HN$), 111.88, 113.78, 115.69, 115.90, 118.30, 127.27, 128.60 (d, J = 8.4), 128.78, 129.19 (d, J = 19.0), 132.60, 134.13, 135.0, 147.14, 162.19, 164.42, 169.50. MS, m/z: 389 (M^+), 390 (M^++1), 407 (M^++2). Analysis calcd. For $C_{23}H_{20}FN_3O_2$: C, 70.94; H, 5.18; N, 10.79. Found: C, 71.18; H, 5.29; N, 10.96.

N-(2-(4-methoxyphenyl)-1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4m):** (81% yield). M.p. 136–138°C. ^{1}H NMR (DMSO, d_6) δ 2.73 (3H, s, NCH_3), 3.48 (2H, s, CH_2CO), 3.73 (3H, s, OCH_3), 5.69 (1H, s, NCHN), 6.78 (1H, d, J = 8.4, ph H), 6.82–6.89 (3H, m, ph H), 7.14 (2H, d, J = 8.4, ph H), 7.24–7.34 (5H, m, ph H), 7.42 (1H, t, J = 7.6, ph H), 7.78 (1H, d, J = 7.6, ph H), 10.41 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.35 ($N\underline{C}H_3$), 40.62 ($\underline{C}H_2CO$), 55.60 (OCH_3), 79.71 ($N\underline{C}HN$), 112.47, 114.38, 115.03, 118.14, 126.97, 128.43, 128.48, 128.69, 129.53, 129.57, 134.98, 135.90, 147.33, 160.27, 160.98, 169.40. MS, m/z: 401 (M^+), 402 (M^++1). Analysis calcd. For

$C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.93; H, 6.00; N, 10.19.

N-(1-methyl-2-(4-nitrophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide **(4n):** (87% yield). M.p. 236–238°C. ^{1}H NMR (DMSO, d_6) δ 2.80 (3H, s, NCH_3), 3.46 (2H, s, CH_2CO), 5.98 (1H, s, NCHN), 6.74 (1H, d, J = 8.4, ph H), 6.88 (1H, t, J = 7.6, ph H), 7.22–7.31 (5H, m, ph H), 7.44–7.52 (3H, m, ph H), 7.80 (1H, d, J = 7.6, ph H), 8.19 (2H, d, J = 8.4, ph H), 10.50 (1H, s, NHCO, exch.). ^{13}C NMR (DMSO, d_6) δ 35.61 ($N\underline{C}H_3$), 40.61 ($\underline{C}H_2CO$), 79.04 ($N\underline{C}HN$), 113.21, 115.07, 118.81, 124.25, 127.02, 128.59, 128.69, 128.77, 129.52, 135.24, 135.68, 144.59, 146.97, 148.39, 160.75, 169.61. MS, m/z: 416 (M^+), 417 (M^++1). Analysis calcd. For $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.52; H, 5.15; N, 13.75.

2.2 | Anticonvulsant screening

The anticonvulsant activity and neurotoxicity screenings were carried out in accordance with the guidelines of the Faculty of Pharmacy, Zagazig University, Egypt, and the whole study was approved by the local authorities, the Ethical Committee for Animal Handling at Zagazig University (ECAHZU), Faculty of Pharmacy, Zagazig University, Egypt, with a registration number (P2-6-2017). Adult male Swiss albino mice (25–30 g) were used as experimental animals, and each mouse was used only once. Animals were purchased from the National Research Center animal house (Cairo, Egypt). The animals were housed at room temperature 22 ± 2°C under a light/dark cycle (12/12) and were allowed free access to food and water. MES and PTZ were the two animal models used for anticonvulsant activity screening, and the rotarod test was used for neurotoxicity screening; the response evaluations were estimated following procedures described elsewhere (Krall, Penry, White, Kupferberg, & Swinyard, 1978). The tested compounds were suspended in a 1% Tween 80/normal saline mixture and injected intraperitoneally at doses of 30, 100, and 300 mg/kg into one to four animals. The anticonvulsant activity and neurotoxicity were then assessed at two different time intervals (0.5 h and 4 h) after administration.

TABLE 1 Preliminary screening results

	Intraperitoneal injection in mice[a]					
	MES screening[b]		PTZ screening[c]		NT screening[d]	
Compound	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4a	–	–	30	100	–	–
4b	–	–	30	–	–	–
4c	30	100	30	30	–	–
4d	300	–	–	–	–	–
4e	30	30	300	300	–	–
4f	30	–	30	30	–	–
4g	100	–	–	–	–	–
4h	300	–	30	–	–	–
4i	300	–	100	100	–	–
4j	–	–	30	–	300	300
4k	100	–	30	100	–	–
4l	100	–	–	30	–	–
4m	300	–	100	–	–	–
4n	30	30	30	–	–	–

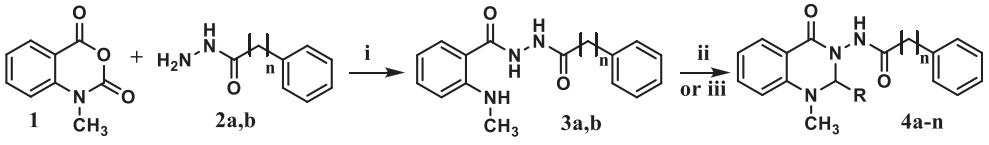
[a] Doses of 30,100 and 300 mg/kg were administered. The animals were examined 0.5 and 4.0 h posttreatment. The dash (–) indicates the absence of activity at the maximum dose administered (300 mg/kg).
[b] Maximal electroshock test.
[c] Pentylenetetrazole test.
[d] Neurotoxicity screening (rotarod test).

2.2.1 | The maximal electroshock (MES) seizure test

In the MES test, animals were subjected to electrical shock through a current of 60 Hz and intensity of 25 mA delivered via ear-lip electrodes for 0.2 s duration. The test compound was considered to be able to inhibit MES-induced seizure spread upon the absence of hind limb tonic extension (Edayadulla & Ramesh, 2015; Krall et al., 1978; Noureldin et al., 2017; Obniska et al., 2015; Obniska et al., 2016).

2.2.2 | The pentylenetetrazol (PTZ) seizure test

In the PTZ test, animals were injected with pentylenetetrazol (85 mg/kg, i.p.) at the predetermined time of testing, and animals were observed over a 30-min period. Failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection. (Edayadulla & Ramesh, 2015; Krall et al., 1978; Noureldin et al., 2017; Obniska et al., 2015; Obniska et al., 2016).



2a, 3a n=0
2b, 3b n=1

4a n=0 R= H	**4h n=1 R= H**
4b n=0 R= CH_3	**4i n=1 R= CH_3**
4c n=0 R= C_6H_5	**4j n=1 R= C_6H_5**
4d n=0 R= 4-ClC_6H_4	**4k n=1 R= 4-ClC_6H_4**
4e n=0 R= 4-FC_6H_4	**4l n=1 R= 4-FC_6H_4**
4f n=0 R= 4-$OCH_3C_6H_4$	**4m n=1 R= 4-$OCH_3C_6H_4$**
4g n=0 R=4-$NO_2C_6H_4$	**4n n=1 R=4-$NO_2C_6H_4$**

SCHEME 1 Synthetic route of target compounds. Reagents and conditions: (i) ethanol/10 drops of glacial acetic acid, reflux, 12 h; (ii) formaline or acetaldehyde, ethanol/10 drops of glacial acetic acid, reflux, 12 h; and (iii) appropriate aromatic aldehyde, glacial acetic acid, reflux, 12 h

2.2.3 | Neurotoxicity-minimal motor impairment (MMI)

The standardized rotarod test was used to determine the neurotoxic effects of the tested compounds. Untreated control mice can maintain their equilibrium when placed on a rotating roller that was set to accelerate from 0 to 40 rpm in 120 s for a prolonged period of time. Acute motor impairment is present when the test animal fails to maintain equilibrium on the revolving roller for at least 1 min in each of three successive trials (Edayadulla & Ramesh, 2015; Krall et al., 1978; Noureldin et al., 2017; Obniska et al., 2015; Obniska et al., 2016).

2.3 | Docking studies

Docking studies were performed on the homology model of diazepam-bound $GABA_A$ receptor reported by Richter et al. (Richter et al., 2012), and the PDB file was downloaded from the Supplementary Material of their published paper using MOE (Molecular Operating Environment [MOE]; MOE, Version, 2018, Chemical Computing Group Inc., Montreal, Quebec, Canada http://www.chemcomp.com). The structures of compounds **4a-n** were drawn using the 2D/3D molecule builder in MOE. The compute module was used to calculate the partial charges and protonate 3D at physiological pH (7.4), followed by optimal energy minimization. The default Triangle Matcher placement method was used for docking. The GBVI/WSA dG scoring function, which estimates the free energy of binding of the ligand in a given pose, was used to rank the final poses.

3 | RESULTS AND DISCUSSION

3.1 | Chemistry

Compounds **(4a-n)** were synthesized in two simple steps according to Scheme 1. N-Methyl isatoic anhydride **(1)** was reacted with the appropriate hydrazide **(2a and b)** in refluxing ethanol with a catalytic amount of glacial acetic acid to give intermediates **3a and b**. These intermediates **(3a and b)** were then cyclized to the target quinazolinones **(4a-n)** using either formalin/acetaldehyde in refluxing ethanol containing a catalytic amount of glacial acetic acid or using the appropriate aromatic aldehyde in refluxing glacial acetic acid to afford compounds **4a, b, h and i** or **4c-g** and **j-n**, respectively.

The structures of the final compounds **(4a-n)** were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The ^{1}H NMR spectra of all compounds **(4a-n)** showed the disappearance of the CONH singlet at 10.08–10.39 ppm and the appearance of an NCHN singlet at 4.62–6.16 ppm. The ^{13}C NMR spectra also revealed an NCN signal at 69.03–79.27 ppm. The ^{1}H NMR, ^{13}C NMR, mass and elemental data of all compounds **(4a-n)** were consistent with the predicted structures.

3.2 | Anticonvulsant screening

An evaluation of the anticonvulsant activities of the newly synthesized quinazolinones **(4a-n)** was carried out using the "gold standard" animal seizure models, the maximal electroshock (MES) and the pentylenetetrazol (PTZ) animal models according to the NIH ADD programme protocol (Stables & Kupferberg, 1997).

In phase I screening, compounds **4a-n** were intraperitoneally (i.p.) injected using doses of 30, 100, or 300 mg/kg, and the anticonvulsant protection was determined at two different time intervals (0.5 h and 4 h) after dosing. The rotarod test was used to assess the potential of the tested compounds to induce neurotoxicity. The results are shown in Table 1.

The outcomes of the preliminary screening revealed that all the synthesized compounds **(4a-n)** had considerable anticonvulsant

TABLE 2 The quantitative pharmacological parameters ED_{50}, TD_{50}, and PI in mice ip

Compound	TPE[a] (h)	ED_{50} MES[b] (mg/kg)	ED_{50} PTZ[b] (mg/kg)	TD_{50} (mg/kg)	PI[c] (TD_{50}/ED_{50})
4a	0.5	ND[d]	4.96 (3.42-7.17)	>500	>100.8 (PTZ)
4b	1.0	ND	3.1 (2.12-4.42)	347.4 (252.7-477.6)	>112 (PTZ)
4c	0.5 (MES) 1.0 (PTZ)	358.9 (243.3-529.4)	8.68 (5.517-13.66)	>500	>1.39 (MES) >57.6 (PTZ)
4e	0.25	189 (81.85-436.3)	ND	>500	>2.65 (MES)
4f	1.0 (MES) 4.0 (PTZ)	82.2 (48.15-140.1)	9.89 (7.969-12.26)	>500	>6.08 (MES) >50.5 (PTZ)
4h	2.0	ND	21.78 (13.92-34.07)	>324.7 (275.3-382.9)	>14.9 (PTZ)
4j	1.0	ND	12 (8.255-17.57)	111.3 (93.17-132.9)	>9.28 (PTZ)
4k	4.0	ND	29.5 (20.10-43.39)	>500	>16.9 (PTZ)
4l	4.0	ND	13.53 (10.63-17.22)	>500	>37 (PTZ)
4n	0.25	40.7 (24.28-68.23)	6 (4.675-7.727)	>500	>12.29 (MES) >83.3 (PTZ)
Ph[e]	1.0	7.1 (5.67-8.90)	>500	42 (33.99-51.93)	5.9 (MES)
VPA[e]	0.5	279 (255-345)	180.2 (158.0-205.4)	367.9 (357.3-378.7)	1.3 (MES) 2.04 (PTZ)

[a] Time of peak effect.
[b] Results are represented as mean ± *SEM* at 95% confidence limit (MES: maximal electroshock test; PTZ: pentylenetetrazol test).
[c] Protective index (TD_{50}/ED_{50}).
[d] ND = not done.
[e] Reference AEDs: Phenytoin (Ph), Valproate (VPA) tested in the same conditions.

activity in the MES and/or PTZ screenings. In the MES test, compounds **4c**, **4e**, **4f** and **4n** showed protective ability at the lowest tested dose (30 mg/kg) at the 0.5 h time interval. Among these compounds, **4e** and **4n** protected the animals at both time intervals, indicating their rapid onset as well as their long duration of action. Compounds **4k**, **4g**, and **4i** were active at a dose of 100 mg/kg. Compounds **4d**, **4h**, **4i**, and **4m** showed protection only at the highest tested dose (300 mg/kg). Notably, the synthesized compounds **(4a-n)** exhibited better anticonvulsant activities in the PTZ screening test, as compounds **4a**, **4b**, **4c**, **4f**, **4h**, **4j**, **4k**, **4l**, and **4n** were active at the 30 mg/kg dose. Moreover, compounds **4c** and **4f** showed a longer lasting protective effect as they remained effective 4 h posttreatment. Compounds **4a** and **4k** also remained active after 4 h but only when a higher dose (100 mg/kg) was used. Compounds **4i** and **4m** exhibited protective effects at 100 mg/kg. Finally, compound **4e** was active only at the highest dose (300 mg/kg).

Most of the tested compounds **(4a-n)** were not neurotoxic according to the rotarod test. Only compound **4j** showed some degree of neurotoxicity at the highest tested dose (300 mg/kg).

Compounds **4a**, **4b**, **4c**, **4e**, **4f**, **4h**, **4j**, **4k**, **4l**, and **4n**, which were active at 30 mg/kg, were selected for phase II screening.

Phase II screening involved the quantitative determination of the median effective dose (ED_{50}), the median toxic dose (TD_{50}), and the protective index (PI), and the results are presented in Table 2. The time of peak effect (TPE) for each of these compounds was estimated at the beginning of the phase II study and was used for the subsequent quantitative studies.

Compound **4n** showed promising activity in both the MES and PTZ tests with ED_{50} values of 40.7 and 6 mg/kg, respectively. In the PTZ test, compounds **4b**, **4a**, **4c**, **4f**, **4j**, and **4i** showed relatively lower ED_{50} values of 3.1, 4.96, 8.68, 9.89, 12, and 13.53, respectively.

The majority of the TD_{50} values of the tested compounds were above 500 except for compounds **4b**, **4h**, and **4j** (TD_{50} values of 347.4, 324.7, and 111.3, respectively).

Notably, the PI values of most of the tested compounds were better than those of the reference drugs (Table 2).

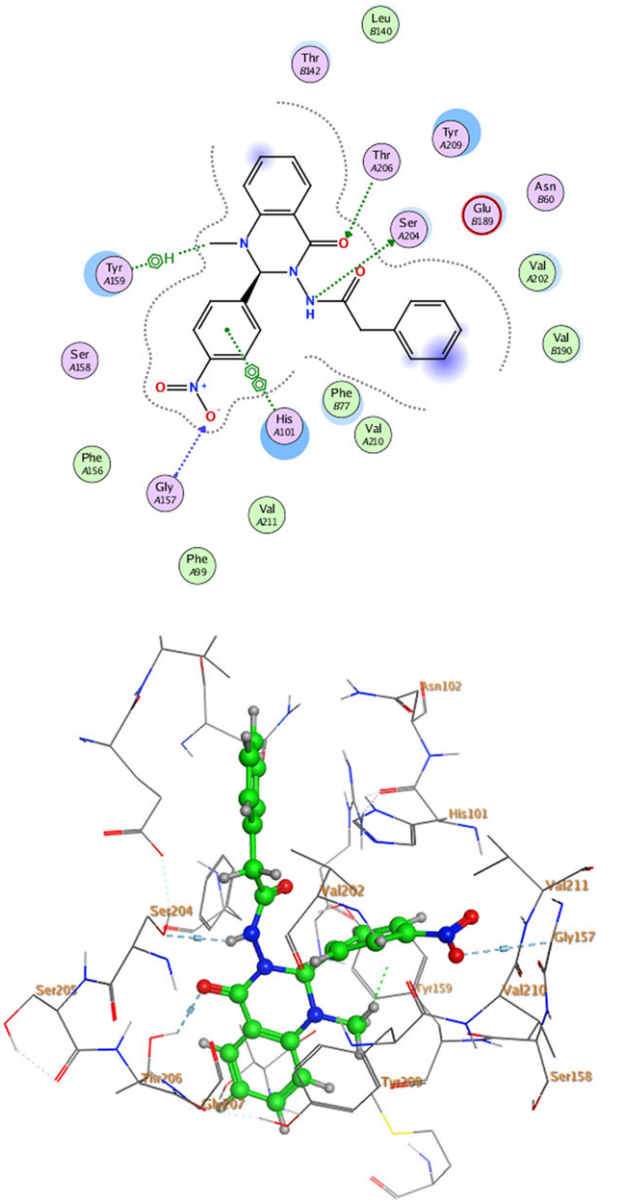


FIGURE 2 2D interaction image of compound 4n in the active site of $GABA_A$ and 3D binding interaction of compound 4n in the active site of $GABA_A$

3.3 | Structure–activity relationship (SAR)

The synthesized compounds **(4a-n)** were designed to include the previously reported anticonvulsant pharmacophoric structural features. To expand the SAR study, we made some structural modifications. The distance between the quinazolinone and the phenyl rings was either 2 or 3 atoms (*n* = 0 or 1). Moreover, Position 2 of the quinazolinone was either unsubstituted or substituted with methyl or phenyl groups, and the phenyl groups were carrying either electron-donating or electron-withdrawing groups (Figure 1).

In general, compounds **4a-g** with *n* = 0 showed better activities and lower ED_{50} values than their analogues (**4h-n**) with *n* = 1 with two exceptions; the ED_{50} of compound **4k** is better than that of its analogue, **4d**, and the ED_{50} of compound **4n** is better than that of its analogue, **4g**.

Series **4a-g** with two atoms distance between the quinazolinone and the phenyl rings (*n* = 0) had lower toxicities compared to those of the three atoms distance series **4h-n** (n = 1). For examples, compounds **4a** and **4c** showed TD_{50} values >500 while their analogues **4h** and **4j** showed TD_{50} values of 324.7 and 111.3, respectively.

Substitution at Position 2 of the quinazolinone ring with phenyl ring was favorable in both series (compounds **4c** and its analogue **4j** had ED_{50} of 8.68 and 12, respectively).

Trials to increase the lipophilicity of the synthesized compounds by incorporation a halogen (either Cl or F) at Position 4 of the phenyl ring (compounds **4d**, **4k**, and **4l**) led to decrease the activity compared to the compounds with unsubstituted phenyl ring (**4c** and **4j**).

The ability of the synthesized compounds to exert better activity in the PTZ test suggests that they may act via a GABAergic activity enhancement mechanism (Bialer & White, 2010; Obniska et al., 2015; Partap et al., 2018).

TABLE 3 Several drug-like properties of compounds **4a-n** calculated using Molinspiration and admetSAR online servers

Compound	M.wt	MiLogP	nOHNH	nON	nRotB	Lipiniski's violations	tPSA	BBB permeability	Probability
Rule	<500	<5	<5	<10	<10	<1			
4a	281.31	1.06	1	5	2	0	52.65	+	.96
4b	295.34	1.42	1	5	2	0	52.65	+	.97
4c	357.41	2.64	1	5	3	0	52.65	+	.98
4d	391.86	3.32	1	5	3	0	52.65	+	.97
4e	375.40	2.81	1	5	3	0	52.65	+	.97
4f	387.44	2.70	1	6	4	0	61.88	+	.96
4g	402.41	2.60	1	8	4	0	98.47	+	.85
4h	295.34	2.16	1	5	3	0	52.65	+	.97
4i	309.37	2.53	1	5	3	0	52.65	+	.97
4j	371.44	3.75	1	5	4	0	52.65	+	.98
4k	405.88	4.42	1	5	4	0	52.65	+	.97
4l	389.43	3.91	1	5	4	0	52.65	+	.97
4m	401.47	3.80	1	6	5	0	61.88	+	.96
4n	416.44	3.70	1	8	5	0	98.47	+	.86

Note. MWt = molecular weight; LogP = octanol/water partition coefficient; nOHNH = number of hydrogen bond donors; nON = number of hydrogen bond acceptors; nRotB = number of rotatable bonds; tPSA, topological polar surface area.

3.4 | In silico studies

3.4.1 | Docking studies

To explore the mechanism of action of our compounds, the docking of compounds **4a-n** into the benzodiazepine binding site of the $GABA_A$ receptor was studied using MOE 2018 software.

The X-ray crystal structure of human $GABA_A$ is not available, so we used the homology model of the diazepam-bound $GABA_A$ receptor (Richter et al., 2012). α1 Thr206, α1 Tyr209, α1 His101, α1 Tyr159, and γ2 Phe77 are key residues in the binding of diazepam (Richter et al., 2012).

For each docked compound, one pose was selected based on the docking score and number of binding interactions. Docking data are summarized in Table SI in supplementary material.

The process was validated by re-docking diazepam into the benzodiazepine binding site of the $GABA_A$ receptor, and its original conformation was reproduced (RMSD: 0.9669 A^0 Score − 6.7575).

The docking scores for the series **4a-n** ranged from −6.2328 to −7.8900. All the compounds **4a-n** showed favorable interactions with the key amino acids. (Table SI in supplementary material.)

The binding poses for compound **4n** (3D and 2D) are shown in Figure 2.

As shown, the carbonyl group of the quinazolinone ring formed hydrogen bonds with Thr206, and the nitro group formed hydrogen bonds with Gly157. His101 formed π–π interactions with the phenyl ring of compound **4n**.

Moreover, a pi-alkyl interaction was observed between Tyr159 and the N-methyl group of the synthesized compound. Ser204 also made hydrogen bond interactions with the amide nitrogen.

Tyr209 and Phe77 are also in close proximity to the docked compound.

Docking studies revealed that our compounds formed favorable binding interactions with key residues in the benzodiazepine binding site of the $GABA_A$ receptor, indicating that binding to $GABA_A$ is a possible mechanism of action for our compounds. However, like most traditional anticonvulsant drugs, other mechanisms could also be involved.

3.4.2 | Drug likeliness parameters

To be an effective anticonvulsant drug, the candidate compounds must be able to cross the BBB to exert their action. They should also possess good pharmacokinetic and oral bioavailability properties (Dehestani et al., 2018; Sangh Partap, Akhtar, Yar, Hassan, & Siddiqui, 2018). The drug-like properties of the designed compounds were predicted using the web tool Molinspiration (www.molinspiration.com) based on Lipinski's "Rule of five" (Lipinski, 2004). Furthermore, the compounds with BBB permeability were predicted via the admetSAR server (http://lmmd.ecust.edu.cn/admetsar1/predict/). The data are listed in Table 3. As seen from the data, all the compounds have a high probability of crossing the BBB. None of the compounds violate Lipinski's rules, making our compounds excellent candidates as CNS-active compounds.

4 | CONCLUSION

A library of 14 compounds **(4a-n)** were designed, synthesized and evaluated for their anticonvulsant activity using the "gold standard" animal seizure models, the MES and PTZ tests. Furthermore, their neurotoxicities were estimated by the rotarod test. *N-(1-Methyl-2-(4-nitrophenyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-phenylacetamide* **(4n)** showed promising activity in both the MES and PTZ seizure models with ED_{50} values of 40.7 and 6, respectively. Among the tested compounds, the six most promising derivatives, **4b**, **4a**, **4c**, **4f**, **4j**, and **4i** showed relatively low ED_{50} values in the PTZ test (3.1, 4.96, 8.68, 9.89, 12, and 13.53, respectively). All the compounds showed no to low neurotoxicity with a wide therapeutic index. Docking studies indicated that binding to the benzodiazepine binding site of the $GABA_A$ receptor is a possible mechanism of action for compound **4n**. Our study demonstrated the potential of the

synthesized molecules as novel drug-like candidates with enhanced anticonvulsant activity and minimal neurotoxicity.

FUNDING INFORMATION

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CONFLICT OF INTEREST

There are no conflicts of interest to declare.

ORCID

Hend Kothayer https://orcid.org/0000-0002-2954-0751

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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