Received: 26 December 2018 | Revised: 14 March 2019 | Accepted: 1 April 2019

DOI: 10.1002/ddr.21538

DDR WILEY

RESEARCH ARTICLE

Synthesis, in vivo anticonvulsant testing, and molecular modeling studies of new nafimidone derivatives

Mustafa F. Acar[1,2] | Suat Sari[1] | Sevim Dalkara[1]

[1]Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Hacettepe University, Ankara, Turkey

[2]Server Gazi Pharmacy, Merkez Efendi, Denizli, Turkey

Correspondence
*Suat Sari, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Hacettepe University, 06100 Ankara, Turkey.
Emails: suat.sari@hacettepe.edu.tr, suat1039@gmail.com

Abstract

An estimated 50 million people suffer epilepsy worldwide and 30% of the cases do not respond to current antiepileptic drugs (AEDs). Here, we report synthesis and anticonvulsant screening of new derivatives of nafimidone, a well-known member of (arylakyl)azole anticonvulsants. The compounds showed promising protection against maximal electroshock (MES)-induced seizures in mice and rats when administered via intraperitoneal (ip) and oral route. Especially, **5b**, **5c**, and **5i** displayed outstanding activity in rats in MES test when given ip (ED_{50}: 16.0, 15.8, and 11.8 mg/kg, respectively). Additionally, **5l** was active against 6 Hz and corneal-kindled mice models. Behavioral toxicity of the compounds was very low and their therapeutic indexes were high compared to some currently available AEDs. A number of pharmaceutically relevant descriptors and properties were predicted for the compounds in silico in comparison with a set of known drugs. Favorable results were obtained such as good blood–brain barrier permeability and high oral absorption, as well as drug-likeness. **5l** was found to show affinity to the benzodiazepine binding site of A-type GABA receptor via molecular docking simulations.

KEYWORDS

(arylalkyl)azole, esterification, molecular docking

1 | INTRODUCTION

Epilepsy, a common neurological disorder characterized by spontaneous and concurrent seizures, usually requires long-term use of antiepileptic drugs (AEDs), making toxicity a major issue. Also 1/3 of an estimated 50 million patients are unresponsive to current AEDs (Dalkara & Karakurt, 2012).

(Arylalkyl)azoles (AAAs) is an antiepileptic class with nafimidone and denzimol as known members (Figure 1; Nardi et al., 1981; Walker, Wallach, & Hirschfeld, 1981). AAA scaffold comprises an aryl moiety, an azole group, and an ethylene linker in between. Many AAAs include small oxygen functional groups on this linker (Dalkara & Karakurt, 2012; Robertson et al., 1986). Previously, some active ether and ester derivatives of AAAs were reported (Karakurt et al., 2006; Karakurt, Özalp, Işık, Stables, & Dalkara, 2010; Sari et al., 2016, 2017; Sari, Kaynak, & Dalkara, 2018). Herein, we present synthesis and anticonvulsant screening of new 2-(1*H*-imidazol-1-yl)-1-(2-naphthyl)ethanol esters (**5a-o**). For anticonvulsant activity, acute (maximal electroshock [MES], subcutaneous metrazol [SCM], 6 Hz psychomotor tests) and chronic (corneal-kindled mice [CKM] and hippocampal kindling) in vivo seizure models were used. Behavioral toxicity of the compounds was evaluated by rotorod and minimal motor impairment tests.

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) is a crucial aspect of drug design (Rankovic, 2015). Thus, we evaluated drug-likeness and certain ADMET properties of our compounds in silico. We also performed docking studies to provide insights into binding properties of **5l** to native (α1β2γ2) A-type GABA receptors ($GABA_ARs$).

Abbreviations: AAA, (arylalkyl)azole; ADMET, absorption, distribution, metabolism, excretion, and toxicity; AED, antiepileptic drug; CBZ, carbamazepine; CKM, corneal-kindled mice; ETSP, epilepsy therapy screening program; ip, intraperitoneal; MES, maximal electroshock; NIH, National Institutes of Health; PHE, phenytoin; SCM, subcutaneous metrazol; TI, therapeutic index.; TPE, time to peak effect; VPA, valproic acid.

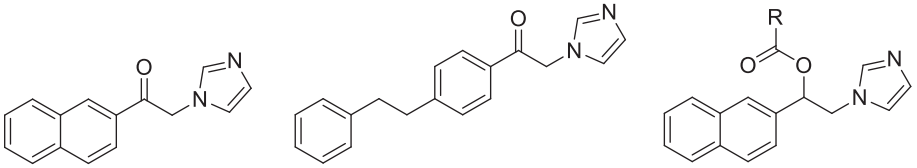

FIGURE 1 Nafimidone, denzimol, and **5a-o**

2 | METHODS

2.1 | Chemistry

All chemicals were purchased from commercial suppliers. Melting points (mp) were determined with Thomas-Hoover capillary melting point apparatus (Swedesboro, NJ, USA) and uncorrected. IR spectra were recorded with PerkinElmer FT-IR System Spectrum BX (Waltham, MA, USA) with attenuated total reflection (ATR) sampling, ^{1}H NMR (400 MHz) and ^{13}C NMR (150 MHz) spectra with Varian Mercury 400 FT (Palo Alto, CA, USA) and Bruker Avonce 600 Ultrashield™ (Billerica, MA, ABD) NMR spectrometers, and mass spectra with Waters Micromass ZQ mass spectrometer (Milford, MA, USA) using electrospray ionization (ESI+) method and MassLynx 4.1 software. Elemental analyses were performed with LECO 932 CHNS apparatus (Saint Joseph, MI, USA) and the results are reported as %. Compounds were dissolved in $CDCl_3$ for NMR spectroscopy. The chemical shifts are reported as δ (ppm) values using TMS as internal reference with splitting patterns designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublet).

2.1.1 | Synthesis of the compounds

Compund **1** was purchased from commercial suppliers and **2-4** were synthesized according to the literature methods (see Supporting Information for details; Baji et al., 1995; Godefroi, Heeres, Van Cutsem, & Janssen, 1969; Immediata & Day, 1940). **5a-o** was afforded by Steglich esterification (Neises & Steglich, 1978): A mixture of *N,N′*-dicyclohexylcarbodiimide (DCC; 4 mmol) and 4-dimethylaminopyridine (DMAP; 0.27 mmol) in dichloromethane (DCM) was added dropwise to a mixture of **4** (4 mmol) and proper carboxylic acid (4 mmol) in DCM at 0–5 °C. The mixture was stirred for 0.5 hr at 0–5°C then for 3–6 hr at room temperature. The precipitate was filtered off and the filtrate was evaporated to dryness. The residue was purified via column chromatography (chloroform–methanol 90:10). All the title compounds except **5a** were converted to their hydrochloride (HCl) salts using gaseous HCl.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl acetate 5a: Off-white powder (0.50 g, 45%). Mp: 72–4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H, CH_3), 4.32 (dd, J_{AB} = 14.4 Hz, J_{AX} = 4.8, H_A, CH_2), 4.38 (dd, J_{BA} = 14.4 Hz, J_{BX} = 7.2, H_B, CH_2), 6.11 (dd, J_{XB} = 7.2 Hz, J_{XA} = 4.8, H_X, CHO), 6.80–7.86 (m, 10H, aromatic); IR (ATR): 3110, 1,729 cm^{-1}; MS (ESI+) *m/z*: 304, 281 (100%) $[M + H]^+$; Anal. calcd. For $C_{17}H_{16}N_2O_2$: C 72.84, H 5.75, N 9.99, found: 72.41, H 6.01, N 9.87.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 2-methylbutanoate hydrochloride 5b: Off-white powder (0.73 g, 51%). Mp: 129–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76–0.82 (m, 3H, CH_2CH_3), 1.10 (d, 3H, $CHCH_3$), 1.39–1.51 (m, H_A, CH_2CH_3), 1.56–1.70 (m, H_B, CH_2CH_3), 2.40–2.49 (m, 1H, $CHCH_3$), 4.72–4.88 (m, 2H, CH_2N), 6.33 (dd, J_{AX} = 7.2 Hz, J_{AY} = 4.8, 1H, CHO), 7.08–9.57 (m, 10H, aromatic); IR (ATR): 3222, 1,738 cm^{-1}; MS (ESI+) *m/z*: 346, 323 (100%) $[M + H]^+$; Anal. calcd. For $C_{20}H_{23}ClN_2O_2$: C 69.94, H 6.46, N 7.81, found: 66.48, H 6.67, N 7.65.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl trimethylacetate hydrochloride 5c: White powder (0.86 g, 60%). Mp: 191–3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 9H, CH_3), 4.72–4.88 (m, 2H, CH_2), 6.28 (dd, J_{AX} = 7.2 Hz, J_{AY} = 4.8, 1H, CHO), 7.55–9.22 (m, 10H, aromatic); IR (ATR): 3088, 1,718 cm^{-1}; MS (ESI+) *m/z* (%): 346 (23), 323 (100) $[M + H]^+$; Anal. calcd. For $C_{20}H_{23}ClN_2O_2.1/2H_2O$: C 65.30, H 6.58, N 7.62, found: 64.94, H 6.69, N 7.59.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 2-methylpentanoate hydrochloride 5d: White powder (0.88 g, 59%). Mp: 168–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76–0.82 (m, 3H, CH_2CH_3), 0.84–1.12 (m, 5H, $CHCH_3$ and CH_2CH_3), 1.26–1.38 (m, H_A, CH_2CH_2), 1.42–1.52 (m, H_B, CH_2CH_2), 2.46–2.58 (m, 1H, COCH), 4.70–4.85 (m, 2H, CH_2N), 6.29–6.35 (m, 1H, CHO), 7.54–9.24 (m, 10H, aromatic); IR (ATR): 3044, 1,717 cm^{-1}; MS (ESI+) *m/z* (%): 360 (25), 337 (100) $[M + H]^+$; Anal. calcd. For $C_{21}H_{25}ClN_2O_2$: C 67.64, H 6.76, N 7.51, found: 67.30, H 6.70, N 7.47.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl but-2-enoate hydrochloride 5e: Off-white powder (0.70 g, 51%). Mp: 187–9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (d, *J* = 5.6 Hz, 3H, CH_3), 4.76 (dd, J_{AB} = 14.4 Hz, J_{AX} = 7.6 Hz, H_A, CH_2), 4.87 (dd, J_{BA} = 14.4 Hz, J_{BX} = 4.0 Hz, H_B, CH_2), 5.92 (d, *J* = 15.6 Hz, 1H, COCH), 6.38 (dd, J_{XA} = 7.6 Hz, J_{XB} = 3.6, H_X, CHO), 7.02–9.39 (m, 11H, $CHCH_3$, aromatic); IR (ATR): 3002, 1,703 cm^{-1}; MS (ESI+) *m/z* (%): 330 (22), 307 (100) $[M + H]^+$; Anal. calcd. For $C_{19}H_{19}ClN_2O_2.1/3H_2O$: C 65.42, H 5.68, N 8.03, found: 65.46, H 5.70, N 7.86.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 2-methylbut-2-enoate hydrochloride 5f: White powder (0.81 g, 56%). Mp: 153–5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (s, 3H, CCH_3), 1.81 (d, *J* = 5.6 Hz, 3H, $CHCH_3$), 4.78 (dd, J_{AB} = 14.0 Hz, J_{AX} = 8.4 Hz, H_A, CH_2), 4.85 (dd, J_{BA} = 14.4 Hz, J_{BX} = 4.0 Hz, H_B, CH_2), 6.34 (dd, J_{XA} = 8.4 Hz, J_{XB} = 4.0, H_X, CHO), 6.95–7.02 (m, 1H, $CHCH_3$), 7.54–9.20 (m, 10H, aromatic); IR (ATR): 3081, 1,693 cm^{-1}; MS (ESI+) *m/z* (%): 344 (23), 321 (100) $[M + H]^+$; Anal. calcd. For $C_{20}H_{21}ClN_2O_2$ C 67.32, H 5.93, N 7.85 found: 67.10, H 6.03, N 7.83.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl hexa-2,4-dienoate hydrochloride 5g: Pale yellow powder (0.70 g, 48%). Mp: 162–5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (d, *J* = 5.2 Hz, 3H, CH_3), 4.79–4.81 (m, 2H, CH_2), 5.94 (d, 1H, *J* = 15.6 Hz, COCH), 6.25–6.41 (m, 3H, $CHCHCH_3$, and CHO), 7.50–9.08 (m, 11H, $COCHCH$, aromatic); ^{13}C NMR

(400 MHz, $CDCl_3$): δ = 18.5, 52.3, 73.2, 117.6, 119.6, 122.7, 123.8, 125.4, 126.6, 126.6, 127.6, 127.9, 128.5, 129.5, 132.5, 132.8, 134.0, 136.0, 141.2, 146.4, 165.1; IR (ATR): 3022, 1,706 cm^{-1}; MS (ESI+) *m/z* (%): 356 (24), 333 (100) $[M + H]^+$; Anal. calcd. For $C_{21}H_{21}ClN_2O_2.H_2O$ C 65.20, H 5.99, N 7.24 found: 64.66, H 5.70, N 7.25.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 4-oxopentanoate hydrochloride 5h: White powder (0.79 g, 53%). Mp: 195–7 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3H, CH_3), 2.52–2.88 (m, 4H, CH_2CH_2), 4.66 (dd, J_{AB} = 14.4 Hz, J_{AX} = 6.0 Hz, H_A, CH_2N), 4.84 (dd, J_{BA} = 14.4 Hz, J_{BX} = 3.2 Hz, H_B, CH_2N), 6.37 (dd, J_{XA} = 5.6 Hz, J_{XB} = 3.2, H_X, CHO), 6.97–9.20 (m, 10H, aromatic); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.3, 29.9, 38.2, 53.6, 73.7, 119.6, 122.1, 123.4, 125.9, 127.0, 127.0, 128.0, 128.4, 129.3, 132.5, 133.2, 133.5, 136.0, 171.8, 207.2; IR (ATR): 3029, 1,728 cm^{-1}; MS (ESI+) *m/z* (%): 360 (22), 337 (100) $[M + H]^+$; Anal. calcd. For $C_{20}H_{21}ClN_2O_3.1/2H_2O$ C 62.91, H 5.81, N 7.34 found: 62.99, H 6.01, N 7.44.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl cyclohexanecarboxylate hydrochloride 5i: White powder (1.02 g, 66%). Mp: 138–40 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09–2.50 (m, 11H, cyclohexane), 4.70–4.83 (m, 2H, CH_2N), 6.31 (dd, J_{AX} = 7.8 Hz, J_{AY} = 4.4, 1H, CHO), 7.52–9.20 (m, 10H, aromatic); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 24.6, 24.6, 25.1, 28.3, 41.9, 52.2, 73.0, 119.6, 122.7, 123.8, 125.4, 126.6, 127.6, 127.9, 128.5, 132.5, 132.8, 134.0, 135.9, 173.8; IR (ATR): 3022, 1,719 cm^{-1}; MS (ESI+) *m/z* (%): 372 (23), 349 (100) $[M + H]^+$; Anal. calcd. For $C_{22}H_{25}ClN_2O_2.1/2H_2O$ C 67.08, H 6.65, N 7.11 found: 67.28, H 6.54, N 7.18.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl phenylacetate hydrochloride 5j: White powder (0.78 g, 50%). Mp: 185–7 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H, $COCH_2$), 4.56 (dd, J_{AB} = 14.4 Hz, J_{AX} = 7.2 Hz, H_A, CH_2N), 4.78 (dd, J_{BA} = 14.4 Hz, J_{BX} = 3.6 Hz, H_B, CH_2N), 6.30 (dd, J_{XA} = 7.6 Hz, J_{XB} = 3.2, H_X, CHO), 6.56–9.28 (m, 15H, aromatic); IR (ATR): 3027, 1,731 cm^{-1}; MS (ESI+) *m/z* (%): 380 (26), 357 (100) $[M + H]^+$; Anal. calcd. For $C_{23}H_{21}ClN_2O_2.1/2H_2O$ C 67.23, H 5.64, N 6.82 found: C 67.28, H 5.95, N 6.77.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 4-phenylbutanoate hydrochloride 5k: White powder (0.83 g, 49%). Mp: 131–3 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87–1.94 (m, 2H, $COCH_2CH_2$), 2.40 (t, J_1 = 7.6 Hz, J_2 = 7.2 Hz, 2H, $CH_2C_6H_5$), 2.58 (t, J_1 = 8 Hz, J_2 = 7.2 Hz, 2H, $COCH_2$), 4.70 (dd, J_{AB} = 14.4 Hz, J_{AX} = 7.6 Hz, H_A, CH_2N), 4.85 (dd, J_{BA} = 14.6 Hz, J_{BX} = 4.0 Hz, H_B, CH_2N), 6.33 (dd, J_{XA} = 7.2 Hz, J_{XB} = 4.0, H_X, CHO), 6.96–9.60 (m, 15H, aromatic); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.0, 32.8, 34.1, 51.0, 73.3, 120.5, 122.4, 123.9, 125.5, 125.9, 126.6, 127.6, 127.9, 128.2, 128.3, 128.4, 132.5, 132.8, 133.9, 136.1, 141.1, 171.7; IR (ATR): 3044, 1,720 cm^{-1}; MS (ESI+) *m/z* (%): 308 (26), 385 (100) $[M + H]^+$; Anal. calcd. For $C_{25}H_{25}ClN_2O_2$ C 71.33, H 5.99, N 6.66 found: C 71.34, H 6.16, N 6.65.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 3-phenylprop-2-enoate hydrochloride 5l: White powder (0.87 g, 54%). Mp: 190–2 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.81 (dd, J_{AB} = 14.4 Hz, J_{AX} = 7.2 Hz, H_A, CH_2N), 4.92 (dd, J_{BA} = 14.4 Hz, J_{BX} = 3.6 Hz, H_B, CH_2N), 6.47 (dd, J_{XA} = 7.6 Hz, J_{XB} = 3.6, H_X, CHO), 6.52 (d, J = 16 Hz, 1H, COCH), 7.06–9.54 (m, 16H, CHC_6H_5 and aromatic); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 52.4, 73.5, 117.2, 119.6, 122.8, 123.9, 125.4, 126.6, 127.7, 127.9, 128.5, 128.5, 128.9130.8, 132.5, 132.8, 133.8, 133.9, 136.1, 145.8, 165.0; IR (ATR): 3000, 1,716 cm^{-1}; MS (ESI+) *m/z* (%): 392 (26), 369 (100) $[M + H]^+$; Anal. calcd. For $C_{24}H_{21}ClN_2O_2.1/2H_2O$ C 69.64, H 5.36, N 6.67 found: C 69.70, H 5.65, N 6.68.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 3-benzoylpropanoate hydrochloride 5m: White powder (0.79 g, 46%). Mp: 184–6 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.72–2.96 (m, 2H, $COCH_2CH_2COC_6H_5$), 3.24–3.50 (m, 2H, $COCH_2CH_2COC_6H_5$), 4.67 (dd, J_{AB} = 14.4 Hz, J_{AX} = 6.0 Hz, H_A, CH_2N), 4.89 (dd, J_{BA} = 14.4 Hz, J_{BX} = 2.8 Hz, H_B, CH_2N), 6.41 (dd, J_{XA} = 5.8 Hz, J_{XB} = 2.8, H_X, CHO), 7.04–9.20 (m, 15H, aromatic); IR (ATR): 3077, 1,722 cm^{-1}; MS (ESI+) *m/z* (%): 422 (27), 399 (100) $[M + H]^+$; Anal. calcd. For $C_{25}H_{23}ClN_2O_2$ C 69.04, H 5.33, N 6.44 found: C 68.77, H 5.27, N 6.49.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl diphenylacetate hydrochloride 5n: Pale yellow powder (1.23 g, 66%). Mp: 182–4 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.70–4.83 (m, 2H, CH_2), 5.13 (s, 1H, COCH), 6.31–6.37 (m, 1H, CHO), 6.51 (m, 20H, aromatic); IR (ATR): 3033, 1,729 cm^{-1}; MS (ESI+) *m/z* (%): 456 (32), 433 (100) $[M + H]^+$; Anal. calcd. For $C_{29}H_{25}ClN_2O_2.1/2H_2O$ C 72.87, H 5.48, N 5.86 found: C 73.01, H 5.99, N 5.75.

2-(1*H*-Imidazol-1-yl)-1-(2-naphthyl)ethyl 4-phenylbenzoate hydrochloride 5o: Pale yellow powder (0.77 g, 42%). Mp: 151–3 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.88–5.04 (m, 2H, CH_2), 6.55–6.62 (m, 1H, CHO), 7.08–9.51 (m, 19H, aromatic); IR (ATR): 3002, 1,713 cm^{-1}; MS (ESI+) *m/z* (%): 442 (31), 419 (100) $[M + H]^+$; Anal. calcd. For $C_{28}H_{23}ClN_2O_2.1/2H_2O$ C 72.49, H 5.21, N 6.04 found: C 72.84, H 5.18, N 6.17.

2.2 | Pharmacology

All the in vivo tests were performed by The epilepsy therapy screening program (ETSP) of the National Institutes of Health (NIH) in compliance with compliance with the U.S. National Research Council's Guide for the Care and Use of Laboratory Animals, the U.S. Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and Guide for the Care and Use of Laboratory Animals.

2.2.1 | MES test

Each compound was given at default doses (30, 100, and 300 mg/kg) to adult male CF1 mice (18–25 g) or Sprague–Dawley rats via ip or oral route. After predetermined time points, the animals were treated with ocular 0.5% tetracaine and delivered 60 Hz corneal stimulation at 50 mA (mice) or 150 mA (rats) for 0.2 s, which typically induces a tonic seizure (rapid spams or jerky movements of the limbs) followed by a clonic phase. Compounds were considered active upon abolition of the hind limb tonic extensor component of the seizure (Castel-Branco, Alves, Figueiredo, Falcao, & Caramona, 2009).

2.2.2 | SCM test

Each compound was given at default doses (30, 100, and 300 mg/kg) to adult male CF1 mice (18–25 g) and Sprague–Dawley rats via ip or oral route. After the determined amount of time 85 mg/kg (mice) or

56.4 mg/kg (rats) metrazol was injected subcutaneously in the midline of the neck, which triggers clonic seizures characterized by spasms of the fore and/or hind limbs, jaws, or vibrissae. The animals were observed for the next 30 min and those without these symptoms were considered protected by the compound (Swinyard, 1989).

2.2.3 | Six hertz psychomotor test

Each compound was given at default doses (30, 100, and 300 mg/kg) to adult male CF1 mice (18–25 g) via ip route. After predetermined time points, the mice were treated with ocular 0.5% tetracaine and delivered 6 Hz corneal stimulation at 32 or 44 mA for 3 s, which induces a seizure with a minimal clonic phase followed by stereotyped, automatistic behaviors including twitching of the vibrissae and Straub-tail. The mice not displaying these behaviors were considered protected by the compound (Barton, Klein, Wolf, & White, 2001).

2.2.4 | CKM test

Adult male CF-1 mice were kindled until each animal underwent five consecutive Stage 5 seizures (fully kindled). The kindling procedure consists of corneal stimulations of 3 mA and 60 Hz for 3 s twice a day. Eight mice were used for each dose (42.5, 85, and 170 mg/kg) at the time to peak effect (TPE) and the behavioral seizure scores (BSS) were rated for each when stimulated in the presence of **5l** (see Table S3 for the scoring criteria; Racine, 1972).

2.2.5 | Hippocampal kindling test

Adult male Sprague–Dawley rats (275–300 g) were surgically implanted with bipolar electrodes into the ventral hippocampus under ketamine–xylazine anesthesia and allowed to recover for 1 week before the rapid hippocampal kindling procedure (Lothman, Perlin, & Salerno, 1988; Lothman, Salerno, Perlin, & Kaiser, 1988), which consists of applying a repeated stimulation regimen on alternating days for a total of five stimulus days (Lothman & Williamson, 1994). During the stimulation regimen, a 50 Hz, 10 s train of 1 ms biphasic 200 μA pulses were delivered every 30 min for 6 hr, thereby giving 12 stimulations per stimulus day. Two rats, which were kindled to display a Stage 5 behavioral seizure, that is, fully kindled, were administered with a nontoxic dose of the test compound to evaluate its ability to modify the fully expressed kindled seizure and afterdischarge duration after a 1-week, stimulation-free period. Each kindled rat was given the kindled stimulation at 15, 45, 75, 105, 135, 165, and 195 min following drug administration. The rats were allowed at least 5 days between tests to "washout" any investigational compound after testing. (The BSS were rated according to the criteria in Table S3.)

2.2.6 | Rotorod and minimal motor impairment tests

The mice with compound were placed on a rod rotating at 6 rpm. Any mouse that fell off the rod three times in a minute was considered intoxicated by the compound (Stables & Kupferberg, 1997).

The animals with compound were monitored for indications of ataxia (circular or zigzag gait, abnormal body posture and spreading legs, tremor, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of righting reflex, and changes in muscle tone). Animals showing at least two of these indications were considered intoxicated by the compound (Stables & Kupferberg, 1997).

2.2.7 | Quantification studies

Quantification of effective and toxic doses (ED_{50} and TD_{50}) was performed at the TPE of each compound in a given test, animal, and route. For TPE determination, animals were tested at 0.25, 0.5, 1.0, 2.0, and 4.0 hr at a given dose to determine the TPE. To obtain biological response data, groups of animals were tested at various doses at the TPE until at least two points were established between 0 and full protection. By applying Probit analysis the ED_{50} and TD_{50}, 95% confidence interval, slope of the regression line, and *SE* were calculated.

2.3 | Molecular modeling

Ligands were modeled and prepared using LigPrep (Schrödinger release 2018-4, LLC, New York, NY 2018), MacroModel (Schrödinger release 2018-4, LLC), and OPLS_2005 force field on Maestro (Schrödinger release 2018-4, LLC; Banks et al., 2005). Their descriptors and properties were calculated using QikProp (Schrödinger release 2018-4, LLC).

The $GABA_AR$ structure (PDB ID: 6D6T; Zhu et al., 2018) was downloaded from the RCSB protein databank (www.rcsb.org; Berman et al., 2000) and prepared for docking using the Protein Preparation Wizard of Maestro (Sastry, Adzhigirey, Day, Annabhimoju, & Sherman, 2013) by treating hydrogens and charges. For receptor grid, the central coordinates of the cocrystallized flumazenil was taken and **5l** was docked 50 times flexibly to $GABA_AR$ using Glide (Schrödinger release 2018-4, LLC) at extra precision (Friesner et al., 2004, 2006; Halgren et al., 2004). To confirm the accuracy of the docking protocol, the cocrystallized flumazenil was re-docked to $GABA_AR$ and the obtained binding mode for flumazenil was close to its original conformation (RMSD 0.62 Å).

3 | RESULTS AND DISCUSSION

3.1 | Chemistry

1-(2-naphthyl)ethanone (**1**) was brominated using bromine (Br_2) and bromic acid ($HBrO_3$) to obtain 2-bromo-1-(2-naphthyl)ethanone (**2**) with which imidazole was alkylated using its excess as base in *N*,*N*-dimethylformamide (DMF) to afford 2-(1*H*-iImidazol-1-yl)-1-(2-naphthyl)ethanone (**3**). Then, **3** was reduced using sodium borohydride ($NaBH_4$) to yield **4**. Compounds **2-4** were previously reported in the literature (Tajana, Portioli, Subissi, & Nardi, 1981). **5a-o** were synthesized by esterification of **4** with various carboxylic acids in the presence of an acyl transfer and dehydration catalyst (DMAP and DCC) and converted to their HCl salts to further purify and improve their aqueous solubility (Scheme 1). Their structures and purity were confirmed by spectral and elemental analyses.

SCHEME 1 Synthesis and molecular structure of **5a-o**

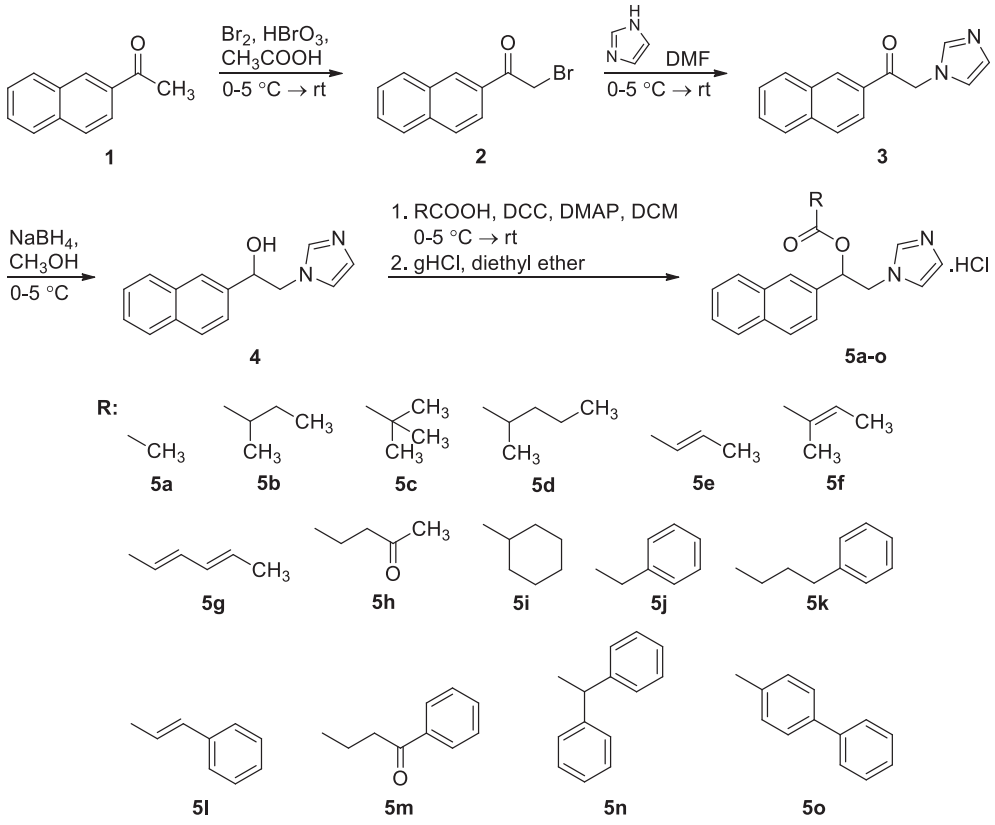

TABLE 1 Anticonvulsant identification results of **5a**, **5d-f**, **5h-m**, and **5o** in mice via ip route

			Compound													
Test	**Time (hr)**	**Dose (mg/kg)**	**5a**	**5d**	**5e**	**5f**	**5h**	**5i**	**5j**	**5k**	**5l**	**5m**	**5o**	**PHE**	**CBZ**	**VPA**
MES	0.5	30	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	**1/1**	0/1
		100	**3/3**	**3/3**	**3/3**	**2/3**	**2/2**	**3/3**	**3/3**	**3/3**	**3/3**	**3/3**	0/3	**1/1**	**1/1**	0/1
		300	**1/1**	**1/1**	0/3[a]	0/3[a]	-	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	0/1
	4	30	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1	0/1
		100	**2/3**	**3/3**	0/3	1/3	1/1	**2/3**	**2/3**	1/3	**2/3**	1/3	1/3	**1/1**	**1/1**	0/1
		300	**1/1**	**1/1**	**1/1**	0/1	-	**1/1**	-	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	0/1
SCM	0.5	30	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
		100	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1
		300	0/1	0/1	-	-	-	0/1	-	0/1	0/1	0/1	0/1	0/1	**1/1**	**1/1**
	4	30	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
		100	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
		300	0/1	0/1	-	-	-	0/1	-	0/1	0/1	0/1	0/1	0/1	**1/1**	0/1
Toxicity	0.5	30	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/4	0/4	0/4
		100	0/4	0/4	0/4	0/4	0/3	0/4	0/4	0/4	0/4	0/4	0/4	**3/4**	**4/4**	0/4
		300	**2/2**[b]	**2/2**[b]	-	-	-	**2/2**[b]	**1/1**[b]	**2/2**	**2/2**[b]	**2/2**[b]	0/2	**4/4**	**4/4**	0/4
	4	30	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
		100	0/4	0/4	0/4	0/4	0/2	0/4	0/4	0/4	0/4	0/4	0/4	**2/2**	0/2	0/2
		300	0/2	**2/2**	0/1	0/1	-	**2/2**	-	0/2	**2/2**	0/2	0/2	**2/2**	**2/2**	0/2

Note. "-" not determined. Results are expressed as the number of animals active/toxic over tested. Data indicating at least 50% activity (or toxicity) is highlighted as bold.

[a]Death.

[b]Clonic seizures.

3.2 | Pharmacology

Oral and ip MES, SCM, and 6 Hz psychomotor tests were used in anticonvulsant identification studies in mice and rats. MES, a model for generalized tonic–clonic seizures, tests a compound's ability to prevent seizure spread (Swinyard, 1989; White, Johnson, Wolf, & Kupferberg, 1995; White, Woodhead, & Franklin, 1995). SCM, a model for human clonic, forebrain seizures, tests a compound's ability to raise seizure threshold (Snead, 1992; Swinyard, 1989). Siz hertz psychomotor test is a model for human partial seizures and tests the ability of a compound to block psychomotor seizures (Barton et al., 2001).

5a, **5d-f**, **5h-m**, and **5o** were tested ip in mice; all the compounds, except **5f**, were protective in the MES test at one of the doses and one of the time points at least (Table 1). No protection was observed at 30 mg/kg, but the compounds were active up to 4 hr except **5f** and **5i**. All but **5o** were protective at 100 mg/kg without neurotoxicity. None was active in the SCM test. According to the activity data of phenytoin (PHE), carbamazepine (CBZ), and valproic acid (VPA) obtained from the PANAChE (Public Access to Neuroactive & Anticonvulsant Chemical Evaluations) database of the NIH, the compounds' activity profile was similar to PHE.

5a, **5b**, **5d**, **5f**, **5g**, **5i**, and **5j-n** were tested in rats using the MES test at time points from 0.25 to 4 hr. Unlike in mice, these compounds were active at 30 mg/kg, except **5f** and **5n** (Table 2). **5b** was active up to 1 hr via ip route and **5i**, **5j**, **and 5l** up to 4 hr orally. None of the compounds manifested toxicity in this test.

Furthermore, **5g**, **5i**, **5k**, **5l**, and **5o** were tested ip in mice using 6 Hz psychomotor test at 75, 100, or 200 mg/kg at time points from 0.25 to 4 hr. **5l** was active up to 2 hr at 200 mg/kg at 32 mA but inactive at 44 mA. **5i** showed protection at the same dose up to 2 hr at 44 mA (Table 3). These compounds did not display toxicity, either.

Quantification studies were performed for **5b**, **5c**, **5g**, **5i**, and **5l** using various tests at their TPE, the time point of the highest activity or toxicity. The results are presented in Table 4 along with the

TABLE 2 Anticonvulsant identification results of **5a**, **5b**, **5d**, **5f**, **5g**, **5i**, and **5j-n** using MES test in rats via ip and oral route

			Compound											
Test	Dose (mg/kg)	Time (hr)	5a[a]	5b[b]	5d[a]	5f[a]	5g[b]	5i[a]	5j[a]	5k[b]	5l[a]	5l[b]	5m[a]	5n[a]	5n[b]
MES	30	0.25	**2/4**	**4/4**	0/4	1/4	**3/4**	**2/4**	1/4	**2/4**	1/4	**2/4**	**2/4**	0/4	0/4
		0.5	**2/4**	**4/4**	0/4	1/4	**4/4**	**2/4**	0/4	1/4	**2/4**	**2/4**	**2/4**	0/4	0/4
		1	**2/4**	**3/4**	**2/4**	0/4	0/4	**3/4**	**2/4**	0/4	**2/4**	1/4	1/4	0/4	0/4
		2	**2/4**	0/4	**2/4**	1/4	1/4	**3/4**	0/4	0/4	**4/4**	0/4	1/4	0/4	0/4
		4	1/4	1/4	0/4	1/4	0/4	**3/4**	**3/4**	0/4	**2/4**	1/4	0/4	0/4	0/4
Tox.	30	0.25	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		0.5	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		1	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		2	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
		4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4

Note. Tox., toxicity. Data indicating at least 50% activity (or toxicity) is highlighted as bold.
[a]Oral route.
[b]Ip route.

TABLE 3 Anticonvulsant identification results of **5g**, **5i**, **5k**, **5l**, and **5o** using 6 Hz psychomotor test in mice via ip route

		32 mA							44 mA		
Test	Time (hr)	Dose (mg/kg)	5g	5k	Dose (mg/kg)	5l	Dose (mg/kg)	5o	Dose (mg/kg)	5i	5l
6 Hz	0.25	100	1/4	0/4	200	**3/4**	75	0/4	200	1/4	0/4
	0.5		**2/4**	0/4		**3/4**		0/4		**3/4**	0/4
	1		0/4	0/4		**2/4**		**2/4**		**2/4**	0/4
	2		0/4	0/4		**2/4**		0/4		**2/4**	0/4
	4		0/4	0/4		0/4		0/4		0/4	0/4
Tox.	0.25	100	0/4	0/4	200	0/4	75	0/4	200	0/4	0/4
	0.5		0/4	0/4		0/4		0/4		0/4	0/4
	1		0/4	0/4		0/4		0/4		0/4	0/4
	2		0/4	0/4		0/4		0/4		0/4	0/4
	4		0/4	0/4		0/4		0/4		0/4	0/4

Note. Data indicating at least 50% activity (or toxicity) is highlighted as bold.

TABLE 4 ED_{50}, TD_{50}, and TI values of **5b**, **5c**, **5g**, **5i**, and **5l**

Compounds	Test	Time (hr)	Animal	Route	ED_{50} or TD_{50} (mg/kg)	95% CI[a]	Slope	SE[b]	TI[c]
5b	MES	0.25	Rat	Ip	16.01	8.26–18.99	11.89	5.51	>5.3
	Tox.	0.25	Rat	Ip	>85	–	–	–	N/A
5c	MES	0.25	Rat	Ip	15.82	11.61–21.0	4.47	1.29	4.9
	Tox.	0.25	Rat	Ip	76.95	67.82–85.06	13.12	3.59	N/A
5g	MES	0.25	Mouse	Ip	51.58	41.65–59.14	8.60	2.51	5.0
	Tox.	0.25	Mouse	Ip	257.20	246.06–309.72	13.23	4.30	N/A
	MES	1	Rat	Oral	36.12	18.30–57.55	2.25	0.62	>13.8
	Tox.	1	Rat	Oral	>500	–	–	–	N/A
5i	MES	0.25	Mouse	Ip	38.07	31.32–49.06	5.13	1.52	5.2
	Tox.	0.25	Mouse	Ip	198.38	157.63–229.47	8.64	2.40	N/A
	MES	0.25	Rat	Ip	11.76	6.50–17.97	2.92	0.92	>21.3
	Tox.	0.25	Rat	Ip	>250	–	–	–	N/A
	MES	1	Rat	Oral	50.89	26.74–102.11	1.58	0.47	>9.8
	Tox.	1	Rat	Oral	>500	–	–	–	N/A
5l	MES	0.5	Mouse	Ip	51.86	37.90–66.73	5.83	1.94	8.2
	6 Hz[d]	0.5	Mouse	Ip	170.39	135.94–206.34	7.16	2.16	2.5
	CKM	0.5	Mouse	Ip	77.44	52.52–109.91	5.31	1.72	5.5
	Tox.	1	Mouse	Ip	426.55	308.40–527.37	7.11	2.36	N/A
	MES	2	Rat	Oral	79.20	44.36–180.6	1.75	0.51	>6.3
	Tox.	2	Rat	Oral	>500	–	–	–	N/A
PHE	MES	1	Mouse	Ip	6.71	5.38–8.37	11.05	3.29	6.1
	Tox.	1	Mouse	Ip	40.63	39.0–42.89	32.85	8.96	N/A
	MES	4	Mouse	Oral	8.59	7.19–9.09	13.21	4.16	10.3
	Tox.	2	Mouse	Oral	88.62	80.39–98.52	18.37	6.49	N/A
	MES	0.25	Rat	Ip	2.39	1.38–3.67	3.05	0.92	6.4
	Tox.	0.5	Rat	Ip	15.21	11.92–19.22	7.55	2.59	N/A
	MES	2	Rat	Oral	28.11	20.73–35.20	4.95	1.38	>35.6
	Tox.	2	Rat	Oral	>1,000	–	–	–	N/A
CBZ	6 Hz[d]	0.25	Mouse	Ip	47.91	27.39–94.16	1.88	0.69	0.95
	Tox.	0.25	Mouse	Ip	45.36	32.87–54.37	6.84	2.05	N/A

Note. TD_{50} values are showed at the intersection of "ED_{50} or TD_{50}" column and "Tox." row highlighted in gray. Data indicating at least 50% activity (or toxicity) is highlighted as bold.

[a]Confidence interval.

[b]Standard error.

[c]Calculated according to formula: TD_{50}/ED_{50}.

[d]32 mA, N/A, not applicable.

therapeutic index (TI) values, as an important indicator of safe dose interval.

5b, **5c**, and **5i** showed outstanding anti-MES profile in rats ip (ED_{50}: 16.01, 15.82, and 11.76 mg/kg; TI: >5.3, 4.9, >21.3, respectively). **5l** showed moderate anti-6 Hz activity and toxicity (ED_{50}: 170.39 mg/kg, TI: 2.5), which was also promising considering that PHE is inactive in 6 Hz model and CBZ's effective dose is not safe (TI: 0.95). The compounds were more active in rats and the peak effect was observed later when given orally. **5i's** ED_{50} increased threefold orally compared to ip. This was more than 10-fold in the case of PHE, thus we can suggest that our compounds had good oral bioavailability.

5l was tested and found active (ED_{50}: 77.44 mg/kg) in the CKM test, a chronic seizure model of human partial seizures for identifying potential compounds, such as levetiracetam (Table 4; Matagne & Klitgaard, 1998; Rogawski, 2006; Rowley & White, 2010). Considering the TD_{50} and the TI value (5.5), **5l** was quite promising compared to VPA (ED_{50}: 174.39 mg/kg and TI: 2.3; CKM quantification for PHE and CBZ is unavailable).

5i and **5l** were tested and failed in hippocampal kindling test in rats, a model for human focal seizures testing compounds' ability to block behavioral seizures and/or decrease the afterdischarge duration (see Supporting Information for details; Lothman, Salerno, et al., 1988).

TABLE 5 QikProp results for **5a-o**

Compounds	Descriptors and properties with their recommended values or ranges										
	#rotor 0–15	donorHB0.0–6.0	acceptHB 2.0–20.0	QPlogPo/w−2.0 to 6.5	QPlogS−6.5 to 0.5	QPPCaco >500 great	QPlogBB −3.0 to 1.2	QPPMDCK >500 great	%HOA >80% is high	RO5	RO3
5a	4	0	4	3.47	−4.07	1,601.35	−0.46	822.96	100	0	0
5b	6	0	4	4.46	−4.96	2,388.09	−0.40	1,267.59	100	0	0
5c	5	0	4	4.42	−4.96	2,439.94	−0.32	1,297.36	100	0	0
5d	7	0	4	5.08	−5.26	3,519.95	−0.32	1927.93	100	1	0
5e	5	0	4	4.24	−4.62	1834.32	−0.50	953.09	100	0	0
5f	5	0	4	4.61	−4.92	2,332.94	−0.40	1,235.98	100	0	0
5g	7	0	4	4.94	−5.18	1823.90	−0.66	947.24	100	0	1
5h	7	0	6	3.39	−4.33	1,279.78	−0.74	645.88	100	0	0
5i	5	0	4	5.10	−5.49	2,401.67	−0.39	1,275.38	100	1	1
5j	6	0	4	5.29	−6.05	1967.24	−0.54	1,027.96	100	1	1
5k	8	0	4	5.96	−6.64	2023.26	−0.65	1,059.63	100	1	1
5l	7	0	4	5.62	−6.30	1842.42	−0.68	957.64	100	1	1
5m	8	0	6	4.55	−6.01	1,297.34	−0.82	655.46	100	0	0
5n	7	0	4	6.94	−8.02	3,795.27	−0.31	2091.43	100	1	1
5o	6	0	4	6.64	−7.72	2,137.78	−0.57	1,124.61	100	1	1

Note. *#rotor*: Number of nontrivial and nonhindered rotatable bonds. *donorHB*: Estimated number of hydrogen bonds donated by the solute to water molecules in an aqueous solution. *acceptHB*: Estimated number of hydrogen bonds accepted by the solute from water molecules in an aqueous solution. *QPlogPo/w*: Predicted octanol/water partition coefficient. *QPlogS*: Predicted aqueous solubility, log S (S in mol/dm^3). *QPPCaco*: Predicted apparent Caco-2 cell permeability (nm/s). Caco-2 cells are a model for the gut–blood barrier. *QPlogBB*: Predicted brain/blood partition coefficient for orally delivered drugs. *QPPMDCK*: Predicted apparent MDCK cell permeability (nm/s). MDCK cells are considered to be a good mimic for the blood–brain barrier. *%HOA*: Predicted human oral absorption %. *RO5*: Number of violations of Lipinski's rule of five: mol_MW <500, QPlogPo/w <5, donorHB ≤5, acceptHB ≤10; the less the RO% value the better. *RO3*: Number of violations of Jorgensen's rule of three. The three rules are QPlogS > −5.7, QP PCaco >22 nm/s; the less the RO% value the better.

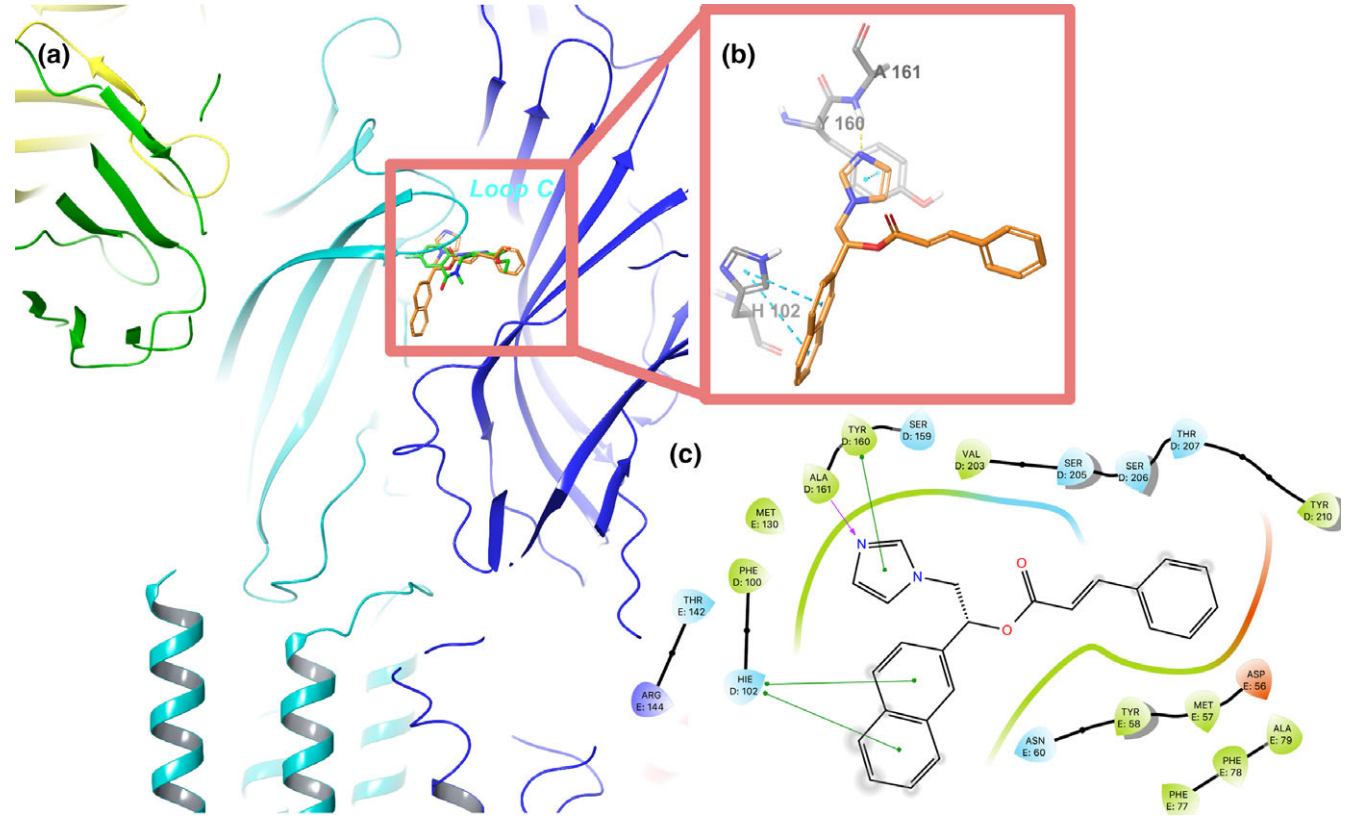

FIGURE 2 Superposition of flumazenil (green) and **5l** (orange) in the BZD binding site of $GABA_AR$ (color ribbons; a), key interactions of **5l** (residues are showed as gray sticks, H bonds as yellow and π–π interactions as blue dashes; b), and 2D interaction diagram of **5l** with $GABA_AR$ (c)

TABLE 6 Docking scores (kcal/mol) of **5a-o** in the BZD binding site of $GABA_AR$

Compounds	Docking score	Compounds	Docking score	Compounds	Docking score
5a	−5.97	**5f**	−7.24	**5k**	−6.63
5b	−7.43	**5g**	−6.63	**5L**	−6.75
5c	−5.34	**5h**	−6.70	**5m**	−6.77
5d	−7.60	**5i**	−7.70	**5n**	−6.60
5e	−7.00	**5j**	−6.01	**5o**	−5.80

3.3 | Prediction of ADMET and drug-likeness

According to QikProp, a software that predicts pharmaceutically relevant descriptors and properties of organic molecules in comparison with a known-drug set, **5a-o** were in accordance with orally available and blood–brain barrier-permeating chemical space with minor exceptions (Table 5; Kelder, Grootenhuis, Bayada, Delbressine, & Ploemen, 1999; Lipinski, Lombardo, Dominy, & Feeney, 2001; Mikitsh & Chacko, 2014). Favorable ADMET properties were predicted for most compounds except **5n** and **5o,** which showed high lipophilicity and low water solubility apparently due to the extra phenyl ring in their ester moieties. These two compounds were among the derivatives with low anticonvulsant activity. QikProp calculated aqueous solubility, high oral absorption, and gut–blood barrier permeability for the compounds (see Supporting Information for details).

3.4 | Molecular docking

Anti-6 Hz and anti-kindling activity is connected with benzodiazepine (BZD)-type allosteric activation of $GABA_AR$ (Albertson, Stark, & Derlet, 1990; Kaminski, Livingood, & Rogawski, 2004; Monaghan, McAuley, & Data, 1999). We previously reported some AAAs with anti-6 Hz and anti-CKM activity to show high affinity to BZD binding site of $GABA_AR$ (Sari et al., 2017). We docked the title compounds to the BZD binding site of $GABA_AR$, which lies at the interface of the extracellular domains of $\alpha1^+$ and $\gamma2^-$ and beneath loop C of $\alpha1$ (Figure 2a). The compounds assumed a common binding orientation with the naphthalene ring parallel to the central pore and close to $\alpha1$ His102, the imidazole close to loop C and the ester portion reaching to the $\gamma2$ subunit. **5l**, active in 6 Hz and CKM tests, bound to the receptor with good affinity making interactions with the key residues

(Table 6). The naphthalene was in π–π interactions with His102 and the imidazole with Tyr160 of α1 (Figure 2b). The latter donated H bond to Ala161. **5l** made van der Waals interactions with residues from both subunits (Figure 2c). **5i**, another derivative with potent anti-6 Hz activity, also made similar interactions, in addition to an H bond with Thr207 of loop C (see Figure S7). Most of these residues were reported to determine binding affinities of BZD-type ligands in alanine scanning, mutagenesis, and related experimental studies (please note that the residue numbering of the α1 subunit of the receptor 6D6T is one higher than the original sequence; Bergmann, Kongsbak, Sørensen, Sander, & Balle, 2013). Similar interactions were also observed between the receptor and co-crystallized flumazenil (Zhu et al., 2018).

4 | CONCLUSION

5a-e and **5f-l** emerged as promising compounds with anticonvulsant activity. Especially, **5b**, **5c**, and **5i** showed outstanding protection in the MES test in rats. Also, **5l** was protective against 6 Hz psychomotor and CKM models. No protection was observed in the SCM and hippocampal kindling tests. The active compounds showed minimal behavioral toxicity, thus had high TI values. These results suggest that our compounds possess potential against generalized tonic–clonic and partial seizures with a wide safe dosage range.

The compounds were predicted to have favorable ADMET properties and comply with the drug-like chemical space except **5n** and **5o**, which were too lipophilic due to the double phenyl ring on their ester moieties and which showed limited anticonvulsant activity. **5l** showed high affinity to the BZD binding site residues of $GABA_AR$ in agreement with its activity profile, making it likely to exert an BZD-type activation of $GABA_AR$, although anticonvulsants are known to act through multiple pathways.

ACKNOWLEDGMENTS

The authors are grateful to the ETSP team for conducting biological experiments and to Prof. Dr. Erhan Palaska for providing the mass data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Suat Sari https://orcid.org/0000-0002-8248-4218

REFERENCES

Albertson, T. E., Stark, L. G., & Derlet, R. W. (1990). Modification of amygdaloid kindling by diazepam in juvenile rats. *Developmental Brain Research*, *51*(2), 249–252. https://doi.org/10.1016/0165-3806(90)90282-4

Baji, H., Flammang, M., Kimny, T., Gasquez, F., Compagnon, P., & Delcourt, A. (1995). Synthesis and antifungal activity of novel (1-aryl-2-heterocyclyl) ethylideneaminooxymethyl-substituted dioxolanes. *European Journal of Medicinal Chemistry*, *30*(7), 617–626. https://doi.org/10.1016/0223-5234(96)88277-8

Banks, J. L., Beard, H. S., Cao, Y., Cho, A. E., Damm, W., Farid, R., … Levy, R. M. (2005). Integrated modeling program, applied chemical theory (IMPACT). *Journal of Computational Chemistry*, *26*(16), 1752–1780. https://doi.org/10.1002/jcc.20292

Barton, M. E., Klein, B. D., Wolf, H. H., & White, H. S. (2001). Pharmacological characterization of the 6 Hz psychomotor seizure model of partial epilepsy. *Epilepsy Research*, *47*(3), 217–227. https://doi.org/10.1016/S0920-1211(01)00302-3

Bergmann, R., Kongsbak, K., Sørensen, P. L., Sander, T., & Balle, T. (2013). A unified model of the GABA A receptor comprising agonist and benzodiazepine binding sites. *PLoS One*, *8*(1), e52323. https://doi.org/10.1371/journal.pone.0052323

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., … Bourne, P. E. (2000). The protein data bank. *Nucleic Acids Research*, *28*(1), 235–242. https://doi.org/10.1093/nar/28.1.235

Castel-Branco, M. M., Alves, G. L., Figueiredo, I. V., Falcao, A. C., & Caramona, M. M. (2009). The maximal electroshock seizure (MES) model in the preclinical assessment of potential new antiepileptic drugs. *Methods and Findings in Experimental and Clinical Pharmacology*, *31*(2), 101–106. https://doi.org/10.1358/mf.2009.31.2.1338414

Dalkara, S., & Karakurt, A. (2012). Recent progress in anticonvulsant drug research: Strategies for anticonvulsant drug development and applications of antiepileptic drugs for non-epileptic central nervous system disorders. *Current Topics in Medicinal Chemistry*, *12*(9), 1033–1071. https://doi.org/10.2174/156802612800229215

Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J. J., Mainz, D. T., … Shenkin, P. S. (2004). Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *Journal of Medicinal Chemistry*, *47*(7), 1739–1749. https://doi.org/10.1021/jm0306430

Friesner, R. A., Murphy, R. B., Repasky, M. P., Frye, L. L., Greenwood, J. R., Halgren, T. A., … Mainz, D. T. (2006). Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. *Journal of Medicinal Chemistry*, *49*(21), 6177–6196. https://doi.org/10.1021/jm051256o

Godefroi, E. F., Heeres, J., Van Cutsem, J., & Janssen, P. A. (1969). The preparation and antimycotic properties of derivatives of 1-phenethylimidazole. *Journal of Medicinal Chemistry*, *12*(5), 784–791. https://doi.org/10.1021/jm00305a014

Halgren, T. A., Murphy, R. B., Friesner, R. A., Beard, H. S., Frye, L. L., Pollard, W. T., & Banks, J. L. (2004). Glide: A new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. *Journal of Medicinal Chemistry*, *47*(7), 1750–1759. https://doi.org/10.1021/jm030644s

Immediata, T., & Day, A. R. (1940). β-Naphthyl derivatives of ethanolamine and n-substituted ethanolamines. *Journal of Organic Chemistry*, *5*(5), 512–527. https://doi.org/10.1021/jo01211a005

Kaminski, R. M., Livingood, M. R., & Rogawski, M. A. (2004). Allopregnanolone analogs that positively modulate GABA receptors protect against partial seizures induced by 6-Hz electrical stimulation in mice. *Epilepsia*, *45*(7), 864–867. https://doi.org/10.1111/j.0013-9580.2004.04504.x

Karakurt, A., Aytemir, M. D., Stables, J. P., Özalp, M., Betül Kaynak, F., Özbey, S., & Dalkara, S. (2006). Synthesis of some Oxime ether derivatives of 1-(2-Naphthyl)-2-(1, 2, 4-triazol-1-yl) ethanone and their anticonvulsant and antimicrobial activities. *Archiv der Pharmazie*, *339*(9), 513–520. https://doi.org/10.1002/ardp.200500248

Karakurt, A., Özalp, M., Işık, Ş., Stables, J. P., & Dalkara, S. (2010). Synthesis, anticonvulsant and antimicrobial activities of some new 2-acetylnaphthalene derivatives. *Bioorganic & Medicinal Chemistry*, *18*(8), 2902–2911. https://doi.org/10.1016/j.bmc.2010.03.010

Kelder, J., Grootenhuis, P. D., Bayada, D. M., Delbressine, L. P., & Ploemen, J. P. (1999). Polar molecular surface as a dominating determinant for oral

absorption and brain penetration of drugs. *Pharmaceutical Research*, *16*(10), 1514–1519. https://doi.org/10.1023/A:1015040217741

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *46*(1-3), 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0

Lothman, E. W., Perlin, J. B., & Salerno, R. A. (1988). Response properties of rapidly recurring hippocampal seizures in rats. *Epilepsy Research*, *2*(6), 356–366. https://doi.org/10.1016/0920-1211(88)90047-2

Lothman, E. W., Salerno, R. A., Perlin, J. B., & Kaiser, D. L. (1988). Screening and characterization of antiepileptic drugs with rapidly recurring hippocampal seizures in rats. *Epilepsy Research*, *2*(6), 367–379. https://doi.org/10.1016/0920-1211(88)90048-4

Lothman, E. W., & Williamson, J. M. (1994). Closely spaced recurrent hippocampal seizures elicit two types of heightened epileptogenesis: A rapidly developing, transient kindling and a slowly developing, enduring kindling. *Brain Research*, *649*(1-2), 71–84. https://doi.org/10.1016/0006-8993(94)91050-2

Matagne, A., & Klitgaard, H. (1998). Validation of corneally kindled mice: A sensitive screening model for partial epilepsy in man. *Epilepsy Research*, *31*(1), 59–71. https://doi.org/10.1016/S0920-1211(98)00016-3

Mikitsh, J. L., & Chacko, A. M. (2014). Pathways for small molecule delivery to the central nervous system across the blood-brain barrier. *Perspectives in Medicinal Chemistry*, *6*, 11–24. https://doi.org/10.4137/PMC.S13384

Monaghan, E. P., McAuley, J. W., & Data, J. L. (1999). Ganaxolone: A novel positive allosteric modulator of the GABA(a) receptor complex for the treatment of epilepsy. *Expert Opinion on Investigational Drugs*, *8*(10), 1663–1671. https://doi.org/10.1517/13543784.8.10.1663

Nardi, D., Tajana, A., Leonardi, A., Pennini, R., Portioli, F., Magistretti, M. J., & Subissi, A. (1981). Synthesis and anticonvulsant activity of N-(benzoylalkyl) imidazoles and N-(. omega.-phenyl-. omega.-hydroxyalkyl) imidazoles. *Journal of Medicinal Chemistry*, *24*(6), 727–731. https://doi.org/10.1021/jm00138a017

Neises, B., & Steglich, W. (1978). Simple method for the esterification of carboxylic acids. *Angewandte Chemie International Edition in English*, *17*(7), 522–524. https://doi.org/10.1002/anie.197805221

Racine, R. J. (1972). Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalography and Clinical Neurophysiology*, *32*(3), 281–294. https://doi.org/10.1016/0013-4694(72)90177-0

Rankovic, Z. (2015). CNS drug design: Balancing physicochemical properties for optimal brain exposure. *Journal of Medicinal Chemistry*, *58*(6), 2584–2608. https://doi.org/10.1021/jm501535r

Robertson, D. W., Krushinski, J. H., Beedle, E., Leander, J. D., Wong, D. T., & Rathbun, R. (1986). Structure-activity relationships of (arylalkyl) imidazole anticonvulsants: Comparison of the (fluorenylalkyl) imidazoles with nafimidone and denzimol. *Journal of Medicinal Chemistry*, *29*(9), 1577–1586. https://doi.org/10.1021/jm00159a004

Rogawski, M. A. (2006). Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Research*, *69*(3), 273–294. https://doi.org/10.1016/j.eplepsyres.2006.02.004

Rowley, N. M., & White, H. S. (2010). Comparative anticonvulsant efficacy in the corneal kindled mouse model of partial epilepsy: Correlation with other seizure and epilepsy models. *Epilepsy Research*, *92*(2), 163–169. https://doi.org/10.1016/j.eplepsyres.2010.09.002

Sari, S., Dalkara, S., Kaynak, F. B., Reynisson, J., Sarac, S., & Karakurt, A. (2017). New anti-seizure (arylalkyl)azole derivatives: Synthesis, in vivo and in Silico studies. *Archiv der Pharmazie*, *350*(6), e201700043. https://doi.org/10.1002/ardp.201700043

Sari, S., Karakurt, A., Uslu, H., Kaynak, F. B., Çalış, Ü., & Dalkara, S. (2016). New (arylalkyl) azole derivatives showing anticonvulsant effects could have VGSC and/or GABA A R affinity according to molecular modeling studies. *European Journal of Medicinal Chemistry*, *124*, 407–416. https://doi.org/10.1016/j.ejmech.2016.08.032

Sari, S., Kaynak, F. B., & Dalkara, S. (2018). Synthesis and anticonvulsant screening of 1,2,4-triazole derivatives. *Pharmacological Reports*, *70*(6), 1116–1123. https://doi.org/10.1016/j.pharep.2018.06.007

Sastry, G. M., Adzhigirey, M., Day, T., Annabhimoju, R., & Sherman, W. (2013). Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. *Journal of Computer-Aided Molecular Design*, *27*(3), 221–234. https://doi.org/10.1007/s10822-013-9644-8

Snead, O. C. (1992). Pharmacological models of generalized absence seizures in rodents. In C. Marescaux, M. Vergnes, & R. Bernasconi (Eds.), *Generalized non-convulsive epilepsy: Focus on GABA-B receptors Journal of Neural Transmission* (Vol. 35) (pp. 7–19). Vienna: Springer.

Stables, J. P., & Kupferberg, H. J. (1997). In G. Avanzini, G. Regesta, P. Tanganelli, & M. Avoli (Eds.), *Molecular and cellular targets for antiepileptic drugs The NIH anticonvulsant drug development (ADD) program: preclinical anticonvulsant* (pp. 191–198). London, England: John Libbey.

Swinyard, E. A. (1989). General principles: Experimental selection, quantification, and evaluation of antiepileptic drugs. In R. Levy, F. Dreifuss, R. Mattson, B. Meldrum, & J. Kiffin Penry (Eds.), *Antiepileptic drugs* (pp. 85–102). New York, NY: Raven Press.

Tajana, A., Portioli, F., Subissi, A., & Nardi, D. (1981). N-Naphthacylimidazoles and N-([beta-naphthyl-beta-hydroxy]ethyl) imidazoles with anticonvulsant activity. *Bollettino Chimico Farmaceutico*, *120*(3), 185–190.

Walker, K. A., Wallach, M. B., & Hirschfeld, D. R. (1981). 1-(Naphthylalkyl)-1H-imidazole derivatives, a new class of anticonvulsant agents. *Journal of Medicinal Chemistry*, *24*(1), 67–74. https://doi.org/10.1021/jm00133a015

White, H. S., Johnson, M., Wolf, H., & Kupferberg, H. (1995). The early identification of anticonvulsant activity: Role of the maximal electroshock and subcutaneous pentylenetetrazol seizure models. *The Italian Journal of Neurological Sciences*, *16*(1-2), 73–77. https://doi.org/10.1007/BF02229077

White, H. S., Woodhead, J., & Franklin, M. (1995). General principles: Experimental selection, quantification, and evaluation of antiepileptic drugs. In R. Levy, F. Dreifuss, R. Mattson, B. Meldrum, & J. Kiffin Penry (Eds.), *Antiepileptic drugs* (pp. 99–110). New York, NY: Raven Press.

Zhu, S., Noviello, C. M., Teng, J., Walsh, R. M., Jr., Kim, J. J., & Hibbs, R. E. (2018). Structure of a human synaptic GABAA receptor. *Nature*, *559*(7712), 67–72. https://doi.org/10.1038/s41586-018-0255-3

SUPPORTING INFORMATION

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

How to cite this article: Acar MF, Sari S, Dalkara S. Synthesis, in vivo anticonvulsant testing, and molecular modeling studies of new nafimidone derivatives. *Drug Dev Res*. 2019;1–11. https://doi.org/10.1002/ddr.21538