DESIGN, SYNTHESIS AND EVALUATION OF SOME NOVEL 3-ALLYL-6-IODO-2-SUBSTITUTED THIOQUINAZOLINONE DERIVATIVES FOR ANTICONVULSANT ACTIVITY

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ABSTRACT

The urgent demand for the development of new antiepileptic drug with a better efficacy inspired us to design and synthesize a new derivatives of the fused heterocyclic analogs 3-allyl-6-iodo-2-(substituted thio)quinazolin-4(3H)-one that prepared and evaluated for their anticonvulsant activity. Compounds **10**, **11**, **12**, **13**, **14** and **22** were found to be the most active anticonvulsant of this series. The achieved results proved that the distinctive compounds could be valuable as a model for future devise, acclimatization and investigation to construct more active analogues.

Key words: synthesis, 3-allyl-6-iodo-2-(substituted thio)quinazolin-4(3H)-one, anticonvulsant screening, pentylenetetrazole.

Introduction

Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. Much efforts devoted in the recent years for the development of novel therapeutics resulted in the availability of several newer drugs as promising anticonvulsants (Stefan, H.; Feuerstein, T, 2007 , Donner, E. J.; Snead, O. C., 2006). However, the currently available anticonvulsants are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with undesirable numerous side effects (Greenwood, R. S., 2000, Namara, M., et al, 2001, Löscher, W.; Schmidt, D., 2002, Bialer, M., et al, 2004).Therefore, continued search for safer and more effective anticonvulsants is urgently necessary.

One of the most frequently encountered heterocycles in medicinal chemistry is 4(3H)-quinazolinones, which have diverse pharmacological activities such as, anticonvulsant (Georgey H , et al, 2008, Sushil KK, et al, 2009, Hanan G, et al, 2008, Wolfe JF, et al, 1990) ,antimicrobial (Sami GA, 2001, Menshawy AM,et al, 2014), hypoglycemic (Mukerji DD, et al, 1985), anti-parkinsonism (Surendra SP, Shiva PS. 1979), antiviral (Pandey VK,et al, 2004), anticancer (Ashraf A. Khalil, et al,2003, Mustafa M. Ghorab ,et al, 1998), antidepressant, (Kashaw SK, et al, 2009, Wang H, et al, 2009, Jatav V, et al, 2008), sedative-hypnotic (Kashaw SK, et al, 2010) and analgesic activity (Mohsen MA, et al, 2010). The present study aimed to synthesize and evaluate the biological activity of some new 2-mercapto-3-allyl-4(3H)-quinazolinone analogs as potential anticonvulsant. The designed target compounds were obtained as outlined in schemes 1–2 starting with 5-iodoanthranilic acid.

Experimental

All melting points shown in (table 1) were taken in open capillaries and are uncorrected. The infrared spectra were recorded on FT/IR-JASCO 4100 using KBr disc technique. Microanalytical data were conducted on a Perkin-Elmer 2408 analyzer, results are within ± 0.4% of the theoretical values, Thin layer chromatography was performed on Merk 5x10 cm plates, percolated with silica gel GF254 using (EtOAc, hexane 1:10) as solvent system and short wavelength UV light for visualization. All fine chemicals and reagents used were purchased from Aldrich chemical Co. U.S.A. ^{1}HNMR was recorded on a Bruker 500 MHz spectrophotometer; Chemical shifts are in γ (ppm) values downfield from Tetramethyl Siloxane as an internal standard. ^{13}C NMR was recorded on a Bruker 125 MHz spectrophotometer. The mass spectra were measured on Waters Micromass (Water AQUITY UPLC System LCT Premier XE Serial no: KE468). A preliminary screening of the anticonvulsant activity of the study compounds has indicated that some of them exhibit significant activity compared to phenobarbitone as standard drug. The starting material 2-amino-5-iodobenzoic acid (**2**) was synthesized in 70% yield by adapting a reported procedure (Klemme C. J. and Hunter J. H.1940).

3-Allyl-2,3-dihydro-6-iodo-2-thioxoquinazolin-4(1H)-one (3)

A mixture of 5-iodoanthranilic acid (5.26 g, 0.02mol) and allylisothiocyanate (2.3 ml, 0.02 mol) in 30 ml ethanol containing triethylamine (2.0 g, 0.02 mol) was heated under reflux for

2 hours. The reaction mixture was poured on ice .The separated solid was filtered, washed with water, dried and crystallized from dioxane (Table 1). ^{1}H NMR (500 MHz, DMSO-d6): δ 5.011-5.020 (d, 2H), 5.132-5.158 (d, 2H), 5.854-5.929(m,1H), 7.179-7.196 (dd, 1H J=8.5 Hz), 8.037-8.054 (dd,1H J=2 and 8.5 Hz), 8.185 (d,1H J=2.0 Hz), 13.035-13.165 (br s,1 H).^{13}C NMR (125 MHz, DMSO-d_6): δ 47.68, 87.99, 117.13, 117.24, 117.79, 131.47, 135.12, 138.42, 143.45, 157.72, 174.89. Anal. for ($C_{11}H_9IN_2OS$) Calcd. /Found (%): C, 38.39 (38.46); H, 2.64 (2.45); N, 8.14 (8.14). MS: [M-1]; Calcd. /Found: 343.1705 (343.0706).

General procedure for the synthesis of 3-allyl-6-iodo-2-(alkylthio)quinazolin-4(3H)-one (4-14)

A mixture of compound 3-allyl-2,3-dihydro-6-iodo-2-thioxoquinazolin-4(1H)-one (**3**) (0.01mol) and appropriate halide (0.01 mol) was heated under reflux for 4-6 hours in (25 ml) acetone in the presence of anhydrous potassium carbonate (1.0 g). The reaction mixture was cooled; the solvent was evaporated under reduced pressure and crystallized from ethanol (Table 1).

3-Allyl-6-iodo-2-(methylthio)quinazolin-4(3H)-one (4)

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.278(s, 3H), 4.682-4.692(d, 2H), 5.081-5.116(d, 1H, J=35 Hz), 5.190-5.211 (d,1H, J=21.0 Hz), 5.861-5.937 (m, 1H),7.343-7.360 (dd,1H, J=8.5 Hz), 8.047-8.064 (dd,1H, J=2.0 and 85 Hz), 8.313-8.317 (d, 1H J=2.0 Hz) .^{13}C NMR (125 MHz, DMSO-d_6) δ 14.52, 45.89, 90.27, 117.40, 120.39, 128.07, 131.09, 134.57, 142.98, 148.08, 158.18, 159.03. MS: [M-1; Calcd. /Found: 357.1975 (357.0787).

3-Allyl-2-(ethylthio)-6-iodoquinazolin-4(3H)-one (5)

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.329-1.359 (t, H, CH_2CH_3-H), 3.214-3.262 (q, 2H), 4.662-4.672 (d, 2H), 5.079-5.113 (dd, 1H J=35.0), 5.185-5.205 (dd, 1H J=20.0), 5.854-5.930 (m, 1H), 7.320-7.337 (dd,1H J=8.5 Hz), 8.042- 8.059 (dd, 1H J=2.0 and 8.5 Hz), 8.311-8.315 (d,1H J=2.0 Hz).^{13}C NMR (125 MHz, DMSO-d_6) δ 13.84, 26.05, 45.85, 90.42, 117.36, 120.48, 128.13, 131.17, 134.55, 142.94, 146.12, 157.55, 159.06. MS: [M-1]; Calcd. /Found: 371.2245 (371.2243).

2-(2-Hydroxyethylthio)-3-allyl-6-iodoquinazolin-4(3H)-one (6)

^{1}H NMR (500 MHz, DMSO-d_6), δ 2.379(s, 1H), 3.925-4.56 (m, 4H), 5.036-5.107 (m, 2H), 5.138-5.148 (d, 2H), 5.879-5.956(m, 1H), 6.999-7.016 (d, 1H J=8.5 Hz), 7.747-7.764 (dd, 1H J=2.0 and 8.5 Hz), 8.068-8.072 (d, 1H J=2.0 Hz).^{13}C NMR (125 MHz, DMSO-d_6) δ 38.91, 39.91, 47.70, 83.91, 115.99, 119.42, 125.28, 133.66, 134.35, 141.42, 146.90, 160.05, 175.58. MS: [M-1]; Calcd. /Found: 387.2235 (387.4303).

3-Allyl-2-(allylthio)-6-iodoquinazolin-4(3H)-one (7)

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.889-3.926 (d, 2H), 4.657-4.666 (d, 2H), 5.073-5.107 (dd, 1H J=34.0 Hz), 5.164-5.167 (d, 1H), 5.186-5.207 (dd,1H J=21.0), 5.849-6.026 (m, 2H),7.301-7.318 (d, 1H J=8.5 Hz), 8.013- 8.034 (dd, 1H J=2.0 and 8.5 Hz), 8.296-8.300 (d, 1H J=2.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.17, 39.50, 45.89, 90.38, 119.19, 120.44, 128.15, 131.10, 132.59, 134.56, 142.98, 145.86, 156.89, 159.04. Anal. for: ($C_{14}H_{13}IN_2OS$) Calcd. /Found (%): C, 43.76 (42.61); H, 3.41 (3.18); N, 7.29 (7.05). MS: [M-1]; Calcd. /Found: 383.2355 (383.2393).

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetamide (8)

^{1}H NMR (500 MHz, DMSO-d_6): δ 4.477(s, 2H), 4.709-4.719 (d, 2H), 5.120-5.155 (dd,1H, J=35.0 Hz), 5.213-5.233 (dd, 1H J=20.0 Hz), 5.875-5.958 (m, 1H), 7.288 (s, 1H), 7.317-7.334 (d, 1H J=8.5 Hz), 7.736 (s, 1H), 8.080- 8.097 (dd,1H J=2.0 and 8.5 Hz), 8.311-8.348 (d,1H J=2.0-Hz).^{13}C NMR (125 MHz, DMSO-d_6) δ 35.73, 46.01, 90.62, 117.58, 120.48, 128.11, 131.07, 134.89, 143.03, 146.12, 156.79, 159.03, 168.56.

2-(4-Nitrobenzylthio)-3-allyl-6-iodoquinazolin-4(3H)-one (9)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.569-4.580 (s, 2H), 4.647-4.659 (dd, 2H), 5.057-5.091 (dd, 1H), 5.179-5.200 (dd, 1H), 5.854-5.909 (m, 1H), 7.454-7.471 (d, 1H J=8.5 Hz), 7.793-7.810 (dd, 2H J=5.0 Hz), 8.092-8.109 (d, 1H J=2.0 and 8.5 Hz), 8.165-8.182 (dd, 2H J=5.0 Hz), 8.321 (d, 1H J=2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.89, 46.42, 89.64, 118.91, 121.08, 121.66, 127.88, 130.39, 131.01 (2), 131.75 (2), 135.40, 135.91, 143.14, 146.57, 156.46, 159.99. MS: [M-1]; Calcd. /Found: 478.2925 (478.1949).

2-(4-Bromobenzylthio)-3-allyl-6-iodoquinazolin-4(3H)-one (10)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.450 (s, 2H), 4.718-4.729 (d, 2H), 5.221-5.256 (dd, 2H), 5.852-5.919 (m, 1H),7.259-7.325 (m, 4H, J=5.0 Hz), 7.430-7.447 (d, 1H, J=8.5 Hz),7.939- 7.956 (dd, 1H, J=2.0 and 8.5 Hz), 8.535-8.538 (d,1H J=2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.05, 39.51, 45.89, 90.88, 117.23, 121.53, 122.48, 124.31, 130.34, 131.71 (2), 134.33 (2), 138.63, 142.54, 146.02, 156.15, 159.32.

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-(4-bromophenyl)acetamide (11)

IR (cm^{-1}): 1689.34 (C=O), 1669.34 (C=O), 3235.97 (NH), ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.195 (s, 2H), 4.719-4.730 (d, 2H), 5.150-5.185 (dd, 1H, J=35.0 Hz), 5.233-5.254 (dd, 1H, J=21.0 Hz), 5.896-5.972 (m, 1H), 7.226-7.243 (d,1H, J=8.5 Hz), 7.488-7.507 (dd, 2H, J=5.0 Hz), 7.567-7.587 (dd, 2H, J= 5.0 Hz), 8.052-8.069 (dd,1H, J=2.0 and 8.5 Hz), 8.323-8.327 (d, 1H J=2.0 Hz) 10.567 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.73, 46.10, 90.67, 115.47, 117.73, 120.60, 120.89, 127.89131.03, 131.63 (2), 134.55 (2), 143.02, 145.51, 156.02, 159.15, 166.32, 173.42. MS: [M-1]; Calcd. /Found: 553.2165 (553.2086), [M+2]: 556.2165 (556.2838).

3-Allyl-2-(benzylthio)-6-iodoquinazolin-4(3H)-one (12)

^{1}H NMR (500 MHz, DMSO-d_6): δ 4.643 (s, 2H), 5.064-5.069 (dd, 2H), 5.164-5.184 (dd, 2H), 5.825-5.901 (m, 1H),7.254-7.269 (dd, 1H J=7.5Hz), 7.303-7.318 (dd, 1H J=7.5 Hz), 7.380-7.397 (d, 1H J=8.5 Hz), 7.480-7.495 (dd, 1H J=7.5 Hz), 8.042- 8.059 (dd, 1H J=2.0 and 8.5 Hz), 8.297-8.30 (d,1H J=2.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.58, 45.90, 90.44, 117.51, 120.50, 127.42, 128.08, 128.43, 129.36 (2), 131.09 (2), 136.41, 142.98, 142.54, 145.94, 157.07, 158.98. Anal. for: ($C_{18}H_{15}IN_2OS$) Calcd. /Found (%): C, 49.78 (49.56); H, 3.48 (3.64); N, 6.45 (6.44).

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-phenylacetamide (13)

^{1}H NMR (500 MHz, DMSO-d_6): δ 4.198 (s, 2H), 4.720-4.730 (dd, 2H), 5.145-5.180 (dd, 1H), 5.232-5.252 (dd, 1H), 5.895-5.971 (m, 1H), 7.060-7.075 (dd, 1H, J=7.5 Hz), 7.258-7.276 (d, 1H, J=8.5 Hz) , 7.314-7.329 (dd, 2H, J=7.5 Hz), 7.583-7.600 (dd, 2H, J=7.5 Hz), 8.054-8.071 (dd, 1H, J=2,8.5Hz), 8.319-8.323 (d, 1H, J=2.0 Hz) 10.433 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.82, 46.10, 90.47, 117.4 2, 119.12, 120.47, 123.46, 127.94, 128.80,

131.01, 134.63 (2), 138.87, 143.09, 145.92, 157.27, 157, 158.97, 165.55. MS: [M-1]; Calcd. /Found: 476.3205 (476.2409).

2-(2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)ethyl)isoindoline-1,3-dione (14)

IR (cm^{-1}): 1693.18, 1708.62, 1770.33(3C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.562-3.611 (t, 2H), 4.131-4.18 (t, 2H), 4.707-4.718 (dd, 2H), 14.195-5.230 (dd, 1H), 5.213-5.233 (dd, 1H), 5.828-5.905 (m, 1H), 7.366-7.383 (d, 1H, J=8.5 Hz), 7.676-7.700 (dd, 2H, J= 3.0 Hz), 7.785-7.810 (dd, 2H, J= 3.0 Hz), 7.914-7.934 (dd,1H, J=2.0 and 8.5 Hz), 8.480-8.484 (d, 1H, J=2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.15, 36.80, 46.44, 89.67, 118.78, 119.30, 120.94, 123.32 (2), 128.33, 130.33, 131.86, 134.10 (2), 135.68, 143.06, 146.54, 156.16, 160.00, 168.08 (2). Anal. for ($C_{21}H_{16}IN_3O_3S$) Calcd. /Found (%): C, 48. 76 (48.14); H, 3.12 (2.57); N, 8.12 (7.88). MS: [M-1]; Calcd. /Found: 516.3415 (516.1837).

Ethyl 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate (15)

A mixture of compound 3-allyl-2,3-dihydro-6-iodo-2-thioxoquinazolin-4(1H)-one (**3**) (344 mg, 0.001mol) and ethyl 2-bromoacetate (167 mg, 0.001mol) was heated was heated under reflux for 4 hours in (25 ml) acetone in the presence of anhydrous potassium carbonate (1 g). The reaction mixture was cooled; the solvent was evaporated under reduced pressure and crystallized from ethanol (Table 1).

IR (cm^{-1}): 1731.76, 1677.77 cm^{-1} (C=O).^{1}H NMR (500 MHz, DMSO-$_{d6}$): δ 1.110-1.241 (t, 3H), 4.067-4.168 (m, 4H), 4.683-4.693 (d, 2H), 5.128-5.163 (dd, 1H, J=35.0 Hz), 5.224-5.244 (dd,1H, J=20), 5.880-5.956 (m, 1H),7.180-7.197 (d, 1H, J=8.5 Hz), 8.040- 8.057 (dd, 1H J=2.0, 8.5 Hz), 8.291-8.295 (d, 1H, J=2.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.12, 34.08, 38.94, 39.61, 61.10, 90.60, 117.66, 120.36, 127.85, 130.91, 134.62, 143.09, 145.75, 156.79, 158.82, 168.12. Anal.for ($C_{15}H_{15}IN_2O_3S$) Calcd. /Found (%): C, 41.87 (42.31); H, 3.51 (3.73); N, 6.51 (6.35). MS: [M-1]; Calcd. /Found: 429.2605 (429.5111).

2-(N-(2-Hydroxyethyl) acetamidothio)-3-allyl-6-iodoquinazolin-4(3H)-one (16)

A mixture of ethyl 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate (**15**) (430 mg, 0.001mol) and ethanolamine (61 mg, 0.001mol) in ethanol was heated under reflux for

2 hours. The reaction mixture was cooled; the solvent was evaporated under reduced pressure and crystallized from ethanol (Table 1).

IR (cm^{-1}): 1685.18, 1659.56 (2C=O), 3270.68 (OH), 3089.04 (NH).

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.222 (s, 1H) 3.134-3.199 (q, 2H), 3.375-3.3.410 (q, 2H), 4.700-4.710 (d, 2H), 4.754-4.776 (d, 2H), 5.080-5.115 (dd,1H, J=35.0 Hz), 5.215-5.235 (dd, 1H J=20.0 Hz), 5.877-5.953 (m, 1H),7.335-7.352 (d,1H, J=8.5 Hz), 8.074- 8.091 (dd, 1H, J=20.0 and 8.5 Hz), 8.322-8.326 (d,1H J=2.0 Hz) 8.299 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.75, 39.61, 41.84, 59.60, 90.43, 117.60, 120.45, 128.13, 131.04, 134.56, 143.03, 145.97, 157.25, 159.02, 166.64. Anal. for ($C_{15}H_{16}IN_3O_3S$) Calcd/Found (%): C, 40.46 (39.06); H, 3.62 (3.51); N, 9.44 (9.03). MS: [M-1]; Calcd. /Found: 444.2755: (444.2892).

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (17)

A mixture of ethyl 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate (**15**) (430 mg, 0.001mol) and hydrazine hydrate (100 mg, 0.002 mol) in ethanol was heated under reflux for 3hours. The reaction mixture was cooled; the solvent was evaporated under reduced pressure and crystallized from acetic acid (Table 1).

IR (cm^{-1}): 1662.34, 1690.22 (2C=O), 3278.39, 3056.83 (NH).

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.787 (br s, 2H), 3.909 (S, 2H), 4.761-4.772 (d, 2H), 5.277-5.312 (dd, 1H, J=35.0 Hz), 5.298-5.318 (dd, 1H, J=20 Hz), 5.864-5.942 (m, 1H),7.287-7.304 (d,1H, J=8.5 Hz),7.973- 7.990 (dd,1H, J=2.0 and 8.5 Hz), 8.560-8.564 (d, 1H, J=2.0 Hz), 8.138 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 33.32, 46.23, 77.05, 90.40, 119.54, 120.98, 127.03, 129.97, 136.11, 143.03, 146.02, 156.98, 159.60, 169.07. MS: [M-1]; Calcd. /Found: 415.2375 (415.3678).

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)acetamide(18)

A mixture of 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (**17**) (416 mg 0.001mol) and tetrachlorophthalic anhydride (285 mg, 0.001mol) in glacial acetic acid (15 ml) was heated under reflux for 18 hours. The reaction mixture was cooled; the solid obtained was filtered, washed with water, dried and crystallized from ethanol (Table 1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.100 (s, 2H), 4.780-4.797 (d, 2H), 5.315-5.350 (dd, 2H, J=35 Hz), 5.889-5.966 (m, 1H), 7.331-7.340 (d, 1H, J=8.5Hz), 7.961-7.978 (dd, 1H, J=2.0 and 8.5 Hz), 8.541-8.553 (d, 1H, J=2.0 Hz), 9.909 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.23, 47.00, 77.05, 90.40, 119.75, 125.68, 127.15, 129.69 (2), 130.44 (2), 136.22 (2), 140.98, 145.68, 156.87, 160.29, 164.68 (2), 169.63. MS: (m/z); [M-1]: Calcd. /Found: 683.1075 (683.1387), [M+2]: 686.1075 (686.2400).

2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-(acetophenyl)acetohydrazide (19)

A mixture of 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide **(17**) (416 mg, 0.001mol) and 2-phenylacetyl chloride (154 mg, 0.001mol) in N,N-dimethylformamide (20 ml) containing pyridine (79 mg, 0.001 mol) was heated under reflux for 20 hours. The reaction mixture was cooled; the solvent was evaporated under reduced pressure and crystallized from ethanol (Table 1).

IR (cm^{-1}): 1681.62, 1621.06, 1665.34 (3C=O, 3197.4, 3131.55 (2NH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.639 (s, 2H), 4.960-4.970 (d, 2H), 5.293-5.313 (dd, 2H), 5.440-5.475 (dd, 2H, J=35.0 Hz), 6.014-6.093 (m, 1H), 7.133 (br s, 1H), 7.169-7.184 (dd, 2H, J=7.5 Hz), 7.235 (br s, 1H), and 7.250-7.265 (dd, 1H, J=7.5 Hz), 7.298-7.313 (dd, 2H, J=7.5 Hz),7.334-7.351 (d, 1H, J=8.5 Hz),7.852- 7.869 (dd,1H, J=2.08.5 Hz),8.662-8.666 (d, 1H, J=2.0 Hz).^{13}C NMR (125 MHz, $CDCl_3$): δ 34.11, 45.60, 77.13, 90.81, 117.42, 118.92, 119.91, 127.66, 127.93, 128.53, 128.73, 129 .34, 129.52, 130.15, 134.02, 138.34, 143.20, 147.38, 148.63, 156.79, 159.19. MS: [M-1]; Calcd. /Found: 533.3725 (533.3240)

1-(2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetyl)-4-allylthiosemicarbazide (20)

A mixture of compound 2- (3 – ally l -3 , 4 – dihydro-6-iodo-4-oxoquinazolin-2-ylthio) acetohydrazide (**17**) (416 mg, 0.001mol) and allylisothiocyanate (99 mg , 0.001mol) in dioxane was heated under reflux for 24 hours The reaction mixture was cooled;the solvent was evaporated under reduced pressure and crystallized from dioxane (Table 1).

^{1}H NMR (500 MHz, DMSO-d_6): δ 4.031(s, 2H), 4.703-4.713 (dd, 2H), 4.956-4.976 (dd, 1H), 4.999-5.033 (dd 2H), 5.118-5.153 (dd, 2H), 5.219-5.239 (dd, 2H), 5.681-5.755 (m,1H), 5.868-5.956 (m, 1H), (d, 1H, J=8.5 Hz),7.374- 7.391 (dd,1H J=2.0 and 8.5 Hz), 8.292-8.308 (d,1H J=2.0 Hz), 9.510 (br s, 1H), 10.263 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.96, 39.60, 45.69, 46.05, 66.33, 90.63, 115.03, 117.62, 120.44, 128.27, 130.99, 134.53, 142.96, 145.87, 157.14, 158.91, 166.61. Anal. for (%): ($C_{17}H_{18}IN_5O_2S_2$) Calcd. /Found (%): C, 39. 62 (39.24); H, 3.52 (3.79); N, 13.59 (13.42). MS: [M-1]; Calcd. /Found: 514.3885 (514.2362).

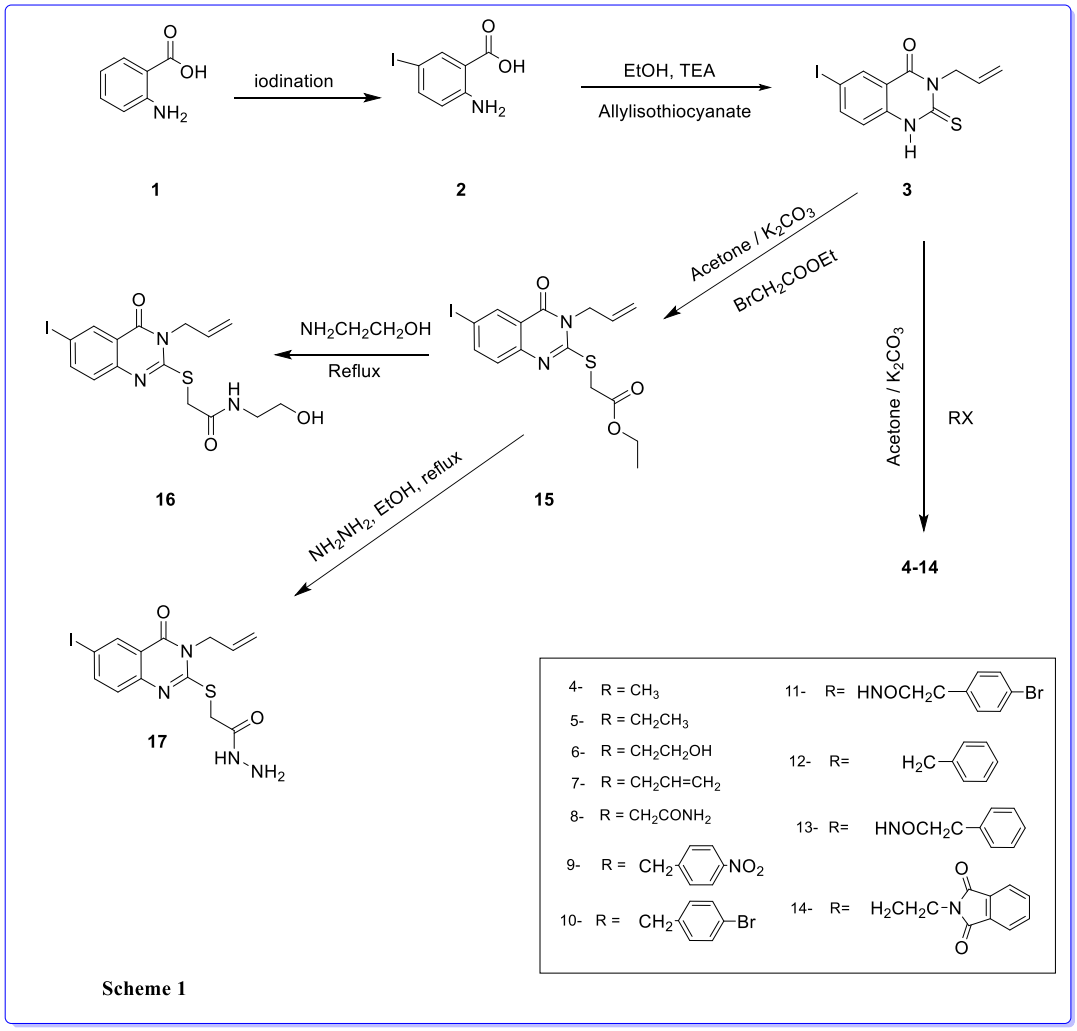
2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N'-tosylacetohydrazide (21)

A mixture of 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (**17**) (416 mg, 0.001mol) and 4-methylbenzene-1-sulfonyl chloride (190 mg, 0.001mol) in dry pyridine (15 ml) was heated under reflux for 24 hours. The reaction mixture was cooled and treated with ice hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.420 (s, 3H), 4.573 (s, 2H), 4.754-4.764 (dd, 2H), 5.248-5.283 (dd, 1H, J=35.0 Hz), 5.310-5.330 (dd, 1H, J=20 Hz), 5.917-6.016 (m, 1H), (dd, 1H, J=8.5 Hz), 7.747- 7.348 (dd, 1H, J=2, 8.5 Hz), 7.764-7.548 (dd, 2H, J=7.5 Hz), 8.004-8.021 (dd, 2H, J=7.5 Hz), 8.647-8.664 (d, 1H, J=2.0 Hz), 8.740 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.10, 39.60, 45.69, 46.05, 77.07, 90.02, 115.84, 117.02, 120.44, 127.34, 127.51, 129.50, 129.81, 131.10, 132.97, 137.18, 137.48, 146.76, 159.14, 161.91.

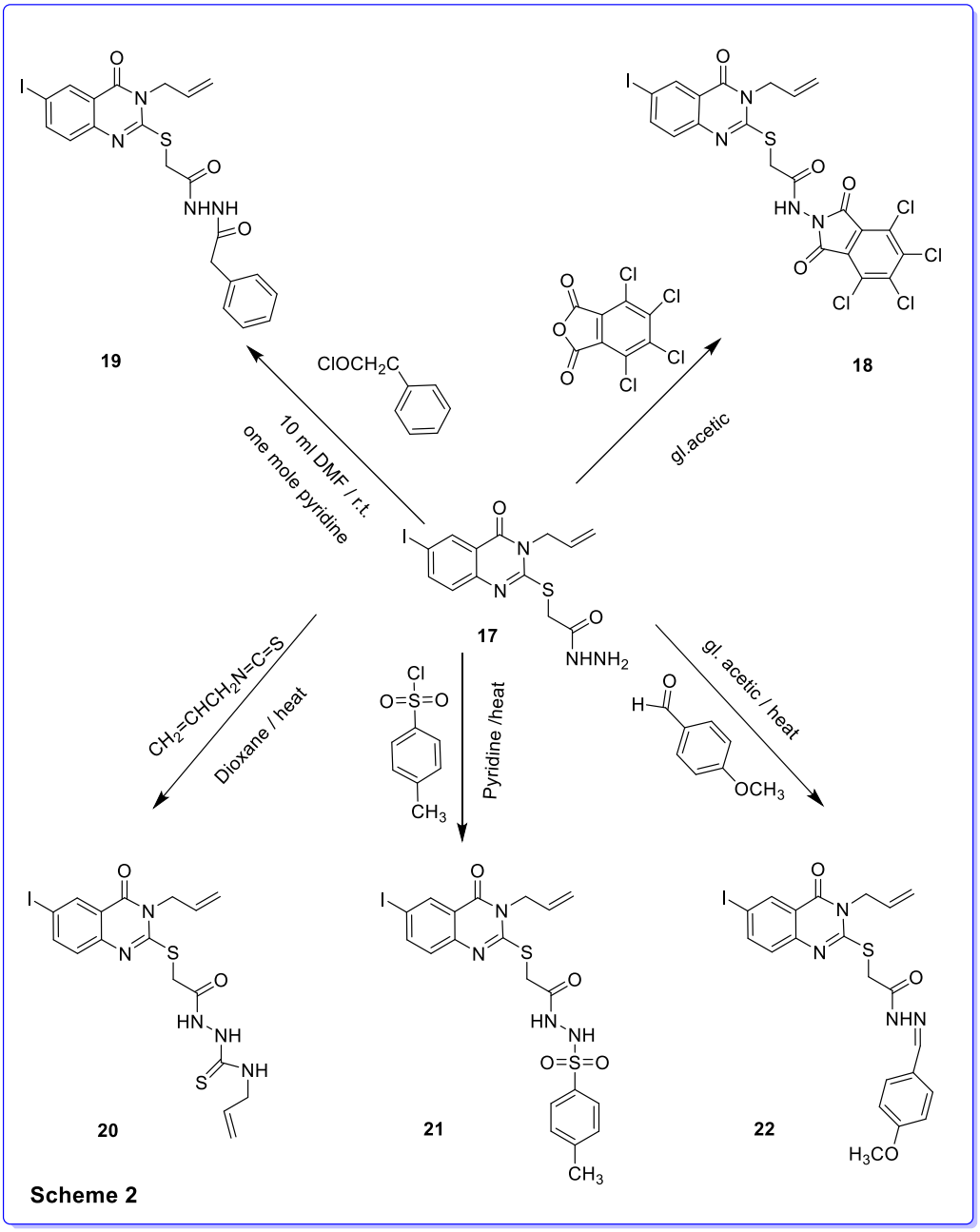
2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-(4-methoxybenzylidene) acetohydrazide (22)

A mixture of 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (**17**) (416 mg, 0.001mol) and 4-methyoxy benzaldehyde (106 mg, 0.001mol) in glacial acetic acid (15 ml) was heated under reflux for 18 hours. The reaction mixture was cooled; the obtained solid was filtered, washed with water, dried and crystallized from acetic acid (Table 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.8171 (s, 2H), 3.900 (s, 3H), 4.992-5.003 (d, 2H), 5.312-5.332 (d, 1H, J=20.0 Hz), 5.471-5.506 (dd,1H, J=35.0 Hz), 6.045-6.124 (m, 1H), 6.940- 6.957 (d, 1H, J=8.5 Hz), 7.076-7.093 (dd, 2H, J=8.0 Hz), 7286-7.300 (d, 1H), 7.531-7.548 (dd, 2H, J=8.0 Hz), 7.773-7.790 (dd,1H, J=2.0 and 8.5 Hz), 8.692-8.696 (d, 1H, J=2.0 Hz), 9.581 (br s, 1H). ^{13}C NMR (125

MHz, $CDCl_3$): δ 29.69, 45.50, 55.52, 76.84, 77.10, 90.74, 114.22, 114.80, 117.39, 119.16, 126.94, 130.09, 130.23, 133.27, 138.27, 142.90, 142.90, 148.27, 156.95, 161.03, 161.67. MS: [M-1]; Calcd. /Found: 533.3725 (533.6813).



Scheme 1


19
18
17
20
21
22
ClOCH2C
10 ml DMF / r.t.
one mole pyridine
gl.acetic
CH2=CHCH2N=C=S
Dioxane / heat
Pyridine /heat
gl. acetic / heat

Scheme 2

Table1: The physicochemical properties of new synthesized compo

No.	Compound	Solvent of crystallization	Melting point	Yield	Molecular Formula
1	3	Dioxane	247-249	70%	$C_{11}H_9IN_2OS$
2	4	Ethanol	293-295	59%	$C_{12}H_{11}IN_2OS$
3	5	Ethanol	275-277	65%	$C_{13}H_{13}IN_2OS$
4	6	Ethanol	281-283	60%	$C_{13}H_{13}IN_2O_2S$
5	7	Ethanol	288-290	76%	$C_{14}H_{13}IN_2OS$
6	8	Ethanol	206-208	63%	$C_{13}H_{12}IN_3O_2S$
9	9	Ethanol	248-250	67%	$C_{18}H_{14}IN_3O_3S$
7	10	Ethanol	298-300	65%	$C_{18}H_{17}BrIN_2OS$
8	11	Ethanol	195-197	72%	$C_{19}H_{18}BrIN_3O_2S$
10	12	Ethanol	223-225	65%	$C_{18}H_{17}IN_2OS$
11	13	Ethanol	180-182	54%	$C_{19}H_{18}IN_3O_2S$
12	14	Ethanol	237-239	45%	$C_{21}H_{16}IN_3O_3S$
14	15	Ethanol	291-293	70%	$C_{15}H_{15}IN_2O_3S$
15	16	Ethanol	231-233	60%	$C_{15}H_{16}IN_3O_3S$
16	17	Ethanol	267-269	75%	$C_{13}H_{13}IN_4O_2S$
17	18	Acetic acid	228-230	66%	$C_{21}H_{11}Cl_4IN_4O_4S$
18	19	Ethanol	235-237	63%	$C_{21}H_{19}IN_4O_3S$
19	20	Dioxane	243-244	65%	$C_{17}H_{18}IN_5O_2S_2$
20	21	Ethanol	211-213	72%	$C_{20}H_{19}IN_4O_4S_2$
21	22	Acetic acid	251-253	67%	$C_{21}H_{19}IN_4O_3S$

Anticonvulsant activity

Materials and method

The compounds were tested against pentylenetetrazol-induced convulsions following the method reported by (Soaje-Echaque E, and Lim RKS, 1962) using phenobarbitone sodium as reference drug. Swiss male albino mice (weigh 20-25 g) are randomly divided into 54 groups, 6 mice per each. The test 18 compounds were suspended in saline solution using few drops of tween-80 in a dose of 200, 400 and 800 mg/kg. The test compounds were injected orally using same dosing volume of 0.33 ml. Phenobarbitone sodium (standard anticonvulsant), was given in doses of 6.25, 12.5 and 25 mg/Kg using the same dosing volume. Pentylenetetrazol (100 mg/Kg) was injected i.p. one hour post test compounds or standard injection. The animals were observed for 2 hours. The animal that showed no tonic convulsions within 1 hour after pentylenetetrazol injections were considered to be protected, the percentage protection was calculated per each dose, effective dose (ED_{50}) that protect 50% of animals against pentylentetrazol induced convulsion was then calculated using INSTAT 2 program (philadelphia). The relative potency of the test compounds to phenobarbitone sodium were calculated and used for comparison between compounds under test as shown in table 2.

Table 2: Screening of anticonvulsant activity of the newly synthesized compounds.

Test compound	Dose mg/Kg	No. of mice	NO. of mice protected	Protection %	Protection ED 50% mg/Kg	Protection ED 50% mmol/Kg
4	200	6	0			2.222
	400	6	2			
	800	6	3	50	800	
5	200	6	0			1.6
	400	6	2	33.3		
	800	6	4	66.6	600	
6	200	6	0		0	0
	400	6	0			
	800	6	1	16.6		
8	200	6	1			0.992
	400	6	3	50	400	
	800	6	5	66.6		
9	200	6	1	16.6		0.833
	400	6	3	50	400	
	800	6	4	66.6		
10	200	6	3	50	200	0.388
	400	6	6	100		
	800	6	6	100		
11	200	6	3	50	200	0.358
	400	6	4	66.6		
	800	6	5	83.3		
12	200	6	3	50	200	0.458
	400	6	6	100		
	800	6	6	100		
13	200	6	3	50	200	0.417
	400	6	4	66.6		
	800	6	5	83.3		
14	200	6	3	50	200	0.385
	400	6	4	66.6		
	800	6	4	66.6		
15	200	6	1	16.6		0.930
	400	6	3	50	400	
	800	6	4	66.6		
16	200	6	0	0		1.797
	400	6	2	33.3		
	800	6	3	50	800	
17	200	6	2	33.3		0.961
	400	6	3	50	400	
	800	6	4	66.6		
18	200	6	2	33.3		0.586
	400	6	3	50	400	
	800	6	4	66.6		
19	200	6	2	33.3		0.749
	400	6	3	50	400	
	800	6	4	66.6		
20	200	6	0	0	0	0
	400	6	0	0		
	800	6	0	0		
21	200	6	0	0		1.403
	400	6	2	33.3		
	800	6	3	50	800	
22	200	6	3	50	200	0.374
	400	6	5	83.3		
	800	6	6	100		
S	12.5	6	6	100		
	6.5	6	3	50	6.5	0.024
	3.25	6	2	33.3		

ED 50: median effective dose; a dose that protect 50% of animals against pentylentetrazol induced convulsion.

ED50 was calculated using INSTAT2 program (computer based statistical program)

Conclusion

The present study, new derivatives of 4(3H)-quinazolinones were synthesized and evaluated for their anticonvulsant activity in mice. The results of this study demonstrated that some 3-allyl-6-iodo-2-(substituted thio)quinazolin-4(3H)-one derivatives possess a good anticonvulsant activity, specially, compounds **10**, **11**, **12**, **13**, **14** and **22** were equipotent regarding their anticonvulsant potency as they induced 50% protection at dose level of 200 mg/kg. Also, compounds **8**, **9**, 1**6**, **17**, **18** and **19** were equipotent regarding their anticonvulsant potency as they induced 50% protection at dose level of 400 mg/kg. Furthermore, compounds **4**, **16** and **21** were equipotent regarding their anticonvulsant potency as they induced 50% protection at dose level of 800 mg/kg. The obtained results showed that compounds **10**, **11**, **12**, **13**, **14** and **22** could be useful as a template for future design, modification and investigation to produce more active analogs.

Results and Discussion

Chemistry

5-Iodo-2-aminobenzoic acid (**2**) was prepared according to a reported procedure (Klemme C. J. and Hunter J. H.1940). 3-Allyl-2, 3-dihydro-6-iodo-2-thioxoquinazolin-4(1H)-one (**3**) as the first key intermediate was obtained in 60% yield by the reaction of 5-Iodo-2-aminobenzoic acid (**2**) with 4-allylisothiocyanate. 2-Mercaptoquinazoline **3** was heated with different halides in dry acetone in the presence of potassium carbonate to afford the corresponding alkyl derivatives (**4**-**15**). Ethyl 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetate (**15**) was refluxed with ethanolamine or hydrazine hydrate 80% in ethanol to get 2-(N-(2-hydroxyethyl)acetamidothio)-3-allyl-6-iodoquinazolin-4(3H)-one (**16**) and 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (**17**) as the second key intermediate (scheme 1). 2-(3-Allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetohydrazide (**17**) was reacted with tetrachlorophthalic anhydride and 2-phenylacetylchloride to obtain 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio) -N- (4,5,6,7-tetrachloro- 1 ,3 - dioxoisoindolin - 2- yl) acetamide (**18**) and 2- (3- ally l-3,4- dihydro -6-iodo-4-oxoquinazolin-2-ylthio)-N-(acetophenyl)

acetohydrazide (**19**) in 66–63 % yield respectively. On the other hand, acid hydrazide **17** was treated with allyl isothiocyanate, 4-methylbenzenesulfonyl chloride and 4-methoxy benzaldehyde to furnish 1-(2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)acetyl)-4-allylthiosemicarbazide (**20**), (2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N'-tosylacetohydrazide (**21**) and 2-(3-allyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylthio)-N-(4 methoxybenzylidene)acetohydrazide (**22**) in 65,72 and 67 % yield respectively (scheme 2).

Anticonvulsant activity

The anticonvulsant activities of the new synthesized compounds were evaluated by the use of standard techniques (Krall, R. L, et al, 1987, Poter, R. J, et al, 1984). The preliminary screening was performed at 200-800 mg/kg of all synthesized compounds (**4**–**22**) by using of pentylenetetrazole (PTZ) induced seizure as a chemical induction method to generate the convulsion (Vogel, H. G., 2002).

The initial anticonvulsant evaluation showed that compound **20** are inactive; however compounds **10**, **11**, **12**, **13**, **14** and **22** were the most active anticonvulsant agents, that caused 50% protection in a dose of 200 mg/Kg body weight while compounds **8**, **9**, **15**, **17**, **18** and **19** were moderate activity as anticonvulsant agents caused 50% protection in a dose of 400 mg/Kg, while, compound **2** exhibit 50% protection in a dose between 400 and 800 mg/Kg. On the other hand, compounds **4**, **16** and **21** were the least active anticonvulsant caused 50% protection in a dose of 800 mg/Kg; the compound **6** exhibited 16.6 % protections at 800 mg/Kg in comparison to phenobarbitone as standard drug (table 2).

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الملخص العربى

تشييد بعض مشتقات الأيودوكينازولين كمضادات للتشنجات العصبية

للسادة الدكاترة

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فى هذا البحث تم تشييد عدد 20 مركبا وسيطا ونهائيا من نواة الأيودوالكينازولين وقد تم إثباتها بطرق التحاليل المختلفة كنقطة الأنصهاروالرنين النووى المغناطيسى ومطياف الكتلة والتحليل الدقيق للعناصر(الكربون والنيتروجين والهيدروجين) لبعض المركبات المشيدة وتم إختبارها كمضادات للتشنجات مقارنة بالفينوباربيتون صوديوم وقد ثبت للمركبات الجديدة فاعلية كمضادات للتشنجات وخاصة المركبات أرقام 10و 11و12و13و14و22 التى ثبت لها فاعلية فى عمل 50% حماية كمضادات للتشنجات.