Synthesis and Anticonvulsant Activity of Certain Substituted Furochromone, Benzofuran and Flavone Derivatives

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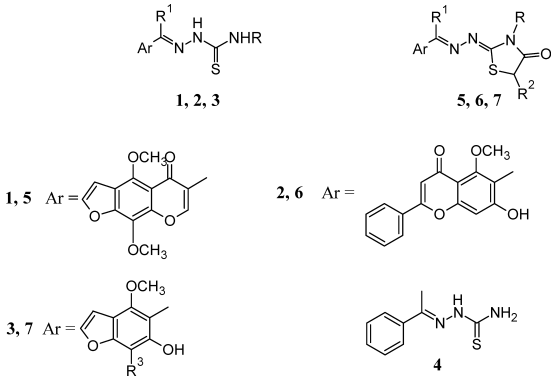
Synthesis of furochromone, 2-phenylchromone (flavone) and benzofuran derivatives substituted with thiosemicarbazide or thiazolidin-4-one moieties were accomplished. All the newly synthesized compounds were tested for their anticonvulsant activity in both subcutaneous pentylenetetrazole induced seizures (scPTZ) and maximal electric shock induced seizures (MES) tests using valproic acid and phenytoin respectively as reference standards. The most active compounds in scPTZ model were 1c, 2b, 5a and 7e showing 100% protection at 300 mg/kg upon intraperitoneal administration. Also, the effect of pre-treatment of three of the most active compounds (1c, 2b, 5a) on 4-amino pyridine-induced lethality in mice was investigated. Pre-treatment with these compounds significantly increased the latency for clonic and tonic seizures and prevented 4-amino pyridine induced death. Hence, this provides evidence for anticonvulsant activity of these compounds, and a neuroprotective activity for them. The structure–activity relationship was studied based on the obtained data.

Key words chromone; flavone; benzofuran; anticonvulsant; neuroprotective activity

Despite the optimal use of the currently available antiepileptic drugs, 30 to 40% of the epileptic population fails to experience seizure control, and others do so only at the expense of significant toxic effects that range in severity from minimal brain impairment to death from aplastic anemia or hepatic failure.[1—3] These facts provoked the need for new anticonvulsant drugs with higher potency and fewer side effects. Several studies reported that chromone derivatives are promising anticonvulsant candidates that perform their activity through a γ-aminobutyric acid (GABA)-mediated mechanism.[4—17] Likewise, flavones (2-phenylbenzopyrons) are with a well known positive GABA-modulating ability; their central activity was attributed to their potential to penetrate the blood–brain barrier which is strongly correlated to their lipophilicity.[18] Semicarbazones and their bioisosteres thiosemicarbazones, have a documented essential role in the design of novel anticonvulsant agents that performing their anticonvulsant activity also through a GABA-mediated mechanism.[19—41] Extensive structure–activity relationship studies proposed certain pharmacophoric requirements for (thio)-semicarbazones interaction at the binding site which are a hydrophobic binding area represented by aryl or heteroaryl group and a hydrogen bonding domain represented by the NH–CO(S)–NH system.[24—26,33,38] It was suggested that (thio)semicarbazones anticonvulsant activity is mediated through GABA-mediated mechanism.[19,22,29,32,37,41]

In the present investigation the two anticonvulsant candidates, chromones or flavones and thiosemicarbazones, were amalgamated to obtain more potent anticonvulsants compounds of series **1** and **2**. In the synthesized hybrid compounds the chromone or the furochromone ring acts as the hydrophobic aryl ring required for binding which itself possesses anticonvulsant tendency. On the other hand, various bicyclic heterocycles containing thiosemicarbazono group showed significant anticonvulsant activity.[33,34,42—44] Herein the tricyclic furochromone moiety was simplified to the bicyclic benzofuran system, which was reported to possess anticonvulsant activity[42—44] to give compounds of series **3**. Obviously, the compounds of this series are the bicyclic analogs



of the reported phenyl congener **4** synthesized by Dimmock *et al*. which showed marked anticonvulsant activity.[20] Replacement of the phenyl ring in **4** by the bicyclic benzofuran structure is thought to increase the hydrophobic aryl area which binds to the binding site and thus may enhance the binding. Moreover, the effect of the hydrophobic group on the terminal amino group of the thiosemicarbazono moiety was studied in the synthesized compounds of series **1**, **2** and **3**.

Due to certain limitations associated with the (thio)semicarbazone functionality, mainly the poor solubility and liability to metabolism[45]; improvement of the molecule, pharmacologically and pharmaceutically, was carried out by replacement of the thiosemicarbazono group with thiazolidin-4-one ring to give the more constrained cyclic derivatives **5**, **6**, **7**. Such particular ring (thiazolidin-4-one) was selected, in part, because of its involvement in molecules that have been reported previously as anticonvulsant agents[46—56]; additionally, being of a similar size and containing atoms that might participate in hydrogen bonding like the parent thiosemicarbazone.[45] Different substituents at position 3 and position 5 in the thiazolidine-4-one nucleus were introduced to study their effect on the anticonvulsant activity.

Results and Discussion

Chemistry According to Chart 1, synthesis of the start-

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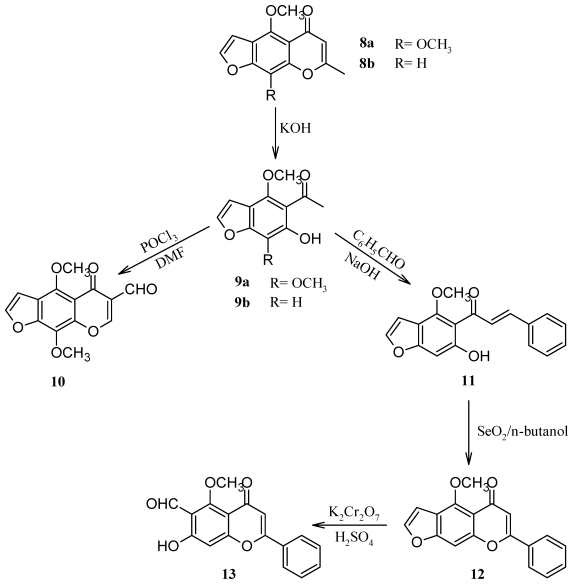

Chart 1

ing two benzofuran ketones **9a** and **9b** the furobenzopyran aldehyde **10** and the flavone aldehyde **13** was accomplished from the naturally occurring furochromones Khellin **8a** and Visnagin **8b**. Ring opening of the γ-pyrone ring with KOH gave the ketones **9a** and **9b** according to the reported procedures.[57,58] Conversion of **9a** to 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde **10** was carried out *via* Vilsmeier–Haack reaction.[59] Subjecting **9b** to Claisen Schmidt condensation with benzaldehyde produced 1-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)-3-phenylprop-2-en-1-one **11**[60] which by oxidative cyclization with selenium dioxide in butanol gave the furoflavone derivative **12**.[61] Cleavage of the furan ring of **12** by chromic acid oxidation gave 7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromene-6-carbaldehyde **13**.[61] Following Chart 2, reaction of the chosen alkyl or phenyl thiosemicarbazides with the aldehyde **10** in ethanol at room temperature gave the thioureas **1a**—**e** and the aldehyde **13** in ethanol with reflux gave the thioureas **2a**—**e** whereas, reaction of **9a** and **9b** with the chosen thiosemicarbazides was carried out in ethanol containing catalytic amount of acetic acid with refluxing for 72 h yielded **3a**—**h**, these later drastic conditions could be attributed to the sterically hindered ketones **9a** and **9b**. Construction of the thiazolidine-4-one derivatives **5**, **6**, **7** was carried out by reaction of the corresponding thiourea derivatives **1**, **2**, **3** with monochloroacetic acid or maleic anhydride according to Charts 3 and 4.

Pharmacological Activity All the newly synthesized compounds in addition to five of the starting or intermediate compounds (methyl thiosemicarbazide, ethyl thiosemicarbazide, **9a**, **10**, **13**) were tested for their potential anticonvulsant activity using subcutaneous pentylenetetrazole induced seizures (scPTZ). Maximal electric shock induced seizures (MES) method was also applied for all the newly prepared compounds. Furthermore, the neuroprotective activity using the 4-amino pyridine (4-AP) method was performed on 3 of the most active compounds after determining their ED_{50}.

Anticonvulsant Activity All the newly synthesized compounds in addition to methyl and ethyl thiosemicar-

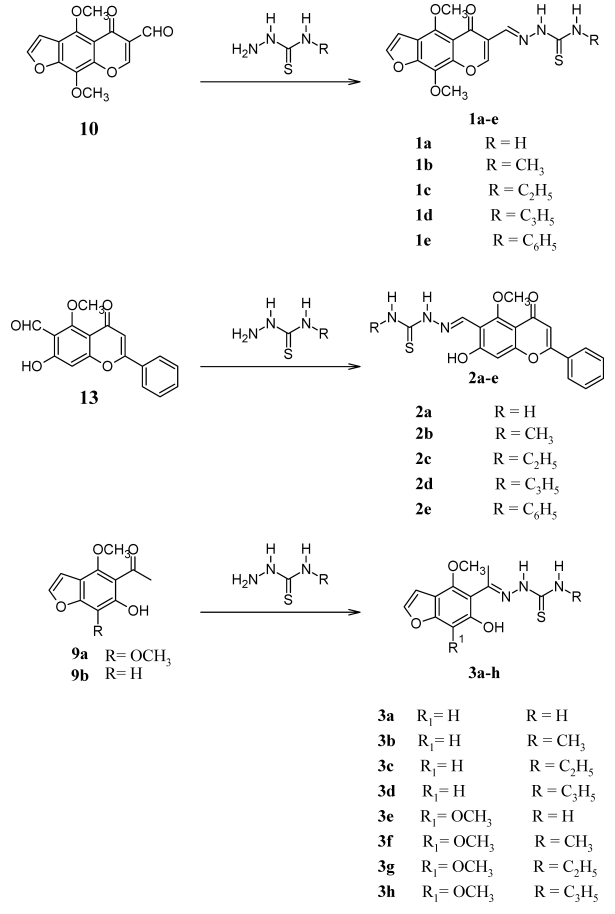

Chart 2

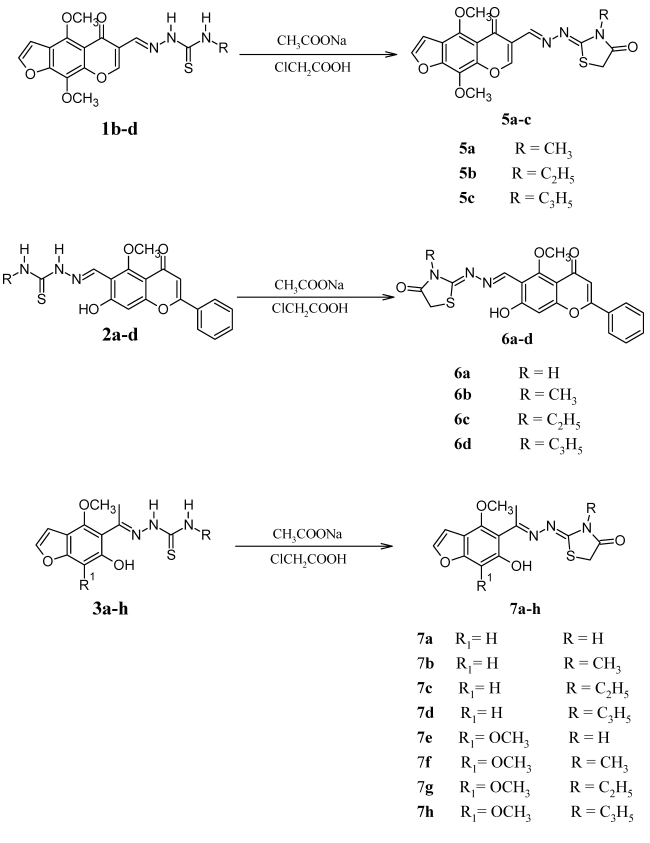

Chart 3

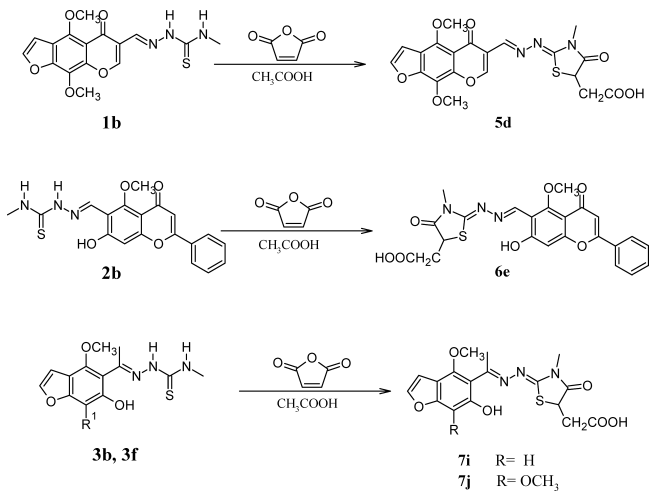

Chart 4

bazides and compounds **9a**, **10**, **13**-used to furnish the designed hybridized final compounds—were tested for their anticonvulsant activity using the scPTZ method. With regard to the furochromone derivatives **1a**—**e** in which the thiosemicarbazono group was attached to the 6-position, compound **1c** showed 100% protection at 300 mg/kg, which is far more than either of its counterparts. Also, **1e** showed 100% protection at a dose of 300 mg/kg. In a dose of 150 mg/kg the protection percent decreased for both **1c** and **1e** to 67 and 83%, which further decreased to 17% and 0% at 75 mg/kg body weight respectively (see Table 1). Compound **1b** showed 50% protection at 300 mg/kg which is lower than both its separate entities. **1d** with an allyl substitution, showed 50% protection at a dose of 300 mg/kg. Compound **1a** which has a free terminal amino group showed no activity. This means that the presence of a terminal substituted amino group is essential for activity. From the above results, presence of the ethyl or phenyl substitution is preferred to methyl or allyl.

Cyclization of the thiosemicarbazono group (**1**) to the constrained (thiazolidin-4-one) derivatives (**5**) retained activity. Activity of compounds **5a** and **5c**; substituted with methyl and allyl increased than the uncyclized giving 100 and 67% protection respectively at 300 mg/kg body weight. The methyl one **5a** even lent 83% at 150 mg/kg and 17% at 75 mg/kg body weight, while the allyl was completely devoid of activity at these doses. On the other hand, the ethyl congener activity was completely abolished as a result of this cyclisation. When an acetic acid moiety was introduced in the 5-position of the thiazolidine-4-one nucleus **5d**; its protection percentage was decreased from 100 to 67. This may be attributed to a corruption in the lipophilicity/hydrophilicity balance.

7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromene-6-carbaldehyde (**13**) was tested using scPTZ method and showed 60% protection at 300 mg/kg body weight. Three compounds **2b**, **2d** and **2e** of the thiosemicarbazono series **2** showed anticonvulsant activity of 100, 83 and 50% protection, respectively, at a dose of 300 mg/kg body weight. Those compounds were the methyl (**2b**), whose percentage protection surpassed both its parts (60 and 20%); the allyl (**2d**) and phenyl (**2e**) substituted ones. The methyl derivative **2b** still showed 100% protection at a dose of 150 mg/kg body weight; while all the others (**2a** and **2c**) were inactive. In this series cyclization of the thiosemicarbazono group (**2**) to thiazolidin-4-one nucleus (**6**) markedly decreased the activity of compound **2b** to the half (**6b** showed 50% protection); while the activity was completely abolished in all the others. Introduction of acetic acid moiety in 5-position of thiazolidin-4-one nucleus giving **6e** abolished the 50% activity that remained for compound **6b**.

Benzofuran ring containing derivatives **3a**—**d** showed a different pattern of activity. The derivative bearing a free amino group **3a** showed 50% protection, the methyl and allyl ones **3b** and **3d** also showed the same percent, while the ethyl **3c** showed a little bit higher percent of 67; all at 300 mg/kg body weight only. When the benzofuran was obtained from khellin (**8a**); the activity profile switched again; the one with a free amino group **3e** and the ethyl derivative **3g** were completely inactive at any of the doses administered in spite of the starting compound **9a** exhibiting 100% protection at 300 mg/kg in scPTZ test. The methyl derivative **3f** together with the allyl **3h**, showed 67% protection at 300 mg/kg body weight only.

The cyclization of the thiosemicarbazono group to the thiazolidin-4-one **7a**—**d** in the benzofurans originating from visnagin (**8b**) completely abolished the activity except that carrying the allyl chain which lent some activity to it; 67% at 300 mg/kg and 17% at 150 mg/kg body weight. On the other hand, those from khellin (**8a**) acted very differently; where the activity was greatly potentiated, except the allyl congener **7h**, which completely lost the activity it had. Derivative having the unsubstituted thiazolidinone ring **7e**, showed the highest activity; 100%, 67% and 17% protection at 300, 150 and 75 mg/kg body weight respectively. When the thiazolidinone ring was methyl substituted **7f**; the activity increased to 83 and 50% at 300 and 150 mg/kg body weight only; compared to its open chain congener (**3f**). The ethyl congener **7g**, acquired mild activity with a 50% protection at 300 mg/kg body weight; compared to **3g**. Introduction of acetic acid moiety in 5-position of the thiazolidin-4-one nucleus **7i** and **7j** abolished the activity.

The ED_{50} for compounds **1c**, **2b** and **5a** was obtained and they were tested for their neuroprotective activity. They were found to significantly increase the latency for clonic and tonic seizures and prevented neurotoxicity associated with 4-amino-pyridine (4-AP) as exemplified in inducing death in mice.

Conclusion

Generally, in the newly synthesized compounds; the bicyclic benzofuran derivatives were less potent than the tricyclic furochromone derivatives indicating the importance of the tricyclic structure for activity; despite the results that showed that bicyclic **9a** from which series 3 and 7 were prepared was the most active (showed 100% protection at 300 mg/kg). Following, was **13** leading to series 2 and 6 then finally **10** which gave series 1 and 5 simultaneously.

Sodium valproate group showed 100% protection at the used dose, while the phenytoin group showed prolonged clonic phase and abolished tonic phase so animals' death occurred without showing tonic phase.

In the MES test; all the tested compounds were inactive

showing no protection against the seizures induced even up to a dose of 300 mg/kg body weight.

As a conclusion; five compounds belonging to the different synthesized series **1c**, **1e**, **2b**, **5a** and **7e** showed 100% protection at a dose of 300 mg/kg in scPTZ test.

Compounds **1c**, **2b**, **5a** were found to counteract the harmful effect of 4-AP. This provides evidence for the anticonvulsant activity of these compounds and indicates a neuroprotective activity for them.

Experimental

Chemistry All melting points are uncorrected and determined by open capillary method using 'Electrothermal capillary melting point apparatus 9100.' Infrared spectra (IR) were recorded as KBr discs using 'Schimadzu 435 IR spectrophotometer.' Proton magnetic resonance (^{1}H-NMR) spectra were carried out using 'Varian Mercury VX-300 NMR spectrophotometer 300 MHz,' 'Varian Gemini 200 MHz' and 'Jeol FX 90 Q 90 MHz FT spectrophotometer' using tetramethylsilane (TMS) as internal standard. Chemical shift values were recorded in ppm on δ scale. Mass spectra were carried out on 'Finnigan Mat SSQ-7000 mass spectrophotometer 70 eV.' Elemental analyses were carried out at the Micro Analytical Center, Faculty of Science, Cairo University; the found values were within the theoretical ones range, unless otherwise indicated. Thin layer chromatography (TLC) was carried out using 'Silica gel/TLC-card DC-Alufolien-Kieselgel F254 (Fluka 60778),' the developing solvent systems used were $CCl_4 : CH_3OH$ (9 : 1) or $CCl_4 : CH_3OH$ (7 : 3), visualization was performed by illumination with UV light source (254 nm).

Compounds throughout this work were chemically named according to the IUPAC system using 'Chemdraw ultra software V.10 Cambridgesoft®.'

1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethanone 9a. 1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethanone 9b Previously reported.[57,58]

4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde 10 Previously reported.[59]

1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)-3-phenylprop-2-en-1-one 11 Previously reported.[60]

4-Methoxy-7-phenyl-5*H*-furo[3,2-*g*]chromen-5-one 12 Previously reported.[61]

7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromene-6-carbaldehyde 13 Previously reported.[61]

2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazinecarbothioamide 1a. 2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]-chromen-6-yl)methylene)-*N*-substituted Hydrazinecarbothioamides 1b—e 4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbaldehyde **10** (1 g, 3.65 mmol) and the appropriate thiosemicarbazide (3.65 mmol) in absolute ethanol (25 ml) were stirred at room temperature for 24 h and the obtained yellow precipitate (**1a**—**e**) was filtered, washed well with hot water, dried and recrystallized from *N*,*N*-dimethylformamide (DMF)/H_2O.

2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazinecarbothioamide 1a 68% yield. mp 203—204 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.96 (3H, s), 4.10 (3H, s), 7.24 (1H, d, J=2 Hz), 8.01, 8.20 (2H, 2s, exch. D_2O), 8.10 (1H, d, J=2 Hz), 8.16 (1H, s), 9.01 (1H, s), 11.52 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3550, 3350, 3150, 1640, 1600, 1580, 1560, 1240. MS *m*/*z*: 347(M^+) (Calcd for $C_{15}H_{13}N_3O_5S$: 347.34). *Anal.* Calcd for $C_{15}H_{13}N_3O_5S$: C, 51.87; H, 3.77; N, 12.10. Found: C, 51.65; H, 4.01; N, 11.80.

2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)-*N*-methylhydrazinecarbothioamide 1b 70% yield. mp 201—202 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.03 (3H, d), 3.99 (3H, s), 4.13 (3H, s), 7.27 (1H, d, J=1 Hz), 8.13 (1H, d, J=1 Hz), 8.15 (1H, s), 8.52 (1H, s, exch. D_2O), 9.02 (1H, s), 11.61 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3375—3200, 1640, 1620, 1590, 1580, 1210. MS *m*/*z*: 360.90 (M^+), 361.90 (M^++1) (Calcd for $C_{16}H_{15}N_3O_5S$: 361.37). *Anal.* Calcd for $C_{16}H_{15}N_3O_5S$: C, 53.18; H, 4.18; N, 11.63. Found: C, 53.30; H, 4.30; N, 11.55.

2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)-*N*-ethylhydrazinecarbothioamide 1c 77% yield. mp 189—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.2 Hz), 3.75—3.97 (2H, m, J=7.2 Hz), 4.10 (3H, s), 4.23 (3H, s), 7.06 (1H, d, J=2 Hz), 7.27 (1H, s, exch. D_2O), 7.68 (1H, d, J=2 Hz), 8.03 (1H, s), 8.43 (1H, s), 8.99 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3350—3250, 1650, 1620, 1580, 1560, 1210. MS *m*/*z*: 375 (M^+), 376 (M^++1) (Calcd for $C_{17}H_{17}N_3O_5S$: 375.400). *Anal.* Calcd for $C_{17}H_{17}N_3O_5S$: C, 54.39; H, 4.56; N, 11.19. Found: C, 54.58; H, 4.60; N, 11.17.

***N*-Allyl-2-((4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazinecarbothioamide 1d** 76% yield. mp 184—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (1H, s, exch. D_2O), 4.11 (3H, s), 4.22 (3H, s), 4.3—5.2 (4H, br m), 5.95—6.20 (1H, m), 7.05 (1H, d, J=2 Hz), 7.67 (1H, d, J=2 Hz), 8.13 (1H, s), 8.43 (1H, s), 9.75 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3470—3300, 1640, 1610, 1580, 1540, 1210. *Anal.* Calcd for $C_{18}H_{17}N_3O_5S$: C, 52.74; H, 4.79; N, 10.25. Found: C, 52.45; H, 4.26; N, 10.60.

2-((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)-*N*-phenylhydrazinecarbothioamide 1e 75% yield. mp 169—170 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.01 (3H, s), 4.13 (3H, s), 7.29—7.44 (5H, m), 7.63 (1H, d, J=2 Hz), 8.16 (1H, d, J=2 Hz), 8.30 (1H, s), 9.27 (1H, s), 10.09 (1H, s, exch. D_2O), 11.97 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3300—3100, 1655, 1600, 1580, 1560, 1210. MS *m*/*z*: 421 (M^+−2) (Calcd for $C_{21}H_{17}N_3O_5S$: 423.44). *Anal.* Calcd for $C_{21}H_{17}N_3O_5S$: C, 59.57; H, 4.05; N, 9.92. Found: C, 59.79; H, 4.00; N, 9.91.

2-((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazinecarbothioamide 2a. 2-((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)-*N*-substituted Hydrazinecarbothioamides 2b—e 7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromene-6-carbaldehyde **13** (1 g, 3.4 mmol) and the appropriate thiosemicarbazide (3.5 mmol) were refluxed in absolute ethanol (20 ml) for 16 h. The yellow product **2a**—**e** was filtered while hot, washed with hot ethanol, left to dry and recrystallized from the suitable solvent.

2-((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazinecarbothioamide 2a 85% yield. mp >350 °C. Crystallization solvent: DMSO/H_2O. ^{1}H-NMR: (DMSO-d_6) δ: 3.39 (1H, s, exch. D_2O), 3.84 (3H, s), 6.81 (1H, s), 7.01 (1H, s), 7.58 (3H, m), 7.95—8.30 (4H, m, exch. D_2O), 8.61 (1H, s), 11.50 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450, 3375, 3250, 3175, 1640, 1620, 1580, 1530, 1215. MS *m*/*z*: 369.40 (M^+) (Calcd for $C_{18}H_{15}N_3O_4S$: 369.39). *Anal.* Calcd for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.78; H, 4.20; N, 11.37.

2-((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)-*N*-methylhydrazinecarbothioamide 2b 80% yield. mp 205—206 °C. Crystallization solvent: DMF/H_2O. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (3H, s), 3.84 (3H, s), 6.81 (1H, s), 7.03 (1H, s), 7.58 (3H, m), 8.05 (2H, m), 8.42 (1H, s, exch. D_2O), 8.62 (1H, br s), 10.85 (1H, s, exch. D_2O), 11.53 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3450 (br), 3250, 1630, 1600, 1560, 1500, 1230. MS *m*/*z*: 383 (M^+), 384.15 (M^++1) (Calcd for $C_{19}H_{17}N_3O_4S$: 383.42). *Anal.* Calcd for $C_{19}H_{17}N_3O_4S$: C, 59.52; H, 4.47; N, 10.96. Found: C, 59.35; H, 4.64; N, 10.88.

***N*-Ethyl-2-((7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazinecarbothioamide 2c** 75% yield. mp 316—317 °C. Crystallization solvent: DMF/H_2O. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t), 3.58 (2H, m), 3.85 (3H, s), 6.78 (1H, s), 6.99 (1H, s), 7.57 (3H, m), 8.03 (2H, m), 8.41 (1H, s, exch. D_2O), 8.60 (1H, br s), 11.00 (1H, s, exch. D_2O), 11.44 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3450, 3250, 1630, 1600, 1550, 1500, 1220. MS *m*/*z*: 397 (M^+), 398 (M^++1) (Calcd for $C_{20}H_{19}N_3O_4S$: 397.45). *Anal.* Calcd for $C_{20}H_{19}N_3O_4S$: C, 60.44; H, 4.82; N, 10.57. Found: C, 60.22; H, 5.14; N, 10.26.

***N*-Allyl-2-((7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazinecarbothioamide 2d** 80% yield. mp >350 °C. Crystallization solvent: DMF/H_2O. IR (KBr) cm^{-1}: 3450 (br), 3250, 1630, 1600, 1560, 1540, 1500, 1220. MS *m*/*z*: 409 (M^+), 410 (M^++1) (Calcd for $C_{21}H_{19}N_3O_4S$: 409.47). *Anal.* Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26. Found: C, 61.63; H, 5.00; N, 9.96.

2-((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)-*N*-phenylhydrazinecarbothioamide 2e 80% yield. mp >350 °C. Crystallization solvent: DMSO/H_2O. IR (KBr) cm^{-1}: 3450 (br), 3150, 1650, 1620, 1580, 1560—1540, 1210. MS *m*/*z*: 445.15 (M^+) (Calcd for $C_{24}H_{19}N_3O_4S$: 445.49). *Anal.* Calcd for $C_{24}H_{19}N_3O_4S$: C, 64.71; H, 4.30; N, 9.43. Found: C, 64.53; H, 4.15; N, 9.44.

2-(1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3a. 2-(1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)-*N*-substituted Hydrazinecarbothioamides 3b—d. 2-(1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3e. 2-(1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)-*N*-substituted Hydrazinecarbothioamides 3f—h A mixture of **9a** or **9b** (3 mmol) and the appropriate thiosemicarbazide (9 mmol) in absolute ethanol (20 ml) and glacial acetic acid (2 ml) was refluxed for 72 h. The reaction solution was concentrated and poured onto ice-water (20 ml). The precipitate **3a**—**h** was collected, washed with hot water, dried, and then it was washed with carbon tetrachloride, dried and recrystallized from methanol.

2-(1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3a 60% yield. mp 196—198 °C. ^{1}H-NMR: ($CDCl_3$) δ: 2.25 (3H, s), 4.12 (3H, s), 6.21 (2H, s, exch. D_2O), 6.75 (1H, s), 6.87 (1H, d, J=1.8 Hz), 7.48 (1H, d, J=1.8 Hz), 8.44, 8.78 (2H, 2s, exch. D_2O). IR (KBr) cm^{-1}: 3400, 3300, 3150, 1620, 1580, 1540—1500, 1205. MS *m/z*: 279(M^+), 280 (M^++1) (Calcd for $C_{12}H_{13}N_3O_3S$: 279.31). *Anal.* Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.43; H, 5.07; N, 14.75.

2-(1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)-*N*-methylhydrazinecarbothioamide 3b 64% yield. mp 185—187 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.19 (3H, d), 4.08 (3H, s), 6.72 (1H, s), 6.82 (1H, d, J=1.8 Hz), 7.64 (1H, d, J=1.8 Hz), 8.18, 8.43, 8.75 (3s, 3H, exch. D_2O); IR (KBr) cm^{-1}: 3350, 3200, 1620, 1600, 1540, 1250. MS *m/z*: 293 (M^+), 294 (M^++1) (Calcd for $C_{13}H_{15}N_3O_3S$: 293.34). *Anal.* Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32. Found: C, 53.22; H, 5.22; N, 14.09.

***N*-Ethyl-2-(1-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3c** 58% yield. mp 178—179 °C. ^{1}H-NMR: ($CDCl_3$) δ: 1.26 (3H, t, J=7.4 Hz), 2.21 (3H, s), 3.63—3.76 (2H, m, J=7.4 Hz), 4.06 (3H, s), 6.72 (1H, s), 6.82 (1H, d, J=1.8 Hz), 7.38 (1H, d, J=1.8 Hz), 7.61, 8.40, 8.90 (3H, 3s, exch. D_2O); IR (KBr) cm^{-1}: 3350, 3300, 3100, 1620, 1590, 1550, 1210. MS *m/z*: 307 (M^+), 308 (M^++1) (Calcd for $C_{14}H_{17}N_3O_3S$: 307.38). *Anal.* Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 13.67. Found: C, 55.60; H, 5.16; N, 13.85.

***N*-Allyl-2-(1-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3d** 65% yield. mp 161—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s), 4.08 (3H, s), 4.27 (1H, s, exch. D_2O), 4.33—5.37 (4H, m (br), 5.90—6.20 (1H, m), 6.69 (1H, s), 6.83 (1H, d, J=2.2 Hz), 7.40 (1H, d, J=2.2 Hz), 7.60 (1H, br s, exch. D_2O), 8.49 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3300, 3150, 1620, 1600, 1540, 1210. MS *m/z*: 319 (M^+), 320 (M^++1) (Calcd for $C_{15}H_{17}N_3O_3S$: 319.39). *Anal.* Calcd for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16. Found: C, 56.37; H, 5.17; N, 13.41.

2-(1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3e 70% yield. mp 192—194 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 4.01 (3H, s), 4.14 (3H, s), 6.28 (2H, br s, exch. D_2O), 6.90 (1H, d, J=2.4 Hz), 7.30 (1H, br s, exch. D_2O), 7.54 (1H, d, J=2.4 Hz), 8.5 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3400, 3250, 3150, 1620, 1600, 1560, 1200. MS *m/z*: 309 (M^+), 310 (M^++1) (Calcd for $C_{13}H_{15}N_3O_4S$: 309.34). *Anal.* Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.58. Found: C, 50.30; H, 5.00; N, 13.63.

2-(1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)-*N*-methylhydrazinecarbothioamide 3f 73% yield. mp 213—215 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 3.20 (3H, d), 3.98 (s, 3H), 4.10 (s, 3H), 6.16 (1H, br s, exch. D_2O), 6.86 (1H, d, J=2.2 Hz), 7.91 (1H, d, J=2.2 Hz), 7.81 (1H, s, exch. D_2O), 8.47 (1H, br s, exch. D_2O). IR (cm^{-1}): 3350, 3250 (NHs, OH), 1610, 1560, 1510—1480 (C=N, NH, C=C), 1230 (C=S). MS *m/z*: 323 (M^+), 324.15 (M^++1) (Calcd for $C_{14}H_{17}N_3O_4S$: 323.37). *Anal.* Calcd for $C_{13}H_{15}N_3O_4S$: C, 52.00; H, 5.30; N, 12.99. Found: C, 51.67; H, 5.04; N, 12.83.

***N*-Ethyl-2-(1-(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3g** 60% yield. mp 218—220 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.5 Hz), 2.17 (3H, s), 5.51—3.56 (2H, m, J=7.5 Hz), 3.92 (s, 3H), 3.95 (s, 3H), 7.16 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=2.4 Hz), 8.32 (1H, br s, exch. D_2O), 8.43 (1H, s, exch. D_2O), 9.51 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3350, 3250, 1610, 1540, 1510—1480, 1210. MS *m/z*: 337 (M^+), 338 (M^++1) (Calcd for $C_{15}H_{19}N_3O_4S$: 337.39). *Anal.* Calcd for $C_{15}H_{19}N_3O_4S$: C, 53.40; H, 5.68; N, 12.45. Found: C, 53.78; H, 5.84; N, 11.98.

***N*-Allyl-2-(1-(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazinecarbothioamide 3h** 75% yield. mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.99 (s, 3H), 4.04 (s, 3H), 4.27 (1H, s, exch. D_2O), 4.32—5.37 (4H, br m), 5.90—6.20 (1H, m), 6.49 (1H, br s, exch. D_2O), 6.87 (1H, d, J=2.24 Hz), 7.46 (1H, d, J=2.24 Hz), 8.61 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3300, 3250, 1610, 1580, 1560, 1210. MS *m/z*: 349 (M^+), 350 (M^++1) (Calcd for $C_{16}H_{19}N_3O_4S$: 349.42). *Anal.* Calcd for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, 5.48; N, 12.03. Found: C, 54.91; H, 5.33; N, 12.22.

2-(((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazono)-3-substituted-1,3-thiazolidin-4-ones 5a—c A mixture of the appropriate thiourea derivative **1b**—**d** (2.5 mmol), anhydrous sodium acetate (0.21 g, 2.6 mmol) and monochloroacetic acid (0.25 g, 2.6 mmol) in glacial acetic acid (15 ml) was refluxed for 16 h with stirring; the reaction mixture was then cooled and poured on ice. The obtained precipitate **5a**—**c** was collected by filtration, washed with water, dried and recrystallized from DMF/H_2O.

2-(((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazono)-3-methyl-1,3-thiazolidin-4-one 5a 62% yield. mp 289—290 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.23 (3H, s), 4.01 (2H, s), 4.06 (s, 3H), 4.19 (s, 3H), 7.33 (1H, d, J=2 Hz), 8.18 (1H, d, J=2 Hz), 8.52 (1H, s), 8.75 (1H, s). IR (KBr) cm^{-1}: 1720, 1655, 1610, 1540. MS *m/z*: 400.90 (M^+), 401.9 (M^++1) (Calcd for $C_{18}H_{15}N_3O_6S$: 401.4). *Anal.* Calcd for $C_{18}H_{15}N_3O_6S$: C, 53.86; H, 3.77; N, 10.47. Found: C, 54.00; H, 3.90; N, 10.35.

2-(((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazono)-3-ethyl-1,3-thiazolidin-4-one 5b 75% yield. mp 244—245 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz), 3.80 (2H, s), 3.92 (2H, q, J=7 Hz), 4.11 (s, 3H), 4.26 (s, 3H), 7.08 (1H, d, J=2 Hz), 7.70 (1H, d, J=2 Hz), 8.66 (1H, s), 8.73 (1H, s). IR (KBr) cm^{-1}: 1710, 1655, 1610, 1560. MS *m/z*: 414.90 (M^+), 415.9 (M^++1) (Calcd for $C_{19}H_{17}N_3O_6S$: 415.4). *Anal.* Calcd for $C_{19}H_{17}N_3O_6S$: C, 54.94; H, 4.12; N, 10.12. Found: C, 54.70; H, 4.30; N, 9.95.

3-Allyl-2-(((4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)hydrazono)-1,3-thiazolidin-4-one 5c 70% yield. mp 247—248 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.04 (2H, s), 4.00 (s, 3H), 4.15 (s, 3H), 4.34 (2H, d, J=5 Hz), 5.23 (2H, d, J=5 Hz), 5.80—6.00 (1H, m), 7.30 (1H, d, J=2 Hz), 8.16 (1H, d, J=2 Hz), 8.45 (1H, s), 8.72 (1H, s). IR (KBr) cm^{-1}: 1720, 1655, 1610, 1560. MS *m/z*: 427.15 (M^+), 428.15 (M^++1) (Calcd for $C_{20}H_{17}N_3O_6S$: 427.44). *Anal.* Calcd for $C_{20}H_{17}N_3O_6S$: C, 56.20; H, 4.01; N, 9.83. Found: C, 55.96; H, 4.12; N, 9.60.

2-(2-(((4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-6-yl)methylene)-hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic acid 5d To a stirred solution of compound **1b** (0.5 g, 1 mmol) in glacial acetic acid (10 ml), maleic anhydride (0.1 g, 1.1 mmol) was added. The reaction mixture was heated under reflux with stirring for 12 h. After cooling, the formed precipitate was filtered and dried to yield **5d** (0.32 g, 50%) which was recrystallized from DMF/H_2O.

50% yield. mp 268—269 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.95 (2H, d,), 3.31 (3H, s), 3.99 (s, 3H), 4.12 (s, 3H), 4.41 (1H, t), 7.29 (1H, d, J=2 Hz), 7.68 (1H, d, J=2 Hz), 8.47 (1H, s), 8.72 (1H, s), 12.50 (1H, br s, exch. D_2O); IR (KBr) cm^{-1}: 3300—2800, 1725 br, 1650, 1620, 1570. MS *m/z*: 459 (M^+), 460 (M^++1) (Calcd for $C_{20}H_{17}N_3O_8S$: 459.43). *Anal.* Calcd for $C_{20}H_{17}N_3O_8S$: C, 52.29; H, 3.73; N, 9.15. Found: C, 52.54; H, 3.87; N, 9.08.

2-(((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)-1,3-thiazolidin-4-one 6a Compound **2a** (1 g, 2.5 mmol) was dissolved in the least amount of dimethyl sulphoxide (12 ml). Anhydrous sodium acetate (0.21 g, 2.6 mmol) and monochloroacetic acid (0.25 g, 2.6 mmol) were added and the reaction mixture was heated with stirring for 8 h in boiling water bath. The produced yellow precipitate **6a** was filtered, dried and recrystallized from dimethyl sulfoxide (DMSO)/H_2O.

70% yield. mp 321—323 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.89 (3H, s), 4.02 (2H, s), 6.82 (1H, s), 7.03 (1H, s), 7.55 (3H, m), 8.03 (2H, m), 8.74 (1H, s), 12.32 (2H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450—3350 (br), 1720, 1640, 1610, 1560, 1540. MS *m/z*: 409 (M^+), 410 (M^++1) (Calcd for $C_{20}H_{15}N_3O_5S$: 409.41). *Anal.* Calcd for $C_{20}H_{15}N_3O_5S$: C, 58.67; H, 3.69; N, 10.26. Found: C, 58.41; H, 4.02; N, 9.95.

2-(((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)-3-substituted-1,3-thiazolidin-4-ones 6b—d To a solution of the chosen thiourea derivative **2b**—**d** (2.5 mmol) in glacial acetic acid (15 ml), anhydrous sodium acetate (0.21 g, 2.6 mmol) and monochloroacetic acid (0.25 g, 2.6 mmol) were added. The reaction mixture was heated under reflux with stirring for 8 h; the obtained yellow precipitate **6b**—**d** was collected, dried and recrystallized from DMF/H_2O.

2-(((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)3-methyl-1,3-thiazolidin-4-one 6b 75% yield. mp 340—341 °C. IR (KBr) cm^{-1}: 3425, 1730, 1650, 1610, 1560. MS *m/z*: 423 (M^+), 424 (M^++1) (Calcd for $C_{21}H_{17}N_3O_5S$: 423.45). *Anal.* Calcd for $C_{21}H_{17}N_3O_5S$: C, 59.57; H, 4.05; N, 9.92. Found: C, 59.86; H, 4.05; N, 9.60.

3-Ethyl-2-(((7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)-1,3-thiazolidin-4-one 6c 78% yield. mp 315—316 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, t), 3.79 (2H, m), 3.92 (3H, s), 4.06 (2H, s), 6.81 (1H, s), 7.02 (1H, s), 7.57 (3H, m), 8.03 (2H, m), 8.84 (1H, s), 12.32 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450 (br), 1720, 1650, 1610, 1550—1490. MS *m/z*: 437.15 (M^+), 438.15 (M^++1) (Calcd for $C_{22}H_{19}N_3O_5S$: 437.47). *Anal.* Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.68; H, 4.43; N, 9.40.

3-Allyl-2-(((7-hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)-1,3-thiazolidin-4-one 6d 75% yield. mp 277—278 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.93 (3H, s), 4.16 (2H, s), 4.37 (d, 2H, J=5 Hz), 5.23 (2H, d, J=5 Hz), 5.85—5.94 (1H, m), 6.84 (1H, s), 7.06 (1H,

s), 7.59 (3H, m), 8.06 (2H, m), 8.82 (1H, s), 12.29 (1H, br s, exch. D_2O); IR (KBr) cm^{-1}: 3475, 1720, 1650, 1610, 1560. MS *m/z*: 449.15 (M^+) (Calcd for $C_{23}H_{19}N_3O_5S$: 449.48). *Anal.* Calcd for $C_{23}H_{19}N_3O_5S$: C, 61.46; H, 4.26; N, 9.35. Found: C, 61.80; H, 4.64; N, 8.78.

2-(2-(((7-Hydroxy-5-methoxy-4-oxo-2-phenyl-4*H*-chromen-6-yl)methylene)hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic Acid 6e A mixture of **2b** (0.77 g, 2 mmol) and maleic anhydride (0.2 g, 2.2 mmol) in glacial acetic acid (10 ml) was refluxed with stirring for 12 h. The reaction mixture was cooled and the resulted precipitate was filtered, left to dry to give 0.6 g of **6e** which was recrystallized from DMF/H_2O.

60% yield. mp 294—295 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, d), 3.18 (3H, s), 3.39 (1H, br s, exch. D_2O), 3.91 (3H, s), 4.53 (1H, t), 6.82 (1H, s), 7.00 (1H, s), 7.48—7.57 (3H, m), 8.03 (2H, br m), 8.81 (1H, s), 12.27 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3425, 3300—2800, 1725 br, 1640, 1610, 1555. MS *m/z*: 481 (M^+) 482 (M^++1) (Calcd for $C_{23}H_{19}N_3O_7S$: 481.47). *Anal.* Calcd for $C_{23}H_{19}N_3O_7S$: C, 57.37; H, 3.98; N, 8.73. Found: C, 57.52; H, 4.07; N, 8.38.

2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7a. 2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-substituted-1,3-thiazolidin-4-ones 7b—d. 2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)-hydrazono)-1,3-thiazolidin-4-one 7e. 2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-substituted-1,3-thiazolidin-4-ones 7f—h A mixture comprised of the appropriate thiourea derivative **3a**—**h** (2.5 mmol), anhydrous sodium acetate (0.21 g, 2.6 mmol) and monochloroacetic acid (0.25 g, 2.6 mmol) in absolute ethanol (20 ml) and glacial acetic acid (2 ml) was refluxed for 16 h with stirring. Then it was concentrated and poured onto crushed ice. The formed precipitate **7a**—**h** was filtered, washed with water, dried and recrystallized from methanol.

2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7a 65% yield. mp 223—225 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.31 (3H, s), 3.87 (2H, s), 3.99 (3H, s), 6.77 (1H, s), 7.06 (1H, d, *J*=2.2 Hz), 7.77 (1H, d, *J*=2.2 Hz), 10.47 (1H, s, exch. D_2O), 11.91 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3500 (br), 1720, 1620, 1560, 1550. MS *m/z*: 319 (M^+), 320 (M^++1) (Calcd for $C_{14}H_{13}N_3O_4S$: 319.34). *Anal.* Calcd for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16. Found: C, 53.00; H, 4.40; N, 12.84.

2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-1,3-thiazolidin-4-one 7b 60% yield. mp 174—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 3.33 (3H, s), 3.83 (2H, s), 4.07 (3H, s), 6.83 (3H, br s, exch. D_2O), 7.43 (1H, d, *J*=2.0 Hz). IR (KBr) cm^{-1}: 3450, 1720, 1590, 1560. MS *m/z*: 333 (M^+), 334 (M^++1) (Calcd for $C_{15}H_{15}N_3O_4S$: 333.37). *Anal.* Calcd for $C_{14}H_{13}N_3O_4S$: C, 54.04; H, 4.54; N, 12.60. Found: C, 54.34; H, 4.88; N, 12.26.

3-Ethyl-2-((1-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7c 55% yield. mp 113—115 °C. IR (KBr) cm^{-1}: 3450, 1710, 1590, 1550. MS *m/z*: 347.05 (M^+), 348.05 (M^++1) (Calcd for $C_{16}H_{17}N_3O_4S$: 347.39). *Anal.* Calcd for $C_{16}H_{17}N_3O_4S$: C, 55.32; H, 4.93; N, 12.10. Found: C, 55.53; H, 5.22; N, 11.76.

3-Allyl-2-((1-(6-hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7d 68% yield. mp 129—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, s), 3.84 (2H, s), 4.06 (3H, s), 4.43—5.42 (4H, br m), 5.95—6.20 (1H, m), 6.83 (2H, s), 7.42 (1H, s), 11.95 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450, 1710, 1620, 1580. MS *m/z*: 359 (M^+), 360 (M^++1) (Calcd for $C_{17}H_{17}N_3O_4S$: 359.40). *Anal.* Calcd for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.48; H, 5.10; N, 11.44.

2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7e 65% yield. mp 200—202 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (1H, br s, exch. D_2O), 2.59 (3H, s), 3.88 (2H, s), 3.99 (s, 3H), 4.10 (s, 3H), 6.84 (1H, d, *J*=2.4 Hz), 7.49 (1H, d, *J*= 2.4 Hz), 11.60 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450 (br), 3200, 1710, 1600, 1540, 1520. MS *m/z*: 349 (M^+), 350 (M^++1) (Calcd for $C_{15}H_{15}N_3O_5S$: 349.36). *Anal.* Calcd for $C_{15}H_{15}N_3O_5S$: C, 51.57; H, 4.33; N, 12.03. Found: C, 51.94; H, 4.70; N, 11.79.

2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-1,3-thiazolidin-4-one 7f 75% yield. mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 3.34 (3H, s), 3.84 (2H, s), 3.98 (3H, s), 4.09 (3H, s), 6.29 (1H, d, *J*=2 Hz), 7.82 (1H, d, *J*=2 Hz), 11.87 (1H, s, exch. D_2O). IR (KBr) cm^{-1}: 3400, 1720, 1600, 1540, 1520. MS *m/z*: 363 (M^+), 364 (M^++1) (Calcd for $C_{16}H_{17}N_3O_5S$: 363.39). *Anal.* Calcd for $C_{15}H_{15}N_3O_5S$: C, 52.88; H, 4.72; N, 11.56. Found: C, 53.14; H, 4.92; N, 11.30.

3-Ethyl-2-((1-(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7g 60% yield. mp 141—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, *J*=7 Hz), 2.66 (3H, s), 3.85 (2H, s), 3.94—3.99 (2H, m, *J*=7 Hz), 4.00 (s, 3H), 4.10 (s, 3H), 6.85 (1H, d, *J*=2.2 Hz), 7.50 (1H, d, *J*=2.2 Hz), 12.00 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3350, 1700, 1600, 1540, 1510, 1480. MS *m/z*: 377 (M^+), 378 (M^++1) (Calcd for $C_{17}H_{19}N_3O_5S$: 377.41). *Anal.* Calcd for $C_{17}H_{19}N_3O_5S$: C, 52.84; H, 5.22; N, 10.87. Found: C, 52.30; H, 4.99; N, 10.88.

3-Allyl-2-((1-(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-1,3-thiazolidin-4-one 7h 68% yield. mp 132—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 3.85 (2H, s), 3.98 (s, 3H), 4.08 (s, 3H), 4.43—5.40 (4H, br m), 5.90—6.20 (1H, m), 6.84 (1H, s), 7.49 (1H, s), 11.90 (1H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450 (br), 1720, 1580, 1520, 1480. MS *m/z*: 389 (M^+), 390 (M^++1) (Calcd for $C_{18}H_{19}N_3O_5S$: 389.42). *Anal.* Calcd for $C_{18}H_{19}N_3O_5S$: C, 55.52; H, 4.92; N, 10.79. Found: C, 55.51; H, 4.88; N, 10.56.

2-(2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic Acid 7i. 2-(2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic Acid 7j To a solution of the appropriate thiourea derivative **3b** or **3f** (1.7 mmol) in glacial acetic acid (10 ml), maleic anhydride (0.16 g, 1.8 mmol) was added and the mixture was refluxed with stirring for 16 h. The reaction solution was concentrated, poured onto ice-water; the produced precipitate **7i**, **7j** was collected, left to dry and then recrystallized from methanol.

2-(2-((1-(6-Hydroxy-4-methoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic Acid 7i 50% yield. mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 2.88—3.01 (2H, d), 3.36 (3H, s), 4.09 (3H, s), 4.36 (1H, t), 6.83 (2H, d), 7.44 (1H, d), 7.60—8.40 (2H, br s, exch. D_2O). IR (KBr) cm^{-1}: 3450 (br), 1730, 1690, 1630, 1600, 1550. MS *m/z*: 391 (M^+), 392 (M^++1) (Calcd for $C_{17}H_{17}N_3O_6S$: 391.40). *Anal.* Calcd for $C_{17}H_{17}N_3O_6S$: C, 52.17; H, 4.38; N, 10.74. Found: C, 52.23; H, 4.12; N, 10.63.

2-(2-((1-(6-Hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)ethylidene)hydrazono)-3-methyl-4-oxo-1,3-thiazolidin-5-yl)acetic Acid 7j 55% yield. mp 144—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s), 2.87—3.01 (2H, d), 3.36 (3H, s), 3.98 (s, 3H), 4.08 (s, 3H), 4.38 (1H, t), 4.99—5.17 (2H, br s, exch. D_2O), 6.84 (1H, d), 7.49 (1H, d). IR (KBr) cm^{-1}: 3550, 3450, 1700 br, 1600, 1560. MS *m/z*: 421 (M^+), 422 (M^++1) (Calcd for $C_{18}H_{19}N_3O_7S$: 421.42). *Anal.* Calcd for $C_{17}H_{17}N_3O_6S$. H_2O: C, 49.20; H, 4.82; N, 9.56. Found: C, 49.17; H, 5.11; N, 9.70.

Anticonvulsant Activity All the newly synthesized compounds were tested for their anticonvulsant activity using the scPTZ[62,63] and MES[64] methods in mice. Also, representatives of the starting and intermediate compounds were tested for their anticonvulsant efficacy using the scPTZ method. In addition the ED_{50} was determined to the most active compounds. Also, the neurotoxicity for the active compounds was performed using the 4-Amino Pyridine (4-AP) method.

Method I: Protection against Pentylenetetrazole Induced Seizures (scPTZ) Albino mice of either sex, weighing 20—30 g, obtained from the animal house of Faculty of Pharmacy, Mansoura University (Mansoura, Egypt) were used in the experiments. Animals were randomly divided into groups, which are test groups, one control group and one reference group; each group consisted of six animals. The tested compounds were suspended in 0.5% methyl cellulose-water mixture as a vehicle, whereas PTZ and sodium valproate were dissolved in saline. The compounds were administered at doses of 75, 150 and 300 mg/kg intraperitoneally (i.p.) to the test groups. In the reference group sodium valproate was administered as a standard pharmacological drug against clonic phase of PTZ-induced seizures at a dose of 650 mg/kg. The control group was treated with the vehicle only. PTZ was applied S.C. at a dose of 85 mg/kg 30 min after injection of the tested compounds, standards or vehicle in the different groups. Each animal was placed into an individual glass cage and observed for 60 min for the appearance of seizures. One clonic seizure for a minimum period of 5 s was considered a threshold of convulsion. Transient intermittent jerks or tremulousness were not taken into account.[63]

Animals showing no threshold convulsion during the period of 60 min were considered protected. The number of protected animals in each group was recorded and the percentage of protected animals in each group was determined.

Method II: Protection against Electrical Shock Induced Seizures (MES) Albino mice of either sex, weighing 20—30 g, obtained from the animal house of Faculty of Pharmacy, Cairo University (Cairo, Egypt) were used in the experiments. Animals were randomly divided into groups, which are test groups, one control group and one reference group; each group consisted of six animals. The tested compounds and the standard reference

phenytoin were suspended in water using few drops of Tween 80. The tested compounds and phenytoin were administered at doses of 75, 150 and 300 mg/kg intraperitoneally (i.p.) to the test groups. The control group was treated with saline only. The animals were stimulated through Auricular electrodes with 18 mA current, shock duration 1 s, frequency of 100 pulse/s and pulse width of 0.5 ms at 0.5 and 4 h from the time of the tested or standard compounds injection using 'CD-S104-Cudos stimulator, (SC-electronics) Brookwood, Surrey, England.' The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity.[64] The number of protected animals in each group was recorded and the percentage of protected animals in each group was determined.

Method III: Protection against 4-Amino Pyridine (4-AP) Induced Seizures Animals (8 groups each of 10 mice) were pretreated with a single injection of valproic acid (300 mg/kg, in distilled water), **1c**, **2b** and **5a** (5, 10, and 10 mg/kg body weight, intraperitoneally (i.p.) suspended with few drops of Tween 80 in distilled water, or distilled water alone (vehicle or control). After 30 min of administration, animals were treated with a single injection of 4-AP (12 mg/kg body weight, intraperitoneally (i.p.), dissolved in water), and were divided as follows:

Group **1**, control [distilled water]; group **2**, [distilled water+4-AP]; group **3**, [valproic acid+water]; group **4**, [valproic acid 300 mg/kg+4-AP]; group **5**, [**1c** 5 mg/kg+water]; group **6**, [**1c** 5 mg/kg+4-AP]; group **7**, [**2b** 10 mg/kg+water]; group **8**, [**2b** 10 mg/kg+4-AP]; group **9**, [**5a** 10 mg/kg+water]; group **10**, [**5a** 10 mg/kg+4-AP].

Pre-treated mice with the newly synthesized compounds or vehicle were placed in individual Plexiglas chambers (20×20×19 cm), and their behavior was observed for 30 min for the appearance of seizures (clonic, tonic) or death. Thereafter the animals were treated with 4-AP and the behavior was observed for additional 60 min for the appearance of seizures (clonic, tonic) or death.[65]

The ED_{50} for the compounds were determined through a pilot study and the therapeutic doses were selected accordingly.[66,67] The dose for valproic acid was based on experimental evidence that doses from 0.1 to 0.4 g/kg are effective in animal models.[68,69] In addition, the convulsive dose of 4-AP was selected in accordance with Wong *et al.* (2002).[70]

Results 1) In the scPTZ test, the anticonvulsant activity results of the newly synthesized compounds and their calculated Log *P* are listed in Table 1.

2) In the MES test, all the tested compounds were considered inactive (doses up to 300 mg/kg showed no protection whereas, phenytoin showed 100% protection in all the used doses).

3) Table 2 show that a single administration of 4-AP (12 mg/kg) caused clonic and tonic seizures in all mice, followed by death of all mice. In contrast, pre-treatment of animals with valproic acid (300 mg/kg) caused a significant latency of clonic seizures and completely prevented the incidence of tonic seizures as well as death. Compound **1c** (5 mg/kg) also caused latency of clonic seizures and completely prevented the incidence of tonic seizures as well as death. The same applies with compounds **2b** and **5a**. Pre-treatment with **2b** (10 mg/kg) or **5a** (10 mg/kg), significantly increased latency for seizures (clonic and tonic) and completely abolished death. On the other hand, pre-treatment with valproic acid, **1c**, **2b**, **5a** reduced the number of animals that presented seizures (clonic and tonic) in relation to animals treated with 4-AP only.

Materials and Methods A) The tested compound or the reference drug (valproic acid) is injected intraperitoneally (i.p.) to groups of 10 mice (18—

Table 1. Number of Animals Protected in Each Group, Its Percentage at Each Dose in scPTZ Method and the Calculated Log *P* Values of the New Compounds

Compound	300 mg/kg	150 mg/kg	75 mg/kg	Log *P*
1a	(0/6) 0%	(0/6) 0%	(0/6) 0%	−0.19
1b	(3/6) 50%	(0/6) 0%	(0/6) 0%	0.33
1c	(6/6) 100%	(4/6) 66.6%	(1/6) 16.6%	0.66
1d	(3/6) 50%	(0/6) 0%	(0/6) 0%	1.16
1e	(6/6) 100%	(5/6) 83.3%	(0/6) 0%	1.99
2a	(0/6) 0%	(0/6) 0%	(0/6) 0%	2.22
2b	(6/6) 100%	(6/6) 100%	(0/6) 0%	2.74
2c	(0/6) 0%	(0/6) 0%	(0/6) 0%	3.08
2d	(5/6) 83.3%	(0/6) 0%	(0/6) 0%	3.57
2e	(3/6) 50%	(0/6) 0%	(0/6) 0%	4.41
3a	(3/6) 50%	(0/6) 0%	(0/6) 0%	0.85
3b	(3/6) 50%	(0/6) 0%	(0/6) 0%	1.37
3c	(4/6) 66.6%	(0/6) 0%	(0/6) 0%	1.71
3d	(3/6) 50%	(0/6) 0%	(0/6) 0%	2.20
3e	(0/6) 0%	(0/6) 0%	(0/6) 0%	0.72
3f	(4/6) 66.6%	(0/6) 0%	(0/6) 0%	1.24
3g	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.58
3h	(4/6) 66.6%	(0/6) 0%	(0/6) 0%	2.08
5a	(6/6) 100%	(5/6) 83.3%	(1/6) 16.6%	0.70
5b	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.04
5c	(4/6) 66.6%	(0/6) 0%	(0/6) 0%	1.40
5d	(4/6) 66.6%	(0/6) 0%	(0/6) 0%	0.42
6a	(0/6) 0%	(0/6) 0%	(0/6) 0%	2.88
6b	(3/6) 50%	(0/6) 0%	(0/6) 0%	3.12
6c	(0/6) 0%	(0/6) 0%	(0/6) 0%	3.46
6d	(0/6) 0%	(0/6) 0%	(0/6) 0%	3.81
6e	(0/6) 0%	(0/6) 0%	(0/6) 0%	2.83
7a	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.51
7b	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.75
7c	(0/6) 0%	(0/6) 0%	(0/6) 0%	2.09
7d	(4/6) 66.6%	(1/6) 16.6%	(0/6) 0%	2.44
7e	(6/6) 100%	(4/6) 66.6%	(1/6) 16.6%	1.39
7f	(5/6) 83.3%	(3/6) 50%	(0/6) 0%	1.62
7g	(3/6) 50%	(0/6) 0%	(0/6) 0%	1.96
7h	(0/6) 0%	(0/6) 0%	(0/6) 0%	2.26
7i	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.16
7j	(0/6) 0%	(0/6) 0%	(0/6) 0%	1.34
Sodium valproate	(6/6) 100%	(6/6) 100%	(6/6) 100%	2.58
Vehicle	(0/6) 0%	(0/6) 0%	(0/6) 0%	

Table 2. Influence of Pre-treatment with Compounds **1c**, **2b**, **5a** and Valproic Acid on Latency for Seizures (Clonic and Tonic) and Death Using 4-AP-Induced Method

Groups	Clonic seizures	Latency for clonic seizures (min)	Tonic seizures	Latency for tonic seizures (min)	Survival
1	0/8	60.00±0.00	0/8	60.00±0.00	8/8
2	8/8[c)]	9.13±1.19[a)]	8/8[c)]	18.13±3.68[a)]	0/8[c)]
3	0/6	60.00±0.00	0/6	60.00±0.00	6/6
4	1/6	48.26±3.57[b)]	0/6[d)]	60.00±0.00[b)]	6/6[d)]
5	0/5	60.00±0.00	0/5	60.00±0.00	5/5
6	6/6	20.17±1.76[b)]	0/6[d)]	60.00±0.00[b)]	6/6[d)]
7	0/5	60.00±0.00	0/5	60.00±0.00	5/5
8	2/7	43.67±10.45[b)]	0/7[d)]	60.00±0.00[b)]	7/7[d)]
9	0/6	60.00±0.00	0/6	60.00±0.00	6/6
10	1/8[d)]	46.50±8.88[b)]	0/8[d)]	60.00±0.00[b)]	8/8[d)]

* Group 1, control [distilled water]; group 2, [distilled water+4-AP]; group 3, [300 mg/kg valproic acid+water]; group 4, [300 mg/kg valproic acid+4-AP]; group 5, [5 mg/kg **1c**+water]; group 6, [5 mg/kg **1c**+4-AP]; group 7, [10 mg/kg **2b**+water]; group 8, [10 mg/kg **2b**+4-AP]; group 9, [10 mg/kg **5a**+water]; group 10, [10 mg/kg **5a**+4-AP]. *a*) Significantly different from distilled water, $p<0.05$ by Mann–Whitney *U*-test. *b*) Significantly different from distilled water+4-AP, $p<0.05$ by Mann–Whitney *U*-test. *c*) Significantly different from distilled water, $p<0.05$ by Fisher exact test. *d*) Significantly different from distilled water+4-AP, $p<0.05$ by Fisher exact test. ** Last animal died at 32.13±6.42 min.

22 g). Another group of 10 mice served as control. Fifteen minutes after injection; 60 mg/kg (Pentylenetetrazole) was injected subcutaneously. Each animal was placed into an individual plastic cage for observation lasting 1 h. Seizures and tonic–clonic convulsions are recorded.[71,72]

B) Male mice (groups of 10 mice) for neuroprotective method (20—25 g), were maintained at 12 h light/dark cycle (07:00—19:00 h lights on) and at a room temperature of 22±2 °C. All animals had free access to food and water. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the German university in Cairo, Cairo, Egypt.

Evaluation The number of protected animals in the treated groups is calculated as percentage of affected animals in the control group. ED_{50} value was then calculated.[69,70]

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