Synthesis of Novel Spiro(indolone-3,2′-[1,3,4]thiadiazol)-2-ones and Evaluation of Their Antidepressant and Anticonvulsant Activities

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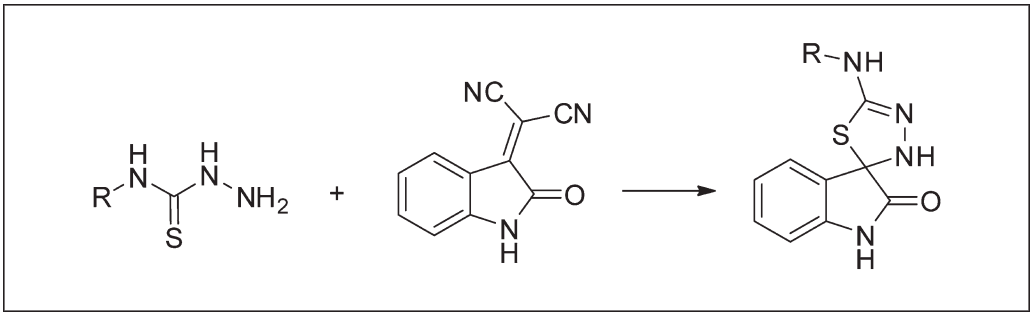

The reaction of 3-(dicyanomethylene)-2-indolone in a solution of ethanol/piperidine with 4-substituted thiosemicarbazides forms the derivatives of 5′-(substituted amino)-3′*H*–spiro(indoline-3,2′-[1,3,4]thiadiazol-2-one. Rationales for these conversions involving the nucleophilic addition on the dicyanomethylene carbon atom are presented. The prepared compounds were evaluated each for antidepressant activity using tail suspension behavioral despair test and anticonvulsant activity against pentylenetetrazol induced seizures in mice.

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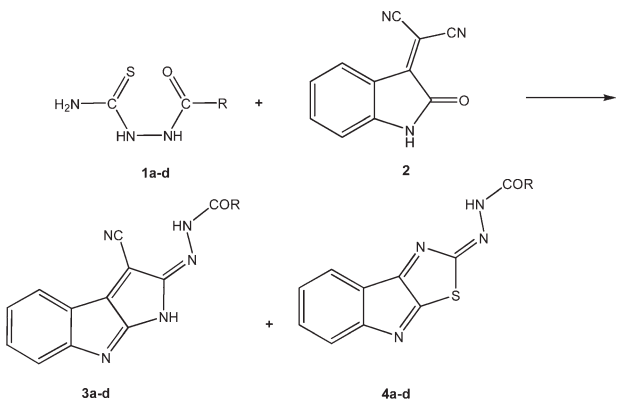
INTRODUCTION

Antidepressants and anticonvulsants are among the most widely utilized drugs for the treatment of central nervous system (CNS) disorders [1–4]. The 1,3,4-thiadiazole core is found to be the active part of several biologically active compounds, including antibacterial [5–8], antifungal [7,8], antitubercular [9–11], analgesic [12], anti-inflammatory [7,8,13], antidepressant [14], and leishmanicidal agents [15]. Isatin is an endogenous compound isolated, and reported to possess a wide range of central nervous system activities [16–18]. Isatin has been identified as a selective inhibitor of monoamine oxidaze B (MAOB), with IC_{50} values of about 5 μ*M* [16,19], it is also considered an endogenous marker of stress and anxiety [20]. Several studies show that isatin exhibits anxiogenic effects at doses of 10–20 mg/kg [21], in contrast to sedative and anticonvulsant effects at doses of 80–200 mg/kg [22]. Furthermore, isatin derivatives are reported to show a variety of biological activities like antibacterial [23], antifungal [24], anti-HIV [25] anticonvulsant [26], antineoplastic [27,28], and DNA gyrase inhibitors [29]. In addition, a number of *N*4-substituted isatin-3-thiosemicarbazones were introduced as urease inhibitors [30,31]. Pharmacophore development for isatin-β-thiosemicarbazones with selective activity toward multidrug-resistant cells has been reported [32]. A novel and a efficient procedure for the synthesis of thiosemicarbazones has been achieved *via* a multicomponents and catalyst-free reaction of phenyl or *p*- chlorophenyl isothiocyanate, hydrazine, and aldehydes or ketones [33]. Besides, thiosemicarbazones are versatile building blocks in the synthesis of densely substituted heterocycles [34–40]. It has been reported earlier that, isatin-3-thiosemicarbazones were cyclized to 5*H*-*as*-triazino[5,6-*b*]indole-3-thiones in aqueous K_2CO_3 [41–43]. 3-(Dicyanomethylene)-2-indolone (**2**), [44] which is a ylidene malononitrile, reacted with *N*,*N*′-diarylaceta-midines to give spiro[2,3-dihydroindol-3,4′-(pyridine)-5′-carbonitriles [45]. An efficient transformation of substituted carbohydrazides with **2** into spiro(indoline-3,2′-oxadiazol)-2-ones and acylpyrazoloindoles has been reported [46]. Recently, we have reported that the reaction of acylthiosemicarbazides **1a–d** with **2** afforded substituted pyrroloindenohydrazide **3a–d** and

Scheme 1



1, 3 and 4: a, R= CH_3; b, R= C_6H_5; c, R= 4-HO-C_6H_4; d, R= 4-Br-C_6H_4-CH_2-

thiazolo[5,4-*b*]indolylidene hydrazide derivatives **4a–d** [47] (Scheme 1). Encouraged by the above-mentioned results, the present work describes the chemical behavior of 4-substituted thiosemicarbazides **5a–f** towards dicyano-methyleneindolone **2**. The isolated compounds **8a–e** were evaluated each for antidepressant activity using tail suspension behavioral despair test [48] and anticonvulsant activity against pentylenetetrazol (PTZ) induced seizures in mice [49].

RESULTS AND DISCUSSION

Chemistry. Heating equimolar amounts of **5a–f** with 3-(dicyanomethylene)-2-indolone (**2**) in ethanol/piperidine under reflux resulted in pink coloration of the solution, which later turned into reddish brown precipitates from **8a–f**. The structures of **8a–f** were delineated from their spectroscopic properties and molecular compositions. The products **8a–f,** obtained from **5a–f,** were found to be formed by reacting one molecule of **5a–f** and one molecule of **2** *via* loss of a molecule of malononitrile. The molecular ions in their EI-mass spectra confirm the molecular masses and the molecular compositions. Furthermore, the common features of the fragmentation patterns supported the assigned structures. The EI-mass spectra of **8a–f** are characterized by molecular ions of high intensity and the loss of 28 a.m.u (dinitrogen or carbonyl group) followed by the loss of 119 a.m.u (most likely PhN=C=O) and RN=C=S from the molecular ion. The IR spectra of **8a–f** showed absorption bands characteristic for NH groups at 3430–3350, 3250–3190, strong carbonyl group at 1710–1695 and C=N at 1625–1620 cm^{-1}. The ^{1}H-NMR spectrum of **8c** clearly showed the presence of three different broad signals with the ratio 1:1:1 at 12.82, 9.75, and 7.65 ppm due to thiadiazole-NH, indole-NH, and allyl-NH, respectively. The ^{1}H-NMR of **8c** clearly indicated the presence of an allyl group which appeared as three multiplets centered at 4.31, 5.28, and 6.0 ppm due to allyl-CH_2N, allyl-CH_2= and allyl-CH=, respectively. The presence of the allyl group was also proved by the ^{13}C-DEPT-NMR spectrum, exhibiting positive signals at 133.78 (allyl-CH=) and negative signals at 47.12, 116.34 due to (allyl-CH_2N and (allyl —CH_2=), respectively. The IR and ^{13}C-NMR spectra of **8a–f** confirmed the disappearance of a thione group, respectively. Instead, signals at 110.10–109.86 (spiro-C-3=C-2′), 162.22–162.86 (C-5′), and 177.18–175.93 ppm (indolone–CO) could be observed, in addition to the aromatic carbons.

In **8d**, mass spectrometry and elemental analysis proved the molecular formula as $C_{15}H_{10}F_2N_4SO$. The IR spectrum revealed absorption bands at υ = 3350–3190, 1710, and 1625 cm^{-1} assigned to NH, CO, and C=N stretching, respectively. Distinctive ^{13}C-NMR signals of **8d** appeared at δc = 176.12 (indolone-CO), 161.18 for (3,5-diflorophenyl), 162.87 (C-5′), 110.08 (C-3=C-2′), 124.86, 125.71, 125.92, 128.26, 129.66, 129.91 (Ar-CH), and 132.66, 141.75, 143.26 (Ar-C) ppm. The analytical data of compound **8a–f** also match those of other isomers of products **7**, **9**, and**10** (Scheme 2).

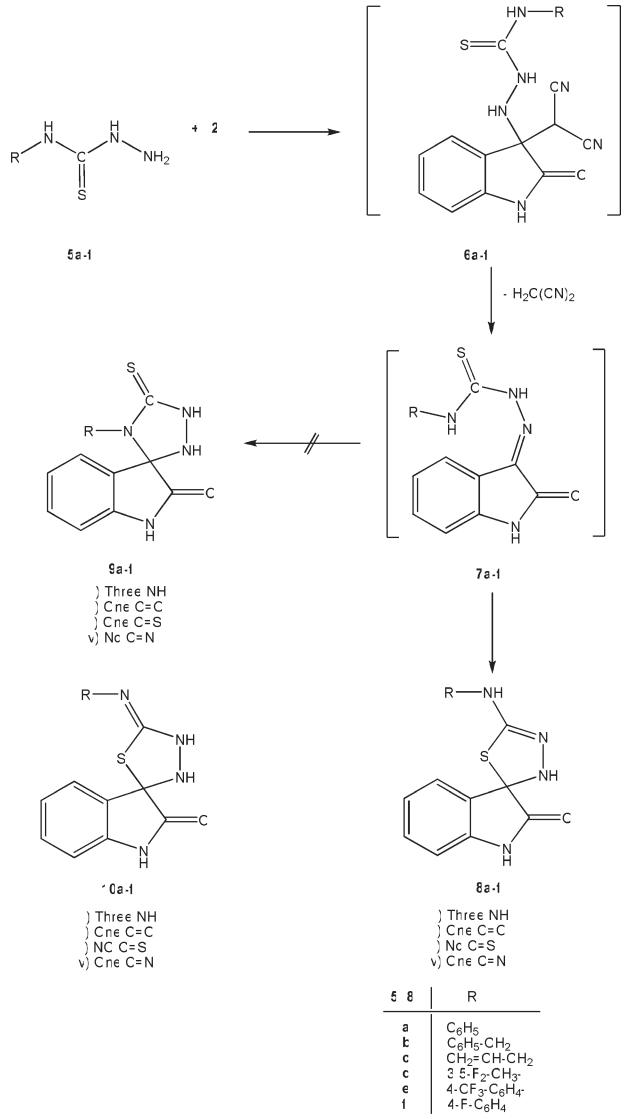
The alternative structures **7** and **9** were ruled out on the basis of ^{1}H-NMR and ^{13}C-NMR spectra. Therefore, we will concentrate on the interplay between the formation of the products **8** and the alternative structures **10**. *A priori* possible isomer structure **10** was ruled out on the basis of ^{1}H-NMR and disappearance of the thiosemicarbazide-N^2-H proton. Moreover, the fact that the in the structures **10**, the NH-thiadiazole in position **3** in not adjacent to C=N double bond should result in considerable lowering of the δ_H value [30] in ^{1}H-NMR spectra which was not the case of **8a–f**. Based on these observations the formation of isomers 10 was excluded.

Nucleophilic attacks of the terminal NH_2 of **5a–f** on C-3 of **2** with elimination of malononitrile from adduct **6** gives rise to indolone **7**. Intramolecular attack of the thione sulfur atom on C-3 of **7** leads to the formation of spiroindoline-3,2′-[1,3,4]thiadiazolone derivatives **8a–f**. The alternative option, namely nucleophilic attack of R-NH-group on C-3 of **7**, is not observed, since a product of structure **9** instead of **8a–f** was not found.

PHARMACOLOGY

Antidepressant activity. The synthesized compounds **8a–e** were screened for antidepressant activity using tail suspension behavioral despair test [48]. This test is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and tricyclic antidepressants [48]. Results of the antidepressant

Scheme 2



activity of the tested compounds and reference drugs are given in Table 1.

Compounds **8d** and **8a** exhibit remarkable antidepressant activity compared with imipramine: their activities are nearly equal 2.5 times the activity of imipramine. Compounds **8c** and **8b** significantly reduced the duration of immobility times to 64.55 and 66.98 s, respectively, compared with 132.00 s reduction of the duration of immobility for imipramine at 10 mg kg^{-1} dose level. Compounds **8c** and **8b** induced remarkable antidepressant activity compared with imipramine, their activities are nearly equal twice the activity of imipramine. Compounds **8c** and **8b** significantly

Anticonvulsant activity. The synthesized compounds **8a–e** were evaluated for anticonvulsant activity against PTZ induced seizures in mice [49]. The results of these experiments are listed in Fig. 1 and were determined using the following formula [50].

$$\% \text{ of protection} = \frac{\text{no.of convulsions of control} - \text{no.of convulsions of treated}}{\text{no. of convulsions of control}} \times 100$$

Compounds **8a**, **8b**, and **8d** exhibited the most protective class of the tested compounds against clonic seizures induced by ip injection of PTZ. They induced 87.78, 73.33, and 67.03% protection, respectively, at a dose level of 20 mg kg^{-1}.

Compound **8a** showed a markedly protective effect nearly equal to phenobarbital sodium at a dose level of 30 mg kg^{-1} and better than phenytoin sodium at a dose level of 30 mg kg^{-1}. Compound **8b** exhibits a remarkable protective effect close to phenobarbital sodium at a dose level of 30 mg kg^{-1} and better than phenytoin sodium at a dose level of 30 mg kg^{-1}. Compound **8d** exhibited a good protective effect compared with phenobarbital sodium at a dose level of 30 mg kg^{-1} and better than phenytoin sodium at a dose level of 30 mg kg^{-1}. Compound **8e** exhibited a moderate protection against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}, it induced 47.03%. Compound **8c** exhibited a weak protection against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}. The results are illustrated in Fig. 1.

Table 1

Antidepressant activities of the tested compounds **8a–e** compared to imipramine.

	Antidepressant activities	
Compounds[a]	Duration of immobility (s) (mean ± S.E.M.)	Change from control (%)
8a	55.10 ± 6.64	−77.35
8b	66.98 ± 5.33	−72.47
8c	64.55 ± 6.44	−72.64
8d	53.21 ± 4.45	−78.13
8e	116.60 ± 4.50	−52.07
Imipramine	132.00 ± 3.60	−45.75
Control	243.30 ± 8.00	–

Values represent the mean ± S.E.M. ($n = 6$)

[a] Tested compounds and imipramine were tested at 10 mg.kg^{-1} dose level, ip. reduced the duration of immobility times to 64.55 and 66.98 s, respectively, compared with 132.00 s reduction for imipramine at 10 mg kg^{-1} dose level. Compound **8e** exhibits antidepressant activity, nearly equaling 1.13 times the activity of imipramine. Compound **8e** significantly reduced the duration of immobility times to 116.60 s compared with 132.00 s reduction for imipramine at 10 mg kg^{-1} dose level.

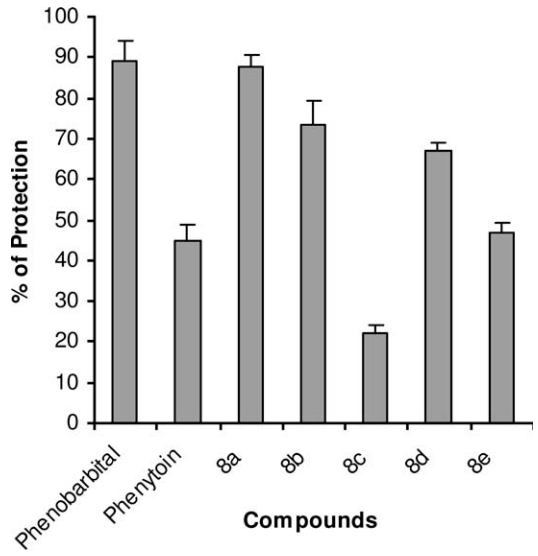


Figure 1. Anticonvulsant activity of compounds **8a–e** expressed as mean ± S.E.M. compared with Phenobarbital sodium and phenytoin sodium at a dose level of 30 mg kg^{-1}. Compounds were tested at 20 mg kg^{-1} dose level, ip. Values represent the mean ± S.E.M. ($n = 6$).

CONCLUSION

The presented synthesis provides insight into the reactions between the electron donating 4-substituted thiosemicarbazides **5a–f** and a suitable electron acceptor, **2** in our case. Spiroindoline-3,2′-[1,3,4]thiadiazolones **8a–f** are formed from **5a–f** and **2** (in presence of a base such as piperidine). The results reported here-in supplement the rich chemistry of 3-(dicyanomethylene)-2-indolone **2**.

The results indicated that all of the tested compounds induced remarkable antidepressant activity compared with imipramine at 10 mg kg^{-1} dose level. Moreover, compounds **8a**, **8b**, and **8d** represented the most protective class of the tested compounds against clonic seizures induced by ip injection of PTZ, their effect nearly close to that of phenobarbital sodium at a dose level of 30 mg kg^{-1}. Therefore, these compounds appear to be promising for their antidepressant and anticonvulsant activities.

EXPERIMENTAL

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Gallenkamp melting point apparatus. The IR spectra were recorded with a Shimadzu 408 (potassium bromide disks). The 400 MHz ^{1}H and 100 MHz ^{13}C-NMR spectra were recorded on a Bruker AM 400 spectrometer with tetramethylsilane as the internal standard, br = broad, s = singlet, m = multiplet. The ^{13}C signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT instrument. Elemental analyses were carried out at the microanalytical center, Cairo University, Egypt.

Starting materials. 4-Substituted thiosemicarbazides **(5a–f)** were synthesized by the reaction of hydrazine hydrate with the proper isothiocyanate according to published procedures in literature: 4-phenyl-thiosemicarbazide (**5a**) [51,52], 4-benzylthiosemicarbazide (**5b**) [33,34], 4-allylthiosemicarbazide (**5c**) [53,54], 4-(3,5-difluoro-phenyl)thiosemicarbazide (**5d**) [55], 4-[4-(trifluoromethyl)-phenyl]thiosemicarbazide (**5e**) [55], 4-(4-fluorophenyl)thio-semicarbazide (**5f**) [56]. 3-(Dicyanomethylene)-2-indolone **2** was prepared according to Fatiadi [44].

Reaction of 4-substituted thiosemicarbazides (5a–f) with 3-(dicyanomethylene)-2-indolone (2). Thiosemicarbazides (**5a–f**) (1.0 mmol) were dissolved in 20 mL absolute ethanol with two drops of piperidine and added to the indolone (**2**) (1 mmol) in 25 mL absolute ethanol, the mixture was heated under reflux for 3h (for run **5a**), 4h (for runs **5b,c**), 7h (for runs **5e,f**), and 5h (for run **5d**) cooled to room temperature. Yellowish brown crystals from compounds **8a–f** were precipitated, filtered, and washed with a small amount of cold ethanol and recrystallized from listed solvents.

5′-(Phenylamino)-3′*H*-spiro(indoline-3,2′-[1,3,4]-thiadiazole)-2-one (8a). This compound was obtained as yellowish brown crystals (acetonitrile), mp 220–222; IR (KBr) υ: NH 3390–3210, CO 1695, C=N 1625, Ar-C=C 1600 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 6.90–7.70 (m, 9H, Ar-H), 8.60 (br, 1H, NHPh), 9.45 (br, 1H, indolone-NH), 12.85 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 110.10 (C-3=C-2′), 124.32, 125.31, 126.50, 128.21, 128.95, 131.65 (Ar-CH), 137.53, 137.84, 141.14 (Ar-C), 162.58 (C-5′), 175.93 (CO); MS: *m/z* 296 (M^+, 51), 268 (100), 203 (6), 179 (9), 161 (10), 150 (14), 104 (12), 93 (18), 77 (15). *Anal*. calcd. for $C_{15}H_{12}N_4OS$: C, 60.79; H, 4.08; N, 18.91; S, 10.82. Found: C, 60.94; H, 3.98; N, 19.06; S, 10.94.

5′-(Benzylamino)-3′*H*-spiro(indoline-3,2′-[1,3,4]thiadiazole)-2-one (8b). This compound was obtained as yellowish brown crystals (acetonitrile), mp 200–202; IR (KBr) υ: NH 3430–3250, CO 1705, C=N 1620, Ar-C=C 1605 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 4.90 (S, 2H, CH_2Ph), 7.05–7.55 (m, 9H, Ar-H), 7.75 (br, 1H, NH-CH_2Ph), 9.70 (br, 1H, indolone-NH), 12.76 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 48.67 (CH_2), 109.86 (C-3=C-2′), 127.56, 128.23, 128.67, 128.95, 129.16, 131.25 (Ar-CH), 132.21, 133.35, 143.14 (Ar-C), 162.61 (C-5′), 173.36 (CO); MS: *m/z* 310 (M^+, 67), 282 (24), 164 (43), 149 (90), 118 (26), 106 (71), 91 (100), 77 (21). *Anal*. calcd. for $C_{16}H_{14}N_4OS$: C, 61.92; H, 4.55; N, 18.05; S, 10.33. Found: C, 62.06; H, 4.39; N, 17.89; S, 10.51.

5′-(Allylamino)-3′*H*-spiro(indoline-3,2′-[1,3,4]thiadiazole)-2-one (8c). This compound was obtained as yellowish brown crystals (ethanol), mp 190–192; IR (KBr) υ: NH 3390–3220, CO 1705, C=N 1620, Ar-C=C 1600 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 4.31 (m, 2H, allyl-CH_2N), 5.28 (m, 2H, allyl-CH_2=), 6.0 (m, 1H, allyl-CH=), 7.08–7.53 (m, 4H, Ar-H), 7.65 (br, 1H, NH-allyl), 9.75 (br, 1H, indolone-NH), 12.82 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 47.12 (allyl-CH_2-N), 110.08 (C-3=C-2′), 116.34 (allyl-CH_2=), 129.15, 129.76, 128.67, 128.95, 129.16, 131.25 (Ar-CH), 133.78 (allyl-CH=), 136.85, 137.22, 142.81 (Ar-C), 162.22 (C-5′), 176.62 (CO); MS: *m/z* 260 (M^+, 23), 232 (21), 161 (18), 147 (46), 113 (51), 91 (100). *Anal*. calcd. for $C_{12}H_{12}N_4OS$: C, 55.37; H, 4.65; N, 21.52; S, 12.32. Found: C, 55.22; H, 4.76; N, 21.39; S, 12.48.

5′-(3,5-Difluorophenylamino)-3′*H*-spiro(indoline-3,2′[1,3,4]-thiadiazole)-2-one (8d). This compound was obtained as pale yellowish-brownish crystals (acetonitrile), mp 260–262; IR (KBr) υ: NH 3350–3190, CO 1710, C=N 1625, Ar-C=C

1605 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 7.02–7.88 (m, 7H, Ar-H), 9.91 (br, 1H, indolone-NH), 10.18 (br, 1H, NH-C_6H_3-F_2), 12.86 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 110.08 (C-3=C-2′), 124.86, 125.71, 125.92, 128.26, 129.66, 129.91 (Ar-CH), 132.66, 141.75, 143.26 (Ar-C), 161.18 (Ar-C-F), 162.87 (C-5′), 176.12 (CO); MS: *m/z* 332 (M^+, 52), 304 (100), 178 (11), 150 (18), 104 (26), 77 (19). *Anal*. calcd. for $C_{15}H_{10}F_2N_4OS$: C, 54.21; H, 3.03; N, 16.86; S, 9.65. Found: C, 54.06; H, 2.91; N, 17.05; S, 9.83.

5′-[(4-Trifluoromethyl)(phenylamino)-3′*H*-spiro-(indoline-3,2′-[1,3,4]thiadiazol)]-2-one (8e). This compound was obtained as pale yellowish brown crystals (acetonitrile), mp 248–250; IR (KBr) υ: NH 3390–3210, CO 1695, C=N 1625, Ar-C=C 1605 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 6.95–7.90 (m, 8H, Ar-H), 9.92 (br, 1H, indolone-NH), 10.18 (br, 1H, NH-Ph), 12.91 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 110.02 (C-3=C-2′), 123.88 (C-F_3), 125.96, 126.18, 127.74, 128.65, 129.26 (Ar-CH), 131.66, 132.74, 142.83, 143.11 (Ar-C), 162.28 (C-5′), 177.18 (CO); MS: *m/z* 364 (M^+, 56), 336 (100), 218 (8), 203 (17), 178 (21), 150 (33), 104 (35), 77 (21). *Anal*. calcd. for $C_{16}H_{11}F_3N_4OS$: C, 52.74; H, 3.04; N, 15.38; S, 8.80. Found: C, 52.92; H, 2.89; N, 15.21; S, 9.02.

5′-(4-Fluorophenylamino)-3′*H*-spiro(indoline-3,2′-[1,3,4]-thiadiazole)-2-one (8f). This compound was obtained as pale yellowish brown crystals (methanol), mp 236–238; IR (KBr) υ: NH 3385–3215, CO 1695, C=N 1620, Ar-C=C 1605 cm^{-1}; ^{1}H-NMR (DMSO-d_6); δ 6.95–7.78 (m, 8H, Ar-H), 9.83 (br, 1H, NH, indolone-NH), 10.26 (br, 1H, NH-C_6H_4-F), 12.76 (br, 1H, thiadiazole-NH); ^{13}C-NMR (DMSO-d_6): δ 109.92 (C-3=C-2′), 125.24, 126.63, 128.55, 129.15, 129.76, 131.25 (Ar-CH), 132.16, 135.77, 142.66 (Ar-C), 160.65 (Ar-C-F), 162.71 (C-5′), 176.53 (CO); MS: *m/z* 314 (M^+, 22), 266 (27), 152 (11), 110 (26), 91 (100). *Anal*. calcd. for $C_{15}H_{11}FN_4OS$: C, 57.31; H, 3.53; N, 17.82; S, 10.20. Found: C, 57.47; H, 3.39; N, 18.03; S, 10.36.

PHARMACOLOGY

Adult male albino Swiss-Webster mice (22 ± 2 g) were obtained from the animal house, Cairo. The mice were housed in a quiet and temperature and humidity-controlled room (22 ± 3°C and 60 ± 5%, respectively) in which a 12 h light/dark cycle was maintained (08.00–20.00 h light). The animals were acclimated to their environment for at least 2 days before the experiments and were allowed free access to food and water before being tested.

Antidepressant activity.. The mice were housed in Plexiglass cages with six animals for each cage. ''Tail suspension test'' a behavioral despair test, was used for evaluating if the compounds have antidepressant activity. On the testing day, mice were assigned into different groups ($n = 6$ for each group). The tested compounds and reference drug (imipramine) were dissolved in carboxy methyl cellulose (CMC) solution (0.5% w/v in water). All the tested compounds **8a–e** (10 mg kg^{-1}) and imipramine (10 mg kg^{-1}) were injected ip to mice at a volume of 0.5 mL per 100 g body weight. Control animals were similarly treated with CMC solution (0.5% w/v in water). One hour later, the mice were suspended by the tail to the edge of a shelf 80 cm above the floor. The tail was secured to the shelf by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of the immobility was recorded for a period of 6 min. Mice were considered immobile only when they hung passively and completely motionless.

Anticonvulsant activity. The synthesized compounds 8**a–e** were evaluated for anticonvulsant activity against PTZ induced seizures in mice [49]. On the testing day, mice were assigned into different groups ($n = 6$ for each group). The tested compounds were dissolved in CMC solution (0.5% w/v in water) and administered to animals at a dose of (20 mg kg^{-1}) ip at a volume of 0.5 mL per 100 g body weight. After1 h, the administration of the tested compound, mice were injected PTZ (80 mg kg^{-1}) as a 0.5% solution ip that produces clonic seizures lasting for a period of at least 5 s in greater than 95% of animals tested. The animals were observed for 30 min, failed to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration was defined as protection). Animals devoid of generalized convulsions were considered to be protected, and the results were represented as percentage protection [50]. Standard drug used was phenobarbital sodium and phenytoin sodium at a dose level of 30 mg kg^{-1}.

Statistical analysis. Results are expressed as mean ± S.E.M.; *n* represents the number of animals. Data obtained from pharmacological experiments were analyzed by one-way analysis of variance. A *P*-value of less than 0.05 was considered statistically significant.

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