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Original article

Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities

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ABSTRACT

Substituted carboxylic acid hydrazides **1a–d** reacted with ethenetetracarbonitril **2** in dimethyl formamide with the formation of diacylhydrazines **4a–d** and 5-amino-1-substiuted pyrazole-3,3,4-tricarbonitriles **5a–d**. On the other hand, **1a–d** reacted with diethyl (*E*)-2,3-dicyanobutenedioate **3** to give oxadiazole derivatives **10a–d** and pyrazolone derivatives **11a–d**, respectively. The prepared compounds **4a–d**, **5a–d** and **11a–d** were evaluated each for antidepressant activity using tail suspension behavioral despair test and anticonvulsant activity against PTZ induced seizures in mice. Compounds **4a** and **4b** induced markedly antidepressant activity compared to imipramine, and their activities as antidepressant nearly equal twice the activity of imipramine at 10 mg kg^{-1} dose level. On the other hand, compounds **11b**, **11a** and **11d** exhibited remarkable protective effect against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}. The results of anticonvulsant activity are nearly close to phenobarbital sodium at a dose level of 30 mg kg^{-1}and more potent than phenytoin sodium at a dose level of 30 mg kg^{-1}.

1. Introduction

Antidepressants and anticonvulsants are among the most widely utilized drugs for the treatment of CNS disorders [1–4]. Considerable interest has been focused on the pyrazole structure, which has been known to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, antihypotensive, and antidepressant activities [5–10]. Moreover, hydrazides and their derivatives have been reported to exhibit various pharmacological activities such HIV-1 integrase inhibitors [11], anti-tubercular [12], antidepressant [13], anticonvulsant [13] and aspartic protease inhibitory activities [14].

Additionally, hydrazide compounds, such as furoic hydrazide, thiophencarboxylic hydrazide and isonicotinic acid hydrazide reacted with a series of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluro-3-alken-2-ones to give 3-alkyl (aryl)-5-trifluoromethyl substiuted pyrazoles [15]. One pot reactions between carboxylic hydrazides and 2-isothiocyanatobenzonitrile afforded pharmacologically relevant 1,2,4-triazolo[1,5-*c*]quinazoline-5-thiones [16]. Hydrazide compounds were also converted to triazole-3-thiols [17], 1,3,4-oxadiazole [18], 1,3,4-oxadiazine [18], pyrazolotriazolopyrimidine [19,20] and pyrazolotriazoloquinoline derivatives [21]. 1,2,4-Triazines were formed *via* the condensation of 1,2-diketones with acylhydrazides and ammonium acetate under traditional thermal and dry media microwave assisted reaction conditions [22,23].

Ethenetetracarbonitrile (tetracyanoethylene) as well as its derivatives containing the dicyanovinylidene moiety are electron deficient substances, and it is well known that their monoelectronic reduction usually results in the formation of fairly long-lived radical anions [24,25], this also applies to other species containing cyano groups bound to a double bond [26–29]. Tetracyanoethylene shows a great affinity for electrons, and is thus a fairly good dehydrogenating agents towards dihydroaromatic and dihydrohetero aromatic systems [30,31]. It behaves as a strong electron acceptor towards suitable electron donors [32–34].

The reaction of methylhydrazine with tetracyanoethylene has been studied in several laboratories [35–37]. A mixture of 1-*N*- and 2-*N*-methyl derivatives of 5-amino-3,4-dicyanopyrazole was isolated [37].

As a part of our program aimed at the development of new simple and efficient procedures for the synthesis of some important heterocyclic systems from hydrazinecarbothioamides, we have recently reported different successful approaches for synthesis of thiazole, thiazine, thiadiazole, thiadiazidine, thiadiazepine, indoazole and pyridazine derivatives [38–42]. Promoted with the above-mentioned studies, this paper reports several heterocyclization of

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1-acylhydrazines **1a–d** using ethenetetracarbonitrile (tetracyanoethylene, **2**) and diethyl (*E*)-2,3-dicyanobutenedioate (dicyanofumarate, **3**) either as a reaction mediator or as a building block Fig. 1. The synthesized compounds including open chain hydrazide derivatives **4a–d** and the cyclized ones including pyrazole derivatives **5a–d** and pyrazolone derivatives **11a–d** were evaluated each for antidepressant activity using tail suspension behavioral despair test [43] and anticonvulsant activity against PTZ induced seizures in mice [44].

2. Results and discussion

2.1. Chemistry

Treatment of **1a–d** with two molar equivalents of **2** in DMF as solvent at room temperature resulted in a green coloration of the solution that quickly turned into brown. Concentration of the mixture to dryness and the residue subjected to vacuum sublimation to remove any unreacted of **2**. Chromatographic separation of the residue in each case gave two zones, containing diacylhydrazines **4a–d** (22–27%) and 5-amino-1-substituted-1*H*-pyrazole-3,3,4-(2*H*)-tricarbonitriles **5a–d** (64–69%). On the other hand, equimolar solutions of **2** and **1a–d** in DMF under the previous mentioned conditions, afforded **5a–d** as major products (38–41%) and **4a–d** as minor products (11–16%), in addition to unreacted **1a–d**. The reaction sequences are outlined in Scheme 2.

The formation of diacylhydrazines **4a–d**, does not take place if tetracyanoethylene **2** is not added to different solutions of **1a–d** in DMF, the presence of **2** is definitely required for the transformation observed. Charge-transfer complexes may (but not necessarily have to) play an intermediate role. Since, the formation of **4a–d** involves intermolecular nucleophilic attacks by hydrazide-NH_2 on the carbonyl group of the adduct **6**. It is conceivable that **2** accelerates the process, possibly through intermediate **6** (Scheme 2), activating the respective C=O bond towards nucleophilic addition from another molecule of **1a–d**. This behavior may well be supported by the polar nature of the solvent stabilizing zwitterionic adduct. After nucleophilic addition; **2** is released with the elimination of one molecule of hydrazine to give **4a–d**.

The structures of **4a–d** are further supported on the basis of their IR, NMR and mass spectral data, and comparison with authentic samples.

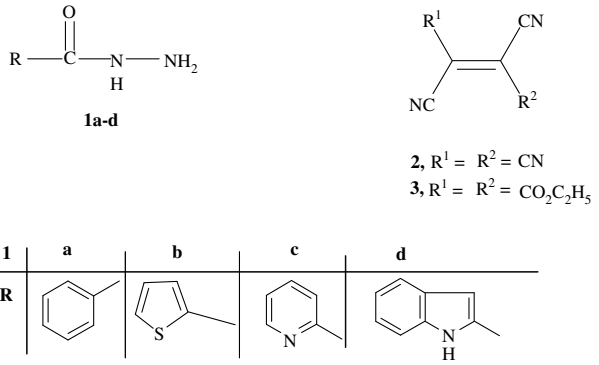


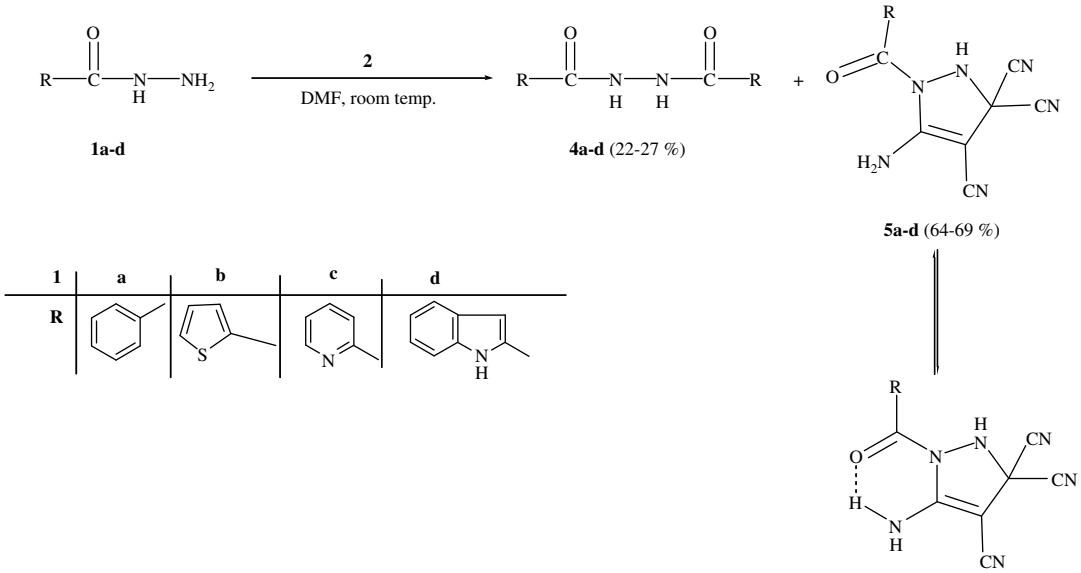
Fig. 1. Different forms of substituted carboxylic acid hydrazides **1a–d**, tetracyanoethylene **2** and dicyanofumarate **3**.

Singh et al. [45] earlier reported that iodobenzene diacetate (IBD) has been found to be an excellent reagent to the oxidation of similar acid hydrazides [R = methyl(phenyl)pyrazolyl, methyl (4-methylquinolinyl)pyrazolyl, phenyl, 4-Cl–C_6H_4, 4-MeO–C_6H_4 and $PhCH_2$] to *N*,*N*^{1}-diacylhydrazines [45].

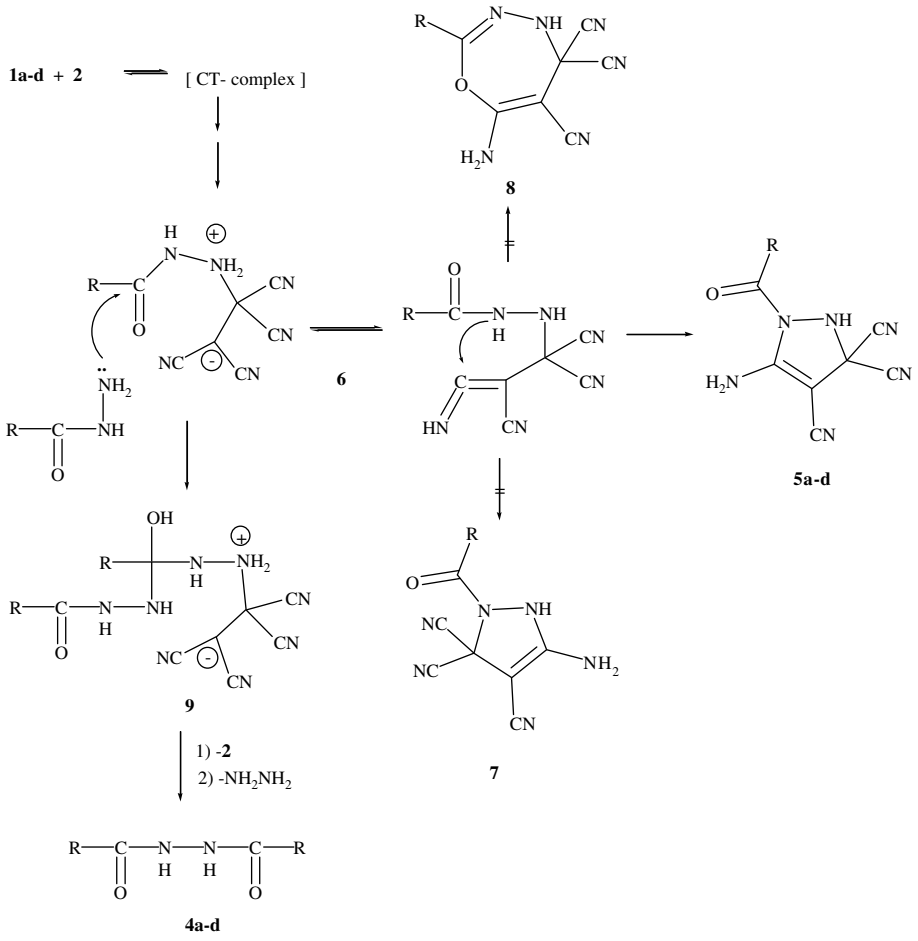
The pyrazole structure in **5a–d** has been assigned on the basis of elemental analysis and spectral data. For example the ^{1}H NMR spectrum of **5b** clearly shows the presence of two broad signals with the ratio of 2:1 centered at δ 6.92 and 11.52 ppm due to exocyclic-NH_2 and pyrazole-NH. The ^{13}C NMR shows signals at δ 46.23 (*C*-3), 117.89, 118.96 (*C*N) and 169.86 (*C*O). Pyrazole *C*-4 and *C*-5 resonate at δ 64.51 and 158.52, respectively, are in accordance with the observed trends in the δ values for C-atoms in push–pull alkenes [46,47]. Further peaks are supported with the assigned structure given in experimental part.

The analytical data of compounds **5** would also match for other isomers of products **7** and **8** (Scheme 1). The alternative structures **7** and **8** could be ruled out on the basis of ^{1}H NMR, ^{13}C NMR, IR and the fragment ions in the mass spectrum of **5b** at 243, 215, 111, 83 and 66.

Furthermore, compound **5b** was also assigned on the basis of intramolecular H-bridge detected by IR (in dilute CCl_4) and ^{1}H NMR (see Section 4) as shown from Scheme 2, structure **5b** fits best to all the spectroscopic data.



Scheme 1. Synthesis of diacylhydrazines **4a-d** and 5-amino-1-substituted pyrazole-3,3,4-tricarbonitriles **5a-d**.



Scheme 2. Mechanism of formation of diacylhydrazines **4a-d** and 5-amino-1-substituted pyrazole-3,3,4-tricarbonitriles **5a-d**.

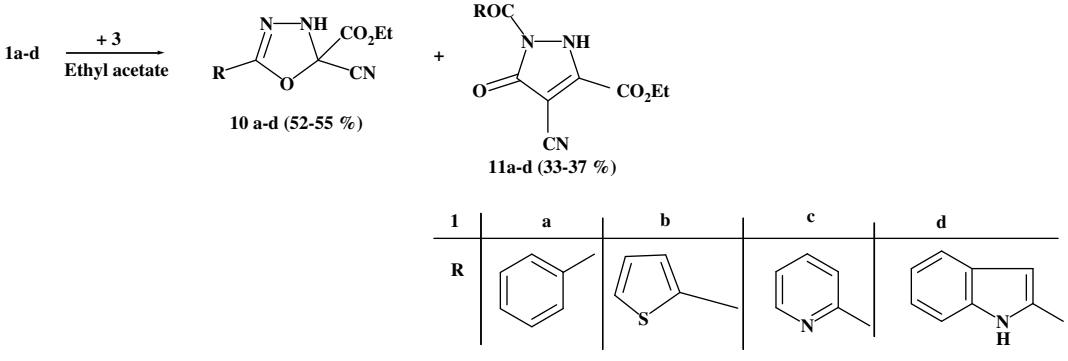
Diethyl (*E*)-2,3-dicyanobutenedioate (dicyanofumarate, **3**) was chosen to compare its reactivity towards the acylhydrazines **1a–d** with **2**. One might expect that acylhydrazines **1a–d** should react with **3** similarly like **2**, but the results were completely different. Not only the structure of the acceptor is the reason for the instability of the CT-complexes and subsequent chemical reaction, but also the electron affinity of the acceptors and ease of undergoing the formation of adduct or tricyanovinylation product is an important factor.

Heating at reflux of equimolar amounts of **1a–d** and **3** in ethyl acetate for 4–18 h afforded the corresponding oxadiazole derivatives **10a–d** and pyrazolone derivatives **11a–d** (Scheme 3).

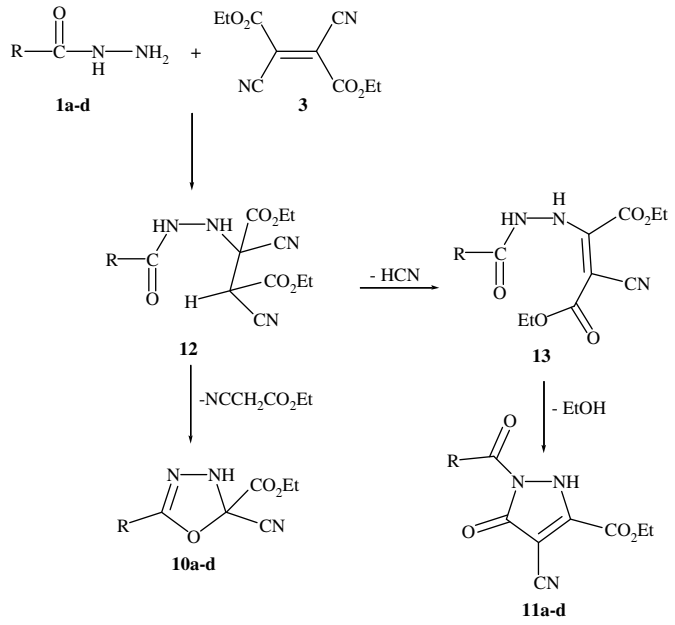
The suggested mechanism for the formation of oxadiazole derivatives **10a–d** and pyrazolone derivatives **11a–d** is illustrated in Scheme 4.

The oxadiazole derivative **10c** exhibited three IR absorption bands at ν 3315 (NH), 1720 (C=O of ester), 2225 (CN) and 1085 (C–O–C).[48] Upon transformation of **1a–d** to **10a–d** the salient features of NMR spectra (including ^{13}C-DEPT spectral) of **10c** are following: signals at δ 14.28 (*C*H$_3$), 61.17 (*C*H$_2$O), 79.89 (*C*-2), 156.24 (*C*-5) and 171.36 (*C*O).

The ^{1}H NMR spectra of compounds **11a–d** show the presence of NH group by broad signals for 1H between δ 12.43 and 12.55 ppm. Signals around 89.19 (C-4), 118.84 (CN), 155.98 (C-3), 165.34 (C-5),



Scheme 3. Synthesis of oxadiazole derivatives **10a–d** and pyrazolone derivatives **11a–d**.



Scheme 4. Mechanism of formation of oxadiazole derivatives **10a–d** and pyrazolone derivatives **11a–d**.

168.49 (ester-CO) and 171.36 (CO) in ^{13}C NMR spectrum of **11d** lend further support to the structures assigned to **11a–d**. The analytical data of compounds **11** would also match for other isomers of products **14** and **15** (Fig. 2). The alternative structures **14** and **15** could be ruled out on the basis of IR, ^{1}H NMR, ^{13}C NMR and the fragment ions in the mass spectrum of **11b** at *m*/*z* 263, 246, 180, 111 and 83. As shown from Fig. 2, structure **11b** fits best to all the spectroscopic data (see Section 4).

2.2. Pharmacology

2.2.1. Antidepressant activity

The synthesized compounds **4a–d**, **5a–d** and **11a–d** were screened for antidepressant activity using tail suspension behavioral despair test [43]. This test is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and tricyclic antidepressants. Results of the antidepressant activity of the tested compounds and reference drug are given in Table 1. Compounds **4a** and **4b** induced markedly antidepressant activity compared to imipramine, their activities as antidepressant nearly equal twice the activity of imipramine. Compounds **4a** and **4b** significantly reduced the duration of immobility times to be 68.23 and 67.58 s, respectively, compared to 132.00 s reduction of the duration of immobility for imipramine at 10 mg kg^{-1} dose level. Compounds **5c**, **11c**, **4c**, **11d**, **11a** and **11b** give good antidepressant activity, their activities nearly equal to 88.60, 86.10, 80.20, 78.10, 71.80 and 66.40% of the activity of imipramine at 10 mg kg^{-1} dose level. Other tested compounds including **4d**, **5d**, **5b** and **5a** exhibited weak antidepressant activity compared to imipramine at 10 mg kg^{-1} dose level.

Table 1
Antidepressant activities of the tested compounds **4a–d**, **5a–d** and **11a–d** compared to imipramine.

Compounds[a]	Antidepressant activities	
	Duration of immobility (s) (mean ± S.E.M.)	Change from control (%)
4a	68.23 ± 1.30	−71.96
4b	67.58 ± 3.90	−72.22
4c	164.50 ± 10.50	−32.39
4d	200.00 ± 10.00	−17.80
5a	220.50 ± 1.50	−9.37
5b	217.50 ± 3.50	−10.60
5c	149.00 ± 2.50	−38.76
5d	200.30 ± 0.88	−17.67
11a	183.90 ± 9.30	−24.41
11b	198.70 ± 6.80	−18.33
11c	153.30 ± 4.60	−36.99
11d	169.00 ± 9.60	−30.54
Imipramine	132.00 ± 2.60	−45.75
Control	243.30 ± 14.42	–

Values represent the mean ± S.E.M. ($n = 6$).
[a] Tested compounds and imipramine were tested at 10 mg kg^{-1} dose level, ip.

2.2.2. Anticonvulsant activity

The synthesized compounds **4a–d**, **5a–d** and **11a–d** were also evaluated for anticonvulsant activity against PTZ induced seizures in mice [44].

The results of these experiments are listed in Fig. 3A–C and were determined using the following formula [49].

$$\%\text{of protection} = \frac{\text{number of convulsions of control} - \text{number of convulsions of treated}}{\text{number of convulsions of control}} \times 100$$

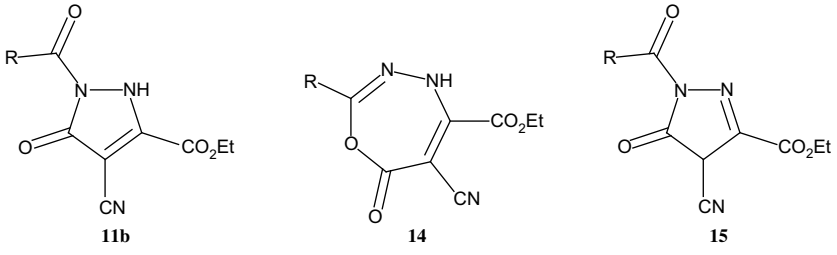


Fig. 2. Different alternative structures **14** and **15** for pyrazolone derivative **11b**.

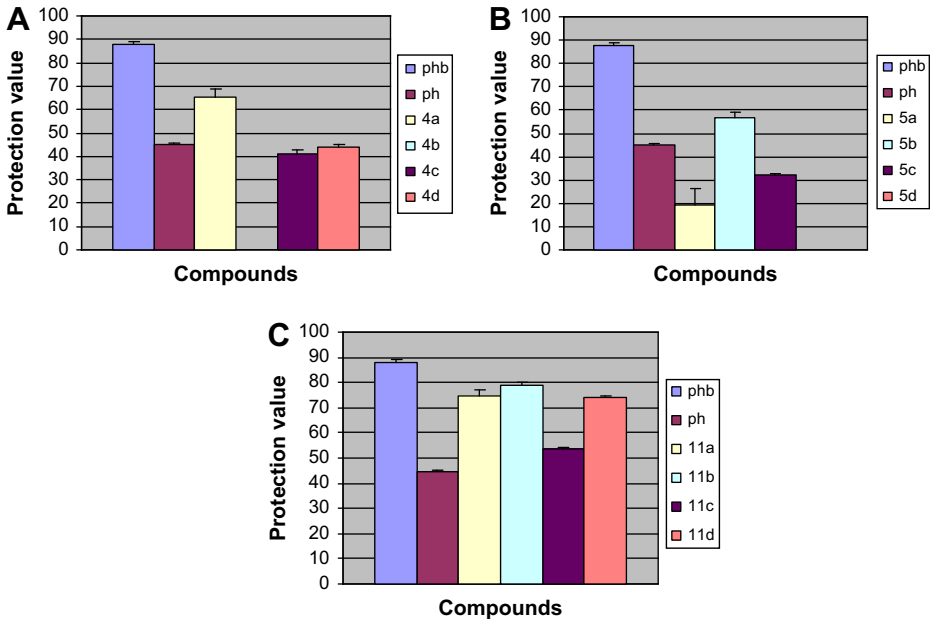


Fig. 3. Anticonvulsant activity of compounds **4a–d**, **5a–d** and **11a–d** expressed as mean ± S.E. compared to phenobarbital sodium (phb) and phenytoin sodium (ph) at a dose level of (30 mg kg^{-1}). Compounds were tested at 20 mg kg^{-1} dose level, ip. values represent the mean ± S.E.M. ($n = 6$).

Compounds **11b**, **11a** and **11d** exhibited the most protective class of the tested compounds against clonic seizures induced by ip injection of PTZ, they induced 78.7, 74.5 and 74% protection, respectively, against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}. Compounds **11b**, **11a** and **11d** exhibited a remarkable protective effect nearly 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}.

Compounds **4a**, **5b** and **11c** exhibited a moderate protection against clonic seizures induced by ip injection of PTZ at a dose level of 20 mg kg^{-1}, they induced 65.1, 56.8 and 53.7%, respectively, protection against clonic seizures induced by ip injection of PTZ. Compounds **4a**, **5b** and **11c** exhibited a moderate protection compared to phenobarbital sodium at a dose level of 30 mg kg^{-1}. Compounds **4d**, **4c** and **5c** 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. 3A–C.

3. Conclusion

Compounds **4a** and **4b** induced remarkable antidepressant activity compared to imipramine at 10 mg kg^{-1} dose level, other compounds including **5c**, **11c**, **4c**, **11d**, **11a** and **11b** give good antidepressant activity. Moreover, compounds **11b**, **11a** and **11d** exhibited the most protective class of the tested compounds against clonic seizures induced by ip injection of PTZ. Other compounds **11b**, **11a** and **11d** exhibited a remarkable protective effect nearly close to phenobarbital sodium at a dose level of 30 mg kg^{-1}. Therefore, they seem to be really promising compounds for their antidepressant and anticonvulsant activities. The synthesis studies should be continued concerning this group of compounds followed with further *in vivo* studies.

4. Experimental

4.1. Chemistry

Melting points have been determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded with a Shimadzu 408 or Bruker Vactor 22 FTIR instruments, using potassium bromide pellets or CCl_4. The ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured in DMSO-d_6 using a Bruker AM400 with TMS as an internal standard, chemical shifts are expressed as δ (ppm), s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad.

Assignment of carbon resonances has been supported by DEPT experiment. Moreover, the signals caused by quaternary carbons were identified by the comparison between ^{13}C NMR and DEPT spectra. Mass spectra have been obtained with a Varian MAT 312 instrument using electron impact ionization (70 eV). Elemental analysis has been detected by the Microanalytical Center, Cairo University, Egypt. Preparation layer chromatography (plc): Glass plates (48 cm × 20 cm) were coated with silica gel Merck Pf_{254} (applied as aqueous slurry and air-dried affording a 1 mm layer). Zones were detected by indicator fluorescence quenching upon 254 nm illuminations, removed from plates and extract with acetone.

4.1.1. Substituted carboxylic hydrazide

1a–d were prepared according to published procedures [18,50–55] as were 2-thiophene carboxylic hydrazide **1b** mp135–137 °C (lit. [50] 134–136 °C); 2-pyridine carboxylic hydrazide **1c** mp 136–138 °C (lit. [52,53], 137 °C); indole-2-carboxylic hydrazide **1d**, mp 243–245 °C (lit. [18,54,55], 246 °C); phenyl carboxylic hydrazide **1a** and diethyl (*E*)-2,3-dicyanobutenedioate **3** (Aldrich) were used as received. Ethentetracarbonitrile (**2**, Merck) was purified by crystallization from chlorobenzene and sublimed.

4.1.2. General procedure for the reaction of substituted carboxylic hydrazides *1a–d* with ethentetracarbonitrile *2*

To a stirred solution of (256 mg; 2.0 mmol) of **2** in 10 mL of dimethylformamide, a solution of 1.0 mmol of **1a–d** was added in a dropwise manner, a spontaneous change of color from yellow to dark green and finally to brown was observed. The mixture was stirred for 4 h and left standing for 48 h at room temperature. After concentration to dryness, the residues were sublimed at 80 °C and then subjected to plc using toluene/ethyl acetate (3:1) as eluent for

the reaction of **1a**, **1b** with **2**. On the other hand, toluene/ethyl acetate (2:1) was used as eluent for the reaction of **1c**, **1d** with **2**. Chromatographic separation of the residue (after sublimation) gave numerous zones, two of which (with high intensity) were removed and extracted. The fastest moving zone contained the pyrazole derivatives **5a–d**, while the slowest moving zone contained the diacylhydrazines **4a–d**. Extraction of the zones with acetone and concentration gave residues, which were rechromatographed and recrystallized to give pure crystals.

4.1.2.1. N′-*Benzoylbenzohydrazide* ***4a***. Yield (65 mg, 27%), mp 239–241 °C (lit. [45,56], 237–238 °C).

4.1.2.2. N′-*(Thiophene-2-carbonyl)thiophen-2-carbohydrazide* ***4b***. Yield (66 mg, 24%), mp 276–278 °C (lit. [56,57], 274–277 °C).

4.1.2.3. N′-*Picolinoylpicolinohydrazide* ***4c***. Yield (56 mg, 23%), mp 224–226 °C (lit. [58] 224–225 °C).

4.1.2.4. N′-*(1*H-*Indole-2-carbonyl)-1*H-*indole-2-carbohydrazide* ***4d***. Yield (80 mg, 25%), mp 355–357 °C (lit. [58] 356.5–357.5 °C).

*4.1.2.5. 5-Amino-1-benzoyl-1*H-*pyrazole-3,3,4-(2*H*)-tricarbonitrile* ***5a***. Pale yellow crystals (ethanol) in (182 mg, 69%), mp 210–212 °C. IR; ν_{max} (KBr) cm^{-1}: 3380, 3300–3220 (NH_2, NH), 2225, 2220 (CN), 1660 (CO), 1585 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 6.98$ (br, 2H, NH_2), 7.57–7.93 (m, 5H, Ar–H), 11.47 (pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 48.48$ (*C*-3), 64.14 (*C*-4), 117.94, 118.18, 119.26 (CN), 127.76, 128.93, 130.17 (Ar–*C*H), 134.36 (Ar–*C*), 158.64 (pyrazole-*C*-5), 170.19 (CO). MS (*m*/*z*, %): 264 (M^+, 33), 237 (18), 171 (26), 105 (100), 66 (71). Anal. Calcd; For $C_{13}H_8N_6O$ (264.08): C, 59.09; H, 3.05; N, 31.80. Found: C, 58.87; H, 2.92; N, 32.04.

*4.1.2.6. 5-Amino-1-(thiophene-2-carbonyl)-1*H-*pyrazole-3,3,4-(2*H*)-tricarbonitrile* ***5b***. Pale yellow crystals (acetonitrile) in (176 mg, 65%), mp 224–226 °C. IR; ν_{max} (KBr) cm^{-1}: 3385, 3310, 3210 (NH_2, NH), 2225, 2220 (CN), 1655 (CO), 1590 (Ar–C═C) ν_{max} (CCl_4, 10^{-3} M, $d = 3$ cm) 3370, 3195 cm^{-1} (broad NH_2 and OH assoc.), 1660 (CO). ^{1}H NMR (DMSO-d_6): $\delta = 6.92$ (br, 2H, NH_2), 7.21–7.87 (thiophene-CH), 11.52 (br, H, pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 46.23$ (*C*-3), 64.51 (*C*-4), 117.89, 118.08, 118.96 (CN), 129.23, 130.34, 131.67 (thiophene-*C*H), 137.69 (thiophene-*C*-2), 158.52 (*C*-5), 169.86 (CO). MS (*m*/*z*, %): 270 (M^+, 27), 243 (31), 215 (23), 111 (100), 83 (69), 66 (49). Anal. Calcd; For $C_{11}H_6N_6OS$ (270.27): C, 48.88; H, 2.24; N, 31.09; S, 11.86. Found: C, 49.08; H, 2.31; N, 30.88; S, 12.05.

*4.1.2.7. 5-Amino-1-picolinoyl-1*H-*pyrazole-3,3,4-(2*H*)-tricarbonitrile* ***5c***. Yellow crystals (ethanol) in (175 mg, 66%), mp 215–217 °C. IR; ν_{max} (KBr) cm^{-1}: 3375, 3300, 3230 (NH_2, NH), 2225, 2220 (CN), 1660 (CO), 1585 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 6.95$ (br, 2H, NH_2), 7.81–8.39 (pyridine-CH), 11.64 (pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 45.96$ (*C*-3), 64.22 (*C*-4), 118.02, 118.28, 119.14 (CN), 126.56, 128.77, 131.12, 142.66 (pyridine-*C*H), 150.34 (pyridine-*C*), 158.56 (*C*-5), 170.12 (CO). MS (*m*/*z*, %): 265 (M^+, 37), 238 (22), 210 (11), 106 (100), 78 (57), 66 (42). Anal. Calcd; For $C_{12}H_7N_7O$ (265.23): C, 54.34; H, 2.66; N, 36.97. Found: C, 54.16; H, 2.59; N, 37.15.

*4.1.2.8. 5-Amino-1-(1*H-*indole-2-carbonyl)-1*H-*pyrazole-3,3,4-(2*H*)-tricarbonitrile* ***5d***. Yellow crystals (acetonitrile) in (194 mg, 64%), mp 276–278 °C. IR; ν_{max} (KBr) cm^{-1}: 3410, 3350–3230 (NH_2, NH), 2225, 2220 (CN), 1650 (CO), 1595 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 6.87$ (br, 2H, NH_2), 7.11–7.67 (m, 5H, Ar–H), 11.41 (br, 1H, pyrazole-NH), 11.76 (br, 1H, indole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 46.18$ (*C*-3), 64.42 (*C*-4), 115.18 (indole-*C*H), 117.93, 118.17, 119.12 (CN), 126.71, 127.16, 128.57, 129.63 (Ar–*C*H), 131.84, 138.66, 139.94 (Ar–*C* and indole-*C*-2), 158.45 (*C*-5), 170.72 (CO). MS (*m*/*z*, %): 303 (M^+, 41), 276 (17), 248 (21), 144 (100), 116 (64), 66 (54). Anal. Calcd; For $C_{15}H_9N_7O$ (303.28): C, 59.40; H, 2.99; N, 32.33. Found: C, 59.23; H, 3.11; N, 32.19.

4.1.3. General procedure for the reaction of substituted carboxylic hydrazides ***1a–d*** *with diethyl (*E*)-2,3-dicyanobutenedioate* ***3***

A solution of (222 mg; 1.0 mmol) of **3** in 30 mL of dry ethyl acetate was heated with 1.0 mmol of **1a–d** and stirred under reflux for 4 h (**a**), 8 h (**b**) and 18 h (**c**,**d**), respectively. During which time the color of the solution changed from colorless to reddish orange. Concentration of the reaction mixture to dryness, the residues was subjected to plc using toluene/ethyl acetate (2:1) as eluent. Chromatographic separation of the residue gave numerous zones, two of which (with high intensity) were removed and extracted. The fastest move zone contained the oxadiazole derivatives **10a–d**, while the slowest moving zone contained the pyrazolone derivatives **11a–d**. Extraction of the zones with acetone and recrystallized gave the pure compounds.

4.1.3.1. Ethyl 2-cyano-5-phenyl-2,3-dihydro-1,3,4-oxadiazole-2-carboxylate ***10a***. Orange crystals (methanol) in (135 mg, 55%), mp 192–194 °C. IR; ν_{max} (KBr) cm^{-1}: 3335 (NH), 2225 (CN), 1715 (CO), 1085 (C–O–C). ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3, $J = 7.12$ Hz), 4.21 (q, 2H, CH_2O, $J = 7.12$ Hz) 7.07–7.64 (m, 5H, Ar–H), 11.93 (br, 1H, oxadiazole–NH). ^{13}C NMR (DMSO-d_6): δ 14.43 (*C*H$_3$), 61.12 (*C*H$_2$O), 80.14 (*C*-2), 118.36 (CN), 126.76, 128.93, 131.12 (Ar–*C*H), 132.77 (Ar–*C*), 156.18 (*C*-5), 171.18 (CO). MS (*m*/*z*, %): 245 (M^+, 39), 218 (22), 190 (16), 105 (100), 77 (86), 65 (56). Anal. Calcd; For $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.57; H, 4.69; N, 16.89.

4.1.3.2. Ethyl 2-cyano-5-(thiophen-2-yl)-2,3-dihydro-1,3,4-oxadiazole-2-carboxylate ***10b***. Pale orange crystals (acetonitrile) in (133 mg, 53%), mp 207–209 °C. IR; ν_{max} (KBr) cm^{-1}: 3320 (NH), 2220 (CN), 1710 (CO), 1080 (C–O–C). ^{1}H NMR (DMSO-d_6): $\delta = 1.22$ (t, 3H, CH_3, $J = 7.10$ Hz), 4.18 (q, 2H, CH_2O, $J = 7.10$ Hz), 7.19–7.18 (m, thiophene-H), 11.87 (br, 1H, oxadiazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.39$ (*C*H$_3$), 61.26 (*C*H$_2$O), 80.26 (*C*-2), 118.67 (CN), 126.84, 127.56, 127.83 (thiophene-*C*H), 129.35 (thiophene-*C*), 156.26 (*C*-5), 171.36 (CO). MS (*m*/*z*, %): 251 (M^+, 53), 224 (37), 196 (63), 111 (100), 45 (86). Anal. Calcd; For $C_{10}H_9N_3O_3S$ (251.26): C, 47.80; H, 3.61; N, 16.72; S, 12.76. Found: C, 48.02; H, 3.52; N, 16. 94; S, 12.54.

4.1.3.3. Ethyl 2-cyano-5-(pyridin-2-yl)-2,3-dihydro-1,3,4-oxadiazole-2-carboxylate ***10c***. Pale orange crystals (methanol) in (135 mg, 55%), mp 202–204 °C. IR; ν_{max} (KBr) cm^{-1}: 3315 (NH), 1720 (CO), 2225 (CN), 1085 (C–O–C). ^{1}H NMR (DMSO-d_6): $\delta = 1.18$ (t, 3H, CH_3, $J = 7.05$ Hz), 4.21 (q, 2H, CH_2O, $J = 7.05$ Hz), 7.58–8.42 (m, 4H, pyridyl-H), 11.89 (br, 1H, oxadiazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.28$ (*C*H$_3$), 61.17 (*C*H$_2$O), 79.89 (*C*-2), 118.72 (CN), 126.18, 127.83, 130.12, 144.11 (pyridyl-*C*H), 147.82 (pyridyl-*C*), 156.24 (*C*-5), 171.36 (CO). MS (*m*/*z*, %): 246 (M^+, 51), 219 (28), 191 (11), 106 (93), 78 (100), 45 (32). Anal. Calcd; For $C_{11}H_{10}N_4O_3$ (246.22): C, 53.66; H, 4.09; N, 22.75. Found: C, 53.48; H, 3.96; N, 22.59.

*4.1.3.4. Ethyl 2-cyano-5-(1*H-*indol-2-yl)-2,3-dihydro-1,3,4-oxadiazole-2-carboxylate* ***10d***. Orange crystals (acetonitrile) in (151 mg, 53%), mp 259–261 °C. IR; ν_{max} (KBr) cm^{-1}: 3340–3305 (NH), 2220 (CN), 1710 (CO), 1080 (C–O–C). ^{1}H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, CH_3, $J = 6.90$ Hz), 4.16 (q, 2H, CH_2O, $J = 6.90$ Hz), 6.98–7.55 (m, 5H, Ar–H), 11.71 (br, 1H, indole-NH), 11.91 (br, 1H, oxadiazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.31$ (*C*H$_3$), 61.33 (*C*H$_2$O), 80.12 (*C*-2), 111.23 (indole-*C*H), 118.65 (CN), 126.26, 126.76, 128.75, 129.24 (Ar–*C*H), 130.61, 131.55, 132.25 (Ar–*C* and indole-*C*-2), 155.93 (*C*-5), 171.42

(CO). MS (*m*/*z*, %): 284 (M^+, 26), 257 (16), 292 (28), 140 (33), 144 (100), 116 (76), 92 (67), 77 (54). Anal. Calcd; For $C_{14}H_{12}N_4O_3$ (284.27): C, 59.15; H, 4.25; N, 19.71. Found: C, 58.92; H, 4.37; N, 19.64.

*4.1.3.5. Ethyl 1-benzoyl-4-cyano-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate* ***11a***. Brown crystals (ethanol) in (99 mg, 35%), mp 227–229 °C. IR; ν_{max} (KBr) cm^{-1}: 3345 (NH), 2220 (CN), 1710, 1680 and 1655 (CO), 1620 (C═N), 1590 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 1.27$ (t, 3H, CH_3, $J = 7.10$ Hz), 4.28 (q, 2H, CH_2O, $J = 7.10$ Hz), 7.36–7.87 (m, 5H, Ar–H), 12.51 (br, 1H, pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.28$ (*C*H_3), 61.49 (*C*H_2O), 88.12 (*C*-4), 118.62 (CN), 128.22, 128.93 and 129.84 (Ar–*C*H), 131.55 (Ar–*C*), 156.11 (*C*-3), 166.53 (*C*-5), 169.23 (*C*O-ester), 171.12 (*C*O). MS (*m*/*z*, %): 285 (M^+, 51), 257 (27), 240 (29), 180 (64), 105 (82), 77 (100), 65 (66). Anal. Calcd; For $C_{14}H_{11}N_3O_4$ (285.25): C, 58.95; H, 3.89; N, 14.73. Found: C, 59.19; H, 4.12; N, 14.51.

*4.1.3.6. Ethyl 1-(thiophene-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate* ***11b***. Brown crystals (acetonitrile) in (107 mg, 37%), mp 237–239 °C. IR; ν_{max} (KBr) cm^{-1}: 3330 (NH), 2225 (CN), 1725, 1675 and 1660 (CO), 1625 (C═N), 1585 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 1.24$ (t, 3H, CH_3, $J = 7.06$ Hz), 4.25 (q, 2H, CH_2O, $J = 7.06$ Hz), 7.19–7.82 (m, 3H, thiophene-H), 12.46 (br, 1H, pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.28$ (*C*H_3), 61.36 (*C*H_2O), 88.38 (*C*-4), 118.76 (CN), 127.83, 128.24 and 128.55 (thiophene-*C*H), 130.12 (thiophene-*C*-2), 155.89 (*C*-3), 165.94 (*C*-5), 168.97 (ester-*C*O), 170.92 (*C*O). MS (*m*/*z*, %): 291 (M^+, 39), 263 (11), 246 (54), 180 (36), 111 (100), 83 (56). Anal. Calcd; For $C_{12}H_9N_3O_4S$ (291.28): C, 49.48; H, 3.11; N, 14.43; S, 11.01. Found: C, 49.61; H, 3.39; N, 14.51; S, 10.87.

*4.1.3.7. Ethyl 1-picolinoyl-4-cyano-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate* ***11c***. Pale brown crystals (acetonitrile) in (103 mg, 36%), mp 231–233 °C. IR; ν_{max} (KBr) cm^{-1}: 3325 (NH), 2215 (CN), 1710, 1680 and 1665 (CO), 1625 (C═N), 1600 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 1.29$ (t, 3H, CH_3, $J = 7.05$ Hz), 4.28 (q, 2H, CH_2O, $J = 7.05$ Hz), 7.61–8.44 (pyridyl-H), 12.45 (br, 1H, pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.29$ (*C*H_3), 61.41 (*C*H_2O), 89.35 (*C*-4), 119.16 (CN), 126.83, 127.22, 130.14, 143.22 (pyridyl-*C*H), 147.12 (pyridyl-*C*-2), 156.24 (*C*-3), 165.54 (*C*-5), 168.84 (ester-*C*O), 171.38 (*C*O). MS (*m*/*z*, %): 286 (M^+, 46), 258 (6), 180 (19), 106 (100), 78 (87). Anal. Calcd; For $C_{13}H_{10}N_4O_4$ (286.24): C, 54.55; H, 3.52; N, 19.57. Found: C, 54.76; H, 3.36; N, 19.69.

*4.1.3.8. Ethyl 1-(1*H*-indole-2-carbonyl)-4-cyano-5-oxo-2,5-dihydro-1*H*-pyrazole-3-carboxylate* ***11d***. Brown crystals (acetonitrile) in (113 mg, 35%), mp 287–289 °C IR; ν_{max} (KBr) cm^{-1}: 3335, 3270 (NH), 2220 (CN), 1715, 1675 and 1660 (CO), 1625 (C═N), 1595 (Ar–C═C). ^{1}H NMR (DMSO-d_6): $\delta = 1.23$ (t, 3H, CH_3, $J = 7.12$ Hz), 4.25 (q, 2H, CH_2O, $J = 7.12$ Hz), 6.72 (indole-CH), 7.22–7.65 (m, 4H, Ar–H), 11.63 (br, 1H, indole-NH), 12.55 (br, 1H, pyrazole-NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.22$ (*C*H_3), 61.72 (*C*H_2O), 89.19 (*C*-4), 111.22 (indole-*C*H), 118.89 (CN), 126.74, 128.12, 128.81, 129.17 (Ar–*C*H), 130.55, 131.67 (Ar–*C*), 155.98 (*C*-3), 165.34 (*C*-5), 168.49 (ester-*C*O), 171.36 (CO). MS (*m*/*z*, %): 324 (M^+, 35), 296 (24), 180 (52), 144 (86), 116 (43), 92 (91), 77 (100), 65 (86). Anal. Calcd; For $C_{16}H_{12}N_4O_4$ (324.29): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.02; H, 3.92; N, 17.45.

4.2. 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.

4.2.1. 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 **4a–d**, **5a–d** and **11a–d** (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 was considered immobile only when they hung passively and completely motionless.

4.2.2. Anticonvulsant activity

The synthesized compounds **4a–d**, **5a–d** and **11a–d** were evaluated for anticonvulsant activity against PTZ induced seizures in mice [44].

On the testing day mice were assigned into different groups ($n = 6$ for each group). The tested compounds were dissolved in carboxymethylcellulose (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. One hour after the administration of the tested compound, mice were injected PTZ (100 mg kg^{-1}) as a 0.5% solution ip that produces clonic seizures lasting for a period of at least five seconds in greater than 95% of animals tested. The animal was observed for 30 min, failure 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 results were represented as percentage protection [49]. Standard drug used was phenobarbital sodium and phenytoin sodium at a dose level of 30 mg kg^{-1}.

4.3. 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 (ANOVA). A *p*-value of less than 0.05 was considered statistically significant.

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References

[1] F. Borsini, A. Meli, Psychopharmacol. 94 (1988) 147–160.
[2] D. Mochizucki, Hum. Psychopharmacol. 19 (2004) S15–S19.
[3] D.A. Williams, T.L. Lemke, Foye's Principles of Medicinal Chemistry, fifth ed. Lippincott Williams & Wilkins, Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo, 2002, pp. 384–403.
[4] M.A. Rogawski, Epilepsy Res. 69 (2006) 273–294.
[5] L.G. Polevoi, Tr. Nauchn. Konf. Aspir. Ordin, 1-yi (Peruyi) Mosk. Med. Inst., Moscow, 1964, pp. 159–161; Chem. Abstr.. 65 (1966) 19147d.

[6] Y.M. Batulin, Farmakol. Toksikol. 31 (1968) 533–536; Y.M. Batulin, Chem. Abstr. 70 (1969) 2236a.
[7] S.S. Parmar, B.R. Pandey, C. Dwivedi, R.D. Harbinson, J. Pharm. Sci. 63 (1974) 1152–1155.
[8] N. Soni, K. Pande, R. Kalsi, T.K. Gupta, S.S. Parmar, J.P. Barthwal, Res. Commun. Chem. Pathol. Pharmacol. 56 (1987) 129–132.
[9] G. Turan-Zitouni, P. Chevallet, F.S. Kilic, K. Erol, Eur. J. Med. Chem. 35 (2000) 635–641.
[10] P. Erhan, A. Mutlu, U. Tayfun, E. Dilek, Eur. J. Med. Chem. 36 (2001) 539–543.
[11] H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G.W.A. Milne, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 40 (1997) 937–941.
[12] T. Aboul-Fadl, F.A. Mohamed, E.A. Hassan, Arch. Pharm. Res. 26 (2003) 778–784.
[13] Z. Özdemir, H.B. Kandilci, B. Gümüsel, Ü. Calis, A.A. Bilgin, Eur. J. Med. Chem. 42 (2007) 373–379.
[14] M.K. Azim, W. Ahmed, I.A. Khan, N.A. Rao, K.M. Khan, Bioorg. Med. Chem. Lett. 18 (2008) 3011–3015.
[15] H.G. Bonacorso, M.R. Oliveira, M.B. Costa, L.B. Dasilva, A.D. Wastowski, N. Zanatta, M.A.P. Martins, J. Heterocycl. Chem. 42 (2005) 631–637.
[16] J. Blank, M. Kandt, W.-D. Pfeiffer, A. Hetzheim, P. Langer, Eur. J. Org. Chem. (2003) 182–189.
[17] F. Gatta, M.R. Del Giudice, A. Borioni, P.A. Borea, S. Dionisotti, E. Ongini, Eur. J. Med. Chem. 28 (1993) 569–576.
[18] S. Pênez, B. Lasheras, C. Oset, A. Monge, J. Heterocycl. Chem. 34 (1997) 1527–1533.
[19] E.I. Al-Afaleq, S.A. Abubshait, Molecules 6 (2001) 621–638.
[20] P.G. Baraldi, B. Cacciari, G. Spalluto, M.J.P.I. Villatoro, C. Zocchi, S. Dionisotti, E. Ongini, J. Med. Chem. 39 (1996) 1164–1171.
[21] P.G. Baraldi, M.A. Tabrizi, D. Preti, A. Bovero, F. Fruttarolo, R. Romagnoli, N. Abdel-Zaid, A.R. Moorman, K. Varani, P.A. Borea, J. Med. Chem. 48 (2005) 5001–5008.
[22] M. Kidwai, P. Sapra, K.R. Bhushan, P. Misra, Synth. Commun. 31 (2001) 1639–1645.
[23] Z. Zhao, W.H. Leister, K.A. Strauss, D.D. Wisnoski, C.W. Lindsley, Tetrahedron Lett. 44 (2003) 1123–1127.
[24] N. Martin, M. Hanack, J. Chem. Soc., Chem. Commun. (1988) 1522–1524.
[25] M. Hirayama, A. Seki, Y. Yamashita, T. Suzuki, T. Miyashi, J. Chem. Soc., Chem. Commun. (1988) 490–491.
[26] F. Gerson, G. Gescheidt, R. Möckel, A. Aumüller, P. Erk, S. Hünig, Helv. Chim. Acta 71 (1988) 1665–1667.
[27] A.A. Hassan, Bull. Soc. Chim. Fr. 131 (1994) 424–428.
[28] D. Döpp, S. Jüschke, G. Henkel, Z. Naturforsch. 57 (2002) 460–470.
[29] D. Döpp, A.A. Hassan, A.M. Nour El-Din, A.E. Mourad, C.W. Lehmann, J. Rust, Tetrahedron 62 (2006) 11618–11626.
[30] A.J. Fatiadi, Synthesis (1986) 249–284 and references cited therein.
[31] D. Döpp, A.A. Hassan, A.E. Mourad, A.M. Nour El-Din, K. Angermund, C. Krüger, C.W. Lehmann, J. Rust, Tetrahedron 59 (2003) 5073–5081.
[32] A.J. Fatiadi, Synthesis (1987) 749–789.
[33] T. Nishio, N. Okuda, J. Org. Chem. 57 (1992) 4000–4005.
[34] P. Bruni, G. Tosi, Gazz. Chim. Ital. 127 (1997) 435–459 and pertinent references cited therein.
[35] C.L. Dickenson, J.K. Williams, B.C. Mckusick, J. Org. Chem. 29 (1964) 1915.
[36] S.M. Hecht, D. Werner, J. Chem. Soc., Perkin Trans. 1 (1973) 1903–1906.
[37] R.A. Earl, R.J. Pugmire, G.R. Revankar, L.B. Townsend, J. Org. Chem. 40 (1975) 1822–1828.
[38] A.A. Hassan, Y.R. Ibrahim, A.A. Semida, A.E. Mourad, Liebigs Ann. Chem. (1994) 989–992.
[39] A.A. Hassan, Phosphorus, Sulfur and Silicon 101 (1995) 189–196.
[40] A.A. Hassan, N.K. Mohamed, A.M. Shawky, D. Döpp, Arkivoc 1 (2003) 118–120.
[41] A.A. Hassan, K.M. El-Shaieb, R.M. Shaker, D. Döpp, Heteroatom Chem. 16 (2005) 12–19.
[42] A.A. Hassan, A.E. Mourad, K.M. El-Shaieb, A.H. Abou-Zied, Z. Naturforsch. 59b (2004) 910–916.
[43] L. Steru, R. Chermat, B. Thierry, P. Simon, Psychopharmacol. 85 (1985) 367–370.
[44] R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg, E.A. Swinyard, Epilepsia 19 (1978) 409–428.
[45] S.P. Singh, H. Batra, P.K. Sharma, J. Chem. Res., Synop. (1997) 468–469.
[46] H.-O. Kalinowski, S. Berger, S. Brann, ^{13}C NMR Spektroskopic, Thieme, Stuttgart, 1984, pp. 121.
[47] K. Gewald, R. Schnidler, J. Prakt. Chem. 332 (1990) 223–228.
[48] D.A. Charistos, G.V. Vagenas, L.C. Tzavellas, C.A. Tsoleridis, N.A. Rodios, J. Heterocycl. Chem. 31 (1994) 1593–1598.
[49] R.A. Turner, Screening Methods in Pharmacology, Academic Press, New York, London, 1964, pp. 165–172.
[50] T. Curtius, J. Thyssen, J. Prakt. Chem. 7 (1902) 65.
[51] M.J. Cook, E.J. Forbes, Tetrahedron 24 (1968) 4501–4508.
[52] G. Struve, J. Prakt. Chem. 52 (1895) 170.
[53] R. Iqbal, F. Malik, J. Chem. Soc. Pak. 6 (1984) 43.
[54] J.I. Marco, J. Heterocycl. Chem. 35 (1998) 475–476.
[55] M.A. Cruces, C. Elorriage, E. Fernandes-Alvarez, Biochem. Pharmacol. 40 (1990) 535–543.
[56] V. Kepe, F. Požgan, A. Golobič, S. Polane, M. Kočevar, J. Chem. Soc. Perkin Trans. 1 (1998) 2813–2816.
[57] G. Kossmehl, G. Manecke, Makromol. Chem. 123 (1969) 233; Chem. Abstr. 71 (1969) 3748b.
[58] H. Zhao, T.R. Burke Jr., Tetrahedron 53 (1997) 4219–4230.