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Synthesis, anticonvulsant, and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles

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Abstract—Treatment of 2-bromoacetylbenzofuran with 1*H*-benzotriazole afforded 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone which reacted with phenylisothiocyanate to give the corresponding thioacetanilide derivatives. Treatment of the latter ethanone and thioacetanilide derivatives with hydrazonoyl chlorides afforded the corresponding pyrazole and 1,3,4-thiadiazole derivatives. The thioacetanilide derivative reacted with α-haloketones and α-halodiketones to afford thiophene and thiazole derivatives, respectively. The newly synthesized compounds were found to possess anticonvulsant and anti-inflammatory activities with the same mechanism of action of selective COX-2 inhibitors.

1. Introduction

Synthetic approaches based on nonsteroidal anti-inflammatory drugs (NSAID) chemical modification have been taken with the aim of improving their profile[1] where the action of NSAID is in lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Very limited work however has been focused on the development of NSAID.[2,3] Benzofuran derivatives were among the COX-2 inhibitors.[4,5] In addition, diverse pharmacological properties have been associated with benzofuran derivatives.[6–10] These include pesticidal and insecticidal,[11] anti-inflammatory,[12] antihistaminic,[13] antiallergic,[14] and antitumor[15] agents. On the other hand, benzotriazole derivatives have shown potential antimycobacterial,[16] antitubercular,[17] antitumor,[18] antiproliferative,[19] anesthetic,[20] and anti-inflammatory[21] activities. Furthermore, pyrazole derivatives were found to possess anti-inflammatory,[22] and antimicrobial[23] activities. In addition, 1,3,4-thiadiazoles were reported as highly anti-inflammatory,[24]antimicrobial,[25] and anticonvulsant[26] agents. In continuation of our research work on the synthesis of benzofuran derivatives,[27–30] we report here some new heteroaromatic derivatives having benzofuran and benzotriazole moieties. The biological activity and structure–activity relationship (SAR) of the newly synthesized compounds were evaluated using Wistar albino mice and some of the obtained products were found to possess anticonvulsant, antinociceptive, and anti-inflammatory activities.

2. Results and discussion

2.1. Chemistry

When 2-bromoacetylbenzofuran (**1**) was treated with 1(*H*)-benzotriazole in refluxing tetrahydrofuran in the presence of triethylamine, it afforded the novel 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone (**2**). The structure of compound **2** was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum showed the presence of a strong absorption peak at 1698 cm^{-1} due to a carbonyl group and its ^1H NMR spectrum revealed a singlet signal at δ 5.3 characteristic of active methylene proton.

Reaction of 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)-ethanone (**2**) with hydrazonoyl chlorides **3a**,**b** in

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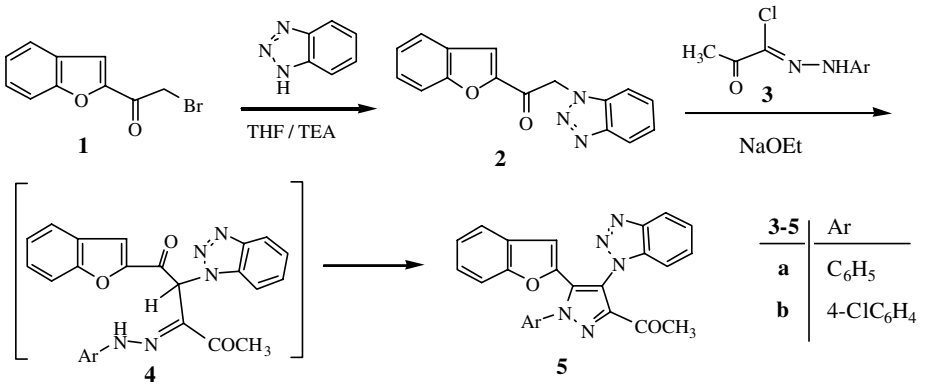
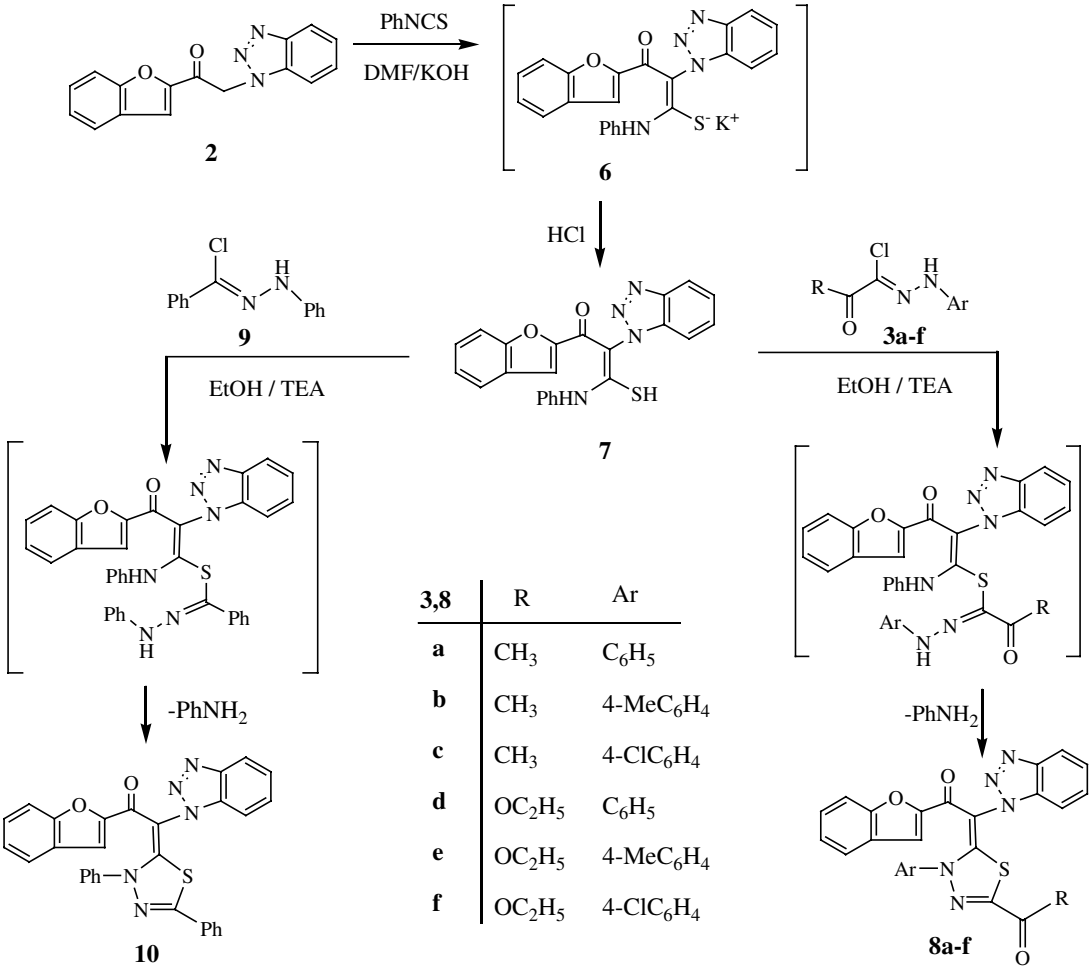


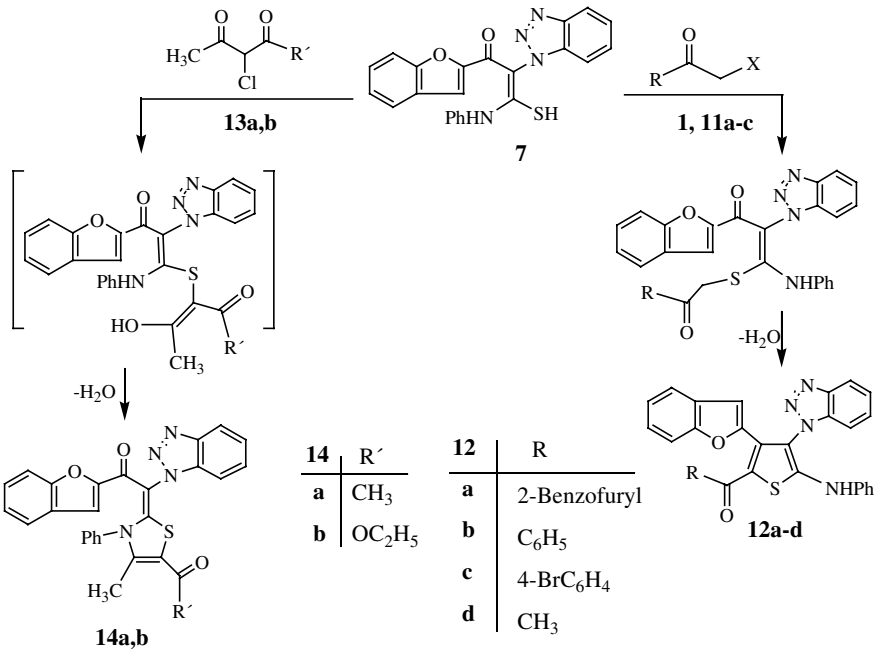
Scheme 1.

ethanolic sodium ethoxide solution at room temperature afforded, in each case, a single product (as examined by TLC). The structure of the isolated products was established as 3-acetyl-1-aryl-5-(benzofuran-2-yl)-4-(benzotriazol-1-yl)pyrazoles **5a**,**b** (Scheme 1) based on their elemental and spectral analyses. The ^{1}H NMR spectra of compounds **5a,b** revealed a singlet signal around δ 2.5 due to $COCH_3$ protons.

Treatment of compound **2** with phenylisothiocyanate and potassium hydroxide in dimethylformamide at room temperature afforded the potassium salt intermediate **6**, which was converted into the thioacetanilide derivative **7** upon treatment with 10% hydrochloric acid (Scheme 3). The thioacetanilide derivative **7** reacted with hydrazonoyl chlorides **3a**–**f** in refluxing ethanol and in the presence of triethylamine to afford, in each case, only one isolable product. Elemental analyses and spectral data of the reaction products were in complete accordance with 1,3,4-thiadiazole structures **8a**–**f** as shown in Scheme 2, typical of our previous results.[31] The IR spectra of the isolated products revealed, in



Scheme 2.



Scheme 3.

all cases, the appearance of two carbonyl absorption bands. The ^{1}H NMR spectrum of **8b** revealed two singlet signals at δ 2.05 and 2.58 characteristic for two methyl groups and that of **8e** revealed a singlet at δ 2.05 characteristic for 4-tolyl protons in addition to a triplet at δ 1.39 and a quartet at δ 4.46 due to CH_3 and CH_2 protons of the ester group, respectively (see experimental part).

Compound **7** reacted similarly with hydrazonoyl chloride **9** to afford 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)-2-(3,5-diphenyl-3*H*-1,3,4- thiadiazol-2-ylidene)ethanone (**10**) based on its elemental analysis and spectral data.

The thioacetanilide derivative **7** reacted also with 2-bromoacetylbenzofuran (**1**) in refluxing ethanol and in the presence of triethylamine to give a single product that was identified, Based on spectral data, as 2-anilino-3-(benzotriazol-1-yl)-4-(2-benzofuryl)-5-(2-benzofuryl)carbonylthiophene **12a**. Compound **12a** showed characteristic NH peak at 3199 cm^{-1} (in its IR spectrum) and at δ 9.65 (in its ^{1}H NMR spectrum). In addition to a peak at *m*/*z* 552 corresponding to its molecular ion in the mass spectrum. Compound **7** reacted similarly with phenacyl bromides **11a,b** and with α-chloroacetone **11c** under the same reaction conditions to give the corresponding thiophene derivatives **12b–d** as depicted in Scheme 3.

Next, compound **7** reacted with α-chloroacetylacetone **13a** and α-chloroethylacetoacetate **13b** under the same reaction conditions to afford, in each case, a single isolable product that was identified as 2-(5-acetyl-4-methyl-3-phenyl-3h-thiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)ethanone (**14a**) and 2-(5-ethoxycarbonyl-4-methyl-3-phenyl-3h-thiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)ethanone (**14b**), respectively. The ^{1}H NMR spectrum of compound **14a** revealed two singlet signals at δ 1.99 and 2.61 due to CH_3 and $COCH_3$ protons, and that of compound **14b** revealed triplet and quartet signals at δ 1.32 and 4.35 due to CH_3 and CH_2 protons of ester group, respectively.

2.2. Pharmacology

2.2.1. Anticonvulsant activity. Selected examples of the newly synthesized benzotriazole derivatives were screened for anticonvulsant activity in maximal electroshock seizure (MES) and subcutaneous metrazole (ScMet) test in mice and the results are given in Table 1. It was found that there was no protection of the solvent in control as well as the test compound **8b**. The reference compound valproic acid and the test compounds **8a** and **8d** were found to be active in ScMet only, whereas the test compounds **8c** and **14b** were active in MES similar to the second reference compound phenytoin. The third reference compound carbamazepine was active both in MES and in ScMet, however none of the studied compounds was active in both MES and ScMet.

2.2.2. Antinociceptive effect. Next, the antinociceptive effect of the synthesized benzotriazole derivatives was also investigated. It was assessed by three different models: the acetic acid-induced writhing test, hot plate test, and tail-flick test. Some of the benzotriazole derivatives exhibited antinociceptive effects as shown in Table 2. Compared with the control, the potency of the tested compounds was found to be as follows: **5b > 8f > 8c > 8a > 14b > 14a > 8b > 8d > 10**. According to the structure–activity relationship (SAR) it is clear that the pyrazole ring system is more active than the 1,3,4-thiadiazole one. Among the same ring system (1,3,4-thiadiazole derivatives **8a–f**), we noticed that the chlorinated ester **8f** and ketone **8c** derivatives are more

Table 1. Anticonvulsant screening of some novel benzotriazole derivatives

Compound	Concentration (mg/kg)		
	MES	ScMet	Neurotoxicity
Control	—	—	—
5b	—	—	30(50%)
7	—	—	100(25%)
8a	—	100(20%)	—
8b	—	—	—
8c	100(33.3%)	—	100(50%)
8d	—	300(60%)	300(25%)
8f	—	—	100(50%)
10	—	—	100(25%)
14a	—	—	30(25%)
14b	100(20%)	—	30(25%)
Phenytoin	30(100%)	—	100(100%)
Carbmazepine	30(100%)	100(100%)	100(100%)
Valproic acid	—	300(100%)	—

MES, maximal electroshock seizure; ScMet, subcutaneous metrazole seizure.
Values in parentheses in the MES and ScMet tests indicate the number of animals protected against the number of animals tested and in the neurotoxicity test indicate the number of animals exhibiting toxicity against the number of animals tested.

effective than their non-chlorinated analogues **8d** and **8a**, respectively.

All the studied compounds significantly reduced the number of writhing and stretching induced by the 0.7% acetic acid solution. The percentage of protection ranged between 6.5% and 53.2%. Aspirin exerted a significant protective effect of 69.4%, as shown in Table 2. The results of hot plate method showed that the test compounds significantly increased the latency to jumping response without affecting the animal's ability to detect pain threshold (licking response) of thermal origin. Morphine exerted also a significant effect in this response. In tail-flick test, morphine was used to induce analgesia, when morphine displaced maximum analgesia.[32] significant analgesia was monitored with test compounds, suggesting that these compounds have central analgesic properties. The results of antinociceptive activity of the mentioned compounds in various models indicate that the newly reported compounds might possess centrally and peripherally mediated antinociceptive properties.

2.2.3. Anti-inflammatory activity. The effect of the new tested compounds and Ibuprofen, as a reference, on carrageenan-induced edema at different time intervals is depicted in Table 3. After 1 h, all the tested benzotriazole compounds (except for **8c** and **8d**) showed a reasonable decrease in the edema size ranging between 7% for compound **10** and 45% for compound **8a**. However, this reduction is still significant from that of control. As shown in Table 3, the thiadiazole derivative **8a** was the most potent anti-inflammatory compound after 2 h. However, compound **8c** showed no inhibitory effect, while ibuprofen was the most effective along the 4 h interval. After 3 h, the inflammation reached the highest size (3.1) and all the tested compounds (except for **8c** and **8d**) were able to decrease the paw edema. Compound **8a** was the most powerful one in minimizing the inflammation size (45% after 2 h).

From the structure–activity relationship (SAR) viewpoint, the anti-inflammatory activity of 5-acetyl-1,3,4-thiadiazole derivatives **8a-c** was found to be high in the case of unsubstituted phenyl derivative **8a** and decreases with substitution in the order: **8a > 8b > 8c**. Also, the anti-inflammation effect of the thiazolidine ester derivative **14b** is higher than that of its acetyl derivative **14a**. In addition, the chlorinated ester derivative of 1,3,4-thiadiazole system **8f** was found to be more effective than its non-chlorinated one **8d**.

2.2.4. Mechanism of action. Acute inflammation depends on the release of chemical mediators which bring about edema formation as a result of extravasations of fluid and proteins from the local microvasculature and accumulation of polymorphonuclear leukocytes at the

Table 2. Antinociceptive effect of some of the synthesized benzotriazole derivatives

Group	Stretching episodes[a] (count/20 min)	Inhibition (%)	Action time[b] (s)	Increase (%)	Analgesia[c] (%)
Control	62 ± 4.9^{a}	—	8.4 ± 1.6^{f}	—	—
5b	29 ± 4.1^{i}	53.2	13.5 ± 1.9^{bc}	60.7	13.7 ± 2.2^{bc}
7	47 ± 4.5^{de}	24.2	11.6 ± 2.0^{bcdef}	38.1	10.8 ± 2.1^{cdef}
8a	38 ± 2.7^{fgh}	38.7	12.6 ± 2.3^{bcd}	50.0	11.1 ± 1.9^{cdef}
8b	50 ± 3.8^{cd}	19.4	10.1 ± 1.2^{def}	20.2	8.4 ± 1.6^{efg}
8c	45 ± 3.8^{def}	27.4	12.7 ± 1.6^{bcd}	51.1	10.0 ± 3.0^{cdef}
8d	58 ± 5.5^{ab}	6.5	8.6 ± 2.3^{f}	12.2	—
8f	41 ± 3.8^{efg}	33.9	13.0 ± 1.4^{bcd}	54.7	11.4 ± 2.0^{bcdef}
10	55 ± 4.6^{abc}	11.3	9.0 ± 2.0^{ef}	7.1	5.6 ± 2.8^{g}
14a	51 ± 3.9^{bcd}	17.7	11.2 ± 2.8^{bcdef}	33.3	9.5 ± 1.8^{defg}
14b	42 ± 4.2^{efg}	32.3	11.5 ± 1.2^{def}	36.9	—
Aspirin	19 ± 3.0^{i}	69.4	NT	—	NT
Morphin	NT	—	20.6 ± 2.6^{a}	145.2	30.1 ± 3.9^{a}

% analgesia = (test latency − control latency) (cut-off time − control latency) × 100.
Values in parentheses are % antinociceptive effect to control group.
Methods a–c indicate the writhing, hot plate and tail-flicks tests, respectively.
NT (not tested). Values represent means ± SD ($n = 10$). Values sharing the same superscript letter are not significantly different from each other ($p < 0.05$) by Duncan's multiple range test.

Table 3. Inhibitory effect of some new benzotriazole derivatives on carrageenan-induced edema of the hind paw in rats

Group	Swelling volume (ml)			
	1 h	2 h	3 h	4 h
Control	1.4 ± 0.08^{bc}	2.2 ± 0.09^{a}	2.9 ± 0.03^{b}	2.4 ± 0.07^{ab}
5b	1.2 ± 0.08^{de} (14)	1.6 ± 0.07^{de} (27)	2.4 ± 0.05^{cd} (17)	2.1 ± 0.07^{de} (13)
7	1.0 ± 0.10^{fg} (29)	1.4 ± 0.05^{fg} (36)	1.9 ± 0.09^{hi} (34)	1.8 ± 0.09^{gh} (25)
8a	0.9 ± 0.07^{gh} (36)	1.2 ± 0.06^{h} (45)	1.8 ± 0.08^{ij} (38)	1.6 ± 0.08^{i} (34)
8b	1.0 ± 0.08^{fg} (29)	1.6 ± 0.04^{dc} (27)	2.3 ± 0.03^{dc} (21)	2.1 ± 0.07^{dc}(13)
8c	1.6 ± 0.05^{a} (-)	2.2 ± 0.09^{a} (-)	2.9 ± 0.11^{b} (-)	2.5 ± 0.05^{a} (-)
8d	1.5 ± 0.03^{ab} (-)	2.3 ± 0.07^{a} (-)	3.1 ± 0.12^{a} (-)	2.3 ± 0.07^{bc}(4)
8f	1.0 ± 0.05^{fg} (29)	1.4 ± 0.03^{fg}(36)	2.0 ± 0.04^{gh} (31)	2.0 ± 0.06^{ef}(17)
10	1.3 ± 0.07^{cd} (7)	1.9 ± 0.08^{b}(14)	2.5 ± 0.07^{c} (14)	2.3 ± 0.06^{bc} (4)
14a	1.1 ± 0.09^{ef} (22)	1.5 ± 0.06^{ef} (32)	2.1 ± 0.06^{fg} (28)	2.0 ± 0.08^{ef}(17)
14b	1.1 ± 0.07^{ef} (22)	1.8 ± 0.07^{bc} (18)	2.2 ± 0.07^{ef} (24)	1.9 ± 0.10^{fg}(21)
Ibuprofen	0.6 ± 0.08^{i} (57)	0.9 ± 0.9^{i}(59)	1.1 ± 0.05^{k}(62)	0.8 ± 0.07^{k}(67)

Values represent means ± SD ($n = 10$). Values sharing the same superscript letter are not significantly different at ($p < 0.05$) Duncan's test. Values in the parentheses are the inhibition % of edema compared to the control at each time interval.

inflammatory site. Winter et al.[33] represented an inflammatory reaction induced in rat hind paw by the subplantar injection of carrageenan. This inflammation model is considered the most conventional one for acute inflammation.

A major mechanism of action of NSAIDs (nonsteroidal anti-inflammatory drugs) is in lowering prostaglandin production through inhibition of cyclooxygenase (COX), which has a dual function, mediation of inflammation and cytoprotection of the stomach and intestine.[34] it was discovered that COX exists in two isoforms, COX-1 and COX-2, which are encoded by two distinct genes. COX-1 is expressed constitutively providing cytoprotection, while COX-2 is transiently upregulated by proinflammatory mediators.[35] This regulated expression suggests that a selective inhibitor of COX-2 may have anti-inflammatory properties and lack the ulcerogenic side effects.[36] This hypothesis has been supported by several studies with selective COX-2 inhibitors, among these reported studies of anti-inflammatory, analgesic agents were benzofuran derivatives.[4,5] Directed by these findings, we studied the anti-inflammatory activity of some benzofuran derivatives, with the same mechanism of action of selective COX-2 inhibtors.

3. Conclusion

Of the benzofuran-benzotriazole-based heterocycles prepared and screened in our study, the pyrazole derivative **5b** showed a higher antinociceptive effect than all other heterocycles. The thiadiazole derivative **8a** was the most potent anti-inflammatory compound after 2 h and it showed also reasonable anticonvulsant activity in ScMet without neurotoxicity.

4. Experimental

4.1. General

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analysis was carried out at the Microanalytical Center of Cairo University. 2-Bromoacetylbenzofuran (**1**),[37] hydrazonoyl chlorides **3a**–**c**,[38] **3d**–**f**,[39] and **9**,[40] phenacyl bromides **11a**, **b**[41] were prepared following the procedures reported in the literature.

4.2. 1-(2-Benzofuryl)-2-(1-benzotriazolyl)ethanone (2)

To a mixture of 2-bromoacetylbenzofuran (**1**) (2.37 g, 10 mmol) and 1*H*-benzotriazole (1.2 g, 10 mmol) in dry tetrahydrofuran (25 ml), triethylamine (1 ml) was added and the mixture was refluxed for 5 h then left to cool. The precipitated triethylamine hydrobromide was filtered off, then the solvent was evaporated to afford a solid product that was filtered off, washed with ethanol, dried, and finally recrystallized from ethanol to afford pale yellow crystals of compound **2** in 2.05 g (74%) yield; mp 160 °C; IR (KBr) ν_{max}/cm^{-1} 1698 (C=O); ^{1}H NMR (DMSO-d_6) δ 5.30 (s, 2H, CH_2), 6.50 (s, 1H, CH-furan), 7.41–7.64 (m, 4H), 7.77–7.94 (m, 3H), 8.10 (d, 1H, $J = 8.4$ Hz); MS *m*/*z* (%) 277 (M^+, 43.7), 248 (9.5), 221 (40.4), 145 (100), 132 (49.8), 104 (18.7), 89 (74.3), 77 (74.5), 63 (26.8), 51 (20.8). Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.63; H, 3.89; N, 15.38.

4.3. 3-Acetyl-1-aryl-4-(1-benzotriazolyl)-5-(2-benzofuryl)pyrazoles 5a,b

1-(2-Benzofuryl)-2-(1-benzotriazolyl)ethanone (**2**) (0.554 g, 2 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.046 g, 2 mmol) and absolute ethanol (25 mL)]. After stirring for 10 min, the appropriate hydrazonyl halides **3a**,**b** (2 mmol) were added and stirring was continued for an additional 30 min. The reaction mixture was then left at room temperature for 12 h. The solid product was collected by filtration, washed with water, and dried. Crystallization

from ethanol afforded the corresponding pyrazole derivatives **5a**,**b**.

4.3.1. 3-Acetyl-4-(1-benzotriazolyl)-5-(2-benzofuryl)-1-phenylpyrazole (5a). Brownish-red solid (0.65 g, 78%); mp 120 °C; IR (KBr) ν_{max}/cm^{-1} 1698 (C=O), 1597 (C=N); ^1H NMR (DMSO-d_6) δ 2.58 (s, 3H, CH_3), 6.10 (s, 1H, CH-furan), 7.02–7.16 (m, 5H), 7.28–7.51 (m, 7H), 7.88 (d, 1H, $J = 8.4$ Hz). MS *m/z* (%) 419 (M^+, 9.8), 376 (5.9), 220 (19.7), 145 (11.2), 118 (4.7), 108 (6.5), 89 (24.3), 77 (100). Anal. Calcd for $C_{25}H_{17}N_5O_2$: C, 71.59; H, 4.09; N, 16.70. Found: C, 71.79; H, 4.20; N, 16.34.

4.3.2. 3-Acetyl-4-(1-benzotriazolyl)-5-(2-benzofuryl)-1-(*p*-chlorophenyl)pyrazole (5b). Brown crystal (0.69 g, 76%); mp 180–182 °C; IR (KBr) ν_{max}/cm^{-1} 1694 (C=O), 1551.83 (C=N); ^1H NMR (DMSO-d_6) δ 2.56 (s, 3H, CH_3), 6.40 (s, 1H, CH-furan), 7.01–7.64 (m, 11H), 7.76 (d, 1H, $J = 8.4$ Hz). Anal. Calcd for $C_{25}H_{16}ClN_5O_2$: C, 66.16; H, 3.55; N, 15.43. Found: C, 66.46; H, 3.75; N, 15.18.

4.4. 1-(2-Benzofuryl)-2-(1-benzotriazolyl)-3-mercapto-3-(*N*-phenylamino)prop-2-enone (7)

To a stirred solution of potassium hydroxide (0.6 g, 10 mmol) in dimethylformamide (50 mL), 1-(2-benzofuryl)-2-(1-benzotriazolyl)ethanone (**2**) (2.77 g, 10 mmol) was added. After stirring for 30 min, phenylisothiocyanate (1.4 g, 10 mmol) was added to the resulting mixture. The stirring was continued for further 6 h then poured over crushed ice containing hydrochloric acid. The solid product was filtered off, washed with water, dried, and finally recrystallized from DMF/H_2O to afford compound **7** as a orange-red powder in 2.84 g (69%) yield; mp 190–192 °C; IR (KBr) ν_{max}/cm^{-1} 3420 (NH), 1692 (C=O); ^1H NMR (DMSO-d_6) δ 6.40 (s, 1H, CH-furan), 7.00–7.80 (m, 12H, ArH), 8.20 (d, 1H, $J = 8.4$ Hz), 12.50 (s, 1H, NH), 14.45 (s, 1H, SH); MS *m/z* (%) 412 (M^+, 5.2), 366 (3.1), 277 (3.6), 145 (27.3), 104 (18.8), 89 (46.5), 77 (100), 63 (30.6), 51 (54.3). Anal. Calcd for $C_{23}H_{16}N_4O_2S$: C, 66.97; H, 3.91; N, 13.58; S, 7.77. Found: C, 67.20; H, 3.68; N, 13.81; S, 7.85.

4.5. Reaction of the thioacetanilide derivative 7 with hydrazonoyl chlorides

To a solution of the thioacetanilide derivative **7** (0.824 g, 2 mmol) in absolute ethanol (20 ml) the appropriate hydrazonoyl chlorides **3a**–**f** or **9** (2 mmol) were added, in the presence of triethylamine (0.3 ml). The reaction mixture was refluxed for 1 h and then allowed to cool. The formed solid product was filtered off, washed with ethanol, and recrystallized from EtOH/DMF to afford the corresponding thiadiazole derivatives **8a**–**f** and **10**.

4.5.1. 2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8a). Yellow crystals (0.62 g, 65%); mp 250 °C; IR (KBr) ν_{max}/cm^{-1} 1687, 1660 (2 C=O), 1591 (C=N); ^1H NMR (DMSO-d_6) δ 2.60 (s, 3H, $COCH_3$), 6.05 (s, 1H, CH-furan), 6.98–7.31 (m, 8H), 7.42–7.53 (m, 4H), 7.85 (d, 1H, $J = 8.4$ Hz). MS *m/z* (%) 479 (M^+, 13.2), 451 (62.4), 386 (17.6), 368 (100), 332 (55.5), 311 (47.3), 216 (24.7), 169 (43.9), 145 (47.0), 77 (70.6), 57 (64.9). Anal. Calcd for $C_{26}H_{17}N_5O_3S$: C, 65.12; H, 3.57; N, 14.61; S, 6.69. Found: C, 65.30; H, 3.25; N, 14.92; S, 6.46.

4.5.2. 2-(5-Acetyl-3-*p*-tolyl-1,3,4-thiadiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8b). Yellow powder (0.66 g, 67%); mp 270-272 °C; IR (KBr) ν_{max}/cm^{-1} 1681, 1670 (2 C=O), 1589 (C=N); ^1H NMR (DMSO-d_6) δ 2.05 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 6.12 (s, 1H, CH-furan), 7.14–7.39 (m, 6H), 7.43–7.58 (m, 5H), 7.79 (d, 1H, $J = 8.26$ Hz). Anal. Calcd for $C_{27}H_{19}N_5O_3S$: C, 65.71; H, 3.88; N, 14.19; S, 6.50. Found: C, 65.86; H, 3.74; N, 14.44; S, 6.43.

4.5.3. 2-[5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2-ylidene]-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8c). Pale brown crystals (0.69 g, 67%); mp 278 °C; IR (KBr) ν_{max}/cm^{-1} 1689, 1678 (2 C=O), 1582 (C=N); ^1H NMR (DMSO-d_6) δ 2.59 (s, 3H, CH_3), 6.09 (s, 1H, CH-furan), 7.03 (d, 2H, $J = 8.7$ Hz), 7.11–7.16 (m, 2H), 7.27 (d, 2H, $J = 7.5$ Hz), 7.36 (d, 2H, $J = 7.5$ Hz), 7.41–7.51 (m, 3H), 7.88 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR δ 26.1, 100.4, 110.1, 111.7, 112, 116.4, 119.9, 122.7, 123.3, 124.2, 126.7, 127.3, 128.2, 128.9, 135.3, 135.6, 145.4, 150.5, 154.8, 155, 160.2, 173.1, 190.2; MS *m/z* (%) 514 (M^+, 9.1), 456 (17.5), 387 (19.8), 340 (26.0), 239 (31.0), 219 (88.1), 190 (28.7), 145 (38.4), 111 (38.1), 89 (100), 75 (33.6). Anal. Calcd for $C_{26}H_{16}ClN_5O_3S$: C, 60.76; H, 3.14; N, 13.63; S, 6.24. Found: C, 60.98; H, 3.37; N, 13.64; S, 6.16.

4.5.4. 2-(5-Ethoxycarbonyl-3-phenyl-1,3,4-thiadiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8d). Orange-yellow needles (0.63 g, 62%); mp 240 °C; IR (KBr) ν_{max}/cm^{-1} 1700, 1665 (2 C=O), 1579 (C=N); ^1H NMR (DMSO-d_6) δ 1.36 (t, 3H, CH_2CH_3, $J = 7.2$ Hz), 4.45 (q, 2H, CH_2CH_3, $J = 7.2$ Hz), 6.05 (s, 1H, CH-furan), 7.00–7.16 (m, 4H), 7.26–7.30 (m, 3H), 7.41–7.52 (m, 5H), 8.20 (d, 1H, $J = 8.4$ Hz); MS *m/z* (%) 509 (M^+, 20), 481 (29), 452 (39.7), 353 (41.5), 336 (49.4), 308 (18.7), 219 (100), 145 (23.9), 89 (49.4), 77 (93). Anal. Calcd for $C_{27}H_{19}N_5O_4S$: C, 63.64; H, 3.76; N, 13.74; S, 6.29. Found: C, 63.85; H, 3.45; N, 13.55; S, 6.48.

4.5.5. 2-[5-Ethoxycarbonyl-3-(p-tolyl)-1,3,4-thiadiazol-2-ylidene]-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8e). Yellowish-green needles (0.69 g, 66%); mp 180 °C; IR (KBr) ν_{max}/cm^{-1} 1751, 1710 (2 C=O), 1578 (C=N); ^1H NMR (DMSO-d_6) δ 1.39 (t, 3H, CH_2CH_3, $J = 7.2$ Hz), 2.05 (s, 3H, *p*-CH_3), 4.46 (q, 2H, CH_2CH_3, $J = 7.2$ Hz), 6.10 (s, 1H, CH-furan), 7.10–7.36 (m, 6H), 7.48–7.54 (m, 5H), 7.90 (d, 1H, $J = 8.4$ Hz); MS *m/z* (%) 523 (M^+, 11.2), 466 (13.7), 367 (27.8), 350 (37.4), 251 (15.3), 219 (85.1), 190 (23.3), 145 (27.0), 116 (10.4), 91 (100), 65 (46.6). Anal. Calcd for $C_{28}H_{21}N_5O_4S$: C, 64.23; H, 4.04; N, 13.38; S, 6.12. Found: C, 64.09; H, 4.30; N, 13.12; S, 6.25.

4.5.6. 2-(5-Ethoxycarbonyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (8f). Yellow solid (0.72 g, 68%); mp 230 °C; IR

(KBr) ν_{max}/cm^{-1} 1745, 1720 (2 C=O), 1584 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.36 (t, 3H, CH_2CH_3, J = 7.2 Hz), 4.44 (q, 2H, CH_2CH_3, J = 7.2 Hz), 6.10 (s, 1H, CH-furan), 7.02–7.34 (m, 6H), 7.44–7.51 (m, 5H), 7.87 (d, 1H, J = 8.4 Hz); MS m/z (%) 543 (M$^+$, 12.0), 515 (15.9), 486 (18.6), 416 (9.6), 387 (30.4), 370 (40.6), 342 (19.2), 239 (26.8), 219 (100), 190 (24.4), 169 (14.0), 145 (34.9), 111 (31.3), 89 (75.4). Anal. Calcd for $C_{27}H_{18}ClN_5O_4S$: C, 59.61; H, 3.34; N, 12.87; S, 5.89. Found: C, 59.87; H, 3.25; N, 12.99; S, 5.75.

4.5.7. 1-(2-Benzofuryl)-2-(1-benzotriazolyl)-2-(3,5-diphenyl-1,3,4-thiadiazol-2-ylidene)-ethanone (10). Brown powder (0.64 g, 63%); mp 290 °C; IR (KBr) ν_{max}/cm^{-1} 1639 (C=O), 1616 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.10 (s, 1H, CH-furan), 7.00–7.65 (m, 15H), 7.85 (d, 1H, J = 8.34 Hz), 7.93–8.05 (m, 2H); ^{13}C NMR δ 99.1, 110.3, 111.1, 111.7, 119.6, 122.5, 123.1, 123.8, 126.8, 126.9, 127, 127.8, 128.5, 129, 129.3, 131.5, 135.7, 137.5, 145.4, 151, 154.7, 156.6, 158.8, 172.3; MS m/z (%) 513 (M$^+$, 12.4), 485 (26.0), 456 (65.0), 353 (60.8), 340 (100), 313 (12.1), 251 (9.8), 247 (15.5), 219 (81.0), 145 (21.9), 89 (37.5), 77 (26.0). Anal. Calcd for $C_{30}H_{19}N_5O_2S$: C, 70.16; H, 3.73; N, 13.64; S, 6.24. Found: C, 70.30; H, 3.97; N, 13.45; S, 6.02.

4.6. Reactions of thioacetanilide derivative 7 with α-haloketones and α-halodiketones

To a mixture of the thioacetanilide derivative **7** (0.824 g, 2 mmol) and the appropriate α-haloketones **1** or **11a–c** or α-halodiketones **13a**, **b** (2 mmol) in absolute ethanol (20 ml), triethylamine (0.3 ml) was added portionwise. The reaction mixture was refluxed for 1 h then left to cool to room temperature. The formed solid product was filtered off, washed with ethanol, and recrystallized from EtOH/DMF to afford the corresponding thiophene derivatives **12a–d** and 1,3,4-thiadiazoles **14a**,**b**, respectively.

4.6.1. 2-(2-Benzofuryl)carbonyl-3-(2-benzofuryl)-4-(1-benzotriazolyl)-5-phenylamino-thiophene (12a). Yellow solid (0.77 g, 70%); mp 218–220 °C; IR (KBr) ν_{max}/cm^{-1} 3199 (NH), 1646 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.30 (s, 2H, CH-furan), 6.90–7.28 (m, 6H), 7.34–7.40 (m, 5H), 7.55–7.63 (m, 4H), 8.20 (d, 2H, J = 8.4 Hz), 9.65 (s, 1H, NH, D_2O-exchangeable); MS m/z (%) 552 (M$^+$, 12), 524 (71.7), 447 (11.7), 379 (100), 346 (11.2), 273 (10.9), 189 (12.0), 145 (47.4), 89 (81.2), 77 (71.4). Anal. Calcd for $C_{33}H_{20}N_4O_3S$: C, 71.72; H, 3.65; N, 10.14; S, 5.80. Found: C, 71.65; H, 3.81; N, 10.10; S, 5.69.

4.6.2. 3-(2-Benzofuryl)-4-(1-benzotriazolyl)-2-benzoyl-5-phenylamino-thiophene (12b). Brown powder (0.66 g, 65%); mp 230–232 °C; IR (KBr) ν_{max}/cm^{-1} 3227 (NH), 1642 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.10 (s, 1H, CH-furan), 7.10–7.25 (m, 8H), 7.34–7.41 (m, 5H), 7.52–7.59 (m, 4H), 8.12 (d, 1H, J = 8.7 Hz), 9.47 (s, 1H, NH, D_2O-exchangeable); MS m/z (%) 512 (M$^+$, 12.5), 484 (35.0), 379 (100), 306 (10), 276 (24), 216 (31), 172 (22.5), 105 (11), 77 (23.5). Anal. Calcd for $C_{31}H_{20}N_4O_2S$: C, 72.64; H, 3.93; N, 10.93; S, 6.26. Found: C, 72.82; H, 4.11; N, 10.61; S, 6.09.

4.6.3. 3-(2-Benzofuryl)-4-(1-benzotriazolyl)-2-(4-bromobenzoyl)-5-phenylamino-thiophene (12c). Pale yellow crystals (0.74 g, 63%); mp 207 °C; IR (KBr) ν_{max}/cm^{-1} 3186 (NH), 1634 (C=O); ^{1}H NMR (DMSO-d_6) δ 6.13 (s, 1H, CH-furan), 7.03–7.48 (m, 12H), 7.61–7.86 (m, 5H), 9.51 (s, 1H, NH);^{13}C NMR δ 110.2, 112.9, 119.2, 121.1, 121.6, 122.8, 124.6, 125.9, 127.1, 128.6, 129.1, 129.6, 130.2, 130.8, 132, 132.4, 133.6, 137.3, 140.1, 144.7, 146.1, 153.5, 153.9, 187.6; MS m/z (%) 591 (M$^+$, 11.3), 562 (94.4), 487 (18.2), 379 (32.6), 348 (4.8), 182 (16.3), 154 (12.9), 77 (9.9). Anal. Calcd for $C_{31}H_{19}BrN_4O_2S$: C, 62.95; H, 3.24; N, 9.47; S, 5.42. Found: C, 63.11; H, 3.60; N, 9.29; S, 5.30.

4.6.4. 2-Acetyl-3-(2-benzofuryl)carbonyl-4-(1-benzotriazolyl)-5-phenylamino-thiophene (12d). Brown solid (0.64 g, 72%); mp 225-227 °C; IR (KBr) ν_{max}/cm^{-1} 3415 (NH), 1646 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.10 (s, 3H, $COCH_3$), 6.63 (s, 1H, CH-furan), 7.15–7.25 (m, 4H), 7.33–7.41 (m, 5H), 7.46–7.56 (m, 3H), 8.05 (d, 1H, J = 8.4 Hz), 9.46 (s, 1H, NH, D_2O-exchangeable); MS m/z (%) 450 (M$^+$, 9.1), 422 (24.2), 379 (100), 345 (14.5), 319 (13.5), 276 (17.5), 216 (13.8), 145 (12.8), 109 (10.7), 77 (50.6). Anal. Calcd for $C_{26}H_{18}N_4O_2S$: C, 69.31; H, 4.03; N, 12.44; S, 7.12. Found: C, 69.40; H, 4.23; N, 12.52; S, 6.95.

4.6.5. 2-(5-Acetyl-4-methyl-3-phenyl-2,3-dihydrothiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (14a). Pale yellow crystals (0.66 g, 67%); mp 260–262 °C; IR (KBr) ν_{max}/cm^{-1} 1645, 1633 (2 C=O); ^{1}H NMR (DMSO-d_6) δ 1.99 (s, 3H, CH_3), 2.61 (s, 3H, $COCH_3$), 6.00 (s, 1H, CH-furan), 7.00–7.12 (m, 3H), 7.22–7.35 (m, 5H), 7.41–7.47 (m, 4H), 7.78 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 14.1, 30.42, 101.7, 110.6, 111.5, 118.8, 119.5, 122.3, 123, 123.7, 126, 126.9, 127.2, 127.7, 128.8, 129.1, 134.8, 136, 145.3, 146.9, 151.3, 154.6, 160., 172.8, 190.6; MS m/z (%) 492 (M$^+$, 13.2), 464 (15.5), 435 (100), 359 (12.2), 319 (32.1), 277 (5.5), 219 (41.4), 201 (12.8), 165 (7.6), 89 (21.22), 77 (36.1). Anal. Calcd for $C_{28}H_{20}N_4O_3S$: C, 68.28; H, 4.09; N, 11.37; S, 6.51. Found: C, 68.47; H, 3.87; N, 11.25; S, 6.58.

4.6.6. 2-(5-Ethoxycarbonyl-4-methyl-3-phenyl-2,3-dihydrothiazol-2-ylidene)-1-(2-benzofuryl)-2-(1-benzotriazolyl)-ethanone (14b). Yellow crystals (0.68 g, 65%); mp 210 °C; IR (KBr) ν_{max}/cm^{-1} 1697, 1647 (2 C=O); ^{1}H NMR (DMSO-d_6) δ 1.32 (t, 3H, CH_2CH_3, J = 7.2 Hz), 2.38 (t, 3H, CH_3), 4.35 (q, 2H, CH_2CH_3, J = 7.2 Hz), 6.30 (s, 1H, CH-furan), 7.05–7.31 (m, 7H), 7.52–7.70 (m, 5H), 8.30 (d, 1H, J = 8.4 Hz); MS m/z (%) 522 (M$^+$, 4), 494 (38.8), 437 (58.4), 349 (29.6), 321 (28.2), 296 (17.7), 245 (11.8), 219 (26.1), 165 (10.3), 89 (43), 77 (89.6). Anal. Calcd for $C_{29}H_{22}N_4O_4S$: C, 66.65; H, 4.24; N, 10.72; S, 6.14. Found: C, 66.77; H, 4.37; N, 10.96; S, 6.02.

5. Pharmacology

5.1. Anticonvulsant activity

5.1.1. Materials and animals. Some of the prepared compounds were screened for anticonvulsant activity

adopting the anticonvulsant drug development (ADD) program protocol.[42,43] The mice used were Wistar albino mice weighing between 19 and 25 g of either sex, produced from National Research Centre, Giza, Egypt, and were housed under suitable laboratory conditions through the period of investigation. Animals were fed standard pellet chow (El-Nasr Chemical Company, Cairo, Egypt) and allowed free access to tap water. The number of animals used in each experiment was six. Dimethyl sulfoxide (DMSO) was used as a solvent for the test compounds. The control was performed with the solvent alone. The compounds were administered intraperitoneally to mice at doses of 30, 100, and 300 mg/kg (body weight).

5.1.2. Methods

5.1.2.1. Electroshock method. Maximal seizures were induced by the application of electrical current to the brain via corneal electrodes. The stimulus parameters for mice were 50 Ma in a pulse of 60 Hz for 200 ms. Abolition of the hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity (Electroshocker, Ugo Basile, Italy).

5.1.2.2. Subcutaneous metrazole seizure pattern test. Metrazole dose of 85 mg/kg administered subcutaneously to mice causes seizures in more than 97% of the animals. This is called the convulsive dose (CD_{97}). The test was carried out by giving the metrazole injection 10 min before the anticipated time of the peak anticonvulsant drug action. The animals were observed during the following 4 h for the occurrence of seizures. A threshold convulsion is defined as one episode of clonic spasms which persists for at least 5 s. Absence of even a threshold convulsion during the period of observation is taken as the endpoint in this test.

5.1.2.3. Rotarod test. The mice were trained to stand on an accelerating rotarod rotating at 10 revs./min. The rod diameter was 3.2 cm (Ugo Basile, Italy). The mice were placed on the rotarod to measure the effect of the drug on their motor performance. The dose at which animals fell off the rotarod was determined. The activities of the compounds in maximum electroshock (MES) and subcutaneous metrazole (ScMet) tests along with their neurotoxicity are shown in Table 1.

5.2. Antinociceptive and anti-inflammatory effects

5.2.1. Materials and animals. The newly synthesized benzotriazole derivatives dissolved in DMSO were administered in a dose of 100 mg/kg (body weight). Both mice and rats used were Wistar albino of either sex, produced from National Research Centre, Giza, Egypt, and were housed under suitable laboratory conditions through the period of investigation. Animals were fed standard pellet chow (El-Nasr Chemical Company, Cairo, Egypt) and allowed free access to tap water.

5.2.2. Methods

5.2.2.1 Writhing test. The acetic acid abdominal constriction test was performed as described by Whittle.[44] Vehicle, aspirin (100 mg/kg), and the testing compound were orally administered to mice 30 min before the experiment. Then 0.1 ml / 10 g of 0.7% acetic acid-saline was injected intraperitoneally 10 min after the injection and the frequency of writhing in mice was counted for the next 10 min.

5.2.2.2. Hot plate test. The hot plate test was used to measure the response latencies according to the method described previously by Eddy and Leimback,[45] with minor modifications. In these experiments, the hot plate (Ugo Basile, Model-DS37) was maintained at 55 ± 0.2 °C. The reaction time was noted by observing either the licking of the hind paws or the jumping movements before and after drug administration. The cut-off time was 20 s and morphine sulfate 10 mg/kg (El-Nasr Pharmaceutical Co.) was administered intraperitoneally and was used as a reference drug.[46]

5.2.2.3. Tail-flick test. The antinociceptive responses were determined by measuring the time required to respond to a radiating thermal stimulus. The rat was restrained so that the radiant heat source was focused onto the base of the tail. An automated tail-flick analgesymeter (Ugo Basile, Italy) was used, and the cut-off time was set at 15 s. For each rat, three determinations were carried out before material administration (control latency). The tail-flick latency responses are expressed as a percentage of analgesia calculated. The intensity of the thermal stimulus was adjusted to obtain control latency between 4 and 6 s.[47]

5.2.2.4. Carrageenan-induced edema in rats. The initial hind paw volume of rats was determined volumetrically. One percent solution of carrageenan in saline (0.1 ml/rat) was injected subcutaneously into the right hind paw 1 h after the test compound had been administered orally. The animals in the control group received vehicle only. Paw volumes were measured up to 4 h at intervals of 60 min and the volume of the edema was measured with plethysmometer 7150 (Ugo Basile, Italy). Ibuprofen, an anti-inflammatory drug, was used as a standard drug.[48]

5.3. Statistics

All data are expressed as means + SEM. The level of statistical significance was determined by analysis of variance followed by Duncan's new multiple range test.

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