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Mohamed I. Hegab[a]; Abdel-Rahman B. A. El-Gazzar[a]; Farouk A. Gad[a]; Mohey Ellithey[b]
[a] Photochemistry Department, National Research Centre, Dokki, Cairo, Egypt [b] Pharmacology Department, National Research Centre, Dokki, Cairo, Egypt

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RESEARCH ARTICLE

Regioselective synthesis and pharmacological activities of spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole derivatives

MOHAMED I. HEGAB*†, ABDEL-RAHMAN B. A. EL-GAZZAR†, FAROUK A. GAD† and MOHEY ELLITHEY‡

†Photochemistry Department, National Research Centre, Dokki, 12622, Cairo, Egypt
‡Pharmacology Department, National Research Centre, Dokki, 12622, Cairo, Egypt

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Some new 3′,5′-substituted-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole and 10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole derivatives **3a–n** were regioselectively synthesized under 1,3-dipolar cycloaddition of 5-thiooxo-5*H*-dibenzo[*a*,*d*]cycloheptene and 5-thiooxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene with a variety of nitrilimines (generated *in situ* via dehydrohalogenation of the corresponding hydrazonoyl chlorides in the presence of triethylamine). The new products were tested for antiinflammatory, analgesic, and ulcerogenic score activities comparable to Indomethacin. Compounds **3i–l** showed significant activity compared to Indomethacin.

Keywords: Regioselective 1,3-dipolar cycloaddition; Spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4] thiadiazole; Nitrilimines; Analgesic; Antiinflammatory; Ulcerogenic

1. Introduction

The five-membered heterocycles could be constructed via, one of the most versatile methods, 1,3-dipolar cycloaddition reaction [1]. Nitrilimines represent an important class of highly reactive 1,3-dipoles used intensively for cycloaddition reactions with numerous unsaturated functional groups [2–13]. Huisgen *et al.* [14, 15] reported the reaction of azomethine oxide with several thiooxoketones to afford 1,4,2-oxathiazolidines. Similarly, diazomethane interacted with thiobenzophenone giving thiadiazoline derivative [16]. On the other hand, regiospecific dipolar cycloaddition reactions of nitrilimines derivatives with thiobenzophenone and 2-thiooxoadamantane have been reported [17, 18].

The 1,3,4-thiadiazole ring containing structure exhibit biological activity, for example leishmanicidal [19], anticonvulsant [20, 21], and antituberculosis [22, 23]. Moreover, several derivatives of 5*H*-dibenzo[*a*,*d*]cycloheptene possess various biological activity, for example

*Corresponding author. Email: apmihegab65@yahoo.com

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antibacteria, antifungi, antihelminths, antiinflammatory, analgesic, antihypertensive, and D-aspartate antagonists [24–27]. In a previous paper, we described the chemistry of 5-thiooxo-5*H*-dibenzo[*a*,*d*]cycloheptene and 5-thiooxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene toward sulfuryl chloride [28]. So, we wish to investigate the reaction of them with variety of nitrilimines and evaluate the biological activity of the new products (analgesic, antiinflammatory, ulcerogenic score).

2. Results and discussion

2.1 *Synthesis*

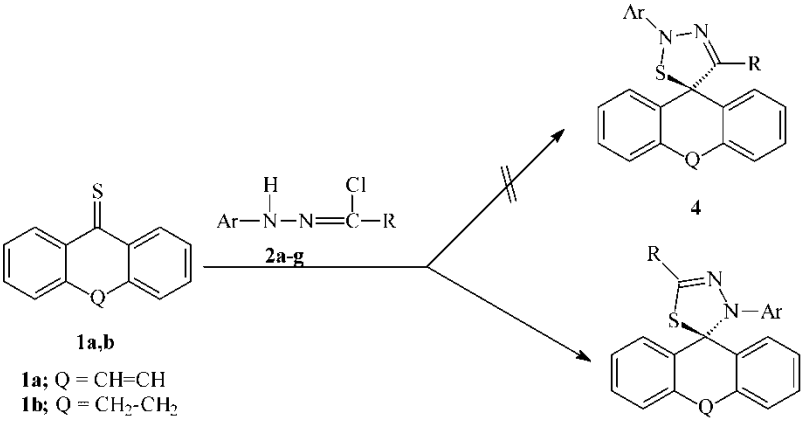
In the present work, the authors wish to explore 1,3-dipolar cycloaddition of sterically hindered 5-thiooxo-5*H*-dibenzo[*a*,*d*]cycloheptene and 5-thiooxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene with variety of nitrilimines. Reaction of thiooxo derivatives **1a,b** with *C*-acetyl-*N*-(4-methylphenyl)hydrazonoyl chloride in refluxing dry benzene containing triethylamine for 6 h afforded 5′-acetyl-3′-(4-methylphenyl)-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (**3a**) and 5′-acetyl-3′-(4-methylphenyl)-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]-thiadiazole (**3b**), respectively as only one product as indicated by *tlc* (scheme 1). The structures of the products **3a,b** were established by elemental analyses and spectral data (IR, ^{1}H and ^{13}C NMR, MS). IR spectra show C=O at υ 1700 cm^{-1} and 1693 cm^{-1}, respectively. ^{1}H NMR of **3a** shows Ph-CH_3 at δ 2.11 ppm as singlet, $COCH_3$ at δ 2.55, 10-CH and 11-CH at δ 6.92 as doublet, J = 12.2 Hz in addition to aromatic protons. In the ^{13}C NMR spectrum of **3a**, appearance of signals at 95.14 (C-5) and 157.72 (C-5′), which are in agreement with that of references [2] and [18], supported structure **3a** but not **4**. The mass spectra of **3a,b** showed the prominent ion peak at m/z 396 (M^+, 20) and m/z 398 (M^+, 23), respectively.

Accordingly, the thiooxo derivatives **1a,b** reacted with *C*-acetyl-*N*-aryl hydrazonoyl chloride derivatives **2b–d** as described above, to afford 5′-acetyl-3′-aryl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole derivatives **3c–h**, respectively (scheme 1). The structures of the products **3c–h** were established by elemental analyses and spectral data (IR, ^{1}H NMR, MS). IR spectra show C=O at υ 1692 cm^{-1} and 1705 cm^{-1}, respectively. ^{1}H NMR spectra showed $COCH_3$ at δ 2.50–2.60, 10-CH and 11-CH at δ 6.85–6.95 as doublet, $J \approx$ 12 Hz, 10-CH_2 and 11-CH_2 at δ 3.30–3.38 as multiplet in addition to aromatic protons. The mass spectra of **3c–h** showed the M^+ as prominent ion peak.

Also, the reaction of thiooxo derivatives **1a,b** with *C*-carboethoxy-*N*-aryl hydrazonoyl chloride derivatives **2e,f** as mentioned above, afforded 5′-carboethoxy-3′-aryl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole derivatives **3i–l**, respectively (scheme 1).

The structures of the products **3i–l** were established by elemental analyses and spectral data (IR, ^{1}H NMR, MS). IR spectra show C=O at υ 1685–1690 cm^{-1}, respectively. ^{1}H NMR spectra showed CH_3CH_2 at δ 1.25–1.35 as triplet, $J \approx$ 7 Hz, CH_3CH_2 at δ 4.30–4.35 as quartet, $J \approx$ 7 Hz, 10-CH and 11-CH at δ 6.90–6.95 as d, $J \approx$ 12 Hz, 10-CH_2 and 11-CH_2 at δ 3.38 as multiplet in addition to aromatic protons. The mass spectra of **3i-l** showed the M^+ as prominent ion peak.

On the other hand, the thiooxo derivatives **1a,b** reacted with *C*-phenyl-*N*-phenyl hydrazonoyl chloride **2g**, as described above, to afford 5′-phenyl-3′-phenyl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole derivatives **3m,n** respectively (scheme 1).



1a; Q = CH=CH
1b; Q = CH_2-CH_2

2a; Ar = 4-$CH_3C_6H_4$, R = $COCH_3$
2b; Ar = 4-ClC_6H_4, R = $COCH_3$
2c; Ar = 4-$NO_2C_6H_4$, R = $COCH_3$
2d; Ar = C_6H_5, R = $COCH_3$
2e; Ar = C_6H_5, R = $COOC_2H_5$
2f; Ar = 4-$CH_3C_6H_4$, R = $COOC_2H_5$
2g; Ar = R = C_6H_5

3a; Q = C_2H_2, Ar = 4-$CH_3C_6H_4$, R = $COCH_3$
3b; Q = C_2H_4, Ar = 4-$CH_3C_6H_4$, R = $COCH_3$
3c; Q = C_2H_2, Ar = 4-ClC_6H_4, R = $COCH_3$
3d; Q = C_2H_4, Ar = 4-ClC_6H_4, R = $COCH_3$
3e; Q = C_2H_2, Ar = 4-$NO_2C_6H_4$, R = $COCH_3$
3f; Q = C_2H_4, Ar = 4-$NO_2C_6H_4$, R = $COCH_3$
3g; Q = C_2H_2, Ar = C_6H_5, R = $COCH_3$
3h; Q = C_2H_4, Ar = C_6H_5, R = $COCH_3$
3i; Q = C_2H_2, Ar = C_6H_5, R = $COOC_2H_5$
3j; Q = C_2H_4, Ar = C_6H_5, R = $COOC_2H_5$
3k; Q = C_2H_2, Ar = 4-$CH_3C_6H_4$, R = $COOC_2H_5$
3l; Q = C_2H_4, Ar = 4-$CH_3C_6H_4$, R = $COOC_2H_5$
3m; Q = C_2H_2, Ar = R = C_6H_5
3n; Q = C_2H_4, Ar = R = C_6H_5

SCHEME 1 Formation of Spirodibenzo[a, d]cycloheptene-5,2′-[1,3,4]thiadiazoles.

The structures of the products **3m,n** were established by elemental analyses and spectral data (^{1}H NMR, MS). ^{1}H NMR spectrum of **3m** showed 6.95 (2H, d, $J = 12$ Hz, 10-CH and 11-CH). The mass spectrum of **3m** showed the prominent ion peak at m/z 416 (M^+, 17). ^{1}H NMR spectrum of **3n** showed 3.38 (4H, m, 10-CH_2 and 11-CH_2). Furthermore, ^{13}C NMR signals at 95.00 (C-5) and 157.65 (C-5′) were compatible with **3n**. The mass spectrum of **3n** showed the prominent ion peak at m/z 418 (M^+, 15)

2.2 *Pharmacological screening*

Anti-inflammatory activity was studied using Carrageenin induced paw edema in rats. The inhibition of edema was evaluated by the comparison of paw volume measured with a plethysmometer, immediately before and 3 h after the injection of carrageenin. Obtained data are given as an arithmetical means of measurements (table 1). Indomethacin was used as a reference drugs. Compounds **3m,n** possess the less anti-inflammatory activity comparable with that of Indomethacin. **3a–h** possess the good anti-inflammatory activity. Compounds **3i–l** showed that, excellent activity compared to the Indomethacin. However, the presence of spiro thiadiazole ring has increased the activity in all cases. The influence of acetyl group at position 2′ in the thiadiazole ring found to be less active compare to ester group at position 2′

Table 1. Pharmacological data of synthesized [1,3,4]thiadiazole derivatives.

Compound	Analgesic activity % protection	Anti-inflammatory activity oedema % Inhibition	Ulcerogenic score
3a	46*	48*	0
3b	42*	46*	0
3c	48*	49*	2
3d	44*	47*	2
3e	40*	44*	4
3f	38*	40*	4
3g	42*	43*	0
3h	40*	43*	0
3i	60*	62*	2
3j	58*	61*	2
3k	62*	63*	4
3l	59*	62*	4
3m	31*	34*	2
3n	30	32*	2
Indomethacin	55*	62*	278*

* $P < 0.05$.

in the thiadiazole ring. The synthesized compounds **3i–l** showed excellent activity indicating that they are more potent compare to the other synthesized compounds (table 1).

3. Experimental

3.1 *Synthesis*

Melting points were determined on open glass capillaries using Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. Microanalyses were performed with all final compounds on Elementar-Vario EL, Microanalytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt. IR spectra were obtained with Brucker-Vector 22 for KBr wafers. (Micro-analytical Center of Cairo University). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in $CDCl_3$ as solvent, ^{13}C spectra were run at 75 MHz in $CDCl_3$ as solvent (Cairo University, Faculty of Science). Splitting patterns were designed as follow: s singlet; d doublet; t triplet; m multiplet. Mass spectra were recorded on Schimadzu GCMS-QP 1000EX (EI, 70 eV) spectrometer (Micro-analytical Center of Cairo University). Compounds **1a,b** [28], **2–8** [29–31] were prepared according to the literature.

3.1.1 Reaction of 1a,b with 2. The appropriate hydrazonoyl chloride **2** (2 mmol) was added to a solution of thiooxo derivative **1a** or **1b** (2 mmol) in dry benzene (20 ml) containing 1 ml TEA. The reaction mixture was heated under reflux for 6 h. The formed solid was removed by filtration and the filtrate was evaporated under reduced pressure till dryness. The residue was treated with ethanol to give the corresponding 1,3,4-thiadiazole products **3a–n**, respectively.

3.1.2 5′-Acetyl-3′-(4-methylphenyl)-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3a). From **1a** and **2a**, yield 56% as yellow crystals from ethanol; m.p. 251–252 °C. IR: υ_{CO} 1700 cm^{-1}; ^{1}H NMR: δ 2.45 (3H, s, CH_3), 2.61 (3H, s, CH_3CO), 6.94 (2H, d,

$J = 12$ Hz, 10-CH and 11-CH), 7.15–7.42 (12H, m, ArH); ^{13}C NMR: δ 25.85 (CH_3), 28.37 CH_3CO), 95.14 (C-5), 117.85, 118.92 (C-10 and C-11), 122.31, 123.40, 126.33, 128.00, 128.21, 128.34, 128.50, 128.71, 129.33, 129.52, 130.21, 130.43, 131.85, 134.66, 138.15, 141.63, 153.65 (Ar−C), 157.72 (C-5′), 190.85 (CO); MS: m/z (%): 396 (M^+, 20), 353 (18), 295 (45), 280 (25), 204 (60), 178 (100), 151 (40). Found: C, 75.35; H, 5.01; N, 6.85; S, 7.90; calcd for $C_{25}H_{20}N_2OS$ (396.49): C, 75.72; H, 5.08; N, 7.06; S, 8.08%.

3.1.3 5′-Acetyl-3′-(4-methylphenyl)-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3b). From **1b** and **2a**, yield 55% as yellow crystals from ethanol; m.p. 225–256 °C. IR: υ_{CO} 1701 cm^{-1}; ^{1}H NMR: δ 2.45 (3H, s, CH_3), 2.61 (3H, s, CH_3CO), 3.25 (4H, m, 10-CH_2 and 11-CH_2), 7.13–7.41 (12H, m, ArH); MS: m/z (%): 398 (M^+, 23), 355 (16), 297 (55), 282 (24), 206 (70), 180 (100), 153 (43). Found: C, 75.35; H, 5.48; N, 6.88; S, 7.87; calcd for $C_{25}H_{22}N_2OS$ (398.52): C, 75.34; H, 5.56; N, 7.03; S, 8.04%.

3.1.4 5′-Acetyl-3′-(4-chlorophenyl)-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3c). From **1a** and **2b**, yield 79% as yellow crystals from ethanol; m.p. 234–236 °C. IR: υ_{CO} 1701 cm^{-1}; ^{1}H NMR: δ 2.55 (3H, s, CH_3CO), 6.85 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.10–7.45 (12H, m, ArH); MS: m/z (%): 416 (M^+, 18), 373 (17), 315 (50), 277 (19), 273 (72), 233 (18), 222 (43), 204 (58), 189 (23), 178 (100), 151 (43). Found: C, 68.93; H, 4.00; N, 6.60; S, 7.50; calcd for $C_{25}H_{17}ClN_2OS$ (416.91): C, 69.13; H, 4.11; N, 6.72; S, 7.68%.

3.1.5 5′-Acetyl-3′-(4-chlorophenyl)-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3d). From **1b** and **2b**, yield 75% as yellow crystals from ethanol; m.p. 204–206 °C. IR: υ_{CO} 1698 cm^{-1}; ^{1}H NMR: δ 2.50 (3H, s, CH_3CO), 3.30 (4H, m, 10-CH_2 and 11-CH_2), 7.15–7.45 (12H, m, ArH); MS: m/z (%): 418 (M^+, 23), 375 (16), 317 (55), 279 (24), 275 (73), 235 (16), 224 (45), 206 (70), 191 (27), 180 (100), 153 (41). Found: C, 68.63; H, 4.50; N, 6.55; S, 7.45; calcd for $C_{24}H_{19}ClN_2OS$ (418.92): C, 68.80; H, 4.57; N, 6.72; S, 7.65%.

3.1.6 5′-Acetyl-3′-(4-nitrophenyl)-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3e). From **1a** and **2c**, yield 65% as yellow crystals from ethanol; m.p. 269–271 °C. IR: υ_{CO} 1703 cm^{-1}; ^{1}H NMR: δ 2.60 (3H, s, CH_3CO), 6.95 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.25–7.50 (12 H, m, ArH); MS: m/z (%): 427 (M^+, 20), 384 (30), 326 (49), 278 (21), 273 (69), 234 (16), 222 (54), 204 (25), 189 (27), 178 (100), 152 (12). Found: C, 67.32; H, 3.89; N, 9.55; S, 7.31; calcd for $C_{24}H_{17}N_3O_3S$ (427.46): C, 67.43; H, 4.00; N, 9.83; S, 7.50%.

3.1.7 5′-Acetyl-3′-(4-nitrophenyl)-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3f). From **1b** and **2c**, yield 65% as yellow crystals from ethanol; m.p. 219–220 °C. IR: υ_{CO} 1705 cm^{-1}; ^{1}H NMR: δ 2.60 (3H, s, CH_3CO), 3.35 (4H, m, 10-CH_2 and 11-CH_2), 7.15–7.45 (12H, m, ArH); MS: m/z (%): 429 (M^+, 18), 386 (26), 328 (50), 280 (24), 275 (65), 236 (16), 224 (45), 206 (30), 191 (27), 180 (100), 153 (12). Found: C, 66.95; H, 4.43; N, 9.72; S, 7.32; calcd for $C_{24}H_{19}N_3O_3S$ (429.47): C, 67.11; H, 4.45; N, 9.78; S, 7.46%.

3.1.8 5′-Acetyl-3′-phenyl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4] thiadiazole (3g). From **1a** and **2d**, yield 64% as yellow crystals from ethanol; m.p. 217–219 °C. IR: υ_{CO} 1695 cm^{-1}; ^{1}H NMR: δ 2.55 (3H, s, CH_3CO), 6.92 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.15–7.48 (13H, m, ArH); MS: m/z (%): 382 (M^+, 14), 339 (15), 281 (50), 273 (40), 222 (20), 204 (22), 189 (14), 178 (56), 152 (12), 129 (20), 117 (19), 111 (13), 97 (30), 83 (43), 72 (71), 56 (100). Found: C, 75.25; H, 4.64; N, 7.19; S, 8.15; calcd for $C_{24}H_{18}N_2OS$ (382.46): C, 75.36; H, 4.74; N, 7.32; S, 8.38%.

3.1.9 5′-Acetyl-3′-phenyl-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3h). From **1b** and **2d**, yield 65% as yellow crystals from ethanol; m.p. 201–203 °C. IR: υ_{CO} 1692 cm^{-1}; ^{1}H NMR: δ 2.58 (3H, s, CH_3CO), 3.38 (4H, m, 10-CH_2 and 11-CH_2), 7.15–7.45 (13H, m, ArH); MS: m/z (%): 384 (M^+, 18), 341 (26), 283 (24), 275 (45), 224 (25), 206 (18), 191 (27), 180 (57), 153 (12), 129 (19), 117 (17), 111 (13), 97 (33), 83 (41), 72 (71), 56 (100). Found: C, 74.75; H, 5.15; N, 7.03; S, 8.15; calcd for $C_{24}H_{20}N_2OS$ (384.48): C, 74.96; H, 5.24; N, 7.28; S, 8.33%.

3.1.10 5′-Carboethoxy-3′-phenyl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4] thiadiazole (3i). From **1a** and **2e**, yield 79% as yellow crystals from ethanol; m.p. 165–168 °C. IR: υ_{CO} 1685 cm^{-1}; ^{1}H NMR: δ 1.35 (3H, t, $J = 7.0$ Hz, CH_3CH_2), 4.30 (2H, q, $J = 7.0$ Hz, CH_3CH_2), 6.90 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.20–7.50 (13H, m, ArH); MS: m/z (%): 412 (M^+, 25), 383 (15), 367 (48), 339 (70), 281 (50), 273 (60), 222 (30), 204 (35), 189 (14), 178 (100), 152 (12). Found: C, 72.67; H, 4.77; N, 6.68; S, 7.58; calcd for $C_{25}H_{20}N_2O_2S$ (412.49): C, 72.78; H, 4.88; N, 6.79; S, 7.77%.

3.1.11 5′-Carboethoxy-3′-phenyl-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3j). From **1b** and **2e**, yield 75% as yellow crystals from ethanol; m.p. 145–146 °C. IR: υ_{CO} 1687 cm^{-1}; ^{1}H NMR: δ 1.35 (3H, t, $J = 7.0$ Hz, CH_3CH_2), 3.38 (4H, m, 10-CH_2 and 11-CH_2), 4.30 (2H, q, $J = 7.0$ Hz, CH_3CH_2), 7.20–7.50 (13 H, m, ArH); MS: m/z (%): 414 (M^+, 15), 385 (18), 369 (48), 341 (74), 283 (50), 275 (40), 224 (60), 206 (75), 191 (18), 180 (100), 152 (10). Found: C, 72.27; H, 5.31; N, 6.68; S, 7.58; calcd for $C_{25}H_{22}N_2O_2S$ (414.51): C, 72.43; H, 5.35; N, 6.75; S, 7.73%.

3.1.12 5′-Carboethoxy-3′-(4-methylphenyl)-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3k). From **1a** and **2f**, yield 73% as yellow crystals from ethanol; m.p. 274–276 °C. IR: υ_{CO} 1687 cm^{-1}; ^{1}H NMR: δ 1.25 (3H, t, $J = 7.0$ Hz, CH_3CH_2), 2.30 (3H, s, CH_3), 4.35 (2H, q, $J = 7.0$ Hz, CH_3CH_2), 6.95 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.20–7.50 (13H, m, ArH); MS: m/z (%): 426 (M^+, 35), 397 (15), 381 (38), 353 (72), 339 (35), 281 (50), 273 (65), 222 (20), 204 (45), 189 (12), 178 (100), 152 (15). Found: C, 72.97; H, 5.00; N, 6.35; S, 7.25; calcd for $C_{26}H_{22}N_2O_2S$ (426.52): C, 73.21; H, 5.18; N, 6.56; S, 7.51%.

3.1.13 5′-Carboethoxy-3′-(4-methylphenyl)-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]-cycloheptene-5,2′-[1,3,4]thiadiazole (3l). From **1b** and **2f**, yield 75% as yellow crystals from ethanol; m.p. 245–248 °C. IR: υ_{CO} 1690 cm^{-1}; ^{1}H NMR: δ 1.35 (3H, t, $J = 7.0$ Hz, CH_3CH_2), 2.30 (3H, s, CH_3), 3.38 (4H, m, 10-CH_2 and 11-CH_2), 4.30 (2H, q, $J = 7.0$ Hz, CH_3CH_2), 7.20–7.50 (13H, m, ArH); MS: m/z (%): 428 (M^+, 15), 399 (18), 383 (48), 355 (74), 341 (48), 283 (56), 275 (40), 224 (60), 206 (74), 191 (20), 180 (100), 152 (10). Found:

C, 72.67; H, 5.351; N, 6.38; S, 7.28; calcd for $C_{26}H_{24}N_2O_2S$ (428.53): C, 72.86; H, 5.64; N, 6.53; S, 7.48%.

3.1.14 5′,3′-Diphenyl-5*H*,3′*H*-spirodibenzo[*a*,*d*]cycloheptene-5,2′-[1,3,4]thiadiazole (3m). From **1a** and **2g**, yield 50% as yellow crystals from ethanol; m.p. 180–182 °C. ^{1}H NMR: δ 6.95 (2H, d, $J = 12$ Hz, 10-CH and 11-CH), 7.09–7.54 (18H, m, ArH); MS: m/z (%): 416 (M^+, 17), 307 (10), 280 (6), 221 (5), 204 (47), 194 (32), 178 (11), 152 (4), 91 (100). Found: C, 80.45; H, 4.70; N, 6.35; S, 7.35; calcd for $C_{28}H_{20}N_2S$ (416.46): C, 80.74; H, 4.84; N, 6.72; S, 7.69%.

3.1.15 5′,3′-Diphenyl-10,11-dihydro-5*H*,3′*H*-spirodibenzo[*a*,*d*]-cycloheptene-5,2′-[1,3,4]thiadiazole (3n). From **1b** and **2g**, yield 50% as yellow crystals from ethanol; m.p. 165–166 °C. ^{1}H NMR: δ 3.38 (4H, m, 10-CH_2 and 11-CH_2), 7.10–7.55 (18H, m, ArH); ^{13}C NMR: δ 28.15, 28.21 (C-10 and C-11), 95.00 (C-5), 122.30, 123.41, 126.35, 128.01, 128.25, 128.34, 128.53, 128.70, 129.32, 130.25, 130.45, 131.81, 134.63, 138.15, 141.65, 144.19, 153.62 (Ar−C), 157.65 (C-5′); MS: m/z (%): 418 (M^+, 15), 309 (18), 282 (8), 223 (6), 206 (44), 191 (20), 180 (10), 152 (10), 91 (100). Found: C, 80.15; H, 5.09; N, 6.38; S, 7.48; calcd for $C_{28}H_{22}N_2S$ (418.54): C, 80.34; H, 5.29; N, 6.69; S, 7.65%.

3.2 *Pharmacology*

3.2.1 Materials and methods. Materials: The new synthesized 1,3,4-thiadiazole derivatives **3a–n** soluble in DMSO (Dimethylsulphoxide), administered intraperitonally (i.p.) in dose of (5 mg/kg b.wt.).

Animals: Both mice and rats used were Wister albino of either sex, produced from (National Research Centre, Giza, Egypt), 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 water. The data for activity and toxicity were evaluated statistically using Student's t-test. A level of $P < 0.05$ was adopted for the test of significance.

3.2.2 Carrageenin test. Carrageenin-induced hind-paw edema in rats was produced by the method of Winter *et al.* [32]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the right hind paw 1 hour after the administration of the test compound. Control animals received only Dimethylsulphoxide solution. Right hind-paw volume was measured with Plethysmometer 7150, (Ugo Basile, Italy), immediately before and 3 hours after the carrageenin injection. The increase of results was matched with that of control rats. Each experiment was made with five groups of rats, 6 animals each (the 1st one was control).

3.2.3 Analgesic activity. The analgesic activity was determined in vivo by using abdominal constriction test induced by acetic acid 0.6% (0.1 ml/10 g) in mice [33]. Albino mice of both sexes (18–22 gm) were used. Compounds were administered i.p (5 mg/Kg). Indomethacin (10 mg/kg) was used as the standard drug under the same conditions.

Acetic acid solution was administered i.p. one hour after administration of the test compounds. Ten minutes after i.p. injection of the acetic acid solution, the number of constrictions per animal was recorded for 20 min. Control animals received on equal volume of vehicle.

Analgesic activity was expressed as percentage of inhibition of constrictions when compared with the vehicle control group.

3.2.4 Ulcerogenic activity. Compounds showed low or no harmful effects on the stomach at the tested dose, when administered twice at a 2 h interval in fasted rats. Indomethacin, at lower doses, produced serious gastric ulcers in all animals [34, 35].

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