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Synthesis of substituted spiro-thiadiazoles via reaction between cyclo-alkylidenehydrazinecarbothioamides and 2,3-diphenyl-cycloprop-2-enone

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Abstract

Substituted spiro thiadiazoles, synthesized by reacting cycloalkylidene-hydrazinecarbothioamides with 2,3-diphenylcycloprop-2-enone in ethanol under stirring and gentle reflux, were thoroughly characterized. Their structures were elucidated using mass spectrometry, IR, and NMR spectroscopy, alongside elemental analysis. Furthermore, X-ray structure analysis provided definitive confirmation for certain compounds. The underlying reaction mechanism leading to the formation of these spiro thiadiazoles was also investigated and discussed.

1. Introduction

Cyclopropenones are commonly employed as electrophilic trapping agents.[1] Owing to the high strain[2] of cyclopropenones, it easily participates in cycloaddition,[3] ring opening,[4] and ring enlargement[5] reactions. Hassan *et al.* reported that a series of thiadiazoles were obtained *via* a catalyst-free reaction between cyclopropenone and alkylidenehydrazine-carbothioamides in dry ethanol.[6] In a different manner, Aly *et al.* reported that the reaction mixture of **cyclopropenone** with ylidene-*N*-phenylhydrazine-carbothioamides in glacial acetic acid at room temperature afforded,2,5,6,7-tetrasubstituted-pyrrolo[2,1-*b*](1,3,5-oxadiazolyl)-2-amines in 60–76% yield[7]. However, substituted thiazinanes were successfully synthesized. It was achieved during the reaction of hydrazinecarbothioamide derivatives with 2,3-diphenylcyclopropenones.[8]

Thiadiazole nucleus is a well-known and one of the most important heterocyclic nuclei, exhibiting various biological activities, such as anti-microbial[9-13], anti-convulsant[14-16], anti-cancer[17,18], anti-viral[19,20], anti-tuberculosis[20,21], anti-inflammatory and analgesic[22-24], diuretic[25], anti-diabetic[26,27],

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anti-depressant[28,29], anti-ulcer[30], anti-leishmanicidal[31,32], anti-influenza[33,34], anti-hypolipidemic, anti-hyperlipidemia[35,36], and anti-hypertensive[37].

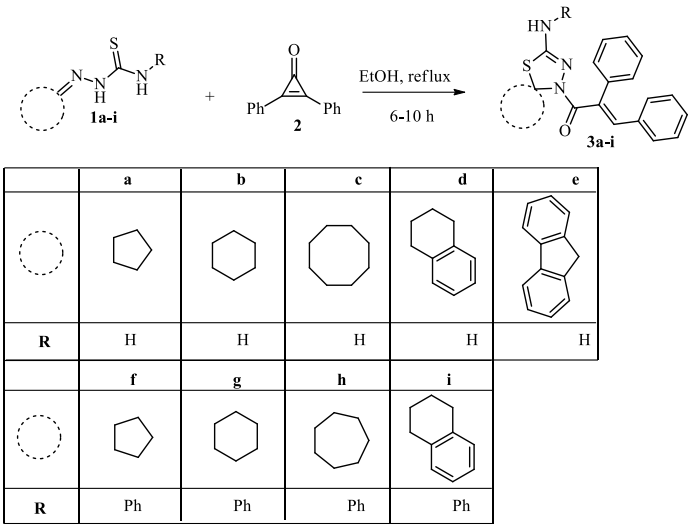
Cunha and Rocha reported that 1,6-diisopropyl-2,7-diphenyl-4-oxaspiro-[2,4]hepta-1,6-dien-5-one was synthesized *via* refluxing 2-isopropyl-3-phenyl-cycloprop-2-en-1-one in dioxane in the presence of copper chloride (CuCl).[38] Spiro heterocyclic compounds were reported during the reaction between substituted cyclopropenones and tri-substituted cyclopropanes in dichloromethane catalyzed by scandium trifluoromethanesulfonate $Sc(OTf)_3$.[39] 1,2-Bis(2-methoxy-5-methylphenyl)-6,7-diphenyl-4-oxaspiro[2,4]hepta-1,6-dien-5-one was obtained *via* the reaction of two derivatives of cyclopropenones together with methyl-*p*-tolylether in the presence of CuBr as a catalyst.[40] Previously, it was also reported that thiazinanones, 2-oxoacenaphthylen-1(2*H*)-ylidene)hydrazineylidene)-5,6-diphenyl-1,3-thiazinan-4-ones were synthesized *via* the reaction of oxoacenaphthylen-hydrazine-carbothioamide derivatives with 2,3-diphenylcycloprop-2-enone in ethanol and catalyzed by triethyl amine[41].

In an attempt to develop effective and safe antibacterial agents, Aly *et al.* synthesized a series of thiazinanones by combining the quinolone scaffold and the 1,3-thiazinan-4-one group by the reaction between ((4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazine-carbothioamides and 2,3-diphenylcycloprop-2-enone in refluxing ethanol in the presence of triethylamine as a catalyst[42].

On the basis of the aforementioned, we encourage carrying out the reaction between cycloalkylidenehydrazinecarbothioamides and 2,3-diphenylcycloprop-2-enone in order to investigate the mechanism and the reactivity of the two starting materials and the type of heterocycles that might be obtained.

2. Results and discussion

In this article, we reported the reaction of cycloalkylidenehydrazinecarbothioamides **1a-i** with 2,3-diphenylcyclopropenones (**2**) in refluxing absolute ethanol for 6-10 h (Scheme 1). From the structural investigation, the IR spectrum of **3a-e** showed the stretching frequency between ν = 3335-3212 cm^{-1} due to NH_2, ν = 2994-2873 cm^{-1} for ali-CH_2. The IR spectra did not reveal any absorptions due to C=S or OH groups. The elemental analysis clearly showed that the products were formed by adding one molecule of **1** to one molecule of **2** without any elimination. The ^{13}C NMR supported the ^{1}H NMR spectroscopic data in elucidation of the structure of compounds **3a-e** (see the experimental section). The ^{1}H NMR spectra of **3a-e** revealed the NH_2 protons together with the aromatic ones. For example, the IR spectrum of compound **3a** showed four characteristic groups NH_2, Ali-CH, carbonyl, and aromatic-CH at υ = 3317, 2958-2876, 1712 (CO), and 1578, respectively. The ^{13}C NMR spectrum showed five distinctive carbon signals of cyclic-CH_2, spiro-C, C=N, and CO at δ = 25.0, 39.4, 88.9,144.9 and 168.0, respectively. The IR spectrum of compound **3e** showed absorptions at υ = 3335 (NH_2), 1708 (CO), and 1594 (Ar-CH). The benzylic-CH appeared in the ^{1}H NMR spectrum as a singlet at δ = 5.23, whereas the NH_2 resonted as a broad singlet at δ = 7.60. The ^{13}C NMR spectrum revealed the spiro-C and C=O carbon signals at δ = 89.7 and 164.6 (see the experimental). Mass spectroscopy revealed the molecular ion peak at *m/z* = 460.



Scheme 1.
Reaction of cycloalkylidenehydrazinecarbothioamides **1a-i** with 2,3-diphenyl-cyclopropenone (**2**); synthesis of substituted spiro thiadiazoles **3a-i**

Moreover, the structure of **3e** and **3f** has been confirmed by a single-crystal X-ray diffraction. Structure analysis (Figures **1**, **2** and supplementary data) confirms the *cissoid* geometry concerning the central C14-C15 double bond (note that the crystallographic numbering does not correspond to the systematic IUPAC numbering rules).

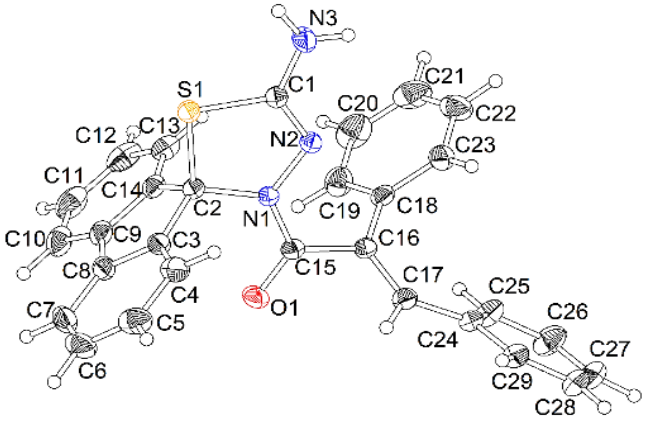


Figure 1. Molecular structure of compound **3e** (ORTEP plot with 50% probability).

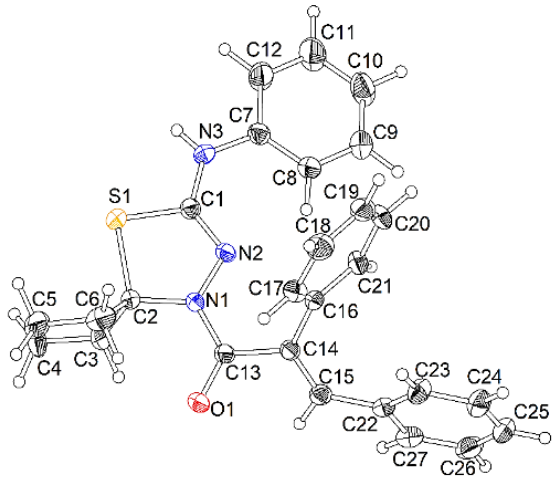
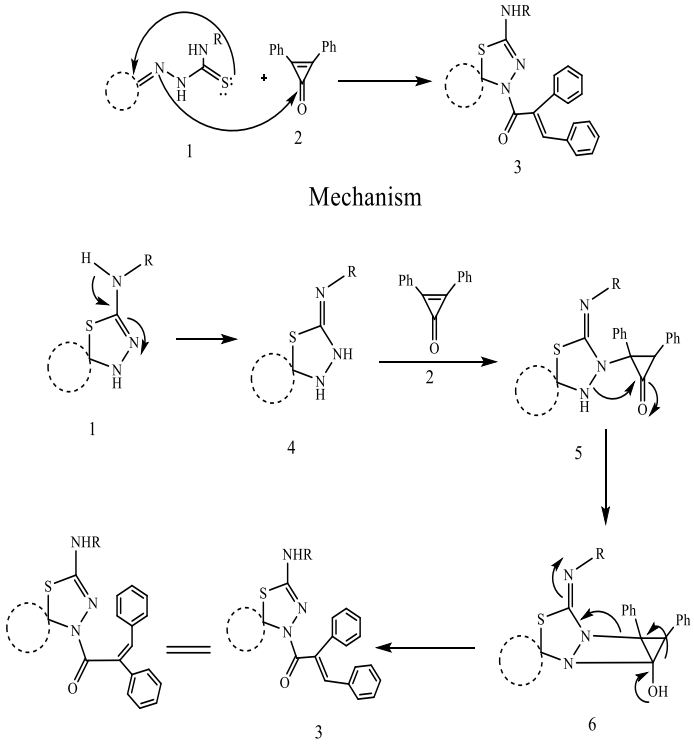


Figure 2. Molecular structure of compound **3f** (ORTEP plot with 50% probability).

The reaction mechanism could be explained as due to an initially internal cyclization by the sulfur lone pair accompanied by amidine-like reaction via nucleophilic attack of the NH-N= group to the electrophilic carbon in compound **2**, and then the intermediate **4a-i** would then be formed (Scheme 2). Subsequently, neutralization would occur to form the corresponding thiadiazoles **3a-i** (Scheme 2).



Scheme 2. Mechanism describes the formation of spiro-diathiazole compounds **3a-i**

3. Experimental

All melting points were determined by using open capillaries on a Gallen Kamp melting point apparatus. Infrared spectra (IR) were performed with Alpha, Bruker instruments with a wavelength from 4000 to 600 cm^{-1} as KBr disks. NMR spectra were recorded on a Bruker AM 400 MHz spectrometer using $CDCl_3$ as a solvent with TMS as the internal standard (δ = 0). The data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, and q = quartet). ^{13}C NMR, TMS (S=O) was used as an internal solvent, and spectra were observed with complete proton decoupling. Mass spectrometers were recorded on a Finnigan MAT instrument (70 ev, EI mode). Elemental analyses for C, H, N, and S were obtained using Elmyer 306.

Starting materials:
substituted cycloalkylidenehydrazinecarbothioamides **1a-i** were prepared according to reported methods.[11,43] The solvent of the reaction was changed to CH_3CN or CH_2Cl_2, CH_3OH, ethyl acetate and tetrahydrofuran. The yields of **3a-i** decreased, and in some cases, such as tetrahydrofuran, only traces of **3a-i** were detected by TLC. On the other hand, increasing one of the reaction partners, such as compound **1** or **2,** led to a significant decrease in the yields.

General procedure for preparation of (*E*)-1-[3-amino-4-thion-1,2-diaza-spiro-2,3-diphenylprop-2-en-1-ones 3a-i
A solution of **1a-i** (1.0 mmol) and cycloprop-2-en-1-one (**2**, 0.21 g, 1.0 mmol) in 30 ml of ethanol as solvent. The reaction mixture was stirred with refluxing for 6-10 h or until the starting material was fully consumed (the reaction was monitored by TLC analyses). The isolated product mixture was filtered, and the precipitate was washed several times with ethanol. The isolated products obtained **3a-i** were recrystallized from suitable solvents.

(*E*)-1-(3-Amino-4-thia-1,2-diazaspiro[4.4]non-2-en-1-yl)-2,3-diphenylprop-2-en-1-one (3a). Colorless crystals (ethanol), m.p. = 178-180°C; IR (KBr): υ = 3317 (NH_2), 2958-2876 (Ali-CH), 1712 (CO), 1578 (Ar-CH); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.52-1.55 (m, 4H, cyclic CH_2), 1.98-2.09 (m, 4H, cyclic-CH_2), 5.93 (s, 1H, benzylic-CH), 6.90-6.93 (m, 2H, Ar-H), 7.00-7.48 (m, 10H, Ar-H and NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.0, 39.4 (cyclic-CH_2), 88.9 (spiro-C), 118.0, 122.6, 127.6, 128.1, 128.4, 129.0, 129.2, 129.6, 131.7 (Ar-CH), 135.9, 136.1 (Ar-C), 144.9 (C=N), 168.0 (CO). Anal. Calcd. For $C_{21}H_{21}N_3OS$: C, 69.39; H, 5.82; N, 11.56; S, 8.82. Found C, 69.44; H, 5.88; N, 11.49; S, 8.76.

(*E*)-1-(3-Amino-4-thia-1,2-diazaspiro[4.5]dec-2-en-1-yl)-2,3-diphenylprop-2-en-1-one (3b). Colorless crystals (methanol), m.p. = 182-184°C; IR (KBr): υ = 3298 (NH_2), 2994-2982 (Ali-CH), 1710 (CO), 1569 (Ar-CH); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.59 (m, 4H, Cyclic CH_2), 1.84-2.09 (m, 6H, cyclic CH_2), 5.23 (s, 1H, benzylic-CH), 6.79-6.93 (m, 2H, Ar-H), 7.01-7.45 (m, 8H, Ar-H), 7.47-7.49 (br, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 24.5, 25.6, 35.8

(cyclic-CH_2), 91.0 (spiro-C), 127.3, 127.6, 127.9, 128.3, 129.1, 129.7, 131.2 (Ar-CH), 136.8, 139.8 (Ar-C), 148.2 (C=N), 168.2 (CO); MS (70 eV, %): *m/z* = 377 (M^+, 61), 207 (100), 179 (92), 154 (24), 136 (18). Anal. Calcd. For $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13; S, 8.49. Found C, 70.08; H, 6.22; N, 11.06; S, 8.41.

(*E*)-1-(3-Amino-4-thia-1,2-diazaspiro[4.4]dodec-2-en-1-yl)-2,3-diphenylprop-2-en-1-one (3c). Colorless crystals (DMF/ethanol), m.p. = 172-174°C; IR (KBr): υ = 3275 (NH_2), 2936-2853 (Ali-CH), 1696 (CO), 1582 (Ar-CH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.41 (m, 2H, cyclic-CH_2) 1.62-1.87 (m, 4H, cyclic CH_2), 1.93-2.69 (m, 8H, cyclic CH_2), 5.86 (s, 1H, benzylic-CH), 6.66-6.97 (m, 2H, Ar-H), 7.50-7.56 (m, 3H, Ar-H), 7.62-7.66 (m, 5H, Ar-H), 7.68-7.70 (br, 2H, NH_2), ^{13}C NMR (101.0 MHz, $CDCl_3$) δ = 21.3, 27.2, 28.8, 39.8 (cyclic-CH_2), 82.6 (spiro-C), 127.2, 128.4, 128.8, 129.3, 129.7, 130.7, 131.4 (Ar-CH), 134.9, 136.2 (Ar-C), 145.5 (C=N), 167.4 (CO). Anal. Calcd. For $C_{24}H_{27}N_3OS$: C, 71.08; H, 6.71; N, 10.36; S, 7.91. Found C, 71.14; H, 6.78; N, 10.30; S, 7.96.

(*E*)-1-(5'-Amino-3,4-dihydro-2*H*,3'*H*-spiro[naphthalene-1,2'-[1,3,4]thiadiazol]-3'-yl)-2,3-diphenylprop-2-en-1-one (3d).

Colorless crystals (ethanol), mp. = 190-192°C; IR (KBr): υ = 3212 (NH_2), 2987-2920 (Ali-CH), 1718 (CO), 1598 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.65 (m, 2H, cyclic CH_2), 1.95-2.08 (m, 2H, cyclic CH_2), 2.52-2.56 (m, 2H, cyclic-CH_2), 5.56 (s, 1H, benzylic-CH), 6.13-6.30 (m, 4H, Ar-H), 6.76-7.01 (m, 2H, Ar-H), 7.15-7.21 (m, 3H, Ar-H), 7.27-7.41 (m, 5H, Ar-H), 7.92 (br, s, 2H, NH_2); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ = 21.4, 25.3, 29.3 (cyclic-CH_2), 86.5 (spiro-C), 124.5, 126.6, 128.1, 128.2, 128.8, 128.9, 129.0, 129.4, 129.6, 129.7, 130.0, (Ar-CH), 130.6, 131.3, 140.1 (Ar-C), 147.8 (C=N), 164.8 (CO). Anal. Calcd. For $C_{26}H_{23}N_3OS$: C, 73.38; H, 5.45; N, 9.87; S, 7.53. Found C, 73.44; H, 5.53; N, 9.81; S, 7.62.

(*E*)-1-(5'-Amino-3'*H*-spiro[fluorene-9,2'-[1,3,4]thiadiazol]-3'-yl)-2,3-diphenylprop-2-en-1-one (3e). Colorless crystals (DMF/ethanol), mp. = 202-204°C; IR (KBr): υ = 3335 (NH_2), 1708 (CO), 1594 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23 (s, 1H, benzylic-CH), 6.93-6.96 (m, 2H, Ar-H), 7.09-7.12 (m, 3H, Ar-H), 7.19-7.23 (m, 2H, Ar-H), 7.27-7.32 (m, 3H, Ar-H), 7.34-7.45 (m, 4H, Ar-H), 7.48-7.58 (m, 4H, Ar-H), 7.60-7.62 (br, 2H, NH_2), ^{13}C NMR (101 MHz, $CDCl_3$): δ = 89.7 (spiro-C), 127.3, 128.0, 128.6, 129.6, 129.7, 130.0 (Ar-CH), 136.5, 139.1, 140.1 (Ar-C), 148.8 (C=N), 164.6 (CO); MS (70 eV, %): *m/z* = 460 (M+1, 92), 459 (M^+, 22), 307 (20), 279 (31), 179 (47), 154 (100), 136 (71). Anal. Calcd. For $C_{29}H_{21}N_3OS$: C, 75.79; H, 4.61; N, 9.14; S, 6.98. Found C, 75.88; H, 4.69; N, 9.23; S, 6.92.

(*E*)-2,3-Diphenyl-1-(3-(phenylamino)-4-thia-1,2-diazaspiro[4.4]non-2-en-1-yl)prop-2-en-1-one (3f). Colorless crystals (DMF/ethanol), mp. = 184-186°C; IR (KBr): υ = 3318 (NH), 2962-2873 (Ali-CH), 1715 (CO), 1584 (Ar-CH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.88 (m, 4H, cyclic CH_2), 1.96-2.24 (m, 4H, cyclic CH_2), 5.95 (s, 1H, benzylic-CH), 6.66-6.90 (m, 2H, Ar-H), 6.96-7.20 (m, 3H, Ar-H), 7.22-7.42 (m, 5H, Ar-H), 7.45-7.52 (m, 5H, Ar-H), 9.12-9.14 (br, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.8, 28.0 (cyclic-CH_2), 86.9 (spiro-C), 127.3, 127.9, 128.4, 129.2, 129.8, 131.0, 131.7 (Ar-CH), 135.2, 137.2, 139.5 (Ar-C), 146.4 (C=N), 164.9 (CO); MS (70 eV, %): *m/z* = 440 (M+1, 26), 439 (M^+, 21), 307 (34), 179 (22), 154 (100), 136 (65). Anal. Calcd. For $C_{27}H_{25}N_3OS$: C, 73.77; H, 5.73; N, 9.56; S, 7.29. Found C, 73.88; H, 5.79; N, 9.51; S, 7.21.

(*E*)-2,3-Diphenyl-1-(3-(phenylamino)-4-thia-1,2-diazaspiro[4.5]dec-2-en-1-yl)prop-2-en-1-one (3g). Colorless crystals (ethanol), m.p. = 208-210°C; IR (KBr): υ = 3263 (NH_2), 2956-2935 (Ali-CH), 1712 (CO), 1614 (Ar-CH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.74 (m, 2H, cyclic CH_2), 1.76-1.90 (m, 4H, cyclic CH_2),1.92-2.34 (m, 4H, cyclic CH_2) 5.85 (s, 1H, benzylic-CH), 6.74-6.84 (m, 2H, Ar-H), 6.94-7.20 (m, 3H, Ar-H), 7.22-7.31 (m, 5H, Ar-H), 7.32-7.54 (m, 5H, Ar-H), 9.21-9.23 (br, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.2, 27.2, 42.2 (cyclic-CH_2), 87.7 (spiro-C), 127.0, 128.0, 128.6, 129.3, 130.0, 130.2, 131.9 (Ar-CH), 134.9, 137.8, 139.7 (Ar-C), 144.7 (C=N), 164.6 (CO); MS (70 eV, %): *m/z* = 454 (M+1, 10), 377 (50), 207 (96), 179 (100), 154 (35), Anal. Calcd. For $C_{28}H_{27}N_3OS$: C, 74.14; H, 6.00; N, 9.26; S, 7.07. Found C, 74.22; H, 6.08; N, 9.18; S, 7.16.

(*E*)-2,3-Diphenyl-1-(3-(phenylamino)-4-thia-1,2-diazaspiro[4.6]undec-2-en-1-yl)prop-2-en-1-one (3h). Colorless crystals (ethanol), m.p. = 198-200°C; IR (KBr): υ = 3271 (NH), 2976-2928 (Ali-CH_2), 1718 (CO), 1590 (Ar-CH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.81 (m, 4H, cyclic CH_2), 1.98-2.19 (m, 4H, cyclic CH_2), 2.33-2.55 (m, 4H, cyclic-CH_2), 5.93 (s, 1H, benzylic-CH), 6.65-6.84 (m, 2H, Ar-H), 6.94-7.21 (m, 3H, Ar-H), 7.24-7.38 (m, 5H, Ar-H), 7.64-7.83 (m, 5H, Ar-H), 9.68 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 24.9, 27.9, 32.4 (cyclic-CH_2), 86.4 (spiro-C), 118.2, 122.7, 125.7, 128.3, 128.6, 129.3, 131.3 (Ar-CH), 136.8, 137.1, 136.5, 140.1 (Ar-C), 147.3 (C=N), 164.4 (CO); MS (70 eV, %): *m/z* = 468 (M+1, 12), 307 (30), 179 (8), 154 (100), 136 (63). Anal. Calcd. For $C_{29}H_{29}N_3OS$: C, 74.49; H, 6.25; N, 8.99; S, 6.86. Found C, 74.54; H, 6.32; N, 8.90; S, 6.78.

(*E*)-2,3-Diphenyl-1-(5'-(phenylamino)-3,4-dihydro-2*H*,3'*H*-spiro[naphthalene-1,2'-[1,3,4]thiadiazol]-3'-yl)prop-2-en-1-one (3i). Colorless crystals (DMF/ethanol), m.p. = 222-224°C; IR (KBr): υ = 3265 (NH), 2986-2921 (Ali-CH_2), 1710 (CO), 1585 (Ar-CH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.87 (m, 2H, cyclic CH_2), 1.91-2.17 (m, 2H, cyclic CH_2), 2.52-2.55 (m, 2H, cyclic-CH_2), 5.96 (s, 1H, benzylic-CH), 7.03-7.14 (m, 4H, Ar-H), 7.15-7.19 (m, 5H, Ar-H), 7.20-7.28 (m, 5H, Ar-H), 7.29-7.38 (m, 5H, Ar-H), 10.05 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 21.7, 28.9, 36.0 (cyclic-CH_2), 85.1 (spiro-C), 118.1, 122.7, 126.6, 127.6, 128.0, 128.3, 128.9, 129.0, 129.3, 129.7, 132.2 (Ar-CH), 135.9, 136.2, 136.5, 138.7, 139.4 (Ar-C), 143.9 (C=N), 167.0 (CO); MS (70 eV, %): *m/z* = 500 (M^+, 18), 307 (31), 207 (47), 179 (69), 154 (100), 136 (66). Anal. Calcd. For $C_{32}H_{27}N_3OS$: C, 76.62; H, 5.43; N, 8.38; S, 6.39. Found C, 76.68; H, 5.52; N, 8.30; S, 6.46.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data set generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Körner Rolf; Rominger, Frank, O.G. Copper(I)-Promoted Synthesis of 4-Oxaspiro[2.4]Hepta-1,6-Dien-5-Ones from Cyclopropenones. *Synthesis (Stuttg).* **2009**, *2009*, 3259–3262, doi:10.1055/s-0029-1216934.
2. Kascheres, A.; Joussef, A.C.; Duarte, H.C. A Route to 2,2-Dihydro-5-Imino-1,2-Oxaphosphol-3-Enes. *Tetrahedron Lett.* **1983**, *24*, 1837–1840, doi:10.1016/S0040-4039(00)81785-2.
3. Wender, P.A.; Paxton, T.J.; Williams, T.J. Cyclopentadienone Synthesis by Rhodium(I)-Catalyzed [3 + 2] Cycloaddition Reactions of Cyclopropenones and Alkynes. *J. Am. Chem. Soc.* **2006**, *128*, 14814–14815, doi:10.1021/ja065868p.
4. Venneri, P.C.; Warkentin, J. Reaction of Dimethoxycarbene with Strained Cyclic Carbonyl Compounds. *Can. J. Chem.* **2000**, *78*, 1194–1203, doi:10.1139/v00-118.
5. Noyori, R.; Umeda, I.; Takaya, H. Nickel(0)-Catalyzed Dimerization Of Cyclopropenones. *Chem. Lett.* **1972**, *1*, 1189–1190, doi:10.1246/cl.1972.1189.
6. Hassan, A.A.; Abdel-Latif, F.F.; Nour El-Din, A.M.; Mostafa, S.M.; Nieger, M.; Bräse, S. Synthesis of (E)-2,5-Disubstituted 1,3,4-Thiadiazolyl-2,3-Diphenylpropenones from Alkenylidene-Hydrazinecarbothioamides. *Tetrahedron* **2012**, *68*, 8487–8492, doi.org/10.1016/j.tet.2012.07.063.
7. Aly, A.A.; Hassan, A.A.; Ameen, M.A.; Brown, A.B. Chemistry of Cyclopropenones: Synthesis of New Pyrrolo[2,1-b]-1,3,4-Oxadiazoles. *Tetrahedron Lett.* **2008**, *49*, 4060–4062, doi:10.1016/j.tetlet.2008.04.066.
8. Hassan, A.A.; Mohamed, N.K.; Aly, A.A.; Tawfeek, H.N.; Hopf, H.; Bräse, S.; Nieger, M. Convenient Diastereoselective Synthesis of Annulated 3-Substituted-(5S*,6S*,Z)-2-(2-(2,4-Dinitrophenyl)Hydrazono)-5,6-Diphenyl-1,3-Thiazinan-4-Ones. *Mol. Divers.* **2019**, *23*, 821–828, doi:10.1007/s11030-018-09912-5.
9. Serban, G.; Stanasel, O; Bota, E.S.S. 2-Amino-1,3,4-Thiadiazole as a Potential Scaffold for Promising Antimicrobial Agents. *Drug Des. Devel. Ther.* **2018**, *12*, 1545–1566.
10. Omar, A.-M.M.E.; Aboulwafa, O.M. Synthesis and in Vitro Antimicrobial and Antifungal Properties of Some Novel 1,3,4-thiadiazole and s -triazolo[3,4- b][1,3,4]Thiadiazole Derivatives. *J. Heterocycl. Chem.* **1986**, *23*, 1339–1341, doi:10.1002/jhet.5570230514.
11. Anthwal, T.; Singh, H.; Nain, S. 1,3,4-Thiadiazole Scaffold: Anti-Microbial Agents. *Pharm. Chem. J.* **2022**, *55*, 1345–1358, doi:10.1007/s11094-022-02580-8.
12. Zhang, R.; Li, B.; Chi, C.; Liu, Y.; Liu, X.; Li, J.; Li, W.; Chen, B. Design, Synthesis, Antiproliferative and Antimicrobial Evaluation of a New Class of Disulfides Containing 1,3,4-Thiadiazole Units. *Med. Chem. Res.* **2022**, *31*, 1571–1583, doi:10.1007/s00044-022-02937-4.
13. Sassiver, M.L.; Shepherd, R.G. 2-Sulfanilamido-5-Methoxy-1,3,4-Thiadiazole and Related Compounds. *J. Med. Chem.* **1966**, *9*, 541–545, doi:10.1021/jm00322a022.
14. Sharma, B.; Verma, A.; Prajapati, S.; Sharma, U.K. Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Thiadiazoles. *Int. J. Med. Chem.* **2013**, *2013*, 1–16, doi:10.1155/2013/348948.
15. Raj, V.; Rai, A.; Singh, M.; Kumar, A.; Kumar, V.; Sharma, S.K. Recent Update on 1, 3, 4-Thiadiazole Derivatives: As Anticonvulsant Agents. *EC Pharm. Sci.* **2015**, *2*, 202–229.
16. Anthwal, T.; Nain, S. 1,3,4-Thiadiazole Scaffold: As Anti-Epileptic Agents. *Front. Chem.* **2022**, *9*, 671212, doi:10.3389/fchem.2021.671212.
17. Szeliga, M. Thiadiazole Derivatives as Anticancer Agents. *Pharmacol. Reports* **2020**, *72*, 1079–1100, doi:10.1007/s43440-020-00154-7.
18. Aliabadi, A. 1,3,4-Thiadiazole Based Anticancer Agents. *Anticancer. Agents Med. Chem.* **2016**, *16*, 1301–1314, doi:10.2174/1871520616666160628100936.
19. Serban, G. Synthetic Compounds with 2-Amino-1,3,4-Thiadiazole Moiety Against Viral Infections. *Molecules* **2020**, *25*, 942, doi:10.3390/molecules25040942.

20. Tatar, E. Synthesis and Biological Evaluation of Some New 1,3,4-Thiadiazole and 1,2,4-Triazole Derivatives from L-Methionine as Antituberculosis and Antiviral Agents. *MARMARA Pharm. J.* **2015**, *2*, 88–88, doi:10.12991/mpj.2015199639.
21. Oruç, E.E.; Rollas, S.; Kandemirli, F.; Shvets, N.; Dimoglo, A.S. 1,3,4-Thiadiazole Derivatives. Synthesis, Structure Elucidation, and Structure−Antituberculosis Activity Relationship Investigation. *J. Med. Chem.* **2004**, *47*, 6760–6767, doi:10.1021/jm0495632.
22. M. H. Shkair, A.; K. Shakya, A.; M. Raghavendra, N.; R. Naik, R. Molecular Modeling, Synthesis and Pharmacological Evaluation of 1,3,4- Thiadiazoles as Anti-Inflammatory and Analgesic Agents. *Med. Chem.* **2016**, *12*, 90–100, doi:10.2174/1573406411666150608102236.
23. Hafez, H.N.; Hegab, M.I.; Ahmed-Farag, I.S.; El-Gazzar, A.B.A. A Facile Regioselective Synthesis of Novel Spiro-Thioxanthene and Spiro-Xanthene-9′,2-[1,3,4]Thiadiazole Derivatives as Potential Analgesic and Anti-Inflammatory Agents. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4538–4543, doi:10.1016/j.bmcl.2008.07.042.
24. A. Muhammad, Z.; S. Masaret, G.; M. Amin, M.; A. Abdallah, M.; A. Farghaly, T. Anti-Inflammatory, Analgesic and Anti-Ulcerogenic Activities of Novel Bis-Thiadiazoles, Bis-Thiazoles and Bis-Formazanes. *Med. Chem.* **2017**, *13*, 226–238, doi:10.2174/1573406412666160920091146.
25. Ghosh, S.; Malik, S.; Jain, B.; Ganesh, N. Synthesis, Characterization and Biological Studies of Zn(II) Complex of Schiff Base Derived from 5-Acetazolamido-1,3,4-Thiadiazole-2-Sulphonamide, A Diuretic Drug. *Asian J. Exp. Sci* **2009**, *23*, 189–192.
26. Datar, P.A. Design and Synthesis of Thiadiazole Derivatives as Antidiabetic Agents. *Med. Chem.* **2014**, *4*, 390–399, doi:10.4172/2161-0444.1000170.
27. Datar, P.; Deokule, T. Development of Thiadiazole as an Antidiabetic Agent- A Review. *Mini-Reviews Med. Chem.* **2014**, *14*, 136–153, doi:10.2174/1389557513666140103102447.
28. Yusuf, M.; Khan, R.A.; Ahmed, B. Syntheses and Anti-Depressant Activity of 5-Amino-1, 3, 4-Thiadiazole-2-Thiol Imines and Thiobenzyl Derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 8029–8034, doi:10.1016/j.bmc.2008.07.056.
29. Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. Synthesis of 2-Amino-5-Sulfanyl-1,3,4-Thiadiazole Derivatives and Evaluation of Their Antidepressant and Anxiolytic Activity. *J. Med. Chem.* **2001**, *44*, 931–936, doi:10.1021/jm001027w.
30. Gomha, S.M.; Edress, M.M.; Muhammad, Z.A.; Gaber, H.M.; Amin, M.M.; Matar, I.K. Synthesis Under Microwave Irradiation and Molecular Docking of Some Novel Bioactive Thiadiazoles. *Mini-Reviews Med. Chem.* **2019**, *19*, 437–447, doi:10.2174/1389557518666180329122317.
31. Tahghighi, A.; Babalouei, F. Thiadiazoles: The Appropriate Pharmacological Scaffolds with Leishmanicidal and Antimalarial Activities: A Review. *Iran. J. Basic Med. Sci.* **2017**, *20*, 613–622, doi:10.22038/ijbms.2017.8828.
32. Bekhit, A.A.; Hassan, A.M.M.; Abd El Razik, H.A.; El-Miligy, M.M.M.; El-Agroudy, E.J.; Bekhit, A.E.-D.A. New Heterocyclic Hybrids of Pyrazole and Its Bioisosteres: Design, Synthesis and Biological Evaluation as Dual Acting Antimalarial-Antileishmanial Agents. *Eur. J. Med. Chem.* **2015**, *94*, 30–44, doi:10.1016/j.ejmech.2015.02.038.
33. Dong, J.; Pei, Q.; Wang, P.; Ma, Q.; Hu, W. Optimized POCl3-Assisted Synthesis of 2-Amino-1,3,4-Thiadiazole/1,3,4-Oxadiazole Derivatives as Anti-Influenza Agents. *Arab. J. Chem.* **2022**, *15*, 103712, doi:10.1016/j.arabjc.2022.103712.
34. Tawfik, S.S.; Farahat, A.A.; A.-A El-Sayed, M.; Tantawy, A.S.; Bagato, O.; Ali, M.A. Synthesis and Anti-Influenza Activity of Novel Thiadiazole, Oxadiazole and Triazole Based Scaffolds. *Lett. Drug Des. Discov.* **2018**, *15*, 363–374, doi:10.2174/1570180814666170512122832.
35. Hamadneh, L.A.; Sabbah, D.A.; Hikmat, S.J.; Al-Samad, L.A.; Hasan, M.; Al-Qirim, T.M.; Hamadneh, I.M.; Al-Dujaili, A.H. Hypolipidemic Effect of Novel 2,5-Bis(4-Hydroxybenzylidenamino)-1,3,4-Thiadiazole as Potential Peroxisome Proliferation-Activated Receptor-α Agonist in Acute Hyperlipidemic Rat Model. *Mol. Cell. Biochem.* **2019**, *458*, 39–47, doi:10.1007/s11010-019-03528-5.
36. Paul, J.; Beena, T.; Neethu, S. Design, Synthesis and Biological Evaluation of Novel Thiadiazole Derivatives as Antihyperlipidemic Agents. *Int. J. Pharm. Chem. Anal.* **2020**, *5*, 16–23, doi:10.18231/2394-2797.2018.0004.
37. Cunha, S.; Rocha, Z.N. da Reatividade de Ciclopropenonas Frente a Nucleófilos e Sua Correlação Com Potenciais de Redução Em Meio Aprótico. *Quim. Nova* **2008**, *31*, 788–792, doi:10.1590/S0100-40422008000400015.
38. Rivero, A.R.; Fernández, I.; Ramírez de Arellano, C.; Sierra, M.A. Synthesis of Oxaspiranic Compounds through [3 + 2] Annulation of Cyclopropenones and Donor–Acceptor Cyclopropanes. *J. Org. Chem.* **2015**, *80*, 1207–1213, doi:10.1021/jo502292y.
39. Syu, J.-R.; Lin, C.-H.; Kuo, C.-W.; Yang, D.-Y. Synthesis of Benzofuran-Containing Spirolactones from Diarylcyclopropenones. *Tetrahedron Lett.* **2014**, *55*, 1207–1211, doi:10.1016/j.tetlet.2013.12.115.
40. Hassan, A.; Mohamed, S.; Nasr, M.K.; El-Shaieb, K.; Abdel-Aziz, A.; Mague, J.; Akkurt, M. The

Behavior of (Cyclic-Alkylidene)Hydrazinecarbothioamides in Cyclization with Dimethyl Acetylenedicarboxylate: (Cyclic-Alkylidene)Hydrazinecarbothioamides in Cyclization with Dimethyl Acetylenedicarboxylate. *J. Heterocycl. Chem.* **2017**, *54*, doi:10.1002/jhet.2803.

41. Aly, A.A.; Sadek, K.U.; Alshammari, M.B.; Ahmad, A.; Aziz, E.A.; Brown, A.B.; Mohamed, A.H. Facile Synthesis of New Thiazinanones Derived by Acenaphythylenone. *J. Sulfur Chem.* **2024**, *45*, 173–183, doi:10.1080/17415993.2023.2281595.
42. Mohamed, A.H.; Mostafa, S.M.; Aly, A.A.; Hassan, A.A.; Osman, E.M.; Nayl, A.A.; Brown, A.B.; Abdelhafez, E.M.N. Novel Quinoline/Thiazinan-4-One Hybrids; Design, Synthesis, and Molecular Docking Studies as Potential Anti-Bacterial Candidates against MRSA. *RSC Adv.* **2023**, *13*, 14631–14640, doi:10.1039/D3RA01721D.
43. Hassan, A.A.; Mohamed, N.K.; Aly, A.A.; Ramadan, M.; Gomaa, H.A.M.; Abdel-Aziz, A.T.; Youssif, B.G.M.; Bräse, S.; Fuhr, O. Synthesis and Antiproliferative Potential of Thiazole and 4-Thiazolidinone Containing Motifs as Dual Inhibitors of EGFR and BRAFV600E. *Molecules* **2023**, *28*, 7951, doi:10.3390/molecules28247951.