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Research Article

SYNTHESIS, SPECTRAL CHARACTERIZATION, AND ANTIPROLIFERATIVE ACTIVITY OF DISPIROPYRROLIDINES CONTAINING 2-THIOXOTHIAZOLIDIN-4-ONE NUCLEUS

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ABSTRACT

Objective: Spiro compounds are present in nature, endowed with deep biological activities. Heterocyclic compounds with a pyrrolidine scaffold are one of the paradigms of organic chemistry that exhibits a wide variety of properties and biological functions. Based on these, seven dispiropyrrolidines have been accomplished by [3+2] cycloaddition reaction from acenaphthenequinone and sarcosine with several dipolaro files such as substituted 5-benzylidene-2-thioxothiazolidin-4-ones.

Methods: Cycloadducts **4a-g** were prepared by conventional method and the structures of the compounds **4a-g** were completely characterized by infrared, ^{1}H, ^{13}C nuclear magnetic resonance spectral data, and elemental analysis. The cytotoxic activity of the synthesized compounds was carried out by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay.

Results: The dispiropyrrolidines **4a-g** were showed a moderate-to-good cytotoxic activity against human cervical cancer lines. Among all the synthesized compounds, **4d** was found to be more potent with human cervical cancer line with an half maximal inhibitory concentration (IC_{50}) value of 5.5 μM.

Conclusion: The synthesized compound **4d** found to be an excellent activity which is nearly closed to reference drug gemcitabine with an IC_{50} value of 4.6 μM.

Keywords: Rhodanine, Acenaphthenequinone, Sarcosine, Antiproliferative activity.

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INTRODUCTION

The 1,3-dipolar cycloaddition reactions [1] have been established as an efficient method for the construction of five-membered nitrogen heterocycles. These five-member heterocycles are very important due to their high regioselectivity and stereoselectivity. A pyrrolidine scaffold is one of the paradigms of organic chemistry that exhibits a wide variety of properties and biological functions [2]. Spirooxindole cores are attractive synthetic targets due to their prevalence in numerous natural products and applications in medicine and therapeutics [3]. In addition, the spirooxindole ring systems are the central skeleton of numerous alkaloids and therapeutically important compounds. More serious diseases such as cancer are considered the second leading cause of death worldwide after cardiovascular diseases. Only in the USA as of 2015, 589,430 cancer patients died and more than 1,658,370 million new cancer cases were identified according to the 2015 cancer data and figures report and it will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 [4]. More than 13 million deaths are expected to occur worldwide by 2030. In India, approximately 1 million new cases occur each year. This is 15% less than in the United States, whose population is one-third that of India. The disturbing fact is that the number of India is expected to double in 20 years, according to the International Agency for Research on Cancer. Cervical cancer is dynamically associated with infection by oncogenic types of human papillomavirus (HPV), which is critical cancer in women. There are more than 100 types of HPV, many of which infect the genital tract. Almost 80% of cases occur in low-income countries or developing countries. This emphasizes that the incessant need to develop new classes of anticancer agents is an important and challenging goal in medical chemistry. Rhodanine-based analogs have been associated with several biological activities such as antibacterial [5,6], antifungal [7], antiviral [8], antimalarial [9], insecticide [10], anti-inflammatory [11], and antidiabetic [12]. Rhodanine and its related compounds are probably due to its affinity for the anticancer agents such as JNK-stimulating phosphate-1 (JSP-1) [13], tumor necrosis factor [14], and antiapoptotic biocomplex BCLXL BH3 [15]. In addition, rhodanine and its analogs have wide industrial applications as vulcanizing agents of synthetic rubber, extreme pressure lubricants, intermediates in the synthesis of dyes, antioxidants, and polishing additives in silver electroplating [16]. The present study has been reported through a highly selective regio- and stereo-scopic cycloaddition reaction derived from acenaphthenequinone and sarcosine with several dipolaro files such as substituted 5-benzylidene-2-thioxothiazolidin-4-ones.

METHODS

Experiments

The complete chemicals were used as laboratory grade purchased from HiMedia Company. The melting points were determined in a digital melting point instrument XT-5 and are incorrect. The infrared (IR) spectra were recorded on a Shimadzu 360 FT-IR spectrometer. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were measured at 400 and 125 MHz, respectively, on a Bruker-400 spectrometer using TMS as internal standard and DMSO-d_6 as a solvent. The elemental analyses for C, H, N, and S were ±0.04% of the theoretical values and determined using a PerkinElmer 240C elemental analyzer.

General procedure for the synthesis of dispiropyrrolidine derivatives (4a-g)

A mixture of acenaphthenequinone (0.0015 mol), sarcosine (0.0015 mol), and substituted 5-benzylidene-2-thioxothiazolidin-4-ones (0.0015 mol) was dissolved in methanol-1,4-dioxane and refluxed for 15–18 h. After

completing the reaction as evident by thin-layer chromatography, the mixture was poured into ice water. The precipitated solid was filtered and purified by recrystallization using ethanol.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(phenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4a)***

^{1}H NMR: δ 2.028 (H-9), 3.648 (H-7a), 3.916 (H-7b), 4.594 (H-6), 7. 432 (H-4′), 7.532 (H-5″, 9″, 10″), 7.678 (H-2′,6′), 7.874 (H-3′,5′), 7.952 (H-8″), 8.136 (H-4″), 8.349 (H-6″), 13.242 (H-3).^{13}C NMR: δ 34.876 (C-9), 49.03 (C-6), 52.09 (C-7), 77.48 (C-5), 81.64 (C-1″), 121.69 (C-5″), 122.32 (C-4′), 123. 96 (C-10″), 127.18 (C-8″), 129. 48 (C-3′, 5′, 9″), 130.58 (C-4″), 130. 81 (C-3″), 132.15 (C-2′,6′), 132. 54(C-4′), 133.06 (C-11″), 133.42 (C-6″), 133.59 (C-7″), 137.314 (C-1′), 143.48 (C-12″), 180.07 (C-4), 201.23 (C-2″), 198.40(C-2). Anal. Calc. for $C_{24}H_{18}N_2O_2S_2$:C, 66.95; H, 4.21; N, 6.51; O, 7.43; S, 14.90. Found: C, 66.97; H, 4.20; N, 6.54; O, 7.46; S, 14.87.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-bromophenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4b)***

^{1}H NMR: δ 2.021 (H-9), 3.658 (H-7a), 3.926 (H-7b), 4.586 (H-6), 7.542 (H-5″, 9″, 10″), 7.652 (H-2′,6′), 7.876 (H-3′,5′), 7.948 (H-8″), 8.146 (H-4″), 8.352 (H-6″), 13.238 (H-3).^{13}C NMR: δ 34.868 (C-9), 49.04 (C-6), 52.02 (C-7), 77.38 (C-5), 81.68 (C-1″), 121.78 (C-5″), 123. 98 (C-10″), 127.11 (C-8″), 129. 38 (C-3′, 5′, 9″), 130.69 (C-4″), 130. 86 (C-3″), 132.14 (C-2′,6′), 132. 56 (C-4′), 133.08 (C-11″), 133.39 (C-6″), 133.54 (C-7″), 137.311 (C-1′), 143.48 (C-12″), 179.09 (C-4), 206.91 (C-2″), 199.56 (C-2). Anal. Calc. for $C_{24}H_{17}BrN_2O_2S_2$: C, 56.58; H, 3.36; Br, 15.68; N, 5.50; O, 6.28; S, 12.59. Found: C, 56.60; H, 3.38; Br, 15.65; N, 5.53; O, 6.31; S, 12.57.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-chlorophenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4c)***

^{1}H NMR: δ 2.025 (H-9), 3.644 (H-7a), 3.919 (H-7b), 4.590 (H-6), 7.534 (H-5″, 9″, 10″), 7.675 (H-2′,6′), 7.870 (H-3′,5′), 7.956 (H-8″), 8.139 (H-4″), 8.348 (H-6″), 13.241 (H-3).^{13}C NMR: δ 34.877 (C-9), 49.06 (C-6), 52.04 (C-7), 77.32 (C-5), 81.66 (C-1″), 121.75 (C-5″), 123. 94 (C-10″), 127.14 (C-8″), 129. 31 (C-3′, 5′, 9″), 130.60 (C-4″), 130. 83 (C-3″), 132.17 (C-2′,6′), 132. 51 (C-4′), 133.03 (C-11″), 133.35 (C-6″), 133.59 (C-7″), 137.311 (C-1′), 143.45 (C-12″), 179.23(C-4), 206.81(C-2″), 199.67(C-2). Anal. Calc. for $C_{24}H_{17}ClN_2O_2S_2$: C, 61.99; H, 3.69; Cl, 7.62; N, 6.02; O, 6.88; S, 13.79. Found: C, 61.96; H, 3.65; Cl, 7.65; N, 6.06; O, 6.90; S, 13.81.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-fluorophenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4d)***

^{1}H NMR: δ 2.032 (H-9), 3.638 (H-7a), 3.914 (H-7b), 4.598 (H-6), 7.538 (H-5″, 9″, 10″), 7.665 (H-2′,6′), 7.868 (H-3′,5′), 7.952 (H-8″), 8.132 (H-4″), 8.339 (H-6″), 13.246 (H-3).^{13}C NMR: δ 34.869 (C-9), 49.05 (C-6), 52.02 (C-7), 77.36 (C-5), 81.68 (C-1″), 121.79 (C-5″), 123. 92 (C-10″), 127.17 (C-8″), 129. 35 (C-3′, 5′, 9″), 130.63 (C-4″), 130. 87 (C-3″), 132.16 (C-2′,6′), 132. 55 (C-4′), 133.06 (C-11″), 133.39 (C-6″), 133.52 (C-7″), 137.316 (C-1′), 143.48 (C-12″), 178.22 (C-4), 203.61(C-2″), 199.52 (C-2). Anal. Calc. for $C_{24}H_{17}FN_2O_2S_2$: C, 64.27; H, 3.82; F, 4.24; N, 6.25; O, 7.13; S, 14.30. Found: C, 64.30; H, 3.83; F, 4.20; N, 6.21; O, 7.15; S, 14.32.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-nitrophenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4e)***

^{1}H NMR: δ 2.04 (H-9), 3.698 (H-7a), 3.70 (H-7b), 4.75 (H-6), 7.672 (H-5″, 9″, 10″), 7.731 (H-2′,6′), 7.869 (H-3′,5′), 7.951 (H-8″), 8.139 (H-4″), 8.372 (H-6″), 13.26 (H-3).^{13}C NMR: δ 34.89 (C-9), 49.12 (C-6), 58.61 (C-7), 76.70 (C-5), 81.72 (C-1″), 121.85 (C-5″), 123. 62 (C-10″), 127.34 (C-8″), 129. 23 (C-3′, 5′, 9″), 130.64 (C-4″), 130. 92 (C-3″), 132.19 (C-2′,6′), 132. 54 (C-4′), 133.08 (C-11″), 133.39 (C-6″), 133.39 (C-7″), 137.326 (C-1′), 147.54 (C-12″), 178.94 (C-4), 206.84(C-2″), 199.25(C-2). Anal. Calc. for $C_{24}H_{17}N_3O_4S_2$: C, 60.62; H, 3.60; N, 8.84; O, 13.46; S, 13.49. Found: C, 60.59; H, 3.61; N, 8.80; O, 13.49; S, 13.47.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-methylphenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4f)***

^{1}H NMR: δ 2.036 (H-9), 2.228 (H-1‴), 3.642 (H-7a), 3.921 (H-7b), 4.594 (H-6), 7.542 (H-5″, 9″, 10″), 7.673 (H-2′,6′), 7.862 (H-3′,5′), 7.955 (H-8″), 8.135 (H-4″), 8.342 (H-6″), 13.243 (H-3).^{13}C NMR: δ 24. 39 (C-1‴) 34.872 (C-9), 49.03 (C-6), 52.11 (C-7), 77.42 (C-5), 81.63 (C-1″), 121.81 (C-5″), 123. 95 (C-10″), 127.12 (C-8″), 129. 42 (C-3′, 5′, 9″), 130.71 (C-4″), 130. 89 (C-3″), 132.09 (C-2′,6′), 132. 43 (C-4′), 133.08 (C-11″), 133.45 (C-6″), 133.42 (C-7″), 137.319 (C-1′), 135.24 (C-4′) 143.52 (C-12″), 178.99 (C-4), 206.02 (C-2″), 199.32 (C-2). Anal. Calc. for $C_{25}H_{20}N_2O_2S_2$: C, 67.54; H, 4.53; N, 6.30; O, 7.20; S, 14.43; Found: C, 67.58; H, 4.54; N, 6.32; O, 7.18; S, 14.46.

1-N-methyl-spiro[2.3^1]acenaphthene-4^1-(4-methoxyphenyl)-spiro[3.5^1]2^{11},4^{11}-thiazolidin-one-3,3^1 pyrrolidine ***(4g)***

^{1}H NMR: δ 2.038 (H-9), 3.98 (H-1‴), 3.652 (H-7a), 3.941 (H-7b), 4.586 (H-6), 7.548 (H-5″, 9″, 10″), 7.675 (H-2′,6′), 7.869 (H-3′,5′), 7.952 (H-8″), 8.138 (H-4″), 8.345 (H-6″), 13.246 (H-3).^{13}C NMR: δ 34.876 (C-9), 49.12 (C-6), 52.19 (C-7), 55.65 (C-1‴) 77.49 (C-5), 81.75 (C-1″), 121.84 (C-5″), 123. 97 (C-10″), 127.14 (C-8″), 129. 51 (C-3′, 5′, 9″), 130.75 (C-4″), 130. 92 (C-3″), 132.19 (C-2′,6′), 132. 44 (C-4′), 133.12 (C-11″), 133.36 (C-6″), 133.51 (C-7″), 137.321 (C-1′), 143.51 (C-12″), 159.02 (C-4′), 179.99 (C-4), 204.52 (C-2″), 199.01 (C-2). Anal. Calc. for $C_{25}H_{20}N_2O_3S_2$: C, 65.20; H, 4.38; N, 6.08; O, 10.42; S, 13.92; Found: C, 65.23; H, 4.34; N, 6.10; O, 10.45; S, 13.90.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay for cytotoxicity screening

The human cervical cancer cell line was obtained from the National Centre for Cell Science (NCCS), Pune, and cultured in Eagle's minimal essential medium containing 10% fetal bovine serum (FBS). The cells were maintained at 37°C, 5% CO_2, 95% air, and 100% relative humidity. Extracts were added to cells cultured in concentrations of 6.25, 12.5, 25, 50, and 100 µg of stock of 1 mg/ml 0.1% DMSO and incubated for 24 h. The percentage difference in viability was determined by a standard MTT assay after 48 h of incubation. The percentage of cell viability was then calculated with respect to control as follows:

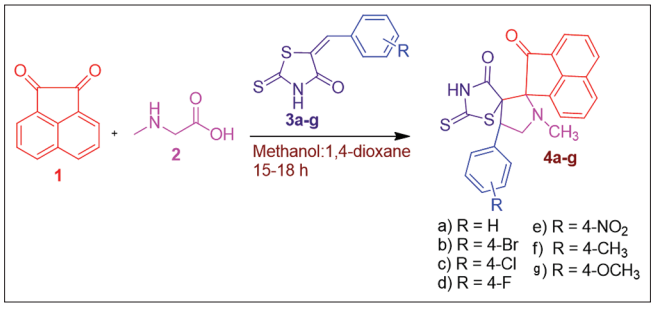
$$\% \text{ Cell viability} = [A] \text{ Test}/ [A]\text{control} \times 100$$

RESULTS AND DISCUSSION

Chemistry

5-benzylidene-2-thioxothiazolidin-4-ones were prepared from rhodanine and various substituted aromatic aldehydes according to the method previously reported [17]. Cycloadducts **4a-g** were prepared by the reaction of different substituted 5-benzylidene-2-thioxothiazolidin-4-ones **3a-g** with azomethine ylide [18] obtained from acenaphthenequinone **1** and sarcosine **2** (**Scheme 1**).

The formation of dispiropyrrolidines **4a-g** was confirmed by spectral (IR,^{1}H NMR, and ^{13}C NMR) and elemental analysis. Among the synthesized compounds, **4c** (Fig. 1) was taken as a representative compound for spectroscopic discussion. The IR spectrum of adduct **4c** showed carbonyl at 1730 cm^{-1} and thiocarbonyl resonated at 1200 cm^{-1}.



Scheme 1: Synthesis of titled compounds 4a-g

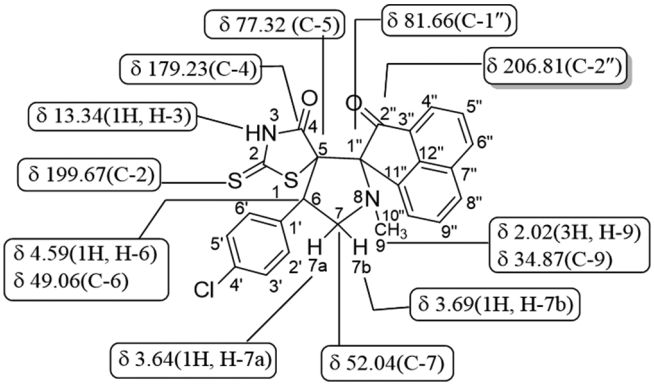


Fig. 1: Selected ^{1}H and ^{13}C chemical shifts of compound 4c

Table 1: *In vitro* antiproliferative activity of compounds 4a-g by MTT assay

Compound	IC_{50} (±SD) µM
4a	36.8 (±1.12)
4b	17.4 (±0.04)
4c	24.2 (±0.12)
4d	05.8 (±0.46)
4e	14.5 (±0.72)
4f	25.4 (±0.35)
4g	28.6 (±0.94)
Gemcitabine	04.6 (±0.44)

IC_{50} values represent the concentration required to decrease cytotoxic activity by 50%. IC_{50}: Half maximal inhibitory concentration, SD: Standard deviation, MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

The sharp peak appeared at 2992 cm^{-1} for the NH group of rhodanine moiety.

In the ^{1}H NMR spectrum (Fig. 1) of compound **4c**, the sharp singlet at δ 2.02 indicates N-CH_3 protons (H-9). The pyrrolidine ring N-CH_2 protons (H-7a and 7b) appeared as a doublet of doublet at δ 3.64 and 3.69. The benzylic proton (H-6) appeared as a doublet at δ 4.59 and the product **4c** exhibited a multiplet at a range δ 7.53–8.34 due to aromatic protons. The peak appeared at δ 13.24 is due to NH proton (H-3) of rhodanine moiety. The cycloadduct **4c** also confirmed by its ^{13}C NMR spectrum (Fig. 1), signals at δ 77.32 and δ 81.66 due to two spiro carbons C-5 and C-1″, respectively. Pyrrolidine ring N-CH_3 carbon C-9 resonated at δ 34.87 and N-CH_2 carbon C-7 also observed at δ 52.04 ppm. The signal at δ 49.06 ppm due to benzylic carbon C-6 and the bunch of peaks at δ 121.75 to δ 143.45 ppm indicates aromatic carbons. The two carbonyl groups observed at δ 206.81(C-2″) and δ 179.23(C-4) ppm and the thiocarbonyl group appeared at δ 199.67(C-2). All other cycloadducts were exhibited identical results.

Antiproliferative activity

In vitro antiproliferative activity for synthesized compounds, **4a-g** was evaluated by the measurement of their cytotoxic properties against human cervical cancer by MTT assay [19] and their results were expressed as half maximal inhibitory concentration (IC_{50}) and depicted in Table 1. In addition, gemcitabine was used as a standard drug.

As shown from Table 1, the synthesized compounds showed moderate-to-good antiproliferative activity against human cervical cancer cell line with the IC_{50} values from 5.8 µM to 36.8 µM. Among the seven tested compounds, compound **4d** showed a better antiproliferative activity due to the higher electronegativity of fluorine substitution. Further, compound **4e** carried nitro atom on the phenyl ring was found to be more potency with the IC_{50} value of 14.5 µM. For bromo and chloro substituent, **4b** and **4c** exhibited an improved antiproliferative activity with the IC_{50} values 17.4 µM and 24.2 µM, respectively. On the other hand, the electron donating substituents **4f** and **4g** found to be moderate potential against human cervical cancer cell lines (IC_{50} 25.4 µM and 28.6 µM, respectively). However, the unsubstituted compound **4a** displayed a lower activity compared to all other synthesized compounds. Among the tested compounds, compound **4d** found to be an excellent activity which is nearly closed to reference drug gemcitabine (IC_{50} 4.6 µM).

CONCLUSION

We have synthesized seven cycloadducts from acenaphthenequinone and sarcosine with several dipolaro files such as substituted 5-benzylidene-2-thioxothiazolidin-4-ones and examined their antiproliferative activity against human cervical cancer cell lines by MTT assay. It seems that the electron withdrawing substituents **4b**, **4c**, **4d**, and **4e** enhanced the activity with IC_{50} values 17.4, 24.2, 5.8, and 14.5 µM, respectively, and more dominant than electron donating substituents such as 4f and 4g with the IC_{50} values are 25.4 and 28.6 µM. Among the tested compounds, compound **4d** showed an excellent activity than all other compounds. As from the results, we may conclude that the electron withdrawing substituents showed better antiproliferative activity than electron donating substituents.

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AUTHORS' CONTRIBUTION

All authors have an equal contribution for this article.

CONFLICTS OF INTEREST

The authors declare that we have no conflicts of interest.

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