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Scientific paper

Synthesis, Characterization and Antimicrobial Evaluation of Novel 6'-Amino-spiro[indeno[1,2-*b*] quinoxaline[1,3]dithiine]-5'-carbonitrile Derivatives

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Abstract

l,3-Dithiin with two sulfurs in its structure is a six-membered, sulfur-containing heterocyclic compound. New derivatives of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile were prepared by the multi-component reaction of active methylene compounds, carbon disulfide, malononitrile and multi-ring compounds containing a carbonyl group in the presence of piperidine as a catalyst at room temperature with high efficiency. The antimicrobial effects including antibacterial and antifungal effects based on inhibition zone diameter (IZD), minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were studied.

Keywords: Multicomponent reaction; sulfur-containing heterocyclic; spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile; carbon disulfide; antimicrobial activity

1. Introduction

Heterocyclic compounds are highly valuable considering their use as a key ingredient in medications.[1] Sulfur-containing heterocyclic compounds are particularly noteworthy in organic chemistry, medicine, and biochemistry due to their structure.[2–3] Spiro heterocyclic compounds lead to the biological activity of these compounds because of the commonality of a carbon between the two rings and the lack of symmetry of these compounds due to the asymmetric nature of carbon spiro compounds.[4–8] Biological activities, such as promising antibacterial, antifungal,[9–11] anti-hyperglycemic,[12] and anti-tubercular[13] effects have been reported for spiro heterocyclic compounds.

l,3-Dithiin is a six-membered sulfur-containing heterocyclic ring with two sulfur atoms at positions 1 and 3. This heterocyclic compound has been reported as an antithrombotic agent found in *Allium sativum*.[14] Other biological properties have also been reported for synthesized heterocyclic compounds containing l,3-dithiin ring.[15–17] These compounds are most often used as a carbon protection groups for the synthesis of heterocyclic compounds.[18–20]

In this study the new derivatives of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile were synthesized using compounds possessing active methylene group, carbon disulfide, malononitrile, 11*H*-indeno[1,2-*b*]quinoxalin-11-one and 1*H*-indene-1,2,3-trione and their biological activities such as antibacterial and antifungal activities were studied.

In our previous report, new derivatives of spiro[indoline-3,4′-[1,3]dithiine] were synthesized by MgO nanoparticles.[17] In this work, the synthesis of derivatives with MgO nanoparticles was investigated but the desired result was not obtained, that could be due to the larger reactant material including 11*H*-indeno[1,2-*b*]quinoxalin-11-one than in the previous work.

2. Experimental

2. 1. Chemistry

The ^{1}H and ^{13}C NMR spectra of compounds in DMSO-d_6 were measured using a Bruker Ultra Shield-250 spectrometer (250 and 75 MHz, respectively). The FT-IR

spectra were taken using the KBr disks by a Bruker Tensor 27 FT-IR spectrometer with absorption given in cm^{-1}. Furthermore, elemental analysis was performed for C, H, N, and S by a Thermo Finnigan Flash EA microanalyzer. The melting point of the compounds was recorded on a Kruss type KSP1 N melting point meter. The concentrations of bacterial, fungal suspensions were determined by using Jenway 6405 UV-VIS spectrophotometer. The reaction progression process was monitored using TLC (silica gel, aluminum sheets) obtained from Merck. Moreover, chemicals and solvents were purchased from Merck and Sigma-Aldrich, and no purification was performed prior to their use.

2. 1. 1. General Procedure for the Preparation of Compounds 7a–c and 10a–d

To a solution of active methylene compound **1a–c** (1 mmol) in 2 mL acetonitrile, 2 mmol piperidine (0.1703 g) and 3 mmol carbon disulfide (0.2284 g) were added, and the mixture was stirred for 0.5 h or 1 h (dimedone for 0.5 h and barbituric acid derivatives for 1 h) at room temperature.

In another container, a mixture of 1 mmol malononitrile (0.066 g), 1 mmol piperidine (0.0852 g), and 1 mmol multi-ring compounds containing a carbonyl group (**4**, **8a–b**) in 2 mL of acetonitrile were stirred for 0.5 h at room temperature. Then, the two mixtures were mixed and stirred at room temperature for 9–12 h. The reaction was monitored using TLC (hexane/ethyl acetate) and, after completion, the precipitate was filtered and recrystallised from acetonitrile to give the pure compounds.

6'-Amino-7,8-dimethyl-2'-(2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)spiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (7a)

Yield: 70%, m.p. 297–298 °C; IR (KBr, cm^{-1}): 3352, 3275 (NH_2), 2164 (CN), 1718, 1673 (CO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.99 (3H, s, Me), 1.05 (3H, s, Me), 2.01–2.25 (4H, m, $2CH_2$), 6.65 (1H, d, J = 7.5 Hz, H-Ar), 6.80–7.01 (3H, m, H-Ar), 7.24 (2H, br s, NH2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.8, 27.9, 33.7, 47.6, 51.3, 58.1, 110.4, 111.5, 117.1, 122.7, 123.6, 129.1, 135.3, 143.4, 160.1, 173.9, 177.9, 193.4, 194.6. Anal. Calcd for $C_{21}H_{16}N_2O_4S_2$: C, 59.42; H, 3.79; N, 6.59; S, 15.11. Found: C, 59.37; H, 3.83; N, 6.62; S, 15.15.

6'-Amino-2'-(4,6-dioxo-2-thioxotetrahydropyrimidin-5(2*H*)-ylidene)-7,8-dimethylspiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (7b)

Yield: 81%, m.p. 273–274 °C; IR (KBr, cm^{-1}): 3129, 3019 (NH_2, NH), 2175 (CN), 1731, 1669 (CO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 6.72 (1H, d, J = 8.25 Hz, H-Ar), 6.79–6.98 (3H, m, H-Ar), 10.24 (1H, s, NH), 10.52 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.2, 80.4, 114.6, 117.6, 122.4, 124.1, 127.6, 128.5, 136.4, 143.1, 143.6, 160.2, 162.7, 174.2, 177.8, 179.7, 180.4. Anal. Calcd for $C_{17}H_8N_4O_5S_2$: C, 49.51; H, 1.95; N, 13.59; S, 15.55. Found: C, 49.32; H, 1.93; N, 13.54; S, 15.57.

6'-Amino-2'-(4,6-dioxo-2-thioxotetrahydropyrimidin-5(2*H*)-ylidene)-7,8-dimethylspiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (7c)

Yield: 77%, m.p. 279–281 °C; IR (KBr, cm^{-1}): 3241 and 3164 (NH, NH_2), 2202 (CN), 1725, 1681 (CO); ^{1}H NMR (250 MHz, DMSO-d_6) δ 6.80 (1H, d, J = 8 Hz, H-Ar), 6.84–7.05 (3H, m, H-Ar), 10.36 (1H, s, NH), 10.54 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.4, 79.3, 111.6, 113.9, 119.2, 124.2, 127.6, 128.2, 132.4, 135.6, 141.9, 161.1, 162.5, 175.1, 178.6, 179.1, 180.2. Anal. Calcd for $C_{17}H_8N_4O_4S_3$: C, 47.65; H, 1.88; N, 13.08; S, 22.45. Found: C, 47.61; H, 1.86; N, 13.10; S, 22.41.

6'-Amino-2'-(4,4-dimethyl-2,6-dioxocyclohexylidene) spiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (10a)

Yield: 85%, m.p. 285–288 °C; IR (KBr, cm^{-1}): 3222 and 3218 (NH_2), 2162 (CN), 1672 (CO); ^{1}H NMR (DMSO-d_6) δ 0.99 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99–2.05 (m, 2H, CH_2), 2.57–2.75 (m, 2H, CH_2), 7.30 (br s, 2H, NH_2), 7.49–7.59 (m, 3H, H-Ar), 7.78 (t, J = 7.75 Hz, 2H, H-Ar), 8.01–8.16 (m, 3H, H-Ar). ^{13}C NMR (DMSO-d_6) δ 27.4, 28.0, 32.4, 47.5, 50.5, 59.0, 112.3, 117.9, 121.9, 124.9, 129.3, 129.5, 129.8, 130.1, 132.8, 136.6, 141.4, 142.1, 152.3, 154.6, 159.3, 165.3, 159.9.185.4. Anal. Calcd for $C_{27}H_{20}N_4O_2S_2$: C, 65.30; H, 4.06; N, 11.28; S, 12.91. Found: C, 65.34; H, 4.08; N, 11.31; S, 12.95.

6'-Amino-2'-(4,4-dimethyl-2,6-dioxocyclohexylidene) -7,8-dimethylspiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (10b)

Yield: 81%, m.p. 264–266 °C; IR (KBr, cm^{-1}): 3313 and 3317 (NH_2), 2193 (CN), 1675 (CO); ^{1}H NMR (DMSO-d_6) δ 0.97 (s, 6H, $2CH_3$), 1.97–1.98 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 3.32 (s, 3H, Me-Ar), 3.35 (s, 3H, Me-Ar), 7.31 (br s, 2H, NH_2), 7.46–7.51 (m, 3H, H-Ar), 7.76 (d, J = 5.5 Hz, 1H, H-Ar), 7.89 (d, J = 5.5 Hz, 1H, H-Ar), 8.0 (t, J = 5.5 Hz, 1H, H-Ar). ^{13}C NMR (DMSO-d_6) δ 20.1, 20.2, 27.5, 27.9, 32.4, 50.6, 112.3, 118.0, 121.7, 124.8, 128.4, 128.5, 129.1, 132.3, 136.9, 139.5, 140.0, 140.2, 140.8, 152.1, 153.6, 159.3, 165.2, 195.4. Anal. Calcd for $C_{29}H_{24}N_4O_2S_2$: C, 66.39; H, 4.61; N, 10.68; S, 12.22. Found: C, 66.43; H, 4.89; N, 10.71; S, 12.19.

6'-Amino-2'-(2,4,6-trioxotetrahydropyrimidin-5 (2*H*)-ylidene)spiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3] dithiine]-5'-carbonitrile (10c)

Yield: 90%, m.p. 273–275 °C; IR (KBr, cm^{-1}): 3372 and 3375 (NH_2), 2189 (CN), 1660 (CO); ^{1}H NMR (DMSO-d_6) δ 7.06 (br s, 2H, NH_2), 7.44–7.50 (m, 3H, H-Ar), 7.72–7.74 (m, 2H, H-Ar), 7.99–8.01 (m, 3H, H-Ar), 9.68 (br s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ 52.8, 113.8, 114.3, 121.5, 121.8, 124.9, 125.0, 128.5, 129.0, 129.4, 132.4, 132.6,

136.7, 141.7, 142.0, 149.8, 152.0, 152.9, 161.0, 164.0, 164.9, 166.7. Anal. Calcd for $C_{23}H_{12}N_6O_3S_2$: C, 57.02; H, 2.50; N, 17.34; S, 13.24. Found: C, 57.05; H, 2.53; N, 17.35; S, 13.26.

6'-Amino-2'-(4,6-dioxo-2-thioxotetrahydropyrimidin-5(2*H*)-ylidene)spiro[indeno[1,2-*b*]quinoxaline-11,4'-[1,3]dithiine]-5'-carbonitrile (10d)

Yield: 88%, m.p. 254–256 °C; IR (KBr, cm^{-1}): 3172 and 3170 (NH_2), 2194 (CN), 1662 (CO); ^{1}H NMR (DMSO-d_6) δ 7.10 (br s, 2H, NH_2), 7.39–7.54 (m, 2H, H-Ar), 7.75–7.86 (m, 3H, H-Ar), 7.96–8.11 (m, 3H, H-Ar), 10.68 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ 57.9, 118.9, 121.6, 125.1, 128.8, 129.2, 129.3, 129.5, 129.6, 129.8, 132.5, 132.7, 136.8, 141.5, 142.1, 153.4, 154.9, 161.0, 162.0, 166.9, 178.9. Anal. Calcd for $C_{23}H_{12}N_6O_2S_3$: C, 55.19; H, 2.42; N, 16.79; S, 19.22. Found: C, 55.23; H, 2.43; N, 16.82; S, 19.19.

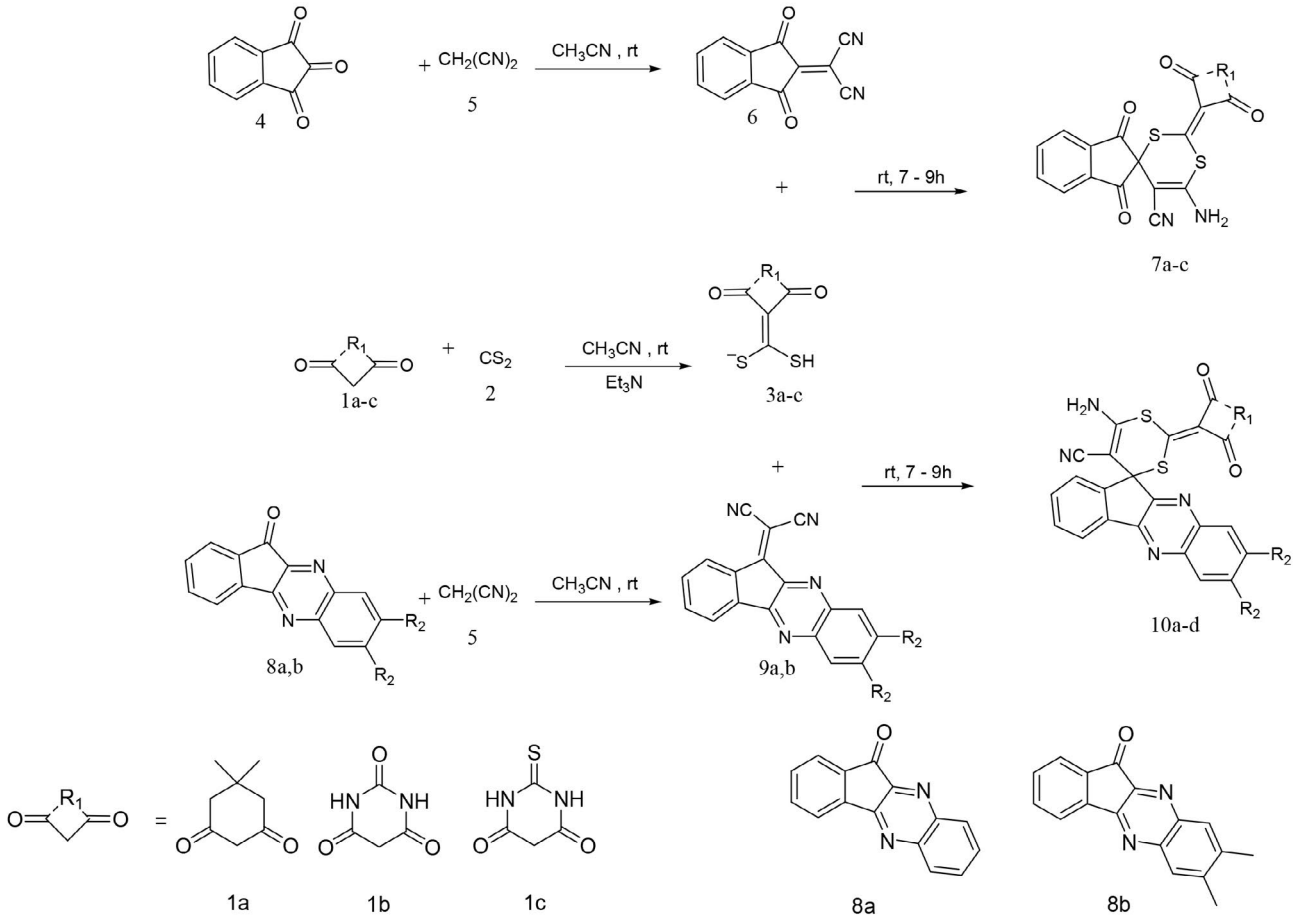
2. 2. *In vitro* Antimicrobial Activity

Antimicrobial properties including broth microdilution and time-kill susceptibility were tested based on the IZD, MIC, MBC and MFC values according to the CLSI (the clinical and laboratory standards institute) guidelines M07-A9, M26-A, M02-A11, M44-A and M27-A2.[17,22–24] Gram-negative pathogenic bacteria including *Pseudomonas aeruginosa* (PTCC 1310), *Escherichia coli* (PTCC 1399), and *Salmonella enterica* subsp. *enterica* (PTCC 1709); Gram-positive strains including *Staphylococcus aureus* (PTCC 1189) and *Staphylococcus epidermidis* (PTCC 1435); fungi including *Fusarium oxysporum* (PTCC 5115) were prepared from the Persian Type Culture Collection (PTCC), Tehran, Iran.

3. Results and Discussion

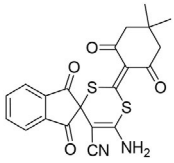
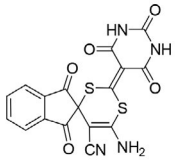
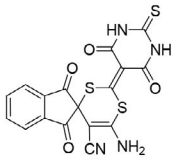
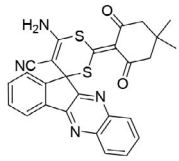
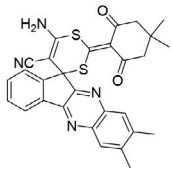
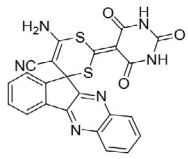
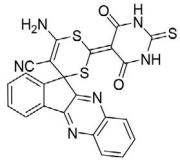
3. 1. Chemistry

Seven 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile derivatives (Table 1) were synthesized using compounds possessing active methylene groups (e.g. dimedone, barbituric acid and thiobarbituric acid), carbon disulfide, malononitrile, and multi-ring compounds containing a carbonyl group (1*H*-indene-1,2,3-trione, 11*H*-indeno[1,2-*b*]quinoxalin-11-one and 7,8-dimethyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one) according to Scheme 1. The presented compounds were synthesized at ambient temperature within the range of yield of 70–90%.



Scheme 1. Multicomponent synthesis of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile derivatives

Table 1. Synthesis of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*] quinoxaline[1,3]dithiine]-5'-carbonitrile derivatives.

Entry	Structure	Time (h)	Yield (%)	m.p. (°C)
7a		10.5	70	297–298
7b		11	81	273–274
7b		12	77	279–281
10a		9.5	85	285–288
10b		10	81	264–266
10c		10	90	273–275
10d		10.5	88	254–256

The structure of prepared compounds were confirmed by spectroscopic data such as ^{1}H NMR, ^{13}C NMR and FT-IR. For example, in the derivative **7a**, amine group appeared in regions 3352, 3275 cm^{-1}, nitrile in 2164 cm^{-1}, and carbonyl in 1718, 1673 cm^{-1} of the FT-IR spectrum. In the ^{1}H NMR spectrum, amine groups appeared at δ 7.24 ppm, methyl groups at δ 0.99, 1.05 ppm, and methylidene groups at δ 2.01, 2.25 ppm; and in the ^{13}H NMR spectrum, methyl groups appeared at δ 27.8, 27.9 ppm, spiro carbon at δ 58.1 ppm, and nitrile carbon at δ 117.1 ppm.

In addition, 2D NMR of **10a** is presented in Fig. 1. In this heteronuclear single quantum correlation (HSQC) spectrum of **10a**, the relationship between the carbons and hydrogens of the dimedone group were visible in aliphatic region along relationship between carbons and hydrogens in the aromatic region.

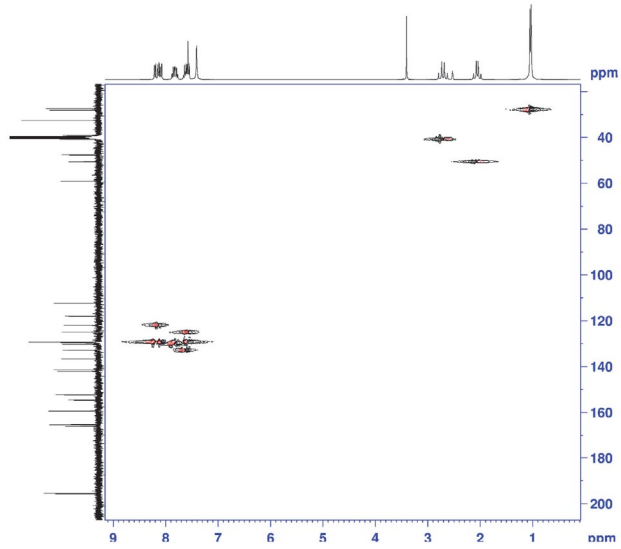


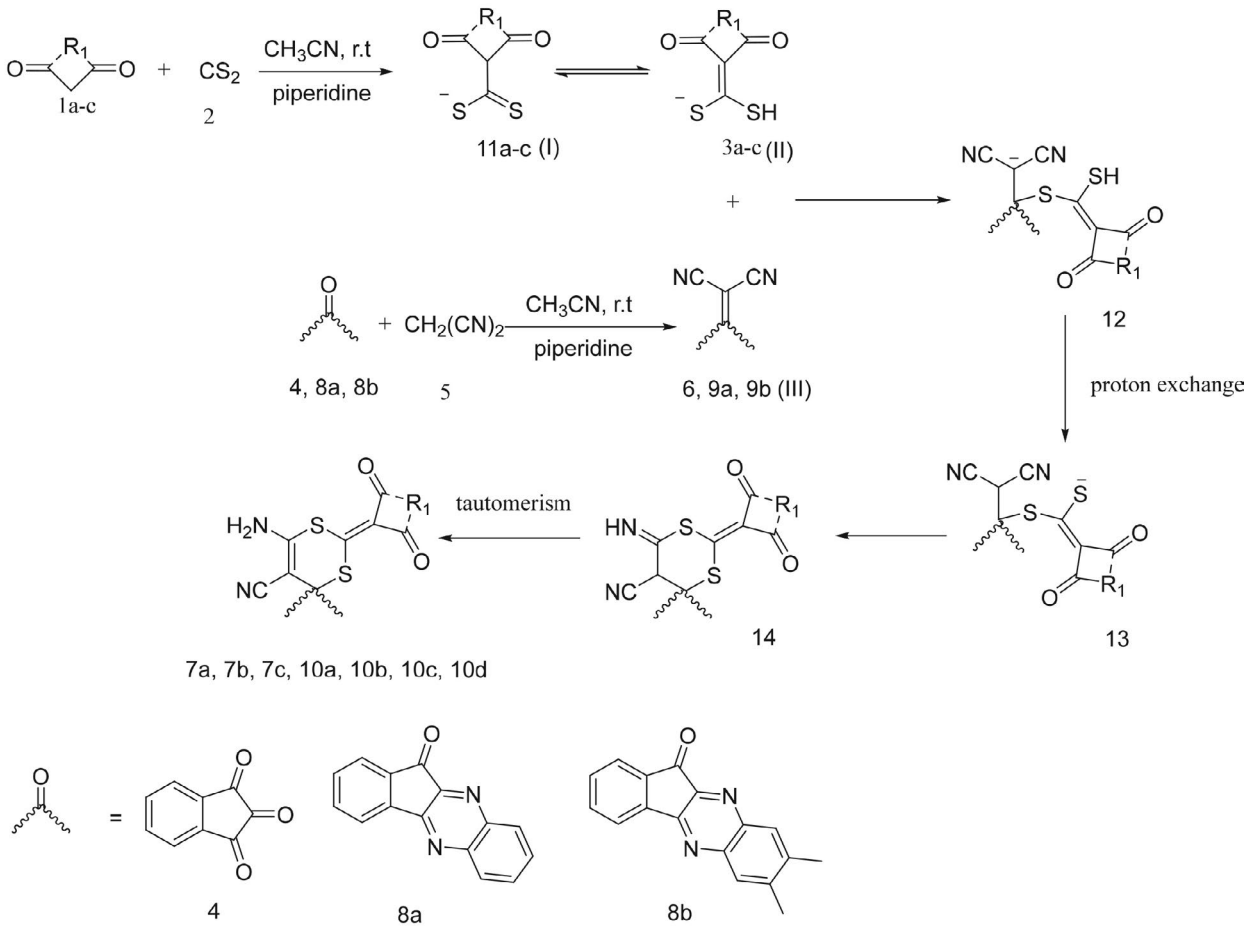
Fig. 1. HSQC spectrum of **10a**

The proposed mechanism for the formation of the prepared compounds is presented in Scheme 2.

Carbon disulfide and active methylene compounds in the presence of a base catalyst form species **I** (**11a–c**) that are in equilibrium with **II** (**3a–c**). From the reaction of multi-ring compounds containing a carbonyl group (**4**, **8a** and **8b**) with malononitrile, compounds **III** (**6**, **9a** and **9b**) are formed. Moreover, from the Michael addition reaction of **II** with **III**, intermediate **12** is formed, leading to the creation of **13** by an intramolecular proton exchange. Upon the nucleophilic sulfur attack on the cyanide group, intermediate **14** is formed, and finally with tautomerism, 6'-amino-2'-(arylidin-ylidene)spiro[aryl-[1,3]dithiine]-5'-carbonitrile derivatives are obtained.

3. 2. Antimicrobial Evaluation

Antibacterial activity of synthetic compounds in comparison with gentamicin and penicillin (as reference drugs) was determined against Gram-positive and Gram-negative bacteria. Antifungal activity of synthetic compounds in comparison with terbinafine and tolnaftate (as reference drugs) was investigated as well. According to the results obtained and presented in Table 2 as the IZD, MIC, MBC and MFC values, the following order of decreasing antimicrobial activity can be established: **10d**, **10c**, **10a**, **10b**, **7c**, **7b** and **7a**. Highest effect of the compound **10d** can be due to the presence of sulfur and pyrazine ring in its structure. In general, the presence of the pyrazine ring had the first priority in antimicrobial effects, followed by the presence of thiobarbituric acid which was



Scheme 2. Proposed mechanism for the synthsis of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile derivatives

Table 2. Antimicrobal activities of derivatives **7a–c** and **10a–d** against Gram-negative, Gram- positive pathogenic bacteria and *Fusarium oxysporum*.

	Bacteria / fungi[a]		Products							Antibacterial and antifungal[b]	
			7a	7b	7c	10a	10b	10c	10d	A	B
gram- negative	1310	IZD	17.63	18.37	18.21	20.73	20.91	22.69	22.86	26.42	–
		MIC	1024	512	256	128	256	64	64	0.12	–
		MBC	2048	1024	512	256	256	256	128	0.5	–
	1399	IZD	–	–	–	–	–	10.23	11.47	23.29	–
		MIC	–	–	–	–	–	1024	256	4	–
		MBC	–	–	–	–	–	2048	512	4	–
	1709	IZD	–	9.92	10.18	–	–	10.53	11.51	20.76	13.57
		MIC	–	1024	512	–	–	256	256	4	8
		MBC	–	2048	1024	–	–	512	512	8	16
gram- positive	1189	IZD	13.99	15.49	16.48	18.26	16.37	17.14	17.68	20.03	21.95
		MIC	1024	1024	512	512	512	256	128	4	0.5
		MBC	2048	1024	512	1024	1024	512	128	8	2
	1435	IZD	–	12.56	13.37	13.46	12.79	15.73	16.19	24.43	25.43
		MIC	–	1024	1024	512	1024	256	128	8	1
		MBC	–	2048	1024	512	2048	512	256	16	2
fungi	5115	IZD	–	11.09	12.35	–	–	12.59	14.97	23.31	–
		MIC	–	256	256	–	–	128	64	32	–
		MFC	–	512	256	–	–	256	128	64	–

[a] IZD values reported as mm; MIC and MFC values reported as μg/mL [b] For bacteria: **A**: gentamicin, **B**: penicillin; for fungi:**A**: terbinafine, **B**: tolnaftate

also effective in this property, after that, the barbituric acid and finally, compounds containing dimedone unit having the least effect.

In antibacterial activity, penicillin has no effect on 1310 and 1399, but **10d** with MIC 64, 256 had the highest impact, respectively. In addition, derivative **10c** on 1399 and all other derivatives on 1310 were effective. In antifungal activity too tolnaftate has no effect on *Fusarium oxysporum*, but derivatives **10d**, **10c**, **7c** and **7b** were effective with MIC 64, 128, 256 and 256, respectively.

4. Conclusions

In summary, we succeeded in synthesizing seven novel derivatives of 6'-amino-2'-(arylidene)spiro[indeno[1,2-*b*]quinoxaline[1,3]dithiine]-5'-carbonitrile starting from compounds possessing active methylene group, carbon disulphide, malononitrile and multi-ring compounds containing a carbonyl group using simple process. Antimicrobial activity of these compounds was evaluated against five Gram-negative and Gram-positive pathogenic bacteria. Additionally, antifungal activity against *Fusarium oxysporum* was determined as well. The results of the antimicrobial study show good effects of derivatives investigated and the relationship between their structures and antimicrobial activity was observed. Some derivatives show better antimicrobial activity than commercial drugs such as penicillin and tolnaftate.

The important advantages of the present study were synthesis of novel heterocyclic compounds containing sulfur with antimicrobial activity, high efficiency, perform the reaction at ambient temperature, the availability, cheap and inexpensive materials

5. Acknowledgements

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Povzetek

l,3-Ditiin z dvema **žveplovima** atomoma v svoji strukturi je **šestčlenska žveplova** heterociklična spojina. S pomočjo multikomponentne reakcije med spojinami z aktivno metilensko skupino, ogljikovim disulfidom, malononitrilom in večkomponentne spojinami, ki vsebujejo karbonilno skupino, smo v prisotnosti piperidina kot katalizatorja pri sobni temperaturi z veliko učinkovitostjo pripravili nove 6'-amino-2'-(ariliden)spiro[indeno[1,2-*b*]kinoksalin[1,3]ditiin]-5'-karbonitrilne derivate. S pomočjo metode merjenja premera cone inhibicije (IZD) in na osnovi tako določenih minimalne inhibitorne (MIC), minimalne baktericidne (MIB) oz. minimalne fungicidne koncentracije (MFC) smo raziskali protimikrobno (t.j. antibakterijsko in antiglivično) učinkovanje pripravljenih spojin.