SYNTHESIS AND BIOLOGICAL EVALUAFION OF SOME NEW ALICYCLICSPIRO-2′-(1′,3′-OXAZOLIDINE) DERIVATIVES

Hassan M. Faidallah[a], E. M. Sharshira*[b] and Mohammed S. M. AL-SAADI[a]

[a]Chemistry Department, Faculty of Medicine, University of King Abdulaziz , Jeddah 21589, Kingdom Saudi Arabia.

[b]Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt;

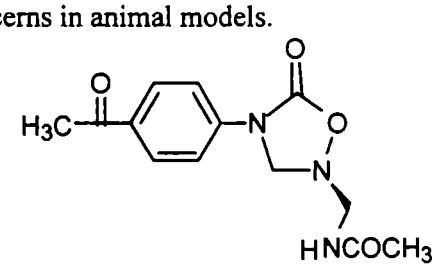
e-mail:dressamsharshira@yahoo.com

Abstract: Condensation of cyclic ketones **1** with ethanolamines gave the corresponding spiro-oxazolidines **2**. The thioamides **3** were obtained in good yields through reaction of **2** with the appropriate isothiocyanate. Reaction of **2** with formaldehyde or acetaldehyde in the presence of the appropriate amine afforded the corresponding aminomethyl spiro-compounds **4** and **5** respectively, in excellent yields. The structures of the isolated compounds were fully determined by spectral methods. Antimicrobial activities of some oxazolidines were also discussed.

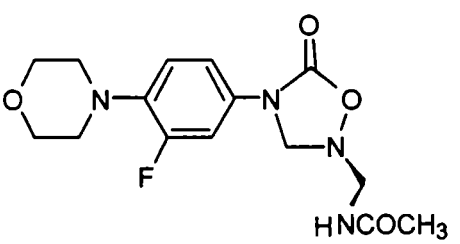
Introduction

Oxazolidines have attracted attention as a new class of orally active synthetic antibiotics with a unique mechanism of bacterial protein synthesis inbibition[1-5]. One of the early oxazolidinones studied in detail was DUP-721 (I)[6] (Figure 1) exhibiting a broad spectrum of antibacterial activity including activity against drug-resistant Gram positive bacteria as well as several anaerobes and *Mycobacterium tuberculosis*.

However, further development of DUP-721 (I) was discontinued because of safety concerns in animal models.



DUP-721 (I)



Linezolid (II)

Figure 1

Continued efforts led to the identification of Linezolid (II)[5,7,8] (Figure 1) with excellent activity against ever increasing *Methicillin Resistant Staphylococcus aureus* (MRSA) and with a better safety profile; Linezolid was approved for clinical use in 2001.

Structural changes at oxazolidine ring including substituents[9-14] and degree of unsaturation[15-18] have also shown antimicrobial activity. These findings encouraged us to synthesize some novel spiro-oxazolidines for biological applications.

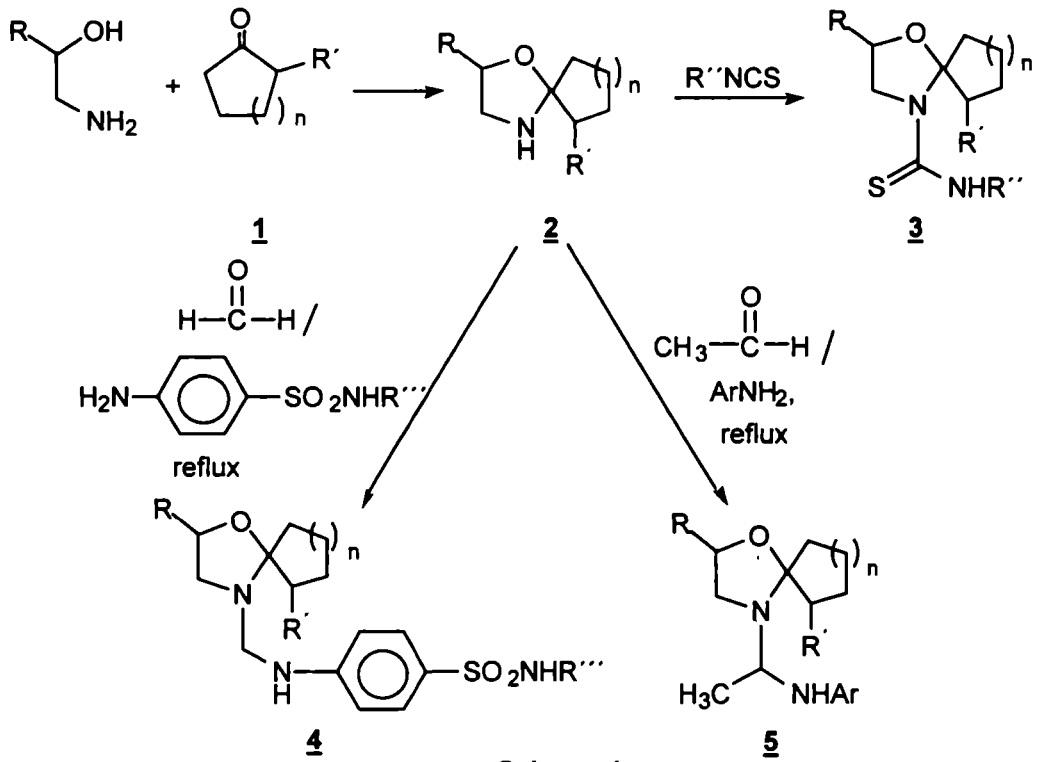
Results and discussion

It has been reported that condensation of ketones with ethanolamine can lead to alkylidene amino alcohols or oxazolidines[19]. However, cyclohexanone and ethanolamine yield cyclohexane spiro-2′-(1′,3′-oxazolidine)[20]. In this report, some new alicyclic spiro-2′-(1′,3′-oxazolidines) have been synthesized by the condensation of the appropriate ketone with ethanolamine as well as substituted ethanolamines with the two fold objective of preparing new spiro compounds and study their biological activities.

The cyclocondensation of ethanolamines with cyclic ketones **1** using a dean-stark trap afforded the spiro oxazolidine derivatives **2** in good yield (77-92%). The physical and analytical data are summarized in Table 1. The structure of the spiro compounds **2** was supported by mass spectra, IR and ^{1}H NMR spectral data (Table 2).

Addition of the spiro compounds **2** across the N=C bond of the appropriate isothiocyanate gave the corresponding thioamides **3** in good yields. The IR spectra of **3** showed a thiocarbonyl absorptions in the region 1080-1155 cm^{-1} as well as an NH band at 3298-3340 cm^{-1}. Their ^{1}H NMR spectra exhibited two triplets at δ 3.55-3.98 and 2.97-3.70 for H-2 and H-3 respectively. The cyclic aliphatic protons appeared in the region δ 1.20-2.16 (Table 2).

Condensation of **2** with formaldehyde and sulfa drugs afforded the corresponding aminomethyl spiro compounds **4** in almost quantitative yields. Acetaldehyde was also used successfully for the condensation between **2** and aromatic amines to give compounds **5** (Scheme 1). The IR spectra of the aminomethyl spiro compounds **4** revealed two characteristic bands at 1365-1380 and 1168-1190 cm^{-1}, indicative of the SO_2N group and two bands at 3150-3190 and 3310-3380 cm^{-1} for the NH bands. Their ^{1}H NMR spectra showed two triplets in the regions δ 3.68-3.81 and 3.42-3.50 for H-2 and H-3 respectively and doublet at 3.85-4.10 for CH_2, the aromatic portons appeared at δ 6.99-8.74 while the cyclic aliphatic portons appeared at 1.25-2.18. The ^{1}H NMR spectra of **5** exhibited a doublet at δ 1.34-1.38 and a multiplet at δ 4.10 - 4.15 for the CH_3 and CH protons respectively (Table 2).



Scheme 1

Antimicrobial activity

Antimicrobial testing of compounds **2-5** (Table 3) was carried out against *Stapylococus* and it was found that compounds **3a1**, **3b1**, **3c1** and **3e1** showed maximum activity (+++) *(MIC = 25 Mg/ml)*, compounds **2a**, **2b**, **2d**, **2e**, **3a2**, **3b2**, **4a1** and **4a3** showed moderate activity (++) (MIC = 50 mg/ml), while compounds **2c** and **2f** exhibited slight activity (+) (MIC = 75 Mg/ml). Against *E. Coli* compounds **3a1**, **3a2**, **3b1** and **3b2** and **3e1** showed maximum activity, while compounds **2b**, **2e**, **3c1**, and **4a1** exhibited moderate activity, while compounds **2a**, **2c**, **2d**, **2f**, **4a2**, **4a3**, and **4c2**, showed slight activity. However, all other compounds were inactive towards the different strains of bacteria. On the other hand, all compounds were inactive towards *C. Albicans.*

Experimental

^{1}H NMR spectra were recorded on Bruker DPX-400FT NMR spectrometers using TMS as internal standard. Mass spectra were determined on a Kratos MS 30. The Infrared spectra were measured on a Nicolet Magna FT 520 spectrophotometer using potassium bromide pellets. Microanalyses were performed on a 2400 Perkin Elmer Series 2 CHNS analyzer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

Spiro Oxazoldine Derivatives 2

A mixture of ethanolamine (6.1g, 0.1 mole) and the appropriate cyclic ketone (0.1 mole) in dry benzene (50 ml) was refluxed using Dean-stark trap until no more water was collected (about 1-2hr). Benzene was then removed under reduced pressure and the residue subjected to column chromatography on silica gel (chloroform / methanol 8:2).

Spiro Oxazolidine Thioamide Derivatives 3

A mixture of the corresponding spiro oxazolidine 2 (0.05 mole), anhydrous, K_2CO_3 (0.1 mole) in dry acetone (100 ml) was stirred and treated at a drop wise rate with a solution of the appropriate isothiocyanate (0.05 mole) in dry acetone (20 ml). After stirring and refluxing the mixture for 6hr, acetone was removed under reduced pressure and the solid residue was dissolved in H_2O. The crude product separated upon acidification with dilute HCl was purified by recrystallization from ethanol.

Spiro Oxazolidine Sulfa Drug Deivatives 4

A mixture of the spiro oxazolidine derivative 2 (0.03 mole) and the sulfa drug (0.03 mole) in absolute ethanol (20 ml) was refluxed with formaldehyde (5 ml, 37%, 0.06 mole), for 4hr. The reaction mixture was then concentrated and the product which separated out was recrystallized from ethanol in needles.

spiro oxazolidine ethylaromatic amine derivatives 5

A solution of the spiro compound 2 (0.03 mole) in absolute ethanol (20 ml) was refluxed with the appropriate aromatic amine (0.03 mole) and acetaldehyde 99%, (2.8 ml, 0.05 mole) for 4hr. The reaction mixture was then concentrated and the solid which separated out recrystallized from ethanol in needles.

Biological Testing

Compounds 2-5 were screened for their antibacterial and antifungal activity following agar-diffusion method[21] using Gram-positive bacteria Stapylococcus and Gram-negative bacteria Escherichia coli. The antifungal testing was carried out against candida albicans.

Acknowledgement

The authors wish to thanks department of biology of King Abdulaziz Universtiy for their helpful contribution and for facilities.

References

(1) M. L. Cohen, *Nature,* **406**, 762 (2000).

(2) S. J. Brickner *Curr. Pharm. Design*, **2**, 175 (1996).

(3) M. R. Barbachyn, S. J. Brickner, G. J. Cleek, R. C. Gadwood, K. C. Grega, S. K. Hendges, D. K. Hutchinson, P. R. Manninen, K. Munesada, R. C. Thomas, L. M. Thomasco, D. S. Toops and D. A. Ulanowicz, In *Antiinfectives: Recent Advances in Chemistry and Structure Activity Relationships*, P. H. Bentley, O;Hanlon, Eds., The Royal society of Chemistry, Hartnolls Limited: Bodmin, Cornwall, 15 (1997).

(4) M. . Barbachyn, S. J. Brickner, R. C. Gadwood, S. A. Garmon, K. C. Grega, D. K. Hutchinson, K. Munesada, R. J. Reischer, M. Taniguchi, L. M. Thomasco, D. S. Toops, H. Yamada, C. W. Ford and G. E. Zurenko, In *Resolving the Antibiotics Paradox*, B. P. Rosen and S. Mobashery, Eds., Kluwer Academc, Plenum Publishers: New York, 219 (1998).

(5) D. A. Shinabarger, *Exp. Opin. Invest. Drugs*, **8**, 1195 (1999); *Chem. abstr.*, **13**, 269300 (1999).

(6) R. B. Fugitt and R. W. Luckenbaugh, *Eur. Pat. Appln.*, **EP 50**, 827 (1982); *Chem. Abstr.*, **97**, 109990 (1982).

(7) J. Lizondo and X. Rabasseda *J. Drugs of Future,* **21**, 1116 (1996).
(8) Jr. R. C. Moellering *Ann. Intern. Med.,* **138**, 135 (2003).
(9) A. Mehta, S. K. Arora, B. Das, A. Ray, S. Rudra and A. Rattan, *Oxazolidinone derivatives as antimicrobials,* WIPO Pat. Appln, WO 02/0627 (2002); *Chem. Abst.,***136**, 134748 (2002).
(10) M. K. Ghorai and K. Ghosh, *Tetrahedron Lett.,* **48** (8), 3191 (2007).
(11) P. Seneci, M. Caspani, F. Ripamontiand R. Ciabatti, *J. Chem. Soc., Perkin Trans I,* 2345 (1994).
(12) M. Georges, D. Mackay and B. Fraser-Reid, *J. Am. Chem. Soc.,* **104**, 1101 (1982).
(13) K. C. Grega, M. R. Barbachyn, S. J. Brickner and S. A. Mizsak, *J. Org. Chem.,* **60**, 5255 (1995).
(14) S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowiez, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford and G. E. Zurenko, *J. Med. Chem.,* **39**, 673 (1996).
(15) H. A. Dondas, C. W. G. Fishwick, R. Grigg and M. T.-Pett, *Tetrahedron,* **59** (50), 9997 (2003).
(16) B. Testa, *Bichemical Pharmacology,* **68** (11), 2097 (2004).
(17) X. Qian, X. Xu, Zhibin Li, Zhong Li and G. Song, *Journal of Fluorine Chemistry,* **125**(11) 1609 (2004).
(18) D. F. Münzer, P. Meinhold, M. W. Peters, S. Feichtenhofer, H. Griengl, F. H. Arnold, A. Glieder and A. de Raadt, Chem. Commun., 2597 (2005).
(19) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.,* **64**, 1503 (1942).
(20) A. I. Vogel, *"A Text book of practical organic chem."* Langmans. Green Co., 3rd Ed., 2129 (1965).
(21) M. C. Bryant, *Antibiotics and their Laboratory centra* V. P. **26**, Butterworth London (1968)

Received on July 27, 2008.

Table 1. Physical and Analytical Data of Compounds 2-5

Compound	n	R	R′	R″	R‴	Ar	Yield [%]	M.P. [°C]	Formula	Calcd . %				Found %			
										C	H	N	S	C	H	N	S
2a	1	H	H				80	oil	$C_7H_{13}NO$	66.14	10.23	11.02		66.18	10.32	11.20	
2b	2	H	H				84	oil	$C_8H_{15}NO$	68.08	10.63	9.93		68.21	10.44	10.02	
2c	3	H	H				78	oil	$C_9H_{17}NO$	69.68	10.96	9.03		69.48	11.12	8.99	
2d	4	H	H				92	oil	$C_{10}H_{19}NO$	71.00	11.24	8.28		69.98	11.32	8.40	
2e	2	H	CH_3				77	oil	$C_9H_{17}NO$	69.68	10.96	9.03		69.70	11.12	9.15	
2f	2	Ph	H				89	oil	$C_{14}H_{19}NO$	77.42	8.75	6.45		77.65	8.88	6.54	
3a1	1	H	H	Ph			84	134	$C_{14}H_{18}N_2OS$	64.12	6.87	10.68	12.21	64.25	6.90	10.70	12.42
3a2	1	H	H	Benzyl			76	128	$C_{15}H_{20}N_2OS$	65.22	7 25	10.14	11.59	65.33	7.50	10.32	11.66
3b1	2	H	H	Ph			81	132	$C_{15}H_{20}N_2OS$	65.22	7.25	10.14	11.59	65.43	7.60	9.88	11.60
3b2	2	H	H	Benzyl			85	120	$C_{16}H_{22}N_2OS$	66.21	7.58	9.65	11.03	66.22	7.60	9.72	11.00
3c1	3	H	H	Ph			77	130	$C_{16}H_{22}N_2OS$	66.21	7.58	9.65	11.03	66.42	7.72	9.66	10.95
3e1	2	H	CH_3	Ph			74	120	$C_{16}H_{22}N_2OS$	66.21	7.58	9.65	11.03	66.42	7.60	9.75	11.12
3e2	2	H	CH_3	Benzyl			81	112	$C_{17}H_{24}N_2OS$	67.10	7.89	9.21	10.53	67.25	7.95	9.02	10.80
4a1	1	H	H		S-diazine[a]		95	200	$C_{18}H_{23}N_5O_3S$	55.53	5.91	17.99	8.23	55.65	6.00	18.12	8.02
4a2	1	H	H		S-thiazole[b]		97	268	$C_{17}H_{22}N_4O_3S_2$	51.78	5.58	14.21	16.24	51.87	5.80	14.11	16.42
4a3	1	H	H		S-methoxypyridazine[c]		93	240	$C_{19}H_{25}N_5O_4S$	54.41	5.96	16.71	7.64	54.34	6.05	16.82	7.55
4c2	3	H	H		S-thiazole[b]		96	276	$C_{19}H_{26}N_4O_3S_2$	54.03	6.16	13.27	15.16	54.12	6.25	13.52	15.23
5a	1	H	H			Ph	81	105	$C_{15}H_{22}N_2O$	73.17	8.94	11.38		73.20	9.02	11.42	
5b	1	H	H			Tolyl	79	110	$C_{16}H_{24}N_2O$	73.85	9.23	10.77		73.94	9.42	10.89	

[a] Pyrimidin-2-yl [b] Thiazol-2-yl [c] 6-Methoxypyridazin-3-yl

Table 2. Spectral Data of Compounds 2-5

	^{1}H NMR (δ / ppm)[a]							IR (cm^{-1})			MS
Compound	H-2 (t, 2H, J=6Hz)	H-3 (t, 2H, J=6Hz)	Cyclic aliph. H (m)	CH_3 (d, 3H, J=6Hz)	ArH (m)	NH (s)	Others	CS	NH	SO_2N	M^+ (relative abundance)
2a	3.65	3.10	1.29-1.95			5.40			3320		127 (10)
2b	3.62	3.13	1.25-1.85			4.92			3375		141 (8)
2c	3.61	3.18	1.20-2.52			5.30			3310		155 (18)
2d	3.68	3.12	1.25-2.65			5.12			3295		169 (14)
2e	3.66	3.25	1.24-2.14	1.27		5.12			3330		155 (12)
2f	3.60	3.11	1.19-2.20		7.15-7.39	5.25			3315		217 (25)
3a1	3.55	2.97	1.28-2.05		7.01-7.41	9.51		1080	3320		
3a2	3.98	3.70	1.36-1.79		7.13-7.51	9.25[b]	4.87(d, 2H, CH_2)	1112	3300		
3b1	3.90	2.99	1.34-1.96		6.95-7.52	9.14		1150	3325		
3b2	3.88	3.62	1.30-2.05		7.15-7.59	9.23[b]	4.82(d, 2H, CH_2)	1095	3298		
3c1	3.68	3.42	1.22-2.12		6.99-7.48	9.42		1110	3340		
3e1	3.64	3.32	1.26-2.16	1.26	7.05-7.51	9.30		1155	3335		
3e2	3.68	3.28	1.20-2.15	1.28	7.10-7.49	9.24[b]	4.80(d, 2H, CH_2)	1148	3300		
4a1	3.81	3.42	1.25-2.02		7.12-8.52	8.12[b],9.70	3.95(d, 2H, CH_2)		3150, 3360	1365,1170	
4a2	3.76	3.49	1.26-2.14		6.99-8.72	8.30[b],9.78	4.10(d, 2H, CH_2)		3172, 3355	1380,1190	
4a3	3.75	3.50	1.30-2.18		7.21-8.65	8.20[b],9.81	3.76(s, 3H, OCH_3), 3.98 (d, 2H, CH_2)		3165, 3380	1375,1168	
4c2	3.68	3.45	1.32-2.12		7.05-8.74	8.18[b],9.80	3.85(d, 2H, CH_2)		3190, 3310	1378,1178	
5a	3.55	3.20	1.28-2.02	1.34		8.52[c]	4.10(m, 1H, CH) 1.34 (d, 3H, CH_3)		3325		
5b	3.58	3.22	1.26-1.99	1.38, 2.34[d]		8.60[c]	4.15(m, 1H, CH) 1.38 (d, 3H, CH_3)		3362		

[a] Solution in a mixture of $CDCl_3$ and DMSO-d_6 [b] triplet [c] doublet [d] singlet

Table 3. Antimicrobial Activities of Synthesized Compounds 2-5 (+++ for maximim activity, MIC 25; ++ for moderate activity, MIC 50; + for slight activity, MIC 75 and - for inactive.

Compound	n	R	R′	R″	R‴	Ar	S. Coccus I. Z.	E. Coli
2a	1	H	H				++	+
2b	2	H	H				++	++
2c	3	H	H				+	+
2d	4	H	H				++	+
2e	2	H	CH_3				++	++
2f	2	Ph	H				+	+
4a1	1	H	H		S-diazine		++	++
4a2	1	H	H		S-Thiazole		–	+
4a3	1	H	H		S-methoxypyridazine		++	+
4c2	3	H	H		S-Thiazole		–	+
5a	1	H	H			Ph	–	–
5b	1	H	H			Tolyl	–	–
3a1	1	H	H	Ph			+++	+++
3a2	1	H	H	Benzyl			++	+++
3b1	2	H	H	Ph			+++	+++
3b2	2	H	H	Benzyl			++	+++
3c1	3	H	H	Ph			+++	++
3e1	2	H	CH_3	Ph			+++	+++