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Synthesis and characterization of a novel series of benzenesulfonylurea and thiourea derivatives of 2*H*-pyran and 2*H*-pyridine-2-ones as antibacterial, antimycobacterial and antifungal agents

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ABSTRACT

Arylhydrazines reacted with dehydroacetic acid (**1**) to give the corresponding 2*H*-pyran-2-one hydrazones (**2**), which on treatment with hydrazine hydrate afforded the corresponding 1-amino-2*H*-pyridin-2-ones (**3**). Reaction of **3** with nitrous acid, aromatic aldehyde and substituted benzenesulfonyl chlorides yielded the corresponding 2*H*-pyridine-2-one derivatives. A series of urea and thiourea derivatives were also prepared. Some of these compounds have shown significant antibacterial and mild to moderate antimycobacterial and antifungal activities.

1. Introduction

In recent years, the number of life threatening infections caused by multi-drug resistant Gram positive and Gram negative pathogenic bacteria has reached an alarming level in many countries around the world; consequently the need for the synthesis of novel antibiotics is a reality. However, investigations in the chemistry and biology of 2-pyrones have become that they constitute an essential pharmacophore in many naturally occurring and biologically active agents [1]. Literature survey revealed that a simple change in the substitution pattern on the 2-pyrone ring often leads to diverse biological activities.

For example, some 2-pyrone derivatives are yeast lipase (CRLI), cholesterol esterase (CRL3) inhibitors [3], anti-inflammatory [4,5] and immune suppressive [6] agents. Particular attention has been focused on the distinctive chemotherapeutic activity of 2-pyrones as cytotoxic agents against some human cancer cell lines [7,8], anti-HIV [9,10] and potential antimicrobial agents [11,12]. On the other hand, a broad spectrum of pharmacological properties has been ascribed to the structurally-relevant 2-pyridone derivatives. In addition to their pronounced effects on the cardiovascular system as cardiotonic [13,14], calcium channel blocking [15] and tissue factor VII inhibitory agents [16], some pyridones were reported to exhibit potential antimicrobial [17-20], antitubercular [21,22], antiamoebic [23], antiparasitic [24], antimalarial [25], antifungal and antiviral [26-28] activities.

N-Substituted pyrazolyl-benzensulfonamides are known to show COX-2 selective inhibition [29], thioureide analogs of 2-phenetilbenzoic acid and pyridazine derivatives carrying urea, thiourea, and sulfonamide moieties were reported to exhibit potential antimicrobial and antifungal activities [30-34]. Hence urea, thiourea and sulfonamides are considered, one of the active areas of medicinal research where efforts are focused in order to have new and better therapeutic agents.

On the basis of these findings, the aim of this study was to synthesize the hybrid molecule through a combination of pyridone and hydrazide pharmacophores in one structure with the hope of obtaining better antibacterial and/or antifungal agents. Therefore, we have synthesized a series of new 2-pyrone and their 2-pyridone analogs (Scheme 1 and 2), carrying urea, thiourea and sulfonamide groups in order to investigate their antibacterial and antifungal activities.

2. Experimental

2.1. Synthesis

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer 297 infrared spectrophotometer using the plate technique. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400-FT spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University, Cairo, Egypt. Follow up of the reactions and checking the homogeneity of the compounds were made by Thin layer chromatography (TLC) on silica gel-protected aluminum sheets (Type 60 F_{254}, Merck) and the spots were detected by exposure to UV lamp at λ = 254 nm. Biological testing was performed in the Faculty of Science, University of Alexandria, Egypt. Dehydroacetic acid was purchased from

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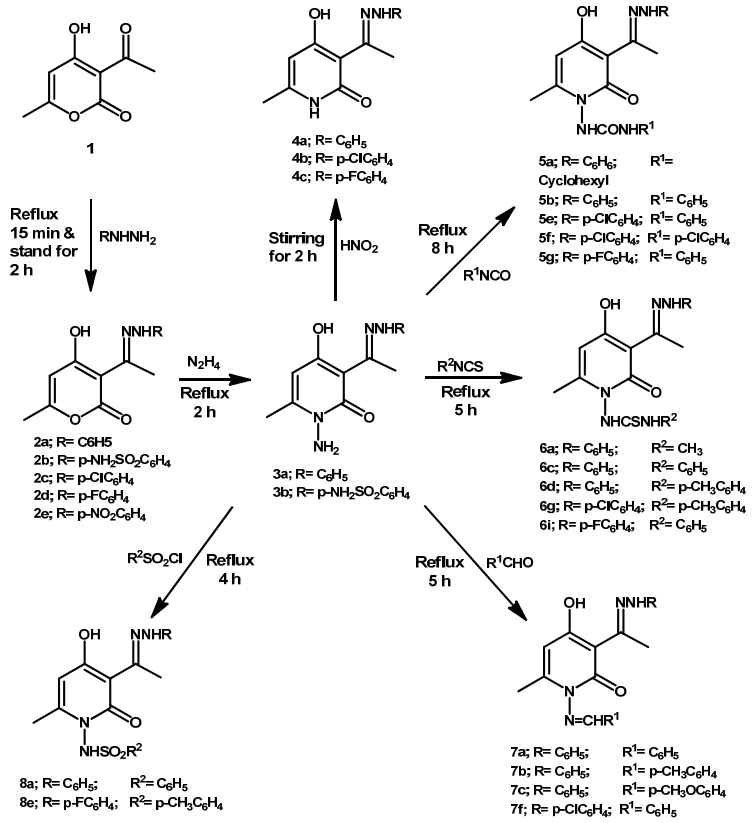
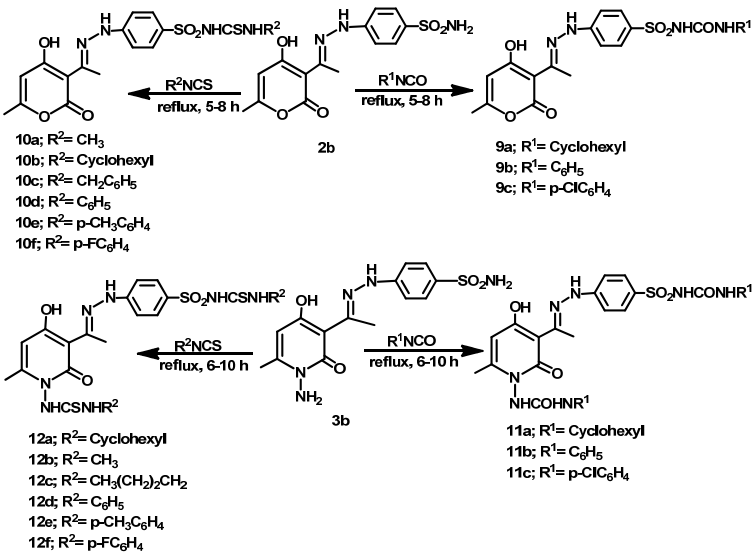


Scheme 1



Scheme 2

Aldrich Chemical Co., Milwaukee, USA and was used without further purification. The characterization data of the synthesized compounds (2-6) (Scheme 1 and 2) are given in Table 1-3.

2.1.1. 4-Hydroxy-6-methyl-3-[1-(substituted-hydrazono) ethyl]pyran-2-ones (2a-e)

To a solution of **1** (10 mmol) in benzene (20 mL) was added the appropriate aryl hydrazine (10 mmol). The mixture was refluxed for 15 min and allowed to stand at room temperature for 2 h. After the mixture was cooled, the hydrazone was collected and recrystallized from ethanol.

2.1.2. 1-Amino-4-hydroxy-6-methyl-3-[1-(substituted-hydrazono)ethyl]-1H-pyridin-2-ones (3a-d)

A solution of the appropriate hydrazone **2** (10 mmol) in ethanol (20 mL) was refluxed with hydrazine hydrate 98% (1.1 mL, 22 mmol) for 2 h. The reaction mixture was concentrated to half its volume and allowed to cool. The solid product separated was filtered, washed with cold ethanol and recrystallized from ethanol.

Table 1. Characterization data of compounds (**2-6**).

Comp.	R	R¹ or R²	Yield (%)	M.p. (°C)	Mol. Formula	Calculated %				Found %			
						C	H	N	S	C	H	N	S
2a	C_6H_5		82	212[a]	$C_{14}H_{14}N_2O_3$	65.11	5.46	10.85		56.21	5.54	10.94	
2b	p-$H_2NSO_2C_6H_4$		85	255	$C_{14}H_{15}N_3O_5S$	49.84	4.48	12.46	9.51	49.72	4.51	12.47	9.62
2c	p-ClC_6H_4		78	218	$C_{14}H_{13}ClN_2O_3$	57.44	4.48	9.57		57.45	4.53	9.62	
2d	p-FC_6H_4		74	212	$C_{14}H_{13}FN_2O_3$	60.87	4.74	14.01		60.81	4.76	13.98	
2e	p-$NO_2C_6H_4$		78	216	$C_{14}H_{13}N_3O_5$	55.45	4.32	13.86		55.48	4.42	13.93	
3a	C_6H_5		69	233	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58		61.84	6.02	20.67	
3b	p-$H_2NSO_2C_6H_4$		70	192	$C_{14}H_{17}N_5O_4S$	47.85	4.88	19.93	9.13	47.92	4.92	20.11	9.23
3c	p-ClC_6H_4		63	250	$C_{14}H_{15}ClN_4O_2$	54.82	4.93	18.26		54.97	5.04	18.18	
3d	p-FC_6H_4		60	216	$C_{14}H_{15}FN_4O_2$	57.92	5.21	19.31		57.84	5.12	19.42	
4a	C_6H_5			204	$C_{14}H_{15}N_3O_2$	65.35	5.88	16.33		65.45	5.97	16.45	
4b	p-ClC_6H_4			231	$C_{14}H_{14}ClN_3O_2$	57.64	4.84	14.41		57.81	4.93	14.38	
4c	p-FC_6H_4			223	$C_{14}H_{14}FN_3O_2$	61.08	5.13	15.26		61.12	5.16	15.37	
5a	C_6H_5	Cyclohexyl	68	169	$C_{21}H_{27}N_5O_3$	63.46	6.85	17.62		63.58	6.92	17.74	
5b	C_6H_5	C_6H_5	70	205	$C_{21}H_{21}N_5O_3$	64.44	5.41	17.89		64.54	5.38	17.92	
5c	C_6H_5	p-ClC_6H_4	68	214	$C_{21}H_{20}ClN_5O_3$	59.23	4.73	16.44		59.34	4.82	16.54	
5d	p-ClC_6H_4	Cyclohexyl	72	264	$C_{21}H_{26}ClN_5O_3$	58.41	6.07	16.21		58.33	6.18	16.38	
5e	p-ClC_6H_4	C_6H_5	74	249	$C_{21}H_{20}ClN_5O_3$	59.23	4.73	16.44		59.28	4.84	16.36	
5f	p-ClC_6H_4	p-ClC_6H_4	70	259	$C_{21}H_{19}Cl_2N_5O_3$	54.79	4.16	15.21		54.82	4.27	15.22	
5g	p-FC_6H_4	C_6H_5	66	218	$C_{21}H_{20}FN_5O_3$	61.61	4.92	17.11		61.73	5.11	17.31	
5h	p-FC_6H_4	p-ClC_6H_4	68	248	$C_{21}H_{19}ClFN_5O_3$	56.83	4.31	15.78		56.71	4.23	15.87	
6a	C_6H_5	CH_3	69	260	$C_{16}H_{19}N_5O_2S$	55.63	5.54	20.27	9.28	55.54	5.48	20.32	9.31
6b	C_6H_5	$CH_3(CH_3)_2CH_2$	66	249	$C_{19}H_{25}N_5O_2S$	58.89	6.51	18.07	8.27	58.97	6.58	17.18	8.38
6c	C_6H_5	C_6H_5	72	254	$C_{21}H_{21}N_5O_2S$	61.91	5.19	17.19	7.87	61.87	5.23	16.76	7.94
6d	C_6H_5	p-$CH_3C_6H_4$	70	262	$C_{22}H_{23}N_5O_2S$	62.69	5.51	16.61	7.61	62.79	5.62	16.58	7.62
6e	C_6H_5	p-FC_6H_4	69	216	$C_{21}H_{20}FN_5O_2S$	59.28	4.74	16.46	7.54	59.41	4.78	16.48	7.53
6f	p-ClC_6H_4	C_6H_5	72	266	$C_{21}H_{20}ClN_5O_2S$	57.07	4.56	15.85	7.26	57.14	4.66	15.92	7.34
6g	p-ClC_6H_4	p-$CH_3C_6H_4$	74	241	$C_{22}H_{22}ClN_5O_2S$	57.95	4.86	15.36	7.03	58.12	4.89	15.44	7.11
6h	p-ClC_6H_4	p-FC_6H_4	68	257	$C_{21}H_{19}ClFN_5O_2S$	54.84	4.16	15.23	6.97	54.86	4.23	15.41	7.04
6i	p-FC_6H_4	C_6H_5	67	252	$C_{21}H_{20}FN_5O_2S$	59.28	4.74	16.46	7.54	59.37	4.86	16.55	7.63
7a	C_6H_5	C_6H_5	72	238	$C_{21}H_{20}N_4O_2$	69.98	5.59	15.55		70.11	5.62	15.64	
7b	C_6H_5	p-$CH_3C_6H_4$	74	226	$C_{22}H_{22}N_4O_2$	70.57	5.92	14.96		70.48	6.02	15.04	
7c	C_6H_5	p-$CH_3OC_6H_4$	68	230	$C_{22}H_{22}N_4O_3$	67.68	5.68	14.35		67.79	5.74	14.42	
7d	C_6H_5	p-ClC_6H_4	72	242	$C_{21}H_{19}ClN_4O_2$	63.88	4.85	14.19		63.92	4.94	14.25	
7e	C_6H_5	2-Thienyl	76	235	$C_{19}H_{18}N_4O_2S$	62.28	4.95	15.29		62.31	5.11	15.41	
7f	p-ClC_6H_4	C_6H_5	78	199	$C_{21}H_{19}ClN_4O_2$	63.88	4.85	14.19		63.77	4.76	14.28	
7g	p-ClC_6H_4	p-ClC_6H_4	76	216	$C_{21}H_{18}Cl_2N_4O_2$	58.75	4.23	13.05		58.84	4.24	13.16	
7h	p-ClC_6H_4	2-Thienyl	72	222	$C_{19}H_{17}ClN_4O_2S$	56.93	4.27	13.98		57.12	4.39	14.01	
7i	p-FC_6H_4	C_6H_5	69	220	$C_{21}H_{19}FN_4O_2$	66.66	5.06	14.81		66.75	5.08	14.92	
7j	p-FC_6H_4	p-ClC_6H_4	66	218	$C_{21}H_{18}ClFN_4O_2$	61.09	4.39	13.57		61.12	4.42	13.64	
7k	p-FC_6H_4	2-Thienyl	68	209	$C_{19}H_{17}FN_4O_2S$	59.36	4.46	14.57		59.43	4.61	15.46	
8a	C_6H_5	C_6H_5	76	178	$C_{20}H_{20}N_4O_4S$	58.24	4.89	13.58	7.77	58.13	4.91	13.62	7.86
8b	C_6H_5	p-$CH_3C_6H_4$	78	162	$C_{21}H_{22}N_4O_4S$	59.14	5.21	13.14	7.52	59.24	5.32	13.24	7.45
8c	p-ClC_6H_4	C_6H_5	77	136	$C_{20}H_{19}ClN_4O_4S$	53.75	4.29	12.54	7.17	53.88	4.41	12.63	7.21
8d	p-FC_6H_4	C_6H_5	76	138	$C_{20}H_{19}FN_4O_4S$	55.81	4.45	13.02	7.45	55.92	4.61	13.12	7.56
8e	p-FC_6H_4	p-$CH_3C_6H_4$	78	164	$C_{21}H_{21}FN_4O_4S$	56.75	4.76	12.61	7.21	56.82	4.79	12.75	7.34
9a		Cyclohexyl	74	172	$C_{21}H_{26}N_4O_6S$	54.53	5.67	12.11	6.93	54.64	5.73	12.21	7.11
9b		C_6H_5	72	192	$C_{21}H_{20}N_4O_6S$	55.26	4.42	12.27	7.02	55.37	4.43	12.36	7.15
9c		p-ClC_6H_4	78	163	$C_{21}H_{19}ClN_4O_6S$	51.38	3.91	11.41	6.53	51.49	4.02	11.56	6.48
10a		CH_3	70	189	$C_{16}H_{18}N_4O_5S_2$	46.82	4.42	13.65	15.62	46.88	4.34	13.78	15.74
10b		Cyclohexyl	72	199	$C_{21}H_{26}N_4O_5S_2$	52.71	5.48	11.71	13.41	52.82	5.52	11.82	13.48
10c		$CH_2C_6H_5$	70	168	$C_{22}H_{22}N_4O_5S_2$	54.31	4.56	11.51	13.18	54.42	4.64	15.68	13.02
10d		C_6H_5	70	152	$C_{21}H_{20}N_4O_5S_2$	53.38	4.27	11.86	13.57	53.51	4.38	11.99	13.43
10e		p-$CH_3C_6H_4$	77	148	$C_{22}H_{22}N_4O_5S_2$	54.31	4.56	11.51	13.18	54.44	4.62	11.54	13.08
10f		p-FC_6H_4	72	151	$C_{21}H_{19}FN_4O_5S_2$	51.42	3.91	11.42	13.07	51.56	4.14	11.58	13.15
11a		Cyclohexyl	72	215	$C_{28}H_{39}N_7O_6S$	55.89	6.53	16.29	5.33	55.92	6.58	16.41	5.38
11b		C_6H_5	70	243	$C_{28}H_{27}N_7O_6S$	57.04	4.62	16.63	5.44	57.13	4.73	16.74	5.42
11c		p-ClC_6H_4	72	236	$C_{28}H_{25}Cl_2N_7O_6S$	51.07	3.83	14.89	4.87	51.12	3.94	14.78	5.96
12a		Cyclohexyl	73	229	$C_{28}H_{39}N_7O_4S_3$	53.06	6.21	15.47	15.18	53.18	6.12	15.52	15.09
12b		CH_3	70	237	$C_{18}H_{23}N_7O_4S_3$	43.45	4.66	19.71	19.33	43.61	4.75	19.83	19.32
12c		$CH_3(CH_2)_2CH_2$	68	244	$C_{24}H_{35}N_7O_4S_3$	49.55	6.06	16.85	16.53	49.64	6.17	16.92	16.64
12d		C_6H_5	70	242	$C_{28}H_{27}N_7O_4S_3$	54.09	4.38	15.77	15.47	54.12	4.42	15.91	15.52
12e		p-$CH_3C_6H_4$	69	250	$C_{30}H_{31}N_7O_4S_3$	55.45	4.81	15.09	14.81	55.54	4.96	15.13	14.71
12f		p-FC_6H_4	67	232	$C_{28}H_{25}F_2N_7O_4S_3$	51.13	3.83	14.91	14.63	51.24	3.74	15.04	14.68

[a]Lit. [7] M.p.: 209 °C.

2.1.3. 4-Hydroxy-6-methyl-3-[1-(substituted-hydrazono) ethyl]-1H-pyridon-2-ones (4a-c)

A solution of the appropriate 1-amino-2-pyridone derivative **3** (2 mmol) in glacial acetic acid (10 mL) was treated (drop wise) with an aqueous solution of sodium nitrite (0.5 g) with stirring for 2 h. The reaction mixture was then poured onto ice cold water and the separated solid was recrystallized from ethanol.

2.1.4. 1-{4-Hydroxy-6-methyl-2-oxo-3-[1-(substituted-hydrazono)ethyl]-2H-pyridin-1-yl}-3-substituted ureas (5a-h)

To the solution to the appropriate aminopyridone **3** (2 mmol) in pyridine (10 mL) was added the appropriate isocyanate (2.1 mmol), and the reaction mixture was heated under reflux for 8 h. After cooling to room temperature, the reaction mixture was poured on crushed ice and the separated solid product was filtered, washed thoroughly with water, dried and crystallized from ethanol.

Table 2. ^{1}H NMR spectral data (δ/ppm)[a] of compounds (**2**-**10**).

Comp.	R	R^1 or R^2	CH_3	H-5	Ar-H	NH	OH	Others
			(*s*, 3H)	(*s*, 1H)	(*m*)	(*s*, 1H)	(*s*, 1H)	
2a	C_6H_5		1.03, 1.52	5.99	6.62-7.01	7.85	14.28	
2b	*p*-$NH_2SO_2C_6H_4$		1.17, 1.62	6.22	6.85-7.72	8.02	14.46	
2c	*p*-ClC_6H_4		0.95, 1.41	6.36	6.45-6.98	7.62	14.82	
2d	*p*-FC_6H_4		1.05, 1.38	6.24	6.48-6.76	7.71	14.26	
2e	*p*-$NO_2C_6H_4$		1.08, 1.47	6.21	6.25-7.01	8.96	15.02	
3a	C_6H_5		1.13, 1.43	5.02	6.62-7.12	7.58	14.52	
3b	*p*-$NH_2SO_2C_6H_4$		1.12, 1.41	5.34	6.47-7.68	7.94	13.84	
4a	C_6H_5		1.03, 1.54	5.52	6.62-7.68	7.72, 8.12	14.92	
4b	*p*-ClC_6H_4		1.12, 1.42	5.34	6.71-7.03	7.64, 8.06	15.03	
4c	*p*-FC_6H_4		0.98, 1.38	5.28	6.74-7.26	7.52, 8.03	14.74	
5a	C_6H_5	Cyclohexyl	1.10, 1.55	5.46	6.81-7.71	6.62, 6.75, 8.57	13.98	1.32-2.63 (*m*, 11H, cyclohexyl)
5b	C_6H_5	C_6H_5	1.04, 1.52	5.29	6.93-7.68	6.74, 6.84, 8.61	14.05	
5e	*p*-ClC_6H_4	C_6H_5	1.18, 1.49	5.34	7.01-7.79	6.88, 6.94, 8.43	13.24	
5f	*p*-ClC_6H_4	*p*-ClC_6H_4	1.05, 1.54	5.22	6.74-7.84	7.26, 8.64, 8.94	14.46	
5g	*p*-FC_6H_4	C_6H_5	0.98, 1.37	5.34	6.62-7.68	7.85, 8.32, 8.75	14.04	
6a	C_6H_5	CH_3	0.95, 1.41	5.29	6.63-7.02	7.24, 7.56, 8.66	15.13	3.45 (*d*, 3H, NCH_3)
6c	C_6H_5	C_6H_5	1.01, 1.46	5.38	6.72-7.41	7.64, 7.83, 9.12	14.28	
6d	C_6H_5	*p*-$CH_3C_6H_4$	1.24, 1.53	5.42	6.83-7.78	7.83, 8.72	12.98	3.13 (*s*, 3H, CH_3)
6g	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	1.18, 1.49	5.39	6.64-7.76	7.94, 8.82	13.56	3.08 (*s*, 3H, CH_3)
6i	*p*-FC_6H_4	C_6H_5	1.07, 1.33	5.26	6.56-7.64	7.74, 7.92, 8.45	14.03	
7a	C_6H_5	C_6H_5	1.12. 1.46	5.28	6.78-7.75	7.95	12.98	8.21 (*s*, 1H, CH=)
7b	C_6H_5	*p*-$CH_3C_6H_4$	1.23, 1.50	5.36	6.67-7.58	8.38	13.56	3.14 (*s*, 3H, CH_3), 8.16 (s, 1H, CH=)
7c	C_6H_5	*p*-$CH_3OC_6H_4$	1.25, 1.46	5.42	6.89-7.79	8.61	13.42	3.85 (*s*, 3H, CH_3O), 8.12 (s, 1H, CH=)
7f	*p*-ClC_6H_4	C_6H_5	1.18, 1.38	5.39	6.77-7.68	8.56	14.05	8.24 (s, 1H, CH=)
8a	C_6H_5	C_6H_5	1.20, 1.36	5.25	6.80-7.72	8.05, 8.42	14.36	
8e	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	1.22, 1.48	5.34	6.74-7.81	8.16, 8.89	13.88	3.12 (*s*, 3H, CH_3)
9a		Cyclohexyl	0.98, 1.50	6.22	6.68-7.42	7.82, 8.05, 8.56	12.98	1.35-2.84 (*m*, 11H, cyclohexyl)
9b		C_6H_5	1.15, 1.54	6.34	6.72-7.64	8.12, 8.34, 8.74	14.45	
10a		CH_3	1.12, 1.49	6.28	6.84-7.36	8.06, 8.42, 8.68	13.92	3.38 (*d*, 3H, CH_3)
10c		$CH_2C_6H_5$	1.20, 1.56	6.42	6.94-7.65	7.98, 8.14, 8.78	12.78	4.57 (*d*, 2H, CH_2)
10d		C_6H_5	1.17, 1.65	6.27	6.68-7.62	7.86, 8.03, 8.66	14.15	
11a		Cyclohexyl	1.14, 1.68	5.28	6.72-7.34	7.94, 8.05, 8.56, 8.84	14.25	1.22-3.05 (*m*, 22H, 2cyclohexyl)
11b		C_6H_5	1.22, 1.56	5.32	6.64-7.58	7.82, 8.14, 8.35, 8.82	13.98	
12a		Cyclohexyl	1.02, 1.59	5.41	6.76-7.49	8.01, 8.25, 8.67, 9.11	13.67	1.18-3.14 (*m*, 22H, 2cyclohexyl)
12d		C_6H_5	1.06, 1.63	5.29	6.65-7.78	8.14, 8.42, 8.90, 9.24	14.18	
12e		*p*-$CH_3C_6H_4$	1.17, 1.65	5.34	6.89-7.82	7.98, 8.06, 8.67, 8.98	14.28	3.12 (*s*, 3H, CH_3), 3.18 (*s*, 3H, CH_3)

[a] Solution in a mixture of $CDCl_3$ and DMSO-d_6.

2.1.5. N^1-{4-Hydroxy-6-methyl-2-oxo-3-[1-(substituted-hydrazono)ethyl]-2H-pyridin-1-yl}-N^3-substituted thioureas (6a-i)

To a solution of the appropriate **3** derivative (2 mmol) in pyridine (10 mL) was added the appropriate isothiocyanate (2.1 mmol), and the reaction mixture was refluxed for 5 h and worked up as above.

2.1.6. 1-(Arylideneamino)-4-hydroxy-6-methyl-3-[1-(substituted-hydrozono)ethyl]-1H-pyridin-2-ones (7a-k)

A mixture of the appropriate **3** derivate (1 mmol) and the appropriate aldehyde (1 mmol) in benzene (10 mL) was refluxed for 5 h. Excess solvent was removed under reduced pressure, and the remaining residue was treated with methanol, filtered and recrystallized from ethanol.

2.1.7. 1-(N-substituted benzenesulfonylamino)-4-hydroxy-6-methyl-3-[1-substituted-hydrazono)ethyl]-1H-pyridin-2-ones (8a-e)

To a solution of the appropriate **3** derivative (1 mmol) in pyridine (10 mL) was added the appropriate benzenesulfonyl chloride derivative (1.1 mmol), and the mixture was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured on crushed ice and the separated solid product was filtered, washed thoroughly with water, dried and crystallized from a mixture of ethanol and benzene.

2.1.8. General procedure for the preparation of N^1-substituted N^3-{4-[(4hydroxy-3-methyl-2-oxopyran-3-yl) ethylidenehydrazino]benzenesulfonyl]}ureas and thioureas (9a-c, 10a-f)

To a solution of **2b** (0.34 g, 1 mmol) in pyridine (10 mL) was added the appropriate isocyanate or isothiocyanate (1.1 mmol), and the reaction mixture was heated under reflux for 5-8 h. After cooling to room temperature, the reaction mixture was poured on crushed ice and the separated solid product was filtered, washed thoroughly with water, dried and crystallized from ethanol.

2.1.9. General procedure for the preparation of 2-pyridone diureas and dithioureas derivatives (11a-c, 12a-f)

To a solution of **3b** (0.35g, 2 mmol) in pyridine (10 mL) was added the appropriate isocyanate or isothiocyanate (4.2 mmol), and the reaction mixture was heated under reflux for 6-10 h. After cooling to room temperature, the reaction mixture was poured on crushed ice and the separated solid product was filtered, washed thoroughly with water, dried and crystallized from the dimethylformamide containing few drops of water.

2.2. Antimicrobial screening

2.2.1. Inhibition zone (IZ) measurement

Standard sterilized filter paper discs (5 mm diameter) impregnated with a solution of the test compound in dimethyl sulfoxide (DMSO) (1 mg/mL) was placed on an agar plate seeded with the appropriate test organism in triplicates. The utilized test organisms were: *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6051) as examples of Gram positive bacteria, *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) as examples of Gram negative bacteria, *Candida albicans* (ATCC 10231) and *Aspergillus niger* (recultured) as representatives of fungi. Ampicillin trihydrate and clotrimazole were used as standard antibacterial and antifungal agents, respectively. DMSO alone

Table 3. ^{13}C NMR spectral data (δ/ppm)[a] of compounds (**2**-**10**).

Comp.	R	R^1 or R^2	CH_3	Pyrone or Pyridone C	ArC	C=N	Others
2a	C_6H_5		13.5, 22.8	92.0, 102.8, 144.1, 161.0, 175.2	115.1, 118.5, 129.3, 140.5	155.6	
2b	*p*-$NH_2SO_2C_6H_4$		12.7, 20.9	94.3, 105.2, 145.4, 160.7, 174.1	117.2, 126.3, 129.4, 137.4	152.4	
2c	*p*-FC_6H_4		11.8, 21.4	95.2, 103.7, 143.1, 160.9, 172.3	116.3, 120.2, 142.3, 152.1	156.3	
3a	C_6H_5		12.0, 20.3	94.4, 103.7, 133.7, 160.2, 171.2	120.2, 126.3, 129.4, 142.3	154.2	
3b	*p*-$NH_2SO_2C_6H_4$			96.6, 108.2, 147.3, 162.8, 173.4	118.6, 125.9, 129.7, 148.3	155.4	
4a	C_6H_5			94.9, 102.6, 138.4, 163.3, 169.9	120.7, 126.3, 129.8, 143.7	157.1	
5b	C_6H_5	Cyclohexyl	11.98, 21.2	92.8, 106.2, 135.8, 161.7, 170.4	121.3, 126.8, 129.5, 138.8	23.1, 29.2, 34.6, 49.5	163.2 (cyclohexyl) (CO)
6a	C_6H_5	CH_3	12.6, 20.7, 32.3	94.6, 109.4, 136.8, 160.4, 168.6	118.9, 126.3, 129.2, 140.4	185.6 (CS)	
6d	C_6H_5	*p*-$CH_3C_6H_4$	13.6, 18.6, 22.3	93.2, 104.6, 135.9, 161.3, 171.8	115.4, 120.3, 122.2, 127.8 128.1, 130.7, 139.2, 140.1	155.8	181.5 (CS)
7a	C_6H_5	C_6H_5	11.6, 20.2	94.6, 110.4, 133.8, 163.6, 168.4	120.2, 121.7, 127.5, 129.8 131.8, 136.7, 137.9, 141.2	152.7	126.2 (CH=)
7b	C_6H_5	*p*-$CH_3C_6H_4$	12.9, 21.4, 23.2	92.6, 108.4, 142.1, 160.5, 171.6	117.3, 121.2, 124.5, 126.4 128.2, 130.6, 138.7, 143.5	156.6	125.4 (CH=)
8a	C_6H_5	C_6H_5	13.7, 20.9	94.6, 105.2, 145.3, 161.9, 170.4	118.8, 121.2, 122.6, 128.4 129.3, 132.6, 138.8, 142.1	155.4 163.8 (cyclohexyl) (CO)	22.9, 28.1, 34.2, 48.4
9a	C_6H_5	Cyclohexyl	12.7, 21.3	93.6, 106.4, 142.7, 160.8, 173.4	118.8, 126.9, 129.4, 142.3	153.4	186.4 (CS)
10a		CH_3	13.2, 20.8, 33.2	98.9, 110.3, 146.2, 161.9, 172.9	120.3, 127.9, 137.2, 142.9		

[a] Solution in a mixture of $CDCl_3$ and DMSO-d_6.

was used as control at the same above-mentioned concentration. The plates were incubated at 37 °C for 24 h for bacteria and 72 h for fungi. The results were recorded for each tested compound as the average diameter of inhibition zones of bacterial growth around the discs in mm (Table 4).

2.2.2. Minimal inhibitory concentration (MIC) measurement

MICs were measured for compounds that showed significant growth inhibition zones (≥ 12 mm) using the two-fold serial dilution technique [35]. The microdilution susceptibility test in Muller-Hinton Broth (Oxoid) and Sabouraud Liquid Medium (Oxoid) was used for the determination of antibacterial and antifungal activity, respectively. Stock solutions of the tested compounds, ampicillin trihydrate and clotrimazole were prepared in DMSO at concentration of 1600 µg/mL followed by two-fold dilution at concentrations of 800, 400, 200, 100, 50, 25, 12.5 and 6.25 µg/mL). The microorganism suspensions at 10^6 CFU/mL (Colony Forming Unit/mL) concentration were inoculated to the corresponding wells. Plates were incubated at 36 °C for 24 h to 48 h and the minimal inhibitory concentrations (MIC) were determined. Control experiments were also done.

2.2.3. Antimycobacterial screening

The available *Mycobacterium tuberculosis* strain was cultured in tubes with 10 µL of a suspension of the strain in physiological saline. The strain was collected from the slant after four weeks incubation [36]. The inoculum was prepared with 3-5 weeks old *M. tuberculosis* colonies from Loewenstein-Jensen slants, emulsified in dilution fluid containing 2% fatty acid free albumin and 0.02% Tween 80, pH = 6.9. Suspensions were then diluted in saline to a turbidity of McFarland no.1 standard and then diluted to obtain inocula of $3x10^5$ cells per well. The MICs measurements were determined by agar dilution technique. Agar supplemented with 10% OADC (oleic acid-albumin-dextrose-catalase) enrichment, was used to prepare quadrant plates with serial DMSO two-fold dilutions of the test compounds. The following concentrations were used: 1000, 500, 250, 125, 62, 32, 16, 8, 4 µg/mL. A 100 µL sample of the mycobacterial suspension was inoculated onto each compound-containing quadrant. Control quadrant consisted of agar alone, culture medium with DMSO and culture medium with reference antimycobacterial drugs; rifampicin and 1HN was performed. All plates were then incubated at 37 °C in a CO_2 (5% CO_2 / 95% humidified air) incubator, for 3-4 weeks. The MIC was defined as the lowest chemical dilution associated with at least a 99% reduction in the number of visible colonies.

Table 4. In vitro antimicrobial activity of the target compounds **2-12**.

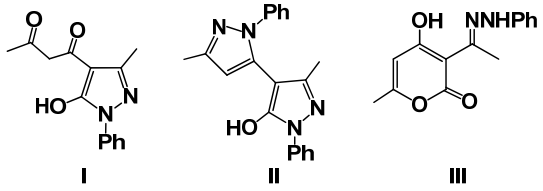
Comp.	*S. aureus* (ATCC 25923)		*B. subtilis* (ATCC 6051)		*E. coli* (ATCC 25922)		*P. aeruginosa* (ATCC 27853)		*C. albicans* (ATCC 10231)	
	IZ[a]	MIC[b]	IZ[a]	MIC[b]	IZ[a]	MIC[b]	IZ[a]	MIC[b]	IZ[a]	MIC[b]
2a	12	>200	10	...[c]	7	...	NA[d]	...	7	...
2b	20	100	17	100	14	200	10	...	14	100
2c	14	100	12	200	8	...	NA	...	9	...
3a	18	100	15	200	9	...	NA	...	9	...
3b	22	100	17	100	14	200	10	...	16	100
3c	24	50	20	50	15	200	11	...	23	50
4a	19	50	18	100	6	...	NA	...	8	...
5a	28	12.5	22	50	17	50	14	200	29	25
5b	12	>200	11	....	8	...	6	...	18	50
5c	23	50	18	100	16	200	11	...	18	50
5d	20	100	17	100	12	200	10	...	14	100
6a	3	...	4	...	NA	...	NA	...	NA	...
6b	5	...	6	...	NA	...	NA	...	NA	...
7a	12	>200	10	...	8	...	NA	...	10	...
7b	6	...	7	...	NA	...	NA	...	NA	...
7c	4	...	3	...	6	...	NA	...	9	...
8a	18	100	16	200	10	...	NA	...	8	...
8b	20	50	18	50	14	200	10	...	16	100
9a	13	>200	10	...	8	...	6	...	14	100
9b	18	100	12	200	10	...	NA	...	9	...
9c	12	>200	9	...	8	...	NA	...	6	...
10a	3	...	4	...	NA	...	NA	...	NA	...
10b	5	...	6	...	NA	...	NA	...	NA	...
11a	14	100	15	200	12	200	10	...	22	50
11b	16	100	17	50	14	100	13	...	18	100
11c	24	50	20	50	10	100	12	...	16	100
12a	3	....	4	...	NA	...	NA	...	2	...
A*	36	12.5	30	25	32	25	27	50	...	...
C**	...	...	...	...	...	...	...	...	42	12.5

[a] Inhibition zone (mm). [b] Minimal inhibitory concentration (µg/mL). [c] ... : not tested. [d] NA: not active. [e] A*: Ampicillin trihydrate; C**: Clotrimazole.

3. Results and discussion

3.1. Chemistry

Dehydroacetic acid has been reported to generate a number of heterocyclic compounds through ring opening and recyclization upon treatment with a variety of binucleophiles [37-41]. In 1991 Bendaas *et al.* reported the synthesis of 4-acylacetyl-5-hydroxy-1-phenylpyrazoles (**I**) [42] (Scheme 3). In more recent work Djerrari *et al.* [43] isolated 3-hydroxy-5-methyl-4-[3-methyl-1-phenylpyrazol-5-yl]-1-phenylpyrazole (**II**) from the reaction of **I** with phenyl hydrazine. However, as early as 1884 Perkin [44] reported that phenylhydrazine reacts readily with dehydroacetic acid in ethanol to yield 3-(1-phenylhydrazonoethyl)dehydroacetic acid (**III**).



Scheme 3

On the basis of the results we investigated the action of aryl hydrazines on **1** following the literature method. We found that the hydrazinolysis reaction of **1** afforded the corresponding hydrazones (**2a-e**).

The IR spectra of these hydrazones revealed carbonyl absorption at 1720-1738 cm^{-1} as well as an OH absorption in the region 3520-3600 cm^{-1}. Their ^1H NMR spectra in agreement with the suggested structures which showed besides the methyl and aromatic protons two singlets at δ 5.99-6.36 and 14.26-15.02 for H-5 and OH, respectively (Table 2). The structures were further confirmed by ^{13}C NMR spectral data (Table 3). Reaction of the hydrazone derivatives **2** with hydrazine hydrate afforded the corresponding 1-amino-2-pyridones **3** which in their turn, were allowed to react with nitrous acid to give the pyridine derivatives **4**. The IR spectra of compounds **3** and **4** exhibited an absorption band at 1655-1668 cm^{-1} due to the carbonyl group and a broad band at 3300-3370 cm^{-1} for the NH_2 or NH absorptions. Their structures were further supported by ^1H and ^{13}C NMR data (Tables 2 and 3). Condensation of 2-pyridones **3** with the appropriate isocyanate and isothiocyanate derivatives in pyridine as alkaline medium afforded the corresponding ureas **5** and thioureas **6**, respectively. The IR spectra of these compounds exhibited a urea carbonyl band at 1647-1668 cm^{-1} in case of compounds **5** and a thiourea carbonyl absorption in the region 1148-1166 cm^{-1} in case of the thiourea derivatives **6**. The ^1H NMR spectra of **5** and **6**, exhibited besides the aromatic and methyl protons, a singlet at δ 5.22-5.46 for H-5 and exchangeable signals in the regions δ 6.62-9.12 and 12.98-15.13 for the NH and OH groups, respectively (Table 2). Their ^{13}C NMR spectra (Tables 3) showed characteristic signals at δ 163.2 and 181.5-185.6 corresponding to the CO and CS, respectively.

On the other hand, condensing the 2-pyridones **3** with the appropriate aldehyde gave rise to the corresponding 1-arylideneamino derivatives **7**. Their ^1H NMR spectra are characterized by the presence of singlets at δ 8.12 to 8.24 due to the CH=N proton (Table 2). Moreover, reacting 1-amino-2-pyridones **3** with benzenesulfonyl chloride and p-toluene-sulfonyl chloride in the presence of pyridine led to the formation of the *N*-substituted benzenesulfonyl derivative **8**. Their IR spectra showed two absorption bands at 1173-1185 cm^{-1} and 1338-1345 cm^{-1} for the SO_2N groups. Their structures were further supported by ^1H and ^{13}C NMR data (Tables 2 and 3). Furthermore condensation of the 2-pyrone hydrazone **2b** with different isocyanates and isothiocyanates yield the corresponding substituted sulfonylureido and sulfonyl-thioureido derivatives **9** and **10**, respectively (Scheme 2). The IR spectra of derivatives **9** showed the sulfonylureido carbonyl absorption at 1658-1662 cm^{-1}, whereas those of derivatives **10** were characterized by the presence of the C=S absorption at 1120-1150 cm^{-1}. The ^1H NMR spectra of urea and thiourea derivatives **9** and **10**, revealed the new NH protons at their expected ranges in addition to other signals assigned for the

ureido and thioureido nitrogens and the respective substituents (Table 2). Their ^{13}C NMR spectra are recorded in Table 4 which showed a urea carbonyl carbon at δ 163.8 and a thiocarbonyl carbon at 186.4 for compounds **9a** and **10a**, respectively. Finally, reacting the 2-pyridone **3b** with 2 moles of the appropriate isocyanate or isothiocyanate in pyridine, afforded the corresponding substituted sulfonylureido and thioureido analogs **11** and **12**, respectively. Their IR and ^{1}H NMR spectral data of some representatives were concordant with the proposed structures showed the functional groups and compounds protons at their expected chemical shifts.

3.2. Antimicrobial screening

Compounds, **2a-c**, **3a-c**, **4a**, **5a-d**, **6a**,**b**, **7a-c**, **8a**,**b**, **9a-c**, **10a**,**b**, **11a-c**, **12a**, were evaluated for their in *vitro* antimicrobial activity against *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6051) as examples of Gram positive bacteria, *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) as examples of Gram negative bacteria, *Candida albicans* (ATCC 10231) and *Aspergillus niger* (recultured) as representatives of fungi. Agar diffusion method was used for the determination of the preliminary antibacterial and antifungal activity. Ampicillin trihydrate and clotrimazole were used as reference drug. The results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial growth around the discs in mm. The minimum inhibitory concentration (MIC) measurement was determined for compounds that showed significant growth inhibition zones (≥ 12 mm) using the two-fold serial dilution method [39]. The IZ (mm) and MIC (μg/mL) values are recorded in Table 4.

The results revealed that most of the tested compounds displayed greater inhibitory effect on the growth of the tested Gram positive strain compared to Gram negative ones. Most of the compounds showed weak or no antibacterial activity against the Gram negative, *P. aeruginosa*. Moreover, few compounds were able to exert potential antifungal activity against *C. albicans,* while, all the tested compounds lacked antifungal activity against the *Aspergillus niger* fungus. A close examination of the structures of the active compounds revealed that the antimicrobial profile of the pyridine-2-one compounds seemed to be more interesting than their corresponding pyran-2-one isosteres, as evidenced by their IZ diameters and MIC values recorded in Table 4.

Among the pyran-2-one series, compound **2a** showed weak antimicrobial activity against all the tested microbial strains (IZ≤ 12 mm). Introduction of chlorine atom in the phenyl group of the hydrazone moiety as in **2c** resulted in a slight improvement in the activity against the Gram positive *S. aureus* and *B. subtilis* (MIC values 100 and 200 μg/mL, respectively). Whereas, replacement of the chlorine atom in **2c** with sulfamyl group resulted in a more potent compound **2b**, with an appreciable broad spectrum of antibacterial activity against the tested Gram positive, Gram negative bacteria (MIC values 100-200 μg/mL), and moderate antifungal activity towards *C. albicans* (MIC 100 μg/mL). On the other hand, bioisosteric shift from the pyran-2-one to the pyridine-2-one structure resulted in an obvious improvement in the antimicrobial spectrum of the target compounds (Table 4). In this view, the prototype **4a** displayed an appreciable activity against the Gram positive *S. aureus* and *B. subtilis* (MIC 50 and 100 μg/mL, respectively) when compared with the bioisosteric pyran-2-one **2a**. Introduction of an amino group at position-1 in the pyridine ring as in compound **3c** resulted in significant change of the overall antimicrobial spectrum. It showed two-fold improvement in the potency against *B. subtilis* when compared with **4a** (MIC 50 *vs* 100 μg/mL, respectively), while it revealed moderate activity against *E. coli* (MIC 200 μg/mL). It also showed antifungal activity towards *C. albicans* (MIC 50 μg/mL). Furthermore, replacement of the 1-amino group in **3a** with a urea moiety (compound **5a** produced the most potent antimicrobial activity in the current series of compounds. Compound **5a** is as potent as ampicillin (MIC 12.5 μg/mL) against *S. aureus,* whereas its activity against *B. subtilis* and *E. Coli* was 50% lower than that of ampicillin (MIC 50 *vs* 25 μg/mL, respectively). Moreover, it displayed a remarkable antifungal activity towards *C. albicans*, which was about 50% of that of Clotrimazole (MIC 25 *vs* 12.5 μg/mL, respectively). However, it is worthy to mention that, structure modification of the urea derivatives to thiourea ones led to almost complete abolishment of the antimicrobial activity (IZ≤ 10 mm).

3.3. Antimycobacterial screening

Determination of *in vitro* antimycobacterial activity of the target compounds **2a-c**, **3a-c**, **4a**, **5a-d**, **6a**,**b**, **7a-c**, **8a**,**b**, **9a-c**, **10a**, **b**, **11a-c**, **12a**; was performed by employing the two-fold agar dilution method slightly modified from that described by Cantos *et al.* [40]. A strain of *Mycobacterium tuberculosis* (locally isolated, Alexandria, Egypt) was utilized in this assay. Rifampicin and isonicotinic acid hydrazide (INH) were used as reference antimycobacterial drugs. The MIC was defined as the lowest concentration of the tested compound that yielded no visible growth on the plate. Among the compounds tested, only compound **7a** was able to exert weak growth inhibitory effect (MIC 250 μg/mL) against the *Mycobacterium tuberculosis* used in this screening, while the rest of the synthesized compounds were totally inactive.

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References

[1]. Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10(1)*, 71-98.
[2]. Douglas, C. J.; Sklenika, H. M.; Shen, H. C.; Mathias, D. S.; Degen, S. J.; Golding, G. M.; Morgan, C. D.; Shin, R. A.; Mueller, K. L.; Scurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55,* 13683-13696.
[3]. Hatch, M. S.; Brown, W. M.; Deck, J. A.; Hunsaker, L. A.; Deck, L. M.; Vander Jagt, D. L. *B. B. A. -Protein Struct. M.* **2002**, *1596*, 381-391.
[4]. Tuchinda, P.; Reutrakul, V.; Claeson, P.; Pongprayoon, U.; Sematong, T.; Santisuk, T.; Taylor, W. C. *Phytochemistry* **2002**, *59*, 169-173.
[5]. Rao, P. N. P.; Uddin, J.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 3972-3990.
[6]. Fujimoto, H.; Okamoto, Y.; Sone, E.; Maeda, S.; Akiyama, K.; Ishibashi, M. *Chem. Pharm. Bull.* **2005**, *53*, 923-929.
[7]. Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3509-3515.
[8]. Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667-2671.
[9]. De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491-2517.
[10]. De Clercq, E. *B. B. A. - Mol. Basis Dis.* **2002**, *1587*, 258-275.
[11]. Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285-4299.
[12]. McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369-385.
[13]. Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M.; Mosti, L. *Bioorg. Med. Chem.* **2003**, *11*, 4749-4759.
[14]. Krauze, A.; Vitolina, R.; Garaliene, V.; Sile, L.; Kluša, V.; Duburs, G. *Eur. J. Med. Chem.* **2005**, *40*, 1163-1167.
[15]. Ochoa, E.; Suarez, M.; Verdecia, Y.; Pita, B.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Duque, J.; Pomes, R. *Tetrahedron* **1998**, *54*, 12409-12420.
[16]. Parlow, J. J.; South, M. S. Tetrahedron **2003**, *59*, 7695-7701.
[17]. Abdel-Aziz, A. A.; El-Subbagh, H. I.; Kunieda, T. *Bioorg. Med. Chem.* **2005**, *13*, 4929-4935.
[18]. Srivastava, B. K.; Solanki, M.; Mishra, B.; Soni, R.; Jayadev, S.; Valani, D.; Jain, M.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 1924-1929.
[19]. Aanandhi, M. V.; George, S.; Vaidhyalingam, V. *Arkivoc* **2008**, *11*, 187-194.

[20]. Narayana, B. L.; Rao, A. R. R.; Rao, P. S. *Eur. J. Med. Chem.* **2009**, *44*, 1369-1376.
[21]. Ranft, D.; Seyfarth, T.; Schaper, K. J.; Lehwark-Yvetot, G.; Bruhn, C.; Buege, A. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 427-430.
[22]. Khoshneviszadeh, M.; Edraki, N.; Javidnia, K.; Alborzi, A.; Pourabbas, B.; Mardaneh, J.; Miri, R. *Bioorg. Med. Chem.* **2009**, *17*, 1579-1586.
[23]. Abid, M.; Kakul Husain, K.; Azam, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4375- 4379.
[24]. Goebel, T.; Ulmer, D.; Projahn, H.; Kloeckner, J.; Heller, E.; Glaser, M.; Ponte-Sucre, A.; Specht, S.; Sarite, S. R.; Hoerauf, A.; Kaiser, A.; Hauber, I.; Hauber, J.; Holzgrabe, U. *J. Med. Chem.* **2008**, *51*, 238-250.
[25]. Rodrigues, T.; Guedes, R. C.; dos Santos, D. J. V. A.; Carrasco, M.; Gut, J.; Rosenthal, P. J.; Moreira, R.; Lopes, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3476-3480.
[26]. Tiwari, A. K.; Mishra, A. K.; Bajpai, A.; Mishra, P.; Sharma, R. K.; Pandey, V. K.; Singh, V. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4581-4585.
[27]. Gudmundsson, K. S.; Johns, B. A.; Wang, Z.; Turner, E. M.; Allen, S. H.; Freeman, G. A.; Boyd, F. L. Jr.; Sexton, C. J.; Selleseth, D. W.; Moniri, K. R.; Creech, K. L. *Bioorg. Med. Chem.* **2005**, *13*, 5346-5361.
[28]. Allen, S. H.; Johns, B. A.; Gudmundsson, K. S.; Freeman, G. A.; Boyd, F. L. Jr.; Sexton, C. H.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2006**, 14, 944-954.
[29]. Croitoru, M.; Pintilie, L.; Tanase, C.; Caproiu, M. T.; Draghici, C. *Rev. Chem. -Bucharest* **2004**, *55(12)*, 993-997.
[30]. Limban, C.; Misisir, A.; Chirita, I.; Ilie, C.; Caproiu, M. T. *Rev. Chem. -Bucharest* **2008**, *59(10)*, 1136-1139.
[31]. Limban, C.; Misisir, A.; Chirita, I.; Niculescu, G. M.; Ilie, C.; Caproiu, M. T. *Rev. Chem. -Bucharest* **2008**, *59(11)*, 1245-1249.
[32]. Limban, C.; Misisir, A.; Chirita, I.; Niculescu, G. M.; Ilie, C.; Caproiu, M. T. *Rev. Chem. -Bucharest* **2009**, *60(7)*, 657-661.
[33]. Morusceag, L.; Misisir, A.; Ilie, C.; Guta, R.; Andreescu, D. N.; Caproiu, M. T. *Rev. Chem. -Bucharest* **2009**, *60(8)*, 805-809.
[34]. Dogruer, D. S.; Urlu, S.; Onkol, T.; Ozcelik, B.; Sahin, M. F. *Turk. J. Chem.* **2010**, *34*, 57-65.
[35]. Conte, J. E.; Barriere, S. L. Manual of Antibiotics and Infectious Disease. 1st ed., Lea and Febiger, USA, 1988, 135-38.
[36]. Mamolo, M. G.; Vio, L. *Il Farmaco* **1992**, *47*, 1055-1066.
[37]. Ait-Baziz, N.; Rachedi, Y.; Silva, A. M. S. *Arkivoc* **2010**, *10*, 86-97.
[38]. Akhrem, A. A.; Moiseenkov, A. M.; Lakhvich, F.A. Smul'Skii, S. P. *Izy. Akad. N. SSR Ser.***1971**, *5*, 1098-1100.
[39]. Habart, M. H.; Pene, C.; Royer, R. *Chim. Ther.* **1973**, 8, 314-318.
[40]. Cantos, A.; De March, P.; Manas, M. M.; Pla, A.; Ferrando, F. S.; Vergili, A. *Bull. Chem. Soc. Japan*. **1987**, *60*, 4425-4431.
[41]. Susnik, I.; Furak, J. V.; Durakovic, S.; Kopuvanoc, S.; Lasniger, J. *Monatsch. Chem.* **1992**, *123*, 817-822.
[42]. Bendaas, A.; Hamdi, M.; Sellier, N. *J. Heterocylic Chem.* **1999**, *36*, 1291-1294.
[43]. Djerrari, B.; Essasi, E.; Fifani, J. *Bull. Soc. Chim. France* **1991**, *128*, 521-524.
[44]. Perkin, Jr., W. H.; Bernhart, C. *Ber*. **1884**, *17*, 1522-1527.