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SYNTHESIS OF PYRAZINAMIDE DERIVATIVES AS LEUCONOSTOC MESENTEROIDES GROWTH INHIBITOR AND OTHER MICROORGANISMS

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Abstract

Synthesis and reactions of 4-pyrazine-2-carboxamido carboxylic acid derivatives **3a-c** were studied. Various N-[4-(5-oxo-oxazol-2-yl)-phenyl]pyrazine-2-carboxamides **7-11** were obtained via condensation of **3c** with different chemical reagents. Interaction of **10b,c** with p-toludine and/or hydrazine hydrate afforded the corresponding N-[4-(1*H*-imidazol-2-yl)phenyl]pyrazine-2-carboxamides **12a,b** respectively. Antimicrobial screening showed that **3c** possess a promising effect against the growth of Leuconostoc sp. and other tested Gram-positive, Gram-negative and fungi**.**

The structures of the newly derivatives were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectra studies.

Keywords: 4-pyrazine-2-carboxamido carboxylic acid derivatives, N-[4-(5-oxo-oxazol-2-yl)phenyl]pyrazine-2-carboxamides, N-[4-(1*H*-imidazol-2-yl)phenyl]pyrazine-2-carbox-amides, 1,2,4-triazine-6-one derivatives, Leuconostoc sp. Growth inhibitor.

Introduction

Pyrazinamide (PZA) is a nicotinamide analogue that has been used as a first-line drug to treat tuberculosis[1]. PZA is bactericidal semidormant, mycobacteria and reduces total treatment time[2], it thought to be a prodrug of pyrazinoic acid, a compound with antimycobacterial activity[3].

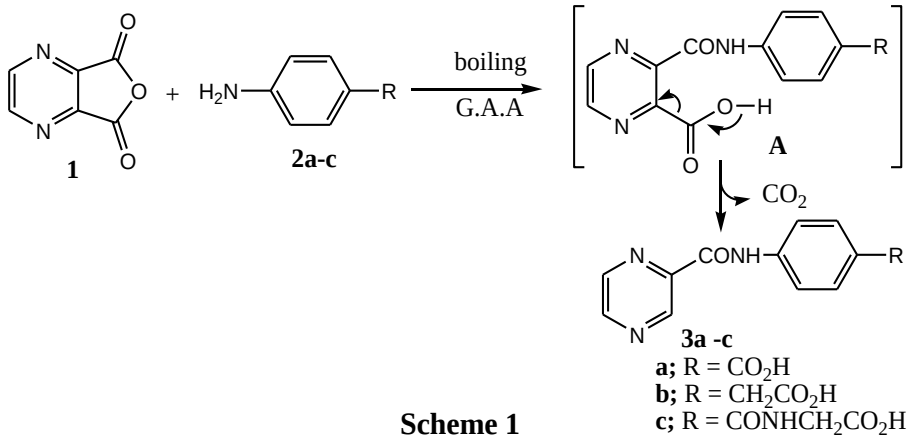
Various compounds possessing -NHCO- grouping, e.g. substituted amides acyl and thioacyl anilides, etc., were found to inhibit photosynthetic electron transport [4-7]. During sugar beet storage and processing sucrose losses due to microbial activity occur, because the formation of slimy microbial polysaccharides which cause sever

processing and quality problems[8-12]. Leuconostoc sp. was suggested to be the reason for slime production in sugar factories[13,14].

The present investigation is ultimate goal the preparation of N-phenylpyrazine-2-carboxamide derivatives with the hope that this may have superior bactericidal properties, specially against Leuconostoc mesentroides, starting with pyrazine-2,3-dicarboxylic acid anhydride **1** [15,16]**.**

Results And Discussion

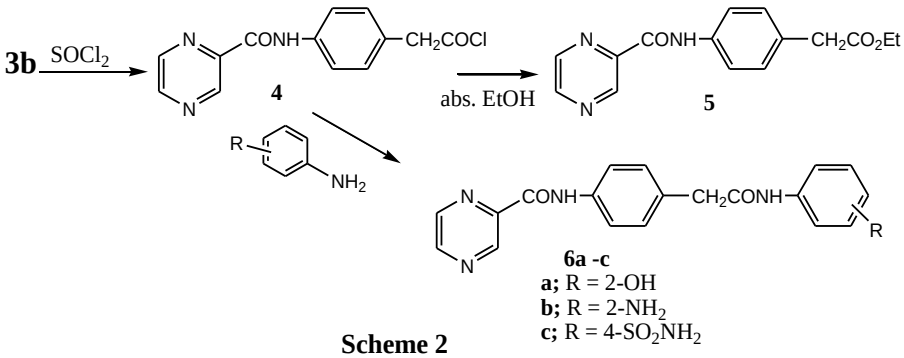
Condensation of **1** with aromatic amino carboxylic acids **2a-c** afforded the corresponding 4-pyrazine-2-carboxamido carboxylic acid derivatives **3a-c** (Scheme 1).



Scheme 1

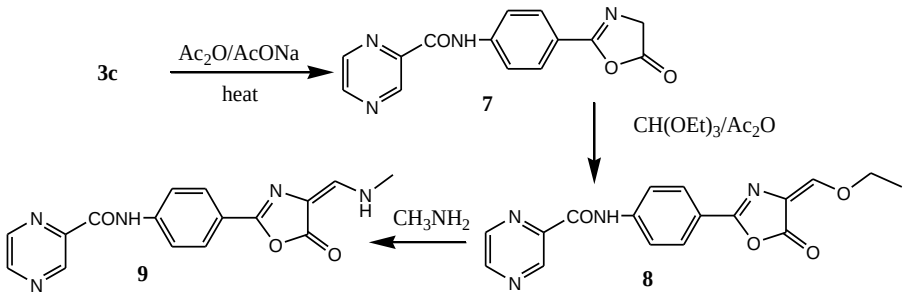
The formation of pyrazine-2-carboxylic acid amide **3** is formed from **1** and the respective amino acid through half acid half carboxamide intermediate **[A]** which underwent spontaneous decarboxylation under the reaction conditions.

Treatment of **3b** with thionyl chloride gave the corresponding 2-[4-(pyrazine-2-carboxamido)phenyl]acetyl chloride 4. the acid chloride was allowed to react with absolute ethanol, which afforded the corresponding ethyl 2-[4-(pyrazine-2-carboxamido)phenyl]acetate **5**. Also, condensa-tion of acid chloride **4** with bifunctional amine in dry ether containing few drops of pyridine gave the corresponding phenylcarbamoyl derivatives **6a-c** respectively (Scheme 2).



Scheme 2

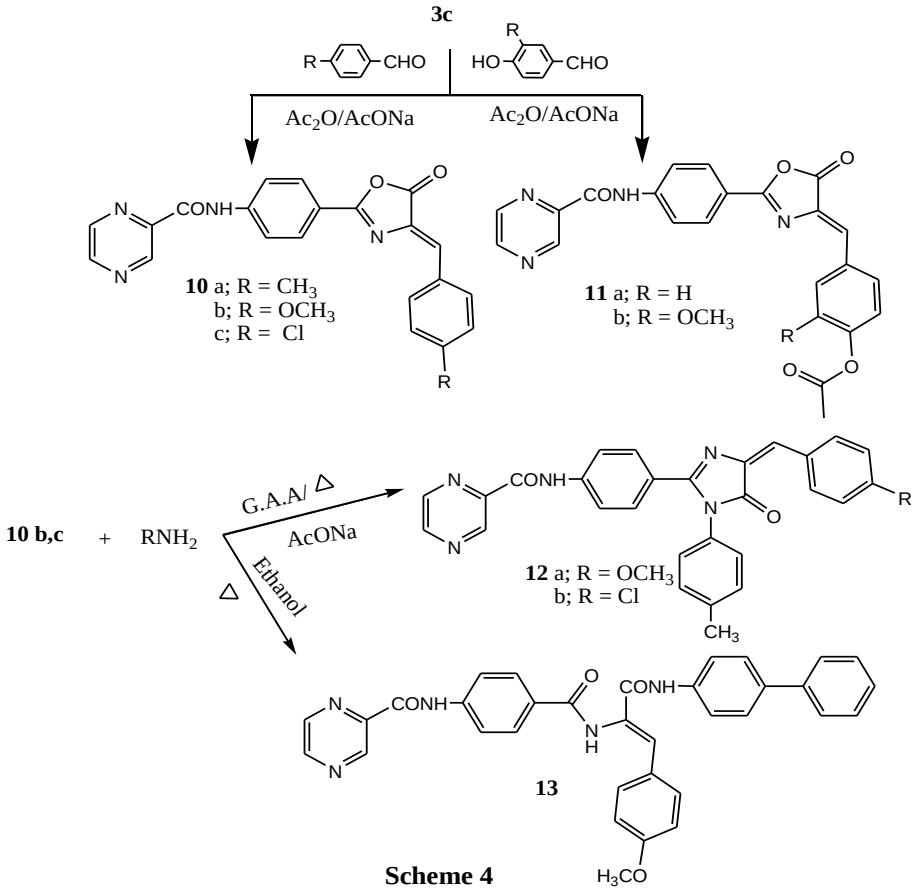
The antibacterial and antitubercular activity of oxazolone derivatives in many active druges[17-28], attract the author to synthesize new compounds containing oxazolone ring incorporated with pyrazine nucleus in order to enhance their biological activities. Thus, treatment of 4-(pyrazine-2-carboxamido)hippuric acid **3c** with Ac_2O/AcONa gave the corresponding N-[4-(4,5-dihydro-5-oxo-oxazol-2-yl)phenyl]pyrazine-2-carboxamide **7** which on treatment with triethylorthoformate in presence of acetic anhydride gave the compound N-[4-(4-ethoxymethylene)-4,5-dihydro-5-oxo-oxazol-2-yl)phenyl]pyrazin-e-2-carboxamide **8**. Treatment of **8** with methylamine led to the formation of the amino compound derivatives **9** as N-[4-(4,5-dihydro-4-methylaminomethylene)-5-oxo-oxazol-2-yl)phenyl]pyrazine-2-carboxamide (Scheme **3**).



Scheme 3

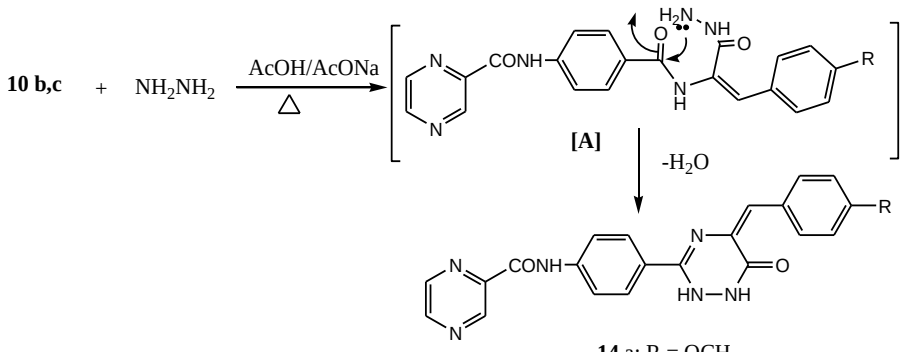
Treatment of **3c** with aromatic aldehyde/Ac_2O-AcONa gave the corresponding N-[4-(4-(arylidine-4,5-dihydro-5-oxo-oxazol-2-yl)phen-yl]pyrazine-2-carboxamide **10a-c.** Condensation of **3c** with phenolic aldehydes in boiling Ac_2O/AcONa afforded the corresponding N-[4-(4-(4-acetyloxy-3-benzylidene)-4,5-dihydro-5-oxo-oxazol-2-yl)phen-yl]pyrazine-2-carboxamide **11a,b** (Scheme 4). Condensation of **10b,c** with p-toulidine in acetic acid / sodium acetate under reflux gave the

corresponding N-[4-(4-(4-methoybenzylidine) /or (4-chlorobenzylidine)-4,5-dihydro-5-oxo-1-phenyl-1*H*-imidazol-2-yl)phenyl]pyrazine-2-carbox-amide **12a,b** respectively, while interaction of **10b** with biphenylamine in boiling ethanol gave the corresponding α-[4-(pyrzine-2-carboxamido)-benzoylamino]-4-methoxycinnamic acid N-biphenylcarboxamide **13** (Scheme 4).



Scheme 4

Reaction of **10b or 10c** with hydrazine hydrate in acetic acid in the presence of sodium acetate cause opening of the oxazolone ring to give the corresponding hydrazide intermediate **[A],** which readily undergoes cyclization uner the reaction conditions to afford the corresponding 1,2,4-triazine-6-one derivatives **14a,b** respectively Addition of nucleophile, ring opening and ring closure in nucleophilic attack on ring systems . (**ANRORC**-mechanism), (Scheme 5).



14 a; R = OCH_3
b; R = Cl

Scheme 5

The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectra studies c.f. experimental part (Table II).

The preliminary antimicrobial screening (Table III) showed that compound **3c** possess a pronounced antimicrobial activity (+++) (MIC 1 mg/1 ml) towards **BS, SA, PA, EC, CA** and leuconostoc mesenteroid growth in liquid culture. The other compounds were less active (+). The present study reveled that the structure of compound with highest inhibitory effect belongs to those in which substitution in carboxamide phenyl part was substituted at 4`-postion with amidoacetic acid **3c**.

Experimental

M.p.s. are uncorrected and were determined on a Stuart Scientific Co. Ltd. Melting point apparatus. IR spectra ν_{max}/cm^{-1} (KBr) were measured on a FT IR/5300 spectrometer. ^{1}HNMR, ^{13}CNMR spectra δ (ppm) on Varian Mercury (300 MHz) spectrometer and mass spectra on a Shimadzu GC-MS.QP 1000EX spectrometer Winniping University, Canada. Elemental analyses were carried out in the Microanalaytical Laboratories of the faculty of Science, Cairo University, and analytical results for (C, H, N) were within ±0.2% of the calculated values.

2,3-Pyrazine dicarboxylic acid anhydride (1):

from pyrazine-2,3-dicarboxylic acid according to Ref [15,16], m.p. 218°C.

Preparation of 4-(pyrazine-2-carboxamido)carboxylic acid derivatives (3a-c):

A mixture of pyrazine-2,3-dicarboxylic anhydride **(1)** (1.5g; 10 mmol) in glacial acetic acid (20 ml) and the corresponding basic amino acid compound (10 mmol)

was refluxed for 3hrs. the solid product, which formed was collected by filtration and recrytstallized from glacial acetic acid to give **3a-c** (Table **I**).

Preparation of 2-[4-(pyrazine-2-carboxamido)phenyl]acetyl chloride (4):

A mixture of **3b** (7.71g; 30 mmol) and thionyl chloride (4 mmol) was refluxed for about one hour in water bath. The excess of thionyl chloride was removed by repeated evaporation to give the corresponding acid chloride **(4)** (Table **I**).

Preparation of ethyl 2-[4-(pyrazine-2-carboxamido)phenyl]acetate (5):

A solution of **4** (1.38g; 5mmol) with (10 ml) ice cooled absolute ethanol was stirred for 1/2 hour, and then boil in water bath for one hour. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from ethanol to give colorless crystals **5** (Table **I**).

Preparation of N-[4-((2-hydroxy(amino)phenylcarbamoyl)methyl)-phenyl]pyrazine-2-carboxamide (6a,b) and N-[4-((4-aminosulphonyl-phenylcarbmoyl)methyl)phenyl]-pyrazine-2-carboxamide (6c).

A mixture of acid chloride **(4)** (1.38g; 5 mmol) and bifunctional amine derivatives (6 mmol) in dry ether (30 ml) containing few drops of pyridine. Then refluxed in water bath for one hour. The reaction mixture was stirred and cooled. The precipitated solid was collected and recrystallized from the suitable solvent to give the corresponding derivatives **6a-c** (Table **I**).

Preparation of N-[4-(4,5-dihydro-5-oxo-oxazol-2-yl)phenyl]pyrazine-2-carboxamide (7).:- A mixture of **3c** (1.5g; 5mmol) with acetic anhydride (10 ml) containing freshly fused sodium acetate (0.5g) was heated on water bath at 90ºC for two hours. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from suitable solvent to give **7** (Table **I**).

Preparation of N-[4-(4-ethoxymethylene)-4,5-dihydro-5-oxo-oxazol-2-yl)phenyl]pyra-zine-2-carboxamide (8):- A mixture of **7** (1.41g; 5mmol) with triethylorthoformate (1.48g; 10 mmol) in presence of (10 ml) acetic anhydride was refluxed for 2 hours. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from suitable solvent to give **8** (Table **I**).

Preparation of N-[4-(4,5-dihydro-4-(methylamino)methylene)-5-oxo-oxazol-2-yl) phen-yl]pyrazine-2-carboxamide (9):- A mixture of **8** (1.01g; 3mmol) with methylamine (0.109g; 3.5mmol) in absolute ethanol (30 ml) was stirred for 2 hours

and the solution was left for overnight, then the precipitated solid was collected and recrystallized from suitable solvent to give **9** (Table **I**).

Preparation of N-[4-(4-(arylidene)-4,5-dihydro-5-oxo-oxazol-2-yl)phenyl]pyrazine-2-carboxamide (10a-c):- A mixture of pyrazine-2-carboxylic acid amide derivative **(3c)** (1.5g; 5mmol) and the respective aromatic aldehyde (5mmol) in acetic anhydride (20 ml) containing freshly sodium acetate (0.5g) was refluxed for 2 hours. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from suitable solvent to give **10a-c** (Table **I**).

Preparation of N-[4-(4-(4-acetyloxy-3-benzylidene)-4,5-dihydro-5-oxo-oxazol-2-yl) phenyl]pyrazine-2-carboxamide (11a,b):- The procedure was similar to that previously described for the preparation of **(10a-c)**.

Preparation of N-[4-(4-benzylidene)-4,5-dihydro-5-oxo-1-phenyl-1H-imidazol-2-yl) phenyl]pyrazine-2-carboxamide derivatives (12a,b):

A mixture of **10** (3mmol) and p-toluidine (0.375g; 3.5mmol) in glacial acetic acid (20 ml) containing freshly fused sodium acetate (0.5g) was refluxed for 3 hours. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from suitable solvent to give **12a,b**, respectively (Table **I**).

Preparation of α-(4-(pyrazine-2-carboxamido)benzoylamino)-4-methoxycinnamic acid-N-biphenylcarboxamide (13).

A mixture of **10b** (1.2g; 3mmol) and biphenylamine (0.592g; 3.5mmol) in ethanol (30 ml) was refluxed for 3 hours. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from suitable solvent to give **13** (Table **I**).

Preparation of 1,2,4-triazine-6-one derivatives (14a,b):

A mixture of **10b** or **10c** (3mmol) and hydrazine hydrate (4mmol) in ethanol (20 ml) was refluxed for 2 hours in water bath. The reaction mixture was cooled. The precipitated solid was collected and recrystallized from glacial acetic acid to give **14a,b**, respectively (Table **I**).

Table I: Elemental analyses data of the newly prepared compounds:

Compd. No.	M.P.[°C] (Solvent)	Color (Yield [%])	Mol. Formula (Mol. Wt.)	Calcd./Found [%]		
				C	H	N
3a	324-326	White	$C_{12}H_9N_3O_3$	59.26	3.73	17.28
		(70)	(243.22)	59.29	3.79	17.19
3b	240-242	White	$C_{13}H_{11}N_3O_3$	60.70	4.31	16.33
		(75)	(257.25)	60.74	4.35	16.29
3c	252-254	White	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66
		(70)	(300.27)	56.10	4.00	18.72
4	254-255	Yellow	$C_{13}H_{10}N_3O_2Cl$	56.64	3.66	15.24
	Benzene	(65)	(275.69)	56.70	3.61	15.21
5	210-212	Colorless	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73
	Ethanol	(60)	(285.30)	63.11	5.35	14.77
6a	238-240	White	$C_{19}H_{16}N_4O_3$	65.51	4.63	16.08
	Ethanol	(75)	(348.36)	65.47	4.69	16.13
6b	266-268	Pale green	$C_{19}H_{17}N_5O_2$	65.70	4.93	20.16
	Ethanol	(70)	(347.38)	65.74	4.90	20.19
6c	300-301	Pale yellow	$C_{19}H_{17}N_5O_4S$	55.47	4.16	17.02
	G.A.A	(72)	(411.44)	55.41	4.22	17.10
7	265-266	Orange	$C_{14}H_{10}N_4O_3$	59.57	3.57	19.85
	Dioxane	(70)	(282.26)	59.62	3.63	19.81
8	218-219	Pale orange	$C_{17}H_{14}N_4O_4$	60.35	4.17	16.56
	Benzene	(75)	(338.32)	60.39	4.22	16.62
9	288-289	Pale green	$C_{16}H_{13}N_5O_3$	59.44	4.05	21.66
	Benzene	(70)	(323.31)	59.53	4.09	21.62
10a	252-253	Yellow	$C_{22}H_{16}N_4O_3$	68.74	4.20	14.58
	G.A.A	(60)	(384.39)	68.69	4.16	14.52
10b	256-257	Yellow	$C_{22}H_{16}N_4O_4$	66.00	4.03	13.99
	Ethanol	(62)	(400.39)	66.05	4.11	13.94
10c	254-255	Yellow	$C_{21}H_{13}N_4O_3Cl$	62.31	3.24	13.84
	G.A.A	(65)	(404.81)	62.39	3.29	13.81
11a	279-280	Yellow	$C_{23}H_{16}N_4O_5$	64.48	3.76	13.08
	G.A.A	(65)	(428.40)	64.42	3.72	13.14
11b	315-316	Yellow	$C_{24}H_{18}N_4O_6$	62.88	3.96	12.22
	Ethanol	(70)	(458.43)	62.93	3.92	12.29
12a	269-270	Yellow	$C_{29}H_{23}N_5O_3$	71.15	4.74	14.31
	Benzene	(65)	(489.53)	71.19	4.79	14.29
12b	267-268	Yellow	$C_{28}H_{20}N_5O_2Cl$	68.09	4.08	14.18
	G.A.A	(60)	(493.95)	68.02	40.2	14.22
13	168-169	Pale orange	$C_{34}H_{25}N_5O_3$	74.03	4.57	12.70
	G.A.A	(75)	(551.6)	74.11	4.62	12.74
14a	278-279	Yellow	$C_{22}H_{18}N_6O_3$	63.76	4.38	20.28
		(70)	(414.42)	63.81	4.42	20.36
14b	288-290	Yellow	$C_{21}H_{15}N_6O_2Cl$	60.22	3.61	20.06
	G.A.A	(72)	(418.84)	60.29	3.65	20.11

G.A.A. = glacial acetic acid

Table II. Spectral data of the prepared compounds

Compd. No.	IR (υ, cm^{-1})	^{1}H NMR, ^{13}C NMR (δ, ppm) and Mass spectrum
3a	3342 (NH), 1690, 1672 (CO).	243 (M^+, 33.1), 199 (M^+-CO_2, 1.1), 120 (3.1),119 (9.9), 80 (54.8), 79 (100), 65 (23.30), 52 (62.8).
3b	3338 (NH), 1718, 1680 (CO).	3.54 (s, 2H, CH_2), 7.22, 7.27, 7.79, 7.83 (AB-q, J = 8.59 Hz, 4H, Ar-H), 8.79, 8.80 (d, J = 1.56 Hz, 1H, H-6), 8.91, 8.92 (d, J = 2.34 Hz, 1H, H-5), 9.29 (s, 1H, H-3),10.69 (s, 1H, NH), 12.25 (s, br, 1H, COOH). 40.27 (CH_2), 120.67 (C-4`), 123.29 (C-2`, 6`), 123.9 (C-3`, 5`) 131.11 (C-1`), 136.75 (C-6), 143.33 (C-5), 145.09 (C-3), 147.79 (C-2), 161.67 (CONH), 172.97 (COOH). 257 (M^+, 65.6), 212 (64.6, M^+-CO_2H), 107 (52.6), 105 (4.4), 79 (100), 52 (60.9).
3c	3379, 3340 (NH), 1728,1681, 1635 (CO)	3.4 (hump, 1H, $NHCH_2$), 3.91, 3.94 (d, J = 5.08 Hz, 2H, CH_2), 7.87, 7.91, 7.99, 8.04 (AB-q, J = 7.42 Hz, 4H, Ar-H), 8.13, 8.82 (d, J = 1.56 Hz, 1H, H-6), 8.94, 8.95 (d, J = 1.95 Hz, 1H, H-5), 9.31 (S, 1H, H-3), 10.94 (s, 1H, CONH). 41.32 (CH_2), 119.93 (C-2`,6`), 123.22 (C-2`, 6`), 128.12 (C-3`, 5`), 129.38 (C-1`), 143.30 (C-6), 144.88 (C-2), 151 (C-4`), 162.06 (CONH), 166.06 (CO), 171.54 (COOH). 300 (M^+, 12), 282 (M^+-H_2O, 4.3), 256 (M^+-CO_2, 19.5) 226 (256-$NHCH_3$, 100), 146 (20.1), 121 (23.3), 80 (14.2), 79 (83.6), 52 (45.3).
5	3336 (NH), 1718, 1676 (CO).	1.25 (t, J= 7.2 Hz, 3H, CH_2CH_3), 3.61 (s, 2H, CH_2CO), 4.15 (q, J = 7.2 Hz, 2H, CH_2CH_3), 7.31, 7.33, 7.87, 7.89 (AB-q, J = 8.4 Hz, 4H, Ar-H), 8.87 (s, 1H, NH), 8.98, 8.99 (d, J = 2.4 Hz, H-5), 9.36 (s,1H, H-3),10.75 (s, 1H, NH). 285 (M^+, 11.4), 257 (58.8), 212 (75.3), 107 (51.3) 79 (100), 52 (43.2).
6a	3350 (NH), 3264 (OH bonded), 1678 (CO).	348 (M^+, 16.5), 239 (42.3), 213 (57), 212 (49.3), 136 (13.5), 109 (88.0), 107 (69.4), 106 (95.3), 80 (39.2), 79 (100), 52 (46).
6b	3346, 3300 (NH), 1676 (CO).	3.61 (s, 2H, CH_2), 5 sets of multiplets at (7.14-7.16), (7.30-7.32), (7.40-7.50), (7.82-7.89) and (9.26-9.30) (10H, Ar-H, NH_2), 8.78 (dd, J = 1.2 Hz, 1H, H-6), 8.92 (s, 1H, H-5), 9.46 (s, 1H, H-3), 10.65 (s, 1H, NH), 10.80 (s, 1H, NH). 347 (M^+, 4.7), 319 (12.4), 239 (15.4), 212 (52.1), 135 (11.1), 134 (32.2), 108 (28), 107 (69.6), 79 (100), 52 (48.4).
6c	3382, 3350, 3282 (NH), 1674, 1660 (CO), 1332, 1154	3.73 (s, 2H, CH_2), 7.28 (s, 2H, SO_2NH_2), 7.38, 7.41, 7.88, 7.91 (AB-q, J = 8.7 Hz, 4H, Ar-H), 7.81 (s, 4H, Ar-H), 8.86, 8.91 (dd, J = 1.8 Hz, 1H, H-6), 8.98, 8.99 (d, J = 2.4 Hz, 1H, H-5), 9.35, 9.36 (d, J = 1.2 Hz, 1H,

	(SO_2)	H-3), 10.52 (s, 1H, NH), 10.75 (s, 1H, NH). 411 (M^+, 21.7), 239 (18.0), 212 (100), 199 (1.51), 172 (2), 107 (54.1), 106 (35.5), 79 (81.9), 52 (29.8).
7	3301.9 (NH), 2850 (C-H aliph.), 1728, 1666 (CO), 1620 (C=N)	
8	3300 (NH), 1791, 1670 (CO).	1.49 (t, J = 7.2 Hz, 3H, CH_3), 4.40, 4.42, 4.45 and 4.47 (q, J = 7.2 Hz, 2H, CH_2), 7.35 (s, 1H, H-6), 7.87, 7.90, 8.09, 8.12 (AB-q, J = 8.7 Hz, 4H, Ar-H), 8.60 (s, 1H, H-5), 8.83, 8.84 (d, J = 2.4 Hz, 1H, H-3), 9.51 (d, J = 0.9 Hz, 1H, CH=), 9.84 (s, 1H, NH).
9	3336, 3160 (NH), 2926 (C-H aliph.), 1730, 1676 (CO), 1640 (C=N).	3.14 , 3.16 (d, J = 5.7 Hz, 3HCH_3), 7.57 (s, 1H, H-6), 7.88, 7.90, 8.07, 8.10 (AB-q, J = 8.1 Hz, 4H, Ar-H), 8.03, 8.05 (d, J = 6.3, Hz, 1H, =CH), 8.89, 8.90 (d, J = 1.2, Hz, 1H, H-5), 9.01, 9.02 (d, J = 1.2 Hz, 1H, H-3), 9.37, 9.38 (d, J = 1.2 Hz, 1H, NH), 10.97 (s, br, 1H, NH). 323 (53.9), 279 (6.8), 244 (0.2), 243 (1), 226 (86.3), 146 (24.4), 121 (30.2), 79 (100), 52 (33.1).
10a	3306 (NH), 1732, 1666 (CO).	2.24 (s, 3H, CH_3), 7.18, 7.23 (d, J = 8.98 Hz, 4H, Ar-H), 7.31 (s, 1H, =CH), 8.03, 8.04 (d, J = 1.56 Hz, 1H, H-6), 8.17, 8.18 (d, J = 2.34 Hz,1H, H-5), 8.66, 8.67 (d, J = 1.17 Hz, 1H, H-3), 9.91 (s, 1H, NH). 402 ($M^+.H_2O$, 1), 384 (M^+, 1.9), 121 (32), 116 (2.1), 103 (3.1), 79 (pyrazin-2-yl cation, 100), 52 (35.5).
10b	3340 (NH), 1789, 1689 (CO).	3.90 (s, 3H, OCH_3), 6.99, 7.02 (d, J = 7 Hz, 4H, Ar-H), 7.21 (s, 1H, CH=), 7.93, 7.97, 8.14, 8.18 (dd, J = 8.8, 8.4 Hz, 4H, Ar-H)), 8.62 (s, 1H, H-6), 8.85, 8.86 (d, J = 2.46 Hz, 1H, H-5), 9.54 (s, 1H, H-3),9 , 92 (s, 1H, NH). 400 (M^+, 17.2), 226 (100), 121 (27.8), 119 (8.6), 107 (12.3), 79 (63.5).
11a	3340 (NH), 1789, 1759, 1681 (CO).	2.34 (s, 3H, CH_3), 7.21 (s, 1H, =CH), 7.22, 7.23, 8.25, 8.26 (AB-q, J = 8.7 Hz, 4H, Ar-H), 7.95, 7.98, 8.86, 8.89 (AB-q, J = 8.4 Hz, Ar-H), 8.62, 8.63 (d, J = 1.5 Hz, 1H, H-6), 8.85, 8.87 (d, J = 2.4 Hz, 1H, H-5), 9.54 (s, 1H, H-3), 9.91 (s, 1H, NH). 428 (M^+, 11.1), 386 (32.1), 226 (100), 146 (15.2), 121 (13.6), 79 (60), 52 (21.2)
11b	3340.5 (NH), 1681.8 (CO).	458 (M^+, 4.7), 416 (25.1), 226 (100), 212 (20.6), 79 (74.2).

12a	3309.6 (NH), 1700, 1689 (CO)	2.86 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.05, 7.09, 7.30, 7.34 (AB-q, J = 8.55 Hz, 4H, Ar-H), 7.17 (s, 1H, CH=), 7.49, 7.53, 8.30, 8.35 (AB-q, J = 8.55 Hz, 4H, Ar-H), 7.87-7.92 (m, 4H, Ar-H), 8.79 (s, 1H, H-6), 8.91 (s, 1H, H-5), 9.27 (s, 1H, H-3), 10.9 (s, 1H, NH). 489 (M^+, 52.5), 315 (20.2), 235 (42.7), 226 (100), 146 (13.4), 91 (98.73), 79(47.0), 65 (69.6), 52 (14.4).
12b	3348 (NH), 1720, 1681 (CO).	2.41 (s, 3H, CH_3), 7.07-7.18 (m, 4H, Ar-H), 7.25 (s, 1H, CH=), 7.42, 7.46, 8.22, 8.26 (AB-q, J = 8.54 Hz, 4H, Ar-H), 7.62, 7.67, 7.74, 7.78 (AB-q, J = 8.8 Hz, 4H, Ar-H), 8.60, 8.61 (d, J = 0.9 Hz, 1H, H-6), 8.84, 8.85 (d, J = 2.2 Hz, 1H, H-5), 9.51 (s, 1H, H-3), 9.81 (s, 1H, NH). 493 (M^+, 26.7), (M^++2, 10.3), 315 (10.8), 235(23.4), 226 (100), 121 (16), 91 (60.8), 79 (65.8), 52(20.7).
13	3355, 3209 (NH), 1697, 1643 (CO).	3.76 (s, 3H, OCH_3), 7.2 (s, 1H, CH=), 6.95-8.15 (m, 17H, Ar-H), 8.8 (s, 1H, H-6), 8.95 (s, 1H, H-5), 9.4 (s, 1H, H-3), 10 (s, 1H, NH), 10.2 (s, 1H, NH), 11 (s, 1H, NH). 55.54 (OCH_3), 114.24, 120.07, 120.70, 126.40, 126.78, 127.19, 128.94, 129.07, 129.19 (Ar-C's), 138.98, 139.86, 141.40, 144.91 (pyrazine-C'S), 135.17 (C-CO), 131,46 (=C), 159.83 (C=N), 162.26 (CO), 164.86 (CO), 165.73 (CO). 551 (M^+-H_2O, 7.9), 402 (1), 401 (5.5), 400 (14.1), 399 (0.9), 297 (3.0), 227 (15.1), 226 (100), 170 (10.2), 169 (66.6), 168 (11.9), 154 (1.7), 152 (11.1), 146 (24.9), 121 (33.3), 107 (14.8), 103 (3.2), 102 (3), 79 (68), 52 (20.2).
14a	3332 (NH), 1789, 1712, 1681 (CO), 1635(C=N), 1596 (C=C)	3.90 (s, 3H, OCH_3), 7.12, 7.15, 8.16, 8.19 (2d, J = 5.2 Hz, 4H, Ar-H), 7.18 (s, 1H, CH=), 7.35 (s, 1H, NH), 8.25 (s, 1H, NH), 8.37, 8.39, 8.50, 8.52 (2d, J = 5.4 Hz, 4H, Ar-H), 8.90, 8.91 (d, J = 0.6 Hz, 1H, H-6), 9.02 (s, 1H, H-5), 9.40 (s, 1H, H-3), 11.08 (s, 1H, NH).
14b	3340 (NH), 1789, 1712, 1681 (CO), 1635(C=N), 1581 (C=C)	418 (M^+, 51.6), M+2 (27.9), 403 (50.8), 240 (43.8), 226 (28.5), 225 (38.5), 224 (7.2), 117 (11.1), 107 (45.9), 91 (24.8), 90 (30.9), 81 (28.7), 80 (27.3), 79 (100), 52 (52).

Biological Activity:

a) Antimicrobial activities

Most of the newly synthesized compounds were tested against different types of Gram-positive bacteria [Bacillus subtilis **NCTC 3610 (BS)**, Staphylococcus aureus **NCTC 6510 (SA)** , Pseudomanas aeruginosa **ATCC 10415 (PA)**] Gram-Negative bacteria [Escherichia coli **ATCC 10416 (EC)**] and unicellular yeast [Candida albicans **ATCC 10231 (CA)** , and filamentous fungi [Aspergillus niger **ATCC 1034 (AN)** (Table **3**).

The tested compounds were dissolved in N,N-dimethylformamide (DMF) to get a solution of 1 mg / ml^{-1} , the inhibition zones were measured at the end of incubation period of 48 h. at 28 ^{0}C. N,N-Dimethylformamide (DMF) showed no inhibition zones .

The activities of this compounds were tested using disk diffusion

Method[29,30] . The area of zone of inhibition was measured using Neomycin and Mycostatine as standard antibiotics . The results are given in (Table **III).**

b) Leuconostoc mesenteroides growth inhibition.

Viscous poly saccharides produced by L . mesenteroides are widely recognized as causing product losses and processing problems in the production of sucrose from sugar cane and sugar beet[31] , therefore the aim of the present investigation was investigate the utility to use the pyrazine-2-carboxamide derivatives as inhibitory compounds for L. mesenteroides. Most strains in liquid culture appear as cocci, occurring singly or in pairs and short chains, however, cells grown in glucose or on solid media may have an elongated or rod shaped morphology[32], therefore the test was carried on liquid culture and the area of zone of inhibition was measure of using Neomycin and Mycostatine as standard antibiotics . The results are given in (Table **III**).

Table III. Antimicrobial activity of the new compounds

Compd. No	*(BS)* NCTC 3610	*(SA)* NCTC 6510	*(PA)* ATCC 10415	*(EC)* ATCC 10416	*(CA)* ATCC 10231	*(AN)* ATCC 1034	*Leuconostoc Mesenteroides Sp.*
3a	+	+	+	+	+	+	+
3b	+	+	+	+	+	+	+
3c	+++	+++	+++	+++	+++	+++	+++
4	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+
10a	+	+	+	+	+	+	+
10b	+	+	+	+	+	+	+
11a	+	+	+	+	+	+	+
11b	+	+	+	+	+	+	+
12b	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+

1 +ve (when inhibition zone up to 8 mm)

2 ++ve (when inhibition zone was between 8-12 mm)

3 +++ve (when inhibition zone was between 12-15 mm)

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