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Antimicrobial activity of various hydantoin derivatives

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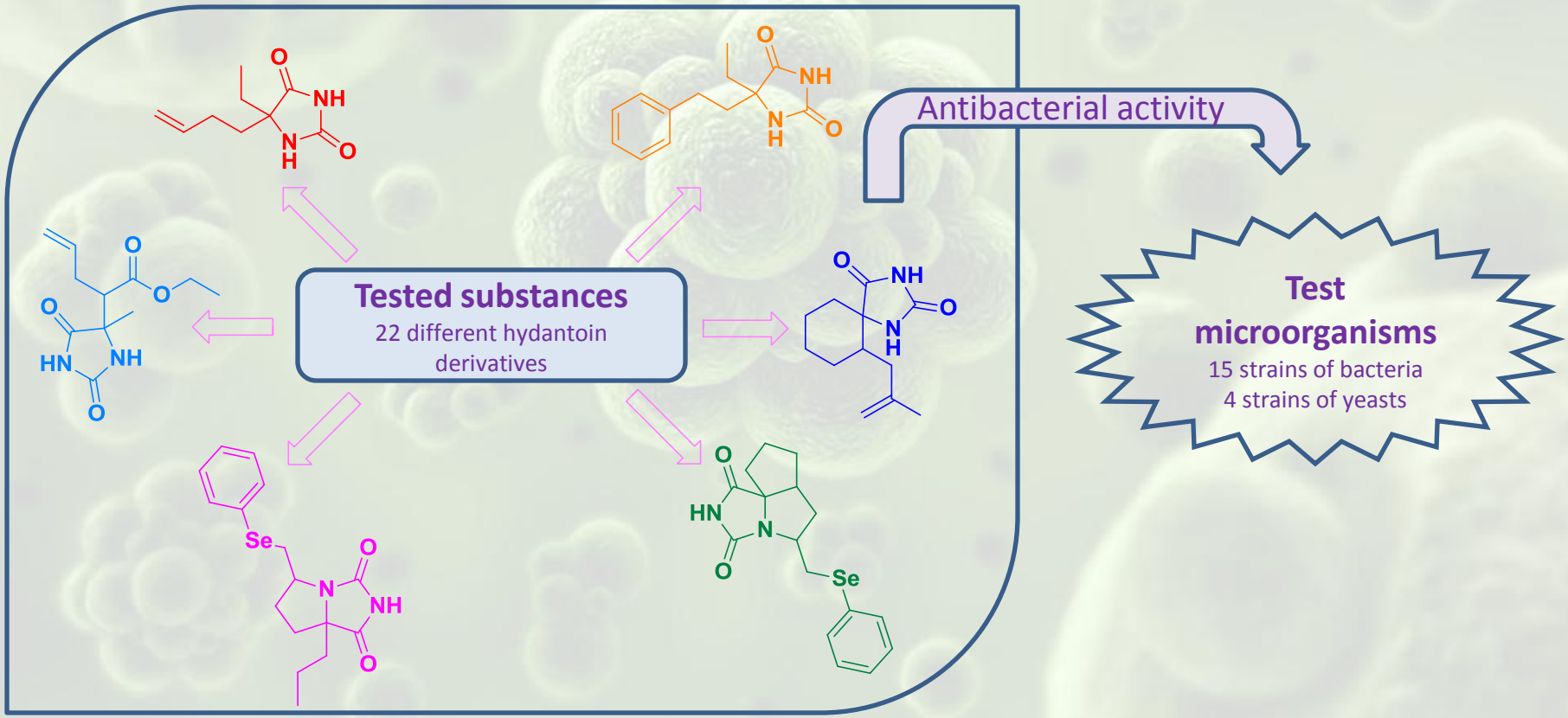
Antimicrobial activity of various hydantoin derivatives

Graphical Abstract



Abstract: A series of 22 synthetic drug-like hydantoin derivatives, including aryl or alkenyl 5,5-disubstituted hydantoins, spirohydantoins and annulated bicyclic and tricyclic hydantoins, was assayed for *in vitro* antibacterial and antifungal activity. The antimicrobial activity was tested by determination of the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) using microdilution method. The tested hydantoin derivatives showed moderate antibacterial and weak antifungal activity. The intensity of acting varied depending on the structure and concentration of the test substances and the type of test organisms. The bicyclic benzeneselenenyl derivatives of hydantoin have shown the highest inhibitory activity. The tested compounds appeared as promising for a fragment-based drug design approach and further bioactivity studies.

Keywords: hydantoins; antibacterial activity; antifungal activity; benzeneselenenyl derivatives

Introduction

- Hydantoin nucleus is integral part of many biologically active compounds such as anti-arrhythmic, anti-convulsive and antitumor agents. The observed activities do not arise from the hydantoin nucleus itself but from different substituents that have been appended to it.

- In particular, spirohydantoins and fused polycyclic hydantoin derivatives have recently attracted much attention in drug discovery due to their various biological activities.

- Hydantoins possess activities against viruses, protozoa, mycobacteria, bacteria and fungi due to their active component urea core.

- Due to the increasing resistance of microorganisms to antibiotics, and also an extensive biological activity exhibited by hydantoins the aim of this study is to investigate the antibacterial and antifungal activity of 22 different hydantoin derivatives.

Results and discussion

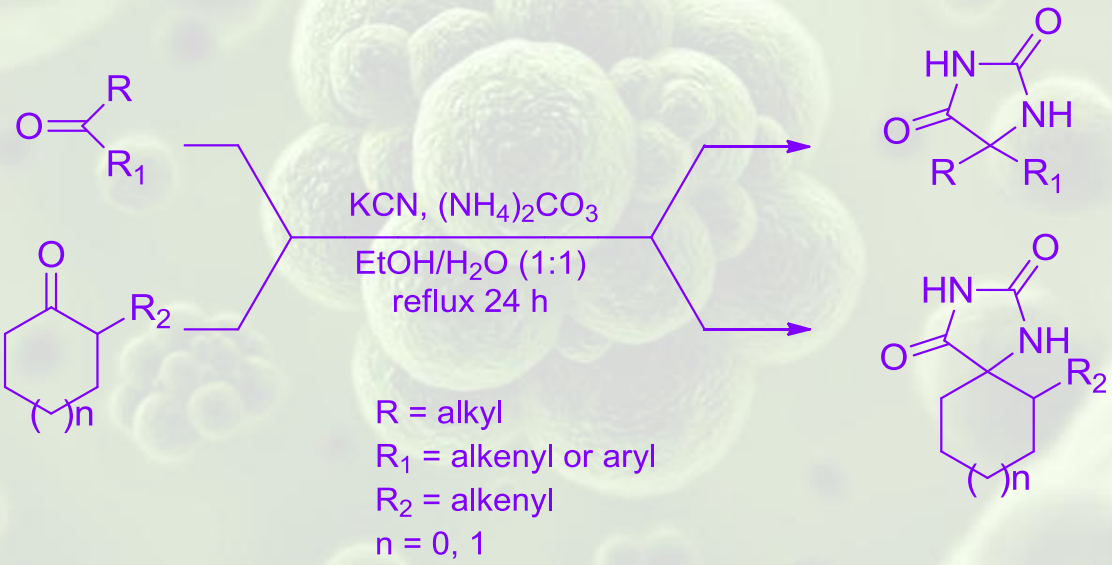
Methodology: Antibacterial activity was tested by determining the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) using micro-dilution method with resazurin.

Test microorganisms

- 15 strains of bacteria
  - 3 probiotics - *Lactobacillus plantarum*, *Bifidobacterium animalis* subsp. *lactis*, *Bacillus subtilis* IP 5832
  - 12 human pathogenic bacteria - *Bacillus subtilis*, *Bacillus pumilus* NCTC 8241, *Staphylococcus aureus*, *S. aureus* ATCC 25923, *Escherichia coli*, *E. coli* ATCC 25922, *Proteus mirabilis*, *P. mirabilis* ATCC 12453, *Pseudomonas aeruginosa*, *P. aeruginosa* ATCC 27853, *Salmonella enterica*, *Salmonella typhymirium*
- 4 strains of yeasts
  - 1 probiotic - *Saccharomyces boulardii*
  - 2 isolates - *Rhodotorula mucilaginosa*, *Candida albicans*
  - 1 standard strain - *C. albicans* ATCC 10231

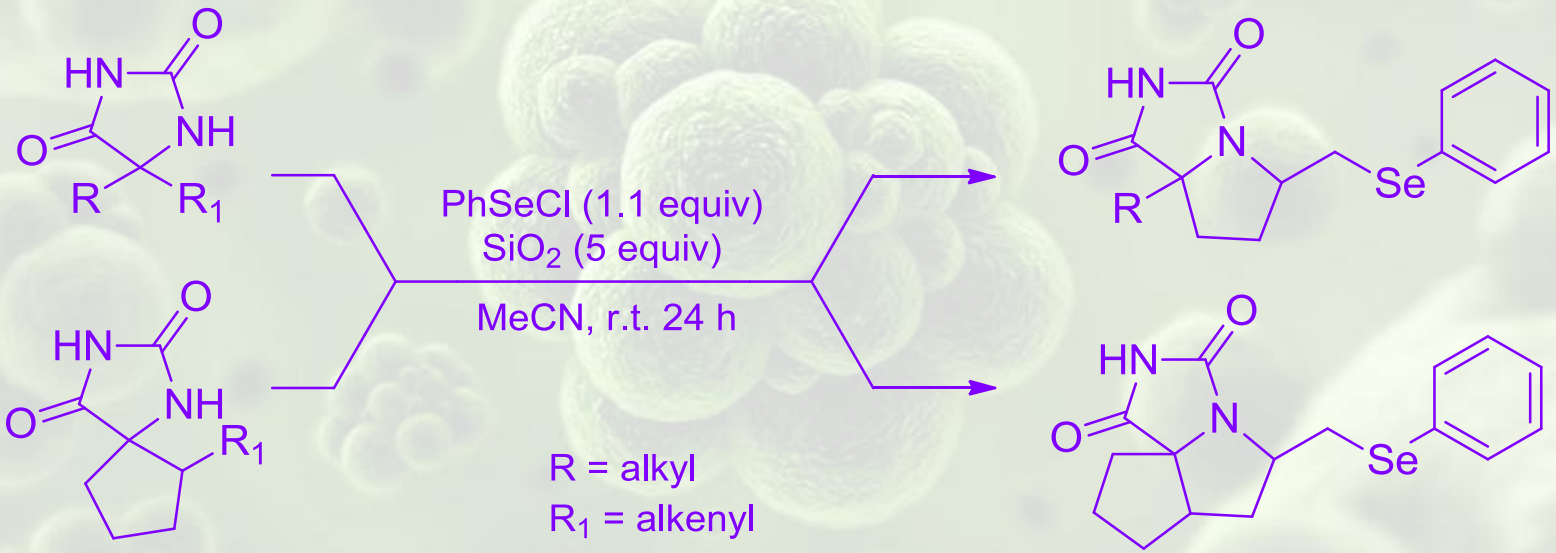
Chemistry

Tested 5,5-substituted hydantoin derivatives and spirohydantoins are synthesized from corresponding ketones and ketoesters using multicomponent Bucherer-Bergs reaction.

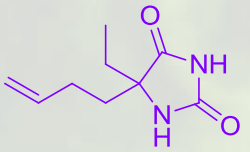


R = alkyl
R_1 = alkenyl or aryl
R_2 = alkenyl
n = 0, 1

Tested bicyclic and tricyclic hydantoin derivatives are synthesized from corresponding 5-alkenyl hydantoins and spirohydantoins by selenium induced intramolecular cyclization.

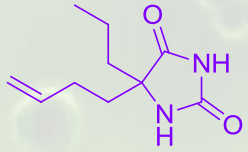


5-Alkenyl hydantoin derivatives



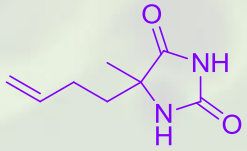
5-But-3-enyl-5-ethyl-imidazolidine-2,4-dione

Hyd1



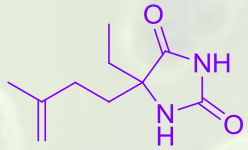
5-But-3-enyl-5-propyl-imidazolidine-2,4-dione

Hyd2



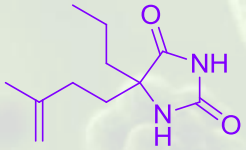
5-But-3-enyl-5-methyl-imidazolidine-2,4-dione

Hyd3



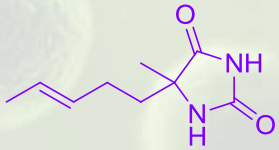
5-Ethyl-5-(3-methyl-but-3-enyl)-imidazolidine-2,4-dione

Hyd4



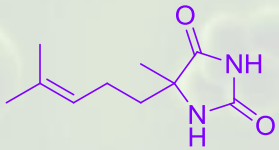
5-(3-Methyl-but-3-enyl)-5-propyl-imidazolidine-2,4-dione

Hyd5



(E)-5-Methyl-5-(pent-3-enyl)-imidazolidine-2,4-dione

Hyd6



5-Methyl-5-(4-methyl-pent-3-enyl)-imidazolidine-2,4-dione

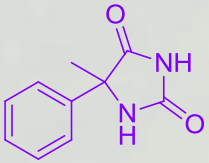
Hyd7

Antimicrobial activity of 5-alkenyl hydantoin derivatives

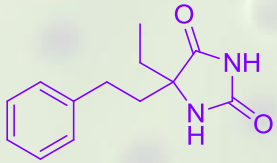
Substances	Hyd1		Hyd2		Hyd3		Hyd4		Hyd5		Hyd6		Hyd7	
Species	[1]MIC	[2]MMC	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC
Lactobacillus plantarum	>1000	>1000	500	500	500	1000	1000	>1000	1000	>1000	1000	>1000	1000	1000
Bifidobacterium animalis subsp. lactis	1000	>1000	**62.5**	500	250	250	125	1000	1000	1000	**62.5**	250	125	500
Bacillus subtilis IP 5832	>1000	>1000	500	1000	1000	1000	>1000	>1000	>1000	>1000	1000	>1000	1000	1000
Bacillus subtilis	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	1000
Bacillus pumilus NCTC 8241	>1000	>1000	>1000	>1000	1000	1000	500	>1000	1000	>1000	500	1000	500	1000
Staphylococcus aureus	500	>1000	>1000	>1000	1000	1000	**62.5**	250	>1000	>1000	1000	>1000	500	>1000
S. aureus ATCC 25923	1000	>1000	>1000	>1000	500	>1000	500	1000	500	>1000	500	>1000	250	1000
Escherichia coli	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	1000	>1000
Proteus mirabilis	>1000	>1000	1000	>1000	1000	>1000	1000	>1000	1000	>1000	1000	1000	1000	>1000
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000
Pseudomonas aeruginosa	1000	>1000	1000	>1000	1000	>1000	250	>1000	1000	>1000	500	>1000	500	>1000
P. aeruginosa ATCC 27853	1000	>1000	1000	>1000	1000	>1000	500	>1000	1000	>1000	**62.5**	>1000	1000	>1000
Salmonella enterica	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Salmonella typhymirium	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Rhodotorula mucilaginosa	500	1000	1000	1000	1000	1000	500	1000	1000	1000	1000	>1000	500	1000
Saccharomyces boulardii	>1000	>1000	1000	>1000	1000	>1000	>1000	>1000	1000	1000	1000	>1000	1000	>1000
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Candida albicans	1000	>1000	1000	>1000	>1000	>1000	1000	>1000	>1000	>1000	1000	>1000	1000	>1000

[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

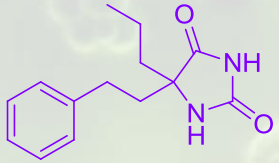
Phenyl hydantoin derivatives



5-Methyl-5-phenylimidazolidine-2,4-dione
Hyd8



5-ethyl-5-phenethylimidazolidine-2,4-dione
Hyd9



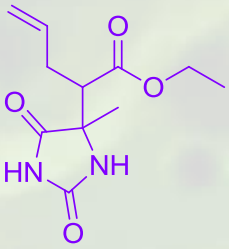
5-phenethyl-5-propylimidazolidine-2,4-dione
Hyd10

Antimicrobial activity

Substances	hydantoins with phenyl group					
	Hyd8		Hyd9		Hyd10	
Species	[1]MIC	[2]MMC	MIC	MMC	MIC	MMC
Lactobacillus plantarum	>1000	>1000	1000	>1000	1000	>1000
Bifidobacterium animalis subsp. lactis	250	1000	1000	1000	500	1000
Bacillus subtilis IP 5832	>1000	>1000	1000	>1000	1000	>1000
Bacillus subtilis	>1000	>1000	>1000	>1000	>1000	>1000
Bacillus pumilus NCTC 8241	>1000	>1000	>1000	>1000	500	>1000
Staphylococcus aureus ATCC 25923	1000	>1000	>1000	>1000	1000	>1000
Staphylococcus aureus	1000	>1000	>1000	>1000	500	>1000
Escherichia coli	>1000	>1000	>1000	>1000	>1000	>1000
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	>1000	>1000
Proteus mirabilis	>1000	>1000	1000	>1000	>1000	>1000
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	>1000	>1000
Pseud. aeruginosa	1000	>1000	500	>1000	500	>1000
Pseud. aeruginosa ATCC 27853	1000	>1000	1000	>1000	1000	>1000
Salmonella enterica	>1000	>1000	>1000	>1000	>1000	>1000
Salmonella typhymirium	>1000	>1000	>1000	>1000	>1000	>1000
Rhodotorula mucilaginosa	1000	1000	1000	1000	1000	1000
Saccharomyces boulardii	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans	1000	1000	1000	>1000	1000	>1000

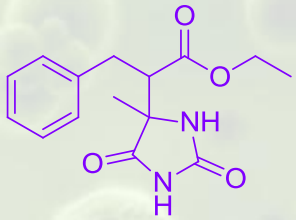
[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

Acetylated hydantoins derivatives



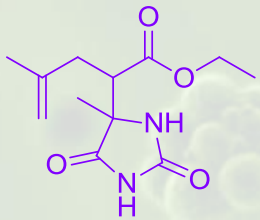
2-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)-pent-4-enoic acid ethyl ester

Hyd11



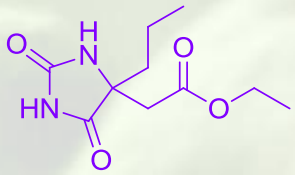
ethyl-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-3-phenylpropanoate

Hyd13



4-Methyl-2-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-pent-4-enoic acid ethyl ester

Hyd12



ethyl-2-(2,5-dioxo-4-propylimidazolidin-4-yl)-acetate

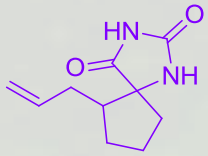
Hyd14

Antimicrobial activity of acetylated hydantoin derivatives

Substances	Hyd11		Hyd12		Hyd13		Hyd14	
Species	[1]MIC	[2]MMC	MIC	MMC	MIC	MMC	MIC	MMC
Lactobacillus plantarum	>1000	>1000	>1000	>1000	1000	>1000	1000	>1000
Bifidobacterium animalis subsp. lactis	>1000	>1000	**250**	1000	500	1000	**250**	1000
Bacillus subtilis IP 5832	>1000	>1000	>1000	>1000	>1000	>1000	1000	1000
Bacillus subtilis	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Bacillus pumilus NCTC 8241	>1000	>1000	1000	>1000	>1000	>1000	1000	>1000
Staphylococcus aureus	>1000	>1000	500	500	1000	>1000	500	>1000
Staphylococcus aureus ATCC 25923	>1000	>1000	1000	>1000	1000	>1000	1000	>1000
Escherichia coli	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Proteus mirabilis	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Pseud. aeruginosa	1000	>1000	1000	>1000	1000	>1000	500	>1000
Pseud. aeruginosa ATCC 27853	1000	>1000	1000	>1000	1000	>1000	1000	>1000
Salmonella enterica	1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Salmonella typhymirium	1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Rhodotorula mucilaginosa	1000	>1000	1000	1000	500	1000	1000	1000
Saccharomyces boulardii	>1000	>1000	1000	>1000	>1000	>1000	>1000	>1000
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans	1000	1000	1000	1000	1000	>1000	1000	>1000

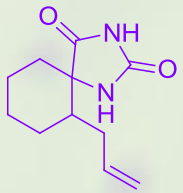
[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

Spiro hydantoins



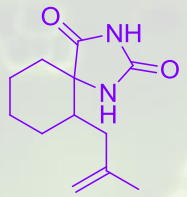
6-allyl-1,3-diazaspiro[4.4]nonane-2,4-dione

Hyd15



6-allyl-1,3-diazaspiro[4.5]decane-2,4-dione

Hyd16



6-(2-methylallyl)-1,3-diazaspiro[4.5]decane-2,4-dione

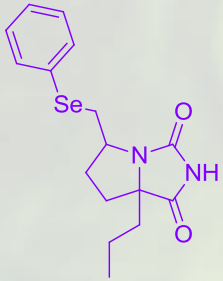
Hyd17

Antimicrobial activity of spiro hydantoins

Substances	Hyd15		Hyd16		Hyd17	
Species	[1]MIC	[2]MMC	MIC	MMC	MIC	MMC
Lactobacillus plantarum	**15.75**	**31.25**	1000	>1000	**15.75**	**31.25**
Bifidobacterium animalis subsp. lactis	-	-	500	1000	125	1000
Bacillus subtilis IP 5832	-	-	1000	>1000	>1000	>1000
Bacillus subtilis	-	-	>1000	>1000	>1000	>1000
Bacillus pumilus NCTC 8241	-	-	1000	>1000	>1000	>1000
Staphylococcus aureus ATCC 25923	-	-	1000	>1000	1000	>1000
Staphylococcus aureus	-	-	1000	>1000	1000	>1000
Escherichia coli	>1000	>1000	>1000	>1000	>1000	>1000
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	>1000	>1000
Proteus mirabilis	1000	>1000	1000	>1000	>1000	>1000
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	>1000	>1000
Pseud. aeruginosa	500	>1000	500	>1000	500	>1000
Pseud. aeruginosa ATCC 27853	500	>1000	1000	>1000	1000	>1000
Salmonella enterica	>1000	>1000	>1000	>1000	>1000	>1000
Salmonella typhymirium	>1000	>1000	>1000	>1000	>1000	>1000
Rhodotorula mucilaginosa	1000	1000	1000	1000	1000	1000
Saccharomyces boulardii	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans	1000	>1000	1000	>1000	1000	>1000

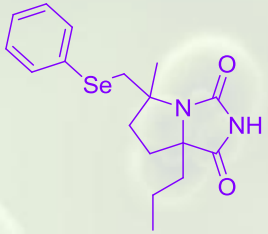
[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

Bicyclic & Tricyclic hydantoin derivatives



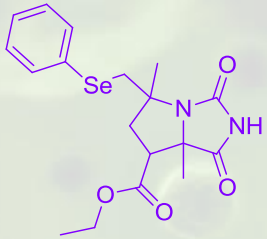
5-phenylselanylmethyl-7a-propyl-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione

Hyd18



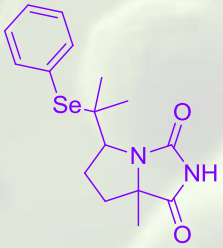
5-methyl-5-phenylselanylmethyl-7a-propyl-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione

Hyd19



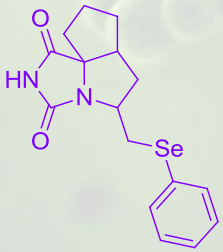
5,7a-dimethyl-1,3-dioxo-5-phenylselanylmethyl-hexahydro-pyrrolo[1,2-c]imidazole-7-carboxylic acid ethyl ester

Hyd20



7a-methyl-5-(1-methyl-1-phenylselanyl-ethyl)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione

Hyd21



5-(phenylselanylmethyl)-hexahydro-1H-cyclopenta[2,3]pyrrolo[1,2-c]imidazole-1,3(2H)-dione

Hyd22

Antimicrobial activity of bicyclic and tricyclic hydantoin derivatives

Substances	Hyd18		Hyd19		Hyd20		Hyd21		Hyd22	
Species	[1]MIC	[2]MMC	MIC	MMC	MIC	MMC	MIC	MMC	MIC	MMC
Lactobacillus plantarum	1000	1000	1000	>1000	500	1000	**62.5**	250	1000	>1000
Bifidobacterium animalis subsp. lactis	1000	1000	250	1000	**62.5**	250	**15.75**	**62.5**	**62.5**	1000
Bacillus subtilis IP 5832	>1000	>1000	>1000	>1000	500	1000	250	1000	>1000	>1000
Bacillus subtilis	>1000	>1000	>1000	>1000	1000	1000	>1000	>1000	>1000	>1000
Bacillus pumilus NCTC 8241	1000	>1000	>1000	>1000	250	500	500	>1000	>1000	>1000
Staphylococcus aureus ATCC 25923	500	>1000	>1000	>1000	500	1000	125	1000	500	>1000
Staphylococcus aureus	1000	>1000	**62.5**	>1000	**<7.81**	**31.25**	**15.75**	**62.5**	1000	>1000
Escherichia coli	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Escherichia coli ATCC 25922	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Proteus mirabilis	>1000	>1000	>1000	>1000	>1000	>1000	1000	>1000	>1000	>1000
Proteus mirabilis ATCC 12453	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Pseud. aeruginosa	1000	>1000	500	>1000	500	>1000	500	>1000	1000	>1000
Pseud. aeruginosa ATCC 27853	1000	>1000	1000	>1000	1000	>1000	1000	>1000	>1000	>1000
Salmonella enterica	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Salmonella typhymirium	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Rhodotorula mucilaginosa	1000	1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Saccharomyces boulardii	1000	1000	>1000	>1000	>1000	>1000	1000	>1000	1000	>1000
Candida albicans ATCC 10231	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Candida albicans	>1000	>1000	>1000	>1000	1000	>1000	1000	>1000	>1000	>1000

[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

Antimicrobial activity of positive control (tetracycline and fluconazole)

Substances	Tetracycline/Fluconazole	
Species	[1]MIC	[2]MMC
Lactobacillus plantarum	0.45	7.81
Bifidobacterium animalis subsp. lactis	31.25	62.50
Bacillus subtilis IP 5832	1.95	15.63
Bacillus subtilis	0.11	1.95
Bacillus pumilus NCTC 8241	0.11	7.81
Staphylococcus aureus ATCC 25923	0.22	3.75
Staphylococcus aureus	0.45	7.81
Escherichia coli	7.81	15.63
Escherichia coli ATCC 25922	15.63	31.25
Proteus mirabilis	250	>250
Proteus mirabilis ATCC 12453	15.63	62.50
Pseudomonas aeruginosa	250	>250
Pseud. aeruginosa ATCC 27853	62.50	125
Salmonella enterica	15.63	31.25
Salmonella typhymurium	15.63	125
Rhodotorula mucilaginosa	62.50	1000
Saccharomyces boulardii	31.25	1000
Candida albicans ATCC 10231	31.25	1000
Candida albicans	62.50	1000

[1]MIC values (μg/ml) – means inhibitory activity.
[2]MMC values (μg/ml) – means microbicidal activity.

Conclusions

- The tested hydantoin derivatives showed moderate antibacterial and weak antifungal activity. The intensity of acting varied depending on the structure and concentration of the test substances and the type of test organisms.

- Hydantoin derivatives generally showed a stronger action against Gram positive bacteria (especially probiotics) than gram negative ones.

- The bicyclic benzeneselenenyl derivatives of hydantoin have shown the highest inhibitory activity probably due to a presence of selenium in their structure. They are most effective against *Staphylococcus aureus,* strain resistant to methicillin.

- The tested compounds appeared as promising for a fragment-based drug design approach and further bioactivity studies.

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