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An efficient conversion of maleimide derivatives to 2-thioxo imidazolidinones

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Abstract: Starting from maleimidederivatives, a series of 2-thioxoimidazolidinones was prepared through two different procedures. These syntheses have achieved in two steps via reaction between maleimide derivatives **1**,semicarbazide hydrochloride **9** and isothiocyanates**5**,the best results being obtained under acid conditions (AcOH or heteropolyacid in ethanol or acétonitrile). The synthesized compounds **11a-f** and substituted thiohydantoins **6a-h**, **8a-h** were screened for their in vitro anti-bacterial activity against four bacterial strains.

Keywords: Maleimide; thiohydantoin; antibacterial activity.

1. Introduction

The thiohydantoin moiety is found in a large number of biologically active compounds.[1]A simple change in the substitution pattern on the thiohydantoin nucleus often leads to incredible diverse biological activities.[2-4] For example, the 5-[(2-phenyl-1*H*-indol-3-yl) methylidene]-2-thioxoimidazolidin-4-one **A** (Figure 1) has been used for its anti HIV properties.[5] Substituted 4-methylene-2-thiohydantoin **B** has displayed Cycline Dependant Kinases (CDK) inhibition in a micromolar range [6] or antileishmanial activity.[7]

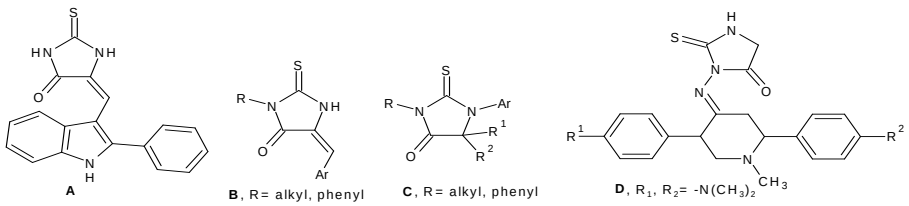

Figure 1. Thiohydantoinswith reported biological activities

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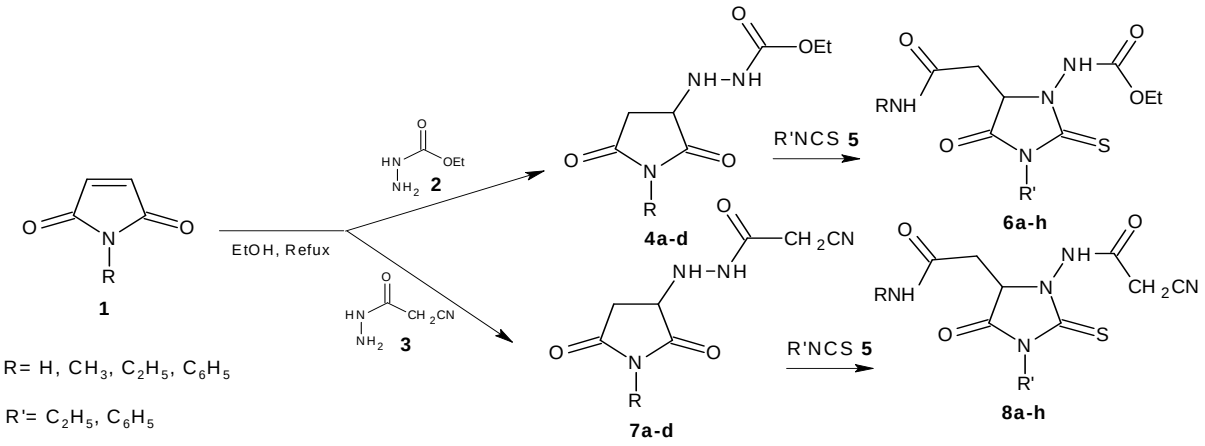
Compound **C** (Figure 1) was claimed to be active for treatment of hormone refractory prostate cancer,[8] whereas 3-[(1-methyl-2,6-diphenyl piperidin-4-yliden)amino]-2-thiohydantoin**D** demonstrated remarkable antimicrobial activity.[9] (Figure 1) Our continued drive towards identifying new biologically active substituted thiohydantoin in particular 1,5substituted thiohydantoins, prompted our investigation on extension of previous work.[10-11] (Scheme 1)



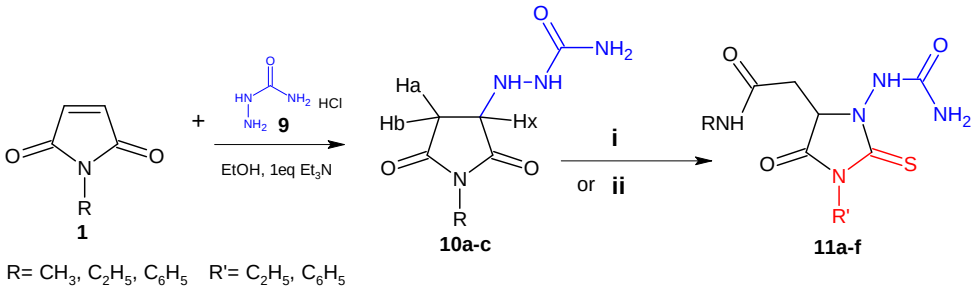
Scheme 1.Synthesis of compounds **6a-h** and **8a-h**

Herein we report the synthesis and the antimicrobial activities for three series of thiohydantoins.

2. Results and Discussion

We have previously described the regiospecific synthesis of thiohydantoins structures [10] **6a-h** and **8a-h** in two steps, from maleimides**1**, hydrazine carboxylate **2** or hydrazine carbocyanate **3** and isothiocyanate reagents **5** (Scheme 1**)**.

We wish to report here an extension of this methodology using semicarbazide hydrochloride **9**as nucleophile. Two protocols of synthesis of compounds **11a-f** have been developed (Scheme 2).



i) Method A: R'NCS **5**, EtOH or CH_3CN

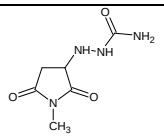
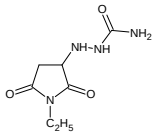
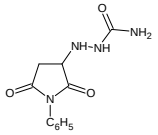
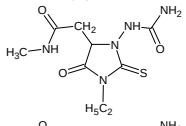
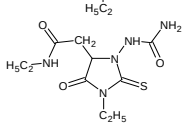
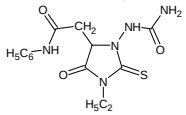
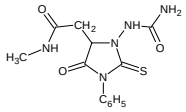
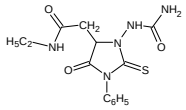
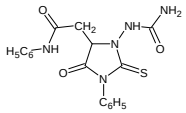
ii) Method B: R'NCS **5**, AcOH or $H_5PMO_{10}V_2O_4$ (0.12 mol%, 1.2 10^{-6} mol), EtOH or CH_3CN

Scheme 2. Synthesis of compounds **11a-f**

Derivatives **11a-f** were synthesised from commercially N-aryl or N-alkylmaleimides**1** and semicarbazide hydrochloride **9**, followed by the coupling with substituted isothiocyanates**5**.The reaction between maleimides**1,**semicarbazide hydrochloride **9** andanequimolar amount of triethylamine in ethanol solution, followed by heating for 6 hours led to the awaiting products **10a-c** with good yields.

The treatment of compounds **10a-c** with ethyl or phenylisothiocyanates **5** under reflux for a period of 6 to 11 hours in ethanol or acetonitrile (Method A), allowed the complete conversion of the starting material **10a-c** to 2-thioxo-imidazolidinones **11a-f**, in good yields (Table 1)

Table 1.Preparation and physical data of derivatives **10** and **11**.

Compound	Structures	Reaction times in absence of catalyst (h)		Reaction times in the presence of $H_5PMo_{10}V_2O_4$ (h)		Yields (%)	MP (°C)
		EtOH	CH_3CN	EtOH	CH_3CN		
10a		6	/	/	/	98	185-188
10b		6	/	/	/	92	
10c		6	/	/	/	66	160
11a		8	9	6	5	44	190
11b		9	10	4	2	56	140
11c		11	11	5	4	60	190
11d		6	7	4	3	63	235
11e		10	11	5	2	69	225
11f		8	9	4	3	71	150

The ^{1}H NMR spectra of compounds **10** showed characteristic patterns of an ABX system corresponding to CH_2-CH fragment. For example concerning compound **10a**, the chemical shift value for H_a, H_b and H_x was observed at 2.32 (J=22 and 10 Hz), 2.57 (J=22 and 5.5 Hz) and 3.96 ppm (J= 10 and 5.5 Hz) respectively and appeared as doublet of doublet (dd), while in the ^{1}H NMR spectrum of derivatives **11** we observe dinstead of an ABX system, the presence of two new signals as doublet at 2,75ppm (J=4Hz) and triplet at 4.40 ppm (J= 4Hz) corresponding to CH_2C=O fragment and CH at position 4 respectively.

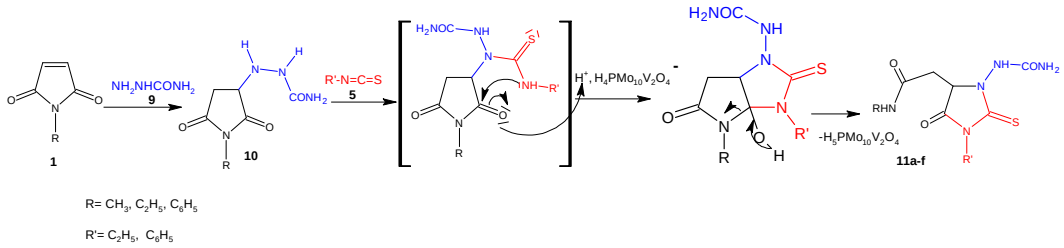
As shown in Table 1, the cyclization reaction times of compounds **11a-f** (6-11 h)were longer comparatively with reaction times of derivatives **6a-h** (1-3 h).

In order to optimize the reaction conditions, the effect of solvents (Method A) or the use of catalysts (Method B) was studied. Two acids were employed: acetic acid (low acid) or heteropolyacid ($H_5PMo_{10}V_2O_4$, strong acid).The cyclization reaction of precursors **10** with isothiocyanates**5** in the

presence of two drops of acetic acid in refluxing ethanol or acetonitrile lead to structures **11**. The addition of AcOH did not significantly increase the rate or the yield.We next prepared the compounds **11** by employing heteropolyacid ($H_5PMo_{10}V_2O_{40}$). The heteropolyacids constitute stronger acids compared with homogeneous acid catalysts such as sulphuricacid.[12-13] In this work, we have used $H_5PMo_{10}V_2O_{40}$ as catalyst. Our concept was that a Keggin acid should be able to promote the condensation of precursors **10** with isothiocyanates**5** to give 2-thioxo-imidazolidinones **11** with shortened reaction times and increased yields.

Compounds **10** reacted with isothiocyanates**5** in the presence of 0.12 mol% (1.2 µmol, 2 10^{-3} g) of $H_5PMo_{10}V_2O_4$ in the same solvents at reflux. The desired products **11** were formed efficiently, and the reaction times in these reactions were shortened from 9 to 4 hours in ethanol, and from 10 to 2 hours in acetonitrile, for derivative **11b**, for example. The results obtained with the Keggin catalyst in different solvents represented in Table 1, clearly show that the best rate was obtained with acetonitrile. In such conditions, the reaction afforded the products **11** in 41-47% yields.

The mechanism of the reaction between compounds **10** and isothiocyanates **5** in the presence of Keggin catalystis showed in Scheme 3.



Scheme 3.Synthetic route to compounds **11**

Materials and methods

Antibacterial Activity

Antibacterial activity of the compounds **6a-h, 8a-h** and **11a-f**, was determined by the well diffusion method.[14-15] Four bacterial strains were selected for this study: *Escherichia coli* ATCC 25992, *Pseudomonas aeruginosa* ATCC 27852, *Staphylococcus aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212. The anti-bacterial activity is presented in Table 2. To realize the bacterial cultures, nutrient broth and Mueller-Hinton agar (Difco) were used as basal medium. We realized a culture of each strain in nutrient broth and after 24 h of incubation at 37 °C, a dilution (10^{-2}) was prepared in sterile physiological water. Muller Hinton agar plates were seeded with a 24 h culture of the bacterial strains. The wells (4 mm in diameter) were cut from the agar and 50 µL of each synthesized compound solution (concentration 0.5 mg/ml in DMSO) was delivered into them. As a control, DMSO (50 µL) was delivered into a well for each Petri dish. Diameter of inhibition zone (mm) was measured after incubation at 37 °C for 24 h.

Antibacterial activity of the synthesized compounds **8a-h**, **6a-h** and **11a-f** was evaluated in vitro against four bacterial species, which are known to cause some infections in humans. Among the tested compound, the most effective one was found to be the structure **8d** (Table 2), for which the biggest inhibition zone represented 24 mm, 23 mm and 22 mm. This compound inhibited the growth of *Escherichia coli*, ATCC 25992 and *Enterococcus feacalis* ATCC 29212, respectively. Molecules **8c**, **8f**, **6e**,and **6f** were also efficient against *Enterococcus feacalis* and the inhibition zone value was 20 mm. It is generally expected that, when antimicrobial activity is measured, most anti-bacterial molecules tested are more active against Gram-positive than against Gram-negative bacteria.[16] In this study, the tested compounds inhibited especially Gram-positivebacteria. None of the compounds **8a-h**, **6a-e** and **11a** did show inhibitory effect against *Escherichia coli*. All compounds have less activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

It is very difficult to explain the activity of the synthesized compound separately against the different bacteria tested. It is known that they can inhibit function of some important molecules such as extracellular and intracellular enzymes and microbial metabolism. They can also causing the degradation of the cell wall with disruption of the cytoplasmic membrane, thus leading leakage of cellular components. We can also assume their influence on the synthesis of DNA and RNA,[17] the synthesis of proteins and other molecules,[18] as well as the formation of complexes with wall.[19]
These mechanisms are not separate targets, some may as a consequence of another mechanism. The antimicrobial action of some agents depends on the type of microorganisms and the arrangement of the outer membrane.[20] The method used to evaluate the antibacterial activity also affects the results. Although, the method of diffusion from wells on agar is more appropriate to study the activity of aqueous extracts and organic compounds.[15, 21]

Table 2. Anti-bacterial activity of molecules **8a-h, 6a-h**and **11 a-f** (zone size, mm).

Compound	*E.coli* ATCC2592	*Staphylococcus aureus* ATCC 25923	*Enterococcus faecalis* ATCC 29212	*Pseudomonas aeruginosa* ATCC 27852
8a	-	-	12	15
8b	-	-	15	16
8c	-	11	20	-
8d	24	10	23	9
8e	-	-	22	9
8f	10	10	20	5
8g	11	-	18	9
8h	-	15	16	9
6a	-	10	15	9
6b	-	15	17	12
6c	-	13	18	9
6d	-	10	19	-
6e	-	-	20	-
6f	12	-	20	9
6g	13	10	17	-
6h	10	13	15	9
11a	-	19	-	-
11b	14	-	-	9
11c	13	15	10	-
11d	12	15	-	10
11e	15	17	9	13
11f	-	18	-	14

Note: control treatment (DMSO) had no inhibitory effect on tested bacteria**.**

3. Conclusion

In summary, we have prepared, for the first time, precursors **10 a-c** by action of maleimides**1**and semicarbazide hydrochloride **9** in ethanol. Compounds **10a-c** were cyclised by reaction with isothiocyanates in ethanol or acetonitrile to afford 2-thioxo-imidazolidinones **11a-f**).In order to optimize the reaction conditions (time and yield),the cyclization reaction of products **10 a-c** was carried out under acidic conditions, using acetic acid or Keggin catalyst ($H_5PMo_{10}V_2O_{40}$) in various solvents (EtOH, CH_3CN The best results were obtained using the heteropolyacid in acetonitrile. Compounds **8a-h**, **6a-h** and **11a-f** were evaluated for their anti-bacterial activity. The derivative **8d** inhibited *Escherichia coli* ATCC 25992 and *Enterococcus feacalis* ATCC 29212 and molecules **8c**, **8f** and **6e**, **6f** were also efficient against *Enterococcus feacalis.*

4. Experimental

All melting points were measured on a Melting Point SMP 1 Stuart Scientific apparatus. The ^{1}H-NMR spectra (250 MHz) and ^{13}C-NMR (63 MHz) were obtained in dimethyl sulfoxide on a Brukerspectrometer, using TMS as an internal standard; chemical shifts are reported as δ units, and mass spectra were recorded onGC-MS- QP2010S. IR spectra were collected on FT/ IR- 4100-A.

General procedure for the synthesis of compounds (10a-c):

A mixture of differently substituted maleimides (10 mmol) and semicarbazide hydrochloride (10 mmol) in the presence of an equimolar amount of triethyl amine (10 mmol) in ethanol (20 mL; 98%) was brought to reflux under magnetic stirring for 6 hours. The white precipitate formed was filtered and recrystallized in ethanol.

2-(1-Methyl-2,5-dioxopyrrolidin-3-yl) hydrazinecarboxamide (10a): White solid, mp 180-185 ^{o}C;IR (KBr, cm^{-1}): 3459, 3266, 3200, 1708, 1581; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 2.32 (dd, 1H, ^{2}J=22 Hz, ^{3}J= 10 Hz, H (C4')), 2.57 (dd, 1H, ^{2}J=22 Hz, ^{3}J= 5.5 Hz, H (C4')), 3.15 (s, 3H, NCH$_3$), 3.96 (dd, 1H,^{3}J= 10 Hz, ^{3}J= 5.5 Hz, H (C3')), 5.59 (s, 1H, NH), 6.06 (s, 2H, NH$_2$), 7.81 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO-d$_6$), δ (ppm): 24.83 (NCH$_3$), 32.37(C4'), 58.48 (C3'), 160.89 (NHCONH$_2$), 176.42 (C5'), 177.63 (C2'); MS: (70 eV), m/z (%): 187 (M+1, 5), 143 (100), 113 (57).

2-(1-Ethyl-2,5-dioxopyrrolidin-3-yl) hydrazinecarboxamide (10b): White solid, mp 175 ^{o}C;IR (KBr, cm^{-1}): 3460, 3260, 3190, 1708, 1590;^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 1.47 (t, 3H, J= 8 Hz, CH$_2$C<u>H</u>$_3$), 2.97 (dd, 1H, ^{2}J$_=$ 22 Hz, ^{3}J=10 Hz, H (C4')), 3.08 (dd, 1H, ^{2}J= 22 Hz, ^{3}J= 5.5 Hz, H (C4')), 3.34 (dd, 1H, ^{3}J= 5.5 Hz, ^{3}J$_=$ 10 Hz, H (C3')), 3.88 (q, 2H, J= 8 Hz, C<u>H</u>$_2$CH$_3$), 5.82 (s, 1H, NH), 6.46 (s, 2H, NH$_2$), 7.67 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO-d$_6$), δ (ppm): 13.23 -CH$_2$<u>C</u>H$_3$, 33.34 (C4'), 33.72 (-<u>C</u>H$_2$CH$_3$), 58.35 (C3'), 160.87 (NHCONH$_2$), 176.14 (C5'), 177.29 (C2'); MS: (70 eV), m/z (%): 201 (M+1, 4), 157 (100), 127 (49).

2-(1-Phenyl-2,5-dioxopyrrolidin-3-yl) hydrazinecarboxamide (10c): White solid, mp 160 ^{o}C;IR (KBr, cm^{-1}): 3465, 3265, 3190, 1708, 1591;^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 2.80 (dd, 1H, ^{3}J=22 Hz, ^{2}J= 10 Hz, H (C4')), 3.04 (dd, 1H, ^{2}J= 22 Hz, ^{3}J= 5.5 Hz, H (C4')), 4.14 (dd, 1H, ^{3}J= 5.5 Hz, ^{3}J=10 Hz, H (C3')), 5.33 (s, 1H, NH), 5.89 (s, 2H, NH$_2$), 7.30 (m, 5H, C<u>H</u>$_{ar}$), 7.31 (s, 1H, NH); ^{13}C NMR (63 MHz, DMSO-d$_6$), δ (ppm): 34.04 (C4'), 58.64 (C3'), 127.45-128.78-129.34-132.79 (<u>C</u>$_{ar}$), 160.86 (NHCONH$_2$), 175.42 (C5'), 176.67 (C2'); MS: (70 eV), m/z (%): 249 (M+1, 4), 205 (100), 175 (37).

General procedure for the synthesis of 2-thioxo-imidazolidinones (11a-f):

Method a: A mixture of compound **10** (10 mmol.)and the appropriate isothiocyanate**5** (11 mmol) was refluxed in 20 mL of ethanol or acetonitrile. The solid was obtained after evaporation of the solvent then recristallization in ethanol.

Method b: To a solution of product **10** (10 mmol.)and the appropriateisothiocyanate**5** was added 0.12 mol% (1.2 µmol, 2×10^{-3}g) of Keggin catalyst (H$_5$PMo$_{10}$V$_2$O$_4$) in 20 mL of ethanol or acetonitrile. The mixed solution was heated atreflux undermagnetic stirring. After cooling to room temperature, the white solid was collected by filtration, andlatterrecrystallizedin ethanol.

2-{3-[(Aminocarbonyl)amino]-1-ethyl-5-oxo-2-thioxoimidazolidin-4-yl}-N-methylacetamide (11a): White solid, mp 190 ^{o}C;IR (KBr, cm^{-1}): 3474, 1620, 1748, 1262; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 1.13 (t, 3H, J= 7Hz, CH$_2$C<u>H</u>$_3$), 3.40 (d, 3H, J= 4.5Hz, NHC<u>H</u>$_3$), 2.75 (d, 2H, J= 4Hz, C<u>H</u>$_2$CO), 3.75 (q, 2H, J= 7Hz, C<u>H</u>$_2$CH$_3$), 4.40 (t, 1H, J= 4Hz, H(C4')), 6.25 (s, 2H, NH$_2$), 8.00 (s, 1H, NH), 8.50 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d$_6$), δ (ppm): 11.90 CH$_2$<u>C</u>H$_3$,

25.07 NHCH$_3$, 35.88 CH$_2$CH$_3$, 39.01 CH$_2$CO, 59.75 (C4'), 156.93 (NHCONH$_2$), 167.76 (NHCOCH$_2$), 171.34 (C5'), 183.37 (C=S); MS: (70 eV), m/z (%): 273 (M+, 3), 44 (100), 58 (26).

2-{3-[(Aminocarbonyl)amino]-1-ethyl-5-oxo-2-thioxoimidazolidin-4-yl}-N-ethylacetamide (11b): White solid, mp 140 ^{o}C; IR (KBr, cm^{-1}): 3475, 1625, 1749, 1263; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 0.98 (t,3H, J= 7 Hz, (CH$_2$CH$_3$)'), 1.12 (t, 3H, J=7 Hz, CH$_2$CH$_3$), 2.68 (d, 2H, J= 4 Hz, CH$_2$CO), 3.02 (q, 2H, J=7 Hz, (CH$_2$CH$_3$))', 3.75 (q, 2H, J= 7 Hz, CH$_2$CH$_3$), 4.44 (t,1H, J= 4 Hz, H(C4')), 6.31 (s, 2H, NH$_2$), 8.05 (s, 1H, NH), 8.50 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d$_6$), δ (ppm): 12.81 CH$_2$CH$_3$, 14.94 (CH$_2$CH$_3$)', 33.69 (CH$_2$CH$_3$)', 36.74 CH$_2$CH$_3$, 39.21 CH$_2$CO, 60.66 (C4'), 157.76 (NHCONH$_2$), 167.54 (NHCOCH$_2$), 172.21 (C5'), 184.26 (C=S); MS: (70 eV), m/z (%): 287 (M+, 4), 44 (100), 72 (10), 59 (7), 59 (7).

2-{3-[(Aminocarbonyl)amino]-1-ethyl-5-oxo-2-thioxoimidazolidin-4-yl}-N-phenylacetamide (11c): White solid, mp 190 ^{o}C; IR (KBr, cm^{-1}): 3498, 1650, 1748, 1201;^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 1.12 (t, 3H, J= 7 Hz, CH$_2$CH$_3$), 2.97 (d, 2H, J= 4 Hz, CH$_2$CO), 3.76 (q, 2H, J= 7 Hz, CH$_2$CH$_3$), 4.53 (t, 1H, J= 4 Hz, H(C4')), 6.30 (s, 2H, NH$_2$), 7.5 (m, 5H, CH$_{ar}$), 8.66 (s, 1H, NH), 10.16 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d$_6$), δ (ppm): 12.31 CH$_2$CH$_3$, 36.33 CH$_2$CH$_3$, 39.20 CH$_2$CO, 60.01(C4'), 119.14-123.26-128.63-138.74(C$_{ar}$), 157.24 (NHCONH$_2$), 166.59 (NHCOCH$_2$), 171.76 (C5'), 183.81 (C=S); MS: (70 eV), m/z (%): 335 (M+, 4), 44 (100), 77 (8), 92 (6).

2-{3-[(Aminocarbonyl)amino]-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl}-N-methylacetamide (11d): White solid, mp 235 ^{o}C; IR (KBr, cm^{-1}): 3475, 1624, 1749, 1263; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 2.85 (d, 2H, J= 4 Hz, CH$_2$CO), 3.42 (d, 3H, J= 7 Hz, NHCH$_3$), 4.63 (t, 1H, J= 4 Hz, H(C4')), 6.38 (s, 2H, NH$_2$), 7.48 (m, 5H, CH$_{ar}$), 8.07 (s, 1H, NH), 8.63 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d$_6$), δ (ppm): 25.15 NHCH$_3$, 32.84 CH$_2$CO, 59.92 (C4'), 128.09-128.46-128.61-133.51(C$_{ar}$), 157.91 (NHCONH$_2$), 167.75(NHCOCH$_2$), 167.91 (C5'), 183.28 (C=S); MS: (70 eV), m/z (%): 321 (M+, 3), 77 (68), 51 (29).

2-{3-[(Aminocarbonyl)amino]-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl}-N-ethylacetamide (11e): White solid, mp 225 ^{o}C; IR (KBr, cm^{-1}): 3479, 1600, 1716, 1234; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 0.99 (t, 3H, J= 7Hz, CH$_2$CH$_3$), 3.01 (d, 2H, J= 4 Hz, CH$_2$CO), 3.05 (q, 2H, J= 7 Hz, CH$_2$CH$_3$), 4.61 (t, 1H, J= 4 Hz, H(C4')), 6.35 (s, 2H, NH$_2$), 7.46 (m, 5H, CH$_{ar}$), 8.08 (s, 1H, NH), 8.59 (s, 1H, NH); ^{13}C NMR (250 MHz, DMSO-d$_6$), δ (ppm): 14.49 CH$_2$CH$_3$, 33.51 CH$_2$CH$_3$, 38.17 CH$_2$CO, 60.53 (C4'), 128.50-128.59-128.78-133.90 (C$_{ar}$), 157.37 (NHCONH$_2$), 167.75 (NHCOCH$_2$), 171.63(C5'), 183.70 (C=S); MS: (70 eV), m/z (%): 335 (M+, 4), 44 (100), 73 (15), 117 (6).

2-{3-[(Aminocarbonyl)amino]-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl}-N-phenylacetamide (11f): White solid, mp 150 ^{o}C; IR (KBr, cm^{-1}): 3459, 1604, 1747, 1260; ^{1}H NMR (250 MHz, DMSO-d$_6$), δ (ppm): 3.17 (d, 2H, J= 4 Hz, CH$_2$CO), 4.78 (t, 1H, J= 4 Hz, H(C4')), 7.37-7.56 (m, 10H, CH$_{ar}$), 6.44 (s, 2H, NH$_2$), 8.85 (s, 1H, NH), 10.27 (s, 1H, NH); ^{13}C NMR (250 MHz,DMSO-d$_6$), δ (ppm): 39.01 CH$_2$CO, 59.58 (C4'), 118.67-122.79-128.16-138.27 (C$_{ar}$), 156.77 (NHCONH$_2$), 166.13(NHCOCH$_2$), 171.29(C5'), 183.32 (C=S); MS: (70 eV), m/z (%): 383 (M+, 3) 44 (100), 77 (41), 92 (9).

References

[1] Karali, N.; Gursoy, A.; Terzioglu, N.; Ozkirimli, S.; Ozer, H.; Ekinci, A. C. Synthesis and preliminary CNS depressant activity evaluation of new 3-[(3-substituted-5-methyl-4-thiazolidinon-2-ylidene)hydrazono]-1H-2- indolinones and 3-[(2-thioxo-3-substituted-4,5-imidazolidinedion-1-yl) imino]-1H-2-indolinones .*Arch. Pharama. Med. Chem.* **1998**, 331, 254-258.

[2] Chaudar, S. K.; Verma, M.; Chatuvedi, A.; Parmar, S. S. Substituted thiazolidones: selective inhibition of nicotinamide adenine dinucleotide-dependent oxidations and evaluation of their CNS activity. *J. Pharm. Sci*. **1975**, 64, 615-617.

[3] Thanusu, J; Kanagarajan, V; Gopalakrishnan, M. Synthesis, spectral analysis and in vitro microbiological evaluation of 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones as a new class of antibacterial and antifungal agents. *Bioorg. Med. Chem. Lett.***2010**, 20, 713–717.

[4] Puszyńska-Tuszkanow, M; Grabowski, T; Daszkiewicz, M; Wietrzyk, J; Filip, B; Maciejewska, G; Cieślak-Golonka, M. Silver (I) complexes with hydantoins and allantoin, Synthesis, crystal and molecular structure, cytotoxicity and pharmacokinetics. *J. Inorg. Biochem*. **2011**, 105, 17–22.

[5] Suzen, S.; Buyukbingol, E. Evaluation of anti-HIV activity of 5- (2-phenyl-3′-indolal)-2-thiohydantoin. *II Farmaco.***1998**, 53, 525-527**.**

[6] Renault, S.; Bertrand, S.; Carreaux, F.; Bazureau, J. P.Parallel Solution-Phase Synthesis of 2-Alkylthio-5-arylidene-3,5-dihydro-4*H*-imidazol-4-one by One-Pot Three-Component Domino Reaction. *J. Comb. Chem.* **2007**, 9, 935-942.

[7] Porwal, S.; Chauhan, S. S.; Chauhan, P. M. S.; Shakya, N.; Verma, A.; Gupta, S. Discovery of novel antileishmanial agents in an attempt to synthesize pentamidine- aplysinopsin hybrid molecule. *J. Med. Chem.* **2009**, 52, 5793-5802.

[8] Sawyers, C. L; Jung, M. E.; Chen, C. D.; Ouk, S; Welsbie, D; Tran, C; Wongvipat, J; Yoo, D. Preparation of diarylhydantoin 3compounds as androgen receptor antagonists useful against hormone refractory prostate cancer.*PCT Int. App. 2006*, WO2006124118 A1 20061123.

[9] Jamal Abdul Nasser, A.; Idhayadhulla, A.; Surendra Kumar, R.; Selvin, J. Synthesis of some 2-Thioxo-imidazolidin-4-one Derivatives and its Antimicrobial Activity.*E-J. Chem.***2010**, 7 (4), 1320-1325.

[10] Bouzroura, S.; Hammal, L.; Nedjar-Kolli, B.; Balegroune, F.; Hamadène, M.; Poulain, S.A Practical synthesis of functionalized 2-thioxoimidazolidine Derivatives. *Synth Commun.***2008**, 38, 448-455.

[11] Bentarzi, Y.; Kolli, B.; Plas, A.; Chalard, P.; Troin, Y.Synthesis of 2-thioxoimidazolin-4-one and thiazolo[3,2-*a*]-benzimidazole derivatives from substituted maleimides. *Arkivoc* **2010**, 328-337.

[12] Maradur, S. P.; Gokavi, G. S.Heteropoly acid catalyzed synthesis of 3,4-dihydropyrimidin-2(1 H)-ones. *Catal.Commun.***2007**, 8, 279-284.

[13] Guo, Y.; Li, K.; Yu, X.; Clark, J. H. Mesoporous $H_3PW_{12}O_{40}$-silica composite: Efficient and reusable solid acid catalyst for the synthesis of diphenolic acid from levulinic acid. *Appl. Catal. B Environ.* **2008**, 81, 182-191.

[14] NCCLS (National Committee for Clinical Laboratory Standards), Performance Standards for Antimicrobial Susceptibility Testing 9th International Supplement, Wayne, PA, M100-S9 **1999**.

[15] Fazeli, M. R.; Amin, G.; Attari, M. M. A.; Ashtiani, H.; Jamalifar, H.; Samadi, N. *Food Control*. **2007**, 18, 646–649.

[16] McCutcheon, A. R.; Ellis, S. M.; Hancock, R. E Towers, G. H. Antibiotic screening of medicinal plants of the British Colombian native peoples. *J. Ethnopharmacol.***1992**, 37, 213-223.

[17] Zhang, H.; Kong, B.; Xiong, Y. L.; Sun, X. Antimicrobial activities of spice extracts against pathogenic and spoilage bacteria in modified atmosphere packaged fresh pork and vacuum packaged ham slices stored at 4 °C. *Meat Sci*. **2009**, 81, 686-692**.**

[18] Balentine, C.W.; Crandall, P.G.; O'Bryan, C.A.; Duong, D.Q.; Pohlman, F.W. The pre- and post-grinding application of rosemary and its effects on lipid oxidation and color during storage of ground beef.*Meat Sci*.**2006**, 73 (3), 413-421.

[19] NgonoBikobo, D. S.;ThéodoreAtchadé, A.; GhogomuTih, R.; Gangoué-Pieboji, J.; Blond, A.; Pegnyemb, D. E.; Bodo, B. Antimicrobial activities of some Ouratea species (Ochnaceae), and Biflavonoids from Ourateaelongata. Asian Chem.Lett.**2009**, 13,59-66.

[20] Zhang, H.; Kong, B.; Xiong, Y. L.; Sun, X. Antimicrobial activities of spice extracts against pathogenic and spoilage bacteria in modified atmosphere packaged fresh pork and vacuum packaged ham slices stored at 4 °C. *Meat Sci*. **2009**, 81(4), 686-692.

[21] Natarajan D.; Britto, J. S.; Srinivasan, K.; Nagamurugan, N.; Mohanasundari, C.; Perumal, G. Anti-bacterial activity of Euphorbia fusiformis-A rare medicinal herb. *J.Ethnopharmacol*. **2005**, 102, 123-126.