Studies on Imidazolones: Synthesis and Biological Evaluation of some New Imidazolone Derivatives

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Abstract: 2-[1-Hydroxy-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-1H-imidazol-2-ylmeth-yl]-isoindole-1,3-dione (1) has been synthesized by treatment of 2-[4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-oxazol-2-ylmethyl]-isoindol-1,3-dione with hydroxyl amine hydrochloride in boiling DMF/ pyridine mixture. The reactions of **(1)** with nitrogen and carbon nucleophiles have been investigated. The structure of these compounds was established on the basis of IR and H-NMR spectroscopy, the antimicrobial activities of the investigated compounds were tested against a Gram positive bacterium i.e. *Staphylococcus aureus*, a Gram negative bacterium i.e. *Escherichia coli* and some fungal plant pathogens i.e. *Aspergillus flavus and Candida albicans* by using the hole plate and filter paper disc method.
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1. Introduction

2-imidazolones are useful as intermediates for polymers, agrochemicals, and pharmaceutical compounds[1]. Several derivatives of 2-imidazolone are biotin antagonists in biological systems, amongst which are compounds capable of inhibiting the growth of malignant tumors[2]. Moreover, some 2-imidazolone compounds are anti-inflammatory agents and useful for the treatment of dermatitis, inflammation of Joints. They also possess antipyretic and analgesic properties[3]. Prompted by there observation and in contamination of our work on the synthesis of nitrogen heterocycles[4,5,6], we thought it worthwhile to synthesis new series of imidazolone with the objective of obtaining new biologically active compounds.

2. Experimental Section

General

All melting points were determined on an electric melting point apparatus, IR spectra (KBr disk) were recorded on Nicolet Magna. IR model 550 spectrophotometers. ^{1}H-NMR spectra were measured on Brucker Wpsy 200 MHz spectrometer in DMSO as the solvent using TMS as an internal standard. The chemical shifts are expressed as ó (PPm). All analysis was carried out at Micro Analytical center, Cairo University, Cairo-Egypt.

All compounds gave satisfactory C, H and N analysis. The starting compounds phthalyl- or tosylamino acids were prepared according to the published procedure. [9]

Synthesis of 2-[1-Hydroxy-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-1H-imida-zol-2-ylmethyl]-isoindole-1,3-dione (1)

A solution of 2-[4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-oxazol-2-ylmethyl]-isoindol-1,3-dione (0.1 mole) in DMF/pyridine mixture was treated with hydroxylamine hydrochloride (0.13 mole). The mixture was heated under reflux for 6 hr. the product obtained after cooling was filtered, crystallized from ethanol to give imidazolone **(1).** This compound was obtained as dark brown powder, yield (45%), m.p.98^{0}C, Anal. Calc. for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43%. Found: C, 64.62; H, 4.33; N, 14.65 %.

Action of phthalyl-amino acids on (1): Formation of (2a-e)

A mixture of imidazolone **(1)** (0.005 mole) and Pht-amino acids (0.005 mole) was dissolved in 30 ml tetrahydrofuran (THF). The mixture was cooled to 0^{0}C and *N,N*-dicyclohexylcarbodiimide (DDC) (0.005 mole) dissolved in 10 ml THF. and added to reaction mixture, the reaction mixture was stirred for 24 hrs at 0^{0}C and another 24 hrs at room temperature. The precipitated *N, N*-dicyclohexylurea was filtered off, and then left at 0^{0}C overnight. The precipitated dicyclo-hexylurea was filtered off and the filtrate evaporated in vacuo and the residual material dissolved in 25 ml ethyl acetate and left for 24 hrs at room temperature the solution was filtrated again from the residual *N,N*-dicyclohexyl-urea. The products were obtained by evaporation of filtrate under vacuo and recrystallized from ethanol to give the compounds **(2a-e).**The physical data of compounds **(2a-e)** were showed in table 1.

Action of tosyl-amino acids on (1): Formation of (12a-d)

A mixture of imidazolone **(1)** (0.005 mole) and Tos-amino acids (0.005 mole) was dissolved in 30 ml tetrahydrofuran (THF). The mixture was cooled to 0^{0}C and N,N-dicyclohexylcarbodiimide (DDC) (0.005 mole) dissolved in 10 ml THF. and added to reaction mixture, the reaction mixture was stirred for 24 hrs at 0^{0}C and another 24 hrs at room temperature. The

precipitated *N, N*-dicyclohexylurea was filtered off, and then left at 0^0C overnight. The precipitated dicyclo-hexylurea was filtered off and the filtrate evaporated in vacuo and the residual material dissolved in 25 ml ethyl acetate and left for 24 hrs at room temperature the solution was filtrated again from the residual *N,N*-dicyclohexyl-urea. The products were obtained by evaporation of filtrate under vacuo and recrystallized from ethanol to give the compounds (3a-d). The physical data of compounds (3a-f) were showed in table 1.

Hydrazinolysis of (2a-e): Formation of (4a-e)

A solution of **(1)** (0.001 mole) was dissolved in 20 ml ethanol and 0.8 ml hydrazine hydrate added. The solution was refluxed for 2 hrs on water bath and left for 24 hrs. at room temperature. Evaporation of the solvent under vacuo gave solid material to which (10 ml) of water was added and the solution acidified with AcOH till (PH=6). Heat for 1 hrs on water bath and the suspension was diluted with (25 ml) of water, cooled to room temperature and filtered off. The filtrate was concentrated and cooled where the product separated. The compounds were recrystallized from ethanol to give **(4a-e).** The physical data of compounds **(4a-e)** were showed in table 1.

3. Results and Discussion

The synthesis of the target compound 2-[1-Hydroxy-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-1H-imida-zol-2-ylmethyl]-isoindole-1,3-dione **(1)** was from the reaction of 2-[4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-oxazol-2-ylmethyl]-iso-indol -1,3-dione with hydroxyl amine hydrochloride in boiling DMF/ pyridine mixture. The reactivity of **(1)** towards different nucleophilic reagents has been described. The structure of this compound was confirmed from their analytical data, different spectroscopic techniques including IR and ^{1}H-NMR. IR spectrum showed strong absorption band at 3480, 3386, 1776-1721& 1672 attribute to υ OH, υ NH, υ of two carbonyl groups of cyclic imides, and imidazolone ring respectively. The ^{1}H-NMR spectrum of compound **(1)** in (DMSO-d_6) showed signals at δ= 2.4-2.6 (d,2H,CH_2CH), 4.36 (s,2H,CH_2NCO), 5.06 (t,1H,CHCH_2), 6.9-7.72 (m,9H, ArH), 8.16 (s,broad,1H,NH), and 10.1 (s,broad,1H,OH).

When imidazolone **(1)** allowed to react with phthalyl-amino acids namely glycine, Alanine, Valine, phenyl alanine, and tryptophan , it yielded (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmeth-yl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(2a),** 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid-2-(1,3-dioxo-1,3-dihydro-iso-indol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(2b),** 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-methyl-butyric acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(2c),** 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-phenyl-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(2d),** 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-(1H-indol-3-yl)-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(2e)** respectively. The IR and ^{1}H-NMR spectrum of compounds **(2a-e)** in (DMSO-d_6) showed in table 2.

However When imidazolone **(1)** allowed to react with tosyl-amino acids namely glycine, alanine, valine, and tryptophan it yielded (Toluene-4-sulfonyl)-acetic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-yl-methyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester**(3a),** 2-(Toluene-4-sulfonyl)-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(3b)**, 3-Methyl-2-(toluene-4-sulfonyl)-butyric acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(3c),** 3-(1H-Indol-3-yl)-2-(toluene-4-sulfonyl)-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmeth-yl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(3d)** respectively. The IR and ^{1}H-NMR spectrum of compounds **(3a-d)** in (DMSO-d_6) showed in table 2.

Hydrazinolysis of compounds **(2a-e)** with hydrazine hydrate in ethanol for 2 hours lead to the formation of the free amino acid derivatives: Amino-acetic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(4a),** 2-Amino-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(4b),** 2-Amino-3-methyl-butyric acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(4c),** 2-Amino-3-phenyl-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(4d),** 2-Amino-3-(1H-indol-3-yl)-propionic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(1H-indol-3-ylmethyl)-5-oxo-4,5-dihydro-imidazol-1-yl ester **(4e)** respectively. The IR and ^{1}H-NMR spectrum of compounds **(4a-e)** in (DMSO-d_6) showed in table 2.

The structures of the above compounds were confirmed from their physical and analytical data (Table 1) and from spectral data (Table 2).

Screening for antimicrobial activity

The behavior of the synthesized organic compounds has been investigated at the Micro analytical unit, Cairo University, Egypt.

The antimicrobial activities of the synthesized compounds were carried out using the filter paper and

hole plate methods [7,8] against a gram positive (*Staphylococcus aureus*), a gram negative (*Escherichia coli*) bacteria in addition to some fungal plant pathogens (*Aspergillus flavus and Candida albicans*).According to the different solubility of the tested compounds one solvent is used (DMSO).

The disks were incubated at 37^0C for 24 hours to permit good diffusion and then incubated at 37^0 C for 24-72 hours to permit good diffusion and then incubated at 37^0 C for 24 hours. After incubation, the zones of inhibition were measured in mm/mg sample. The results are listed in (Table 3).

Table 1. Characterization data of the synthesized compounds.

Comp.	m.p.	(Yield %)	Mol. Formula (M Wt)	Calc. (found) %		
				C	H	N
1	156-158	55	$C_{21}H_{16}N_4O_4$ 388.38	64.94 64.62	4.15 4.33	14.43 14.65
2a	113	53	$C_{31}H_{21}N_5O_7$ 575.53	64.69 64.45	3.68 3.31	12.17 12.14
2b	104	68	$C_{32}H_{23}N_5O_7$ 589.55	65.19 65.30	3.93 3.82	11.88 11.51
2c	64	65	$C_{34}H_{27}N_5O_7$ 617.61	66.12 66.32	4.41 4.68	11.34 11.25
2d	50	70	$C_{38}H_{27}N_5O_7$ 665.65	68.57 68.55	4.09 4.13	10.52 10.66
2e	106	30	$C_{40}H_{28}N_6O_7$ 704.69	68.18 68.35	4.00 4.22	11.93 11.65
3a	82	43	$C_{30}H_{25}N_5O_7S$ 599.62	60.09 60.12	4.20 4.62	11.68 11.78
3b	117	30	$C_{31}H_{27}N_5O_7$ S 613.64	60.68 60.44	4.43 4.25	11.41 11.12
3c	98	68	$C_{33}H_{31}N_5O_7$ S 641.69	61.77 61.86	4.87 4.44	10.91 10.62
3d	99	85	$C_{39}H_{32}N_6O_7$ S 728.77	64.27 64.99	4.43 4.78	11.53 11.77
4a	194	77	$C_{23}H_{19}N_5O_5$ 445.43	62.02 62.35	4.30 4.47	15.72 15.63
4b	206	75	$C_{24}H_{21}N_5O_5$ 459.45	62.74 62.85	4.61 4.43	15.24 15.55
4c	210	77	$C_{26}H_{25}N_5O_5$ 487.51	64.06 64.36	5.17 5.22	14.37 14.44
4d	229	79	$C_{30}H_{25}N_5O_5$ 535.55	67.28 67.66	4.71 4.98	13.08 13.44
4e	216	60	$C_{32}H_{26}N_6O_5$ 574.59	66.89 66.65	4.56 4.33	14.63 14.85

[a] All the synthesized compounds were recrystallized from ethanol.

Table 2. ^{1}H-NMR, and IR data of prepared compounds.

Comp.	H^1-NMR δ/ppm[b]	IR (KBr) cm^{-1}	
		ν OH,NH and NH2	$^{\nu}$ C=O
1	2.4-2.6 (d,2H, CH_2CH). 4.36 (s,2H,CH_2NCO), 5.02 (t,1H, CH CH_2), 6.9-7.72 (m,9H,ArH) , 8.16 (s,broad,1H,NH) 10.1 (s,broad,1H,OH)	(3480) 3386	(1776-1721) (cyclic imide) 1672 (imidazolone)
2a	2.5-2.8 (d,2H,CH_2CH), 4.32 (s,4H,2xCH_2NCO), 5.01 (t,1H, $CHCH_2$), 7.5-7.6 (m,13H,ArH), 7.9 (s,broad,1H, NH),	3327	(1772-1730) (cyclic imide) 1720 (O-C=O)

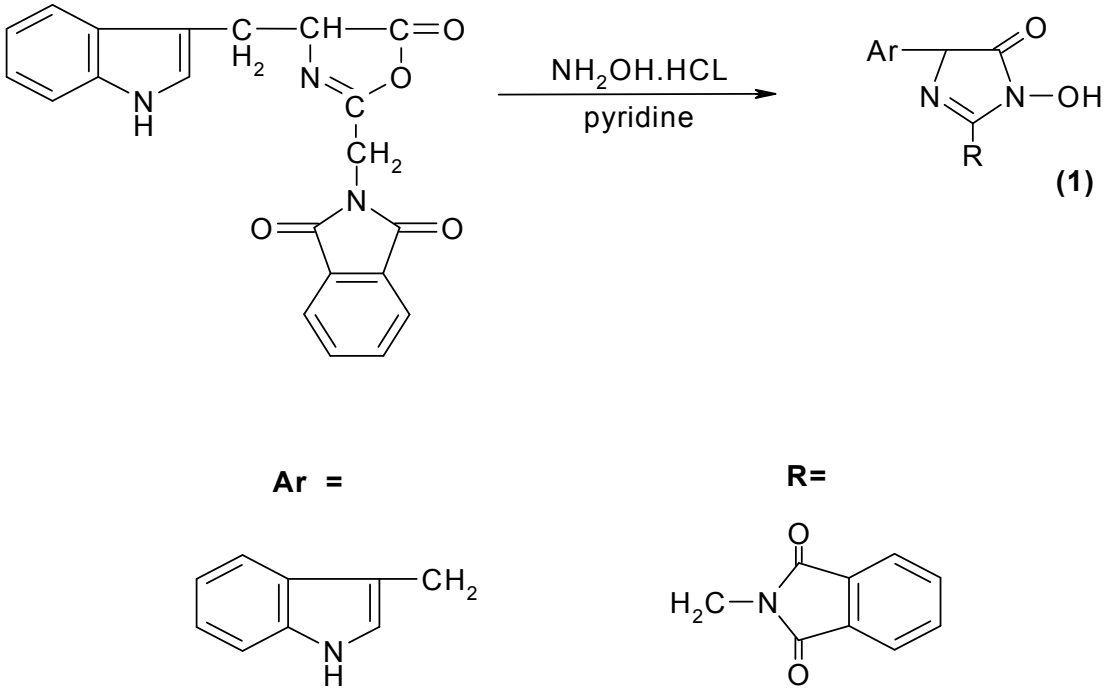
2b	1.1 (d,3H,CH_3), 2.5-2.6 (d,2H,CH_2CH). 4.23 (s,2H,CH_2NCO), 5.06 (t,1H, CH CH_2), 5.24 (q,1H,CHCH3), 6.7-7.69 (m,13H,ArH), 8.15(s,broad,1H, NH),	3380	(1769-1732) (cyclic imide) 1711 (O-C=O)
2c	2.4-2.5 (d,2H,CH_2CH). 4.16 (s,2H,CH_2NCO), 4.59 (m,2H,$CH(CH_3)_2$), 4.65 (d,6H,2xCH_3), 5.06 (t,1H,$CHCH_2$), 5.26 (d,1H,CHCH), 6.8-7.9 (m,13H,ArH), 8.12 (s,broad,1H, NH),	3388	(1776-1730) (cyclic imide) 1713 (O-C=O)
2d	2.2-2.3 (d,4H,2xCH_2CH). 4.62(s,2H,CH_2NCO), 5.04 (t,2H,2x$CHCH_2$), 6.7-7.76(m,18H,ArH), 8.14(s,broad,1H, NH),	3386	(1770-1729) (cyclic imide) 1710 (O-C=O)
2e	2.1-2.3 (d,4H,2xCH_2CH). 4.35 (s,2H,CH_2NCO), 5.03 (t,2H, 2x$CHCH_2$), 6.8-7.5(m,18H,ArH), 8.14(s,broad,2H,2xNH),	3349	(1765-1725) (cyclic imide) 1711 (O-C=O)
3a	2.1 (s,3H,ArCH_3), 2.4-2.5 (d,2H,CH_2CH). 4.61 (s,2H,CH_2NCO), 5.06 (t,1H, CH CH_2), 5.23 (s,2H,CH_2NH), 6.8-7.5 (m,13H,ArH), 8.1 (s,broad,1H, NH), 8.82-9.2 (s,broad,1H, $NHSO_2$)	3385	2931 (CH_3) (1768-1729) (cyclic imide) 1390-1231 (SO2)
3b	1.2 (d,3H,CH_3), 2.0 (s,3H,ArCH_3), 2.5-2.6 (d,2H,CH_2CH), 4.63(s,2H,CH_2NCO), 5.02 (t,1H, $CHCH_2$), 5.5 (q,1H,$CHCH_3$), 7.4-7.7 (m,13H,ArH) 8.16(s,broad,1H, NH), 8.6-8.95 (s,broad,1H, $NHSO_2$)	3329	2925 (CH_3) 1717 (cyclic imide) 1383-1240 (SO2)
3c	2.1(s,3H,ArCH_3), 2.4-2.5 (d,2H,CH_2CH). 4.12(s,2H,CH_2NCO), 4.51 (m,2H,$CH(CH_3)_2$), 4.63 (d,6H,2xCH_3), 5.01 (t,1H, $CHCH_2$), 5.22 (d,2H,CHCH), 6.99-7.9 (m,13H,ArH) 8.12(s,broad,1H, NH), 8.6-9.0(s,broad,1H, $NHSO_2$)	3387	2921 (CH_3) (1771-1732) (cyclic imide) 1385-1234 (SO2)
3d	2.0 (s,3H,ArCH_3), 2.7-2.8 (d,4H,2xCH_2CH). 4.32 (s,2H,CH_2NCO), 5.0 (t,2H, 2xCH CH_2), 7.0-7.5 (m,18H,ArH), 8.1 (s,broad,2H, 2xNH), 8.88-9.3(s,broad,1H, $NHSO_2$)	3388	2927 (CH_3) 1716 (cyclic imide) 1387-1332 (SO2)

4a	2.4-2.5 (d,2H, CH_2CH). 4.61(s,2H,CH_2NCO), 5.03 (t,2H, $CHCH_2$), 5.1 (s,2H, CH_2NH_2). 5.42 (t,broad,2H,NH_2), 7.1-7.9 (m,9H,ArH) 8.01 (s,broad,1H, NH),	3384 (3167)	(1775-1714) (cyclic imide)
4b	1.1 (d,3H,CH_3), 2.5-2.6 (d,2H,CH_2CH). 4.17 (s,2H,CH_2NCO), 5.06 (t,1H, CH CH_2), 5.24(q,1H,CHCH3), 5.55 (d,broad,2H,NH_2), 6.9-7.69 (m,9H,ArH), 8.14 (s,broad,1H, NH),	3359 (3151)	(1776-1731) (cyclic imide)
4c	2.4-2.5 (d,2H,CH_2CH). 4.12(s,2H,CH_2NCO), 4.58 (m,2H,$CH(CH_3)_2$), 4.61(d,6H,2xCH_3), 5.02 (t,1H, $CHCH_2$), 5.2 (d,1H, CHCH), 5.85(d,broad,2H,NH_2), 7.2-7.6 (m,9H,ArH), 8.16 (s,broad,1H, NH),	3365 (3172)	(1776-1728) (cyclic imide)
4d	2.2-2.3 (d,4H,2xCH_2CH). 4.23 (s,2H,CH_2NCO), 5.04 (t,2H,2x$CHCH_2$), 5.5 (d,broad,2H,NH_2), 7.4-7.8 (m,14H,ArH), 8.01 (s,broad,1H, NH),	3327 (3155)	(1770-1729) (cyclic imide)
4e	2.4-2.5 (d,4H,2xCH_2CH). 4.14 (s,2H,CH_2NCO), 5.03 (t,2H, 2xCH CH_2), 5.59 (d,broad,2H,NH_2), 6.8-7.6 (m,14H,ArH), 8.0 (s,broad,2H,2xNH),	3320 3162	(1773-1732) (cyclic imide)

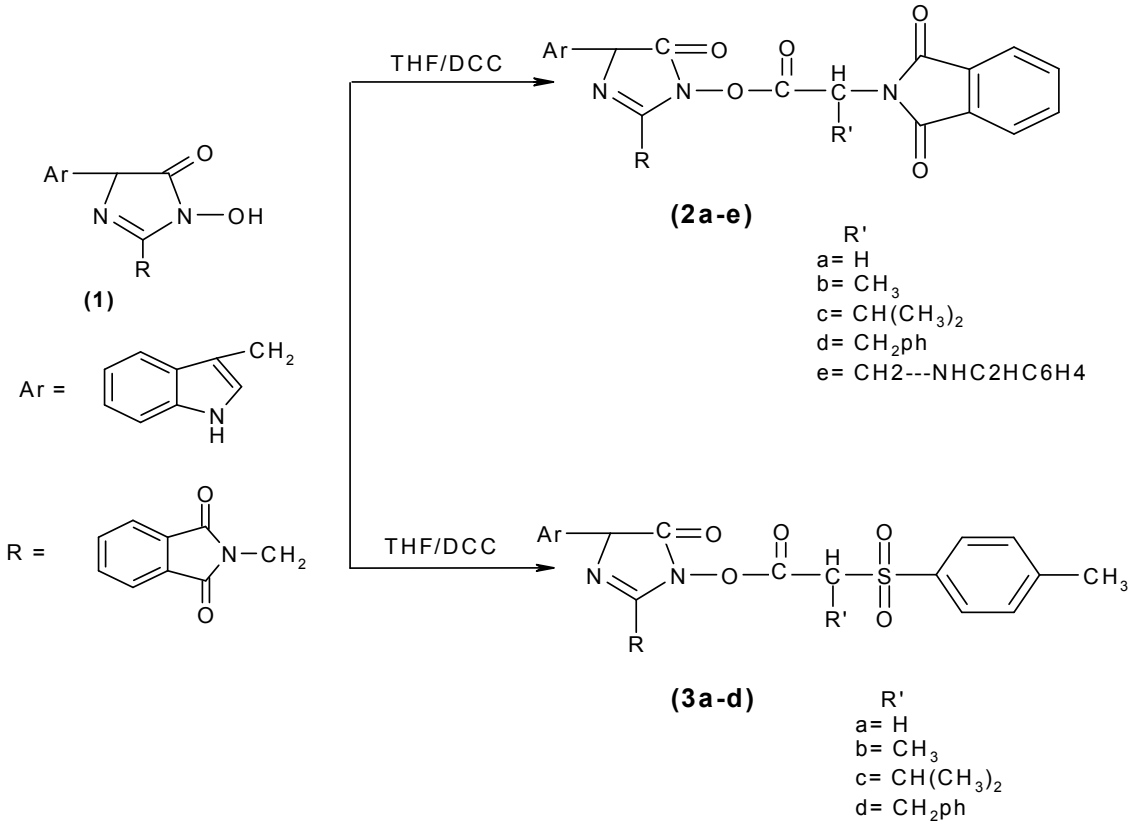
[b] All NH signals were exchangeable with deuterium oxide D_2O.

Table 3. Relative activity of some compounds against (G^+), (G^-) bacteria and fungi.

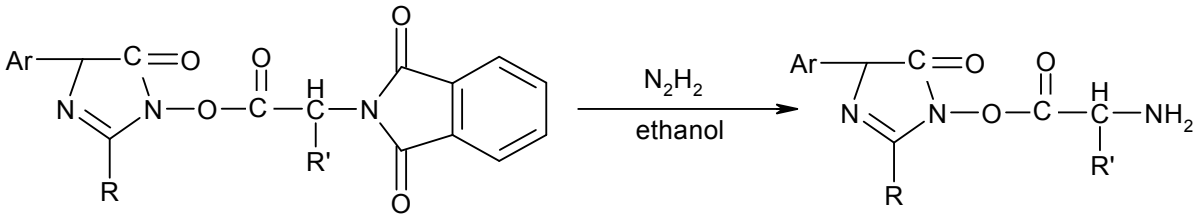
sample		Inhibition zone diameter (mm / mg sample)			
		Escherichia coli (G^-)	**Staphylococcus aureus (G^+)**	**Aspergillus flavus (fungus)**	**Candida albicans (fungus)**
standard	**Tetracycline** (Antibacterial Agent)	**30**	**28**	**--**	**--**
	Amphotericin B (Antifungal agent)	**--**	**--**	**18**	**19**
1		13	13	0.0	0.0
2d		15	14	0.0	0.0
2e		15	16	0.0	12
3b		14	16	0.0	0.0
3c		14	15	0.0	12
3d		14	15	0.0	12
4a		13	15	0.0	0.0
4c		13	14	0.0	0.0
4d		13	15	0.0	0.0



Scheme I. Synthesis of imidazolone 1.



Scheme II. Reactions of imidazolone compound 1.



(2a-e) **(4a-e)**

R'
a= H
b= CH_3
c= $CH(CH_3)_2$
d= CH_2ph
e= CH2---NHC2HC6H4

Scheme III. Formation of free amino acid derivatives (4a-e).

Conclusion

The most active compounds against the Gram negative and positive bacteria found to be 2d, 2e, 3b, 3c & 3d. However, the rest of compounds showed moderate action on the Gram negative bacteria. Furthermore, all the tested compounds showed no antifungal activities on the tested compounds except compounds 2e, 3c, & 3d show moderate antifungal activities.

Acknowledgements

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List of abbreviations

IR: Infrared	H^1-NMR: Proton Nuclear Magnetic Resonance
DMSO: Dimethylsulfoxide	TMS: Tetramethylsilane
Comp.: Compound	m.p.: Melting point
Mol: Molecular	M.wt: Molecular weight
Calc.: Calculated	DMF: Dimethyl formamide
G-: Gram Negative	G+: gram Positive
D_2O: Deuterium oxide	d_6: Deutrated DMSO

6/12/2012

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