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Synthesis and Biological Evaluation of Hydrazide based Formamides Derivatives

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Abstract

Hydrazide based formamides were synthesized from substituted hydrazides. And their structures were confirmed by FTIR and Elemental Analyzer studies. The main aim of this study is to investigate Enzyme inhibition activity, antioxidant activity and antimicrobial activity against all synthesized formamide derivatives. Linoleic acid and Lipoxygenase enzyme were used for enzyme inhibition activity while Baicalein used as a standard. Similarly Ferric thiocyanate method was used for the determination of (ABTS) radical cation scavenging method, (FRAP), ferric reducing antioxidant power and (DPPH) antioxidant power. Moreover antimicrobial activity was evaluated of hydrazide based formamides against gram negative, gram positive bacteria and fungus as well.

Keywords: Formamides, Lipoxygenase, Antimicrobial activity, Antioxidant Activity.

Introduction

Hydrazide based formamides contain appreciable range of antimicrobial activities. Because formamides hinder the folic acid production[1, 2] they are considered as bacteriostatic. Because folic acid takes important role in Bacterial cell division and cell growth. Due to such importance of antimicrobial activity of formamides[3-5] antimicrobial activity has also been evaluated of all new formamides derivatives. Sulfonamides contains indole moiety due to which it potent HIV non nucleoside reverse transcriptase inhibitor.[6] While HIV reverses transcriptase (HIV-RT) plays an essential role in the life cycle of HIV replication.[7]

Materials and Methods

For the synthesis of hydrazide based formamides first substituted esters was synthesized, for this substituted carboxylic acid allowed to react with methanol in the presence of conc. H_2SO_4. Purify the ester (a) by solvent extraction method and then recrystallized with methanol. Secondly, to obtain substituted hydrazide (b), different esters refluxed with hydrated hydrazine in the presence of methanol. Purification of substituted hydrazides was done by filtration and then crystallization (Figure 1).

Finally, to obtain desired product (c), substituted hydrazides were allowed to react with phenyl chloroformate in the presence of $NaHCO_3$. Whole mixture was stirred for two hours at 25 °C. Wash the reaction mixture with dilute HCl to remove the impurities. Hydrazide based formamides [(i), (ii), (iii), (iv) and (v)] were obtained in solid form after drying the precipitate (Figure 2).

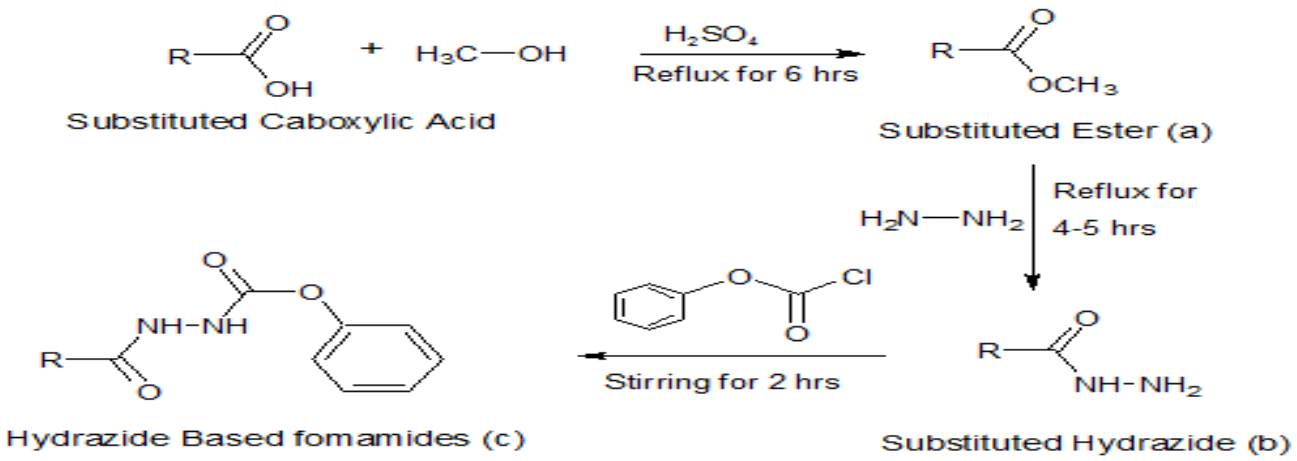


Figure 1: Formation of hydrazide based formamides

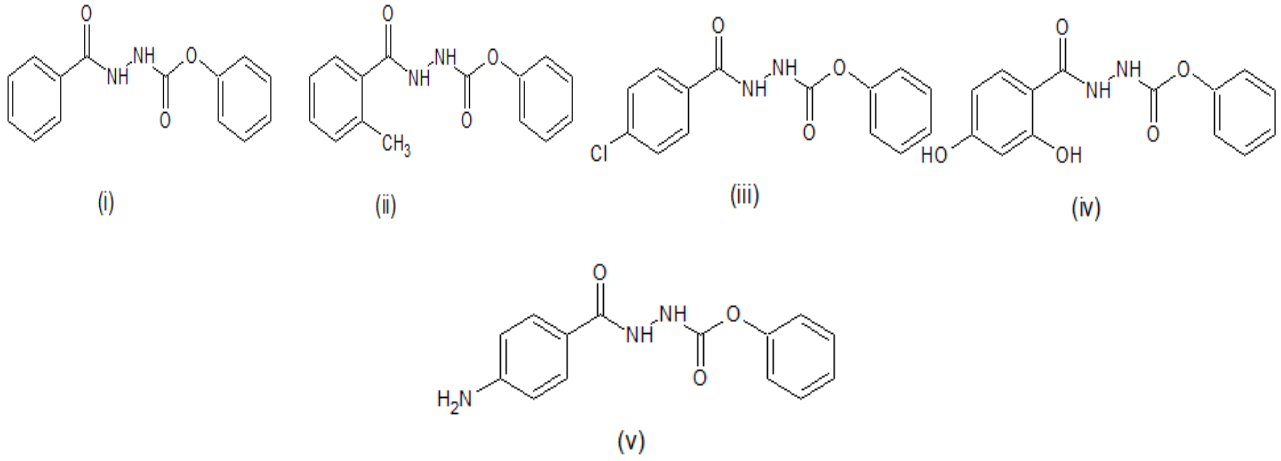


Figure 2: Different hydrazide based formamides

Result and Discussion

FTIR analysis and Elemental analysis of all formamides derivatives was done from Material Chemistry Lab, GC University, Lahore as shown in Table No. 1

Table No. 1:

Product Code	M.p. °C	Rf Value	% age Yield	Molecular Formula	IR spectrum	Elemental Analyzer
i)	122°C	0.74	77 %	$C_{14}H_{12}N_2O_3$	3265 N–H Str, 2910 C–H Str, 1645 C=0 Str, 1490 C=C 1212 C–0 Str (Sp^2)	C 65.59% H 4.64% N 10.91% S 0 %
ii)		0.44	67 %	$C_{15}H_{14}N_2O_3$	3149 N–H Str, 2913 C–H Str, 1673 C=O Str, 1488 C=C, 1247 C–O (Sp^2)	C 56.58% H 4.4% N 17.6% S 0 %

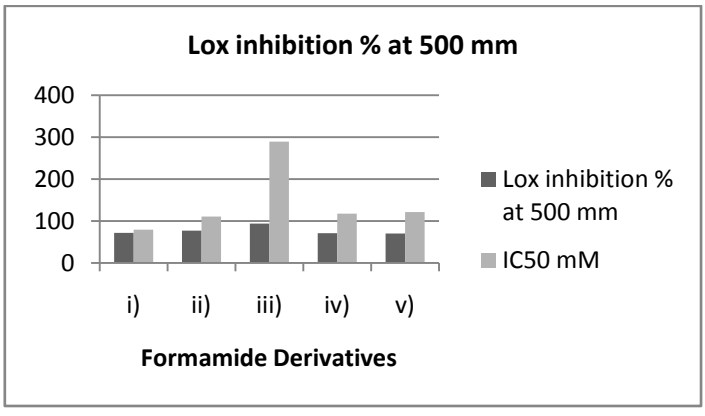
iii)	209°C	0.47	80%	$C_{14}H_{11}ClN_2O_3$	3354 N–H Str, 3053 Ar C–H Str, 2873 al: C–H Str 1692 C=O Str, 1486, 1558,1600 C=C (Ar) 1283 C–O Str, 880 C–Cl Str 1330 C–N Str	C 57.81% H 3.75% N 9.62%, S 0%
iv)	190°C	0.43	74%	$C_{14}H_{12}N_2O_5$	3410 N–H Str 2910 C–H Str, 1738C=O Str 1489, 1610 C=C Str 1218 C –O (Sp^2) 779 C–Cl	C 58.32% H 4. % N 9.7% S 0 %
v)	240°C	0.43	86%	$C_{14}H_{13}N_3O_3$	3299 N–H Str, 1741C=O Str, 1492, 1543, 1604 C=C Str, 1203 C–O Str, 760 C–Cl	C 61.98% H 4.78% N 10.33% S 0 %

Lipoxygenase Inhibition Assay

Lipoxygenase Inhibition assay of all synthesized derivatives of formamides at 500 µM, as their results are shown in Table No. 2. Results show that phenyl 2-(4-chlorobenzoyl) hydrazinecarboxylate (iii) show larger LOX inhibition assay while remaining formamide derivatives show same LOX inhibition value at 500 µM.

Table No. 2:

Formamide Derivatives	LOX inhibition % at 500 µm	IC_{50} µM
i)	72	79.2
ii)	77	110.5
iii)	94	289
iv)	71	117.4
v)	70	121.5



Antioxidant Activity

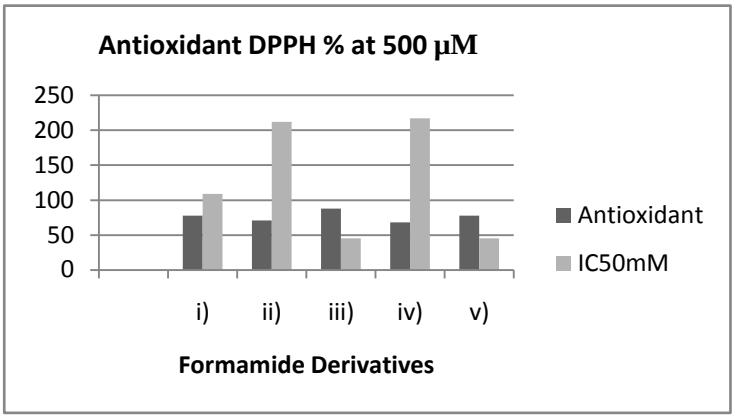
Antioxidant activity of all formamides derivatives were tested in the form of different activity like radical scavenging action over ABTS assay, Metal chelating action over Metal chelating activity and Ferric reducing antioxidant control over FRAP assay.

DPPH Radical Scavenging Assay:

DPPH Radical Scavenging Assay of all synthesized fromamide derivatives are shown in Table No. 3. phenyl 2-(4-chlorobenzoyl) hydrazinecarboxylate (iii) also shows maximum Antioxidant DPPH % at 500 µM on the other hand phenyl 2-(2,4-dihydroxybenzoyl) hydrazinecarboxylate shows smallest antioxidant DPPH % value.

Table No. 3:

Formamide Derivatives	Antioxidant DPPH % at 500 µM	IC50µM
i)	78	109
ii)	71	212
iii)	88	45.5
iv)	68	217
v)	78	45.3

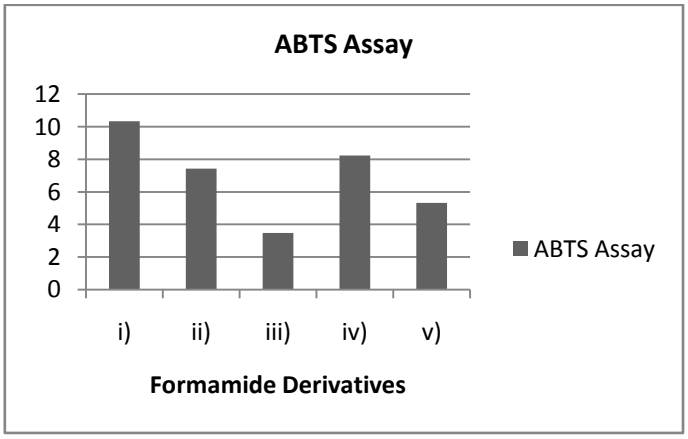


ABTS Assay

From ABTS assay, determines the free radical scavenging activity of all synthesized formamides derivatives, which are shown in Table No. 4. Result shows that phenyl 2-benzoylhydrazinecarboxylate (i) has the highest free radical scavenging ability on the other hand phenyl 2-(4-chlorobenzoyl) hydrazinecarboxylate (ii) indicates least free radical scavenging ability.

Table No. 4:

Formamide Derivative	ABTS Assay
i)	10.33
ii)	7.42
iii)	3.47
iv)	8.22
v)	5.32

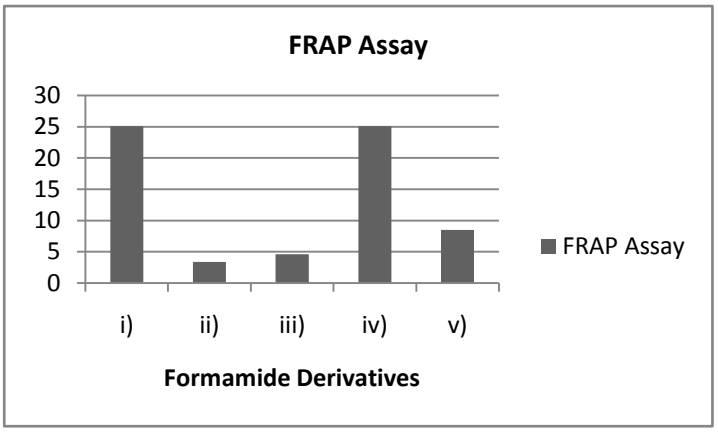


FRAP Assay

This assay defines the ferric reducing antioxidant power of chemical compounds. FRAP results of all formamides derivatives are shown in Table No. 5 which indicates that phenyl 2-benzoylhydrazinecarboxylate (i) and phenyl 2-(2,4-dihydroxybenzoyl)hydrazinecarboxylate (ii) show extreme reducing potential.

Table No. 5:

Formamide Derivative	FRAP Assay
i)	25.08
ii)	3.392
iii)	4.632
iv)	25.08
v)	8.48



Antimicrobial activity evaluation

All the synthesized formamide derivatives were calculated for antimicrobial activity against gram negative, gram positive bacteria and fungus. Results are shown in Table No. 6, which indicates that inconstant activity of formamide derivative against different strains.

Table No. 6:

Formamide Derivative	*E. coli*	*Bacillus Subtilis*	*Typhimusium Salmonella*	*Staphlococcus aureus*	*Candida albicans*
i)	Nil	Nil	10mm	Nil	16mm
ii)	Nil	18mm	Nil	12mm	27mm
iii)	Nil	Nil	12mm	Nil	Nil
iv)	11 mm	20mm	20mm	20mm	10mm
v)	Nil	Nil	Nil	Nil	25mm

Conclusion

Synthesized formamides show fluctuation in results against their antioxidant studies. Majority of the produced formamides are inactive against E coli bacteria but on the other hand most of the formamide derivatives are dynamic against *Candida albicans*.

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