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Evaluation of the antimicrobial activity and cytotoxic effect of some uridine derivatives

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Abstract

Nucleoside analogues may represent good candidates for the discovery of new antimicrobial agents, therefore, a series of uridine derivatives (2-13) was assessed for their antibacterial and antifungal activities, and the relationship between the structure and activity of these molecules was outlined. The 2-bromobenzoylation of uridine derivatives was evaluated for *in vitro* antibacterial and antifungal screening studies against a number of human and plant pathogenic microorganisms by disc diffusion and food poisoned methods, respectively. From the antibacterial screening results, it was revealed that the test chemical 4 and 6 very significantly inhibited the growth of all Gram-positive and Gram-negative bacterial strains used. The inhibition of *E. coli* by 4 (14 mm), of *S. typhi*by 4 (15 mm), of *B. subtilis*by 6 (12 mm), of *B. cereus* by 6 (14 mm) were remarkable. However, the test chemical 10 inhibited the highest mycelial growth of *Rhizopus nigricans* (60.0%) against all examined fungal pathogens. For comparative studies, two standard antibiotics, Ampicillin and Nystatin, were also determined. In addition to that the toxicity results of brine shrimp lethality assay displayed the test chemicals 6, 7 and 8 highest levels of mortality (i.e., ~80% death) among all tested chemicals. Hence, uridine derivatives bearing various acyl substituents in the ribose moiety may represent good lead compounds for the future discovery of novel antibacterial and/or antifungal agents.

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Introduction

Infectious diseases worldwide have been known to beacause of morbidity, disability and mortality. Approximately 15 million people die eachyear due to infectious diseases-nearly all live in developing countries (WHO, 2008). Indiscriminate and unconcerned use of antibiotics has led to increased microbial resistance. Consequently, newer agents have been brought in at increased economic costs to the patient but theytoo have becomein efficacious in due course and pose worldwide a great threat to human health. So, noble, emerging and re-emerging infectious diseases have becomea focus for the development of new cost-effective drug in bothdeveloped and developing countries. So, the finding of new drugisvery important for the treatment.

Uridine (1) is a molecule (known as nucleoside) that is formed when uracil is attached to a ribose ring via β-N_1-glycosidic bond. Uridine is one of the four basic components of robonucleic acid (RNA). Upon digestion of foods containing RNA, uridine is released from RNA and is absorbed intact in the gut. Uridine is found in sugarcane, tomatos, broccoli, liver, pancreas etc. Uridine has anti depression activity, asthmatic airway inflammation, hepatocyte proliferation (Carlezon *et al*., 2005; Jonas *et al*., 2001).

Nucleosides and nucleotides play important roles in cell physiology both as nutrients and modulators of cellular homeostasis. They are implicated in crucial processes such as DNA and RNA synthesis, cell signaling, and metabolic regulation. Moreover, nucleoside and nucleobase analogs are currently used in the treatment of solid tumors, lymphoproliferative diseases, viral infections such as hepatitis and AIDS, and some inflammatory diseases such as Crohn (Jordheim *et al*., 2013; Minuesa *et al*., 2011).

In medicine several nucleoside analogues are used as antiviral or anticancer agents (Jordheim *et al*., 2013; Marçal *et al*., 2016). The viral polymerase incorporates these compounds with non-canonical bases. These compounds are activated in the cells by being converted into nucleotides. They are administered as nucleosides since charged nucleotides cannot easily cross cell embranes. Moreover, nucleoside analogues exhibited antibacterial and antifungal activities against some pathogenic microorganisms (Alan *et al*., 1988; Richa *et al*., 2007).

Literature survey revealed that a wide variety of biologically active substances contain aromatic, heteroaromatic and acylsubstituents (Gupta *et al*., 1997). It is also known that the combination of two or more potent acyl substituents in a single molecular framework enhances the biological profile many foldthanits parent nuclei (Kabir *et al*., 1998). The benzene and substituted benzene nucleus play important role as common denominator for various biological activities. In the context of ourstudies, we observed that some acylated derivatives of D-glucose (Kabir *et al*., 2009), D-mannose (Kabir *et al*., 2004) and uridine (Kawsar *et al*., 2015) also exhibited effective antibacterial and antifungal activities. In view of the above mentioned facts and in continuation of ourwork on synthesis of biologically important nucleoside derivatives, we report herein the results of antibacterial, antifungal and toxicity activities of a series of uridine derivatives containing various prospective biologically potent acyl substituents in a single molecular framework.

Materials and methods

Test compounds

Twelve partially protected derivatives of uridine (2-13) (Fig. 1) were used as test chemicals. The chemicals (2-13) were synthesized, isolated, purified and characterized in the Laboratory of Carbohydrate and Nucleoside Chemistry, Department of Chemistry, University of Chittagong. The antimicrobial activity of the chemicals was done in the Microbiology Laboratory, Department of Microbiology, University of Chittagong.

Bacterial and fungal micro-organisms

The antibacterial activities of acylated uridine compounds 2-13 (Fig. 1) were studies against two

Gram-positive and three Gram-negative micro-organisms *viz. Bacillus subtilis* BTCC 17, *Bacillus cereus* BTCC 19, *Escherichia coil* ATCC 25922, *Pseudomonas aeruginosa* CRL (ICDDR,B) and *Salmonella typhi*AE 14612. Antifungal activities of the compounds were also studied against two fungi *viz. Aspergillus niger* ATCC 16404 and *Rhizopus nigricans* ATCC 6227b.

Antibacterial activity test

The antibacterial activities of the synthesized compounds (**2-13**) were detected by disc diffusion method (Bauer *et al.*, 1966) with little modification (Miah *et al.*, 1990). Sterilized paper discs of 4 mm in diameter and Petri dishes of 150 mm in diameter were used throughout the experiment.

The autoclaved Mueller-Hinton agar medium, cooled to 45˚C, was poured into sterilized Petri dishes to a depth of 3 to 4 mm and after solidification of the agar medium; the plates were transferred to an incubator at 37˚C for 15 to 20 minutes to dry off the moisture that developed on the agar surface.

The plates were inoculated with the standard bacterial suspensions (as McFarland 0.5 standard) followed by spread plate method and allowed to dry for three to five minutes. Dried and sterilized filter paper discs were treated separately with 50 µg dry weight/disc from 2% solution (in $CHCl_3$) of each test chemical using a micropipette, dried in air under aseptic condition and were placed at equidistance in a circle on the seeded plate. A control plate was also maintained in each case without any test chemical.

These plates were kept for 4-6 hours at low temperature (4-6˚C) and the test chemicals diffused from disc to the surrounding medium by this time. The plates were then incubated at 35±2˚C for 24 hours to allow maximum growth of the organisms. The antibacterial activity of the test agent was determined by measuring the mean diameter of zone of inhibitions in millimeter. Each experiment was repeated thrice. All the results were compared with the standard antibacterial antibiotic ampicillin (20 µg/disc, BEXIMCO Pharm Bangladesh Ltd).

Antifungal activity test

Antifungal activity of the acylated uridine compounds (2-13) was assessed by food poison technique (Grover & More, 1962) with some modification (Miah *et al.*, 1990). Two percent solution of the test chemical (in $CHCl_3$) was mixed with sterilized melted Saburaud agar medium to obtain the desired concentration (2%) and this was poured in sterilized Petri dishes. At the center of each plate, 5 days old fungal mycelial block (4 mm in diameter) was inoculated and incubated at 27˚C. A control set was also maintained in each experiment. Linear mycelial growth of fungus was measured after 3-5 days of incubation. The percentage inhibition of radial mycelial growth of the test fungus was calculated as follows:

$$I = \left\{\frac{C-T}{C}\right\} \times 100$$

Where, I = Percentage of inhibition, C = Diameter of the fungal colony in control ($CHCl_3$), T = Diameter of the fungal colony in treatment. All the results were compared with the standard antifungal antibiotic nystatin (100 µg/ml medium, MEXIMCO Pharm Bangladesh Ltd.).

Toxicity activity test

For toxicity activity assessment brine shrimp lethality assay of the uridine derivatives were performed according to McLaughlin *et al.* method (1991).

Results and discussion

Twelve acylated derivatives (2-13) (Fig. 1) of uridine (1) were chosen as the test chemicals for the present investigation. As our present investigations the test chemicals were subjected for antimicrobial evaluation against five human pathogenic bacteria and two plant pathogenic fungi. The results of antibacterial activity of the test chemicals (2-13) were measured in terms of zone of inhibition in mm and are presented in Table 1 and Fig. 2.

A) Effect of test chemicals on bacteria

The inhibition zones against the selected bacteria due to the effect of compounds are mentioned in Table 1.

Table 1. Zone of inhibition observed against Gram+Ve and Gram-Ve test organisms by the test chemicals.

Compound no.	Zone of inhibition (mm) at 200 µg dw/disc				
	Gram +Ve bacteria		Gram -Ve bacteria		
	B. subtilis	*B. cereus*	*E. coli*	*P. aeruginosa*	*S. typhi*
2	8	8	NF	NF	6
3	6	7	7	7	NF
4	9	11	*14	*14	*15
5	6	7	6	NF	NF
6	*12	*14	*12	8	*12
7	6	NF	NF	NF	6
8	8	7	NF	6	NF
9	7	8	NF	NF	NF
10	NF	NF	6	NF	7
11	NF	NF	NF	NF	7
12	8	9	NF	NF	NF
13	*14	*14	9	NF	*12
**Ampicillin	*22	*15	*19	*17	*20

N.B: '*' = marked inhibition, '**' = standard antibiotic, 'NF' = not found, 'dw' = dry weight.

Bacillus subtilis BTCC 17

The *in vitro* growth inhibitions of this Gram positive bacterium due to the treatment of different test chemicals are shown in Table 1 and (Fig. 2). It was found that, the inhibition zone of the derivatives 6 (12 mm) and 13 (14 mm) derivatives were more effective than that of other chemicals such as 2, 3, 4, 5, 7, 8, 9 and 12 which were somewhat less effective. The rest of the chemicals such as 10 and 11 did not show any inhibition. All of these test chemicals were, however, less active against this bacterial strain than standard antibiotic, Ampicillin (22 mm) in case of this bacterial strain.

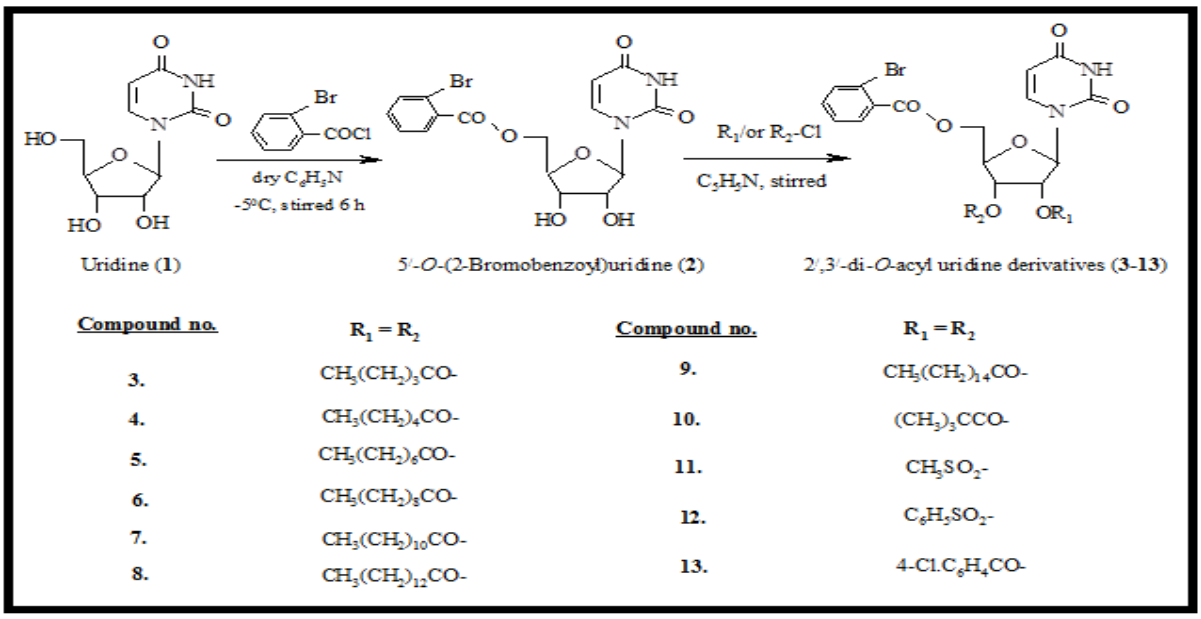
Table 2. Antifungal activities of the test chemicals and nystatin.

Compound no	% Inhibition of fungal mycelial growth[a](100 µg (dw)/ml medium)	
	Aspergillus niger	*Rhizopus nigricans*
2	NF	NF
3	20	15
4	11	14
5	NF	25
6	NF	32
7	19	20
8	10	*52
9	*58	36
10	20	*60
11	NF	18
12	18	20
13	NF	NF
**Nystatin	*66.41	*63.10

N.B: '*' = marked inhibition, '**' = standard antibiotic, 'NF' = not found, 'dw' = dry weight,
[a]growth measured-radial growth in cm.

Bacillus cereus BTCC 19

The inhibition zone for this Gram positive organism by different uridine derivatives treatment is mentioned in Table 1. It was observed that only derivative **6** (14 mm) and **13** (14 mm) derivative were more prone towards inhibition against this bacterium than that of the other chemicals and showed the nearest activity with the standard antibiotic, Ampicillin (15 mm). Most of the chemicals indicated lower potentiality against these human pathogens.



Compound no.	$R_1 = R_2$	Compound no.	$R_1 = R_2$
3.	$CH_3(CH_2)_3CO$-	9.	$CH_3(CH_2)_{14}CO$-
4.	$CH_3(CH_2)_4CO$-	10.	$(CH_3)_3CCO$-
5.	$CH_3(CH_2)_6CO$-	11.	CH_3SO_2-
6.	$CH_3(CH_2)_8CO$-	12.	$C_6H_5SO_2$-
7.	$CH_3(CH_2)_{10}CO$-	13.	4-Cl.C_6H_4CO-
8.	$CH_3(CH_2)_{12}CO$-		

Fig. 1. The structure of synthesized uridine derivatives (2-13).

Escherichia coli ATCC 25922

The diameter zone of inhibition of *Escherichia coli* after different chemicals treatments is presented in Table 1 and (Fig. 2). The inhibition zone of the derivatives 4 (14 mm) and 6 (12 mm) derivatives were more effective than that of other chemicals such as 3, 5, 10 and 13 which were somewhat less effective. However, most of the test chemicals were found less effective against this bacterial strain than standard antibiotics, Ampicillin (19 mm) in case of this bacterial strain.

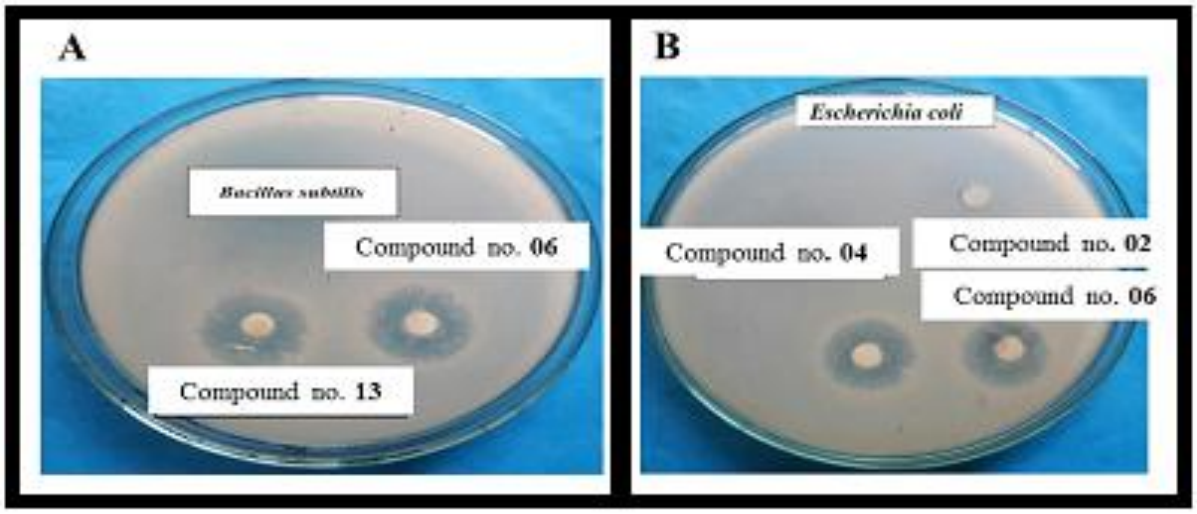


Fig. 2. % Zone of inhibition of the compounds 06 and 13 against A: *Bacillus subtilis* and the compounds 02, 04 and 06 against B: *Escherichia coli.*

Pseudomonas aeruginosa CRL (ICDDR,B)

The screening data presented in Table 1 suggests that the inhibition zone of the derivatives 4 (14 mm) were showed maximum inhibition against this bacterium. It was found that the chemicals 3, 6, and 8 showed some inhibition against this pathogen. The rest of the chemicals were unable to show any inhibition.

Salmonella typhi AE 14612

The screening data presented in Table 1 suggests that the test chemicals 4 (15 mm), 6 (12 mm) and 13 (12 mm) were more effective than other chemicals.

Chemicals 2, 7, 10 and 11 showed were less active against this bacterium. Chemicals 3, 5, 8, 9 and 12 were found to be inactive against this bacterial strain. In this case, none of the compounds showed more activity than the standard antibiotics, Ampicillin (20 mm).

In our own work (Kabir *et al.*, 1998, 2003; Kawsar *et al.*, 2015), it was examined that selectively acylated uridine derivatives 4, 6 and 13 were more effective against Gram positive bacteria and Gram negative bacteria. Some acylated compounds were less effective against Gram positive as well as Gram negative bacteria. In general, it has been noticed that antibacterial results of the selectively acylated uridine derivatives obtained by using various acylating agents follow the order for Gram positive organisms: 13 > 6 > 4 > 12 > 2 > 8 > 9 > 3 = 5 > 7 and Gram negative bacteria follow the order: 4 > 6 > 13 > 3 > 10 > 11 > 2 = 5 = 7 = 8.

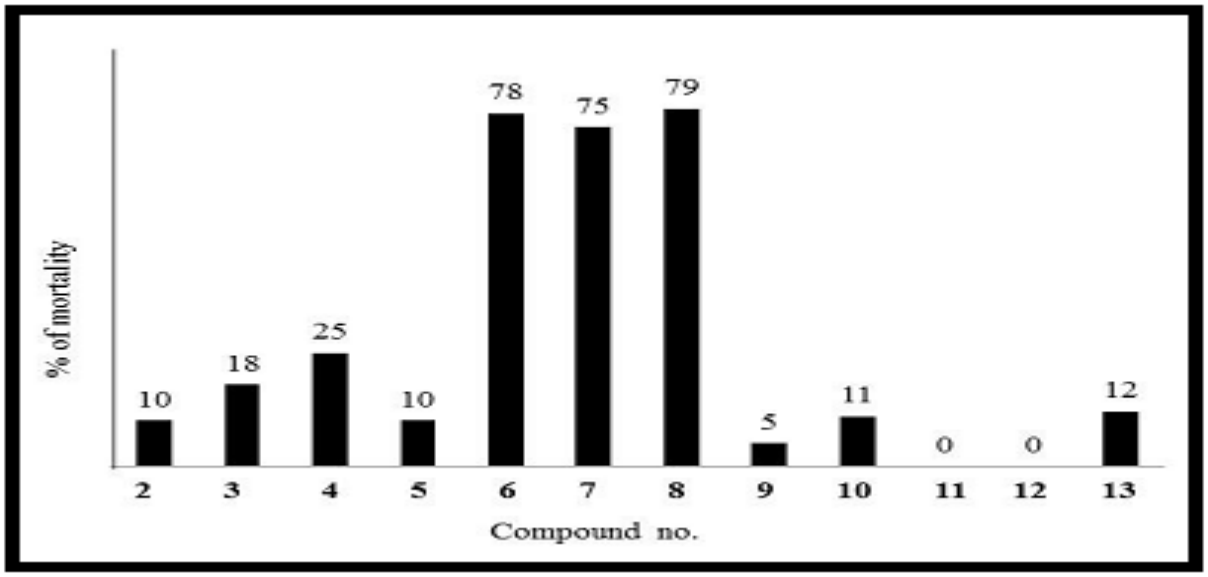


Fig. 3.% of mortality of the tested compounds by brine shrimp lethality assay.

From the experimental results obtained by using a number of selected human pathogenic bacteria (as shown in Table 1) we found that selectively acylated derivatives 4, 6 and 13 showed highest inhibition against Gram positive bacteria while compounds 4, 6 and 13 were also very active against Gram negative bacteria. Another noteworthy observation was that the uridine derivatives were found comparatively equally effective against both Gram positive microorganisms and Gram negative microorganisms.

The results reported in Table 1 revealed that the hydrophobicity is the primary contributor to antibacterial activity. Here the hydrophobicity of the molecules increased gradually from compound 2 to 9. The hydrophobicity of materials is an important parameter with respect to such bioactivity as toxicity or alteration of membrane integrity, because it is directly related to membrane permeation (Kim *et al.*, 2007). Hunt (1975) also proposed that the potency of aliphatic alcohols is directly related to their lipid solubility through the hydrophobic interaction between alkyl chains from alcohols and lipid regions in the membrane. We believe that a similar hydrophobic interaction might occur between the acyl chains of uridine accumulated in the lipid like nature of the bacteria membranes. As a consequence of their hydrophobic interaction, bacteria lose their membrane permeability, ultimately causing death of the bacteria (Hunt 1975; Judge *et al.*, 2013; Kim *et al.*, 2007).

B) Effect of test chemicals on fungi

The results of the percentage inhibition of fungi (*Aspergillus niger* and *Rhizophers nigricans*) due to

treatment of compounds (2-13) are presented in Table 2.

Aspergillus niger ATCC 16404

The percent inhibitions of mycelial growth of plant pathogenic *Aspergillus niger* for different chemical treatment are shown in Table 2. It is evident that chemicals 9 (58.0%), was found to be very active against the test fungus. Whereas, the remaining test chemicals such as 2, 3, 4, 5, 6, 7, 8, 10, 11, 12 and 13 were found less effective against this plant pathogenic fungi. Chemicals palmitoyl derivatives 9 (58.0%) showed the highest inhibition which is near to that of standard antibiotic, Nystatin (66.40%).

Rhizophers nigricans ATCC 6227b

The mycelial growth inhibition of *Rhizophers nigricans* due to the treatment by different test chemicals are mentioned in Table 2. It was found that, test chemical 8 (52.0%), 10 (60.0%), showed effective inhibition against the fungus. The chemicals 3 (15.0%), 4 (14.0%), 5 (25.0%), 7 (20.0%), 6 (14.0%), 9 (22.0%), 11 (18.0%) and 13 (20.0%) were less effective against this fungal species. Among these compounds pivaloyl derivative 10 (60.0%) showed the highest inhibition against this fungus.

As seen in ourprevious investigations (Kawsar *et al*., 2014; 2015) the presence of someacyl groups in the test chemicals increased the antimicrobial capacity, here in this investigation we found that the presence of hexanoyl, decanoyl, 4-chlorobenzoyl etc. acyl groups improved the antimicrobial power of the test chemicals which was in accordance without previous work (Kawsar *et al*., 2013).

C) Effect of test chemicals on toxicity

The toxicity activity of the acylated derivatives of uridine in the brine shrimp lethality bioassay (Fig. 3) shows the percentage of mortality of shrimps at 24 hrs and 48 hrs. Mortality of the nauplii was noticed in the experimental groups at the same time the control group remained unchanged. The number of survived nauplii in each vial was counted and the results were noted. From these data the percent of mortality of the shrimp was calculated for every concentration of each chemical. In the bioassay, the test chemicals showed a significant cytotoxicity activity in the brine shrimp lethality bioassay indicating that these compounds are biologically active. The compounds showed different rate mortality with different concentrations. The mortality of brine shrimp was found to increase with the increase of concentrations of compounds. It is evident from the results of brine shrimp lethality testing that the test chemicals 5´-*O*-(2-Bromobenzoyl)-2,´3´-di-*O*-decanoyluridine (6), 5´-*O*-(2-Bromobenzoyl)-2´,3´-di-*O*-lauroyluridine (7) and 5´-*O*-(2-Bromobenzoyl)-2´, 3´-di-*O* myristoyl uridine (8) showed highest levels of toxicity (i.e., ~80% death) indicating its higher mortality. Fig. 3.

Conclusions

In the present investigation, we observed that the introduction of some specific functionalities in the test chemicals improved their antimicrobial and toxicityactivities. In thisseries the presence of hexanoyl, decanoyl, 4-chlorobenzoyl and substituted benzoyl groups might be responsible for the improvement of the antimicrobial and toxicity capacity of the test chemicals. We also found that compound 4, 6 and 13 were very sensitive towards all of both Gram-positive and Gram-negative bacterial organisms. It is expected that this piece work employing uridine derivatives as test chemicals will help further work to the development of pesticides and medicine for human and plant disease control. So it is hoped that the tested uridine derivatives might show potential antiviral, antituberculatic and anti-inflammatory activities.

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