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# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW PHENYTOIN DERIVATIVES AND THEIR ACYCLIC NUCLEOSIDE ANALOGS

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*New phenytoin derivatives and their N-substituted acyclic nucleoside analogs were prepared. The synthesized compounds were tested for their antimicrobial activity against Escherichia coli, Staphylococcus aureus, and Streptomyces Sp. Most of the tested compounds exhibited moderate to high antimicrobial activity while a few compounds were found to exhibit little or no activity against the tested microorganisms.*

**Keywords:** acyclic nucleosides, phenytoin derivatives, sugar hydrazones, antimicrobial activity.

Phenytoin (5,5-diphenylhydantoin) (**1**) is one of the most widely used drugs in the therapy of epilepsy. The risks associated with the use of this formulation are obvious, taking into account its high acidity, as well as the precipitation of the free acid [1]. The classical prodrug approach to improve membrane permeability of drug molecules employs lipophilic derivatives to increase passive membrane penetration. In recent years, different nutrient transporters (i.e., oligopeptide, amino acid, and glucose transporters) have been identified and cloned. The active nutrient transport systems have become a target for prodrug design [2]. Hydrazones have been demonstrated to possess antimicrobial, antibacterial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular, and antitumor activities [3-5], among others. In addition, some of the new hydrazide-hydrazones [6] that have been recently synthesized were active against the same strain of *Mycobacterium tuberculosis* H37Rv between the concentrations of 0.78–6.25 μg/ml. These compounds were reported to have inhibitory activity in mice infected with various strains of *M. tuberculosis* [7] and showed less toxicity [8]. Some hydrazide-hydrazones were reported to have lower toxicity than hydrazides because of blockage of the $NH_2$ group. A number of studies were devoted to the *in vitro* and *in vivo* metabolism of hydrazide-hydrazones. In *in vitro* metabolism studies, it has been found that hydrazide-hydrazones undergo hydrolytic reactions, the aromatic rings undergoing aromatic hydroxylation reactions [9, 10]. Furthermore, nucleoside analogs are structurally, metabolically, and pharmacodynamically related agents that have diverse biological actions and therapeutic effects, including antiviral [11, 12] and antitumor activities [13-15]. The above facts and our interest [16-20] in the attachment of carbohydrate moieties to newly synthesized heterocycles in order to find new biologically active lead compounds promoted us to synthesize new substituted phenytoins and their acyclic nucleoside analogs and evaluate their antimicrobial activity.

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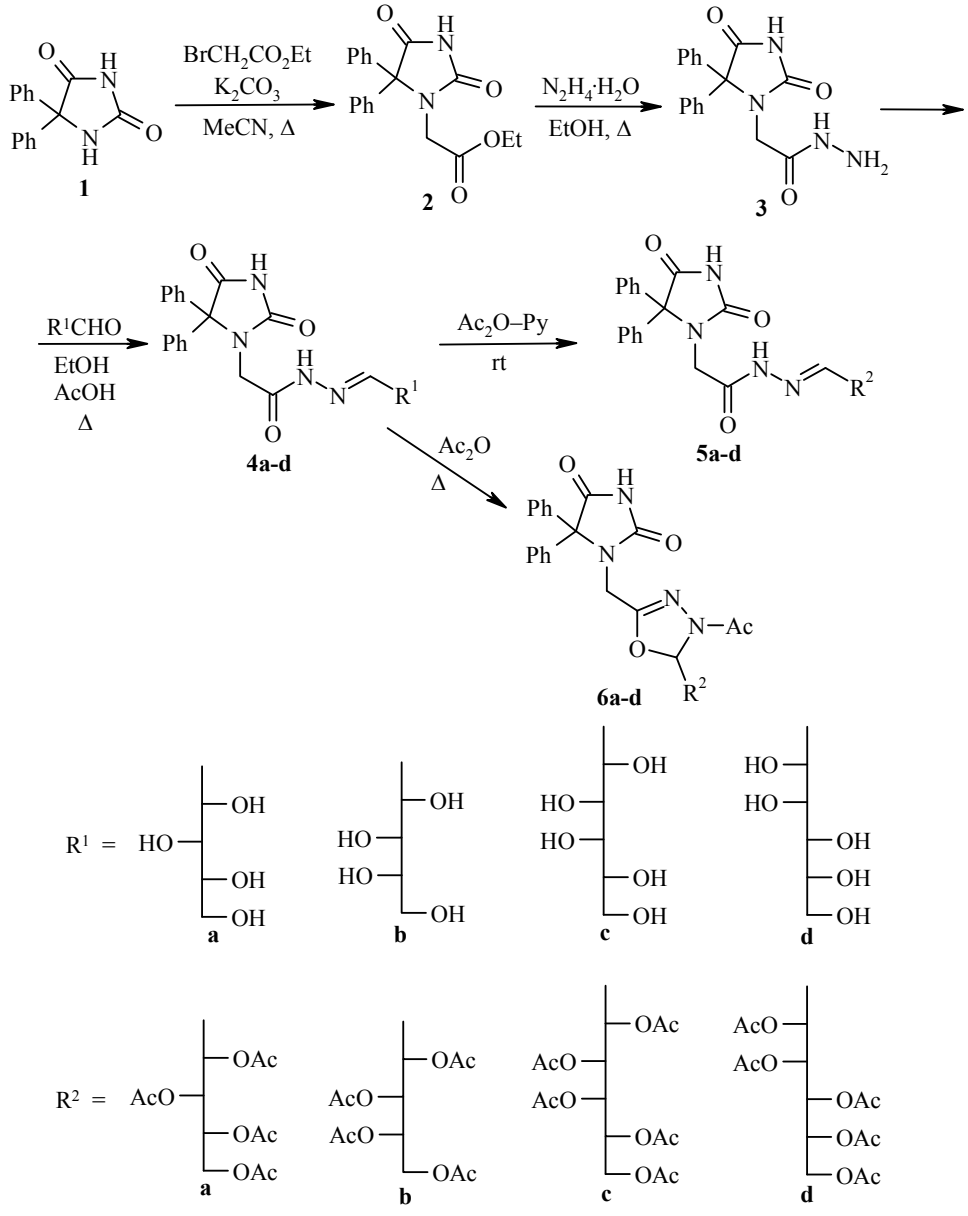
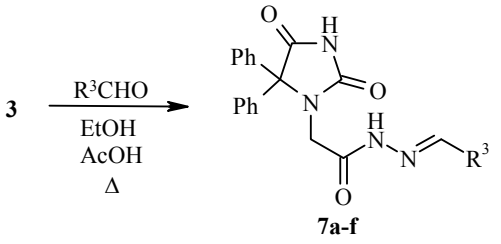
In this investigation, phenytoin (**1**) was allowed to react with ethyl bromoacetate in dry acetone and in the presence of anhydrous potassium carbonate to afford 1-ethoxycarbonylmethylphenytoin (**2**) [21]. Treatment of compound **2** with hydrazine hydrate in ethanol at reflux temperature gave the corresponding hydrazide **3** in 90% yield. The structures of products **2** and **3** were confirmed by $^1$H NMR and mass spectra, which agreed with the assigned structures. 1-Phenitoinylacetic acid hydrazide (**3**) was allowed to react with D-xylose, L-arabinose,




D-galactose, and D-mannose in an aq. ethanolic solution with a catalytic amount of acetic acid, and the corresponding sugar *N*-acylhydrazones **4a-d** were obtained in 85–87% yields. The structures of these compounds were confirmed by analytical and spectral data. The IR spectra of compounds **4a-–d** showed the presence of characteristic absorption bands corresponding to the hydroxy groups in the region 3340–3415 cm$^{-1}$. The $^1$H NMR spectra showed signals of the sugar chain protons at 3.24-4.19 ppm and the H-1' methine proton as a doublet in the range 7.10-7.18 ppm. Treatment of the sugar hydrazones **4a-d** with acetic anhydride in pyridine at room temperature gave the corresponding per-*O*-acetyl derivatives **5a-d** in 95–97% yields. The $^1$H NMR spectra of compounds **5a-d** showed the signals of the *O*-acetyl group protons at 1.94-2.16 ppm. The

rest of the sugar protons appeared in the range 4.10-5.80 ppm. The reaction of sugar arylhydrazones with boiling acetic anhydride is well known to give either the corresponding per-*O*,*N*-acetyl derivatives or the respective per-*O*,*N*-acetyl-1,3,4-oxadiazoline derivatives [11, 22-24]. In our case, reaction of the sugar hydrazones **4a-d** with acetic anhydride at 100°C gave the sugar-substituted 1,3,4-oxadiazoline derivatives **6a-d** in 80–85% yields. The $^1$H NMR spectra of compounds **6a-d** showed signals of the *O*- and *N*-acetyl group methyl protons. The rest of the sugar chain protons appeared in the range 4.00-5.47 ppm. Phenytoin hydrazide **3** was refluxed with various aromatic aldehydes in ethanol and in the presence of a catalytic amount of acetic acid to afford the corresponding Schiff bases **7a-f** in 90-95% yields.




**7a-f**

**7 a** $R^3$ = 2-$BrC_6H_4$, **b** $R^3$ = 4-$ClC_6H_4$, **c** $R^3$ = 4-$FC_6H_4$,
**d** $R^3$ = 4-$Me_2NC_6H_4$, **e** $R^3$ = 5-methylfuran-2-yl, **f** $R^3$ = pyren-1-yl

The synthesized compounds were evaluated for their antimicrobial activity against *Escherichia coli* (gram-negative bacteria), *Staphylococcus aureus* (gram-positive bacteria), and *Streptomyces* Sp. The values of minimal inhibitory concentrations (MIC) of the tested compounds are presented in Table 1.

The MIC values of the most active compounds were in accord with the results obtained in the primary screening. The results revealed that the compounds showed varying degrees of inhibition against the tested microorganisms. In general, compounds **5d**, **6d**, and **7c**,**e** displayed the highest activity against *Staphylococcus*

TABLE 1. Minimal Inhibitory Concentrations of the Title Compounds,* μg/ml

| Compound | *Escherichia coli* | *Staphylococcus aureus* | *Streptomyces* Sp. |
|---|---|---|---|
| **4a** | 500 | 250 | 500 |
| **4b** | 500 | 225 | 475 |
| **4c** | 100 | 125 | 100 |
| **4d** | 250 | 500 | 225 |
| **5a** | 125 | 225 | 125 |
| **5b** | 100 | 125 | 125 |
| **5c** | 125 | 225 | 125 |
| **5d** | 100 | 100 | 75 |
| **6a** | 250 | 125 | 75 |
| **6b** | 500 | 500 | 100 |
| **6c** | 250 | 250 | 100 |
| **6d** | 100 | 100 | 250 |
| **7a** | 125 | 125 | 100 |
| **7b** | 500 | 500 | 75 |
| **7c** | 100 | 100 | 225 |
| **7d** | 125 | 225 | 250 |
| **7e** | 75 | 75 | 75 |
| **7f** | 125 | 225 | 250 |
| Penicillin | 45 | 34 | 31 |

* Negative control DMSO, no activity.

*Aureus*, followed by compounds **4c**, **5b**, **6a**, and **7a**. Compounds **4c**, **5b**,**d**, **6d**, **7c**, and **7e** displayed the highest inhibition activity against *Escherichia coli* with an MIC value of 75–100 μg/ml, followed by derivatives **5a**,**c**, **7a**,**d**, and **7f**. Compounds **4c**, **5d**, **6a-c**, **7a**,**b**,**e** revealed the highest activity against *Streptomyces* Sp.

In conclusion, new phenytoin *N*-substituted acyclic nucleoside analogs were prepared and studied for their antimicrobial activity. Substitution at the free N-1 in the phenytoin moiety afforded compounds with increased inhibitory activities with respect to the three microorganisms.

## EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer model 1720 FTIR spectrometer in KBr pellets. $^1$H NMR spectra were recorded on a Varian Gemini 200 NMR spectrometer at 300 MHz in DMSO-$d_6$ with TMS as internal standard. Elemental analyses were performed on a 2400 CHN Perkin Elmer Elemental Analyzer at the Microanalytical Data Center at the Faculty of Science, Cairo University, Egypt. Melting points were determined with a Kofler block apparatus and are uncorrected. The progress of the reactions was monitored by TLC using silica gel plates 60 F 245 (5% MeOH in $CH_2Cl_2$).

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)acetohydrazide (3)**. A solution of the ester **2** [21] (3.38 g, 10 mmol) in EtOH (20 ml) and hydrazine hydrate (10 ml) was refluxed for 4 h. The solvent was removed under reduced pressure, and the remaining precipitate was collected, dried, and recrystallized from EtOH. Yield 2.91 g (90%). White powder, mp 172-174°C. IR spectrum, ν, cm$^{-1}$: 1695 (C=O), 3427 (NH). $^1$H NMR spectrum, δ, ppm: 4.57 (2H, s, $NCH_2$); 5.80 (2H, br. s, $NH_2$); 7.23-7.43 (10H, m, H Ph); 8.22 (1H, br. s, NH); 9.92 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 324 $[M]^+$ (25). Found, %: C 62.88; H 4.68; N 17.09. $C_{17}H_{16}N_4O_3$. Calculated, %: C 62.95; H 4.97; N 17.27.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(alditolylmethylidene)acetohydrazides 4a-d (General Method)**. Hydrazide **3** (3.24 g, 10 mmol) in EtOH (10 ml) was added to a vigorously stirred solution of the corresponding monosaccharide (10 mmol) in $H_2O$ (2 ml) and AcOH (1 ml). The mixture was heated to reflux, and the resulting solution was concentrated under reduced pressure and left to cool. The formed precipitate was collected by filtration, washed with water and cold EtOH, dried, and recrystallized from EtOH to afford the corresponding sugar hydrazones **4a**–**d**.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(D-xylotetritolylmethylidene)acetohydrazide (4a)**. Yield 3.96 g (87%). White powder, mp 164-166°C. IR spectrum, ν, cm$^{-1}$: 3300 (NH), 3415 (OH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.26-3.55 (5H, m, 2',3',4'-CH, 5'-$CH_2$), 4.48 (2H, br. s, 2OH); 4.60 (2H, s, $NCH_2$); 5.21 (2H, br. s, 2OH); 7.13 (1H, d, *J* = 2.5, 1'-CH); 7.23-7.37 (10H, m, H Ph); 9.62 (1H, br. s, NH); 11.08 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 456 $[M]^+$ (11). Found, %: C 57.50; H 5.11; N 12.19. $C_{22}H_{24}N_4O_7$. Calculated, %: C 57.89; H 5.30; N 12.27.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(L-arabinotetritolylmethylidene)acetohydrazide (4b)**. Yield 3.87 g (85%). White powder, mp 172-174°C. IR spectrum, ν, cm$^{-1}$: 3432 (NH), 3345 (OH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.24-3.45 (5H, m, 2',3',4'-CH, 5'-$CH_2$); 4.40 (2H, br. s, 2OH); 4.58 (2H, s, $NCH_2$); 5.18 (2H, br. s, 2OH); 7.18 (1H, d, *J* = 2.5, 1'-CH); 7.23-7.42 (10H, m, H Ph); 9.63 (1H, br. s, NH); 11.12 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 456 $[M]^+$ (11). Found, %: C 57.61; H 5.07; N 12.03. $C_{22}H_{24}N_4O_7$. Calculated, %: C 57.89; H 5.30; N 12.27.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(D-galactopentitolylmethylidene)acetohydrazide (4c)**. Yield 4.18 g (86%). White powder, mp 200-202°C. IR spectrum, ν, cm$^{-1}$: 3270 (NH), 3340 (OH). $^1$H NMR spectrum, δ, ppm: 3.24-3.85 (5H, m, 3',4',5'-CH, 6'-$CH_2$); 4.19-4.21 (1H, m, H-2'); 4.42 (1H, br. s, OH); 4.61 (2H, br. s, 2OH); 4.60 (2H, s, $NCH_2$); 5.03 (2H, br. s, 2OH); 7.18-7.40 (11H, m, H Ph, 1'-CH); 9.30 (1H, br. s, NH); 11.04 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 486 $[M]^+$ (32). Found, %: C 56.60; H 5.21; N 11.30. $C_{23}H_{26}N_4O_8$. Calculated, %: C 56.79; H 5.39; N 11.52.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(D-mannopentitolylmethylidene)acetohydrazide (4d)**. Yield 4.22 g (87%). White powder, mp 192-194°C. IR spectrum, ν, $cm^{-1}$: 3425 (NH), 3340 (OH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.27-4.15 (6H, m, 2',3',4',5'-CH, 6'-$CH_2$); 4.53 (3H, br. s, 3OH); 4.61 (2H, s, $NCH_2$); 4.75 (2H, br. s, 2OH); 7.10 (1H, d, *J* = 2.5, 1'-CH); 7.28-7.38 (10H, m, H Ph); 9.60 (1H, br. s, NH); 11.11 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 486 $[M]^+$ (27). Found, %: C 56.55; H 5.13; N 11.25. $C_{23}H_{26}N_4O_8$. Calculated, %: C 56.79; H 5.39; N 11.52.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(tetra- and penta-*O*-acetylalditolylmethylidene)acetohydrazides 5a-d (General Method)**. Acetic anhydride (1.02 g, 10 mmol) was added to a solution of sugar hydrazones **4a-d** (1 mmol) in pyridine (7 ml) with stirring at room temperature overnight. The resulting solution was poured onto crushed ice, and the product that separated was collected by filtration, washed with a saturated solution of $NaHCO_3$ followed by water, and then dried. The products were recrystallized from EtOH to afford *O*-acetyl derivatives **5a-d**.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(2,3,4,5-tetra-*O*-acetyl-D-xylotetritolylmethylidene)-acetohydrazide (5a)**. Yield 5.99 g (96%). White powder, mp 140-142°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.96 (3H, s), 2.04 (3H, s), 2.10 (3H, s), and 2.12 (3H, s, 4$CH_3CO$); 4.15-4.17 (2H, m, 5'-$CH_2$); 4.23-4.28 (1H, m, H-4'); 4.58 (2H, s, $NCH_2$); 5.60-5.64 (1H, m, H-3'); 5.76-5.80 (1H, m, H-2'); 7.26 (1H, d, *J* = 2.5, H-1'); 7.35-7.45 (10H, m, H Ph); 9.14 (2H, br. s, 2NH). Mass spectrum, *m/z* ($I_{rel}$, %): 624 $[M]^+$ (5). Found, %: C 57.45; H 5.10; N 8.65. $C_{30}H_{32}N_4O_{11}$. Calculated, %: C 57.69; H 5.16; N 8.97.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(2,3,4,5-tetra-*O*-acetyl-L-arabinotetritolylmethylidene)-acetohydrazide (5b)**. Yield 5.92 g (95%). White powder, mp 137-139°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s), 2.04 (3H, s), 2.10 (3H, s), and 2.13 (3H, s, 4$CH_3CO$); 4.17-4.19 (2H, m, 5'-$CH_2$); 4.25-4.27 (1H, m, 4'-CH); 4.55 (2H, s, $NCH_2$); 5.60-5.63 (1H, m, 3'-CH); 5.74-5.77 (1H, m, 2'-CH); 7.27 (1H, d, *J* = 2.5, 1'-CH); 7.34-7.61 (10H, m, H Ph); 9.11 (2H, br. s, 2NH). Mass spectrum, *m/z* ($I_{rel}$, %): 624 $[M]^+$ (9). Found, %: C 57.53; H 5.06; N 8.54. $C_{30}H_{32}N_4O_{11}$. Calculated, %: C 57.69; H 5.16; N 8.97.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(2,3,4,5,6-penta-*O*-acetyl-D-galactopentitolylmethylidene)acetohydrazide (5c)**. Yield 6.75 g (97%). White powder, mp 120-122°C. $^1$H NMR spectrum, δ, ppm: 1.95 (3H, s), 2.02 (3H, s), 2.10 (3H, s), 2.13 (3H, s), and 2.16 (3H, s, 5$CH_3CO$); 4.11-4.15 (2H, m, 6'-$CH_2$); 4.54-4.57 (1H, m, 5'-CH); 4.63 (2H, s, $NCH_2$); 4.74-4.78 (1H, m, H-4'); 5.19-5.21 (1H, m, H-3'); 5.49-5.53 (1H, m, 2'-CH); 7.25-7.38 (11H, m, H Ph, 1'-CH); 9.16 (2H, br. s, 2NH). Mass spectrum, *m/z* ($I_{rel}$, %): 696 $[M]^+$ (13). Found, %: C 56.67; H 5.03; N 7.87. $C_{33}H_{36}N_4O_{13}$. Calculated, %: C 56.89; H 5.21; N 8.04.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(2,3,4,5,6-penta-*O*-acetyl-D-mannopentitolylmethylidene)acetohydrazide (5d)**. Yield 6.61 g (95%). White powder, mp 102-103°C. $^1$H NMR spectrum, δ, ppm: 1.94 (3H, s), 2.03 (3H, s), 2.10 (3H, s), 2.12 (3H, s), and 2.15 (3H, s, 5$CH_3CO$); 4.10-4.13 (2H, m, 6'-$CH_2$); 4.54-4.58 (1H, m, 5'-CH); 4.60 (2H, s, $NCH_2$); 4.72-4.76 (1H, m, 4'-CH); 5.18-5.22 (1H, m, 3'-CH); 5.52-5.55 (1H, m, 2'-CH); 7.28-7.41 (11H, m, H Ph, 1'-CH); 9.16 (2H, br. s, 2NH). Mass spectrum, *m/z* ($I_{rel}$, %): 697 $[M+H]^+$ (10). Found, %: C 56.60; H 5.00; N 7.83. $C_{33}H_{36}N_4O_{13}$. Calculated, %: C 56.89; H 5.21; N 8.04.

**1-[4-Acetyl-5-(tetra- and penta-*O*-acetylalditolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-5,5-diphenylimidazolidine-2,4-diones 6a-d (General Method).** A solution of sugar hydrazones **4a-d** (1 mmol) in acetic anhydride (5 ml) was heated at 100°C for 3 h. The resulting solution was poured onto crushed ice, and the product that separated was collected by filtration, washed with a saturated solution of $NaHCO_3$ followed by water, and then dried. The products were recrystallized from EtOH to give oxadiazolines **6a-d**.

**1-[4-Acetyl-5-(1,2,3,4-tetra-*O*-acetyl-D-xylotetritolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-5,5-diphenylimidazolidine-2,4-dione (6a)**. Yield 0.53 g (80%). Pale-yellow resin. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s), 1.98 (3H, s), 2.01 (3H, s), 2.10 (3H, s), and 2.29 (3H, s, 5$CH_3CO$); 3.85 (2H, s, $NCH_2$); 4.01-4.04 (1H, m) and 4.09-4.13 (1H, m, 4"-$CH_2$); 4.98-5.01 (1H, m, 3"-CH); 5.18-5.22 (1H, m, 2"-CH); 5.40 (1H, dd, *J* = 3.2, *J* = 6.2, 1"-CH); 5.95 (1H, d, *J* = 6.2, H-5'); 7.25-7.39 (10H, m, H Ph); 11.15 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 667 $[M+H]^+$ (9). Found, %: C 57.44; H 5.05; N 8.33. $C_{32}H_{34}N_4O_{12}$. Calculated, %: C 57.66; H 5.14; N 8.40.

**1-[4-Acetyl-5-(1,2,3,4-tetra-*O*-acetyl-L-arabinotetritolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-5,5-diphenylimidazolidine-2,4-dione (6b)**. Yield 0.55 g (82%). Pale-yellow resin. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s), 1.97 (3H, s), 2.04 (3H, s), 2.13 (3H, s), and 2.23 (3H, s, 5$CH_3$CO); 3.88 (2H, s, $NCH_2$); 4.00-4.04 (1H, m) and 4.12-4.15 (1H, m, 4"-$CH_2$); 5.07–5.10 (1H, m, 3"-CH); 5.22-5.25 (1H, m, 2"-CH); 5.47 (1H, dd, *J* = 3.2, *J* = 6.2, 1"-CH); 5.98 (1H, d, *J* = 6.2, H-5'); 7.25-7.43 (10H, m, H Ph); 11.12 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 667 $[M+H]^+$ (7). Found, %: C 57.40; H 5.00; N 8.23. $C_{32}H_{34}N_4O_{12}$. Calculated, %: C 57.66; H 5.14; N 8.40.

**1-[4-Acetyl-5-(1,2,3,4,5-penta-*O*-acetyl-D-galactopentitolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-5,5-diphenylimidazolidine-2,4-dione (6c)**. Yield 0.59 g (80%). Pale-yellow resin. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s), 1.96 (3H, s), 2.01 (3H, s), 2.10 (3H, s), 2.19 (3H, s), and 2.28 (3H, s, 6$CH_3$CO); 3.93 (2H, s, $NCH_2$); 4.05-4.08 (1H, m) and 4.12-4.15 (1H, m, 5"-$CH_2$); 4.94-4.99 (1H, m, 4"-CH); 5.23-5.26 (1H, m, 3"-CH); 5.33-5.36 (1H, m, 2"-CH); 5.43 (1H, dd, *J* = 3.2, *J* = 6.2, 1"-CH); 5.94 (1H, d, *J* = 6.2, H-5'); 7.25-7.35 (10H, m, H Ph); 10.90 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 738 $[M]^+$ (9). Found, %: C 56.76; H 5.02; N 7.39. $C_{35}H_{38}N_4O_{14}$. Calculated, %: C 56.91; H 5.19; N 7.58.

**1-[4-Acetyl-5-(1,2,3,4,5-penta-*O*-acetyl-D-mannopentitolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl]-5,5-diphenylimidazolidine-2,4-dione (6d)**. Yield 0.62 g (85%). Pale-yellow resin. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s), 1.99 (3H, s), 2.03 (3H, s), 2.10 (3H, s), 2.13 (3H, s), and 2.29 (3H, s) (6$CH_3$CO); 3.95 (2H, s, $NCH_2$); 4.11-4.14 (1H, m) and 4.17-4.20 (1H, m, 5"-$CH_2$); 4.99-5.02 (1H, m, 4"-CH); 5.19-5.23 (1H, m, 3"-CH); 5.31-5.34 (1H, m, 2"-CH); 5.43 (1H, dd, *J* = 3.2, *J* = 6.2, 1"-CH); 5.99 (1H, d, *J* = 6.2, H-5'); 7.25-7.38 (10H, m, H Ph); 9.20 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 738 $[M]^+$ (13). Found, %: C 56.68; H 5.07; N 7.33. $C_{35}H_{38}N_4O_{14}$. Calculated, %: C 56.91; H 5.19; N 7.58.

**Schiff Bases 7a-f (General Method)**. A solution of compound **3** (3.24 g, 10 mmol) and an aromatic aldehyde (10 mmol) in abs. EtOH (50 ml) and AcOH (1 ml) was refluxed for 6–8 h (TLC). The solvent was evaporated under reduced pressure and the residue was collected by filtration and recrystallized from EtOH.

***N*'-(2-Bromobenzylidene)-2-(2,4-dioxo-5,5-diphenylimidazolidin-1-yl)acetohydrazide (7a)**. Yield 4.51 g (92%). White powder, mp 290-292°C. $^1$H NMR spectrum, δ, ppm: 4.51 (2H, s, $NCH_2$); 7.25-7.59 (14H, m, H Ph, H Ar); 8.40 (2H, br. s, CH=N, NH); 9.93 (1H, br. s, NH). Mass spectrum (for $^{79}$Br isotope), *m/z* ($I_{rel}$, %): 490 $[M]^+$ (10). Found, %: C 58.50; H 3.73; N 11.29. $C_{24}H_{19}BrN_4O_3$. Calculated, %: C 58.67; H 3.90; N 11.40.

***N*'-(4-Chlorobenzylidene)-2-(2,4-dioxo-5,5-diphenylimidazolidin-1-yl)acetohydrazide (7b)**. Yield 4.10 g (92%). White powder, mp 310-312°C. $^1$H NMR spectrum, δ, ppm: 4.59 (2H, s, $NCH_2$); 7.29-7.79 (14H, m, H Ph, H Ar); 8.48 (2H, br. s, CH=N, NH); 9.99 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 446 $[M]^+$ (13). Found, %: C 64.33; H 4.13; N 12.29. $C_{24}H_{19}ClN_4O_3$. Calculated, %: C 64.50; H 4.29; N 12.54.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(4-fluorobenzylidene)acetohydrazide (7c)**. Yield 4.00 g (93%). White powder, mp 320-322°C. $^1$H NMR spectrum, δ, ppm: 4.62 (2H, s, $NCH_2$); 7.32-7.75 (14H, m, H Ph, H Ar); 8.50 (2H, br. s, CH=N, NH); 10.02 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 430 $[M]^+$ (22). Found, %: C 66.88; H 4.32; N 12.93. $C_{24}H_{19}FN_4O_3$. Calculated, %: C 66.97; H 4.45; N 13.02.

***N*'-[4-(Dimethylamino)benzylidene]-2-(2,4-dioxo-5,5-diphenylimidazolidin-1-yl)acetohydrazide (7d)**. Yield 4.32 g (95%). White powder, mp 334-336°C. $^1$H NMR spectrum, δ, ppm: 2.95 (6H, s, 2$CH_3$); 4.55 (2H, s, $NCH_2$); 7.22-7.55 (14H, m, H Ph, H Ar); 8.30 (2H, br. s, CH=N, NH); 9.92 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 455 $[M]^+$ (17). Found, %: C 68.33; H 5.44; N 15.17. $C_{26}H_{25}N_5O_3$. Calculated, %: C 68.56; H 5.53; N 15.37.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-[5-(methylfuran-2-yl)methylidene]acetohydrazide (7e)**. Yield 3.95 g (95%). White powder, mp 265-267°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, $CH_3$); 4.53 (2H, s, $NCH_2$); 6.24 (1H, d, *J* = 3.4, H-4 Fur); 6.79 (1H, d, *J* = 3.4, H-3 Fur); 7.22-7.55 (10H, m, H Ph); 8.22 (2H, br. s, CH=N, NH); 9.99 (1H, br. s, NH). Mass spectrum, *m/z* ($I_{rel}$, %): 416 $[M]^+$ (25). Found, %: C 66.19; H 4.73; N 13.22. $C_{23}H_{20}N_4O_4$. Calculated, %: C 66.34; H 4.84; N 13.45.

**2-(2,4-Dioxo-5,5-diphenylimidazolidin-1-yl)-*N*'-(pyren-1-ylmethylidene)acetohydrazide (7f)**. Yield 4.82 g (90%). White powder, mp 284-286°C. $^1$H NMR spectrum, δ, ppm: 4.55 (2H, s, $NCH_2$); 7.22-7.55 (10H,

m, H Ph); 7.70-7.85 (9H, m, H Pyrene); 8.52 (2H, br. s, CH=N, NH); 10.02 (1H, br. s, NH). Mass spectrum, *m*/*z* ($I_{rel}$, %): 536 $[M]^+$ (23). Found, %: C 76.00; H 4.43; N 10.31. $C_{34}H_{24}N_4O_3$. Calculated, %: C 76.11; H 4.51; N 10.44.

**Antimicrobial Testing.** The hole plate method was the most suitable technique for investigating the antibacterial activities of the different compounds. Nutritive agar plates seeded with the test organisms (three plates for each organism) were allowed to solidify, and then 5 mm diameter holes were formed in the plates using a cork borer. Each hole was filled with one drop of the ethanolic solution of the tested compound, while the hole in the center of the plate was filled with one drop of ethanol. Plates were separately incubated at the optimum temperature for each test organism for 24 h. Inhibition zones (zones with no growth) around the holes were measured as an indicator of the antibacterial action [25, 26].

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