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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antitubercular activity of nucleoside analogs based on L-ascorbic acid and bases

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Abstract 5,6-*O*-isopropylidene-2,3-di-*O*-methyl ascorbic acid (**2**), obtained by reaction of acetone with ascorbic acid (**1**) followed by methylation with methyl iodide, on 1,8-Diazabicyclo[5.4.0]undec-7-ene-catalyzed elimination of acetone moiety led to the formation of respective 2,3-di-*O*-methyl didehydro-L-ascorbic acid (**4**) in good yield. The latter, on methanesulfonylation with methanesulfonyl chloride and subsequent reaction of the crude methanesulfonyloxy derivative with imidazole, benzimidazole, and adenine resulted in the corresponding tetronolactonyl nucleoside analogs **5**, **6,** and **7**. Compound **5** on reaction with benzyl amine led to the *N*-benzylated teramyl nucleoside analog, while compounds **6** and **7** did not react under similar conditions. All the synthesized compounds were evaluated for their antitubercular activity against *M. tuberculosis* $H_{37}R_a$ and $H_{37}R_v$, exhibiting a minimum inhibitory concentration (MIC) of more than12.5 μg/mL.

Keywords Ascorbic acid · Vitamin C · Nucleosides · Adenine · Tetramic acid

Introduction

Ascorbic acid, commonly known as vitamin C, has served as an excellent scaffold for the synthesis of many biologically active compounds (Cinatl *et al*., 1995; Bram *et al*. 1980; Grdisa *et al*., 1995). Its antioxidant activity and the immunomodulatory activities of many of its *O*-alkyl derivatives have been studied extensively (Olabisi and Wimalasena, 2004). Ascorbic acid is basically a tetranolactone and the two enols at the 2- and 3- positions play a crucial role both in organic synthesis and in eliciting the

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biological response. Replacement of the ring oxygen atom with sulfur in the tetranolactone results in thionotetranolactone, a pharmacophore in compounds exhibiting antimalarial and antitubercular activities via Fatty acid synthetase-II inhibition. One of such compounds possessing the thiotetranolactone moiety, thiolactomycin, is under preclinical development as a new antitubercular drug (Miyakawa *et al*., 1982; Kremer *et al*., 2000). However, replacement of the ring oxygen with nitrogen atom results in tetramates, another moiety found in a variety of antibiotics (Royles, 1995; Ley *et al*., 1992; Wang *et al*., 2003; Elbe *et al*., 1956) and anti-HIV (Roggoet *et al*., 1994), anticancer, and antitumor agents (Holtzel *et al*., 2000; Iwata *et al*., 2005). Very recently a few reports have come to light where ascorbic-based nucleosides were prepared as antiviral and antitumor agents (Malic *et al*., 2000). Nucleoside analogs themselves are known for their diverse range of biological activities (Mishra *et al*., 2005). Ascorbic acid has also been used in the synthesis of pyrano[3,4-b]indoles and a variety of other heterocycles by Preobrzhenskaya and co-workers (Larvrenov *et al*., 2005; Preobrzhenskaya and Korolev 2000).

In our continuing program aimed towards the development of new antitubercular agents we were curious to synthesize certain teramic-acid-based nucleosides and investigate their antitubercular activity. Our curiosity arose due to the fact that many purines, nucleoside analogs, and thiolactomycins have displayed significant antitubercular activity (Miyakawa *et al*., 1982; Kremer *et al*., 2000; Somu, 2006). Thus herein we describe the methodology to synthesize tetranolactonyl and tetramyl nucleoside analogs. The synthesized compounds were evaluated for their antitubercular activities.

Results and discussion

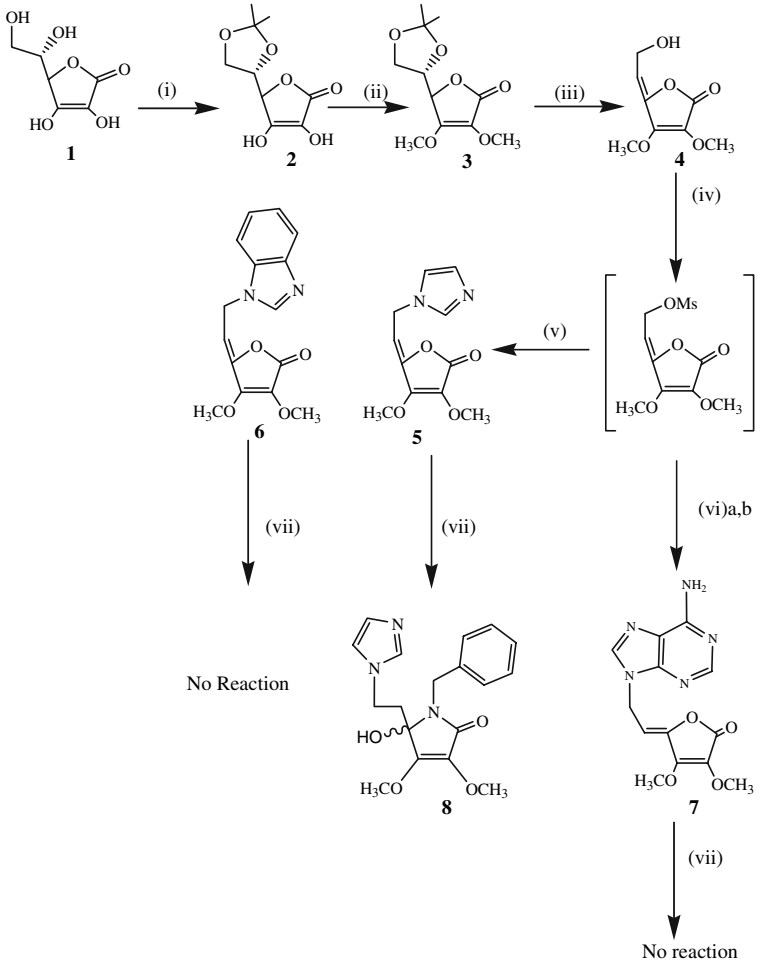
The synthetic strategy involves the reaction of ascorbic acid (**1**) with acetone in the presence of a catalytic amount of acetyl chloride, leading to selective protection of the 5,6-diol to give 5,6-*O*-isopropylidene-L-ascorbic acid (**2**) in quantitative yield. This compound (**2**) was methylated with methyl iodide in dimethyl sulfoxide (DMSO)/acetone (1:4) as the solvent in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB) to give 2,3-*O-bis*-methyl-5,6-O-isopropylidene ascorbic acid (**3**) (Khan and Adams, 1999). The latter was reacted with DBU (50 mol%) using Tetrahydrofuran as the solvent, leading to the elimination of a molecule of acetone to give 3,4-*bis*-methyl-5-(2-hydroxyethylidene)-5*H*-furan-2-one (**4**) (Singh *et al*., 2006). Compound **4** was treated with methanesulfonyl chloride in dry CH_2Cl_2 in the presence of a catalytic compound of triethylamine, resulting in the intermediate methanesulfonyloxy derivative (**5**), which was used as such in the subsequent steps of the desired synthesis.

The intermediate methanesulfonyloxy derivative (**4**) was reacted with imidazole and a catalytic amount of DBU (25 mol%) in dry toluene at 120°C to give (*Z*)-5-[2-(imidazol-1-yl)ethylidene]-3,4-dimethoxy-5H-furan-2-one (**5**) at 65.7% yield.

A similar reaction of compound **5** with benzimidazole gave the corresponding (*Z*)-5-[2-(benzimidazol-1-yl) ethylidene]-3,4-dimethoxy-5H-furan-2-one (**6**) in good yield.

To prepare the adenine derivative of thiotetranolactone, the adenine was persilylated by refluxing it with 1,1,1,3,3,3-Hexamethyldisilazane in anhydrous toluene in the presence of a catalytic amount of $(NH_4)_2SO_4$ under a nitrogen atmosphere for 3–4h. The silyated adenine thus obtained was reacted with methanesulfonyloxy tetranolactone derivative **5** as above using DBU (25 mol%) in refluxing toluene to give (*Z*)-5-[2-(adenin-9-yl) ethylidene]-3,4-dimethoxy-5H-furan-2-one (**7**) at 10% yield (Scheme 1).

The reaction of the imidazolyl tetranolactone **6** with benzyl amine in ethanol gave the corresponding tetramate, 1-benzyl-5-hydroxy-5-(2-imidazol-1-yl-ethyl)-3,4-dimethoxy-1,5-dihydro-pyrrol-2-one (**8**) at very good yield. Similar reactions of



Scheme 1 (i)Acetone, Acetylchloride,30°C, 4 h (ii) MeI, TBAB, DMSO:Acetone (1:4), K2CO3, 30°C, 18h (iii) THF , DBU, 30°C, 7 h (iv) Methanesulphonyl chloride, CH2Cl2, Et3N, 0–30°C, 5h (v) imidazole or benzimidazole,Toluene, DBU, 120°C, 3–6 h.(vi) *a*. adenine, HMDS, (NH4)2SO4, reflux, 3h; *b*. DBU, 120°C, 3–4h (vii) Ethanol, benzyl amine 3–4 h

compounds **6** and **7** did not afford the desired tetramates. The possible reason for the inertness of (*Z*)-5-[2-(benzimidazol-1-yl)ethylidene]-3,4-dimethoxy-5H-furan-2-one (**6**) and (*Z*)-5-[2-(adenin-9-yl)ethylidene]-3,4-dimethoxy-5H-furan-2-one (**7**) towards benzyl amine may be due the steric hindrance offered during reaction by the bulky benzimidazole and adenine moieties. Thus among the compounds **5**, **6,** and **7** described above only (*Z*)-5-[2-(imidazol-1-yl)ethylidene]-3,4-dimethoxy-5H-furan-2-one (**5**) undergoes a ring-opening reaction with the benzyl amine to give the enol-keto-amide, leading to compound **8**. The structures of all the products synthesized were established on the basis of their spectroscopic data and analysis (see the Experimental Section).

Biological activity

The ascorbic-acid-based nucleosides **5**, **6**, **7,** and **8** were evaluated for their antitubercular activity against *M. Tuberculosis* $H_{37}R_a$ by Micro alamar blue essay technique (Collins and Franzblan, 1997); while the agar microdilution method (Saito *et al*., 1991) was used against $H_{37}R_v$. As evident from Table 1 none of the compounds showed significant activity against *M. tuberculosis* $H_{37}R_A$ and the virulent $H_{37}R_A$ strains since the MIC values for them are greater than 25 μg/mL as compared to the standard drug Isoniazid. One of the possible reasons for their inactivity against mycobacterium may be their transport or instability in the cellular medium.

In summary, we have developed a simple method for the synthesis of tetranolctonyl nucleosides which can be manipulated to tetramyl nucleoside analogs. The compounds have been screened against *M. tuberculosis* and exhibited MIC values above 25 μg/mL.

Experimental section

5,6-*O*-isopropylidene-L-ascorbic acid (**2**)

To a magnetically stirred solution of ascorbic acid (30 g, 170.4 mmol) in acetone (120 mL), acetyl chloride (3 ml, 42.6 mmol) was added and the reaction mixture stirred for 2–3 h at ambient temperature. The reaction mixture was kept for 7–8 h in

Table 1 Antimycobacterial activity of synthesized compounds **5–8**

Sample number	Compound	$H_{37}R_a$ MIC (μgmL^{-1})	$H_{37}Rv$ MIC (μgmL^{-1})
1	5	>12.5	>25
2	6	>12.5	>25
3	7	>12.5	>25
4	8	>12.5	>25
INH	–	–	0.65

MIC = minimum inhibitory concentration

freezer, the solid separated was filtered and washed with cold acetone and was dried to give compound **2** as colorless granules (27 g, 73.7%), m.p. 195–198°C. lit m.p.

2,3-Dimethoxy-5, 6-*O*-isopropylidene-L-ascorbic acid (**3**)

A mixture of compound **2** (25 g, 115.7 mmol) and anhydrous K_2CO_3 (32 g, 231.4 mmol) in acetone:dimethyl sulfoxide (4:1, 250 mL) was magnetically stirred for 25 min. A solution of methyl iodide (14.9 mL, 231.4 mmol) was dissolved slowly in acetone (30 mL) for 30 min, followed by the addition of tetrabutylammonium bromide (2.0 g) and stirring overnight at ambient temperature. The result was filtered and the filtrate thus obtained was evaporated under reduced pressure to give the crude mass, which was dissolved in ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford a crude solid, which was chromatographed over silica gel (230–400 mesh) using a gradient of hexane-EtOAc (17:3) as eluent to give the compound **3** as a colorless solid (22 g, 78%).

(*Z*)-3,4-Dimethoxy-5-(2-hydroxyethylidene)-5*H*-furan-2-one (**4**)

To a magnetically stirred solution of compound **3** (20 g, 81.96 mmol) in THF (80 mL), DBU (6.2 mL, 50 mol%) was added slowly and the reaction mixture was stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was dissolved in ethyl acetate (100 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude mass, which was chromatographed over silica gel (230–400 mesh) using hexane:ethyl acetate (9:1) as eluent to give the above compound **4** as a colorless solid (10 g, 65.7%), m.p. 60°C, infrared(IR) (neat) 3391, 1688 cm^{-1}, MS (FAB) 187$(M + H)^+$ ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.39 (bs, 1H), 3.92 (s, 3H, OCH_3), 4.16 (s, 3H, -OCH_3), 4.41 (d, J = 7.0, 2H, OCH_2), 5.50 (t, J = 7.0 Hz, 1H, = CH−); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.6, 59.9, 60.6, 108.1, 125.0, 142.3, 149.1, 164.7.

Preparation of the intermediate 5-(2-methanesulfonyloxy ethylidene)-3,4-dimethoxy-5H-furan-2-one

To a stirring solution of compound **4** (2 g, 10.65 mmol) and triethylamine (1 mL) in anhydrous dichloromethane (10 mL) a solution of methanesulfonyl chloride (1.11 mL, 10.65 mmol) in CH_2Cl_2 (2 ml) was added slowly at 0°C during 5 min. The reaction mixture was brought to 30°C and stirring continued for a further hour. The solvent was evaporated under reduced pressure and the residue thus obtained was dissolved in ethyl acetate (100 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude mass of the title compound, which was used as such in the subsequent reactions.

(*Z*)-5-[2-(Imidazol-1-yl)ethylidene]-3, 4-dimethoxy-5*H*-furan-2-one (5)

A mixture of the above crude methanesulfonyloxy derivative (1 g, 3.78 mmol) imidazole (0.257 g, 3.78 mmol) and DBU (0.285 mL, 25 mol%) in anhydrous toluene was stirred at 120°C for 5 h. The solvent was evaporated under reduced pressure and the residue thus obtained was dissolved in ethyl acetate (100 mL) and washed with water (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude mass, which was chromatographed over silica gel (230–400 mesh) using a gradient of hexane:ethylacetate (3:2) as eluent to give the above compound **6** as a light yellow foam (1 g, 65.7%), as foam IR (KBr) υ_{max} 3210, 1775 ; FABMS 237(M + H)$^+$; ^{1}H NMR (200Mz, $CDCl_3$) δ 3.95 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 4.81 (d, J = 7.4 Hz, 2H, CH_2), 5.73 (t, J = 7.4 Hz, 1H, = CH), 6.93, 7.07 (2s, 2H, imidazole CH), 7.51 (s, 1H, imidazolyl CH); analysis calculated for $C_{11}H_{12}N_2O_4$ C, 55.92; H, 5.12, N, 11.85; found: C, 55.87; H, 5.08; N, 11.93.

(*Z*)-5-[2-(Adenin-9-yl)ethylidene]-3,4-dimethoxy-5*H*-furan-2-one (**7**)

Adenine (1.5 g, 11.1 mmol) was refluxed in anhydrous toluene with HMDS in the presence of a catalytic amount of $(NH_4)_2SO_4$ under an N_2 atmosphere for 3–4 h and the excess reagent and solvent were removed under reduced pressure to give the silylated adenine derivative. A mixture of this silylated adenine derivative, the above intermediate methanesulfonyloxy derivative (1 g, 3.78 mmol), and DBU (0.285 mL, 50 mol%) in anhydrous toluene (5 mL) was stirred at 120°C for 5 h. The solvent evaporated, and the residue thus obtained was dissolved in chloroform and washed with water and the organic layer dried (Na_2SO_4) and solvent-evaporated under reduced pressure to afford a crude mass. The latter was chromatographed over an SiO_2 column using CH_2Cl_2:MeOH (9:1) as eluent to give the title compound **7** as colorless granules (0.32 g) at 10% yield: m.p. 138–140°C; IR (KBr) υ_{max} 3210, 1775 ; FABMS 304(M + H)$^+$; ^{1}H NMR (200Mz, DMSO) δ 3.82 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 5.15 (d, J = 7.0 Hz, 2H, CH_2), 5.73 (t, J = 7.0 Hz, 1H, = CH), 7.76 (s, 1H, CH), 7.95 (br, 2H, NH_2), 8.14 (s, 1H, CH); analysis calculated for $C_{13}H_{13}N_5O_4$ C, 51.48; H, 4.29, N, 23.10; found: C, 51.40; H, 4.32; N, 23.18.

1-Benzyl-5-hydroxy-5-(2-imidazol-1-yl-ethyl)-3,4-dimethoxy-1,5-dihydro-pyrrol-one (**8**)

A solution of compound **5** (0.2 g, 0.847 mmol) and benzylamine (0.09 mL 0.847 mmol) in ethanol (1 mL) was stirred at 40°C for 5 h. The solvent was evaporated to a crude product which was chromatographed over silica gel (230–400 mesh) using a gradient of hexane:ethylacetate (3:2) as eluent to give compound **8** as a light yellow foam. Yield (174 mg, 60 %); IR (KBr) υ_{max} 3210, 1775 cm^{-1}; FABMS 343(M + H)$^+$; ^{1}H NMR (200Mz, $CDCl_3$) δ 2.00– 2.24 (m, 2H, H-6), 3.22– 3.40 (m, 2H, H-7), 3.85 (s, 3H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.21 (d, J = 15.2 Hz, 1 H,

NCH_{2A}), 4.90 (d, J = 15.2 Hz, 1 H, NCH_{2B}), 6.30 (s, 1H, imidazole H), 6.85 (m, 2H, imidazole CH), 7.33–7.43 (m, 5H, Ar-H); analysis calculated for $C_{18}H_{21}N_3O_4$: C, 62.93; H, 6.16, N, 12.24; found: C, 62.90; H, 6.16; N, 12.24.

Antitubercular screening

Activity against *M. tuberculosis* $H_{37}R_a$ strain

All the compounds synthesized were evaluated for their efficacy against *M. tuberculosis* $H_{37}R_a$ at concentrations ranging from 100 μg mL^{-1} to 1.56 μg mL^{-1} using twofold dilutions in the initial screen. Log phase culture of *M. tuberculosis* $H_{37}R_a$ was diluted so as to give a final optical density $(OD)_{550\ nm}$ of 0.05 in Sauton's medium. In 96-well white plates, 190 µl of culture is dispensed in each well. A dimethyl sulfoxide (DMSO) solution of test compounds was dispensed into 96-well plates so as to make the final test concentration 25 μg mL^{-1} (5 µgtest compound dispensed in 10 µl of DMSO). Then the plate was incubated at 37°C in 5% CO_2 for 5 days. On fifth day 15 µl Alamar blue solution was added to the each well of plate. The plate was again incubated overnight at 37 °C in 5% CO_2. The fluorescence was read on a BMG Polar Star with an excitation frequency of 544 nm and emission frequency of 590 nm. The compounds that were found active to be (>90% inhibition compared with control) at this concentration were then tested at six serial dilutions from 50 to 1.56 μg mL^{-1}.

Activity against *M. tuberculosis* $H_{37}R_v$ strain

Drug susceptibility and determination of MIC of the test compounds/drugs against *M. tuberculosis* $H_{37}R_v$ was performed by the agar microdilution method where twofold dilutions of each test compound added to 7H10 agar supplemented with oleic acid-albumin-dextrosecatalase and organism. A culture of *M. tuberculosis* $H_{37}R_v$ growing on Lowenstein Jensen medium was harvested in 0.85% saline with 0.05% Tween-80. A 1 μg mL^{-1} concentration suspension of the extracts/compounds was prepared in DMSO. This suspension was added to (in tubes) 7H10 middle Brook's medium (containing 1.7 ml medium and 0.2 ml OADC supplement) at different concentrations of compound, keeping the volume constant, i.e., 0.1 mL. The medium was allowed to cool with the tubes in a slanting position. These tubes were then incubated at 37°C for 24 h followed by streaking of *M. tuberculosis* $H_{37}R_v$ (5×10^4 bacilli per tube). These tubes were then incubated at 37°C. Growth of bacilli was observed after 30 days of incubation. Tubes containing the compounds were compared with control tubes in which medium alone was incubated with $H_{37}R_v$. The concentration at which complete inhibition of colonies occurred was taken as the active concentration of test compound.

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