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Synthesis and Characterization of New Schiff Bases Heterocyclic Compounds and Their N-Acyl, Thiourea and Imidazole Derived from D-Erythroascorbic Acid

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Abstract The new Schiff bases derived from D-erythroascorbic acid containing heterocyclic unit were synthesized by condensation of D-erythroascorbic acid with aromatic amine (containing 1,3,4-oxadiazole or 1,3,4-thiadiazole unit) in dry benzene using glacial acetic acid as a catalyst. D-erythroascorbic acid[IV] was synthesized by four steps (Scheme 1), while the primary aromatic amine which is containing 1,3,4-oxadiazole[VII] or 1,3,4-thiadiazole[XII] synthesized by the reaction of 4-methoxybenzoyle- hydrazine[VI] with 4-aminobenzoic acid or by the reaction tuloic acid with thiosemicarbazide, respectively in the presence of $POCl_3$. The new imidazole derivatives were synthesized by three-steps reactions starting with corresponding Schiff bases[VIII] or[XIII]. N-acyl compounds[IX]a,b and[XIV]a,b were synthesized by addition reaction of acid chloride to imine group of Schiff bases in dry benzene. The second step include reaction of thiourea with N-acyl derivatives in Na_2CO_3 medium to yield N-thiourea compounds[X]a,b and[XV]a,b. The third step involves cyclization reaction of N-thiourea derivatives with benzoin in DMF to result new imidazole derivatives[XI]a,b and[XVI]a,b. The structure of the synthesized compounds have been characterized by their melting points, elemental analysis and by their spectral data; FTIR, UV-Vis, mass, ^{1}HNMR, and ^{13}CNMR spectroscopy. All the synthesized compounds have been screened for their antibacterial activities. They exhibited good antibacterial activity against Escherichia coli (G-) and Staphylococus aureus (G+).

Keywords Schiff bases, L-Ascorbic acid, Imidazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole

1. Introduction

D-erythroascorbic acid derivatives shows antitumor and antiviral activities[1,2]. Schiff bases are used as substrates in the preparation of a large of bioactive and industrial compounds via ring closure, cycloaddiation and replacement reactions. In addition, Schiff bases are well known to have biological activities[3-5].

The thioureas have been shown to possess antifungal properties, antimicrobial[6] and potential antiviral agents, [7,8] also these compounds have been widely used in enantioselective synthesis such as in Mannich reaction, Michael addition and so on[9].

Imidazoles like all azoles are five membered ring systems, [10] occurs in purine nucleus and in histidine[11,12]. The imidazoles derivatives have useful applications in such areas as medical fields: anti-histamine drugs, antifungi,[13] antitumor,[14] anti-inflammatory activity and anticonvulsant activity[15].

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To the best of our knowledge that the synthesis of imidazoles derivatives derived from D-erythroscorbic acid are not reported in literature. Thus, we report herein the synthesis, characterization and antibacrial activity of new derivatives of imidazole containing D-erythroscorbic acid

2. Experimental

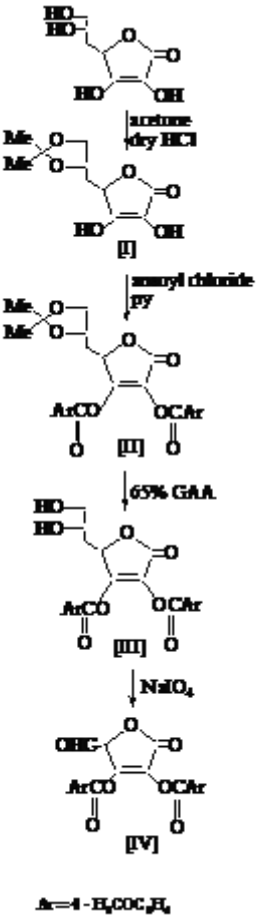
2.1. Materials

All the chemicals were supplied from Aldrich-Sigma Chemicals Co. and used as received. FTIR spectra were recorded using potassium bromide discs on a 8400s Shimadzu spectrophotometer. The ^{1}H NMR spectra were recorded on Bruker AMX-300 spectrometer at 300 MHz, using deutrated chloroform or DMSO as solvent with TMS as an internal standard. Elemental analysis (C,H,N) were carried out using a Perkin-Elmer model 2400 instrument. Uncorrected melting points (uncorrected) were determined by using hot-stage Gallen Kamp melting point apparatus. UV-vis spectra of solutions were performed on CECL 7200 England Spectrophotometer using $CHCl_3$ as a solvent. Mass spectra were recorded on IEOL JMS-7 high resolution instrument. ^{13}C-NMR spectra of the compounds were recorded on a varian Mercury plus 100 MH_Z spectrometer.

2.2. Synthesis Procedures

All compounds were synthesized according to Schemes 1 to 3, and the following procedures. All known compounds gave acceptable elemental analysis, FTIR and NMR spectra that matched data reported in the cited references.

Compounds[I] to[IV] were synthesised following the Scheme 1.



Scheme 1. The synthesis rout for Compounds[I] to[IV]

2.2.1. Preparation of 5,6-O-isopropylidene-L-ascorbic acid[I]

This compound was prepared from the reaction of L-ascorbic acid with Acetone in a acidic media, following Salomon method[16].

2.2.2. Preparation of 2,3-O-dianisoyl-5,6-O-isopropylidene-L- ascorbic acid[II]

To a cold solution of[I] (10 g, 46 mmol) in pyridine (50 mL), anisoyl chloride was added (22.3 g, 129 mmol) with stirring for 2 hrs, then kept in dark place at room temperature for 24 hrs. The mixture was poured into ice-water the oil layer was extracted with (150 mL) chloroform, washed with water and dried over anhydrous magnesium sulfate. Filtered and the solvent evaporated, purified from chloroform: petroleum ether (1:5) to give[II] (76.5%) as a pale yellow solid, m.p (102 -104℃), R_f = 0.80 (benzene/heptanol 5:5).

2.2.3. Preparation of 2,3-O-dianisoyl-L-ascorbic acid[III]

Compound[II] (10 g, 24 mmol) was dissolved in a mixture of (65%) acetic acid (30 mL), absolute methanol (10 mL) and stirred for 48 hrs at room temperature. To the resulting solution a benzene (40mL) was added and evaporated to yield[III],[17] (78%) as a white crystals, m.p (130-132℃), R_f = 0.42 (benzene/ methanol 4:6).

2.2.4. Preparation of pentulosono-lacton-2,3-ene-dianisoate [IV]

To a stirred solution of sodium periodate (5.6 g) in distilled water (60 mL) at (0℃), a solution of[III] (10 g, 26 mmol) in absolute ethanol (60 mL) was added dropwise. After stirring15 min, ethylene glycol (0.5 mL) was added and stirring for one hour. The mixture was extracted with ethyl acetate (3x50 mL)[17]. The extracts dried over anhydrouse $MgSO_4$, filtered and the solvent evaporated, the residue recrystallized from benzene to yield[IV] (45%) as a white crystals, m.p (156-158 ℃), R_f=0.70 (benzene / methanol 6:4).

Compounds[V] to[XI] were synthesised following the Scheme 2.

2.2.5. Preparation of Methyl 4-Methoxybenzoate[V]

This compound was prepared following the procedure described by Vog el[18], m.p.(49-51℃).

2.2.6. Preparation of Methoxy Benzoyl Hydrazine[VI]

This compound was prepared following the procedure described by Smith[19]. m.p.(135-137℃).

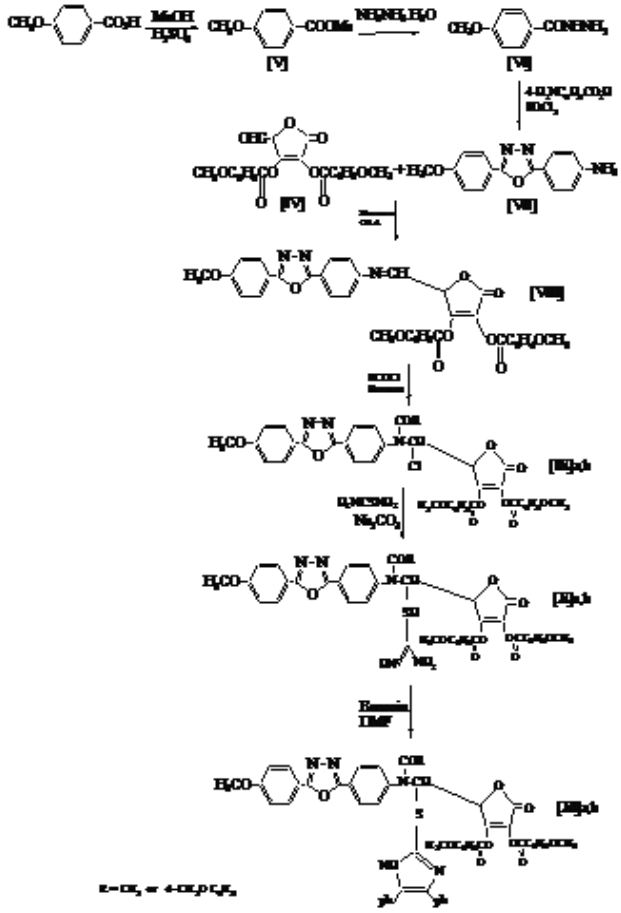
2.2.7. Preparation of 2-(4′-aminophenyl)-5-(4″-methoxy - phenyl) -1,3,4-oxadiazole[VII]

A mixture of 4-methoxybenzoyl hydrazine (10 mmol), 4-aminobenzoic acid (10 mmol) and phosphorus oxy chloride (5 mL) was refluxed for 7 hrs. The cold reaction mixture was poured into ice-water and made basic by adding sodium bicarbonate solution. The formed solid was filtered, dried and purified. Yield: 89%; m.p. = 196 ^{o}C (ethanol);[20]. IR(KBr) ν cm^{-1}: 3350-3200 (NH_2), 2935-2841(C-H), 1610 (C=N), 1245 (sym. C-O-C), 1070 (asym. C-O-C); ^{1}H NMR (TMS) δ ppm: 6.70-8.01 (m, 8 H, ArH), 3.90 (s, 3 H, OCH_3), 1.60-1.75 (s, 2H, NH_2) ^{13}C NMR (CDCl3,75 MHz): δ 162.2 (C- NH_2), 114.5-128.6 (aromatic and olefinic carbons), 101.8 (C-1), 80.0, 79.1, (O-C=N), 55.5 (OCH_3); Anal. Calcd. for $C_{15}H_{13}O_2N_3$ (267): C, 67.42; H, 4.87; N, 15.73. Found: C, 67.89; H, 5.44; N, 15.49.

2.2.8. Preparation of Schiff bases[VIII]

A mixture of new primary amine compounds[VII] (10 mmol), aldehyde[IV] (10 mmol), dry benzene (15 mL) and 2 drops of glacial acetic acid was refluxed for 6hrs. The

solvent was evaporated under vacuum and the residue crystallized from chloroform.



Scheme 2. The synthesis rout for Compounds[V] to[XI]

2.2.9. Compound[VIII]

Yield: 75%; m.p. = 178-180 °C (chloroform); IR(KBr) ν cm^{-1}: 1635 (C=N), 1685 (C=C), 1770 (C=O); ^{1}H NMR (TMS) δ ppm: 10.3 (s, 1H, CH=N), 7.10-8.20 (m, 16 H, ArH), 3.85 (s, 9 H, OCH_3), 3.99 (s, 1H, lacton); Anal. Calcd. for $C_{36}H_{27}O_{10}N_3$ (661): C, 65.36; H, 4.08; N, 6.35. Found: C, 65.18; H, 4.28; N, 6.45.

2.2.10. Preparation of N-(acetyl or anisoyl) Derivatives[IX] a,b

To a stirred solution of Schiff bases[VIII] (10 mmol) in 10 mL dry benzene was added dropwise acetyl or anisoyl chloride (12 mmol) after cooling , the reaction mixture was refluxed for 1 hour. The solvent was evaporated and the residue was washed with water for many times and recrystallized from petroleum ether.

2.2.11. Compound[IX]$_a$

Yield: 60%; m.p. = 122-124 °C (petroleum ether); IR(KBr) ν cm^{-1}: 2939-2843 (C-H), 1767(C=O lactone), 1687(C=C), 1708 (C=O amide), 748 (C-Cl); ^{1}H NMR (TMS) δ ppm: 7.30 (s, 1H, CH=N), 7.00-8.04 (m, 16 H, ArH), 3.85 (s, 9 H, OCH_3), 2.88 (s, 3 H, CH_3), 3.98 (s, 1H, lacton); Anal. Calcd. for $C_{38}H_{30}O_{11}N_3Cl$ (739.5): C, 61.66; H, 4.06; N, 5.68. Found: C, 61.53; H, 4.31; N, 5.79.

2.2.12. Compound[IX]$_b$

Yield: 65%; m.p. = 146-148℃ (petroleum ether); IR(KBr) ν cm^{-1}: 2935-2839 (C-H), 1771(C=O lactone), 1686(C=C), 1700(C=O amide), 767 (C-Cl); Anal. Calcd. for $C_{44}H_{34}O_{12}N_3Cl$ (831.5): C, 63.50; H, 4.09; N, 5.05. Found: C, 63.37; H, 4.28; N, 5.19.

2.2.13. Preparation of N-(acetyl or anisoyl)Thioureas Derivatives[X]a,b

A mixture of compound[IX]$_{a,b}$ (10 mmol), thiourea (10 mmol), anhydrous sodium carbonate (10 mmol), 20 mL analar acetone was refluxed for 4 hrs with stirring. The reaction mixture was cooled and poured into ice water. The product was filtered off and recrystalized from ethyl acetate to give colored compounds[X]a,b.

2.2.14. Compound[X]$_a$

Yield: 60%; m.p. = 240-242 °C (petroleum ether); IR(KBr) ν cm^{-1}: 3393-3200 (NH_2), 1700 (C=C), 1630 (C=N), 840 (C-S); ^{1}H NMR (TMS) δ ppm: 7.88 (s, 1H, NH), 6.95-7.08 (m, 12 H, ArH), 3.44-3.49 (s, 2 H, NH_2), 3.79 (s, 6 H, OCH_3), 2.07 (s, 3 H, CH_3), 2.72 (s, 3 H, $COCH_3$), 3.88 (s, 1H, lacton); Anal. Calcd. for $C_{39}H_{33}O_{11}N_5S$ (779): C, 60.08; H, 4.24; N, 8.99. Found: C, 59.89; H, 4.23; N, 8.74.

2.2.15. Compound[X]$_b$

Yield: 45%; m.p.=213-215℃ (petroleum ether); IR(KBr) ν cm^{-1}: 3375-3232(NH_2), 2924-2850 (C-H), 1721(C=C), 1640(C=N), 841 (C-S); Anal. Calcd. for $C_{45}H_{37}O_{12}N_5S$ (871): C, 62.00; H, 4.25; N, 8.04. Found: C, 61.98; H, 4.21, N, 8.17.

2.2.16. Preparation of Diphenylimidazoles Derivatives[XI] a,b

To a stirred solution of compound[X] (10 mmol) in dry DMF (10 mL), the benzoin (10 mmol) was added. The reaction mixture was refluxed for 5 hrs. After cooling, drops of water were added with stirring until a precipitate separated out. The precipitate was filtered, dried and recrystalized from petroleum ether.

2.2.17. Compound[XI]$_a$

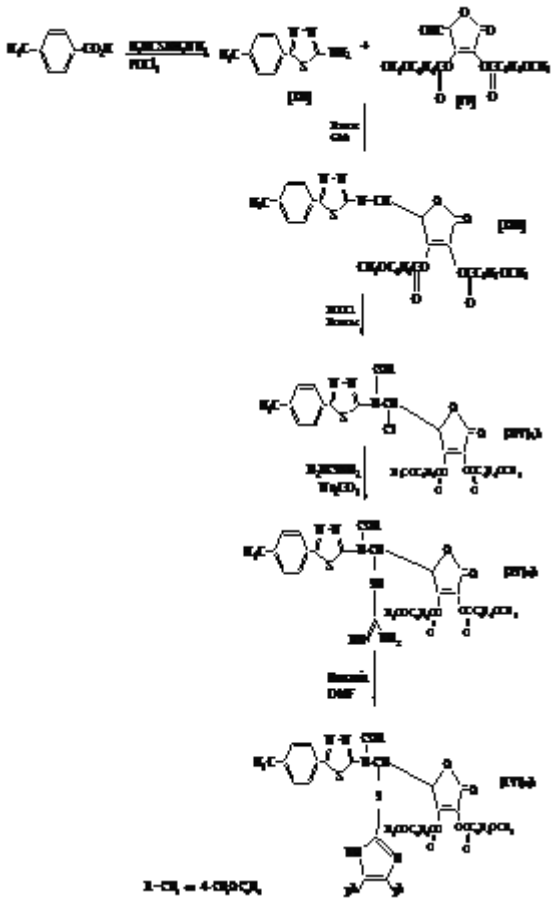
Yield: 50%; m.p. = 112-114 °C (petroleum ether); IR(KBr) ν cm^{-1}: 3280(NH_2),, 2926-2854(C-H), 1685(C=C), 1591(C=N), 875 (C-S); Anal. Calcd. for $C_{53}H_{41}O_{11}N_5S$ (855): C, 74.39; H, 4.80; N, 8.19. Found: C, 74.53; H, 4.71; N, 8.29.

2.2.18. Compound[XI]$_b$

Yield: 40%; m.p. = 120 °C (petroleum ether); IR(KBr) ν cm^{-1}: 3236(NH_2), 2924-2846(C-H), 1685(C=C), 1597(C=N), 841 (C-S); ^{1}H NMR (TMS) δ ppm: 8.06 (s, 1H, NH), 7.07-7.20 (m, 10 H, ph), 7.66-7.93 (s, 20 H, ArH), 3.86 (s, 12 H, OCH_3), 3.74 (s, 1 H, C_4 lacton), 7.35 (s, 1 H, C_5 lacton),

3.88 (s, 1H, lacton); Anal. Calcd. for $C_{59}H_{45}O_{12}N_5S$ (1047): C, 67.62; H, 4.30; N, 6.69. Found: C, 67.77; H, 4.17; N, 6.79.

Compounds[XII] to[XVI] were synthesised following the Scheme 3.



Scheme 3. The synthesis rout for Compounds[XII] to[XVI]

2.2.19. preparation of 2-amino-5-(4`-tolyl)-1,3,4-thiadiazole[XII]

A mixture of tuloic acid (10 mmol), thiosemicarbazide (10 mmol), and phosphorus oxy chloride (5 mL) was refluxed gently for 6 hrs. After cooling, ice water (50 mL) was added in portions with stirring. The yellow precipitate was filtered, washed with water , dried and crystallized from ethanol yield(68%), m.p.(246-248℃)[21].

2.2.20. Preparation of Schiff bases [XIII]

A mixture of new primary amine compounds[VIII] (10 mmol), aldehyde[IV] (10 mmol), dry benzene (15 mL) and 2 drops of glacial acetic acid was refluxed for 6hrs. The solvent was evaporated under vacuum and the residue crystallized from chloroform.

2.2.21. Compound[XIII]

Yield: 60%; m.p. = 162-164 ^oC (chloroform); IR(KBr) ν cm^{-1}: 1636(C=N), 1685 (C=C), 1771(C=O); ^1H NMR (TMS) δ ppm: 8.9 (s, 1H, CH=N), 6.99-7.90 (m, 12 H, ArH), 3.81 (s, 6 H, OCH_3), 2.35 (s, 3 H, CH_3), 3.98 (s, 1H, lacton); Anal. Calcd. for $C_{30}H_{23}O_8N_3S$ (585): C, 61.45; H, 3.93; N, 7.18. Found: C, 61.44; H, 4.13; N, 7.91.

2.2.22. Preparation of N-(acetyl or Anisoyl) Derivatives [XIV] a, b

To a stirred solution of Schiff bases[XIII] (10 mmol) in 10 mL dry benzene was added dropwise acetyl or anisoyl chloride (12 mmol) after cooling , the reaction mixture was refluxed for 1 hour. The solvent was evaporated and the residue was washed with water for many times and recrystallized from petroleum ether.

2.2.23. Compound[XIV]a

Yield: 65%; m.p. = 146-148 ^oC (petroleum ether); IR(KBr) ν cm^{-1}: 2900-2843(C-H), 177(C=O lactone)0, 1685(C=C), 1708(C=O amide), 1685(C=C), 772 (C-Cl); Anal. Calcd. for $C_{32}H_{26}O_9N_3SCl$ (663.5): C, 57.87; H, 3.92; N, 6.33. Found: C, 57.73; H, 4.10; N, 6.45.

2.2.24. Compound[XIV]$_b$

Yield: 50%; m.p. = 179-180℃ (petroleum ether); IR(KBr) ν cm^{-1}: 2925-2850(C-H), 1775(C=O lactone), 1685(C=C), 1720(C=O amide), 1687(C=C), 772 (C-Cl); Anal. Calcd. for $C_{38}H_{30}O_{10}N_3SCl$ (655.5): C, 69.57; H, 4.58; N, 6.41. Found: C, 69.43; H, 4.54; N, 6.27 .

2.2.25. Preparation of N-(acetyl or anisoyl)Thioureas Derivatives[XV] a,b

A mixture of compound[XIV]a,b (10 mmol), thiourea (10 mmol), anhydrous sodium carbonate (10 mmol), 20 mL analar acetone was refluxed for 4 hrs with stirring. The reaction mixture was cooled and poured into ice water. The product was filtered off and recrystalized from ethyl acetate to give colored compounds[XV].

2.2.26. Compound[XV]a

Yield: 45%; m.p. = 213-215℃ (petroleum ether); IR(KBr) ν cm^{-1}: 3421-3160(NH_2), 2918-2856(C-H), 1730(C=C), 1610(C=N), 1560, 823 (C-S); Anal. Calcd. for $C_{33}H_{29}O_9N_5S_2$ (703): C, 56.33; H, 4.13; N, 9.96. Found: C, 56.19; H, 4.01, N, 10.09.

2.2.27. Compound[XV]b

Yield: 45%; m.p. = 198-200℃ (petroleum ether); IR(KBr) ν cm^{-1}: 3305-3109(NH_2), 2924-2850(C-H), 1693(C=C), 1577(C=N), 817 (C-S); Anal. Calcd. for $C_{39}H_{33}O_{10}N_5S_2$ (795): C, 58.87; H, 4.15; N, 8.81. Found: C, 58.77; H, 4.09, N, 8.41.

2.2.28. Preparation of Diphenylimidazoles Derivatives[XVI] a,b

To a stirred solution of compound[XV] (10 mmol) in dry DMF (10 mL), the benzoin (10 mmol) was added. The reaction mixture was refluxed for 5 hrs. After cooling, drops of water were added with stirring until a precipitate separated out. The precipitate was filtered, dried and recrystallized from petroleum ether.

2.2.29. Compound[XVI]a

Yield: 50%; m.p. = 90℃ (petroleum ether); IR(KBr) ν cm^{-1}: 3317(NH_2), 2924-2852(C-H), 1678(C=C), 1595(C=N), 875 (C-S); Anal. Calcd. for $C_{47}H_{37}O_9N_5S_2$ (879): C, 64.16; H, 4.21; N, 7.96. Found: C, 64.24; H, 4.19; N, 8.09.

2.2.30. Compound[XVI]$_b$

Yield: 50%; m.p. =130-132℃ (petroleum ether); IR(KBr) ν cm^{-1}: 3228(NH_2), 2926-2848(C-H), 1680(C=C), 1590(C=N), 840 (C-S); Anal. Calcd. for $C_{53}H_{41}O_{11}N_5S$ (855): C, 74.39; H, 4.80; N, 8.19. Found: C, 74.53; H, 4.71; N, 8.29.

3. Results and Discussion

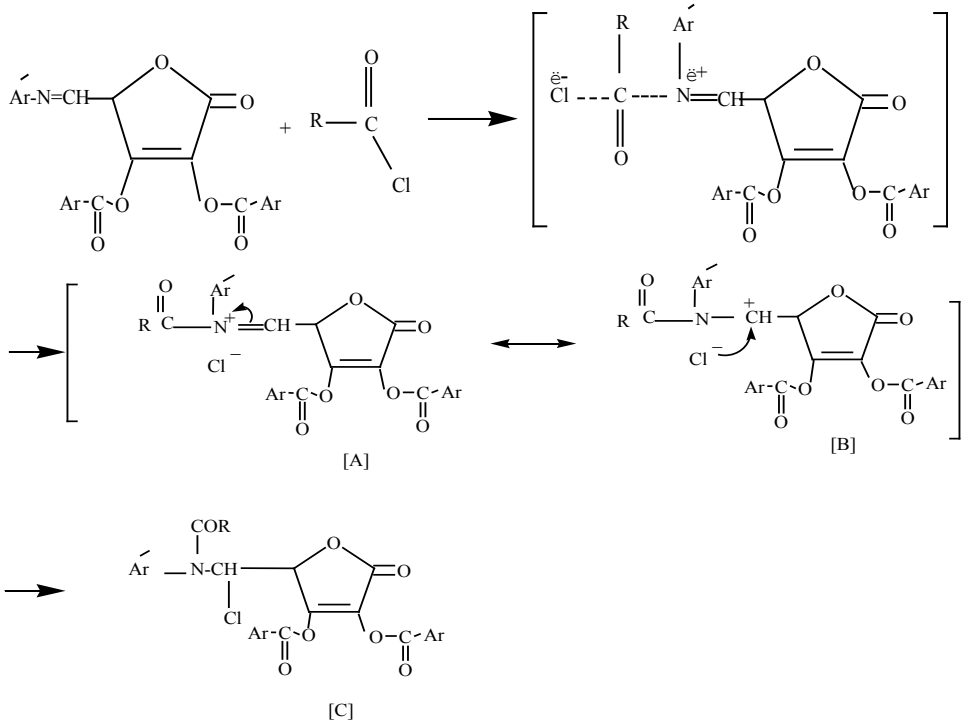
5,6-O-isopropylidene-L-ascorbic acid[I] was prepared by the reaction of L-ascorbic acid with acetone in dry HCl[16]. Compound[I] reacts with excess of anisoyl chloride in dry pyridine to give the corresponding ester[II].

Glycols[III] oxidized by periodate, which is cleaves the C_5-C_6 bond (bearing OH groups) and formation the aldehyde compound D-erythroascorbic acid[IV][22-24]. Methyl-4 -methoxy benzoate[V] was obtained by esterification of 4-methoxy benzoic acid (anisic acid) with methanol[25]. The reaction of 4-methoxybenzoate with hydrazine hydrate in ethanol under reflux give 4-methoxybenzoyl hydrazine[VI] in good yield. Condensation of acid hydrazid with 4-aminobenzoic acid in the presence of dehydrating agent phosphorus oxychloride yielded the oxadiazole derivative [VII].

The reaction of tuloic acid with thiosemicarbazide in the presence of phosphorous oxychloride under reflux for 8 hrs leads to formation 2-amino-5-(4′-tolyl)-1,3,4-thiodiazole [VIII].

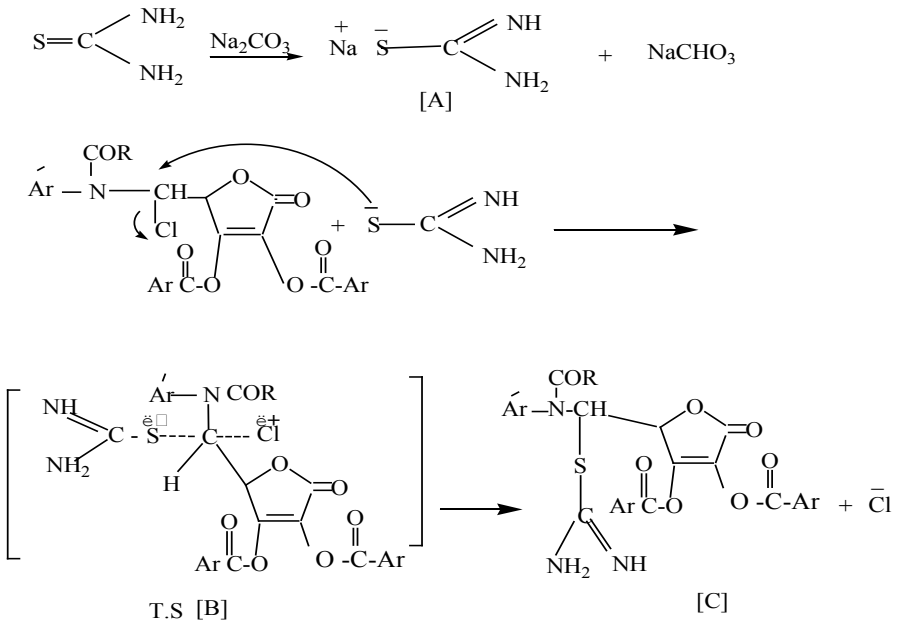
The novel Schiff bases[VIII] and[XIII] were synthesized by refluxing equemolare of D-erythroascorbic acid[VI] with amino compounds[VII] or[XII] in dry benzene with some drops of glacial acetic acid.

Compounds[IX] or[XIV] were synthesized by refluxing acetyl or anisoyl chloride with Schiff bases[XIII] or[XIII] in dry benzene. The reaction is initiated by attack of the azomethine nitrogen at the carbonyl group of acid chloride (acetyl or anisoyl chloride)[26], displacing the chlorine as a chloride anion and forming the iminium cation[A] which can be represented by structure[B] too. In both structure[A] and[B] the positively charged on nitrogen in[A] and the positively charged on carbon in[B] are linked to strong electron withdrawing groups and are unlikely to form, therefore, N-acyl derivatives are best represented by the covalent structure[C] (Scheme 4).



Scheme 4. Mechanism for the synthesis of compounds[IX] or[XIV]

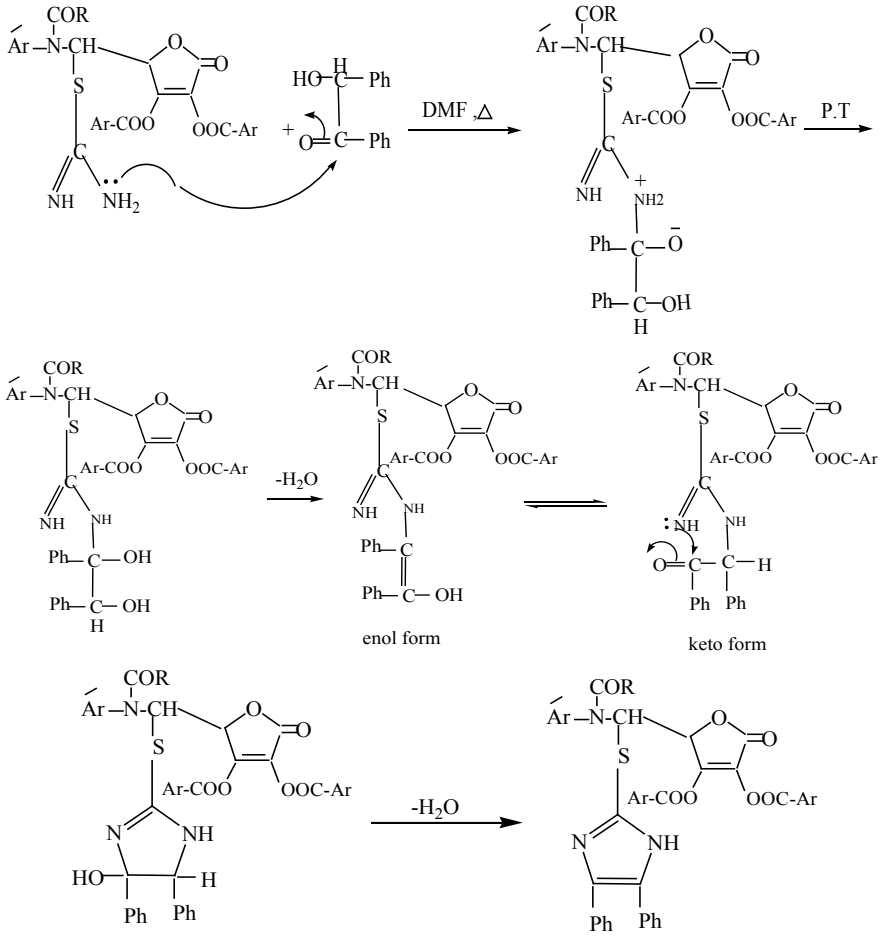
A mixture of compound[IX] or[XIV], thiourea, anhydrous sodium carbonate in acetone was refluxed for 4 hrs with stirring to yield thiourea derivatives[X] or[XV]. The mechanism may be proposed for this reaction as indicated in Scheme 5[26]:



Scheme 5. Mechanism for the synthesis of compounds[X] or[XV]

The reaction in basic medium is converted the thiourea into the sodium salt of thiourea[A], which is attacks the carbon of C-Cl group in an SN^2 like mechanism as in T.S[B] with displacement of Cl^- to yield thiourea derivatives[C].

The novel imidazole derivatives[XI] or[XVI] were synthesized by refluxing compounds[XII]$_{a-d}$ with benzoin in DMF for 5 hrs. The following mechanism is proposed[26] for this reaction (Scheme 6):



Scheme 6. Mechanism for the synthesis of compounds[XI] or[XVI]

3.1. Biological Activity

The antibacterial activity of the synthesized compounds was performed according to the agar diffusion method[27]. The synthesized compounds were tested against E.coli and Staph. aureus. Each compound was dissolved in DMSO to give concentration 1ppm. The plates were then incubated at 37℃ and examined after 24 hrs. The zones of inhibition formed were measured in millimeter and are represented by (-), (+), (+ +) and (+ + +) depending upon the diameter and clarity as in Table 1. All the compounds exhibit the highest or low biological activity against both the organisms. Compounds showed good inhibition against of the two types of the bacteria, this could be related to the presence of the D-erythroascorbic acid, imine linkage or imidazole ring.

Table 1. Antibacterial activity of the synthesized compounds[IV]-[XVI]

Comp. No.	E Coli(G-)	Staph. aurus(G+)	Comp. No.	E. Coli(G-)	Staph. aurus(G+)
[IV]	+ +[a]	+ +	[XI]a	+ + +	+ + +
[V]	+ + +	+ + +	[XI]b	+	+
[VI]	+ + +	+ + +	[XII]	+	+
[VII]	+	+ + +	[XIII]	+	+
[VIII]	+	+	$[XIV]_a$	+	+
$[IX]_a$	+ +	+ +	[XIV]b	+	+
$[IX]_b$	+	+ +	[XV]a	+	+
[X]a	+	+	[XV]b	+	+
[X]b	+	+	[XVI]a	+ + +	+ + +

[a]Key to symbols: highly active = + + + (mor than)15 mm, moderately active = + + (11-15) mm and slightly active = + (5-10) mm

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