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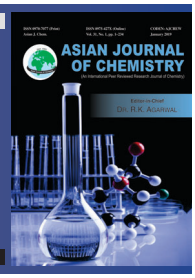

Synthesis and Antimicrobial Evaluation of New Pyrrolo-isoxazolidine Derivatives

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In the present study, pyrrolo-isoxazolidines **3(a-l)** and **4(a-e), 4g, 4i, 4j** have been synthesized by using the 1,3-dipolar cycloaddition reactions of nitrones **1(a-l)** with ester substituted N-aryl maleimide (**2b**). These heterocycles have been obtained in *cis* and *trans* diastereomeric forms. The structures of newly synthesized heterocycles have been confirmed from their spectroscopic parameters such as IR, ^{1}H NMR, ^{13}C NMR and ESI-MS. The *in vitro* antimicrobial evaluation of these compounds were also investigated. Most of the prepared heterocycles showed significant antimicrobial properties. C_3-phenyl substituted products exhibited the remarkable antibacterial behaviours while C_3-thienyl/furyl substituted heterocycles proved themselves potent antifungal agents.

Keywords: Nitrones, N-Aryl-maleimide, Cycloaddition, Pyrrolo-isoxazolidines, Antimicrobial activities.

INTRODUCTION

The studies of cycloaddition reactions are concerned with crucial group of organic processes, which are associated with immense synthetic applications. These protocols take place by the involvement of cyclic transition state and proceed through the concerted mechanism [1]. The [3+2]-cycloaddition reactions are one of the very important tools for the formation of five membered heterocycles [2]. Nitrones and azomethine ylides are the useful 1,3-dipoles as they lead to the generation of numerous hetrocycles by reacting with variety of dipolarophiles. The generally used dipolarophiles in these reactions are the activated alkene and alkyne derivatives [3]. Huisgen has suggested that these reactions occur through concerted mechanism and they involve the stereospecificity and regioselectivity in their pathways [4]. The commonly used 1,3-dipoles are nitrones, azomethine imines, azomethine ylides, diazoalkanes, azides, nitrile oxides, nitrile imines, nitrile ylides and ozone [5]. Among these dipoles, nitrones are the very important synthones that are found to play a vital role in the field of heterocyclic synthesis [6]. The important feature of nitrones is that they may react with variety of dipolarophiles to provide various ring sized products from three membered to macrocycles. These intermediates are prepared by using the condensation reaction of N-phenylhydroxylamine with appropriate carbonyl compounds [7-11].

The most significant aspect of the above 1,3-dipolar cycloaddition reaction is their capability to generate the three adjoining stereogenic centres through the regioselective and stereoselective way [12]. These aspects have attracted the much attentions of the researchers to utilize these reactions in the formation of five membered heterocyclic products which are realized in the *cis* and *trans* diastereomeric forms [13,14]. The noticeable characteristic of these processes has been the incorporation of multiple sterocentres in a single stage reactions [15].

The five membered heterocycles having nitrogen and oxygen at the adjacent positions are called as isoxazoles while their half reduced and tetrahydro forms are regarded as isoxazolines and isoxazolidines, respectively [16-18]. The cycloaddition reactions of nitrones with N-aryl-maleimides is an attractive and versatile protocol for the synthesis of regio and stereoselective pyrrolo-isoxazolidine scaffolds [19,20]. The reactions of nitrones with alkene occur *via* the involvement of 4π and 2π-electrons system which suggested their occurrence under the thermal modes [5]. Pyrrolo-isoxazolidine derivatives exhibit a wide diversity of biological activities like antibacterial [21], antifungal [22], anti-inflammatory [23], anticancer [24], anticonvulsant [25], antitubercular [26], anti-influenza [27], anti-HIV [28] and antistress [29]. Some of these heterocycles are also reported as broad spectrum antibiotics due to their actions against the Gram-positive bacteria [30].

In the literature 1,3-dipolar cycloaddition reactions of N-aryl-maleimide with variety of nitrones have been fully exploited bearing the various substituent upon the N-aryl group of maleimide as well as on the N-imino aryl/heteroaryl rings of the nitrone [12-14,31]. Thus, the present study has been taken up with a view to fill the gap in the literature and to explore the antimicrobial studies of final heterocyclic products [7].

By considering these aspects in view, we have focused our present researches upon the extensive 1,3-dipoar cycloaddition reactions of ester substituted N-aryl maleimide with variously substituted N-imino aryl nitrones in order to obtain new pyrrolo-isoxazolidines. The major interest behind the synthesis of these hetreocycles was to investigate the effect of the nature of C_3-aryl ring upon the antimicrobial properties of the proposed heterocycles.

EXPERIMENTAL

The melting points reported are uncorrected and checked with the open capillary method in paraffin wax. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. Waters ESI-MS was used to obtain the mass spectra of the prepared compounds. Both ^{1}H NMR and ^{13}C NMR spectra of the given compounds were recorded on the Bruker Spectrometer at 400 MHz and 100 MHz, respectively. In the NMR scanning tetramethylsilane was added in the form of standard molecule. The progress of the given reactions has been monitored with the help of TLC plates, which were coated with silica gel. The iodine vapours were used as the visualizing agent for the TLC plates. The nitrones **1(a-l)** were prepared and identified according to the literature methods [32-34].

General procedure for the synthesis of N-aryl nitrones: A mixture of nitrobenzene (5.0 g, 0.040 mol), ammonium chloride (2.5 g, 0.046 mol) and H_2O (100.0 mL) was mechanically stirrred for 1 h and zinc dust (5.9 g, 0.090 mol) was slowly added to this mixture. Zinc dust was added in such a way so that temperature of the reaction mixture could not rise above the 60-70 °C. The formation of pale yellow reaction mixture after the addition of whole zinc dust indicated the complete reduction of nitrobenzene to N-phenylhydroxylamine. The resulting mixture was filtered and thoroughly washed with warm water. The equimolar quantity of aromatic aldehydes **(a-l)** and chloroform (15 mL) were added to the filtrates and the mixture was stirred till solids were formed. The crude substances were purified by their crystallization in MeOH, which finally yielded the pure nitrones **1(a-l)** [32-34].

General procedure for the synthesis of methyl 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoate: To a well stirred solution of maleic anhydride (2.0 g, 0.020 mol) and toluene (20 mL) was slowly added methyl-4-aminobenzoate (3 g, 0.020 mol). After 1 h a solid substance was separated out which was filtered and dried under pressure. At the end maleanilic acid (**2a**) was realized in the pure form by performing its crystallization in EtOH (yellow solid; yield: 4.0 g, 80 %, m.p.: 200-202 °C). Further the mixture of maleanilic acid **2a** (3.0 g, 0.012 mol), sodium acetate (0.5 g, 0.006 mol) and acetic anhydride (20.0 mL) was refluxed for 2 h on a water bath. After the completion of reaction (as checked by TLC), the mixture was decomposed by the slow addition to the crushed ice which upon appropriate shaking provided a light yellow solid. This product was further crystallized from hexane:ethyl acetate (1:1) to provide pure compound **2b**. White solid; m.p. 150-152 °C; yield: 70 %; IR (KBr, ν_{max}, cm^{-1}): 1696, 1710 (C=O) and 1750 (ester C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (2H, dd, $J_{m,o}$ = 1.7, 7.1 Hz, H-3′, 5′), 7.51 (2H, dd, $J_{m,o}$ = 2.2, 9.0 Hz, H-2′, 6′), 6.88 (2H, s, H-3, 4), 3.93 (3H, s, OC***H*****$_3$**); ESI-MS: *m/z* 232 (M+1, 15 %), 231 (M$^+$, 100 %); Anal. calcd. (%) for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06; Found (%): C, 62.09; H, 3.90; N, 6.03.

Synthesis of pyrrolo-isoxazolidines 3a and 4a: A mixture of nitrone **1a** (0.8 g, 0.004 mol) and compound **2b** (1.0 g, 0.004 mol) was vigorously refluxed by using dry toluene (25.0 mL) as the solvent. The reaction mixture was allowed to refluxed for 4 h when whole of the reactant was converted into products (as checked by TLC). The resulting mixture was concentrated under vacuum to provide a mass, which was loaded over a silica-gel column (100-200 mesh) packed in pure hexane. Further, elution of column with hexane:EtOAc (2:1) yielded two new products **3a** and **4a.**

cis*-Methyl-4-[(*3H,3aH,6aH*)-4,6-dioxo-2,3-diphenyl-hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (3a):** Off white solid; m.p. 186-188 °C; yield: 37 %; IR (KBr, ν_{max}, cm^{-1}): 1691, 1716 (C=O), 1739 (ester C=O), 2951 (aliphatic C-H) and 3290 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (2H, dt, $J_{p,o}$ = 1.1, 7.3 Hz, H-3‴, 5‴), 7.66 (2H, d, J_o = 7.9 Hz, H-2‴, 6‴), 7.46 (2H, d, J_o = 7.5 Hz, H- 2″, 6″), 7.21 (3H, m, H-3″, 4″, 5″), 6.98 (3H, m, H-3′, 4′, 5′), 6.81 (2H, dd, $J_{m,o}$ = 2.1, 7.3 Hz, H-2′, 6′), 5.17 (1H, d, $J_{3,3a}$ = 8.0 Hz, H-3), 5.06 (1H, d, $J_{6a,3a}$ = 6.80 Hz, H-6a), 3.93 (1H, dd, $J_{3a,3}$ = 8.0 Hz, $J_{3a,6a}$ = 6.4 Hz, H-3a), 3.88 (3H, s, OCH*****$_3$**); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.91, 168.32 (C=O), 167.34 (ester C=O), 147.96 (C-1‴), 145.42 (C-1′), 131.66 (C-4‴), 128.64 (C-1″), 128.41 (C-3‴, 5‴), 127.58 (C-2‴, 6‴), 126.38 (C-3″, 5″), 124.59 (C-2″, 6″), 123.07 (C-3′, 5′), 121.79 (C-4″), 119.54 (C-4′), 116.84 (C-2′, 6′), 76.82 (C-6a), 64.39 (C-3), 51.86 (O***C***H$_3$), 48.56 (C-3a); ESI-MS: *m/z* 429 (M+1, 27 %), 428 (M$^+$, 100 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_5$: C, 70.09; H, 4.71; N, 6.54; Found (%): C, 69.81; H, 4.73; N, 6.51.

trans*-Methyl-4-[(*3H,3aH,6aH*)-4,6-dioxo-2,3-diphenyl-hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (4a):** Off white solid; m.p. 168-170 °C; yield: 20 %; IR (KBr, ν_{max}, cm^{-1}): 1696, 1714 (C=O), 1740 (ester C=O), 2957 (aliphatic C-H) and 3288 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (2H, dd, $J_{p,o}$ = 0.8, 7.6 Hz, H-3‴, 5‴), 7.62 (2H, d, J_o = 8.1 Hz, H-2‴, 6‴), 7.43 (2H, d, J_o = 7.7 Hz, H- 2″, 6″), 7.23 (3H, m, H-3″, 4″, 5″), 6.94 (3H, m, H- 3′, 4′, 5′), 6.89 (2H, dd, $J_{m,o}$ = 2.8, 7.2 Hz, H-2′, 6′), 5.78 (1H, s, H-3), 5.23 (1H, d, $J_{6a,3a}$ = 6.7 Hz, H-6a), 4.13 (1H, d, $J_{3a,6a}$ = 6.7 Hz), 3.89 (3H, s, OCH*****$_3$**); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.32, 167.68 (C=O), 166.82 (ester C=O), 149.23 (C-1‴), 143.16 (C-1′), 130.51 (C-4‴), 130.13 (C-1″), 129.17 (C-3‴, 5‴), 128.24 (C-2‴, 6‴), 125.09 (C-3″, 5″), 124.47 (C-2″, 6″), 123.27 (C-3′, 5′), 120.46 (C-4″), 118.13 (C-4′), 116.96 (C-2′, 6′), 77.89 (C-6a), 64.78 (C-3), 51.35 (O***C***H$_3$), 49.26 (C-3a); ESI-MS: *m/z* 451 (M+Na, 98 %), 429 (M+1, 32 %); Anal.

calcd. (%) for $C_{25}H_{20}N_2O_5$: C, 70.09; H, 4.71; N, 6.54; Found (%): C, 70.37; H, 4.69; N, 6.49.

Synthesis of pyrrolo-isoxazolidines 3b and 4b: The compounds **3b** and **4b** were prepared by treating nitrone **1b** (0.9 g, 0.004 mol) with maleimide **2b** (1.0 g, 0.004 mol) by following the similar protocol as given earlier for **3a** and **4a.**

cis*-Methyl-4-[(*3H,3aH,6aH*)-3-(2-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (3b):** Off white solid; m.p. 133-135 °C; yield: 38 %; IR (KBr, ν_{max}, cm^{-1}): 1699, 1713 (C=O), 1741 (ester C=O), 2952 (aliphatic C-H), 3285 (aromatic C-H) and 3405 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (1H, s, OH***), 7.88 (2H, dt, $J_{p,o}$ = 1.0, 7.1 Hz, H-3‴, 5‴), 7.65 (2H, d, J_o = 8.8 Hz, H-2‴, 6‴), 7.43 (1H, dd, $J_{m,o}$ = 1.4, 7.7 Hz, H-6″), 7.20 (2H, t, J_o = 7.7 Hz, H-4″, 5″), 7.11 (1H, td, $J_{m,o}$ = 1.6, 8.2 Hz, H-3″), 6.94 (3H, m, H- 3′, 4′, 5′), 6.81 (2H, m, H-2′, 6′), 5.19 (1H, d, $J_{3,3a}$ = 8.2 Hz, H-3), 5.10 (1H, d, $J_{6a,3a}$ = 6.5 Hz, H-6a), 3.91 (1H, dd, $J_{3a,3}$ = 8.2 Hz, $J_{3a,6a}$ = 6.5 Hz, H-3a), 3.82 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.46, 168.18 (C=O), 165.76 (ester C=O), 154.71 (C-2″), 148.93 (C-1‴), 143.10 (C-1′), 130.27 (C-4‴), 128.75 (C-1″), 128.37 (C-3‴, 5‴), 127.68 (C-2‴, 6‴), 125.09 (C-6″), 124.26 (C-4″), 122.59 (C-3′, 5′), 119.38 (C-5″), 118.65 (C-4′), 116.88 (C-2′, 6′), 115.40 (C-3″), 76.94 (C-6a), 65.70 (C-3), 51.83 (O***C***H$_3$), 48.58 (C-3a); ESI-MS: *m/z* 467 (M+Na, 14 %), 444 (M^+, 100 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.28; H, 4.51; N, 6.27.

trans*-Methyl-4-[(*3H,3aH,6aH*)-3-(2-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (4b):** Off white solid; m.p. 115-117 °C; yield: 20 %; IR (KBr, ν_{max}, cm^{-1}): 1699, 1712 (C=O), 1743 (ester C=O), 2954 (aliphatic C-H), 3281 (aromatic C-H) and 3404 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (1H, s, OH***), 7.85 (2H, dd, $J_{p,o}$ = 0.9, 7.5 Hz, H-3‴, 5‴), 7.64 (2H, d, J_o = 7.8 Hz, H-2‴, 6‴), 7.48 (1H, dd, $J_{m,o}$ = 2.1, 8.0 Hz, H-6″), 7.22 (2H, t, J_o = 7.9 Hz, H-4″, 5″), 7.16 (1H, dd, $J_{m,o}$ = 1.8, 8.0 Hz, H-3″), 6.98 (3H, m, H- 3′, 4′, 5′), 6.80 (2H, m, H-2′, 6′), 5.80 (1H, s, H-3), 5.25 (1H, d, $J_{6a,3a}$ = 6.8 Hz, H-6a), 4.15 (1H, d, $J_{3a,6a}$ = 6.8 Hz, H-3a), 3.84 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.85, 169.01 (C=O), 167.24 (ester C=O), 155.01 (C-2″), 149.84 (C-1‴), 145.41 (C-1′), 132.20 (C-4‴), 130.02 (C-1″), 128.94 (C-3‴, 5‴), 128.02 (C-2‴, 6‴), 126.78 (C-6″), 125.04 (C-4″), 122.82 (C-3′, 5′), 120.04 (C-5″), 118.98 (C-4′), 117.82 (C-2′, 6′), 115.10 (C-3″), 77.45 (C-6a), 66.08 (C-3), 51.57 (O***C***H$_3$), 49.13 (C-3a); ESI-MS: *m/z* 468 (M+Na+1, 60 %), 467 (M+Na, 100 %), 445 (M+1, 50 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.32; H, 4.57; N, 6.32.

Synthesis of pyrrolo-isoxazolidines 3c and 4c: The reaction of compounds **1c** (0.9 g, 0.004 mol) and **2b** (1.0 g, 0.004 mol) in the same manner as described above for **3a** and **4a** resulted in the formation of two new diastereomers **3c** and **4c.**

cis*-Methyl-4-[(*3H,3aH,6aH*)-3-(3-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (3c):** Off white solid; m.p. 160-162 °C; yield: 50 %; IR (KBr, ν_{max}, cm^{-1}): 1696, 1715 (C=O), 1740 (ester C=O), 2953 (aliphatic C-H), 3283 (aromatic C-H) and 3408 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.37 (1H, s, OH***), 7.86 (2H, dd, $J_{p,o}$ = 0.6, 7.9 Hz, H-3‴, 5‴), 7.63 (2H, d, J_o = 7.2 Hz, H-2‴, 6‴), 7.47 (2H, d, J_o = 7.5 Hz, H-5″, 6″), 7.18 (2H, t, J_o = 7.0 Hz, H-2″, 4″), 6.91 (3H, m, H- 3′, 4′, 5′), 6.78 (2H, dd, $J_{m,o}$ = 2.4, 7.7 Hz, H-2′, 6′), 5.23 (1H, d, $J_{3,3a}$ = 8.2 Hz, H-3), 5.16 (1H, d, $J_{6a,3a}$ = 6.2 Hz, H-6a), 3.88 (1H, dd, $J_{3a,3}$ = 8.2 Hz, $J_{3a,6a}$ = 6.2 Hz, H-3a), 3.85 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.96, 167.20 (C=O), 166.78 (ester C=O), 153.82 (C-3″), 148.08 (C-1‴), 144.64 (C-1′), 131.81 (C-4‴), 129.73 (C-1″), 129.03 (C-3‴, 5‴), 128.46 (C-2‴, 6‴), 125.63 (C-5″), 124.84 (C-3′, 5′), 123.34 (C-4′), 120.68 (C-6″), 119.03 (C-2′, 6′), 117.87 (C-2″), 114.71 (C-4″), 76.84 (C-6a), 64.86 (C-3), 52.09 (O***C***H$_3$), 49.08 (C-3a); ESI-MS: *m/z* 445 (M+1, 27 %), 444 (M^+, 100 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.83; H, 4.52; N, 6.33.

trans*-Methyl-4-[(*3H,3aH,6aH*)-3-(3-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (4c):** Off white solid; m.p. 145-147 °C; yield: 26 %; IR (KBr, ν_{max}, cm^{-1}): 1698, 1714 (C=O), 1742 (ester C=O), 2950 (aliphatic C-H), 3289 (aromatic C-H) and 3409 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (1H, s, OH***), 7.82 (2H, dd, $J_{p,o}$ = 0.8, 7.1 Hz, H-3‴, 5‴), 7.67 (2H, d, J_o = 7.6 Hz, H-2‴, 6‴), 7.42 (2H, d, J_o = 7.8 Hz, H- 5″, 6″), 7.19 (2H, t, J_o = 7.2 Hz, H-2″, 4″), 6.92 (3H, m, H- 3′, 4′, 5′), 6.75 (2H, dd, $J_{m,o}$ = 2.5, 7.1 Hz, H-2′, 6′), 5.80 (1H, s, H-3), 5.30 (1H, d, $J_{6a,3a}$ = 6.4 Hz, H-6a), 4.10 (1H, d, $J_{3a,6a}$ = 6.4 Hz, H-3a), 3.86 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.02, 167.43 (C=O), 166.01 (ester C=O), 154.43 (C-3″), 148.94 (C-1‴), 144.08 (C-1′), 132.63 (C-4‴), 129.05 (C-1″), 128.84 (C-3‴, 5‴), 128.32 (C-2‴, 6‴), 126.20 (C-5″), 124.17 (C-3′, 5′), 123.79 (C-4′), 121.26 (C-6″), 120.06 (C-2′, 6′), 118.09 (C-2″), 114.22 (C-4″), 76.13 (C-6a), 65.94 (C-3), 51.34 (O***C***H$_3$), 48.65 (C-3a); ESI-MS: *m/z* 446 (M+2, 12 %), 445 (M+1, 100 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.35; H, 4.56; N, 6.26.

Synthesis of pyrrolo-isoxazolidines 3d and 4d: Heterocycles **3d** and **4d** could become available from the dipolar cycloaddition reaction of **1d** (0.9 g, 0.004 mol) and **2b** (1.0 g, 0.004 mol) under the usual reaction conditions.

cis*-Methyl-4-[(*3H,3aH,6aH*)-3-(4-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (3d):** Off white solid; m.p. 210-212 °C; yield: 55 %; IR (KBr, ν_{max}, cm^{-1}): 1696, 1718 (C=O), 1741 (ester C=O), 2952 (aliphatic C-H), 3285 (aromatic C-H) and 3402 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (1H, s, OH***), 7.82 (2H, dt, $J_{p,o}$ = 0.9, 7.3 Hz, H-3‴, 5‴), 7.62 (2H, d, J_o = 8.0 Hz, H-2‴, 6‴), 7.45 (2H, d, J_o = 7.1 Hz, H-2″, 6″), 7.24 (2H, t, J_o = 7.7 Hz, H-3″, 5″), 6.93 (3H, m, H- 3′, 4′, 5′), 6.71 (2H, dd, $J_{m,o}$ = 2.5, 7.3 Hz, H-2′, 6′), 5.18 (1H, d, $J_{3,3a}$ = 8.4 Hz, H-3), 5.11 (1H, d, $J_{6a,3a}$ = 6.6 Hz, H-6a), 3.94 (1H, dd, $J_{3a,3}$ = 8.4 Hz, $J_{3a,6a}$ = 6.6 Hz, H-3a), 3.86 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.15, 168.32 (C=O), 165.81 (ester C=O), 155.08 (C-4″), 147.18 (C-1‴), 144.47 (C-1′), 130.87 (C-4‴), 130.04 (C-1″), 128.05 (C-3‴, 5‴), 127.14 (C-2‴, 6‴), 125.42 (C-2″, 6″), 124.31 (C-3′, 5′), 122.79 (C-4′), 119.55 (C-2′, 6′), 118.78 (C-3″, 5″), 77.58 (C-6a), 66.34 (C-3), 51.90 (O***C***H$_3$), 48.74 (C-3a); ESI-MS: *m/z* 468 (M+Na+1, 35 %), 444 (M^+,

100 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.34; H, 4.51; N, 6.27.

trans*-Methyl-4-[(*3H,3aH,6aH*)-3-(4-hydroxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl]benzoate (4d):** Off white solid; m.p. 193-195 °C; yield: 24 %; IR (KBr, ν_{max}, cm^{-1}): 1695, 1721 (C=O), 1742 (ester C=O), 2953 (aliphatic C-H), 3286 (aromatic C-H) and 3406 (O-H); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 10.53 (1H, s, OH***), 7.84 (2H, dt, $J_{p,o}$ = 0.8, 7.9 Hz, H-3‴, 5‴), 7.65 (2H, d, J_o = 7.7 Hz, H-2‴, 6‴), 7.43 (2H, d, J_o = 7.6 Hz, H- 2″, 6″), 7.28 (2H, t, J_o = 7.2 Hz, H-3″, 5″), 6.96 (3H, m, H- 3′, 4′, 5′), 6.74 (2H, dd, $J_{m,o}$ = 2.1, 7.8 Hz, H-2′, 6′), 5.83 (1H, s, H-3), 5.26 (1H, d, $J_{6a,3a}$ = 6.9 Hz, H-6a), 4.10 (1H, d, $J_{3a,6a}$ = 6.9 Hz, H-3a), 3.82 (3H, s, OC***H*$_3$**); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 168.34, 168.03 (C=O), 166.39 (ester C=O), 153.93 (C-4″), 148.07 (C-1‴), 145.87 (C-1′), 132.02 (C-4‴), 130.40 (C-1″), 129.95 (C-3‴, 5‴), 128.34 (C-2‴, 6‴), 126.16 (C-2″, 6″), 125.48 (C-3′, 5′), 123.47 (C-4′), 120.47 (C-2′, 6′), 119.43 (C-3″, 5″), 77.23 (C-6a), 65.78 (C-3), 52.16 (O***C***H$_3$), 49.32 (C-3a); ESI-MS: *m/z* 467 (M+Na, 100 %), 445 (M+1, 26 %); Anal. calcd. (%) for $C_{25}H_{20}N_2O_6$: C, 67.56; H, 4.54; N, 6.30; Found (%): C, 67.28; H, 4.52; N, 6.28.

Synthesis of pyrrolo-isoxazolidines 3e and 4e: The compounds **3e** and **4e** were realized easily from the cycloaddition reaction of **1e** (0.8 g, 0.004 mol) and **2b** (1.0 g, 0.004 mol) by following the similar protocol as depicted above for **3a** and **4a.**

cis*-Methyl-4-((*3H,3aH,6aH*)-4,6-dioxo-2-phenyl-3-(*p*-tolyl)hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3e):** Off white solid; m.p. 176-178 °C; yield: 44 %; IR (KBr, ν_{max}, cm^{-1}): 1698, 1720 (C=O), 1738 (ester C=O), 2959 (aliphatic C-H) and 3282 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.89 (2H, dd, $J_{p,o}$ = 0.7, 7.8 Hz, H-3‴, 5‴), 7.66 (2H, d, J_o = 7.0 Hz, H-2‴, 6‴), 7.40 (2H, d, J_o = 7.5 Hz, H- 2″, 6″), 7.30 (2H, t, J_o = 7.2 Hz, H-3″, 5″), 6.98 (3H, m, H- 3′, 4′, 5′), 6.75 (2H, dd, $J_{m,o}$ = 2.4, 7.8 Hz, H-2′, 6′), 5.20 (1H, d, $J_{3,3a}$ = 8.3 Hz, H-3), 5.08 (1H, d, $J_{6a,3a}$ = 6.0 Hz, H-6a), 3.92 (1H, dd, $J_{3a,3}$ = 8.3 Hz, $J_{3a,6a}$ = 6.0 Hz, H-3a), 3.82 (3H, s, OCH*$_3$**), 2.5 (3H, s, C***H*$_3$**); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 168.82, 168.18 (C=O), 167.24 (ester C=O), 148.52 (C-1‴), 145.21 (C-1′), 132.98 (C-4‴), 128.71 (C-1″), 128.03 (C-4″), 127.54 (C-3‴, 5‴), 126.11 (C-2‴, 6‴), 125.38 (C-2″, 6″), 122.47 (C-3′, 5′), 121.66 (C-4′), 119.48 (C-3″, 5″), 116.89 (C-2′, 6′), 77.34 (C-6a), 65.64 (C-3), 52.32 (O***C***H$_3$), 49.42 (C-3a), 21.4 (C_4″-CH_3); ESI-MS: *m/z* 465 (M+Na, 98 %), 443 (M+1, 40 %); Anal. calcd. (%) for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33; Found (%): C, 70.29; H, 4.98; N, 6.30 %.

trans*-Methyl-4-((*3H,3aH,6aH*)-4,6-dioxo-2-phenyl-3-(*p*-tolyl)hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (4e):** Off white solid; m.p. 161-163 °C; yield: 32 %; IR (KBr, ν_{max}, cm^{-1}): 1699, 1718 (C=O), 1741 (ester C=O), 2956 (aliphatic C-H) and 3284 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.86 (2H, dd, $J_{p,o}$ = 1.0, 8.0 Hz, H-3‴, 5‴), 7.63 (2H, d, J_o = 7.4 Hz, H-2‴, 6‴), 7.42 (2H, d, J_o = 7.8 Hz, H- 2″, 6″), 7.23 (2H, t, J_o = 7.0 Hz, H-3″, 5″), 6.95 (3H, m, H- 3′, 4′, 5′), 6.72 (2H, dd, $J_{m,o}$ = 2.6, 7.3 Hz, H-2′, 6′), 5.86 (1H, s, H-3), 5.29 (1H, d, $J_{6a,3a}$ = 6.7 Hz, H-6a), 4.08 (1H, d, $J_{3a,6a}$ = 6.7 Hz, H-3a), 3.87 (3H, s, OCH*$_3$**), 2.5 (3H, s, C***H*$_3$**); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 169.22, 168.32 (C=O), 165.98 (ester C=O), 148.29 (C-1‴), 143.31 (C-1′), 130.59 (C-4‴), 129.13 (C-1″), 128.29 (C-4″), 127.33 (C-3‴, 5‴), 125.94 (C-2‴, 6‴), 124.22 (C-2″, 6″), 123.52 (C-3′, 5′), 119.38 (C-4′), 118.97 (C-3″, 5″), 116.44 (C-2′, 6′), 76.93 (C-6a), 64.05 (C-3), 51.77 (O***C***H$_3$), 48.30 (C-3a), 21.6 (C_4″-***C***H$_3$); ESI-MS: *m/z* 443 (M+1, 28 %), 442 (M^+, 100 %); Anal. calcd. (%) for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33; Found (%): C, 70.31; H, 4.99; N, 6.36.

Synthesis of pyrrolo-isoxazolidine (3f): The reaction of nitrone **1f** (0.9 g, 0.004mol) and compound **2b** (1.0 g, 0.004 mol) could be able to provide **3f** under the conditions as given above **(3a** and **4a)**.

cis*-Methyl-4-((*3H,3aH,6aH*)-3-(4-methoxyphenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3f):** Off white solid; m.p. 190-192 °C; yield: 45 %; IR (KBr, ν_{max}, cm^{-1}): 1693, 1712 (C=O), 1742 (ester C=O), 2952 (aliphatic C-H) and 3281 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.83 (2H, dd, $J_{p,o}$ = 1.0, 7.8 Hz, H-3‴, 5‴), 7.69 (2H, d, J_o = 7.6 Hz, H-2‴, 6‴), 7.41 (2H, d, J_o = 7.9 Hz, H- 2″, 6″), 7.20 (2H, t, J_o = 7.5 Hz, H-3″, 5″), 6.95 (3H, m, H- 3′, 4′, 5′), 6.79 (2H, dd, $J_{m,o}$ = 2.4, 8.0 Hz, H-2′, 6′), 5.20 (1H, d, $J_{3,3a}$ = 8.3 Hz, H-3), 5.09 (1H, d, $J_{6a,3a}$ = 6.1 Hz, H-6a), 3.92 (1H, dd, $J_{3a,3}$ = 8.3 Hz, $J_{3a,6a}$ = 6.1 Hz, H-3a), 3.90 (3H, s, C_4″-OCH*$_3$**), 3.81 (3H, s, C_4‴-OC***H*$_3$**); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 168.58, 167.43 (C=O), 166.41 (ester C=O), 155.41 (C-4″), 149.19 (C-1‴), 143.84 (C-1′), 130.24 (C-4‴), 130.81 (C-1″), 129.06 (C-3‴, 5‴), 128.87 (C-2‴, 6‴), 126.22 (C-2″, 6″), 124.33 (C-3′, 5′), 123.53 (C-4′), 120.84 (C-2′, 6′), 119.45 (C-3″, 5″), 75.06 (C-6a), 66.28 (C-3), 55.9 (C_4″-O***C***H$_3$) 51.58 (C_4‴-O***C****H*$_3$**), 48.23 (C-3a); ESI-MS: *m/z* 481 (M+Na, 100 %), 459 (M+1, 25 %); Anal. calcd. (%) for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11; Found (%): C, 67.84; H, 4.82; N, 6.08.

Synthesis of pyrrolo-isoxazolidines 3g and 4g: The products **3g** and **4g** were synthesized from the reaction of nitrone **1g** (0.9 g, 0.004 mol) and maleimide **2b** (1.0 g, 0.004 mol) by following the usual protocols as stated above for **3a** and **4a.**

cis*-Methyl-4-((*3H,3aH,6aH*)-3-(4-chlorophenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3g):** Off white solid; m.p. 202-204 °C; yield: 51 %; IR (KBr, ν_{max}, cm^{-1}): 1691, 1714, (C=O), 1741 (ester C=O), 2954 (aliphatic C-H) and 3285 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.90 (2H, dt, $J_{p,o}$ = 0.8, 7.2 Hz, H-3‴, 5‴), 7.60 (2H, d, J_o = 7.6 Hz, H-2‴, 6‴), 7.48 (2H, d, J_o = 8.0 Hz, H- 2″, 6″), 7.28 (2H, t, J_o = 7.4 Hz, H-3″, 5″), 6.91 (3H, m, H- 3′, 4′, 5′), 6.82 (2H, dd, $J_{m,o}$ = 2.5, 7.6 Hz, H-2′, 6′), 5.17 (1H, d, $J_{3,3a}$ = 7.9 Hz, H-3), 5.02 (1H, d, $J_{6a,3a}$ = 6.2 Hz, H-6a), 3.89 (1H, dd, $J_{3a,3}$ = 7.9 Hz, $J_{3a,6a}$ = 6.2 Hz, H-3a), 3.84 (3H, s, OCH*$_3$**); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 168.08, 167.91 (C=O), 165.75 (ester C=O), 149.91 (C-1‴), 143.80 (C-1′), 131.71 (C-4‴), 129.69 (C-1″), 128.56 (C-4″), 127.54 (C-3‴, 5‴), 125.44 (C-2‴, 6‴), 124.64 (C-2″, 6″), 122.33 (C-3′, 5′), 119.56 (C-4′), 118.68 (C-3″, 5″), 116.15 (C-2′, 6′), 75.64 (C-6a), 64.91 (C-3), 52.29 (O***C***H$_3$), 49.15 (C-3a); ESI-MS: *m/z* 464 (M+2, 32 %), 462 (M^+, 94 %); Anal. calcd. (%) for $C_{25}H_{19}N_2O_5Cl$: C, 64.87; H, 4.14; N, 6.05; Found (%): C, 64.61; H, 4.12; N, 6.02.

trans*-Methyl-4-((*3H,3aH,6aH*)-3-(4-chlorophenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (4g):** Off white solid; m.p. 183-185 °C; yield: 27 %; IR (KBr, ν_{max}, cm^{-1}): 1698, 1713 (C=O), 1744 (ester C=O), 2951 (aliphatic C-H) and 3284 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (2H, dt, $J_{p,o}$ = 1.0, 7.3 Hz, H-3‴, 5‴), 7.61 (2H, d, J_o = 7.1 Hz, H-2‴, 6‴), 7.43 (2H, d, J_o = 7.8 Hz, H- 2″, 6″), 7.21 (2H, t, J_o = 7.9 Hz, H-3″, 5″), 6.94 (3H, m, H- 3′, 4′, 5′), 6.80 (2H, dd, $J_{m,o}$ = 2.3, 7.4 Hz, H-2′, 6′), 5.84 (1H, s, H-3), 5.30 (1H, d, $J_{6a,3a}$ = 6.6 Hz, H-6a), 4.14 (1H, d, $J_{3a,6a}$ = 6.6 Hz, H-3a), 3.90 (3H, s, OCH₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.71, 167.88 (C=O), 166.08 (ester C=O), 147.83 (C-1‴), 144.37 (C-1′), 130.60 (C-4‴), 130.34 (C-1″), 129.16 (C-4″), 128.88 (C-3‴, 5‴), 126.68 (C-2‴, 6‴), 124.87 (C-2″, 6″), 123.58 (C-3′, 5′), 120.85 (C-4′), 118.05 (C-3″, 5″), 117.26 (C-2′, 6′), 76.48 (C-6a), 66.45 (C-3), 51.89 (O***C***H$_3$), 48.70 (C-3a); ESI-MS: *m/z* 464 (M+2, 12 %), 462 (M^+, 33 %); Anal. calcd. (%) for $C_{25}H_{19}N_2O_5Cl$: C, 64.87; H, 4.14; N, 6.05; Found (%): C, 64.59; H, 4.16; N, 6.03.

Synthesis of pyrrolo-isoxazolidine (3h): The heterocycle **3h** was obtained from the reaction of **1h** (1.0 g, 0.004 mol) and **2b** (1.0 g, 0.004 mol) by following the above described procedures.

cis*-Methyl-4-((*3H,3aH,6aH*)-3-(4-nitrophenyl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3h):** Off white solid; m.p. 220-222 °C; yield: 48 %; IR (KBr, ν_{max}, cm^{-1}): 1346, 1518 (NO_2), 1699, 1715 (C=O), 1739 (ester C=O), 2956 (aliphatic C-H) and 3280 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (2H, dt, $J_{p,o}$ = 1.0, 7.8 Hz, H- 3‴, 5‴), 7.78 (2H, d, J_o = 7.8 Hz, H-3″, 5″), 7.68 (2H, d, J_o = 8.0 Hz, H-2‴, 6‴), 7.52 (2H, d, J_o = 7.4 Hz, H-2″, 6″), 6.99 (3H, m, H- 3′, 4′, 5′), 6.88 (2H, dd, $J_{m,o}$ = 2.2, 8.1 Hz, H-2′, 6′), 5.21 (1H, d, $J_{3,3a}$ = 8.1 Hz, H-3), 5.12 (1H, d, $J_{6a,3a}$ = 6.3 Hz, H-6a), 3.90 (1H, dd, $J_{3a,3}$ = 8.1 Hz, $J_{3a,6a}$ = 6.3 Hz, H-3a), 3.80 (3H, s, OCH₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.43, 168.75 (C=O), 165.74 (ester C=O), 148.76 (C-1‴), 144.67 (C-1′), 132.17 (C-4‴), 129.44 (C-1″), 128.46 (C-4″), 127.98 (C-3‴, 5‴), 125.87 (C-2‴, 6‴), 125.81 (C-3′, 5′), 122.61 (C-2″, 6″), 119.03 (C-4′), 118.83 (C-3″, 5″), 117.51 (C-2′, 6′), 77.46 (C-6a), 65.18 (C-3), 51.05 (O***C***H$_3$), 49.38 (C-3a); ESI-MS: *m/z* 475 (M+2, 3 %), 474 (M+1, 27 %), 473 (M^+, 100); Anal. calcd. (%) for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88; Found (%): C, 63.16; H, 4.02; N, 8.84.

Synthesis of pyrrolo-isoxazolidines 3i and 4i: The heterocycles **3i** and **4i** were obtained in the pure by using the cycloaddition process of **1i** (0.8 g, 0.004mol) and **2b** (1.0 g, 0.004 mol) under the above described conditions**.**

cis*-Methyl-4-((*3H,3aH,6aH*)-4,6-dioxo-2-phenyl-3-(thiophen-2-yl)hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3i):** Off white solid; m.p. 214-216 °C; yield: 31 %; IR (KBr, ν_{max}, cm^{-1}): 1695, 1711 (C=O), 1740 (ester C=O), 2957 (aliphatic C-H) and 3285 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (2H, dd, $J_{p,o}$ = 1.0, 7.2 Hz, H-3‴, 5‴), 7.72 (1H, d, $J_{3″,4″}$ = 3.7 Hz, H-3″),7.68 (2H, d, J_o = 7.9 Hz, H-2‴, 6‴), 7.61 (1H, d, $J_{5″,4″}$ = 5.0 Hz, H-5″), 7.21 (1H, dd, $J_{4″,3″}$ = 3.7 Hz, $J_{4″,5″}$ = 5.0 Hz, H-4″), 6.91 (3H, m, H- 3′, 4′, 5′), 6.74 (2H, dd, $J_{m,o}$ = 2.5, 7.8 Hz, H-2′, 6′), 5.22 (1H, d, $J_{3,3a}$ = 8.1 Hz, H-3), 5.13 (1H, d, $J_{6a,3a}$ = 6.5 Hz, H-6a), 3.95 (1H, dd, $J_{3a,3}$ = 8.1 Hz, $J_{3a,6a}$ = 6.5 Hz, H-3a), 3.86 (3H, s, OCH₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.82, 167.83 (C=O), 166.72 (ester C=O), 148.19 (C-1‴), 145.09 (C-1′), 144.56 (C-2″), 131.72 (C-4‴), 130.58 (C-5″), 129.84 (C-3‴, 5‴), 128.95 (C-2‴, 6‴), 125.11 (C-3′, 5′), 122.64 (C-4′), 1l20.78 (C-3″), 119.94 (C-4″), 117.34 (C-2′, 6′), 77.78 (C-6a), 64.53 (C-3), 51.38 (O***C***H$_3$), 48.62 (C-3a); ESI-MS: *m/z* 436 (M+2, 5 %), 435 (M+1, 24 %), 434 (M^+, 100); Anal. calcd. (%) for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18; N, 6.45 %, S, 7.38; Found (%): C, 63.83; H, 4.16; N, 6.42 %, S, 7.35.

trans*-Methyl-4-((*3H,3aH,6aH*)-4,6-dioxo-2-phenyl-3-(thiophen-2-yl)hexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (4i):** Off white solid; m.p. 199-202 °C; yield: 22 %; IR (KBr, ν_{max}, cm^{-1}): 1696, 1716 (C=O), 1744 (ester C=O), 2955 (aliphatic C-H) and 3282 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (2H, dd, $J_{p,o}$ = 0.7, 7.9 Hz, H-3‴, 5‴), 7.76 (1H, d, $J_{3″,4″}$ = 3.8 Hz, H-3″),7.67 (2H, d, J_o = 7.5 Hz, H-2‴, 6‴), 7.63 (1H, d, $J_{5″,4″}$ = 5.1 Hz, H-5″), 7.23 (1H, dd, $J_{4″,3″}$ = 3.6 Hz, $J_{4″,5″}$ = 5.1 Hz, H-4″), 6.95 (3H, m, H- 3′, 4′, 5′), 6.73 (2H, dd, $J_{m,o}$ = 2.4, 7.7 Hz, H-2′, 6′), 5.81 (1H, s, H-3), 5.31 (1H, d, $J_{6a,3a}$ = 6.8 Hz, H-6a), 4.16 (1H, d, $J_{3a,6a}$ = 6.8 Hz, H-3a), 3.88 (3H, s, OCH₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.04, 168.94 (C=O), 167.18 (ester C=O), 147.55 (C-1‴), 144.52 (C-1′), 143.07 (C-2″), 132.23 (C-4‴), 130.22 (C-5″), 129.37 (C-3‴, 5‴), 127.28 (C-2‴, 6‴), 126.85 (C-3′, 5′), 123.06 (C-4′), 121.27 (C-3″), 120.29 (C-4″), 117.76 (C-2′, 6′), 75.89 (C-6a), 66.91 (C-3), 52.58 (O***C***H$_3$), 49.12 (C-3a); ESI-MS: *m/z* 458 (M+Na+1, 24 %), 457 (M+Na, 48 %), 435 (M+1, 8 %); Anal. calcd. (%) for $C_{23}H_{18}N_2O_5S$: C, 63.58; H, 4.18; N, 6.45; S, 7.38; Found (%): C, 63.32; H, 4.20; N, 6.40; S, 7.41.

Synthesis of pyrrolo-isoxazolidines 3j and 4j: The usual reaction of **1j** (0.7 g, 0.004 mol) and **2b** (1.0 g, 0.004 mol) under the above described conditions furnished two new products **3j** and **4j**.

cis*-Methyl-4-((*3H,3aH,6aH*)-3-(furan-2-yl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)-benzoate (3j):** Off white solid; m.p. 218-220 °C; yield: 35 %; IR (KBr, ν_{max}, cm^{-1}): 1692, 1710 (C=O), 1741 (ester C=O), 2953 (aliphatic C-H) and 3283 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (2H, dd, $J_{p,o}$ = 0.8, 7.1 Hz, H-3‴, 5‴), 7.66 (2H, d, J_o = 7.9 Hz, H-2‴, 6‴), 7.52 (1H, d, $J_{3″,4″}$ = 1.7 Hz, H-3″), 6.93 (3H, m, H- 3′, 4′, 5′), 6.88 (1H, d, $J_{5″,4″}$ = 3.4 Hz, H-5″), 6.76 (2H, dd, $J_{m,o}$ = 2.3, 7.3 Hz, H-2′, 6′), 6.68 (1H, dd, $J_{4″,3″}$ = 1.7 Hz, $J_{4″,5″}$ = 3.4 Hz, H-4″), 5.16 (1H, d, $J_{3,3a}$ = 8.3 Hz, H-3), 5.06 (1H, d, $J_{6a,3a}$ = 6.3 Hz, H-6a), 3.91 (1H, dd, $J_{3a,3}$ = 8.3 Hz, $J_{3a,6a}$ = 6.3 Hz, H-3a), 3.87 (3H, s, OCH₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.44, 167.05 (C=O), 165.49 (ester C=O), 155.96 (C-2″), 149.40 (C-1‴), 143.23 (C-1′), 130.58 (C-4‴), 129.74 (C-5″), 128.44 (C-3‴, 5‴), 127.50 (C-2‴, 6‴), 125.86 (C-3′, 5′), 123.51 (C-4′), 116.19 (C-2′, 6′), 109.75 (C-3″), 106.17 (C-4″), 75.99 (C-6a), 66.18 (C-3), 52.36 (O***C***H$_3$), 48.25 (C-3a); ESI-MS: *m/z* 441 (M+Na, 38 %), 419 (M+1, 26 %); Anal. calcd. (%) for $C_{23}H_{18}N_2O_6$: C, 66.03; H, 4.34; N, 6.70; Found (%): C, 65.77; H, 4.30; N, 6.67.

***trans*-Methyl-4-((*3H,3aH,6aH*)-3-(furan-2-yl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-**

yl)benzoate (4j): Off white solid; m.p. 205-207 °C; yield: 20 %; IR (KBr, ν_{max}, cm^{-1}): 1694, 1718, (C=O), 1742 (ester C=O), 2950 (aliphatic C-H) and 3286 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (2H, dd, $J_{p,o}$ = 0.9, 7.3 Hz, H-3‴,5‴), 7.64 (2H, d, J_o = 7.6 Hz, H-2‴, 6‴), 7.53 (1H, d, $J_{3'',4''}$ = 1.6 Hz, H-3″), 6.96 (3H, m, H- 3′, 4′, 5′), 6.86 (1H, d, $J_{5'',4''}$ = 3.5 Hz, H-5″), 6.75 (2H, dd, $J_{m,o}$ = 2.0, 7.8 Hz, H-2′, 6′), 6.64 (1H, dd, $J_{4''},_{3''}$ = 1.6 Hz, $J_{4''},_{5''}$ = 3.5 Hz, H-4″), 5.85 (1H, s, H-3), 5.21 (1H, d, $J_{6a,3a}$ = 6.7 Hz, H-6a), 4.11 (1H, d, $J_{3a,6a}$ = 6.7 Hz, H-3a), 3.81 (3H, s, OC***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.95, 168.74 (C=O), 167.09 (ester C=O), 154.28 (C-2″), 147.22 (C-1‴), 144.31 (C-1′), 132.18 (C-4‴), 129.14 (C-5″), 128.96 (C-3‴, 5‴), 128.01 (C-2‴, 6‴), 126.37 (C-3′, 5′), 122.76 (C-4′), 117.78 (C-2′, 6′), 110..04 (C-3″), 106.68 (C-4″), 76.35 (C-6a), 65.89 (C-3), 51.93 (O***C***H_3), 49.87 (C-3a); ESI-MS: *m/z* 441 (M+Na, 12 %), 418 (M^+, 30 %); Anal. calcd. (%) for $C_{23}H_{18}N_2O_6$: C, 66.03; H, 4.34; N, 6.70; Found (%): C, 66.29; H, 4.32; N, 6.73.

Synthesis of pyrrolo-isoxazolidines (3k): The product **3k** was obtained by treating nitrone **1k** (0.9 g, 0.004 mol) with maleimide **2b** (1.0 g, 0.004mol) under the similar conditions as explained earlier for **3a** and **4a**.

cis*-Methyl-4-((*3,3aH,6aH*)-3-(5-methylthiophen-2-yl)-4,6-dioxo-2-phenylhexahydro-*5H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3k):** Off white solid; m.p. 216-218 °C; yield: 38 %; IR (KBr, ν_{max}, cm^{-1}): 1690, 1710 (C=O), 1741 (ester C=O), 2953 (aliphatic C-H) and 3285 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (2H, dd, $J_{p,o}$ = 0.7, 7.8 Hz, H-3‴, 5‴), 7.68 (2H, d, J_o = 7.5 Hz, H-2‴, 6‴), 7.59 (1H, d, $J_{3'',4''}$ = 3.7 Hz, H-3″), 6.91 (3H, m, H-3′, 4′, 5′), 6.83 (2H, dd, $J_{m,o}$ = 2.2, 7.9 Hz, H-2′, 6′), 6.76 (1H, d, $J_{4'',3''}$ = 3.6 Hz, H-4″), 5.28 (1H, d, $J_{3,3a}$ = 8.2 Hz, H-3), 5.02 (1H, d, $J_{6a,3a}$ = 6.2 Hz, H-6a), 3.97 (1H, dd, $J_{3a,3}$ = 8.2 Hz, $J_{3a,6a}$ = 6.2 Hz, H-3a), 3.80 (3H, s, OCH₃***), 2.50 (3H, s, C***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.71, 167.99 (C=O), 166.89 (ester C=O), 148.12 (C-1‴), 144.19 (C-1′), 143.18 (C-2″), 136.23 (C-5″), 132.93 (C-4‴), 128.92 (C-3‴, 5‴),127.32 (C-2‴, 6‴), 125.84 (C-3′, 5′), 122.46 (C-4′), 120.75 (C-3″), 120.69 (C-4″), 117.93 (C-2′, 6′), 77.93 (C-6a), 64.54 (C-3), 52.07 (O***C***H_3), 49.28 (C-3a), 15.4 (C_5''-***C***H_3); ESI-MS: *m/z* 450 (M+2, 12 %), 449 (M+1, 30 %); Anal. calcd. (%) for $C_{24}H_{20}N_2O_5S$: C, 64.27; H, 4.50; N, 6.25; S, 7.15; Found (%): C, 64.01; H, 4.47; N, 6.22; S, 7.12.

Synthesis of pyrrolo-isoxazolidines (3l): The heterocycle **3l** was prepared from the reaction of nitrone **1l** (0.8 g, 0.004 mol) and maleimide **2b** (1.0 g, 0.004 mol) under the same conditions as discussed formerly for **3a** and **4a.**

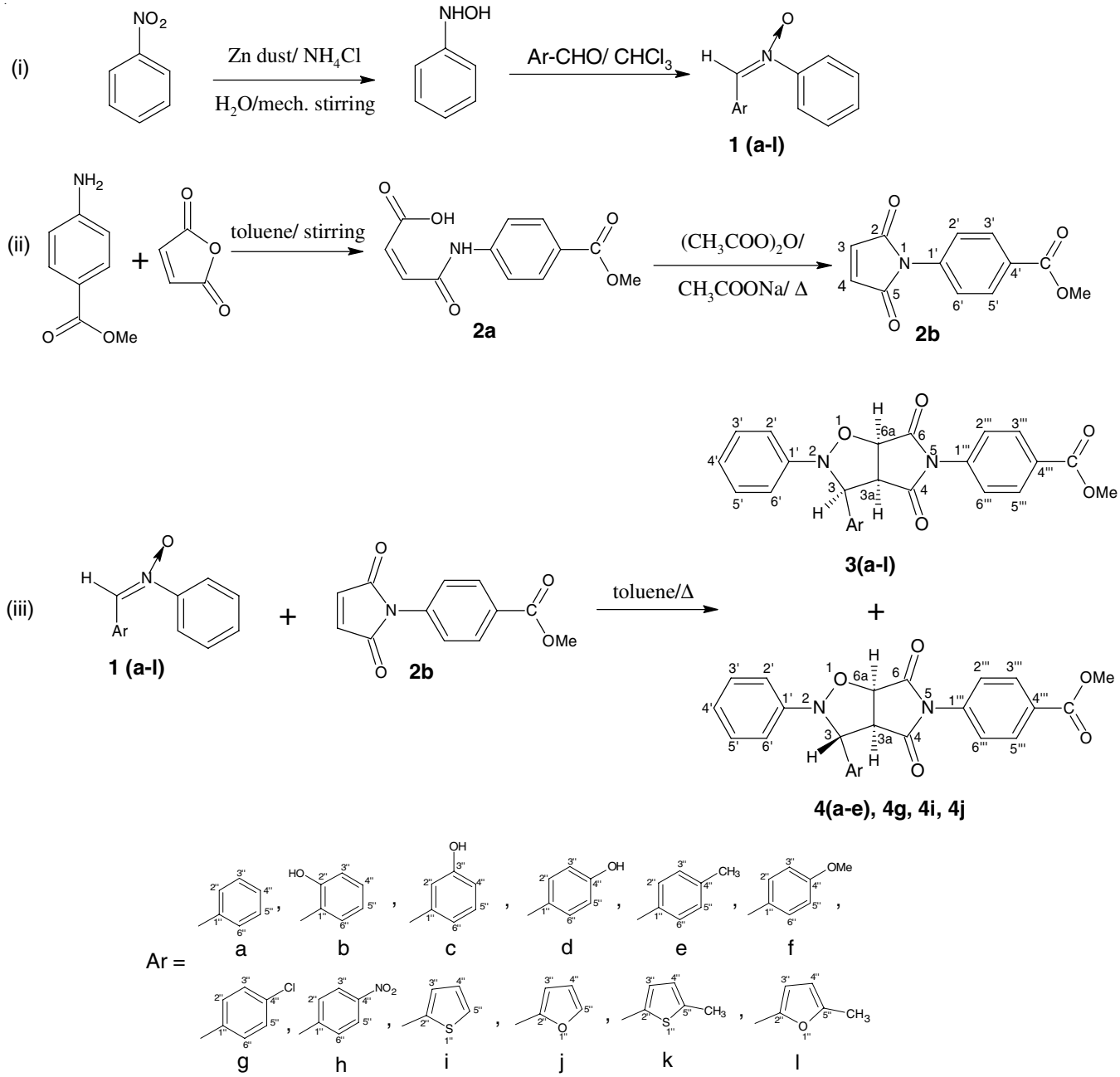
cis*-Methyl-4-((3*H*,3a*H*,6a*H*)-3-(5-methylfuran-2-yl)-4,6-dioxo-2-phenylhexahydro-5*H*-pyrrolo[3,4-d]isoxazol-5-yl)benzoate (3l):** Off white solid; m.p. 208-210 °C; yield: 40 %; IR (KBr, ν_{max}, cm^{-1}): 1697, 1719 (C=O), 1743 (ester C=O), 2958 (aliphatic C-H) and 3287 (aromatic C-H); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (2H, dt, $J_{p,o}$ = 1.0, 7.4 Hz, H-3‴, 5‴), 7.69 (2H, d, J_o = 7.1 Hz, H-2‴, 6‴), 7.60 (1H, d, $J_{3'',4''}$ = 3.5 Hz, H-3″), 6.98 (3H, m, H- 3′, 4′, 5′), 6.84 (2H, dd, $J_{m,o}$ = 2.5, 7.6 Hz, H-2′, 6′), 6.60 (1H, d, $J_{4'',3''}$ = 3.5 Hz, H-4″), 5.24 (1H, d, $J_{3,3a}$ = 8.0 Hz, H-3), 5.11 (1H, d, $J_{6a,3a}$ = 6.1 Hz, H-6a), 3.85 (1H, dd, $J_{3a,3}$ = 8.0 Hz, $J_{3a,6a}$ = 6.1 Hz, H-3a), 3.89 (3H, s, OCH₃***), 2.24 (3H, s, C_5''-C***H₃***); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.23, 168.01 (C=O), 165.50 (ester C=O), 153.89 (C-2″), 148.72 (C-1‴), 145.13 (C-1′), 142.86 (C-5″), 132.36 (C-4‴), 129.11 (C-3‴, 5‴), 128.34 (C-2‴, 6‴), 126.06 (C-3′, 5′), 123.59 (C-4′), 121.95 (C-3″), 116.89 (C-2′, 6′), 107.88 (C-4″), 76.12 (C-6a), 65.88 (C-3), 51.67 (O***C***H_3), 48.93 (C-3a), 13.8 (C_5''-***C***H_3); ESI-MS: *m/z* 434 (M+2, 3 %), 433 (M+1, 26 %), 432 (M^+, 100 %); Anal. calcd. (%) for $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48; Found (%): C, 66.39; H, 4.64; N, 6.51.

RESULTS AND DISCUSSION

The syntheses of pyrrolo-isoxazolidines **3(a-l)** and **4(a-e), 4g, 4i, 4j** was initiated from the reaction of nitrobenzene with zinc dust in the presence of NH_4Cl/H_2O to provide nitrones **1(a-l)**. The N-aryl maleimide (**2b**) required for these reactions was prepared in two steps starting from the reaction of maleic anhydride with methyl-4-aminobenzoate which led to the formation of N-aryl maleanilic acid (**2a**) [4,35]. The latter was cyclized by refluxing under $CH_3COO^-Na^+/Ac_2O$ conditions to yield product **2b**. The extensive 1,3-dipolar cycloaddition reactions of prepared nitrones **1(a-l)** were carried out by refluxing with **2b** in the presence of dry toluene. After the completion of these reactions, the mixtures were concentrated under the reduced pressure (**Scheme-I**). The resulting masses were purified by using the silica-gel column chromatography which provided two types of diastereomeric products **3(a-l)** and **4(a-e), 4g, 4i, 4j.** The elemental analysis results were helpful to confirm the purity of prepared heterocycles and their structures were characterized on the basis of their spectral data (IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS).

IR spectra of **3(a-l)** and **4(a-e), 4g, 4i, 4j** showed intense absorptions in the carbonyl group region at 1744-1738, 1721-1710 and 1699-1691 cm^{-1} which suggested the presence of three C=O groups in their structures (two of succinimide moiety and one belonging to ester). The aromatic and aliphatic C-H stretching frequencies were observed in 3290-3280 and 2959-2950 cm^{-1} region, respectively. In the heterocycle **3h** two additional bands were observed at 1518 and 1346 cm^{-1} which proved the presence of NO_2 group in this molecules. The appearance of broad bands at 3409-3402 cm^{-1} in the IR spectra of **3(b-d)** and **4(b-d)** indicated the presence of O-H group in their molecular structures.

^{1}H NMR spectra (400 MHz, DMSO-d_6) of the newly prepared diastereomers **3(a-l)** and **4(a-e), 4g, 4i, 4j** were very helpful to confirm their structures. The *p*-disubstituted benzene ring present on the N-atom of succinimide moiety provided appropriate doublet of triplets and doublet of doublets at δ 7.90-7.82 (H-3‴, 5‴) and 7.71-7.60 (H-2‴, 6‴), respectively having coupling values of $J_{p,o}$ = 1.1-0.6, 8.0-7.1 and J_o = 8.8-7.0 Hz, respectively. Three hydrogens H-3′, 4′, 5′ belonging to the N-phenyl ring of isoxazolidine moiety were responsible to generate mutiplets at δ 6.99-6.91 (3H) while H-2′, 6′ associated to the same ring were found to be centred at δ 6.89-6.71 in the form of well defined doublet of doublets ($J_{m,o}$ = 2.8-2.0, 8.1-7.1). Many substituted C_3-aryl rings furnished the signals of appropriate multiplicity at the suitable positions in the aromatic region. The singlets integrating for three protons



Scheme-I: Synthesis of pyrrolo-isoxazolidines **3(a-l)** and **4(a-e), 4g, 4i, 4j**

at δ 3.89-3.80 were easily assignable to COOC***H₃*** group present at the *para* position of the 5-N aromatic ring. In compounds **3(b-d)** and **4(b-d)**, *O-H* substituents belonging to C_3-aromatic ring were fully confirmed by the appearance of the D_2O exchangeable singlets at δ 10.36-10.53. Three protons singlets located at δ 3.90 and 2.50 could be easily allotted to OC***H₃*** **(3f)** and C***H₃*** **(3e-4e)** group, respectively. Similarly, methyl group belonging to C_3-thienyl (**3k**) and C_3-furyl (**3l**) rings were able to produce three protons singlets at δ 2.50-2.24. The interesting feature of the ^{1}H NMR spectra of the prepared diastereomers was the signal of H-3, H-6a and H-3a. In **3(a-l)**, doublets at δ 5.28-5.16, doublets at δ 5.16-5.02 and well splitted doublet of doublets at δ 3.97-3.85 were easily assigned to H-3, H-6a and H-3a, respectively. The proton H-3 appeared more downfield than H-6a and H-3a owing to its direct bonding with electronegative nitrogen atom while its benzylic nature also seems to be contributing to its downfield appearance. The inter-relationship between these hydrogens was established on the basis of their mutual coupling constants. The coupling values of $J_{3,3a}$ = 8.4-7.9 Hz and $J_{6a,3a}$ = 6.6-6.0 Hz in heterocycles **3(a-l)** describe the *cis* relationship between H-3 and H-3a as well as H-6a and H-3a. This observation certainly proves that all the three protons H-3, H-6a and H-3a are *cis* among to each other and present on the same side of molecular framework.

Similarly, three noticeable hydrogens H-3, H-6a and H-3a in **4(a-e), 4g, 4i 4j** were found to be resonating at δ 5.86-5.78 (s), 5.31-5.21 (d) and 4.16-4.08 (d), respectively. The singlet appearance of H-3 in these heterocycles suggested that this hydrogen has not been able to couple with adjacent proton

and it has *trans* relationship with H-3a. Coupling values of 6.9-6.4 Hz between H-3a and H-6a certainly established their *cis* dispositions with respect to each other.

It is evident from the above discussion that stereochemical relationship between H-6a and H-3a is similar in the both diastereomers while H-3 and H-3a are *cis* in **3(a-l)** but these hydrogens are found to be *trans* oriented to each other in **4(a-e), 4g, 4i** and **4j**. It may easily described that cycloadducts **3(a-l) and 4(a-e), 4g, 4i, 4j** have similar configurations at C-3a and C-6a while it seems to be opposite at C-3 position.

^{13}C NMR spectra (100 MHz, DMSO-d_6) of the both types of diastereomers **3(a-l)** and **4(a-e), 4g, 4i, 4j** were very instrumental to confirm their carbon skeletons. The location of three downfield signals at δ 169.91-168.02, 169.01-167.05 and 167.34-165.49 were able to confirm the presence of three C=O groups in these molecules. Three appropriate signals were easily resonating at δ 149.91-147.18 (C-1‴), 145.87-143.10 (C- 1′) and132.98-130.24 (C- 4‴). The isoxazolidine ring carbon C-3 revealed the signals at δ 66.91-64.05 while carbon atoms C-6a and C-3a present at the junction of the two heterocyclic rings yielded two appropriate resonances at δ 77.93-75.06 and 49.87-48.23, respectively. The methyl group of ester moiety (COO***C***H$_3$) furnished suitable signals at δ 52.58-51.05. In the compounds **3e**, **4e** and **3(k-l)** addional signals were also located at δ 21.6-21.4 due to the presence of ***C***H$_3$ group at the C$_3$-aromatic/hetero aromatic ring. The O***C***H$_3$ group located at the same aromatic ring (**3f)** also generated an appropriate signal at δ 55.9. The resonances of the remaining aromatic ring carbon atoms were centered at the suitable δ values.

The proposed structures of **3(a-l)** and **4(a-e), 4g, 4i, 4j** were further corroborated from their ESI-MS spectral data.

Antimicrobial activity of 3(a-l) and 4(a-e), 4g, 4i, 4j: The *in vitro* antifungal and antibacterial activities of the newly prepared products **3(a-l)** and **4(a-e), 4g, 4i, 4j** were attempted against the three fungal and four bacterial species (two Gram-negative and two Gram-positive) such as *Aspergillius janus*, *Penicillium glabrum*, *Aspergillus niger*, *Escherichia coli, Klubsellia pneumonia, Bacillius subtilis, Staphylococcus aureus*, respectively. Serial tube dilution method was applied for the MIC evaluation of these compounds [36-38]. Amoxicillin has been used as the standard drug for antibacterial analysis while antifungal study was carried out against the fluconazole. The lowest concentration of the given compound required to control the growth of microorganisms after overnight incubation was considered as minimum inhibitory concentrations (MIC). The MIC of the tested compounds was determined at the concentrations of 128, 64, 32, 16, 8 and 4 μg/mL against the above said microorganisms. DMSO was used for preparing the stock solutions. Standard drug and DMSO were used as positive and negative control, respectively.

The bacterial and fungal susceptibility of the tested compounds were examined through the appearance of turbidity after the above mentioned durations. The observed MIC values were compared with positive controls, which are presented in Table-1.

It is evident from Table-1 that heterocycles **3b, 4b, 3c, 4c, 3d** and **4d** displayed potent behaviours against *Escherichia coli, Klubsellia pneumonia, Bacillius subtilis, Staphylococcus aureus* at the MIC of 8 μg/mL while compounds **3i, 4i, 3j, 4j, 3k** and **3l** were found to be significantly active (MIC-8 μg/mL) against *Aspergillius janus*, *Penicillium glabrum*, *Aspergillus niger*. Products **3e** and **4e** showed MIC of 8 μg/mL against *Klubsellia pneumonia* and *Bacillius subtilis*, respectively. The product **3f** was also found to inhibit the growth of *Escherichia coli and Staphylococcus aureus* at the MIC of 8 and 16 μg/mL, respectively. The diastereomers **3g** and **4g** could provide noticeable activity (MIC-8 μg/mL) against *Aspergillius janus* and *Penicillium glabrum*, respectively. The product **3h** demonstrated

TABLE-1
MIC (μg/mL) DATA OF PYRROLO-ISOXAZOLIDINES **3(a-l)** AND **4(a-e), 4g, 4i, 4j**

Compd. No.	Gram-negative bacteria		Gram-positive bacteria		Fungi		
	E. coli	*K. pneumonia*	*B. subtilis*	*S. aureus*	*A. janus*	*P. glabrum*	*A. niger*
3a	32	64	32	**16**	64	32	**16**
4a	**16**	32	64	32	**16**	32	32
3b	**8**	**8**	**16**	**16**	32	**16**	32
4b	**8**	**16**	**8**	**8**	32	64	32
3c	**8**	**8**	**16**	**8**	**16**	32	64
4c	**16**	**16**	**8**	**16**	64	**16**	32
3d	**8**	**8**	**16**	**16**	32	32	**16**
4d	**16**	**8**	**8**	**8**	32	**16**	64
3e	64	**8**	32	64	32	64	**16**
4e	32	32	**8**	32	**16**	32	32
3f	**8**	32	32	**16**	32	32	**16**
3g	64	**16**	64	**16**	**8**	64	32
4g	32	32	**16**	32	32	**8**	64
3h	**16**	32	32	**16**	32	**16**	**8**
3i	64	32	32	32	**8**	**8**	**16**
4i	32	**16**	32	64	**8**	**8**	**8**
3j	64	32	**16**	32	**16**	**8**	**8**
4j	**16**	32	64	32	**8**	**16**	**8**
3k	32	**16**	32	**16**	**16**	**8**	**8**
3l	**16**	64	32	32	**8**	**16**	**8**
Amoxicillin	4	4	2	2	–	–	–
Fluconazole	–	–	–	–	2	2	2

remarkable results against *Aspergillus niger* at the MIC of 8 µg/mL. Table-1 clearly describes that compounds **3a** and **4a** exhibited moderate level of actions against *Escherichia coli, Staphylococcus aureus, Aspergillius janus* and *Aspergillus niger* at the MIC of 16 µg/mL. It is also clear from these results that most of the prepared compounds exhibited moderate activity against the tested microorganisms (MIC-16 µg/mL).

It may be derived from the above mentioned antimicrobial evaluation results that the thiophene/furan based pyrroloisoxazolidines **3(i-l), 4i** and **4j** revealed better antifungal properties whereas phenyl substituted products **3(a-h)** and **4(a-e), 4g** were able to exhibit the promising antibacterial properties.

Conclusion

It may be concluded that in the present study we have investigated the applications of 1,3-dipolar cycloaddition reactions for the synthesis of new pyrrolo-isoxazolidines which have been realized in the two diastereomeric forms (*cis* and *trans*). The stereochemistry of prepared products has been ascertained on the basis of the coupling values. Most of the prepared diastereomeric heterocycles exhibited significant antimicrobial activites. C_3-phenyl substituted products exhibited the noticeable antimicrobial behaviours while C_3-thienyl/furyl substituted heterocycles proved themselves potent antifungal agents. Thus, nature of the C_3-aryl group has been found to affect the antimicrobial activities of the prepared heterocycles.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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