Synthesis of some novel enzyme inhibitors and antibacterial agents derived from 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol

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Keeping in mind the pharmacological importance of the 1,3,4-oxadiazole moiety, a series of new S-substituted derivatives, 5a-h, of 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol (3) were synthesized. The reaction of p-toluenesulfonyl chloride (a) and ethyl isonipecotate (b) produced ethyl 1-(4-tosyl)piperidin-4-carboxylate (1) which was further transformed into 1-(4-tosyl)piperidin-4-carbohydrazide (2) by hydrazine hydrate in methanol. Compound 2 was refluxed with CS² in the presence of KOH to synthesize 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol (3). The desired compounds, 5a-h, were synthesized by stirring 3 with aralkyl halides, 4a-h, in DMF using NaH as an activator. The structures of synthesized compounds were elucidated by ’H-NMR, IR and EI-MS spectral studies. These compounds were further evaluated for enzyme inhibitory activity against lipoxigenase and alpha-glucosidase, along with antibacterial activity against Gram-negative and Gram-positive bacteria.

Uniterms: 1,3,4-Oxadiazole/antibacterial activity. 1,3,4-Oxadiazole/enzyme inhibitory activity. Isonipecotato. Sulfonamida.

INTRODUCTION

Scientists have been working to develop new drugs for combating and controlling different diseases for decades. This task has been taken up by chemists and pharmacologists to design and synthesize novel drugs to treat various disorders and diseases in plants, animals and especially humans, resulting in the emergence of various drugs. Sulfonamide, oxadiazole and piperidine derivatives with significant pharmacological activities have been introduced. 1,3,4-Oxadiazoles comprise a class of heterocyclic compounds that have a wide variety of biological activities. Their derivatives show, for example, remarkable antiproliferative (El-Din et al., 2015), antihepatitis (Tan et al., 2006), antitumor (Zhang et al., 2014), antinflammatory (Omar et al., 1996), and antibacterial (Bhardwaj et al., 2009; Li et al.,...
MATERIAL AND METHODS

General

The melting points of synthesized compounds were determined with a Griffin and George melting point apparatus using an open capillary tube and were uncorrected. The purity of the synthesized compounds was confirmed using thin-layer chromatography (TLC), performed on aluminum plates pre-coated with silica gel G-25-UV254, carried out under different solvent systems with varying ratios of ethyl acetate and n-hexane to obtain a single spot, visualized using a 254-nm UV lamp. The IR spectra were recorded using the KBr pellet method on a Jasco-320-A spectrometer (wave number in cm⁻¹). Proton nuclear magnetic resonance spectra were recorded in CDCl₃ solvent on a Bruker spectrometer operating at 400 MHz. Chemical shifts are given in ppm. Mass spectra (EI-MS) were recorded on a JMS-HX-110 spectrometer, with a data system.

Preparation of ethyl 1-(4-tosyl)piperidin-4-carboxylate (1)

Ethyl isoniazidolate (b; 15.0 mmol) was dissolved in 15 mL distilled water in a 250 mL round bottom (RB) flask. Then p-toluenesulfonyl chloride (a; 15.0 mmol) was added to the reaction mixture gradually over 15-20 minutes. The pH was maintained at 9.0 by basic aqueous solution of Na₂CO₃ (5%) at room temperature. The reaction mixture was stirred for 3-4 hours and monitored using TLC. At the completion of the reaction, concentrated HCl (11 M, 2 mL) was slowly added to adjust the pH to 6.0 and allowed to stand for 10-15 minutes. The precipitate was filtered and washed with cold distilled water to yield on drying the desired white-colored compound 1. White amorphous solid; yield: 89%; M.P.: 70-72 ºC; molecular formula: C₁₅H₁₂NO₄S; molecular weight: 311; IR (KBr, cm⁻¹) vₙmax: 3067 (C-H stretching of aromatic ring), 1732 (C=O stretching), 1353 (C=O aromatic stretching), 1335 (-SO₂- stretching), 1079 (C-O bond stretching); ¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.62 (d, J = 8.0 Hz, 2H, H-2'' & H-6''), 7.32 (d, J = 8.0 Hz, 2H, H-3'' & H-5''), 3.98 (q, J = 7.2 Hz, 2H, O-CH₂), 3.71-3.68 (m, 2H, H-3'), 2.54-2.48 (m, 2H, H-2' & H-6'), 2.42 (s, 3H, CH₃), 2.10-2.08 (m, 2H, H-3' & H-5'), 1.60-1.86 (m, 2H, H-2' & H-6'), 1.15 (t, J = 7.2 Hz, CH₃); EI-MS (m/z): 311 [M]+, 266 [C₁₃H₁₀NO₅S]+, 184 [C₁₀H₈NO₃S]+, 170 [C₆H₇NO₂S]+, 155 [C₅H₆O₂S]+, 91 [C₄H₇]+.

Preparation of 1-(4-tosyl)piperidin-4-carbohydrazide (2)

Ethyl 1-(4-tosyl)piperidin-4-carboxylate (1; 13.0 mmol) was dissolved in 20 mL methanol in a 250 mL RB flask. Hydrazine hydrate (80%, 10 mL) was added dropwise to the reaction mixture, which was then refluxed for 4-5 hours. Completion of the reaction was determined by TLC. At the end of the reaction, excess solvent was evaporated to yield a white crystalline product, compound 2, which was washed with cold distilled water and dried. White crystalline solid; yield: 91%; M.P.: 128-130 ºC; molecular formula: C₁₅H₁₃N₂O₄S; molecular weight: 297; IR (KBr, cm⁻¹) vₙmax: 3348 (N-H stretching), 3063 (C-H stretching of aromatic ring), 1682 (C=O stretching), 1534 (C=C aromatic stretching), 1339 (-SO₂- stretching); ¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.61 (d, J = 8.0 Hz, 2H, H-2'' & H-6''), 7.33 (d, J = 8.0 Hz, 2H, H-3'' & H-5''), 3.72-3.69 (m, 2H, H-3'), 2.54-2.48 (m, 2H, H-2' & H-6'), 2.42 (s, 3H, CH₃), 2.12-2.10 (m, 2H, H-3' & H-5'), 1.58-1.84 (m, 2H, H-3' & H-5'); EI-MS (m/z): 297 [M]+, 266 [C₁₃H₁₀NO₅S]+, 238 [C₁₀H₈NO₃S]+, 184 [C₁₀H₈NO₃S]+, 170 [C₆H₇NO₂S]+, 155 [C₅H₆O₂S]+, 91 [C₄H₇]+.

Preparation of 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol (3)

1-(4-Tosyl)piperidin-4-carbohydrazide (2;
Synthesis of some novel enzyme inhibitors and antibacterial agents derived from 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol

A calculated amount of 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol (3; 8.0 mmol) was added to a 50-mL RB flask. N,N-Dimethylformamide (DMF, 10 mL) was added to dissolve 3, followed by the addition of sodium hydride (8.0 mmol) to the reaction mixture at room temperature and stirring for 0.5 hour. The aralkyl halides 4a-h were then added in an equimolar ratio to 3, and the reaction was further stirred for 3-4 hours. The progress of reaction was monitored with TLC until a single spot was obtained. Distilled water was added to the reaction mixture, and products 5a-h were recovered by filtration, which were then washed and dried.

4-(2-(Benzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine (5a)

White crystalline solid; yield: 85%; M.P.: 128-130 °C; molecular formula: C_{18}H_{16}N_{2}O_{5}S_{2}; molecular weight: 429; IR (KBr, cm⁻¹) ν_max: 3047 (C-H stretching of aromatic ring), 1649 (C=N stretching of oxadiazole ring), 1544 (C=C aromatic stretching), 1339 (SO₂ stretching), 1248 & 1079 (C-O-C bond stretching); 1H-NMR (400 MHz, CDCl₃, δ / ppm): 7.62 (d, J = 8.0 Hz, 2H, H-2’ & H-6’), 7.53 (d, J = 6.8 Hz, 1H, H-3’’), 7.37 (dd, J = 7.6, 1.2 Hz, 1H, H-6’’), 7.31 (d, J = 8.0 Hz, 2H, H-2’’ & H-6’’), 7.24-7.17 (m, 2H, H-3’ & H-5’), 1.98-1.90 (m, 2H, H-3’ & H-5’); EIMS (m/z): 465 [M⁺], 266 [C₁₃H₁₀NO₂S]⁻, 238 [C₁₂H₁₀NO₂S]⁻, 184 [C₈H₆NO₂S]⁻, 170 [C₂H₅NO₂S]⁻, 91 [C₃H₇]⁻, 83 [C₂H₅N]⁻, 71 [C₅H₇F]⁻.

4-(2-(4-Fluorobenzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine (5b)

White amorphous solid; yield: 83%; M.P.: 135-137 °C; molecular formula: C_{18}H_{22}FN_{2}O_{5}S_{2}; molecular weight: 447; IR (KBr, cm⁻¹) ν_max: 3055 (C-H stretching of aromatic ring), 1658 (C=N stretching of oxadiazole ring), 1554 (C=C aromatic stretching), 1361 (SO₂ stretching), 1256 & 1087 (C-O-C bond stretching), 1178 (C-F bond stretching); 1H-NMR (400 MHz, CDCl₃, δ / ppm): 7.62 (d, J = 8.0 Hz, 2H, H-2’ & H-6’), 7.35 (dd, J = 8.0 Hz, 2H, H-3’ & H-5’), 6.98 (br. t, J_{ab,b,b} = 8.8 Hz, 2H, H-3’’ & H-5’’), 4.37 (s, 2H, CH₂), 3.67-3.64 (m, 2H, H-2’ & H-6’), 2.85-2.78 (m, 1H, H-4’), 2.59-2.53 (m, 2H, H-3’ & H-5’), 2.42 (s, 3H, CH₃), 2.10-2.06 (m, 2H, H-3’ & H-5’), 1.98-1.89 (m, 2H, H-3’ & H-5’); EIMS (m/z): 447 [M⁺], 266 [C₁₃H₁₀NO₂S]⁻, 238 [C₁₂H₁₀NO₂S]⁻, 184 [C₈H₆NO₂S]⁻, 170 [C₂H₅NO₂S]⁻, 109 [C₃H₇F]⁻, 91 [C₃H₇]⁻, 83 [C₂H₅N]⁻, 83 [C₂H₅F]⁻, 64 [C₅H₇]⁻, 51 [C₅H₇F]⁻.
4-(2-(3-Chlorobenzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine (5d)

Fluffy white amorphous solid; yield: 78%; M.P.: 168-170 °C; molecular formula: C_{12}H_{14}ClNO_{5}S; molecular weight: 463; IR (KBr, cm\(^{-1}\)) \(\nu_{max}\): 3049 (C-H stretching of aromatic ring), 1639 (C=N stretching of oxadiazole ring), 1543 (C=C aromatic stretching), 1356 (-SO\(_2\) stretching), 1243 & 1078 (C-O-C bond stretching), 701 (C-Br bond stretching); \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta / ppm\)): 7.63 (d, \(J = 8.4\) Hz, 2H, H-2'' & H-6''), 7.37 (s, 1H, H-2'''), 7.31 (d, \(J = 8.4\) Hz, 2H, H-3'' & H-5''), 7.28-7.22 (m, 3H H-4'' to H-6''), 4.35 (s, 2H, CH\(_2\)-7''), 3.67-3.64 (m, 2H, H-2'' & H-6''), 2.86-2.78 (m, 1H, H-4'), 2.59-2.53 (m, 2H, H-2' & H-6'), 2.42 (s, 3H, CH\(_3\)-4'), 2.10-2.06 (m, 2H, H-3' & H-5'), 1.98-1.89 (m, 2H, H-3' & H-5'); EIMS (m/z): 465 [M+2]\(^+\), 266 [C\(_9\)H\(_6\)NO\(_5\)S]\(^+\), 155 [C\(_6\)H\(_5\)NO\(_2\)S]\(^+\), 95 [C\(_4\)H\(_3\)Cl]\(^+\), 91 [C\(_3\)H\(_2\)]\(^+\), 83 [C\(_3\)H\(_2\)N]\(^+\), 64 [C\(_3\)H\(_4\)]\(^+\), 51 [C\(_3\)H\(_3\)].

4-2(4-Chlorobenzylthio)-1,3,4-oxadiazol-5-yl-1-(4-tosyl)piperidine (5e)

White amorphous solid; yield: 85%; M.P.: 210-212 °C; molecular formula: C\(_{12}\)H\(_{14}\)ClNO\(_5\)S; molecular weight: 463; IR (KBr, cm\(^{-1}\)) \(\nu_{max}\): 3049 (C-H stretching of aromatic ring), 1639 (C=N stretching of oxadiazole ring), 1543 (C=C aromatic stretching), 1356 (-SO\(_2\) stretching), 1243 & 1078 (C-O-C bond stretching), 699 (C-Cl bond stretching); \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta / ppm\)): 7.62 (d, \(J = 8.4\) Hz, 2H, H-2'' & H-6''), 7.27 (d, \(J = 8.4\) Hz, 2H, H-3'' & H-5''), 7.33-7.24 (m, 4H, H-2'' to H-6''), 4.35 (s, 2H, CH\(_2\)-7''), 3.67-3.64 (m, 2H, H-2'' & H-6''), 2.84-2.79 (m, 1H, H-4'), 2.59-2.53 (m, 2H, H-2' & H-6'), 2.42 (s, 3H, CH\(_3\)-4'), 2.10-2.05 (m, 2H, H-3' & H-5'), 1.98-1.88 (m, 2H, H-3' & H-5'); EIMS (m/z): 465 [M+2]\(^+\), 266 [C\(_9\)H\(_6\)NO\(_5\)S]\(^+\), 155 [C\(_6\)H\(_5\)NO\(_2\)S]\(^+\), 95 [C\(_4\)H\(_3\)Cl]\(^+\), 91 [C\(_3\)H\(_2\)]\(^+\), 83 [C\(_3\)H\(_2\)N]\(^+\), 64 [C\(_3\)H\(_4\)]\(^+\), 51 [C\(_3\)H\(_3\)].

4-(2-(4-Bromobenzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine (5f)

White amorphous solid; yield: 83%; M.P.: 190-192 °C; molecular formula: C\(_{12}\)H\(_{14}\)BrNO\(_5\)S; molecular weight: 443; IR (KBr, cm\(^{-1}\)) \(\nu_{max}\): 3067 (C-H stretching of aromatic ring), 1655 (C=N stretching of oxadiazole ring), 1554 (C=C aromatic stretching), 1365 (-SO\(_2\) stretching), 1259 & 1093 (C-O-C bond stretching); \(^{1}H\)-NMR (400 MHz, CDCl\(_3\), \(\delta / ppm\)): 7.63 (d, \(J = 8.0\) Hz, 2H, H-2'' & H-6''), 7.32-7.30 (m, 3H, H-3'', H-5'' & H-3'''), 7.18-7.10 (m, 3H, H-4'' to H-6''), 4.43 (s, 2H, CH\(_2\)-7''), 3.67-3.64 (m, 2H, H-2' & H-6'), 2.85-2.79 (m, 1H, H-4'), 2.60-2.55 (m, 2H, H-2' & H-6'), 2.42 (s, 3H, CH\(_3\)-4'), 2.39 (s, 3H, CH\(_3\)-2''), 2.11-2.07 (m, 2H, H-3' & H-5'), 1.99-1.93 (m, 2H, H-3' & H-5'); EIMS (m/z): 443 [M]\(^+\), 266 [C\(_{11}\)H\(_{10}\)NO\(_5\)S]\(^+\), 184 [C\(_{10}\)H\(_{9}\)NO\(_3\)S]\(^+\), 170 [C\(_7\)H\(_6\)NO\(_2\)S]\(^+\), 106 [C\(_5\)H\(_4\)S]\(^+\), 91 [C\(_3\)H\(_2\)]\(^+\), 83 [C\(_3\)H\(_2\)N]\(^+\), 65 [C\(_3\)H\(_3\)]\(^+\), 51 [C\(_3\)H\(_4\)]\(^+\).
Biological activity assays

Lipoxygenase inhibition assay

Lipoxygenase activity was assayed according to a previously reported method (Baylac, Racine, 2003; Nafeesa et al., 2015). The change in absorbance was determined at 234 nm for all the test compounds.

α-Glucosidase inhibition assay

α-Glucosidase inhibitory activity was performed according to a previously reported method (Abbasi et al., 2014; Chapdelaine et al., 1978). The change in absorbance was determined at 400 nm for all the test compounds.

Antibacterial activity assay

The antibacterial activity was performed under aseptic conditions in sterile 96-well microplates. The principle of the method is that as microbial cell population increases during log phase growth, there is an increase in the absorbance of the broth medium (Kaspady et al., 2009; Nafeesa et al., 2015). Ciprofloxacin was used as reference standard.

Statistical analysis

Minimum inhibitory concentration (MIC) for antibacterial activity and IC\textsubscript{50} (concentration causing 50% inhibition) for enzyme inhibition was determined with suitable dilutions for each sample, and results were calculated using EZ-Fit software (Perrella Scientific Inc., Amherst, NH, USA). The results are presented as mean ± SEM for triplicate determinations after statistical analysis performed with MS Excel 2010.

RESULTS AND DISCUSSION

The goal of our study was to produce S-substituted derivatives of oxadiazole compounds having p-toluene sulfonyl and piperidine moieties and also to screen them for enzyme inhibitory activity. A series of derivatives, 5a-h, were synthesized according to the protocol given in Figure 1. The different aralkyl groups are given in Table I.

Chemistry

Compound 5a was synthesized as a white crystalline compound. The molecular formula C\textsubscript{21}H\textsubscript{23}N\textsubscript{3}O\textsubscript{3}S\textsubscript{2} was established with molecular ion peak m/z 429 in EIMS and by proton counting using \textsuperscript{1}H-NMR spectra. The IR spectrum gave absorption bands at 3047, 1649, 1544, 1339, 1248 and 1079 cm\textsuperscript{-1}, which were assigned to C-H (stretching of aromatic ring), C=N (stretching of oxadiazole ring), C=C (aromatic stretching), -SO\textsubscript{2} (stretching), and C-O-C (stretching of oxadiazole ring), respectively. In EIMS spectra, the peak at m/z 266 showed cleavage...
of the benzyl sulfide group along with partial cleavage of the oxadiazole ring in 5a, while the peak at m/z 155 showed the presence of the p-toluenesulfonyl group and the peak at m/z 83 the presence of a piperidine moiety. The other prominent fragments are given in Figure 2. In the aromatic region of 1H-NMR, signals appeared at δ 7.62 (d, J = 8.0 Hz, 2H, H-2'' & H-6'') and 7.31 (d, J = 7.6 Hz, 2H, H-3'' & H-5''), which were assigned to the toluenesulfonyl moiety; the signals appearing at δ 7.38-7.26 (m, 5H, H-2''' to H-6'''') were assigned to the mono-substituted benzene ring of the benzyl moiety. The signals resonating at δ 3.66-3.63 (m, 2H, H-e-2' & H-e-6'), 2.84-2.79 (m, 1H, H-4'), 2.60-2.53 (m, 2H, H-e-2' & H-e-6'), 2.10-2.05 (m, 2H, H-e-3' & H-e-5') and 1.98-1.89 (m, 2H, H-a-3' & H-a-5') were assigned to the piperidine moiety; and the signal at 4.40 (s, 2H, CH2-7''') was assigned to the methylene group of the benzyl moiety. On the basis of the above findings, the structure of 5a was determined to be 4-(2-(benzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine. In a similar way, the structures of other synthesized compounds were characterized by using 1H-NMR, IR and EIMS data.

### Enzyme inhibitory activity (in vitro)

The screening of synthesized compounds against the enzymes lipoxygenase and α-glucosidase revealed that most of the compounds were moderate to weakly moderate inhibitors of these enzymes. The experimental results are given in Table II below. Screening of these synthesized compounds proved 5b to be the most active inhibitor against lipoxygenase. Other compounds showed no activity, except 5d against this enzyme. Only the S-substituted benzyl compound containing fluorine at the para position showed better activity against this enzyme. The better activity of 5b was attributed to the presence of a fluorne at position ‘4’ in the benzyl moiety. The compounds 5d and 5f remained inactive against α-glucosidase. 5b showed the highest inhibitory activity with an IC50 of 181.92 ± 0.17 µM compared to 38.25 ± 0.12 µM of acarbose, the reference standard. The high inhibitory activity of this compound could be attributed to the S-substituted benzyl moiety containing a highly electronegative group at the para position, which showed the best catalysis-blocking capability. The other compounds showed moderately weak inhibition, but all 4-substituted halogenated benzyl group-containing compounds had relatively better activity in a sequential order. The IC50 values of 4-substituted halogenated benzyl group-containing compounds indicated that the presence of small and more electronegative atoms leads to better inhibition of the enzyme. The inhibition order of molecules containing 4-substituted halogenated benzyl group was fluorinated > chlorinated > brominated. The overall descending order of inhibitory activity of the synthesized molecules was as follows, 5b, 5e, 5c, 5a, 5g and 5h.

### Antibacterial activity (in vitro)

The in vitro MIC and percentage inhibition results for antibacterial activity of the synthesized compounds against Gram-positive and Gram-negative bacteria are given in Tables III and IV, using ciprofloxacin as reference standard. All the synthesized compounds displayed strong to moderate antibacterial activity against all the bacterial strains studied except for Staphylococcus aureus against which only 5h was moderately active. Compounds 5a and

<table>
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<th>Comp.</th>
<th>R</th>
<th>Comp.</th>
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<tr>
<td>5a</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Cl})</td>
<td>5e</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Cl})</td>
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<tr>
<td>5b</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{F})</td>
<td>5f</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Br})</td>
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<td>5c</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Cl})</td>
<td>5g</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Br})</td>
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<tr>
<td>5d</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Cl})</td>
<td>5h</td>
<td>-(\text{CH}_2)-(\text{H}_2)-3''(\text{Br})</td>
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Synthesis of some novel enzyme inhibitors and antibacterial agents derived from 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol

5g showed strong to moderate activity and 5b showed moderate activity against all strains except Staphylococcus aureus. 5h exhibited moderate activity against all except Pseudomonas aeruginosa. The compounds 5d and 5e were active against only three strains, Salmonella typhi, Escherichia coli and Bacillus subtilis. 5f was active only

### TABLE II - Enzyme inhibitory activity against lipoxygenase and α-glucosidase enzymes

<table>
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<th>Compound</th>
<th>Lipoxygenase (LOX)</th>
<th>α-Glucosidase</th>
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<td>Inhibition (%) at 0.5 mM</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; µM</td>
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<tr>
<td>5a</td>
<td>47.81 ± 0.06</td>
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<tr>
<td>5b</td>
<td>99.12 ± 0.41</td>
<td>78.38 ± 0.12</td>
</tr>
<tr>
<td>5c</td>
<td>11.71 ± 0.14</td>
<td>-</td>
</tr>
<tr>
<td>5d</td>
<td>56.95 ± 0.33</td>
<td>229.72 ± 0.16</td>
</tr>
<tr>
<td>5e</td>
<td>12.25 ± 0.89</td>
<td>-</td>
</tr>
<tr>
<td>5f</td>
<td>47.43 ± 0.56</td>
<td>-</td>
</tr>
<tr>
<td>5g</td>
<td>11.62 ± 0.41</td>
<td>-</td>
</tr>
<tr>
<td>5h</td>
<td>14.37 ± 0.29</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td>93.79 ± 1.27</td>
<td>22.41 ± 1.3</td>
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</table>

Note: a = Baicalein, b = Acarbose. IC<sub>50</sub> values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ-Fit Enzyme Kinetics software (Perrella Scientific Inc.)

FIGURE 2 - Proposed mass fragmentation pattern of 4-(2-(benzylthio)-1,3,4-oxadiazol-5-yl)-1-(4-tosyl)piperidine (5a).
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against two strains, *Salmonella typhi* and *Bacillus subtilis*, while 5e showed no activity at all. Against *Salmonella typhi*, the three compounds 5e, 5f and 5g were the most efficient with MIC values of 9.15 ± 0.24, 8.24 ± 0.90 and 9.69 ± 0.16 µM, respectively, relative to 7.45 ± 0.58, MIC of reference. Against *Escherichia coli*, the two compounds 5d and 5e showed the lowest MIC values, i.e., 9.78 ± 0.66 and 10.09 ± 0.05 µM, respectively, relative to that of the reference, 7.16 ± 0.58 µM. 5a, 5f and 5g inhibited *Bacillus subtilis* with MIC values of 9.65 ± 0.24, 9.10 ± 0.41 and 9.27 ± 0.17 µM, respectively, compared to 7.14 ± 0.18 µM for the reference drug. The overview of the most active compounds revealed that the nature and position of halogen-substitution in the molecule greatly affected the biological behavior of the molecules.

**CONCLUSION**

The structures of the synthesized compounds are supported by spectroscopic data. From enzyme inhibition and antibacterial data, it was evident that different S-substituted derivatives of 5-(1-(4-tosyl)piperidin-4-yl)-1,3,4-oxadiazol-2-thiol are valuable enzyme inhibitors and potential antibacterial agents. It is interesting and worth knowing that α-glucosidase is inhibited by all 4-halogenated benzyl S-substituted compounds while lipoxygenase is inhibited by only 4-fluoro benzyl S-substituted compounds. This information could be used for selective inhibition of alpha-glucosidase and lipoxygenase and may be of use in drug discovery programs. The antibacterial activity suggested that compounds 5a, 5f and 5g against *Bacillus subtilis*, 5d against *Escherichia coli* and 5e, 5f and 5g against *Salmonella typhi* could be considered for further in vivo evaluation by the pharmaceutic industry.

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