Evaluation of Sulfonamide Derivatives of Dagenan Chloride as Lipoxygenase and α-Glucosidase Inhibitors

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Abstract

Purpose: To study the enzyme inhibition activity of various sulfonamides derived from dagenan chloride.

Methods: The synthesis of N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (3) was carried out by gearing up 1-naphthylamine (1) with dagenan chloride (2) in water in the presence of Na\(_2\)CO\(_3\) solution. Further, compound 3 was treated with various alkyl/aralkyl halides (4a-o) to yield 5a-o in an aprotic polar solvent, DMF (dimethylformamide), using LiH as activator. The structures of all the synthesized molecules were corroborated by infra red spectroscopy (IR), proton nuclear magnetic resonance (1H-NMR) and electron impact mass spectrometry (EI-MS) and screened against lipoxygenase and α-glucosidase using baicalein and acarbose as reference standards, respectively.

Results: Molecules 5e and 5j showed good lipoxygenase inhibition activity with IC\(_{50}\) (50 % inhibition concentration) value of 132.21 ± 0.73 and 133.33 ± 0.87 μmol/L, respectively, relative to reference, while 5m was the most active inhibitor of α-glucosidase with IC\(_{50}\) of 19.41 ± 0.55 μmol/L relative to reference.

Conclusion: Most of the synthesized compounds are good inhibitors of lipoxygenase but moderate inhibitors of α-glucosidase enzyme. These molecules should be evaluated for their in vivo activity to determine their potentials as anti-inflammatory and anti-diabetic drugs.

Keywords: 1-Naphthylamine, Sulfonamide, Lipoxygenase, α-Glucosidase, Dagenan chloride, Enzyme inhibitor, Anti-inflammatory, Anti-diabetic

INTRODUCTION

Sulfonamides have been used as therapeutic agent, first as antibacterial agents but later extended to treat other diseases. The first sulfonamide which was identified as the active in vivo metabolite of red azo dye was prontosil [1-3]. In addition, sulfonamides are known to inhibit various enzymes such as carbonic anhydrase [4]. Sulfonamides due to their resemblance to p-aminobenzoic acid (PABA), act as competitive inhibitors and so block the synthesis of tetrahydrofolic acid required by bacteria for growth [3,5].

Lipoxygenase (EC 1.13.11.12) extensively exists in animals and plants. Iron (Fe\(^{3+}\)) structurally present in lipoxygenase gets oxidized to catalytically active Fe\(^{3+}\) products including hydro peroxide derivatives such as 15-hydroperoxy-
eicosatetraenoic acid (15-HPETE), leukotrienes from arachidonic acid as a substrate, and 13-
hydroperoxy-octadecadienoic acid (13-HPODE) from linoleic acid as a substrate [6]. One of the
key products of lipoxygenases consists of bioactive lipids known as leukotrienes [7].
Leukotrienes are potential mediators of various inflammatory disorders such as bronchial asthma
[8]. α-Glucosidase (EC 3.2.1.20) is located in the brush-border surface membrane of small
intestinal cells [9]. α-Glucosidase inhibitors are used as oral anti-diabetic drugs for patients with
type-2 diabetic mellitus. Postprandial hyperglycemia has a vital role in the
development of type-2 diabetes and complications associated with this disease such as nephropathy, neuropathy, micoangiopathy and macroangiopathy [10]. The inhibitors of this enzyme can retard the liberation of D-glucose of
oligosaccharides and disaccharides from dietary complex carbohydrates and delay glucose
absorption, resulting in reduced postprandial hyperglycemia [11].

Literature survey has revealed that even minor modifications in the structure of molecules can
be responsible for varied anti-microbial activities. In continuation of our previous work in this regard
[12-14], new sulfonamides derived from dagenan chloride have been synthesized in order to
assess their enzyme inhibition activities.

**EXPERIMENTAL**

Thin layer chromatography (TLC) was performed on pre-coated silica gel G-25-UV254 plates using
ethyl acetate and n-hexane solvent systems, with detection under 254 nm. 1H-NMR spectra, with δ-
values in ppm and J-values in Hz, were recorded in CDCl3 using Bruker spectrometer at 400 MHz.
IR spectra was recorded by KBr pellet method using Jasco-320-A spectrophotometer. Mass
spectra was measured on Finnigan MAT-112 instrument and melting point on Gallonkamp
apparatus by open capillary tube and was uncorrected.

**Procedure for synthesis of N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (3)**

An equimolar mixture of 1-naphthylamine (1; 10.0 mmol) and dagenan chloride (2; 10.0 mmol)
was suspended in 25 mL water, in a round bottom (RB) flask (100 ml), with pH = 9, adjusted
and maintained by aqueous Na2CO3 at room temperature. The reaction solution was stirred for
2 h and monitored by TLC. Concentrated HCl was added gradually to adjust the pH to 2.0. The
precipitate was collected by filtration, washed with distilled water and dried to afford compound
3. The product was re-crystallized from methanol.

**General procedure for synthesis of N-
alkyl/aralkyl-N-(naphthalen-1-yl)-4-
acetamidobenzenesulfonamide (5a-o)**

Molecule 3 (0.1 mmol) was taken in a RB flask (50 ml) and dissolved in DMF (10.0 ml), followed
by the addition of LiH (0.1 mmol). The mixture was stirred for 30 min at room temperature and then alkyl/aralkyl halides (4a-o) were added. Further stirring was continued for 3 h along with
TLC monitoring. The products, 5a-o, were precipitated by adding water and were isolated by
filtration, washing with distilled water; and crystallized from methanol.

**Lipoxygenase assay**

Lipoxygenase activity was assayed by a previously reported method [15] with slight
modifications. Lipoxygenase assay mixture was prepared with sodium phosphate buffers, test
compound and enzyme. After thoroughly mixing, pre-reading and pre-incubating, substrate was
added. The variation in absorbance was noted after incubation. The experiments were performed in triplicate with baicalein as reference.

**α-Glucosidase assay**

α-Glucosidase inhibition activity was performed following a slightly modified method [11]. Like
lipoxygenase assay, α-glucosidase assay was carried out using phosphate buffer saline, test
compound and enzyme. After mixing, pre-incubation and pre-reading, a substrate (p-
nitrophenyl glucopyranoside) was added for initiation. The absorbance was noted after
incubation. The experiments were performed in triplicate with acarbose as reference.

**Statistical analysis**

Determinations were carried out in triplicate and statistical analysis was performed using
Microsoft Excel 2010, and the results presented as mean ± SEM. IC50 values (concentration at
which there is 50% in enzyme catalyzed reaction) compounds were calculated using EZ-
Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA). IC50 values were calculated
(as mean of three independent experiments) from the graph by dilution of compounds to
different concentrations. The statistical analysis included 85% CL.
**RESULTS**

The spectral data for the synthesized molecules (3, 5a-o) are as follows.

**N-(Naphthalen-1-yl)-4-acetamidobenzenesulfonamide (3)**

Move Amorphous Solid; Yield: 80 %; M.P.: 222 °C; Molecular Formula: C_{19}H_{18}N_{2}O_{2}S; Molecular Mass: 340; IR (KBr, cm\(^{-1}\)) \(\lambda_{\text{max}}\): 3080 (Ar C=S), 1650 (Ar C=C), 1645 (\=N=O). 1H-NMR (CDCl\(_3\), 400 MHz, \(\delta/ppm\): 8.24 (d, \(J = 8.4\) Hz, 2H, H-3' & H-5'), 7.80 (d, \(J = 6.4\) Hz, 1H, H-4), 7.66 (dd, \(J = 6.4, 1.9\) Hz, 1H, H-5), 7.66 (dd, \(J = 6.4, 1.9\) Hz, 1H, H-8), 7.49 (dt, \(J = 8.4, 3.6\) Hz, 1H, H-6), 7.49 (dt, \(J = 8.4, 3.6\) Hz, 1H, H-7), 7.43 (t, \(J = 8.0\) Hz, 1H, H-3), 7.35 (d, \(J = 6.4\) Hz, 1H, H-2), 6.66 (d, \(J = 8.4\) Hz, 2H, H-2' & H-6'), 2.16 (s, 3H, -CO-CH\(_3\))

**N-Ethyl-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5a)**

Move Amorphous Solid; Yield: 70 %; M.P.: 186 °C; Molecular Formula: C\(_{20}\)H\(_{26}\)N\(_2\)O\(_3\)S; Molecular Mass: 368; IR (KBr, cm\(^{-1}\)) \(\lambda_{\text{max}}\): 3080 (Ar C=S), 1650 (Ar C=C), 1645 (\=N=O), 1390 (SO\(_2\)); ¹H-NMR (CDCl\(_3\), 400 MHz, \(\delta/ppm\): 7.97 (d, \(J = 7.9\) Hz, 2H, H-3' & H-5'), 7.84 (dd, \(J = 8.0, 4.2\) Hz, 1H, H-5), 7.82 (dd, \(J = 8.0, 3.4\) Hz, 1H, H-8), 7.75 (d, \(J = 7.9\) Hz, 1H, H-4), 7.67 (t, \(J = 11.2\) Hz, 1H, H-3), 7.50 (d, \(J = 6.0\) Hz, 1H, H-2), 7.38 (t, \(J = 7.9\) Hz, 1H, H-6), 7.38 (dt, \(J = 8.0, 7.9\) Hz, 1H,
H-7, 7.05 (d, J = 7.9 Hz, 2H, H-2' & H-6'), 3.23 (q, J = 7.2 Hz, 2H, H-1''), 3.76 (t, J = 6.7 Hz, 3H, CH2-2''), 2.21 (s, 3H, -CO2CH3); EI-MS (m/z): 368 (9 %), 275 (13 %), 198 (5 %), 134 (9 %), 127 (100 %), 102 (4 %), 65 (43 %), 51 (5 %), 29 (5 %).

**N-(Propan-2-yl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5c)**

Pink Crystalline Solid; Yield: 70 %; M.P: 225 °C; Molecular Formula: C20H17NO4S; Molecular Mass: 382; IR (KBr, cm⁻¹) νmax: 3690 (νN≡O), 1667 (O=C), 1621 (C=S), 1529 (C=C), 1412 (C-O), 1256 (C-S), 1107 (C-NH2), 1051 (C-O-C), 1012 (C-S-S-C), 876 (C-C).

**N-(Propan-2-yl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5d)**

Move Amorphous Solid; Yield: 80 %; M.P: 177 °C; Molecular Formula: C20H17NO4S; Molecular Mass: 380; IR (KBr, cm⁻¹) νmax: 3082 (νN≡O), 1679 (C=O), 1647 (C=O), 1398 (C=S), 1108 (C-O), 1003 (C-S-S-C), 868 (C-C).

**N-(Butan-2-yl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5e)**

Black Sticky Solid; Yield: 65 %; Molecular Formula: C27H22N2O4S; Molecular Mass: 396; IR (KBr, cm⁻¹) νmax: 3015 (νC-H), 1657 (νN≡O), 1396 (νS=O), 1619 (C-H), 1569 (C=C), 1405 (νS=O), 1275 (C-O), 1150 (C-S-S-C), 1072 (C-O-C), 770 (C-C).
N-(2-Chlorobenzyl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonylamide (5k)

Move Amorphous Solid; Yield: 68 %; M.P: 160 °C; Molecular Formula: C_{25}H_{23}N_{2}O_{3}SCl; Molecular Mass: 464; IR (KBr, cm⁻¹) vmax: 3019 (Ar-C-H), 1673 (Ar-C=C), 1657 (-HNC=O), 1382 (SO₂⁻), 765 (C-Cl); 1H-NMR (CDCl₃, 400 MHz, δ/ppm): 8.98 (d, J = 7.6 Hz, 1H, H-8), 7.84 (d, J = 8.0 Hz, 2H, H-3' & H-5''), 7.73-7.71 (m, 2H, H-2' & H-6'), 7.41-7.33 (m, 2H, H-4' & H-7), 7.11-7.07 (m, 1H, H-3), 7.05-6.99 (m, 4H, H-3'' to H-6''), 6.95 (d, J = 7.2 Hz, 1H, H-2), 6.91 (d, J = 8.0 Hz, 2H, H-2' & H-6'), 6.95 (d, J = 7.2 Hz, 1H, H-2), 4.86 (s, 2H, H-7''), 2.20 (s, 3H, -COCH₃); EI-MS (m/z): 466 (2 %), 464 (6 %), 275 (7 %), 198 (16 %), 134 (11 %), 127 (37 %), 125 (100 %), 102 (1 %), 98 (23 %), 65 (51 %), 51 (6 %).

N-(4-Chlorobenzyl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonylamide (5i)

Purple Crystalline Solid; Yield: 78 %; M.P: 186 °C; Molecular Formula: C_{25}H_{23}N_{2}O_{3}SCl; Molecular Mass: 464; IR (KBr, cm⁻¹) vmax: 3039 (Ar-C-H), 1679 (Ar-C=C), 1649 (-HNC=O), 1379 (SO₂⁻), 769 (C-Cl); 1H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.88 (d, J = 8.0 Hz, 2H, H-3' & H-5''), 7.75-7.73 (m, 2H, H-5 & H-6), 7.63 (t, J = 9.2 Hz, 1H, H-8), 7.40-7.36 (m, 2H, H-4 & H-7), 7.26 (t, J = 10.4 Hz, 1H, H-3), 7.13 (d, J = 8.4 Hz, 2H, H-3'' & H-5''), 7.05 (d, J = 8.4 Hz, 2H, H-2' & H-6''), 6.88 (d, J = 7.2 Hz, 1H, H-2), 6.84 (d, J = 7.2 Hz, 2H, H-2' & H-6'), 4.77 (s, 2H, H-7''), 2.18 (s, 3H, -COCH₃); EI-MS (m/z): 466 (1 %), 464 (3 %), 275 (9 %), 198 (13 %), 134 (10 %), 127 (42 %), 125 (100 %), 102 (2 %), 98 (19 %), 65 (33 %), 51 (6 %).

N-(4-Bromobenzyl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonylamide (5m)

Move Amorphous Solid; Yield: 80 %; M.P: 179 °C; Molecular Formula: C_{25}H_{23}N_{2}O_{3}SBr; Molecular Mass: 509; IR (KBr, cm⁻¹) vmax: 3027 (Ar-C-H), 1679 (Ar-C=C), 1657 (-HNC=O), 1398 (SO₂⁻), 680 (C-Br); 1H-NMR (CDCl₃, 400 MHz, δ/ppm): 7.88 (d, J = 8.0 Hz, 2H, H-3' & H-5''), 7.75 (dd, J = 6.8, 3.4 Hz, 1H, H-8), 7.63-7.58 (m, 2H, H-5 & H-6), 7.14-7.10 (m, 2H, H-4 & H-7), 7.28 (d, J = 8.4 Hz, 2H, H-3'' & H-5''), 7.23 (d, J = 7.6 Hz, 2H, H-2' & H-6'), 7.01 (t, J = 6.8 Hz, 1H, H-3), 6.99 (d, J = 8.0 Hz, 2H, H-2' & H-6''), 6.83 (d, J = 7.2 Hz, 1H, H-2), 2.93 (s, 2H, H-7''), 2.17 (s, 3H, -COCH₃); EI-MS (m/z): 511 (4 %), 509 (4 %), 275 (7 %), 198 (31 %), 170 (100 %), 143 (15 %), 134 (12 %), 127 (35 %), 102 (3 %), 65 (46 %), 51 (9 %).
N-(2-Phenylethyl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5n)

Move Sticky Solid; Yield: 60 %; Molecular Formula: C_{25}H_{26}N_{2}O_{3}S; Molecular Mass: 444; IR (KBr, cm⁻¹) v_{max}: 3015 (Ar C=C), 1680 (Ar C=C), 1657 (HNC-O), 1395 (SO₂); H-NMR (CDCl₃, 400 MHz, δ/ppm): 8.11 (d, J = 9.2 Hz, 2H, H-3' & H-5'), 7.84 (dd, J = 8.0, 7.6 Hz, 1H, H-8), 7.65-7.56 (m, 2H, H-5 & H-6), 7.53-7.46 (m, 2H, H-4 & H-7), 7.35 (t, J = 8.0 Hz, 1H, H-3), 3.02-2.78 (1H, H-6').

Table 1: Enzyme inhibition activity of synthesized molecules

| Compound | Lipoygenase enzyme inhibition (%) | IC₅₀ (µM) | α-Glucosidase enzyme inhibition (%) | IC₅₀ (µM) |
|----------|----------------------------------|----------|----------------------------------|----------|
| 3        | 98.02±0.97                       | 171.93±0.89 | -2.33±0.12                       | -        |
| 5a       | 97.13±0.87                       | 260.24±0.92 | 5.48±0.17                        | -        |
| 5b       | 92.34±13.77                      | 299.24±0.94 | 85.31±3.34                      | 189.23±1.52|
| 5c       | 68.12±1.13                       | 341.6±0.97  | 93.42±3.22                      | 349.21±1.93|
| 5d       | 47.13±0.78                       | -         | 57.21±2.31                      | >450     |
| 5e       | 99.41±0.97                       | 132.21±0.73 | 33.41±0.14                      | -        |
| 5f       | 81.49±1.34                       | 273.61±0.89 | 30.90±1.7                       | -        |
| 5g       | 39.60±0.67                       | -         | -3.01±3.12                      | -        |
| 5h       | 96.95±1.63                       | 256.41±0.76 | 67.58±2.64                      | 388.21±1.27|
| 5i       | 63.76±0.69                       | 355.61±0.88 | 30.55±2.34                      | -        |
| 5j       | 98.51±1.18                       | 133.33±0.87 | 93.11±2.12                      | 139.27±1.81|
| 5k       | 3.23±0.08                        | -         | 2.71±1.55                       | -        |
| 5l       | 2.87±2.15                        | -         | 8.45±1.34                       | -        |
| 5m       | 95.93±1.23                       | 139.72±0.51 | 83.21±1.25                      | 19.41±0.55|
| 5n       | 8.12±0.77                        | -         | 4.63±1.22                       | -        |
| 5o       | 86.93±0.89                       | 256.6±0.69  | 83.21±3.75                      | 341.33±2.43|
| Control  | 93.79±1.27                       | 22.4±1.3   | 92.23±0.14                      | 38.25±0.12|

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Anti-enzymatic activity

Among the synthesized molecules, almost all of them remained active against lipoxygenase enzyme relative to baicalein, a reference standard with IC₅₀ value of 22.4 ± 1.3 µmoles. N-(butan-1-yl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5e) and N-benzyl-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5j) showed good lipooxygenase activity due to small aliphatic and unsubstituted aralkyl groups and IC₅₀ values of 132.21 ± 0.73 and 133.33 ± 0.87 µmoles/L, respectively.

The α-glucosidase enzyme activity results for the synthesized derivatives (5a-o) demonstrate that a few were active with excellent inhibitory potential, based on IC₅₀ values (Table 1). Among these molecules, 5b, 5c, 5i, 5j, 5m and 5o were active but N-(propan-1-yl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5b), N-benzyl-N-(naphthalen-1-yl)-4-acetamidobenzene sulfonamide (5j) and N-(4-bromobenzyl)-N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide (5m) were good inhibitors with IC₅₀ values of 189.23 ± 1.52, 139.27 ± 1.81 and 19.41 ± 0.55 µmoles/L respectively, relative to acarbose with IC₅₀ value of 38.25 ± 0.12 µmoles/L. The compound, 5m, showed good activity against both lipooxygenase and α-glucosidase.
DISCUSSION

The sulfonamide (compound 3) was obtained as an amorphous powder. Its molecular formula was determined through HR-MS showing [M]+ peak at m/z 340.3962 corresponding to the molecular formula C_{18}H_{16}N_{2}O_{3}S (Calcd. for 340.4162). The molecular formula is also supported by the protons in its ^1H-NMR spectrum. The signals in its ^1H-NMR spectrum, appearing at δ 8.24 (d, J = 8.4 Hz, 2H, H-3' & H-5') and δ 6.66 (d, J = 13.6 Hz, 2H, H-2' & H-6') are typical for the protons of the p-substituted ring and a singlet at δ 2.16 (s, 3H, -COCH$_3$) for acetamyl group. Naphthyl group showed different signals at δ 7.80 (d, J = 6.4 Hz, 1H, H-4), 7.66 (dd, J = 6.4, 1.9 Hz, 1H, H-5), 7.66 (dd, J = 6.4, 1.9 Hz, 1H, H-8), 7.49 (dt, J = 8.4, 3.6 Hz, 1H, H-6), 7.49 (dt, J = 8.4, 3.6 Hz, 1H, H-7), 7.43 (t, J = 8.0 Hz, 1H, H-3) and 7.35 (d, J = 6.4 Hz, 1H, H-2). On the basis of the above cumulative evidence, the structure of 3 was assigned as N-(naphthalen-1-yl)-4-acetamidobenzenesulfonamide. The mass fragmentation pattern of N-benzyl-N-(naphthalen-1-yl)-4-acetamidobenzene sulfonamide (5j) is outlined in Figure 1. Similarly, the proposed structures of other compounds were corroborated.

The compounds bearing sulfamoyl moiety have previously been synthesized by our group [12,13] and their biological activities have been shown to be related to structural modification in the molecules. The overview of compounds showing activity against both enzymes revealed that molecules bearing small N-substitution like propyl group were better inhibitors because of best fit to active site of enzyme. Also N-substitution by benzyl and 4-bromobenzyl presented better result owing to their ability to generate better π-π interactions with the active site. Thus the compounds 5b, 5j and 5m remained significantly efficient among the whole series of synthesized molecules.

![Figure 1: Mass fragmentation pattern of N-benzyl-N-(naphthalen-1-yl)-4-acetamidobenzene sulfonamide (5j)](image-url)
CONCLUSION

Good yield has been obtained for all the synthesized compounds and definitive spectral structural elucidation attained. The synthesized compounds (5a-o) show potent anti-enzymatic activity against the two enzymes tested, especially lipoxygenase.

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