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ARTICLE

Aldose Reductase Inhibitory Activity Studies of Substituted 3-Sulfenylindoles

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ABSTRACT

Sulfenylindoles obtained by direct sulfenylation of indoles using diphenyl disulphide in the presence of catalytic amount of iodine in DMSO have been studied for aldose reductase inhibitory activity. As expected, different 3-sulfenylindoles derivatives that are synthesized exhibit good-to-excellent aldose reductase inhibitory activity.

KEYWORDS

3-Sulfenylindoles, Diphenyl disulphide, Aldose reductase inhibitory activity, Enzyme.

Asian Journal of Organic & Medicinal Chemistry

Volume: 3 Year: 2018
Issue: 3 Month: July–September
pp: 60–64
DOI: https://doi.org/10.14233/ajomc.2018.AJOMC-P98

Received: 18 December 2017
Accepted: 22 February 2018
Published: 25 September 2018

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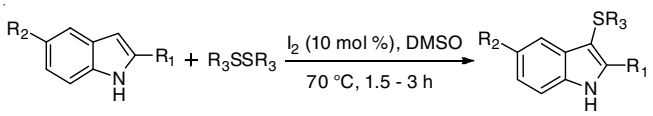
INTRODUCTION

Indole is an important heterocycle present in a variety of pharmaceutically important products and natural products [1]. Literature studies reveal that the indoles have a protective effect against estrogen-related cancer such as breast, colon, uterus and other types of cancer [2]. At present, there are about 1500 indole alkaloids containing simple and complex indole derivatives, and a large number of them are at the fore of drug development. Among the different indole derivatives, 3-thiophenylindole has been shown to display potent anticancer activity and has gained popularity as a useful therapeutic phytochemical [3]. The observed activity is being attributed to vinyl sulfenyl moiety at 3-position and electron-donating groups on phenyl ring seem to enhance the observed activity in 2.0 to 4.5 μm range. The proposed mechanism of action involves inhibition of tubulin assembly that plays an important role in demobilization of chromosomes during cell division. They are also known to inhibit MCF-7 cell growth at nanomolar concentrations. It is remarkable to note that 3,4,5-trimethoxy-substituted arylthioindoles showed potencies comparable to those of the reference compounds colchicine and combretastatin A-4 in both assembly of tubulin and inhibition of cell growth assays. 5-Chloro-3-(phenylsulfonyl) indole-2-carboxamide has been reported to be a novel, non-nucleoside inhibitor of HIV-1 reverse transcriptase [4].

Also, 3-thioindoles have recently attracted the attention of pharmaceutical industries due to their therapeutic applications in different disease states such as cancer [2], HIV [4], obesity [5], heart disease [6] and allergies [7]. As part of our ongoing research on sulfenylindoles, an efficient strategy is developed for the synthesis of 3-sulfenylindoles using easily

available benchtop reagents (**Scheme-I**). Herein, we report the aldose reductase inhibitory (ARI) activity of the synthesized 3-sulfenylindoles.



Scheme-I: Sulfenylation of substituted indoles using iodine

Aldose reductase belongs to aldo-keto reductase superfamily of proteins and it is the key enzyme that brings about the conversion of glucose into sorbitol, first and rate-limiting step of polyol pathway. It is an NADPH-dependent cytosolic enzyme composed of 315 amino acid residues. The protein is devoid of any structural carbohydrate, lipid or metal ion and the catalytic site consists of hydrophobic residues and an anion well, which includes NADPH or $NADP^+$. The enzyme exhibits broad substrate specificity and catalyzes the reduction of aldehydes produced in the biological system and hence plays a very important role in the clearance of toxic aldehydes from the system. It also plays a osmoregularity role in renal homeostasis through fluctuation in the concentration of osmolyte sorbitol. Under hyperglycemic conditions, enhanced concentration of glucose triggers the polyol pathway, leading to accumulation of hydrophilic sorbitol, which cannot diffuse through the membrane. This electrolyte imbalance causes hydration, osmotic stress and membrane damage. Further, reduced levels of NADPH and increased ratio of NADPH/$NADP^+$ followed by reduced levels of the important antioxidant GSH lead to the development of microvascular diabetic complications [8-12]. Hence, targeting aldose reductase in the polyol pathway is of therapeutic significance to combat the development of late diabetic complications and aldose reductase inhibitors have received great attention [9-11,13-16]. Although a large variety of small-molecule aldose reductase inhibitors have been reported, only a few have reached clinical trials. Orally active alrestatin was reported in 1973 and was tested on diabetic neuropathy patients [17]. There is a great need for the development of new therapeutically active aldose reductase inhibitors. Since 3-sulfenylindoles have been shown to display interesting biological activities, we explored its aldose reductase inhibitor activity on aldose reductase obtained from bovine lens and the results are presented herein.

EXPERIMENTAL

General procedure: A mixture of an indole (0.4 mmol), disulfide (0.24 mmol) and I_2 (10 mol %) in DMSO (2 mL) was stirred at 70 ºC for 0.5 to 3 h until complete consumption of the starting material as monitored by TLC. After completion of the reaction, 5 % sodium thiosulphate solution (5 mL) was added and extracted with dichloromethane (2 × 15 mL). The combined dichloromethane extracts were washed with brine solution and dried over anhydrous sodium sulphate, and the evaporation of solvent under the reduced pressure afforded 90 to 98 % yield of the desired product.The product was purified by passing through 100 to 200 mesh silica gel column using chloroform and ethyl acetate as an eluent to afford the sulfenylindole product.

Enzyme inhibitory assay: Aldose reductase obtained from the bovine lens was assayed as per the method reported by Hayman and Kinoshita [18]. The incubation mixture for assay consisted of phosphate buffer (0.067 M; final pH of reaction mixture was 6.2), lithium sulphate (0.2 M), NADPH (5×10^{-5} M), enzyme solution (100 µL), DL-glyceraldehyde (5×10^{-4} M) and distilled water made to a final volume of 3 mL with or without inhibitor.The inhibitor was dissolved in DMSO to get the desired concentration and the blank contains all the reagents except substrate DL-glyceraldehyde. The addition of NADPH initiates the reaction which was followed by UV spectrophotometer at 340 nm [18].

Spectral data

3-(Phenylthio)-1*H*-indole (1): Off white solid; m.p.: 151-153 ºC. IR (KBr, μ_{max}, cm^{-1}): 3397.1, 3109.5, 3080.8, 2923.9, 2853.8, 1564.3, 1547.7, 1451.8, 1364.09, 1088.4, 1024.9, 790.8, 818.5, 751.1 and 518.8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03-7.19 (m, 6H), 7.28 (d, 2H, *J* = 7.6 Hz), 7.45 (d, 1H, *J* = 8.0 Hz), 7.5 (d, 1H, *J* = 2.5 Hz), 7.61 (d, 1H, *J* = 8.0 Hz), 8.41 (br, 1H). EI-MS: *m/z* (rel.abund.%): 224 (M^{-1}, 100).

5-Bromo-2-methyl-3-(phenylthio)-1*H*-indole (2): Off white solid; m.p.: 156-159 ºC. IR (KBr, μ_{max}, cm^{-1}): 3354.3, 3115.7, 3075.7, 2914.1, 2823.3, 1557.3, 1550.2, 1461.7, 1344.2, 1087.4, 1024.1, 809.2, 801.0, 762.1 and 510.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 6.69-7.78 (m, 3H), 7.12-7.25 (m, 4H), 7.65 (s, 1H), 10.11 (s, 1H). EI-MS: *m/z* (rel.abund.%): 318 (M, 100), 320 (M, 98 (Br).

5-Bromo-3-(4-chlorophenylthio)-2-methyl-1*H*-indole (3): White solid; m.p.: 153-155 ºC. IR (KBr, μ_{max}, cm^{-1}): 3354.9, 3116.2, 3074.2, 2912.9, 2824.7, 1554.9, 1555.4, 1464.4, 1342.7, 1083.6, 1025.7, 801.2, 801.5, 762.6 and 510.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H),6.69-7.79 (m, 3H), 7.11-7.25 (m, 3H), 7.66 (s, 1H), 10.12 (s, 1H). EI-MS *m/z* (rel.abund.%): 352 (M, 80), 354 (M, 100 (Br, Cl)).

5-Bromo-3-(3-chloro-4-fluorophenylthio)-2-methyl-1*H*-indole (4): Pale pink solid; m.p.: 129-131 ºC. IR (KBr, μ_{max}, cm^{-1}): 33574.1, 3112.4, 3072.1, 2922.1, 2834.2, 1559.1, 1553.9, 1466.6, 1344.3, 1080.5, 1030.1, 810.2, 807.3, 769.3, 520.8 and 517.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 6.81-7.06 (m, 3H), 7.17-7.35 (m, 3H), 7.64 (d, *J* = 1.8 Hz, 1H), 8.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.14, 98.88, 112.24, 114.42, 116.70, 116.99, 121.26, 121.40, 121.64, 125.22, 125.31, 125.36, 127.25, 131.77, 134.06, 135.36, 135.41, 142.73, 154.34 and 157.61. HRMS: Found mass 369.94848, calculated mass 369.94690 with m.f.: $C_{15}H_{11}NSBrClF$.

5-Bromo-2-methyl-3-(3,4,5-trimethoxyphenylthio)-1*H*-indole (5): White solid; m.p.: 165-168 ºC. IR (KBr, μ_{max}, cm^{-1}): 3294.9, 3126.5, 3094.7, 2915.3, 2834.4, 1543.5, 1547.4, 1454.4, 1345.2, 1089.2, 1027.1, 821.2and 810.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.67 (s, 6H), 3.78 (s, 3H), 6.27 (s, 2H), 7.17-7.27 (m, 2H), 7.70 (s, 1H), 8.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.14, 55.97, 60.83, 99.20, 102.80, 112.20, 114.04, 121.35, 124.98, 132.00, 134.01, 135.44, 142.59 and 153.41. HRMS: Found mass 408.02841, calculated mass 408.02635, with m.f.: $C_{18}H_{19}O_3NSBr$.

3-(Naphthalen-2-ylthio)-1*H*-indol-5-ol (6): White solid; m.p.: 170-173 ºC. IR (KBr, μ_{max}, cm^{-1}): 3402.4, 3394.0, 3108.1, 3055.6, 1620.8, 1588.4, 1486.8, 1464.9, 1181.1, 850.6, 816.7

and 797.9. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.69-6.74 (m, 2H), 7.21 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz), 7.32 (d, 1H, *J* = 8.4 Hz), 7.36-7.44 (m, 2H), 7.48 (d, 1H, *J* = 1.5 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 3.0 Hz), 7.75-7.81 (m, 2H), 8.81 (s, 1H), 11.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 97.77, 102.12, 112.51, 112.91, 122.45, 124.21, 125.12, 126.61, 127.60, 128.306, 129.64, 130.79, 131.03, 132.62, 133.27, 137.00 and 151.684. HRMS: Found mass 292.08014, calculated mass 292.07906 with m.f.: $C_{18}H_{14}NOS$.

4-Methoxy-3-(3,4,5-trimethoxyphenylthio)-1*H*-indole-2-carboxylic acid (7): Off white solid; m.p.: 161-164 ºC. IR (KBr, μ_{max}, cm^{-1}): 3331.4, 3173.9, 2995.9, 2958.2, 2837.9, 1677.5, 1628.5, 1587.9, 1509.1, 1459.4, 1437.9, 1388.5, 1327.8, 1208.7, 1047.8, 1024.1, 969.0, 799.8 and 637.2. ^{1}H NMR (500 MHz, $CDCl_3$ and DMSO-d_6): δ 3.66 (s, 6H), 3.73 (s, 3H), 3.74 (s, 3H), 6.40 (s, 2H), 6.91-6.95 (m, 2H), 7.42 (d, 1H, *J* = 8.2 Hz), 11.27 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$ and DMSO-d_6): δ 55.13, 55.63, 60.31, 100.31, 104.41, 107.45, 113.58, 116.72, 129.37, 129.80, 131.12, 132.39, 135.50, 152.81, 154.51 and 162.03. HRMS: Found mass 390.10309, calculated mass 390.10118 with m.f.: $C_{19}H_{20}NO_6S$.

Methyl-3-(3,4-dimethoxyphenylthio)-5-methoxy-1*H*-indole-2-carboxylate (8): Off white solid; m.p.: 140-143 ºC. IR (KBr, μ_{max}, cm^{-1}): 3320.3, 2974.0, 2950.1, 2903.5, 2834.8, 2251.9, 1679.3, 1634.5, 1579.8, 1503.9, 1452.93, 1271.1, 1233.1, 1208.3, 1168.6, 1024.7, 810.0, 729.4and 508.9. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 6.72, (d, 1H, *J* = 8.3 Hz), 6.83 (dd, 1H, *J* = 2.1, *J* = 8.4 Hz), 6.90-6.91 (m, 2H), 6.99 (dd, 1H, *J* = 2.1, *J* = 9.4 Hz), 7.30 (d, 1H, *J* = 9.4 Hz), 9.09 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.13, 55.53, 55.90, 55.96, 101.42, 111.67, 112.71, 113.04, 117.96, 121.60, 127.83, 128.09, 130.25, 130.97, 147.81, 144.12, 155.10 and 161.63. HRMS: Found mass 374.10827, calculated mass 374.10657 with m.f.: $C_{19}H_{21}NO_5S$.

Methyl-5-methoxy-3-(phenylthio)-1*H*-indole-2-carboxylate (9): Off white solid; m.p.: 206-209 ºC. IR (KBr, μ_{max}, cm^{-1}): 3305.2, 3072.5, 2988.1, 2941.2, 2834.1, 2699.7, 1933.6, 1879.9, 1682.5, 1582.4, 1507.9, 1476.2, 1454.0, 1439.3, 1438.3, 1340.8, 1258.8, 1207.9, 1169.1, 1120.1, 1023.4, 969.8, 687.7 and 518.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.95 (s, 3H), 6.96 (d, 1H, *J* = 2.0 Hz), 7.10 (dd, 1H, *J* = 2.0 Hz, 8.8 Hz), 7.05-7.10 (m, 1H), 7.15-7.20 (m, 4H), 7.33 (d, 1H, *J* = 8.8 Hz), 9.31 (s, 1H). EI-MS: *m/z* (rel. abund.%): 312 (M^{-1}, 100).

Ethyl-3-(4-chlorophenylthio)-5-methoxy-1*H*-indole-2-carboxylate (10): Off white solid; m.p.: 166-168 ºC. IR (KBr, μ_{max}, cm^{-1}): 3279.0, 3073.7, 2981.2, 2936.2, 2906.2, 2833.2, 1682.4, 1507.1, 1474.4, 1453.0, 1418.6, 1254.8, 1209.2, 1166.8, 1010.5 and 813.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 7.2 Hz), 3.78 (s, 3H), 4.34 (q, 2H, *J* = 7.2 Hz), 7.02-7.23 (m, 5H), 7.29 (s, 1H), 7.33-7.44 (m, 1H), 9.27 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.33, 55.99, 61.42, 101.01, 108.72, 113.20, 128.11, 128.15, 128.78, 129.25, 130.73, 130.83, 130.92, 136.71, 155.49 and 161.03. HRMS: Found mass 362.06196, calculated mass 362.06177 with m.f.: $C_{18}H_{17}NO_3Cl$.

Ethyl-5-methoxy-3-(phenylthio)-1*H*-indole-2-carboxylate (11): White solid; m.p.: 144-146 ºC. IR (KBr, μ_{max}, cm^{-1}): 3305.9, 3071.5, 2986.8, 2939.2, 2903.0, 2831.1, 2699.3, 1936.3, 1879.9, 1682.3, 1582.8, 1507.4, 1476.3, 1454.4, 1439.3, 1438.4, 1340.4, 1258.4, 1207.0, 1169.7, 1120.8, 1058.6, 1024.4, 966.8 and 687.7. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.2 Hz), 3.73 (s, 3H), 4.36 (q, 2H, *J* = 7.2 Hz), 6.97 (d, 1H, *J* = 2.0 Hz), 7.10 (dd, 1H, *J* = 2.0 Hz, 8.8 Hz), 7.06-7.10 (m, 1H), 7.15-7.20 (m, 4H), 7.33 (d, 1H, *J* = 8.8 Hz), 9.29 (s, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 14.12, 55.54, 61.35, 101.18, 109.46, 113.09, 118.00, 125.17, 127.08, 128.67, 129.06, 130.82, 130.86, 137.93, 155.28 and 161.26. HRMS: Found mass 350.08369, calculated mass 350.08214 with m.f.: $C_{18}H_{17}NO_3SNa$.

3-(3,4,5-Trimethoxyphenylthio)-1*H*-indole (12): Off white solid; m.p.: 139-142 ºC. IR (KBr, μ_{max}, cm^{-1}): 3396.1, 3109.5, 3082.2, 2923.9, 2853.8, 1561.3, 1547.4, 1451.9, 1364.1, 1088.9, 1024.0, 818.1 and 803.2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (s, 6H), 3.77 (s, 3H), 6.39 (s, 2H), 7.15-7.18 (m, 1H), 7.24 (d, 1H, *J* = 8.4 Hz), 7.42(d, 1H, *J* = 8.4 Hz), 7.48 (d, 1H, *J* = 2.1 Hz), 7.64 (d, 1H, *J* = 7.3 Hz), 8.53 (s, 1H). EI-MS: *m/z* (rel. abund.%): 316 (M^{+1}, 100).

RESULTS AND DISCUSSION

The observed inhibitory activity of sulfenylindoles is given in Table-1. As anticipated, all the derivatives exhibited good activity in 20 to 50 μM range. Among them, entries 1, 2, 3, 9, 10 and 11 exhibited activity better than well-known inhibitor quercetin, while entry 4, 5, 6, 7, 8 and 12 exhibit good activity in 40-50 μM range. The substituents on indole moiety and disulphide seem to have an impact on the observed activity. In comparison, 2-methyl indoles display less activity and further substitution on both the rings leads to a reduction in activity. On the other hand, ethyl carboxylate group at 2-position seems to enhance activity and tolerates substituents on the aromatic ring of indole and sulfide. The hydrolysis of ester to carboxylic acid reduces aldose reductase inhibitor activity. It looks like lipophilicity of sulfenylindoles plays a crucial role in determining the activity.

Conclusion

In conclusion, as envisaged, 3-sulfenyl indole derivatives studied display good-to-excellent aldose reductase inhibitor (ARI) activity and the nature of substituents on aromatic ring of indole and sulfide exerts a profound effect on the observed activity.

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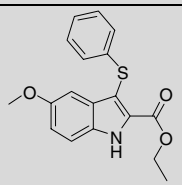
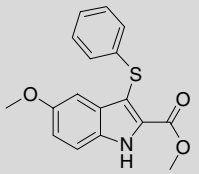
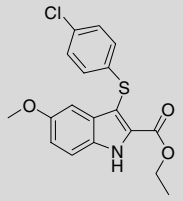
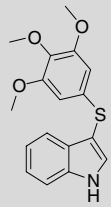
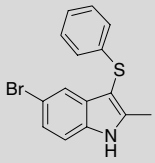
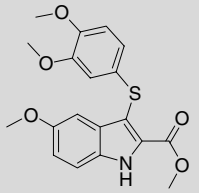
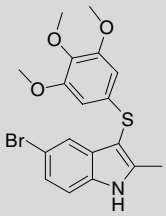
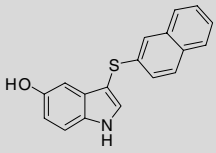
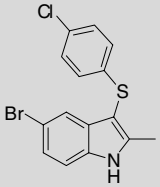
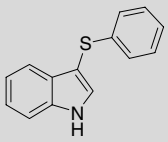
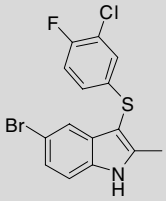
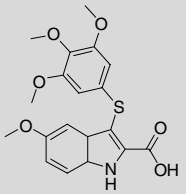
TABLE-1
ALDOSE REDUCTASE inhibition ACTIVITY OF 3-SULFENYLINDOLES

S. No	Indole	Concentration	Inhibition (%)	$IC_{50\ \mu m}$	S. No	Indole	Concentration	Inhibition (%)	$IC_{50\ \mu m}$
1		20 µM	95.40	9.93	7		50 µM	93.75	12.18
2		20 µM	98.43	9.45	8		40 µM	98.43	10.02
3		20 µM	97.70	9.87	9		20 µM	98.85	9.52
4		20 µM	89.65	10.58	10		20 µM	95.31	9.94
5		50 µM	98.85	11.23	11		20 µM	97.70	9.87
6		50 µM	93.75	11.15	12		30 µM	93.75	15.12
					13	Quercetine	30	98.97	10

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