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Bezafibrate Scaffold Derived Hydrazide-Hydrazones: Synthesis and Antioxidant Activities

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A NEW series of Bezafibrate derived hydrazide-hydrazone analogues were generated by using some five membered, fused heterocyclic and aromatic aldehydes. All the hydrazones were obtained in good yields from methanol at 60-80 °C for 5-8 hours stirring. Moreover, the compounds were also screened for their anti-oxidant activity potentiality at four different concentrations using DPPH method. Among these compounds, compound **6k** analogue of bezafibrate was found to be the most active at all the tested concentrations (≈ 40% inhibition at 25 **µg**/mL) followed by **6j** (4-hydroxy, 3-methoxy 5-bromo analogue ≈ 35% at 25 **µg**/mL) compared to standard ascorbic acid (49.6% at 25 **µg**/mL).

Keywords: Bezafibrate, Hydrazide-hydrazone, Antioxidant, Ascorbic acid.

Introduction

Basically hydrazines possess versatile biological activities. In recent years, a lot of biologically important hydrazide–hydrazone derivatives with a number of functional groups have been synthesized from many different carbonyl compounds. They were found to possess anticancer [1-4], anti-inflammatory [5], anticonvulsant [6], antiviral [7], and antiprotozoal [8] anti-tumoral [9] , anti-microbial [10-15], analgesic [16], anti-platelet [17], antimycobacterial [18], and anti-tubercular [19] activities. The main route to synthesize hydrazide–hydrazone derivatives is the heating of suitable hydrazides with different aldehydes in various organic solvents like ethanol, methanol or butanol [20-23]. Recently, hydrazide-hydrazones of bezafibrate scaffolds, were synthesized and screened for antimicrobial activity [20-22]. Moreover, the results of antimicrobial activity of these compounds were found to be significant and supporting the biological importance of the hydrazide-hydrazones. In the present investigation some new heterocyclic aldehyde derived bezafibrate hydrazide-hydrazones were attempted (Scheme 1) and screened for antioxidant activity.

Experimental

Materials and methods

All the reactions were carried out in oven-dried glassware (120 °C). Ethyl acetate and hexanes from Merck Chemical Co. were dried and distilled from CaH_2. Tetrahydrofuran from Chemlabs Chemicals Co. was dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. Acetonitrile, ethanol were purchased from Merck Chemicals.

Thin layer chromatography (TLC) was performed on percolated plates (silica gel 60 F_{254}), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycleultra pure

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silica gel (particle size 40–63 µm, 100–200 mesh). Proton NMR spectra were obtained on Bruker (400 MHz) spectrometer by use of dimethylsulfoxide-d_6 (DMSO) as solvent and TMS as internal standard. Proton NMR chemical shifts were referenced to residual protonated solvents (δ 2.5 ppm for dimethylsulfoxide). Carbon-13 NMR spectra were obtained on a MR (100 MHz) and Bruker spectrometer by use of dimethylsulfoxide as the solvent TMS as internal standard.

Preparation of N-(4-hydroxyphenethyl)-4-chlorobenzamide (3)[14]:

To a solution of 4-(2-aminoethyl) phenol (**1,** 25 g, 0.18 mol) in tetrahydrofuran (100 mL) was added sodium bicarbonate (16.84 g, 0.20 mol) followed by water (25 mL) and cooled to 0-5 °C. To the above reaction mixture, 4-chlorobenzoylchloride (**2**, 33.5 g, 0.20 mol) was added over a period of 20 min and stirred at the same temperature for 3h. The reaction was monitored by using T.L.C, after completion of the reaction, water (225 mL) was added and stirred at 0-5 °C for 1 h, the pure solid **3** obtained was filtered, washed with water (50 mL) and dried under vacuum to yield 45 g (91 %) as an off white solid. M.p: 181-183 °C and the reported value is 180-182°C[14].

Ethyl 2-(4-(2-(4-chlorobenzamido) ethyl) phenoxy)-2-methylpropanoate (4)[14]:

To a solution of 4-chloro-N-(4-hydroxyphenethyl)benzamide (**3**, 50 g, 0.18 mol), in methyl isobutyl ketone (125 mL) was added potassium carbonate(62.6 g, 0.45 mol), and ethanol (125 mL) was heated at 85 °C for 30 min and added tetrabutylamonium bromide-TBAB (11.7 g, 0.0362) followed by ethyl α-bromoisobutyrate (77.8 g,0.40 mol) at the same temperature. The reaction mixture was heated to 85 °C for 24 h. The reaction was monitored by T.L.C, after completion of the reaction, mixture was cooled to room temperature for 30 min and filtered to discard the inorganic salts. The filtrate was concentrated at 40 °C to obtain the crude compound. This crude compound was purified in a mixture of acetone (150 mL) and water (500 mL), to give compound **4** with an yield of 59 g (88 %) as a white solid. M.p: 43-45 °C and the reported value is 46-48 °C[14].

4-Chloro-N-(4-((1-hydrazinyl-2-methyl-1-oxopropan-yl) oxy) phenethyl) benzamide (5) [14]:

To a solution of compound (**4)**, (20 g, 0.05 mol) in methanol (100 mL) 80 % aqueous; hydrazine-hydride (16.03 g, 0.26 mol) was added and heated to 45-50 °C for 15 h. The completion of the reaction was monitored by TLC, and after completion of reaction the reaction mixture was cooled to room temperature and the precipitated solid was filtered and washed with methanol (50 mL) to afford compound **5** to yield 18.50 g, (86 %) as a white solid. Further, the compound **5** was confirmed by MP and comparison of the spectral data with the literature data[14]. This compound (**5**) used as a starting material to synthesise the following hyrazide-hydrazone analogues (**6a-6l**). M.p: 131-133 °C and the reported value is 134-136 °C[14].

*General experimental procedure for the synthesis of the hydrazide-hydrazones derivatives ((**6a-6l**)) [14]:*

To a suspension of compound **5**, (0.1 g, 0.266 mmol) in methanol (10 mL) at 15-25 °C appropriate aldehyde (**a-l**, 0.266 mmol) was added and heated to 60 °C for 5-8 h. The reaction was monitored by using TLC, and after completion of the reaction the mixture was cooled to 0-5 °C and maintained for 30 min. The reaction mixture was allowed precipitate, and solids were filtered and purified by column chromatography.

4-Chloro-N-2{4-[1-(furan-2-ylmethylene-hydrazinocarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide (6a):

White solid; Yield: 86% ; M.p: 134-136 °C; IR (KBr): υ_{max} 3431(N-H), 2930(alkyl C-H), 2862(alkyl C-H), 1640(C=C), 1549(Ar- C=C), 1278(C-O), 1225(C-O), 1090(C-O-C) cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d_6) : δ 11.52 (s, 1H, N<u>H</u>-N), 8.62 (t, 1H, *J* = 5.2 Hz, N<u>H</u>-CH_2), 8.31 (s, 1H, N=C<u>H</u> (or) H-5″), 7.83 (dd, 1H, *J* = 8.8 Hz, H-4″), 7.82 (d, 2H, *J* = 8.8 Hz, H-2,6), 7.52 (d, 2H, *J* = 8.4 Hz, H-3,5), 7.16 (d, 2H, *J* = 8.4 Hz, H-3′,5′), 6.86 (dd, 1H, *J* = 8.8 Hz, H-2″), 6.84 (d, 2H, *J* = 8.8 Hz, H-2′,6′), 6.62 (dd, 1H, *J* = 2.0, 3.2 Hz, H-3″), 3.44 (q, 2H, *J* = 6.8Hz, H-8′), 2.78 (t, 2H, *J* = 8.0 Hz, H-7′), 1.48 (s, 6H, 2xC<u>H</u>$_3$); ^{13}C NMR (100Hz, DMSO-d_6): 170.1 (C-<u>C</u>=O-NH-N), 165.0 (C-<u>C</u>=O-NH-CH_2), 152.8 (C-1′), 149.4 (C-1″), 145.0 (C-4″), 137.9 (C-4), 135.8 (C-1), 133.5 (C-4′), 133.3 (C-5″), 129.3 (C-2,6), 128.9 (C-3,5), 128.2 (C-3′,5′), 119.9 (C-2′,6′) 113.1 (C-2″), 112.0 (C-3″), 79.9 (O-<u>C</u>-CH_3), 40.8 (NH-<u>C</u>H_2-8′), 34.1 (Ph-<u>C</u>H_2-7′), 24.8 (C-2<u>C</u>H_3) ; ESI-MS: *m/z*, 470.2 $(M+H)^+$ for $C_{24}H_{24}ClN_3O_4$.

4-Chloro-N-(2-{4-[1-methyl-1-(thiophene-2-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6b):

White solid; Yield: 83%; M.p: 164-166°C; IR (KBr): υ_{max} 3459(N-H), 2985(alkyl C-H), 2864(alkyl C-H), 1665(C=C), 1532(Ar- C=C), 1273(C-O), 1225(C-O), 1089(C-O-C), cm^{-1}; ^1H NMR: (400 MHz, DMSO-d_6) : δ 11.51 (s, 1H, NH-N), 8.63 (t, 1H, *J* = 5.2 Hz, NH-CH_2), 7.82 (d, 2H, *J* = 2.0 Hz, H-2,6), 7.66 (s, 1H, N=CH (or) H-5″), 7.53 (d, 2H, *J* = 2.0 Hz, H-3,5), 7.38 (s, 1H, H-4″), 7.17 (d, 2H, *J* = 8.4 Hz, H-3′, 5′), 7.13 (d, 1H, *J* = 2.8 Hz, H-2″), 6.86 (d, 2H, *J* = 8.8 Hz, H-2′,6′), 3.47 (q, 2H, *J* = 6.8 Hz, H-8′), 2.80 (t, 2H, *J* = 7.6 Hz, H-7′), 1.48 (s, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 170.0 (C-C=O-NH-N), 165.0 (C-C=O-NH-CH_2), 152.8 (C-1′), 143.2 (C-1″), 139.0 (C-4″), 136.1 (C-4), 135.8 (C-1), 133.5 (C-4′), 133.3 (C-5″), 130.6 (C-2,6), 129.3 (C-3,5), 128.9 (C-3′,5′), 128.2 (C-2″), 127.7 (C-3″), 119.9 (C-2′,6′) 79.9 (O-C-CH_3), 40.8 (NH-CH_2-8′), 34.1 (Ph-CH_2-7′), 24.8 (2xCH_3); ESI-MS: *m/z*, 470.2 $(M+H)^+$ for $C_{24}H_{24}ClN_3O_3S$.

4-Chloro-N-(2-{4-[1-methyl-1-(thiophene-3-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6c):

White solid; Yield: 86% ; M.p: 185-187°C; IR (KBr): υ_{max} 3391(N-H), 2939(alkyl C-H), 2874(alkyl C-H), 1638(C=C), 1542(Ar- C=C), 1274(C-O), 1225(C-O), 1089(C-O-C) cm^{-1}; ^1H NMR: (400 MHz, DMSO-d_6) δ 11.42 (brs, 1H, NH-N), 8.63 (t, 1H, *J* = 5.2 Hz, NH-CH_2), 8.44 (brs, 1H, N=CH (or) H-5″), 7.85 (d, 2H, *J* = 1.2 Hz, H-2,6), 7.81 (d, 2H, *J* = 8.4 Hz, H-4″), 7.62 (d, 1H, *J* = 8.8 Hz, H-3″), 7.52 (d, 2H, *J* = 8.8 Hz, H-3′,5′), 7.43 (s, 1H, H-4″), 7.17 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 6.86 (d, 2H, *J* = 8.4 Hz, H-2″), 3.47 (q, 2H, *J* = 6.8 Hz, H-8′), 2.79 (t, 2H, *J* = 7.6 Hz, H-7′), 1.48 (brs, 6H, 2xCH_3) ; ^{13}C NMR (100Hz, DMSO-d_6): 170.0 (C-C=O-NH-N), 165.0 (C-C=O-NH-CH_2), 152.9 (C-1′), 143.8 (C-1″), 137.4 (C-4″), 135.8 (C-4), 133.4 (C-1), 133.3 (C-4′), 129.3 (C-5″), 128.9 (C-2,6), 128.2 (C-3,5) 127.9 (C-3′,5′), 127.5 (C-2′,6′), 124.6 (C-2″), 119.9 (C-3″), 79.9 (O-C-CH_3), 40.8 (NH-CH_2-8′), 34.1 (Ph-CH_2-7′), 24.9 (C-2xCH_3) ; ESI-MS: *m/z*, 470.3 $(M+H)^+$ for $C_{24}H_{24}ClN_3O_3S$.

4-Chloro-N-(2-{4-[1-methyl-1-(4-methyl-thiophene-2-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6d):

White solid; Yield: 89% ; M.p: 153-156°C; IR (KBr): υ_{max} 3392(N-H), 2994(alkyl C-H), 2852(alkyl C-H), 1648(C=C), 1545(Ar- C=C), 1274(C-O), 1222(C-O), 1094(C-O-C) cm^{-1}; ^1H NMR: (400 Hz; DMSO-d_6) : δ 11.43 (s, 1H, NH-N), 8.72 (s, 1H, NH-CH_2), 8.65 (t, 1H, *J* = 6.0 Hz, N=CH (or) H-5″), 7.83 (d, 2H, *J* = 8.8 Hz, H-2,6), 7.56 (s, 1H, H-4″), 7.53 (d, 2H, *J* = 8.4 Hz, H-3,5), 7.18 (d, 2H, *J* = 8.8 Hz, H-3′,5′), 6.95 (d, 1H, *J* = 4.8 Hz, H-3″), 6.86 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 3.47 (q, 2H, *J* = 6.4 Hz, H-8′), 2.80 (t, 2H, *J* = 7.6 Hz, H-7′), 2.26 (brs, 3H, H-2″), 1.47 (brs, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.7 (C-C=O-NH-N), 165.0 (C-C=O-NH-CH_2), 152.9 (C-1′), 149.5 (C-1″), 145.1 (C-4″), 137.9 (C-4), 135.6 (C-1), 133.5 (C-4′), 133.2 (C-5″), 129.4 (C-2,6), 128.9 (C-3,5), 128.2 (C-3′,5′), 120.0 (C-2′,6′) 113.1 (C-2″), 112.0 (C-3″), 80.0 (O-C-CH_3), 40.9 (NH-CH_2-8′), 34.5 (Ph-CH_2-7′), 25.0 (C-2CH_3); ESI-MS: m/z, 484.3 $(M+H)^+$ for $C_{25}H_{26}ClN_3O_3S$.

4-Chloro-N-(2-{4-[1H-indole-2-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6e):

White solid; Yield: 83% ; M.p: 178-180°C; IR (KBr): υ_{max} 3393(N-H), 2987(alkyl C-H), 2935(alkyl C-H), 1643(C=C), 1540(Ar- C=C), 1316(C-O), 1226(C-O), 1096(C-O-C) cm^{-1}; ^1H NMR: (400 MHz, DMSO-d_6): δ 11.53 (s, 1H, =C-NH), 11.15 (s, 1H, NH-N), 8.61 (t, 1H, *J* = 5.6 Hz, NH-CH_2), 8.55 (s, 1H, H-2″), 8.24 (d, 1H, *J* = 7.6 Hz, H-3″), 7.83-7.80 (m, 2H, *J* = 2.8 Hz, H-2,6), 7.72 (d, 1H, *J* = 2.8 Hz, H-9″), 7.54 -7.49 (m, 2H, *J* = 8.8 Hz, H-3,5), 7.44 (d, 1H, *J* = 8.4 Hz, H-6″), 7.22 -7.12 (m, 4H, H-3′,5′, 4″,5″), 6.89 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 3.47 - 3.4 (m, 2H, H-8′), 2.79 (t, 2H, *J* = 7.6 Hz, H-7′), 1.50 (brs, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.2 (O=C-NH-N), 165.0 (O=C-NH-C), 153.0 (C-1′), 145.2 (C-1″), 136.9 (C-4), 135.8 (C-1), 133.3 (C-9″), 129.9 (C-2″), 129.3 (C-2,6), 128.9 (C-3,5), 128.2 (3′,5′), 124.3 (C-8″), 122.5 (C-3″), 121.8 (C-5″), 120.2 (C-4″), 119.9 (C-2′,6′), 111.7 (C-6″), 111.6 (C-7″), 40.8 (NH-CH_2-8′), 34.1 (C-7′), 25.0 (2xCH_3); ESI-MS: *m/z*, 503.3 $(M+H)^+$ for $C_{28}H_{27}ClN_4O_3$.

4-Chloro-N-(2-{4-[6-bromo-1-methyl-1H-indole-2-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6f):

White solid; Yield: 84% ; M.p: 190-192°C; IR (KBr): υ_{max} 3314(N-H), 2930(alkyl C-H), 2864(alkyl C-H), 1668(C=C), 1550(Ar- C=C), 1295(C-O), 1228(C-O), 1089(C-O-C) cm^{-1}; ^1H NMR: (400 Hz, DMSO-d_6): δ 11.24 (s, 1H, NH-N), 8.62 (t, 1H, *J* = 4.4 Hz, -NH-CH_2), 8.51 (d, 1H, *J* = 2.0 Hz, H-2″), 8.42 (t, 1H, *J* = 8.4 Hz, H-3″), 7.82 (d, 2H, *J* = 8.4 Hz, H-2, 6), 7.79 (d, 1H, *J* = 8.4 Hz, H-7″), 7.54 -7.38 (m, 4H, *J* = 8.4 Hz, H-3′,5′, 5″,6″), 7.17 (d, 2H, *J* = 8.8 Hz, H-3,

5), 6.89 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 3.81 (s, 3H, H-9″), 3.47 (q, 2H, *J* = 6.8 Hz, H-8′), 2.79 (t, 2H, *J* = 6.8 Hz, H-7′), 1.50 (m, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.4 (O=C-NH-N), 165.0 (O=C-NH-C), 152.9 (C-1′), 144.2 (C-1″), 136.3 (C-4), 135.8 (C-1), 133.4 (C-9″), 129.3 (C-2″), 128.9 (C-2,6), 128.2 (C-3,5), 125.1 (C-3′,5′), 124.1 (C-8″), 120.0 (C-3″), 113.3 (C-5″), 112.3 (C-4″), 111.8 (C-6″), 111.6 (C-7″), 40.8 (NH-CH_2-8′), 34.1 (C-7′), 25.0 (2xCH_3) ; ESI-MS: *m/z* 595.2 $(M+H)^+$ for $C_{29}H_{28}BrClN_4O_3$.

4-Chloro-N-(2-{4-[1-Benzyl-6-bromo-1H-indole-2-ylmethylene-hydrazinocarbonyl)-ethoxy]-phenyl}-ethyl)-benzamide (6g):

White solid; Yield: 86% ; M.p: 173-175 °C; IR (KBr): υ_{max} 3393(N-H), 2940(alkyl C-H), 2855(alkyl C-H), 1675(C=C), 1560(Ar- C=C), 1298(C-O), 1224(C-O), 1091(C-O-C) cm^{-1} ; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 11.30 (s, 1H, N<u>H</u>-N), 8.63 (t, 1H, *J* = 5.6 Hz, -N<u>H</u>-CH_2), 8.54 (d, 1H, H-3″), 7.99 (s, 1H, H-7″), 7.82 (d, 2H , *J* = 8.4 Hz, H-2,6), 7.82 (d, 2H, *J* = 8.4 Hz, H-3′,5′), 7.52 (d, 2H, *J* = 8.4 Hz, H-5″,6″), 7.36-7.22 (m, 5H , *J* = 2.0 Hz, H-2‴, 6‴), 7.17 (d, 2H, *J* = 8.8 Hz, H-7‴), 6.88 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 5.46 (d, 2H, H-9″), 3.47 (q, 2H, *J* = 6.4 Hz, H-8′), 2.79 (t, 2H, *J* = 7.6 Hz, H-7′), 1.50 (m, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.4 (O=C-NH-N), 165.0 (O=C-NH-C), 153.2 (C-1′), 144.0 (C-1″), 137.2 (C-4), 135.8 (C-1), 134.3 (C-9″), 133.3 (C-2″), 129.3 (C-2,6), 128.9 (C-3,5), 128.6 (C-3′,5′), 127.5 (C-8″), 127.0 (C-3″), 126.5 (C-5″), 125.5 (C-4″), 124.3 (C-2′,6′), 113.5 (C-6″), 112.7 (C-7″), 40.8 (NH-CH_2-8′), 34.1 (C-7′), 25.0 (2xCH_3); ESI-MS: *m/z* 671.4 $(M+H)^+$ for $C_{35}H_{32}BrClN_4O_3$.

4-Chloro-N-(2-{4-[1-[4-Dimethylamino-benzylidene-hydrazinocarbonyl)-1-methyl)-ethoxy]-phenyl}-ethyl)-benzamide (6h):

White solid; Yield: 84% ; M.p: 193-195°C; IR (KBr): υ_{max} 3394(N-H), 2991(alkyl C-H), 2866(alkyl C-H), 1638(C=C), 1547(Ar- C=C), 1274(C-O), 1225(C-O), 1087(C-O-C) cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d_6): δ 11.18 (s, 1H, -N<u>H</u>-N), 8.63 (t, 1H, *J* = 5.6Hz, -N<u>H</u>-CH_2), 8.25 (s,1H, -N=C-<u>H</u>) 7.82 (d, 2H, *J* = 6.0 Hz, H-2, 6), 7.52 (m, 4H, *J* = 8.4 Hz, H-2″,3″, 5″,6″), 7.16 (d, 2H, *J* = 8.4 Hz, H-3,5), 6.86 (dd, 4H, *J* = 8.4 Hz, H-2′,6′), 3.47 (q, 2H, *J* = 6.8 Hz, H-8′), 2.97 (m, 6H, N-(C<u>H</u>$_3$)$_2$), 2.79 (t, 2H, H-7′), 1.47 (m, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.5 (O=<u>C</u>-NH-N), 165.0 (O=<u>C</u>-NH-CH_2), 152.9 (C-1′), 151.4 (C-1″), 148.9 (C-4″), 135.8 (C-4), 133.3 (C-1), 129.3 (C-4′), 128.9 (C-5″), 128.3 (C-2,6), 128.2 (C-3,5), 121.5 (C-3′,5′), 119.9 (C-2′,6′), 112.7 (C-2″), 111.2 (C-3″), 79.9 (O-<u>C</u>-2CH_3), 40.8 (NH-<u>C</u>H_2), 34.1 (Ph-CH_2-7′), 24.9 (C-2x<u>C</u>H_3); ESI-MS: *m/z* 507.4 $(M+H)^+$ for $C_{28}H_{31}ClN_4O_3$.

4-Chloro-N-(2-(4-((1-(3-bromo-4-hydroxy-benzylidene-hydrazinocarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide (6i):

White solid; Yield: 82% ; M.P: 166-168°C; IR: (KBr): υ_{max} 3333(N-H), 2931(alkyl C-H), 2863(alkyl C-H), 1639(C=C), 1552(Ar- C=C), 1275(C-O), 1228(C-O), 1094(C-O-C) cm^{-1}; ^{1}H NMR: (400 Hz; DMSO-d_6) : δ 11.95 (s, 1H, -O<u>H</u>), 11.23 (s, 1H, N<u>H</u>-N), 8.62 (t, 1H, *J* = 5.6Hz, N<u>H</u>-CH_2), 8.59 (s, 1H, H-7″), 7.82 (d, 2H, *J* = 8.8 Hz, H-2,6), 7.70 (d, 1H, *J* =8.4 Hz, H-3′,5′), 7.51 (d, 2H, *J* = 8.4 Hz, H-3,5), 7.42 (dd, 1H, *J* = 2.4, 8.4 Hz, H-6″), 7.17 (d, 2H, *J* = 8.4 Hz, H-3′,5′), 6.89 (d, 1H, *J* = 8.8 Hz, H-5″), 6.86 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 3.47 (q, 2H, *J* = 6.4 Hz, H-8′), 2.78 (t, 2H, *J* = 7.6 Hz, H-7), 1.49 (bs, 6H, 2xC<u>H</u>$_3$); ^{13}C NMR (100 Hz, DMSO-d_6): 170.3 (O=<u>C</u>-NH-N), 165.0 (O=<u>C</u>-NH-C), 156.4 (C-4″), 152.7 (C-1′), 146.4 (C-7″), 135.8 (C-3″), 133.6 (C-4), 133.5 (C-1″), 130.5 (C-4′), 129.4 (C-2,6), 128.9 (C-3,5), 128.2 (C-3′,5′), 121.2 (C-2″), 120.1 (C-2′,6′), 118.7 (C-6″), 110.3 (C-5″), 79.8 (O-<u>C</u>$(CH_3)_2$), 40.8 (C-8′), 34.2 (C-7′), 24.8 (2x<u>C</u>H_3); ESI-MS: *m/z* 558.0 $(M+H)^+$ for $C_{26}H_{25}BrClN_3O_4$.

4-Chloro-N-(4-((1-(3-bromo-4-hydroxy-5-methoxybenzylidene-hydrazinocarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide (6j):

White solid; Yield: 85%; M.P.: 193-195°C; IR: (KBr): υ_{max} 3327(N-H), 2927(alkyl C-H), 2856(alkyl C-H), 1646(C=C), 1539(Ar- C=C), 1287(C-O), 1226(C-O), 1094(C-O-C) cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d_6) δ 11.52 (s, 1H,-O<u>H</u>), 8.65 (t, 1H, *J* = 5.2Hz, N<u>H</u>-CH_2), 8.26 (s, 1H, H-7″), 7.82 (d, 2H, *J* = 8.4 Hz, H-2,6), 7.52 (d, 2H, *J* = 8.4 Hz, H-2″), 7.33 (d, 2H, *J* = 1.6 Hz, H-3,5), 7.17 (d, 2H, *J* = 8.4 Hz, H-3′,5′), 6.85 (d, 2H, *J* = 8.4 Hz, H-6″), 3.88 (s, 3H, H-3″), 3.46 (m, 3H, *J* = 8.0 Hz, H-8′), 2.79 (t, 2H, *J* = 8.0 Hz, H-7′), 1.48 (bs, 6H, 2xCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.9 (O=C-NH-N), 165.0 (O=C-NH-C), 152.9 (C-4″), 148.6 (C-1′), 147.1 (C-7″), 135.8 (C-3″), 133.4 (C-4), 133.3 (C-1″), 129.3 (C-4′), 128.9 (C-2, 6), 128.2 (C-3, 5), 124.33 (C-3′, 5′), 119.9 (C-2″), 109.2 (C-2′, 6′), 108.2 (C-6″), 104.8 (C-5″), 100.6 (C-3″), 79.8 (O-<u>C</u>$(CH_3)_2$), 40.8 (C-8′), 34.2 (C-7′), 24.8 (2xCH_3); ESI-MS:

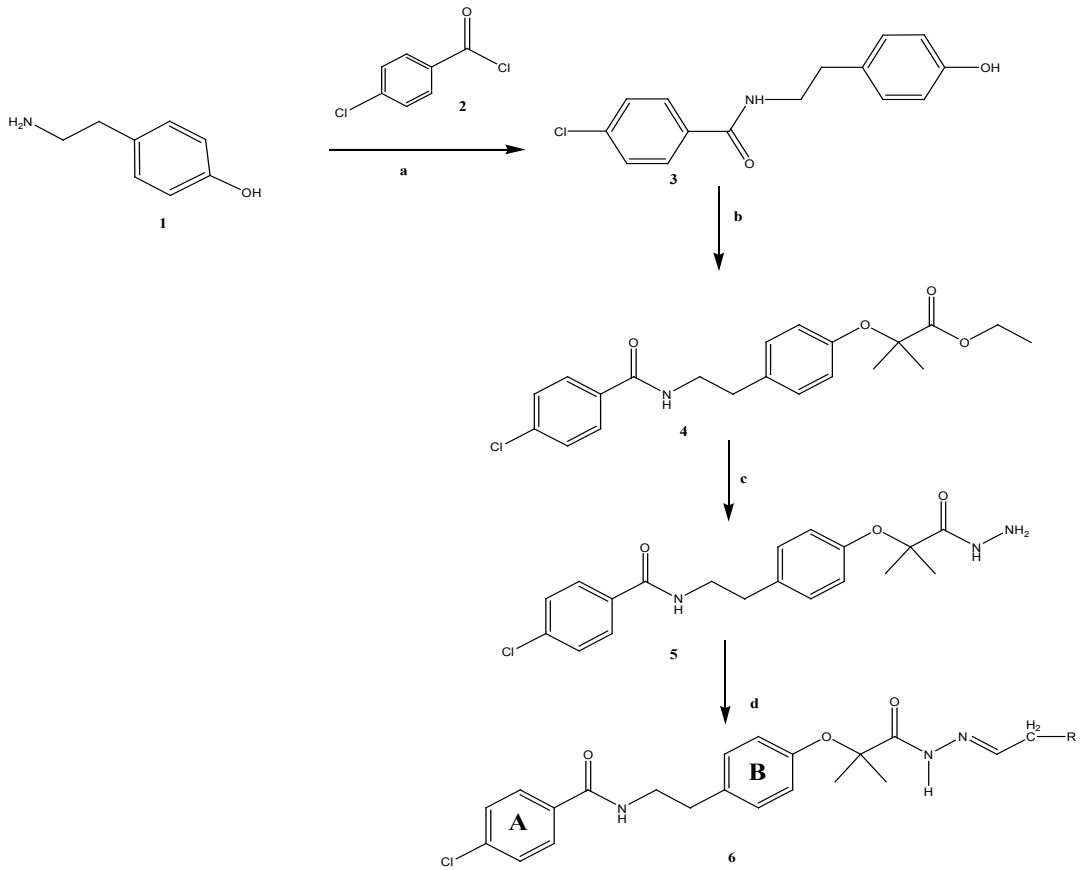
m/z 590.0 $(M+H)^+$ for $C_{27}H_{27}BrClN_3O_5$.

4-Chloro-N-(2-{4-[1-(4-hydroxy-3-methoxy-5-methyl-benzylidene-hydrazinocarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide (6k):

White solid; Yield: 83% ; M.P: 196-198°C; IR: (KBr): υ_{max} 3410(N-H), 2936(alkyl C-H), 2877(alkyl C-H), 1634(C=C), 1537(Ar- C=C), 1281(C-O), 1225(C-O), 1113(C-O-C) cm^{-1}; ^1H NMR: (400 MHz, DMSO-d_6) δ 11.37 (s, 1H, -OH), 8.87 (s, 1H, NH-N), 8.63 (s, 1H, *J* = 5.6 Hz, NH-CH_2), 8.28 (s, 1H, H-7″), 7.83 (d, 2H, *J* = 8.4 Hz, H-2,6), 7.52 (d, 2H, *J* = 8.4 Hz, H-3′,5′), 7.17 (d, 2H, *J* = 8.8 Hz, H-3,5), 6.91 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 6.86 (d, 2H, *J* = 8.4 Hz, H-2″,6″), 3.80 (s, 6H, *J* = 8.4 Hz, H-3″,5″), 3.47 (q, 2H, *J* = 6.8 Hz, H-8′), 2.80 (t, 2H, *J* = 7.6 Hz, H-7′), 1.49 (bs, 6H, 2XCH_3); ^{13}C NMR (100Hz, DMSO-d_6): 169.9 (O=C-NH-N), 165.0 (O=C-NH-C), 152.9 (C-4″), 148.6 (C-1′), 148.1 (C-7″), 138.1 (C-3″), 135.8 (C-4), 133.4 (C-1″), 129.3 (C-4′), 128.9 (C-2,6), 128.2 (C-3,5), 124.5 (C-3′,5′), 119.8 (C-2″), 108.2 (C-6″), 104.7 (C-2″,6′), 104.8 (C-5″), 100.6 (C-3″), 79.8 (O-C(CH_3)$_2$), 40.8 (C-8′), 34.2 (C-7′), 24.8 (2xCH_3); ESI-MS: *m/z* 524.1 $(M+H)^+$ for $C_{28}H_{30}ClN_3O_5$.

4-Chloro-N-(2-{4-[1-(2,3-dimethoxy-6-nitro-benzylidene-hydrazinocarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide (6l):

White solid; Yield: 83% ; M.P: 196-198°C; IR: (KBr): υ_{max} 3326(N-H), 2937(alkyl C-H), 2855(alkyl C-H), 1637(C=C), 1561(Ar- C=C), 1283(C-O), 1222(C-O), 1073(C-O-C) cm^{-1}; ^1H NMR: (400 MHz, DMSO-d_6): δ 11.91 (s, 1H, -OH), 8.94 (s, 1H,NH-N), 8.62 (t, 1H, *J* = 5.6Hz,



Reagents and conditions:

a) 4-chloro,benzoylchloride, THF, $NaHCO_3$, 0-5 °C, 3 h; b) Ethyl-α-bromoisobutyrate, TBAB, K_2CO_3,MIBK, ethanol, 85 °C, 24 h; c) Aqueous hydrazine-hydrate (80%), methanol, 45-50 °C, 15 h; d) Aldehyde (**a-l**), methanol, 60 °C, 5-8 h.

Scheme 1: Synthesis of hydrazide-hydrazone derivatives of Bezafibrate scaffold (6a-l).

NH-CH_2), 7.82 (d, *J* = 8.4 Hz, H-7″), 7.62 (d, 2H, *J* = 2.8 Hz, H-2,6), 7.52(d, 2H, *J* = 2.8 Hz, H-3′,5′), 7.18 (d, 2H, *J* = 8.4 Hz, H-3,5), 6.88 (d, 2H, *J* = 8.4 Hz, H-2′,6′), 3.94 (m, 6H, H-5″,6″), 3.48 (q, 2H, *J* = 7.2 Hz, H-8′), 2.80 (t, 2H, *J* = 7.2 Hz, H-7′), 1.49 (bs, 6H, 2xCH_3) ; ^{13}C NMR (100Hz, DMSO-d_6): 170.4 (O=C-NH-N), 165.0 (O=C-NH-C), 152.8 (C-4″), 149.6 (C-1′), 143.5 (C-7″), 141.4 (C-3″), 135.8 (C-4), 133.3 (C-1″), 129.4 (C-4′), 128.9 (C-2,6), 128.2 (C-3,5), 123.1 (C-3′,5′), 120.1 (C-2″), 108.2 (C-6″), 104.7 (C-2′,6′), 104.1 (C-5″), 100.6 (C-3″), 79.9 (O-C(CH_3)$_2$), 40.8 (C-8′), 34.1 (C-7′), 24.8 (2xCH_3); ESI-MS: *m/z* 569.1(M+H)$^+$ for $C_{28}H_{29}ClN_4O_7$.

Procedure for antioxidant activity:

2,2-Diphenyl-1-picryl hydrazyl (DPPH) Free radical scavenging activity:

The DPPH free radical scavenging activity of the different extracts was measured according to the method of Ai Lan Chew *et al*. (2012) [21]. The crude extracts in different concentrations viz., 25 µg/mL, 50 µg/mL, 100 µg/mL and 200 µg/mL were prepared in DMSO. One ml of each concentration was mixed with 4 mL of 0.004% (w/v) solution of DPPH prepared in methanol. The reaction mixture was kept for incubation in dark for 30 minutes. Methanol was used as control and Ascorbic acid was used as positive control. The absorbance was measured at 517 nm. The DPPH scavenging activity (%) was calculated by using the following formula DPPH scavenging activity (%) = [(A0 – As) / A0] × 100, Where, A0 -- absorbance of the control, As -- absorbance of the plant sample.

Results and Discussion

The preparation of hydrazide-hydrazone derivatives **6a-l** is provided in Scheme 1. Benzoylation of 4-(2-aminoethyl)phenol **1** with 4-chlorobenzoyl chloride **2** in presence of sodium bicarbonate in tetrahydrofuran:water at 0-5 ℃ for 3 h gave N-(4- hydroxyphenethyl)-4-chlorobenzamide **3** in 91 % yield. Esterification of benzamide **3** with ethyl α-bromoisobutyrate in presence of potassium carbonate and catalaytic quantity of tetrabutylamonium bromide in methyl isobutyl ketone:ethanol at 85 ℃ for 30 min yielded ethyl 2-(4-(2-(4-chloro enzamido) ethyl)phenoxy)-2-methylpropanoate **4** in 88 % yield. Reaction of ethyl ester derivative with hydrazine-hydrate in methanol at 45-50 ℃ for 15 h resulted in the key intermediate 4-chloro-N-(4-((1-hydrazinyl-2-methyl-1-oxopropan-2-yl)oxy)phenethyl) benzamide **5** in 86 % yield. Condensation of hydrazide **5** with various aromatic and heteroaromatic aldehydes **a-l** afforded hydrazide-hydrazone derivatives **6a-l** in quantitative yields (**Table 1**). The newly synthesized compounds **6a-l,** were characterised utilizing analytical techniques such as ^{1}H NMR, ^{13}C NMR, IR and Mass analyses. All the synthesized compounds were exhibited anti-oxidant activity at four different concentrations (25, 50, 100, 200 **µg**/mL) using DPPH method (**Table 2**).

In the present investigation a series of heterocyclic (**6a-6g**) and (**6h-6l**) aryl hydrazones were reported as shown in Table 1. The heterocyclic hydrazones were obtained at an yield of 71 to 87%. Among them the compound **6a** with furan-2-aldehyde showed highest yield (87.45%), followed by compound **6b** obtained by the condensation of thiophene-2-aldehyde (85.54%). Further, thiophene-3-aldehyde was also produced the respective hydrazone (**6c**) with reasonably good yield of 75.75%. Moreover, another 5-membered aldehyde namely 3-methyl thiophene-2-aldehyde was also generated the respective hydrazone (**6d**) with 75.75%. The author also prepared three hydrazones (**6e-6g**) with 3-different indole moieties. Among the three hydrazones, the hydrazone **6e** formed with indole without any substitution was obtained with good yield (77.45%) followed by the indole aldehyde with N-methyl,5-bromo substitutions (**6f**), (71.75%) and **6g** with (N-benzyl and 5-bromo substitutions) (70.54%).

In the second type of hydrazones substituted benzaldehydes with same hydrazide the compound **6h** with *para*-N,N-di-methyl substitution and compound (**6k**) with *meta*-methoxy, methyl, *para*-hydroxy substitutions on the aromatic ring were found to be obtained with highest yields 82.54%, and 81.96% respectively. Further the compounds and **6i** with *meta*-bromo, *para*-hydroxy, **6j** with *meta*-methoxy, bromo, *para*-hydroxy and **6l** with ortho-Nitro, methoxy, para-methoxy substitutions were obtained in almost equal amounts as 76.27%, 75.33% and 74.35% respectively. Therefore all the products were confirmed by spectral analysis with their strucutures.

SAR study: When compared to standard ascorbic acid (49.68% at 25g/ mL) the compound **6k** with para-hydroxyl, meta-bromo, and methyl substitutions showed almost comparable activity (40.07% at 25g/mL). Further, the compound **6j** with the same para-hydroxyl with meta-bromo

Table 1: Synthesis details of Hydrazide-Hydrazone derivatives **6a-6l**

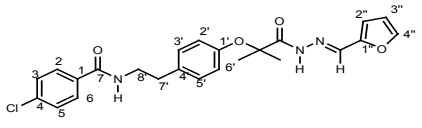
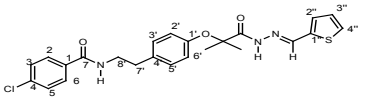
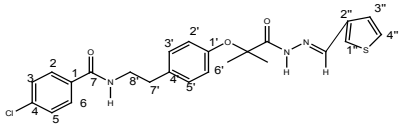
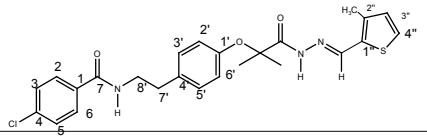
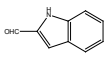
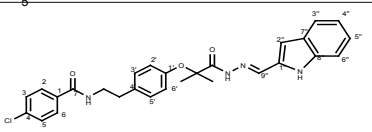
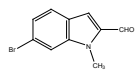
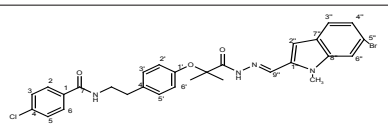
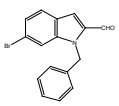
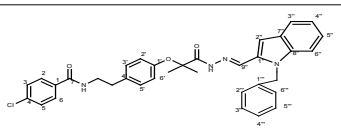
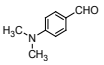
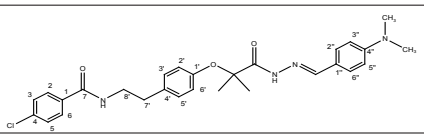
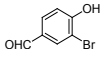
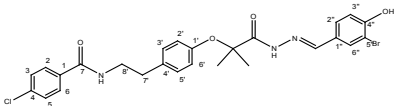
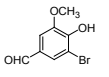
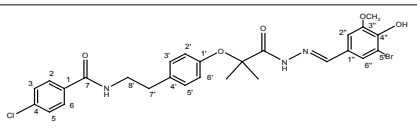
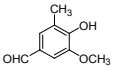
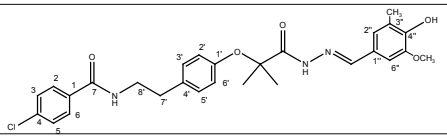
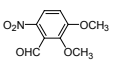
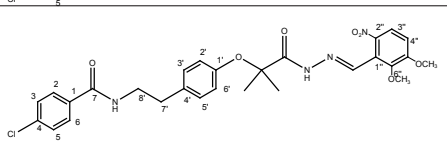
C. No	R-CHO	Product	Yield %	Mobile Phase System for TLC only.	R_f
6a			87.45	Ethyl acetate : Hexane 60:40	0.75
6b			85.54.	Ethyl acetate : Hexane 80:20	0.81
6c			76.80	Ethyl acetate : Hexane 50:50	0.82
6d			75.75	Ethyl acetate : Hexane 60:40	0.74
6e			77.45	Ethyl acetate :Hexane 40:60	0.22
6f			71.75	Hexane: Ethyl acetate 50:50	0.82
6g			70.54	Hexane: Ethyl acetate 60:40	0.42
6h			82.54	Ethyl acetate :Hexane 50:50	0.78
6i			76.27	Ethyl acetate : Hexane 60:40	0.88
6j			75.33	Ethyl acetate : Hexane 70:30	0.83
6k			81.96	Ethyl acetate : Hexane 70:30	0.62
6l			74.35.	Ethyl acetate : Hexane 50:50	0.78

TABLE 2: Antioxidant activity data of novel Hydrazide-Hydrazone derivatives of Bezafibrate scaffold 6a-6l

Compd. No.	25 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL
6a	12.98 %	14.48 %	15.23 %	15.73 %
6b	18.22 %	19.35 %	20.22 %	20.72 %
6c	6.11 %	6.86 %	8.11 %	9.11 %
6d	14.85 %	15.35 %	16.22 %	18.22 %
6e	12.98 %	13.60 %	14.10 %	14.48 %
6f	2.37 %	3.37 %	3.99 %	4.99 %
6g	15.98 %	16.72 %	17.47 %	18.10 %
6h	12.73 %	13.60 %	14.60 %	15.60 %
6i	21.59 %	22.09 %	22.97 %	23.84 %
6j	34.83 %	35.58 %	36.20 %	37.07 %
6k	40.07 %	40.94 %	41.44 %	42.07 %
6l	14.23 %	14.98 %	15.85 %	16.47 %
Ascorbic acid	49.68 %	50.56 %	51.18 %	52.30 %

and methoxy substitutions followed the same trend at all the three tested concentrations (34.83 to 36.20). However, a close look at different types of substitutions on hydrazones viz. 5-membered, fused ring systems, substituted phenyl ring systems indicate that the hydrazones with phenyl and fused ring substitutions were found better. Moreover, the compound **6i** having para-hydroxy but with only meta-bromo substitutions showed moderate activity (22% at 25 µg/mL). But the compound **6l** with meta-methoxy, ortho-methoxy, and Nitro substitutions further lowered the antioxidant activity. From the above comparision compounds having electron releasing groups showed better antioxidant activity.All the synthesised hydrazide-hydrazone derivatives (**6a-6l**) were screened for their anti-oxidant activity using DPPH method and ascorbic acid was used as standard.

Among them the compound **6k** with *meta*-methoxy, methyl, para-hydroxy substitutions was found to be more active with more than 40 % inhibition at all the four tested concentrations, followed compound **6j** *meta*-methoxy, bromo, *para*-hydroxy substitutions with around 35-37 % inhibition at all the tested concentrations. In the remaining compounds, the compound **6c** was showed lowest inhibition (6 %), among the other compounds.

In summary, the hydrazones formed with 5-membered heterocyclic aldehydes particularly with thiophene aldehydes were obtained with good yields compared to substituted benzaldehyde hydrazones and indole hydrazones. However, the yields of these reactions clearly indicating that a more number of heterocyclic hydrazones may be synthesised by using the present protocol towards the development of potential anti-oxidants.

Conclusions

A series of new hydrazide-hydrazone derivatives **6a-6l** were synthesised from bezafibrate scaffold and characterized by spectral data. Out of these compounds the **6k** and **6j** compounds exhibited good antioxidant activity.

Conflict of interest

The authors declare no conflict of interest.

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