Supporting Information

Lipid-lowering (Hetero)Aromatic Tetrahydro-1,4-Oxazine Derivatives with Antioxidant and Squalene Synthase Inhibitory Activity

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1. Preparation of intermediate and starting materials

Trans-2-methylamino-cyclohexanol:[22] To a solution of cyclohexene oxide (55.7 mmol) in 20 mL methanol and 15mL aqueous solution (40%) of methylamine, was stirred for 19 h at RT. The product was isolated by vacuum distillation (bp_4 66-69^{o}C). Yield 70%.

2-(4-Acetylphenyl)thiophene (23):[24] To a solution of 4-bromoacetophenone (15 mmol) in dry tetrahydrofuran (40 ml), 2-(tributylstannyl)thiophene (16.5 mmol) and dichlorobis(triphenylphosphine) palladium II (0.75 mmol) were added under a nitrogen atmosphere.[25] The mixture was refluxed for 2 h, ether was added (160 ml), the mixture was filtered, the filtrate was concentrated and the residue was

flash chromatographed (ethyl acetate : petroleum ether 1: 7) to give 2-(4-acetylphenyl)thiophene. Yield 54%, m.p. 120-122 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ 2.60 (s, 3H), 7.10-8.05 (m, 7H).

2-(4-Bromoacetylphenyl)thiophene (24) 2-Bromo-5-(4-bromoacetylphenyl)thiophene (25): Bromine (25 mmol) was added to 2-(4-acethylphenyl)thiophene (23) (10 mmol) in chloroform (45 ml) with stirring. After 1 h at room temperature, the mixture was washed with a 5% NaOH solution, water, dried (Na_2SO_4), the solvent was distilled off and the residue (mixture of products 24 and 25) was flash chromatographed (petroleum ether : dichloromethane 1:2) to give 2-(4-bromoacelylphenyl)thiophene (24), yield 32%, m.p. 113-115 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ 4.50 (s, 2H), 7.10-8.07 (m, 7H), Anal. ($C_{12}H_9BrOS\cdot 0.3CH_2Cl_2$), C, H, and 2-Bromo-5-(4-bromoacetylphenyl)thiophene (25), yield 33%, m.p. 130-132 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ 4.40 (s, 2H), 7.10-8.10 (m, 6H). Anal. ($C_{12}H_8Br_2OS$), C, H.

2-(Acetylphenyl)benzothiazole (26):[26] A suspension of sodium hydride (128 mmol) in dry tetrahydrofuran was added slowly to a solution of 2-aminothiophenol (32 mmol) in dry tetrahydrofuran (80 ml). To this mixture 4-acetylbenzonitrile (32 mmol) in dry tetrahydrofuran (25 ml) was added slowly. The mixture was heated at 60 ^{o}C for 3 h, cooled, and a saturated aqueous NaCl solution (200 ml) was added. The precipitate was collected, dissolved in chloroform, washed with water, dried (Na_2SO_4), concentrated and flash chromatographed (chloroform), to give 2-(acetylphenyl) benzothiazole. Yield 35%, m.p. 180-190 ^{o}C (decom). ^{1}H-NMR ($CDCl_3$) δ 2.68 (s, 3H), 7.40-8.20 (m, 8H).

2-(4-Bromoacetylphenyl)benzothiazole (27):[27] Bromine (7.64 mmol) was added to a stirred suspension of 2-(acetylphenyl)benzothiazole (26) (6.95 mmol) in chloroform (20 ml) and the mixture was refluxed for 1.5 h. The precipitate was collected, washed with cold chloroform and flash chromatographed (dichloromethane) to give 2-(4-bromoacetylphenyl)benzothiazole. Yield 40%, m.p. 151-152 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ 4.50 (s, 2H), δ 7.40-8.25 (m, 8H). Anal. ($C_{15}H_{10}BrNOS$), C, H, N.

4-(2'-Fluorophenyl)acetophenone (28), 4-(4'-Fluorophenyl)acetophenone (29) and 4-(4'-Chorophenyl)acetophenone (30): A solution of (commercially available) 2-fluoro- or 4-fluoro- or 4

chloro-1,1'-biphenyl (15 mmol) in 30 mL dry carbon disulfide was stirred at room temperature, aluminum trichloride (33 mmol) was added and the mixture was refluxed for 5 min. Acetic anhydride (15 mmol) was added dropwise and the mixture was refluxed for 2 h. The reaction mixture was poured into crushed ice and hydrochloric acid 36% was added (5 ml). The product was extracted by ether, the organic phase was washed with water and sodium bicarbonate solution 5%, dried (Na_2SO_4), concentrated and flash chromatographed (petroleum ether-ethyl acetate 15:1). 4-(2'-Fluorophenyl)acetophenone (28):[28] Yield: 31%, m.p. 78-80°C. ^{1}HNMR ($CDCl_3$) δ 2.65 (s, 3H), 7.10-8.10 (m, 8H). 4-(4'-Fluorophenyl)acetophenone (29):[29] Yield 37.5%. m.p. 78-80°C. ^{1}HNMR ($CDCl_3$) δ: 2.65 (s, 3H), 7.11-8.10 (m, 8H). 4-(4'-Chlorophenyl)acetophenone (30): [30] Yield: 15%, m.p. 97-99°C. ^{1}HNMR ($CDCl_3$) δ: 2.70 (s, 3H), 7.40-8.12 (m, 8H).

4-(2'-Fluorophenyl)-bromoacetophenone (31), 4-(4'-Fluorophenyl)bromoacetophenone (32), 4-(4'-Chlorophenyl)-bromoacetophenone (33): A solution of 28 or 29 or 30 (12.78 mmol) in 18 mL chloroform was stirred at 10°C and bromine (5.39 mmol) was added dropwise. The reaction mixture was stirred for 1h and then diluted with 18 mL chloroform, washed with water, sodium bicarbonate solution 5%, dried (Na_2SO_4) and concentrated to give the crude product. 4-(2'-Fluorophenyl)-bromoacetophenone (31):[28] was purified by recrystalisation from abs. ethanol. Yield: 65%, m.p. 71-73°C. ^{1}HNMR: ($CDCl_3$) δ: 4.5 (s, 2H), 7.10-8.12 (m, 8H). 4-(4'-Fluorophenyl)bromoacetophenone (32) was purified by flash chromatography (dichloromethane-petroleum ether 1:2) Yield: 70%, m.p. 102-103°C. ^{1}HNMR: ($CDCl_3$) δ: 4.5 (s, 2H), 7.10-8.10 (m, 8H). Anal. ($C_{14}H_{10}BrFO$), C, H. 4-(4'-Chlorophenyl)-bromoacetophenone (33)[31] was purified by flash chromatography (petroleum ether-ethyl acetate 20:1). Yield: 65%, m.p. 125-127°C. ^{1}HNMR ($CDCl_3$) δ: 4.5 (s, 2H), 7.45-8.10 (m, 8H).

4-(4'-Bromophenyl)-bromoacetophenone (34):[32] Bromine (12.79 mmol) was added to a solution of (commercially available) 4-(4'-bromophenyl)acetophenone (11.63 mmol) in 25 mL chloroform, stirred at room temperature for 1 h, diluted with chloroform, washed with water, dried (Na_2SO_4), concentrated

and flash chromatographed (dichloromethane-petroleum ether 3:2). Yield: 60%, m.p. 143-146°C. ^{1}HNMR ($CDCl_3$) δ: 4.45 (s, 2H), 7.44-8.12 (m, 8H).

2. ^{1}HNMR data for compounds **4**, **5**, **9**, **11**, **12**, **13**, **16**, **17**, **19**, **20** and **21**

3-[4-(2-Thienyl)phenyl]-octahydro-1,4-pyrido[2,1-c]oxazin-3-ol hydrobromide (4). ^{1}H-NMR ($CDCl_3$) δ 1.20-2.17 (m, 6H), 2.40-3.00 (m, 2H), 3.39-3.57 (m, 3H), 3.89 (dd, J_1=13.0 Hz, J_2=3.0 Hz, 1H), 4.22 (d, J=8.0 Hz, 1H), 4.52 (dd, J_1=13.0 Hz, J_2=3.0 Hz, 1H), 6.92 (s, 1H), 7.05 (m, 1H), 7.26-7.32 (m, 1H), 7.59 (d, J=7.6 Hz, 2H), 7.65 (d, J=8.0 Hz, 2H), 10.9 (bs, 1H).

2-[4-(2-Bromo-5-thienyl)phenyl]-4-methylmorpholin-2-ol hydrobromide (5). ^{1}H-NMR ($CDCl_3$ with drops of DMSO-d_6) δ 2.60 (s, 3H), 3.10-3.20 (m, 5H), 3.70 (dd, J_1=12.6 Hz, J_2=3.3 Hz, 1H), 4.30 (dt, J_1=12.5 Hz, J_2=3.2 Hz, 1H), 6.74 (d, J=4.0 Hz, 1H), 6.80 (d, J=4.0 Hz, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 10.05 (bs, 1H).

2-[4-(2-Benzothiazolyl)phenyl]-4-methyl-octahydro-1,4-benzoxazin-2-ol hydrobromide (9). ^{1}H-NMR ($CDCl_3$) δ 1.20-1.48 (m, 4H), 1.80-2.40 (m, 4H), 2.70-3.00 (m, 5H), 3.10 (m, 1H), 3.70 (d, J=13.5 Hz, 1H), 4.50 (m, 1H), 7.39-8.15 (m, 8H), 10.55 (bs, 1H).

2-[4-(2-Fluorophenyl)phenyl]-4-methyl-morphonyl-2-ol hydrobromide (11). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 2.90 (s, 3H), 3.05-3.50 (m, 5H), 4.00 (dd, J_1=12.5 Hz, J_2=3.2 Hz, 1H), 4.60 (dt, J_1=12.0 Hz, J_2=2.7 Hz,1H), 7.10-7.75 (m, 8H), 10.4 (bs, 1H).

2-[4-(2-Fluorophenyl)phenyl]-4-methyl-octahydro-1,4-benzoxazine-2-ol hydrobromide (12). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 0.85-1.60 (m, 9H), 1.90 (m, 1H), 2.20 (s, 3H), 2.40 (m, 1H), 2.90 (d, J=11.6 Hz, 1H), 3.60 (dt, J_1=11.6 Hz, J_2=2.9 Hz, 1H), 6.50-7.06 (m, 8H), 9.6 (bs, 1H).

3-[4-(2-Fluorophenyl)phenyl]-octahydro-1,4-pyrido[2,1-c]oxazine-3-ol hydrobromide (13).

^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 1.20-2.17 (m, 7H), 2.40-3.00 (m, 2H), 3.39-3.57 (m, 3H), 3.59 (dd, J_1=13.0 Hz, J_2=3.0 Hz, 1H), 3.89 (dt, J_1=13.0 Hz, J_2=2.0 Hz, 1H), 7.10-7.70 (m, 8H), 10.1 (bs, 1H).

3-[4-(4-Chlorophenyl)phenyl]-octahydro-1,4-pyrido[2,1-c]oxazine-3-ol hydrobromide (16). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 1.20-2.07 (m, 7H), 2.83-3.26 (m, 5H), 3.66 (dd, J_1=12.1 Hz, J_2=3.6 Hz, 1H), 4.10 (t, J=12.46 Hz, 1H), 7.10-7.70 (m, 8H), 10.08 (bs, 1H).

2-[4-(4-Bromophenyl)phenyl]-4-methyl-morphonyl-2-ol hydrobromide (17). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 2.37 (s, 3H), 2.90-3.00 (m, 4H), 3.30 (m, 1H), 3.50 (dd, J_1=12.7 Hz, J_2=3.3 Hz, 1H), 4.01 (dt, J_1=12.5 Hz, J_2=3.2 Hz, 1H), 6.88 (bs, 1H), 6.96-7.27 (m, 8H).

3-[4-(4-Bromophenyl)phenyl]-octahydro-1,4-pyrido[2,1-c]oxazine-3-ol hydrobromide (19). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 1.20-2.02 (m, 7H), 3.06-3.33 (m, 4H), 3.65 (m, 1H), 3.83 (d, J=12.3 Hz, 1H), 4.05 (t, J=12.5 Hz, 1H), 7.03-7.52 (m, 8H), 10.55 (bs, 1H).

2-[4-(4-Fluorophenyl)phenyl]-4-methyl-morphonyl-2-ol hydrobromide (20). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 2.70 (s, 3H), 2.80-3.40 (m, 5H), 3.80 (dd, J_1=12.2 Hz, J_2=3.0 Hz, 1H), 4.50 (dt, J_1=12.1 Hz, J_2=2.9 Hz, 1H), 6.90-7.50 (m, 8H), 9.5 (bs, 1H).

2-[4-(4-Fluorophenyl)phenyl]-4-methyl-octahydro-1,4-benzoxazine-2-ol hydrobromide (21). ^{1}HNMR ($CDCl_3$+DMSO-d_6) δ 1.40-2.30 (m, 9H), 2.70 (s, 3H), 2.85 (m, 1H), 3.05 (d, J=11.6 Hz, 1H), 3.65 (d, J=11.6 Hz, 1H), 4.50 (dt, J_1=11.0 Hz, J_2=3.9 Hz, 1H), 6.50 (bs, 1H), 7.06-7.80 (m, 8H).

3. Elemental analyses data

Compound	Formula	% calculated	% found
2	$C_{15}H_{18}BrNO_2S \cdot 0.5\ H_2O$	C 49.32	C49.13
		H 5.24	H 5.19
		N 3.83	N 3.77
3	$C_{19}H_{24}BrNO_2S \cdot 2.2\ H_2O$	C 50.64	C 50.61
		H 6.37	H 6.31
		N 3.11	N 3.46
4	$C_{18}H_{22}BrNO_2S \cdot H_2O$	C 52.05	C 52.07
		H 5.85	H 6.07
5	$C_{15}H_{17}Br_2NO_2S \cdot H_2O$	C 39.75	C 40.1
		H 4.23	H 4.28
		N 3.09	N 3.29
6	$C_{19}H_{23}Br_2NO_2S \cdot H_2O$	C 44.99	C 45.02
		H 4.97	H 5.18
		N 2.76	N 3.10
7	$C_{18}H_{21}Br_2NO_2S$	C 45.99	C 45.52
		H 4.45	H 4.46
8	$C_{18}H_{19}BrN_2O_2S$	C 53.08	C 52.73
		H 4.7	H 4.65
9	$C_{22}H_{25}BrN_2O_2S \cdot 2H_2O$	C 53.12	C 52.87
		H 5.88	H 5.80
		N 5.63	N 5.69
10	$C_{21}H_{23}BrN_2O_2S \cdot 0.6CH_2Cl_2$	C 52.06	C52.17
		H 4.89	H 4.94
		N 5.62	N 5.75
11	$C_{17}H_{19}BrFNO_2$	C 55.45	C 55.60

		H 5.20	H 5.21
		N 3.80	N 4.20
12	$C_{21}H_{25}BrFNO_2 \cdot 0.5H_2O$	C 58.48	C 58.45
		H 6.07	H 5.91
		N 3.25	N 3.06
13	$C_{20}H_{23}BrFNO_2 \cdot 3H_2O$	C 51.96	C 52.37
		H 6.32	H 6.67
14	$C_{17}H_{19}BrClNO_2 \cdot 0.3H_2O$	C 52.34	C 52.25
		H 5.06	H 5.07
		N 3.59	N 3.65
15	$C_{21}H_{25}BrClNO_2 \cdot 0.8H_2O$	C 55.66	C 55.65
		H 5.92	H 5.94
		N 3.09	N 3.22
16	$C_{20}H_{23}BrClNO_2 \cdot H_2O$	C 54.25	C 54.09
		H 5.69	H 5.72
		N 3.16	N 3.50
17	$C_{17}H_{19}Br_2NO_2$	C 46.60	C 46.51
		H 4.60	H 4.25
18	$C_{21}H_{25}Br_2NO_2$	C 52.20	C 51.85
		H 5.21	H 4.98
19	$C_{20}H_{23}Br_2NO_2 \cdot 0.5H_2O$	C 50.23	C 50.15
		H 5.06	H 4.88
20	$C_{17}H_{19}BrFNO_2$	C 55.45	C 55.19
		H 5.20	H 5.27
		N 3.80	N 3.96
21	$C_{21}H_{25}BrFNO_2 \cdot 0.5H_2O$	C 58.47	C 58.45
		H 6.08	H 5.91
		N 3.25	N 3.06
22	$C_{20}H_{23}BrFNO_2$	C 58.83	C59.04

		H 5.68	H 5.77
24	$C_{12}H_9BrOS \cdot 0.3CH_2Cl_2$	C 48.18	C 48.23
		H 3.16	H 2.98
25	$C_{12}H_8Br_2OS$	C 40.03	C 40.14
		H 2.24	H 2.26
27	$C_{15}H_{10}BrNOS$	C 54.23	C 53.96
		H 3.03	H 3.10
		N 4.22	N 4.10
32	$C_{14}H_{10}BrFO$	C 57.36	C 57.50
		H 3.44	H 3.46