JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

Synthesis of Some New 1,3,4-Thiadiazole Derivatives Derived from Cholic Acid and Evaluation of their Biological Activity

Intisar Q. Mahmood Al-araj[1*], Rana A. Saeed[2], Linda R. Abdul-Raheem[1], Amena A. Ahmed[1]

[1] Chemistry Dept, College of Education for Pure Science, University of Mosul, Mosul, Iraq.
[2]Pharmacy Dept, Mosul Technical Institute, Mosul, Iraq.

Supplementary information

Nuclear Magnetic Resonance (NMR) Data and Spectra:

2-Amino-5-choly-1,3,4-thiadiazol (1)

^{1}H NMR (400 MHz, DMSO-d_6 , δ, ppm): 5.05 (1H, s, OH), 4.55 (1H, s, OH), 4.47 (1H, s, OH), 4.28 (2H, s, NH_2), 3.44 (1H, dt, *J*= 10.2, 7.3 Hz, CH-OH), 3.34 (1H, t, *J*= 3.1 Hz, CH-OH), 3.18 (1H, p, *J* =7.5 Hz, CH-OH), 2.74 (2 H, t, *J*= 5.3 Hz, CH_2 thiadiazol), 2.07-1.04 (22H, m, Choly), 1.01 (3H, s, CH_3), 1.00 (3H, d, *J* 2.3 Hz, CH_3), 0.98 (3H, s, CH_3).

4-(1-((5-Choly-1,3,4-thiadiazol-2-yl)imino)ethyl)aniline (2)

1H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.41 (2H, d, *J*= 7.5 Hz, Ar-H), 6.68 (2H, d, *J*= 7.5 Hz, Ar-H), 5.49 (2H, s, NH_2), 4.61 (1H, s, OH), 4.56 (1H, s, OH), 4.47 (1H, s, OH), 3.57 (1H, dd, *J*= 13.3, 7.0 Hz, CH-OH), 3.34 (1H, t, *J*= 7.5 Hz, CH-OH), 3.18 (1H, p, *J* =7.5 Hz, CH-OH), 2.74 (2H, t, *J* =5.4 Hz, CH_2), 2.42 (3H, s, CH_3C=N), 1.90 –1.04 (22H, m, Choly), 1.00 (3H, s, CH_3), 0.98 (3H, d, *J* =6.8 Hz, CH_3), 0.94 (3H, s, CH_3).

Ethyl (4-(1-((5-choly-1,3,4-thiadiazol-2-yl) imino) ethyl) phenyl) glycinate (3)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.46 (2H, d, *J*= 7.5 Hz, Ar-H), 6.59 (2H, d, *J*= 7.5 Hz, Ar-H), 6.52 (1H, s, N-H), 4.55 (1H, s, O-H), 4.48 (2H, s, O-H), 4.15 (2H, q, *J* =5.9 Hz, CH_2 ester), 4.04 (2H, d, *J*= 18.2 Hz, CH_2C=O), 3.57 (1H, td, *J*= 7.3, 5.6 Hz, CH-OH), 3.37 – 3.31 (1H, m, CH-OH), 3.18 (1H, p, *J*= 7.5 Hz, CH-OH), 2.75 (2H, t, *J*= 5.3 Hz, CH_2 thiadiazol),

2.37 (3H, s, CH_3C=N), 1.89 –1.04 (25H, m, Choly), 1.00 (3H, s,CH_3), 0.98 (3H, d, *J* =4.9 Hz, CH_3), 0.94 (3H, s, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6 , δ, ppm): 184.3 (C=N), 174.7 (C-thiadiazol), 170.2 (C=O), 148.9 (C-Ar), 129.0 (C-Ar), 127.6 (C-Ar), 116.3 (C-Ar), 72.8, 70.8, 69.7, 60.6 (C-ester), 47.9, 46.4, 44.7, 43.0, 42.8, 41.2, 37.6, 35.8, 35.0, 34.7, 34.2, 34.1, 33.2, 28.8, 27.9, 27.4, 26.9, 26.3, 23.9, 22.1, 17.7, 14.0, 12.6.

2-((4-(1-((5-Choly-1,3,4-thiadiazol-2-yl) imino) ethyl) phenyl) amino) acetohydrazide (4)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.51 (1H, s, N-H), 7.46 (2H, d, *J*= 7.5 Hz, Ar-H), 7.10 (1H, s, N-H), 6.61 (2H, d, *J*= 7.7 Hz, Ar-H), 4.56 (2H, s, OH), 4.48 (1H, s, OH), 4.04 (1H, s, a-CH_2-NH), 3.88 (1H, s, b-CH_2-NH), 3.57 (1H, td, *J* =7.2, 6.2 Hz, CH-OH), 3.34 (1H, t, *J* =7.4 Hz, CH-OH), 3.18 (1H, p, *J*= 7.5 Hz, CH-OH), 2.79 (2H, t, *J*= 5.4 Hz CH_2 thiadiazol), 2.67 (1H, s, NH_2), 2.63 (1H, s, NH_2), 2.40 (3H, s, CH_3-C=N), 1.91 –1.04 (22H, m, Choly), 1.00 (3H, br.d, *J*= 2.5 Hz, CH_3), 0.99 (3H, s, CH_3), 0.94 (3H, s, CH_3)

2-((4-(1-((5-Choly-1,3,4-thiadiazol-2-yl)imino)ethyl)phenyl)glycyl)hydrazine-1-carbothioam-ide(5)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.05 (1H, s, NH-C=S), 7.87 (1H, s, NH-C=O), 7.47 (2H, d, *J*= 7.5 Hz, Ar-H), 6.66 (2H, d, *J*= 7.5 Hz, Ar-H), 6.18 (2H, s, NH_2), 4.76 (1H, s, O-H), 4.69 (1H, s, NH), 4.56 (1H, s, O-H), 4.48 (1H, s, O-H), 4.01 (1H, s, a-CH_2C=O), 3.73 (1H, s, b-CH_2C=O), 3.57 (1H, td, *J*= 7.2, 5.9 Hz, CH-OH), 3.34 (1H, t, *J*= 7.4 Hz, CH-OH), 3.18 (1H, p, *J*= 7.5 Hz, CH-OH), 2.76 (2H, t, *J*= 7.9 Hz, CH_2thiadiazol), 2.37 (3H, s, CH_3-C=N), 1.90-1.04 (22H, m, Choly), 1.01 (3H, s, CH_3), 0.99 (3H, d, *J*= 6.8 Hz, CH_3), 0.94 (3H, s, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6 , δ, ppm): 184.3 (C=N), 181.3 (C=S), 174.7 (C-thiadiazol), 170.2 (C-thiadiazol), 169.7 (C=O), 148.9 (C-Ar), 129.0 (C-Ar), 127.6(C-Ar), 116.3(C-Ar), 72.8 (C-OH), 70.8(C-OH), 69.7(C-OH), 47.9, 46.4, 43.8, 43.0, 42.8, 41.2, 37.6, 35.8, 35.0, 34.7, 34.2, 34.1, 33.2, 28.8, 27.9, 27.4, 26.9, 26.3, 23.9, 22.1, 17.7, 12.6.

5-(((4-(1-((5-Choly-1,3,4-thiadiazol-2-yl)imino)ethyl)phenyl)amino)methyl)-4H-1,2,4-triazole-3,4-diamine (6)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.46 (2H, d, *J* =7.5 Hz, Ar-H), 6.63 (2H, d, *J* =7.5 Hz, Ar-H), 6.02 (1H, s, NH), 5.42 (1H, s, a-NH_2-N), 4.74 (1H, s, OH), 4.60 (1H, s, OH), 4.56 (2H, s, NH_2), 4.47 (1H, s, OH), 4.43 (1H, s, a-CH_2 triazole), 4.35 (1Hs, b-CH_2 triazole), 3.82 (1H, s, b-NH_2-N), 3.57 (1H, td, *J*= 7.2, 6.2 Hz, CH-OH), 3.34 (1H, t, *J* =7.5 Hz, CH-OH), 3.18 (1H, p, *J*= 7.5 Hz, CH-OH), 2.74 (2H, t, *J* =5.4 Hz, CH_2 thiadiazol), 2.42 (3H, s, CH_3C=N), 1.90 - 1.04 (22H, m, Choly), 1.02 (3H, s, CH_3), 0.99 (3H, d, *J*= 7.0 Hz, CH_3), 0.95 (3H, s, CH_3)

N-((4,5-bis((4-chlorobenzylidene)amino)-4H-1,2,4-triazol-3-yl)methyl)-4-(1-((5-choly-1,3,4-thiadiazol-2-yl)imino)ethyl)aniline (7)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.83 (1H, s, CH=N), 8.66 (1H, s,CH=N), 8.02 (1H, d, *J*= 1.4 Hz, Ar-H), 8.00 (1H, d, *J* =1.4 Hz, Ar-H), 7.60 (1H, d, *J*= 1.2 Hz, Ar-H), 7.58 (1H, d, *J*= 1.3 Hz, Ar-H), 7.50 (4H, m, Ar-H), 7.37 (1H, t, *J*= 6.5 Hz, NH), 7.27 (1H, d, *J* =1.3 Hz, Ar-H), 7.25 (1H, d, *J*= 1.3 Hz, Ar-H), 6.78 (1H, d, *J*= 1.4 Hz, Ar-H), 6.77 (1H, d, *J*= 1.3 Hz, Ar-H), 4.61 (1H, dd, *J*= 17.3, 6.4 Hz, a-CH_2NH), 4.47 (1H, dd, *J*= 17.3, 6.4 Hz, b-CH_2NH),4.41, (1H, d, *J* =7.3 Hz, OH), 4.28 (1H, d, *J*= 6.0 Hz, OH), 3.97 – 3.83 (3H, m, CH-OH), 3.62 (1H, d, *J*= 6.6 Hz, OH), 2.81 (1H, dt, *J* =16.2, 8.8 Hz, a-CH_2 thiadiazol), 2.33 (1H, dt, *J*= 16.2, 8.8 Hz, b-CH_2 thiadiazol), 2.20 (3H, s, CH_3C=N), 1.91-1.04 (22H, m, choly), 0.84 (3H, dd, *J* =5.8, 1.5 Hz, CH_3), 0.81 (3H, q, *J*= 1.6 Hz, CH_3), 0.77 (3H, t, *J*= 1.5 Hz, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6 , δ, ppm): 184.3(C=N), 174.7(C-thiadiazol), 170.2(C-thiadiazol), 167.7(HC=N), 163.7(C-triazole), 160.7(HC=N, 152.4(C-triazole), 148.9(C-Ar), 138.6(C-Cl), 138.5(C-Cl), 133.8((C-Ar), 130.9(C-Ar), 130.7(C-Ar), 130.0(C-Ar), 129.8(C-Ar), 129.6(C-Ar), 129.0(C-Ar), 127.6(C-Ar), 116.3(C-Ar), 72.8(C-OH), 70.8(C-OH), 69.7(C-OH), 47.9, 46.4, 43.0, 42.8, 41.2, 38.0, 37.6, 35.8, 35.0, 34.7, 34.2, 34.1, 33.2, 28.8, 27.9, 27.4, 26.9, 26.3, 23.9, 22.1, 17.7, 12.6

5-(((4-(1-((5-Choly-1,3,4- thiadiazol-2-yl) imino) ethyl) phenyl) amino) methyl)-1,3,4-oxadiazol-2-amine (8)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.46 (2H, d, *J* 7.5 Hz, Ar-H), 6.58 (2H, d, *J* 7.7 Hz, Ar-H), 6.15 (1H, s, NH), 4.56 (1H, s, OH), 4.54 (1H, s, OH), 4.48 (1H, s, OH), 4.42 (1H, s, a-CH_2 oxadiazole), 4.30 (2H, s, NH_2), 4.27 (1H, s, b-CH_2 oxadiazole), 3.57 (1H, td, *J* 7.0, 5.6 Hz, CH-OH), 3.34 (1H, t, *J* 7.4, Hz, CH-OH), 3.18 (1H, p, *J* 7.5, Hz, CH-OH), 2.72 (2H, t, *J* 7.9, Hz, CH_2 thiadiazol), 2.40 (1H, s, CH_3-C=N), 1.91 –1.07 (24H, m, Choly), 1.00 (3H, d, *J* 6.5, Hz, CH_3), 0.99 (3H, s, CH_3), 0.94 (3H, s, CH_3).

N-((5-((4-chlorobenzylidene)amino)-1,3,4-oxadiazol-2-yl)methyl)-4-(1-((5-Choly-1,3,4-thiadiazol-2-yl)imino) ethyl)aniline (9)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.34 (1H, s, HC=N), 8.04 – 7.98 (2H, m, Ar-H), 7.62 – 7.56 (2H, m, Ar-H), 7.37 (1H, t, *J* =7.7 Hz, NH), 7.28 – 7.22 (2H, m, Ar-H), 6.75 – 6.69 (2H, m, Ar-H), 4.55 (1H, dd, *J*= 17.3, 7.7Hz, a-CH_2 oxadiazole), 4.41 (1H, d, *J* =7.1 Hz, OH), 4.31 (1H, dd, *J*= 17.3, 7.6 Hz, b-CH_2 oxadiazole), 4.27 (1H, d, *J*= 6.0 Hz OH), 4.00 – 3.92 (1H, m, CH-OH), 3.95 – 3.88 (1H, m, CH-OH), 3.91 – 3.83 (1H, m, CH-OH), 3.62 (1H,

d, *J*= 6.4 Hz, OH), 2.84 – 2.70 (1H, m, a-CH_2thiadiazol), 2.40 – 2.27 (1H, m, b-CH_2thiadiazol), 2.19 (3H, s, CH_3-C=N), 1.92-1.10 (22H, m, Choly), 0.90 (3H, dd, *J*= 5.6, 1.5 Hz, CH_3), 0.81 (3H, q, *J*= 1.6 Hz, CH_3), 0.77 (3H, t, *J*= 1.5 Hz, CH_3).

5-(((4-(1-((5-choly-1,3,4- thiadiazol-2-yl) imino) ethyl) phenyl) amino) methyl)-1,3,4-thiadiazol-2-amine (10)

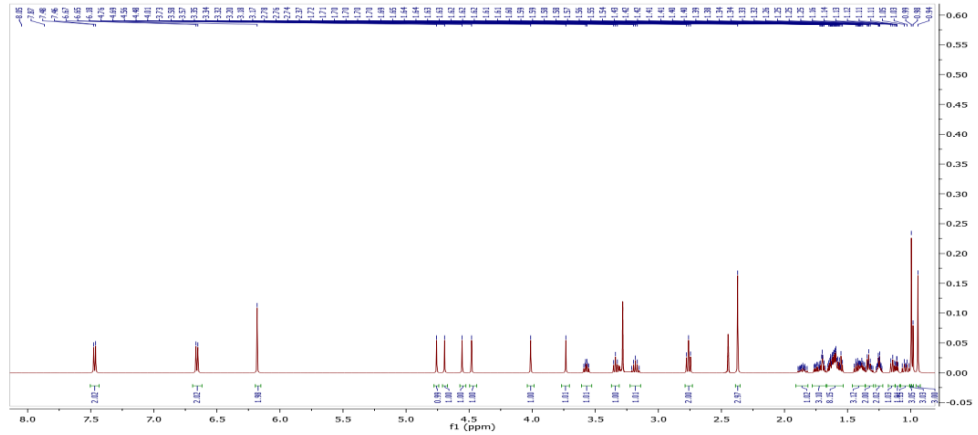
^{1}H NMR (400 MHz, DMSO-d_6 δ, ppm): 7.46 (2H, d, *J* 7.5 Hz, Ar-H), 6.58 (2H, d, *J* =7.5 Hz, Ar-H), 6.08 (1H, s, NH), 5.83 (1H, s, OH), 4.63 (1H, s, OH), 4.49 (1H, s, OH), 4.35 (1H, s, CH_2-NH), 4.24 (1H, s, NH_2), 4.19 (1H, s, CH_2-NH), 3.57 (1H, td, *J*= 7.2, 5.9 Hz, CH-OH), 3.37 – 3.30 (1H, m, CH-OH), 3.18 (1H, p, *J* =7.5 Hz, CH-OH), 2.44 (1H, s, CH_3-C=N), 1.90 - 1.04 (27H, m, Choly), 1.00 (3H, s, CH_3), 0.98 (3H, d, *J*= 6.5 Hz, CH_3), 0.96 (3H, s, CH_3)

N-((5-((4-chlorobenzylidene)amino)-1,3,4-thiadiazol-2-yl)methyl)-4-(1-((5-choly-1,3,4-thiadiazol-2-yl)imino)ethyl)aniline (11)

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.76 (1H, s, H-C=N), 8.04 – 7.98 (2H, m, Ar-H), 7.62 – 7.56 (2H, m, Ar-H), 7.37 (1H, t, *J* 7.8 Hz, NH), 7.27 – 7.21 (2H, m, Ar-H), 6.74 – 6.68 (2H, m, Ar-H), 4.60 (1H, dd, *J* 11.2, 7.8 Hz, a-CH_2-NH), 4.40 (1H, d, *J* 7.3 Hz, OH), 4.27 (1H, dd, *J* 10.9, 7.2 Hz, a-CH_2-NH), 4.26 (1H, d, *J* 3.8 Hz, OH), 4.01 – 3.94 (1H, m, CH-OH), 3.96 – 3.89 (1H, m, CH-OH), 3.92 – 3.83 (1H, m, CH-OH), 3.64 (1H, d, *J* 6.6 Hz, OH), 2.75 (1H, dt, *J* 16.5, 8.8 Hz, a-CH_2 thiadiazol), 2.43 – 2.32 (1H, m, b-CH_2 thiadiazol), 2.20 (3H, s, CH_3-C=N), 1.90 (2H, m, CH_2-CH_2), 1.75 – 1.03(20 H, m, Choly) , 0.91 (3H, dd, *J* 5.8, 1.5 Hz, CH_3), 0.81 (3H, q, *J* 1.6 Hz, CH_3), 0.77 (3H, t, *J* 1.5 Hz, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6 , δ, ppm): 184.2 (C=N), 174.9(C-thiadiazol), 174.8(C-thiadiazol), 171.3 (C-thiadiazol), 170.2(C-thiadiazol), 168.4 (C=N), 148.9(C-Cl), 138.5 (C-Ar), 133.8(C-Ar), 130.8(C-Ar), 129.6(C-Ar), 129.0(C-Ar), 127.6(C-Ar), 116.3(C-Ar), 72.8(C-OH), 70.8 (C-OH), 69.7(C-OH), 47.9, 46.4, 42.9, 42.7, 41.2, 40.7, 37.6, 35.8, 35.0, 34.7, 34.2, 34.1, 33.2, 28.8, 27.9, 27.4, 27.0, 26.3, 23.9, 22.1, 17.7, 12.6

^{1}H-NMR of some synthesized compounds (5,6,8,9) respectively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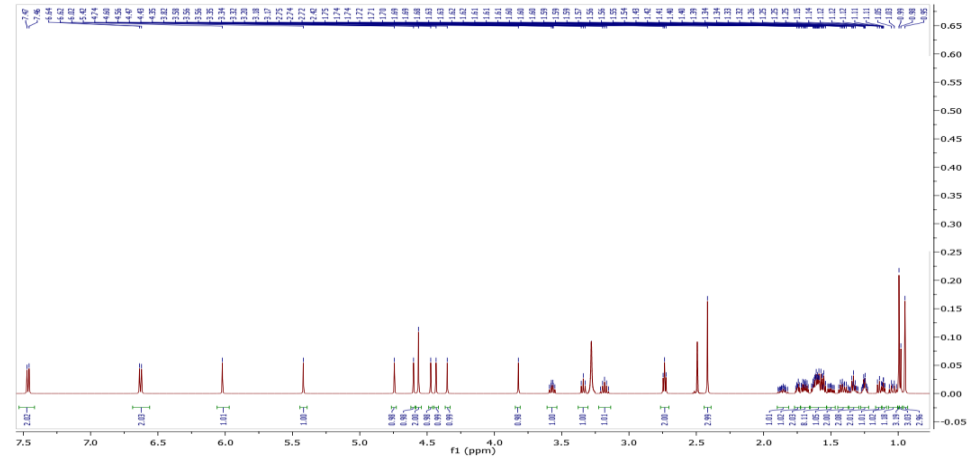
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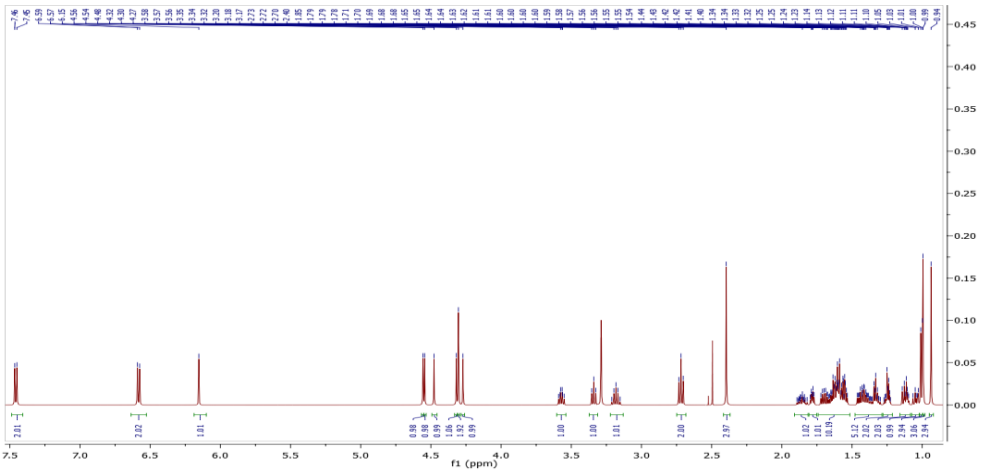
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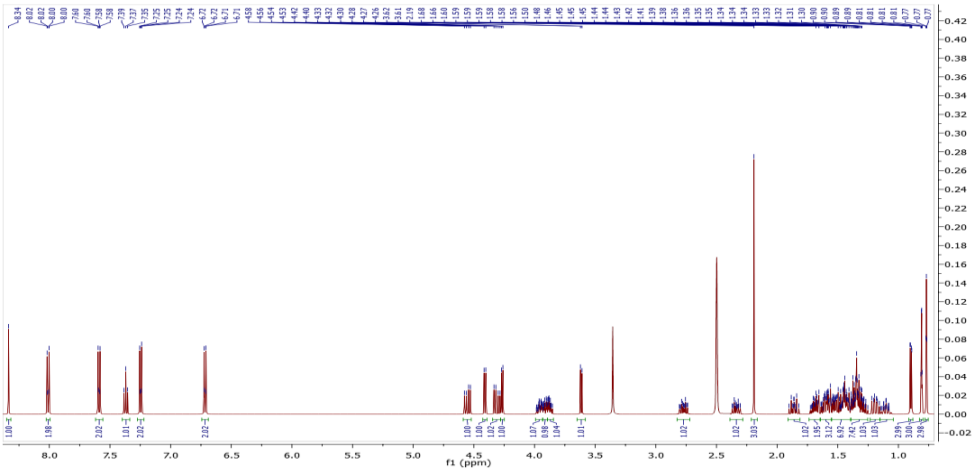
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