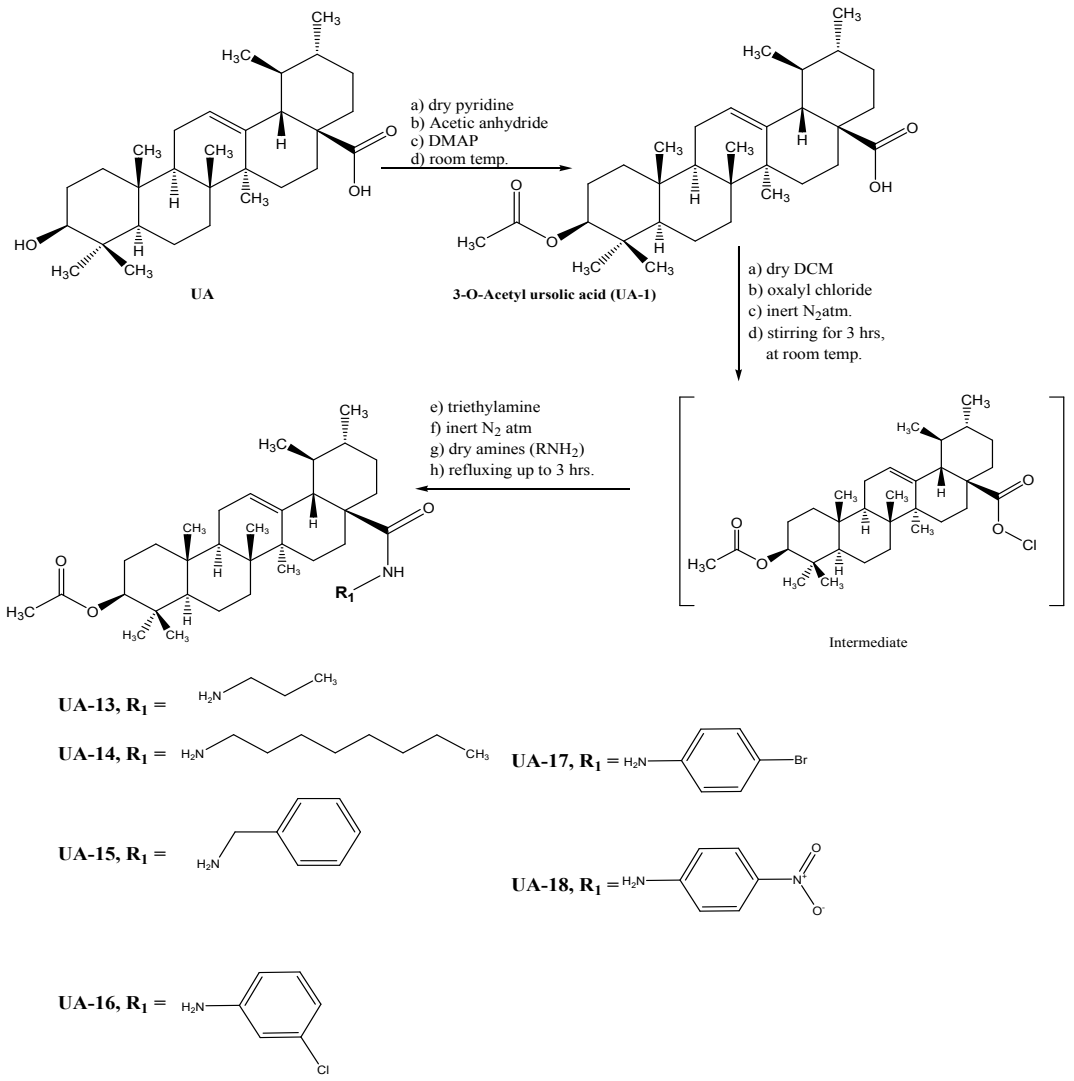
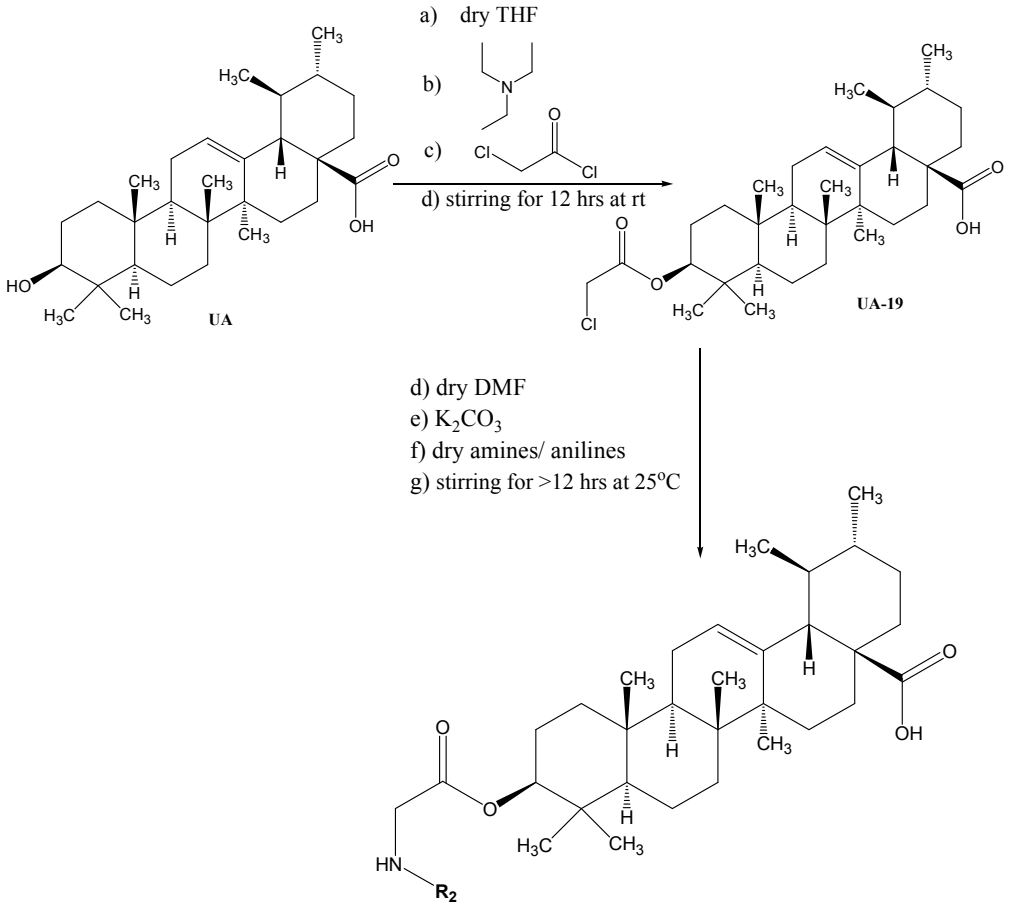
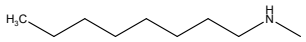
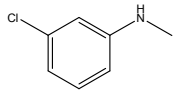
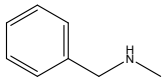


Scheme-1: The schematic mechanism of UA derivatives (UA-1 to UA-18)



UA-20, R_2 = 

UA-21, R_2 = 

UA-22, R_2 = 

Scheme-2: The schematic mechanism of UA derivatives (UA-19 to UA-22).

Semisynthesis of virtually active derivatives of UA:

For the semisynthesis of amide derivatives of ursolic acid (UA) in alkaline conditions, the hydroxyl group of UA was protected with acetate. The protected 3-O-acetylursolic acid (UA-1) was obtained by reacting UA with acetic anhydride (2 equiv.) in the presence of dry pyridine. In Scheme 1, UA-1 was reacted with oxalyl chloride (1–2 equiv.) in dry dichloromethane (DCM) under a nitrogen atmosphere. After 3 h of stirring, the respective dry amines (1.5 equiv.) for amides were added under a nitrogen atmosphere. The resulting airtight reaction mixture was refluxed for 3-4 h and the progress of the reaction was monitored by TLC [CHCl3: MeOH, 9.5: 0.5], which resulted in the formation of the desired amide derivatives (10-11).

In Scheme 2, amines were substituted at position C-3 and total 3 derivatives were prepared (28). The products were further purified by column chromatography, which afforded the desired analogs in yields of 40–80%. All the analogs were characterized on the basis of their ^{1}H and ^{13}C NMR spectroscopic data (10-11).

Propyl 3-O-acetyl-urs-12-en -28-amide (UA-13):

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5

(C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

Octyl 3-O-acetyl-urs-12-en -28-amide (UA-14):

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5 (C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

Benzyl 3-O-acetyl-urs-12-en -28-amide (UA-15)

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5 (C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

3-chloro 3-O-acetyl-urs-12-en -28-anilamide (UA-16)

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C

NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5 (C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

4-bromo 3-O-acetyl-urs-12-en -28-anilamide (UA-17)

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5 (C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

4-nitro 3-O-acetyl-urs-12-en -28-anilamide (UA-18)

^{1}H NMR ($CDCl_3$): δ 0.77.0.78, 0.98, 1.09, 1.14 (3H each all s, 5 x tert.CH_3) 0.92 & 0.96 (3 H each d, J=6.4 & 7.3 Hz, 2x sec CH_3), 4.52 (1H, t, J= 8.1 Hz, 3 α-H), 5.30 (1H, m, H-12), 5.87 (1H, brs, NH), 3.31 (2H, m, C-1^{1}), 1.92 (2H, m, C-2 ^{I}) 0.78 (3H, brs c-8^{I}), 1.25 (10 H, brs 3^{I}-7^{I}). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 81.2 (C-3), 39.9 (C-4), 55.7 (C-5), 18.5 (C-6), 33.4 (C-7), 42.4 (C-8), 47.9 (C-9), 38.1 (C-10), 23.8 (C-11), 125.4 (C-12), 138.6 (C-13), 42.4 (C-14), 28.3 (C-15), 24.6 (C-16), 48.4 (C-17), 53.3 (C-18), 39.5 (C-19), 39.3 (C-20), 31.1 (C-21), 37.2 (C-22), 28.5 (C-23), 17.1 (C-24), 15.9 (C-25), 17.5 (C-26), 23.9 (C-27), 177.9 (C-28), 17.5 (C-29), 21.6 (C-30), 178.3 (C-31), 21.5 (C-32), 40.1 (C-1'), 33.2 (C-2'), 32.2 (C-3'), 29.6 (C-4'), 29.5 (C-5'), 27.21 (C-6'), 22.9 (C-7'), 14.4 (C-8')

3-O-Chloro acetyl -urs-12-en -28-oic acid (UA-19)

^{1}H NMR ($CDCl_3$): 5.28 (1H, m, H-12), 4.5 (1H, m, H-3), 4.03 & 4.07 (2H, two d, J = 14.6 Hz, -$COOCH_2Cl$), 2.2 (1H, d, J = 9.9 Hz, H-18 β). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 78.7 (C-3), 79.9 (C-4), 56.3 (C-5), 19.1 (C-6), 39.9 (C-7), 40.4 (C-8), 47.0 (C-9), 37.7 (C-10), 23.9 (C-11), 123.0 (C-12), 139.6 (C-13), 42.9 (C-14), 28.9 (C-15), 25.2 (C-16), 48.5 (C-17), 54.0 (C-18), 30.5 (C-19), 39.7 (C-20), 31.3 (C-21), 37.6 (C-22), 29.0 (C-23), 15.8 (C-24), 16.4 (C-25), 17.5 (C-26), 24.1 (C-27), 179.7 (C-28), 17.7 (C-29), 21.4 (C-30) 165.4 (C-1”), 46.4 (C-2”).

3-O- octylamide -urs-12-en -28-oic acid (UA-20)

^{1}H NMR ($CDCl_3$): 5.29 (1H, m, H-12), 3.9 (1H, m, H-3), 3.4 (2H, d, -$COOCH_2$), 2.4 (1H, brs, NH), 2.1 (2H, m, C-1”), 1.05 (2H, m C-2”), 1.25-1.39 (H, brs 3”-7”), 0.98 (3H, brs C-8”). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 78.7 (C-3), 79.9 (C-4), 56.3 (C-5), 19.1 (C-6), 39.9 (C-7), 40.4 (C-8), 47.0 (C-9), 37.7 (C-10), 23.9 (C-11), 123.0 (C-12), 139.6 (C-13), 42.9 (C-14), 28.9 (C-15), 25.2 (C-16), 48.5 (C-17), 54.0 (C-18), 30.5 (C-19), 39.7 (C-20), 31.3 (C-21), 37.6 (C-22), 29.0 (C-23), 15.8 (C-24), 16.4 (C-25), 17.5 (C-26), 24.1 (C-27), 179.7 (C-28), 17.7 (C-29), 21.4 (C-30), 169.8 (C-1’), 55.4 (C-2’), 42.2-13.7 (C-1”- C-8”).

3-O- 3-chloroanilamide-urs-12-en -28-oic acid (UA-21)

^{1}H NMR ($CDCl_3$): 5.29 (1H, m, H-12), 3.9 (1H, m, H-3), 3.4 (2H, d, -$COOCH_2$), 4.4 (1H, brs, NH), 6.4 (H, Ar, C-2”), 6.7 (H, Ar, C-4”), 7.4 (H, Ar, C-5”), 6.9 (H, Ar C-6”). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 78.7 (C-3), 79.9 (C-4), 56.3 (C-5), 19.1 (C-6), 39.9 (C-7), 40.4 (C-8), 47.0 (C-9), 37.7 (C-10), 23.9 (C-11), 123.0 (C-12), 139.6 (C-13), 42.9 (C-14), 28.9 (C-15), 25.2 (C-16), 48.5 (C-17), 54.0 (C-18), 30.5 (C-19), 39.7 (C-20), 31.3 (C-21), 37.6 (C-22), 29.0 (C-23), 15.8 (C-24), 16.4 (C-25), 17.5 (C-26), 24.1 (C-27), 179.7 (C-28), 17.7 (C-29), 21.4 (C-30), 169.9 (C-1’), 56.1 (C-2’), 142.3 (C-1”), 111.9 (C-2”), 134.3 (C-3”), 115.8 (C-4”), 129.7 (C-5”), 109.6 (C-6”).

3-O- Benzylamide -urs-12-en -28-oic acid (UA-22)

^{1}H NMR ($CDCl_3$): 5.29 (1H, m, H-12), 3.9 (1H, m, H-3), 3.4 (2H, d, -$COOCH_2$), 2.54 (1H, brs, NH), 3.8 (2H, s, -CH_2-), 7.1-7.5 (H, Ar, C-2-6). ^{13}C NMR: 39.5 (C-1), 28.3 (C-2), 78.7 (C-3), 79.9 (C-4), 56.3 (C-5), 19.1 (C-6), 39.9 (C-7), 40.4 (C-8), 47.0 (C-9), 37.7 (C-10), 23.9 (C-11), 123.0 (C-12), 139.6 (C-13), 42.9 (C-14), 28.9 (C-15), 25.2 (C-16), 48.5 (C-17), 54.0 (C-18), 30.5 (C-19), 39.7 (C-20), 31.3 (C-21), 37.6 (C-22), 29.0 (C-23), 15.8 (C-24), 16.4 (C-25), 17.5 (C-26), 24.1 (C-27), 179.7 (C-28), 17.7 (C-29), 21.4 (C-30), 169.9 (C-1'), 55.4 (C-2'), 52.8 (Bz-CH_2), 136.5 (C-1"), 126.7 (C-2", C-6"), 127.3 (C-3", C-5"), 125.1 (C-4").