Extending the scope of oleic acid catalysis in diversity-oriented synthesis of chromene and pyrimidine based scaffolds

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Materials and methods

All the chemicals were received from sigma Aldrich, Loba chemicals, Merck, Avra synthesis or SD Fine chemicals. The Oleic acid was obtained from (Pdt No: 61821625001730) Merck chemicals, and its used as such any further purification The 2-hydroxychalcone were synthesized through reported Literature. Melting points were found via microscopic melting point apparatus and those were uncorrected. Subsequently the characterization of NMR (H\textsuperscript{1}) were determined by a Bruker Av-300MHz spectrometer TMS as internal standard and CDCl\textsubscript{3}, DMSO-d6 as external solvent. Labomed LX- 400 Microscope were used for images. All the reactions were carried out to the 10 ML round bottom flask with magnetic stirrer.

General procedure for synthesis of 4H-chromene derivatives synthesis (3a-g)

The 2-hydroxychalcone (1.0 mmol) and indole (1mmol, 117 mg) were added to the mixture of oleic acid (40 \(\mu\)L) in water at room temperature. Then the reaction mixture was refluxed 4 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Then the reaction mixture was extracted with ethyl acetate (2 \(\times\) 20 mL) and the combined extracts were washed with water (1 \(\times\) 10 mL) and dried over anhydrous sodium sulphate. The solvents were removed under reduced pressure and the crude residue was purified through the silica gel column chromatography (elutent ethyl acetate, hexane solvent mixture). Eventually pale red solid was obtained with good yield.

3-(2-phenyl-4H-chromen-4yl)-1H-indole (3a)

Yield = 228 mg (71 \%) Brown solid. Mp 99-101°C (Lit 100-102 °C). \(\text{H}^1\) NMR (300 MHz, CDCl\textsubscript{3}, \(\delta\) ppm): 5.17 (d, \(J = 3.9\) Hz, 1H), 5.68 (d, \(J = 4.2\) Hz, 1H), 6.92 (td, \(J = 7.8, 1.8\) Hz, 1H), 7.02-7.19 (m, 6H), 7.31-7.39 (m, 4H), 7.62 (d, \(J = 7.8\) Hz, 1H), 7.72 (d, \(J= 7.2\) Hz, 2H), 7.99(brs, 1H).

2-methyl-3-(2-phenyl-4H-chromen-4yl)-1H-indole (3b)

Yield = 217 mg (67 \%) Brown solid, Mp 97-99°C (Lit 97-98°C). \(\text{H}^1\) NMR (300 MHz, CDCl\textsubscript{3}, \(\delta\) ppm): 2.39 (s, 3H), 5.19 (d, \(J = 3.6\) Hz, 1H), 5.57 (d, \(J = 3.6\) Hz, 1H), 6.86-6.98 (m, 3H), 7.04-7.15 (m, 3H), 7.27-7.40 (m, 4H), 7.45 (d, \(J = 7.8\) Hz, 1H), 7.72 (dd, \(J= 7.8, 1.2\) Hz, 2H), 7.78(brs, 1H)
**5-methoxy-3-(2-phenyl-4H-chromen-4-yl)-1H-indole (3c)**

Yield = 220 mg (68 %) Gum-like red (lit1) oil., H1 NMR (300 MHz, CDCl3, δ ppm): 3.74 (s, 3H), 5.13 (d, J = 3.9 Hz, 1H), 5.67 (d, J = 3.7 Hz, 1H), 6.82 (dd, J = 8.7, 2.4 Hz, 1H), 6.93 (td, J = 7.8, 1.8 Hz, 1H), 7.06 (t, J = 2.7 Hz, 2H), 7.11-7.23 (m, 3H), 7.31-7.47 (m, 3H), 7.72 (dd, J = 7.8, 1.2 Hz, 2H), 7.91 (brs, 1H).

**3-[2-(2-bromophenyl)-4H-chromen-4-yl]-1H-indole (3d)**

Yield = 242 mg (60 %) Gum-like red (lit1). H1 NMR (300 MHz, CDCl3, δ ppm): 5.17 (d, J = 3.9 Hz, 1H), 5.35 (d, J = 3.9 Hz, 1H), 6.92 (dd, J = 7.8, 1.2 Hz, 1H), 7.04-7.08 (m, 2H), 7.10-7.15 (m, 3H), 7.20 (td, J = 7.8, 1.8 Hz, 2H), 7.30 (td, J = 7.5, 1.2 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.47 (dd, J = 7.8, 1.5 Hz, 1H), 7.62 (dd, J = 8.1, 1.2 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H) 8.01 (brs, 1H).

**3-[2-(4-chlorophenyl)-4H-chromen-4-yl]-1H-indole (3e)**

Yield = 246 mg (69 %) Brown solid, Mp 80-81 °C (Lit 84-86 °C)1. H1 NMR (300 MHz, CDCl3, δ ppm): 5.16 (d, J = 4.2 Hz, 1H), 5.66 (d, J = 3.9 Hz, 1H), 6.93 (td, J = 6.9, 1.5Hz, 1H), 7.02-7.08 (m, 2H), 7.13 (td, J = 7.8, 1.5 Hz, 2H), 7.17-7.20 (m, 2H), 7.33 (dt, J = 8.7, 2.4 Hz, 2H), 7.37 (d, J = 0.6 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.65 (dt, J = 8.7, 2.4 Hz, 2H), 8.03 (brs, 1H).

**3-[2-(4-methoxyphenyl)-4H-chromen-4-yl]-1H-indole (3f)**

Yield = 247 mg (70 %) Brown solid, Mp 97-98°C (Lit 97-98°C)1. H1 NMR (300 MHz, CDCl3, δ ppm): 3.82 (s, 3H), 5.15 (d, J = 3.9 Hz, 1H), 5.55 (d, J = 3.9 Hz, 1H), 6.87-6.95 (m, 3H), 7.02-7.21 (m, 6H), 7.35 (d, J = 8.1 Hz, 1H), 7.61-7.68 (m, 3H), 8.02 (brs, 1H).

**3-[2-(4-methylphenyl)-4H-chromen-4-yl]-1H-indole (3g)**

Yield = 235 mg (70 %) Gum-like red oil (lit1). H1 NMR (300 MHz, CDCl3, δ ppm): 2.36 (s, 3H), 5.15 (d, J = 3.9 Hz, 1H), 5.62 (d, J = 3.9 Hz, 1H), 6.90 (td, J = 8.1, 1.8Hz, 1H), 7.04 (td, J = 7.8, 0.9 Hz, 2H), 7.09-7.24 (m, 6H), 7.34 (d, J = 7.8, Hz, 1H), 7.61 (dd, J = 8.1, 0.9 Hz, 3H), 7.98 (brs, 1H).

**General procedure for synthesis of 4H-chromene derivatives synthesis (3h-n)**

To a stirred solution of 2-hydroxy aldehyde (1 mmol), malononitrile (1 mmol, 66 µL) and indole (1 mmol, 117 mg) were added to the oleic acid (40 µL) in water (3 mL) at room temperature. The reaction mixture was stirred further 3 hours. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (2 x 20 mL) and the combined extracts were washed with water (1 x 10 mL). The organic layer was dried over sodium sulphate, filtered and the solvent were removed under reduced pressure. After that the crude was purified through
the silica gel column chromatography eluted by ethyl acetate, hexane solvent mixture. Eventually dark yellow solid was obtained with good yield.

2-amino-4-(1H-indol-3-yl)-4H-chromene-3-carbonitrile (3h)
Yield = 236 mg (82 %) Yellow solid Mp 192–194 °C (Lit 193–194 °C) H^1 NMR (300 MHz, DMSO(d6), δ ppm): 4.99 (s, 1H), 6.83-6.89 (m, 3H), 6.99-7.08 (m, 4H), 7.19-7.24 (m, 2H), 7.29-7.35 (m, 2H), 10.93 (s, 1H).

2-amino-4-(1-methyl-1H-indol-3-yl)-4H-chromene-3-carbonitrile (3i)
Yield = 256 mg (85 %) Yellow solid. Mp 200-202 °C (Lit 202°C) H^1 NMR (300 MHz, DMSO(d6), δ ppm): 3.74 (s, 3H), 4.99 (s, 1H), 6.89-7.13 (m, 6H), 7.21 (t, J = 8.1 Hz, 1H), 7.28 (d, J = 9.9 Hz, 2H), 7.38 (d, J = 8.4 Hz, 1H).

3-amino-1-(1H-indol-3-yl)-1H-benzof[chromene-2-carbonitrile (3j)
Yield = 259 mg (77 %) Yellow solid. Mp 212–214 °C (Lit 215–217 °C) H^1 NMR (300 MHz, DMSO(d6), δ ppm): 5.62 (s, 1H), 6.79-6.86 (m, 3H), 6.96 (t, J = 7.2 Hz,1H), 7.20 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz,1H), 7.35-7.44 (m, 4H), 7.84-7.90 (m, 2H), 8.10 (d, J = 7.8 Hz, 1H), 10.90 (s, 1H).

2-amino-4-(1-methyl-1H-pyrrol-2-yl)-4H-chromene-3-carbonitrile (3k)
Yield = 210 mg (85%) Yellow solid. Mp 196-198 °C, H^1 NMR (300 MHz, DMSO(d6), δ ppm): 3.43 (s, 3H), 4.97 (s, 1H), 5.76-5.87 (m, 2H), 6.59 (s, 1H), 6.92-7.11 (m, 5H), 7.56 (t, J = 7.5 Hz, 1H).

2-amino-4-(1H-pyrrol-2-yl)-4H-chromene-3-carbonitrile (3l)
Yield = 200 mg (84%) Gray colour solid. Mp 195-197°C (Lit 195-197 °C) H^1 NMR (300 MHz, DMSO(d6), δ ppm): 4.75 (s, 1H), 5.82-5.88 (m, 2H), 6.59 (s, 1H), 6.88 (s, 2H), 6.98-7.09 (m, 2H), 7.16-7.24 (m, 2H), 10.69 (s, 1H).

2-amino-4-(2-methyl-1H-indol-3-yl)-4H-chromene-3-carbonitrile (3m)
Yield = 238 mg (79 %) Yellow solid. Mp 186–188°C (Lit 187–188 °C) H^1 NMR (300 MHz, DMSO (d6), δ ppm): 2.44 (s, 3H), 5.06 (s, 1H), 6.76-6.79 (m, 3H), 6.90-7.06 (m,5H), 7.16-7.24 (m, 2H), 10.85 (s, 1H).

2-amino-4-(6-methoxy-1H-indol-3-yl)-4H-chromene-3-carbonitrile (3n)
Yield = 257 mg (81 %) Yellow solid. Mp 199-201 °C (Lit 198-200 °C) H^1 NMR (300 MHz, DMSO(d6), δ ppm): 3.65 (s, 3H), 4.96 (s, 1H), 6.68-6.76 (m, 2H), 6.83 (s,2H), 6.99-7.12 (m, 3H), 7.21 (t,J = 10.5 Hz,3H), 10.76 (s, 1H).
Intermediate isolation from the reaction mixture (Scheme 3 in main article)

5-[(2-hydroxyphenyl)methylidene]-1,3-diazinane-2,4,6-trione (6)
Yield = 180 mg (78%) Orange solid. Mp >260 °C H¹ NMR (300 MHz, DMSO(d6), δ ppm): 6.82 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.61 (s, 1H), 10.63 (s, 1H), 11.15 (s, 1H), 11.31 (s, 1H).

General procedure for synthesis of Synthesis of 5-(2,3,4,5-tetrahydro-1H-chromeno-[2,3-d]pyrimidin-5-yl)pyrimidiones (7a-c)
To a stirred solution of salicylaldehyde or 5-bromo salicylaldehyde (0.5 mmol) and barbituric acid or thiobarbituric acid (1 mmol) in water (3 mL), oleic acid (40 µL) was added and the mixture was heated at 50 °C for 1 hour. After completion the reaction indicated by TLC, the reaction mixture was cooled and filtered. The precipitate was washed with ethanol to afford pure product.

5-(2,4-Dioxo-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (7a)
Yield = 157 mg (92%) white solid. Mp >225°C (Lit 268-270 °C) H¹ NMR (300 MHz, DMSO(d6), δ ppm): 3.85 (d, J = 2.1 Hz, 1H), 4.71 (d, J = 2.1 Hz, 1H), 7.08-7.24 (m, 3H), 7.31-7.36 (m, 1H), 10.99 (s, 1H), 11.19 (s, 1H), 11.30 (s, 1H), 11.98 (s, 1H).

5-(4-oxo-2-sulfanylidene-1H,2H,3H,4H,5H-chromeno[2,3-d]pyrimidin-5-yl)-2-sulfanylidene-1,3-diazinane-4,6-dione (7b)
Yield = 170 mg (91%) white solid. Mp >225°C (Lit > 300 °C) H¹ NMR (300 MHz, DMSO(d6), δ ppm): 5.12 (s, 1H), 6.99 (d, J = 7.5 Hz, 1H), 7.11 (s, 2H), 7.22 (s, 1H), 11.94 (brs, 1H), 12.24 (brs, 1H), 12.34 (s, 1H), 13.29 (s, 1H).

5-(2,4-Dioxo-7-bromo-2,3,4,5-tetrahydro-1Hchromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (7c)
Yield = 185 mg (88%) white solid. Mp >225°C (Lit > 240-242 °C) H¹ NMR (300 MHz, DMSO(d6), δ ppm): 3.93 (brs, 1H), 4.72 (brs, 1H), 7.10 (s, 1H), 7.29 (s, 1H), 7.52 (d, J = 3.9 Hz, 1H) 11.10 (s, 1H), 11.23 (s, 1H), 11.37 (s, 1H), 12.06 (s, 1H).
General procedure for synthesis of C-glycosylated pyrimidine-fused heterocycle (8)

To a stirred mixture of barbituric acid (1 mmol, 128 mg), D-glucose (0.5 mmol, 90 mg) and oleic acid (40 µL) in ethanol (3 mL) at 50 °C was stirred 12 h. After completion the reaction confirmed by TLC, the reaction mixture cooled at room temperature and filtered. The mixture washed with ethanol thrice and evaporated reduced pressure affords a pure product.

5-((1R,2S,3S,4S)-1,2,3,4,5-Pentahydroxypentyl)-5,9-dihydro-2H-pyrano[2,3-d:6,5-d′]dipyrimidine-2,4,6,8(1H,3H,7H)-tetraone (8)

Yield = 284 mg (71 %) white solid. Mp 200-201°C (Lit 202-204°C) \(^1\) H\(^1\) NMR (300 MHz, DMSO(d6), δ ppm): 2.50-2.98 (m, 2H), 3.11 (t, \(J = 7.1\) Hz, 1H), 3.26-3.30 (m, 1H), 3.39-3.35 (m, 2H), 3.61-3.70 (m, 5H), 3.89(s, 1H) 11.07 (s, 2H), 11.12 (s, 1H), 11.21(s, 1H).

General procedure for synthesis of pyrazolo pyranopyrimidine derivatives synthesis 10a-f

To a stirred solution of hydrazine hydrate (1 mmol, 50 µL) and ethylacetoacetate (1 mmol, 130 µL) in water (3 mL), oleic acid (40 µL) was added and the mixture was refluxed over 30 min. Next an appropriate amount aromatic aldehyde (1 mmol), barbituric acid (128 mg, 1 mmol) were added in the reaction mixture was further refluxed for an appropriate time. After completion the reaction indicated by TLC, the reaction mixture was cooled and filtered. The precipitate was washed with ethanol to afford pure product.

3-Methyl-4-(4-nitrophenyl)-1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione(10 a)

Yield = 296 mg (87 %) white solid. Mp >225°C (Lit 233-234°C) \(^5\) H\(^1\) NMR (300 MHz, DMSO(d6), δ ppm): 2.25 (s, 3H), 5.51 (s, 1H), 7.31(d, \(J = 8.7\) Hz, 2H), 8.11 (d, \(J = 8.4\) Hz, 2H), 10.25 (s, 2H), 13.40 (brs, 1H).

3-Methyl-4-(3-nitrophenyl)-1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (10 b)

Yield = 283 mg (83 %) white solid. Mp >225°C (Lit 266-267°C) \(^5\) H\(^1\) NMR (300 MHz, DMSO(d6), δ ppm): 2.09 (s, 3H), 5.30 (s, 1H), 7.31(s, 2H), 7.63 (s, 1H), 7.91 (s, 1H), 10.05 (s, 2H), 13.19 (brs, 1H).
3-Methyl-4-phenyl-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (10c)
Yield = 230 mg (78 %) white solid. Mp 216-218°C (Lit 218-219°C)\(^5\) H\(^1\) NMR (300 MHz, DMSO (d6), δ ppm): 2.23 (s, 3H), 5.43 (s, 1H), 7.04-7.13 (m, 3H), 7.18-7.23 (m, 2H), 10.18 (s, 2H), 13.14 (brs, 1H).

3-Methyl-4-(4-methylphenyl)-1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (10d)
Yield = 254 mg (82 %) white solid. Mp 197-198 °C (Lit 200-201°C)\(^5\) H\(^1\) NMR (300 MHz, DMSO (d6), δ ppm): 2.08 (s, 3H), 2.11 (s, 3H), 4.73 (s, 1H), 7.03-7.24 (m, 4H), 10.93 (s, 2H), 11.74 (brs, 1H).

3-Methyl-4-(2-nitrophenyl)-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (10e)
Yield = 291mg (85 %) pale yellow solid. Mp 207-208°C (Lit 208-209°C)\(^5\) H\(^1\) NMR (300 MHz, DMSO (d6), δ ppm): 2.21 (s, 3H), 5.77 (s, 1H), 7.33-7.41 (m, 2H), 7.50-7.76 (m, 2H) 10.16 (s, 2H), 13.19 (brs, 1H)

4-(4-Chlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3',5,6]-pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (10f)
Yield = 264 mg (80 %) white solid. Mp 220-222°C (Lit 222-223°C)\(^5\) H\(^1\) NMR (300 MHz, DMSO (d6), δ ppm): 2.08 (s, 3H), 2.11 (s, 3H), 4.73 (s, 1H), 7.03-7.24 (m, 4H), 10.93 (s, 2H), 11.74 (brs, 1H).

Procedure for synthesis of curcumin-based pyrano[2,3-d]pyrimidine 11:
To a magnetically stirred solution of curcumin (0.5 mmol, 184 mg), 4-chlorobenzaldehyde (0.5 mmol, 70 mg) and barbituric acid (0.5 mmol, 62 mg) in EtOH (2 ml) was oleic acid (40 µL) at reflux temperature of EtOH. The mixture was stirred for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture cooled down to room temperature and then the precipitate filtered, washed with EtOH (3 x 5 mL) thrice and dried under vacuum.
Progress of the reaction monitored as photograph.

A) Initial reaction mixture of curcumin, 4-chlorobenzaldehyde, barbituric acid and oleic acid in ethanol

B) Homogeneous solution of the reaction mixture after 2 hours.

C) After completion of the reaction precipitate was formed

7-((E)-4-Hydroxy-3-methoxystyrlyl)-5-(4-chlorophenyl)-6-((E)-3-(4-hydroxy-3-methoxyphenyl) acryloyl)-1H-pyran [2,3-d]pyrimidine-2,4(3H,5H)-dione (11)

Yield = 261 mg (87 %) yellow solid. Mp 228-230 °C (lit 152-156 °C ). H NMR (300 MHz, DMSO(d6), δ ppm): 3.71 (s, 6H), 5.19 (s, 1H), 6.14(d, J = 15.6, 1H), 6.50 (d, J = 8.1 Hz, 2H), 6.61-6.82 (m, 5H), 6.88-6.97 (m, 2H), 7.23-7.38 (m, 4H), 9.09 (s, 1H), 9.67 (s, 1H), 11.25 (s, 1H), 11.32 (s, 1H).

References:

Light microscopic images of oleic acid in water

A) Light microscopic image of oleic acid (40 µL) in water (3 mL)
B) Light microscopic image of Indole (1 mmol), salicylaldehyde (1 mmol) and oleic acid (40 µL) in water (3 mL)
Current Data Parameters
NAME  03698-1
EXPN  1
PROCN  1

F2 - Acquisition Parameters
Date_  20130708
Time  14.19
INSTRUM  spect
PROBHD  5 mm BBBO BB-1H
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  15
DS  2
SWH  6180.119 Hz
FIDRES  0.094423 Hz
AQ  5.2953587 sec
RG  228
DW  80.800 usec
DE  6.000 usec
TE  300.00 K
D1  1.00000000 sec
TDD  1

--------- CHANNEL f1 ---------
NUC1  1H
P1  8.60 usec
PLI  -2.00 db
SP01  300.138534 MHz

F2 - Processing parameters
SI  32768
SF  300.1299999 MHz
WDM  EM
SSB  0
LB  0.30 Hz
GB  0
PC  1.00