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A simple, efficient synthesis and molecular docking studies of 2-styrylchromones

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Abstract: 2-Styrylchromones have been synthesized successfully by using eco-friendly, recoverable and reusable PEG-400 as reaction medium in the presence of the catalytic amount of piperidine under warm conditions through 1,5-diphenylpenta-2,4-dien-1-ones as intermediates followed by oxidative cyclization with iodine in the same reaction vessel starting from 2-hydroxyacetophenones and cinnamaldehydes. The synthesized compounds were characterized by some physical methods and spectral data like IR, NMR, and LCMS etc. *In silico* molecular docking study was performed for all the synthesized compounds to know their ability in inhibiting pancreatic *α*-amylase enzyme. In this study, the compounds 24, 25, 26 & 28 with binding energies, -8.7, -8.8, -8.6 and -8.4 kcal/mol respectively were found to be more active amongst the synthesized when compared with standard drug, acarbose (-8.2 kcal/mol).

Keywords: 2-Styrylchromones; eco-friendly; PEG-400; molecular docking; acarbose; α-amylase.

1. Introduction

2-Styrylchromones are the new class of oxygen containing heterocyclic compounds, play an important role in nature due to their wide range of biological activities[1-3] including pharmacological and biocidal activities[4-7]. These biological activities are due to the number and position of various substituents in the core structure which create great demand for their synthesis in past few years.

However, several attempts were made to synthesize[8-15] 2-styrylchromones, still there is a large scope for the efficient and eco-friendly routes to synthesize novel and potent bioactive analogues. This motivated many researchers as a result of which a large variety of 2-styrylchromones derivatives were reported[6,10,16-19] as potential therapeutic agents.

Chromone (benz-γ-pyrone or 4H-chromen-4-one) derivatives (Figure 1) with styryl group at 2[nd] position have attracted a great deal of attention by virtue of their substantial anti-oxidant[20], anti-cancer,[21] anti-proliferal[22], anti-tumor[23] and anti-viral[24] activities. Some research on chromone derivatives demonstrated their potentiality as anti-diabetic agents[25,26].

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All these widespread biological activities and scarcity of 2-styrylchromones in nature[27,28] along with some others[29-33] promoted us to synthesize a series of 2-styrylchromones from simple starting compounds with an efficient way and to screen them for their anti-diabetic activity using *in silico* molecular docking studies.

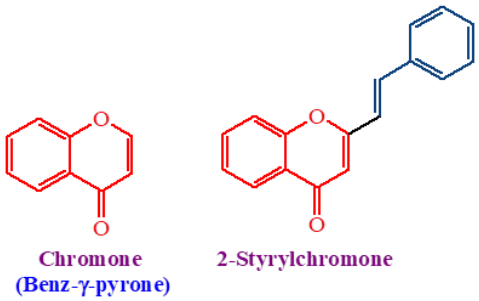


Figure 1. Structures of chromone and its derivative

2. Experimental

2.1. Methods & Materials:

All chemicals needed for experimental part were purchased from National Scientific Products, Guntur. The melting point of all the synthesized compounds were determined in open capillary tubes using melting point apparatus. The synthesized compounds were characterized by various spectroscopic methods like FTIR, ^{1}H & ^{13}C-NMR (Bruker, 400 MHz), LCMS and elemental analysis (Vario El-III). With the help of Marvin view software, the structures of all the compounds were drawn, optimized and converted them into required format. 1-Click docking software powered by Auto Dock Vina docking algorithm *was used for in silico* molecular docking study[34, 35].

2.2. Synthetic Procedure for 2-Styrylchromones Preparation (20-31):

The substituted acetophenone and cinnamaldehyde in 1:1 molar ratio were dissolved in 5 mL of PEG-400 and stirred at 40-50 °C with 0.4 mL of piperidine for about half an hour. The progress of the reaction was monitored by TLC using hexane:ethylacetate (9:1) as eluent. All the intermediate compounds were obtained in yellow colour.

The reaction intermediate (1,5-diphenylpenta-2,4-dien-1-one) thus obtained was dissolved in 5 mL of PEG in the same round bottom flask and a catalytic amount (10 mg) of powdered iodine was added to it. The reaction mixture was refluxed in an oil bath with intermittent shaking for 3-4 hours at ≈140 °C. Then the reaction mixture was cooled to room temperature, poured on to crushed ice with stirring and allowed the ice to melt. The chromone was filtered, washed with sodium thiosulfate solution until the washings were free from iodine, followed by with water. The product was dried and then purified using adsorption (column) chromatographic method using hexane:ethylacetate (9.5:0.5 and 9:1) as eluent and then recrystallized from ethanol.

The structures of all the synthesized compounds were characterized from their spectral data.

*6-Hydroxy-2-(3, 4-dimethoxystyryl) chromone (**20**)*: Pale brown solid (285 mg, 82.3%), m.p 208-210 °C; IR (KBr) υ_{max}: 3435, 2892, 1621, 1522, 1227, 1108, 1032, 829, 775 cm^{-1}; ^{1}H-NMR (DMSO-d$_6$): δ 9.87 (1H, br, s, Ar-OH), 7.58 (1H, d, *J*=8.9 Hz, H-8), 7.50(1H, d, *J*=1.7 Hz, H-2′), 7.31 (1H, d, *J*=16.1 Hz, H-*β*), 7.19 (1H, d, *J*=2.8 Hz, H-5), 7.06 (1H, dd, *J*=8.9, 2.8 Hz, H-7), 6.98 (1H, dd, *J*=8.1, 1.7 Hz, H-6′), 6.87 (1H, d, *J*=16.1 Hz, H-*α*), 6.73 (1H, d, *J*=8.1 Hz, H-5′), 6.30 (1H, s, H-3), 3.83-3.92 (6H, s, Ar-OCH$_3$); ^{13}C-NMR ((DMSO-d$_6$): δ 175.8(C-4), 163.6(C-2), 154.2(C-6), 149.5(C-3'), 149.3 (C-8a), 149.1 (C-4'), 136.5 (C-*β*), 127.6 (C-1'), 124.8 (C-4a), 122.3(C-7), 121.8(C-6'), 119.1(C-8), 118.7 (C-*α*), 115.4(C-5'), 114.6(C-5), 109.2(C-2'), 106.9(C-3) and 55.7(OMe-4'), 56.4(OMe-3'); LC-MS (ESI, negative ion mode), *m/z:* 323 [M-H]$^-$; elemental analysis for $C_{19}H_{16}O_5$, found (calcd): C 70.35 (70.37); H 5.01 (4.94).

*6-Methoxy-2-(3, 4-dimethoxystyryl)chromone (**21**):* Snuff color solid (287 mg, 84.9%), m.p. 186-187 °C (lit[2], 159-161°C); IR (KBr) υ_{max}: 2983, 2835, 1632, 1527, 1218, 1110, 830, 781 cm^{-1}; ^{1}H-NMR

(DMSO-d_6): δ 7.56 (1H, d, *J*=8.9 Hz, H-8), 7.48(1H, d, *J*=1.7 Hz, H-2′), 7.35 (1H, d, *J*=16.2 Hz, H-*β*), 7.32 (1H, d, *J*=2.8 Hz, H-5), 7.16 (1H, dd, *J*=8.9, 2.8 Hz, H-7), 6.98 (1H, dd, *J*=8.1, 1.7 Hz, H-6′), 6.85 (1H, d, *J*=16.2 Hz, H-*α*), 6.71 (1H, d, *J*=8.1Hz, H-5′), 6.31(1H, s, H-3), 3.83 (6H, s, Ar-OCH_3), 3.67(3H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 175.6(C-4), 163.6(C-2), 156.3(C-6), 149.8(C-3'), 149.4 (C-8a), 149.2(C-4'), 135.8(C-*β*), 128.3(C-1'), 125.2(C-4a), 121.7(C-7), 119.8(C-6'), 119.3(C-8), 118.9(C-*α*), 115.6 (C-5'), 115.2(C-5), 111.3(C-2'), 106.7(C-3) and 55.8 (OMe-4',6), 56.2(OMe-3'); LC-MS (ESI, negative ion mode): *m/z*: 337 $[M-H]^-$; elemental analysis: for $C_{20}H_{18}O_5$, found (calcd): C 70.97(71.00); H 5.35(5.32).

*7-Hydroxy-2-(3, 4-dimethoxystyryl)chromone (**22**)*: Brick red solid (265 mg, 81.7%), m.p. 223-225 °C; IR(KBr) υ_{max}: 3429, 2924, 1629, 1608, 1458, 1225, 1131, 865 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.67 (1H, br, s, Ar-OH), 7.78 (1H, d, *J*=8.6 Hz, H-5), 7.36 (1H, d, *J*=16.1 Hz, H-*β*), 7.13 (1H, d, *J*=2.0 Hz, H-2′), 6.98(1H, dd, *J*=8.2, 2.0 Hz, H-6′), 6.88 (1H, d, *J*=16.1 Hz, H-*α*), 6.65 (1H, d, *J*=2.2 Hz, H-8), 6.52 (1H, dd, *J*=8.6, 2.2 Hz, H-6), 6.78 (1H, d, *J*=8.2 Hz, H-5′), 6.29 (1H, s, H-3), 3.88 (3H, s, Ar-OCH_3), 3.67(3H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.8(C-4), 164.3(C-7), 162.4(C-2), 156.2(C-8a), 149.3(C-3'), 148.8(C-4'), 136.5(C-*β*), 134.7(C-5), 127.3(C-1'), 120.7(C-6'), 116.8(C-*α*), 116.3(C-5'), 115.8(C-4a), 113.7(C-2'), 112.5(C-6), 107.6(C-3), 103.8(C-8), and 56.3(OMe-4'), 55.8(OMe-3'); LC-MS (ESI negative ion mode): *m/z*: 323 $[M-H]^-$; elemental analysis for $C_{19}H_{16}O_5$, found (calcd): C 70.98; (70.37); H 5.40 (4.94).

*7-Methoxy-2-(3, 4-dimethoxystyryl)chromone (**23**)*: Yellowish orange solid (285 mg, 84.3%), m.p. 179-181 °C (lit[2], 198-199 °C); IR(KBr) υ_{max}: 2933, 2835, 1634, 1605, 1468, 1242, 1162, 847 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.86 (1H, d, *J*=8.6 Hz, H-5), 7.38 (1H, d, *J*=16.3 Hz, H-*β*), 7.15 (1H, d, *J*=2.0 Hz, H-2′), 7.02(1H, dd, *J*=8.2, 2.0 Hz, H-6′), 6.89 (1H, d, *J*=16.3 Hz, H-*α*), 6.77 (1H, d, *J*=8.2 Hz, H-5′), 6.69 (1H, d, *J*=2.2 Hz, H-8), 6.55 (1H, dd, *J*=8.6, 2.2 Hz, H-6), 6.31 (1H, s, H-3), 3.90-3.86 (6H, s, Ar-OCH_3), 3.65(3H, s, Ar-OCH_3). ^{13}C-NMR ((DMSO-d_6): δ 176.5(C-4), 165.8(C-7), 162.6(C-2), 156.7(C-8a), 149.4 (C-3'), 149.1(C-4'), 136.7(C-*β*), 134.9(C-5), 127.6(C-1'), 121.8(C-6'), 117.2(C-*α*), 116.6(C-5'), 115.4(C-4a), 113.4 (C-2'), 112.2(C-6), 107.3(C-3), 103.2(-C8), and 56.8 (OMe-4'7), 55.6(OMe-3'); LC-MS (ESI negattive ion mode): *m/z*: 337 $[M-H]^-$; elemental analysis for $C_{20}H_{18}O_5$, found (calcd): C 70.28(71.00); H 5.37(5.32).

*7-Hydroxy-2-(4-hydroxy-3-methoxystyryl)chromone (**24**)*: Brick red solid (252 mg, 80.7%), m.p. 258-260 °C (lit[44], 260-262 °C); IR(KBr) υ_{max}: 3365, 2918, 1636, 1618, 1564, 1468, 1328, 1272, 1169, 836 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.67 (1H, br, s, Ar-OH), 8.85 (1H, br, s, Ar-OH), 7.83 (1H, d, *J*=8.6 Hz, H-5), 7.55 (1H, d, *J*=16.0 Hz, H-*β*), 7.12 (1H, d, *J*=2.0 Hz, H-2′), 7.02 (1H, dd, *J*=8.2, 2.0 Hz, H-6′), 6.94 (1H, d, *J*=16.0 Hz, H-*α*), 6.87 (1H, d, *J*=2.2 Hz, H-8), 6.85 (1H, dd, *J*=8.6, 2.2 Hz, H-6), 6.82 (1H, d, *J*=8.2 Hz, H-5′), 6.23 (1H, s, H-3), 3.85(3H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.2(C-4), 163.1 (C-7), 162.2(C-2), 157.1(C-8a), 148.5(C-3'), 148.2 (C-4'), 136.4(C-*β*), 126.9(C-5), 126.3(C-1'), 122.4(C-6'), 117.6 (C-*α*), 116.3(C-5'), 115.5(C-4a), 114.6(C-2'), 113.4 (C-6), 108.7(C-3), 102.3(C-8), and 55.8(OMe-3'); LC-MS (ESI, negative ion mode): *m/z*: 309 ($[M-H]^-$; elemental analysis for $C_{18}H_{14}O_5$: found (calcd): C 69.65 (69.68); H, 4.6 (4.5).

*7-Methoxy-2-(4-hydroxy-3-methoxystyryl)chromone (**25**)*: Brown solid (270 mg, 83.3%), m.p. 227-229 °C; IR(KBr) υ_{max}: 3303, 2919, 1628, 1609, 1535, 1448, 1219, 1017, 771 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.07 (1H, br, s, Ar-OH), 7.72 (1H, d, *J*=8.6 Hz, H-5), 7.57 (1H, d, *J*=16.1 Hz, H-*β*), 7.15 (1H, d, *J*=2.0 Hz, H-2′), 7.03 (1H, dd, *J*=8.2, 2.0 Hz, H-6′), 6.93 (1H, d, *J*=16.1 Hz, H-*α*), 6.86 (1H, d, *J*=2.2 Hz, H-8), 6.84(1H, dd, *J*=8.6, 2.2 Hz, H-6), 6.80 (1H, d, *J*=8.2 Hz, H-5′), 6.27 (1H, s, H-3), 3.83-3.85 (6H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 175.9(C-4), 163.7(C-7), 161.9(C-2), 157.3 (C-8a), 149.5(C-3'), 148.0(C-4'), 136.4(C-*β*), 126.8(C-5), 126.4 (C-1'), 122.5(C-6'), 118.1(C-*α*), 116.3(C-5'), 115.2 (C-4a), 114.9(C-2'), 114.0(C-6), 107.9(C-3), 101.9(C-8), and 55.7-55.9(OMe-3',7); LC-MS (ESI, negative ion mode): *m/z*: 323 $[M-H]^-$; elemental analysis for $C_{19}H_{16}O_5$: found (calcd): C, 70.36(70.37); H, 4.97 (4.93).

*6-Hydroxy-2-(4-hydroxy-3-methoxystyryl)chromone (**26**)*: Light yellow solid (255 mg, 82.2%), m.p. 265-267 °C (lit[44], 268-270 °C). IR (KBr) υ_{max}: 3454, 2986, 1636, 1591, 1535, 1463, 1269, 1204, 1023, 835 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.89 (1H, br, s, Ar-OH), δ 9.55 (1H, br, s, Ar-OH), 7.54 (1H, d, *J*=8.9 Hz, H-8), 7.53(1H, d, *J*=1.7 Hz, H-2′), 7.27 (1H, d, *J*=16.0 Hz, H-*β*), 7.26 (1H, d, *J*=2.8 Hz, H-5), 7.23 (1H, dd, *J*=8.9, 2.8 Hz, H-7), 7.10 (1H, dd, *J*=8.1, 1.7 Hz, H-6′), 7.02 (1H, d, *J*=16.0 Hz, H-*α*), 6.80 (1H, d, *J*=8.1 Hz, H-5′), 6.29 (1H, s, H-3), 3.85 (3H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.5(C-

4), 162.2 (C-2), 154.5(C-6), 150.2(C-8a), 149.2(C-3'), 148.3(C-4'), 136.5(C-*β*), 126.3(C-1'), 123.9(C-4a), 123.1(C-7), 122.1 (C-6'), 118.8(C-8), 117.5(C-*α*), 115.6(C-5'), 111.2(C-5), 108.5(C-2'), 107.9(C-3) and 55.8(OMe-3'); LC-MS (ESI, negative ion mode): *m/z*: 309 $[M-H]^-$; elemental analysis for $C_{18}H_{14}O_5$: found (calcd): C 69.62 (69.68); H 4.3 (4.5).

*6-Methoxy-2-(4-hydroxy-3-methoxystyryl)chromone (**27**)*: Greenish yellow color solid (272 mg, 83.9%), m.p. 231-233 °C (lit[44], 230-232 °C); IR (KBr) υ_{max}: 3238, 1641, 1608, 1530, 1380, 1273, 1132, 827 cm^{-1}; ^{1}H-NMR (DMSO-d_6) : δ 9.54 (1H, br, s, Ar-OH), 7.65 (1H, d, *J*=9.0 Hz, H-8), 7.59 (1H, d, *J*=16.1 Hz, H-*β),* 7.55 (1H, d, *J*=2.2 Hz, H-2′), 7.38-7.31 (2H, m, H-5 & 7), 7.12 (1H, dd, *J*=8.1, 2.2 Hz, H-6′), 7.03 (1H, d, *J*=16.1 Hz, H-*α*), 6.80 (1H, d, *J*=8.1 Hz, H-5′), 6.35 (1H, s, H-3), 3.86 (6H, s, 2xAr-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.7(C-4), 163.8(C-2), 156.3(C-6), 150.4(C-3'), 149.2(C-8a), 148.1(C-4'), 137.2(C-*β*), 126.8(C-1'), 124.5(C-4a), 123.1(C-7), 122.6 (C-6'), 120.2(C-*α*), 117.3(C-8), 115.9 (C-5'), 111.3(C-5), 108.7(C-2'), 105.2(C-3) and 55.9 (OMe-3',6); LC-MS (ESI, negative ion mode): *m/z*: 323 $[M-H]^-$; elemental analysis for $C_{19}H_{16}O_5$: found (calcd): C, 70.33 (70.37); H, 5.00 (4.94).

*7-Hydroxy -2-(4-methoxystyryl)chromone (**28**)*: Orange color solid (240 mg, 81.6%), m.p. 250-253 ºC (lit[11], 248-251 °C). IR (KBr) υ_{max}: 3431, 2956, 2833,1635,1609, 1513, 1465, 1234,1137,843,813,765 cm^{-1}; ^{1}H-NMR (DMSO-d_6):δ 9.76 (1H, br, s, Ar-OH); 7.84(1H, d, *J*=8.7 Hz, H-5); 7.54 (1H, d, *J*=16.0 Hz; H-*β*); 7.51(2H, d, *J*=8.6 Hz, H-2′,6′); 6.97(1H,d, *J*=16.0 Hz,H-*α*); 6.88 (1H, d, *J*=2.2 Hz,H-8); 6.85(1H, dd, *J*=8.6, 2.2 Hz-H-6); 6.82(2H, d, *J*=8.6 Hz, H-3′,5′); 6.25(1H, s, H-3); 3.85(3H, s.Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.3(C-4), 164.8(C-7), 161.8(C-2), 158.0 (C-8a), 157.5 (C-4'), 136.5(C-*β*), 130.2(C-5), 123.3(C-1'), 125.5(C-2',6'), 117.6(C_α), 115.3(C-3',5'), 114.6(C-4a), 108.7 (C-6), 106.3(C-3), 103.3(C-8), and 55.8 (OMe-4'); LCMS (ESI, negative ion mode): *m/z*: 293 $[M-H]^-$; elemental analysis: for $C_{18}H_{14}O_4$: found (calcd): C 73.23 (73.46); H 4.75(4.76).

*7-Methoxy-2-(4-methoxystyryl)chromone (**29**)*: Yellowish orange solid (255 mg, 82.8%), m.p. 172-175 ºC (lit[42,] 140-141 °C,); IR (KBr) υ_{max}: 2935, 2819, 1623, 1605, 1511, 1436, 1233, 1125, 812, 763 cm^{-1}; ^{1}H-NMR (DMSO-d_6):δ 7.74 (1H, d, *J*=8.8 Hz, H-5); 7.57 (1H, d, *J*=16.1 Hz; H-*β*); 7.55 (2H, d, *J*=8.6 Hz, H-2′,6′); 6.88(1H, d, *J*=16.1 Hz, H-*α*); 6.91 (1H, d, *J*=2.2 Hz, H-8); 6.89(1H, dd, *J*=8.6, 2.2 Hz-H-6); 6.85(2H, d, *J*=8.6 Hz, H-3′,5′); 6.29(1H, s, H-3); 3.85(6H, s, Ar-OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.2 (C-4), 165.6(C-7), 162.1(C-2), 157.9(C-8a), 157.6 (C-4'), 136.7 (C-*β*), 129.8(C-5), 123.4(C-1'), 125.7(C-2',6'), 118.2 (C-*α*), 116.6(C-3',5'), 114.8(C-4a), 110.8(C-6), 106.6(C-3), 102.7(C-8), and 56.2 (OMe-4',7); LCMS (ESI, negative ion mode): *m/z*: 307 $[M-H]^-$; elemental analysis for $C_{19}H_{16}O_4$: found (calcd): C-74.01(74.02); H-5.23, (5.19).

*6-hydroxy-2-(4-methoxystyryl)chromone (**30**)*: Brown color solid (240 mg, 81.6%). m.p. 256-257 °C (lit[41], 257-259 °C); IR (KBr) υ_{max}: 3345, 2936, 1631, 1617, 1465, 1247, 1167 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.82 (1H, br, s, Ar-OH), 7.67 (1H, d, *J*=8.5 Hz, H-8), 7.55 (1H, d, *J*=16.2 Hz, H-*β*), 7.42 (2H, d, *J*=8.4 Hz, H-2',6'), 7.30 (2H, m, H-5,7), 6.91 (1H, d, *J*=16.2 Hz, H-*α*), 6.82 (2H, d, *J*=8.4 Hz, H-3',5'), 6.38 (1H, s, H-3), 3.89 (3H, s, OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 176.6(C-4), 162.8(C-2), 158.3 (C-4') , 149.7(C-6), 148.6(C-8a), 136.8(C-*β*), 126.8(C-2',6'), 125.3 (C-1'), 123.8(C-4a), 123.7(C-7), 118.8(C-8), 117.3(C-*α*), 115.1(C-3',5'), 113.2(C-5), 107.3(C-3), and 55.7 (OMe-4'); LCMS (ESI, negative ion mode): *m/z*: 293 $[M-H]^-$; elemental analysis for $C_{l8}H_{14}O_4$: found (calcd): C, 73.44 (73.46); H, 4.73 (4.76).

*6-methoxy-2-(4-methoxystyryl)chromone (**31**)*: Pale yellow color solid (258 mg, 83.7%); m.p. 167-169 °C (lit[41], 167-169 °C); IR (KBr) υ_{max}: 2985, 2838, 1632,1607,1565,1436, 1243, 1168 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 7.73 (1H, d, *J*=8.7 Hz, H-8), 7.58 (1H, d, *J*=16.3 Hz, H-*β*), 7.51(2H, d, *J*=8.3 Hz, H-2',6'), 7.42-7.33(2H, m, H-5,7), 7.02(1H, d, *J*=16.3 Hz, H-*α),* 6.80 (2H, d, *J*=8.3 Hz, H-3',5'), 6.34 (1H, s, H-3), 3.93(3H, s, OCH_3), 3.85(3H, s, OCH_3); ^{13}C-NMR ((DMSO-d_6): δ 175.9(C-4), 163.5 (C-2), 159.1 (C-4'), 151.9(C-6), 149.2(C-8a), 136.5(C-*β*), 126.9(C-2',6'), 125.6(C-1'), 123.5(C-4a), 122.6(C-7), 118.4 (C-8), 117.8(C-*α*), 114.9(C-3',5'), 113.6(C-5), 106.8(C-3), and 55.8 (OMe-4',6); LCMS (ESI, negative ion mode): *m/z*: 307 ([M-H]$^-$; elemental analysis for $C_{19}H_{16}O_4$: found (calcd): C 73.98 (74.01); H 5.21 (5.23).

2.3 In Silico Molecular Docking Studies with α-Amylase

Molecular docking studies of the prepared compounds were performed against *α*-amylase enzyme, in order to understand the possible binding mechanism prior to their synthesis. Marvin view software was utilized to optimize the structures of the title compounds and the standard drug acarbose. In order to reveal the binding modes of the title compounds, docking simulation was performed targeting the crystal structure of pancreatic alpha amylase which was retrieved from RCSB, Protein Data Bank (PDB ID: 3IJ8) and the structure was optimized by removing the water molecules, hetero atoms, and co-factors. Hydrogen bonds, missing atoms, and charges were computed. The PDB structures of target protein (A) and standard drug, acarbose (B) were shown in Figure 1. The molecular docking method was performed using 1-click docking online server tool, which uses a Vina filter and dock multiple ligands into a single target with default binding site X: 7.2178, Y: 16.2957, Z: 42.1167. The docked process and interactions of compounds and protein were analyzed by using Discovery studio Visualizer[36] V16.1.0.15350.

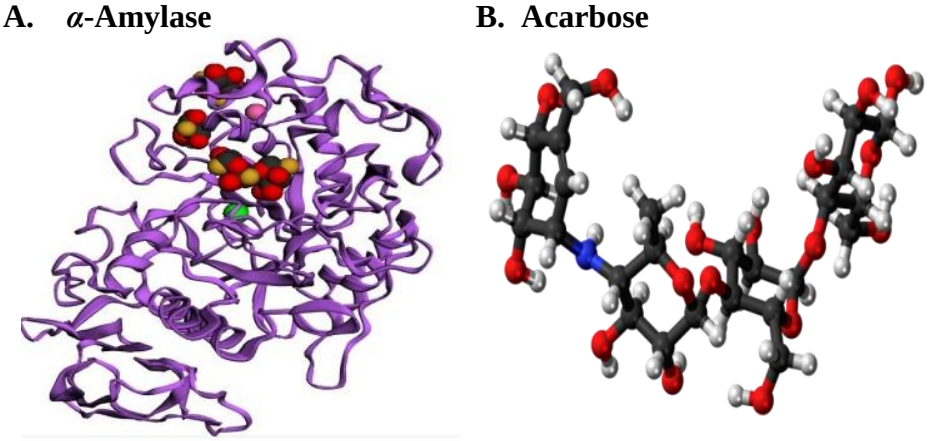


Figure 2. PDB Structures of target protein (**A**) and standard drug (**B**).

3. Results and Discussion

3.1. Chemistry

For a long time different methods[4,8, 37-39] have been developed for the synthesis of wide variety of analogues, but Aldol condensation and Baker-venkataraman rearrangement are the most common methods to synthesize (*E*)-2-styrylchromoes from *o*-hydroxyacetopenones and cinnamaldehydes or cinnamic acids. The detailed synthetic methods, reactivity and biological activites of 2-styrylchromones were discussed by Silva etal[40]. In all above methods, majority of synthetic routs[41-43] were multistep and also frequently involving protection-deprotection steps[44]. So the use of protecting groups makes the entire synthetic plan more complex since it requires at least two additional steps. At the same time, it is desirable to design synthetic procedure with high selectivity, high-yielding, clean and manipulatively easy.

Based on the above facts and literature survey, we focused on the use of PEG-400[45, 46] which is an excellent solvent and, non-toxic, thermally stable, eco-friendly, recoverable and reusable[47,48] reaction medium/condensing agent[49-51].With the previous experience in the synthesis, we have started preparation of 2-styrylchromones using PEG-400 as a solvent cum condensing agent at 40-50 °C temperature followed by oxidative cyclization with iodine at ≈140 °C.

In majority of cases iodine was used for oxidative cyclization in DMSO under different conditions to get flavones[52] and other chromone derivatives[40,53]. Iodine was also used by Pinto[54] and Silva for iodination of chromones to enhance their biological activities and also as condensing (dehydrating) agent to convert *β*-diketones into respective chromone derivatives.

Before the use of PEG-400, we tried with Polyphosphoric acid (PPA) alone and also along with some solvents like ethanol, methanol etc. But the yield of products was very low even on long stirring for about several hours. Later we have carried out the optimization of reaction conditions (Table 1) with the starting materials and found that the products were obtained in good yield at high purity when the reaction was run under warm conditions in PEG-400 by using piperidine in trace amounts. Initially, we have prepared 1, 5-diphenylpenta-2,4-dienones from *o*-hydroxy- acetophenones and connamaldehydes in the first step. These compounds were then converted into corresponding 2-styrylchromones by means of oxidative cyclization in PEG-400 using iodine as oxidizing agent, Scheme 1.

After following the above method for 2-3 compounds, just we have run the entire synthetic process in the same reaction vessel without isolation and purification of dienones. The completion of reaction for each corresponding product was scrutinized by TLC. Even the two steps were made to complete in the same vessel, there was no that much decrease in the yield of final products. The physical data of synthesized products was given in the Table 2.

Initially, the synthesized compounds were identified by LCMS and IR spectrum. Of course 2D-NMR[55] is also useful in structural eiucidation, 1D-NMR spectroscopy which is the most powerful technique to illustrate the structure of organic compounds was used for the structural elucidation of 2-styrylchromones. The pair of doublets at δ 6.81-7.03 and 7.27-7.57 ppm represents two hydrogens of a double bond (C_α-C_β) of styryl group. The trans configuration of α and β (vicinal) protons was established from the large coupling constants ($J_{H\alpha}$-$J_{H\beta}$,) at around 16 H_Z. The presence of –OH and –OCH_3 at two benzene nuclei was distinguished by resonance peaks at δ 9.07-9.81 ppm and 3.83-3.92 ppm respectively. The C-3 proton was highly shielded which gave a strong peak in the range of 6.29-6.34 ppm. All these structural features were well supported by ^{13}C-NMR spectra and the hydroxyl and methoxyl substituted aromatic carbons were easily identified by larger δ values about 149-163 ppm.

All the synthesized compounds were given an intensified molecular ion peak in negative ion mode at their respective molecular mass. The presences of various functional groups like C=O, -C-O-C-, -OH, -OCH_3 were well recognized from their IR spectra.

3.2. In Silico Molecular Docking Studies

Based on important activities of some other chromones including 2-styrylchromones [41,43,44,56, 57-62], the docking studies were performed for the synthesized compounds (**20-31)** to understand their binding interactions with the active site of the pancreatic α-amylase enzyme (PDB ID: 3IJ8) using 1-click docking online server tool. All most all the 12 compounds in this series were found to be active. From the docking results, it was observed that the compounds **24**, **25, 26** and **28** were exhibited good binding energies (-8.7, -8.8, -8.6 and -8.4 kcal/mol) with the target enzyme, α-amylase when compared with the reference drug (-8.3 kcal/mol) and were fitted in the active site of the target gene properly. Binding energies and bonding pose of ligands with target enzyme were presented in detail in Table 3. 2D ligand interactions of most active compounds (**28**, **26, 24** and **25**) with the target enzyme were shown in Table 4.

The compound **25** is the most active compound in this series and the binding mode shows that the chrome nucleolus and phenyl group of compound **25** forms π-π stacking with Trp59 and Tyr62 respectively. Additionally, the compound was also found to have hydrophobic interactions with Leu165, Leu162, Ala198, Tyr62, Trp59, Trp58 and Trp59. In compound **24**, the chromone ring forms π-π stacking with Trp59. Additionally, Leu165, Leu162, Ala198, Tyr62, Trp59 and Trp58 formed hydrophobic contacts with compound **24**. The binding mode orientation of the compound **26** showed that the chromone ring forms π-π stacking with Trp59.

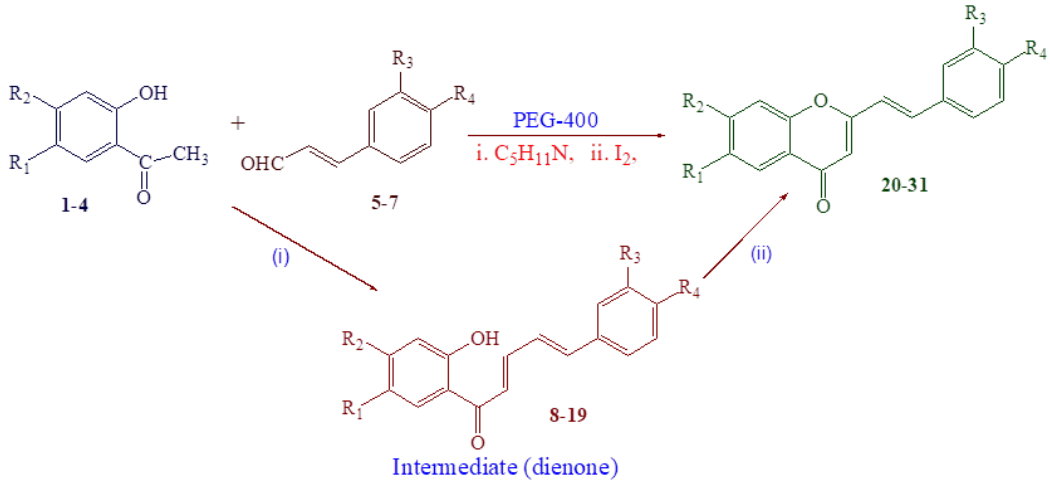
Table 1. Optimization of reaction conditions:

S.No.	Solvent	Reagent	Temp.(°C)	Time (hrs.)	Yield (%)
1	PPA	-	RT	3-4	ND
2	EtOH	PPA	RT	3	Very poor
3	MeOH	PPA	40-50	2-3	10-20
4	PEG-400	-	RT	3-5	ND
5	PEG-400	-	90-100	3	10-20
6	PEG-400	Et_3N	40-50	1-2	25-30
7	PEG-400	Et_2NH	40-50	1-2	≈30
8	PEG-400	Piperidine	40-50	0.5	85-87

Additionally, Ala198, Leu162, Leu165, Tyr62, Trp59 and Trp58 forms hydrophobic contacts with compound **26**. In compound **28**, the chromone ring forms π-π stacking with His201. Additionally, Val234, Ile235, Ala198, Tyr151, Leu162, Leu165, Tyr62, Trp59 and Trp58 form hydrophobic contacts with compound **24**. Additionally, the oxygen atom of chrome ring forms hydrogen bond with Tyr 151.

Table 2. Physical data of synthesized compounds

Entry	Molecular formula	Substituents				M.P. (°C)	Yield (%)
		R_1	R_2	R_3	R_4		
20	$C_{19}H_{16}O_5$	OH	H	OMe	OMe	208-210	82.3
21	$C_{20}H_{18}O_5$	OMe	H	OMe	OMe	186-187	84.9
22	$C_{19}H_{16}O_5$	H	OH	OMe	OMe	223-225	81.7
23	$C_{20}H_{18}O_5$	H	OMe	OMe	OMe	179-181	84.3
24	$C_{18}H_{14}O_5$	H	OH	OMe	OH	258-260	80.7
25	$C_{19}H_{16}O_5$	H	OMe	OMe	OH	227-229	83.3
26	$C_{18}H_{14}O_5$	OH	H	OMe	OH	265-267	82.2
27	$C_{19}H_{16}O_5$	OMe	H	OMe	OH	231-233	83.9
28	$C_{18}H_{14}O_4$	H	OH	H	OMe	250-253	81.6
29	$C_{19}H_{16}O_4$	H	OMe	H	OMe	172-175	82.8
30	$C_{18}H_{14}O_4$	OH	H	H	OMe	256-257	81.6
31	$C_{19}H_{16}O_4$	OMe	H	H	OMe	167-169	83.7



Scheme 1. Preparation of 2-styrylchromones

(i) PEG-400, $C_5H_{11}N$, 40-50 °C, 0.5 hrs. (ii) PEG-400, I_2, ≈140 °C, 3-4 hrs

Table 3. Bonding interactions of the title lead compounds (20-31) and standard with α-amylase

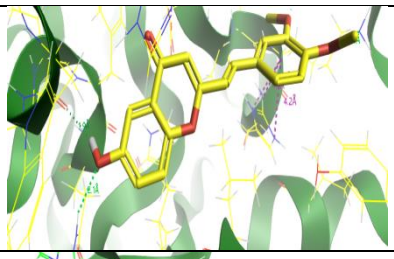
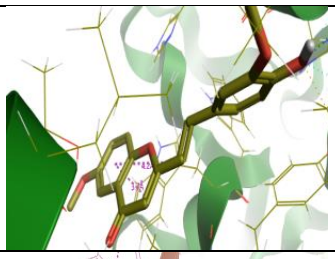
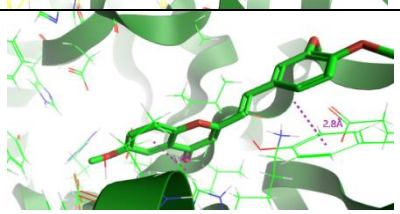
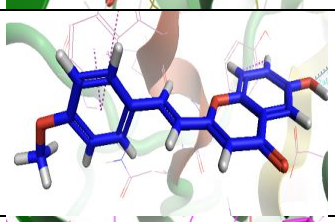
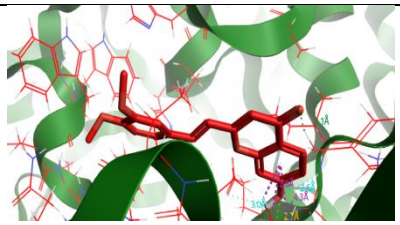
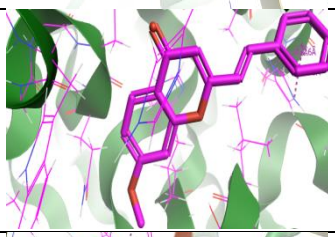
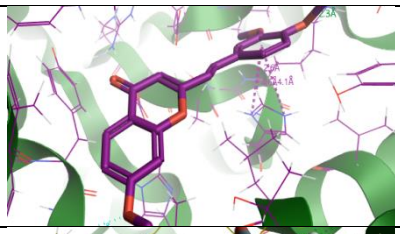
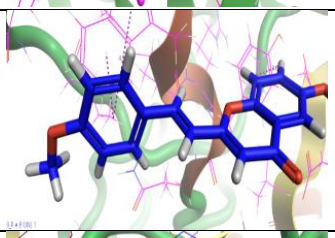
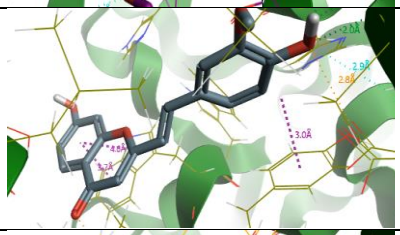
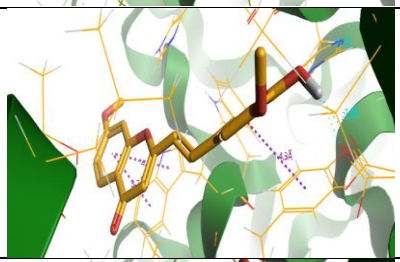
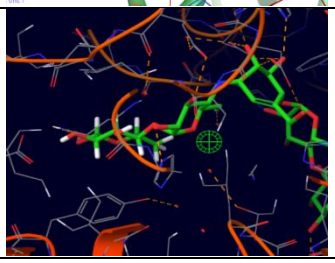
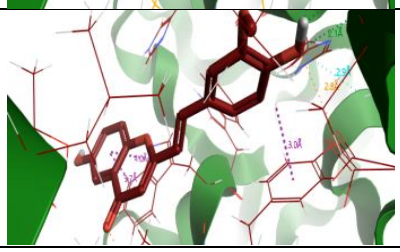
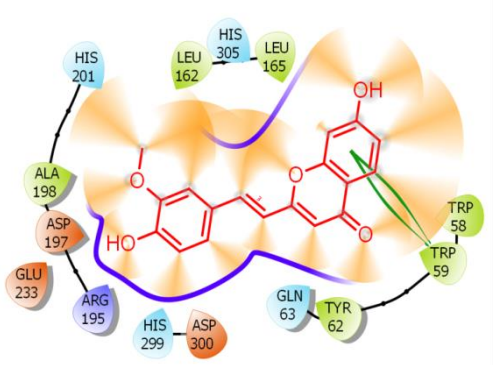
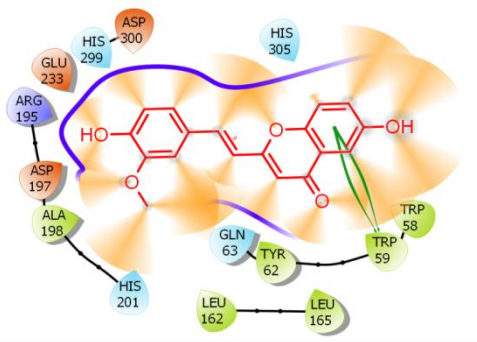
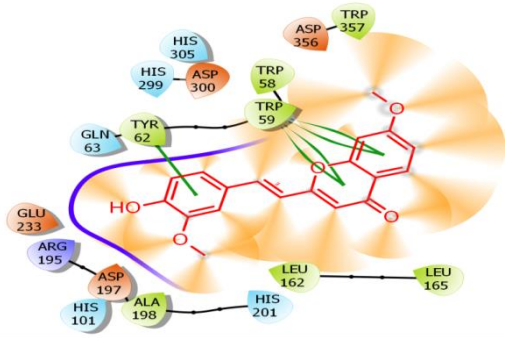
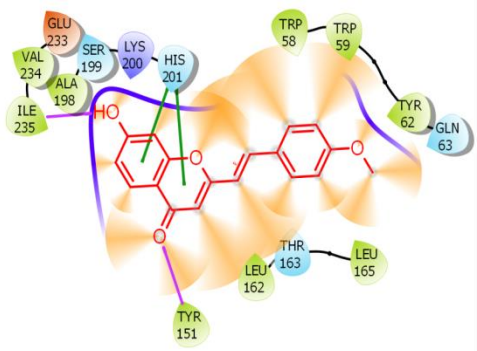
Compd.	Image	BE (kcal/ mol)	Compd.	Image	BE (kcal/ mol)
20		-8.1	**27**		-8.2
21		-7.8	**28**		-8.4
22		-8.3	**29**		-7.8
23		-8.1	**30**		-7.9
24		-8.7	**31**		-7.6
25		-8.8	**Acarbose**		-8.3
26		-8.6			

Table 4. 2D Lig Plot images of compounds **24**, **25**, **26** and **28**

Compd	2D structure	Compd	2D structure
24		**26**	
25		**28**	

4. Conclusion

We have attempted a new way for the synthesis of 2-styrylchromones with PEG-400 in the presence of catalytic amounts of piperidine and iodine. The way, we proceeded was satisfactory in the completion of the reaction, yield and purity of final products. In silico molecular docking study was also performed for all the ligands against human α-amylase enzyme. The study established that the compounds 24 (4',7-OH, 3'-OMe), 25 (33',7-OMe, 4'-OH), 26 (4',6-OH, 3'-OMe) and 28 (4'-OMe, 7-OH) were exhibited higher binding energies (-8.7, -8.8, -8.6 and -8.4 Kcal/mol) with the target enzyme than the reference drug, acarbose (-8.2 kcal/mol) which shows that the synthesized compounds will become the promising next-generation anti-diabetic agents.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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