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Synthesis and characterization of 3-arylidenechroman-4-ones and their inhibitory effects on platelet aggregation activity

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ABSTRACT

*A series of 3-arylidenechroman-4-one derivatives (1-16) have been synthesized in good yields from chroman-4-one and different substituted aldehydes by the Claisen-Schmidt condensation. All the synthesized compounds were characterized by using spectroscopic analyses including IR, ^{1}H NMR, ^{13}C NMR, EIMS and HREIMS. The synthesized compounds were screened for in vitro inhibitory effects on aggregation of washed rabbit platelets induced by adenosine diphosphate (20 µM) and collagen (10 µg/mL). Compounds **1** (81.3%), **11** (88.7%), and **13** (85.0 %) were showed potent inhibitory effects on ADP-induced aggregation activity, in which their structures possessed 2-thiophene, 3,5-dimethoxybenzene and 2,3-dimethoxybenzene moieties in the B-ring, respectively.*

Keywords: 3-arylidenechroman- 4-one derivatives; Claisen-Schmidt condensation; spectroscopic and spectrometric analysis; platelet aggregation activity

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INTRODUCTION

Platelet aggregation plays a central role in thrombosis (clot formation). Platelet-mediated thrombus formation in the coronary artery is a primary factor in the development of thrombotic disorders such as unstable angina, myocardial infarction stroke [1-2], and peripheral vascular diseases [3]. Normally, the blood is not aggregated in the blood vessels, but on an occasion of bleeding, blood aggregation is generated as a physiological defense reaction. Platelet aggregation is caused by physiological substances such as thrombin and prostaglandin endoperoxide and can lead an arterial thrombosis [4]. Platelet aggregation is induced by the action of endogenous agonists such as arachidonic acid (AA), adenosine diphosphate (ADP), platelet-activating factor (PAF), thrombin (Thr) and collagen (Col) [5]. The inhibition of platelet function represents a promising approach for the treatment of these diseases. Many antiplatelet drugs have been used clinically, and have certain disadvantages such as notable side effects and inefficient therapy [6-7]. Therefore, searching for more effective and safer antiplatelet agents with fewer side effects is extremely important. Homoisoflavones are a class of naturally occurring oxygen hetero cyclic compounds. It occupied a special place in the field of hetero cycles as this skeleton is an integral part of many natural compounds. It is structurally related to flavonoid consisted a sixteen carbon skeleton, which includes a chromanone or chromane ring system with a benzyl or benzylidene group at C-3 position. Both natural and synthetic chromone derivatives are

known to exhibit numerous biological activities including antifungal, antihistaminic, anti-inflammatory, antioxidant, and antiviral effects [8-17]. Thiochromones and their derivatives are reported to show medicinal properties [18-19]. The current literature shows that there has been a growing trend towards synthesis of heterocyclic containing these two rings [20-21]. As a continuation of our efforts, we synthesized and reported the structures of heterocyclic homoisoflavanones by condensing different substituted aldehydes with 4-chromanone to obtain 3-arylidene chroman-4-one derivatives **1-16** (Scheme1). In the present study, we would report the characterization of 3-arylidene chroman-4-one derivatives and evaluated for their *in vitro* inhibitory effects on aggregation of washed rabbit platelet induced ADP (20 μM) and Col (10 μg/mL).

MATERIALS AND METHODS

Chemistry

All the chemicals and reagents were of analytical grade and were used without further purification. All the reaction and purity of synthesized compounds were deduced by thin layer chromatography (TLC) using silica-G plates. The plates were developed by exposing to the iodine vapors. All the synthesized compounds (**1-16, Scheme-1**) were characterized by spectroscopic and spectrometric analyses including IR, ^{1}H-, ^{13}C-NMR, EIMS and HREIMS techniques to confirm the presence of proposed ring systems. IR spectra were determined on a Shimadzu FT-IR Prestige 21 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer, using tetramethylsilane (TMS) as internal standard and all chemical shifts were reported in parts per million (ppm, δ). EIMS and HREIMS spectra were obtained on a VG-70-250S mass spectrometer. Column chromatography was performed on silica gel (70–230 mesh, 230–400 mesh). Purity of the compounds were checked by TLC plates on Pre coated Kieselgel 60 F254 plates (Merck) using *n*-hexane/ethyl acetate as an eluent in the different ratios and the spots were examined under a UV lamp.

Table1. Inhibitory effects of compounds 1-16 on platelet aggregation induced by ADP and Collagen

Inducer / Compound	Inhibition percentage (%)	
	ADP	Col
1	81.3	59.9
2	38.0	10.2
3	54.9	73.3
4	60.6	71.7
5	43.3	48.1
6	66.8	32.1
7	31.5	3.9
8	41.5	48.7
9	69.0	69.9
10	54.1	35.4
11	88.7	19.5
12	61.5	0.0
13	85.0	15.0
14	36.4	0.0
15	66.4	55.1
16	47.8	18.9

General procedure for the synthesis of 3-arylidenechroman-4-ones (1-16):

A mixture of chroman-4-one and corresponding aldehydes in methanol (30 mL) then slowly added to the solution 30% KOH (30 mL) were stirred at room temperature for a period of 24 h (monitored by TLC) [22]. After this period, the alcohol was distilled off and the resulting material was treated with water and acidified dil. HCl (30%). The viscous mass was extracted in separating funnel with ethyl acetate (3X50 mL). The ethyl acetate was evaporated under reduced pressure in the rotavapour to obtain residue. This was further purified by over a silica gel chromatography eluted with a mixture of *n*-hexane-EtOAc to obtain compounds **1-16** in good yields.

Spectral data of synthesized isoxazole compounds

(*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (1). Chroman-4-one (1.48 g, 0.01 moles) and 2-thiophene carboxaldehyde (1.12 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **1** (pale yellow solid, 2.1 g, 87%). IR (neat) ν_{max}: 3097, 2920, 1662, 1600, 1581, 1469, 1334, 1303, 1211, 1141, 1107, 1041, 983, 948, 856, 829, 752, 713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (2H, d, J = 8.7 Hz), 7.59 (1H, d, J = 5.1 Hz), 7.50 (1H, m), 7.34 (1H, d, J = 2.7 Hz), 7.17 (1H, t, J = 8.7 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.98 (2H, d, J = 8.2 Hz), 5.46 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.2, 160.9, 137.6, 135.6, 133.9, 130.9, 128.7, 128.1, 127.8, 127.1 (x2), 121.8, 117.7, 67.7. EIMS *m/z* (% *rel. int.*): 242 ([M]$^{+}$, 100), 241 (14), 213 (26), 181 (3), 134 (8), 122 (37), 121 (72), 120 (5), 96 (7), 92 (9), 57 (10).HREIMS *m/z*calcd for $C_{14}H_{10}O_2S$, 242.0402; found, 242.0405.

(*E*)-3-((3-methylthiophen-2-yl)methylene)chroman-4-one (2). Chroman-4-one (1.48 g, 0.01 moles) and 3-methyl-2-thiophenecarboxaldehyde (1.26 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **2** (pale yellow solid, 2.1 g, 82%). IR (neat) ν_{max}: 1654, 1600, 1570, 1465, 1303, 1261, 1211, 1153, 1103, 1041, 983, 948, 744, 605cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.08 (1H, br s), 8.02 (1H, dd, J = 1.8, 7.8 Hz), 7.50 (2H, m), 7.06 (1H, t, J = 7.8 Hz), 6.99 (2H, t, J = 7.8 Hz), 5.48 (2H, s), 2.44 (3H, s).^{13}C NMR (75 MHz, $CDCl_3$): δ181.5, 160.9, 144.0, 135.5, 131.2, 130.9, 129.2, 127.7, 127.2, 126.0, 121.9, 121.7, 117.7, 67.7, 14.6.EIMS *m/z* (% *rel. int.*): 256 ([M]$^+$, 100), 255 (15), 242 (8), 241 (45), 237 (18), 227 (12), 213 (12), 159 (6), 136 (16), 135 (66), 134 (17), 121 (42), 110 (5), 97 (12), 91 (21), 65 (6).HREIMS *m/z*calcd for $C_{15}H_{12}O_2S$, 256.0558; found, 256.0559.

(*E*)-3-(furan-2-ylmethylene)chroman-4-one (3). Chroman-4-one (1.48 g, 0.01 moles) and 2-furaldehyde (0.96 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **3** (pale yellow solid, 1.75 g, 77%). IR (neat) ν_{max}: 1666, 1600, 1469, 1396, 1319, 1257, 1215, 1145, 1026, 918, 883, 833, 752, 601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.99 (1H, d, J = 1.2 Hz), 7.61 (1H, s), 7.46 (2H,m), 7.05 (1H, t, J = 7.2 Hz), 6.98 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 3.3 Hz), 6.54 (1H, dd, J = 3.3, 1.2Hz), 5.59 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ181.6, 161.3, 151.2, 145.6, 135.6, 127.7, 126.6, 121.9, 121.7, 121.6, 118.5, 117.8, 112.6, 67.9.EIMS *m/z* (% *rel. int.*): 226 ([M]$^+$, 100), 225 (14), 197 (44), 169 (15), 141 (8), 121 (20), 120 (12), 106 (14), 105 (12), 92 (9), 78 (19), 65 (4).HREIMS *m/z*calcd for $C_{14}H_{10}O_3$, 226.0630; found, 226.0630.

(*E*)-3-((5-metnylfuran-2-yl)methylene)chroman-4-one (4). Chroman-4-one (1.48 g, 0.01 moles) and 5-methyl-2-furaldehyde (1.10 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/$CHCl_3$(1:1) yield **4** (yellow solid, 1.90 g, 79%). IR (neat) ν_{max}: 2920, 2850, 1666, 1608, 1570, 1516, 1469, 1311, 1261, 1219, 1141, 1026, 956, 756, 721, 601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.00 (1H, dd, J = 1.8, 8.1 Hz), 7.47 (2H, m), 7.00 (2H, m), 6.67 (1H, d, J = 3.0 Hz), 6.17 (1H, d, J = 3.0 Hz), 5.58 (2H, s), 2.40 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ181.7, 161.3, 156.6, 149.9, 135.3, 127.7, 124.9, 122.1, 121.9, 121.6, 120.5, 117.7, 109.3, 68.0, 14.1.EIMS *m/z*(% *rel. int.*): 240([M]$^+$, 100), 239 (17), 225 (25), 211 (12), 197 (38), 169 (13), 121 (13), 120 (26), 119 (13), 105 (12), 91 (10), 77 (7), 65 (6).HREIMS*m/z*calcd for $C_{15}H_{12}O_3$, 240.0786; found, 240.0785.

(*E*)-3-((1-methyl-1H-pyrrol-2-yl)methylene)chroman-4-one (5). Chroman-4-one (1.48 g, 0.01 moles) and N-methylpyrrole-2-carboxaldehyde (1.09 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **5** (pale yellow solid, 1.70 g, 71%). IR (neat) ν_{max}:1647, 1600, 1573, 1473, 1415, 1384, 1323, 1296, 1257, 1172, 1072, 1045, 995, 956, 914, 729, 648 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (1H, t, J = 8.4 Hz), 7.78 (1H, d, J = 9.6 Hz), 7.45 (1H, d, J = 8.1 Hz), 6.97 (3H, m), 6.30 (2H, m), 5.39 (2H, s), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ181.1, 160.6, 135.3, 128.3, 127.7, 127.5, 124.7, 123.4, 121.9, 121.5, 117.6, 115.8, 109.8, 68.2, 34.5. EIMS *m/z*(% *rel. int.*): 239 ([M]$^+$, 100), 238 (23), 210 (19), 121 (19), 119 (32), 118 (69), 117 (9), 104 (8), 94 (5), 91 (6), 77 (4).HREIMS *m/z*calcd for $C_{15}H_{13}O_2N$, 239.0946; found, 239.0945.

(*E*)-3-(4-methoxybenzylidene)chroman-4-one (6). Chroman-4-one (1.48 g, 0.01 moles) and 4-methoxy benzaldehyde (1.36 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **6** (pale yellow solid, 2.1 g, 79%). IR (neat) ν_{max}: 2916, 2839, 1666, 1600, 1508, 1465, 1319, 1257, 1211, 1180, 1149, 1111, 1026, 956, 914, 825, 748, 675 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.02 (1H, dd, J = 1.2, 9.0 Hz), 7.83 (1H, s), 7.46 (1H, m), 7.26 (2H, d, J = 9.0 Hz), 7.05 (1H, t, J = 7.6 Hz), 6.96 (3H, m), 5.38 (2H, s), 3.85 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.1, 160.9, 160.6, 137.2, 135.6, 132.0 (x2), 128.8, 127.8, 126.9, 122.0, 121.7, 117.7, 114.2 (x2), 67.7, 55.3.EIMS *m/z*(% *rel. int.*): 266 ([M]$^+$, 100), 265 (39), 256 (7), 251 (14), 237 (12), 235 (8), 223 (6), 146 (29), 145 (14), 131 (17), 121 (44), 103 (17), 92 (7), 77 (11).HREIMS *m/z*calcd for $C_{17}H_{14}O_3$, 266.0943; found, 266.0943.

(*E*)-3-(4-(3-methylbut-2-enyloxy)benzylidene)chroman-4-one (7). Chroman-4-one (1.48 g, 0.01 moles) and 4-*O*-prenylbenzaldehyde (1.90 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **7** (pale yellow solid, 1.92 g, 60%). IR (neat) ν_{max}: 2962, 2858, 1658, 1585, 1508, 1473, 1423, 1377, 1319, 1257, 1215, 1180, 1149, 1118, 1018, 829, 752, 570 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.02 (1H, d, J = 7.5 Hz), 7.83 (1H, br s), 7.47 (1H, t, J = 7.5 Hz), 7.27 (2H, d, J = 8.7 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.96 (3H, m), 5.49 (1H, t, J = 6.6 Hz), 5.38 (2H, s), 4.56 (2H, d, J = 6.6 Hz), 1.81 (3H, s), 1.76 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.2, 160.9, 160.0, 138.8, 137.4, 135.6, 132.0 (x2), 128.7, 127.8, 126.9, 122.1, 121.8, 119.1, 117.8, 114.9 (x2), 67.8, 64.9, 25.8, 18.2.EIMS *m/z*(% *rel. int.*): 320 ([M]$^+$, 2), 253 (17), 252 (100), 251 (33), 235 (6), 223 (8), 132 (11), 131 (15), 121 (35), 92 (7), 69 (34).HREIMS *m/z*calcd for $C_{21}H_{20}O_3$, 320.1412; found, 320.1415.

(*E*)-3-(4-(dimethylamino)benzylidene)chroman-4-one (8). Chroman-4-one (1.48 g, 0.01 moles) and N,N-dimethylbenzaldehyde (1.49 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **8** (pale yellow solid, 1.89 g, 68%). IR (neat) ν_{max}: 1654, 1604, 1566, 1523, 1458, 1365, 1319, 1222, 1192, 1141, 1033, 995, 956, 810, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (1H, d, *J* = 7.5 Hz), 7.84 (1H, s), 7.47 (1H, d, *J* = 6.9 Hz), 7.28 (2H, d, *J* = 9.0 Hz), 7.06 (1H, t, *J* = 7.5 Hz), 6.97 (1H, d, *J* = 8.1 Hz), 6.74 (2H, d, *J* = 9.0 Hz), 5.45 (2H, s), 3.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.0, 160.7, 151.1, 138.2, 135.2, 132.5 (x2), 127.7, 126.0, 122.3, 122.2, 121.6, 117.6, 111.7 (x2), 68.1, 40.0 (x2). EIMS *m/z*(% *rel. int.*): 279 ($[M]^+$, 100), 278 (30), 250 (14), 159 (30), 158 (47), 144 (6), 143 (5), 139 (6), 115 (14), 92 (5).HREIMS *m/z*calcd for $C_{18}H_{17}O_2N$, 279.1259; found, 279.1256.

(*E*)-3-benzylidenechroman-4-one (9). Chroman-4-one (1.48 g, 0.01 moles) and benzaldehyde (1.06 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **9** (pale yellow solid, 2.2 g, 93%). IR (neat) ν_{max}: 3062, 1674, 1604, 1469, 1311, 1265, 1211, 1149, 1107, 1029, 995, 956, 837, 759, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ8.03 (1H, d, *J* = 7.5 Hz), 7.88 (1H, s), 7.46 (4H, m), 7.30 (2H, d, *J* = 6.9 Hz), 7.07 (1H, t, *J* = 7.5 Hz), 6.96 (1H, d, *J* = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.1, 161.0, 137.4, 135.8, 134.3, 130.8, 129.9 (x2), 129.4, 128.6 (x2), 127.8, 121.9, 121.8, 117.8, 67.5.EIMS *m/z*(% *rel. int.*): 236 ($[M]^+$, 100), 235 (73), 207 (16), 179 (5), 178 (6), 131 (9), 121 (51), 116 (25), 115 (66), 92 (20), 89 (10), 77 (6), 63 (14).HREIMS *m/z*calcd for $C_{16}H_{12}O_2$, 236.0837; found, 236.0839.

(*E*)-3-((*E*)-3-phenylallylidene)chroman-4-one (10). Chroman-4-one (1.48 g, 0.01 moles) and cinnamaldehyde (1.32 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **10** (pale yellow solid, 2.01 g, 77%). IR (neat) ν_{max}: 2850, 1662, 1604, 1469, 1392, 1327, 1257, 1215, 1141, 1103, 1018, 92, 829, 752, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (1H, d, *J* = 6.6 Hz), 7.49 (4H, d, *J* = 9.0 Hz), 7.37 (3H, d, *J* = 6.6 Hz), 7.03 (3H, d, *J* = 16.2 Hz), 6.98 (1H, s), 5.26 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ181.9, 161.3, 143.3, 135.9 (x2), 135.5, 129.5, 129.0, 128.8 (x2), 127.8, 127.4 (x2), 122.3, 121.8, 121.5, 117.8, 66.9.EIMS *m/z*(% *rel. int.*): 262 ($[M]^+$, 100), 261 (45), 247 (6), 185 (16), 171 (27), 142 (21), 141 (48), 131 (14), 128 (7), 121 (56), 115 (31), 105 (10), 92 (13), 77 (14), 63 (9).HREIMS *m/z*calcd for $C_{18}H_{14}O_2$, 262.0994; found, 262.0992.

(*E*)-3-(3,5-dimethoxybenzylidene)chroman-4-one (11). Chroman-4-one (1.48 g, 0.01 moles) and 3,5-dimethoxybenzaldehyde (1.66 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **11** (yellow solid, 2.4 g, 81%). IR (neat) ν_{max}: 2935, 2839, 1670, 1604, 1469, 1300, 1265, 1203, 1157, 1107, 1064, 1033, 995, 937, 837, 756, 678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (1H, dd, *J* = 1.2, 8.1 Hz), 7.99 (1H, s), 7.50 (1H, m), 7.07 (1H, t, *J* = 7.5 Hz), 6.97 (1H, d, *J* = 8.1 Hz), 6.51 (1H, d, *J* = 1.8 Hz), 6.43 (2H, d, *J* = 1.8 Hz), 5.35 (2H, s), 3.82 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 161.1, 160.8 (x2), 137.4, 136.1, 135.8, 131.2, 127.9, 121.9, 121.8, 117.9, 107.8 (x2), 101.3, 67.6, 55.4 (x2). EIMS *m/z*(% *rel. int.*): 296 ($[M]^+$, 33), 295 (4), 265 (8), 175 (5), 168 (8), 167 (12), 166 (100), 165 (40), 148 (27), 147 (15), 137 (16), 135 (22), 122 (20), 121 (62), 120 (13), 109 (13), 95 (10), 92 (16), 77 (14), 63 (18), 58 (16).HREIMS *m/z*calcd for $C_{18}H_{16}O_4$, 296.1049; found, 296.1049.

(*E*)-3-(benzo[d][1,3]dioxol-5-ylmethylene)chroman-4-one (12). Chroman-4-one (1.48 g, 0.01 moles) and 3,4-methylenedioxybenzaldehyde (1.66 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **12** (pale yellow solid, 2.2 g, 79%).IR (neat) ν_{max}:2897, 1662, 1593, 1477, 1446, 1315, 1261, 1145, 1103, 1033, 918, 867, 813, 756, 721, 671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ8.00 (1H, d, *J* = 9.0 Hz), 7.77 (1H, s), 7.47 (1H, t, *J* = 7.2 Hz), 7.06 (1H, t, *J* = 7.2 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 6.84 (3H, m), 6.03 (2H, s), 5.35 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.0, 160.9, 148.8, 148.0, 137.3, 135.7, 129.3, 128.4, 125.3, 122.0, 121.8, 117.8, 109.8, 108.6, 101.6, 67.7.EIMS *m/z*(% *rel. int.*): 280 ($[M]^+$, 100),279 (28), 251 (9), 221 (8), 160 (35), 159 (20), 130 (6), 121 (71), 102 (31), 76 (11), 75 (6), 63 (8), 57 (7).HREIMS *m/z*calcd for $C_{17}H_{12}O_4$, 280.0736; found, 280.0735.

(*E*)-3-(2,3-dimethoxybenzylidene)chroman-4-one) (13). Chroman-4-one (1.48 g, 0.01 moles) and 2,3-dimethoxybenzaldehyde (1.66 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **13** (pale yellow solid, 2.2 g, 74%). IR (neat) ν_{max}:2935, 2835, 1670, 1604, 1469, 1311, 1273, 1222, 1149, 1072, 1033, 995, 898, 752, 640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (1H, d, *J* = 7.2 Hz), 7.95 (1H, s), 7.47 (1H, t, *J* = 7.2 Hz), 7.07 (2H, m), 6.73 (1H, d, *J* = 7.2 Hz), 5.18 (2H, s), 3.89 (3H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.3, 161.3, 152.9, 148.0, 135.7, 133.2, 131.8, 128.7, 127.8, 123.8, 122.0 (x2), 121.7, 117.8, 113.6, 68.2, 61.1, 55.8.EIMS *m/z*(% *rel. int.*): 296 ($[M]^+$, 69), 281 (10), 267 (6), 266 (40), 265 (100), 250 (21), 221 (12), 161 (41), 160 (17), 146 (9), 121 (32), 118 (28), 115 (11), 92 (30), 77 (13), 63 (23).HREIMS *m/z*calcd for $C_{18}H_{16}O_4$, 296.1049; found, 296.1050.

(*E*)-3-(2,4-dimethoxybezylidene)chroman-4-one (14). Chroman-4-one (1.48 g, 0.01 moles) and 2,4-dimethoxybenzaldehyde (1.66 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (8:2) yield **14** (pale yellow solid, 2.4 g, 81%).IR (neat) ν_{max}:2927, 2843, 1666, 1600, 1500, 1465, 1307, 1269, 1211, 1157, 1114, 1026, 960, 925, 829, 756, 729, 675, 636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ8.03 (1H, br s), 8.01 (1H, m), 7.47 (1H, m), 7.04 (1H, t, J = 7.5 Hz), 6.96 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.51 (2H, m), 5.25 (2H, br s), 3.85 (3H, s), 3.84 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.4, 162.5, 161.0, 159.7, 135.4, 133.6, 131.4, 128.9, 127.8, 122.2, 121.6, 117.7, 116.5, 104.4, 98.4, 68.2, 55.5, 55.4.EIMS *m/z*(% *rel. int.*): 296 ($[M]^+$, 24), 281 (10), 266 (19), 265 (100), 165 (7), 161 (21), 121 (14), 118 (4), 97 (5), 77 (5), 71 (6), 57 (10).HREIMS *m/z*calcd for $C_{18}H_{16}O_4$, 296.1049; found, 296.1046.

(*E*)-3-(2,5-dimethoxybenzylidene)chroman-4-one (15). Chroman-4-one (1.48 g, 0.01 moles) and 2,5-dimethoxybenzaldehyde (1.66 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **15** (pale yellow solid, 2.6 g, 88%). IR (neat) ν_{max}: 2943, 2835, 1670, 1604, 1469, 1307, 1222, 1149, 1041, 1022, 921, 871, 810, 759, 709, 594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (1H, d, J = 6.9 Hz), 7.95 (1H, s), 7.46 (1H, t, J = 6.9 Hz), 7.06 (1H, t, J = 7.2 Hz), 6.92 (3H, m), 6.65 (1H, d, J = 6.6 Hz), 5.22 (2H, s), 3.81 (3H, s), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.3, 161.2, 153.0, 152.4, 135.6, 133.5, 131.1, 127.8, 124.1, 122.1, 121.7, 117.8, 116.1, 115.6, 111.8, 68.0, 55.9, 55.8.EIMS *m/z*(% *rel. int.*): 296($[M]^+$, 16),266 (19), 265 (100), 161 (13), 121 (6), 118 (7), 92 (4).HREIMS *m/z*calcd for $C_{18}H_{16}O_4$, 296.1049; found, 296.1050.

(*E*)-3-(2,3,4-trimethoxybenzylidene)chroman-4-one (16). Chroman-4-one (1.48 g, 0.01 moles) and 2,3,4-trimethoxybenzaldehyde (1.96 g, 0.01 moles) were treated as described above mentioned general method. The crude product was purified by CC eluting *n*-hexane/EtOAc (9:1) yield **16** (pale yellow solid, 2.85 g, 87%). IR (neat) ν_{max}: 2939, 2839, 1670, 1608, 1589, 1465, 1415, 1300, 1284, 1230, 1145, 1099, 1049, 995, 929, 837, 806, 759, 725, 682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (1H, d, J = 7.8 Hz), 7.93 (1H, s), 7.47 (1H, t, J = 7.2 Hz), 7.05 (1H, t, J = 7.2 Hz), 6.95 (1H, d, J = 8.1 Hz), 6.81 (1H, d, J = 8.1 Hz), 6.71 (1H, d, J = 8.7 Hz), 5.23 (2H, s), 3.93 (3H, s), 3.90 (3H, s), 3.89 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ182.3, 161.1, 155.2, 153.1, 142.3, 135.6, 133.3, 130.0, 127.8, 125.3, 122.1, 121.7, 121.4, 117.7, 106.9, 68.1, 61.4, 60.9, 56.0.EIMS *m/z*(% *rel. int.*): 326 ($[M]^+$, 7), 296 (20), 295 (100), 279 (5), 196 (4), 191 (5), 121 (7), 120 (4), 58 (28).HREIMS *m/z*calcd for $C_{19}H_{18}O_5$, 326.1154; found, 326.1155.

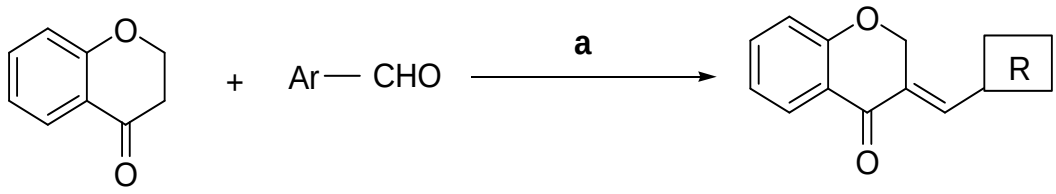
ANTIPLATELET AGGREGATION ACTIVITY

Preparation of the platelet suspension

Washed platelet suspension was prepared as previously described with some modifications [23-25]. In brief, blood was collected from the marginal ear vein of New Zealand White rabbits into tubes containing one-sixth volume of acid-citrate dextrose as anticoagulant. The blood was centrifuged at 1000 *g* for 8 min. at room temperature. The upper portion was kept as platelet-rich plasma (PRP) after mixing with EDTA to a final concentration of 5mM and re centrifuged at 2000 *g* for 12 min. The platelet pellet was suspended in modified Ca^{2+}-free Tyrode′s buffer (137 mM NaCl, 2.8 mM KCl, 2 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 5 mM glucose, 10 mM HEPES) with 0.35% bovine serum albumin, heparin (50 unit/mL), and apyrase (1unit/mL) and then was incubated at 37 °C for 20 min. After centrifugation at 2000*g* for 6 min, the washed platelet pellet was re suspended in Tyrode's buffer containing 1 mM Ca^{2+}. For the aggregation test, the platelet numbers were counted by hemacytometer and adjusted to 2.5×10^8 platelets/mL.

Measurement of platelet aggregation

Platelet aggregation was measured turbidimetrically with a light-transmission Platelet Aggregation Chromogenic Kinetic System PACK4 (Helena Laboratories, Beaumont TX) with some modifications [23-25]. The platelet suspension was stirred at 900 rpm and incubated with an appropriate amount of vehicle (dimethyl sulfoxide, DMSO) or various concentrations of test compounds in DMSO at 37 °C for 2 min. Aggregation was induced with ADP (20 μM) or Col (10 μg/mL). The transmission of washed platelet suspension was assigned 0% aggregation while transmission through Tyrode′s buffer was assigned 100% aggregation. The extent of platelet aggregation was measured as the maximal increase in light transmission within 4 min after the addition of an inducer. To eliminate or minimize any possible effects of the solvent, the final concentration of DMSO in the platelet suspension was fixed at 0.5%. The inhibition percentages of aggregation are presented as mean values ($n \geq 2$).



4-chromanone

1. R = 2-thiophene
2. R = 3-methyl-2-thiophene
3. R = 2-furan
4. R = 5-methyl-2-furan
5. R = N-methyl-2-pyrrole
6. R = 4-methoxybenzene
7. R = 4-O-prenylbenzene
8. R = 4-N,N-dimethylbenzene
9. R = benzene
10. R = cinnamyl
11. R = 3,5-dimethoxybenzene
12. R = 3,4-methylenedioxybenzene
13. R = 2,3-dimethoxybenzene
14. R = 2,4-dimethoxybenzene
15. R = 2,5-dimethoxybenzene
16. R = 2,3,4-trimethoxybenzene

Scheme 1: (a) 30% KOH solution in methanol stirring at room temperature at 24 hr

RESULTS AND DISCUSSION

The IR spectra of these synthetic compounds exhibited carbonyl absorption bands around 1647-1674 cm^{-1}. In the ^{1}H-NMR spectra the characteristic resonance signal for H-2 around at δ 5.18- 5.59 and ^{13}C NMR spectrum displayed characteristic signal of C-2 around at δ 68.2- 66.9. The chemical shift for carbonyl carbons (C-4) appeared in the downfield region at δ 182.4- 181.1. We evaluated inhibition effects for**1-16** on ADP and Collagen induced washed platelet aggregation **(Table.1).** Compound **1** showed potent inhibitory effect 81.3% on ADP and 59.9% collagen induced aggregation. While the methyl derivative of **1**decreased inhibitory effects observe on both ADP (38%) and collagen (10.2%)-induced aggregation. Compounds **3** and **4** with furan and 5-methylfuran have ring-B moieties, respectively, showed significant inhibition on ADP (54.9% and 60.6%) and collagen (73.3% and 71.7%) induced aggregation. Compounds **6** and **9** showed significant inhibitory effects on ADP (66.8% and 69.0%)-induced aggregation with benzene and 4-methoxybenzene rings as ring-B moieties. Compounds **11**(88.7%), **13**(85%) and **15** (66.4%) having 3,5-dimethoxy, 2,3-dimethoxy, and 2,5-dimethoxybenzene ring as ring-B moieties, respectively, showed potent inhibition on ADP-induced aggregation. It can be concluded that, all the synthesized 3-arylidenechroman-4-ones (**1-16**) from substituted and heterocyclic aldehydes. Among the **16** compounds screened for *in vitro* inhibitory effects on aggregation of platelets induced ADP and collagen showed potent inhibitory effect on ADP (**1, 11** and **13**), and collagen (**3, 4** and **9**) induced aggregation activity. The results indicate that some 3-arylidenechroman-4-ones were relatively significant inhibitors of platelet aggregation.

CONCLUSION

Present study described the synthesis of some 3-arylidene-4-one derivatives. All the synthesized compounds were characterized by IR and ^{1}H &^{13}C-NMR and mass spectral analysis and evaluated for antiplatelet aggregation activity. The results indicated that compounds **3, 4** and **9** were showed potent inhibitory effect on collage and **1, 11** and **13** were potent on ADP.

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