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SYNTHESIS OF 1,4-BIS SPIROCHROMANONE SUBSTITUTED BENZENES USING SUZUKI CROSS COUPLING AND THEIR ANTIMICROBIAL ACTIVITY

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Abstract: 1,4-Bis spirochromanone substituted benzenes **(6a-h)** were synthesized using 4-chloro-3-formylspirochromanones **(4a-d)** and benzene-1,4-diboronic acid **(2)** using Suzuki cross coupling conditions. All the synthesized compounds were screened for their in vitro antimicrobial activity. Compounds **6a, 6b, 6e** and **6f** shown good antimicrobial activity against all the tested organisms.

Key words: Spirochromanone, Suzuki coupling, Antimicrobial activity.

Introduction

Natural and synthetic flavones, chromones and spirochromanones are reported to have antimalarial[1], antiarrhythmic[2], free radical scavenging[3] and antihypertensive[4] activity. The spiro-heterocyclic moiety is key structure present in a variety of natural products and drugs **(Fig. 1)**. Synthetic flavones, flavone-8-acetic acid[5] and flavopiridol[6] are anti-cancer drugs. Similarly 8-substituted flavones demiflin and flavoxate are coronary vasodilator[7] and diuretic[8] drugs respectively.

Chromone derived drugs include sorbinil (diabetes)[9], cromakalim (cardiac)[10] and centochroman (contraceptive). Substituted chromans show a variety of biological action and several of these compounds are used as drugs. Sorbinil and methosorbinil are aldose reductase inhibitors and are used in the treatment of diabetes. Cromakalim is an ATP sensitive potassium channel opener and is used for the treatment of cardiac problems[11]. 7,8-Dihydroxy-3-amino-chroman-4-ol and 6,7-dihydroxy-3-amino-chroman-4-ol have adrenergic receptor antagonist action. 6-Hydroxychroman derivative has dopamine agonist activity. Rotenone isolated from *Derris elliptica*, a chromanochroman, is a natural insecticide.

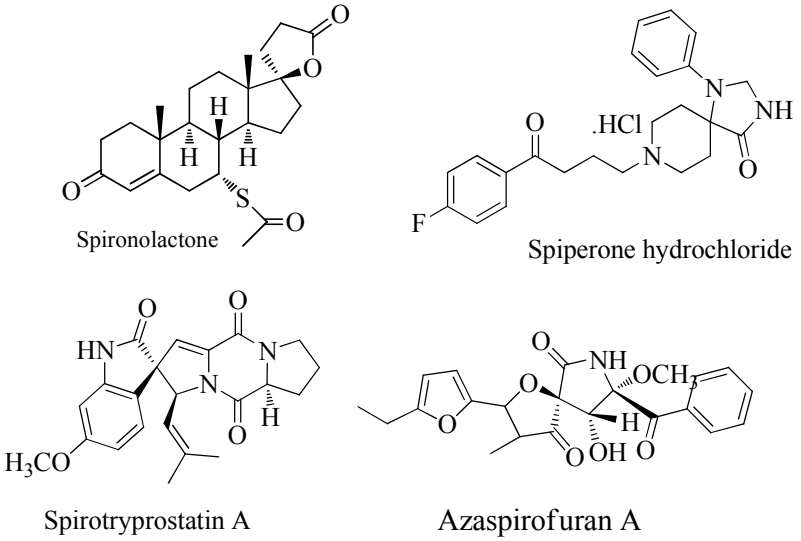
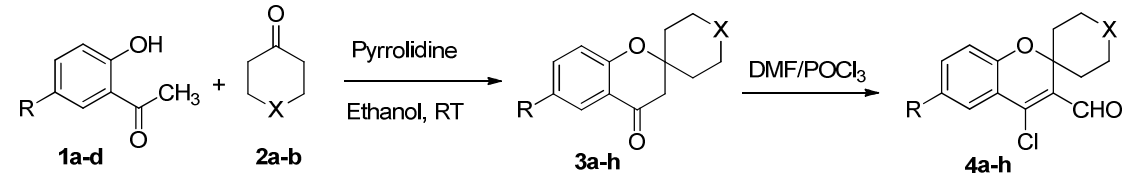


Figure. 1. Representative examples of drugs and natural products containing spiro moieties.

Results & Discussion

To synthesize 1,4-bis spirochromanonebenzenes **(6a-h)** we have started from 2-hdroxyacetophenones **(1a-d)**. The reaction of substituted 2-hydroxyacetophenones with cycloalkanones **(2a-b)** using pyrrolidine as catalyst gave substituted spirochromanones[12]**(3a-h)**. This on reaction with DMF/$POCl_3$ yielded 4-chloro-3-formylspirochromanones **(4a-h) (Scheme-1).**

Scheme-1



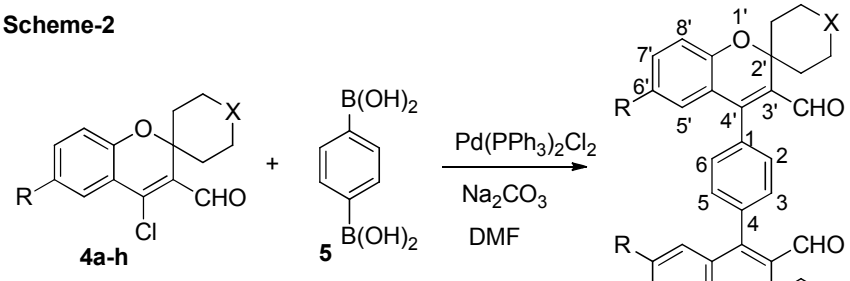
1a, R=Cl
1b, R=CH_3
1c, R=H
1d, R=Br

2a, X=CH_2
2b, X=Nil

4a, R=Cl;X=CH_2 4e, R=Cl;X=Nil
4b, R=CH_3;X=CH_2 4f, R=CH_3;X=Nil
4c, R=H;X=CH_2 4g, R=H;X=Nil
4d, R=Br;X=CH_2 4h, R=Br;X=Nil

These 4-chloro-3-formylspirochromanones **(4a-h**) on reaction with benzene-1,4-diboronic acid **(5)** using Suzuki cross coupling gave 1,4-bis spirochromanonebenzenes **(6a-h) (Scheme-2)**. All the synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data.

Scheme-2



6a, R=Cl;X=CH_2 6e, R=Cl;X=Nil
6b, R=CH_3;X=CH_2 6f, R=CH_3;X=Nil
6c, R=H;X=CH_2 6g, R=H;X=Nil
6d, R=Br;X=CH_2 6h, R=Br;X=Ni

IR spectrum of **6a** showed characteristic peak at 1698cm^{-1}. ^{1}H-NMR spectrum of **6a** shown formyl peak at δ 9.75 as singlet (2H) and other peaks appeared at 7.62 (m, 4H), 7.40 (d, 2H,), 6.85 (d, 2H,), 1.90-2.55 (m, 10H, cyclohexane). In ^{13}C-NMR of **6a** peaks appeared at δ 192.1, 154.0, 152.3, 137.5, 136.4, 135.4, 132.5, 131.2, 131.0, 130.5, 126.5, 123.5. Mass spectrum of **6a** shown peak at m/z 599 [M+H], 601 [M+H+2].

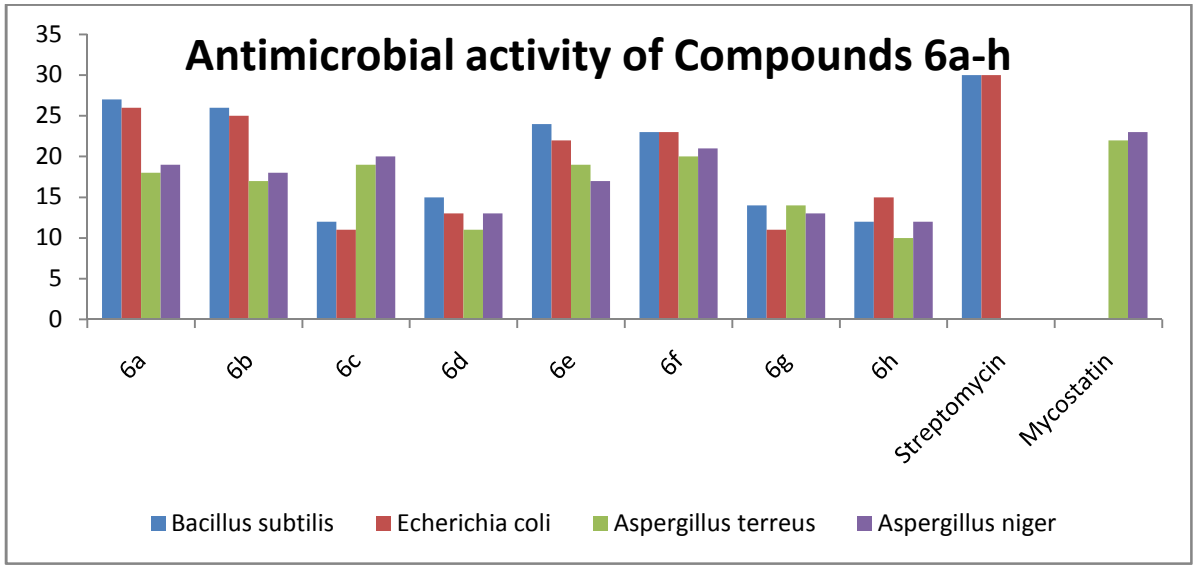
Antimicrobial activity

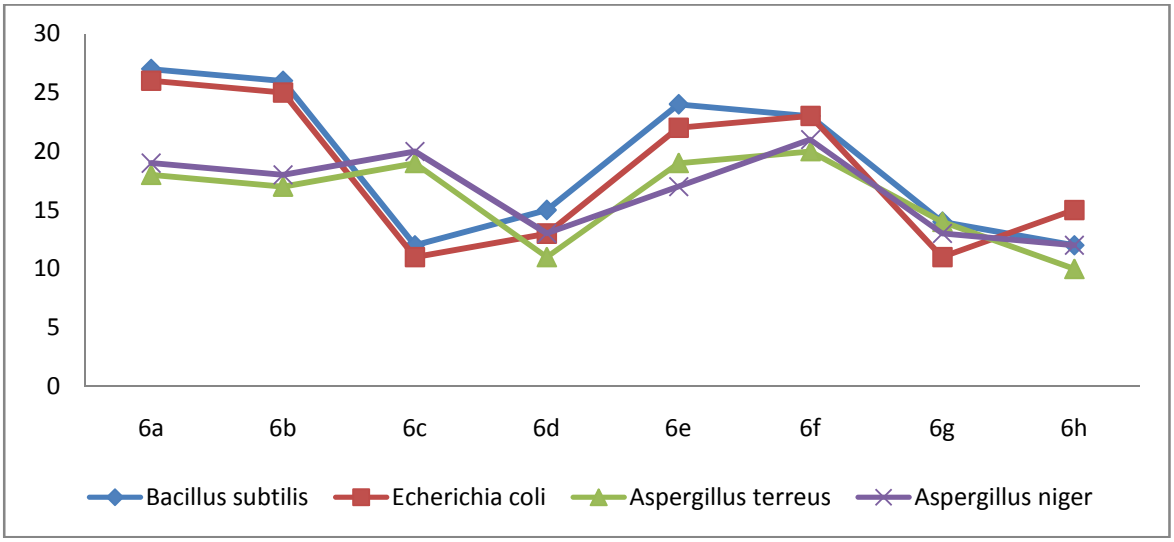
All the synthesized compounds were screened in vitro for their antimicrobial activity against Gram positive bacteria *Bacillus subtilis* (MTCC 121) and Gram negative bacteria *Escherichia Coli* (MTCC 7390) using streptomycin as standard and antifungal activity against *Aspergillus terreus* and *Aspergillus niger*. The activity was determined using disc diffusion method by measuring the zone inhibition in mm. The compounds were used at the concentration of 50µg/ml in DMSO.

Table-1: Antimicrobial activity of Compounds **6a-h**

No	Zone of Inhibition (in mm)			
	Gram-positive Bacteria	Gram-negative Bacteria	Fungi	
	Bacillus subtilis	*Echerichia coli*	*Aspergillus terreus*	*Aspergillus niger*
6a	27	26	18	19
6b	26	25	17	18
6c	12	11	19	20
6d	15	13	11	13
6e	24	22	19	17
6f	23	23	20	21
6g	14	11	14	13
6h	12	15	10	12
*	30	30	-	-
**	-	-	22	23

*Streptomycin
**Mycostatin





From the screening studies it is evident that the synthesized compounds **6a, 6b, 6e** and **6f** shown good antmicrobial activity against all the tested organisms.

Conclusion

1,4-Bis spirochromanones substituted benzene **(6a-h)** were synthesized using 4-chloro-3-formylspirochromanones **(4a-d)** and benzene-1,4-diboronic acid **(2)** using Suzuki cross coupling conditions. All the synthesized compounds were screened for their in vitro antibacterial activity. Compounds **6a, 6b, 6e** and **6f** shown good antimicrobial activity against all the tested organisms

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Experimental

General procedure for the synthesis of spiro[chromene-2,1'-cyclalkan]-3-carbaldehydes (4a-h)

To spiro[chroman-2,1'-cycloalkan]-4-one **(3a-h)** (10mmol) in dry DMF (50 mmols) a freshly distilled dry phosphorous oxychloride (9mmol) was added with constant stirring at 0^{o}C. The reaction mixture was kept overnight and poured into crushed ice. The yellow compound that separated was filtered and washed with water. The product on chromatography over silicagel gave 4-chlorospiro[chromene-2,1'-cycloalkan]-3-carbaldehydes **(4a-h)**. This was recrystallised from chloroform to give pale yellow needles.

4, 6-dichlorospiro[chromene-2,1'-cyclohexan]-3-carbaldehyde (4a)

yellow solid; mp 92 °C; yield 90%; IR (KBr) (cm^{-1}): 1689 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.24 (s, 3-CHO), 7.64 (d, J= 2.5 Hz, H-5), 7.30 (dd, J= 8.5, 2.5 Hz, H-7), 6.85 (d, J= 8.5 Hz, H-8), 1.29-2.15 (m, H-2', 3', 4', 5', 6'); ^{13}C-NMR ($CDCl_3$, 75.5MHz): δ 188.9, 152.4, 143.0, 133.4, 132.7, 126.5, 125.4, 121.5, 118.4, 81.9, 32.4, 24.5, 20.9; ESIMS: *m/z* 297 [M+H], 299[M+H+2], 301[M+H+4].

4-chloro-6-methylspiro[chromene-2, 1'-cyclohexan]-3-carbaldehyde (4b)

yellow solid; mp 87 °C; yield 85%; IR (KBr) (cm^{-1}): 1688 (CHO); ^{1}H-NMR ($CDCl_3$, 00MHz): δ 10.23 (s, 3-CHO), 7.48 (d, J= 2.5 Hz, H-5), 7.20 (dd, J= 8.5, 2.5 Hz, H-7), 6.80 (d, J= 8.5 Hz, H-8), 2.38 (s, 6-CH_3), 1.28-2.15 (m, H-2', 3', 4', 5', 6'); ^{13}C-NMR ($CDCl_3$,

50MHz): δ 188.0, 152.4, 143.0, 133.4, 132.7, 126.5, 125.4, 121.5, 118.4, 81.9, 32.4, 24.5, 20.9, 20.4; EIMS: *m/z* 277[M+H], 279[M+H+2].

4-chlorospiro[chromene-2, 1'-cyclohexan]-3-carbaldehyde (4c)

yellow solid; mp 71 °C; yield 93%; IR (KBr) (cm^{-1}): 1698 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.22 (s, 3-CHO), 7.65 (d, J= 8.7 Hz, H-5), 7.34 (dd, J= 8.7, 2.8 Hz, H-7), 6.97 (dd, J = 8.7, 2.8 Hz, H-6), 6.85 (d, J= 8.7 Hz, H-8), 1.60-2.15 (m, H-2', 3', 4', 5', 6'); ^{13}C-NMR ($CDCl_3$, 50MHz): δ 189.2, 154.2, 143.2, 133.9, 132.2, 125.9, 121.5, 120.1, 117.1, 81.5, 32.6, 24.7, 21.1; ESIMS: *m/z* 263 [M+H], 265[M+H+2].

4-chloro-6-bromospiro[chromene-2, 1'-cyclohexan]-3-carbaldehyde (4d)

yellow solid; mp 97 °C; yield 87%; IR (KBr) (cm^{-1}): 1668 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.20 (s, 3-CHO), 7.61 (d, J= 2.4 Hz, H-5), 7.27 (dd, J= 8.4, 2.4 Hz, H-7), 6.81 (d, J= 8.4 Hz, H-8), 1.26-2.10 (m, H-2', 3', 4', 5', 6'); ^{13}C-NMR ($CDCl_3$, 50MHz): δ 191.0, 151.8, 142.3, 133.1, 132.3, 125.8, 124.6, 121.2, 117.8, 81.1, 32.2, 24.1, 20.5; ESIMS: *m/z* 341[M+H], 343[M+H+2], 345[M+H+4].

4,6-dichlorospiro[chromene-2, 1'-cyclopentan]-3-carbaldehyde (4e)

yellow solid; mp 86 °C; yield 89%; IR (KBr) (cm^{-1}): 1697 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.23 (s, 3-CHO), 7.63 (d, J= 2.5 Hz, H-5), 7.28 (dd, J= 8.5, 2.4 Hz, H-7), 6.76 (d, J= 8.5 Hz, H-8), 1.79-2.20 (m, H-2', 3',4', 5'). ^{13}C-NMR ($CDCl_3$, 50MHz): δ 188.8, 152.6, 142.5, 133.3, 130.9, 126.5, 125.2, 121.5, 118.4, 91.0, 37.3, 24.0; ESIMS: *m/z* 283 [M+H], 285[M+H+2], 287[M+H+4].

4-chloro-6-methylspiro[chromene-2,1'-cyclopentan]-3-carbaldehyde (4f)

yellow solid; mp 84 °C; yield 89%; IR (KBr) (cm^{-1}): 1687 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.21 (s, 3-CHO), 7.65 (d, J= 8.7 Hz, H-5), 7.30 (dd, J= 8.7, 2.8 Hz, H-7), 6.95 (dd, J = 8.7, 2.8 Hz, H-6), 6.87 (d, J= 8.7 Hz, H-8), 2.35 (s, 6-CH_3), 1.80-2.10 (m, H-2', 3', 4', 5'); ^{13}C-NMR ($CDCl_3$, 50MHz): δ 189.0, 154.2, 144.3, 133.7, 130.2, 125.8, 121.4, 120.1, 117.0, 90.5, 37.1, 24.0, 20.7; ESIMS: *m/z* 263 [M+H], 265[M+H+2].

4-chlorospiro[chromene-2, 1'-cyclopentan]-3-carbaldehyde (4g)

yellow solid; mp 78 °C; yield 89%;IR (KBr) (cm^{-1}): 1692 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.20 (s, 3-CHO), 7.61 (d, J= 8.7 Hz, H-5), 7.33 (dd, J= 8.7, 2.8 Hz, H-7), 6.93 (dd, J = 8.7, 2.8 Hz, H-6), 6.82 (d, J= 8.7 Hz, H-8), 1.82-2.12 (m, H-2', 3', 4', 5'); ^{13}C-NMR ($CDCl_3$, 50MHz): δ 189.9, 153.8, 145.1, 133.2, 129.8, 126.2, 122.1, 119.8, 116.8, 90.1, 36.9, 23.8; ESIMS: *m/z* 249 [M+H], 251[M+H+2].

4-chloro-6-bromospiro[chromene-2, 1'-cyclopentan]-3-carbaldehyde (4h)

yellow solid; mp 98 °C; yield 92%; IR (KBr) (cm^{-1}): 1658 (CHO); ^{1}H-NMR ($CDCl_3$, 200MHz): δ 10.25 (s, 3-CHO), 7.68 (d, J= 2.5 Hz, H-5), 7.30 (dd, J= 8.5, 2.4 Hz, H-7), 6.79 (d, J= 8.5 Hz, H-8), 1.60-2.13 (m, H-2', 3',4', 5'). ^{13}C-NMR ($CDCl_3$, 50MHz): δ 189.1, 153.5, 143.6, 134.1, 131.1, 126.3, 124.1, 121.3, 119.1, 91.5, 37.1, 24.2; ESIMS: *m/z* 327 [M+H], 329[M+H+2], 331[M+H+4].

Synthesis of 1,4-bis spirochromanonebenzenes (6a-d)

Spiro[chromene-2,1'-cyclohexan/cyclopentan]-3-carbaldehyde **(4a-h)** (1mmol) was stirred in the presence of 4 mol% of dichlorobis(triphenylphosphine) palladium at RT under nitrogen for 30 min in DMF (10 mL) and Na_2CO_3 (1 mL of 2M aqueous solution). Phenyl-1,4-diboronic acid **(5)** (3 equiv) was added and the mixture was stirred for 30 min. The reaction mixture was heated at 80ºC for 16 hours, cooled and 30% hydrogen peroxide was added to oxidize excess arylboronic acid. The reaction mixture was diluted with chloroform (50mL), washed with water (3 x 3mL). The aqueous layers were combined and further extracted with chloroform (3 x 5mL). The organic extracts were combined, dried (Na_2SO_4) and the solvent evaporated. The residue was purified column chromatography using pet.ether to **6a-h**.

1,4-di-(6-chloro-3-formyl[chroman-2,1'-cyclohexan-4yl)benzene (6a)
Yellow solid; 1mp 79 °C; IR (KBr): 1698 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): 9.75 (s, 2H, CHO), 8.05 (d, 2H, H-5'), 7.62 (m, 4H, H-2,3,5,6), 7.40 (d, 2H, H-7'), 6.85 (d, 2H, H-8'), 1.90-2.55 (m, 10H, cyclohexane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.1, 154.0, 152.3, 137.5, 136.4, 135.4, 132.5, 131.2, 131.0, 130.5, 126.5, 123.5, 115.0, 82.5, 37.5, 30.2, 23.5; ESIMS: 599 [M+H], 601[M+H+2]. *Anal*. Calcd. for $C_{36}H_{32}Cl_2O_4$: C, 72.12; H, 5.38; Found: C, 72.09; H, 5.35.

1,4-di-(6-methyl-3-formyl[chroman-2,1'-cyclohexan-4yl)benzene (6b)
Yellow solid; yield 72%; mp 86 °C; IR (KBr): 1689 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.58 (s, 2H, CHO), 7.98 (d, 2H, H-5'), 7.60 (m, 4H, H-2,3,5,6), 7.38 (d, 2H, H-7'), 6.90 (d, 2H, H-8'), 2.50 (s, 3H, CH_3), 1.70-2.40 (m, 10H, cyclohexane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.1, 154.0, 152.3, 137.5, 136.4, 135.4, 132.5, 131.2, 131.0, 130.5, 126.5, 123.5, 115.0, 82.5, 37.5, 30.2, 23.5; ESIMS: m/z 559 [M+H]. *Anal*. Calcd. for $C_{38}H_{38}O_4$: C, 81.69; H, 6.86; Found: C, 81.64; H, 6.82.

1,4-di-(3-formyl[chroman-2,1'-cyclohexan-4yl)benzene (6c)
Yellow solid; yield 68%; mp 93 °C; IR (KBr): 1695 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.65 (s, 2H, CHO), 8.20 (d, 2H, H-5'), 7.80 (d, 2H, H-6'), 7.62 (m, 4H, H-2,3,5,6), 7.40 (d, 2H, H-7'), 6.90 (d, 2H, H-8'), 1.60-2.20 (m, 10H, cyclohexane); ^{13}C-NMR ($CDCl_3$, 400MHz): δ 192.1, 154.0, 152.3, 137.5, 136.4, 135.4, 132.5, 131.2, 131.0, 130.5, 126.5, 123.5, 115.0, 82.5, 37.5, 30.2, 23.5; ESIMS: m/z 531[M+H]. *Anal*. Calcd. for $C_{36}H_{34}O_4$: C, 81.48; H, 6.46; Found: C, 81.45; H, 6.42.

1,4-di-(6-bromo-3-formyl[chroman-2,1'-cyclohexan-4yl)benzene (6d)
Yellow solid; yield 72%; mp 68 °C; IR (KBr): 1686cm^{-1} (C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.70 (s, 2H, CHO), 8.02 (d, 2H, H-5'), 7.60 (m, 4H, H-2,3,5,6), 7.41 (d, 2H, H-7'), 6.86 (d, 2H, H-8'), 1.80-2.51 (m, 10H, cyclohexane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.1, 154.0, 152.3, 137.5, 136.4, 135.4, 132.5, 131.2, 131.0, 130.5, 126.5, 123.5, 115.0, 82.5, 37.5, 30.2, 23.5; ESIMS: m/z 687 [M+H], 689 [M+H+2]. *Anal*. Calcd. for $C_{36}H_{32}Br_2O_4$: C, 62.81; H, 4.69; Found: C, 62.78; H, 4.64.

1,4-di-(6-chloro-3-formyl[chroman-2,1'-cyclohpentan-4yl)benzene (6e)
Yellow solid; yield 68%; mp 71 °C; yield 62%; IR (KBr): 1657 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.80 (s, 2H, CHO), 8.02 (d, 2H, H-5'), 7.50 (m, 4H, H-2,3,5,6), 7.36 (d, 2H, H-7'), 6.82 (d, 2H, H-8'), 1.88-2.40 (m, 8H, cyclopentane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.3, 153.8, 151.9, 137.6, 136.2, 135.1, 132.8, 130.8, 130.6, 130.4, 125.6, 122.8, 116.1, 83.1, 37.1, 30.3, 23.1; ESIMS: m/z 571 [M+H], 573 [M+H+2]. *Anal*. Calcd. for $C_{34}H_{28}Cl_2O_4$: C, 71.46; H, 4.94; Found: C, 71.41; H, 4.88.

1,4-di-(6-methyl-3-formyl[chroman-2,1'-cyclohpentan-4yl)benzene (6f)
Yellow solid; yield 66%; mp 72 °C; yield 65%; IR (KBr): 1667 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.63 (s, 2H, CHO), 7.99 (d, 2H, H-5'), 7.58 (m, 4H, H-2,3,5,6), 7.41 (d, 2H, H-7'), 6.96 (d, 2H, H-8'), 2.55 (s, 3H, CH_3), 1.76-2.34 (m, 8H, cyclopentane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.3, 153.8, 152.5, 138.2, 137.2, 136.1, 131.6, 131.1, 129.8, 129.6, 125.5, 123.1, 115.8, 82.1, 37.3, 30.1, 23.3; ESIMS: m/z 531 [M+H]. *Anal*. Calcd. for $C_{36}H_{34}O_4$: C, 81.48; H, 6.46; Found: C, 81.44; H, 6.41.

1,4-di-(3-formyl[chroman-2,1'-cyclohpentan-4yl)benzene (6g)
Yellow solid; yield 74%; mp 65 °C; yield 69; IR (KBr): 1678 cm^{-1}(C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.68 (s, 2H, CHO), 8.12 (d, 2H, H-5'), 7.78 (d, 2H, H-6'), 7.61 (m, 4H, H-2,3,5,6), 7.38 (d, 2H, H-7'), 6.83 (d, 2H, H-8'), 1.64-2.24 (m, 8H, cyclopentane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 191.8, 153.8, 152.1, 138.1, 137.1, 136.4, 132.4, 131.6, 131.2, 131.0, 126.6, 123.8, 116.6, 82.3, 37.1, 30.1, 23.1; ESIMS: m/z 503 [M+H]. *Anal*. Calcd. for $C_{34}H_{30}O_4$: C, 81.25; H, 6.02; Found: C, 81.20; H, 6.05.

1,4-di-(6-bromo-3-formyl[chroman-2,1'-cyclohpentan-4yl)benzene (6h)
Yellow solid; yield 72%; mp 68 °C; yield 71; IR (KBr): 1681cm^{-1} (C=O)**;** ^{1}H-NMR ($CDCl_3$, 400MHz): δ 9.76 (s, 2H, CHO), 8.10 (d, 2H, H-5'), 7.64 (m, 4H, H-2,3,5,6), 7.45 (d, 2H, H-7'), 6.88 (d, 2H, H-8'), 1.70-2.41 (m, 8H, cyclopentane); ^{13}C-NMR ($CDCl_3$, 100MHz): δ 192.2, 153.8, 152.5, 136.5, 136.2, 135.6, 133.4, 132.2, 131.5, 131.1, 126.2, 123.1, 115.1, 82.1, 37.2, 30.5, 23.1; ESIMS: m/z 659 [M+H], 661 [M+H+2]. *Anal*. Calcd. for $C_{34}H_{28}Br_2O_4$: C, 61.84; H, 4.27; Found: C, 61.83; H, 4.22.

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