Cumhuriyet Sci. J., 44(4) (2023) 678-686
DOI: https://doi.org/10.17776/csj.1341173

Cumhuriyet Science Journal

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Synthesis and Characterization of Novel 2,4-Diaryloctahydro-2*H*-Chromene Derivatives with Four Stereocenters

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Research Article

History
Received: 11/08/2023
Accepted: 13/11/2023

ABSTRACT

Chromene derivatives are among the natural compounds and they can also be easily obtained synthetically. They are one of the most commonly used skeletons in heterocyclic chemistry. Chromene derivatives are used in the cosmetic and pigment industries as well as having a wide spectrum of biological activity. Synthesis of chromene derivatives and their application areas is a current topic. In this study, it is aimed to synthesis and characterization of new chromene derivatives by catalysis of molecular iodine starting from 1,5-diol derivatives with chiral centers. In this context, 8 new 2,4-diaryloctahydro-2H-chromene derivatives were synthesized in high yields and their structure determinations were made by spectroscopic methods (1H-NMR, 13C-NMR, 2D-NMR, GCMS and FTIR) and their stereochemistry was determined.

Keywords: Chalcone, 1,5-Diol, Chromene, Iodine.

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Introduction

Today, many synthetic or natural compounds, which used as drugs in medical therapy, are in the class of heterocyclic compounds. Among heterocyclic compounds, the six-membered oxygen-containing heterocyclic compound adjacent to the benzene ring is known as chroman (benzodihydropyran or 3,4-dihydro-*2H*-chromene) (**I**) [1]. The chroman ring is a pharmacologically important structural unit and it is found in the structure of e vitamins and some drugs that are troglitazone used as an antidiabetic [2], ormeloxifene used as a selective estrogen receptor [3] and nebivolol used in the treatment of high blood pressure and heart failure [4].

Chromene derivatives are obtained by the placement of various functional groups in different positions on the chromane skeleton (I).

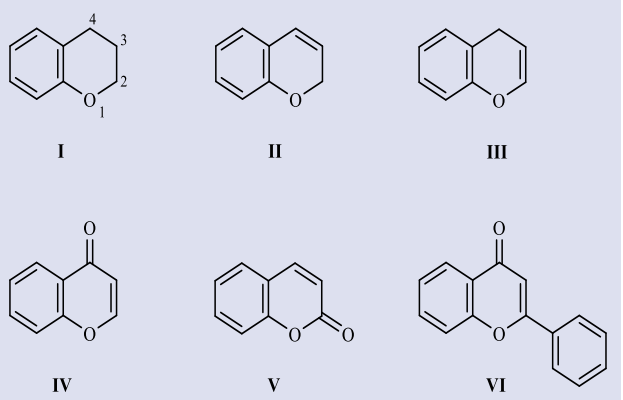


Figure 1. Chromane and chromene derivatives

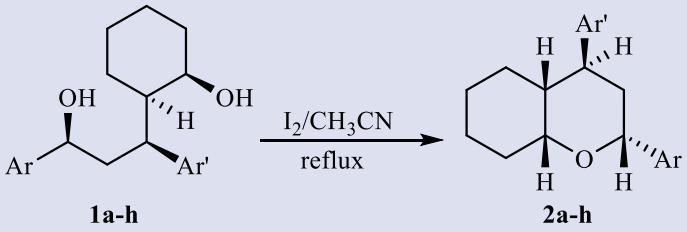
2H-Chromene derivatives (II) are formed by the double bond between of carbons 3 and 4, *4H*-chromene derivatives (III) are formed by the double bond between of carbons 2 and 3 on this skeleton, and *4H*-chromen-4-one derivatives (IV) are formed with the carbonyl group in the 4 position. In addition, coumarin (V) and flavonoid (VI) derivatives have this basic skeleton (Figure 1) [5].

Chromene derivatives are widely found in nature and can be easily obtained by synthesis. Due to their bioactive potential, they are one of the most commonly used skeletons in heterocyclic chemistry. It is known that chromene derivatives have a wide spectrum of biological activity [6]. While some chromene derivatives act as sex pheromones [7], some are used as drugs especially as antifungal [8] and antimicrobial agents [9]. In addition, chromene derivatives are also used in the cosmetics and pigment industries [10]. When the studies on the activity of chromene derivatives are examined, it is seen that these compounds have important biological activities such as antimalarial, antituberculosis [11], anti-cancer [12], potassium channel opener [13], anti-HIV activity [14] and antioxidant [15]. Synthesis and application areas of chromene derivatives is a current and interesting subject and there are many studies in the literature, and new ones are added to these studies every day.

Molecular iodine, which is used as an effective catalyst in various organic synthesis reactions, stands out as a clean and non-toxic Lewis acid catalyst compared to metallic catalysts [16]. In addition to being a cheap and easily available compound, its use in reactions and its removal from the reaction medium are carried out by

uncomplicated simple methods [17]. Iodine catalyzes C-C, C-N, C-O and C-S bond formations, allowing the synthesis of heteroatom-containing polyfunctional compounds and the formation of molecular diversity [16], [18], [19]. Molecular iodine, which is widely used especially in Michael addition reactions also plays an important role in condensation, cycloaddition, esterification, etherization and production of cyclic ethers [20], [21].

In the light of this information, here in this study, first time molecular iodine-catalyzed synthesis of new 2,4-diaryloctahydro-2*H*-chromene derivatives with four stereo centers (Figure 2) was carried out over 1,5-diols that we synthesized in our previous studies [22], [23]. The method we used and the reaction we performed are capable of guiding and giving ideas to researchers working in this field in the design and synthesis of various functional new compounds.



a: Ar = 4-CH_3Ph Ar' = 4-CH_3Ph **e:** Ar = 4-OCH_3Ph Ar' = 4-OCH_3Ph
b: Ar = 4-OCH_3Ph Ar' = 4-ClPh **f:** Ar = 4-CH_3Ph Ar' = 4-OCH_3Ph
c: Ar = 4-ClPh Ar' = 4-OCH_3Ph **g:** Ar = 4-OCH_3Ph Ar' = 4-CH_3Ph
d: Ar = 4-BrPh Ar' = 4-OCH_3Ph **h:** Ar = 4-CH_3Ph Ar' = 2-thiophen

Figure 2. The general route for the preparation of 2,4-diaryloctahydro-2*H*-chromene derivatives (2a-h)

Material and Methods

^{1}H- NMR, ^{13}C-NMR and 2D-NMR spectra were measured on a Bruker Avance DPX-400 NMR (Nuclear Magnetic Resonance, 400 MHz) instrument in $CDCl_3$ and (D_6)DMSO at 25 °C. δ in ppm relative to Me_4Si (δ 0.00) for ^{1}H-NMR, $CDCl_3$ (δ 77.0) and (D_6)DMSO (δ 39.5) for 13C-NMRspectra as internal standards, *J* in Hz. GC-MS (Gas chromatography-mass spectrometry) spectra were measured on a PerkinElmer Clarus 500 instrument. All the FTIR (Fourier Transform Infra-Red) spectra were measured on a JASCO FT/IR-430 spectrometer.

General Procedure for the Synthesis of Chromene Derivatives

The synthesis of 1,5-diols, which are used as starting compounds in the synthesis of chromene derivatives, has been reported in our previous studies [22], [23].

To a solution of 1,5-diol derivative (1 mmol) (1a-h) in CH_3CN (10 mL) was added molecular iodine (I_2, 10% mole) and the mixture was refluxed for 6 hours. At the end of the reaction, the mixture was taken into a separatory funnel and sodium thiosulfate solution (10%) was added, and the organic phase was separated by extraction with $CHCl_3$ (3x20 mL). After drying over Na_2SO_4 and removing the solvent, the crude product was purified on a silica gel column eluting with $CHCl_3$/n-hexane (3:7).

rel-(2*R*,4S,4a*R*,8a*R*)-2,4-di-*p*-tolyloctahydro-2*H*-chromene (2a): Yield 84%, yellow viscous liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.10 (s, 4H), 4.82 (dd, *J* = 11.6, 2.4 Hz, 1H), 4.14 (dt, *J* = 12.4, 4.8 Hz, 1H), 3.16 (td, *J* = 12.2, 3.7 Hz, 1H), 2.31 (s, 6H), 2.26 – 2.19 (m, 1H), 1.96 (ddd, *J* = 13.2, 3.7, 2.5 Hz, 1H), 1.87 (dt, *J* = 5.6, 3.5 Hz, 1H), 1.78 (dd, *J* = 25.0, 12.2 Hz, 2H), 1.49 – 1.38 (m, 1H), 1.33 – 1.24 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 141.5, 140.9, 136.3, 135.4, 129.4 (2C), 128.9 (2C), 127.6 (2C), 126.2 (2C), 75.5, 71.4, 43.3, 40.7, 38.6, 26.9, 25.5, 25.4, 21.1, 21.0, 20.2. IR (KBr, cm^{-1}): 3018, 2931, 2856, 1513, 1450, 1375, 1139, 1085, 1029, 981, 811, 721, 572, 514. GC/MS (m/z) (%): 321 (M^+, 2.1), 302 (4.9), 228 (32.8), 185 (28.7), 131 (41.2), 118 (100.0), 105 (82.5), 91 (44.6).

rel-(2*R*,4S,4a*R*,8a*R*)-4-(4-chlorophenyl)-2-(4-methoxyphenyl)octahydro-2*H*-chromene (2b): Yield 80%, colorless viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.18 (dt, *J* = 12.4, 4.8 Hz, 1H), 3.81 (s, 3H), 3.22 (td, *J* = 12.2, 3.4 Hz, 1H), 2.21 (bd, *J* = 12.4 Hz, 1H), 2.02-1.91 (m, 3H), 1.80-1.73 (m, 3H), 1.44-1.27 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ158.9, 142.7, 135.2, 131.9, 128.8 (2C), 128.7 (2C), 127.2 (2C), 113.7 (2C), 76.1, 71.5, 55.3, 42.7, 40.6, 39.0, 26.8, 25.5, 25.4, 20.3. IR (KBr, cm^{-1}): 2998, 2935, 2856, 1614, 1513, 1490, 1450, 1367, 1301, 1245, 1174, 1139, 1087, 1029, 1012, 827, 549, 522. GC/MS (m/z) (%): 359 (M^+, 1.6), 258 (16.4), 205 (18.4), 151 (20.6), 134 (100.0), 121 (73.3), 108 (55.2), 91 (31.9), 77 (34.8).

rel-(2*R*,4S,4a*R*,8a*R*)-2-(4-chlorophenyl)-4-(4-methoxyphenyl)octahydro-2*H*-chromene (2c): Yield 84%, yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.88 (d, *J* = 11.6 Hz, 1H), 4.24-4.19 (m, 1H), 3.82 (s, 3H), 3.23-3.19 (m, 1H), 2.39 (bd, *J* = 12.4 Hz, 1H), 2.05-1.91 (m, 3H), 1.79-1.73 (m, 3H), 1.51 (bd, *J* = 12.4 Hz, 1H), 1.37-1.31 (m, 3H). ^{13}C-NMR (100

MHz, $CDCl_3$, ppm): δ158.2, 141.9, 136.1, 132.8, 128.4 (2C), 128.3 (2C), 127.3 (2C), 113.9 (2C), 76.3, 71.5, 55.2, 43.1, 40.8, 38.6, 26.8, 25.5, 25.4, 20.3. IR (KBr, cm^{-1}): 2996, 2933, 2856, 1610, 1511, 1490, 1450, 1375, 1247, 1178, 1083, 1037, 1014, 827, 561, 530. GC/MS (m/z) (%): 358 (M^+, 5.0), 259 (20.8), 201 (13.4), 147 (37.1), 134 (100.0), 121 (91.4), 91 (31.4), 77 (21.2).

rel-(2*R*,4*S*,4a*R*,8a*R*)-2-(4-bromophenyl)-4-(4-methoxyphenyl)octahydro-2*H*-chromene (2d): Yield 81%, colorless viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.48 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.85 (dd, *J* = 11.4, 1.8 Hz, 1H), 4.20 (td, *J* = 8.6, 4.8 Hz, 1H), 3.81 (s, 3H), 3.18 (td, *J* = 12.0, 3.6 Hz, 1H), 2.25 (bd, *J* = 11.4 Hz, 1H), 2.02-1.91 (m, 3H), 1.78-1.71 (m, 3H), 1.51 (bd, *J* = 11.4 Hz, 1H), 1.35-1.25 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 158.2, 142.4, 136.1, 131.3 (2C), 128.8 (2C), 127.7 (2C), 120.1, 113.9 (2C), 76.3, 71.5, 55.3, 43.1, 40.8, 38.6, 26.8, 25.5, 25.4, 20.3. IR (KBr, cm^{-1}): 2996, 2933, 2856, 1610, 1511, 1486, 1450, 1247, 1178, 1085, 1072, 1035, 1010, 827, 559, 530. GC/MS (m/z) (%): 403 (M^+, 2.5), 303 (17.7), 201 (22.3), 147 (46.8), 134 (100.0), 121 (94.3), 91 (37.9), 77 (30.4).

rel-(2*R*,4*S*,4a*R*,8a*R*)-2,4-bis(4-methoxyphenyl)octahydro-2*H*-chromene (2e): Yield 73%, yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.90-6.86 (m, 4H), 4.83 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.17 (dt, *J* = 12.4, 4.6 Hz, 1H), 3.81 (s, 3H), 3.18 (td, *J* = 12.0, 3.4 Hz, 1H), 2.27-2.22 (m, 1H), 2.00-1.91 (m, 3H), 1.82-1.72 (m, 3H), 1.48 (bd, *J* = 12.0 Hz, 1H), 1.35-1.28 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ158.8, 158.0, 136.3, 135.4, 128.3 (2C), 127.2 (2C), 113.9 (2C), 113.7 (2C), 75.8, 71.7, 55.3, 55.2, 42.9, 40.9, 38.6, 26.8, 25.5, 25.4, 20.3. IR (KBr, cm^{-1}): 2996, 2933, 2856, 1612, 1511, 1463, 1450, 1375, 1301, 1247, 1176, 1139, 1083, 1035, 1012, 829, 738, 565, 528. GC/MS (m/z) (%): 353 (M^+, 2.5), 244 (52.0), 201 (23.8), 147 (33.0), 134 (100.0), 121 (90.3), 91 (32.9), 77 (18.5).

rel-(2*R*,4*S*,4a*R*,8a*R*)-4-(4-methoxyphenyl)-2-(*p*-tolyl)octahydro-2*H*-chromene (2f): Yield 79%, yellow viscous liquid. ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.06-4.02 (m, 1H), 3.68 (s, 3H), 3.16-3.10 (m, 1H), 2.24 (s, 3H), 2.19-2.09 (m, 2H), 1.84 (bd, *J* = 12.4 Hz, 1H), 1.78-1.76 (m, 1H), 1.68-1.52 (m, 2H), 1.33-1.11 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 158.1, 141.0, 136.4, 136.2, 128.9 (2C), 128.5 (2C), 126.1 (2C), 114.2 (2C), 75.6, 71.5, 55.2, 43.5, 40.9, 38.3, 26.8, 25.5, 25.4, 21.1, 20.2. IR (KBr, cm^{-1}): 3027, 2996, 2933, 2856, 1610, 1511, 1450, 1375, 1247, 1178, 1083, 1037, 829, 813, 563, 520. GC/MS (m/z) (%): 338 (M^+, 0.7), 239 (16.4), 228 (58.0), 201 (30.5), 147 (59.0), 134 (100.0), 121 (91.6), 105 (45.4), 91 (55.9), 77 (16.7).

rel-(2*R*,4*S*,4a*R*,8a*R*)-2-(4-methoxyphenyl)-4-(*p*-tolyl)octahydro-2*H*-chromene (2g): Yield 82%, yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.16 (s, 4H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.18 (dt, *J* = 12.4, 4.8 Hz, 1H), 3.82 (s, 3H), 3.20 (td, *J* = 12.0, 3.6 Hz, 1H), 2.36 (s, 3H), 2.30-2.28 (m, 1H), 2.00-1.91 (m, 2H), 1.88-1.74 (m, 3H), 1.49 (bd, *J* = 12.4 Hz, 1H), 1.35-1.26 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ158.8, 141.2, 135.8, 135.4, 129.2 (2C), 127.4 (2C), 127.2 (2C), 113.7 (2C), 76.3, 71.7, 55.3, 42.8, 40.7, 39.1, 26.9, 25.5, 25.4, 21.0, 20.3. IR (KBr, cm^{-1}): 3004, 2933, 2857, 1612, 1511, 1450, 1301, 1245, 1174, 1083, 1035, 815, 736, 551, 524. GC/MS (m/z) (%): 338 (M^+, 0.6), 244 (34.0), 201 (20.5), 185 (32.3), 135 (63.1), 118 (100.0), 105 (54.6), 91 (43.0), 77 (20.7).

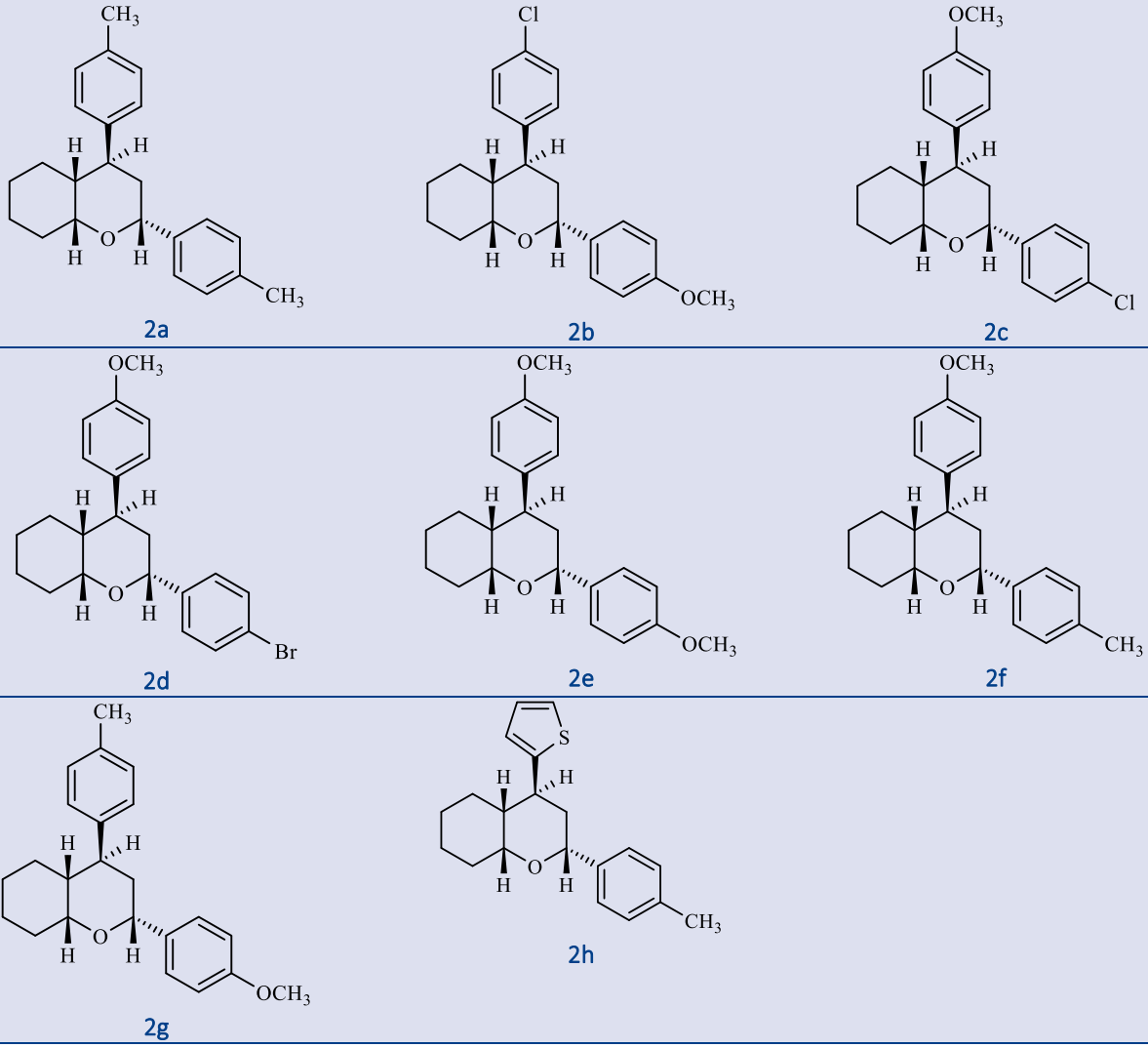
rel-(2*R*,4*S*,4a*R*,8a*R*)-4-(thiophen-2-yl)-2-(*p*-tolyl)octahydro-2*H*-chromene (2h): Yield 70%, yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.22-7.18 (m, 3H), 6.98 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.89 (d, *J* = 3.2 Hz, 1H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.20 (dt, *J* = 12.4, 4.6 Hz, 1H), 3.60 (td, *J* = 12.0, 3.2 Hz, 1H), 2.37 (s, 3H), 2.25-2.17 (m, 1H), 2.00-1.85 (m, 2H), 1.79-1.65 (m, 4H), 1.41-1.35 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 148.3, 139.9, 137.0, 129.0 (2C), 126.5, 125.8 (2C), 123.6, 122.8, 76.2, 71.9, 44.2, 42.6, 35.1, 26.9, 25.5 (2C), 21.1, 20.3. IR (KBr, cm^{-1}): 3023, 2933, 2856, 1513, 1448, 1367, 1265, 1247, 1135, 1085, 1039, 813, 740, 694, 563. GC/MS (m/z) (%): 314 (M^+, 0.7), 227 (43.1), 177 (17.1), 134 (31.5), 110 (100.0), 97 (53.9), 91 (31.3), 79 (19.1).

Results and Discussion

In our previous study, we synthesized 1,5-diols starting from chalcones [22], [23]. In this study, we carried out the synthesis of eight new chromene derivatives that have four stereogenic centers. The 2,4-diaryloctahydro-2*H*-chromene derivatives (2a-h) were obtained by reaction of 1,5-diols (1a-h) with molecular iodine in CH_3CN at reflux condition in high yields. The synthesized new compounds and their structures are shown in Table 1.

The mechanism of the transformation of 1,5-diols to 2,4-diaryloctahydro-2*H*-chromene derivatives in the presence of iodine can be explained as shown Figure 3. As a result of the interaction of iodine with the oxygen atom in the benzylic position, a polarization occurs on the 1,5-diol. Thus generating an electron-deficient centre (δ+). Through the transition state, the electron-rich oxygen atom (δ-) in the structure attacks the benzylic position and realized the cyclisation. Meanwhile, the hydroxyl group in the benzylic position takes the hydrogen and leaves as a water molecule [24]. The resulting cyclization yields new 2,4-diaryloctahydro-2*H*-chromene derivatives with four stereocenters (2a-h).

Table 1. Synthesized 2,4-diaryloctahydro-2*H*-chromene derivatives (2a-h)



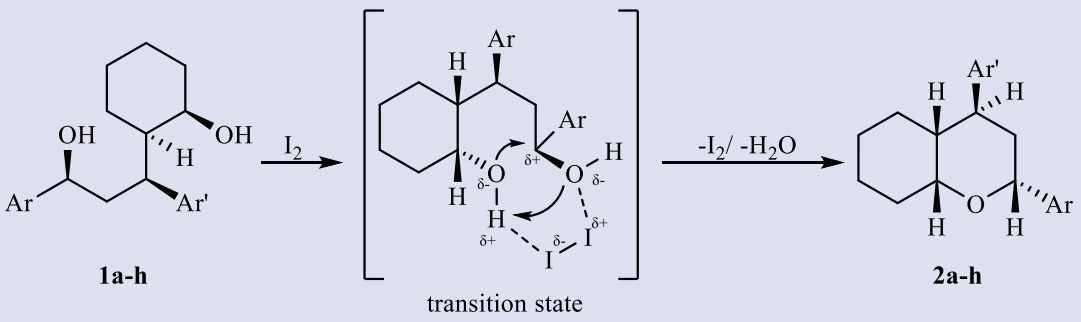


Figure 3. Proposed reaction mechanism

The structures of the synthesized new chromenes were determined by spectroscopic analysis studies (^{1}H-NMR, ^{13}C-NMR, 2D-NMR, FTIR and GC/MS). The full analysis of ^{1}H-NMR, ^{13}C-NMR, COSY and HETCOR spectra of 2a confirmed the presence of chromene structure (Figure 4, Figure 5, Figure 6 and Figure 7). Moreover, the stereochemistry of 2a was predicted from NOESY analysis. In the NOESY spectrum of compound 2a, a strong correlations between the H-C4 signal at 2.23 ppm and the H-C1 signal at 4.82 ppm was observed. In addition, a strong correlation between the H-C4 signal at 2.23 ppm and the H-C5 signal at 4.15 ppm was observed (Figure 8). In the ^{1}H-NMR spectrum of 2a, the H-C1 proton gave a doublet of doublets at 4.82 (J = 11.6, 2.4 Hz) ppm. Additionally the signals of the H-C5, H-C3 and H-C4 protons of 2a in the spectrum were observed as doublet of triplets at 4.14 (J = 12.4, 4.8 Hz), triplet of doublets at 3.16 (J = 12.2, 3.7 Hz) and multiplet 2.27-2.20 ppm respectively. The methylene protons in the structure resonate by giving an AB spin system. The A part of the AB system gave doublet of doublets of doublets at 1.96 (J = 13.2, 3.7, 2.5 Hz) ppm, while the B part gave doublet of

doublets at 1.78 (J = 25.0, 12.2 Hz) ppm respectively. All the aliphatic and aromatic signals in the spectrum were consistent with the structure of 2a (Figure 4). In the ^{13}C-NMR spectrum, it is seen that the C1 and C5 etheric carbons in the chromene structure resonate at 72.0 ppm and 76.3 ppm respectively, and the other aliphatic and aromatic signals are in full harmony with the structure (Figure 5).

The absorption bands seen at 3014-2856 cm^{-1} in the FTIR spectrum of 2a result from the stretching vibration of the aliphatic and aromatic C-H units in the structure. Aromatic C-C stretch bands arising from aromatic rings in the structure are seen at 1513 and 1450 cm^{-1} in the spectrum. The asymmetric stretch band of the C-O-C bridge, which indicates the presence of the chromene ring, is located at 1085 cm in the spectrum, while the symmetric stretch band is seen as a weak peak at 890 cm^{-1}. The band seen at 811 cm^{-1} in the spectrum proves that the substituents in the aromatic rings are in the para position (Figure 9).

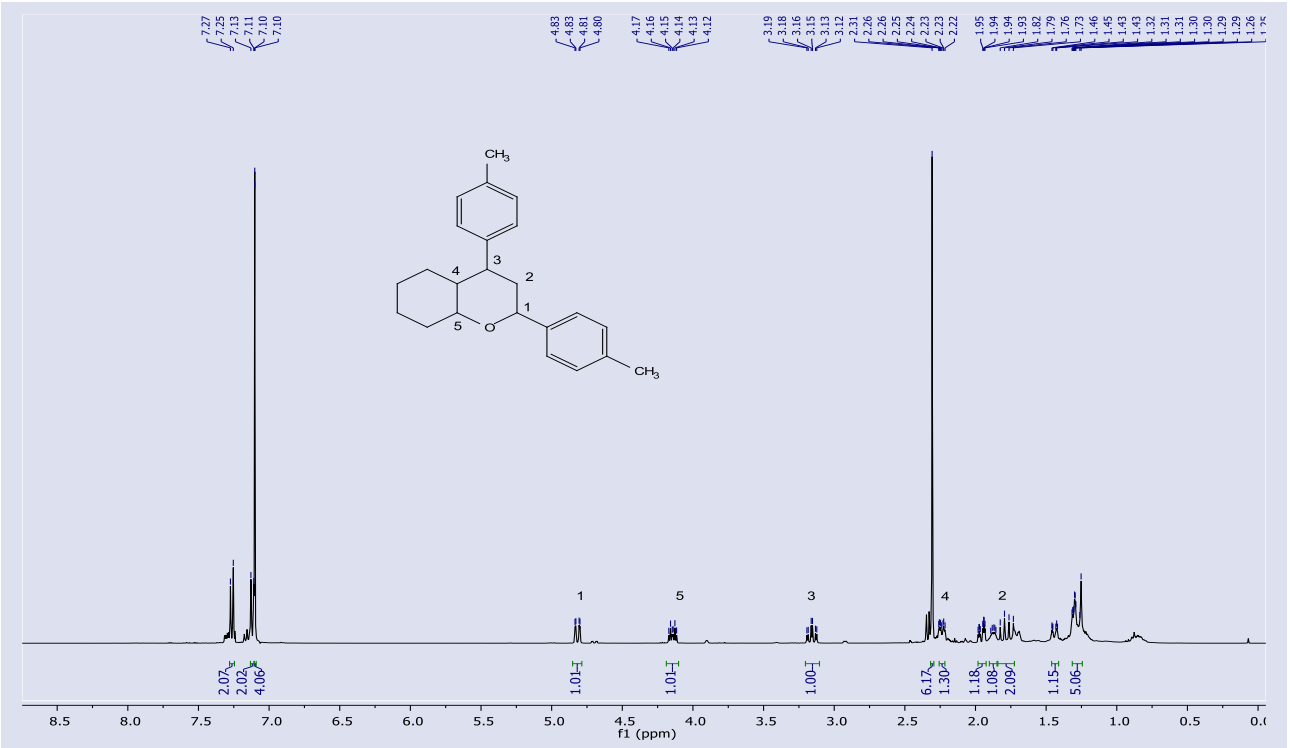


Figure 4. ^{1}H-NMR spectrum of 2a

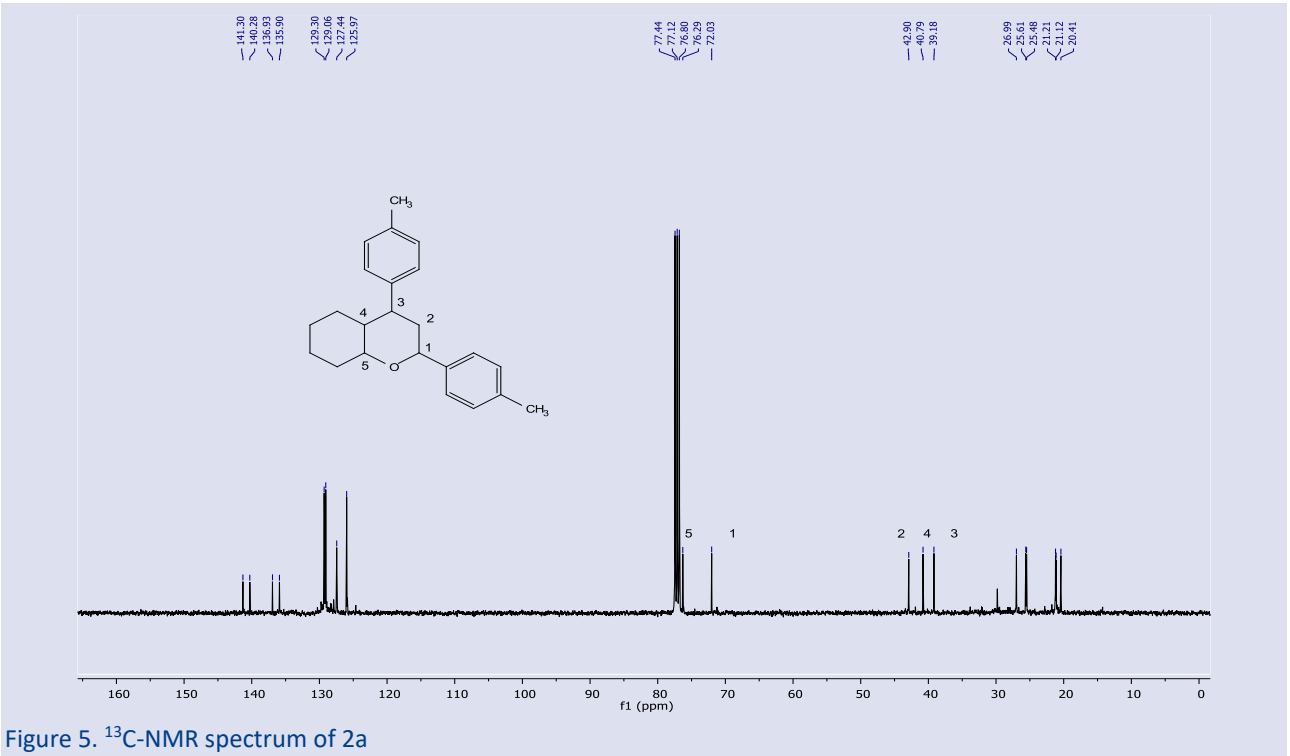


Figure 5. ^{13}C-NMR spectrum of 2a

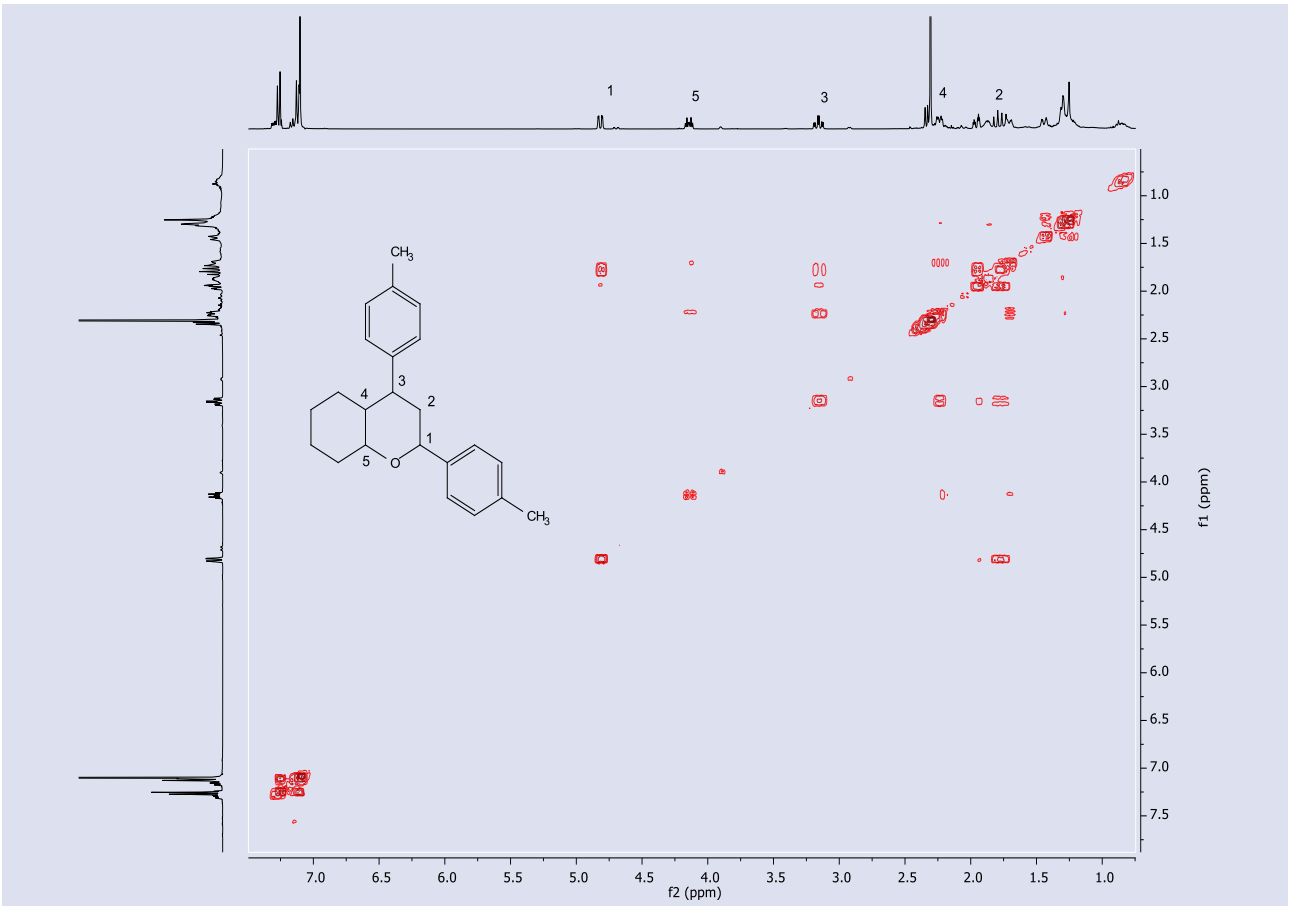


Figure 6. COSY spectrum of 2a

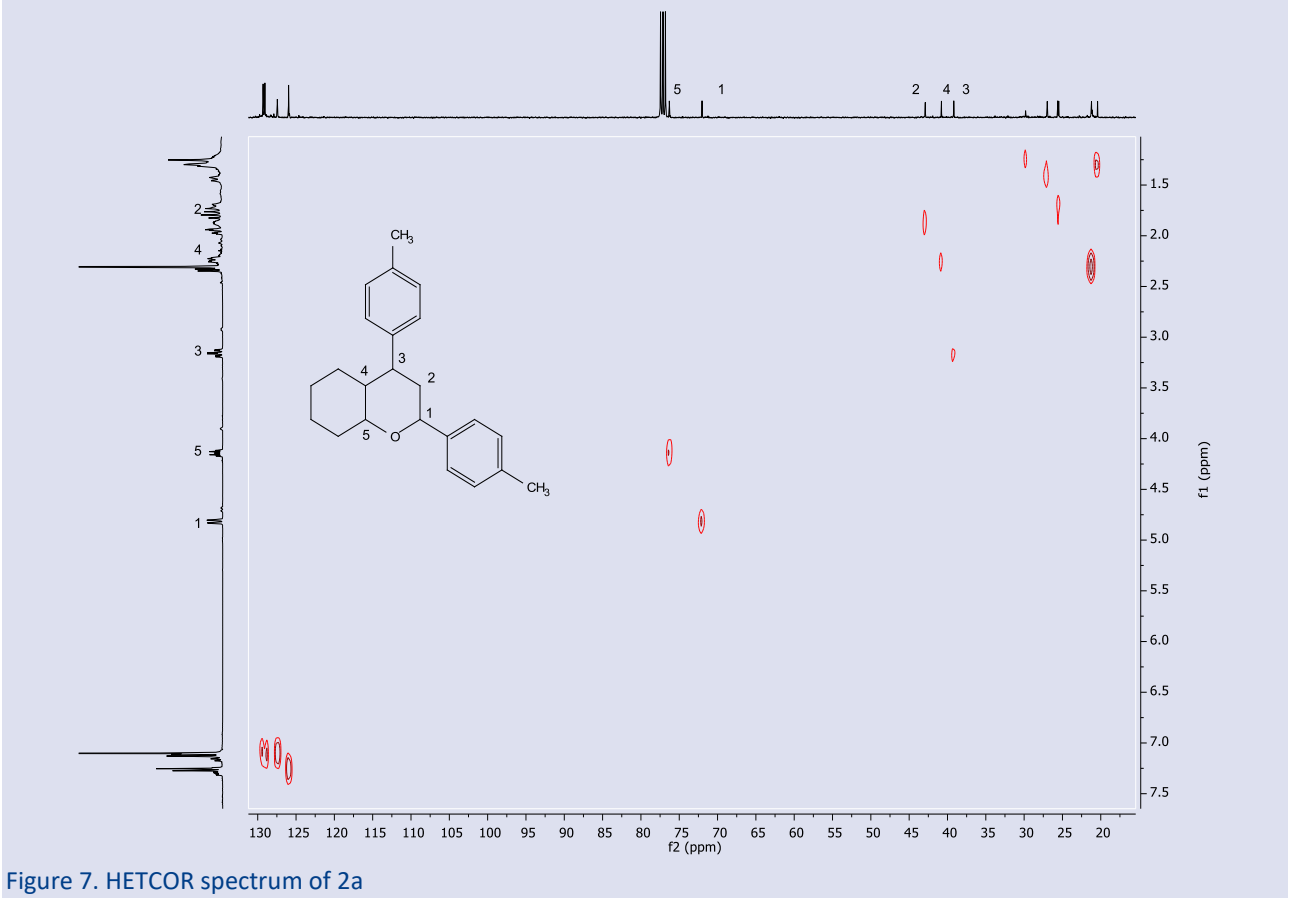


Figure 7. HETCOR spectrum of 2a

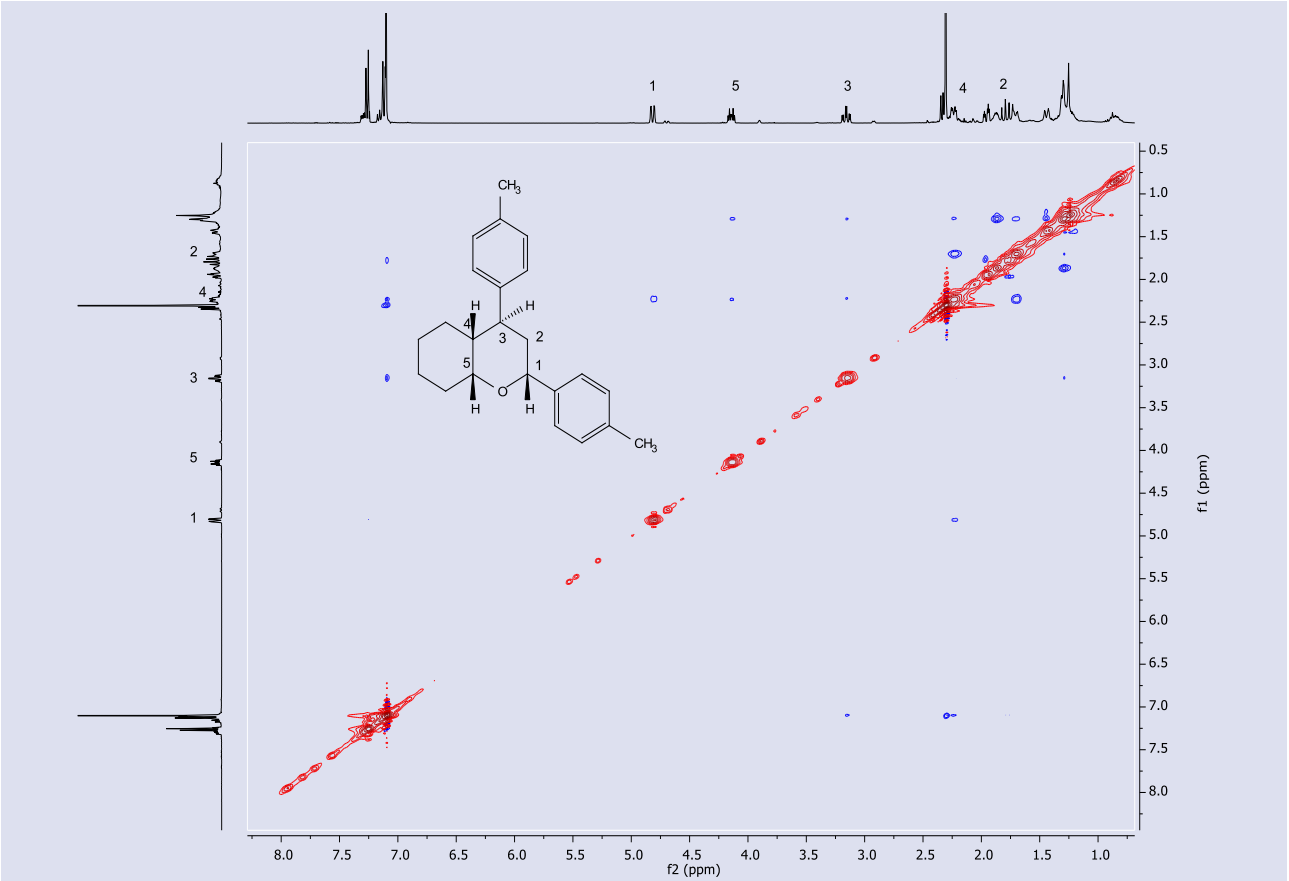


Figure 8. NOESY spectrum of 2a

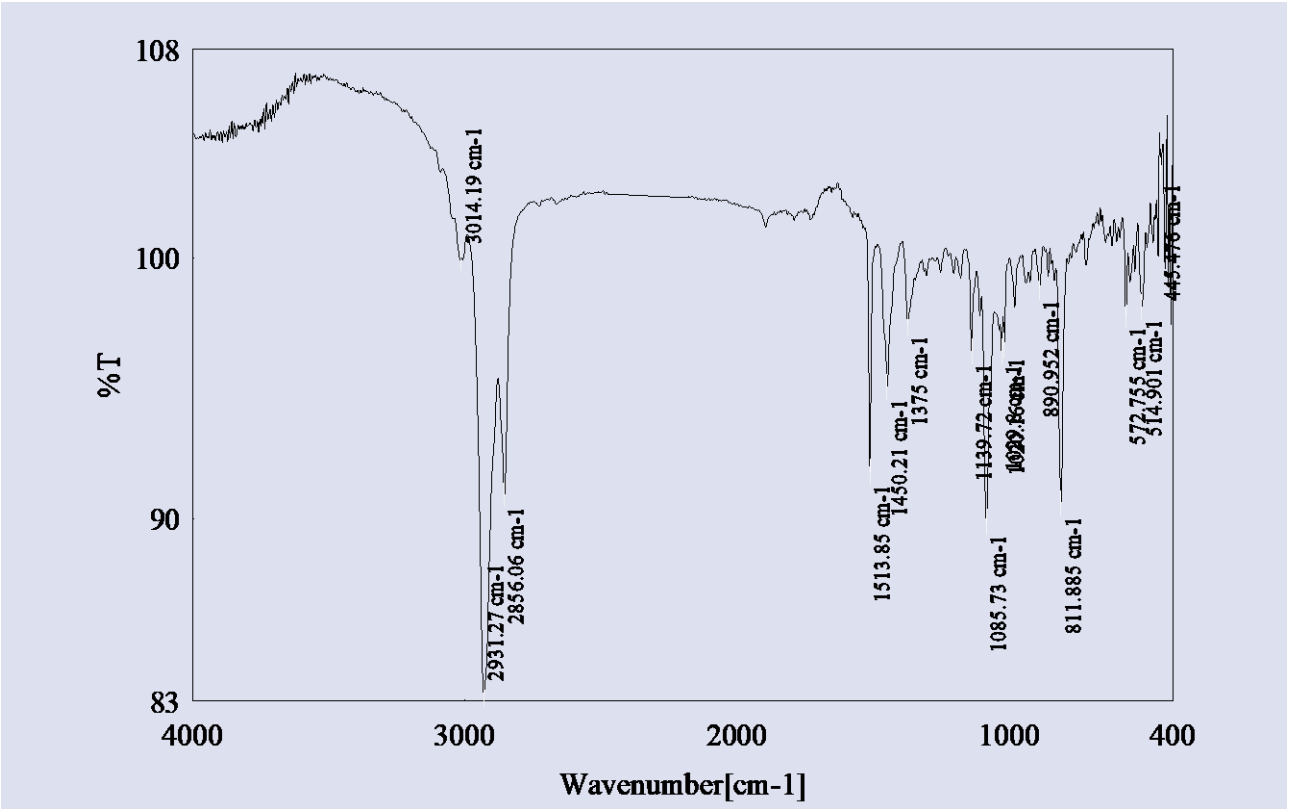


Figure 9. FTIR spectrum of 2a

Conclusion

It is known that chromene derivatives are compounds with high biological activity potential as well as being

natural compounds [6]. At the same time, chromene derivatives are among the important compounds that are used in industry [25]. In this respect, the synthesis and application areas of chromene derivatives is a current issue that attracts the attention of researchers. In the present study, eight novel 2,4-diaryloctahydro-2*H*-chromene derivatives (2a-h) were synthesized from molecular iodine catalysed cyclization of 1,5-diols (1a-h) that we synthesized in our previous studies [22], [23]. The chemical structures of the synthesized new compounds were determined by spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, 2D-NMR, FT-IR, and GC-MS). Although various chromene derivatives and various synthesis methods are reported in the literature, there is no study on the synthesis of iodine-catalyzed chromene derivatives over 1,5-diols. This study demonstrated a route for converting 1,5-diols to cyclic ethers under mild conditions in high yield with iodine. The synthesized compounds are new chiral chromene derivatives with four different stereocenters and are not included in the literature. The 2D-NMR analyzes performed support the proposed configurations of the compounds. The method used can be useful and applicable in synthesizing and developing new chiral compounds with high bioactive potential and multifunctionality. In this respect, this study will make an important contribution to the literature.

Conflicts of interest

There are no conflicts of interest in this work.

Acknowledgements

The authors are indebted to the Gaziosmanpaşa University (Grant BAP-201194) for financial support of this work.

References

[1] Eicher T., Hauptmann S. & Speichcr, A., *The Chemistry of Heterocycles: Structure, Reactions, Synthesis and Applications.*2nd ed. Weinheim (2004) 341-345.

[2] Wen Z., Yang K.-C., Deng J.-F. & Chen L., Advancements in the preparation of 4H-chromenes: an overview, *Advanced Synthesis & Catalysis*, 365 (2023) 1290-1331.

[3] Singh M. M., Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders, *Medicinal Research Reviews*, 21 (2001) 302-347.

[4] Hilas O. & Ezzo D., Nebivolol (bystolic), a novel beta blocker for hypertension, *Pharmacy and Therapeutics*, 34(4) (2009) 188-192.

[5] Mamaghani M., Nia H. R., Tavakoli F. & Jahanshahi P., Recent Advances in the MCRs Synthesis of Chromenes: A Review, *Current Organic Chemistry*, 22(17) (2018) 1704 - 1769.

[6] Raj V. & Lee J., 2H/4H-Chromenes-a versatile biologically attractive scaffold, *Frontiers in Chemistry*, 8(623) (2020) 1-23.

[7] Bianchi G. & Tava, A., Synthesis of (2R)-(+)-2,3-Dihydro-2,6-dimethyl-4H-pyran-4-one, a Homologue of Pheromones of a Species in the Hepialidae Family, *Agricultural and Biological Chemistry*, 51 (1987) 2001-2002.

[8] Tangmouo J. G., Meli A. L., Komguem J., Kuete V., Ngounou F. N., Lontsi D., Beng V. P., Houdhary M. L. & Sondengam B. L., Crassiflorone, a new naphthoquinone from Diospyros crassiflora (Hien), *Tetrahedron Letter*, 47 (2006) 3067-3070.

[9] Kitamura R. O. S., Romoff P., Young M. C. M., Kato M. J. & Lago J. H. G., Chromenes from Peperomia serpens (Sw.) Loudon (Piperaceae), *Phytochemistry*, 67 (2006) 2398-2402.

[10] Ellis G. P., The Chemistry of Heterocyclic Compounds. In: Weissberger, A. & Taylor, E. C. (Eds). *Chromenes. Chromanes and Chromones*. 2nd ed. New York and London: John Wiley and Sons. (1977) Chapter 11, 11-139.

[11] McCracken S. T., Kaiser M., Boshoff H. I., Boyd P. D. W. & Copp B. R., Synthesis and antimalarial and antituberculosis activities of a series of natural and unnatural 4-methoxy-6-styryl-pyran-2-ones, dihydro analogues and photo-dimers, *Bioorganic & Medicinal Chemistry*, 20 (2012) 1482-1493.

[12] Mohareb R. M. & Schatz J., Anti-tumor and anti-leishmanial evaluations of 1,3,4-oxadiazine, pyran derivatives derived from cross-coupling reactions of β-bromo-6H-1,3,4-oxadiazine derivatives, *Bioorganic & Medicinal Chemistry*, 19 (2011) 2707-2713.

[13] Press J. B., McNally J. J., Sanfilippo P. J., Addo M. F., Loughney D., Giardino E., Katz L. B., Falotico R. & Haertlein B. J., Novel thieno[2,3-b]- and [3,4-b]pyrans as potassium channel openers, Thiophene systems-XVII, *Bioorganic & Medicinal Chemistry*, 1 (1993) 423-435.

[14] Tummino P. J., Prasad J. V. N. V., Ferguson D., Nouhan C., Graham N., Domagala J. M., Ellsworth E., Gajda C., Hagen S. E., Lunney E. A., Para K. S., Tait B. D., Pavlovsky A., Erickson J. W., Gracheck S., McQuade T.J. & Hupe D.J., Discovery and optimization of nonpeptide HIV-1 protease inhibitors, *Bioorganic & Medicinal Chemistry*, 4 (1996) 1401-1410.

[15] Jayaprakasha G. K., Rao L. J. & Sakariah K. K., Antioxidant activities of flavidin in different in vitro model systems, *Bioorganic & Medicinal Chemistry*, 12 (2004) 5141-5146.

[16] Yusubov M.S. & Zhdankin V. V., Iodine catalysis: A green alternative to transition metals in organic chemistry and technology, *Resource-Efficient Technologies*, 1 (2015) 49-67.

[17] Prajapati D. & Gohain M., Iodine a Simple, Effective and Inexpensive Catalyst for the Synthesis of Substituted Coumarins, *Catalysis Letters*, 119 (2007) 59-63.

[18] Zhang H., Wang H., Jiang Y., Cao F., Gao W., Zhu L., Yang Y., Wang X., Wang Y., Chen J., Feng Y., Deng X., Lu Y., Hu X., Li X., Zhang J., Shi T. & Wang Z., Recent Advances in Iodine-Promoted C−S/N−S Bonds Formation, *Chemistry-A European Journal*, 26 (2020) 17289-17317.

[19] Samanta S. & Mondal S., Iodine-Catalyzed or -Mediated Reactions in Aqueous Medium, *Asian Journal of Organic Chemistry*, 10 (2021) 2503-2520.

[20] Breugst M. & von der Heiden D., Mechanisms in Iodine Catalysis, *Chemistry-A European Journal*, 24 (2018) 9187-9199.

[21] Kasashima Y., Fujimoto H., Mino T., Sakamoto M., Fujita T., An Efficient Synthesis of Five-membered Cyclic Ethers from 1,3-Diols Using Molecular Iodine as a Catalyst, *Journal of Oleo Science*, 57 (2008) 437-443.

[22] Gezegen H., Tutar U., & Ceylan M., Synthesis and antimicrobial activity of racemic 1,5-diols: 2-(1,3-diaryl-3-hydroxypropyl)cyclohexan-1-ol derivatives, *Helvetica Chimica Acta*, 99 (2016) 608-616.

[23] Çelik İ., Akkurt M., Gezegen H., Üremiş M. M. & Duteanu N., 2-[1-(4-Bromophenyl)-3-hydroxy-3-(4-methoxyphenyl)propyl]cyclohexanol, *Acta Crystallographica Section E*, E69 (2013) o1091-o1092.

[24] Jereb M. & Vrazic D., Iodine-catalyzed Transformation of Aryl-substituted Alcohols Under Solvent-free and Highly Concentrated Reaction Conditions, *Acta Chimica Slovenica*, 64 (2017) 747-762.

[25] El-Sayed R., Mohamed K.S. & Fadda A. A., Synthesis and evaluation of some chromene derivatives as antioxidant with surface activity, *Afinidad Journal of Chemical Engineering Theoretical and Applied Chemistry*, 75 (2018) *581*, 66-75.