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A complicated path of salicylaldehyde through the Biginelli reaction: a case of unexpected spiroketalization

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ABSTRACT

Cyclocondensation of salicylaldehydes with alkyl acetoacetates and 2-aminobenzothiazoles or 2-amino-5-methylthiazole under classical Biginelli reaction conditions gives rare hetarylamino substituted 2,2′-spirobischromanecarboxylate derivatives. The mechanism and observed stereoselectivity of the unexpected pseudo-four-component process are discussed.

1. Introduction

Spiroketals are prominent structural subunits embedded in numerous natural products of plant, fungi, bacterial, insect and marine origin. Most of the naturally occurring substances with various complexity, such as steroidal saponins, polyketide antibiotics, polyether ionophores, macrolides and pheromones exhibit important biological properties.[1] In this respect even relatively simple spiroketal structures display useful pharmacological effects. Not only potential medicinal importance but also rather delicate relationship between anomeric and non-anomeric configurations, access to less stable isomers, development of general and stereocontrolled methods to 'contrathermodynamic' (non-anomeric) congeners and generation of stereodiversified libraries make spiroketal ring system an attractive target.[1]

In the course of our research focused on salicylaldehyde (**1a**) as a fundamental constituent of oxygen-bridged pyrimidines[2] we have recently found that the replacement of urea/thiourea by 3-amino-1,2,4-triazole in the Biginelli reaction led quite unexpectedly to novel spirocyclic structure **2**[2d] (Fig. 1). For a better understanding of the pseudo-four-component process, we selected some substituted 2-aminobenzothiazoles **4a**–**e** and 2-amino-5-methylthiazole (**5**) substrates to reduce the number of reaction centres acting in the above aminotriazole educt. The present paper reports on the unexpected formation of a benzannelated spiroketal ring system in the Biginelli-like reaction using salicylaldehydes **1**, alkyl acetoacetates **3** and the chosen isothiourea analogues.

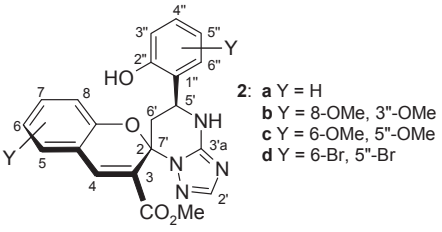

Fig. 1. Unconventional product of the Biginelli-like reaction with 3-amino-1,2,4-triazole.

2. Results and discussion

We began our investigations with the heterocyclization of methyl acetoacetate (**3a**), 2-aminobenzothiazole (**4a**) with 2 M equiv of salicylaldehyde (**1a**) under similar conditions as reported for the transformation of aminotriazole.[2d] Thus, ethanolic solution of the reactants was allowed to reflux gently in the presence of the HCl catalyst for 14 h, at the end of which period a white

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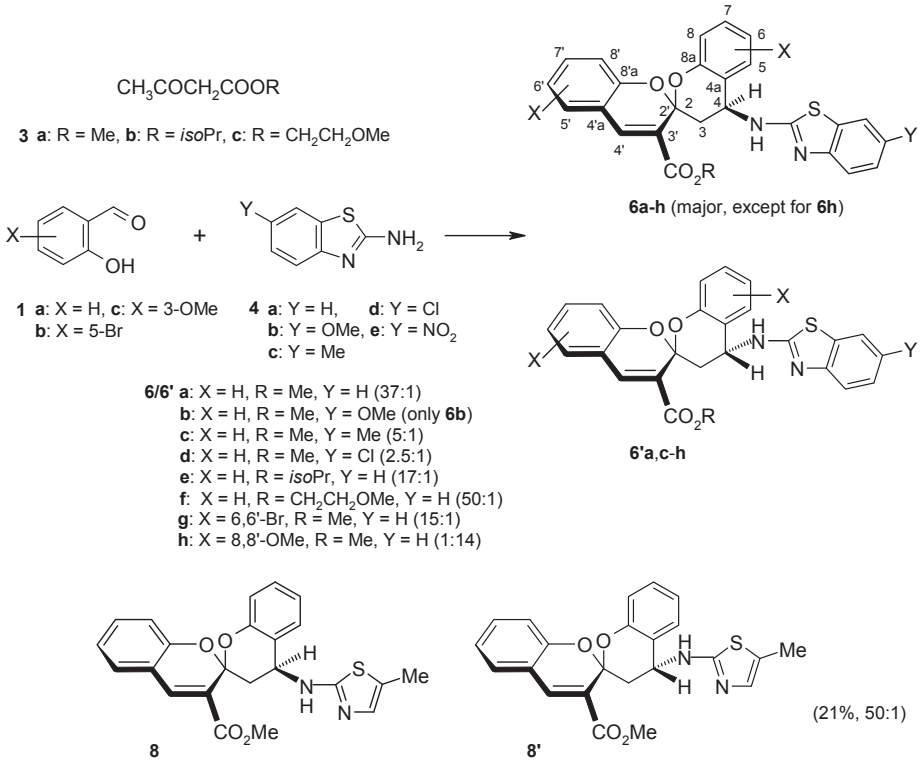
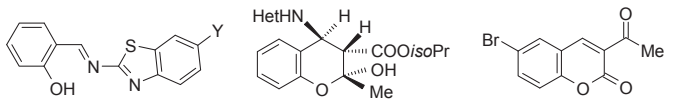
precipitate separated. The molecular formula, $C_{26}H_{20}N_2O_4S$, of isolated compound **6a** corresponds to an adduct combining the above ester **3a**, amine **4a** and aldehyde **1a** in a 1:1:2 manner by loss of three molecules of water. Although the NMR spectra of the product **6a** are similar to those of spiro-fused heterocycle **2a**, thereby showing the presence of some common structural elements, the diagnostic N,O-spiro ^{13}C resonance (δ_C 85.6 for C-2 in **2a**) was lacking. Instead, a new quaternary sp^3 carbon atom was observed at δ_C 98.1. Such a peculiar downfield shift is anticipated for a O–C–O moiety where increased substituent electronegativities would induce a higher degree of deshielding. This assumption was supported by comparison of the critical ^{13}C chemical shift value with literature data reported for ketals and spiroketals typically lying close to 100 ppm.[3] In addition, the absence of free hydroxyl groups permitted the deduction that both of the phenolic functionalities have been incorporated in the formation of the key spiroketal substructure. According to a careful NMR analysis, the other part of the molecule contains a CH_2CHNH segment of which a two-carbon link belonging to the oxacyclic system is tethered to the phenylene skeleton via the methine carbon on the one hand and to the spiro centre through the methylene terminus on the other. Hence, the secondary amino group must be flanked by the spiroketal and benzothiazole pendants. Two types of ^{15}N nuclei were differentiated by means of ^1H, ^{15}N correlation spectroscopy (HSQC for the protonated nitrogen, HMBC for the heteroaromatic ring nitrogen atom). Not surprisingly, the second half of the [6,6]-spiroketal core consists of an unsaturated chromene ring carrying a methoxycarbonyl function, thus being reminiscent of **2a**. Having collected the above molecular features, we concluded that the product structure is spiro[chroman-2,2′-chromene]-3′-carboxylate **6a** as outlined in Scheme 1. A complete ^1H and ^{13}C signal assignment of **6a** was achieved using 2D NMR methods (COSY, HSQC, HMBC). Nevertheless, the ^1H NMR spectrum of the crude product showed that two diastereomers, **6a** and **6′a** were formed. Both isomers could be easily recognized mainly due to different positions of their H-4 ($\Delta\delta$ 0.34 ppm) resonances. Integration of the corresponding signals, being well separated from the rest of the spectrum, allowed us to estimate the isomer relation **6a**/**6′a** in a ratio 37:1. Evidently, the explored multicomponent condensation is highly diastereoselective. Based on the NMR spectra, the examined diastereomers retain the same configuration at the spiro carbon while the amine residue alternates between two possible positions on the C-4 ring carbon. The relative stereochemistry of **6a** was established from the 1D-NOESY and ROESY measurements. In particular, the ROESY experiment displayed convincing and even complementary dipole–dipole interactions between the aliphatic methine H-4 and aromatic H-8′ protons. As seen from the Dreiding model of **6a**, H-4 faces the oxygen atom belonging to the chromene ring whereas the secondary amine moiety, which is also bonded to C-4 has to occupy the opposite side of the partially saturated oxacyclic skeleton. Besides that, the N–H bond became aligned with one of the neighbouring methylene hydrogen linkages. The former H-4 proton was found downfield from that of the epimer **6′a**, which by contrast is characterized by a reverse arrangement. The observed deshielding seems to reflect a relationship between the H-4 and O-1′ atoms. Accordingly, the higher chemical shift of H-4 in **6a** is possibly due to the anisotropy effect of this proximal and eclipsing oxygen, thereby parallelling the situation in some spiroketal derivatives.[3b] Note that the presented structural findings have been confirmed by single crystal X-ray diffraction analysis made on other derivatives (see below).

To exploit the synthetic potential of the multicomponent cyclization, we examined other aminobenzothiazole substrates. The treatment of salicylaldehyde (**1a**) and methyl ester **3a** with 2-amino-6-methoxy- (**4b**) or 2-amino-6-methyl-benzothiazole (**4c**) provided, under similar conditions, the desired spiroketals **6b** and **6c**, respectively. Besides the target products, small amounts of azomethines **7b** and **7c**, arising from aldehyde and amine condensation, were isolated from the filtrate (Fig. 2). As for stereoselectivity, cyclocondensation of **4b** resulted in a single isomer **6b** whereas reaction of **4c** gave an epimeric mixture of **6c**/**6′c** in a ratio 5:1. Moreover, we found that longer time led to a decrease of



Scheme 1. Biginelli-like condensation of salicylaldehydes with aminobenzothiazoles and 2-amino-5-methylthiazole.



7 b: Y = OMe, **c**: Y = Me **9** Het = benzothiazol-2-yl **10**

Fig. 2. Isolated by-products **7b**,**c**, **9** and **10**.

diastereoselectivity. In contrast to the above amines, the cyclization with 2-amino-6-chlorobenzothiazole (**4d**) appeared to be more complex and was less diastereoselective (**6d**/**6′d** ratio of 2.5:1). On the other hand, 2-amino-6-nitrobenzothiazole (**4e**), which is rather insoluble in ethanol, proved to be resistant to spiroketalization under the given conditions (Scheme 1).

Of the thiazole series, just 2-amino-5-methyl member **5** was successfully converted to provide the expected spiroketal with excellent diastereoselectivity, **8**/**8′**=50:1 (Scheme 1). Since this compound occurred in a single crystal form, we determined its X-ray structure[4] to support our postulated assignment and to establish the overall molecular conformation. The crystal structure unequivocally confirmed that the spatial features (Fig. 3) are in accordance with the above conclusions judged from the NMR spectra.

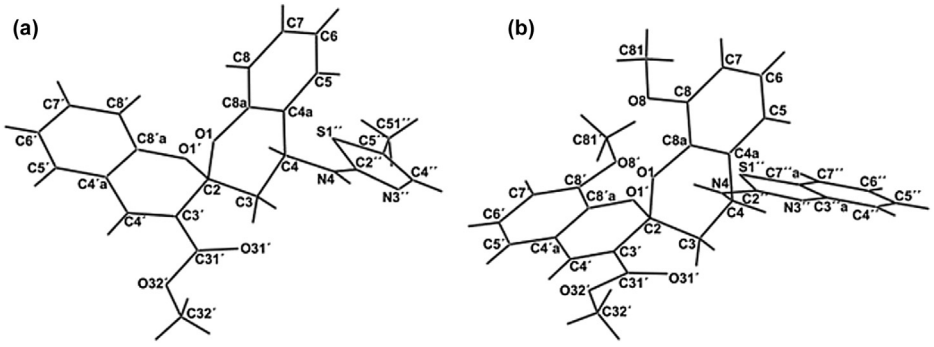


Fig. 3. Perspective views of (a) spiroketal **8** (left), and (b) **6′h** (right).

Next, we tested the applicability of the studied reaction with two other acetoacetates. Both esters, isopropyl **3b** and 2-methoxyethyl **3c**, produced the corresponding spiroketals in a highly diastereoselective fashion, **6e**/**6′e** 17:1 and **6f**/**6′f** 50:1, respectively (Scheme 1). Furthermore, in the former case the minor chromane by-product **9** (Fig. 2) was isolated from the mother liquor. The relative stereochemistry of **9** followed from X-ray crystallography[4] (Fig. 4).

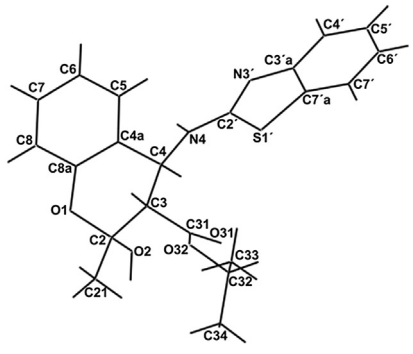


Fig. 4. Perspective view of chromane **9**.

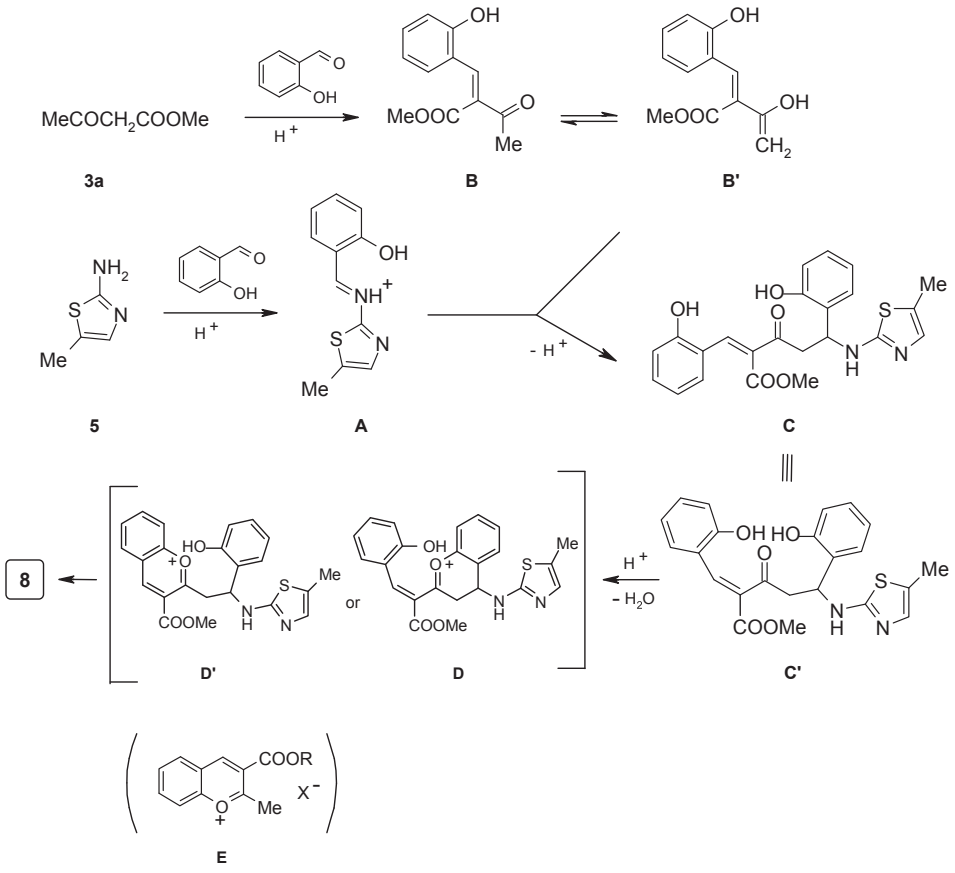
It was also of interest to inspect the behaviour of some substituted salicylaldehydes in the cyclocondensation with amine **4a** and ester **3a**. Whereas 5-bromo-2-hydroxybenzaldehyde **1b** reacted in an usual mode furnishing a mixture of epimers **6g** and **6′g** 15:1, together with 3-acetyl-6-bromocoumarin (**10**) (Fig. 2), the 3-methoxy representative **1c** gave the opposite diastereomer **6′h** as the dominant form (**6h**/**6′h** 1:14) (Scheme 1). As expected, the methine H-4 signal in **6′h** moved upfield (δ_H 5.61) when compared to that of **6h** (δ_H 5.79). The relative stereochemistry of the major isomer **6′h** was again assigned on the basis of NOESY exhibiting a significant correlation of the NH with the spatially adjacent MeO-8′ protons and afterwards confirmed by a single crystal X-ray diffraction[4] (Fig. 3).

The prepared spiroketals were obtained as stable crystalline colourless compounds. Generally, the achieved yields were modest and almost constant regardless of the nature of the substituent (20–29%), except for the condensation between salicylaldehyde, 2-aminobenzothiazole and methyl acetoacetate displaying a slightly higher efficiency (36%). By contrast, in most cases the determined stereoselectivities were found to be good to high.

A plausible mechanism for the studied reaction can be envisioned to involve the generation of analogous initial condensation adducts, azomethine **A** and butenone **B** (Scheme 2), which have been proposed as precursors of the aforementioned spiropyrimidine **2**.[2d] Then, the enol form of the constituent **B** attacks the aldimine **A** forming intermediate **C** via a Mannich-like process. The postulated dihydroxy ketone structure **C**, being similar to the widely used building blocks for the spiroketal synthesis,[1] undergoes subsequent dehydrative cyclization to yield the desired spiro derivative **8**. It is noteworthy that the two feasible intervening carboxonium ions, **D** and **D′**, originating from both phenolic hydroxyl functionalities, can be implicated in the spiroketalization (Scheme 2). Interestingly, although the formation of the species **D** by more nucleophilic aminobenzyl phenol in **C′** should be favoured, the final S_N1 closure[5] might also occur through the alternative pyrylium cation **D′** considering its aromatic character and hence an inherent higher thermodynamic stability. Indeed, the significant energy difference of 15.1 kcal/mol between both carboxonium intermediates was obtained by using ab initio MP2/6-31G(d)//HF/6-31G(d) calculations. Recently similar mechanisms have also been described by research groups of Zhu[6] and Pyne[7] to explain the formation of related amino substituted spiroketal structures.

Theoretically, the spiroketalization sequence might also occur via initial formation of a chromenylium structure **E** (Scheme 2) whose acidic methyl group would then add to the aldimine **A**. Nevertheless, this route can be ruled out since the condensation between salicyladehyde and β-ketoesters to the ion **E** requires a strong acid medium ($HClO_4$/HOAc/Ac_2O).[8]

It was somewhat surprising that the opposite isomer **6′h** significantly prevailed over isomer **6h**, which typically predominates. Nevertheless, this dramatic change in the diastereoselectivity may be due to hydrogen bonding between the NH group and the two available adjacent acceptors, the O-1′ atom along with the OMe oxygen situated on the C-8′. This so-called bifurcated hydrogen



Scheme 2. Plausible spirocyclization mechanism leading to compound **8**.

bond was characterized by the bond lengths and angles, NH···O-1′: 2.163 Å, 121.1°; NH···OMe-8′: 2.449Å, 169.6°, and is believed to be a medium strength hydrogen bond.[9] Consequently, the observed hydrogen bond could be capable of steering the reaction towards formation of 'anomalous' diastereomer **6′h**. It seems therefore likely that **6′h** is a product of thermodynamic control. Likewise, ab initio MP2/6-31G(d)//HF/6-31G(d) calculations predicted the structure **6′h** to be more stable than its counterpart **6h** (ΔE_{rel}=−5.9 kcal/mol). Such an energy difference can be attributed to the existence of the bifurcated hydrogen bond in **6′h**. To elucidate the reversed situation when the 'normal' diastereomers predominated, we carried out calculations for a model pair of **8**/**8′**. In this instance the 'anomalous' minor isomer **8′** was found only 1.6 kcal/mol lower in energy than **8** as computed at the same level of theory as above. Although the obtained results support again the thermodynamic preference of the opposite isomer **8′**, the estimated value is, however, not large enough to guarantee its preferential formation. As expected, the diastereomer couple **6a**/**6′a** also showed an analogous energy difference (ΔE_{rel}=−1.7 kcal/mol). Disregarding the thermodynamic stabilities of the products, the observed diastereomeric ratios suggest that the determined stereoselectivities might be the consequence of a kinetically governed process. Correspondingly, treatment with a catalytic amount of HCl in ethanol for 6 days at rt converted **6e** into **6′e**, setting their population at a ratio of 60:40. Thus, the observed slow equilibration towards the opposite isomer was consistent with the kinetic control of the reaction.

Since the formation of the Mannich adduct **C** is not diastereoselective, the resulting stereochemistry must be established only in the course of the spirocyclization. We have therefore presumed that the observed stereoselectivity could be explained by the involvement of the carboxonium intermediate **D**. Its two possible stereochemical models, **D1** and **D2**, possessing *o*-hydroxystyryl and secondary amine groups in an *anti* or *syn* relationship were postulated for final ring closure (Fig. 5). However, due to steric repulsion between these large moieties, the amine functionality

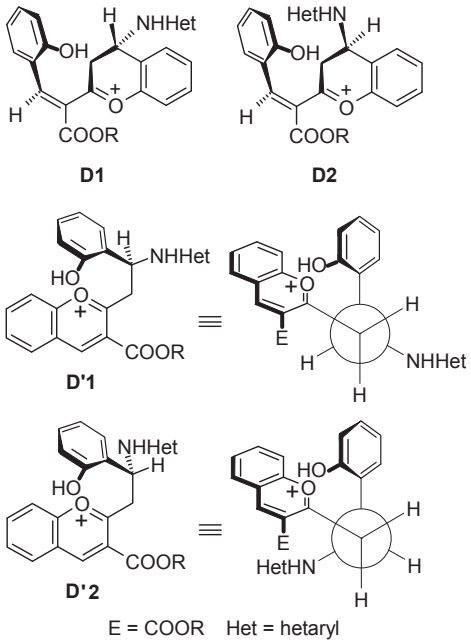


Fig. 5. Transition state conformations leading to spiro products **6** or **8**.

prefers to occupy the opposite face of the forming oxonium ring, thus adopting a more advantageous distal equatorial position as viewed by the **D1** assemblage. This *anti* type configuration of the intermediate satisfies the stereochemistry of the kinetic product **6**. It should be noted that a shorter interatomic distance between the phenolic oxygen and the contiguous amine hydrogen in **D2** (~2.3 Å) enables the O···HN hydrogen bonding. Nevertheless, the benefit arising from the mentioned steric relief overrides the stabilization of the *syn* form by the potential hydrogen bonding. Besides, the oxygen atom involved in hydrogen bonding would certainly become less nucleophilic.

Alternatively, final spirocyclization may also be rationalized in terms of two transition states derived from the carboxonium ion **D′**. Due to a higher conformational freedom, the saturated side chain in **D′** enables the placement of the 2-hydroxyphenyl functionality in a better bonding contact than does the 2-hydroxystyryl moiety in the species **D**. Accordingly, the proposed arrangement **D′1** with a *gauche* positioned chromene and aryl moieties (Fig. 5) is expected to yield the major isomer **6**. On the other hand, pre-transition state conformer **D′2** involving two unfavourable *gauche* interactions should lead to the minor diastereomer **6′**. The steric encumbrance imposed by the position of the oxygen ring and the two vicinal bulky groups makes **D′2** somewhat less favoured than **D′1**. For that reason the reaction channel through **D′1** appears to be the pathway with a lower overall activation energy leading to the dominant kinetic isomer **6**.

3. Conclusion

In summary, we have elucidated the structures of unconventional products formed in the Biginelli-like reaction of salicylaldehydes with alkyl acetoacetates and 2-aminobenzothiazoles or 2-amino-5-methylthiazole. The identified alkyl 4-hetarylamino substituted spiro[chroman-2,2′-chromene]-3′-carboxylates constitute a group of hitherto unreported compounds obtained in the name reaction using salicylaldehyde as an aldehyde component. Formation of these heterocycles contrasts the pyrimidine derivatives produced normally by the Biginelli cyclization. The properly functionalized spiroketals are considered to be valuable bioactive preparates, being primarily suitable for screening as potential Akt inhibitors for cancer treatment.[10]

4. Experimental

4.1. General

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The IR spectra were recorded on a Nicolet Impact 400D spectrophotometer (taken as KBr discs). The NMR spectra were measured in DMSO-d_6 on a Varian VNMRS 600 (for **6a**–**c**, **e**–**h** and **8**) or Varian Unity-Inova 300 (for **6d** and **9**) instruments using TMS as internal standard. The MS (ESI^+) spectrum was obtained on an Agilent 6520 Q-TOF mass spectrometer. Elemental analyses were taken on a Carlo-Erba Elemental Analyzer 1012 apparatus. The X-ray diffraction data were collected on an Oxford Diffraction Xcalibur (Ruby, Gemi) diffractometer.

4.2. General procedure for the synthesis of spiroketal derivatives 6 and 8

To a solution of amine **4** or **5** (4.0 mmol) in dry EtOH (15 mL) were added alkyl acetoacetate **3** (4.0 mmol) and aldehyde **1** (8.0 mmol). The mixture containing four drops of concd HCl was refluxed for 14–17 h until the completion of reaction was confirmed by TLC. While compound **6a** precipitated during the reaction, the other products crystallized after removal of the solvent and trituration of an oily residue with a small volume of MeCN. The by-products **7b**, **7c**, **9**, **10**[2d] and another crop of spiroketals were isolated from the filtrate upon standing. The crude spiro products were then recrystallized from MeCN (dioxane for **6′h**) to give pure diastereomer as white crystalline solids.

4.2.1. Methyl (2R,4R*)-4-(benzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6a**).* Yield 36%; mp 235–237 °C; IR: ν_{max} 1716, 1612, 1575, 1450, 1207, 1191, 1032, 753 cm^{-1}; ^1H NMR: δ 2.77 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.22 (t, 1H, J=13.2 Hz, H_b-3), 3.78 (s, 3H, OMe), 5.80–5.86 (m, 1H, H-4), 6.73 (d, 1H, J=8.4 Hz, H-8), 7.00 (d, 1H, J=8.4 Hz, H-8′), 7.01 (t, 1H, J=8.4 Hz, H-6), 7.06 (t, 1H, J=7.8 Hz, H-6″), 7.13 (t, 1H, J=8.4 Hz, H-6′), 7.18 (t, 1H, J=8.4 Hz, H-7), 7.25 (t, 1H, J=7.8 Hz, H-5″), 7.38–7.42 (m, 2H, H-5 and H-7′), 7.45 (d, 1H, J=7.8 Hz, H-4″), 7.61 (d, 1H, J=8.4 Hz, H-5′), 7.72 (d, 1H, J=7.8 Hz, H-7″), 8.01 (s, 1H, H-4′), 8.57 (d, 1H, J=9.0 Hz, NH); ^{13}C NMR: δ 34.2 (CH_2), 45.8 (CH), 52.0 (OMe), 98.1 (C-2 spiro), 116.3 (CH-8′), 116.6 (CH-8), 118.2 (CH-4″), 118.8 (C-4′a), 121.0 (CH-7″), 121.2 (CH-6″), 121.7 (CH-6), 122.6 (CH-6′), 122.7 (C-3′), 123.9 (C-4a), 125.6 (CH-5″), 126.8 (CH-5), 128.9 (CH-7), 129.4 (CH-5′), 130.4 (C-7″a), 132.9 (CH-7′), 136.3 (CH-4′), 150.9 (C-8a), 151.0 (C-8′a), 152.3 (C-3″a), 164.0 (COO), 166.3 (C-2″); ESI MS: (m/z) 1009 $[2M+DMSO+NH_4+H]^{2+}$, 913 $[2M+H]^+$, 457 $[M+H]^+$. Anal. Calcd for $C_{26}H_{20}N_2O_4S$ (456.52): C, 68.41; H, 4.42; N, 6.14%. Found: C, 68.28; H, 4.20; N, 6.33%.

4.2.2. Methyl (2R,4R*)-4-(6-methoxybenzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6b**).* Yield 24%; mp 232–233 °C; IR: ν_{max} 1711, 1615, 1471, 1216, 1187, 1030, 928, 881, 753 cm^{-1}; ^1H NMR: δ 2.75 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.19 (t, 1H, J=13.2 Hz, H_b-3), 3.75 (s, 3H, OMe), 3.78 (s, 3H, ester OMe), 5.74–5.80 (m, 1H, H-4), 6.71 (dd, 1H, J=7.8, 1.2 Hz, H-8), 6.85 (dd, J=7.8, 1.8 Hz, H-5″), 7.00 (dd, 1H, J=7.8, 1.8 Hz, H-8′), 7.01 (dt, 1H, J=7.8, 1.2 Hz, H-6), 7.13 (dt, 1H, J=7.8, 1.8 Hz, H-6′), 7.17 (t, 1H, J=7.8 Hz, H-7), 7.35 (d, 1H, J=7.8 Hz, H-4″), 7.36 (d, 1H, J=1.8 Hz, H-7″), 7.38–7.41 (m, 2H, H-5 and H-7′), 7.61 (dd, 1H, J=7.8, 1.8 Hz, H-5′), 8.01 (s, 1H, H-4′), 8.34 (d, 1H, J=9.0 Hz, NH); ^{13}C NMR: δ 34.3 (CH_2), 45.7 (CH), 52.1 (ester OMe), 55.6 (OMe), 98.1 (C-2 spiro), 105.7 (CH-7″), 113.1 (CH-5″), 116.4 (CH-8′), 116.6 (CH-8), 118.6 (CH-4″), 118.8 (C-4′a), 121.7 (CH-6), 122.6 (C-3′), 122.7 (CH-6′), 124.1 (C-4a), 126.9 (CH-5), 128.9 (CH-7), 129.5 (CH-5′), 131.5 (C-7″a), 132.9 (CH-7′), 136.3 (CH-4′), 146.4 (C-3″a), 150.9 (C-8a), 151.0 (C-8′a), 154.5 (C-6″), 164.0 (COO), 164.7 (C-2″). Anal. Calcd for $C_{27}H_{22}N_2O_5S$ (486.54): C, 66.65; H, 4.56; N, 5.76%. Found: C, 66.38; H, 4.42; N, 5.93%.

4.2.3. Methyl (2R,4R*)-4-(6-methylbenzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6c**).* Yield 22%; mp 224–227 °C; IR: ν_{max} 1708, 1594, 1537, 1445, 1219, 1111, 1030, 884, 758 cm^{-1}; ^1H NMR: δ 2.33 (s, 3H, Me), 2.75 (dd, 1H, J=12.6, 6.0 Hz, H_a-3), 3.19 (t, 1H, J=12.6 Hz, H_b-3), 3.78 (s, 3H, OMe), 5.76–5.82 (m, 1H, H-4), 6.72 (dd, 1H, J=7.8, 1.8 Hz, H-8), 7.00 (dt, 1H, J=7.8, 1.8 Hz, H-6), 7.01 (d, 1H, J=7.8 Hz, H-8′), 7.06 (d, 1H, J=7.8 Hz, H-5″), 7.13 (t, 1H, J=7.8 Hz, H-6′), 7.17 (t, 1H, J=7.8 Hz, H-7), 7.33 (d, 1H, J=7.8 Hz, H-4″), 7.39 (d, 1H, J=7.8 Hz, H-5), 7.40 (dt, 1H, J=7.8, 1.8 Hz, H-7′), 7.52 (s, 1H, H-7″), 7.61 (dd, 1H, J=7.8, 1.8 Hz, H-5′), 8.01 (s, 1H, H-4′), 8.44 (d, 1H, J=8.4 Hz, NH); ^{13}C NMR: δ 20.7 (Me), 34.3 (CH_2), 45.7 (CH), 52.0 (ester OMe), 98.1 (C-2 spiro), 116.4 (CH-8′), 116.6 (CH-8), 117.9 (CH-4″), 118.8 (C-4′a), 120.9 (CH-7″), 121.7 (CH-6), 122.6 (C-3′), 122.7 (CH-6′), 124.0 (C-4a), 126.6 (CH-5″), 126.9 (CH-5), 128.9 (CH-7), 129.4 (CH-5′), 130.3 (C-6″), 130.5 (C-7″a), 132.9 (CH-7′), 136.2 (CH-4′), 150.2 (C-3″a), 150.9 (C-8a), 151.0 (C-8′a), 164.0 (COO), 165.6 (C-2″). Anal. Calcd for $C_{27}H_{22}N_2O_4S$ (470.54): C, 68.92; H, 4.71; N, 5.95%. Found: C, 69.19; H, 4.52; N, 5.77%.

4.2.4. Methyl (2R,4R*)-4-(6-chlorobenzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6d**).* Yield 21%; mp

214–215 °C; IR: ν_{max} 1716, 1614, 1465, 1212, 1194, 1024, 926, 886, 753 cm^{-1}; ^1H NMR: δ 2.77 (dd, 1H, J=12.9, 6.0 Hz, H_a-3), 3.20 (t, 1H, J=12.9 Hz, H_b-3), 3.78 (s, 3H, OMe), 5.75–5.85 (m, 1H, H-4), 6.72 (d, 1H, J=8.1 Hz, H-8), 6.97–7.50 (m, 8H, H_{ar}), 7.61 (d, 1H, J=7.5 Hz, H-5′), 7.78 (d, 1H, J=2.1 Hz, H-7″), 8.01 (s, 1H, H-4′), 8.73 (d, 1H, J=8.7 Hz, NH). Anal. Calcd for $C_{26}H_{19}ClN_2O_4S$ (490.96): C, 63.61; H, 3.90; N, 5.71%. Found: C, 63.30; H, 4.21; N, 6.00%.

4.2.5. Isopropyl (2R,4R*)-4-(benzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6e**).* Yield 29%; mp 210–212 °C; IR: ν_{max} 1707, 1604, 1573, 1456, 1445, 1207, 1193, 1099, 1014, 918, 887, 753 cm^{-1}; ^1H NMR: δ 1.27 (d, 3H, J=6.6 Hz, Me), 1.30 (d, 3H, J=6.6 Hz, Me), 2.75 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.21 (t, 1H, J=13.2 Hz, H_b-3), 5.04 (sep, 1H, J=6.6 Hz, OCH), 5.78–5.84 (m, 1H, H-4), 6.73 (dd, 1H, J=8.4, 1.2 Hz, H-8), 6.99 (dd, 1H, J=7.8, 1.8 Hz, H-8′), 7.00 (dt, 1H, J=8.4, 1.2 Hz, H-6), 7.06 (dt, 1H, J=7.8, 1.2 Hz, H-6″), 7.13 (dt, 1H, J=7.8, 1.8 Hz, H-6′), 7.17 (dt, 1H, J=8.4, 1.2 Hz, H-7), 7.25 (dt, 1H, J=7.8, 1.2 Hz, H-5″), 7.38 (dd, 1H, J=8.4, 1.2 Hz, H-5), 7.39 (dt, 1H, J=7.8, 1.8 Hz, H-7′), 7.45 (dd, 1H, J=7.8, 1.2 Hz, H-4″), 7.61 (dd, 1H, J=7.8, 1.8 Hz, H-5′), 7.72 (dd, 1H, J=7.8, 1.2 Hz, H-7″), 7.94 (s, 1H, H-4′), 8.57 (d, 1H, J=8.7 Hz, NH); ^{13}C NMR: δ 21.5 (Me), 21.6 (Me), 34.3 (CH_2), 45.8 (CH), 68.3 (OCH), 98.2 (C-2 spiro), 116.3 (CH-8′), 116.6 (CH-8), 118.2 (CH-4″), 118.8 (C-4′a), 121.0 (CH-7″), 121.2 (CH-6″), 121.7 (CH-6), 122.7 (CH-6′), 123.2 (C-3′), 123.9 (C-4a), 125.6 (CH-5″), 126.8 (CH-5), 128.9 (CH-7), 129.4 (CH-5′), 130.4 (C-7″a), 132.7 (CH-7′), 135.7 (CH-4′), 150.9 (C-8a), 151.0 (C-8′a), 152.3 (C-3″a), 163.0 (COO), 166.3 (C-2‴). Anal. Calcd for $C_{28}H_{24}N_2O_4S$ (484.57): C, 69.40; H, 5.00; N, 5.78%. Found: C, 69.33; H, 4.90; N, 5.73%.

4.2.6. 2-Methoxyethyl (2R,4R*)-4-(benzothiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**6f**).* Yield 20%; mp 186–187 °C; IR: ν_{max} 1708, 1607, 1573, 1485, 1447, 1210, 1190, 1163, 1131, 1060, 1003, 916, 885, 752 cm^{-1}; ^1H NMR: δ 2.77 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.22 (t, 1H, J=13.2 Hz, H_b-3), 3.28 (s, 3H, OMe), 3.62 (t, 2H, J=4.8 Hz, CH_2OMe), 4.29–4.33 (m, 2H, OCH_2), 5.79–5.86 (m, 1H, H-4), 6.72 (d, 1H, J=8.4 Hz, H-8), 7.00 (d, 1H, J=7.8 Hz, H-8′), 7.01 (t, 1H, J=8.4 Hz, H-6), 7.06 (t, 1H, J=7.8 Hz, H-6″), 7.13 (t, 1H, J=7.8 Hz, H-6′), 7.17 (t, 1H, J=8.4 Hz, H-7), 7.25 (t, 1H, J=7.8 Hz, H-5″), 7.40 (d, 1H, J=8.4 Hz, H-5), 7.41 (t, 1H, J=7.8 Hz, H-7′), 7.46 (d, 1H, J=7.8 Hz, H-4″), 7.63 (d, 1H, J=7.8 Hz, H-5′), 7.72 (d, 1H, J=7.8 Hz, H-7″), 7.98 (s, 1H, H-4′), 8.57 (d, 1H, J=9.0 Hz, NH); ^{13}C NMR: δ 34.2 (CH_2), 45.8 (CH), 58.1 (OMe), 63.8 (OCH_2), 69.6 (CH_2OMe), 98.2 (C-2 spiro), 116.4 (CH-8′), 116.6 (CH-8), 118.2 (CH-4″), 118.8 (C-4′a), 121.0 (CH-7″), 121.2 (CH-6″), 121.7 (CH-6), 122.6 (C-3′), 122.7 (CH-6′), 123.9 (C-4a), 125.6 (CH-5″), 126.8 (CH-5), 128.9 (CH-7), 129.5 (CH-5′), 130.4 (C-7″a), 132.9 (CH-7′), 136.2 (CH-4′), 150.9 (C-8a), 151.0 (C-8′a), 152.3 (C-3″a), 163.4 (COO), 166.3 (C-2″). Anal. Calcd for $C_{28}H_{24}N_2O_5S$ (500.57): C, 67.19; H, 4.83; N, 5.60%. Found: C, 67.31; H, 4.93; N, 5.67%.

4.2.7. Methyl (2R,4R*)-4-(benzothiazol-2-ylamino)-6,6′-dibromospiro[chroman-2,2′-chromene]-3′-carboxylate (**6g**).* Yield 20%; mp 243–245 °C; IR: ν_{max} 1717, 1604, 1562, 1474, 1447, 1265, 1209, 1198, 1114, 1023, 926, 901, 888, 817, 755 cm^{-1}; ^1H NMR: δ 2.80 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.17 (t, 1H, J=13.2 Hz, H_b-3), 3.78 (s, 3H, OMe), 5.74–5.85 (m, 1H, H-4), 6.73 (d, 1H, J=8.7 Hz, H-8), 7.01 (d, 1H, J=8.7 Hz, H-8′), 7.07 (t, 1H, J=7.8 Hz, H-6″), 7.26 (t, 1H, J=7.8 Hz, H-5″), 7.35 (dd, 1H, J=8.7 and 2.1 Hz, H-7), 7.46 (d, 1H, J=7.8 Hz, H-4″), 7.48 (d, 1H, J=2.1 Hz, H-5), 7.54 (dd, 1H, J=8.7 and 2.1 Hz, H-7′), 7.72 (d, 1H, J=7.8 Hz, H-7″), 7.86 (d, 1H, J=2.1 Hz, H-5′), 8.00 (s, 1H, H-4′), 8.60 (d, 1H, J=8.7 Hz, NH); ^{13}C NMR: δ 33.7 (CH_2), 45.6 (CH), 52.3 (OMe), 98.4 (C-2 spiro), 113.5 and 114.2 (C-6/C-6′), 118.4 (CH-4″), 118.8 (CH-8′), 119.2 (CH-8), 120.9 (C-4′a), 121.1 (CH-7″), 121.4 (CH-6″), 123.5 (C-3′), 125.8 (CH-5″), 126.5 (C-4a), 129.3 (CH-5), 130.5 (C-7″a), 131.5 (CH-5′), 131.8 (CH-7), 135.2 (CH-4′ and CH-7′), 149.9 and 150.1 (C-8a/C-8′a), 152.1 (C-3″a), 163.7 (COO), 166.2 (C-2″). Anal. Calcd for $C_{26}H_{18}Br_2N_2O_4S$ (611.94): C, 50.99; H, 2.96; N, 4.58%. Found: C, 50.74; H, 3.23; N, 4.77%.

4.2.8. Methyl (2R,4S*)-4-(benzothiazol-2-ylamino)-8,8′-dimethoxyspiro[chroman-2,2′-chromene]-3′-carboxylate (**6′h**).* Yield 20%; mp 231–232 °C; IR: ν_{max} 3385, 1715, 1541, 1481, 1459, 1441, 1265, 1203, 1188, 1109, 1028, 977, 947, 782, 757 cm^{-1}; ^1H NMR: δ 2.67 (dd, 1H, J=15.0, 3.0 Hz, H_a-3), 3.37 (overlapped by HDO signal, H_b-3), 3.61 (s, 3H, 8-OMe), 3.79 (s, 3H, ester OMe), 3.86 (s, 3H, 8′-OMe), 5.59–5.63 (m, 1H, H-4), 6.91 (dd, 1H, J=7.8, 1.2 Hz, H-7), 6.95 (t, 1H, J=7.8 Hz, H-6), 7.07 (t, 1H, J=7.8 Hz, H-6′), 7.08 (t, 1H, J=7.8 Hz, H-6″), 7.13 (dd, 1H, J=7.8, 1.2 Hz, H-5), 7.18 (d, 1H, J=7.8 Hz, H-7′), 7.21 (d, 1H, J=7.8 Hz, H-5′), 7.28 (t, 1H, J=7.8 Hz, H-5″), 7.50 (d, 1H, J=7.8 Hz, H-4″), 7.56 (d, 1H, J=9.6 Hz, NH), 7.72 (d, 1H, J=7.8 Hz, H-7″), 7.99 (s, 1H, H-4′); ^{13}C NMR: δ 34.6 (CH_2), 46.4 (CH), 52.1 (ester OMe), 55.5 (8-OMe), 56.2 (8′-OMe), 98.7 (C-2 spiro), 112.0 (CH-7), 115.4 (CH-7′), 118.5 (C-4′a and CH-4″), 120.5 (CH-5), 121.07 (CH-5′), 121.13 (CH-7″), 121.5 (CH-6″), 121.8 (CH-6), 122.4 (CH-6′), 122.5 (C-3′), 124.1 (C-4a), 125.8 (CH-5″), 130.1 (C-7″a), 136.1 (CH-4′), 139.7 (C-8′a), 139.8 (C-8a), 147.0 (C-8′), 148.3 (C-8) 152.4 (C-3″a), 164.0 (COO), 165.3 (C-2″). Anal. Calcd for $C_{28}H_{24}N_2O_6S$ (516.14): C, 65.10; H, 4.69; N, 5.43%. Found: C, 65.34; H, 4.43; N, 5.67%.

4.2.9. Methyl (2R,4R*)-4-(5-methylthiazol-2-ylamino)spiro[chroman-2,2′-chromene]-3′-carboxylate (**8**).* Yield 21%; mp 216–217 °C; IR: ν_{max} 1717, 1593, 1484, 1448, 1293, 1207, 1135, 1113, 1091, 1035, 1028, 995, 948, 886, 770, 757 cm^{-1}; ^1H NMR: δ 2.34 (d, 1H, J=1.2 Hz, Me), 2.66 (dd, 1H, J=13.2, 6.0 Hz, H_a-3), 3.12 (t, 1H, J=13.2 Hz, H_b-3), 3.77 (s, 3H, OMe), 5.52–5.62 (m, 1H, H-4), 6.69 (dd, 1H, J=7.8, 1.2 Hz, H-8), 6.72 (d, 1H, J=1.2 Hz, H-4″), 6.96 (dd, 1H, J=7.8, 1.2 Hz, H-8′), 6.99 (dt, 1H, J=7.8, 1.2 Hz, H-6), 7.11 (dt, 1H, J=7.8, 1.2 Hz, H-6′), 7.15 (t, 1H, J=7.8 Hz, H-7), 7.37 (dt, J=7.8, 1.2 Hz, H-7′), 7.38 (d, 1H, J=7.8 Hz, H-5), 7.59 (dd, 1H, J=7.8, 1.2 Hz, H-5′), 7.84 (d, 1H, J=9.0 Hz, NH), 7.98 (s, 1H, H-4′); ^{13}C NMR: δ 12.2 (Me), 34.9 (CH_2), 46.1 (CH), 52.6 (OMe), 98.8 (C-2 spiro), 116.9 (CH-8′), 117.1 (CH-8), 119.4 (C-4′a), 120.4 (C-5″), 122.1 (CH-6), 123.2 (CH-6′), 123.3 (C-4a), 125.3 (C-3′), 127.4 (CH-5), 129.2 (CH-7), 130.0 (CH-5′), 133.4 (CH-7′), 135.9 (CH-4″), 136.7 (CH-4′), 151.5 (C-8a), 151.6 (C-8′a), 164.6 (COO), 167.9 (C-2″). Anal. Calcd for $C_{23}H_{20}N_2O_4S$ (420.48): C, 65.70; H, 4.79; N, 6.66%. Found: C, 65.78; H, 4.82; N, 6.73%.

4.2.10. Isopropyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**9**).* Yield 6%; mp 145–146 °C (toluene); IR: ν_{max} 3304, 1709, 1558, 1447, 1249, 1179, 1102, 926, 753 cm^{-1}; ^1H NMR: δ 1.04 (d, 3H, J=6.0 Hz, Me), 1.11 (d, 3H, J=6.0 Hz, Me), 1.61 (s, 3H, Me-2), 2.94 (d, 1H, J=12.0 Hz, H-3), 4.91 (sep, 1H, J=6.0 Hz, OCH), 5.68–5.78 (m, 1H, H-4), 6.78 (d, 1H, J=7.8 Hz, H-8), 6.88 (t, 1H, J=7.8 Hz, H-6), 7.05 (t, 1H, J=7.8 Hz, H-6′), 7.06 (br s, 1H, OH), 7.16 (t, 1H, J=7.8 Hz, H-7), 7.21 (d, 1H, J=7.8 Hz, H-5), 7.25 (t, 1H, J=7.8 Hz, H-5′), 7.42 (d, 1H, J=7.8 Hz, H-4′), 7.69 (d, 1H, J=7.8 Hz, H-7′), 8.41 (d, 1H, J=9.0 Hz, NH); ^{13}C NMR: δ 21.2 (Me), 21.5 (Me), 27.0 (Me-2), 49.5 (CH-4), 53.7 (CH-3), 67.7 (OCH), 97.0 (C-2), 116.5 (CH-8), 118.2 (CH-4′), 120.7 (CH-6), 120.9 (CH-7′), 121.1 (CH-6′), 123.9 (C-4a), 125.6 (CH-5′), 126.8 (CH-5), 128.5 (CH-7), 130.3 (C-7′a), 151.2 and 152.5 (C-8a/C-3′a), 168.8 (COO), N–C–S(=N) not observed. Anal. Calcd for $C_{21}H_{22}N_2O_4S$ (398.13): C, 63.30; H, 5.57; N, 7.03%. Found: C, 63.09; H, 5.34; N, 7.22%.

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