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Three-component reaction and organocatalysis in one: synthesis of densely substituted 4-aminochromanes

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ABSTRACT

Cyclocondensation of salicylaldehydes with alkyl acetoacetates and 2-aminobenzothiazoles or 2-aminothiadiazole/thiazoles under L-proline catalysis gives 4-hetarylamino substituted chromanecarboxylate derivatives. The mechanism involving the Mannich/hemiketalization cascade reaction and the observed stereoselectivity of the three component process are discussed.

1. Introduction

The chromane skeleton represents a key structural unit found in a plethora of natural products like flavans and isoflavans.[1] This privileged heterocyclic entity is also an essential feature of more complex compounds including vitamin E, tocopherols and cannabinoids.[2] Among the numerous types of bioactive functionalized chromanes,[3] the 4-amino derivatives have received unusual interest because of their ability to act as ATP-sensitive potassium channel openers.[4] Cromakalim (**1**, Fig. 1) being a lead compound of K_{ATP} activators has had a pivotal influence in the development of new promising cardioprotective agents for myocardial ischemia.[5] Moreover, potassium channels have become attractive pharmacological targets for novel therapeutic strategies in the treatment of hypertension, asthma, urinary incontinence, epilepsy and certain neurodegenerative diseases, glaucoma and diabetes.[5]

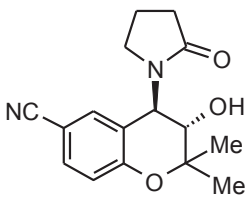

Fig. 1. Pharmacologically valuable cromakalim **1**.

Most of synthetic approaches to the 4-aminochromane framework involve reactions between *o*-hydroxybenzaldimines and electron-rich cyclic or open-chain alkenes catalyzed by several Lewis[6] and Brønsted[7] acids. An alternative route making use of salicylaldehyde Schiff bases consists in their $Sc(OTf)_3$ promoted cyclization with 2,2-dimethoxypropane.[8] Besides, an intramolecular etherification of bromo substituted β-aminoalcohols mediated by CuI/8-hydroxyquinoline constitutes an another preparative protocol.[9] Notably, an adaption of the established imine method for chiral organocatalysts and complexes has permitted development of an enantioselective entry to this molecular architecture.[10]

Recently we have found[11] that the cyclocondensation of salicylaldehydes **2** with alkyl acetoacetates **3** and 2-aminobenzothiazoles **4** or 2-amino-5-methylthiazole **5b** under classical Biginelli reaction conditions (concd HCl catalysis) gave hetarylamino substituted spiroketals **6** (Fig. 2) instead of the expected pyrimidine[12a,b] or oxygen-bridged pyrimidine scaffold.[12a,c] In one case we succeeded in identifying a minor chromane by-product (namely **7b**,

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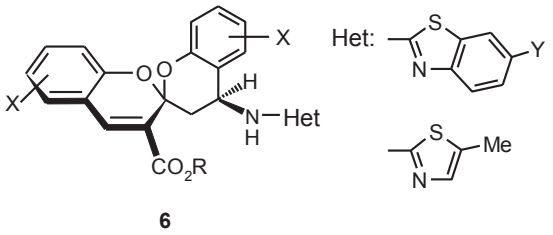
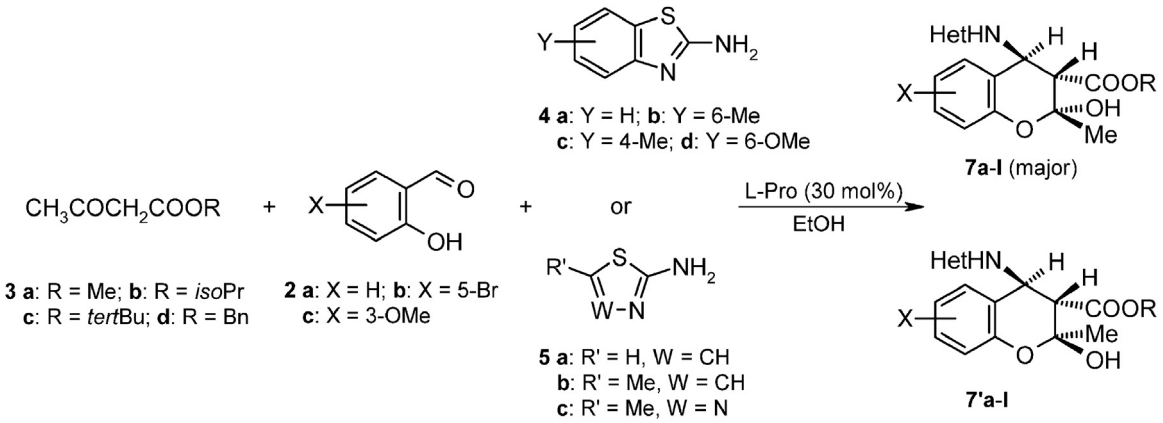
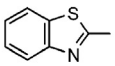
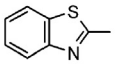
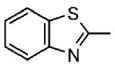
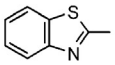
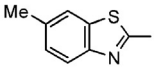
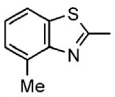
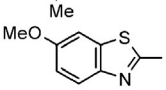
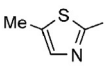
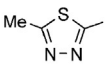
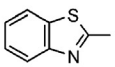
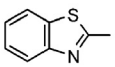


6

Fig. 2. Spirobischromane product formed under Biginelli conditions.

Scheme 1).[11] It was therefore of interest to study whether a modification of the above experimental procedure might affect the reaction outcome. The widely used organocatalysis by L-proline in diverse multicomponent processes[13] prompted us to examine this amino acid as a promoter for the previously studied transformation. In pursuing our work on the conformationally restricted heterocycles,[11,12] we report here a practical one-pot synthesis of highly substituted 4-aminochromanes. Generally, in this case construction of these bicyclic molecules involves the formation of three new bonds (one C–C, one C–N, and one C–O) and three consecutive stereocenters in one synthetic step.



Product	R	X	Het	Yield[a] [%]	dr[b]
7/7'a	Me	H		45	77:23
7/7'b	*iso*Pr	H		71	82:18
7/7'c	*tert*Bu	H		69	84:16
7/7'd	Bn	H		50	86:14
7/7'e	*tert*Bu	H		57	85:15
7/7'f	*tert*Bu	H		78	84:16
7/7'g	*tert*Bu	H		42	77:23
7/7'h	*tert*Bu	H		53	75:25
7/7'i	*tert*Bu	H		70	80:20
7/7'j	*tert*Bu	H		50	80:20
7/7'k	*tert*Bu	6-Br		63	82:18
7/7'l	*tert*Bu	8-OMe		58	80:20

[a] Isolated yield.

[b] Determined by ^{1}H NMR of the crude product.

Scheme 1. L-Proline catalyzed three-component reaction.

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2. Results and discussion

At the outset of our work, we reacted salicylaldehyde **2a**, methyl acetoacetate **3a** and 2-aminobenzothiazole **4a** as the model compounds at the same molar ratio (2:1:1) used for the spiroketalization mentioned above.[11] Unfortunately, refluxing ethanolic solution of the substrates in the presence of 15 mol % L-proline resulted in substantial decomposition progressing with the time of heating. However, when the mixture was stirred at ambient temperature for a prolonged time period, a white solid could be isolated through filtration. Its ^{1}H NMR spectrum closely resembled to that of the foregoing aminochromane **7b**, and, hence, the product structure must correspond to the methyl ester analogue **7a**. In addition, elemental analysis data for the isolated substance showed satisfactory agreement with the empirical formula of $C_{19}H_{18}N_2O_4S$ corresponding to derivative **7a**, thereby confirming equimolar ternary adduct formation in this organocatalytic three-component cyclization. A control experiment indicated that no cyclization proceeded in the absence of the catalyst. To identify the optimal conditions, several different solvents, catalyst loading and reaction times were evaluated (Table 1). Taken together, the screening attempts revealed that using 30 mol % charge of L-proline in ethanol for 45 h afforded the desired compound in an improved yield of 45%. According to the ^{1}H NMR spectrum, particularly due to differentiated doublets of H-3 ($\Delta\delta$ 0.15 ppm), the obtained product was a mixture of two diastereomers **7a** and **7′a** in a 77:23 ratio (Scheme 1). Regarding other reaction media, DMF and DMSO also functioned well, although they showed certain drawbacks due to slightly lower yields and a more complicated work-up procedure (Table 1). Surprisingly, the same three-component condensation reaction did not take place in acetonitrile, while a 1:1 proton-transfer compound **8** of the catalyst and amine substrate **4a** was formed. Based on the ^{1}H NMR spectrum, and in agreement with an earlier experimental study on dissociation constants of substituted 2-aminobenzothiazoles,[14] the protonation by the proline carboxylic group is believed to occur on the ring nitrogen atom (Fig. 3). The fact that an equimolar mixture of the two constituents alone underwent conversion to prolinate **8** in essentially quantitative yield (85%), may be seen as a proof of the observed transformation. Moreover, a similar proton-transfer process between 2-amino-6-methylbenzothiazole and dipicolinic acid has recently been described.[15] With regard to the proline behavior, our literature survey revealed in this context only an article referring to in situ generation of triethylammonium prolinate.[16] Curiously enough, according to a database search 2-aminobenzothiazol-3-ium prolinate **8** proves to be the first isolated and characterized 1:1 proton-transfer derivative in the proline family.

Table 1
Reaction optimization for the synthesis of **7**/**7′a**

Entry	Solvent	L-Proline [mol %]	Time [h]	Isolated yield [%]
1	EtOH	15	25	26
2	EtOH	25	25	31
3	EtOH	30	25	34
4	EtOH	30	30	38
5	EtOH	30	35	42
6	EtOH	30	45	45
7	DMF	30	45	32
8	DMSO	30	45	35

With the optimized conditions in hand, we first explored the scope of the reaction with various acetoacetates. The isopropyl (**3b**), *tert*-butyl (**3c**) and benzyl (**3d**) esters produced the corresponding aminochromanes **7** and **7′** in good yields (50–71%). The determined diastereomeric ratio (dr) values (**7b**/**7′b** 82:18, **7c**/**7′c** 84:16, **7d**/**7′d** 86:14) which are slightly higher than that for the methyl derivative reflect the bulkiness of the alcohol moieties.

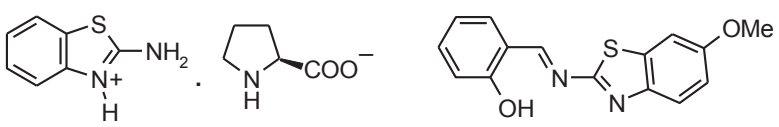
Next, the synthetic utility of the studied heterocyclization was tested by modifying the amine component while the salicylaldehyde (**2a**) and *tert*-butyl 3-oxobutanoate (**3c**) input was fixed. As shown in Scheme 1, we were successful in converting both selected 2-aminobenzothiazoles **4b**–**d**, two 2-aminothiazoles **5a**,**b** as well as 2-amino-5-methylthiadiazole **5c** to the desired chromanes **7e**–**j** in moderate to good yields (42–78%) with average drs of 80:20. Nevertheless, the cyclocondensation with 2-amino-6-methoxybenzothiazole **4d** proceeded very slowly and a small quantity of the unreacted intermediary azomethine **9**[11] (Fig. 3) was isolated even after 7 days.

On the other hand, the employment of salicylaldehydes **2b**,**c** enabled us to install a substituent onto the benzene ring of the chromane skeleton in the products **7k**,**l** (Scheme 1).

As to the minor isomer **7′**, we suppose that it differs from **7** only in the configuration at C-2 while their relative stereochemistry between the C-3 and C-4 positions remained intact. This finding relies on the similar vicinal coupling constants $J_{H\text{-}3,H\text{-}4}$, the values of which for the H-3 doublet signal amount to 12 Hz in **7** and to 9.6–10.5 Hz in **7′**, respectively. Since such $J_{H,H}$ magnitudes correspond obviously to a *trans*-diaxial relationship of H-3 and H-4 in both cases, the diastereomers **7** and **7′** must possess an opposite configuration at the stereogenic C-2 atom.

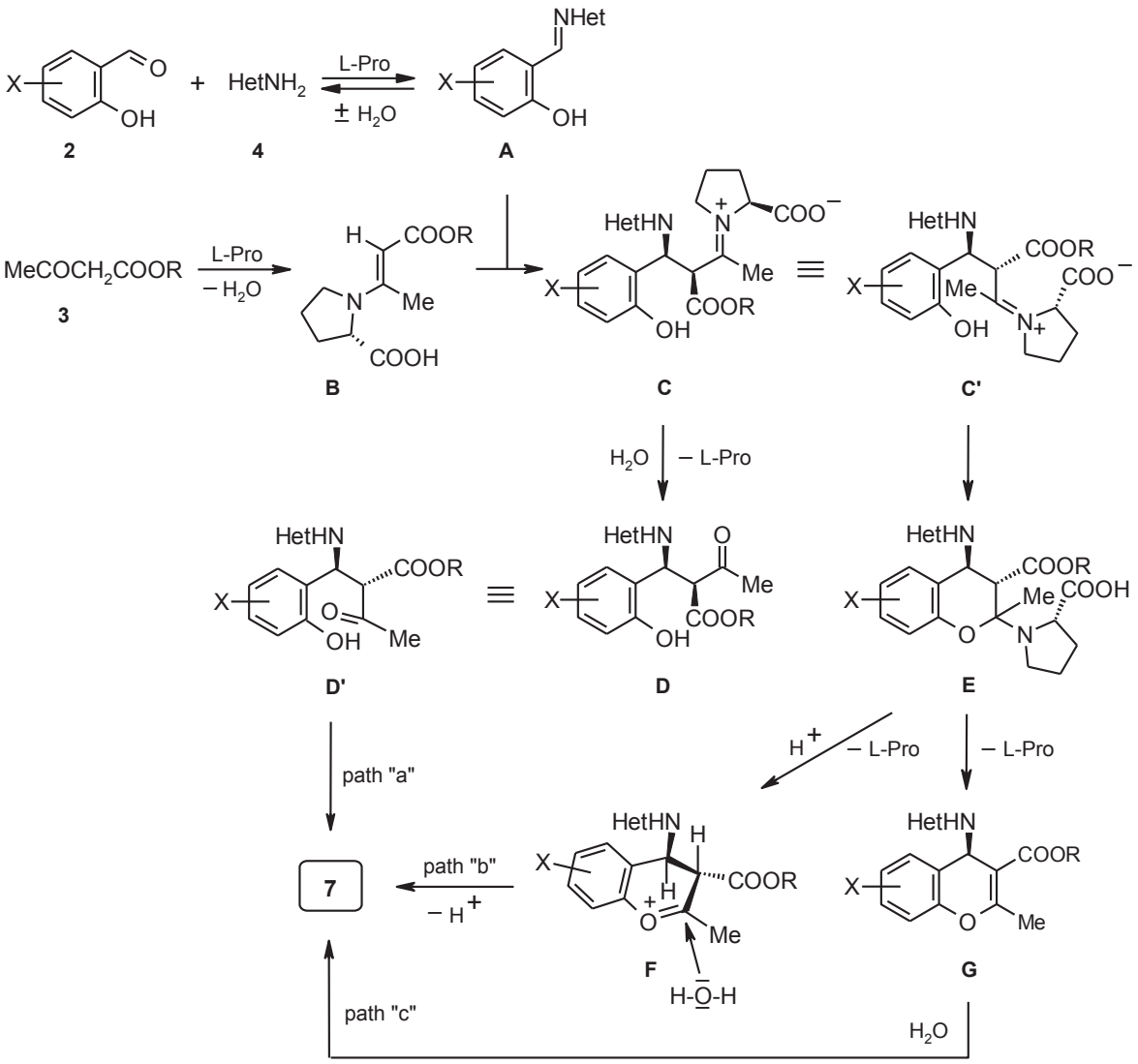
During the course of this work, we attempted to dehydrate the crude 2-hydroxychromane **7b**/**7′b** by a treatment with *p*-TosOH (25 mol %). Interestingly, instead of the expected water elimination a conversion to single diastereomer **7b** occurred (dr=95:5) under prolonged stirring of ethanolic or acetone solution at room temperature. The isomerization has been successfully undertaken with all diastereomeric mixtures, except for **7a**/**7′a** and **7i**/**7′i**. In most cases chromanes **7** were isolated in good yields (80–90%) and high purity (dr=95:5).

A plausible mechanism for the studied multicomponent cyclization is outlined in Scheme 2. The reaction pathway commences with the L-proline catalyzed formation of 2-hydroxybenzaldimine **A** from salicylaldehyde **2** and heterocyclic amine **4** or **5**. The condensation is apparently facilitated by activation of the aldehyde carbonyl oxygen via intermolecular hydrogen bonding with the acidic group of the catalyst, since this reaction does not take place in the absence of the L-proline. In contrast, the catalytic aldimine generation represents a fast step because separation of the Schiff base could be observed within a short time. A simultaneously occurring dehydrative condensation between acetoacetate **3** and proline gives β-enamino ester **B** which then adds diastereoselectively to the preformed imine **A** to produce intermediary iminium ion **C**. Its sequential hydrolysis liberates *syn*-Mannich



8 **9**

Fig. 3. Isolated by-products **8** and **9**.



Scheme 2. Plausible mechanisms leading to compound **7**.

adduct **D** with concomitant release of the catalyst molecule. Finally, the key precursor **D** undergoes intramolecular hemiketalization reaction to yield the 4-aminochromane product diastereomers **7** and **7′**. Nevertheless, the stereochemistry observed for the major isomer **7** with an axial hydroxyl group suggests a stereocontrol arising as a consequence of the anomeric effect. This stereoelectronic phenomenon thus favors the formation of the thermodynamically more stable α-lactol form **7**. As to the invoked fundamental stabilizing interaction, its existence in the 2-hydroxy- and 2-alkoxychromanes had long been recognized from NMR conformational analysis of $^{3}J_{HH}$ coupling constants.[17]

The observed *syn*-selectivity can be rationalized in terms of the Houk–List paradigm[18] for the organocatalytic Mannich reaction. In agreement with this concept we postulated a simple stereochemical model that features the proton transfer from proline carboxyl to imine nitrogen along with an additional hydrogen bonding between the phenolic hydroxyl and ester carbonyl oxygen (Fig. 4). The above mentioned intervening non-covalent interactions thus allowed organizing both (*E*)-configurated components into a 15-membered cyclic transition state assembly through an *Si*, *Si* approach.

An alternative plausible pathway can be envisaged to involve, at first, a ring closure of the above intermediate **C** into chromane skeleton **E**, followed by the generation of the cyclic oxocarbenium ion **F** together with proline elimination. The resulting addition of water to the postulated cationic species **F** then leads to the desired anomeric lactols **7** and **7′**. In this case, the preferable formation of isomer **7** can be explained by the axial nucleophilic attack of H_2O on the *Si*-face of the 3,4-dihydrochromenium C-2 center. On the other hand, *Re*-approach to the transient ion **F**, adopting a sofa-like conformation with the C-3 out of plane, would encounter a destabilizing 1,2-diaxial interaction between the incoming water molecule and H-3 atom (Scheme 2). However, in contrast to the recently reported synthesis of 2-alkoxychromenes through trapping of the heteroaromatic 1-benzopyrylium cation with alcohols,[13g,k] our attempts to detect the potential 2-ethoxy-2-methylchromane derivatives in the crude products by NMR spectroscopy failed. In the light of the given facts the mechanistic rationale discussed here appears therefore less probable.

Nevertheless, there is yet another possible pathway from **E** to diastereoisomers **7** and **7′**. It consists in the acidic H-3 hydrogen assisted elimination of proline leading to 4*H*-chromene **G** followed by the final addition of water (Scheme 2). Unfortunately, such an explanation when confronted with a reported competing formation of 2-alkoxy- and hydroxychromenes via similar chromene intermediate,[13l] seems to be rather debatable, too.

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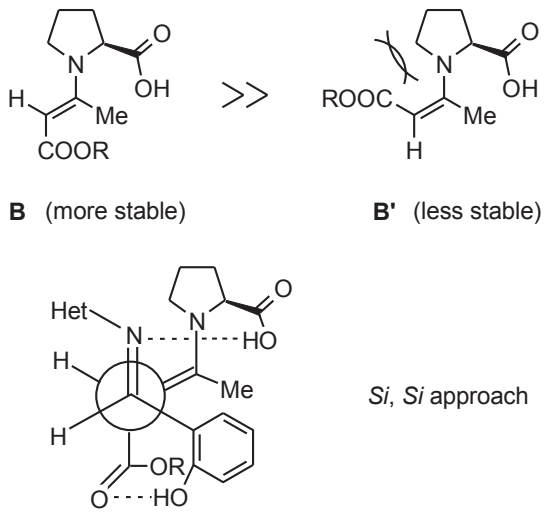

Fig. 4. Transition state structure of the Mannich reaction.

In order to gain a better understanding of the stereochemical aspects of the studied reaction, some obtained chromanes were subjected to isomer stability evaluation. Thus, NMR monitoring of the pure diastereomer **7e** in DMSO-d_6 solution has shown that equilibrium between epimers **7e** and **7′e** was established within about 16 h while the content of both forms corresponded approximately to the composition found in the crude product. The anomeric ratio at equilibrium remained almost unchanged although some decomposition was observed. Accordingly, we conclude that the stereochemical outcome of the reaction is determined by thermodynamic equilibration. This interconversion process between both anomers takes place most probably through the common open-chain form **D** (see Scheme 2). In support of such a structure, an analogous hydroxyketone existing in a fast dynamic equilibrium with 2-methylchroman-2,4-diol can be mentioned.[19]

Apparently, DFT quantum chemical calculations (B3LYP/6-311++G**) carried out on the compound **7c** showed that the major isomer represents the most stable form of the four theoretically possible diastereomers originating from the presence of three stereogenic centers in the molecule. The minor component **7′c** was found to be approximately 2.6 kcal/mol higher in energy than the diastereomer **7c**. Moreover, as revealed by the computations, the α-hydroxyl in the hemiketal **7c** is held in place by a hydrogen bond to the proximal ester carbonyl oxygen (OH···O=C–O 2.03 Å), thereby increasing the stability of this anomer. The observed lower wavenumber of ν(C=O) at 1708 cm^{-1} matches well with an ester carbonyl group arrested by a hydrogen bridge. On the other hand, β-oriented hydroxyl in **7′c** tends to interact rather with the O-1 chromane atom (OH···O1 2.43 Å) than with the ester alkoxy oxygen (OH···O–C=O 3.13 Å), as seen from the respective calculated hydrogen bond lengths.

Despite the relatively low solubility of the aminochromane products, we attempted to analyze the pure diastereomer **7c** by using chiral HPLC. The resulting chromatogram, however, surprisingly contained four peaks evidently corresponding to two pairs of enantiomers arising from the anomerization process during the HPLC experiment. Chiral separation of the crude product **7c** gave essentially the same chromatographic profile. In addition to the two smaller and slower eluting peaks, there were other two faster and poorly resolved peaks with the second being the major one. The variation of experimental conditions regarding the column type, flow rate and mobile phase composition nevertheless did not improve the separation. Quite gratifyingly, by manually collecting fractions of the main component from two non-preparative analyses, it was possible to gain a sufficient amount of the sample for the electronic CD spectra recording. The obtained evaporation residue was dissolved in MeCN and immediately subjected to the chiroptical measurement. The experimental ECD curve is plotted in Fig. 5a. The simulated spectra for the enantiomeric pair of **7c**, 2*R*,3*S*,4*S* and 2*S*,3*R*,4*R* (Fig. 6), computed with the time-dependent DFT at the CAM-B3LYP-SCFR(acetonitrile)/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory are displayed in Fig. 5b. As can be seen, the calculated spectrum for the 2*R*,3*S*,4*S* isomer and the experimental trace could be satisfactorily related to each other when considering their overall shape. In particular, there is a predicted strong electronic transition near 195 nm being similar in relative intensity and sign with the observed positive Cotton effect. Even though the two negative bands at higher wavelength of the theoretical spectrum appear somewhat weaker compared to the experimental pattern, they still reproduce acceptably the observed CD profile.

Thus, the determined absolute stereostructure proves to be in accord with the explanation based on the stereochemical model given in Fig. 4. Moreover, following our findings resulting from the circular dichroism investigation we may conclude that the predominant enantiomer formed in the L-proline catalyzed three-

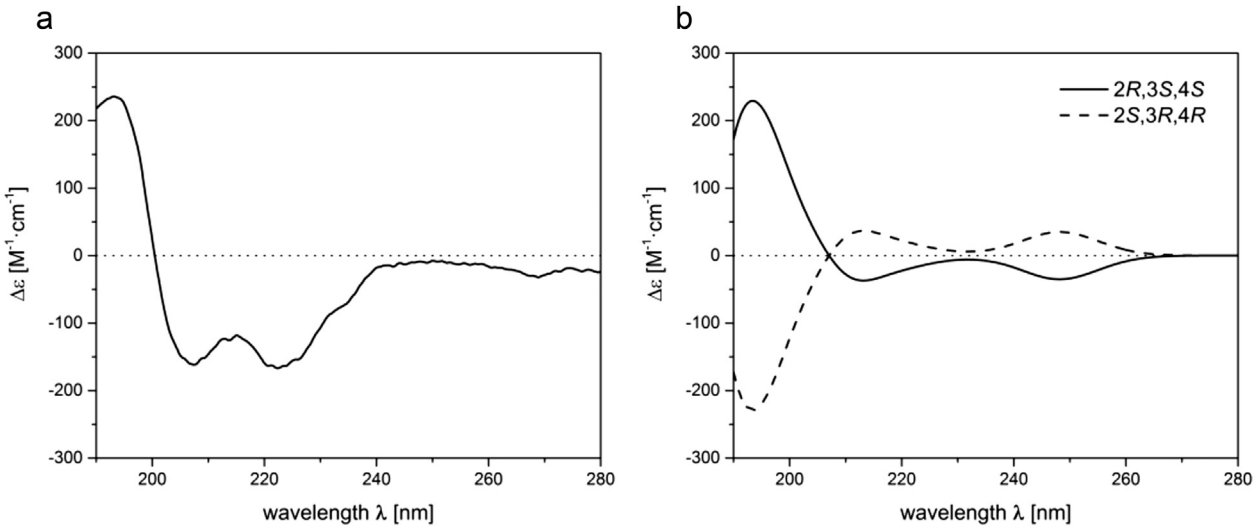

Fig. 5. (a) Experimental (left), and (b) calculated (right) CD spectra of **7c**.

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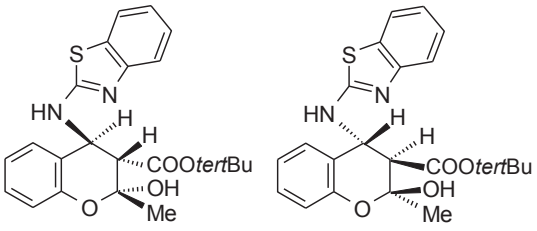

Fig. 6. Examined enantiomers of **7c**.

component reaction is expected to be the chromane **7** having the 2*R*,3*S*,4*S* stereochemistry.

3. Conclusion

In summary, the cyclization of salicylaldehydes with alkyl acetoacetates and 2-aminobenzothiazoles or 2-aminothiadiazole/thiazoles catalyzed with L-proline affords under mild conditions alkyl 4-hetarylamino-2-hydroxy-2-methyl-3,4-dihydro-2*H*-chromene-3-carboxylates. The formation of these heterocycles is different from the hetarylamino substituted 2,2′-spirobischromanecarboxylate derivatives produced by employing classical Biginelli protocol (HCl catalyst). The three component process proceeds via tandem Mannich/hemiketalization reaction sequence. Based on the CD spectra and quantum chemical calculations, the absolute stereochemistry of the major enantiomer was established as 2*R*,3*S*,4*S*.

4. Experimental

4.1. General

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The IR (FT-ATR) spectra were recorded on a Nicolet 6700 spectrophotometer. The NMR spectra were measured in DMSO-d_6 on a Varian Unity-Inova 300 instruments using TMS as internal standard. The MS (ESI-) spectrum was obtained on an Agilent 6410 Triple Quadrupole mass spectrometer. Elemental analyses were taken on a Carlo-Erba Elemental Analyzer 1012 apparatus. Optical rotations were determined with a POLAR L-μP polarimeter (IBZ Messtechnik). Chiral phase HPLC analysis was done on a Knauer instrument system using Daicel Chiralpak AS-H (25×0.46 cm) column, *n*-hexane/isopropanol (92:8) as the eluent, and a flow rate of 0.6 mL/min. CD spectra were measured in acetonitrile on a Jasco J-815 spectropolarimeter with 2 mm path length.

4.2. General procedure for the synthesis of chromane derivatives 7

To a solution of amine **4** or **5** (2.0 mmol) in dry EtOH (15 mL) were added alkyl acetoacetate **3** (2.1 mmol), aldehyde **2** (2.0 mmol) and L-proline (69 mg, 30 mol%). The mixture was stirred for 40–45 h at room temperature until the completion of reaction was confirmed by TLC. While most of the compounds precipitated during the reaction, the other products (**7e**, **7j**, **7k**) crystallized after removal of the solvent and trituration of an oily residue with a small volume of *iso*PrOH–H_2O. Another crop of chromanes were isolated from the filtrate upon standing. Obtained solids were washed with water and diethylether.

The crude products (1.0 mmol) were then dissolved in acetone or methanol and isomerized by treatment of *p*-TosOH (48 mg, 25 mol%) at room temperature for 40 h. The solution was concentrated in vacuo, the resulting oil was dissolved in minimal volume of aqueous ethanol and allowed to crystallize. The pure diastereomers were obtained as white crystalline solids.

4.2.1. Methyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7a**).* Isolated yield 0.333 g (45%), isomerization was not successful; mp 156–158 °C (EtOH); R_f (EtOAc) 0.61; IR: ν_{max} 3311, 1717, 1544, 1453, 1244, 1227, 749 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.59 (s, 3H, Me-2), 3.05 (d, 1H, *J*=12 Hz, H-3), 3.62 (s, 3H, OMe), 5.60–5.70 (m, 1H, H-4), 6.79 (d, 1H, *J*=7.8 Hz, H-8), 6.87 (t, 1H, *J*=7.8 Hz, H-6), 7.05 (t, 1H, *J*=7.8 Hz, H-6′), 7.17 (t, 1H, *J*=7.8 Hz, H-7), 7.20 (br s, 1H, OH), 7.21 (d, 1H, *J*=7.8 Hz, H-5), 7.25 (t, 1H, *J*=7.8 Hz, H-5′), 7.41 (d, 1H, *J*=7.8 Hz, H-4′), 7.69 (d, 1H, *J*=7.8 Hz, H-7′), 8.42 (d, 1H, *J*=9.0 Hz, NH); ^{1}H NMR (DMSO-d_6, minor isomer **7′a**, only resolved resonances): δ 1.49 (s, 3H, Me-2), 3.20 (d, 1H, *J*=9.6 Hz, H-3), 3.46 (s, 3H, OMe), 5.48–5.54 (m, 1H, H-4), 7.64 (d, 1H, *J*=7.5 Hz, H-7′), 8.49 (d, 1H, *J*=9.0 Hz, NH). Anal. Calcd for $C_{19}H_{18}N_2O_4S$ (370.42): C, 61.61; H, 4.90; N, 7.56%. Found: C 61.32; H, 5.05; N, 7.34%.

4.2.2. Isopropyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7b**).* Isolated yield 0.565 g (71%), isomerization 90%; mp 146–148 °C (EtOH); mp 145–146 °C: Ref. 11; R_f (EtOAc) 0.62. Spectral data and X-ray structure: Ref. 11.

4.2.3. tert-Butyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7c**).* Isolated yield 0.569 g (69%), isomerization 83%; mp 158–159 °C (EtOH); R_f (EtOAc) 0.71; IR: ν_{max} 3290, 1708, 1556, 1445, 1252, 1142, 1097, 928, 752 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.28 (s, 9H, 3Me), 1.59 (s, 3H, Me-2), 2.82 (d, 1H, *J*=12 Hz, H-3), 5.65–5.75 (m, 1H, H-4), 6.77 (d, 1H, *J*=7.8 Hz, H-8), 6.87 (t, 1H, *J*=7.8 Hz, H-6), 7.02 (br s, 1H, OH), 7.04 (t, 1H, *J*=7.8 Hz, H-6′), 7.15 (t, 1H, *J*=7.8 Hz, H-7), 7.21 (d, 1H, *J*=7.8 Hz, H-5), 7.24 (t, 1H, *J*=7.8 Hz, H-5′), 7.41 (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). Anal. Calcd for $C_{22}H_{24}N_2O_4S$ (412.50): C, 64.06; H, 5.86; N, 6.79%. Found: C 64.21; H, 6.01; N, 6.55%.

4.2.4. Benzyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7d**).* Isolated yield 0.446 g (50%), isomerization 81%; mp 137–139 °C (EtOH); R_f (EtOAc) 0.63; IR: ν_{max} 3313, 1716, 1557, 1252, 1083, 1047, 920, 752 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.57 (s, 3H, Me-2), 3.08 (d, 1H, *J*=12 Hz, H-3), 5.13 (dd, 2H, *J*=21.0, 12.6 Hz, OCH_2), 5.74–5.83 (m, 1H, H-4), 6.79 (d, 1H, *J*=7.8 Hz, H-8), 6.88 (t, 1H, *J*=7.8 Hz, H-6), 7.07 (t, 1H, *J*=7.8 Hz, H-6′), 7.10–7.28 (m, 4H, H-5+H-7+H-5′+OH), 7.42 (d, 1H, *J*=7.8 Hz, H-4′), 7.71 (d, 1H, *J*=7.8 Hz, H-7′), 8.48 (d, 1H, *J*=9.3 Hz, NH). Anal. Calcd for $C_{25}H_{22}N_2O_4S$ (446.13): C, 67.25; H, 4.97; N, 6.27%. Found: C 67.38; H, 5.07; N, 6.19%.

4.2.5. tert-Butyl (2R,3S*,4S*)-4-(6-methylbenzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7e**).* Isolated yield 0.486 g (57%), isomerization 76%; mp 149–151 °C (EtOH); R_f (EtOAc) 0.61; IR: ν_{max} 3319, 1704, 1581, 1556, 1257, 1143, 930, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.29 (s, 9H, 3Me), 1.60 (s, 3H, Me-2), 2.33 (s, 3H, Me-6′), 2.81 (d, 1H, *J*=12 Hz, H-3), 5.66–5.74 (m, 1H, H-4), 6.77 (d, 1H, *J*=7.8 Hz, H-8), 6.86 (t, 1H, *J*=7.8 Hz, H-6), 6.98 (br s, 1H, OH), 7.05 (d, 1H, *J*=7.8 Hz, H-5′), 7.15 (t, 1H, *J*=7.8 Hz, H-7), 7.21 (d, 1H, *J*=7.8 Hz, H-5), 7.29 (d, 1H, *J*=7.8 Hz, H-4′), 7.49 (s, 1H, *J*=7.8 Hz, H-7′), 8.29 (d, 1H, *J*=9.0 Hz, NH). Anal. Calcd for $C_{23}H_{26}N_2O_4S$ (426.53): C, 64.77; H, 6.14; N, 6.57%. Found: C 64.92; H, 6.01; N, 6.38%.

4.2.6. tert-Butyl (2R,3S*,4S*)-4-(4-methylbenzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7f**).* Isolated yield 0.665 g (78%), isomerization 52%; mp

137–139 °C (EtOH); R_f (EtOAc) 0.64; IR: ν_{max} 3286, 1711, 1596, 1552, 1449, 1366, 1252, 1145, 917, 756 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.30 (s, 9H, 3Me), 1.61 (s, 3H, Me-2), 2.43 (s, 3H, Me-4′), 2.84 (d, 1H, J=12 Hz, H-3), 5.64–5.74 (m, 1H, H-4), 6.77 (d, 1H, J=7.8 Hz, H-8), 6.87 (t, 1H, J=7.8 Hz, H-6), 6.94 (t, 1H, J=7.8 Hz, H-6′), 7.00 (br s, 1H, OH), 7.07 (d, 1H, J=7.8 Hz, H-5′), 7.15 (t, 1H, J=7.8 Hz, H-7), 7.24 (d, 1H, J=7.8, H-5), 7.51 (d, 1H, J=7.8 Hz, H-7′), 8.37 (d, 1H, J=9.0 Hz, NH). Anal. Calcd for $C_{23}H_{26}N_2O_4S$ (426.53): C, 64.77; H, 6.14; N, 6.57%. Found: C 64.52; H, 6.31; N, 6.28%.

4.2.7. tert-Butyl (2R,3S*,4S*)-4-(6-methoxybenzothiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7g**).* Isolated yield 0.355 g (42%), isomerization 71%; mp 155–156 °C (EtOH); R_f (EtOAc) 0.64; IR: ν_{max} 3486, 1722, 1606, 1581, 1560, 1477, 1248, 1230, 1159, 1031, 911, 835, 757 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.30 (s, 9H, 3Me), 1.59 (s, 3H, Me-2), 2.81 (d, 1H, J=12 Hz, H-3), 3.75 (s, 3H, MeO-6′), 5.63–5.70 (m, 1H, H-4), 6.76 (d, 1H, J=7.8 Hz, H-8), 6.85 (d, 1H, J=7.8, H-5′), 6.87 (t, 1H, J=7.8 Hz, H-6), 6.97 (br s, 1H, OH), 7.14 (t, 1H, J=7.8 Hz, H-7), 7.21 (d, 1H, J=7.8 Hz, H-5), 7.31 (d, 1H, J=7.8 Hz, H-4′), 7.34 (d, 1H, J=1.8 Hz, H-7′), 8.18 (d, 1H, J=9.6 Hz, NH). Anal. Calcd for $C_{23}H_{26}N_2O_5S$ (422.53): C, 62.43; H, 5.92; N, 6.33%. Found: C 62.55; H, 6.04; N, 6.09%.

4.2.8. tert-Butyl (2R,3S*,4S*)-4-(thiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7h**).* Isolated yield 0.384 g (53%), isomerization 43%; mp 125–126 °C (EtOH); R_f (EtOAc) 0.57; IR: ν_{max} 3311, 1709, 1557, 1253, 1144, 1099, 917, 750 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (s, 9H, 3Me), 1.57 (s, 3H, Me-2), 2.85 (d, 1H, J=12 Hz, H-3), 5.40–5.45 (m, 1H, H-4), 6.63 (d, 1H, J=3.9 Hz, H-5′), 6.74 (d, 1H, J=7.8 Hz, H-8), 6.86 (t, 1H, J=7.8 Hz, H-6), 6.89 (br s, 1H, OH), 7.01 (d, 1H, J=3.9 Hz, H-4′), 7.13 (t, 1H, J=7.8 Hz, H-7), 7.17 (d, 1H, J=7.8 Hz, H-5), 7.93 (d, 1H, J=9.0 Hz, NH); ^{13}C NMR (DMSO-d_6): δ 27.0 (Me-2), 27.5 (Me ester), 50.1 (CH-4), 54.6 (CH-3), 80.2 (OC_q ester), 97.1 (C-2), 106.1 (CH-5′), 116.4 (CH-8), 120.5 (CH-6), 124.6 (C-4a), 126.8 (CH-5), 128.2 (CH-7), 138.6 (CH-4′), 151.3 (C-8a), 168.7 (COO), 169.5 (C-2′). Anal. Calcd for $C_{18}H_{22}N_2O_4S$ (362.44): C, 59.65; H, 6.12; N, 7.73%. Found: C 59.90; H, 6.01; N, 7.55%.

4.2.9. tert-Butyl (2R,3S*,4S*)-4-(5-methylthiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7i**).* Isolated yield 0.527 g (70%), partial isomerization; mp 137–138 °C (EtOH); R_f (EtOAc) 0.55; IR: ν_{max} 3295, 1708, 1557, 1363, 1251, 1141, 1087, 909, 759 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (s, 9H, 3Me), 1.56 (s, 3H, Me-2), 2.22 (s, 3H, Me-5′), 2.83 (d, 1H, J=12 Hz, H-3), 5.33–5.39 (m, 1H, H-4), 6.66 (s, 1H, H-4′), 6.73 (d, 1H, J=7.8 Hz, H-8), 6.85 (t, 1H, J=7.8 Hz, H-6), 6.88 (br s, 1H, OH), 7.12 (t, 1H, J=7.8 Hz, H-7), 7.18 (d, 1H, J=7.8 Hz, H-5), 7.69 (d, 1H, J=9.0 Hz, NH); ^1H NMR (DMSO-d_6, minor isomer **7′i**, only resolved resonances): δ 1.11 (s, 9H, 3Me), 1.45 (s, 3H, Me-2), 2.15 (s, 3H, Me-5′), 2.96 (d, 1H, J=10.2 Hz, H-3), 5.22–5.28 (m, 1H, H-4), 7.73 (d, 1H, J=9.0 Hz, NH). Anal. Calcd for $C_{19}H_{24}N_2O_4S$ (376.47): C, 60.62; H, 6.43; N, 7.44%. Found: C, 60.88; H, 6.29; N, 7.39%.

4.2.10. tert-Butyl (2R,3S*,4S*)-4-(5-methyl-1,3,4-thiadiazol-2-ylamino)-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7j**).* Isolated yield 0.377 g (50%), isomerization 34%; mp 125–127 °C (EtOH); R_f (EtOAc) 0.40; IR: ν_{max} 3282, 1709, 1548, 1363, 1251, 1145, 1125, 1091, 918, 766 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.34 (s, 9H, 3Me), 1.58 (s, 3H, Me-2), 2.47 (s, 3H, Me-5′), 2.87 (d, 1H, J=12 Hz, H-3), 5.32–5.39 (m, 1H, H-4), 6.75 (d, 1H, J=7.8 Hz, H-8), 6.87 (t, 1H, J=7.8 Hz, H-6), 6.94 (br s, 1H, OH), 7.12–7.18 (m, 2H, H-5+H-7), 8,00 (d, 1H, J=9.0 Hz, NH). Anal. Calcd for $C_{18}H_{23}N_3O_4S$ (377.46): C, 57.28; H, 6.14; N, 11.13%. Found: C, 57.15; H, 6.04; N, 11.27%.

4.2.11. tert-Butyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-6-bromo-2-hydroxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7k**).* Isolated yield 0.619 g (63%), isomerization 68%; mp 147–148 °C (EtOH); R_f (EtOAc) 0.66; IR: ν_{max} 3295, 1707, 1557, 1449, 1254, 1143, 1103, 893, 750 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (s, 9H, 3Me), 1.60 (s, 3H, Me-2), 2.83 (d, 1H, J=12 Hz, H-3), 5.68–5.75 (m, 1H, H-4), 6.78 (d, 1H, J=7.8 Hz, H-8), 7.07 (t, 1H, J=7.8 Hz, H-6′), 7.18 (br s, 1H, OH), 7.26 (t, 1H, J=7.8 Hz, H-5′), 7.26 (overlapped s, 1H, H-5), 7.33 (d, 1H, J=7.8 Hz, H-7), 7.44 (d, 1H, J=7.8 Hz, H-4′), 7.71 (d, 1H, J=7.8 Hz, H-7′), 8.48 (d, 1H, J=9.0 Hz, NH). Anal. Calcd for $C_{22}H_{23}BrN_2O_4S$ (491.40): C, 53.77; H, 4.72; N, 5.70%. Found: C, 53.98; H, 4.51; N, 5.64%.

4.2.12. tert-Butyl (2R,3S*,4S*)-4-(benzothiazol-2-ylamino)-2-hydroxy-8-methoxy-2-methyl-3,4-dihydro-2H-chromene-3-carboxylate (**7l**).* Isolated yield 0.513 g (58%), isomerization 71%; mp 137–139 °C (EtOH); R_f (EtOAc) 0.56; IR: ν_{max} 3289, 1712, 1557, 1448, 1267, 1149, 1090, 924, 750 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.29 (s, 9H, 3Me), 1.61 (s, 3H, Me-2), 2.81 (d, 1H, J=12 Hz, H-3), 3.73 (s, 3H, MeO-8), 5.67–5.74 (m, 1H, H-4), 6.78–6.86 (m, 3H, H-5+H-6+H-7), 7.01 (br s, 1H, OH), 7.03 (t, 1H, J=7.8 Hz, H-6′), 7.24 (t, 1H, J=7.8 Hz, H-5′), 7.40 (d, 1H, J=7.8 Hz, H-4′), 7.69 (d, 1H, J=7.8 Hz, H-7′), 8.38 (d, 1H, J=9.6 Hz, NH). Anal. Calcd for $C_{23}H_{26}N_2O_5S$ (442.53): C, 62.43; H, 5.92; N, 6.33%. Found: C, 62.66; H, 6.12; N, 6.11%.

4.3. Preparation of 2-aminobenzothiazol-3-ium L-prolinate (8)

To a solution of L-proline (115 mg, 1.0 mmol) in acetonitrile (55 mL) was added amine **4a** (0.155 g, 1.0 mmol) under stirring at room temperature. After 20 h the separated solid was collected and washed with acetonitrile and ether. Compound **8** was obtained as a white powder (0.229 g, 86%), mp 210–212 °C; $[\alpha]_D^{25}$=−36.9 (c=1, EtOH); IR: ν_{max} 3388, 1640, 1606, 1536, 1444, 754 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.65–1.70 (m, 1H, H-4b proline), 1.74–1.79 (m, 1H, H-4a), 1.91–1.95 (m, 1H, H-3b), 1.97–2.03 (m, 1H, H-3a), 2.98–3.02 (m, 1H, H-5b), 3.18–3.36 (m, 1H, H-5a), 3.62–3.64 (m, 1H, H-2), 7.00 (t, 1H, J=7.8 Hz, H_{Ar}-6), 7.19 (t, 1H, J=7.8 Hz, H_{Ar}-5), 7.32 (d, 1H, J=7.8 Hz, H_{Ar}-4), 7.47 (s, 2H, NH), 7.64 (d, 1H, J=7.8 Hz, H_{Ar}-7), 8.20–8.80 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.9 (CH_2-4 proline), 28.9 (CH_2-3), 45.2 (CH_2-5), 60.7 (CH-2), 117.7 (CH_{Ar}-4), 120.7 (CH_{Ar}-6/CH_{Ar}-7), 120.8 (CH_{Ar}-7/CH_{Ar}-6), 125.4 (CH_{Ar}-5), 130.9 (C_{Ar}-7a), 152.8 (C_{Ar}-3a), 166.4 (C_{Ar}-2), 169.3 (COO); ESI MS (m/z) 342 [M-H+DMSO]$^-$. Anal. Calcd for $C_{12}H_{15}N_3O_2S$ (265.33): C, 54.32; H, 5.70; N, 15.84%. Found: C, 54.54; H, 5.51; N, 16.01%.

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