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Proline-mediated formation of novel chroman-4-one tetrahydropyrimidines

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ABSTRACT

Novel tricyclic *N*-benzylated chroman-4-one tetrahydropyrimidine derivatives have been prepared through a multi-component reaction between various 2-substituted chroman-4-one derivatives, *N*-methylenebenzylamine and a catalytic amount of proline under mild reaction conditions. The tricyclic structure of **1a** was determined by NMR spectroscopy and confirmed by X-ray crystallography. An additional product, **2a**, was isolated from the reaction mixture and its structure and conformation were determined by a combination of theoretical (Monte Carlo conformational search) and NMR-based (NOE and $^3J_{HH}$ couplings) conformational analysis. The NMR analysis revealed one preferred geometry for **1a** and **2a** in $CHCl_3$ solution.

1. Introduction

Substituted chroman-4-ones are regarded as common structures for drug design.[1] Along with related, higher order oxygen-containing ring systems, they are frequently found in plants and marine organisms[2] and have been shown to possess antioxidant,[3] antiviral[4] and antibacterial[5] activities. Protocols for the preparation of substituted chromones and chroman-4-ones have been developed by our group with the most recent progress being the incorporation of a carboxy functionality in the 6-position[6,7] and an amino group in the 3-position (Fig. 1).[7–9] Such chromone/chroman-4-ones have been designed as potential β-turn peptidomimetics.[9]

As an extension of these studies we explored the use of the Mannich reaction to introduce an aminomethyl group in the 3-position of the 2-alkyl-chroman-4-one scaffold. However, this reaction did not result in the desired product, instead tricyclic chroman-4-one derivatives were isolated. Herein, we report the synthesis and conformational analysis of these novel chroman-4-one tetrahydropyrimidines.

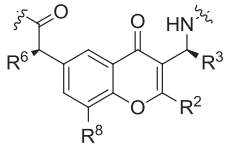

Fig. 1. The 2,3,6,8-tetrasubstituted chromone system as a potential β-turn mimetic.

2. Results and discussion

As found in the present study a proline-mediated Mannich reaction resulted in the unexpected formation of two novel tricyclic derivatives **1** and **2** (Fig. 2). This fact indicates a yet unexplored potential of the amino acid-catalyzed Mannich reaction. The new compounds are expected to be of interest due to their high structural similarity to derivatives with significant pharmacological activities.[10,11] Examples of such compounds are the amine containing tricyclic chroman-4-one analogues of **3**, which exhibit anti-inflammatory[12] and antiplatelet[13] activities (Fig. 2) whereas the Biginelli analogue **4**[14] belongs to a type of structures shown to act as calcium channel blockers.[15]

2.1. Synthesis

For the synthesis of the title compounds, the racemates of 8-bromo-6-chloro-2-alkyl substituted chroman-4-ones **5a–c** (Scheme 1) were used. They were synthesized via a microwave promoted two-component reaction using commercially available

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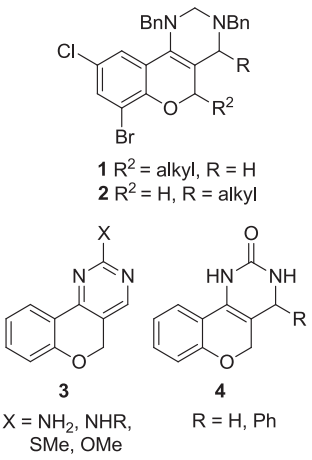
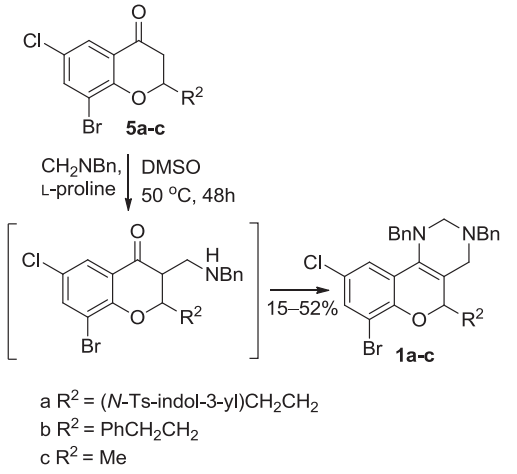


Fig. 2. The novel tricyclic chroman-4-one derivatives **1** and **2** along with the structurally related compounds **3** and **4**, which were reported to exhibit promising pharmacological activities.

3-bromo-5-chloro-2-hydroxyacetophenone and an aldehyde in the presence of *N*,*N*-diisopropylamine (DIPA) in ethanol.[8] As L-proline is known to efficiently catalyze asymmetric Mannich reactions[16–18] it was chosen for the corresponding reactions of derivatives **5a**–**c**. Interestingly, reacting **5a** with an excess of *N*-methylenebenzylamine[19] (5 equiv) and a catalytic amount of L-proline (0.3 equiv) in DMSO at 50 °C for 48 h afforded instead the novel tricyclic derivative **1a** in 52% yield (Scheme 1). The chroman-4-one **5b** substituted with a phenethyl group in the 2-position and **5c** with a considerably smaller 2-methyl substituent were also examined (Scheme 1). Applying the identical reaction conditions, an excess of *N*-methylenebenzylamine in DMSO in the presence of a catalytic amount of L-proline, the products **1b** and **1c** were formed but in lower yields (26% and 15%, respectively) as compared to **1a**. An attempt to synthesize a derivative with a 2-phenyl substituent was unsuccessful.



Scheme 1. The L-proline catalyzed formation of tricyclic derivatives **1a**–**c**.

The structure of **1a** was determined by HMBC, HSQC and NOESY-based NMR spectroscopic investigation and was confirmed by X-ray crystallography (Fig. 3). Remarkably, the bulky substituent in the 5-position prefers to adopt an axial orientation.

Compounds **1a**–**c** are formed via a Biginelli-type mechanism.[15] Proline is suggested to catalyze the enolization of the chroman-4-one (Scheme 2) instead of mediating enamine formation, which was previously proposed for L-proline.[16] This conclusion is based on

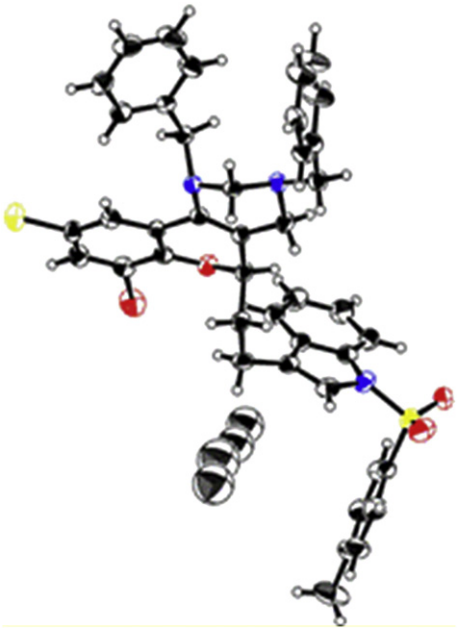
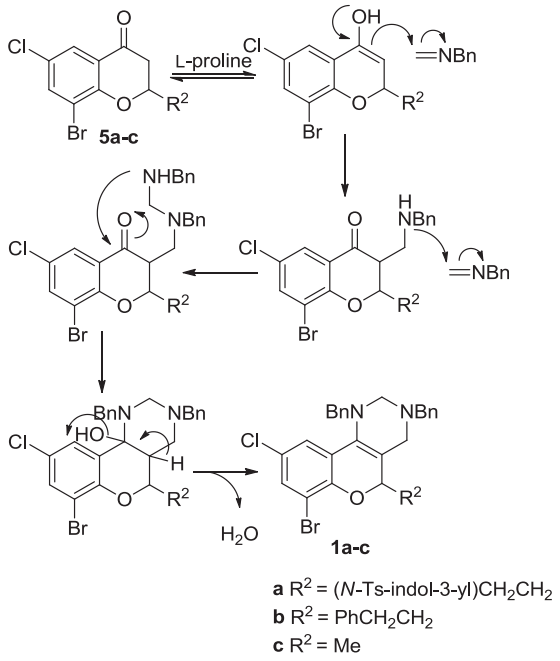


Fig. 3. The crystal structure of the tricyclic derivative **1a**.

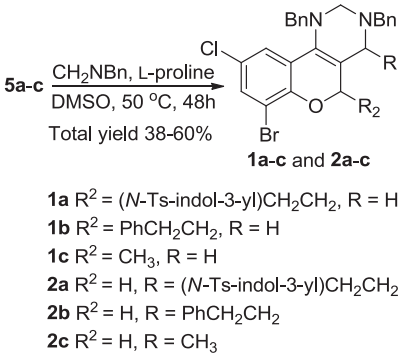
experiments using additional secondary amine sources such as DIPA and pyrrolidine, which were shown to mainly react as nucleophiles leading to ring opening of the chroman-4-one ring (according to ^{1}H NMR spectroscopic analysis of the crude reaction mixture). In addition, upon heating a mixture of L-proline and chroman-4-one **1a** at 50 °C no enamine formation was observable by ^{1}H NMR spectroscopy. Hence, in the proposed mechanism the enol of **5a**–**c** attacks the preformed *N*-methylenebenzylamine providing the Mannich product as an intermediate. The subsequent nucleophilic attack of the newly formed amino function on a second *N*-methylenebenzylamine gives the aminal of which one amino group attacks the carbonyl functionality in the chroman-4-one. Subsequent dehydration provides the tetrahydropyrimidine ring and thus the final product.



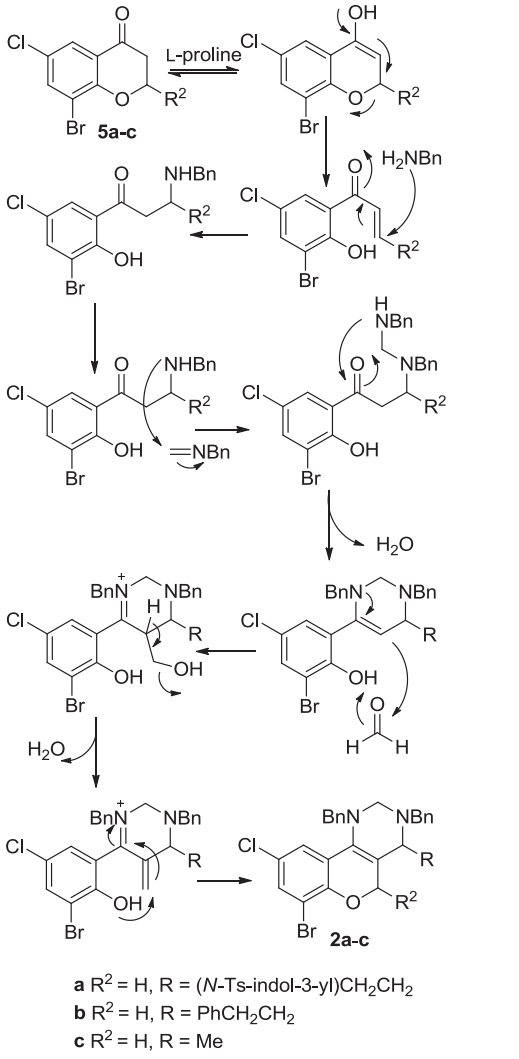
Scheme 2. Proposed mechanism for the synthesis of derivatives **1a**–**c**.

In an attempt to optimize the yield of the tricyclic derivatives **1a**–**c** a series of reaction conditions were examined. The use of smaller amounts of *N*-methylenebenzylamine, shorter reactions times or higher temperatures (20 min or 2 h at 80, 120 or 150 °C under microwave irradiation) resulted in lower conversions. Similar observations were made upon variation of the chiral catalysts (sarcosine, L-pipecolic acid), the use of achiral catalysts (glycine, DIPA, DIPEA or pyrrolidine), racemic catalyst (D/L-proline) or alteration of solvents (THF or DMF). Neither the change of substrate structure by removal of substituents or by introduction of electron donating (OMe) or electron withdrawing (NO_2 or Cl) groups in the 6-position of the chroman-4-one resulted in improved yields. Further attempts on reacting **5a** with electrophiles such as *N*-methylene *p*-anisidine imine provided only traces of the Mannich product along with numerous impurities. Using dibenzyl imine as the electrophile resulted only in recovered starting material.

The isolated yields of derivatives **1a**-**c** were moderate due to the competing formation of additional heterocyclic products. For example, the synthesis of **1a** also yielded **2a** in 7% isolated yield (Scheme 3). As expected the formation of analogous products was detected also in the synthesis of **1b** and **1c** (**2b** and **2c** in 26% and 23% yields, respectively). Compound **2a** was found to have identical molecular weight to **1a**, but showed a different ^{1}H NMR spectrum and chromatographic behaviour. Therefore additional HMBC and NOESY-based NMR spectroscopic investigations were performed, as described in detail below.



Scheme 3. The L-proline-mediated formation of tricyclic derivatives **1a**–**c** and **2a**–**c**.



Scheme 4. A proposed mechanism for the formation of compounds **2a**–**c**.

The mechanism for the formation of compounds **2a**–**c** is suggested to occur via a nucleophilic attack by benzylamine on the chroman-4-one ring system as shown in Scheme 4. Benzylamine is most likely formed by partial hydrolysis of *N*-methylenebenzylamine. However, using dry DMSO as the solvent and molecular sieves (4 Å) or $MgSO_4$ as drying agents did not prevent the decomposition of *N*-methylenebenzylamine and hence the formation of the heterocyclic products **2a**–**c**.

2.2. Conformational analysis of 1a and 2a

Small molecules encompassing flexible bonds commonly exist in solution as a mixture of rapidly interconverting conformers.[20] Their solution structure usually cannot be correctly represented by a single averaged structure, but is preferably described as the probability-weighted ensemble of several conformations present in solution. The determination of such ensembles is possible, although not yet extensively carried out, by deconvolution of their time-averaged spectroscopic data.[21,22] For elucidation of the structure of **2a** as well as the available conformational space of the tricyclic backbones of **1** and **2** a combined computational and NMR spectroscopic approach was utilized. A Monte Carlo conformational search followed by molecular mechanics minimization of the generated structures was performed using the OPLS-2005 all atom force field[23] and the Born solvation model for chloroform,[24] as implemented in the MacroModel program (v. 9.7).[25]

The mixed torsions/low mode method was employed and conformations within 21 kJ/mol from the global minimum were kept. This protocol yielded two distinct conformational families for **1a** and **2a**. Because of the uncertainty and force field dependency of the energies of computationally derived conformations, the predicted populations of theoretical ensembles do not necessarily represent the molecular structure present in solution,[20,26,27] yet allow their determination when utilized in combination with experimental data.[20,22] Accordingly, the set of structures derived by the conformational analysis was evaluated in a subsequent NAMFIS (NMR analysis of molecular flexibility in solution) analysis.[28] Distances were determined by acquisition of NOE-buildups with five mixing times (100, 150, 200, 250, and 400 ms) using the initial rate approximation,[29] whereas scalar couplings were obtained from standard ^{1}H and P.E. COSY[30] spectra. Despite the few available protons on the tricyclic backbone of **1a** and **2a**, a sufficient number of NOEs were observed for description of the orientation of their flexible fragments (Fig. 4). As enantiomeric mixtures yield a single set of NMR signals, the conformational analysis of **1a** and **2a** was carried out without chiral separation. Assignment of the diastereotopic CH_2 protons was based on relative NOE intensities and corresponded to the expected

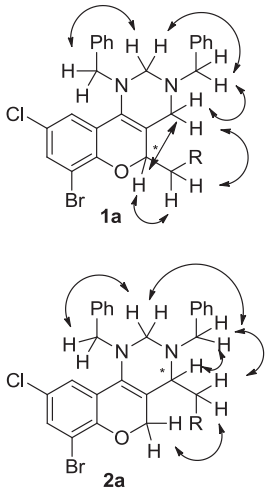


Fig. 4. NOE correlations observed in NMR spectra of **1a** and **2a** in chloroform. Two and six additional *J*-couplings, respectively, are described in Supplementary data.

distances, when starting the identification from the chiral centres (Fig. 4). The solution ensembles were determined by identification of the geometries truly present in solution from the theoretically predicted conformational pool using experimental selection criteria. Hence, 8 and 11 possibly time-averaged NMR-derived distances and dihedral angles were used to deconvolute the conformational pool of **1a** and **2a** using the NAMFIS protocol. Details of the analysis, including the comparison of the observed and the calculated distances are given in Supplementary data.

The analysis of **1a** indicated one preferred conformation in solution. This geometry showed dihedral angles corresponding to those observed in the solid state by X-ray analysis including also the axially positioned 5-substituent (Fig. 5a).

Compound **2a** was revealed to also prefer a single conformation (Fig. 5b) in which the large 4-substituent is equatorially oriented. Thus, the refinement revealed that only one of the computationally predicted conformational families exists in solution for **1a** and **2a**. It should be underlined that application of the NAMFIS protocol ensures that the identified geometries are the real solution structures and therefore are pharmacologically relevant.

Given our aim to use chroman-4-one/chromone scaffolds as novel mimetics of bioactive peptides it was especially interesting to find that the tricyclic cores of **1a** and **2a** efficiently mimic a native type VIII β-turn (Fig. 6; see the Experimental section for details on the calculations). Their Cl- and Br-substitutions provide possibilities for selective functionalization through Pd-mediated cross-coupling reactions,[6] and thereby allow broad applicability. However, any further investigations in this direction are outside the scope of the present study.

3. Conclusions

A one-pot proline catalyzed synthetic route to novel chroman-4-one tetrahydropyrimidine derivatives **1a**–**c** and **2a**–**c** has been developed. The reactions are proposed to proceed through an L-proline-mediated enolization mechanism. Depending on the identity of the 2-substituent of the chroman-4-one products were obtained in varying yields. Combined NMR spectroscopic and theoretical conformational analysis of **1a** and **2a** revealed the presence of a single geometry in solution, which for **1a** was revealed to be identical to its solid state (X-ray) structure. The obtained products are of considerable interest due to their potential pharmaceutical applicability. Their use as potential scaffolds for type VIII *β*-turn peptidomimetics will be further explored.

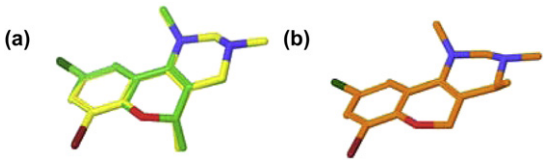


Fig. 5. (a) The solution structure of the core of **1a** (yellow) overlapped with its X-ray derived conformation (green). (b) The solution conformation of the tricyclic core of **2a**, as identified by NAMFIS analysis.

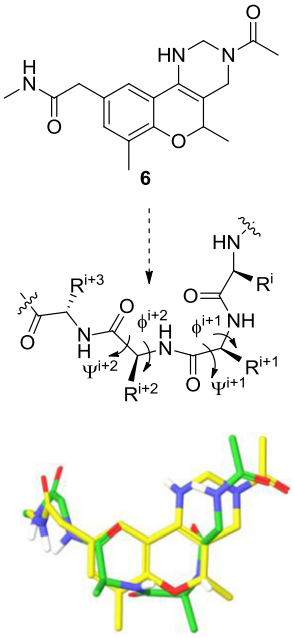


Fig. 6. Alignment of a modified structure of the tricyclic derivative **6** and a type VIII β-turn ($\Phi^{(i+1)}=-60°$, $\psi^{(i+1)}=-30°$, $\Phi^{(i+2)}=-120°$ and $\psi^{(i+2)}=120°$).[31]

4. Experimental section

4.1. General

Commercially available chemicals were used without prior purification. The reactions were monitored by thin-layer chromatography (TLC) on silica plated aluminium sheets (Silica gel 60 F_{254}, E. Merck). Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, manually or using a Biotage SP4 Flash+ instrument). Microwave reactions were carried out using a Biotage Initiator™ Sixty with fixed hold time modus in 2–5 mL or 10–20 mL capped microwave vials. IR was recorded with a Chiral*IR*-2x™ from BioTools. Every compound was dissolved in 0.5 mL $CDCl_3$. High-resolution mass spectral analysis (Q-TOF-MS) was performed at Stenhagen Analyslab AB, Gothenburg, Sweden. Elemental analyses were performed at Kolbe Mikroanalytisches Laboratorium, Mülheim and der Ruhr, Germany.

NMR spectra were recorded on JEOL GX-270 (400 MHz) or Varian Unity Innova (800 MHz) spectrometer. Assignments of signals of derivatives **1a** and **2a** were made using HMBC, HSQC and NOESY spectra. The samples were dissolved in $CDCl_3$. Chemical shifts are reported in parts per million with the solvent residual peak as internal standard: $CDCl_3$ [$CHCl_3$ δ_H 7.26, $CDCl_3$ δ_C 77.0]. The NOE buildup studies were performed on 0.5 mmol/dm^3 solutions at mixing times of 100, 150, 200 and 250 and 400 ms. Distances were calculated with a reference distance of 1.78 Å for geminal protons. NOE peak intensities were calculated using normalization of both cross-peaks with both diagonal peaks according to $([xpeak_1 \times xpeak_2])/([diagpeak_1 \times diagpeak_2])^{0.5}$. Five mixing times yielding

a linear (r^2>0.95) initial NOE rate were used to estimate the σ_{ij} buildup rates according to the equation $r_{ij}=r_{ref}(\sigma_{ref}/\sigma_{ij})^{(1/6)}$, where r_{ij} is the distance between protons i and j and σ_{ij} is the normalized intensity obtained from NOE experiments. The $^3J_{HH}$ couplings were derived from E.COSY experiments.

The computer based studies were performed using the MacroModel program (v. 9.7)[25] as implemented in Maestro (v. 9.0). The conformational search for **1a** and **2a** was performed using the OPLS-2005 force field and the Born solvation model for chloroform. The number of torsional rotations were restricted to 3^6 and the cut off was set to 0.5 Å. The conformational search was performed using the mixed torsions/low mode method with 5000 steps. The minimization method used was PRCG (Polak-Ribiere Conjugate Gradient) with a maximum of 500 iterations. Conformations within 21 kJ/mol from the global minimum were retained. This resulted in 2000 (**1a**) and 1351 (**2a**) conformations, respectively. The conformations were subsequently re-minimized using TNCG (truncated Newton conjugate gradient) using the same criteria as described above. The repeated minimization gave 162 (**1a**) and 349 (**2a**) conformations, respectively, where conformations within 21 kJ/mol from the global minimum were retained.

4.2. Synthesis of chroman-4-ones 5a–c

*4.2.1. 8-Bromo-6-chloro-2-(2-(1-tosyl-1H-indol-3-yl)ethyl)-chroman-4-one (**5a**).* The chroman-4-one was synthesized according to the procedure reported by Fridén-Saxin et al.[8] To an ethanolic solution (2.5 mL) of 3′-bromo-5′-chloro-2′-hydroxyacetophenone (0.250 g, 1.002 mmol, 1 equiv) 3-(1-tosyl-1*H*-indol-3-yl) propanal (0.146 mL, 1.10 mmol, 1.1 equiv) and DIPA (0.154 mL, 1.10 mmol, 1.1 equiv) were added. The reaction was run in a microwave cavity for 1 h at 170 °C. The reaction mixture was diluted with Et_2O and the phases were separated. The organic phase was washed with NaOH (aq, 1%), HCl (aq, 0.1 M), water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The obtained crude product was purified by flash chromatography using EtOAc/heptane (2.5%) yielding **5a** as an orange oil (0.31 g, 88%) as previously reported.[8]

*4.2.2. 8-Bromo-6-chloro-2-phenethylchroman-4-one (**5b**).* 3′-Bromo-5′-chloro-2′-hydroxyacetophenone (1.38 g, 5.54 mmol) was reacted with 3-phenylpropanal (2.00 g, 6.10 mmol) and DIPA (0.856 mL, 6.10 mmol) in ethanol (15 mL) following the general procedure. Purification by flash chromatography using toluene/heptane (50%) afforded **5b** as a yellow solid (2.28 g, 74%) as previously reported.[8]

*4.2.3. 8-Bromo-6-chloro-2-methylchroman-4-one (**5c**).* 3′-Bromo-5′-chloro-2′-hydroxyacetophenone (1.51 g, 6.05 mmol), acetaldehyde (0.373 mL, 6.61 mmol) and DIPA (0.932 mL, 6.61 mmol) were reacted following the general procedure. Purification by flash chromatography using EtOAc/heptane (1:9) gave **5c** (0.47 g, 28%) as a yellow oil. R_f=0.77 (5% EtOAc/heptane); IR 3158, 2906, 2362, 2332, 1819 cm^{-1}; ^1H NMR (400 MHz) δ 7.80 (d, J=2.6 Hz, 1H), 7.70 (d, J=2.6 Hz, 1H), 4.72–4.62 (m, 1H), 2.78–2.65 (m, 2H), 1.59 (d, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 190.4, 156.7, 138.4, 126.8, 125.8, 122.1, 112.5, 75.4, 43.7, 20.7; HRMS (Q-TOF-MS) $[M+H]^+$, calcd for $C_{10}H_9BrClO_2$: 274.9474, found: 274.9429.

4.3. Synthesis of the tricyclic derivatives 1a–c and 2a–c

*4.3.1. 1,3-Dibenzyl-7-bromo-9-chloro-5-(2-(1-tosyl-1H-indol-3-yl) ethyl)-2,3,4,5-tetrahydro-1H-chromeno[4,3-d]pyrimidine (**1a**) and 1,3-dibenzyl-7-bromo-9-chloro-4-(2-(1-tosyl-1H-indol-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-chromeno[4,3-d]pyrimidine (**2a**).* Chroman-4-one **5a** (0.100 g, 0.179 mmol, 1 equiv) was dissolved in DMSO (2.5 mL). *N*-Methylenebenzylamine[19] (0.106 g, 0.895 mmol, 5 equiv) and L-proline (6.18 mg, 0.054 mmol, 0.3 equiv) were added. The reaction mixture was stirred at 50 °C for 48 h. The reaction was quenched with NH_4Cl (satd, aq) followed by the addition of EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed three times with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum. Purification by flash chromatography using a gradient of heptane/toluene (20%) gave **1a** (72 mg, 52%) and **2a** (10 mg, 7%) as orange oils.

*4.3.1.1. Compound **1a**.* R_f=0.4 (5% EtOAc/toluene); IR 3160, 2362, 2337, 1822, 1794, 1453, 1375 cm^{-1}; ^1H NMR (400 MHz) δ 8.03 (d, J=8.2 Hz, 1H), 7.75 (d, J=8.2 Hz, 2H), 7.51–7.16 (m, 18H), 4.68–4.61 (m, 1H), 4.03–3.92 (m, 2H), 3.59–3.47 (m, 3H), 3.32 (d, J=11.1 Hz, 1H), 3.19 (d, J=16.9 Hz, 1H), 3.09–2.85 (m, 3H), 2.33 (s, 3H), 2.19–2.06 (m, 1H), 1.93–1.82 (m, 1H); ^{13}C NMR (100 MHz) δ 148.2, 144.6, 138.2, 137.7, 135.3, 135.2, 134.7, 131.2, 130.8, 129.7 (2C), 128.8, 128.4, 128.3, 128.2, 127.3, 127.1, 126.6, 126.5, 124.6, 123.0, 122.7, 121.9, 121.4, 119.8, 119.4, 113.7, 111.3, 77.3, 67.3, 59.0, 54.4, 52.8, 32.8, 21.4, 20.8. Anal. Calcd for $C_{42}H_{37}BrClN_3O_3S\cdot$EtOAc: C, 63.70; H, 5.23; N, 5.06. Found: C, 64.10; H, 5.60, N, 5.06.

*4.3.1.2. Compound **2a**.* R_f=0.5 (5% EtOAc/toluene); IR 3159, 3022, 2988, 2363, 2333, 1792, 1470, 1457, 1377 cm^{-1}; ^1H NMR (400 MHz) δ 7.99 (d, J=8.3 Hz, 1H), 7.74 (d, J=8.3 Hz, 2H), 7.44 (d, J=7.4 Hz, 1H), 7.39–7.13 (m, 17H), 4.74 (d, J=13.5 Hz, 1H), 4.55 (d, J=13.5 Hz, 1H), 4.13–4.02 (m, 2H), 3.95 (d, J=13.6 Hz, 1H), 3.85 (d, J=11.8 Hz, 1H), 3.57–3.44 (m, 2H), 3.21 (br s, 1H), 2.88–2.70 (m, 2H), 2.34 (s, 3H), 2.16–2.01 (m, 1H), 2.00–1.85 (m, 1H); ^{13}C NMR (100 MHz) δ 150.6, 144.7, 138.5, 138.1, 136.5, 135.3, 135.2, 131.2, 130.9, 129.8, 128.9, 128.5, 128.4, 128.0, 127.4, 127.2, 126.8, 126.6, 124.6, 123.2, 123.1, 123.0, 122.5, 121.9, 119.3, 117.0, 113.8, 110.8, 67.0, 64.7, 58.5, 57.1, 54.6, 30.5, 21.5, 19.8. Anal. Calcd for $C_{42}H_{37}BrClN_3O_3S\cdot H_2O$: C, 63.28; H, 4.93; N, 5.27. Found: C, 63.21; H, 4.99; N, 5.20.

*4.3.2. 1,3-Dibenzyl-7-bromo-9-chloro-5-phenethyl-2,3,4,5-tetrahydro-1H-chromeno[4,3-d]pyrimidine (**1b**) and 1,3-dibenzyl-7-bromo-9-chloro-4-phenethyl-2,3,4,5-tetrahydro-1H-chromeno[4,3-d] pyrimidine (**2b**).* Chroman-4-one **5b** (0.100 g, 0.275 mmol) was reacted with *N*-methylenebenzylamine[19] (0.163 g, 1.37 mmol) and L-proline (9.44 mg, 0.082 mmol) according to the general procedure. Purification by flash chromatography using EtOAc/heptane (5:95→4:6) followed by toluene/heptane (3:7→1:1) as eluents gave **1b** (42 mg, 26%) and **2b** (42 mg, 26%) as yellow oils.

*4.3.2.1. Compound **1b**.* R_f=0.7 (10% EtOAc/hexane); IR 3159, 3020, 2364, 2337, 1689, 1454 cm^{-1}; ^1H NMR (400 MHz) δ 7.39–7.15 (m, 17H), 4.68–4.61 (m, 1H), 4.03–3.92 (m, 2H), 3.55–3.48 (m, 3H), 3.26–3.12 (m, 2H), 3.00–2.91 (m, 2H), 2.83–2.75 (m, 1H), 2.09–2.00 (m, 1H), 1.82–1.74 (m, 1H); ^{13}C NMR (100 MHz) δ 148.4, 141.2, 138.3, 137.7, 134.6, 131.2, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 127.3, 127.2, 126.5, 126.0, 122.7, 121.4, 119.9, 111.4, 77.5, 67.4, 59.1, 54.5, 52.8, 35.2, 31.7; HRMS (Q-TOF-MS) $[M+H]^+$, calcd for $C_{33}H_{31}BrClN_2O$: 585.1308, found: 585.1320.

*4.3.2.2. Compound **2b**.* R_f=0.6 (10% EtOAc/hexane); IR 3156, 3083, 3067, 3027, 2931, 2362, 2335, 1700 cm^{-1}; ^1H NMR (400 MHz) δ 7.39–7.13 (m, 17H), 4.82 (d, J=13.4 Hz, 1H), 4.65 (d, J=13.4 Hz, 1H), 4.06–3.91 (m, 3H), 3.80 (d, J=11.6 Hz, 1H), 3.51–3.40 (m, 2H), 3.24–3.20 (m, 1H), 2.91–2.68 (m, 2H), 2.16–2.05 (m, 1H), 1.97–1.86 (m, 1H); ^{13}C NMR (100 MHz) δ 150.5, 142.3, 138.7, 138.1, 136.3, 131.1, 128.9, 128.5, 128.42 (2C), 128.40, 128.1, 127.2, 127.1, 126.7, 125.8, 123.1, 121.8, 117.6, 110.7, 67.0, 64.7, 58.7, 56.8, 54.6, 33.0, 30.7; HRMS

(Q-TOF-MS) $[M+H]^+$, calcd for $C_{33}H_{31}BrClN_2O$: 585.1308, found: 585.1309.

*4.3.3. 1,3-Dibenzyl-7-bromo-9-chloro-5-methyl-2,3,4,5-tetrahydro-1H-chromeno[4,3-d]pyrimidine (**1c**) and 1,3-dibenzyl-7-bromo-9-chloro-4-methyl-2,3,4,5-tetrahydro-1H-chromeno[4,3-d]pyrimidine (**2c**).* Chroman-4-one **5c** (0.100 g, 0.363 mmol) was reacted with *N*-methylenebenzylamine[19] (0.216 g, 1.82 mmol) and L-proline (12.5 mg, 0.109 mmol) according to the general procedure. Purification by flash chromatography using EtOAc/heptane (5→40%) followed by toluene as the eluent afforded **1c** (27 mg, 15%) and **2c** (41 mg, 23%) as yellow oils.

*4.3.3.1. Compound **1c**.* R_f=0.5 (10% EtOAc/toluene); IR 3161, 3081, 3030, 2363, 2338, 1692, 1457 cm^{-1}; ^1H NMR (400 MHz) δ 7.40–7.18 (m, 12H), 4.88 (q, J=6.5 Hz, 1H), 4.01–3.91 (m, 2H), 3.56–3.47 (m, 3H), 3.34 (d, J=11.0 Hz, 1H), 3.18 (d, J=16.8 Hz, 1H), 3.06 (d, J=16.8 Hz, 1H), 1.39 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz) δ 148.7, 138.3, 134.3, 131.1, 128.9, 128.5 (2C), 128.4 (2C), 128.3, 127.4, 127.1, 126.3, 121.3, 111.3, 99.9, 74.7, 67.3, 59.1, 54.5, 52.6, 19.4. Anal. Calcd for $C_{26}H_{24}BrClN_2O\cdot 0.5H_2O$: C, 61.86; H, 4.99; N, 5.55. Found: C, 61.91; H, 5.24; N, 5.49.

*4.3.3.2. Compound **2c**.* R_f=0.7 (5% EtOAc/toluene); IR 3159, 3074, 3028, 2973, 2930, 2826, 2359, 2336, 1651, 1559 cm^{-1}; ^1H NMR (400 MHz) δ 7.51–6.99 (m, 12H), 4.83 (d, J=13.3 Hz, 1H), 4.64 (d, J=13.3 Hz, 1H), 3.93–3.84 (m, 2H), 3.76 (d, J=13.6 Hz, 1H), 3.67 (d, J=11.4 Hz, 1H), 3.53 (d, J=13.6 Hz, 1H), 3.41–3.26 (m, 2H), 1.26 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz) δ 150.4, 138.7, 138.3, 135.1, 131.1, 128.9, 128.5, 128.4, 127.2, 127.1, 126.7, 123.4, 121.8, 120.6, 110.5, 99.9, 67.6, 63.1, 55.3, 54.3, 54.2, 16.0. HRMS (Q-TOF-MS) $[M+H]^+$, calcd for $C_{26}H_{25}^{77}BrClN_2O$: 495.0839, found: 495.0836.

4.4. Conformational analysis of general type VIII β-turns and derivatives 6 and 2a

For evaluation of the potential applicability of these novel ring systems as peptidomimetics their most stable conformations were compared to that of various β-turn conformations of peptides. An initial analysis indicated that the tricyclic ring systems of **1a** and **2a** mimic a type VIII β-turn. The conformational analyses were made on simplified structures of **1** denoted **6** (Fig. 6) and **2** (not shown) with methyl groups as substituents in the 5- and 7-positions, mimicking the possible orientation of attached chains. One nitrogen atom in the tetrahydropyrimidine ring was acetylated to correspond to the *N*-terminus of a peptide and the *C*-terminal was methylamidated. A low energy conformation of the novel ring system in **6** obtained from the NAMFIS calculations was aligned with an energy minimized type VIII β-turn with the amino acid sequence Ac–Gly-Ala-Ala-Gly–NHMe as shown in Fig. 6.[31,32] The dihedral angles of the β-turn VIII was constrained according to previously defined angles ($\Phi^{(i+1)}$=−60°, $\psi^{(i+1)}$=−30°, $\Phi^{(i+2)}$=−120° and $\psi^{(i+2)}$=120°).[31] The type VIII β-turn of the peptide was energy minimized using OPLS-2005 as the force field in a simulated water environment. The PRCG method was used with 500 iterations.

4.5. X-ray diffraction

Crystals of **1a** were obtained by recrystallization from EtOAc/hexane (1:1). The crystal structure determination was carried out on a Rigaku Saturn CCD area detector with graphite monochromated Mo Kα radiation (l=0.71073 Å) using χ and θ scans.[33] The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods and was refined by full-matrix least-squares on F.[34,35] Hydrogen atoms were refined using the riding model. The crystal data and experimental parameters are summarized in Supplementary data. Crystallographic data (excluding structure factors) for the structure **1a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 838242. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

NMR spectra of compounds **1a**–**c**, **2a**–**c** and **5c**; results from NAMFIS calculations of **1a** and **2a**; crystal data and refinement of **1a**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.077.

References and notes

1. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
2. Hong, B. C.; Kotame, P.; Tsai, C. W.; Liao, J. H. *Org. Lett.* **2010**, *12*, 776–779.
3. Lee, H.; Lee, K.; Jung, J. K.; Cho, J.; Theodorakis, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2745–2748.
4. Yu, D. L.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K. H. *Med. Res. Rev.* **2003**, *23*, 322–345.
5. Cottiglia, F.; Dhanapal, B.; Sticher, O.; Heilmann, J. *J. Nat. Prod.* **2004**, *67*, 537–541.
6. Dahlén, K.; Wallén, E. A.; Grøtli, M.; Luthman, K. *J. Org. Chem.* **2006**, *71*, 6863–6871.
7. Ankner, T.; Fridén-Saxin, M.; Pemberton, N.; Seifert, T.; Grøtli, M.; Luthman, K.; Hilmersson, G. *Org. Lett.* **2010**, *12*, 2210–2213.
8. Fridén-Saxin, M.; Pemberton, N.; Andersson, K. D.; Dyrager, C.; Friberg, A.; Grøtli, M.; Luthman, K. *J. Org. Chem.* **2009**, *74*, 2755–2759.
9. Wallén, E. A. A.; Dahlén, K.; Grøtli, M.; Luthman, K. *Org. Lett.* **2007**, *9*, 389–391.
10. Skrabek, R. Q.; Galimova, L.; Ethans, K.; Perry, D. *J. Pain* **2008**, *9*, 164–173.
11. Simon-Levert, A.; Arrault, A.; Bontemps-Subielos, N.; Canal, C.; Banaigs, B. *J. Nat. Prod.* **2005**, *68*, 1412–1415.
12. Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Filippelli, W.; Falcone, G.; Motola, G.; Mazzeo, F. *Farmaco* **1999**, *54*, 95–100.
13. Bruno, O.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocelli, E.; Ballabeni, V.; Chiavarini, M.; Bertoni, S.; Tognolini, M.; Impicciatore, M. *Bioorg. Med. Chem.* **2001**, *9*, 629–636.
14. Wang, Z. T.; Xu, L. W.; Xia, C. G.; Wang, H. Q. *Tetrahedron Lett.* **2004**, *45*, 7951–7953.
15. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
16. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748.
17. Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.
18. Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8–27.
19. Axén, A.; Grennberg, H.; Gogoll, A. *J. Chem. Res.* **1998**, 712–713.
20. Nevins, N.; Cicero, D.; Snyder, J. P. *J. Org. Chem.* **1999**, *64*, 3979–3986.
21. Erdelyi, M.; d'Auvergne, E.; Navarro-Vazquez, A.; Leonov, A.; Griesinger, C. *Chem.—Eur. J.* **2011**, *17*, 9368–9376.
22. Erdelyi, M.; Pfeiffer, B.; Hauenstein, K.; Fohrer, J.; Gertsch, J.; Altmann, K. H.; Carlomagno, T. *J. Med. Chem.* **2008**, *51*, 1469–1473.
23. Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem.* **2001**, *105*, 6474–6487.
24. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129.
25. *MacroModel v. 9.7*; Schrodinger: 2007; www.schrodinger.com.
26. Agrafiotis, D. K.; Gibbs, A. C.; Zhu, F. Q.; Izrailev, S.; Martin, E. *J. Chem. Inf. Model.* **2007**, *47*, 1067–1086.
27. Bonnet, P.; Agrafiotis, D. K.; Zhu, F. Q.; Martin, E. *J. Chem. Inf. Model.* **2009**, *49*, 2242–2259.
28. Cicero, D. O.; Barbato, G.; Bazzo, R. *J. Am. Chem. Soc.* **1995**, *117*, 1027–1033.
29. Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302–324.
30. Griesinger, C.; Sorensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1987**, *75*, 474–492.
31. Hutchinson, E. G.; Thornton, J. M. *Protein Sci.* **1994**, *3*, 2207–2216.
32. Floquet, N.; Hery-Huynh, S.; Dauchez, M.; Derreumaux, P.; Tamburro, A. M.; Alix, A. J. P. *Biopolymers* **2004**, *76*, 266–280.
33. *CrystalClear Software User's Guide*; Rigaku Corporation, Molecular Structure Corporation, (c): 2000; www.rigaku.com.
34. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435–435.
35. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *The DIRDIF-99 Program System*; University of Nijmegen: The Netherlands, 1999.