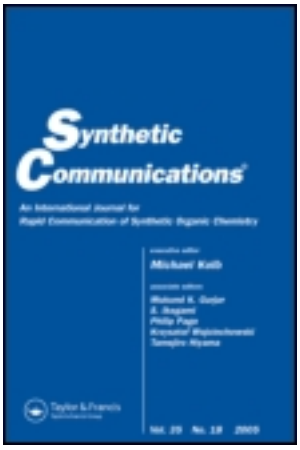

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Convenient Synthesis and Reactivity of Ethyl 8-amino-6-methyl-2,3-dihydro-4H-

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Convenient Synthesis and Reactivity of Ethyl 8-amino-6-methyl-2,3-dihydro-4*H*-1-benzopyran-2-carboxylate

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Abstract: We report and comprehensively describe the synthesis and reactivity of ethyl 8-amino-6-methyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate. This peptidomimetic building block provides a constrained template that allows for the introduction of various functionalities in a specific spatial orientation.

Keywords: Benzopyranes, 3,4-dihydro-2*H*-1-benzopyran derivatives, reduction, RGD mimetic

INTRODUCTION

The past decade has witnessed major advances in the field of GPIIb/IIIa (fibrinogen receptor) antagonists that are based predominantly on the Arg-Gly-Asp (RGD) minimal amino acid sequence. A large number of non-peptide RGD mimetics have been synthesized to obtain potent and orally deliverable compounds.[1] However, no such drug has yet passed clinical trials and new compounds with high affinity for the fibrinogen receptor and potential oral activity are still of interest.[2] A rigid scaffold that would bear the aspartate and guanidine mimicking elements in their proper spatial orientation is a promising key to molecules with high affinity for GP IIb/IIIa.[3] Numerous bicyclic scaffolds have been used as peptidomimetic blocks for this purpose. These include indole,[3] 3,4-dihydro-2*H*-benzopyran and

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tetrahydronaphthalene,[4] 3-oxo-1,4-benzodiazepine,[5] benzimidazole, benzoxazole,[6] and pyrrolidone.[7]

We have designed and synthesized the hitherto unknown compound ethyl 8-amino-6-methyl-2,3-dihydro-4*H*-1-benzopyran-2-carboxylate. This heterocycle constitutes a scaffold suitable for introducing various functionalities to achieve the specific spatial orientation of the pharmacophoric groups required for interaction with the receptor binding sites (Figure 1). The parent bicycle has proven its versatility in the synthesis of novel dopamine D_2 partial agonists.[8] The similar basic structures were prepared as components of receptor molecules.[9]

The synthesis of ethyl 8-amino-6-methyl-2,3-dihydro-4*H*-1-benzopyran-2-carboxylate is outlined in Scheme 1. Treatment of the starting 2′-hydroxy-5′-methylacetophenone (commercially available from Acros Organics) with nitric acid in glacial acetic acid (**1**) gave the corresponding nitro compound (**2**).[10] This was followed by Claisen condensation of acetophenone **2** with diethyl oxalate to give **3**. The later was subjected to intramolecular addition with subsequent dehydration under acidic conditions. An similar condensation route (steps 2 and 3, Scheme 1) was reported by Barker and Ellis,[11] whereas Naylor et al. reported a condensation procedure with previous benzylation of the phenol compound.[12] A one-step transformation of **4** to **6** was achieved by catalytic hydrogenation. To the best of our knowledge, the detailed synthetic procedure of this step has not been published yet. This prompted us to intensely explore reaction conditions of this one-step multiple reduction. An initial attempt, using palladium on activated charcoal (10%) as the catalyst under normal conditions (1 bar, rt), resulted in reduction of the nitro group (**5**). The hydrogenation reaction proceeded further under higher pressure and temperature (7 bar, 50°C), but after 5 h MS analysis still showed the presence of peaks with m/z 235 (**6**) and 251 (presumably **7**). The presence of

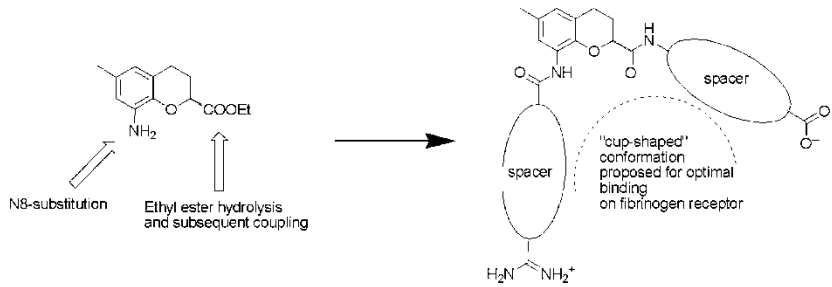
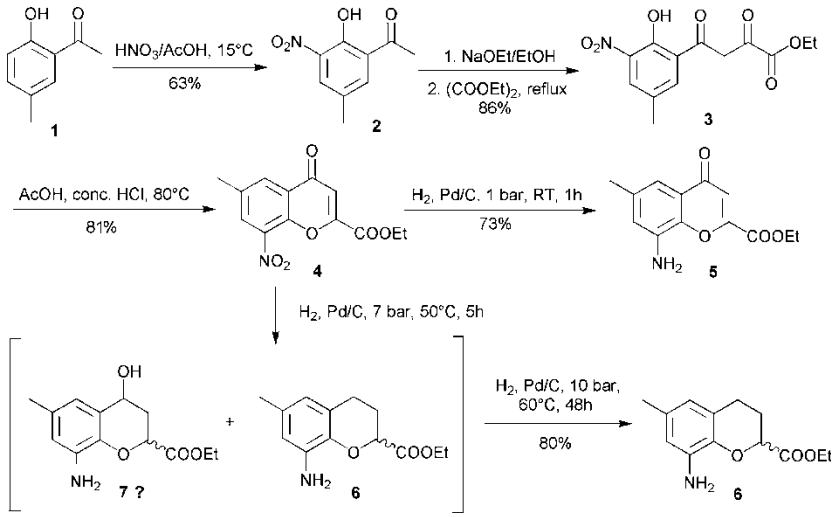


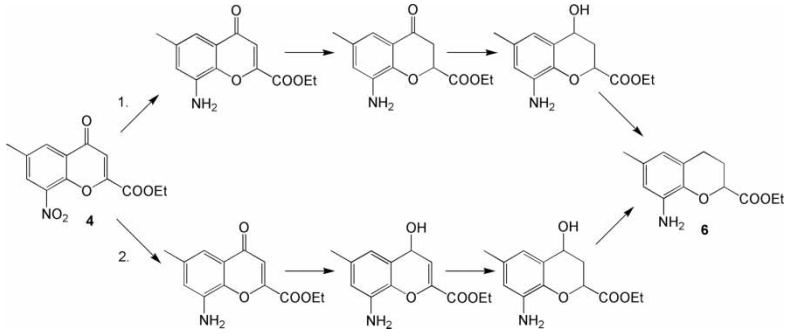
Figure 1. Ethyl 8-amino-6-methyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate as a scaffold suitable for introducing various functionalities at positions 2 and 8 by formation of amide bonds. The constrained scaffold is supposed to mimic "cup-shaped" conformation of the RGD tripeptide that could lead to more potent GPIIb/IIIa antagonists (the term "cup-shaped" originally refers to the conformation of the RGD-sequence peptide backbone in reported peptide antagonists).[1a,4]



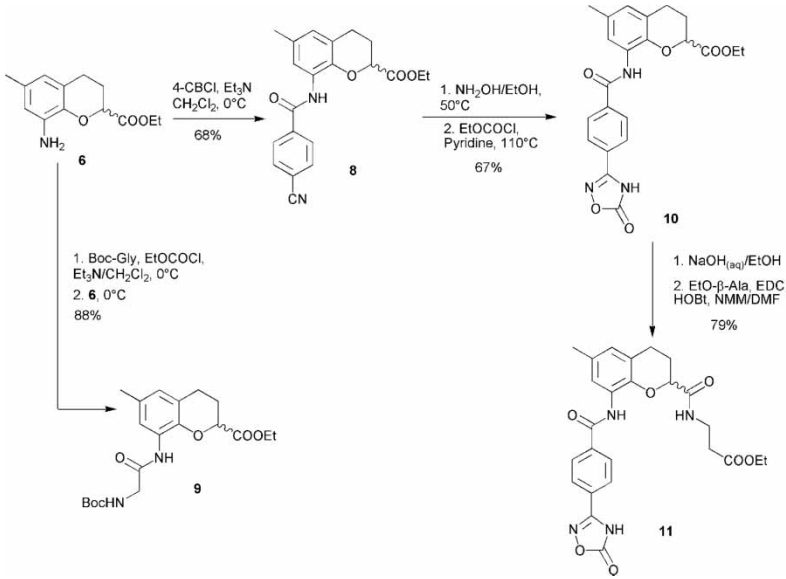
Scheme 1.

the higher m/z peak suggested that the reduction proceeds in the following order: the reduction of the nitro group to an amine, double bond hydrogenation, and further reduction of the keto group to methylene via a hydroxy derivative (1, Scheme 2), although the alternative pathway seems possible (2, Scheme 2). The reaction went to completion under more rigorous conditions (10 bar, 60°C, 48 h).

The reactivity of the bicyclic product was studied by derivatization of **6** at positions 2 and 8 (Scheme 3). At position 8, only coupling with strong electrophilic species such as acyl halides or anhydrides was achieved. This is due to extremely low nucleophilic character of the amino group at position 8. At position 2, facile amide bond formation was observed after ethyl ester alkali-mediated saponification.



Scheme 2.



Scheme 3.

CONCLUSIONS

In conclusion, we report an efficient and simple protocol for the synthesis of ethyl 8-amino-6-methyl-2,3-dihydro-4*H*-1-benzopyran-2-carboxylate. This bicyclic compound can be readily substituted at the amino group at position 8 and the carboxyl group at position 2. Thus it can be envisaged as a template that allows introduction of various functionalities in specific spatial orientations. Utilization of this template for the preparation of new GPIIb/IIIa antagonists is under progress.

EXPERIMENTAL

General

Chemicals from Aldrich Chemical Co., Fluka, and Acros Organics were used without further purification. Anhydrous solvents were prepared according to standard procedures.[13] Analytical TLC was performed on Merck silica-gel (60 GF 254) plates (0.25 mm) and components were visualized with ultraviolet light (254-nm wavelength). Column chromatography was carried out on silica gel 60 (particle size 240–400 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AVANCE DPX_{300} spectrometer in $CDCl_3$ or DMSO-d_6

solution with TMS as the internal standard. IR spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrometer. Microanalyses were performed on a Perkin-Elmer C, H, N analyzer 240 C. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer. All yields relate to purified products.

1-(2-Hydroxy-5-methyl-3-nitrophenyl)-1-etanone 2. To a cooled (15°C) solution of 2′-hydroxy-5′-methylacetophenone (**1**, 15.20 g, 101 mmol) in 90 mL of glacial acetic acid the nitric acid (65%, 5.0 mL, 110 mmol) was added stepwise and the mixture stirred for 4 h. The temperature was allowed to rise to rt and stirring continued overnight. The pale yellowish crystals, which precipitated from the reaction mixture, were filtered off and recrystallized from ethanol. Yield: 12.3 g (63%). Mp 129–131°C. (KBr, cm^{-1}): 3460, 3077, 1654, 1578, 1526, 1458, 1362, 1344, 1267, 1181, 1107, 979, 876, 802, 759, 661, 586. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.86 (d, 1H, $J = 2.0$ Hz, Ar-H), 8.09 (d, 1H, $J = 2.0$ Hz, Ar-H), 12.87 (s, 1H, OH) ppm. MS (EI) = 195 (M^+). Anal. calcd. for $C_9H_9N_1O_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.12; H, 4.33; N, 6.95.

Ethyl 4-(2-hydroxy-5-methyl-3-nitrophenyl)-2,4-dioxobutanoate 3. To a solution of sodium (4.60 g, 200 mmol) in anhydrous ethanol (100 mL) 2′-hydroxy-5′-methyl-3′-nitroacetophenone (**2**, 9.76 g, 50.0 mmol) was added during vigorous stirring. After 30 min of stirring, diethyl oxalate (20.4 mL, 150 mmol) was added and the reaction mixture heated under reflux for a further 2 h. The reaction mixture was allowed to cool to rt and was poured over the mixture of 60 mL of 4 M HCl and 90 g of ice. The precipitated crystals were filtered off, dried at high temperature (60°C), and ccompound recrystallized from ethanol. Yield: 12.7 g (86%). Mp 146–149°C. IR (KBr, cm^{-1}): 3444, 1731, 1628, 1530, 1458, 1269, 1075, 979, 832, 790, 747. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.21 (t, 3H, $J = 7.1$ Hz, $CH_2\underline{CH_3}$), 2.37 (s, 3H, Ar-CH_3), 3.06 (d, 1H, $J = 16.5$ Hz, $COCH_2CO$), 3.44 (d, 1H, $J = 16.5$ Hz, $COCH_2CO$), 4.22 (q, 2H, $J = 7.1$ Hz $\underline{CH_2}CH_3$), 7.86 (d, 1H, $J = 2.0$ Hz, Ar-H), 8.06 (d, 1H, $J = 2.0$ Hz, Ar-H), 8.69 (s, 1H, OH) ppm. MS (FAB) = 296 (MH^+). Anal. calcd. for $C_{13}H_{13}N_1O_7$: C, 52.88; H, 4.44; N, 4.74. Found: C, 52.62; H, 4.21; N, 4.54.

Ethyl 6-methyl-8-nitro-4-oxo-4*H*-chromene-2-carboxylate 4. Compound **3** (8.86 g, 30.0 mmol) was dissolved in 75 mL of glacial acetic acid and 5 mL of conc. HCl. The reaction mixture was heated at 80°C for 2 h, allowed to cool to rt, and poured onto 30 g of ice. The precipitated product was filtered off and purified with column chromatography using $CHCl_3$ as an eluent. Yield: 6.70 g (81%). Mp 148–151°C. IR (KBr, cm^{-1}): 3478, 3076, 2986, 1750, 1663, 1625, 1540, 1474, 1355, 1268, 1243, 1187, 1096, 1020, 872, 835, 781. ^{1}H NMR (DMSO-d_6, 300 MHz): δ1.46 (t, 3H, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 2.57 (s, 3H, Ar-CH_3), 4.48 (q, 2H, $J = 7.0$, Hz $\underline{CH_2}CH_3$), 7.17 (s, 1H, CO–CH =), 8.22 (s, 1H, Ar-H), 8.26 (s, 1H, Ar-H) ppm. MS (EI) = 277 (M^+). Anal. calcd. for $C_{13}H_{11}N_1O_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 55.90; H, 3.65; N, 4.72.

Ethyl 8-amino-6-methyl-4-oxo-4*H*-chromene-2-carboxylate 5. Argon was bubbled into a solution of **4** (0.277 g, 1.00 mmol) in glacial acetic acid (12 mL) and palladium (10% by weight, 10% on active charcoal) was added stepwise. Hydrogen was bubbled into the suspension and stirring continued under 1 atm of hydrogen at rt until no nitro compound was detected with TLC. After the catalyst was filtered off, 30 mL of water was added and crude Na_2CO_3 used to adjust the pH to ~8. Water phase was extracted with 3 × 30 mL of ethyl acetate and the organic phase was collected, dried over Na_2SO_4, and evaporated under vacuum to give crude product. The pure crude product was obtained using column chromatography with $CHCl_3$ as an eluent. Yield: 0.179 g (73%). Mp 127–132°C. IR (KBr, cm^{-1}): 3447, 3342, 1741, 1638, 1485, 1365, 1278, 1250, 1100, 1019, 837, 782, 628, 548. ^1H NMR ($CDCl_3$, 300 MHz): δ1.42 (t, 3H, $J = 7.1$ Hz, $CH_2\underline{CH_3}$), 2.34 (s, 3H, Ar-CH_3), 4.35 (s, 2H, NH_2), 4.44 (q, 2H, $J = 7.1$ Hz $\underline{CH_2}CH_3$), 6.87 (s, 1H, CO–CH =), 7.04 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H) ppm. MS (EI) = 247 (M^+). HRMS calcd. for $C_{13}H_{13}N_1O_4$: 247.085050. Found: 247.084458.

Ethyl 8-amino-6-methyl-2-chromanecarboxylate 6. Argon was bubbled into a solution of **4** (1.00 g, 4.04 mmol) and conc. HCl (0.20 mL) in anhydrous ethanol (120 mL) and palladium (10% by weight, 10% on active charcoal) was added stepwise. The reaction mixture was placed in the Parr high-pressure apparatus. Hydrogen was bubbled into the suspension and stirring continued under 7 bar of hydrogen at 50°C for the period of 5 h. A small amount of reaction mixture was filtered and the solvent evaporated under vacuum. The oily residue was analysed with mass spectrometry to confirm the formation of desired product. The rest of the reaction mixture was continued stirring under 10 bar of hydrogen at 60°C until the completion of the reaction was detected with TLC (another 48 h). The catalyst was filtered off and the solvent evaporated under vacuum. The residue was dissolved in 30 mL of water and crude Na_2CO_3 was added to adjust the pH (~8). Water phase was extracted with 3 × 30 mL of ethyl acetate and the organic phase collected, dried over Na_2SO_4, and evaporated under vacuum to give a dark brown oily product. Yield: 0.761 g (80%). IR (KBr, cm^{-1}): 2930, 1731, 1494, 1378, 1215, 1093, 857. ^1H NMR ($CDCl_3$, 300 MHz): δ1.31 (t, 3H, $J = 6.6$ Hz, $CH_2\underline{CH_3}$), 2.19 (s, 3H, Ar-CH_3), 2.24 (m, 2H, $CH_2\underline{CH_2}CH$), 2.74 (m, 2H, $\underline{CH_2}CH_2CH$), 3.76 (s, 2H, NH_2), 4.26 (q, 2H, $J = 6.6$ Hz $\underline{CH_2}CH_3$), 4.71 (m, 1H, $CH_2CH_2\underline{CH}$), 6.28 (s, 1H, Ar-H), 6.41 (s, 1H, Ar-H) ppm. MS (EI) = 236 (M^+). Anal. calcd. for $C_{13}H_{17}N_1O_3 \times 0.25\ H_2O$: C, 65.25; H, 7.37; N, 5.85. Found: C, 65.47; H, 7.59; N, 5.69.

Ethyl 8-[(4-cyanobenzoyl)amino]-6-methyl-2-chromanecarboxylate 8. To a cooled (−10°C) solution of amine (0.500 g, 2.13 mmol) and triethylamine (0.30 mL, 2.13 mmol) in distilled dichloromethane (20 mL), 4-cyanobenzoyl chloride (0.353 g, 2.13 mmol) was added stepwise and the mixture stirred for 6 h. During stirring, the temperature was allowed to rise to rt. The reaction

mixture was washed with water (20 mL), 10% aqueous citric acid (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude residue was recrystallized from ethanol to give white crystals. Yield: 0.528 g (68%). Mp 169–172°C. IR (KBr, cm^{-1}): 3327, 2229, 1730, 1655, 1550, 1466, 1222, 1028, 857, 668. ^1H NMR ($CDCl_3$, 300 MHz): δ1.33 (t, 3H, $J = 7.0$ Hz, $CH_2\underline{CH_3}$), 2.18 (m, 1H, $CH_2\underline{CH_2}CH$), 2.33 (s, 3H, Ar-CH_3), 2.37 (m, 1H, $CH_2\underline{CH_2}CH$), 2.80 (m, 2H, $\underline{CH_2}CH_2CH$), 4.29 (q, 2H, $J = 7.0$ Hz, $\underline{CH_2}CH_3$), 4.79 (m, 1H, $CH_2CH_2\underline{CH}$), 6.69 (s, 1H, Ar-H), 7.81 (d, 2H, $J = 8.7$ Hz, AB-Ar), 8.04 (d, 2H, $J = 8.7$ Hz, A′B′-Ar) 8.19 (s, 1H, Ar-H), 8.66 (s, 1H, Ar-NHCO) ppm. MS (EI) = 365 (M^+). Anal. calcd. for $C_{21}H_{20}N_2O_4 \times 0.75\ H_2O$: C, 66.75; H, 5.73; N, 7.41. Found: C, 66.50; H, 5.99; N, 7.80.

Ethyl 8-({2-[(*tert*-butyloxycarbonyl)amino]acetyl}amino)-6-methyl-2-chromanecarboxylate 9. To a cooled (0°C) solution of Boc-Glycine (0.410 g, 2.34 mmol) and triethylamine (0.384 mL, 2.76 mmol) in distilled dichloromethane (30 mL), ethyl chloroformate (0.22 mL, 2.34 mmol) was added stepwise. After 15 min of stirring, the compound **6** (0.500 g, 2.125 mmol), dissolved in 10 mL of distilled dichloromethane, was added. The stirring was continued overnight and the temperature was allowed to rise to rt. The reaction mixture was washed with water (30 mL), 0.01 M HCl (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under vacuum to give pale brown oily compound. Yield 0.737 g (88%). IR (KBr, cm^{-1}): 3392, 2981, 1718, 1542, 1458, 1368, 1250, 1201, 1168, 1096, 1026, 856, 778. ^1H NMR (DMSO-d_6, 300 MHz): δ1.31 (t, 3H, $J = 7.1$ Hz, $CH_2\underline{CH_3}$), 1.48 (s, 9H, 3 × CH_3), 2.19 (m, 2H, $CH_2\underline{CH_2}CH$), 2.37 (s, 3H, Ar-CH_3), 2.75 (m, 2H, $\underline{CH_2}CH_2CH$), 3.98 (d, 2H, $J = 4.9$ Hz, $\underline{CH_2}NHCO$), 4.26 (q, 2H, $J = 7.1$ Hz $\underline{CH_2}CH_3$), 4.75 (m, 1H, $CH_2CH_2\underline{CH}$), 5.23 (s, 1H, $CH_2\underline{NH}CO$), 6.61 (s, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 8.27 (s, 1H, Ar-NHCO) ppm. MS (EI) = 392 (M^+). HRMS calcd. for $C_{20}H_{28}N_2O_6$: 392.195650. Found: 392.194737.

Ethyl 6-methyl-8-{[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzoyl]amino}-2-chromanecarboxylate 10. To a suspension of hydroxylammonium chloride (0.765 g, 11.0 mmol) in anhydrous ethanol (20 mL), triethylamine (1.53 mL, 11.0 mmol) was added and the resulting solution stirred for 20 min, after which a solution of **8** (1.380 g, 3.78 mmol) in anhydrous ethanol (10 mL) was added and the mixture was heated at 50°C overnight. The product was precipitated by cooling in the refrigerator and filtered off. The crude product was used without further purification in the next step; in 1.0 g of the latter (2.52 mmol) in freshly distilled pyridine (15 mL), argon was bubbled for 5 min. Afterward, ethyl chloroformate (0.26 mL, 2.77 mmol) was added dropwise, stirred for 45 min in an ice bath and then 30 min at rt. Again, the argon was bubbled in and the mixture heated under reflux (∼120°C) overnight. The solvent was evaporated under vacuum and the

water (30 mL) was poured onto crude residue. The water phase was acidified with 1 M HCl (pH ≅ 2) and extracted with ethyl acetate (3 × 30 mL). Collected organic phase was washed with 1 M HCl (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under vacuum. Yield: 0.69 g (67%). Mp 255–260°C. IR (KBr, cm^{-1}): 3384, 3196, 2977, 1737, 1650, 1546, 1462, 1220, 866, 670. ^{1}H NMR (DMSO-d_6, 300 MHz): δ1.20 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 2.05 (m, 1H, $CH_2\underline{CH_2}CH$), 2.23 (s, 3H, Ar-CH_3), 2.27 (m, 1H, $CH_2\underline{CH_2}CH$), 2.64 (m, 1H, $\underline{CH_2}CH_2CH$), 2.81 (m, 1H, $\underline{CH_2}CH_2CH$), 4.16 (q, 2H, $J = 7.2$ Hz $\underline{CH_2}CH_3$), 4.92 (m, 1H, $CH_2CH_2\underline{CH}$), 6.75 (d, 1H, $J = 1.5$ Hz, Ar-H), 7.53 (d, 1H, $J = 1.5$ Hz, Ar-H), 7.96 (d, 2H, $J = 8.7$ Hz, AB-Ar), 8.10 (d, 2H, $J = 8.7$ Hz, A′B′-Ar), 9.43 (s, 1H, Ar-$\underline{NH}$CO) ppm. MS (FAB) = 424 (MH^+). Anal. calcd. for $C_{22}H_{21}N_3O_6$: C, 62.41; H, 5.00; N, 9.92. Found: C, 62.14; H, 5.18; N, 9.65.

Ethyl 3-{[(6-methyl-8-{[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) benzoyl]amino}-3,4-dihydro-2*H*-chromen-2-yl)carbonyl]amino}propanoate 11. To a dispersion of **10** (0.660 g, 1.56 mmol) in 96% ethanol (30 mL), 1 M NaOH (4.70 mL, 4.70 mmol) was added and stirred at rt until no starting compound was detected by TLC. The solvent was evaporated under vacuum and residue dissolved in water (10 mL). The water phase was acidified with 1 M HCl (pH ≅ 2) and the precipitated product was filtered off and dried at 60°C (M = 0.502 g, 81%). The crude product was used without further purification in the next step; to a cooled (−10°C) solution of carboxylic acid (0.180 g, 0.46 mmol) and ethyl β-alanine (0.078 g, 0.50 mmol) in anhydrous *N,N*-dimethylformamide (15 mL), 1-hydroxybenzotriazole (HOBt) monohydrate (0.084 g, 0.55 mmol) and *N*-methylmorpholine (0.15 mL, 1.4 mmol) were added. The pH of the mixture was checked with wet pH-indicator strip (∼8) and *N*-ethyl-*N*′-(dimethylaminopropyl)carbodiimide hydrochloride (EDC × HCl) (0.115 g, 0.59 mmol) was added. The temperature was allowed to rise to rt and the mixture was stirred until complete conversion to the final product was detected with TLC. The solvent was evaporated and the residue was dissolved in ethyl acetate (20 mL), washed with aqueous citric acid (10%, 2 × 20 mL) and brine (20 mL), and dried over Na_2SO_4. The solvent was evaporated under vacuum to yield crude amorphus product. Yield: 0.221 g (79%). Mp 198–205°C. IR (KBr, cm^{-1}): 3360, 3090, 1797, 1727, 1652, 1548, 1466, 1220, 1077, 939, 858, 735, 674. ^{1}H NMR (DMSO-d_6, 300 MHz): δ1.10 (t, 3H, $J = 7.2$ Hz, $CH_2\underline{CH_3}$), 2.07 (m, 2H, $CH_2\underline{CH_2}CH$), 2.23 (s, 3H, Ar-CH_3), 2.28 (t, 2H, $J = 3.8$ Hz, $CONHCH_2\underline{CH_2}CO$), 2.73 (m, 2H, $\underline{CH_2}CH_2CH$), 3.42 (m, 2H, $CONH\underline{CH_2}CO$), 3.95 (q, 2H, $J = 7.2$ Hz $\underline{CH_2}CH_3$), 4.67 (m, 1H, $CH_2CH_2\underline{CH}$), 6.79 (s, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.98 (d, 2H, $J = 8.5$ Hz, AB-Ar), 8.14 (d, 2H, $J = 8.5$ Hz, A′B′-Ar), 8.54 (t, 1H, $J = 5.1$ Hz, $CH_2\underline{NH}CO$), 10.00 (s, 1H, Ar-NHCO) ppm. MS (FAB) = 495 (MH^+). Anal. calcd. for $C_{25}H_{26}N_4O_7 \times 0.5\ H_2O$: C, 59.84; H, 5.41; N, 11.13. Found: C, 60.13; H, 5.41; N, 10.99.

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