Synthesis of the Imidazole-Derived AT_1-Selective ANG II Receptor Antagonist HR 720 Utilizing Reductive Amination as Key Step

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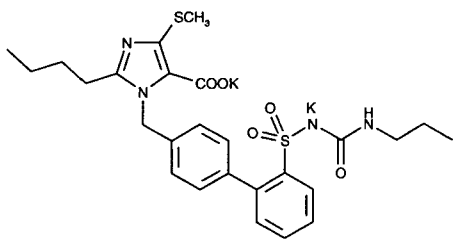
The straightforward synthesis of the (1-methylbiphenylsulfonyl)-urea substituted imidazole HR 720, an orally active ANG II receptor antagonist, by reductive amination of 2′-sulfonamidobiphenylcarbaldehydes, derived from Suzuki-type phenyl-phenyl coupling procedures, as key step is described.

Antagonists of the angiotensin II (ANG II) receptors are the newest entity to the therapeutic armory for the treatment of hypertensive diseases.[1] The prototype and most advanced compound of this class is the AT_1-selective antagonist losartan (DUP 753, Cosaar)[2] developed by DuPont-Merck, which has already demonstrated an excellent safety and tolerability profile in long-term clinical trials in patients with essential hypertension.[3]

The discovery of losartan and its oral efficacy instigated major work by many pharmaceutical companies towards the synthesis of other non-peptide ANG II antagonists. Albeit a great variety of very potent compounds have been reported,[4] the majority of them still contained the biphenyltetrazole moiety of losartan. Although serving as a powerful acidic group at the 2′-biphenyl position which is essential for gaining oral activity, the common 2′-tetrazole also may be responsible for rapid metabolism and clearance via glucuronidation[5] resulting in loss of biological efficacy.

Recently, (imidazolylbiphenylyl)sulfonylureas and -sulfonylcarbamates have been described as new non-tetrazole ANG II receptor antagonists.[6] The most promising compound derived from this series is the orally active, AT_1-selective antagonist HR 720 **(1)** with a 2′-propylsulfonylurea substituent as isosteric surrogate for the tetrazole moiety.



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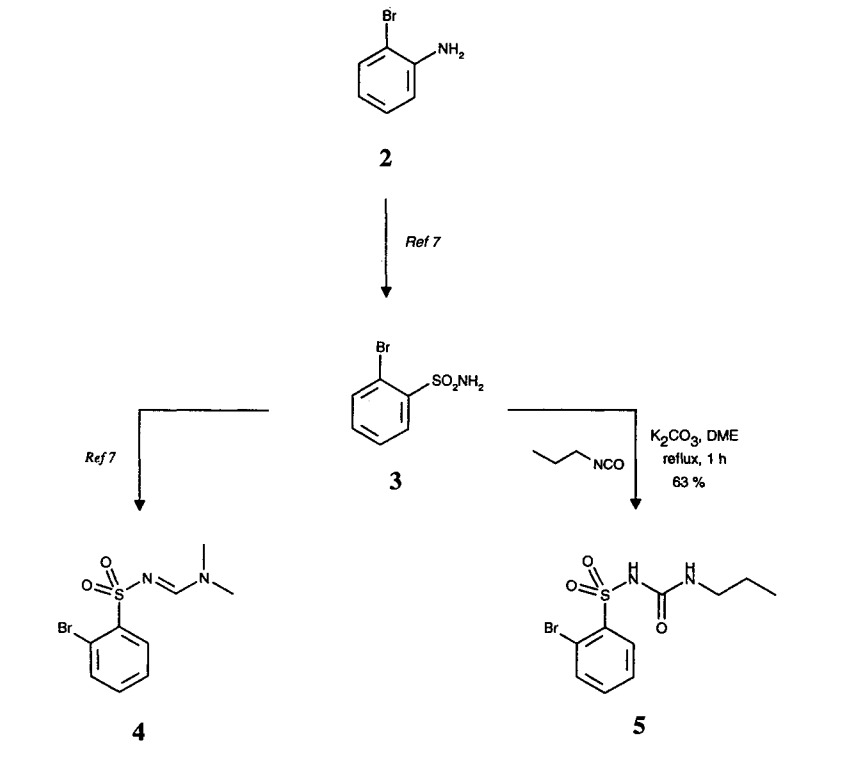
This compound exhibits favourable pharmacological properties when compared to the analogous tetrazole derivative as well as to DUP 753 or its active metabolite EXP 3174.[6]

Originally, HR 720 **(1)** was synthesized like many other ANG II antagonists by a convergent approach via *N*-alkylation of the appropriate imidazole with the requisite 4′-bromomethyl-1,1′-biphenyl.[6] Here we describe an alternative preparative access for 1-alkylated imidazoles by reductive amination of the biphenyl 4′-carbaldehydes **6** and **7** as key synthetic step. This pathway provides intermediates suitable for the introduction of a variety of substituents for the future imidazole positions 2 and 4 during the course of the synthesis and avoids N_1/N_3-regioisomer separation associated with the current *N*-alkylations on a preformed imidazole. The first segment of this approach was the synthesis of aldehydes **6** and **7** as outlined in Scheme 1.

The biphenyl-4′-carbaldehyde **6** has been prepared recently in good yield, employing a Suzuki-type coupling procedure, from 1-bromo-*N*-[(dimethylamino)methylene]benzene-2-sulfonamide **(4)** and 4-formylbenzeneboronic acid in a way which is suitable even for large-scale preparations.[7] Similar Pd(0)-catalysed coupling of 1-bromo-*N*-[(propylamino)carbonyl]benzene-2-sulfonamide **(5)** with 4-formylbenzeneboronic acid provided in comparable yield aldehyde **7** which is already linked with the final 2-propylsulfonylurea residue.[8] This avoids the need for a protection/deprotection sequence of reactions within the pathway towards **1**. The synthesis of both bromides started from 2-bromobenzenesulfonamide **(3)** derived from 2-bromoaniline **(2)** by diazotization, Cu(I)-mediated sulfonyl chloride formation in a sulfur dioxide/acetic acid solution followed by treatment with aqueous ammonia in a one-pot procedure. Subsequent reaction with $DMF/POCl_3$[7] or propyl isocyanate provided the desired bromides **4** and **5**, respectively. The application of these aldehydes **6** and **7** for the synthesis of HR 720 **(1)** is shown in Scheme 2.

The reductive amination of the aldehydes **6** and **7** with the freshly prepared tosylate of ethyl aminocyanoacetate **(9)** provided the desired secondary amines **10** and **11** in yields of 72% and 68%, respectively. In both reactions sodium triacetoxyborohydride formed in situ from $NaBH_4$ and glacial acid was used as the reducing agent for the intermediate imines derived from the acid catalysed condensation of the components.[9,10] The *N*-acylated compound **13** was derived either immediately by acylation of **11** with pentanoyl chloride or from **12** by amidine deprotection with hydrogen chloride in 1,2-dimethoxyethane (DME) followed by treatment of the 2-biphenylsulfonamide derivative obtained with propyl isocyanate.[6] The yield of **13** via acylation of **11** is moderate (40%) due to the formation of ethyl cyano[({2′-[(*N*-pentanoylamino)sulfonyl]1,1′-biphenyl-4-yl}methyl)-*N*-pentanoylamino]acetate **(17)**, the yield of which could be decreased by using lower reaction temperatures.

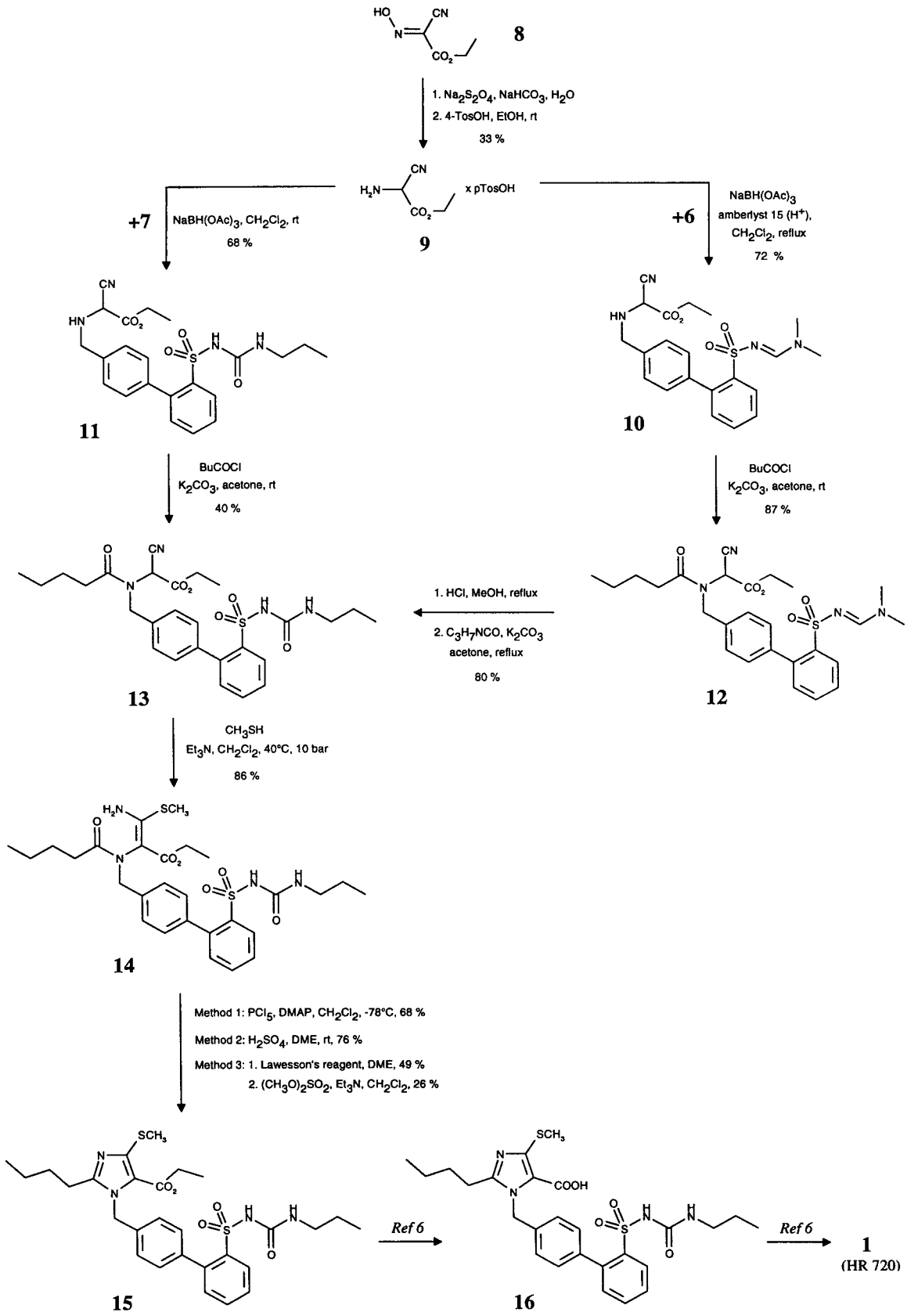


Scheme 1

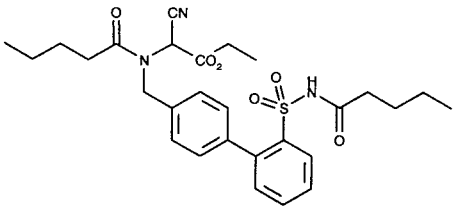
Compound **14** was obtained in excellent yield by addition of methyl mercaptan to the nitrile as described for the synthesis of the appropriate unsubstituted imidazole.[6] The following intramolecular cyclisation to the 1*H*-imidazole **15** was achieved in similar good yields (68% and 78%, respectively) either using PCl_5/DMAP at low temperature (−78 °C)[6] or H_2SO_4 in DME at ambient temperature. Alternatively, the ester **15** was also obtained in moderate yield by two-step procedure via the corresponding 1-thioxo derivative of **14** prepared by treatment with Lawesson's reagent[11] (accompanied by the formation of 9% of **15**) followed by *S*-alkylation with dimethyl sulfate which facilitates the intramolecular nucleophilic attack on the thioamide group. Saponification of the resultant ethyl ester **15** in aqueous methanolic NaOH solution furnished the imidazole-5-carboxylic acid **16** which finally was converted into its dipotassium salt **1** (HR 720), which exhibits a higher stability towards decarboxylation than its precursor.[6]

In summary, the present paper describes an alternative and convenient synthesis of the (imidazolylbiphenyl)sulfonylurea HR 720 **(1)**, a promising, orally active, non-tetrazole ANG II receptor antagonist. The key step is the reductive amination of 4′-formylbiphenyl-2-sulfonamide derivatives with ethyl aminocyanoacetate. This pathway avoids N_1/N_3 imidazole isomer separation associated with the common convergent approach to imidazole derived ANG II antagonists via *N*-alkylation of an entire imidazole moiety and provides preparatively useful intermediates for the synthesis of compounds in new imidazole series.

Solvents and other reagents were used without further purification unless otherwise stated. Column chromatography was carried out on E. Merck silica gel 60 (0.04–0.063 mm). The NMR spectra were recorded on a Bruker AM 270. Chemical shifts are reported as δ values from an internal TMS standard. Positive FAB mass spectra were obtained on a Kratos MS 902 in a 3-nitrobenzylic alcohol matrix using xenon as the target gas. DCI mass spectra were meas-



Scheme 2



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ured on a Kratos MS 80 RFA using isobutane as reagent gas. Elemental analyses were determined by the analytical laboratories, Hoechst AG.

1-Bromo-*N*-[(propylamino)carbonyl]benzene-2-sulfonamide (5):
A mixture of 2-bromobenzenesulfonamide (**3**; 3.5 g, 15.0 mmol) and K_2CO_3 (4.1 g, 30.0 mmol) in DME (50 mL) was refluxed for 1 h. After addition of propyl isocyanate (3.0 mL, 30.0 mmol) the mixture was refluxed for an additional 12 h. The pH of the mixture was adjusted to 5–6 at 0 °C using an aqueous solution of 5% $NaHSO_4$ followed by extraction with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Crystallization from EtOAc (40 mL) furnished 3.0 g (64%) of **5** as a white solid.

^{1}H NMR (DMSO-d_6): δ = 8.10 (m, 1H), 7.85 (m, 1H), 7.62 (m, 2H), 6.40 (t, J = 7.0 Hz, 1H), 2.90 (dd, J = 9.5, 7.0 Hz, 2H), 1.35 (m, J = 7.0 Hz, 2H), 0.75 (t, J = 7.0 Hz, 3H).

MS(DCI): m/z = 321/323 ($M+H^+$).

Anal. calc. for $C_{10}H_{13}BrN_2O_3S$ (321.2): C 37.40, H 4.08, N 8.72; found: C 37.2, H 4.2, N 8.6.

4′-Formyl-*N*-[(propylamino)carbonyl]-(1,1′-biphenyl)-2-sulfonamide (7):
To a solution of **5** (770.0 mg, 2.4 mmol) and Ph_3P (70.0 mg, 0.3 mmol) in toluene (10 mL) was added Cs_2CO_3 (1.17 g, 3.6 mmol) in water (10 mL). The mixture was flushed with argon and $Pd(OAc)_2$ (30.0 mg, 0.1 mmol) was added at 60 °C. After 10 min, 4-formylbenzeneboronic acid[7] (390.0 mg, 2.6 mmol) was added. The mixture was stirred for 5 h at 75 °C. After concentration and addition of buffer (pH 5, 100 mL), the mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography with EtOAc/heptane (2 : 1) provided 620.0 mg (75%) of **7**; mp 160 °C.

^{1}H NMR (DMSO-d_6): δ = 10.10 (s, 1H), 9.92 (s, 1H), 8.1–7.9 (m, 3H), 7.4–7.8 (m, 4H), 7.1–7.4 (m, 1H), 2.85 (dd, J = 9.5, 7.0 Hz, 2H), 1.32 (m, J = 9.5, 7.0 Hz, 2H), 1.04 (t, J = 7.0 Hz, 3H).

MS(DCI): m/z = 347 ($M+H^+$).

Anal. calc. for $C_{17}H_{18}N_2O_4S$ (346.4): C 58.94, H 5.24, N 8.09; found: C 59.1, H 5.2, N 8.2.

Ethyl Aminocyanoacetate 4-Toluenesulfonate (9):
Ethyl (*E*)-cyanohydroxyiminoacetate (**8**; 50.0 g, 35.2 mmol) was dissolved in water (440 mL) and sat. aq $NaHCO_3$ solution (340 mL). $Na_2S_2O_4$ (150 g, 95.0 mmol) was added and the resulting mixture stirred at 35 °C for 30 min. The mixture was saturated with NaCl (20 g), extracted with CH_2Cl_2 (5 × 150 mL), the combined extracts dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O (220 mL) and the solution treated with TsOH (44.0 g, 23.2 mmol) in EtOH (110 mL). After addition of Et_2O (740 mL) and cooling, the precipitate was removed by filtration, washed with cold Et_2O (200 mL), and dried under reduced pressure to provide 35.2 g (33%) of **9** as a white solid; mp 128–130 °C.

Anal. calc. for $C_{12}H_{16}N_2O_5S$ (300.3): C 47.99, H 5.37, N 9.33; found: C 48.0, H 5.2, N 9.2.

Ethyl Cyano[({2′-[(dimethylamino)methylene]aminosulfonyl}1,1′-biphenyl-4-yl)methylamino]acetate (10):
A solution of **6**[7] (12.3 g, 29.2 mmol) in CH_2Cl_2 (60 mL) was added to a mixture of **9** (13.0 g, 43.3 mmol) and the ion exchange resin Amberlyst 15 (H^+) (1.0 g) in CH_2Cl_2 (30 mL). After stirring for 7 h at reflux this solution was added to a suspension prepared by introduction of glacial AcOH (14.2 mL) to a suspension of $NaBH_4$ (3.1 g, 82.1 mmol) in CH_2Cl_2 (60 mL) at 10 °C followed by stirring at r.t. for 1 h. After the addition was complete, stirring was continued at r.t. for 14 h. After filtration of the precipitate the separated organic layer was washed with water (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by chromatography using CH_2Cl_2/EtOAc (85 : 15) as eluent provided 9.0 g (72%) of **10** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 8.27 (m, 1H), 7.51 (m, 2H), 7.39 (s, 3H), 7.22 (m, 1H), 7.16 (s, 1H), 4.38 (br d, 1H), 4.35 (q, J = 7.0 Hz, 2H), 4.06 (d, J = 14.0 Hz, 1H), 3.94 (d, J = 14.0 Hz, 1H), 2.79 (s, 3H), 2.78 (s, 3H), 2.21 (br m, 1H), 1.37 (t, J = 7.0 Hz, 3H).

MS (FAB): m/z = 429 ($M+H^+$).

Anal. calc. for $C_{21}H_{24}N_4O_4S$ (428.5): C 58.86, H 5.65, N 13.08; found: C 58.7, H 5.6, N 13.0.

Ethyl Cyano[({2′-[(propylamino)carbonyl]aminosulfonyl}1,1′-biphenyl-4-yl)methylamino]acetate (11):
A solution of **7** (2.0 g, 5.77 mmol) and **9** (1.83 g, 6.10 mmol) in CH_2Cl_2 (40 mL) was stirred at 35 °C for 6 h. This solution was added to a suspension of $NaBH_4$ (0.44 g, 11.55 mmol) and glacial AcOH (2 mL) in CH_2Cl_2 (30 mL) at 10 °C, and the mixture was stirred for 16 h. After addition of water (10 mL), the organic layer was separated, washed with water (2 × 10 mL), dried (Na_2SO_4), and evaporated. Chromatography using CH_2Cl_2/MeOH (30 : 1) as eluent provided 1.8 g (68%) of **11** as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 8.17, (dd, J = 1.0, 8.0 Hz, 1H), 7.7–7.3 (m, 7H), 6.46 (br, 1H), 5.92 (br t, J = 6.0 Hz, 1H), 4.34 (m, 3H), 4.05 (s, 2H), 3.07 (dt, J = 6.0 Hz, 2H), 2.70 (br, 1H), 1.35 (m, 5H), 0.76 (t, J = 7.0 Hz, 3H).

MS (FAB): m/z = 459 ($M+H^+$).

Anal. calc. for $C_{22}H_{26}N_4O_5S$ (458.5): C 57.63, H 5.72, N 12.22; found: C 57.7, H 5.6, N 12.0.

Ethyl Cyano{[({2′-[(dimethylamino)methylene]aminosulfonyl}1,1′-biphenyl-4-yl)methyl]-2-pentanoylamino}acetate (12):
Pentanoyl chloride (3.33 mL, 28.0 mmol) was added dropwise to a mixture of **10** (11.1 g, 25.9 mmol) and K_2CO_3 (5.54 g, 40.0 mmol) in anhyd acetone (200 mL). After stirring for 20 h at r.t., the mixture was filtered and dried. Purification by chromatography with CH_2Cl_2/EtOAc (85 : 15) gave 11.6 g (87%) of **12** as a white solid; mp 117 °C.

^{1}H NMR (DMSO-d_6): δ = 8.08 (m, 1H), 7.60 (m, 2H), 7.4–7.2 (m, 5H), 5.83 (s, 1H), 4.96 (d, J = 17.5 Hz, 1H), 4.71 (d, J = 17.5 Hz, 1H), 4.20 (q, J = 7.55 Hz, 2H), 2.84 (s, 3H), 2.73 (s, 3H), 2.46 (m, 2H), 1.52 (m, 2H), 1.30 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 6.0 Hz, 3H).

MS (DCI) m/z = 513 ($M+H^+$).

Anal. calc. for $C_{26}H_{32}N_4O_5S$ (512.6): C 60.92, H 6.29, N 10.93; found: C 60,8, H 6.3, N 10.9.

Ethyl Cyano{[({2′-[(propylamino)carbonylamino]sulfonyl}1,1′-biphenyl-4-yl)methyl]-2-pentanoylamino}acetate (13):
(1). From **11**: Pentanoyl chloride (0.45 mL, 3.80 mmol), followed by K_2CO_3 (0.79 g, 5.71 mmol) were added slowly to a solution of **11** (1.7 g, 3.71 mmol) in anhyd acetone (50 mL), and the mixture was stirred at r.t. for 6 h. Filtration and evaporation of the filtrate yielded crude product which was purified by chromatography with CH_2Cl_2/EtOAc (4 : 1) as eluent to provide 812.0 mg (40%) of **13** as a white solid.

(2). From **12**: A solution of **12** (20.0 g, 39.0 mmol) in MeOH (200 mL) and conc. HCl (100 mL) was refluxed for 1 h. After cooling to r.t., the pH of the solution was adjusted to 6 by addition of 6 N

NaOH. The mixture was extracted with EtOAc (4 × 150 mL) and the combined organic layers were washed with water (50 mL) and brine. The solvents were evaporated and the residue purified by chromatography with EtOAc/heptane (4 : 1) as eluent to yield 7.3 g (41 %) of the desired deprotected 2′-sulfonamide as a colourless oil.

^{1}H NMR ($CDCl_3$): δ = 8.15 (dd, J = 1.0, 8.0 Hz, 1 H), 7.64–7.30 (m, 7 H), 5.62 (s, 1 H), 4.80 (s, 2 H), 4.32 (br s, 2 H), 4.26 (q, J = 7.5 Hz, 2 H), 2.53 (m, 2 H), 1.70 (m, 2 H), 1.34 (m, 5 H), 0.92 (t, J = 7.5 Hz, 3 H).

MS (DCI): m/z = 458 ($M+H^+$).

A solution of the above 2′-sulfonamide (7.2 g, 15.7 mmol), K_2CO_3 (6.5 g, 46.9 mmol) and propyl isocyanate (1.48 mL, 15.0 mmol) in anhyd acetone (180 mL) was refluxed for 2.5 h. After cooling, the pH of the mixture was adjusted to 4 by addition of 2N HCl and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2/water (100 mL) followed by extraction with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried and evaporated to dryness. The crude product was purified by recrystallization from EtOAc (80 mL) to afford 6.5 g (80 %) of **13**; mp 131–133 °C.

^{1}H NMR ($CDCl_3$): δ = 8.22 (dd, J = 0.8, 8.5 Hz, 1 H), 7.7–7.5 (m, 2 H), 7.45–7.28 (m, 5 H), 6.54 (br, 1 H), 5.80 (s, 1 H), 5.53 (br t, J = 5.0 Hz, 1 H), 4.80 (s, 2 H), 4.28 (q, J = Hz, 2 H), 3.02 (dt, J = 5.0, 7.2 Hz, 2 H), 2.62 (t, J = 7.5 Hz, 2 H), 1.75 (m, 2 H), 1.45–1.30 (m, 7 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.78 (t, J = 7.2 Hz, 3 H).

MS (FAB) m/z = 543 ($M+H^+$).

Anal. calc. for $C_{27}H_{34}N_4O_6S$ (542.7): C 59.76, H 6.32, N 10.32; found: C 59.7, H 6.2, N 10.3.

Ethyl 3-Amino-2-[(2′-{[(propylamino)carbonyl]aminosulfonyl}1,1′biphenyl-4-yl)methyl]-2-(pentanoyl)amino-3-methylthioprop-2-enoate (14):

A cooled (−20 °C) solution of **13** (8.5 g, 15.7 mmol) and Et_3N (2.4 mL, 17.2 mmol) in anhyd CH_2Cl_2 (100 mL) was saturated with methyl mercaptan (1.5 g). The resulting solution was maintained under a N_2 pressure of 10 bar at 40 °C for 48 h. After concentration, the resulting residue was purified by chromatography using CH_2Cl_2/MeOH (20 : 1) as eluent to give 8.0 g (86 %) of **14** as a white foam.

^{1}H NMR ($CDCl_3$): δ = 8.18 (dd, J = 1.0, 8.5 Hz, 1 H), 7.55 (m, 2 H), 7.30 m, 5 H), 6.64 (br, 1 H), 5.94 (br, t, 1 H), 4.83 (d, J = 14.0 Hz, 1 H), 4.56 (d, J = 14.0 Hz, 1 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.03 (m, 2 H), 2.32 (s, 3 H), 2.20 (m, 2 H), 1.60 (m, 2 H), 1.35 (m, 4 H), 1.26 (t, J = 8.0 Hz, 3 H), 0.92 (t, J = 6.0 Hz, 3 H), 0.77 (t, J = 7.0 Hz, 3 H).

MS (FAB): m/z = 591 ($M+H^+$).

Anal. calc. for $C_{28}H_{38}N_4O_6S_2$ (590.8): C 56.93, H 6.48, N 9.48; found: C 56.8, H 6.5, N 9.3.

Ethyl 2-Butyl-4-methylthio-1-[(2′-{[(propylamino)carbonyl]aminosulfonyl}1,1′-biphenyl-4-yl)methyl]-1*H*-imidazole-5-carboxylate (15):

Method 1: Under Ar, PCl_5 (180.0 mg, 0.85 mmol) was suspended in CH_2Cl_2 (15 mL). After cooling to −78 °C, a solution of 4-dimethylaminopyridine[12] (230.0 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) was added. Stirring was continued for 10 min at −78 °C, and then a solution of **14** (500.0 mg, 0.85 mmol) in CH_2Cl_2 (25 mL) was slowly added. The mixture was allowed to warm up to r.t. and stirring was continued for an additional 18 h. The precipitate was removed by filtration and the filtrate washed with water (2 × 20 mL) and brine. Drying (Na_2SO_4), evaporation of the solvent and purification by chromatography with CH_2Cl_2/MeOH (20 : 1) as eluent afforded a pale yellow foam, which provided after crystallization from EtOAc/heptane 330.0 mg (68 %) of **15** as a white solid.

Method 2: Conc. H_2SO_4 (1.0 mL) was added to a solution of **14** (200.0 mg, 0.34 mmol) in DME (5 mL). The solution was stirred at r.t. for 1 h. After cooling, water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (10 mL), dried, and concentrated under reduced pressure. The yellow solids obtained were recrystallized from EtOAc (12 mL) to yield 140.0 mg (76 %) of **15**.

Method 3: A solution of **14** (1.0 g, 1.69 mmol) and Lawesson's reagent (342.0 mg, 0.85 mmol) in DME (10 mL) was stirred at r.t. for 2 d. The mixture was concentrated in vacuo and the residue dissolved in CH_2Cl_2/water (60 mL). The organic layer was separated, washed with water (10 mL), dried and evaporated. Purification of the crude product by chromatography with EtOAc/hexane (1 : 1) as eluent provided 506.0 mg (49 %) of the desired 1-thiopentyl amide as a pale yellow oil [MS (FAB) m/z = 607 ($M+H^+$)] and together with 80.0 mg (9 %) of the imidazole **15**. A solution of the thus obtained thioamide (150.0 mg, 0.25 mmol), Et_3N (34 μL, 0.25 mmol) and $(CH_3O)_2SO_2$ (24 μL, 0.25 mmol) in CH_2Cl_2 (5 mL) was refluxed for 15 h. After cooling to 20 °C the mixture was washed with water (2 × 4 mL) and brine, dried, and concentrated under reduced pressure. Chromatography using EtOAc/heptane (2 : 1) as eluent provided 35.0 mg (26 %) of **15**; mp 140–142 °C.

^{1}H NMR ($CDCl_3$): δ = 8.13 (dd, J = 9.0, 1.0 Hz, 1 H), 7.58 (m. 2 H), 7.34 (m, 3 H), 7.08 (d, J = 8.5 Hz, 2 H), 6.08 (br t, J = 6.0 Hz, 1 H), 5.52 (s, 2 H), 4.25 (q, J = 7.0 Hz, 2 H), 3.03 (m, 2 H), 2.70 (m, 2 H), 2.60 (s, 3 H), 1.68 (m, 2 H), 1.35 (m, 7 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.78 (t, J = 6.5 Hz, 3 H).

MS (FAB): m/z = 573 ($M+H^+$).

Anal. calc. for $C_{28}H_{36}N_4O_5S_2$ (572.8): C 58.72, H 6.34, N 9.78; found: C 58.6, H 6.3; N 9.8.

2-Butyl-4-methylthio-1-[(2′-{[(propylamino)carbonyl]aminosulfonyl}1,1′biphenyl-4-yl)methyl]-1*H*-imidazole-5-carboxylic Acid (16):[6]

A solution of **15** (130.0 mg, 0.23 mmol) in MeOH (10 mL) and 2N NaOH (3.1 mL) was stirred at r.t. for 18 h. The mixture was evaporated and the residue taken up in water (5 mL). The resulting aqueous solution was acidified by addition of 2N HCl and the white precipitate was collected by filtration. Drying of the crystals in vacuo yielded 115.0 mg (93 %) of **16**; mp 126–128 °C.

^{1}H NMR ($CDCl_3$): δ = 8.14 (dd, J = 1.0, 8.5 Hz, 1 H), 7.50 (m, 2 H), 7.35 (m, 3 H), 7.08 (d, J = 7.5 Hz, 2 H), 6.20 (br t, 1 H), 5.44 (s, 2 H), 2.95 (m, 2 H), 2.70 (m, 2 H), 2.52 (s, 3 H), 1.65 (m, 2 H), 1.34 (m, 4 H), 0.90 (t, J = 6.5 Hz, 3 H), 0.74 (t, J = 7.5 Hz, 3 H).

MS (FAB) m/z = 545 ($M+H^+$).

Anal. calc. for $C_{26}H_{32}N_4O_5S_2$ (544.7): C 57.33, H 5.92, N 10.29; found: C 57.1, H 5.8, N 10.1

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