Journal of Enzyme Inhibition and Medicinal Chemistry, April 2004 Vol. 19 (2), pp. 137–143

Design and Synthesis of Indole and Tetrahydroisoquinoline Hydantoin Derivatives as Human Chymase Inhibitors

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(Received 12 September 2003; In final form 20 October 2003)

The synthesis of new potential inhibitors of human chymase is described. Treatment of dihydroimidazo[1,5-*a*]indole and [1,5-*b*]isoquinoline-dione with thioaryl followed by oxidation gave the *N*-arylsulfonylmethyl of polycyclic hydantoin derivatives 3, 5 and 6.

Keywords: Indoles; Tetrahydroisoquinoline hydantoins; Human chymase; Inhibitors

INTRODUCTION

Human chymase (EC 3.4.21.39) is a chymotrypsin-like serine protease with a single glycoprotein ($M_r \sim 30.000$) and is stored in the secretory granules of mast cells in an active form.[1] The physiological and pathological roles of chymase have not been fully elucidated.[2]

Studies have demonstrated that chymase generates angiotensin II from angiotensin I in several species including humans[3,4] and could be implicated in blood pressure regulation. Chymase has also been implicated in inflammatory disorders through the activation of interstitial collagenase[5] and degradation of various components of the extracellular matrix.[6] Specific inhibitors of chymase are suitable tools to investigate the physiological functions of chymase and have a useful therapeutic potential. Several peptidic chymase inhibitors have been synthesised[7,8] with high inhibitory potency, however their peptide structure limited their therapeutic use.

Non peptidic inhibitors have been reported[9] none of which is orally potently active. In the search for new ligands targeting the chymase enzyme, we initiated a focussed library synthesis based on the hydantoin skeleton. Niwata *et al.*[10] have described 3-(phenylsulfonyl)-1-phenylimidazolidine-2,4-diones **1** with interesting activities and we have recently described the synthesis of active 1,5-dibenzyl-3-(arylsulfonyl) imidazolidine-2,4-diones **2**.[11] Consequently we decided to synthesize three different families of compounds which possess a strained conformation as potential chymase inhibitors **3**, **4** and **5** (Scheme 1).

MATERIALS AND METHODS

Chemistry

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Advance DPX250 instrument (250.131 Hz). The coupling constants are recorded in Hz and the chemical shifts are reported in ppm (δ, ppm) downfield from Me_4Si, which was used as internal standard. IR spectra were obtained on a Perkin-Elmer FT Paragon 1000 PC spectrometer. MS spectra were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography on silica gel (Merck 230–400 mesh). Analytical thin-layer chromatography was carried out on silica gel (Merck 60 F_{254}) plates. Elemental analyses for carbon, hydrogen, nitrogen

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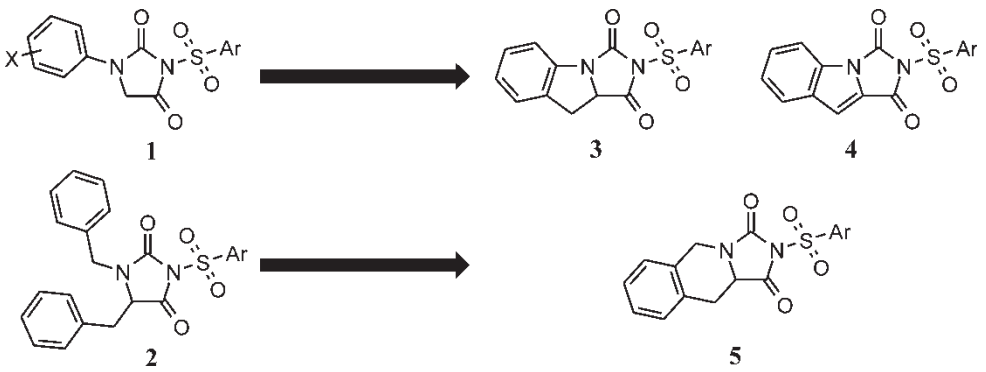
ISSN 1475-6366 print/ISSN 1475-6374 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/14756360310001650200



SCHEME 1 Design aspect for the new series of compounds **3**, **4** and **5**.

and sulfur were conduced with a Carlo Erba 1108 analyzer. All compounds submitted for testing had analytical results within ±0.4% of the theoretical values. Reactions were carried out under a nitrogen atmosphere in anhydrous solvents.

9,9a-Dihydro-1H-imidazo[1,5-A]indole-1,3(2H)-dione 7

To a solution of indoline-2-carboxylic acid (10.00 g, 61.3 mmol) in water (100 mL) was added potassium isocyanate (9.93 g, 122 mmol). The mixture was refluxed for 3 h then acidified to pH = 1 with hydrochloric acid (37%) under reflux for 2h and then evaporated. The crude product was extracted with acetone under reflux and filtered to afford **7** as a white solid (49% yield). mp 153°C. IR 1735 cm^{-1} (C═O), ^{1}H NMR (d6-DMSO) δ 3.30 (dd, 2H, J = 9.3, 3.0 Hz, H_9), 5.02 (t, 1H, J = 9.3 Hz, H_{9a}), 7.06–7.33 (m, 4H, CHAr), 11.26 (sl, 1H, NH). ^{13}C-NMR (d_6-DMSO) δ 31.4 (1C, CH_2, C_3), 64.7 (1C, CH, C_2), 117.0 (1C, CHAr), 125.5 (1C, CHAr), 126.2 (1C, CHAr), 128.3 (1C, CHAr), 134.3 (1C, Cq), 142.0 (1C, Cq), 175.8 (1C, C═O). m/z = 189 (M + 1). Elemental analysis ($C_{10}H_8N_2O_2$) C, H, N.

General Procedure for Preparation of Compounds 3a–d, 5a–b and 5d

2-(4-Methylphenylsulfonyl)-9,9a-dihydro-1*H*-imidazo[1,5-*A*]indole-1,3(2*H*)-dione **3a**

To a stirred solution of methyl trifluoromethanesulfonate (721 μL, 6.38 mmol) in tetrahydrofuran (50 mL) at 0°C was added *p*-toluenesulfonyl imidazole (1.21 g, 6.38 mmol). After being at this temperature for 0.3 h the solution was mixed with a solution of compound **7** (1.00 g, 5.32 mmol) and triethylamine (1.11 mL, 7,97 mmol) in tetrahydrofuran (25 mL) and the reaction stirred overnight at room temperature. The reaction mixture was hydrolyzed and extracted with EtOAc. The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography with petroleum ether–ethyl acetate (2/1, v/v) as eluent to give a white solid (59% yield) **3a**. mp 188–190°C. IR cm^{-1} 1725 (C═O). ^{1}H NMR ($CDCl_3$) δ 4.46 (s, 3H, CH_3), 3.22–3.48 (m, 2H, H_9), 4.97 (t, 1H, J = 10.1 Hz, H_{9a}), 7.12–7.49 (m, 6H, 2CHTs and 4CHAr), 8.08 (d, 2H, J = 8.4 Hz, CHTs). ^{13}C NMR ($CDCl_3$) δ 22.2 (1C, CH_3), 31.6 (1C, CH_2, C_3), 63.1 (1C, CH, C_2), 117.6 (1C, CHAr), 125.7 (1C, CHAr), 126.4 (1C, CHAr), 128.9 (1C, CHAr), 129.2 (2C, CHTs), 130.5 (2C, CHTs), 132.2 (1C, Cq), 134.8 (1C, Cq), 140.2 (1C, Cq), 146.9 (1C, Cq), 151.5 (1C, Cq, C═O), 168.8 (1C, Cq, C═O). m/z = 343 (M + 1). Elemental analysis ($C_{17}H_{14}N_2O_4S$) C, H, N, S.

2-(3,4-dimethylphenylsulfonyl)-9,9a-dihydro-1*H*-imidazo[1,5-*A*]indole-1,3(2*H*)-dione **3b**

This was prepared from compound **7** (1.00 g, 5.32 mmol) and 3,4-dimethylphenylsulfonyl imidazole (1.64 g, 6.38 mmol): white solid (60% yield), mp 198–200°C. IR cm^{-1} 1725 (C═O). ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 6H, $2CH_3$), 3.24–3.49 (m, 2H, H_9), 4.98 (t, 1H, J = 9.8 Hz, H_{9a}), 7.00–7.50 (m, 5H, CHAr), 7.92–7.94 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ 20.2 (1C, CH_3), 20.6 (1C, CH_3), 31.6 (1C, CH_2, C_3), 63.1 (1C, CH, C_2), 117.7 (1C, CHAr), 125.7 (1C, CHAr), 126.4 (1C, CHAr), 126.7 (1C, CHAr), 128.9 (1C, CHAr), 129.6 (1C, CHAr), 130.9 (1CH, CHAr), 132.3 (1C, Cq), 134.9 (1C, Cq), 138.8 (1C, Cq), 140.2 (1C, Cq), 145.8 (1C, Cq), 151.6 (1C, C═O), 168.9 (1C, C═O). m/z = 357 (M + 1). Elemental analysis ($C_{18}H_{16}N_2O_4S$) C, H, N, S.

2-(3,4-dichlorophenylsulfonyl)-9,9a-dihydro-1*H*-imidazo[1,5-*A*]indole-1,3(2*H*)-dione **3c**

This was prepared from compound **7** (1.00 g, 5.32 mmol) and 3,4-dichlorophenylsulfonyl imidazole (1.73 g, 6.38 mmol): white solid (62% yield), mp 152–153°C. IR 1698 cm^{-1} (C═O). ^{1}H NMR ($CDCl_3$) δ 3.27–3.56 (m, 2H, H_9), 5.04 (t, 1H, J = 9.8 Hz, H_{9a}), 7.17–7.34 (m, 3H, CHAr), 7.46 (d, 1H, J = 7.8 Hz, CHAr), 7.67 (d, 1H, J = 8.5 Hz, H_{12}), 8.02 (dd, 1H, J = 8.5, 2.2 Hz, H_{11}), 8.25 (d, 1H, J = 2.2 Hz, H_{10}). ^{13}C NMR ($CDCl_3$) δ 31.4 (1C, C_9), 63.2 (1C, C_{9a}), 117.5 (1C, CHAr), 125.9 (1C, CHAr), 126.6 (1C, CHAr), 128.2 (1C, CHAr), 129.0 (1C, CHAr), 130.9 (1C, CHAr), 131.9

(1CH, CHAr), 132.2 (1C, Cq), 134.6 (1C, Cq), 137.2 (1C, Cq), 139.8 (1C, Cq), 140.8 (1C, Cq), 150.9 (1C, C═O), 168.5 (1C, C═O). m/z = 397 (M + 1)2Cl^{35}, 399 (M + 1)Cl^{35} + Cl^{37}, 301 (M + 1)2Cl^{37}. Elemental analysis ($C_{16}H_{10}Cl_2N_2O_4S$) C, H, N, S.

2-(2-Naphthylsulfonyl)-9,9a-dihydro-1*H*-imidazo[1,5-*A*]indole-1,3(2*H*)-dione **3d**

This was prepared from compound **7** (1.00 g, 5.32 mmol) and 2-naphthylsulfonyl imidazole (1.64 g, 6.38 mmol): white solid (65% yield), mp 176–178°C. IR 1769 cm^{-1} (C═O). ^{1}H NMR ($CDCl_3$) δ 3.15–3.46 (m, 2H, H_9), 4.95 (t, 1H, J = 9.8 Hz, H_{9a}), 7.00–7.29 (m, 3H, CHAr), 7.42 (d, 1H, J = 7.7 Hz, CHAr), 7.59–7.72 (m, 2H, CHAr), 7.87–8.01 (m, 3H, CHAr), 8.01 (dd, 1H, J = 8.7, 1.6 Hz, CHAr), 8.75 (d, 1H, J = 1.2 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ 31.4 (1C, C_9), 63.1 (1C, C_{9a}), 117.5 (1C, CHAr), 123.0 (1C, CHAr), 125.8 (1C, CHAr), 126.3 (1C, CHAr), 128.4 (1C, CHAr), 128.6 (1C, CHAr), 128.8 (1C, CHAr), 130.1 (1C, CHAr), 130.2 (1C, CHAr), 130.5 (1C, CHAr), 131.5 (1C, CHAr), 132.,2 (1C, Cq), 132.4 (1C, Cq), 134.6 (1C, Cq), 136.2 (1C, Cq), 140.1 (1C, Cq), 151.5 (1C, C═O), 169.0 (1C, C═O). m/z = 379 (M + 1). Elemental analysis ($C_{20}H_{14}N_2O_4S$) C, H, N, S.

2-(4-Methylphenylsulfonyl)-10,10a-dihydroimidazo[1,5-*B*]isoquinoline-1,3(2*H*,5*H*)-dione **5a**

This was prepared from compound **8** (1.00 g, 4.95 mmol) and *p*-toluenesulfonyl imidazole (1.13 g, 5.94 mmol): white solid (71% yield). mp 259–261°C. IR 1781 cm^{-1} (C═O). ^{1}H NMR (d_6- DMSO) δ 2.43 (s, 3H, CH_3), 2.98 (dd, 1H, J = 15.4, 5.0 Hz, H_{10}), 3.13 (dd, 1H, J = 15.4, 5.0 Hz, H_{10}), 4.35 (d, 1H, J = 17.1 Hz, H_5), 4.42–4.48 (m, 1H, H_{10a}), 4.77 (d, 1H, J = 17.1 Hz, H_5), 7.24 (s, 4H, CHAr), 7.51 (d, 2H, J = 8.2 Hz, CHTs), 7.94 (d, 2H, J = 8.2 Hz, CHTs). ^{13}C NMR (d_6-DMSO) δ 22.1 (1C, CH_3), 30.0 (1C, CH_2, C_{10}), 42.1 (1C, CH_2, C_5), 55.1 (1C, CH, C_{10a}), 127.5 (1C, CHAr), 127.7 (2C, CHAr), 128.2 (2C, CHAr), 130.1 (1C, CHAr), 130.9 (2C, CHAr), 131.5 (1C, Cq), 132.0 (1C, Cq), 136.2 (1C, Cq), 146.8 (1C, Cq), 149.9 (1C, Cq, C═O), 169.2 (1C, Cq, C═O). m/z = 357 (M + 1). Elemental analysis ($C_{18}H_{16}N_2O_2S$) C, H, N, S.

2-(3,4-Dimethylphenylsufonyl)-10,10a-dihydroimidazo[1,5-*B*]isoquinoline-1,3(2*H*,5*H*)-dione **5b**

This was prepared from compound **8** (1.00 g, 4.95 mmol) and 3,4-dimethylphenylsulfonyl imidazole (1.40 g, 5.94 mmol): white solid (62% yield). mp 265–267°C. IR 1732 cm^{-1} (C═O). ^{1}H NMR (d_6-DMSO) δ 2.34 (s, 6H, 2CH_3), 2.99 (dd, 1H, J = 15.5, 5.0 Hz, H_{10}), 3.13 (dd, 1H, J = 15.5, 5.0 Hz, H_{10}), 4,35 (d, 1H, J = 17.4 Hz, H_5), 4.42–4.47 (m, 1H, H_{10a}), 4.77 (d, 1H, J = 17.4 Hz, H_5), 7,24 (s, 4H, CHAr), 7.47 (d, 1H, J = 7.8 Hz, CHAr), 7.79 (d, 1H, J = 7.8 Hz, CHAr), 7.81 (s, 1H, CHAr). ^{13}C NMR (d_6-DMSO) δ 20.2 (1C, CH_3), 20.5 (1C, CH_3), 30.0 (1C, CH_2), 42.1 (1C, CH_2), 55.1 (1C, CH), 126.4 (1C, CHAr), 127.5 (1C, CHAr), 127.7 (1C, CHAr), 129.0 (1C, CHAr), 130.1 (1C, CHAr), 131.2 (1C, CHAr), 131.5 (1C, Cq), 132.0 (1C, Cq), 135.8 (1C, Cq), 139.0 (1C, Cq), 145.8 (1C, Cq), 149.9 (1C, Cq, C═O), 169.2 (1C, Cq, C═O). m/z = 371 (M + 1). Elemental analysis ($C_{19}H_{18}N_2O_4S$) C, H, N, S.

2-(2-Naphtylsulfonyl)-10,10a-dihydroimidazo[1,5-*B*]isoquinoline-1,3(2*H*,5*H*)-dione **5d**

This was prepared from compound **8** (1.00 g, 4.95 mmol) and 2-naphthylsulfonyl imidazole (1.53 g, 5.94 mmol): white solid (68% yield). mp 254–256°C. IR 1732 cm^{-1} (C═O). ^{1}H NMR (d_6-DMSO) δ 3.01 (dd, 1H, J = 15.5, 5.0 Hz, H_{10}) 3.12 (dd, 1H, J = 15.5, 5.0 Hz, H_{10}), 4.34 (d, 1H, J = 16.9 Hz, H_5), 4.45–4.49 (m, 1H, H_{10a}), 4.77 (d, 1H, J = 16.9 Hz, $H_{5'}$), 7.21 (s, 4H, CHAr), 7.69–7.83 (m, 2H, CHAr), 8.02–8.32 (m, 4H, CHAr), 8.80 (s, 1H, CHAr). ^{13}C NMR (d_6-DMSO) δ 30.0 (1C, CH_2, C3), 42.1 (1C, CH_2, C8), 55.1 (1C, CH, C2), 123.1 (1C, CHAr), 127.4 (1C, CHAr), 127.6 (2C, CHAr), 128.8 (2C, CHAr), 130.1 (1C, CHAr), 130.7 (1C, CHAr), 130.9 (1C, CHAr), 131.1 (1C, CHAr), 131.2 (1C, CHAr), 131.5 (1C, Cq), 132.0 (1C, Cq), 132.3 (1C, Cq), 135.5 (1C, Cq), 136.1 (1C, Cq), 149.9 (1C, C═O), 169.2 (1C, C═O). m/z = 393 (M + 1). Elemental analysis ($C_{21}H_{16}N_2O_4S$) C, H, N, S.

General Procedure for Preparation of Compounds 4a–d

2-(4-Methylphenylsulfonyl)-1*H*-imidazo-[1,5-*A*]indole-1,3(2*H*)-dione **4a**

To a stirred solution of compound **3a** (500 mg, 1.46 mmol) in carbon tetrachloride (100 mL) was added *N*-bromosuccinimide (286 mg, 1.60 mmol). After being heated under reflux for 1 h and cooled to room temperature, this solution was then washed with 10% K_2CO_3 solution. The organic layer was dried over MgSO4, filtered and evaporated under reduced pressure to give the crude product. The residue was recrystallised from methylene chloride/pentane to furnish **4a** as a white solid (85% yield). mp 237–240°C. IR 1712 cm^{-1} (C═O). ^{1}H NMR (d_6-DMSO) δ 2.43 (s, 3H, CH_3), 7.38 (t, 1H, CHAr), 7.50–7.63 (m, 4H, 2CHTs and 2CHAr), 7.80 (d, 1H, J = 2.6 Hz, CHAr), 7.84 (d, 1H, J = 2.6 Hz, CHAr), 7.99 (d, 2H, J = 2.3 Hz, CHTs). ^{13}C NMR (d_6-DMSO) δ 22.0 (1C, CH_3), 111.6 (1C, CHAr), 114.1 (1C, CHAr), 125.5 (1C, CHAr), 125.6 (1C, CHAr), 127.7 (1C, Cq), 129.1 (2C, CHTs), 129.8 (1C, Cq), 130.9 (2C, CHTs), 133.2 (2C, CHAr et Cq), 135.5 (1C, Cq), 144.2 (1C, C═O), 144.7 (1C, Cq), 154.9 (1C, C═O). m/z = 341 (M + 1). Elemental analysis ($C_{17}H_{12}N_2O_4S$) C, H, N, S.

2-(3,4-Dimethylphenylsulfonyl)-1*H*-imidazo-[1,5-*A*]indole-1,3(2*H*)-dione **4b**

This was prepared from compound **3b** (500 mg, 1.40 mmol): white solid (68% yield). mp 223–225°C.

IR 1710 cm^{-1} (C═O). ^1H NMR (d_6-DMSO) δ 2.33 (s, 6H, $2CH_3$), 7.34–7.63 (m, 4H, CHAr), 7.88–7.86 (m, 4H, CHAr). ^{13}C NMR (d_6-DMSO) 20.2 (1C, CH_3), 20.5 (1C, CH_3), 111.5 (1C, CHAr), 114.1 (1C, CHAr), 125.6 (1C, CHAr), 125.7 (1C, CHAr), 126.6 (1C, CHAr), 127.7 (1C, Cq), 129.2 (1C, CHAr), 129.8 (1C, CHAr), 131.2 (1C, CHAr), 133.2 (1C, Cq), 135.6 (1C, Cq), 139.9 (1C, Cq), 144.2 (1C, Cq), 145.8 (1C, Cq), 155.0 (1C, C═O), 177.6 (1C, C═O). m/z = 355 (M + 1). Elemental analysis ($C_{18}H_{14}N_2O_4S$) C, H, N, S.

2-(3,4-Dichlorophenylsulfonyl)-1*H*-imidazo-[1,5-*A*]indole-1,3(2*H*)-dione **4c**

This was prepared from compound **3c** (500 mg, 1.26 mmol): white solid (58% yield). mp 251–253°C. IR 1710 cm^{-1} (C═O). ^1H NMR (d_6-DMSO) δ 7.42 (t, 1H, J = 7.6 Hz, 1CHAr), 7.59 (s, 1H, CHAr), 7.63 (t, 1H, J = 7.6 Hz, CHAr), 7.85 (d, 2H, J = 8.0 Hz, CHAr), 7.99–8.09 (m, 2H, CHAr), 8.20 (d, 1H, J = 0.9 Hz, CHAr). ^{13}C NMR (d_6-DMSO) δ 111.8 (1C, CHAr), 114.3 (1C, CHAr), 125.6 (1C, CHAr), 125.7 (1C, CHAr), 127.1 (1C, Cq), 129.5 (1C, CHAr), 130.1 (1C, CHAr), 131.0 (1C, CHAr), 132.8 (1C, CHAr), 133.2 (1C, Cq), 135.3 (1C, Cq), 137.6 (1C, Cq), 142.3 (1C, Cq), 143.2 (1C, Cq), 154.1 (1C, C═O), 177.4 (1C, C═O). m/z = 395 (M + 1)$2Cl^{35}$, 397 (M + 1)Cl^{35} + Cl^{37}, 399 (M + 1)$2Cl^{37}$. Elemental analysis ($C_{16}H_8Cl_2N_2O_4S$) C, H, N, S.

2-(2-Naphthylsulfonyl)-1*H*-imidazo-[1,5-*A*]indole-1,3(2*H*)-dione **4d**

This was prepared from compound **3d** (500 mg, 1.32 mmol): white solid (68% yield). mp 240–242°C. IR 1724 cm^{-1} (C═O). ^1H NMR ($CDCl_3$) δ 7.36 (t, 1H, J = 8.0 Hz, CHAr), 7.53–7.83 (m, 6H, CHAr), 8.04–8.09 (m, 2H, CHAr), 8.22–8.32 (m, 2H, CHAr), 8.83 (d, 1H, J = 1.0 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ 111.5 (1C, CHAr), 114.1 (1C, CHAr), 123.4 (1C, CHAr), 125.5 (1C, CHAr), 125.6 (1C, CHAr), 127.8 (1C, Cq), 128.8 (2C, CHAr), 129.8 (1C, CHAr), 130.5 (1C, CHAr), 130.7 (1C, CHAr), 130.9 (1C, CHAr), 131.2 (1C, CHAr), 132.3 (1C, Cq), 133.2 (2C, Cq), 135.3 (1C, Cq), 136.2 (1C, Cq), 144.2 (1C, Cq, C═O), 155.0 (1C, Cq, C═O). m/z 337 (M + 1). Elemental analysis ($C_{20}H_{12}N_2O_4S$) C, H, N, S.

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid 9

A suspension of phenylalanine (37.5 g, 226 mmol) hydrochloric acid (290 mL) and formaldehyde (90 mL) was heated under reflux for 3 h. After cooling to room temperature the precipitate was filtered and dissolved in a mixture of ethanol/water 2/1 (1000 mL) and adjusted to pH 7–8. After 2 h at 0°C the precipitate was filtered, washed with water and dried under vacuum to give a white solid **9** (62% yield). mp => 300°C. IR 3226 cm^{-1} (NH), 1723 (C═O).

10,10a-Dihydroimidazo[1,5-B]isoquinoline-1,3(2H,5H)-dione 8

To a stirred solution of the acid **9** (20.00 g, 113 mmol) in water (100 mL) was added potassium isocyanate (18.3 g, 226 mmol). The reaction mixture was stirred at reflux for 3 h, then brought to pH 1 with dilute HCl and stirred again under reflux for 2 h. The solvent was then evaporated and the residue recrystallized from acetone to give a white solid **8** (53% yield). mp 227–230°C. IR 3256 cm^{-1} (NH), 1757 (C═O). ^1H NMR (d_6-DMSO) δ 2.84 (dd, 1H, J = 15.4, 4.8 Hz, H_{10}), 3.13 (dd, 1H, J = 15.4, 4.8 Hz, H_{10}), 4.20 (d, 1H, J = 11.4 Hz, H_{10a}), 4.30 (d, 1H, J = 16.8 Hz, H_5), 4.78 (d, 1H, J = 16.8 Hz, H_5), 7.24 (s, 4H, CHAr), 10.96 (sl, 1H, NH). ^{13}C NMR (d_6-DMSO) δ 30.6 (1C, CH_2, C_{10}), 41.7 (1C, CH_2, C_5), 59.9 (1C, CH, C_{10a}), 127.5 (3C, CHAr), 130.1 (1C, CHAr), 132.6 (2C, Cq), 156.4 (1C, Cq, C═O), 175.4 (1C, Cq, C═O). m/z = 203 (M + 1). Elemental analysis ($C_{11}H_{10}N_2O_2$) C, H, N.

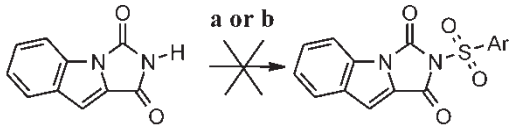
Pharmacology

Recombinant human chymase was prepared according to the procedure of Ferry *et al.*[18] Expressed human prochymase was purified from the culture medium of transfected African green monkey kidney cells (COS-1) using gel filtration and heparin chromatography. Prochymase was activated by cathepsin C. Activated chymase was separated from cathepsin C using the same heparin chromatography. The inhibitory activity of the compounds was expressed as IC_{50} (concentration inhibiting 50% of the chymase activity). For some weakly active compounds, results are expressed as the percentage of inhibition observed at 10 μM.

RESULTS AND DISCUSSION

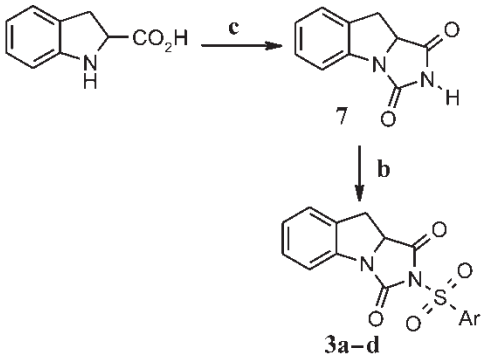
Chemistry

First, we decided to obtain compounds diversely substituted **4** via a direct sulfonylation of 1*H*-imidazo[1,5-a]indole-1,3(2*H*)-dione **6**. The synthesis of **6** was described in a five steps procedure[12] with 24% overall yield starting from methyl indol-2-carboxylate. All attempts here to introduce the arylsulfonyl moiety on **6** using the respective aryl sulfonyl chloride failed. This unreactivity of **6** must be attributed to the low nucleophilic power of the nitrogen. Therefore we treated compound **6** by Rapoport's procedure[13] which is described as allowing sulfonylation of a less reactive nitrogen but unfortunately this methodology also failed (Scheme 2).Then in order to decrease the aromatic character of **6** we used its saturated analogue **7** where the nitrogen by having a higher nucleophilic character should permit sulfonylation.



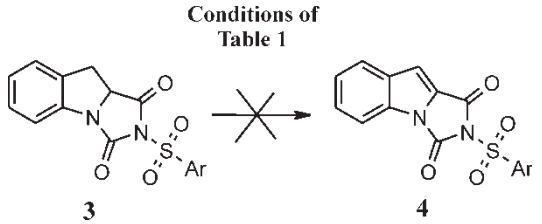
a: Arylsulfonyl chloride/base;
b: Rapoport sulfonylation methodology's

SCHEME 2 Attempted conversion of compound **6** to compound **4**.



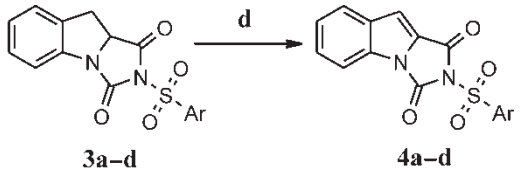
c: i) KNCO/ H_2O /reflux ii) HCl 37%/reflux (49%)
b: Rapoport sulfonylation methodology's

SCHEME 3 Synthesis of the series **3a–d**.



SCHEME 4 Attempted oxidation of compound **3** to compound **4** using conditions in Table 1.

Compound **7** has not been described previously but it can be obtained in a one pot reaction in 49% yield as follows. Indoline-2-carboxylic acid was condensed with potassium cyanate in water and subsequent cyclization under acidic conditions led to the desired compound **7**. Compound **7** was then submitted to sulfonylation using Rapoport's methodology to afford compounds **3a–d** in satisfactory yields. (Scheme 3, Table 2). The next step in the synthetic sequence concerned the oxidation of **3**, but all the classical methodologies using a oxidants such as manganese dioxide, cerium ammonium nitrate, manganese acetate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, palladium on charcoal didn't give the expected compound **4** but recovery of starting material except for manganese acetate where degradation occurred (Scheme 4, Table 1).



d: i) NBS/CCl_4/AIBN ii) H_2O

SCHEME 5 Synthesis of the series **4a–d**.

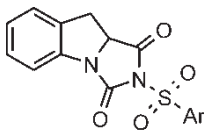
Fortunately the compounds **4** could be obtained using a bromination–debromination sequence. Treatment of **3a–d** with *N*-bromosuccinimide in boiling carbon tetrachloride with a catalytic amount of 2,2′-azobisisobutyronitrile led, after water hydrolysis, to compounds **3a–d** in good yield (Scheme 5, Table 3). Using the same procedure, compound **6** could be obtained from **7** in 89% yield in only two steps, which is superior to Rabbat's method in five steps which used indoline-2-carboxylic acid as starting compound.[12]

The 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione **8** was obtained in two steps starting from phenylalanine. Following Pictet-Spengler's cyclization method, phenylalanine was treated with formaldehyde in acidic conditions to provide the 1, 2, 3, 4-tetrahydro-3-isoquinolinecarboxylic acid **9** in 62% yield. Treatment of **9** with potassium cyanate in boiling water following by reaction under acidic conditions afforded **8** in 53% yield. Application of Rapoport's sulfonylation methodology to compound **8** gave **5a–c** in satisfactory yields

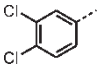
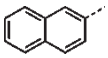
TABLE 1 Attempted methodologies for oxidation of compound **3**

Reagent	Solvent	Temperature	Product
Pd/C 10 to 30%	Ethyl acetate	Reflux	Starting material
Pd/C 10 to 30%	2-Ethoxyethyl ether	180°C	Starting material
MnO_2	Chloroform	Reflux	Starting material
CAN	Tertbutanol/water	80°C	Starting material
S_8	Xylene	Reflux	Starting material
Manganese acetate	Acetic acid	Reflux	Degradation
DDQ	Toluene	Reflux	Starting material
p-Chloranile	toluene	reflux	Starting material

TABLE 2 IC_{50} values for **3a–d** to inhibitors of human chymase



3a–d

Compound	Ar	Yield	mp °C	IC_{50}* μM
3a		59%	188–190	171.5 ± 37.5
3b		60%	198–200	205.5 ± 56
3c		62%	152–153	373.5 ± 145
3d		65%	176–178	86.77 ± 15.5

*The results are the mean ± spread of two determinations.

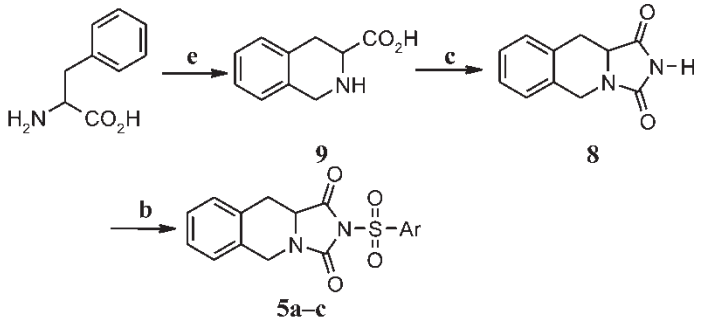
(Scheme 6, Table 4). Compounds submitted for testing had analytical results 0.4% of the theoretical values.

Pharmacology

The enzyme inhibitory activities were measured by the methodology previously described by Ferry *et al.*[14] Inhibition activities are expressed as IC_{50} values (concentration inhibiting 50% of the enzyme activity) and are summarized in Tables 2, 3 and 4. The strained conformation of compound **1** by incorporation in the indoline skeleton (compounds **3a–d**) lead to poorly active inhibitors. The increase in the planarity using indole derivatives induced a decrease in the activity (compounds **4a–d** in comparison to **3a–d**). The best results were obtained with the 2-naphthylsulfonyl group in accord with Niwata *et al.*'s results[10] which claimed the importance of a big hydrophobic group at this position. The tetrahydroisoquinoline skeleton afforded a better activity than that of **3** and **4**, however these compounds 5**a–c**, were less active than the parent compound **2**. Analogous results are observed concerning the role played by the arylsulfonyl group. In conclusion, we have obtained new compounds as the polycyclic hydantoins **3**, **4** and **5**. Unfortunately these derivatives have shown a relatively poor activity.

Acknowledgements

We are grateful to Les Laboratoires Servier (Courbevoie, France) for their multivarious support.

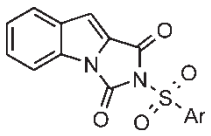


9 **8** **5a–c**

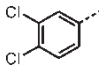
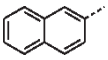
e: HCHO 37%/HCl 37%/ H_2O /reflux (62%)
c: i) KNCO/ H_2O /reflux ii) HCl 37%/reflux (53%)
b: Rapoport sulfonylation methodology

SCHEME 6 Synthesis of the series **5a–c**.

TABLE 3 IC_{50} values for **4a–d** as inhibitors of human chymase

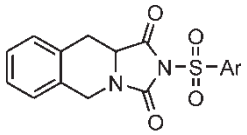


4a–d

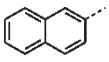
Compound	Ar	Yield	mp °C	IC_{50}* μM
4a		85%	237–240	>1000
4b		68%	223–225	>1000
4c		58%	251–253	308 ± 60
4d		68%	240–242	123 ± 22

*The results are mean ± spread of two determinations.

TABLE 4 IC_{50} values for **5a–c** as inhibitors of human chymase



5a–c

Compound	Ar	Yield	mp °C	IC_{50} μM
5a		71%	259–261	49 ± 2 n = 2
5b		62%	265–267	42.75 ± 6.2 n = 2
5d		68%	254–256	17.54 ± 8.8 n = 4

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