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ASYMMETRIC SYNTHESIS OF NOVEL (1*H*-BENZO[d]IMIDAZOL -2-YLTHIO)- AND (DI-*n*-BUTYLAMINO-2-YLTHIO)ACETAMIDES

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Abstract: Asymmetric synthesis of novel (1*H*-benzo[d]imidazol-2-ylthio)- and (di-*n*-butylamino)acetamides is described. The *o*-nitrobenzyl oxime ethers were reduced with borane in the presence of oxazaborolidenes derived from norephedrine or diphenylvalinol and diphenylphosphinic amide was reduced with modified sodium tetrahydroborate catalyzed with β-ketoiminato cobalt(II) complex to the corresponding amines with high yields and moderate enantiomeric excess. Reaction of amines with 2-chloroacetyl chloride and next with thiobenzimidazole or *n*-dibutylamine gave corresponding products with high yields.

Keywords: asymmetric synthesis, acetamides, oxazaborolidines, benzimidazoles

Imidazoles and benzimidazoles exhibit very important physiological activity, e.g., anti-hypertensive (1), anti-inflammatory (2), antimicrobial (3, 4), antiviral (5), antifungal (6) and anticancer activity (7). Recently, it has been observed that some structures containing (1*H*-imidazol-2-ylthio)acetamide moiety are very active inhibitors of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (8-10) the key target for inhibition of HIV-1 replication (Fig. 1).

Also the synthesis of certain (benzazole-2-ylthio)acetamide derivatives containing 5-methoxy-2,3-dihydrobenzofuran moiety was reported, together with a research on their antihypertensive activity (11), (Fig. 1) and on other interesting biological activities (12, 13). Benzimidazole derivatives, as well as other heterocyclic compounds, are known to be the structural isosters of naturally occurring nucleotides. This resemblance to natural products allows them to easily interact with the biopolymers and results in their lower toxicities in the chemotherapeutic approach (14). Fast spreading of drug resistance is a serious and well recognized global threat, and methods of its preventing are widely discussed in the scientific world (15-17). Among them, the synthesis of novel potential pharmaceutics seems to be a particularly attractive solution. Especially, systems combining multiple biolabile components could become new efficient and effective drugs defeating the drug resistant microorganisms and viruses. Examples of containing two biolabile components, are benzimidazole and 2,3-dihydrobenzofurane, described in (11-13). Although these compounds are potential effective drugs, their asymmetric synthesis have not been yet reported.

Since pharmacological effect of potential drugs depends sensitively on the stereochemistry, herein an asymmetric synthesis of novel (1*H*-benzo[d]imi-

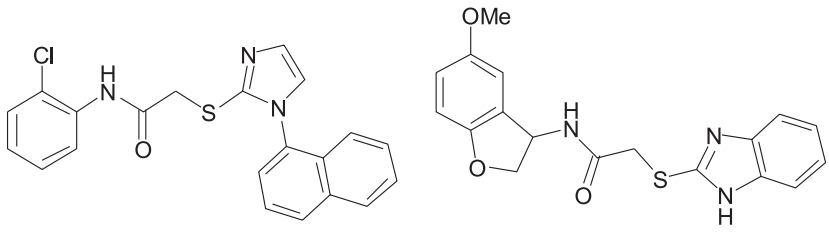

Figure 1. Azole derivatives as potent anti-HIV and antihypertensive drugs

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dazol-2-ylthio)- and (di-*n*-butylamino-2-ylthio)-acetamides with 6-methoxy-2,3-dihydrobenzofurane and 1-phenylethyl moiety *via* enantioselective reduction of oxime *O*-nitrobenzyl ethers and diphenylphosphinic amide, as a key transformation generating a stereogenic center, is reported.

EXPERIMENTAL

Materials and Methods

All experiments were carried out under nitrogen atmosphere. Reagents were generally the best quality commercial grade and used without further purification. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian Gemini 200 MHz multinuclear instrument and on a Bruker AMX 300 MHz instrument. Optical rotations were measured on a PolAAr 3000 automatic polarimeter. GC analyses were performed on a Perkin-Elmer AutoSystem XL chromatograph. Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were performed by Instrumental Analysis Laboratory, Department of Chemistry, Nicolaus Copernicus University, Toruń, and Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warszawa. Silica gel 60, E. Merck 230–400 mesh, was used for preparative column chromatography. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV_{254} 0.2 mm plates. THF was freshly distilled from sodium benzophenone ketyl. Benzene and toluene were freshly distilled from calcium hydride. 6-Hydroxy-2,3-dihydrobenzofuran-3-one (18) and its 6-methoxy derivative (19), were prepared according to the literature procedures. β-Ketoiminato cobalt(II) complex catalyst (TCI) and (–)-norephedrine (Aldrich), benzimidazole and 2-chloroacetyl chloride were commercial materials.

(*Z*)-6-Methoxy-2,3-dihydrobenzofuran-3-one oxime 2-nitrobenzyl ether (2)

A solution of (*Z*)-6-methoxy-2,3-dihydrobenzofuran-3-one oxime **1** (3.58 g, 20 mmol) in DMF (20 mL) was added to a mixture of sodium hydride (0.60 g, 25 mmol) and DMF (40 mL) at 0°C, and the mixture was stirred for 3 h at room temperature (rt). A solution of 2-nitrobenzyl bromide (5.40 g, 25 mmol) in DMF (40 mL) was then added and stirring was continued for 24 h at rt. Water (300 mL) was added and the mixture was kept in a refrigerator for 3 h. The precipitated solid was filtered off, washed with water (50 mL), and the product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate, 80 : 20, v/v). Yield 5.14 g (82%); m.p. 115–117°C, (> 99% *Z*); ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 3.83 (s, 3H, CH_3); 5.06 (s, 2H, CH_2); 5.15 (s, 2H, CH_2); 6.48 (d, J = 2.2 Hz, 1H, CH); 6.62 (dd, J = 2.2 Hz, J = 8.6 Hz, 1H, CH); 7.30–7.65 (m, 4H, CH); 8.02 (d, J = 8.6 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 55.32 (CH_3); 71.65 (CH_2); 76.30 (CH_2); 96.05 (CH); 109.18 (CH); 122.50 (CH); 127.78 (CH); 127.98 (CH); 128.05 (CH); 128.30 (CH); 112.13 (C); 137,70 (C); 147.60 (C); 156.74 (C); 163.87 (C); 167.28 (C). Analysis: calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91%; found: C, 61.22; H, 4.53; N, 8.84%.

(*R*)-(–)-3-Amino-6-methoxy-2,3-dihydrobenzofurane (4)

A 1.24 M borane–tetrahydrofuran solution (24.2 mL, 30 mmol) was added to a solution of (1*R*,2*S*)-(–)-norephedrine **3** (2.27 g, 15 mmol) in tetrahydrofuran (20 mL) and the mixture was stirred for 4 h at 0°C. A solution of **2** (2.20 g, 7 mmol) in tetrahydrofuran (10 mL) was added, and stirring was continued for 72 h at rt. A 2 M hydrochloric acid (90 mL) was added and the mixture was stirred for 30 h at rt. Tetrahydrofuran was removed under vacuum and the precipitated solid was filtered off, washed with diethyl ether (10 mL), and added to water (50 mL). The mixture was basified with solid sodium hydroxide to pH 12. The mixture was extracted with diethyl ether (2 × 100 mL) and the extract was dried with anhydrous magnesium sulfate, the solvent was removed, and the product was isolated by column chromatography on silica gel (ethyl acetate/methanol/triethylamine, 70 : 30 : 1, v/v/v). Yield 0.69 g (60%); $[\alpha]_D^{20}$ – 21.0 (c 1.8, $CHCl_3$), 90% ee (*R*), hydrochloride, m.p. 160–162°C (decomp.). Lit. (19) $[\alpha]_D^{20}$ 12.5 (c 1.8, $CHCl_3$), 57% ee (*S*), hydrochloride, m.p. 162–163°C (decomp.). HPLC analysis of benzamide derivative on the OD-H chiral column (*n*-hexane/isopropanol, 90 : 10, v/v), 90% ee (*R*), 0.6 mL/min, t_R 30.25 (*R*), 32.81 (*S*). Racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.62 (br s, 2H, NH_2); 3.77 (s, 3H, CH_3); 4.39 (dd, J = 4.2 Hz, J = 9.3 Hz, 1H, CH_2); 4.56 (dd, J = 4.2 Hz, J = 7.8 Hz, 1H, CH); 4.66 (dd, J = 7.8 Hz, J = 9.3 Hz, 1H, CH_2); 6.39 (d, J = 2.2 Hz, 1H, CH); 6.47 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H, CH); 7.18 (d, J = 8.2 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 53.26 (CH); 55.25 (CH_3); 80.63 (CH_2); 96.02 (CH); 106.61 (CH); 123.03 (C); 124.43 (CH); 160.85 (C); 161.08 (C). Analysis: calcd. for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; N, 6.95%; found: C, 53.44; H, 5.98; N. 6,88%.

(*R*)-(+)-2-Chloro-*N*-(6-methoxy-2,3-dihydrobenzofuran-3-yl)acetamide (5)

This compound was prepared from **4** as described above: Yield 1.10 g (55.8%), m.p. 136-139°C, $[\alpha]_D^{20}$ 10.4 (c 1.4, $CHCl_3$), 90% ee (*R*). ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 3.79 (s, 3H, CH_3); 4.07 (s, 2H, CH_2); 4.38 (dd, *J* = 3.4 Hz, *J* = 10.4 Hz, 1H, CH_2); 4.73 (dd, *J* = 7.4 Hz, *J* = 10.4 Hz, 1H, CH_2); 5.52 (dd, *J* = 7.4 Hz, *J* = 3.4 Hz, 1H, CH); 6.44 (d, *J* = 2.4 Hz, 1H, CH); 6.51 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H, CH); 6,77 (br s, 1H, NH); 7,2 (d, *J* = 8.4 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, δ, ppm): 42.30 (CH_2); 51.76 (CH); 55.56 (CH_3); 78.42 (CH_2); 96.49 (CH); 107.64 (CH); 117.02 (C); 125.50 (CH); 162.36 (C); 165.83 (C). Analysis: calcd. for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.00; N, 5.80%; found: C, 54.59; H, 4.94; N, 5.87%.

(*R*)-(–)-2-(1*H*-Benzo[d]imidazol-2-yltio)-*N*-(6-methoxy-2,3-dihydrobenzofuran-3-yl)acetamide (6)

This compound was prepared from **5** as described above: Yield 1.0 g (78%), m.p. 110-114°C, $[\alpha]_D^{20}$ –41.7 (c 0.55, $CHCl_3$), 90% ee (*R*). ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 2.17 (s, 2H, CH_2); 3.74 (s, 3H, CH_3); 4.34 (dd, *J* = 4.0 Hz, *J* = 10.1 Hz, 1H, CH_2); 4.65 (dd, *J* = 7.8 Hz, *J* = 10.1 Hz, 1H, CH_2); 5.37 (dd, *J* = 4.0 Hz, *J* = 7.8 Hz, 1H, CH); 6.34-6.36 (m, 2H, CH); 7.00 (d, *J* = 9.0 Hz, 1H, CH); 7.13-7.25 (m, 2H, CH); 7.36-7.48 (m, 2H, CH). ^{13}C NMR ($CDCl_3$, δ, ppm): 35.10 (CH_2); 51.96 (CH); 55.43 (CH_3); 78.06 (CH_2); 96.21 (CH); 107.18 (CH); 114.28 (2CH); 117.43 (C); 122.16 (2CH); 125.45 (CH); 139.59 (C); 150.10 (C); 161.63 (C); 161.89 (C); 169.82 (C). Analysis: calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82; S, 9.02%; found: C, 60.88; H, 4.89; N, 11.75; S, 8.84%.

(*S*)-(–)-1-Phenylethylamine (7)

Prepared from (*E*)-acetophenone oxime benzyl ether by reduction with borane/(1*R*,2*S*)-(–)-norephedrine following the reported methodology (19), oil, 80%, $[\alpha]_D^{20}$ –29.8 (c 10, EtOH), 99% ee. Lit. (19) –29.8 (c 2.0, MeOH), 99% ee.

(*S*)-(–)-1-(4-Methoxyphenyl)ethylamine (8)

Prepared from (*E*)-4-methoxyacetophenone oxime 2-nitrobenzyl ether by reduction with borane/(*S*)-(–)-diphenylvalinol following the reported methodology (19), oil, 75%, $[\alpha]_D^{20}$ –28.9 (c 2.0, MeOH), 98.8% ee. Lit. (19) –29.0 (c 2.0, MeOH), 98.8% ee.

(*E*)-*N*-(1-(4-Methoxyphenyl)ethylidene)-*P*,*P*-diphenylphosphinic amide (10)

Triethylamine (2.45 g, 24,2 mmol) was added to a solution of (*E*)-4-methoxyacetophenone oxime (**9**) (4.00 g, 24.2 mmol), in mixture of Et_2O/*n*-hexane (82 mL) and cooled to –40°C. Next, the solution of chlorodiphenylphosphine (5.35 g, 24.2 mmol) in dichloromethane (7.2 mL) was added to the mixture. The solution was stirred at –40°C for 3 h and next 1.5 h at rt. The precipitated solid was filtered off, washed with diethyl ether (15 mL); Yield 6.10 g (72%); m.p. 120-122°C. ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 2.92 (d, 3H, CH_3, *J* = 2.0 Hz); 3,88 (s, 3H, CH_3); 6,95 (d, 2H, CH, *J* = 8.6Hz, AA'BB'); 7.35-7.40 (m, 6H, CH_{ar}); 7.80-8.00 (m, 4H, CH_{ar}); 8.08 (d, 2H, CH, *J* = 8.6 Hz, AA'BB'). ^{13}C NMR ($CDCl_3$, δ, ppm): 22,70 (CH_3); 55.38 (CH_3); 113.67 (2CH); 128.13 (2CH); 128.37 (2CH); 130.01 (2CH), 131.11 (CH); 131.17 (CH); 131.34 (2CH); 131.53 (2CH); 133.78 (C); 136.39 (C), 163.13 (2C), 180.42 (C). ^{31}P NMR ($CDCl_3$, δ, ppm): 18.71 (P).

(*S*)-(–)-*N*-(1-(4-Methoxyphenyl)ethyl)-*P*,*P*-diphenylphosphinic amide (12)

Under argon atmosphere, in a pre-cooled vessel at 0°C, were placed fine grained $NaBH_4$ (0.059 g, 1.50 mmol), $CHCl_3$ (10.0 mL), EtOH (0.088 mL, 1.50 mmol), and THFA (2.0 mL, 20.6 mmol), and stirring of the mixture was continued for 3 h. While maintaining the pre-modified borohydride solution at 0°C, it was slowly added to a solution of cobalt(II) catalyst (*S*,*S*)-**11** (14 mg, 0.02 mmol) and *N*-diphenylphosphinic amide **10** (0.35 g, 1.0 mmol) in $CHCl_3$ (5.0 mL), and stirring of the mixture was continued for 4 h at 0°C. The reaction was quenched by addition of saturated aqueous ammonium chloride and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and the excess solvents were removed under reduced pressure. The product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate, 90 : 10, v/v). Yield 0.052 g (99%); 126-127°C, $[\alpha]_D^{20}$ –41.7 (c 1.5, $CHCl_3$). Purification by column chromatography on silica gel (n-hexane : ethanol 90:10, v/v) gave the corresponding amine in 85% yield (148.0 mg). HPLC analysis on the OD-H chiral column (*n*-hexane/ethanol, 90 : 10, v/v), 83% ee (*S*), t_R 16.77 min. and 18.47 min. Racemate was also analyzed. ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 1.54 (d, 3H, CH_3, *J* = 6.6 Hz); 3.10-3.25 (m, 1H, CH); 3.78 (s, 3H, CH_3); 4.22-4.40 (m, 1H, NH); 6.80-6.90 (m, 2H, CH); 7.20-7.60 (m, 7H, CH_{ar}); 7.75-8.00 (m, 5H, CH_{ar}). ^{13}C NMR ($CDCl_3$, δ, ppm): 25.82 (CH_3);

50.45 (CH); 55.23 (CH_3); 113.84 (2CH); 127.16 (2CH); 128.21 (CH); 128.29 (CH); 128.47 (CH); 128.54 (CH); 131.69 (2CH); 131.84 (CH); 131.93 (CH); 132.29 (CH); 132.48 (CH); 133.67 (C); 134.56 (C); 137.41 (C); 158.57 (C). ^{31}P ($CDCl_3$, δ, ppm): 22.58 (P). Analysis: calcd. for $C_{21}H_{22}NO_2P$: C, 71.78; H, 6.31; N, 3.99%; found: C, 71.71; H, 6.29; N, 4.02.

(*S*)-(–)-2-Chloro-*N*-(1-phenylethyl)acetamide (13). Typical procedure

Triethylamine (1.7 g, 16.5 mmol) and 2-chloroacetyl chloride (1.86 g, 16.5 mmol) were added to the solution of **7**, 99% ee (*S*), (2.0 g, 16.5 mmol) in benzene (60 mL), and the mixture was stirred for 2.5 h at rt. The precipitated solid was filtered off, washed with benzene (20 mL), and the product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate 80 : 20, v/v). Yield 2.70 g, (82.8%), m.p. 96-98°C, $[\alpha]_D^{20}$ –56.0 (c 1.7, $CHCl_3$), 99% ee (*S*). Lit. (20) m.p. 101-102°C, $[\alpha]_D^{20}$ –57.5 (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 1.54 (d, *J* = 6.8 Hz, 3H, CH_3); 4.02 (d, *J* = 18.4 Hz, 1H, CH_2); 4.13 (d, *J* = 18.4 Hz, 1H, CH_2); 5.14 (quintet, *J* = 7.0 Hz, 1H, CH); 6.80 (br s, 1H, NH); 7.20-7.40 (m, 5H, CH). ^{13}C NMR ($CDCl_3$), δ, ppm): 21.64 (CH_3); 42.61 (CH_2); 49.25 (CH); 126.06 (2CH); 127.61 (CH); 128.78 (2CH); 142.32 (C), 164.95 (CO).

(*S*)-(–)-2-Chloro-*N*-(1-(4-methoxyphenyl)ethyl)acetamide (14)

This compound was prepared from **8** as described above. Yield 2.63 g (98.2%), m.p. 93-95°C, $[\alpha]_D^{20}$ –77.4 (c 1.2, $CHCl_3$), 99% ee (*S*). ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 1.52 (d, *J* = 7.0 Hz, 3H, CH_3); 3.80 (s, 3H, CH_3); 4.00 (d, *J* = 15.0 Hz, 1H, CH_2); 4.07 (d, *J* = 15.0 Hz, 1H, CH_2); 5.09 (quintet, *J* = 7.2 Hz, 1H, CH); 6.70 (br s, 1H, NH); 6.83 (d, *J* = 8.5 Hz, 2H, CH, AA'BB'); 7.23 (d, *J* = 8.5 Hz, 2H, CH, AA'BB'). ^{13}C NMR ($CDCl_3$, δ, ppm): 21.48 (CH_3); 42.60 (CH_2); 48.69 (CH); 55.27 (CH_3); 114.11 (2CH); 127.31 (2CH); 134.38 (C); 159.03 (C), 164.89 (CO). Analysis: calcd. for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; N, 6.15%; found: C, 49.97; H, 6.17; N, 6.19%.

(*S*)-(–)-2-(*n*-Dibutylamino)-*N*-(1-phenylethyl)-acetamide (15). Typical procedure

Dibutylamine (1.50 g, 11.5 mmol) was added to the solution of **13**, 99% ee, (1.14 g, 5.8 mmol) in benzene (20 mL), and the mixture was stirred under reflux for 8 h, then cooled to rt and filtered through Celite pad and concentrated to dryness. The product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate, 80 : 20, v/v), and pale yellow oil was obtained. Yield 1.23 g (73.2%), $[\alpha]_D^{20}$ –52.9 (c 2.4, $CHCl_3$), 99% ee (*S*). ^{1}H NMR ($CDCl_3$, 200 MHz, δ, ppm): 0.87 (t, *J* = 6.8 Hz, 6H, CH_3); 1.18-1.40 (m, 8H, $4CH_2$); 1.48 (d, *J* = 7.0 Hz, 3H, CH_3); 2.43 (t, *J* = 6.6 Hz, 4H, CH_2); 2.95 (d, *J* = 16.0 Hz, 1H, CH_2); 3.05 (d, *J* = 16 Hz. 1H, CH_2); 5.14 (dq, *J* = 8.6 Hz, *J* = 7.2 Hz, 1H, CH); 7.20-7.40 (m, 5H, CH); 7.70 (br d, *J* = 8.6 Hz, 1H, NHCO). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.97 ($2CH_3$); 20.57 ($2CH_2$); 22.05 (CH_3); 29.70 ($2CH_2$); 48.05 (CH); 55.36 ($2CH_2$); 58.86 (CH_2); 126.03 (2CH); 127.20 (CH); 128.58 (2CH); 143.41 (C), 170.96 (CO). Analysis: calcd. for $C_{18}H_{30}N_2O$: C, 74.44, H, 10.41, N, 9.65%; found: C, 74.52; H, 10.38; N, 9.73%.

(*S*)-(–)-2-(*n*-Dibutylamino)-*N*-[1-(4-methoxyphenyl)ethyl]acetamide (16)

This compound was prepared from **14** as described above: *n*-hexane/ethyl acetate (70 : 30, v/v). Yield 1.06 g (65.4%), pale yellow oil, $[\alpha]_D^{20}$ –52.8 (c 2.0, $CHCl_3$), 99% ee (*S*). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 0.87 (t, *J* = 7.2 Hz, 6H, CH_3); 1.25 (sextet, *J* = 6.9 Hz, 4H, CH_2); 1.30-1.43 (m, 4H, CH_2); 1.46 (d, *J* = 6.9 Hz, 3H, CH_3); 2.42 (t, *J* = 6.9 Hz, 4H, CH_2); 2.92 (d, *J* = 17.0 Hz, 1H, CH_2); 2.97 (d, *J* = 17.1 Hz, 1H, CH_2); 3.28 (s, 3H, CH_3); 5.09 (dq, *J* = 8.4 Hz, *J* = 6.9 Hz, 1H, CH); 6.86 (d, *J* = 9.0 Hz, 2H, CH, AA'BB'); 7.23 (d, *J* = 9.0 Hz, 2H, CH, AA'BB'); 7.61 (d, *J* = 8.4 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.88 ($2CH_3$); 20.46 ($2CH_2$); 21.80 (CH_3); 29.55 ($2CH_2$); 47.32 (CH); 55.13 (CH_3); 55.21 ($2CH_2$); 58.70 (CH_2); 113.95 (2CH); 127.08 (2CH); 135.44 (C); 158.61 (C), 170.76 (CO). Analysis: calcd. for $C_{19}H_{32}N_2O_2$: C, 71.21%, H, 10.06%, N, 8.74%; found: C, 71.19; H, 10.04; N, 8.70%.

(*S*)-(–)-2-(1*H*-Benzo[d]imidazol-2-ylthio)-*N*-(1-phenylethyl)acetamide (17). Typical procedure

Thiobenzimidazole (0.76 g, 5.1 mmol), and dry potassium carbonate (0.70 g, 5.1 mmol) were added to the solution of **13**, 99% ee (*S*) (1.0 g, 5.1 mmol) in acetone (35 mL), and the mixture was stirred under reflux for 10 h, then cooled to room temperature, filtered through Celite pad and concentrated to dryness. The crude product was crystallized from ethanol. Yield 1.30 g (82.8%), m.p. 198-202°C, $[\alpha]_D^{20}$ 40.2 (c 1.9, DMSO), 99% ee (*S*). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.35 (d, *J* = 6.9 Hz, 3H, CH_3); 2.17 (s, 1H, NH); 3.70 (d, *J* = 14.5 Hz, 1H, CH_2); 3.75 (d, *J* = 14.5 Hz, 1H, CH_2); 4.86 (q, *J* = 6.9 Hz, 1H, CH); 5.50-6.50 (br s, 1H, NH); 7.05-

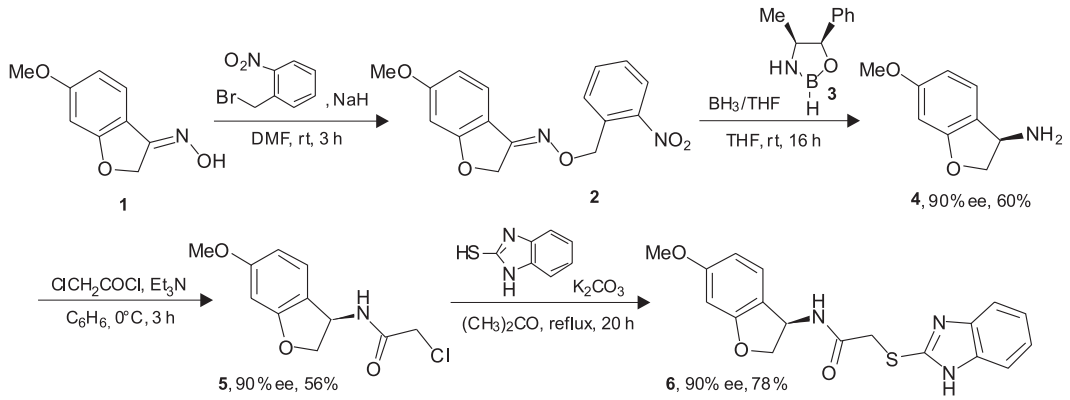
7.20 (m, 7H, CH); 7.45-7.52 (m, 2H, CH). Analysis: calcd. for $C_{17}H_{17}N_3OS$: C, 65.57, H, 5.50, N, 13.49; S, 10.30%; found: C, 65.64; H, 5.54; N, 13.41; S, 10.25%.

(*S*)-(+)-2-(1*H*-Benzo[d]imidazol-2-ylthio)-*N*-(1-(4-metoxyphenyl)ethyl)acetamide (18)

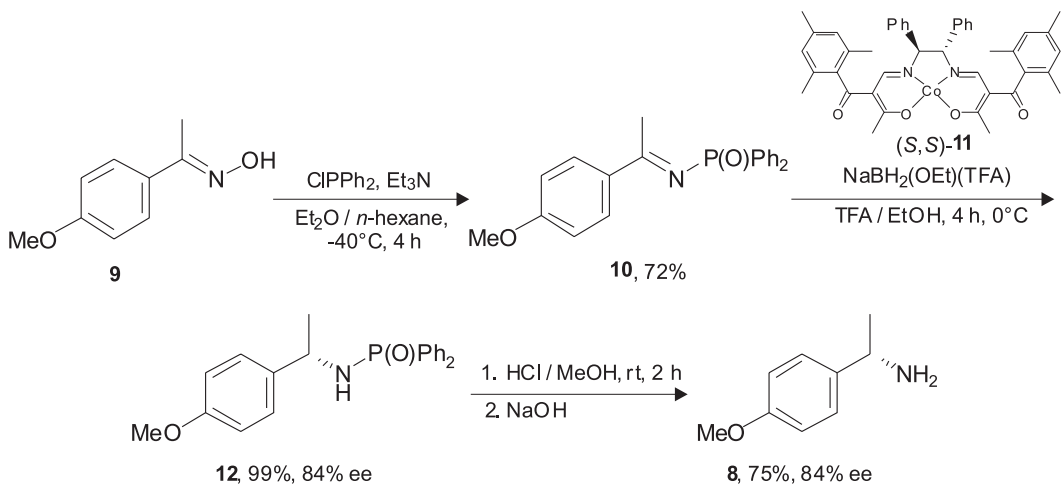
This compound was prepared from **14** as described above. Yield 1.71 g (95.4%), m.p. 75-78°C, $[\alpha]_D^{20}$ +32.9 (c 1.0, DMSO), 99% ee (*S*). ^{1}H NMR (DMSO-d_6, 200 MHz, δ, ppm): 1.29 (d, *J* = 7.0 Hz, 3H, CH_3); 2.07 (s, 1H, NH); 3.68 (s, 3H, CH_3); 3.82 (d, *J* = 15.0 Hz, 1H, CH_2); 3.92 (d, *J* = 15.0 Hz, 1H, CH_2); 4.81 (quintet, *J* = 7.6 Hz, 1H, CH); 6.77 (d, *J* = 8.6 Hz, 2H, CH, AA'BB'); 6.93-7.04 (m, 2H, CH); 7.18 (d, *J* = 8.6 Hz, 2H, CH, AA'BB'); 7.30-7.41 (m, 2H, CH); 9.53 (d, *J* = 7.6 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 22.68 (CH_3); 35.05 (CH_2); 47.78 (CH); 54.97 (CH_3); 113.51 (2CH); 113.86 (2CH); 119.84 (2CH); 126.95 (2CH); 136.29 (C); 141.91 (2C), 152.45 (C); 157.91 (C); 167.45 (C). Analysis: calcd. for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31; S 9.39%; found: C, 63.29; H, 5.55; N, 12.24; S, 9.37%.

RESULTS AND DISCUSSION

As a model compounds we chose 6-methoxy-2,3-dihydrobenzofuran-3-one oxime (**1**), which was converted into their pure *Z*-izomer of 2-nitrobenzyl ether **2**. The reduction of (*Z*)-6-methoxy-2,3-dihydrobenzofuran-3-one 2-nitrobenzyl oxime ether (**2**) with excess of borane–tetrahydrofuran complex in the presence of (1*R*,2*S*)-(–)-norephedrine (**3**) gave



Scheme 1. Asymmetric synthesis of (*R*)-2-(1*H*-benzo[d]imidazol-2-ylthio)-*N*-(6-methoxy-2,3-dihydrobenzofuran-3-yl)acetamide **6**.



Scheme 2. Enantioselective reduction of *P*,*P*-diphenylphosphinic amide **10** with a modified sodium tetrahydroborate catalyzed with β-ketoiminato cobalt(II) complex (*S*,*S*)-**11**.

(*R*)-6-methoxy-2,3-dihydrobenzofuran-3-amine (**4**) with 60% yield. HPLC analysis of benzamide derivative of **4** on the OD-H chiral column showed 90% ee (*R*) (Scheme 1). The racemate was also analyzed. The reaction of amine **4** with 2-chloroacetyl chloride in the presence of triethylamine gave (*R*)-2-chloro-*N*-(6-methoxy-2,3-dihydrobenzofuran-3-yl)acetamide (**5**) with 56% yield. The alkylation of benzimidazole can be effective with potassium carbonate or sodium hydride in dimethylformamide, tetrabutylamonium bromide/triethylamine in acetonitrile, potassium carbonate or cesium carbonate in acetone (21-28). In this paper, we report the selective alkylation of SH group of thiobenzimidazole in good yield (78-99%) using potassium carbonate in acetone under reflux.

Consequently, the reaction of chloroacetamide **5** with thiobenzimidazole in acetone in the presence of potassium carbonate gave after crystallization the desired product **6** with 78% yield and 90% ee. The structure of **6** was confirmed by ^{1}H, ^{13}C NMR and elemental analysis. We think that this method can be successfully applied to the synthesis of other analogues including the lately described 5-methoxy analogue of **6** (11-13).

The procedure described above and efficient sequence of transformations were used to synthesize (1*H*-benzo[d]imidazol-2-ylthio)- and (di-*n*-butylamino-2-ylthio)acetamides with 1-phenylethyl moiety.

(*S*)-(–)-1-Phenylethylamine (**7**) and (*S*)-(–)-1-(4-methoxyphenyl)ethylamine (**8**) were prepared from the corresponding 2-nitrobenzyl oxime ethers with high yield and 99% enantiomeric excess using our recently described procedure (26).

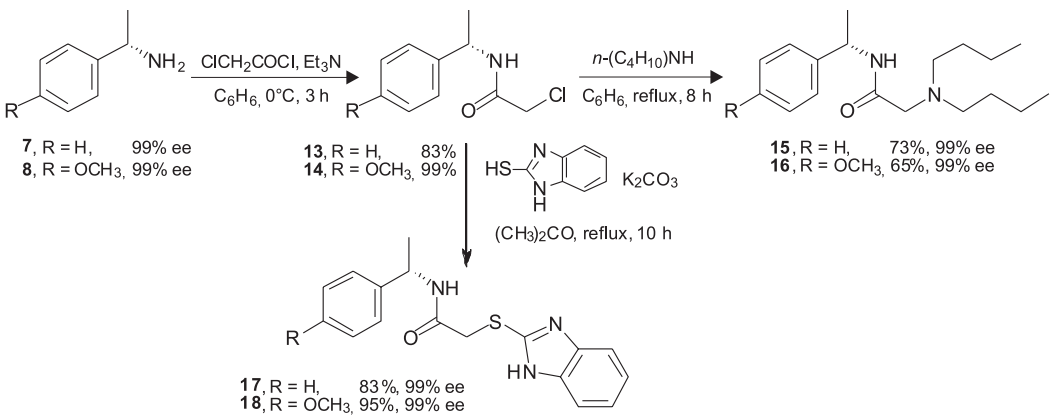
Additionally, (*E*)-1-(4-methoxyphenyl)ethanone oxime (**9**) was converted into *N*-(1-(4-methoxyphenyl)-ethylidene)-*P*,*P*-diphenylphosphinic amide (**10**) in the reaction with chlorodiphenylphosphine in the presence of triethylamine with 72% yield. The reduction of **10** with a modified sodium tetrahydroborate catalyzed with β-ketoiminato cobalt(II) complex (*S*,*S*)-**11** gave product **12** with 99% yield. HPLC analysis of **12** on the OD-H chiral column showed 84% ee (*S*) (Scheme 2). The racemate was also analyzed.

Product **12** after hydrolysis with hydrochloric acid gave the desired amine **8** with 75% yield and with moderate selectivity, 84% ee (Scheme 2) (29-31).

Then, the reaction of **7** and **8** with 2-chloroacetyl chloride in the presence of triethylamine was carried out, resulting in **13** with 83% yield, and **14** with 99% yield, respectively (Scheme 3).

Introduction of *n*-butyl group into bioactive molecules increases their therapeutic efficiency due to an increase in lipophilicity (32). Benzimidazole derivatives were chosen mainly because they are structural isosteres of naturally occurring nucleotides, which allows them to interact easily with the biopolymers of the living systems (14).

The reaction of acetamides **13** and **14** with *n*-dibutylamine and thiobenzimidazole gave (di-*n*-butylamino-2-ylthio)acetamides **15** of 73% and **16** of 65% yield, and (1*H*-benzo[d]imidazol-2-ylthio)acetamides **17** of 83% and **18** of 95% yield, respectively, all with 99% ee. All acetamides were easily purified by column chromatography or by crystallization. Structures of **13**-**18** were fully char-



Scheme 3. Asymmetric synthesis of (*S*)-(1-phenylethyl)acetamides **15**-**18**.

Table 1. Calculated properties for acetamides **6**, **15**-**18**.

Acetamides	ALOGPS	KoWWIN	XLOGP2	TPSA	MW	nON	nNHOH	Lipinski rule
6	2.81	2.53	2.41	76,24	304	6	2	+
15	4.13	3.98	4.46	32,34	312	3	1	+
16	4.32	4.06	4.09	41,57	338	4	1	+
17	3.34	2.97	2.32	57,78	280	4	2	+
18	3.67	3.05	3.13	67.01	305	5	2	+

nON - numbers of hydrogen bonds acceptors, nNHOH - numbers of hydrogen bonds donors, TPSA - topological polar surface area, MW - molecular weight.

acterized by ^{1}H, ^{13}C NMR and elemental analysis.

One of the most important properties of the drug is its lipophilicity, which can be predicted using theoretical methods implemented in e.g., ALOGPS 2.1 (33-37), LogKow (KoWWIN) [38], and XLOGP2 (39, 40) programs. The ALOGPS 2.1 program performs the lipophilicity calculation based on the efficient partition algorithm and the associative neutral network approach. The LogKow (KoWWIN) program estimates the logarithm of the octanol / water partition coefficient (log P) of organic compounds and drugs using an atom / fragment contribution method developed at Syracuse Research Corporation. The XLOGP2 uses atom-additive method applying corrections.

All these programs are commonly used for the calculation of lipophilicity, due to their well established accuracy, and were used in the present investigations for acetamides (Tab. 1) (41).

Computed values, depending on the software used, differ by as much as one log P unit. Lipophilicity was determined only theoretically because of the insolubility of investigated compounds in the required solvents (42). Molecular Polar Surface Area (PSA), defined as the sum of surface contributions of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule, has been shown to correlate well with drug transport properties, such as intestinal absorption, or blood-brain barrier penetration (43-45). Current methodologies to calculate PSA, however, are relatively time consuming, because of the necessity to create a reasonable 3D molecular geometry and to calculate the surface itself. Therefore, we decided to use very fast methodology to calculate the PSA from fragment contributions named topological PSA (TPSA). TPSA calculations show that all compounds may exhibit good absorption and blood-brain barrier penetration. Additionally, as shown above, all reported compounds fulfill the Lipinski's Rule of Five, which thus can be attractive subject of further studies as potential drugs.

CONCLUSIONS

A convenient asymmetric synthesis of novel (1*H*-benzo[d]imidazol-2-ylthio)- and (di-*n*-butylamino)-acetamides with high yield and moderate to high enantiomeric excess by enantioselective reduction of 2-nitrobenzyl oxime ethers and diphenylphosphinic amide as a key transformation has been developed. Results of theoretical calculations suggest that the reported compounds may have interesting pharmacological properties.

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