2-Arylpropionyl chlorides in kinetic resolution of racemic 3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazines

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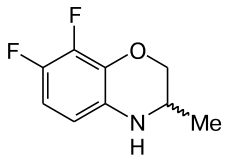
Kinetic resolution of racemic 3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazines in the reaction with chiral 2-arylpropionyl chloride predominantly yielded *R**,*R**-diastereomers. Ibuprofen acyl chloride as acylating agent was found to be more selective and sensitive to the changes in the reaction temperature as compared to naproxen acyl chloride and 2-phenylpropionyl chloride.

Key words: kinetic resolution, 2-arylpropionic acids, acyl chlorides, acylation, 3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine, naproxen, ibuprofen, carboxamides, amines, enantiomers, diastereoselectivity.

Kinetic resolution (KR)[1] based on the difference in the transformation rates of individual stereoisomers of a racemate in the reactions with an asymmetric agent or a catalyst is successfully used for the preparation of optically pure biologically active compounds and intermediate products of their synthesis.[2—4] Kinetic resolution is often used to obtain chiral amines in enantiomerically pure forms by acylation in the presence of either acylating enzymes[5—8], or synthetic acyl transfer catalysts.[9—13] In the last years, a lot of attention is attracted by methods of KR using enantiomerically pure chiral acylating agents.[14—19]

One of the approaches to KR of racemic amines consists in the use of chiral acyl chlorides as acylating agents. Such an approach, which allows one to obtain individual enantiomers of chiral heterocyclic amines in high enough yields, is being successfully developed in our research group during last years.[20—25]

It is known[26—29] that 2-arylpropionic acid derivatives can be used for the KR of racemic amines and alcohols. (*S*)-Naproxen ((2*S*)-2-(6-methoxynaphth-2-yl)propionic acid) acyl chloride was for the first time used for the KR of racemic heterocyclic amines,[20,21] including 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (**1**) and 3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (**2**). We found the optimum conditions to carry out the process, whose selectivity was evaluated based on the diastereomeric excess (*de* (%)) of the amides formed, and developed efficient method for the preparation of optically pure (*S*)-enantiomer of amine **1**[30] — the key intermediate in the synthesis of antibacterial agent Levofloxacin.



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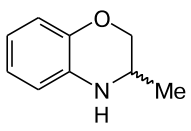

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At the same time, the regularities between the structure of reagents used in KR and stereochemical result of the process are not still found. Therefore, information on the KR results with the use of maximum structurally different resolution agents is very important. One of the possible approaches to the search for efficient resolution agents consists in the running the reaction between racemic amine and racemic acylating agent. The reaction results in the formation of two pairs of diastereomeric amides, (*S*,*S*)—(*R*,*R*) and (*R*,*S*)—(*S*,*R*), whose ratio (*dr*) is equal to the selectivity factor $s = k_{fast}/k_{slow}$,[1,26,31] where k_{fast} and k_{slow} are the rate constants of the reactions for the fast and slow reacting enantiomer, respectively. It should be emphasized that in this case the ratio of concentrations of diastereomeric products depends on neither the proportion of the starting reactants, nor the reaction time. In addition, chiral compounds, which are of interest as potential agents for KR, most often are available in the form of racemates (excluding some groups of substances, for example, amino acid derivatives).

The purpose of the present work is to evaluate diastereoselectivity of acylation of racemic heterocyclic amines **1** and **2** with 2-arylpropionyl chlorides, *viz.*, naproxen (2-(6-methoxynaphth-2-yl)propionic acid) acyl chloride (**3**), ibuprofen (2-(4-isobutylphenyl)propionic acid) acyl chloride (**4**), and 2-phenylpropionyl chlorides (**5**), under conditions of kinetic resolution.

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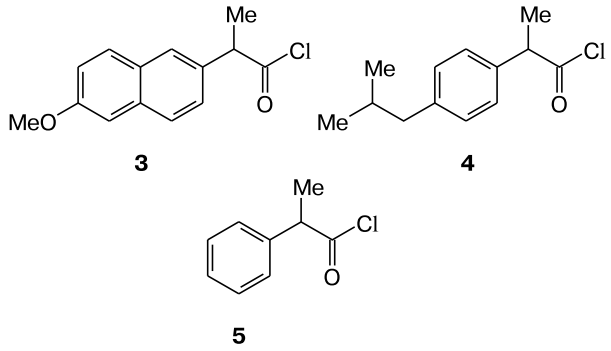
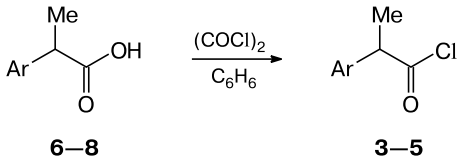


Results and Discussion

Acyl chlorides **3—5** were obtained upon the action of oxalyl chloride on the corresponding 2-arylpropionic acids **6—8** in benzene in 95—97% yields and chemical purity >98% (from the ^{1}H spectral data) (Scheme 1). The freshly prepared acyl chlorides were used in the acylation without additional purification.

Scheme 1



6—8 **3—5**

Ar = 6-methoxynaphth-2-yl (**3**, **6**), 4-$Me_2CHCH_2C_6H_4$ (**4**, **7**), Ph (**5**, **8**)

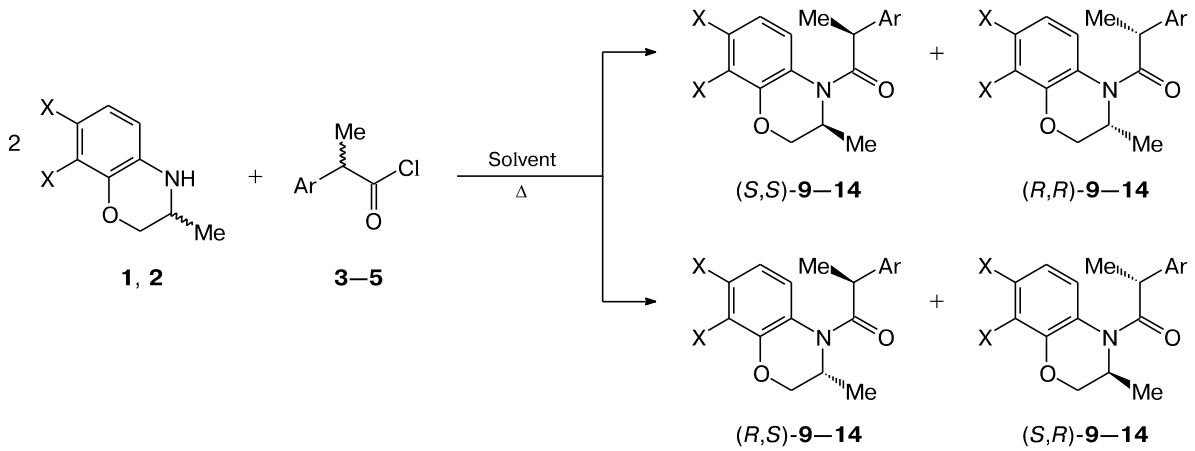
Acylation of racemic amines **1** and **2** with racemic acyl chlorides **3—5** was carried out with the reactant ratio 2 : 1 in toluene, dichloromethane, and acetonitrile for 6 h at +20 and −20 °C (Scheme 2). The initial concentration of the starting racemic amine was 0.1 mol L^{-1}.

The forming mixture of diastereomeric amides was analyzed by HPLC and ^{1}H and ^{19}F NMR spectroscopy. For the assignment of stereoconfiguration of compounds obtained, (*S*,*S*)-diastereomers of amides **11—14** were alternatively synthesized starting from (*S*)-amines and (*S*)-acyl chlorides **4** and **5**, the former are identical to the mixture of (*S*,*S*)- and (*R*,*R*)-diastereomers in their retention time (HPLC) and signals in the NMR spectra.

As in the case of acylation of amines **1** and **2** with (*S*)-naproxen acyl chloride,[20,21] the use of acyl chlorides **4** and **5** led to the enrichment of amides **11—14** with (*S*,*S*)- and (*R*,*R*)-diastereomers (see Scheme 2). In the reaction of racemic amines **1** and **2** and racemic acyl chlorides **3—5**, the formed mixtures of amides **9—14** contained a small amount of minor (*R*,*S*)- and (*S*,*R*)-diastereomers. Therefore, starting from (*S*)-amines **1** and **2** and (*RS*)-acyl chlorides **4** and **5**, the mixtures of (*S*,*S*)- and (*S*,*R*)-amides **11—14** with the enhanced content of (*S*,*R*)-diastereomer were synthesized in order to unambiguously determine retention time by HPLC and positions of signals in the NMR spectra.

The signals of the methine protons and protons of the methyl groups at the asymmetric carbon atoms were considered as diagnostic signals in the ^{1}H NMR spectra, which allowed us to conclude on the diastereomeric composition of the amide mixtures. For the amides studied in the present work it was found that in the ^{1}H NMR spectra recorded at room temperature, the signals for the CH_3 and CH groups of the acyl and amine fragments are noticeably broadened, apparently, due to both the retarded rotation around the amide bond and the conformation lability of the heterocyclic fragment. When ^{1}H NMR spectra of amides **11—14** were recorded in DMSO-d_6 at 100 °C, the narrowing of the signals was observed and the spectra be-

Scheme 2



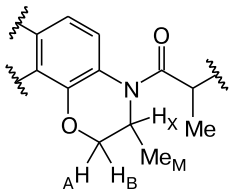
X = F (**1**, **9**, **11**, **13**), H (**2**, **10**, **12**, **14**); Ar = 6-methoxynaphth-2-yl (**3**, **9**, **10**), 4-$Me_2CHCH_2C_6H_4$ (**4**, **11**, **12**), Ph (**5**, **13**, **14**)

came well resolute and suitable for the quantitative determination of diastereomeric composition (Table 1). Such a phenomenon has been observed earlier[20,21] for the diastereomeric amides of naproxen with heterocyclic amines.

To evaluate selectivity of acylation, the *dr* values for amides **9**—**14** were determined by HPLC from the ratio of areas under the peaks of (*S*,*S*)—(*R*,*R*)- and (*R*,*S*)—(*S*,*R*)-diastereomers. The averaged values from two—four parallel determinations are given in Table 2.

For all the acyl chlorides studied, the highest selectivity of acylation was observed in toluene at −20 °C; the selectivity decreased in more polar solvents (see Table 2).

Table 1. Diagnostic signals in the ^{1}H NMR spectra of amides **11**—**14** (400 MHz, DMSO-d_6, 100 °C)



Compound	δ (*J*/Hz)			
	Amine fragment		Acyl fragment	
	Me	H_X	Me	CH
(*S*,*S*)-**11**	0.71 (d, *J* = 6.7)	4.76 (qdd, $J_{M,X}$ = 6.7, $J_{B,X}$ = 2.8, $J_{A,X}$ = 1.5)	1.37 (d, *J* = 6.7)	4.34 (q, *J* = 6.7)
(*R*,*S*)-**11**	1.14 (d, *J* = 6.7)	4.65 (qdd, $J_{M,X}$ = 6.7, $J_{B,X}$ = 2.8, $J_{A,X}$ = 1.5)	1.39 (d, *J* = 6.7)	4.17 (q, *J* = 6.7)
(*S*,*S*)-**12**	0.73 (d, $J_{M,X}$ = 6.9)	4.69 (qdd, $J_{M,X}$ = 6.9, $J_{B,X}$ = 3.0, $J_{A,X}$ = 1.7)	1.39 (d, *J* = 6.8)	4.37 (q, *J* = 6.8)
(*R*,*S*)-**12**	1.11 (d, $J_{M,X}$ = 6.9)	4.64 (m)	1.38 (d, *J* = 6.7)	4.18 (q, *J* = 6.7)
(*S*,*S*)-**13**	0.72 (d, $J_{M,X}$ = 6.8)	4.77 (qdd, $J_{M,X}$ = 6.8, $J_{B,X}$ = 2.8, $J_{A,X}$ = 1.4)	1.39 (d, *J* = 6.6)	4.38 (q, *J* = 6.6)
(*R*,*S*)-**13**	1.15 (d, $J_{M,X}$ = 6.9)	4.66 (qdd, $J_{M,X}$ = 6.9, $J_{B,X}$ = 2.8, $J_{A,X}$ = 1.5)	1.42 (d, *J* = 6.6)	4.21 (q, *J* = 6.6)
(*S*,*S*)-**14**	0.75 (d, $J_{M,X}$ = 6.9)	4.71 (qdd, $J_{M,X}$ = 6.8, $J_{B,X}$ = 3.0, $J_{A,X}$ = 1.7)	1.41 (d, *J* = 6.8)	4.42 (q, *J* = 6.8)
(*R*,*S*)-**14**	1.12 (d, $J_{M,X}$ = 6.9)	4.65 (m)	1.41 (d, *J* = 6.8)	4.22 (q, *J* = 6.8)

Table 2. The ratio of diastereomers (*dr*) in the acylation products of racemic amines **1** and **2** with racemic acyl chlorides **3**—**5**

Amine	Acylating agent	Solvent	*T* /°C	*dr**
1	**3**	$PhCH_3$	+20	97.8 : 2.2
	3	$PhCH_3$	−20	98.5 : 1.5
	3	CH_2Cl_2	+20	96.0 : 4.0
	3	CH_2Cl_2	−20	96.6 : 3.4
	3	MeCN	+20	91.0 : 9.0
	3	MeCN	−20	89.7 : 10.3
	4	$PhCH_3$	+20	97.9 : 2.1
	4	$PhCH_3$	−20	99.0 : 1.0
	4	CH_2Cl_2	+20	95.5 : 4.5
	4	CH_2Cl_2	−20	97.9 : 2.1
	4	MeCN	+20	91.0 : 9.0
	4	MeCN	−20	94.1 : 5.9
	5	$PhCH_3$	+20	96.9 : 3.1
	5	$PhCH_3$	−20	98.6 : 1.4
	5	CH_2Cl_2	+20	94.5 : 5.5
	5	CH_2Cl_2	−20	94.5 : 5.5
	5	MeCN	+20	88.4 : 11.6
	5	MeCN	−20	89.2 : 10.8
2	**3**	$PhCH_3$	+20	97.0 : 3.0
	3	$PhCH_3$	−20	98.2 : 1.8
	3	CH_2Cl_2	+20	93.7 : 6.3
	3	CH_2Cl_2	−20	95.5 : 4.5
	3	MeCN	+20	87.2 : 12.8
	3	MeCN	−20	87.9 : 12.1
	4	$PhCH_3$	+20	98.2 : 1.8
	4	$PhCH_3$	−20	99.0 : 1.0
	4	CH_2Cl_2	+20	95.9 : 4.1
	4	CH_2Cl_2	−20	96.8 : 3.2
	4	MeCN	+20	91.6 : 8.4
	4	MeCN	−20	96.6 : 3.4
	5	$PhCH_3$	+20	97.0 : 3.0
	5	$PhCH_3$	−20	97.2 : 2.8
	5	CH_2Cl_2	+20	92.2 : 7.8
	5	CH_2Cl_2	−20	91.0 : 9.0
	5	MeCN	+20	83.2 : 16.8
	5	MeCN	−20	85.5 : 14.5

* *dr* = ((*S*,*S*)—(*R*,*R*))/((*R*,*S*)—(*S*,*R*)) (from the HPLC data (Reprosil 100 Si); see Experimental).

The acylation of amine **1** was more stereoselective when ibuprofen acyl chloride (**4**) was used as compared to naproxen acyl chloride (**3**) and 2-phenylpropionyl chloride (**5**). In the case of acylation with acyl chlorides **3** and **5** in dichloromethane and acetonitrile, the reaction temperature affected little the stereochemical result of the reaction. Stereoselectivity of acylation with acyl chloride **4** noticeably depended on the temperature (for instance, *dr* for amides **11** were 95.0 : 5.0 and 97.9 : 2.1 in CH_2Cl_2 at +20 and −20 °C, respectively).

Acylation of nonfluorinated amine **2** was characterized by the same regularities. Thus, in the case of the

reaction of amine **2** with acyl chloride **4** at reduced temperatures, a somewhat increase in stereoselectivity was observed (*dr* for amides **12** were 98.2 : 1.8 and 99.0 : 1.0 in toluene at +20 and −20 °C, respectively), while the stereochemical result of acylation of amine **2** with acyl chloride **5** virtually did not depend on temperature (*dr* for amides **14** were 97.0 : 3.0 and 97.2 : 2.8 in toluene at +20 and −20 °C, respectively).

In conclusion, it was found that among compounds studied, ibuprofen acyl chloride (**4**) is an acylating reagent the most selective and sensitive to the changes in the reaction temperature as compared to naproxen acyl chloride (**3**) and 2-phenylpropionyl chlorides (**5**).

At the present, we continue our studies on the search for the new efficient agents for resolution among 2-arylpropionic acid derivatives and on the prospects for their practical use in the resolution of racemic amines.

Experimental

(*RS*)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (**1**) and (*RS*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (**2**) were obtained according to the known procedure.[32] (*S*)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine and (*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine were obtained as described earlier.[20] (*S*)-Naproxen, ibuprofen, (2*RS*)-phenylpropionic and (2*S*)-phenylpropionic acids are commercially available reagents. (*S*)-Ibuprofen was synthesized by resolution of a racemate by fractional crystallization of diastereomeric salts with quinine from the acetone—methanol solvent mixture and subsequent crystallization of the sodium salt according to the known method.[33] (*RS*)-Naproxen was obtained by racemization of (*S*)-naproxen by melting with DBU according to the described method.[34] All the solvents were purified using standard procedures just before use. Column flash-chromatography was performed on silica gel 60 (230—400 mesh) (Lancaster). Melting points were determined on a SMP3 instrument (Barloworld Scientific). ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 376 MHz, respectively) with Me_4Si and hexafluorobenzene as internal standards. ^{1}H NMR spectra of chlorides **3**—**5** were recorded in $CDCl_3$ at room temperature, ^{1}H NMR spectra of amides **11**—**14**, in DMSO-d_6 at 100 °C. Specific rotation was determined on a Perkin—Elmer M 341 polarimeter (the units are (deg mL) (g dm)$^{-1}$; the units for concentration of solutions are g (100 mL)$^{-1}$).

Analysis of diastereomeric composition of amides **9**—**14** by HPLC was performed on a Knauer Smartline-1000 chromatograph (Germany) using a 4.6×250-mm column filled with ReproSil 100 Si, 5 μm sorbent (Elsiko, Russia); the rate of elution was 1 mL min^{-1}; detection was at 220 nm, the hexane—propan-2-ol was a liquid phase (80 : 1 for **9**, 100 : 1 for **10**, and 200 : 1 for **11**—**14**). Mass spectra were recorded after chromatographic resolution on a Shimadzu LCMS-2010 instrument (a Phenomenex Luna C18(2) column, 150×2.0 mm, 3 μm, 100 Å, the acetonitrile—water (75 : 25) mixture was a liquid phase, the rate of elution was 1.0 mL min^{-1}, the column temperature was 60 °C) with a quadrupole analyzer (in the positive or negative modes); chemical ionization at atmospheric pressure (APCI), the source temperature was 400 °C. Elemental analysis was performed on a PE 2400 II elemental analyzer (Perkin—Elmer Instruments, USA).

2-Arylpropionyl chlorides 3—5 (general procedure). Oxalyl chloride (175 μL, 2.0 mmol) was added to a suspension of acid **6**—**8** (1.0 mmol) in benzene (5 mL) with stirring. The reaction mixture was stirred for 6 h at room temperature, concentrated *in vacuo*, and dried over P_2O_5.

(*RS*)-2-(6-Methoxynaphth-2-yl)propionyl chloride (3). The yield was 97%, pale yellow crystals, m.p. 76 °C. ^{1}H NMR ($CDCl_3$), δ: 1.67 (d, 3 H, Me, J = 6.9 Hz); 3.92 (s, 3 H, OMe); 4.24 (q, 1 H, CH, J = 6.9 Hz); 7.10—7.80 (m, 6 H, Ar).

(*S*)-2-(4-Isobutylphenyl)propionyl chloride ((*S*)-4). The yield was 95%, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 0.91 (d, 6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.7 Hz); 1.59 (d, 3 H, CH_3, J = 7.1 Hz); 1.86 (m, 1 H, $CH_2C\underline{H}(CH_3)_2$); 2.57 (d, 2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.5 Hz); 4.10 (q, 1 H, CH, J = 7.1 Hz); 7.15, 7.20 (both m, 4 H, Ar).

(*RS*)-2-(4-Isobutylphenyl)propionyl chloride (4). The yield was 95%, colorless oil. ^{1}H NMR spectrum is identical to that of compound (*S*)-**4**.

(*S*)-2-Phenylpropionyl chloride ((*S*)-5). The yield was 95%, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 1.60 (d, 3 H, Me, J = 6.8 Hz); 4.13 (q, 1 H, CH, J = 6.8 Hz); 7.28—7.41 (m, 5 H, Ph).

(*RS*)-2-Phenylpropionyl chloride (5). The yield was 95%, colorless oil. ^{1}H NMR spectrum is identical to that of compound (*S*)-**5**.

Kinetic resolution (general procedure). A solution of acyl chloride **3**—**5** (0.15 mmol) in the corresponding solvent (toluene, dichloromethane, or acetonitrile) (1.5 mL) was added in one portion to a thermostated solution of amine **1** or **2** (0.3 mmol) in the same solvent (1.5 mL) at a given temperature. The reaction mixture was thermostated for 6 h at the given temperature, washed with aqueous HCl (1 *M*, 2×3 mL) (in the case of the reaction in acetonitrile, aq. HCl (1 *M,* 5 mL) was added to the reaction mixture, followed by extraction the amide with benzene); the organic layer was washed with brine (4×3 mL), 5% aq. $NaHCO_3$ (2×3 mL), water (2×3 mL), dried with $MgSO_4$, and concentrated. The residue was dried *in vacuo* over P_2O_5. Diastereomeric composition of amides **9**—**14** was determined by HPLC (ReproSil 100Si).

The mixtures of amides and individual (*S*,*S*)-diastereomers **9** and **10** have been described earlier.[20]

Synthesis of (*S*,*S*)-amides 11—14 (general procedure). A solution of (*S*)-acyl chloride **4** or **5** (1 mmol) in toluene (10 mL) was added to a solution of (*S*)-amine **1** or **2** (2 mmol) in toluene (10 mL) at +20 °C. The reaction mixture was thermostated for 6 h at +20 °C; washed with aq. HCl (1 *M*, 2×3 mL), brine (4×3 mL), 5% aq. $NaHCO_3$ (2×3 mL), water (2×3 mL), dried with $MgSO_4$, and concentrated. The residue was dried *in vacuo* over P_2O_5. (*S*,*S*)-Amides **11** and **12** were isolated by flash-chromatography on silica gel (eluent, benzene), (*S*,*S*)-amides **13** and **14**, by recrystallization from the EtOH—water solvent mixture.

***N*-[(2*S*)-2-(4-Isobutylphenyl)propionyl]-7,8-difluoro-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine ((*S*,*S*)-11).** The yield was 68%, colorless oil, $[\alpha]_D^{20}$ +96.0 (*c* 1.06, $CHCl_3$), *de* ≥ 99.9%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): τ = 8.6 min. ^{1}H NMR (DMSO-d_6), δ: 0.71 (d, 3 H, Me benzoxazine, J = 6.7 Hz); 0.83 (d, 6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.8 Hz); 1.37 (d, 3 H, Me ibuprofen, J = 6.7 Hz); 1.80 (m, 1 H,

$CH_2C\underline{H}(CH_3)_2$); 2.40 (d, 2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.1 Hz); 4.01 (dd, 1 H, C(2)H_B benzoxazine, J = 11.1 Hz, J = 2.8 Hz); 4.22 (dd, 1 H, C(2)H_A benzoxazine, J = 11.1 Hz, J = 1.5 Hz); 4.34 (q, 1 H, CH ibuprofen, J = 6.8 Hz); 4.76 (qdd, 1 H, C(3)H benzoxazine, J = 6.7 Hz, J = 2.8 Hz, J = 1.5 Hz); 6.82 (ddd, 1 H, C(6)H benzoxazine, J = 10.1 Hz, J = 9.4 Hz, J = 8.1 Hz); 7.04 (m, 4 H, C_6H_4 ibuprofen); 7.54 (ddd, 1 H, C(5)H benzoxazine, J = 9.4 Hz, J = 5.3 Hz, J = 2.5 Hz). ^{19}F NMR (DMSO-d_6), δ: 1.69 (ddd, 1 F, C(8)F, J = 21.2 Hz, J = 8.1 Hz, J = 2.5 Hz); 20.5 (m, 1 F, C(7)F). Found (%): C, 67.89; H, 5.33; N, 4.36. $C_{18}H_{17}F_2NO$. Calculated (%): C, 68.13; H, 5.40; N, 4.41. MS (APCI), m/z (I_{rel} (%)): 374 $[M + H]^+$ (100), 415 $[M + H + CH_3CN]^+$ (5.99).

***N*-[(2*S*)-2-(4-Isobutylphenyl)propionyl]-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine ((*S*,*S*)-12).** The yield was 70%, colorless oil, $[\alpha]_D^{20}$ +84.25 (*c* 1.0, $CHCl_3$), *de* ≥ 99.9%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): τ = 6.8 min. ^{1}H NMR (DMSO-d_6), δ: 0.73 (d, 3 H, Me benzoxazine, J = 6.9 Hz); 0.83 (d, 6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.6 Hz); 1.39 (d, 3 H, Me ibuprofen, J = 6.8 Hz); 1.80 (m, 1 H, $CH_2C\underline{H}(CH_3)_2$); 2.40 (d, 2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.1 Hz); 3.91 (dd, 1 H, C(2)H_B benzoxazine, J = 10.8 Hz, J = 3.0 Hz); 4.06 (dd, 1 H, C(2)H_A benzoxazine, J = 10.8 Hz, J = 1.7 Hz); 4.37 (q, 1 H, CH ibuprofen, J = 6.8 Hz); 4.69 (qdd, 1 H, C(3)H benzoxazine, J = 6.9 Hz, J = 3.0 Hz, J = 1.7 Hz); 6.78 (dd, 1 H, C(8)H benzoxazine, J = 8.1 Hz, J = 1.6 Hz); 6.86 (ddd, 1 H, C(7)H benzoxazine, J = 8.1 Hz, J = 7.2 Hz, J = 1.3 Hz); 7.00 (ddd, 1 H, C(6)H benzoxazine, J = 8.3 Hz, J = 7.2 Hz, J = 1.6 Hz); 7.03 (m, 4 H, C_6H_4 ibuprofen); 7.65 (dd, 1 H, C(5)H benzoxazine, J = 8.3 Hz, J = 1.3 Hz). MS (APCI), m/z (I_{rel} (%)): 338 $[M + H]^+$ (100), 379 $[M + H + CH_3CN]^+$ (4.3).

***N*-[(2*S*)-2-Phenylpropionyl]-7,8-difluoro-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine ((*S*,*S*)-13).** The yield was 65%, colorless crystals, m.p. 165 °C (EtOH—water), $[\alpha]_D^{20}$ +127.4 (*c* 1.0, $CHCl_3$), *de* ≥ 99.9%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): τ = 11.1 min. ^{1}H NMR (DMSO-d_6), δ: 0.72 (d, 3 H, Me benzoxazine, J = 6.8 Hz); 1.39 (d, 3 H, Me phenylpropionic acid, J = 6.6 Hz); 4.02 (dd, 1 H, C(2)H_B benzoxazine, J = 10.9 Hz, J = 2.8 Hz); 4.23 (dd, 1 H, C(2)H_A benzoxazine, J = 10.9 Hz, J = 1.4 Hz); 4.38 (q, 1 H, CH phenylpropionic acid, J = 6.6 Hz); 4.77 (qdd, 1 H, C(3)H benzoxazine, J = 6.8 Hz, J = 2.8 Hz, J = 1.4 Hz); 6.84 (ddd, 1 H, C(6)H benzoxazine, J = 10.2 Hz, J = 9.0 Hz, J = 8.2 Hz); 7.12—7.30 (m, Ph); 7.55 (ddd, 1 H, C(5)H benzoxazine, J = 9.0 Hz, J = 5.3 Hz, J = 2.5 Hz). ^{19}F NMR (DMSO-d_6), δ: 1.75 (ddd, 1 F, C(8)F, J = 21.2 Hz, J = 8.0 Hz, J = 2.5 Hz); 20.58 (m, 1 F, C(7)F). Found (%): C, 67.89; H, 5.33; N, 4.36. $C_{18}H_{17}F_2NO_2$. Calculated (%): C, 68.13; H, 5.40; N, 4.41.

***N*-[(2*S*)-2-Phenylpropionyl]-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine ((*S*,*S*)-14).** The yield was 55%, white crystals, m.p. 76 °C (EtOH—water), $[\alpha]_D^{20}$ +136.2 (*c* 1.0, $CHCl_3$), *de* ≥ 99.9%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): τ = 7.6 min. ^{1}H NMR (DMSO-d_6), δ: 0.75 (d, 3 H, Me benzoxazine, J = 6.9 Hz); 1.41 (d, 3 H, Me phenylpropionic acid, J = 6.8 Hz); 3.92 (dd, 1 H, C(2)H_B benzoxazine, J = 10.8 Hz, J = 3.0 Hz); 4.07 (dd, 1 H, C(2)H_A benzoxazine, J = 10.8 Hz, J = 1.7 Hz); 4.42 (q, 1 H, CH phenylpropionic acid, J = 6.8 Hz); 4.71 (qdd, 1 H, C(3)H benzoxazine, J = 6.9 Hz, J = 3.0 Hz, J = 1.7 Hz); 6.77 (dd, 1 H, C(8)H benzoxazine, J = 8.2 Hz, J = 1.4 Hz); 6.87 (ddd, 1 H, C(7)H benzoxazine, J = 8.2 Hz, J = 7.3 Hz, J = 1.4 Hz); 7.00 (ddd, 1 H, C(6)H benzoxazine, J = 8.2 Hz, J = 7.3 Hz, J = 1.6 Hz); 7.10—7.28 (m, Ph); 6.77 (dd, 1 H, C(5)H benzoxazine, J = 8.2 Hz, J = 1.4 Hz). Found (%): C, 76.77; H, 6.75; N, 4.85. $C_{18}H_{19}NO_2$. Calculated (%): C, 76.84; H, 6.81; N, 4.98.

Synthesis of amides 11—14 (a mixture of diastereomers). A solution of (*RS*)-acyl chloride **4** or **5** (1 mmol) in toluene (10 mL) was added to a solution of (*S*)-amine **1** or **2** (2 mmol) in toluene (10 mL) at +20 °C. The reaction mixture was thermostated for 6 h at +20 °C; washed with aq. HCl (1 *M*, 2×3 mL), brine (4×3 mL), 5% aq. $NaHCO_3$ (2×3 mL), water (2×3 mL), dried with $MgSO_4$, and concentrated. The residue was dried *in vacuo* over P_2O_5. Diastereomers **11—14** were isolated by flash-chromatography on silica gel (eluent, benzene).

***N*-[(2*RS*)-2-(4-Isobutylphenyl)propionyl]-7,8-difluoro-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (11).** The yield was 55%, colorless oil, *de* 0. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): $\tau_{(R,S)}$ 5.6 min, $\tau_{(S,S)}$ 8.6 min. ^{1}H NMR (DMSO-d_6), δ: 0.71 (d, 0.5×3 H, Me benzoxazine, J = 6.7 Hz); 0.83 (d, 0.5×6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.8 Hz); 0.87 (d, 0.5×6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.8 Hz); 1.14 (d, 0.5×3 H, Me benzoxazine, J = 6.7 Hz); 1.37 (d, 0.5×3 H, Me ibuprofen, J = 6.8 Hz); 1.39 (d, 0.5×3 H, Me ibuprofen, J = 6.7 Hz); 1.80 (m, 0.5×1 H, $CH_2C\underline{H}(CH_3)_2$); 1.85 (m, 0.5×1 H, $CH_2C\underline{H}(CH_3)_2$); 2.40 (d, 0.5×2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.1 Hz); 2.44 (d, 0.5×2 H, $C\underline{H}_2CH(CH_3)_2$, J = 6.9 Hz); 3.58 (dd, 0.5×1 H, C(2)H_B benzoxazine, J = 11.0 Hz, J = 2.8 Hz); 4.01 (dd, 0.5×1 H, C(2)H_B benzoxazine, J = 11.0 Hz, J = 2.8 Hz); 4.16 (dd, 0.5×1 H, C(2)H_A benzoxazine, J = 11.0 Hz, J = 1.5 Hz); 4.17 (q, 1 H, CH ibuprofen, J = 6.7 Hz); 4.22 (dd, 0.5×1 H, C(2)H_A benzoxazine, J = 11.1 Hz, J = 1.5 Hz); 4.34 (q, 0.5×1 H, CH ibuprofen, J = 6.8 Hz); 4.65 (qdd, 1 H, C(3)H benzoxazine, J = 6.7 Hz, J = 2.8 Hz, J = 1.5 Hz); 4.76 (qdd, 0.5×1 H, C(3)H benzoxazine, J = 6.7 Hz, J = 2.8 Hz, J = 1.5 Hz); 6.82 (ddd, 1 H, C(6)H benzoxazine, J = 10.1 Hz, J = 9.4 Hz, J = 8.1 Hz); 7.04 (m, 0.5×4 H, C_6H_4 ibuprofen); 7.12, 7.23 (both m, 0.5×4 H, C_6H_4 ibuprofen); 7.55 (m, 1 H, C(5)H benzoxazine). ^{19}F NMR (DMSO-d_6), δ: 1.69 (ddd, 0.5×1 F, C(8)F, J = 21.2 Hz, J = 8.1 Hz, J = 2.5 Hz); 2.08 (ddd, 0.5×1 F, C(8)F, J = 22.2 Hz, J = 9.4 Hz, J = 2.8 Hz); 20.50 (m, 1 F, C(7)F). Found (%): C, 70.48; H, 6.89; N, 3.91. $C_{22}H_{25}F_2NO_2$. Calculated (%): C, 70.76; H, 6.75; N, 3.75.

***N*-[(2*RS*)-2-(4-Isobutylphenyl)propionyl]-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (12).** The yield was 62%, colorless oil, *de* 70%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): $\tau_{(R,S)}$ 4.8 min, $\tau_{(S,S)}$ 6.8 min. ^{1}H NMR (DMSO-d_6), δ: 0.73 (d, 0.85×3 H, Me benzoxazine, J = 6.9 Hz); 0.83 (d, 0.85×6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.6 Hz); 0.87 (d, 0.15×6 H, $CH_2CH(C\underline{H}_3)_2$, J = 6.6 Hz); 1.11 (d, 0.15×3 H, Me benzoxazine, J = 6.9 Hz); 1.38 (d, 0.15×3 H, Me ibuprofen, J = 6.7 Hz); 1.39 (d, 0.85×3 H, Me ibuprofen, J = 6.8 Hz); 1.80 (m, 1 H, $CH_2C\underline{H}(CH_3)_2$); 2.40 (d, 0.85×2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.1 Hz); 2.44 (d, 0.15×2 H, $C\underline{H}_2CH(CH_3)_2$, J = 7.1 Hz); 3.61 (dd, 0.15×1 H, C(2)H_B benzoxazine, J = 10.8 Hz, J = 2.1 Hz); 3.91 (dd, 0.85×1 H, C(2)H_B benzoxazine, J = 10.8 Hz, J = 3.0 Hz); 4.02 (dd, 0.15×1 H, C(2)H_A benzoxazine, J = 10.8 Hz, J = 1.7 Hz); 4.06 (dd, 0.85×1 H, C(2)H_A benzoxazine, J = 10.8 Hz, J = 1.7 Hz); 4.18 (q, 0.15×1 H, CH ibuprofen, J = 6.7 Hz); 4.37 (q, 0.85×1 H, CH ibuprofen, J = 6.8 Hz); 4.64 (m, 0.15×1 H, C(3)H benzoxazine); 4.69 (qdd, 0.85×1 H, C(3)H benzoxazine, J = 6.9 Hz, J = 3.0 Hz, J = 1.7 Hz); 6.78 (dd, 0.85×1 H, C(8)H benzoxazine, J = 8.1 Hz, J = 1.6 Hz); 6.82 (m, 0.15×1 H, C(8)H benzoxazine); 6.80 (m, 0.15×1 H,

C(7)H benzoxazine); 6.86 (ddd, 0.85×1 H, C(7)H benzoxazine, J = 8.1 Hz, J = 7.2 Hz, J = 1.3 Hz); 7.00 (ddd, 1 H, C(6)H benzoxazine, J = 8.3 Hz, J = 7.2 Hz, J = 1.6 Hz); 7.03 (m, 0.85×4 H, C_6H_4 ibuprofen); 7.12, 7.23 (both m, 0.15×4 H, C_6H_4 ibuprofen); 7.65 (dd, 1 H, C(5)H benzoxazine, J = 8.3 Hz, J = 1.3 Hz). Found (%): C, 78.25; H, 8.36; N, 4.13. $C_{22}H_{27}NO_2$. Calculated (%): C, 78.30; H, 8.06; N, 4.15.

***N*-[(2*RS*)-2-Phenylpropionyl]-7,8-difluoro-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (13).** The yield was 60%, colorless crystals, m.p. 160 °C, *de* 10%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): $\tau_{(R,S)}$ 6.2 min, $\tau_{(S,S)}$ 11.1 min. ^{1}H NMR (DMSO-d_6), δ: 0.72 (d, 0.55×3 H, Me benzoxazine, J = 6.8 Hz); 1.15 (d, 0.45×3 H, Me benzoxazine, J = 6.9 Hz); 1.39 (d, 0.55×3 H, Me phenylpropionic acid, J = 6.6 Hz); 1.42 (d, 0.45×3 H, Me phenylpropionic acid, J = 6.6 Hz); 3.62 (dd, 0.45×1 H, $C(2)H_B$ benzoxazine, J = 10.9 Hz, J = 2.8 Hz); 4.02 (dd, 0.55×1 H, $C(2)H_B$ benzoxazine, J = 10.8 Hz, J = 3.0 Hz); 4.17 (dd, 0.45×1 H, $C(2)H_A$ benzoxazine, J = 10.9 Hz, J = 1.5 Hz); 4.21 (q, 0.45×1 H, CH phenylpropionic acid, J = 6.6 Hz); 4.23 (dd, 0.55×1 H, $C(2)H_A$ benzoxazine, J = 10.8 Hz, J = 1.4 Hz); 4.38 (q, 0.55×1 H, CH phenylpropionic acid, J = 6.8 Hz); 4.66 (qdd, 0.45×1 H, C(3)H benzoxazine, J = 6.9 Hz, J = 2.8 Hz, J = 1.5 Hz); 4.77 (qdd, 0.55×1 H, C(3)H benzoxazine, J = 6.8 Hz, J = 2.8 Hz, J = 1.4 Hz); 6.84 (ddd, 1 H, C(6)H benzoxazine, J = 10.2 Hz, J = 9.0 Hz, J = 8.2 Hz); 7.12—7.30 (m, Ph); 7.55 (ddd, 1 H, C(5)H benzoxazine, J = 9.0 Hz, J = 5.3 Hz, J = 2.5 Hz). ^{19}F NMR (DMSO-d_6), δ: 1.75 (ddd, 0.55×1 F, C(8)F, J = 21.2 Hz, J = 8.0 Hz, J = 2.5 Hz); 2.13 (ddd, 0.45×1 F, C(8)F, J = 21.2 Hz, J = 8.0 Hz, J = 2.5 Hz); 20.58 (m, 1 F, C(7)F). Found (%): C, 68.12; H, 5.37; N, 4.37. $C_{18}H_{17}F_2NO_2$. Calculated (%): C, 68.13; H, 5.40; N, 4.41.

***N*-[(2*RS*)-2-Phenylpropionyl]-(3*S*)-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (14).** The yield was 55%, colorless crystals, m.p. 70—71 °C, *de* 60%. HPLC (ReproSil 100 Si, hexane—propan-2-ol (200 : 1)): $\tau_{(R,S)}$ 5.6 min, $\tau_{(S,S)}$ 7.6 min. ^{1}H NMR (DMSO-d_6), δ: 0.75 (d, 0.8×3 H, Me benzoxazine, J = 6.9 Hz); 1.12 (d, 0.2×3 H, Me benzoxazine, J = 6.9 Hz); 1.41 (d, 3 H, Me phenylpropionic acid, J = 6.8 Hz); 3.65 (m, 0.2×1 H, $C(2)H_B$ benzoxazine); 3.92 (dd, 0.8×1 H, $C(2)H_B$ benzoxazine, J = 10.8 Hz, J = 3.0 Hz); 4.02 (m, 0.2×1 H, $C(2)H_A$ benzoxazine); 4.07 (dd, 0.8×1 H, $C(2)H_A$ benzoxazine, J = 10.8 Hz, J = 1.7 Hz); 4.22 (q, 0.2×1 H, CH phenylpropionic acid, J = 6.8 Hz); 4.42 (q, 0.8×1 H, CH phenylpropionic acid, J = 6.8 Hz); 4.65 (m, 0.2×1 H, C(3)H benzoxazine); 4.71 (qdd, 0.8×1 H, C(3)H benzoxazine, J = 6.9 Hz, J = 3.1 Hz, J = 1.7 Hz); 6.77 (dd, 0.8×1 H, C(8)H benzoxazine, J = 8.2 Hz, J = 1.4 Hz); 6.82 (m, 0.2×1 H, C(8)H benzoxazine); 6.85 (m, 1 H, C(7)H benzoxazine); 6.87 (ddd, 0.8×1 H, C(7)H benzoxazine, J = 8.2 Hz, J = 7.3 Hz, J = 1.4 Hz); 7.00 (ddd, 1 H, C(6)H benzoxazine, J = 8.2 Hz, J = 7.3 Hz, J = 1.6 Hz); 7.10—7.28 (m, Ph); 6.77 (dd, 1 H, C(5)H benzoxazine, J = 8.2 Hz, J = 1.4 Hz). Found (%): C, 76.56; H, 6.97; N, 4.75. $C_{18}H_{19}NO_2$. Calculated (%): C, 76.84; H, 6.81; N, 4.98.

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