Synthesis of 1-[(1*R*)-1-(6-Fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted Phenyl Ureas and Their Inhibition Activity to Acetylcholinesterase and Butyrylcholinesterase

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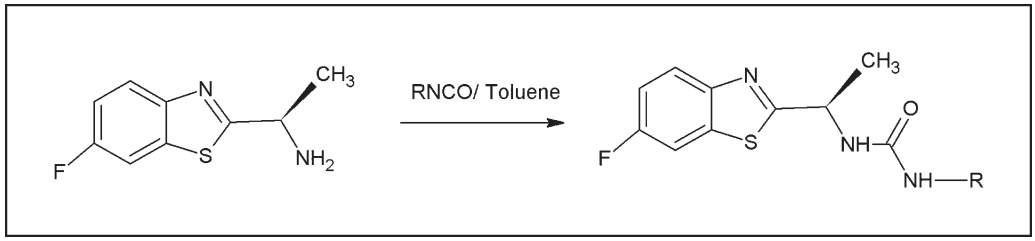

A series of novel 1-[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted phenyl ureas were synthesized by the condensation of (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine with substituted phenyl isocyanates under mild conditions. Their structures were confirmed ^{1}H, ^{13}C, and ^{19}F NMR spectra, and elemental analyses. The optical activities were confirmed by optical rotation measurements. The inhibition activity of 1-[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted phenyl ureas to acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE) was also tested. Preliminary bioassay indicated that the target ureas displayed excellent acetylcholinesterase and butyrylcholinesterase inhibition activity.

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INTRODUCTION

The search for new and potent cholinesterase inhibitors (CHEIs) is an ongoing quest mobilizing many organic chemistry groups around the world. It was shown that these molecules can treat the late symptoms of Alzheimer's disease (AD) and as well as act as neuroprotecting agents [1].

There are two major forms of cholinesterases (CHEs)—acetylcholinesterase (ACHE, EC 3.1.1.7) and butyrylcholinesterase—also called pseudocholinesterase or nonspecific cholinesterase (BCHE, EC 3.1.1.8) in vertebrates. These enzymes belong to the group of serine hydrolases and are responsible for the breakdown of neurotransmitter acetylcholine (ACH) and butyrylcholine (BCH), respectively [2].

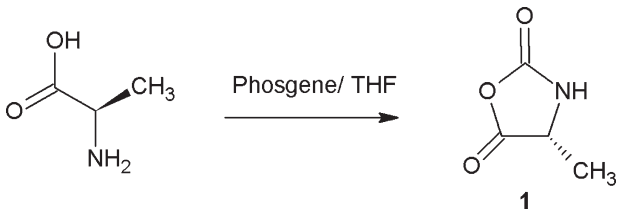
In AD, the loss of cholinergic neurotransmission in the brain is accompanied by a reduced concentration of ACH and contributes to the salient cognitive and behavioral disturbances characteristic of AD [1].

CHEIs increase the amount of ACH available for neuronal and neuromuscular transmission through their ability to reversibly or irreversibly inhibit the activity of CHEs [3]. Therefore, CHEIs have become the main approach to symptomatic treatment of AD [4].

RESULTS AND DISCUSSION

The key intermediate, **2** required for the synthesis of the title compounds was prepared according to the procedure outlined in the Schemes 1 and 2. (4*R*)-4-Methyl-1,3-oxazolidine-2,5-dione (**1**) was prepared by reaction of D-alanine with phosgene in THF according to reported method (Scheme 1) [5]. (1*R*)-1-(6-Fluoro-1,3-benzothiazol-2-yl)ethanamine *p*-toluenesulfonic salt (**2**) was prepared by three-step process according to reported method (Scheme 2) [6,7]. Compound **1** reacted with water solution of potassium hydroxide in the first step to give 2-aminobenzothiol potassium salt, which reacted with compound **1** in the second step to give product **2** hydrochloride. Product **2** *p*-toluenesulfonic salt was prepared by reaction of product **2** hydrochloride with *p*-toluenesulfonic acid in water. The measured melting points as well as the ^{1}H, ^{13}C NMR chemical shifts of the known compound **1** agree with the literature data [5,8]. A series of unreported ureas **3a–j** were synthesized by the two steps process. Compound **2** *p*-toluenesulfonic salt was transformed by 15% aqueous solution of sodium hydroxide to compound **2** base in the first step. In this work, a series of 10 new optical active unsymmetrical ureas **3a–j** were synthesized (Scheme 3). Compound

Scheme 1. Synthetic route to compound **1**.



2 reacted with corresponding substituted phenyl isocyanates under mild conditions in good yields (85–88%) in the second step. Low solubilities of prepared ureas in toluene were used for preparation of high quality products. Unreacted compound **2-**base and isocyanates were very good soluble in toluene and they could by remove from products by toluene wash. The structures of the prepared products were confirmed by ^{1}H, ^{13}C, ^{19}F NMR, and elemental analyses.

R= **a**: phenyl, **b**: benzyl, **c**: 2,6-diisopropylphenyl, **d**: 3-chloro-4-methylphenyl, **e**: 3,5-dichlorophenyl, **f**: 3,5-dimethylphenyl, **g**: 4-isopropylphenyl, **h**: 4-chlorophenyl, **i**: 4-cyanophenyl, **j**: 4-nitrophenyl.

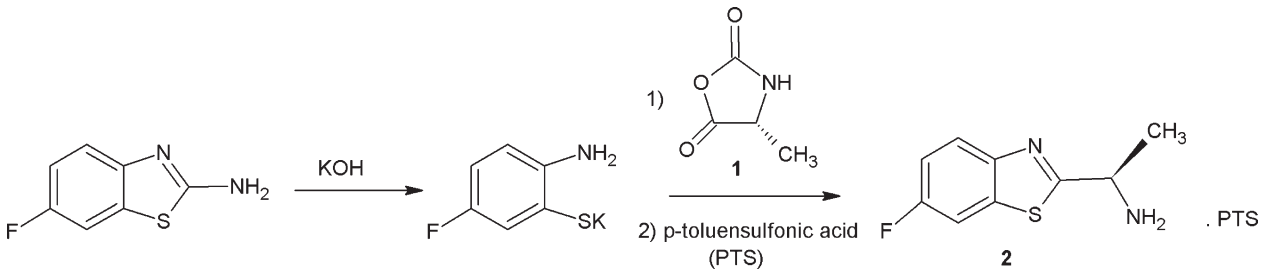
The structures of substituents, molecular formulas, yields, and melting points are compiled in Table 1. The structures of compounds **3a–j** were deduced from their spectroscopic data. ^{1}H NMR spectra of compounds **3** showed the presence of two NH ureas proton peaks typical for unsymmetrical ureas. The first NH(6′-H) proton signal displayed singlet and second NH(1-H) proton signal displayed doublet with $J = 7$ Hz. NH proton (1-H) was coupled by presence CH group. This CH group was coupled to quintet by CH_3 group proton (2-H) and NH urea group protons (1-H) with $J = 7$ Hz too. The proton 4-H signal was displayed doublet with $J = 9$ Hz. The fluorine couplings were not observed in compound **3a–j** in contrast to compound **2**. The proton 4-H signal in compound 2 was displayed doublet of doublet with $J = 9$ Hz and fluorine coupling through four bonds with $^{4}J(^{19}F,^{1}H) = 4.8$ Hz. The proton 5-H signal should be displayed doublet of doublet of doublet. The proton signal was coupled by proton through three bonds with $^{3}J = 9$ Hz, through four bonds with $^{4}J = 2.6$ Hz and by fluorine through three bonds with $^{3}J(^{19}F,^{1}H) = 9$ Hz. Because the values of coupling constants ^{3}J and $^{3}J(^{19}F,^{1}H)$ were the same, the proton signal was displayed doublets of triplets. The proton 6-H signal was displayed doublets of doublets. The proton signal was coupled by protons through four bonds with $^{4}J = 2.5$ Hz and by fluorine through three bonds with $^{3}J(^{19}F,^{1}H) = 9$ Hz. Proton numbering for assignment of ^{1}H NMR shifts is illustrated in Schemes 4 and 5. The ^{13}C NMR spectrum showed two peaks in the alkyl region indicating the presence of the CH_3—CH— group. Seven peaks were assignable to 6-substituted benzothiazole group. Other peaks were assignable to substituted phenyl groups. All peaks of 6-substituted benzothiazole group were duplex by fluorine coupling to doublets. The optical activities were confirmed by optical rotation measurements. The optical rotation measurements were performed in aceton ($c = 0.2-1$).

Determination of IC_{50}. The effectiveness of the inhibitor could be described by the 50% inhibitory concentration IC_{50}. The IC_{50}, or the half maximal inhibitory concentration, represents the concentration of an inhibitor that is required for 50% inhibition of the enzyme. (Sometime it is referred to as the negative logarithm of the molar concentration inhibiting the enzyme activity by 50%, $pI_{50} = -\log IC_{50}$). IC_{50} values are dependent on conditions under which they are measured. The results of IC_{50} determination are compiled in Table 2.

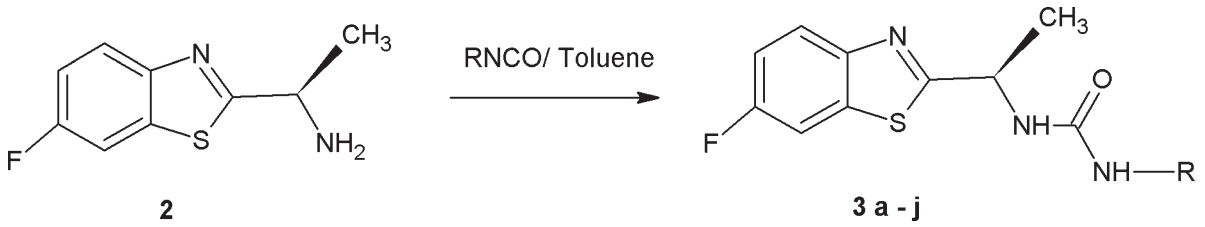
From the obtained results it follows that all tested compounds inhibit ACHE as well as BCHE. Generally, it is possible to conclude that inhibition of BCHE by the tested compounds is stronger than of ACHE. This could be caused by several structural differences between the hydrophobic gorge of active centre in ACHE and BCHE. At the base of the gorge in ACHE, the binding of the substrate is represented by two phenylalanine molecules whose aromatic residues protrude into the gorge. In BCHE, these molecules are replaced by two smaller amino acid molecules—valine and leucine. This conformational change creates a larger space within the deepest area of the gorge of BCHE to allow the fit of larger-size substrates and inhibitors of BCHE [9,10].

In conclusion, a series of novel 1-[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted phenyl ureas

Scheme 2. Synthetic route to compound **2**.



Scheme 3. Synthetic route to compound **3**.

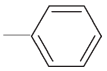
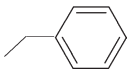
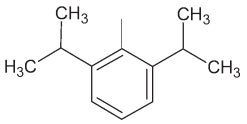
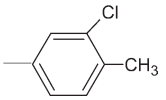
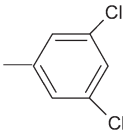
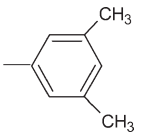
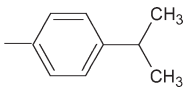
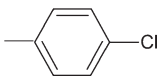
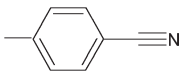
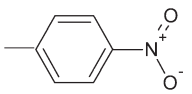


2 **3 a - j**

were synthesized by the condensation of (1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine with substituted phenyl isocyanates under mild conditions in good yields (85–88%). The inhibition activity of 1-[(1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-substituted phenyl ureas to acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE) was also tested. Preliminary bioassay indicated that the target ureas displayed excellent acetylcholinesterase and butyrylcholinesterase inhibition activity.

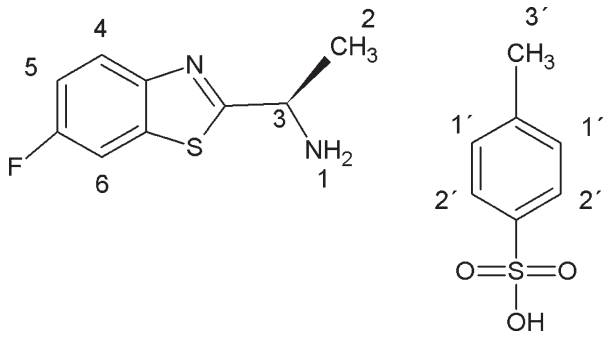
Table 1

Synthesis of compounds **3a–j**.

Compound[a]	R	Mol. formula	Yield (%)	Mp (°C)
3a		$C_{16}H_{14}FN_3OS$	85	226–228
3b		$C_{17}H_{16}FN_3OS$	84	214–215
3c		$C_{22}H_{26}FN_3OS$	86	213–214
3d		$C_{17}H_{15}ClFN_3OS$	86	210–211
3e		$C_{16}H_{12}Cl_2FN_3OS$	88	239–240
3f		$C_{18}H_{18}FN_3OS$	86	233–234
3g		$C_{19}H_{20}FN_3OS$	87	175–176
3h		$C_{16}H_{13}ClFN_3OS$	86	248–249
3i		$C_{17}H_{13}FN_4OS$	86	220–221
3j		$C_{16}H_{13}FN_4O_3S$	85	224–226

[a] All the products were characterized by NMR and elemental analyses.

Scheme 4. Proton numbering for the assignment of ^{1}H NMR shifts (compound **2**).



EXPERIMENTAL

General data. The purity of ureas was checked by elemental analysis using an automatic analyzer EA 1108 (Fisons). ^{1}H, ^{13}C, and ^{19}F NMR spectra of the model compounds were measured at 25°C using their solutions in DMSO-d_6 on a Bruker Avance 400 apparatus at 400.13 MHz (^{1}H), 100.62 MHz (^{13}C), 376.46 MHz (^{19}F). The chemical shifts were referenced to the solvent signal. The optical rotation was measured on a Perkin–Elmer 341 instrument, concentration *c* is given in g/100 mL. Melting points were determined by open capillary method and were uncorrected. Elemental analyses were performed with Fisons Instruments1108 CHN elemental analyzer.

The IC_{50} values were determined by spectrophotometric Ellman's method [11].

The substituted aromatic isocyanates, 6-fluoro-1,3-benzothiazol-2-amine, other reagents, and solvents were purchased from commercial sources (Sigma-Aldrich, Merck). Commercial grade reagents were used without a further purification.The required compounds (4*R*)-4-methyl-1,3-oxazolidine-2,5-dione (1) and (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine *p*-toluenesulfonic salt (2) were synthesized by reported method [5–7]. Their structures of the products were confirmed by ^{1}H, ^{13}C, NMR, meeting point and elemental analyses.

Yields, melting points, ^{1}H, ^{13}C, and ^{19}F NMR shifts, results of the optical rotation measurings and elemental analyses of ureas **3a–j** are given in the text below.

(1R)-1-(6-Fluoro-1,3-benzothiazol-2-yl)ethanamine 4-toluenesulfonate (2) This compound was obtained as white powder. Yield: 81%, m.p. 241–242°C ^{1}H NMR (400.13 MHz, DMSO-d_6)**:** δ = 1.66 (d, 3H, 2-H, *J* = 6.8 Hz), 2.28 (s, 3H, 3′-H), 5.01 (k, 1H, 3-H, *J* = 6.8 Hz), 7.10 (d, 2H, 2′-H, *J* = 8.0 Hz), 7.37 [dt, 1H, 5-H, *J* = 2.4, 9.2 Hz, $^3J(^{19}F, ^1H)$ = 9.2 Hz],

Scheme 5. Proton numbering for the assignment of ^{1}H NMR shifts (compounds **3a–j**).

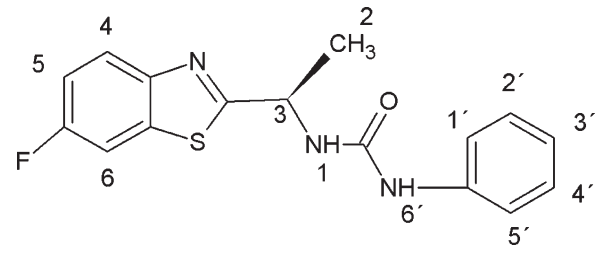


Table 2

The IC_{50} values of tested ureas **3a–j.**

Compound	IC_{50} (μmol/L) Acetylcholinesterase **ACHE**	Butyrylcholinesterase **BCHE**
3a	39.3	3.65
3b	46.1	35
3c	50.5	28.8
3d	15.2	14.1
3e	72.7	35.5
3f	58.9	50.8
3g	60.6	50.1
3h	36.9	43.9
3i	39.4	7.54
3j	26.9	22.9

7.48 (d 2H, 1′-H, *J* = 8.0 Hz), 8.09 [dd, 1H, 4-H, *J* = 9.2 Hz, $^4J(^{19}F, ^1H)$ = 4.8 Hz], 8.12 [dd, 1H, 6-H, *J* = 2.4 Hz, $^3J(^{19}F, ^1H)$ = 8.4 Hz], 8.74 (s, 2H, 1-H) NH_2; ^{13}C NMR (100.62 MHz, DMSO-d_6): 19.9, 20.9, 48.4, 109.0 [d, $^2J(^{19}F, ^{13}C)$ = 27.4 Hz], 115.5 [d, $^2J(^{19}F, ^{13}C)$ = 24.9 Hz], 124.3 [d, $^3J(^{19}F, ^{13}C)$ = 9.6 Hz], 125.7, 128.5, 136.4 [d, $^3J(^{19}F, ^{13}C)$ = 11.9 Hz], 138.5, 144.9, 148.8, 160.1 [d, $^1J(^{19}F, ^{13}C)$ = 243.5 Hz], 169.1; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −115.21. Anal. Calcd. for $C_{16}H_{17}FN_2O_3S_2$ (368.44): C, 52.16; H, 4.65; N, 7.60. Found: C, 52.00; H, 4.82; N, 17.51.

General procedure for synthesis of ureas 3a–j. To the suspension of (1*R*)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethanamine *p*-toluenesulfonic salt (**2**) (0.01 mole) and toluene (50 mL) was added the 15% aqueous solution of sodium hydroxide (0.011 mole), the mixture was stirred at room temperature for 0.5 h. The toluene phase was separated and filtered. The toluene solution of R–1-(6-fluorobenzthiazole-2-yl)ethylamine (0.01 mole) was treated with a solution of corresponding substituted phenyl isocyanate (0.01 mole) in toluene (20 mL) at room temperature. The separated solid was collected by filtration, dried to give compounds **3a–j** in 84–88% yields.

1-[(1R)-1-(6-Fluoro-1,3-benzothiazol-2-yl)ethyl]-3-phenylurea (3a). This compound was obtained as white powder. Yield: 85%; m.p. 226–228°C; $[\alpha]_D^{20}$ = +48.7° (acetone *c* = 1); ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.60 (d, 3H, 2-H, *J* = 7.2 Hz) CH_3, 5.19 (kv, 1H, 3-H, *J* = 7.2 Hz) CH, 6.93 (t, 1H, 3′-H, *J* = 7.4 Hz), 7.08 (d, 1H, 1-H, *J* = 7.2 Hz) NH urea, 7.24 (t, 2H, 2′-H, 4′-H, *J* = 7.4), 7.37 [dt, 1H, 5-H, *J* = 2.7, 9.0 Hz, $^3J(^{19}F, ^1H)$ = 9.0 Hz], 7.41 (d 2H, ′1′-H, 5′-H, *J* = 7.4 Hz), 7.97 (d, 1H, 4-H, *J* = 8.9 Hz), 7.99 [dd, 1H, 6-H, *J* = 2.8 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz], 8.67 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.9, 48.1, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 25.2 Hz], 117.9, 121.6, 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 9.1 Hz], 128.8, 135.8 [d, $^3J(^{19}F, ^{13}C)$ = 11.1 Hz], 140.0, 149.8 [d, $^5J(^{19}F, ^{13}C)$ = 2.0 Hz], 154.6, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 177.2 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.70. Anal. Calcd. for $C_{16}H_{14}FN_3OS$ (315.37): C, 60.94; H, 4.47; N,13.32. Found: C, 61.22; H, 4.60; N, 13.38.

1-Benzyl-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3b). This compound was obtained as white powder. Yield: 84%; m.p. 214–215°C; $[\alpha]_D^{20}$ = −17.0° (acetone *c* = 0.2); ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.59 (d, 3H, 2-H, *J* = 7.2 Hz),

4.30 (d, 2H J = 6.0 Hz) CH_2-benzyl, 5.16 (kv, 1H, 3-H, J = 7.2 Hz), 5.6 (t, 1H, 3′-H, J = 6 Hz), 7.02 (d, 1H, 1-H, J = 7.2 Hz) NH urea, 7.25–7.34 (m, 5H, 1′-H, 2′-H, 4′-H, 5′-H), 7.36 [dt, 1H, 5-H, J = 2.6, 9.0 Hz, $^3J(^{19}F, ^1H)$ = 9.0 Hz], 7.99 (d, 1H, 4-H, J = 4.9 Hz), 8.01 [dd, 1H, 6-H, J = 2.6 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz]; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.9, 42.9, 48.1, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 24.1 Hz], 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 9.1 Hz], 126.7, 127.0, 128.3, 135.7 [d, $^3J(^{19}F, ^{13}C)$ = 11.1 Hz], 140.4, 149.8 [d, $^5J(^{19}F, ^{13}C)$ = 1.0 Hz], 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 177.9 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.86. Anal. Calcd. for $C_{17}H_{16}FN_3OS$ (329.39): C, 61.99; H, 4.90; N,12.76. Found: C, 61.92; H, 5.02; N, 12.82.

1-(2,6-Diisopropylphenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3c). This compound was obtained as white powder. Yield: 86%; m.p. 213–214°C, $[\alpha]_D^{20}$ = +18.6° (acetone c = 1); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.10 (b, 3H) CH_3-isopropyl, 1.15 (d, 3H, J = 6.8 Hz) CH_3-isopropyl, 1.59 (d, 3H, 2-H, J = 7.2 Hz), 3.20 (b, 2H) CH-isopropyl, 5.17 (kv, 1H, 3-H, J = 7.2 Hz), 7.11–7.25 (m, 4H, 1-H, 2′-H, 3′-H, 4′-H), 7.36 [dt, 1H, 5-H, J = 2.4, 8.8 Hz, $^3J(^{19}F, ^1H)$ = 8.8 Hz], 7.61 (s, 1H, 6′-H) NH urea, 7.95 [dd, 1H, 6-H, J = 4.8 Hz, $^3J(^{19}F, ^1H)$ = 8.8 Hz], 8.01 (d, 1H,4-H, J = 6.8 Hz); ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.9, 27.8, 48.2, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 25.1 Hz], 122.7, 123.5 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 126.9, 135.7 [d, $^3J(^{19}F, ^{13}C)$ = 11.1 Hz], 146.5, 149.8, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 177.7; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.82. Anal. Calcd. for $C_{22}H_{26}FN_3OS$ (399.52): C, 66.14; H, 6.56; N,10.52. Found: C, 66.22; H, 6.46; N, 10.61.

1-(3-Chloro-4-methylphenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3d). This compound was obtained as white powder. Yield: 86%; m.p. 210–211°C; $[\alpha]_D^{20}$ = +77.9° (acetone c = 1); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.59 (d, 3H, 2-H, J = 7.1 Hz), 2.22 (s, 3H) CH_3, 5.17 (kv, 1H, 3-H, J = 7.1 Hz), 7.12–7.20 (m, 3H, 1-H, 4′-H, 5′-H), 7.36 [dt, 1H, 5-H, J = 2.6, 9.1 Hz, $^3J(^{19}F, ^1H)$ = 9.1 Hz], 7.66 (d, 1H, 1′-H, J = 2.0 Hz), 7.97 (d, 1H, 4-H, J = 8.8 Hz), 7.99 [dd, 1H, 6-H, J = 3.0 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz], 8.80 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 18.8, 20.8, 48.2, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 24.1 Hz], 116.6, 117.8, 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 127.9, 131.1, 133.1, 135.7 [d, $^3J(^{19}F, ^{13}C)$ = 11.1 Hz], 139.2, 149.8 [d, $^5J(^{19}F, ^{13}C)$ = 1.0 Hz], 154.5, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 176.9 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.67. Anal. Calcd. for $C_{17}H_{15}ClFN_3OS$ (363.84): C, 56.12; H, 4.16; N,11.55. Found: C, 56.10; H, 4.26; N, 11.51.

1-(3,5-Dichlorophenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3e). This compound was obtained as white powder. Yield: 88%; m.p. 239–240°C; $[\alpha]_D^{20}$ = +66.9° (acetone c = 0.3); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.59 (d, 3H, 2-H, J = 7.1 Hz), 5.18 (kv, 1H, 3-H, J = 7.1 Hz), 7.10 (t, 1H, 3′-H, J = 1.8 Hz), 7.36 [dt, 1H, 5-H, J = 2.6, 9.2 Hz, $^3J(^{19}F, ^1H)$ = 9.2 Hz], 7.39 (d, 1H, 1-H, J = 7.1 Hz) NH urea, 7.50 (d, 2H, 1′-H, 5′-H, J = 1.8 Hz), 7.97 (d, 1H, 4-H, J = 9.0 Hz), 7.99 [dd, 1H, 6-H, J = 3.3 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz], 9.10 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.4, 48.1, 108.6 [d, $J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.6 [d, $^2J(^{19}F, ^{13}C)$ = 25.2 Hz], 115.8, 120.4, 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 9.1 Hz], 134.1, 135.7 [d, $^3J(^{19}F, ^{13}C)$ = 12.1 Hz], 142.4, 149.5, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 176.3 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.58. Anal. Calcd. for $C_{16}H_{12}Cl_2FN_3OS$ (384.26): C, 50.01; H, 3.15; N,10.94. Found: C, 50.09; H, 4.26; N, 10.85.

1-(3,5-Dimethylphenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3f). This compound was obtained as white powder. Yield: 86%; m.p. 233–234°C; $[\alpha]_D^{20}$ = +51.2° (acetone c = 0.3); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.59 (d, 3H, 2-H, J = 7.2 Hz), 2.20 (s, 6H) CH_3, 5.16 (kv, 1H, 3-H, J = 7.2 Hz), 6.56 (s, 3′-H, 1H), 7.03 (s, 2H, 1′-H, 5′-H), 7.06 (d, 1H, 1-H, J = 7.2 Hz) NH urea, 7.37 [dt, 1H, 5-H, J = 2.6, 9.2 Hz, $^3J(^{19}F, ^1H)$ = 9.2 Hz], 7.97 (d, 1H, 4-H, J = 8.8 Hz), 7.99 [dd, 1H, 6-H, J = 3.0 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz], 8.50 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.9, 21.1, 48.1, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 24.1 Hz], 115.7, 123.2, 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 9.1 Hz], 135.7 [d, $^3J(^{19}F, ^{13}C)$ = 12.1 Hz], 137.7, 139.8, 149.8 [d, $^5J(^{19}F, ^{13}C)$ = 2.0 Hz], 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 177.3 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.72. Anal. Calcd. for $C_{18}H_{18}FN_3OS$ (343.42): C, 62.95; H, 5.28; N, 12.24. Found: C, 63.06; H, 5.46; N, 12.18.

1-(4-Isopropylphenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3g). This compound was obtained as white powder. Yield: 87%; m.p. 175–176°C; $[\alpha]_D^{20}$ = +58.7° (acetone c = 1); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.15 (d, 6H, J = 6.8 Hz) CH_3–isopropyl, 1.59 (d, 3H, 2-H, J = 7.2 Hz), 2.80 (sept., 1H, J = 7.2 Hz) CH-isopropyl, 5.18 (kv, 1H, 3-H, J = 7.2 Hz), 7.03 (d, 1H, 1-H, J = 7.2 Hz) NH urea, 7.10 (d, 2H, 1′-H, 5′-H, J = 8.4 Hz), 7.32 (d, 2H, 2′-H, 4′-H, J = 8.4 Hz), 7.37 [dt, 1H, 5-H, J = 2.7, 9.2 Hz, $^3J(^{19}F, ^1H)$ = 9.2 Hz], 7.97 (d, 1H, 4-H, J = 9.2 Hz) 7.99 [dd, 1H, 6-H, J = 3.1 Hz, $^3J(^{19}F, ^1H)$ = 8.9 Hz], 8.58 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.9, 24.0, 32.8, 48.1, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.5 [d, $^2J(^{19}F, ^{13}C)$ = 24.1 Hz], 118.1, 123.6 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 126.4, 135.8 [d, $^3J(^{19}F, ^{13}C)$ = 12.1 Hz], 137.7, 141.7, 149.9 [d, $^5J(^{19}F, ^{13}C)$ = 1.0 Hz], 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 177.3 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.73. Anal. Calcd. for $C_{19}H_{20}FN_3OS$ (357.45): C, 63.84; H, 5.64; N,11.76. Found: C, 63.75; H, 5.82; N, 11.66.

1-(4-Chlorophenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]urea (3h). This compound was obtained as white powder. Yield: 86%; m.p. 248–249°C; $[\alpha]_D^{20}$ = +68.6° (acetone c = 1); ^1H NMR (400.13 MHz, DMSO-d_6): δ = 1.59 (d, 3H, 2-H, J = 7.2 Hz), 5.18 (kv, 1H, 3-H, J = 7.2 Hz), 7.13 (d, 1H, 1-H, J = 7.3 Hz) NH urea, 7.27 (d, 2H, 1′-H, 5′-H, J = 9.0 Hz), 7.37 [dt, 1H, 5-H, J = 2.6, 9.0 Hz, $^3J(^{19}F, ^1H)$ = 9.0 Hz], 7.45 (d, 2H, 2′-H, 4′-H, J = 9.0 Hz), 7.97 (d, 1H, 4-H, J = 9.2 Hz),7.99 [dd, 1H, 6-H, J = 2.5 Hz, $^3J(^{19}F, ^1H)$ = 9.0 Hz], 8.82 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.8, 48.1, 108.6 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.6 [d, $^2J(^{19}F, ^{13}C)$ = 25.1 Hz], 119.4, 123.7 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 125.0, 128.6, 135.8 [d, $^3J(^{19}F, ^{13}C)$ = 12.1 Hz], 139.0, 149.8, 154.5, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 242.5 Hz], 176.9 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.66. Anal. Calcd. for $C_{16}H_{13}ClFN_3OS$ (349.81): C, 54.94; H, 3.75; N, 12.01. Found: C, 55.02; H, 4.00; N, 12.12.

1-(4-Cyanophenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]urea (3i). This compound was obtained as white powder. Yield: 86%; m.p. 220–221°C; $[\alpha]_D^{20}$ = +98.2° (acetone c

= 1); ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.60 (d, 3H, 2-H, J = 7.2 Hz), 5.21 (kv, 1H, 3-H, J = 7.2 Hz), 7.37 [dt, 1H, 5-H, J = 2.6, 9.2 Hz, $^3J(^{19}F, ^1H)$ = 9.2 Hz], 7.38 (d, 1H, 1-H, J = 7.2 Hz) NH urea, 7.60 (d, 2H, 1′-H, 5′-H, J = 8.9 Hz), 7.69 (d, 2H, 2′-H, 4′-H, J = 8.9 Hz), 7.97 (d, 1H, 4-H, J = 8.5 Hz), 7.99 [dd, 1H, 6-H, J = 2.5 Hz, $^3J(^{19}F, ^1H)$ = 8.8 Hz], 9.26 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.7, 48.2, 103.0, 108.7 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.6 [d, $^2J(^{19}F, ^{13}C)$ = 24.1 Hz], 117.8, 119.4, 123.7 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 133.3, 135.8 [d, $^3J(^{19}F, ^{13}C)$ = 12.1 Hz], 144.5, 149.7, 154.1, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 241.5 Hz], 176.4 [d, $^4J(^{19}F, ^{13}C)$ = 3.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.58. Anal. Calcd. for $C_{17}H_{14}FN_4OS$ (340.37): C, 59.99; H, 3.85; N,16.46. Found: C, 59.89; H, 4.00; N, 16.55.

1-(4-Nitrophenyl)-3-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl) ethyl]urea (3j). This compound was obtained as yellowish powder. Yield: 85%; m.p. 224–226°C; $[\alpha]_D^{20}$ = +128.0° (acetone c = 1) ; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 1.62 (d, 3H, 2-H, J = 7.2 Hz), 5.22 (kv, 1H, 3-H, J = 7.2 Hz), 7.37 [dt, 1H, 5-H, J = 2.5, 9.1 Hz, $^3J(^{19}F, ^1H)$ = 9.1 Hz], 7.43 (d, 1H, 1-H, J = 7.5 Hz) NH urea,7.65 (d, 2H, 1′-H, 5′-H, J = 9.1 Hz), 7.98 (d, 1H, 4-H, J = 8.8 Hz), 7.99 [dd, 1H, 6-H, J = 2.5 Hz, $^3J(^{19}F, ^1H)$ = 8.8 Hz], 8.15 (d, 2H, 2′-H, 4′-H, J = 9.1 Hz), 9.49 (s, 1H, 6′-H) NH urea; ^{13}C NMR (100.62 MHz, DMSO-d_6): 20.7, 48.2, 108.7 [d, $^2J(^{19}F, ^{13}C)$ = 27.2 Hz], 114.6 [d, $^2J(^{19}F, ^{13}C)$ = 25.2 Hz], 117.2, 123.7 [d, $^3J(^{19}F, ^{13}C)$ = 10.1 Hz], 125.2, 135.8 [d, $^3J(^{19}F, ^{13}C)$ = 11.1 Hz], 140.8, 146.6, 149.7 [d, $^5J(^{19}F, ^{13}C)$ = 1.0 Hz], 154.0, 159.5 [d, $^1J(^{19}F, ^{13}C)$ = 241.5 Hz], 176.2 [d, $^4J(^{19}F, ^{13}C)$ = 4.0 Hz]; ^{19}F NMR (376.46 MHz, DMSO-d_6): δ = −116.54. Anal. Calcd. for $C_{16}H_{13}FN_4O_3S$ (360.36): C, 53.33; H, 3.64; N,15.55. Found: C, 53.43; H, 3.46; N, 15.61.

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