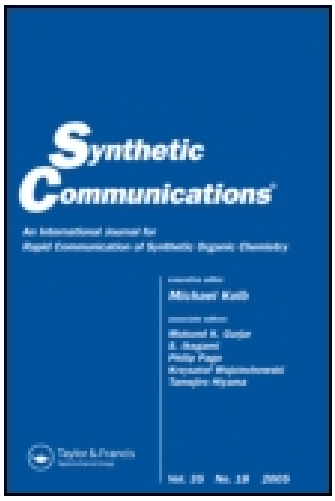

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Introduction of a Carbohydrate Moiety into the Structure of Thiourea Compounds Targeting HIV-1 Reverse Transcriptase

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ABSTRACT

We developed a novel approach to introduce a carbohydrate moiety into the structure of thiourea compounds targeting the NNI binding pocket of the HIV-1 reverse transcriptase. The described method involves the synthesis of an amino-substituted carbohydrate moiety which is then condensed with various thiocarbonylimidazole derivatives of substituted aromatic amines.

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INTRODUCTION

The reverse transcriptase (RT) enzyme of the human immunodeficiency virus (HIV-1) is responsible for the reverse transcription of retroviral RNA to proviral DNA.[1] Because of its pivotal role in HIV-1 replication, RT serves as a molecular target for drugs aimed at treating AIDS.[2] We have previously reported the structure-based design of several thiourea compounds (**Z**, Fig. 1) as promising non-nucleoside inhibitors (NNI) of RT.[3–11] Although these thiourea derivatives are potent anti-HIV agents, their poor bioavailability limits their therapeutic potential. In order to eliminate this disadvantage, we have developed a synthetic strategy for introduction of a carbohydrate side chain which may improve the bioavailability of thiourea derivatives. This strategy may also result in increased intracellular concentrations of the thiourea compounds.

RESULTS AND DISCUSSION

Synthesis of several new carbohydrate-containing thiourea compounds, was initiated using several water soluble secondary amines prepared from D-glucose. In order to prepare water soluble chiral amines of furanosaccharides, diacetone-D-glucose was chosen as the starting material **1,** which was prepared from D-glucose and acidic (H_2SO_4) acetone, as described in the literature.[12] The crystalline furano sugar **1** on benzylation with NaH-BnBr-DMF at 0°C gave benzyl ether **2** with a 92% yield. Regioselective hydrolysis of **1**,**2** with 0.8% H_2SO_4 yielded diol (**3,4**) which was oxidatively cleaved with sodium metaperiodate to yield aldehydes which on immediate reaction with fluorophenethyl amine in CH_2Cl_2/Na_2SO_4 yielded the corresponding imines. These imines without isolation were immediately reduced with $NaBH_4$–MeOH at 0°C to obtain the corresponding secondary amines (**5,6**) (Sch. 1).

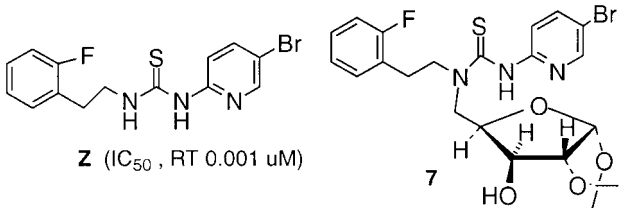
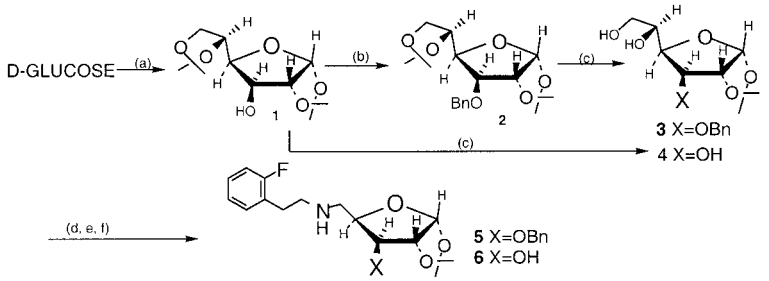


Figure 1.

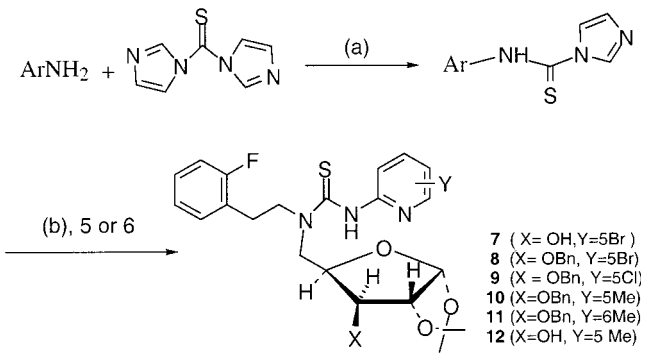
Substituted pyridyl thiocarbonylimidazole derivaties were prepared using the respective primary amines and thiocarbonyldiimidazole in acetonitrile at room temperature for 48 h (Sch. 2). The condensation of secondary amines (**5,6**) with appropriately substituted pyridyl thiocarbonylimidazole derivatives in DMF at 90°C for 15 h and workup furnished the final products (**7–12**).

CONCLUSION

We have developed an efficient method for the introduction of a carbohydrate moiety into the structure of thiourea compounds with anti-



Scheme 1. *Reagents and conditions*: (a) CH_3COCH_3, H_2SO_4/0°C; (b) NaH, DMF, BnBr, 0°C; (c) 0.8% H_2SO_4, MeOH, r.t., 3 h; (d) $NaIO_4$, CH_2Cl_2, Satd. $NaHCO_3$, 0°C, 2 h; (e) fluorophenethyl amine, CH_2Cl_2, r.t., 1 h; (f) $NaBH_4$, MeOH, 12 h.



Scheme 2. *Reagents and conditions*: (a) acetonitrile/N_2, r.t., 48 h; (b) DMF, 90°C, 15 h.

HIV activity. It is hoped that improved in vivo efficacy may be observed for these derivatives due to increased bioavailability and improved cellular uptake. Further work is in progress to evaluate the biological activity as well as bioavailability of these novel furanosyl thioureas.

EXPERIMENTAL

3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-a-D-glucofuranose (2). To a solution of 1,2:5,6-di-*O*-isopropylidine-a-D-glucofuranose (**1**) (6.0 g, 23.0 mmol) in dimethylformamide (40 mL) was added sodium hydride (1.33 g, 55.1 mmol) at 0°C. After stirring for 15 min benzyl bromide (5.1 g, 30.0 mmol) was added and further stirred for 30 min. After this period, the excess sodium hydride was quenched with methanol (1 mL) and the resulting mixture was poured into ice cold water and extracted with ether (2×100 mL). The organic layer was washed with additional water and the ether layer dried over anhydrous magnesium sulfate. Concentration of solvent and purification by silica gel chromatography (hexane/ethylacetate, 5:1) gave the title compound as a colorless oil (7.55 g, 94%). ^{1}H NMR ($CDCl_3$) d: 7.45–7.22 (m, 5H, ArH), 5.85 (d, 1H, $J = 3.8$ Hz, H-1), 4.76–4.25 (m, 5H, H-3-6, 6[1]), 4.15–3.19 (m, 3H, H-2, O**CH$_2$**Ph), 1.50, 1.44, 1.36, 1.31 (4s, 12H, $4 \times CH_3$); LCMS (ESI) calcd. for (M+H): 351.4, Found: 351.2; Anal. calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.09; H, 7.45.

3-*O*-benzyl-1,2-*O*-isopropylidene-a-D-glucofuranose (3). A solution of compound (**2**) (7.0 g, 20.0 mmol) in methanol (40 mL) and 0.8% aqueous sulfuric acid (40 mL) was stirred for 12 h. After completion of the reaction as evidenced by TLC, solid barium carbonate was added to the reaction mixture and the pH was adjusted to 7.0. The solid mass obtained was filtered off and the filtrate concentrated in vaccuum to yield a viscous liquid which was chromatographed (hexane/ethylacetate, 3:7) to furnish the title compound as a syrup (5.4 g, 87%). $[\alpha]_D = -39.4°$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) d: 7.45–7.22 (m, 5H, ArH), 5.9 (d, 1H, $J = 3.8$ Hz, H-1), 4.72 (d, 1H, $J = 11.5$ Hz, O**CH$_2$**Ph), 4.58 (d, 1H, $J = 3.8$ Hz, H-2), 4.52 (d, 1H, $J = 11.2$ Hz, O**CH$_2$**Ph), 4.14–3.6 (m, 5H, H-3-6, 6[1]), 2.45 (brs, 1H, OH), 1.48, 1.3 (2s, 6H, $2 \times CH_3$); LCMS (ESI) calcd. for (M+H): 311.34, Found: 311.35; Anal. calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.89; H, 7.11. (Lit.[13] C, 61.99; H, 7.19).

1,2-*O*-isopropylidene-a-D-glucofuranose (4). Compound **4** was prepared from **1** (5 g, 19.2 mmol) in methanol (40 mL) and 0.8% aqueous sulfuric acid (40 mL) as described for compound **3**: (3.6 g, 92%) as a solid.

M.p.: 159–160°C; $[\alpha]_D = -13.5°$ (*c* 1.0, H_2O); ^{1}H NMR (D_2O) d: 5.86–5.85 (d, 1H, $J = 3.6$ Hz, H-1), 4.54–4.53 (d, 1H, $J = 3.6$ Hz, H-2), 4.16–4.15 (d, 1H, $J = 2.4$ Hz, H-3), 3.92–3.91 (d, 1H, $J = 2.4$ Hz, H-4), 3.41–3.74 (m, 3H, H-5,6,6[1]), 1.35, 1.20 (2s, $2 \times CH_3$); LCMS (ESI) calcd. for (M+H): 221.2, Found: 221.3; Anal. calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.28; H, 7.39. (Lit.[13] C, 49.26; H, 7.44).

[((4*S*,1*R*,5*R*)-7,7-dimethyl–2,6,8-trioxa–4-phenoxybicyclo [3.3.0] oct-3yl) methyl] [2-(2-flurophenyl] amine (5). To a solution of diol **3** (8 g, 25.8 mmol) in dichloromethane and saturated sodium bicarbonate solution (4.0 mL) was added sodium metaperiodate (11.0 g, 53.2 mmol) at 0°C and stirred for 2 h at room temperature. After completion of the reaction anhydrous sodium sulphate (20 g) was added to the reaction mixture, filtered and filterate concentrated to obtain the aldehyde (5.8 g, 82%) as a syrup. To a solution of aldehyde (5.8 g, 22.1 mmol) and fluorophenethylamine (3.07 g, 22.1 mmol) in dichloromethane (20 mL) was added anhydrous sodium sulphate (10 g) and stirred vigorously for 30 min. After completion of the reaction , it was filtered off and filtrate concentrated to obtain imine (7.0 g, 18.2 mmol) which was dissolved in methanol (20 mmol) and sodium borohydride (1.69 g, 45.6 mmol) was added at 0°C. Reaction was monitored by TLC, after completion of the reaction, methanol was removed under reduced pressure to obtain a residue which was dissolved in ethylacetate (150 mL), washed with saturated sodium chloride solution (2×50 mL), dried and concentrated to obtain a syrupy residue which was purified by silica gel (60–120 mesh, hexane: EtOAc, 1:1) to obtain the title compound **5** (5.6 g, 80%) as a colorless syrup. ^{1}H NMR ($CDCl_3$) d: 7.33–6.98 (m, 9H, ArH), 5.90–5.89 (d, 1H, $J = 3.3$ Hz, H-1), 4.73–4.69 (d, 1H, $J = 12$ Hz, O**C**$\mathbf{H_2}$Ph), 4.68–4.67 (d, 1H, $J = 3.6$ Hz, H-5), 4.53–4.49 (d, 1H, $J = 11.7$ Hz, O**C**$\mathbf{H_2}$Ph), 4.42–4.38 (m, 1H, H-3), 3.99–3.98 (d, 1H, $J = 3$ Hz, H-4), 2.99–2.74 (m, 6H, N-**C**$\mathbf{H_2}$-Sug, Ar-**C**$\mathbf{H_2}$-**C**$\mathbf{H_2}$-N), 1.48, 1.32 (2s, 6H, $2 \times CH_3$); LCMS (ESI) calcd. for (M+H) 389.46, Found: 389.48; Anal. calcd. for $C_{22}H_{27}FNO_4$: C, 68.02; H, 7.0; N, 3.6. Found: C, 68.0; H, 6.99; N, 3.56.

(2*S*, 1*R*, 5*R*)-3-({[2-(-fluorophenyl) ethyl]amino} methyl)-7,7-dimethyl-4,6,8-trioxa bicyclo [3.3.0] octan-2-ol (6). Compound **6** was prepared from **4** (3.5 g, 15.9 mmol), saturated sodium bicarbonate (3.0 mL), sodium periodate (6.7 g, 31.8 mmol) anhydrous sodium sulphate (10 g), fluorophenethylamine (3.2 g, 23.0 mmol and sodium borohydride (0.74 g, 19.6 mmol) as described for compound **5**: (4.4 g, 83%) as a semisolid: ^{1}H NMR ($CDCl_3$) d: 7.24–6.98 (m, 4H, ArH), 5.90–5.89 (d, 1H, $J = 3.3$ Hz, H-5), 4.56–4.43 (d, 1H, $J = 3.9$ Hz, H-1), 4.23–4.15 (m, 2H, H-2,3), 2.96–2.77 (m, 6H, N-**C**$\mathbf{H_2}$-Sug, Ar-**C**$\mathbf{H_2}$-**C**$\mathbf{H_2}$-N), 1.44, 1.28 (2s, 6H, $2 \times CH_3$); LCMS (ESI) calcd. for (M+H) 312.35, Found: 312.36; Anal. calcd. for

$C_{16}H_{22}FNO_4$: C, 61.72; H, 7.12; N, 4.49. Found: C, 61.65; H, 7.01; N, 4.31.

Preparation of Thiocarbonylimidazole Derivatives of Pyridyl Compounds

In a 500 mL RB flask under nitrogen was added 8.6 g (50 mmol) of substituted-2-aminopyridine and 250 mL of anhydrous acetonitrile. The contents were stirred at room temperature and 1.1 Eq. of 1,1′-thiocarbonyldiimidazole was introduced. The contents were allowed to stir for 48 h when a precipitate appeared. The precipitate was filtered and washed with dry acetonitrile (2×50 mL), dried under vaccum to furnish the required thiocarbonylimidazole derivative as a crisp solid (95%). This was used as such without further purification in the next step.

General Procedure for the Synthesis of Halo Pyridyl-Fluorophenethyl-a-D-Glucofuranosyl Thioureas (7–12)

To a stirred solution of secondery amine in dimethyl formamide (20 mL) was added 1.2 Eq. of the respective pyridyl thiocarbonylimidazole precursor and the contents were heated to 90°C for 15 h over an oil bath. The mixture was cooled to room temperature and poured into crushed ice cold water to obtain a precipitate which was filtered, washed with water (2×50 mL) and dried under vacuum. The solid was then extracted with chloroform, washed successively with brine, water and the resulting organic layer was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave crude glucofuranosyl thioureas. The crude material was subjected to column chromatography over silica gel (hexane/ethylacetate 7:3) to obtain analytical pure sample of the thioureas in 75–80% yield as light yellow solids and semi solids.

(2*S*,1*R*,5*R*) - 3- [({[(5-bromo(2-pyridyl))amino]thioxomethyl}[2 -fluorophenyl) ethyl] amino)methyl]- 7, 7-dimethyl-4,6,8-trioxabicyclo [3.3.0] octan-2-ol (7). $[\alpha]_D = -0.045°$(*c* 1, MeOH); M.p.: 74–75°C; ^{1}H NMR ($CDCl_3$) d: 9.6 (brs, 1H, NH), 8.19 (m, 2H, ArH), 7.76–7.72 (dd, 1H, $J = 2.4$, 2.1 Hz, ArH), 7.32–6.90 (m, 4H, ArH), 5.90–5.89 (d, 1H, $J = 3.3$ Hz, H-5), 4.56–4.55 (d, 1H, $J = 2.7$ Hz, H-1), 4.33–3.64 (m, 6H, –CH_2-N-CH_2-, H-2,3), 3.16–3.14 (m, 2H, Ar-**CH_2**, –CH_2-N), 1.40, 1.25 (2s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) d: 180.8, 162.6, 159.4, 152.1, 147.8, 139.9, 131.1, 128.5, 124.3, 119.5, 115.4, 115.1, 112.0, 104.4, 85.0, 78.0, 73.8, 52.4, 49.2, 26.7, 26.5; LCMS (ESI) calcd. for (M+H) 526.07,

Found: 526.0; HPLC R_t: 9.14 min, % purity 97.1; Anal. calcd. for $C_{22}H_{25}BrFN_3O_4S$: C, 50.2; H, 4.79; N, 7.98 Found: C, 49.66; H, 4.80; N, 8.03.

({[(4*S*, 1*R*, 5*R*)-7,7-dimethyl-2, 6, 8-trioxa-4-(phenylmethoxy) bicyclo [3.3.0] oct-3-yl]methyl}[2-(2-fluorophenyl)ethyl]amino[(5-bromo(2-pyridyl)amino] methane-1-thione (8). $[\alpha]_D = -0.074^\circ$(*c* 1, MeOH); M.p.: 64–65°C; ^{1}H NMR ($CDCl_3$) d: 9.10 (brs, 1H, NH), 8.30–8.27 (m, 2H, ArH), 7.73–7.69 (dd, 1H, $J = 2.7$ Hz, 2.1 Hz, ArH), 7.40–6.99 (m, 9H, ArH), 6.10–6.08 (d, 1H, $J = 3.9$ Hz, H-1), 4.73–4.69 (d, 1H, $J = 12$ Hz, O**CH$_2$**Ph), 4.68–4.67 (d, 1H, $J = 3.6$ Hz, H-5), 4.53–4.49 (d, 1H, $J = 11.7$ Hz, O**CH$_2$**Ph), 4.43–3.65 (m, 6H, H-3,4, CH_2-N-CH_2), 3.19–3.07 (m, 2H, Ar-**CH$_2$**, –CH_2-N), 1.48, 1.32 (2s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$): 181.0, 162.5, 159.3, 152.1, 148.4, 138.8, 136.6, 131.2, 131.2, 128.5, 128.3, 128.2, 128.1, 127.6, 125.1, 124.3, 117.6, 115.2, 115.0, 113.9, 112.0, 105.0, 82.0, 78.7, 71.8, 52.5, 51.2, 26.7, 26.2; LCMS (ESI) calcd. for (M+H) 617.5, Found: 617.2; HPLC R_t: 13.6 min, % purity 99.8; Anal. calcd. for $C_{29}H_{31}BrFN_3O_4S$: C, 56.50; H, 5.07; N, 6.82 Found: C, 56.14; H, 5.09; N, 6.84.

({[(4*S*, 1*R*, 5*R*)-7,7-dimethyl-2, 6, 8-trioxa-4-(phenylmethoxy) bicyclo [3.3.0] oct-3-yl] methyl}[2-(2-fluorophenyl)ethyl] amino[(5-chloro(2-pyridyl) amino] methane-1-thione (9). $[\alpha]_D = -0.077^\circ$(*c* 1, MeOH); M.p.: 59–60°C; ^{1}H NMR ($CDCl_3$) d: 9.14 (brs, 1H, NH), 8.31–8.28 (d, 1H, $J = 9$ Hz, ArH), 8.18–8.17 (d, 1H, $J = 2.4$ Hz, ArH), 7.58–7.55 (dd, 1H, $J = 2.4$, 2.7 Hz, ArH), 7.38–6.97 (m, 9H, ArH), 6.08–6.07 (d, 1H, $J = 3.6$ Hz, H-1), 4.71–4.67 (d, 1H, $J = 11.7$ Hz, O**CH$_2$**Ph), 4.66–4.65 (d, 1H, $J = 3.9$ Hz, H-5), 4.51–4.47 (d, 1H, 11.7 Hz, O**CH$_2$**Ph), 4.42–3.63 (m, 6H, H-3,4, CH_2-N-CH_2), 3.22–3.03 (m, 2H, Ar-**CH$_2$**, –CH_2-N), 1.45, 1.30 (2s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) d: 181.1, 162.5, 159.3, 151.7, 146.1, 136.6, 136.2, 131.3, 128.5, 128.4, 128.3, 128.1, 127.7, 125.9, 124.2, 117.2, 115.3, 115.0, 112.1, 105.0, 82.0, 81.7, 78.7, 71.8, 52.5, 51.2, 26.7, 26.2; LCMS (ESI) calcd. for (M+H) 572.1, Found: 572.2; HPLC R_t: 34.1 min, % purity 96.3; Anal. calcd. for $C_{29}H_{31}ClFN_3O_4S$: C, 60.89; H, 5.46; N, 7.34. Found: C, 60.52; H, 5.52; N, 7.54.

({[(4*S*, 1*R*, 5*R*)-7,7-dimethyl-2, 6, 8-trioxa-4-(phenylmethoxy) bicyclo [3.3.0] oct-3-yl] methyl}[2-(2-fluorophenyl)ethyl] amino[(5-methyl(2-pyridyl) amino] methane-1-thione (10). $[\alpha]_D = -0.053^\circ$ (*c* 1, MeOH); M.p.: 50–52°C; ^{1}H NMR ($CDCl_3$): 8.78 (brs, 1H, ArH), 8.03 (brs, 2H, ArH), 7.45–7.41 (dd, 1H, $J = 2.1$, 2.4 Hz, ArH), 7.37–696 (m, 9H, ArH), 6.04–6.03 (d, 1H, $J = 3.9$ Hz, H-1), 4.70–4.66 (d, 1H, $J = 12$ Hz, O**CH$_2$**Ph), 4.63–4.62 (d, 1H, $J = 3.9$ Hz, H-5), 4.53–4.49 (d, 1H, 11.7 Hz, O**CH$_2$**Ph) 420–3.73 (m, 6H, H-3,4, CH_2-N-CH_2), 3.21–3.06 (m, 2H, Ar-**CH$_2$**, –CH_2-N), 2.52 (s, 3H, Ar-CH_3), 1.45, 1.29 (2s, 6H,

$2 \times CH_3$); ^{13}C NMR ($CDCl_3$) d: 181.1, 162.6, 159.4, 136.8, 131.3, 131.2, 128.5, 128.2, 128.1, 128.0, 127.0, 124.2, 115.2, 114.9, 111.9, 105.0, 82.2, 81.8, 79.0, 71.8, 52.3, 51.0, 26.8, 26.2, 17.8; LCMS (ESI) calcd. for (M+H) 552.68, Found: 552.2; HPLC R_t: 24.6 min, % purity 99.7; Anal. calcd. for $C_{30}H_{34}FN_3O_4S$: C, 65.32; H, 6.21; N, 7.62. Found: C, 65.20; H, 6.27; N, 7.58.

({[(4*S*, 1*R*, 5*R*)-7,7-dimethyl-2, 6, 8-trioxa-4-(phenylmethoxy) bicyclo [3.3.0] oct-3-yl] methyl}[2-(2-fluorophenyl)ethyl] amino[(6-methyl(2-pyridyl) amino] methane-1-thione (11). $[\alpha]_D = -0.047^\circ$ (*c* 1, MeOH); M.p.: 57–58°C; ^1H NMR ($CDCl_3$): 7.51–6.68 (m, 11H, ArH), 6.68 (brs, 1H, ArH), 6.0–5.99 (d, 1H, $J = 3$ Hz, H-1), 4.70–4.66 (d, 1H, $J = 12$ Hz, O**CH$_2$**Ph), 4.63–4.61 (d, 1H, $J = 3.9$ Hz, H-5), 4.56–4.52 (d, 1H, $J = 12$ Hz, O**CH$_2$**Ph), 4.11–3.75 (m, 6H, H-3,4, CH_2-N-CH_2), 3.22–3.12 (m, 2H, Ar-**CH$_2$**, –CH_2-N), 2.40 (s, 3H, Ar-CH_3), 1.45, 1.25 (2s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) d: 181.1, 162.6, 159.4, 136.9, 131.3, 128.4, 128.1, 127.9, 127.6, 124.1, 115.2, 114.9, 111.8, 104.9, 82.2, 81.6, 77.4, 76.5, 71.8, 52.1, 50.9, 26.8, 26.3, 22.5; LCMS (ESI) calcd. for (M+H) 552.68, Found: 552.2; HPLC R_t: 27.8 min, % purity 99.6; Anal. calcd. for $C_{30}H_{34}FN_3O_4S$: C, 65.32; H, 6.21; N, 7.62. Found: C, 65.16; H, 6.32; N, 7.52.

(2*S*,1*R*,5*R*)-3-[({[(5-methyl(2-pyridyl))amino]thioxomethyl}[2-fluorophenyl) ethyl] amino)methyl]-7,7-dimethyl-4,6,8-trioxabicyclo [3.3.0] octan-2-ol (12). $[\alpha]_D = -0.045^\circ$ (*c* 1, MeOH); M.p.: 74–75°C; ^1H NMR ($CDCl_3$): 9.52 (brs, 1H, ArH), 8.13 (m, 2H, ArH), 7.74–7.70 (dd, 1H, $J = 2.4$, 2.1 Hz, ArH), 7.22–6.89 (m, 4H, ArH), 5.90–5.89 (d, 1H, $J = 3.3$ Hz, H-5), 4.56–4.55 (d, 1H, $J = 2.7$ Hz, H-1), 4.29–3.72 (m, 6H, H-2,3, CH_2-N-CH_2), 3.20–3.12 (m, 2H, Ar-**CH$_2$**, –CH_2-N), 2.38 (s, 3H, Ar-CH_3), 1.39, 1.27 (2s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) d: 180.8, 162.6, 159.4, 152.1, 147.8, 139.9, 131.1, 128.5, 124.3, 119.5, 115.4, 115.1, 112.0, 104.4, 85.0, 73.8, 52.4, 49.2, 26.7, 26.5, 18.2; LCMS (ESI) calcd. for (M+H) 462.56, Found: 462.52; HPLC R_t: 10.2 min, % purity 99.1; Anal. calcd. for $C_{23}H_{28}FN_3O_4S$: C, 59.85; H, 6.11; N, 9.11. Found: C, 59.78; H, 6.07; N, 9.03.

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