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CHEMISTRY

# Novel Binary Compounds Derived from 1,2,4-Thiadiazole

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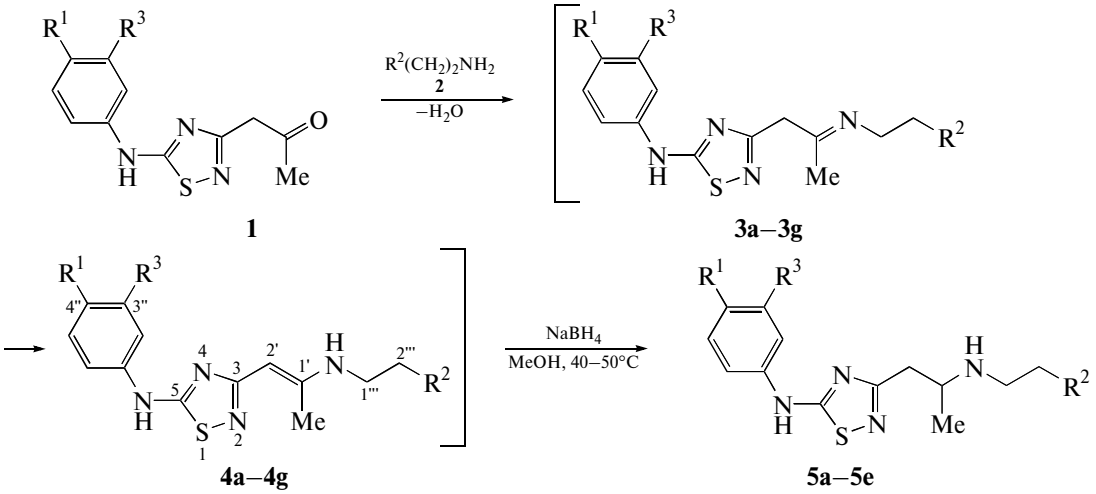
The design of multifunctional pharmaceuticals with a broad spectrum of activity that are capable of interacting with several targets is one of the promising directions of contemporary medicinal chemistry. Recently, molecules containing pharmacophoric thiadiazole fragment and showing interesting pharmaceutical properties [1], including neuroprotective [2], have attracted much attention as promising therapeutics. In continuation of our studies, we developed a method of synthesis of 1,2,4-thiadiazole derivatives containing biogenic amines as a second pharmacophore or nitroxy group as a nitrogen oxide NO producer. We showed recently that *N*,*N*-disubstituted 5-amino-3-(2-nitroxypropyl)-1,2,4-thiadiazoles are efficient blocators of glutamate-stimulated $^{45}Ca^{2+}$ uptake [3] and, therefore, can affect pathological processes in different neurodegenerative diseases [4].

We used 5-amino-3-(2-oxopropyl)-1,2,4-thiadiazoles (**1**) as initial compounds, they were obtained by the reaction of different amines with 3-isothiocyanato-5-methylisoxazole [3]. The presence of oxo group in their molecule provides an opportunity for further modification of the parent compound by introducing different pharmacophoric groups. Thus, enamines (**4a**–**4g**) were prepared in almost quantitative yield by the reaction of compound **1** with amines (**2**) in methanol. Initially formed "classical" Shiff base (imine **3a**–**3g**) undergoes in situ rearrangement into vinylamine (**4a**–**4g**). This is confirmed by $^1$H NMR. The spectra of these compounds show a signal of one proton at the double bond at 5.15–5.20 ppm (enamine form, **4a**–**4g**) and the lack of signal of two protons at 3.5 ppm (imine form, **3a**–**3g**). Amines **2** used were primary amines (preferably those showing neurotropic physiological activity, for example, tryptamine, substituted phenethylamines, aminoalcohols), as well as 2-nitroethanolamine as a pharmacophore containing an NO-releasing group.

Enamines **4a**–**4g** isolated by filtration were reduced with sodium borohydride at 40–50°C to give amino derivatives **5a**–**5e**.




**Scheme 1**

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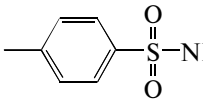
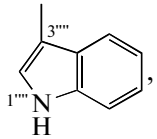
**4a**, **5a**: $R^1$ = 4''-F, $R^2$ = OH, $R^3$ = H;
**4b**, **5b**: $R^1$ = 4''-Cl, $R^2$ = $CH_2OH$, $R^3$ = 3''-Cl;
**4c**, **5c**: $R^1$ = H, $R^2$ =  , $R^3$ = H;
**4d**, **5d**: $R^1$ = 3''-Cl, $R^2$ =  , $R^3$ = 4''-F;
**4e**, **5e**: $R^1$ = 4''-Cl, $R^2$ =  , $R^3$ = H;
**4f**: $R^1$ = 4''-$CF_3$, $R^2$ = $ONO_2$, $R^3$ = H;
**4g**: $R^1$ = 4''-Cl, $R^2$ = $ONO_2$, $R^3$ = H.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Bruker CXP-200 spectrometer (Germany), chemical shifts are given in the δ scale relative to $Me_4Si$. Melting points were determined using a Boetius hot-stage apparatus and were uncorrected. Evaporation of solutions was performed with the use of a rotor evaporator in a vacuum of a water-jet pump.

**Procedure of synthesis of N-substituted [3-(1'-aminopropyl)-1,2,4-thiadiazol-5-yl]-arylamines (5a–5g).** A solution of amine **2** (0.01 mol) in 10 mL of methanol was added dropwise to a solution of 1,2,4-thiadiazole **1** (0.01 mol) in 10 mL of methanol with stirring, and the reaction mixture was stirred at ambient temperature for 2–5 h until precipitate appeared. The precipitate of enamine **4a**–**4g** was separated by filtration, washed with methanol, and dried. The resulting enamine was suspended in 20 mL of methanol, heated to 40–50°C, 1.5 equiv. of sodium borohydride was added, and the mixture was stirred for 2 h. The precipitate gradually dissolved. After the reaction completion, the mixture was cooled, methanol was evaporated, and the residue was diluted with 20 mL of water and extracted with methylene chloride (3 × 10 mL). The combined organic extract was dried with sodium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated. The residue was recrystallized to give [3-(2'-aminopropyl)-1,2,4-thiadiazol-5-yl]phenylamines (**5a**–**5e**). We failed to reduce compounds **5f** and **5g** with sodium borohydride.

**1'''-{2'-[5-(4''-Fluorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylvinylamino}ethanol (4a).** Pale yellow crystals, mp 165–167°C. Yield 96%.

$^1$H NMR (DMSO-$d_6$, δ, ppm): 8.31 (1H, t, *J* 6.0 Hz, N<u>H</u>$CH_2$), 7.57 (1H, dd, *J* 4.9, 9.0 Hz, $H_{arom}$), 7.06 (2H, t, *J* 8.8 Hz, $H_{arom}$), 5.03 (1H, s, CH), 4.63 (1H, t, *J* 4.9 Hz, OH), 3.57 (2H, m, NHC<u>H</u>$_2$), 3.34 (2H, q, *J* 5.5 Hz, $CH_2O$), 2.02 (3H, s, $CH_3$).

**1'''-{2'-[5-(3'',4''-Dichlorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylvinylamino}propanol (4b).** Pale yellow crystals, mp 172–174°C. Yield 93%.

$^1$H NMR (DMSO-$d_6$, δ, ppm): 10.64 (1H, s, NH), 8.18 (1H, t, *J* 5.8 Hz, N<u>H</u>$CH_2$), 7.88 (1H, d, *J* 1.8 Hz, $H_{arom}$), 7.39 (2H, m, $H_{arom}$), 5.04 (1H, s, CH), 4.24 (1H, t, *J* 4.9 Hz, OH), 3.50 (2H, q, *J* 5.7 Hz, NHC<u>H</u>$_2$), 3.30 (2H, q, *J* 6.4 Hz, $CH_2O$), 2.01 (3H, s, $CH_3$), 1.69 (2H, m, $CH_2$).

**[3-(1'-Phenylethylaminopropenyl)-1,2,4-thiadiazol-5-yl]phenylamine (4c).** Pale yellow crystals, mp 153–155 °C. Yield 90%.

$^1$H NMR ($CDCl_3$, δ, ppm): 8.56 (1H, br s, NH), 8.37 (1H, t, *J* 5.8 Hz, N<u>H</u>$CH_2$), 7.31 (10H, m, $H_{arom}$), 5.14 (1H, s, CH), 3.56 (2H, q, *J* 6.7 Hz, NHC<u>H</u>$_2$), 2.96 (2H, t, *J* 7.0 Hz, $CH_2$), 1.99 (3H, s, $CH_3$).

**4-(2'''-{2'-[5-(3''-Chloro-4''-fluorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylvinylamino}ethyl)-benzenesulfonamide (4d).** White crystals, mp 213–215°C. Yield 87%.

$^1$H NMR (DMSO-$d_6$, δ, ppm): 10.38 (1H, br s, NH), 8.33 (1H, t, *J* 5.8 Hz, N<u>H</u>$CH_2$), 7.90 (1H, dd, *J* 2.8, 6.7 Hz, $H_{arom}$), 7.77 (2H, d, *J* 8.4 Hz, $H_{arom}$), 7.45 (1H, m, $H_{arom}$), 7.40 (2H, d, *J* 8.4 Hz, $H_{arom}$), 7.18 (1H, t, *J* 8.7 Hz, $H_{arom}$), 7.11 (2H, br s, $NH_2$), 5.11 (1H, s, CH), 3.54 (2H, m, NHC<u>H</u>$_2$), 2.96 (2H, t, *J* 7.1 Hz, $CH_2$), 2.00 (3H, s, $CH_3$).

**(4''-Chlorophenyl)-(3-{1-[2'''-(1H''''-indol-3''''-yl)ethylamino]-1'-methylethyl}-1,2,4-thiadiazol-5-yl)amine (4e).** White crystals, mp 133–135°C. Yield 85%.

$^1$H NMR ($CDCl_3$, δ, ppm): 9.15 (1H, br s, NH), 8.43 (1H, t, *J* 5.6 Hz, N<u>H</u>$CH_2$), 8.08 (1H, s, $NH_{ind}$),

7.66 (3H, m, $H_{arom}$), 7.29 (6H, m, $H_{arom}$), 5.14 (1H, s, CH), 3.63 (2H, q, *J* 5.6 Hz, NHC$\underline{H}_2$), 3.11 (2H, t, *J* 6.9 Hz, $CH_2$), 2.01 (3H, s, $CH_3$).

**(4''-Trifluoromethylphenyl)-{3-[1'-(2'''-nitroxyethylamino)propenyl]-1,2,4-thiadiazol-5-yl}amine (4f).** Dark brown crystals, mp 147–149°C. Yield 93%.

$^1$H NMR ($CDCl_3$, δ, ppm): 8.47 (1H, t, *J* 6.4 Hz, N$\underline{H}CH_2$), 7.58 (4H, s, $H_{arom}$), 5.21 (1H, s, CH), 4.59 (2H, t, *J* 5.6 Hz, $CH_2ONO_2$), 3.61 (2H, q, *J* 5.6 Hz, NHC$\underline{H}_2$), 2.00 (3H, s, $CH_3$).

**(4''-Chlorophenyl)-{3-[1'-(2'''-nitroxyethylamino)propenyl]-1,2,4-thiadiazol-5-yl}amine (4g).** Brown crystals, mp 186–188°C. Yield 92%.

$^1$H NMR (DMSO-$d_6$, δ, ppm): 10.57 (1H, s, NH), 8.36 (1H, t, *J* 6.5 Hz, N$\underline{H}CH_2$), 7.53 (1H, d, *J* 9.0 Hz, $H_{arom}$), 7.25 (1H, d, *J* 9.0 Hz, $H_{arom}$), 5.12 (1H, s, CH), 4.60 (2H, t, *J* 5.5 Hz, $CH_2ONO_2$), 3.61 (2H, q, *J* 5.7 Hz, NHC$\underline{H}_2$), 2.02 (3H, s, $CH_3$).

**1'''-{2'-[5-(4''-Fluorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylethylamino}ethanol (5a).** Pale yellow crystals, mp 144–146°C. Yield 82%.

$^1$H NMR (DMSO-$d_6$, δ, ppm): 7.52 (1H, m, $H_{arom}$), 7.04 (2H, m, $H_{arom}$), 3.46 (2H, t, *J* 5.5 Hz, NHC$\underline{H}_2$), 3.10 (1H, sextet, *J* 6.3 Hz, CH), 2.73 (4H, m, C$\underline{H}_2$CHMe, $CH_2O$), 1.21 (3H, d, *J* 6.3 Hz, $CH_3$).

**1'''-{2'-[5-(3'',4''-Dichlorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylethylamino}propanol (5b).** White crystals, mp 147–149°C. Yield 79%.

$^1$H NMR ($CDCl_3$, δ, ppm): 7.60 (1H, d, *J* 2.3 Hz, $H_{arom}$), 7.24 (2H, m, $H_{arom}$), 3.77 (2H, t, *J* 5.0 Hz, NHC$\underline{H}_2$), 3.34 (1H, m, CH), 2.97 (4H, m, C$\underline{H}_2$CHMe, $CH_2O$), 1.72 (2H, m, $CH_2$), 1.21 (3H, d, *J* 6.3 Hz, $CH_3$).

**[3-(1'-Phenylethylaminopropyl)-1,2,4-thiadiazol-5-yl]phenylamine (5c).** Crystallizing oil. Yield 78%.

$^1$H NMR ($CDCl_3$, δ, ppm): 7.32 (2H, m, $H_{arom}$), 7.15 (8H, m, $H_{arom}$), 3.13 (1H, sextet, *J* 6.3 Hz, CH), 2.78 (6H, m, $3CH_2$), 1.05 (3H, d, *J* 6.3 Hz, $CH_3$).

**4-(2'''-{2'-[5-(3''-Chloro-4''-fluorophenylamino)-1,2,4-thiadiazol-3-yl]-1'-methylethylamino}ethyl)-benzenesulfonamide (5d).** White crystals, mp 110–112°C. Yield 81%

$^1$H NMR ($CD_3CN$, δ, ppm): 8.04 (1H, dd, *J* 2.8, 6.7 Hz, $H_{arom}$), 7.90 (2H, d, *J* 8.4 Hz, $H_{arom}$), 7.50 (4H, m, $H_{arom}$), 3.38 (1H, sextet, *J* 8.4 Hz, CH), 3.00 (6H, m, $3CH_2$), 1.27 (3H, d, *J* 6.3 Hz, $CH_3$).

**(4''-Chlorophenyl)-(3-{1'-[2'''-(1H''''-indol-3''''-yl)ethyl-amino]-1'-methylethyl}-1,2,4-thiadiazol-5-yl)amine (5e).** Yellowish crystals, mp 75–77°C. Yield 86%.

$^1$H NMR ($CDCl_3$, δ, ppm): 7.95 (1H, s, $NH_{ind}$), 7.55 (3H, m, $H_{arom}$), 7.03 (6H, m, $H_{arom}$), 3.15 (1H, sextet, *J* 6.4 Hz, CH), 2.93 (4H, m, $CH_2CH_2$), 2.78 (2H, dd, *J* 2.8, 6.7 Hz, CHC$\underline{H}_2$), 1.08 (3H, d, *J* 6.3 Hz, $CH_3$).

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