Synthesis of New Tetrazole-Substituted Pyroaminoadipic and Pipecolic Acid Derivatives

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Racemic 5-aryl- and 5-(arylmethyl)tetrazolyl-substituted pyroaminoadipic and pipecolic acid derivatives were diastereoselectively synthesized from dimethyl *meso*-2,5-dibromoadipate (**1**) in good yields under mild reaction conditions. The key step of this reaction sequence is the selective *N*2-alkylation of 5-substituted tetrazoles with **1**. The reactive 2-bromo-5-tetrazolyladipate derivatives **2a**–**g** were generated and treated with sodium azide, followed by Pd/C-catalyzed hydrogenation, to provide lactams **4a**–**g**. The chemoselective reduction of the amide carbonyl group of **4a**–**g** with BH_3, followed by acid hydrolysis, provided 5-tetrazolylpipecolic acids in racemic form.

Introduction

Heterocyclic α-amino acids are of particular importance in various fields, especially in biochemistry, enzymology, and pharmacology.[1−3] Among the heterocyclic substituents that are currently being studied the tetrazole ring is considered as a functional isosteric group to a carboxylic acid in medicinal chemistry.[4] This ring contains an acidic hydrogen atom and can represent an effective alternative to carboxylic acids for the design of biologically active compounds with a particular resistance to metabolic degradation.[5] However, some studies have shown that tetrazoles without the acid functionality can also be effective and these are more widely available.[6] A few reports in the literature describe tetrazolic α-amino acids. One can cite, in particular, the *cis*-4-(tetrazolylalkyl)piperidine-2-carboxylic acids such as LY233053 (Figure 1), which is known for its selective and potent antagonist activity at the NMDA receptor,[2] and LY300020, which is an agonist of the AMPA receptor.[3] Since the discovery of D,L-α-aminoadipic acid as a selective antagonist of the NMDA receptor,[7] several modified structures have been prepared to study the structure−activity relationship.[2,8−10]

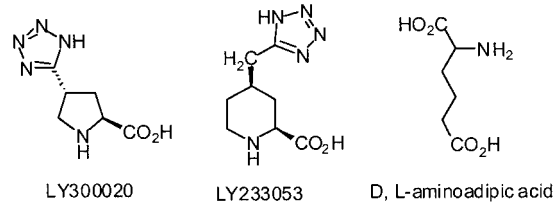

Figure 1. Bioactive tetrazolic amino acids

In order to study the effects of the substituents on α-aminoadipic acid in the neuroexcitatory activity of the acid, we decided to prepare different pyroaminoadipates **4a**−**g**, precursors of δ-substituted aminoadipic acids and also the 5-substituted pipecolic acid derivatives **5a**−**g**. The substituents which were considered are 5-aryltetrazoles and 5-(arylmethyl)tetrazoles. The synthetic strategy relies on the double substitution of dimethyl *meso*-2,5-dibromoadipate (**1**) successively by substituted tetrazoles and sodium azide. The first substitution is a selective *N*-alkylation of the tetrazole ring on one of the brominated centers followed by an azidation on the second center. A hydrogenation/cyclization step provides the six-membered ring. The final product is obtained after reduction and hydrolysis.

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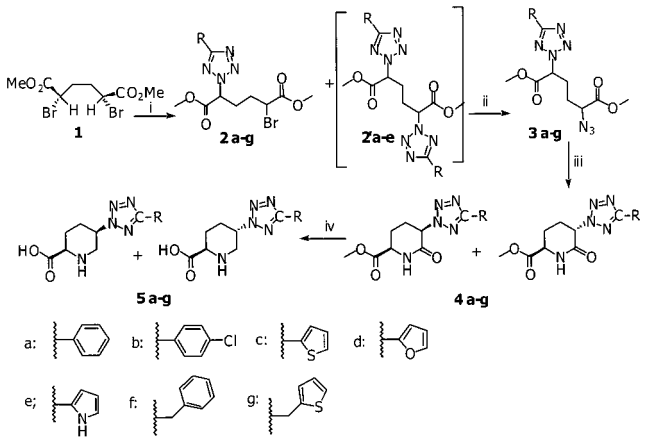
Results and Discussion

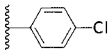
According to the synthetic approach described in Scheme 1, we initially studied the reaction of an equimolar quantity of tetrazole with dimethyl *meso*-2,5-dibromoadipate (**1**), which is easily obtained from adipic acid.[11]



Scheme 1. Reagents: (i) substituted tetrazole, NEt_3, acetone, room temp.; (ii) NaN_3, acetone, room temp.; (iii) 5% Pd/C, MeOH, H_2 (1 atm), room temp.; (iv) a) BH_3·THF, −10 °C, b) 6 N HCl, propylene oxide, CH_2Cl_2

This reaction, which was carried out in acetone in the presence of 1.5 equiv. of triethylamine, led mainly to the product of monosubstitution.[12] However, the formation of products of disubstitution (**2′a**−**e**) was also observed, and the experimental results showed that, although the ratio between mono- and disubstituted products depended somewhat on the R group, it was primarily dependent on the concentration of the reaction mixture. We hoped that by moving from 5-aryltetrazoles to the more hindered 5-(arylmethyl)tetrazoles we could favor the monosubstitution. Indeed, compounds **2f** and **2g** were obtained as the sole products whatever the concentration; **2′f** and **2′g** were not detected by ^{1}H NMR spectroscopy. These results are summarized in Table 1.

Table 1. Substitution reactions of **1** with various tetrazoles

Products **2**, **2'**	R	Isolated yield of **2** (%)	Isolated yield of **2'** (%)
a		70	20
b		60	18
c		74	10
d		65	2
e		76	2
f		90	0
g		66	0

The tetrazole ring is a system of the azapyrrole type and therefore two tautomeric forms can exist. During our synthesis, in all cases we obtained only one of the two *N*-regioisomers, as detected by ^{1}H NMR spectroscopy and confirmed by X-ray analysis of products **4a**[13] and **4c**[14] (Figure 2). All the 5-aryltetrazoles and the 5-(arylmethyl)tetrazoles obtained are *N2*-isomers. This result is in agreement with the literature, where spectroscopic data[15,16] have shown that 2*H*-tetrazole is more stable than the tautomeric 1*H*-isomer. The 2-bromo-5-tetrazolyladipate derivatives **2a**−**g** were purified by column chromatography and were isolated in good yields. The use of acetonitrile as solvent resulted in lower yields. In the absence of triethylamine, the 5-aryl- and 5-(arylmethyl)tetrazoles were inert towards the dibromo derivative.

For the preparation of 5-substituted tetrazoles we extended the method described by Koguro,[17] which is based on the reaction of variously substituted nitriles with sodium azide in the presence of an amine salt in toluene (Scheme 2).

The bromo derivatives **2a**−**g** were treated with 3 equiv. of sodium azide in acetone[18] to give **3a**−**g** in high yields (90−95%) as a mixture of diastereoisomers rising from suc-

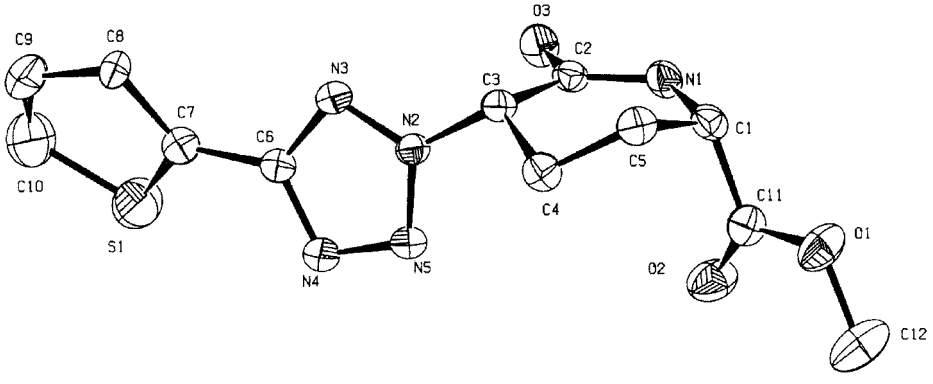
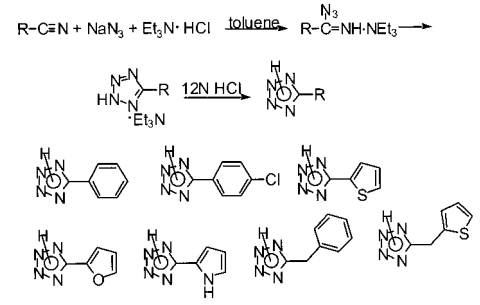


Figure 2. X-ray crystal structure of **4c**



Scheme 2

cessive non-stereocontrolled S_N2 reactions. While double substitutions of **1** with one nucleophile to give cyclic compounds have been reported,[19−26] to the best of our knowledge these are the first examples of successive substitutions with two different nucleophiles. Reduction of **3a**−**g** by catalytic hydrogenation over Pd/C in methanol[18] led quantitatively to the corresponding substituted pyroaminoadipic acids **4a**−**g** by an intramolecular aminolysis. LC/MS analysis of **4a**−**g** on a chiral column showed the presence in all cases of a racemic mixture composed of two diastereoisomers in a 5:1 ratio. In the cases of **4a** and **4c** the major isomer was separated by crystallization and analyzed by X-ray crystallography. The relative stereochemistry of the methoxycarbonyl groups in the C1 position and the tetrazolyl ring in the C3 position was determined (Figure 2). The *cis* isomer is the major product in the reaction mixture. The obtention of this isomer can be explained by successive S_N2 reactions of the bromine atoms of *meso*-**1**, which, after cyclization, would orientate the two substituents in a *cis* position. Nevertheless, this control is not total since some *trans* isomer was also obtained. Diastereomerically pure *cis*-**4a** and *cis*-**4c** and the mixture of diastereoisomers for **4b** and **4d**−**g** were used as such in the next step. Lactams **4a**−**g** were reduced with BH_3 in THF at −10 °C.[27] Subsequent acid hydrolysis (6 N HCl, 60 °C, 12 h) and neutralization with propylene oxide yielded the (±)-5-(5′-aryltetrazolyl)- and (±)-5-[5′-(arylmethyl)tetrazolyl]pipecolic acids. In the cases of **4a** and **4c**, the reaction was carried out on the crystallized *cis* isomer to provide the corresponding *cis*-disubstituted pipecolic acid.

Conclusion

The present study describes an efficient synthesis of racemic 5-(5′-aryltetrazolyl)- and 5-[5′-(arylmethyl)tetrazolyl]-pipecolic acids starting from dimethyl *meso*-2,5-dibromoadipate. The 5-aryltetrazoles and the 5-(arylmethyl)tetrazoles were selectively introduced in the 5-position of the piperidine ring with good chemical yields and diastereoselectivity (65% *de*). In two cases the *cis* diastereoisomer of the tetrazole-substituted pipecolic acid was obtained by crystallization of one of the synthetic intermediates followed by hydride reduction. Further investigation of the successive substitutions of dimethyl *meso*-2,5-dibromoadipate (**1**) to prepare biologically active compounds is currently underway in our laboratory.

Experimental Section

General: ^1H and ^{13}C NMR analyses were performed with 200 MHz and 400 MHz NMR spectrometers. Infrared spectra were recorded by diffuse reflectance or by transmittance as a micro cup of KBr or by transmittance in KBr plates. Mass spectra (electrospray ionization mode, ESIMS) were recorded with a Platform II quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer (Micromass, Manchester, U.K.) was calibrated in the positive-ion ESI mode. The samples were dissolved in H_2O/CH_3CN (50:50 by volume). The high resolution mass spectra were measured with a JEOLJMS-SX-102A mass spectrometer. The chiral HPLC analyses were carried out at a wavelength of 250 nm, with a Chiracel OD column (5 μm, 250 × 4.6 mm) and a flow rate of 1 mL/min (eluent: hexane/2-propanol, 70:30).

Dimethyl (*R*,*S*)-2,5-Dibromohexanedioate (1): $SOCl_2$ (1680 mmol, 200 g) was added to adipic acid[11] (685 mmol, 100 g). The reaction mixture was stirred at 70−80 °C for 3 h, then concentrated under reduced pressure. Br_2 (1560 mmol, 250 g) was added dropwise to the resulting acyl chloride. The reaction mixture was stirred at room temperature for 12 h then added to 500 mL of MeOH at −5 °C and stirred at 20 °C for 12 h. The mixture was cooled and the precipitate was filtered, washed several times with cold methanol, and then recrystallized from methanol. The filtrate was concentrated, dissolved in 500 mL of Et_2O, washed successively with 2% aqueous sodium bisulfite solution, 3% aqueous $NaHCO_3$ solution, and water, dried with K_2CO_3, concentrated, crystallized, and recrystallized from MeOH. The solids were collected together to give 183 g (80%) of the title compound. M.p. 76−77 °C. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 4.30−4.23 (m, 2 H), 3.80 (s, 6 H), 2.36−2.35 (m, 2 H), 2.10−2.02 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 32.80, 44.66, 53.56, 170.03 ppm. MS (electrospray): *m*/*z* = 335 [M + 1].

General Procedure for the Synthesis of Tetrazoles: A mixture of a nitrile[17] (1 equiv.), NaN_3 (1.3 or 3 equiv.), and $Et_3N{\cdot}HCl$ (1.3 or 3 equiv.) in toluene (50−150 mL) was heated to 100 °C for 24 h with stirring. After cooling, the product was extracted with water. 36% HCl was added dropwise to the aqueous layer to precipitate the tetrazole. After filtration, the solid was dried under reduced pressure and recrystallized from $EtOAc/Et_2O$ to yield the tetrazole.

5-Phenyl-1*H*-tetrazole:[17] The general procedure was applied with benzonitrile (1030 mg, 10 mmol), NaN_3 (840 mg, 13 mmol), and $Et_3N{\cdot}HCl$ (1781 mg, 13 mmol) to afford 1310 mg (90% yield) of the title compound as a white solid. M.p. 214−216 °C (ref.[17] 217−218 °C). ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 7.5 (s, 3 H), 8.05 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 127.5, 129.7, 131.6, 206.6 ppm. MS (electrospray): *m*/*z* = 147 [M + 1]

5-(4-Chlorophenyl)-1*H*-tetrazole: The general procedure was applied with 4-chlorobenzonitrile (1370 mg, 10 mmol), NaN_3 (840 mg, 13 mmol), and $Et_3N{\cdot}HCl$ (1781 mg, 13 mmol) to afford 1260 mg (70% yield) of the title compound as a white solid. M.p. 265−266 °C (ref.[30] 258 °C). ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 7.5 (m, 4 H), 7.9 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 128.1, 130.9, 132.1, 132.1, 132.7, 132.9, 206.0 ppm. MS (electrospray): *m*/*z* = 181 [M + 1] ^{35}Cl, 183 [M + 1] ^{37}Cl.

5-(Thiophen-2-yl)-1*H*-tetrazole: The general procedure was applied with thiophene-2-carbonitrile (1090 mg, 10 mmol), NaN_3

(1300 mg, 20 mmol), and $Et_3N{\cdot}HCl$ (2740 mg, 20 mmol) to afford 1360 mg (90% yield) of the title compound as a greenish solid. M.p. 205−206 °C. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 7.2 (m, 1 H), 7.75 (dd, J_1 = 1.2, J_2 = 3.9 Hz, 1 H), 7.8 (d, J = 1.27 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 128.8, 129.3, 130.2, 153.1, 205.9 ppm. MS (electrospray): m/z = 153 [M + 1].

5-(Furan-2-yl)-1*H*-tetrazole: The general procedure was applied with furan-2-carbonitrile (930 mg, 10 mmol), NaN_3 (1300 mg, 20 mmol), and $Et_3N{\cdot}HCl$ (2740 mg, 20 mmol) to afford 1110 mg (82% yield) of the title compound as a reddish solid. M.p. 203−204 °C (ref.[30] 199−200 °C). ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 6.75 (dd, J_1 = 1.9, J_2 = 1.7 Hz, 1 H), 7.3 (d, J = 12 Hz, 1 H), 7.9 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 112.7, 113.2, 140.9, 146.1, 206.2 ppm. MS (electrospray): m/z = 137 [M + 1].

5-(1*H*-Pyrrol-2-yl)-1*H*-tetrazole: The general procedure was applied with 1*H*-pyrrole-2-carbonitrile (920 mg, 10 mmol), NaN_3 (1300 mg, 20 mmol), and $Et_3N{\cdot}HCl$ (2740 mg, 20 mmol) to afford 1180 mg (88% yield) of the title compound as a yellowish solid. M.p. 224−226 °C. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 6.1 (dd, J_1 = 2.7, J_2 = 1.0 Hz, 1 H), 6.7 (d, J_1 = 2.3, J_2 = 1.2 Hz, 1 H), 6.91 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 106.3, 110.3, 122.9, 145.1, 206.2 ppm. MS (electrospray): m/z = 136 $[M + 1]^+$, 177 [M + K].

5-Benzyl-1*H*-tetrazole: The general procedure was applied with phenylacetonitrile (1170 mg, 10 mmol), NaN_3 (1300 mg, 20 mmol), and $Et_3N{\cdot}HCl$ (2740 mg, 20 mmol) to afford 1440 mg (90% yield) of the title compound as a white solid. M.p. 121−122 °C (ref.[31] 125−126 °C) ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 4.4 (s, 2 H), 7.4 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 29.6, 127.6, 129.2, 136.1, 206.9 ppm. MS (electrospray): m/z = 161 [M + 1].

5-(Thiophen-2-ylmethyl)-1*H*-tetrazole: The general procedure was applied with thiophen-2-ylacetonitrile (1230 mg, 10 mmol), NaN_3 (1950 mg, 30 mmol), and $Et_3N{\cdot}HCl$ (4110 mg, 30 mmol) to afford 1460 mg (88% yield) of the title compound as a greenish solid. M.p. 225−230 °C. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 4.65 (s, 2 H), 6.93 (m, 1 H), 7.05 (m, 1 H), 7.3 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 24.2, 125.8, 127.4, 127.6, 137.6, 207.5 ppm. MS (electrospray): m/z = 167 [M + 1].

Synthesis of Dimethyl 2-Bromo-5-(5-substituted tetrazol-2-yl)hexanedioates 2 and Dimethyl 2,5-Bis(5-substituted tetrazol-2-yl)hexanedioates 2′: NEt_3 (15 mmol) was added dropwise to a solution of 5-substituted tetrazole (10 mmol) in 240 mL of anhydrous acetone.[12] The mixture was stirred at room temperature for 15 min, and dimethyl (*R*,*S*)-2,5-dibromohexanedioate (1.1 mol), dissolved in the minimum amount of acetone, was then added. The reaction mixture was stirred for 24 h and concentrated under reduced pressure. Column chromatography (silica gel; hexane/diethyl ether, 70:30) afforded the title compound.

Dimethyl 2-Bromo-5-(5-phenyltetrazol-2-yl)hexanedioate (2a): The general procedure was applied with 5-phenyl-1*H*-tetrazole (1460 mg, 10 mmol) to afford 3050 mg (70% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3004 (s), 2955 (m), 1748 (s), 1262 (m), 1001 (s), 760 (l) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.8 (m, 1 H), 2.05 (m, 1 H), 2.4 (m, 1 H), 3.6 (s, 6 H), 4.2 (m, 1 H), 7.3 (dd, J_1 = 3.5, J_2 = 6.9 Hz, 3 H), 8.1 (dd, J_1 = 2.1, J_2 = 1.38 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 28.8, 31.1, 44.6, 53.4, 54.4, 65.1, 127.4, 127.3, 129.3, 130.9, 165.6, 167.7, 169.7 ppm. HRMS calcd. for $C_{15}H_{17}BrN_4O_4$: 397.0511; found 397.0557.

Dimethyl 2-Bromo-5-[5-(4-chlorophenyl)tetrazol-2-yl]hexanedioate (2b): The general procedure was applied with 5-(4-chlorophenyl)-1*H*-tetrazole (1810 mg, 10 mmol) to afford 2850 mg (60% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3066 (s), 3008 (s), 2953 (m), 2849 (s), 1756 (s), 1267 (m), 1205 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.75 (m, 1 H), 2.1 (m, 1 H), 2.4 (m, 2 H), 3.58 (s, 6 H) 5.62 (q, J = 5 Hz, 1 H), 7.3 (m, 2 H), 7.5 (m, 1 H), 7.9 (m,1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.7, 28.9, 31.1, 44.5, 53.5, 65.0, 126.2, 126.5, 131.2, 131.8, 133.4, 163.8, 167.6, 169.6 ppm. HRMS calcd. for $C_{15}H_{16}BrClN_4O_4$: 431.433; found 431.0118.

Dimethyl 2-Bromo-5-[5-(thiophen-2-yl)tetrazol-2-yl]hexanedioate (2c): The general procedure was applied with 5-(thiophen-2-yl)-1*H*-tetrazole (1520 mg, 10 mmol) to afford 3280 mg (74% yield) of the title compound as a greenish oil. IR (neat): $\tilde{\nu}$ = 3109 (s), 3004 (s), 2954 (m), 2848 (s), 1748 (s), 1266 (m), 1205 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.9 (m, 1 H), 2.05 (m, 1 H), 2.37 (m, 1 H), 2.52 (m, 1 H), 3.6 (s, 6 H), 4.2 (m, 1 H), 5.6 (m, 1 H), 7 (s, 1 H), 7.35 (s, 1 H), 7.7 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 28.7, 31.1, 44.6, 53.4, 54.2, 65.1, 128.4, 128.6, 128.7, 128.9, 161.6, 167.5, 169.69, 169.71 ppm. HRMS calcd. for $C_{13}H_{16}BrN_4O_4S$: 403.0076; found 403.0070.

Dimethyl 2-Bromo-5-[5-(furan-2-yl)tetrazol-2-yl]hexanedioate (2d): The general procedure was applied with 5-(furan-2-yl)-1*H*-tetrazole (1360 mg, 10 mmol) to afford 2760 mg (65% yield) of the title compound as a reddish oil. IR (neat): $\tilde{\nu}$ = 3134 (s), 3010 (s), 2955 (m), 2848 (s), 1747 (s), 1267 (m), 1001 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.7 (m, 1 H), 1.95 (m, 1 H), 2.3 (m, 1 H), 2.5 (m, 1 H), 3.6 (s, 6 H), 4.2 (m, 1 H), 5.6 (q, J = 5 Hz, 1 H), 6.4 (s, 1 H), 7 (s, 1 H), 7.5 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 28.6, 31.0, 44.5, 53.4, 53.7, 64.9, 112.16, 112.21, 142.8, 144.9, 158.7, 167.5, 169.7 ppm. HRMS calcd. for $C_{13}H_{16}BrN_4O_5$: 387.0304; found 387.0291.

Dimethyl 2-Bromo-5-[5-(1*H*-pyrrol-2-yl)tetrazol-2-yl]hexanedioate (2e): The general procedure was applied with 5-(1*H*-pyrrol-2-yl)-1*H*-tetrazole (1350 mg, 10 mmol) to afford 3220 mg (76% yield) of the title compound as a yellowish oil. IR (neat): $\tilde{\nu}$ = 3380 (s), 3295 (s), 3004 (s), 2954 (m), 2848 (s), 1746 (s), 1268 (m), 1201 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.85 (m, 1 H), 2.1 (m, 1 H), 2.4 (m, 1 H), 2.6 (m, 1 H), 3.7 (s, 6 H), 4.25 (m, 1 H), 5.6 (q, J = 4.9 Hz, 1 H), 6.3 (s, 1 H), 6.9 (s, 1 H), 7 (s, 1 H), 10.2 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 28.8, 31.1, 44.6, 53.6, 64.8, 110.6, 110.9, 119.4, 121.8, 160.6, 167.8, 170.0 ppm. HRMS calcd. for $C_{13}H_{17}BrN_5O_4$: 386.0464; found 386.0505.

Dimethyl 2-(5-Benzyltetrazol-2-yl)-5-bromohexanedioate (2f): The general procedure was applied with 5-benzyl-1*H*-tetrazole (1600 mg, 10 mmol) to afford 4060 mg (90% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3066 (s), 3008 (s), 1746 (s), 1237 (m), 783 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.68 (m,1 H), 2 (m, 1 H), 2.35 (m, 2 H), 3.62 (s, 6 H), 4.20 (m, 1 H), 4.25 (s, 2 H), 5.5 (dd, J_1 = 5, J_2 = 4 Hz, 1 H), 7.125 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.6, 31.1, 32.1, 44.5, 53.5, 64.0, 127.3, 127.5, 129.1, 129.4, 136.6, 166.2, 167.7, 169.6 ppm. HRMS calcd. for $C_{16}H_{19}BrN_4O_4$: 411.0668; found 411.0717.

Dimethyl 2-Bromo-5-[5-(thiophen-2-ylmethyl)tetrazol-2-yl]hexanedioate (2g): The general procedure was applied with 5-(thiophen-2-ylmethyl)-1*H*-tetrazole (1660 mg, 10 mmol) to afford 3020 mg (66% yield) of the title compound as a greenish oil. IR (neat): $\tilde{\nu}$ = 3109 (s), 3005 (s), 2954 (m), 2847 (s), 1758 (l), 1436 (s) 1268 (m), 700 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.8 (m, 1 H), 2.1 (m, 1 H), 2.4 (m, 1 H), 2.6 (m, 1 H), 3.7 (s, 6 H), 4.2 (m, 1 H), 4.5 (s, 2 H), 5.5 (q, J = 5.5 Hz, 1 H), 6.9 (s, 2 H), 7.2 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 26.7, 28.8, 31.2, 44.4, 53.5, 64.7, 125.2, 126.7,

127.4, 138.5, 165.6, 167.6, 169.8 ppm. HRMS calcd. for $C_{14}H_{17}BrN_4O_4S$: 417.0232; found 417.0231.

Dimethyl 2,5-Bis(5-phenyltetrazol-2-yl)hexanedioate (2′a): The general procedure was applied with 5-phenyl-1*H*-tetrazole (1460 mg, 10 mmol) to afford 1046 mg (20% yield) of the title compound as a white solid. IR (neat): $\tilde{\nu}$ = 3036 (s), 2953 (s), 1731 (s), 1438 (m), 1311 (m), 1146 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.3 (m, 2 H), 2.4 (m, 2 H), 3.7 (s, 6 H), 5.5 (m, 2 H), 7.4 (m, 6 H), 8.05 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.2, 53.7, 64.3, 64.7, 126.9, 127.0, 128.91, 128.94, 130.6, 130.65, 165.6, 167.5 ppm. HRMS calcd. for $C_{22}H_{23}N_8O_4$: 463.1842; found 463.1870.

Dimethyl 2,5-Bis[5-(4-chlorophenyl)tetrazol-2-yl)hexanedioate (2′b): The general procedure was applied with 5-(4-chlorophenyl)-1*H*-tetrazole (1810 mg, 10 mmol) to afford 1049 mg (18% yield) of the title compound as a white solid. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.3 (m, 2 H), 2.4 (m, 2 H), 3.7 (s, 6 H), 5.5 (m, 2 H), 7.2 (m, 4 H), 8.10 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.2, 53.7, 64.3, 64.7, 126.9, 127.0, 128.91, 128.94, 130.60, 130.65, 165.6, 167.5 ppm. HRMS calcd. for; found $C_{22}H_{21}Cl_2N_8O_4$: 531.1063; found 531.1049.

Dimethyl 2,5-Bis[5-(thiophen-2-yl)tetrazol-2-yl]hexanedioate (2′c): The general procedure was applied with 5-thiophen-2-yl-1*H*-tetrazole (1520 mg, 10 mmol) to afford 521 mg (10% yield) of the title compound as a greenish solid. IR (neat): $\tilde{\nu}$ = 3035 (s), 2952 (s), 1738 (s), 1439 (m), 1319 (m), 1155 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.34 (m, 2 H), 2.61 (m, 2 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 5.57 (dd, J_1 = 5.4, J_2 = 4.4 Hz, 2 H), 7.04 (m, 2 H), 7.19 (m, 2 H), 7.74 (dd, J_1 = 1.2, J_2 = 3.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.09, 27.13, 27.31, 27.37, 53.22, 53.25, 53.6, 53.7, 64.3, 64.5, 64.7, 64.8, 127.9, 128.0, 128.35 128.37, 130.6, 131.0, 161.6, 166.87, 166.94, 167.1, 167.3, 169.45 169.46 ppm. HRMS calcd. for $C_{18}H_{19}N_8O_4S_2$: 475.0971; found 475.0959.

Dimethyl 2,5-Bis[5-(furan-2-yl)tetrazol-2-yl]hexanedioate (2′d): The general procedure was applied with 5-furan-2-yl-1*H*-tetrazole (1360 mg, 10 mmol) to afford 97 mg (2% yield) of the title compound as a reddish solid. IR (neat): $\tilde{\nu}$ = 3030 (s), 2950 (s), 1745 (s), 1438 (m), 1319 (m), 1159 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.4 (m, 2 H), 2.7 (m, 2 H), 3.70 (s, 3 H), 3.78 (s, 3 H), 5.6 (dd, J_1 = 9.3, J_2 = 16.4 Hz, 2 H), 6.58 (m, 2 H), 7.18 (dd, J_1 = 2.5, J_2 = 2.9 Hz, 2 H), 7.6 (dd, J_1 = 9.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.06, 27.11, 27.28, 27.30, 53.19, 53.22, 53.5, 53.6, 64.4, 64.8, 64.96, 64.98, 111.82, 111.87, 112.06, 112.13, 115.6, 115.7, 144.55, 144.59, 145.7, 145.8, 166.80, 166.82, 169.50, 169.52 ppm. HRMS calcd. for $C_{18}H_{19}N_8O_6$: 443.1428; found 443.1415.

Dimethyl 2,5-Bis[5-(1*H*-pyrrol-2-yl)tetrazol-2-yl)hexanedioate (2′e): The general procedure was applied with 5-(1*H*-pyrrol-2-yl)-1*H*-tetrazole (1350 mg, 10 mmol) to afford 96 mg (2% yield) of the title compound as a yellowish solid. IR (neat): $\tilde{\nu}$ = 3416 (s), 3036 (s), 2953 (s), 1737 (s), 1435 (m), 1318 (m), 1154 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.2 (m, 2 H), 2.6 (m, 2 H), 3.70 (s, 3 H), 3.77 (s, 3 H), 5.6 (m, 2 H), 6.4 (m, 2 H), 6.9 (dd, J_1 = 2.9, J_2 = 1.1 Hz, 2 H), 7.4 (dd, J_1 = 1.4, J_2 = 2.6 Hz 2 H), 9.5 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.0, 27.1, 53.1, 53.22, 53.24, 53.52, 53.55, 53.6, 64.2, 64.3, 64.5, 64.6, 110.34, 110.38, 110.46, 110.48, 110.5, 119.13, 119.16, 119.2, 120.9, 121.06 167.05, 167.06, 167.2, 169.4, 169.5 ppm. HRMS calcd. for $C_{18}H_{21}N_{10}O_4$: 441.4293; found 441.1759.

Dimethyl Synthesis of 2-Azido-5-(5-substituted tetrazol-2-yl)hexanedioates 3: The appropriate dimethyl 2-bromo-5-(5-substituted tetrazol-2-yl)hexanedioate **2a**−**g** (2 mmol) and NaN_3 (7 mmol) were dissolved in 10 mL of anhydrous acetone.[18] The reaction mixture was stirred at room temperature for 24 h. After filtration of the formed precipitate, the solvent was evaporated under reduced pressure. Column chromatography (silica gel; hexane/diethyl ether, 50:50) afforded the title compound.

Dimethyl 2-Azido-5-(5-phenyltetrazol-2-yl)hexanedioate (3a): The general procedure was applied with **2a** (794 mg, 2 mmol) to afford 3240 mg (90% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3074 (s), 3036 (s), 3006 (s), 2955 (m), 2109 (s), 1753 (s), 1255 (m), 1204 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.5 (br. s, 2 H), 2.4 (m, 2 H), 3.65 (s, 6 H), 3.9 (m, 1 H), 5.6 (q, J_1 = 3, J_2 = 1.9 Hz, 1 H), 7.4 (dd, J_1 = 1, J_2 = 4.4 Hz, 3 H), 8.1 (dd, J_1 = 2.8, J_2 = 4.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.4, 27.8, 53.8, 54.2, 61.3, 65.0, 127.3, 127.4, 129.3, 130.9, 165.7, 167.8, 170.50, 170.52 ppm. HRMS calcd. for $C_{15}H_{18}N_7O_4$: 360.1420; found 360.1473.

Dimethyl 2-Azido-5-[5-(4-chlorophenyl)tetrazol-2-yl]hexanedioate (3b): The general procedure was applied with **2b** (866 mg, 2 mmol) to afford 3620 mg (92% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3004 (s), 2955 (m), 2848 (s), 2109 (s), 1752 (s), 1255 (m), 1204 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.53 (br. s, 2 H), 2.5 (m, 1 H), 3.7 (s, 6 H), 3.95 (m, 1 H), 5.6 (m, 1 H), 7.3 (m, 2 H), 7.45 (m, 1 H), 7.9 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.4, 31.1, 53.2, 54.8, 61.3, 64.9, 126.5, 127.3, 131.2, 131.8, 133.5, 163.9, 167.6, 170.5 ppm. HRMS calcd. for $C_{15}H_{17}ClN_7O_4$: 394.1031; found 394.1051.

Dimethyl 2-Azido-5-[5-(thiophen-2-yl)tetrazol-2-yl]hexanedioate (3c): The general procedure was applied with **2c** (804 mg, 2 mmol) to afford 3290 mg (94% yield) of the title compound as a greenish oil. IR (neat): $\tilde{\nu}$ = 3007 (s), 2955 (m), 2847 (m), 2109 (s), 1754 (s), 1267 (m), 1202 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.50 (m, 2 H), 2.5 (m, 2 H), 3.7 (s, 6 H), 3.9 (m, 1 H), 5.55 (m, 1 H), 7.1 (dd, J_1 = 3.7, J_2 = 1.3 Hz, 1 H), 7.4 (s, 1 H), 7.75 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.3, 27.8, 53.2, 53.9, 61.3, 65.0, 128.4, 128.7, 128.8, 129.0, 161.9, 167.6, 170.5 ppm. HRMS calcd. for $C_{13}H_{16}N_7O_4S$: 350.1213; found 350.1205.

Dimethyl 2-Azido-5-[5-(furan-2-yl)tetrazol-2-yl)hexanedioate (3d): The general procedure was applied with **2d** (772 mg, 2 mmol) to afford 2800 mg (80% yield) of the title compound as a reddish oil. IR (neat): $\tilde{\nu}$ = 3007 (s), 2955 (m), 2109 (s), 1754 (s), 1267 (m), 1202 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.47 (m, 2 H), 2.49 (m, 2 H), 3.61 (s, 6 H), 3.95 (m, 1 H), 5.6 (m, 1 H), 6.45 (s, 1 H), 7.05 (s, 1 H), 7.5 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.5, 27.7, 53.1, 54.7, 61.2, 65.0, 112.2, 112.2, 142.8, 144.9, 158.8, 167.5, 170.41 ppm. HRMS calcd. for $C_{13}H_{16}N_7O_5$: 350.1213; found 350.1205.

Dimethyl 2-Azido-5-[5-(1*H*-pyrrol-2-yl)tetrazol-2-yl]hexanedioate (3e): The general procedure was applied with **2e** (770 mg, 2 mmol) to afford 2930 mg (84% yield) of the title compound as a yellowish oil. IR (neat): $\tilde{\nu}$ = 3468 (m), 3006 (s), 2955 (m), 2109 (s), 1754 (s), 1266 (m), 1200 (m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.5 (m, 2 H), 2.5 (m, 2 H), 3.63 (s, 6 H), 3.9 (m, 1 H), 5.5 (m, 1 H), 6.2 (s, 1 H), 6.9 (d, J = 2.4 Hz, 2 H), 10 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.3, 27.8, 53.3, 53.9, 61.3, 64.9, 110.6, 110.8, 119.5, 121.6, 160.6, 167.9, 170.6 ppm. HRMS calcd. for $C_{13}H_{17}N_8O_4$: 349.1373; found 349.1385.

Dimethyl 2-Azido-5-(5-benzyltetrazol-2-yl)hexanedioate (3f): The general procedure was applied with **2f** (822 mg, 2 mmol) to afford 3440 mg (92% yield) of the title compound as a colorless oil. IR (neat): $\tilde{\nu}$ = 3032 (s), 2955 (m), 2109 (s), 1752 (s), 1256 (m), 1207

(m) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.4 (m, 2 H), 2.4 (m, 2 H), 3.6 (s, 6 H), 3.8 (m, 1 H), 4.15 (s, 2 H), 5.4 (m, 1 H), 7.2 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.4, 27.9, 32.2, 53.3, 53.8, 61.3, 64.9, 127.3, 129.1, 129.2, 136.8, 166.3, 167.7, 170.4 ppm. HRMS calcd. for $C_{16}H_{20}N_7O_4$: 374.1577; found 374.1571.

Dimethyl 2-Azido-5-[5-(thiophen-2-ylmethyl)tetrazol-2-yl]hexanedioate (3g): The general procedure was applied with **2g** (832 mg, 2 mmol) to afford 3050 mg (84% yield) of the title compound as a greenish oil. IR (neat): $\tilde{\nu}$ = 3027 (s), 3003 (s), 2955 (m), 2109 (s), 1754 (s), 1237 (m), 1207 (m), 788 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.3 (m, 2 H), 2.3 (m, 2 H), 3.5 (s, 6 H), 3.75 (m, 1 H), 4.2 (s, 2 H), 5.35 (m, 1 H), 6.65 (d, J = 3.5 Hz, 2 H), 7 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 27.3, 27.8, 26.6, 53.0, 53.5, 61.3, 64.8, 125.2, 126.6, 127.4, 138.6, 165.6, 167.7, 170.5 ppm. HRMS calcd. for $C_{14}H_{18}N_7O_4S$: 364.1210; found 364.1202.

Synthesis of Methyl 6-Oxo-5-(5-substituted tetrazol-2-yl)piperidine-2-carboxylates 4: 5% Pd/C or $Pd(OH)_2$/C (500 mg) was added to the appropriate dimethyl 2-azido-5-(5-substituted tetrazol-2-yl)hexanedioate **3** (10 mmol) in 30 mL of anhydrous MeOH[18] and the reaction mixture was stirred at room temperature under hydrogen (1 atm) for 24 h. The catalyst was then filtered off through Celite, and the filtrate was concentrated under reduced pressure and the product precipitated by addition of Et_2O. The product was recrystallized from ethyl acetate. The NMR spectroscopic data are given for the major isomer.

4a: The general procedure was applied with **3a** (3600 mg, 10 mmol) to afford 2400 mg (80% yield) of the title compound as a colorless solid. M.p. 144−146 °C. IR (neat): $\tilde{\nu}$ = 3441 (m), 3166 (s), 3007 (s), 2936 (s), 1743 (s), 1670 (m) 1272 (m), 808 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.2 (m, 2 H), 2.5 (m, 2 H), 3.7 (s, 3 H), 4.2 (m, 1 H), 5.5 (m, 1 H), 6.8 (br. s, 1 H), 7.4 (m, 3 H), 8 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.5, 26.3, 53.5, 54.7, 61.9, 127.4, 127.61, 127.64, 129.2, 130.79, 130.82, 165.0, 170.7, 171.1 ppm. HRMS calcd. for $C_{14}H_{16}N_5O_3$: 302.1259; found 302.1253.

4b: The general procedure was applied with **3b** (3930 mg, 10 mmol) to afford 2680 mg (80% yield) of the title compound as a white solid. IR (neat): $\tilde{\nu}$ = 3367 (s), 2956 (s), 2253 (s), 1750 (s), 1671 (m) 1232 (m), 732 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.2 (m, 4 H), 3.75 (s, 3 H), 4.3 (m, 1 H), 5.7 (m, 1 H), 7.4 (m, 3 H), 8.1 (m, 1 H), 8.7 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 21.6, 31.3, 52.1, 54.6, 65.2, 126.5, 127.5, 129.3, 130.9, 131.2, 163.7, 166.4, 171.6, 173.4 ppm. HRMS calcd. for $C_{14}H_{14}ClN_5O_3$: 335.0785; found 335.0798.

4c: The general procedure was applied with **3c** (3490 mg, 10 mmol) to afford 2460 mg (80% yield) of the title compound as a greenish solid. M.p. 155−158 °C. IR (neat): $\tilde{\nu}$ = 3368 (s), 3154 (s), 2156 (s), 1748 (s), 1675 (m), 1227 (m), 727 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.3 (m, 4 H), 3.8 (s, 6 H), 4.2 (m, 1 H), 5.55 (m, 1 H), 6.9 (br. s, 1 H), 7.2 (m, 1 H), 7.5 (dd, J_1 = 1.3, J_2 = 3.8 Hz, 1 H), 7.83 (dd, J_1 = 1, J_2 = 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.6, 26.2, 53.5, 54.7, 62.0, 128.3, 128.4, 128.5, 129.3, 161.7, 165.4, 171.2 ppm. HRMS calcd. for $C_{12}H_{14}N_5O_3S$: 308.0817; found 308.0805.

4d: The general procedure was applied with **3d** (3500 mg, 10 mmol) to afford 2330 mg (80% yield) of the title compound as a reddish solid. IR (neat): $\tilde{\nu}$ = 3453 (s), 3107 (s), 2945 (m), 1755 (s), 1673 (m), 1213 (m), 1002 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2 (m, 2 H), 2.4 (m, 2 H), 3.6 (s, 3 H), 4.3 (m, 1 H), 5.6 (m, 1 H), 6.5 (s, 1 H), 7.1 (s, 1 H), 7.6 (s, 1 H), 8.6 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.6, 26.9, 53.4, 54.9, 62.2, 112.0, 112.1, 142.9, 158.6, 166.0, 170.8, 170.9, 171.6 ppm. HRMS calcd. for $C_{12}H_{14}N_5O_4$: 292.1046; found 292.1053.

4e: The general procedure was applied with **3e** (3480 mg, 10 mmol) to afford 2380 mg (82% yield) of the title compound as a yellowish solid. IR (neat): $\tilde{\nu}$ = 3455 (s), 3443 (s), 3261 (s), 2940 (m), 1743 (s), 1225 (m), 1000 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.4 (m, 4 H), 3.5 (s, 3 H), 4 (m, 1 H), 4.7 (br. s, 1 H), 5.5 (m, 1 H), 6 (m, 1 H), 6.6 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.6, 29.2, 52.8, 54.3, 64.8, 109.4, 110.3, 119.1, 121.5, 160.8, 168.2, 172.5 ppm. HRMS calcd. for $C_{12}H_{15}N_6O_3$: 291.1206; found 291.1236.

4f: The general procedure was applied with **3f** (3740 mg, 10 mmol) to afford 2520 mg (80% yield) of the title compound as a white solid. IR (neat): $\tilde{\nu}$ = 3366 (s), 3150 (s), 2155 (s), 1747 (s), 1671 (m), 1228 (m), 730 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.1 (m, 4 H), 3.6 (s, 3 H), 4.2 (m, 3 H), 5.7 (m, 1 H), 7.3 (m, 6 H), 8.6 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 24, 26, 32.5, 53.0, 54.4, 61.9, 127.2, 129.0, 129.0, 129.1, 129.2, 136.9, 166.4, 169.7, 171.8 ppm. HRMS calcd. for $C_{15}H_{18}N_5O_3$: 316.1410; found 316.1407.

4g: The general procedure was applied with **3g** (3690 mg, 10 mmol) to afford 2640 mg (82% yield) of the title compound as a white solid. IR (neat): $\tilde{\nu}$ = 3450 (s), 3102 (s), 3130 (m), 2940 (m), 1756 (s), 1672 (m), 1210 (m), 1000 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 2.1 (m, 2 H), 2.4 (m, 2 H), 3.8 (s, 3 H), 4.3 (m, 1 H), 4.5 (s, 2 H), 5.7 (m, 1 H), 6.9 (m, 2 H), 7.2 (s, 1 H), 8.7 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.6, 26.6, 33.3, 53.0, 61.9, 65.5, 125.1, 126.7, 127.4, 138.7, 166.1, 171.6, 173.4 ppm. HRMS calcd. for $C_{13}H_{16}N_5O_3S$: 322.0974; found 322.0962.

Synthesis of 5-(5-Substituted tetrazol-2-yl)piperidine-2-carboxylic Acids 5: A solution of borane (10 mmol, 1 M in THF) in 4 mL of THF was added at −10 °C to a solution of the appropriate methyl 6-oxo-5-(5-substituted tetrazol-2-yl)piperidine-2-carboxylate **4** (1 mmol).[27] The reaction mixture was maintained at −10 °C during the addition, then stirred at −5 °C for 24 h and concentrated under reduced pressure. The mixture was hydrolyzed by addition of 6 N HCl at 60 °C during 12 h and then propylene oxide was added. The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried with Na_2SO_4, filtered, and concentrated to yield the title compound. The NMR spectroscopic data are given for the major isomer.

5a: The general procedure was applied with **4a** (301 mg, 1 mmol) to afford 220 mg (80% yield) of the title compound as a white solid. M.p. 147−149 °C. IR (neat): $\tilde{\nu}$ = 3346 (s), 3232 (s), 3120 (s), 2954 (m), 1738 (s), 1208 (m), 917 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.2 (m, 2 H), 2 (br. s, 1 H), 2.5 (m, 2 H), 3.5 (m, 2 H), 3.8 (m, 1 H), 4.75 (m, 1 H), 7.4 (m, 3 H), 8.1 (m, 2 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.0, 27.9, 48.1, 52.6, 63.1, 127.2, 127.4, 127.7, 129.3, 130.8, 165.1, 173.6 ppm. HRMS calcd. for $C_{13}H_{15}N_5O_2$: 273.1227; found 273.1229.

5b: The general procedure was applied with **4b** (335 mg, 1 mmol) to afford 240 mg (80% yield) of the title compound as a white solid. IR (neat): $\tilde{\nu}$ = 3355 (m), 3236 (m), 2926 (s), 1736 (s), 1090 (s), 919 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.5 (m, 2 H), 2 (m, 2 H), 2.5 (br. s, 1 H), 3.25 (m, 2 H), 4.25 (m, 1 H), 5.12 (m, 1 H), 7.25 (m, 3 H), 8.25 (m, 1 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 22.4, 32.3, 58.6, 59.5, 66.9, 127.6, 129.3, 130.9, 131.7, 133.5, 164.1, 165.3, 170.4 ppm. HRMS calcd. for $C_{13}H_{15}ClN_5O_2$: 308.091; found 308.182.

5c: The general procedure was applied with **4c** (307 mg, 1 mmol) to afford 220 mg (80% yield) of the title compound as a greenish

solid. M.p. 159−162 °C, IR (neat): $\tilde{\nu}$ = 3321 (s), 3153 (s), 2984 (m), 1792 (s), 1164 (m), 916 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.6 (m, 2 H), 2.25 (m, 2 H), 2.95 (br. s, 1 H), 3.25 (m, 2 H), 3.75 (m, 1 H), 4.8 (s, 1 H), 7.2 (dd, J_1 = 3.8, J_2 = 1.2 Hz, 1 H), 7.5 (dd, J_1 = 1, J_2 = 4.3 Hz, 1 H), 7.85 (dd, J_1 = 1, J_2 = 2.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.6, 28.1, 48.2, 57.1, 65.6, 128.3, 128.3, 128.35, 129.4, 161.2, 170.2 ppm. HRMS calcd. for $C_{11}H_{14}N_5O_2S$: 280.0868; found 280.1320.

5d: The general procedure was applied with **4d** (291 mg, 1 mmol) to afford 220 mg (80% yield) of the title compound as a reddish solid. IR (neat): $\tilde{\nu}$ = 3356 (s), 3156 (s), 2950 (s), 1758 (s), 1130 (m), 915 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.25 (m, 2 H), 1.25 (m, 2 H), 2 (m, 1 H), 3.5 (m, 2 H), 3.9 (m, 1 H), 4.2 (m, 1 H), 6.6 (s, 1 H), 7.3 (s, 1 H), 7.6 (m, 1 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.1, 28.1, 47.1, 56.9, 65.3, 113.1, 113.2, 143.2, 159.0, 165.9, 170.1 ppm. HRMS calcd. for $C_{11}H_{13}N_5O_3$: 263.1018; found 263.1021.

5e: The general procedure was applied with **4e** (290 mg, 1 mmol) to afford 210 mg (79% yield) of the title compound as a yellowish solid. IR (neat): $\tilde{\nu}$ = 3612 (s), 3095 (s), 2963 (m), 1742 (s), 1144 (m), 846 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.25 (m, 2 H), 1.75 (m, 2 H), 2.25 (br. s, 1 H), 3.25 (m, 2 H), 3.7 (m, 1 H), 3.8 (m, 1 H), 5.2 (s large, 1 H), 6.4 (s, 1 H), 7 (s, 1 H), 7.3 (s, 1 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.1, 29.8, 37.5, 55.4, 63.1, 110.2, 110.6, 120.8, 125.9, 161.1, 171.1 ppm. HRMS calcd. for $C_{11}H_{14}N_6O_2$: 262.1178; found 262.1183.

5f: The general procedure was applied with **4f** (315 mg, 1 mmol) to afford 220 mg (80% yield) of the title compound as a colorless solid. IR (neat): $\tilde{\nu}$ = 3362 (m), 3032 (s), 2932 (s), 1759 (s), 1181 (s), 910 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.5 (m, 2 H), 2 (s large, 1 H), 2.3 (br. s, 1 H), 3.25 (m, 2 H), 4.25 (m, 2 H), 4.75 (m, 1 H), 7.25 (m, 5 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 23.9, 28.0, 32.27 48.5, 57.0, 58.4, 127.2, 127.3, 129.0, 129.2, 129.2, 137.0, 165.3, 165.5 ppm. HRMS calcd. for $C_{14}H_{18}N_5O_2$: 288.146; found 288.182.

5g: The general procedure was applied with **4g** (321 mg, 1 mmol) to afford 240 mg (82% yield) of the title compound as a greenish solid. IR (neat): $\tilde{\nu}$ = 3342 (m), 3128 (s), 2877 (m), 1769 (m), 1142 (m), 1076 (s) cm^{-1}. ^1H NMR ($CDCl_3$, $SiMe_4$): δ = 1.3 (m, 2 H), 1.7 (m, 2 H), 2 (br. s, 1 H), 3.4 (m, 2 H), 3.6 (m, 1 H), 4.75 (m, 1 H), 7 (m, 2 H),7.25 (m, 1 H), 11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, $SiMe_4$): δ = 22.3, 26.9, 32.0, 55.4, 63.0, 64.2, 125.0, 126.5, 127.4, 138.9, 164.7, 165.3 ppm. HRMS calcd. for $C_{12}H_{16}N_5O_2S$: 294.1025; found 294.1371.

X-ray Crystallographic Analysis of 4c: Suitable crystals of this compound were grown at room temperature from a solution in diethyl ether and ethyl acetate by slow concentration. Crystal data: $C_{24}H_{26}O_6N_{10}S_2$, M_r = 614.67, triclinic, space group $P\bar{1}$, a = 10.5536(2) Å, b = 10.8755(3) Å, c = 13.5015(4) Å, α = 80.150(1)°, β = 69.243(1)°, γ = 89.363(1)°, V = 1425.64(6) $Å^3$, Z = 2, $D_{calcd.}$ = 1.432 $Mg\cdot m^{-3}$, $F(000)$ = 640, μ(Mo-K_α) = 0.245 mm^{-1}, crystal dimensions = 0.05 × 0.12 × 0.15 mm. Crystal setting and data collection were performed with an Enraf−Nonius kappa-CCD diffractometer with Mo-K_α radiation (λ = 0.71069 Å). Intensities were collected in the ω-scan mode. The reflections were measured in the range $-12 \le h \le 13$, $-13 \le k \le 14$, $0 \le l \le 17$ ($4° < \theta < 28°$). An absorption correction was not applied. A total of 11200 reflections were averaged according to the point group symmetry −1 resulting in 6354 unique reflections (R_{int} = 0.024). The structure was solved by direct methods using the ShelxS 97 package,[28] which allowed us to locate most non-hydrogen atoms. The remaining atoms were located after successive Fourier syntheses. The atomic parameters were refined with the ShelxL 97 package.[29] Full-matrix least-squares refinement on F^2 was performed, minimizing $w(F_o^2 - F_c^2)^2$, first with isotropic then with anisotropic thermal parameters for the non-hydrogen atoms. The hydrogen atoms were placed in their theoretical positions and allowed to ride on the carbon and nitrogen atoms to which they are attached. The refinement (386 parameters) converged at R_1 = 0.079, wR_2 = 0.220, S = 1.044 for 4542 reflections with $I > 2\sigma(I)$. In the final difference Fourier map maximum and minimum electron densities were 0.925 and −0.683 $e\cdot Å^{-3}$ respectively.

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