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Efficient Synthesis of 1-Substituted-4-phenyl-1, 4-dihydro-5*H*-tetrazole-5-thione and (1-Phenyl-1*H*-tetrazol-5-yl)thioacetyl Derivatives

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ABSTRACT: *A new and convenient synthesis of a variety of N- and S-substituted tetrazoles has been developed* via *azide and Mannich reaction methods. Compounds were characterized by elemental analysis, MALDI MS, and* ^{1}*H NMR data.*
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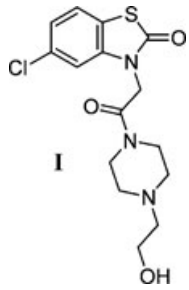
INTRODUCTION

Substituted tetrazoles [1,2] are well known as an excellent nonclassical carboxylic acid bioisosteres in biological molecules [3,4]. Recently, X-ray crystal structure revealed that the tetrazolate moiety of several nonpeptide antagonists was proved to form a hydrogen bond with protonated lysine and histidine at the active site of the angiotensin II receptor [3,5,6].

Waisser et al. [7] reported that substituted benzyl sulfanyl group enhances the antimycobacterial activity of 1-aryl-5-alkylsulfanyltetrazoles. *Tiaramide* **I** and other benzothiazolone acetamides are shown to inhibit prostoglandin synthesis and have significant analgesic and anti-inflammatory activities [8–10].



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RESULTS AND DISCUSSION

In this study, we report an efficient synthesis of a series of tetrazoles containing a variety of functional methyl amino and acetamide moieties at positions 1 and 5, respectively, as represented in Schemes 1–3, for a significant structure–activity relationship study.

Our synthetic strategy is dependent on the regioselective reactions of thioamides, which gives *S*- and *N*-substituted derivatives [11–13]. Thus, the reaction of 1 molar equivalent of the selected 1-phenyl-4,5-dihydro-1*H*-1,2,3,4-tetrazole-5-thione (**1**) with 1 molar equivalent of secondary amines and excess formaldehyde regioselectively gives a reasonable amount of *N*-methyl amino tetrazole **2a–c**. The

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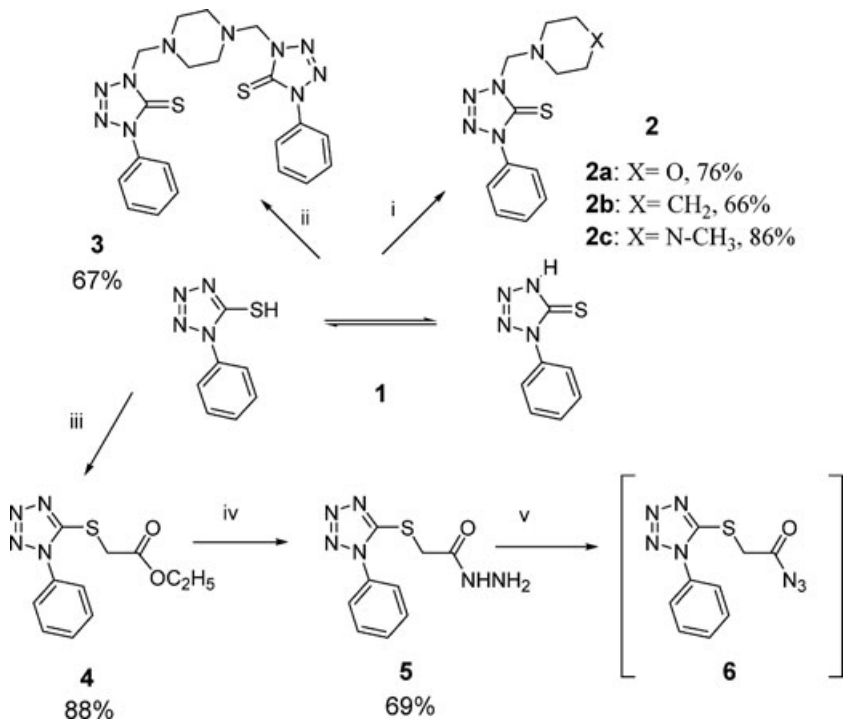
N-substitution is due to strong Coulumbic attraction between the hard part of the ambident nucleophile and the electrophile [12]. However, treatment of 2 molar equivalents of tetrazole **1** with 1 molar equivalent of piperazine and excess formaldehyde, under the same reaction conditions, afforded bis methyl amino piperazine **3**.

The elemental analysis together with MALDI MS of both structures **2a–c** and **3** agreed with the molecular formula of these compounds. The MALDI of **2a** gave 300.3 corresponding to $(M + Na)^+$. The ^1H NMR spectra were used as a major tool in identifying the *N*-substitution. Thus, ^1H NMR spectra showed a singlet at 5.33 ppm, characteristic for NCH_2N, and other peaks from secondary amine and tetrazole moieties are also clearly shown in the Experimental section.

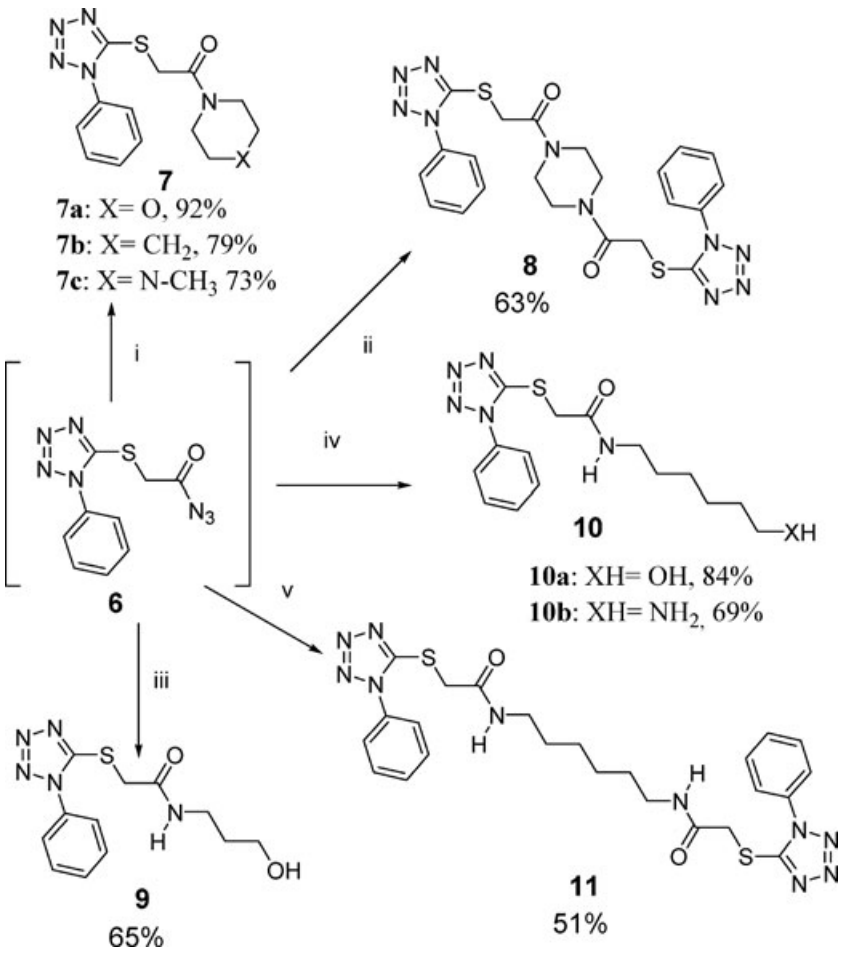
The azide derivative **6** was proved to be highly versatile intermediate, forming a variety of acetamides. This extensive structure modification of the selected tetrazole molecules **1** could affect the biological activity. The synthesis of tetrazole acetamides via azide-coupling method is shown in Schemes 1–3. The reaction of 1-phenyl-4,5-dihydro-1*H*-1,2,3,4-tetraazole-5-thione (**1**) with chloroethyl acetate in the presence of K_2CO_3 furnished the regioselective *S*-alkylation reaction product **4** [13,14]. The expected *S*-alkylation reaction was favored because of an interaction between the HOMO of the nucleophile and the LUMO of the electrophile to produce the *S*-attack [13]. Hydrazinolysis of **4** afforded hydrazide **5**, which was subsequently converted into azide **6** by treatment with $NaNO_2$ and HCl mixture (Scheme 1).

The in situ generated azide **6** solution extracted with ethyl acetate was used without isolation and purification. One molar equivalent of the amine was treated with 1 molar equivalent of the in situ generated ethyl acetate solution of azide **6** at −5°C. A variety of *S*-substituted acetamides of tetrazoles **7a–c**, **9**, and **10a,b** were obtained in moderate to good yields. However, employing 1 molar equivalent of the amine (piperazine and 1,6-diamino hexane) with 2 molar equivalents of the intermediate azide produced bistetrazoles derivatives **8** and **11**, respectively (Scheme 2). The long-chain derivatives **9–11** were designed to increase the lipophilicity of the tetrazole moiety, which is an important factor when designing a drug molecule able to pass through the cell membrane.

The ^1H NMR spectra of the *S*-acylated derivatives showed a singlet, typically associated with a SCH_2CO group appeared at 4.50 ppm for short-chain derivatives **9**, **7a–c**, **8** and 4.06 ppm for long-chain substituents **10a,b**, and **11**. The structure of hydroxy



SCHEME 1 Reagents and conditions: (i) CH_2O, secondary amine, ethanol, 25°C, 2 h; (ii) CH_2O, piperazine, ethanol, 25°C, 2 h; (iii) $ClCH_2COOC_2H_5$, Et_3N, EtOH, 85°C, 6 h; (iv) $NH_2NH_2{\cdot}H_2O$, EtOH, 85°C, 3 h; and (v) $NaNO_2$, HCl, −5°C, 30 min.

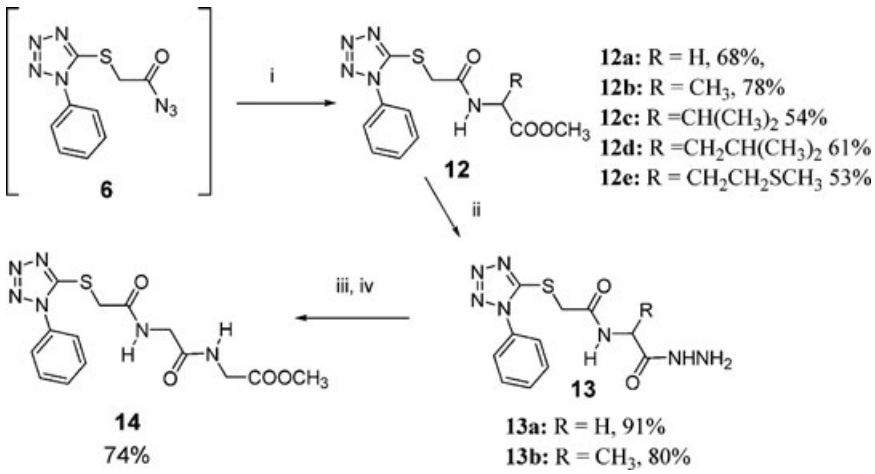


SCHEME 2 Reagents and conditions: (i) secondary amine, ethyl acetate, 25°C, 24 h; (ii) piperazine, ethyl acetate, 25°C, 24 h; (iii) 1-propanol amine, ethyl acetate, 25°C, 24 h; (iv) 1,6-diamino hexane or 1-hexanol amine, ethyl acetate, 25°C, 24 h; (v) 1,6-diamino hexane, ethyl acetate, 25°C, 24 h.

derivatives **9** and **10a** was confirmed by measuring the ^{1}H NMR spectrum in $CDCl_3$ and $CDCl_3/D_2O$. The ^{1}H NMR spectrum of **9** in $CDCl_3$ showed a quartet at 3.42 ppm, while giving a triplet at 3.42 ppm in $CDCl_3/D_2O$ characteristic for $NHC\underline{H}_2CH_2$. Furthermore, an exchangeable hydroxyl group appeared at 2.83 ppm. The structure of the bis derivatives **8** and **11** was simply deduced by comparing the intensity of bi-nucleophilic amine residue to a tetrazole thioacetyl moiety.

In addition, our next target was the elongation of the side chain at the thioacetyl group by coupling with amino acid. It was designed to increase the binding affinity of tetrazole moiety by interacting with the receptor recognition sites. Several coupling reagents were employed in the literature to introduce peptide bonds by the reaction of acid derivatives with amino acid methyl ester. Among those were 1-hydroxy-benzotriazole (HOBt) [15,16] and *N*,*N*-dicyclohexylcarbodiimide (DCC) [17]. HOBt is widely used as an additive to decrease racemization in the carbodiimide peptide coupling. Our choice was azide coupling following Sahin et al.'s method [18–20], which was reported to minimize the degree of racemization in amino acid coupling. Thus, azide **6** reacts with amino acid methyl ester. HCl (Gly, Ala, Val, Leu, Meth) in the presence of Et_3N afforded peptides **12a–e** in good yield. Hydrazinolysis of **12a,b** afforded hydrazides **13a,b** (Scheme 3).

The structure assignments of the amino acid derivatives **12a–e** were based on elemental analysis, MALDI, and ^{1}H NMR spectra. The MALDI spectra of **12b** gave 330.5 corresponding to $(M + Na)^+$. Significantly, *S*-alkylation site ($SC\underline{H}_2CO$ group) was indicated as a singlet in the ^{1}H NMR spectrum at 4.03 ppm for all amino acid derivatives **12a–e**. The ^{1}H NMR spectrum of methyl *N*-{[(1-phenyl-1*H*-tetrazol-5-yl)thio]acetyl}alaninate (**12b**) displayed multiplet resonance at δ 4.62–4.47 ppm



SCHEME 3 (i) amino acid methyl ester hydrochloride, Et_3N, ethyl acetate, 25°C, 24 h; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, 85°C, 3 h; (iii) $NaNO_2$, HCl, −5°C, 30 min; (iv) glycine methyl ester hydrochloride, Et_3N, ethyl acetate, 25°C, 24 h.

characteristic for NHCH group, whereas a broad signal was observed at 7.48 ppm for a NH group. Additional evidence for the structure of glycine acetamide derivative **12a** was the dipeptide **14** formation via the azide-coupling method as described above.

CONCLUSION

In summary, we describe a simple, convenient, and practical method for the extensive modification of the structure of the selected 1-phenyl-4,5-dihydro-1*H*-1,2,3,4-tetrazole-5-thione (**1**) regioselectively at positions 1 and 5 via the azide-coupling method and the Mannich reaction, respectively, with lipophilic amines, secondary amines, and amino acids.

EXPERIMENTAL

Solvents were purified and dried in the usual way. The boiling range of the petroleum ether used was 35–65°C. Thin layer chromatography (TLC): silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Melting points were determined on a Büchi 510 melting-point apparatus, and the values are uncorrected. NMR spectra were measured with Bruker AC 250 (250 MHz). TMS (0.00 ppm) or the signal of the deuterated solvent was used as internal standard. FAB-MS modified Finningan MAT 312/ AMD 5000 spectrometer was used at 790 eV and $T = 70$ MALDI-MS, the mass spectra were measured with a KRATOS Analytical Kompact spectrometer. Microanalyses were performed at the Microanalytical Center, Chemistry Department, Konstanz University, Germany.

The starting compounds 1, 5 were prepared according to the method described by Waisser et al. [14].

Mannich Reaction

General Procedure. To the suspension of tetrazole **1** (1.78 g, 0.01 mol) in ethyl alcohol (30 mL, absolute), formaldehyde (30%, 0.9 mL, 0.03 mol), and the desired secondary amine (0.01 mol) were added dropwise with stirring. The reaction mixture was further stirred for 1–2 h at room temperature and was concentrated under reduced pressure and cooled. The solid obtained was filtered and crystallized from ethyl alcohol.

*1-(Morpholin-4-yl-methyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**2a**).* (Amine = morpholine), white powder (2.1 g, 76%), mp 154°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.03$–7.91 (m, 2H, Ar-H), 7.66–7.47 (m, 3H, Ar-H), 5.33 (s, 2H, CH_2), 3.71 (t, 4H, $J = 4.94$ Hz, $2OCH_2$), 2.89 (t, 4H, $J = 4.94$ Hz, $2NCH_2$), (MALDI, positive mode, matrix: DHB): $m/z = 300.3$ $(M + Na)^+$. $C_{12}H_{15}N_5OS$ (277.3): C, 51.97; H, 5.45; N, 25.25; S, 11.56. Found: C, 51.76; H, 5.24; N, 25.12; S, 11.43.

*1-Phenyl-4-(piperidin-1-yl-methyl)-1,4-dihydro-5H-tetrazole-5-thione (**2b**).* (Amine = piperidine), white powder (1.8 g, 66%), mp 112°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.01$–7.84 (m, 2H, Ar-H), 7.65–7.44 (m, 3H, Ar-H), 5.32 (s, 2H, CH_2), 2.78 (t, 4H, $J = 5.1$ Hz, $2NCH_2$), 1.69–1.54 (m, 4H, $2CH_2$), 1.47–1.32 (m, 2H, CH_2). (MALDI, positive mode, matrix: DHB): $m/z = 298.4$ $(M + Na)^+$. $C_{13}H_{17}N_5S$ (275.4): C, 56.70; H,

6.22; N, 25.43; S, 11.64. Found: C, 56.64; H, 6.21; N, 25.33; S, 11.52.

*1-[(4-Methylpiperazin-1-yl)methyl]-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**2c**).* (Amine = *N*-methyl piperazine), white powder (2.5 g, 86%), mp 139°C. ^{1}H NMR ($CDCl_3$): δ = 8.01–7.86 (m, 2H, Ar-H), 7.62–7.35 (m, 3H, Ar-H), 5.33 (s, 2H, CH_2), 3.29–3.12 (m, 8H, $4CH_2$), 2.87 (s, 3H, CH_3). (MALDI, positive mode, matrix: DHB): m/z = 313.4 $(M+Na)^+$. $C_{13}H_{18}N_6S$ (290.4): C, 53.77; H, 6.25; N, 28.94; S, 11.04. Found: C, 53.75; H, 6.24; N, 28.91; S, 11.04.

*1,1′-[Piperazine-1,4-diyl-bis-(methylene)]-bis-(4-phenyl-1,4-dihydro-5H-tetrazole-5-thione) (**3**).* To the suspension of tetrazole **1** (1.78 g, 0.01 mol) in absolute ethyl alcohol (30 mL), formaldehyde (30%, 0.9 mL, 0.03 mol) and the desired secondary amine (0.005 mol) were added dropwise with stirring. The reaction mixture was further stirred for 2 h at room temperature, concentrated under reduced pressure, and cooled. The solid obtained was filtered and crystallized from ethyl alcohol. White powder (3.1 g, 67%), mp 187°C. ^{1}H NMR ($CDCl_3$): δ = 7.96–7.84 (m, 4H, Ar-H), 7.61–7.42 (m, 6H, Ar-H), 5.28 (s, 4H, $2CH_2$), 2.88 (s, 8H, $4CH_2$). (MALDI, positive mode, matrix: DHB): m/z = 489.6 $(M+Na)^+$. $C_{20}H_{22}N_{10}S_2$ (466.6): C, 51.48; H, 4.75; N, 30.02; S, 13.74. Found: C, 51.46; H, 4.69; N, 29.99; S, 13.73.

*Ethyl[(1-phenyl-1H-tetrazol-5-yl)thio] Acetate (**4**).* To a mixture of tetrazole **1** (1.78 g, 0.01 mol) and K_2CO_3 (1.38 g, 0.01 mol) in dry acetone (30 mL), ethyl chloroacetate (1.1 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h, filtered, then concentrated under reduced pressure. The solid obtained was filtered and recrystallized from ethyl alcohol. White powder (2.3 g, 88%), mp 113°C. ^{1}H NMR ($CDCl_3$): δ = 7.66–7.47 (m, 5H, Ar-H), 4.31 (q, 2H, J = 6.9 Hz, OCH_2), 4.26 (s, 2H, SCH_2), 1.29 (t, 3H, J = 7.1 Hz, CH_3); (MALDI, positive mode, matrix: DHB): m/z = 287.3 $(M+Na)^+$. $C_{11}H_{12}N_4O_2S$ (264.3): C, 49.99; H, 4.58; N, 21.20; S, 12.13. Found: C, 49.63; H, 4.37; N, 21.11; S, 11.94.

*2-[(1-Phenyl-1H-tetrazol-5-yl)-thio]Acetohydrazide (**5**)* [14]. To a solution of the ester derivatives **4** (1.78 g, 0.01mol) in absolute ethyl alcohol (30 mL), hydrazine hydrate (0.74 mL, 0.015 mol) was added and the reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled and evaporated under reduced pressure till dried. The precipitated residue was crystallized from ethyl alcohol. White crystal (2.1 g, 69%), mp 164°C. ^{1}H NMR ($CDCl_3$): δ = 8.23 (bs, 2H, NH_2) 7.68–7.45 (m, 5H, Ar-H), 3.98 (s, 2H, SCH_2); (MALDI, positive mode, matrix: DHB): m/z = 273.3 $(M+Na)^+$. $C_9H_{10}N_6OS$ (250.3): C, 43.19; H, 4.03; N, 33.58; S, 12.81. Found: C, 43.12; H, 3.84; N, 33.18; S, 12.69.

*[(1-Phenyl-1H-tetrazol-5-yl)thio] Acetyl Azide (**6**).* To a cold solution (~ -5°C) of hydrazide **5** (2.50 g, 0.01 mmol) in 1 N HCl solution (20 mL) and acetic acid 96% (3 mL), 5 mL water solution of $NaNO_2$ (1.38 g, 0.02 mmol) was added. The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was extracted three times with 30 mL ethyl acetate. The combined yellow syrup extract was washed several times with 3% solution of $NaHCO_3$ and water till it became neutral and was finally dried over Na_2SO_4. The in situ generated azide **6** was used without further isolation and purification.

4-{[(1-Phenyl-1H-tetrazol-5-ptyl)thio]} Acetamide Derivatives

General Procedure. To the previously prepared cold ethyl acetate solution of azide **6** (from 0.01 mol hydrazide), a solution of appropriate amines (0.01 mol) in ethyl acetate (20 mL) was added dropwise with stirring. The reaction mixture was kept at -5°C for 12 h, then at room temperature for another 12 h. The reaction mixture was washed with 0.5 N HCl, water and 3% solution of $NaHCO_3$ and dried over Na_2SO_4. The solution was evaporated to dryness, and the residue was recrystallized from ethyl acetate/petroleum ether to give the desired product.

*4-{[(1-Phenyl-1H-tetrazol-5-yl)thio]acetyl} Morpholine (**7a**).* (Amine = morpholine), white powder (2.8 g, 92%), mp 138°C. ^{1}H NMR ($CDCl_3$): δ = 7.67–7.52 (m, 5H, Ar-H), 4.49 (s, 2H, SCH_2), 3.79–3.55 (m, 8H, $4CH_2$). (MALDI, positive mode, matrix: DHB): m/z = 328.3 $(M+Na)^+$. $C_{13}H_{15}N_5O_2S$ (305.4): C, 51.13; H, 4.95; N, 22.94; S, 10.50. Found: C, 51.12; H, 4.95; N, 22.87; S, 10.49.

*1-{[(1-Phenyl-1H-tetrazol-5-yl)thio]acetyl} Piperidine (**7b**).* (Amine = piperidine), white powder (2.4 g, 79%), mp 73°C. ^{1}H NMR ($CDCl_3$): δ = 7.67–7.48 (m, 5H, Ar-H), 4.53 (s, 2H, SCH_2), 3.68–3.46 (m, 4H, $2NCH_2$), 1.86–1.57 (m, 6H, $3CH_2$). (MALDI, positive mode, matrix: DHB): m/z = 326.4 $(M+Na)^+$. $C_{14}H_{17}N_5OS$ (303.4): C, 55.42; H, 5.65; N, 23.08; S, 10.57. Found: C, 55.41; H, 5.64; N, 23.08; S, 10.55.

*1-Methyl-4-{[(1-phenyl-1H-tetrazol-5-yl)thio] acetyl} Piperazine (**7c**).* (Amine = *N*-methyl piperazine), white powder (2.2 g, 73%), mp 112°C. ^{1}H

NMR ($CDCl_3$): δ = 7.65–7.52 (m, 5H, Ar-H), 4.51 (s, 2H, CH_2), 3.74–3.61 (m, 4H, $2NCH_2$), 2.51 (t, 2H, J = 4.94 Hz, $C\underline{H}_2NCH_3$), 2.48 (t, 2H, J = 4.94 Hz, $C\underline{H}_2NCH_3$), 2.34 (s, 3H, CH_3) (MALDI, positive mode, matrix: DHB): m/z = 341.4 $(M + Na)^+$. $C_{14}H_{18}N_6OS$ (318.4): C, 52.81; H, 5.70; N, 26.39; S, 10.07. Found: C, 52.69; H, 5.63; N, 26.29; S, 10.01.

*N-(3-Hydroxypropyl)-2-[(1-phenyl-1H-tetrazol-5-yl)thio] Acetamide (***9***).* (1,3-Amino propanol), white powder (1.9 g, 65%), mp 74°C. ^{1}H NMR ($CDCl_3$): δ = 7.62–7.49 (m, 5H, Ar-H), 4.06 (s, 2H, SCH_2), 3.76 (t, 1H, J = 7.1 Hz, NH), 3.64 (t, 2H, J = 7.1 Hz, OCH_2), 3.42 (q, 2H, J = 7.1 Hz, NCH_2), 2.82 (bs, 1H, OH), 1.78–1.66 (m, 2H, CH_2), $CDCl_3/D_2O$, δ = 7.62–7.51 (m, 5H, Ar-H), 4.06 (s, 2H, SCH_2), 3.64 (t, 2H, J = 7.1 Hz, OCH_2), 3.42 (t, 2H, J = 7.1 Hz, NCH_2), 1.78–1.66 (m, 2H, CH_2) (MALDI, positive mode, matrix: DHB): m/z = 316.3 $(M + Na)^+$. $C_{12}H_{15}N_5O_2S$ (293.3): C, 49.13; H, 5.15; N, 23.87; S, 10.93. Found: C, C, 49.05; H, 5.12; N, 23.52; S, 10.79.

*N-(6-Hydroxyhexyl)-2-[(1-phenyl-1H-tetrazol-5-yl) thio] Acetamide (***10a***).* (1,6-Aminohexanol), white powder (2.8 g, 84%), mp 216°C. $CDCl_3$: δ = 7.59–7.48 (m, 5H, Ar-H), 7.18 (bs, 1H, NH), 4.04 (s, 2H, SCH_2), 3.59 (t, 2H, J = 7.0 Hz, OCH_2), 3.27 (q, 2H, J = 7.1 Hz, NCH_2), 2.33 (bs, 1H, OH), 1.62–1.26 (m, 8H, $4CH_2$). $CDCl_3/D_2O$ δ = 7.59–7.48 (m, 5H, Ar-H), 4.04 (s, 2H, SCH_2), 3.59 (t, 2H, J = 7.1 Hz, OCH_2), 3.27 (t, 2H, J = 7.1 Hz, NCH_2), 1.78–1.66 (m, 2H, CH_2), (MALDI, positive mode, matrix: DHB): m/z = 358.4 $(M + Na)^+$. $C_{15}H_{21}N_5O_2S$ (335.4): C, 53.71; H, 6.31; N, 20.88; S, 9.56. Found: C, 53.66; H, 6.31; N, 20.79; S, 9.54.

*N-(6-Aminohexyl)-2-[(1-phenyl-1H-tetrazol-5-yl) thio] Acetamide (***10b***).* (1,6-Aminohexane), white powder (2.3 g, 69%), mp 105°C. ^{1}H NMR ($CDCl_3$): δ = 7.63–7.52 (m, 5H, Ar-H), 7.16 (bs, 1H, NH), 3.92 (s, 2H, SCH_2), 3.27 (q, 2H, J = 7.1 Hz, NCH_2), 1.58–1.29 (m, 10H, $5CH_2$), (MALDI, positive mode, matrix: DHB): m/z = 357.4. $(M + Na)^+$. $C_{15}H_{22}N_6OS$ (334.4): C, 53.87; H, 6.63; N, 25.13; S, 9.59. Found: C, 53.81; H, 6.63; N, 25.06; S, 9.58.

N,N′-(Alkyldiamino)bis{2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide}

General Procedure. To a recently generated azide solution **6** in ethyl acetate (from 0.01 mol hydrazide), a solution of the appropriate diamine (0.005 mol) in ethyl acetate (20 mL) was added dropwise with stirring. The reaction mixture was kept at −5°C for 12 h, then at room temperature for another 12 h. The reaction mixture was washed with 0.5 N HCl, water, and 3% solution of $NaHCO_3$ and dried over Na_2SO_4. The solution was evaporated to dryness, and the residue was recrystallized by ethyl acetate/petroleum ether to give the desired product.

*1,4-Bis{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} piperazine (***8***).* (Amine = piperazine), white powder (3.3 g, 63%), mp 95°C. ^{1}H NMR ($CDCl_3$): δ = 7.65–7.52 (m, 10H, Ar-H), 4.48 (s, 4H, $2CH_2$), 3.92–3.81 (m, 4H, $2NCH_2$), 3.75–3.63 (m, 4H, $2NCH_2$). (MALDI, positive mode, matrix: DHB): m/z = 545.6 $(M + Na)^+$. $C_{22}H_{22}N_{10}O_2S_2$ (522.6): C, 50.56; H, 4.24; N, 26.80; S, 12.27. Found: C, 50.49 H, 4.21; N, 26.77; S, 12.14.

*N,N′-(Iminodihexane-6,1-diyl)bis{2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide} (***11***).* (Amine = 1,6-hexandiamine), white powder (2.8 g, 51%), mp 145°C. ^{1}H NMR ($CDCl_3$): δ = 7.63–7.49 (m, 8H, Ar-H), 7.28–7.12 (m, 3H, Ar-H, NH), 3.95 (s, 4H, $2SCH_2$), 3.26 (q, 4H, J = 7.0 Hz, $2NCH_2$), 1.59–1.43 (m, 8H, $2CH_2$), 1.38–1.20 (m, 8H, $2CH_2$), (MALDI, positive mode, matrix: DHB): m/z = 575.7 $(M + Na)^+$. $C_{24}H_{28}N_{10}O_2S_2$(552.7): C, 52.16; H, 5.11; N, 25.34; S, 11.60. Found: 52.13; H, 5.09; N, 25.28; S, 11.59.

Methyl N-{[(1-phenyl-1H-tetrazol-5-yl) thio] acetyl} Amino Ester

General Procedure. To a recently generated azide solution **6** in ethyl acetate (from 0.01 mol hydrazide), appropriate amino ester hydrochloride (0.01 mol) and triethyl amine (1 mL, 0.01 mol) was added. The reaction mixture was kept at −5°C for 12 h, and then at room temperature for another 12 h. The reaction mixture was washed with 0.5 N HCl, water, and 3% solution of $NaHCO_3$ and dried over Na_2SO_4. The solution was evaporated to dryness, and the residue was recrystallized by ethyl acetate–petroleum ether to give the desired product.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Glycinate (***12a***).* (Amino acid = glycine), white powder (2.3 g, 68%), mp 87°C. ^{1}H NMR ($CDCl_3$): δ = 7.63–7.43 (m, 6H, Ar-H, NH), 4.08 (s, 2H, SCH_2), 4.03 (s, 2H, $NHC\underline{H}_2$), 3.72 (s, 3H, OCH_3), (MALDI, positive mode, matrix: DHB): m/z = 330.3 $(M + Na)^+$. $C_{12}H_{13}N_5O_3S$ (307.3): C, 46.90; H, 4.26; N, 22.79; S, 10.43. Found: C, 46.89; H, 4.24; N, 22.78; S, 10.41.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Alaninate (***12b***).* (Amino acid = L-alanine), white powder (2.5 g, 78%), mp 67°C. ^{1}H NMR ($CDCl_3$):

δ = 7.58–7.53 (m, 5H, Ar-H), 7.48 (bs, 1H, NH), 4.62–4.47 (m, 1H, C<u>H</u>CH$_3$), 4.03 (s, 2H, SCH$_2$), 3.71 (s, 3H, OCH$_3$), 1.42 (d, 3H, J = 12.0 Hz, CHC<u>H</u>$_3$), (MALDI, positive mode, matrix: DHB): m/z = 344.3 (M + Na)$^+$. $C_{13}H_{15}N_5O_3S$ (321.4): C, 48.59; H, 4.70 N, 21.79; S, 9.98. Found: C, 48.56; H, 4.68 N, 21.73; S, 9.90.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Valinate (***12c***).* (Amino acid = L-valine), white powder (1.9 g, 55%), mp 59°C. ^{1}H NMR (CDCl$_3$): δ = 7.63–7.58 (m, 5H, Ar-H), 7.50 (bs, 1H, NH), 4.59–4.48 (m, 1H, NHC<u>H</u>), 4.04 (s, 2H, SCH$_2$), 3.72 (s, 3H, OCH$_3$), 2.29–2.12 (m, 1H, C<u>H</u>CH$_3$), 0.95–0.82 (m, 6H, 2CH$_3$), (MALDI, positive mode, matrix: DHB): m/z = 372.4 (M + Na)$^+$. $C_{15}H_{19}N_5O_3S$ (349.4): C, 51.56; H, 5.48 N, 20.04; S, 9.18. Found: C, 51.56; H, 5.47 N, 20.02; S, 9.17.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Leucinate (***12d***).* (Amino acid = L-leucine), white powder (2.2 g, 61%), mp 51°C. ^{1}H NMR (CDCl$_3$): δ = 7.63–7.53 (m, 5H, Ar-H), 7.36 (bs, 1H, NH), 4.63–4.51 (m, 1H, NHC<u>H</u>), 4.08 (s, 2H, SCH$_2$), 3.74 (s, 3H, OCH$_3$), 1.68–1.52 (m, 2H, CHC<u>H</u>$_2$), 1.80–1.26 (m, 1H, C<u>H</u>CH$_3$), 1.03–0.84 (m, 6H, 2CH$_3$), (MALDI, positive mode, matrix: DHB): m/z = 386.4 (M + Na)$^+$. $C_{16}H_{21}N_5O_3S$ (363.4): C, 52.88; H, 5.82 N, 19.27; S, 8.82. Found: C, 52.86; H, 5.82 N, 19.24; S, 8.80.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Methioninate (***12e***).* (Amino acid = L-methionine), yellow oil (2.0 g, 53%), ^{1}H NMR (CDCl$_3$): δ = 7.68 (bs, 1H, NH), 7.61–7.45 (m, 5H, Ar-H), 4.76–4.64 (m, 1H, NHC<u>H</u>), 4.08 (s, 2H, SCH$_2$), 3.71 (s, 3H, OCH$_3$), 2.51 (t, 2H, J = 7.1 Hz, SC<u>H</u>$_2$), 1.92–2.22 (m, 5H, SCH$_3$, C<u>H</u>$_2$CH), (MALDI, positive mode, matrix: DHB): m/z = 404.5 (M + Na)$^+$. $C_{15}H_{19}N_5O_3S_2$ (381.5): C, 47.23; H, 5.02 N, 18.36; S, 16.81. Found: C, 47.18; H, 4.85 N, 18.26; S, 16.79.

*N^2-{[(1-Phenyl-1H-tetrazol-5-yl)thio]acetyl} Glycine Hydrazide (***13a***).* (Amino acid = glycine), white powder (2.8 g, 91%), mp 189°C. ^{1}H NMR (CDCl$_3$): δ = 9.05 (bs, 1H, NH), 8.60 (bs, 1H, NH), 7.63–7.55 (m, 5H, Ar-H), 4.24 (s, 2H, SCH$_2$), 3.66 (bs, 2H, NH$_2$), 3.33–3.23 (m, 2H, NHC<u>H</u>$_2$), (MALDI, positive mode, matrix: DHB): m/z = 330.3 (M + Na)$^+$. $C_{11}H_{13}N_7O_2S$ (307.3): C, 42.99; H, 4.26 N, 31.90; S, 10.43. Found: 42.85; H, 4.19 N, 31.87; S, 10.38.

*N^2-{[(1-Phenyl-1H-tetrazol-5-yl)thio]acetyl} Alanine Hydrazide (***13b***).* (Amino acid = L-alanine), white powder (2.6 g, 80%), mp 163°C. ^{1}H NMR (CDCl$_3$): δ = 9.18 (bs, 1H, NH), 8.66 (bs, 1H, NH), 7.71–7.57 (m, 5H, Ar-H), 4.31–4.15 (s, 3H, SCH$_2$, NHC<u>H</u>), 3.49 (bs, 2H, NH$_2$), 1.29–1.16. (m, 3H, CHC<u>H</u>$_3$), (MALDI, positive mode, matrix: DHB): m/z = 344.4 (M + Na)$^+$. $C_{12}H_{15}N_7O_2S$ (321.4): C, 44.85; H, 4.70 N, 30.51; S, 9.98. Found: C, 44.61; H, 4.63 N, 30.49; S, 9.87.

*Methyl N-{[(1-phenyl-1H-tetrazol-5-yl)thio]acetyl} Glycylglycinate (***14***).* White powder (2.7 g, 74%), mp 150°C. ^{1}H NMR (CDCl$_3$): δ = 7.70 (bs, 1H, NH), 7.58–7.53 (m, 5H, Ar-H), 7.33 (bs, 1H, NH), 4.14–4.08 (m, 4H, 2NHC<u>H</u>$_2$), 4.01 (s, 2H, SCH$_2$), 3.71 (s, 3H, OCH$_3$), (MALDI, positive mode, matrix: DHB): m/z = 387.4 (M + Na)$^+$. $C_{14}H_{16}N_6O_4S$ (364.4): C, 46.15; H, 4.43 N, 23.06; S, 8.80. Found: C, 46.13; H, 4.37 N, 23.04; S, 8.78.

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