Article

J. Mex. Chem. Soc. **2013**, *57(4)*, 283-289

ISSN 1870-249X

Efficient Synthesis of 1,5-disubstituted-1*H*-tetrazoles by an Ugi-azide Process

Luis Edilberto Cárdenas-Galindo,[1] Alejandro Islas-Jácome,[1] Carlos Jesús Cortes-García,[1] Laurent El Kaim,[2,*] and Rocío Gámez-Montaño[1,*]

[1] Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, C. P. 36050, Guanajuato, Gto, México. Tel: +52-(473)-7320006, ext. 8191 rociogm@ugto.mx

[2] UMR 7652, (Ecole Polytechnique/ENSTA/CNRS), Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75015 Paris, France. Tel: +33-(145)-52553 laurent.elkaim@ensta.fr

Received January 22, 2013; Accepted May 28, 2013.

Abstract. A series of eighteen novel 1,5-disubstituted-1*H*-tetrazoles has been prepared with moderate to good overall yields using an Ugi-azide reaction as key step under mild conditions. Tetrazoles are heterocyclic systems present in several synthetic products which have privileged biological activity. Therefore, in this paper we describe the synthesis of novel compounds containing the tetrazole moiety, which could present biological activity.
Keywords: Multicomponent reactions, Ugi-azide, 1,5 dipolar electrocyclization, tetrazole, azide, isocyanide.

Resumen. Fue preparada una serie de dieciocho nuevos tetrazoles-1*H*-1,5-disubstituidos con rendimientos de moderados a buenos utilizando una reacción Ugi-azida como proceso clave bajo condiciones suaves. Los tetrazoles son sistemas heterocíclicos presentes en diversos productos sintéticos con actividad biológica privilegiada. En este trabajo describimos la síntesis de nuevos compuestos con el núcleo de tetrazol, los cuales podrían presentar actividad biológica.
Palabras clave: Reacciones de multicomponentes, Ugi-azida, electrociclización 1,5 dipolar, tetrazol, azida, isonitrilo.

Introduction

Tetrazoles are an important class of heterocycles, which are present in various compounds of great interest in medicinal chemistry because of their privileged biological activity. For example, losartan **1** is an angiotensin II receptor antagonist [1]. Tomelukast (L-171883, **2**) [2], mimics the cystein-ylglycine terminus of growth hormone LTD_4 and also functions as a potent anti-asthmatic drug [3] and BMS-317180 (**3**) is a potent oral agonist of the human growth hormone secretagogue (GHS) receptor [4], (Fig. 1).

Various methodologies for preparing compounds with a tetrazole ring system [5] have been developed, among the most important are those based on azides on cyanides [6] reactions, for example, Aldhoun *et al* described a short route based on [2, 3]-dipolar cycloadditions using TMSCN and several azides as starting materials to access a series of 1,5-disubstituted-1*H*-tetrazoles with good to excellent overall yields [7]. Multicomponent reactions (MCR) have also been exploited to obtain compounds with a tetrazole ring system in short reactions time with good overall yields [8]. Hulme, who has been a pioneer in this field, reported in 2002 a rapid preparation of norstatine analogs, which include the tetrazole ring system based on a Passerini-type multicomponent reaction with $TMSN_3$ and several isocyanides as starting materials in excellent overall yields [9]. Additionally, Kazemizadeh *et al*, recently published a novel methodology to prepare a series of 1,5-disubstituted-1*H*-tetrazoles which was based on the use of a three component reaction as key-step process using isocyanides, $TMSN_3$ and several carbodiimides as starting materials [10]. Among multicomponent reactions, the Ugi-type MCR combined with subsequent post-condensation processes present several advantages over other methodologies for the 1,5-disubstituted-1*H*-tetrazoles synthesis [11]. In this context, important efforts have been made by the Dömling's research group for the preparation of novel Ugi-tetrazoles of great interest in medicinal chemistry [12]. Also, Marcaccini reported the synthesis of a series of tetrazoyl isoindolinones via a tandem Ugi-4CR/amidation with moderate to

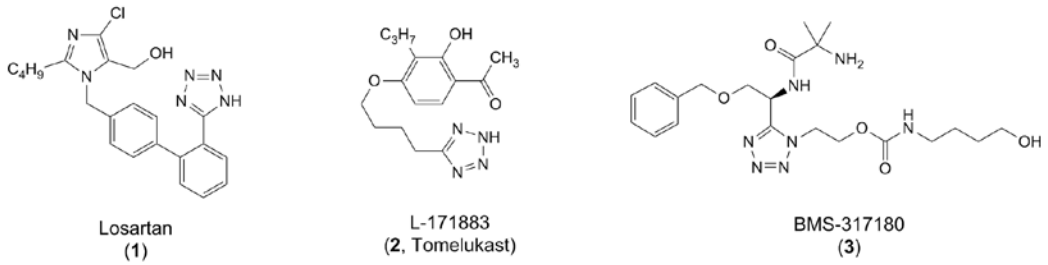


Fig. 1. Tetrazoles of great interest in medicinal chemistry.

good overall yields [13]. More recently, Hulme *et al* published an elegant synthesis of a novel 1,5-disubstituted-1*H*-tetrazoles series with moderate yields based on the Ugi-azide process [14].

The most important feature of the Ugi-3CR is the ease to construct structural diversity and to access to compound libraries by changing one of the starting materials [15]. In this context, series of different fused tetrazolopiperazines have been prepared with tosylate-substituted isocyanides[16], isocyanoesters [17], fluoroaryl isocyanides [18], or Schöllkopf isocyanides [19].

Results and Discussion

In this work, we describe a rapid preparation of a series of eighteen 1,5-disubstituted-1*H*-tetrazoles (**4a-r**) with good to excellent overall yields (70-94%) based on the use of a catalyst free optimized Ugi-azide process employing commercially available aryl-ethanamine derivatives **5**, aldehydes **6**, isocyanides **7** and $TMSN_3$ (**8**) in MeOH under mild conditions (room temperature), (Scheme 1).

As depicted in Scheme 1, most of the compounds were obtained with really high yields, see for example **4f** (91%), **4i** (94%) and **4p** (96%). Thus, yields are independent of the electronic and structural nature of substituents in the starting materials. As can be seen in the multicomponent process, aryl-ethanamines, aryl, alkyl aldehydes and isocyanides were used showing the generality of the methodology. In fact, no significant changes have been observed in the yields. Steric effects, which commonly take importance in the Ugi-3CR, had no influence on the yields of the corresponding 1,5-disubstituted-1*H*-tetrazoles. Lower yields for the compounds **4e** and **4k** (which have the lowest steric factor) can be explained by the low boiling point of acetaldehyde, which hampers its experimental manipulation. Thus, the main contribution of our work is the operational simplicity of this multicomponent methodology to access to libraries of novel 1,5-disubstituted-1*H*-tetrazoles under mild conditions in relatively short reaction time. This latter is in comparison with other reports in which high temperatures, catalysts or strong acidic media are required [20].

We are currently exploiting a comprehensive study of the reactivity of other amines in this Ugi-azide process such as polysubstituted benzylamines and anilines. In this work, the resulting 1,5-disubstituted-1*H*-tetrazoles (**4a-r**) are aryl-ethanamine derivatives with possible biological activity.

The reaction mechanism by which the synthesis of 1,5-disubstituted-1*H*-tetrazoles **4a-r** occurs is depicted in Scheme 2. First, condensation occurs between amines **5** and aldehydes **6** to produce imines **9**, which are converted into corresponding iminium ions **10** by hydrazoic acid. Then, isocyanide **7** undergoes an α-nucleophilic addition to produce nitrilium ions **11**, which are attacked by the azide anion to give intermediates **12**, which carry out a 1,5 dipolar electrocyclization to afford the 1,5-disubstituted-1*H*-tetrazoles series **4** [21].

Conclusions

We prepared a series of eighteen novel 1,5-disubstituted-1*H*-tetrazoles with good to excellent overall yields in one simple operational reaction step using mild conditions at room temperature. With these tetrazoles, we will study other combinations of multicomponent reactions with other miscellaneous post-condensations methodologies.

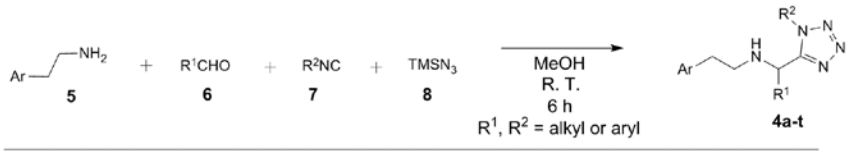
Experimental Part

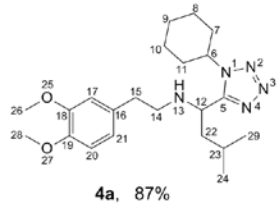
Starting materials were obtained from Aldrich (México) and were used without further purification. IR Spectra: Perkin Elmer Spectrum 100FT-IR spectrometer, ν_{max} in cm^{-1}. ^1H and ^{13}C-NMR Spectra: *Bruker* (400 and 100 MHz, resp.), V*arian* (300 and 75 MHz resp.) and (200 and 50 MHz resp.), in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

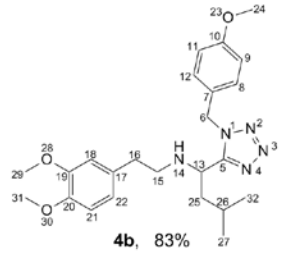
General method*:* Amine **5** (1.0 M) (1.0 equiv.) aldehyde **6** (1.0 equiv.), isocyanide **7** (1.0 equiv.) and azidotrimethylsilane **(8)** (1.0 equiv.) were disolved in MeOH in a round-bottom flask equipped with a magnetic stirrer bar. The resulting mixture was stirred for 6h under an inert nitrogen atmosphere at room temperature. The solvent was evaporated under reduced pressure until dryness, then the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over $NaSO_4$. The resulting product was purified by column chromatography on silica gel using a mixture of Hex-AcOEt (3:1 V/V) as eluent to afford compounds **(4a-r)**.

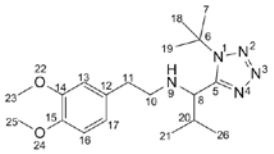
1-(1-cyclohexyl-1H-tetrazol-5-yl)-N-(3,4-dimethoxyphenethyl)-3-methylbutan-1-amine **(4a)**. The general method was followed using homoveratrylamine **(5a)** (300 mg, 1.66 mmol), isovaleraldehyde **(6a)** (143 mg, 1.66 mmol), cyclohexylisocyanide **(7a)** (181 mg, 1.66 mmol), and azidotrimethylsilane **(8)** (191 mg, 1.66 mmol), producing 578 mg (87%) of **4a** as a yellow solid; R_f = 0.61 Hex-AcOEt (3:1 V/V); m.p. 62-63°C; FT-IR (ATR) ν_{max} 3345, 1515, 1260, 1236, 1094, 1027 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz): δ 0.86 (d, *J* = 6.6 Hz, 3H, C*H*$_3$ of *i*-Bu), δ 0.92 (d, *J* = 6.6 Hz, 3H, C*H*$_3$ of *i*-Bu), 1.25 – 1.40 (m, 3H, C*H*$_2$ of Cy, C*H*-23), 1.40 – 1.49 (m, 2H, C*H*$_2$ of Cy), 1.60-1.73 (m, 2H, C*H*$_2$-22), 1.75 (d, *J* = 8.4 Hz, 1H, N*H*-13), 1.83-2.05 (m, 6H, C*H*$_2$ of Cy), 2.59-2.62 (m, 1H, C*H*$_2$-14), 2.65-2.71 (m, 3H, C*H*$_2$-15, C*H*$_2$-14), 3.85 (s, 6H, C*H*$_3$-26, 28), 4.21 (t, *J* = 7.4 Hz, C*H*-12), 4.53 (tt, *J* = 11.5, 3.7, Hz, 1H, C*H*-6), 6.65-6.68 (m, 2H, C*H*-20, 21), 6.78 (d, *J* = 8.0 Hz, 1H, C*H*-17); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 22.9, 22.9 (24, 29), 25.2 (9), 25.3 (23), 25.8, 25.8, 33.4, 33.6 (7, 8, 10, 11), 36.2 (15), 44.1 (22), 49.1 (14), 52.4 (12), 56.2, 56.3 (26, 28), 111.7, 112.1, 120.9 (17, 20 ,21), 132.3 (16), 147.9, 149.3 (18, 19), 155.8 (5).

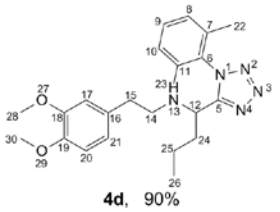
N-(3,4-dimethoxyphenethyl)-1-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-3-methylbutan-1-amine **(4b).** The general method was followed using homoveratrylamine **(5a)** (400 mg, 2.21 mmol), isovaleraldehyde **(6a)** (190 mg, 2.21 mmol), 4-me-

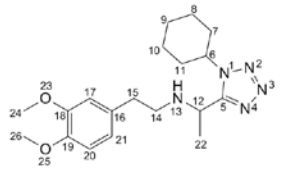


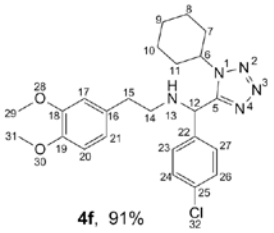

4a, 87%

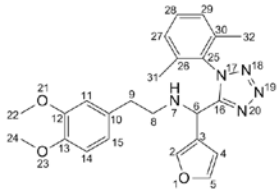

4b, 83%

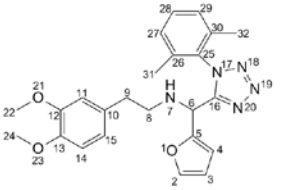

4c, 91%

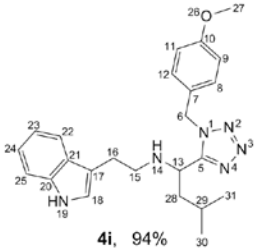

4d, 90%

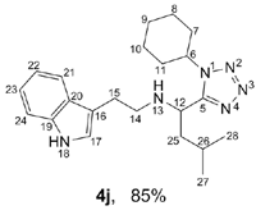

4e, 71%

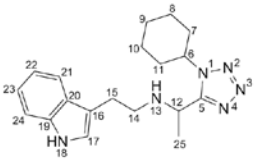

4f, 91%

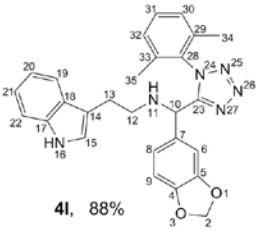

4g, 84%

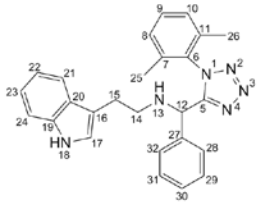

4h, 88%

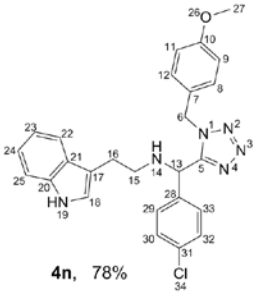

4i, 94%

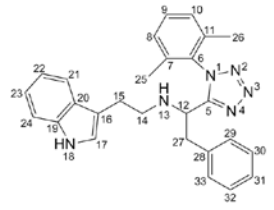

4j, 85%

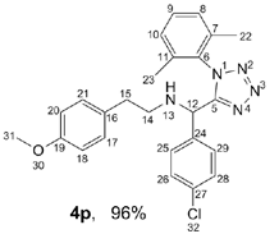

4k, 74%

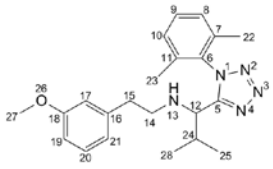

4l, 88%

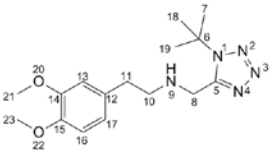

4m, 78%


4n, 78%

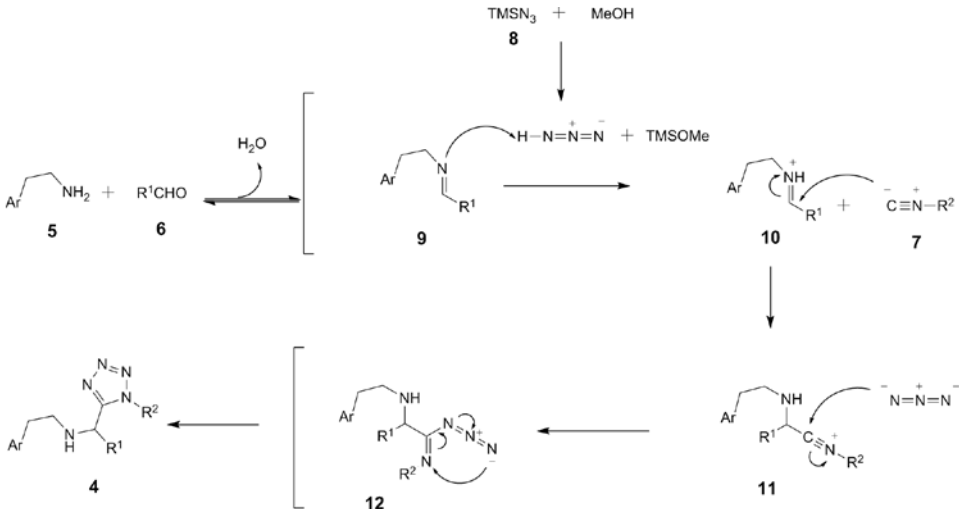

4o, 70%


4p, 96%


4q, 89%


4r, 80%

Scheme 1. Synthesis of 1,5-disubstituted-1*H*-tetrazoles **4a-r**.



Scheme 2. Reaction mechanisms for the formation of 1,5-disubstituted-1*H*-tetrazoles **4a-r**.

thoxy-benzylisocyanide **(7b)** (325 mg, 2.21 mmol), and azidotrimethylsilane **(8)** (254 mg, 2.21 mmol), producing 805 mg (83%) of **4b** as a yellow oil; R_f = 0.58 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3321, 1513, 1275, 1258, 1140, 1027 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.71 (d, 3H, *J* = 6.5 Hz, C*H*$_3$ of *i*-Bu), 0.83 (d, 3H, *J* = 6.5 Hz, C*H*$_3$ of *i*-Bu), 1.30 (s, 1H, N*H*-14), 1.35 (dt, 1H, *J* = 13.7, 6.7 Hz, C*H*-26), 1.41-1.57 (m, 2H, C*H*$_2$-25), 2.51-2.63 (m, 4H, C*H*$_2$-15,16), 3.79 (s, 3H, C*H*$_3$-24), 3.87 (s, 6H, C*H*$_3$-29, 31), 4.15 (t, 1H, *J* = 7.5 Hz, C*H*-13), 5.51 (dd, 2H, ^2J = 21.7, 15.2 Hz, C*H*$_2$-6), 6.63 – 6.66 (m, 2H, C*H*-21, 22), 6.80 (d, 1H, *J* = 8.0 Hz, C*H*-18), 6.86 (m, 2H, C*H*-9, 11), 7.14 (d, 2H, *J* = 8.7 Hz, C*H*-8, 12); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 22.6, 22.8 (27, 32), 25.1 (26), 36.1 (16), 43.5 (25), 49.0 (15), 50.9 (6), 52.3 (13), 55.7 (24), 56.3, 56.4 (29, 31), 111.7 (18), 112.2 (22), 114.7 (9, 11), 120.9 (21), 126.5 (7), 129.4 (8, 12), 132.4 (17), 148.0, 149.4 (19, 20), 156.8 (5), 160.2 (10).

1-(1-(tert-butyl)-1H-tetrazol-5-yl)-N-(3,4-dimethoxyphenethyl)-2-methylpropan-1-amine **(4c)**. The general method was followed using homoveratrylamine **(5a)** (250 mg, 1.38 mmol), isobutyraldehyde **(6b)** (99 mg, 1.38 mmol), *t*-butyl isocyanide **(7c)** (115 mg, 1.38 mmol), and azidotrimethylsilane **(8)** (159 mg, 1.38 mmol), producing 454 mg (91%) of **4c** as a yellow oil; R_f = 0.90 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3335, 1514, 1260, 1235, 1138, 1027 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.00 (dd, 6H, *J* = 17.8, 6.7 Hz,C*H*$_3$-21, 26), 1.72 (s, 9H, C*H*$_3$-7, 18, 19), 1.87 (s, 1H, N*H*-9), 2.13 (dt, 1H, *J* = 13.6, 7.0 Hz, C*H*-20), 2.65-2.70 (m, 4H, C*H*$_2$-10, 11), 3.85 (d, 6H, *J* = 1.3 Hz, C*H*$_3$-23, 25), 6.65-6.68 (m, 2H, C*H*-13, 17), 6.77 (d, 1H, *J* = 8.7 Hz, C*H*-16); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 17.6, 20.5 (21, 26), 30.4 (18, 19), 32.8 (20), 36.1 (11), 48.4 (10), 55.8, 55. 9 (23, 25), 59.7 (8), 61.3 (6), 11.2, 111.9 (13, 16), 120.5 (17), 132.2 (12), 147.4, 148.8 (14, 15), 157.0 (5).

N-(3,4-dimethoxyphenethyl)-1-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)butan-1-amine **(4d)**. The general method was followed using homoveratrylamine **(5a)** (100 mg, 0.55 mmol), butyraldehyde **(6c)** (40 mg, 0.55 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (60 mg, 0.55 mmol), and azidotrimethylsolane **(8)** (64 mg, 0.55 mmol), roducing 203 mg (90%) of **4d** as a yellow oil; R_f = 0.68 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3323, 1514, 1260, 1235, 1139, 1027 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.81 (t, 3H, *J* = 7.3 Hz, C*H*$_3$-26), 1.29 (dq, 2H, *J* = 14.9, 7.5 Hz, C*H*$_2$-25), 1.64-1.80 (m, 2H, C*H*$_2$-24), 1.92 (d, 6H, *J* = 4.5 Hz, C*H*$_3$-22, 23), 2.61-2.68 (m, 2H, C*H*$_2$-14), 2.68-2.84 (m, 2H, C*H*$_2$-15), 3.64 (t, 1H, *J* = 6.5 Hz, C*H*-12), 3.86 (d, 6H, *J* = 1.8 Hz, C*H*$_3$-28, 30), 6.62-6.71 (m, 2H, C*H*-17, 21), 6.74-6.82 (m, 1H, C*H*-20), 7.15-7.26 (m, 2H, C*H*-8, 10), 7.38 (t, 1H, *J* = 7.6 Hz, C*H*-9); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 13.8 (26), 17.5, 17.6 (22, 23), 19.0 (25), 35.8 (24), 36.1 (15), 48.5 (14), 52.4 (12), 56.0, 56.0 (28, 30), 111.5 (17), 112.0 (20), 120.7 (21), 129.0, 129.0 (8, 10), 130.9 (9), 132.0 (6), 132.2 (16), 135.7, 136.0 (7, 11), 147.6, 149.0 (18, 19), 158.0 (5).

1-(1-cyclohexyl-1H-tetrazol-5-yl)-N-(3,4-dimethoxyphenethyl)ethanamine **(4e)**. The general method was followed using homoveratrylamine **(5a)** (500 mg, 2.76 mmol), acetaldehyde **(6d)** (122 mg, 2.76 mmol), cyclohexylisocyanide **(7a)** (301 mg, 2.76 mmol), and azidotrimethylsilane **(8)** (318 mg, 2.76 mmol), producing 704 mg (71%) of **4e** as a yellow oil; R_f = 0.42 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3320, 1514, 1260, 1235, 1139, 1026 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.22-1.39 (m, 4H, C*H*$_2$ of Cy), 1.47 (d, 3H, *J* = 6.8 Hz, C*H*$_3$-22), 1.72 (d, 1H, *J* = 10.1 Hz, N*H*-13), 1.84-2.00 (m, 6H, C*H*$_2$ of Cy), 2.62-2.70 (m, 3H, C*H*$_2$-15,C*H*$_2$-14), 2.73-2.76 (m, 1H, C*H*$_2$-14), 3.81 (s, 3H, C*H*$_3$ of OMe), 3.82 (s, 3H, C*H*$_3$ of OMe), 4.24 (q, 1H, *J* = 6.8 Hz, C*H*-12), 4.45-4.53 (m, 1H, C*H*-6), 6.64-6.67 (m, 2H, C*H*-17, 21), 6.75 (d, 1H, *J* = 7.9 Hz, C*H*-20); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 20.8 (22), 25.2, 25.8, 33.4, 33.4 (7, 8, 9, 10, 11), 36.3 (15), 49.0 (14), 49.1 (12), 56.2, 56.3 (24, 26), 58.2 (6), 111.7 (20), 112.2 (21), 120.9 (17), 132.3 (16), 148.0, 149.4 (18, 19), 156.4 (5).

N-((4-chlorophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2-(3,4-dimethoxyphenyl)ethanamine **(4f)**. The general method was followed using homoveratrylamine **(5a)** (500

mg, 2.76 mmol), 4-chlorobenzaldehyde **(6e)** (388 mg, 2.76 mmol), cyclohexylisocyanide **(7a)** (301 mg, 2.76 mmol), and azidotrimethylsilane **(8)** (318 mg, 2.76 mmol), producing 1145 mg (91%) of **4f** as a white solid; R_f = 0.19 Hex-AcOEt (3:1 V/V); m.p. 109-110°C; FT-IR (ATR) ν_{max} 3301, 1514, 1471, 1275, 1260, 768, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.20-1.23 (m, 3H, C*H*$_2$ of Cy), 1.48 (d, 1H, *J* = 10.5 Hz, C*H*$_2$ of Cy), 1.58 (d, 1H, *J* = 11.0 Hz, C*H*$_2$ of Cy), 1.66 (s, 1H, C*H*$_2$ of Cy), 1.81 (t, 4H, *J* = 9.5 Hz, C*H*$_2$ of Cy), 2.18 (s, 1H, N*H*-13), 2.73-2.82 (m, 4H, C*H*$_2$-14, 15), 3.82 (s, 3H, C*H*$_3$ of OMe), 3.83 (s, 3H, C*H*$_3$ of OMe),4.21 (tt, 1H, *J* = 11.5, 3.8 Hz, C*H*-6), 5.21 (s, 1H, C*H*-12), 6.67-6.71 (m, 2H, C*H*-20, 21), 6.77 (d, 1H, *J* = 8.1 Hz, C*H*-17), 7.22 (d, 2H, *J* = 8.1 Hz, C*H*-23, 27), 7.29 (d, 2H, *J* = 8.4 Hz, C*H*-24, 26); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 25.1, 25.7, 33.0 (7, 8, 9, 10, 11), 36.2 (15), 49.3 (14), 56.3, 56.3 (29, 31), 57.3 (12), 58.4 (6), 111.8 (17), 112.3, 121.0 (20, 21), 128.9 (23, 27), 129.6 (24, 26), 132.2 (16), 134.8 (25) 137.0 (22), 148.1, 149.4 (18, 19), 154.6 (5).

2-(3,4-dimethoxyphenyl)-N-((1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)(furan-3-yl)methyl)ethanamine **(4g)**. The general method was followed using homoveratrylamine **(5a)** (250 mg, 1.38 mmol), 3-furaldehyde **(6f)** (133 mg, 1.38 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (181 mg, 1.38 mmol), and azidotrimethylsilane **(8)** (159 mg, 1.38 mmol), producing 502 mg (84%) of **4g** as a white solid; R_f = 0.65 Hex-AcOEt (3:1 V/V); m.p. 63-64°C; FT-IR (ATR) ν_{max} 3326, 1514, 1258, 1234, 1139, 1025 cm^{-1}; ^{1}H-NMR ($(CD_3)_2SO$, 300 MHz): δ 1.57 (s, 3H, C*H*$_3$ of Ph*Me*$_2$), 1.90 (s, 3H, C*H*$_3$ of Ph*Me*$_2$), 2.26 (d, 1H, *J* = 14.4 Hz, N*H*-7), 2.55-2.70 (m, 4H, C*H*$_2$-8,9), 3.76 (s, 6H, C*H*$_3$-22, 24), 4.79 (*CH*-6), 6.41 (d, 1H, *J* = 1.4 Hz, C*H*-4), 6.63-6.68 (m, 2H, C*H*-14, 15), 6.77 (dd, 1H, *J* = 7.9, 4.1 Hz, C*H*-11), 7.23-7.29 (m, 3H, C*H*-2, 27, 29), 7.40-7.47 (m, 2H, C*H*-5, 28); ^{13}C-NMR ($(CD_3)_2SO$, 75 MHz): δ 14.9, 15,3 (31, 32), 33.3 (9), 46.3 (8, 6), 53.8, 53.9 (22, 24), 107.7 (4), 110,1 (11), 110.6 (14), 118.7, (15), 126.9, 127.0 (27, 29), 129.2 (28), 129.6 (3), 130.4 (25), 133.8, 133.9 (26, 32), 139.1 (2), 141.9 (5), 145.6, 147.0 (12, 13), 154.6 (16).

2-(3,4-dimethoxyphenyl)-N-((1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)(furan-2-yl)methyl)ethanamine **(4h)**. The general method was followed using homoveratrylamine **(5a)** (180 mg, 0.99 mmol), 2-furaldehyde **(6g)** (95 mg, 0.99 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (130 mg, 0.99 mmol), and azidotrimethylsilane **(8)** (114 mg, 0.99 mmol), producing 379 mg (88%) of **4h** as a yellow solid; R_f = 0.68 Hex-AcOEt (3:1 V/V); m.p. 84-86°C; FT-IR (ATR) ν_{max} 3326, 1514, 1257, 1233, 1141, 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.60 (s, 3H, C*H*$_3$ of Ph*Me*$_2$), 1.91 (s, 3H, C*H*$_3$ of Ph*Me*$_2$), 2.16 (s, 1H, N*H*-7), 2.76 (dd, 4H, *J* = 14.2, 5.2, Hz,C*H*$_2$-8, 9), 3.84 (s, 3H, C*H*$_3$ of OMe), 3.86 (s, 3H, C*H*$_3$ of OMe), 4.83 (s, 1H, C*H*-6), 6.03 (d, 1H, *J* = 3.1 Hz, C*H*-3), 6.25 (dd, 1H, *J* = 3.0, 1.8, Hz, C*H*-4), 6.67-6.68 (m, 2H, C*H*-11, 14), 6.75-6.79 (m, 1H, C*H*-15), 7.11-7.21 (m, 2H, C*H*-27, 29), 7.28 (d, 1H, *J* = 3.5 Hz, C*H*-5), 7.36 (t, 1H, *J* = 7.6 Hz, C*H*-28); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 17.1, 17.5 (31, 32), 35.9 (9), 47.8 (8), 51.0 (6), 56.0, 56.1 (22, 24), 109.0 (4), 110.7 (3), 111.4 (15), 112.0 (11), 120.7 (14), 128.8, 128.9 (27, 29), 131.1 (28), 131.7 (25), 132.0 (10), 135.8, 136.7 (26, 30), 143.1 (5), 147.7, 149.1 (12, 13), 150.2 (2), 155.2 (16).

N-(2-(1H-indol-3-yl)ethyl)-1-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-3-methylbutan-1-amine **(4i)**. The general method was followed using tryptamine **(5b)** (500 mg, 3.12 mmol), isovaleraldehyde **(6a)** (269 mg, 3.12 mmol), 4-methoxy-benzylisocyanide **(7b)** (459 mg, 3.12 mmol), and azidotrimethylsilane **(8)** (360 mg, 3.12 mmol), producing 1272 mg (94%) of **4i** as an amber oil; R_f = 0.42 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3320, 3056, 1612, 1456, 1249, 1177 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.53 (d, 3H, *J* = 6.4 Hz, C*H*$_3$ of *i*-Bu), 0.79 (d, 3H, *J* = 6.4 Hz, C*H*$_3$ of *i*-Bu), 1.30 (tt, 1H, *J* = 13.2, 6.5 Hz, C*H*-29), 1.39-1.54 (m, 3H, C*H*$_2$-28,N*H*-14), 2.61-2.67 (m, 1H, C*H*$_2$-16), 2.71-2.77 (m, 1H,C*H*$_2$-16), 2.85 (t, 2H, *J* = 6.5 Hz, C*H*$_2$-15), 3.76 (s, 3H, C*H*$_3$-27), 4.18 (t, 1H, *J* = 7.5 Hz, C*H*-13), 5.42 (d, 1H, *J* = 15.6 Hz, C*H*$_2$-6), 5.44 (d, 1H, *J* = 15.6 Hz, C*H*$_2$-6), 6.81- 6.83 (m, 2H, C*H*-9, 11), 6.95 (s, 1H, C*H*-18), 7.05-7.07 (m, 2H, C*H*-8, 12), 7.13 (t, 1H, *J* = 7.4 Hz, C*H*-23), 7.21 (t, 1H, *J* = 7.4 Hz, C*H*-24), 7.38 (d, 1H, *J* = 8.0 Hz, C*H*-22), 7.54 (d, 1H, *J* = 7.8 Hz, C*H*-25), 8.36 (s, 1H, N*H*-19); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 22.7 (30, 31), 25.1 (29), 26.1 (16), 43.5 (28), 48.0 (15), 50.8 (6), 52.4 (13), 55.7 (27), 111.7 (22), 113.9 (21), 114.7 (9, 11), 119.1 (25), 119.7 (23), 122.4 (18), 122.5 (24), 126.6 (7), 127.8 (17), 129.4 (8, 12), 136.8 (20), 156.9 (5), 160.2 (10).

N-(2-(1H-indol-3-yl)ethyl)-1-(1-cyclohexyl-1H-tetrazol-5-yl)-3-methylbutan-1-amine **(4j)**. The general method was followed using tryptamine **(5b)** (500 mg, 3.12 mmol), isovaleraldehyde **(6a)** (269 mg, 3.12 mmol), cyclohexylisocyanide **(7a)** (341 mg, 3.12 mmol), and azidotrimethylsilane **(8)** (360 mg, 3.12 mmol), producing 1009 mg (85%) of **4j** as a white solid; R_f = 0.61 Hex-AcOEt (3:1 V/V); m.p. 99-101°C; FT-IR (ATR) ν_{max} 3310, 3157, 1619, 1454, 1119, 1101 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.86 (d, 3H, *J* = 6.6 Hz, C*H*$_3$ of *i*-Bu), 0.92 (d, 3H, *J* = 6.6 Hz, C*H*$_3$ of *i*-Bu), 1.28-1.40 (m, 3H, C*H*$_2$ of Cy, C*H*-26), 1.41-1.49 (m, 2H, C*H*$_2$ of Cy), 1.55 (s, 1H, N*H*-13),1.62-1.71 (m, 2H, C*H*$_2$-25), 1.92-2.07 (m, 6H, C*H*$_2$ of Cy), 2.69-2.75 (m, 1H, C*H*$_2$-14), 2.80-2.86 (m, 1H, C*H*$_2$-14), 2.88-2.94 (m, 2H, C*H*$_2$-15), 4.25 (t, 1H, *J* = 7.4 Hz, C*H*-12), 4.60 (tt, 1H, *J* = 11.4, 3.6, Hz, C*H*-6), 7.00 (s, 1H, C*H*-17), 7.12 (t, 1H, *J* = 7.4 Hz, C*H*-22), 7.12 (t, 1H, *J* = 7.5 Hz, C*H*-23), 7.38 (d, 1H, *J* = 8.1 Hz, C*H*-21), 7.56 (d, 1H, *J* = 7.9 Hz, C*H*-24), 8.05 (s, 1H, N*H*-18); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 22.9, 23.1 (27, 28), 24.9 (9), 25.3 (26), 25.8, 25.9, 32.6, 34.0 (7, 8, 10, 11), 35.7 (15), 43.7 (25), 51.4 (14), 52.7 (12), 111.3 (16), 111.5 (24), 116.5 (21), 120.2, (22) 121.3 (23), 123.2 (17) 127.8 (20), 137.0 (19), 162.7 (5).

N-(2-(1H-indol-3-yl)ethyl)-1-(1-cyclohexyl-1H-tetrazol-5-yl)ethanamine **(4k).** The general method was followed using tryptamine **(5b)** (500 mg, 3.12 mmol), acetaldehyde **(6d)** (137 mg, 3.12 mmol), cyclohexylisocyanide **(7a)** (341 mg, 3.12 mmol), and azidotrimethylsilane **(8)** (360 mg, 3.12 mmol), producing 782 mg (74%) of **4k** as a white-yellow solid; R_f = 0.35 Hex-AcOEt (3:1 V/V); m.p. 102-104°C; FT-IR (ATR) ν_{max} 3392, 3182, 1617, 1455, 1434, 1146, 1117 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.28-1.39 (m, 4H, *CH*$_2$ of Cy), 1.50 (d,

2H, *J* = 6.8 Hz, CH_3-25), 1.77 (s, 1H, N*H*-13), 1.90-2.07 (m, 6H, CH_2 of Cy), 2.79 (m, 1H, CH_2-14), 2.88-3.01 (m, 3H, $CH_2$14, CH_2-15), 4.30 (q, 1H, *J* = 6.8 Hz, C*H*-12), 4.57 (tt, 1H, *J* = 11.1, 3.7 Hz, C*H*-6), 7.03 (d, 1H, *J* = 2.1 Hz, C*H*-17), 7.13 (t, 1H, *J* = 7.9 Hz, C*H*-22), 7.21 (t, 1H, *J* = 7.1 Hz, C*H*-23), 7.38 (d, 1H, *J* = 8.1 Hz, C*H*-24), 7.58 (d, 1H, *J* = 7.8 Hz, C*H*-21), 8.11 (s, 1H, N*H*-18); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 21.0 (25), 25.3 (9), 25.8 (8, 10), 26.2 (15), 33.5 (7, 11), 48.1 (14), 49.3 (12), 58.3 (6), 111.6 (24), 113.9 (16), 119.1 (21), 119.8 (22), 122.3 (17) 122.5 (23), 127.8 (20), 136.8 (19), 156.5 (5).

N-(benzo[d][1,3]dioxol-5-yl(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)-2-(1H-indol-3-yl)ethanamine **(4l)**. The general method was followed using tryptamine **(5b)** (350 mg, 2.18 mmol), 1,3-Benzodioxole-5-carbaldehyde **(6h)** (328 mg, 2.18 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (287 mg, 2.18 mmol), and azidotrimethylsilane **(8)** (252 mg, 2.18 mmol), producing 897 mg (88%) of **4l** as a yellow solid; R_f = 0.29 Hex-AcOEt (3:1 V/V); m.p. 70-72°C; FT-IR (ATR) ν_{max} 3409, 3311, 1608, 1501, 1483, 1242, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.30 (d, 3H, *J* = 1.8 Hz, CH_3 of Ph*Me*$_2$), 1.84 (d, 3H, *J* = 1.8 Hz, CH_3 of Ph*Me*$_2$), 2.23 (s, 1H, N*H*-11), 2.84-2.96 (m, 4H, CH_2-12, 13), 4.57 (d, 1H, *J* = 2.3 Hz, C*H*-10), 5.87 (dd, 1H, *J* = 2.6, 1.7 Hz, CH_2-2), 6.29 (dt, *1H*, *J* = 8.0, 2.0 Hz, C*H*-9), 6.53 (dd, 1H, *J* = 7.9, 2.5 Hz, C*H*-8), 6.57 (t, 1H, *J* = 1.8 Hz, C*H*-6), 6.99 (s, 1H, C*H*-15), 7.02-7.07 (m, 2H, C*H*-19, 22), 7.13-7.17 (m, 2H, C*H*-30, 32), 7.30-7.33 (m, 2H, C*H*-20, 21), 7.47 (d, 1H, *J* = 7.9 Hz, C*H*-31) , 8.31 (s, 1H, N*H*-16); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.7, 17.1 (34,35), 25.5 (13), 47.4 (12), 57.5 (10), 101.1 (2), 107.7 (6), 107.9 (8), 111.2 (20), 113.0 (14), 118.5 (31), 119.0 (19), 121.3 (9), 121.8 (30), 122.1 (15), 127.2 (18), 128.5 (31), 128.6 (19), 130.8 (21), 131.2 (28), 131.5 (7), 135.2 (17), 136.3, 136.6 (29, 33), 147.6, 147.9 (4, 5), 156.9 (23).

N-((1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)(phenyl)methyl)-2-(1H-indol-3-yl)ethanamine **(4m)**. The general method was followed using tryptamine **(5b)** (158 mg, 0.99 mmol), benzaldehyde **(6i)** (105 mg, 0.99 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (129 mg, 0.99 mmol), and azidotrimethylsilane **(8)** (114 mg, 0.99 mmol), producing 325 mg (78%) of **4m** as a white solid; R_f = 0.64 Hex-AcOEt (3:1 V/V); m.p. 91-93°C; FT-IR (ATR) ν_{max} 3180, 3056, 1618, 1456, 1340, 1105 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.15 (s, 3H, CH_3 of Ph*Me*$_2$), 1.84 (s, 3H, CH_3 of Ph*Me*$_2$), 2.35 (s, 1H, N*H*-13), 2.79-2.96 (m, 4H, CH_2-14, 15), 4.67 (s, 1H,C*H* 12), 6.92-7.04 (m, 5H, *CH*-17, 22, 28, 29, 32), 7.08-7.20 (m, 5H, C*H*- 8, 23, 10, 30, 31), 7.32 (dd, 2H, *J* = 7.6, 4.9 Hz, C*H*- 9, 24), 7.46 (d, 1H, *J* = 7.7 Hz, C*H*- 21), 8.37 (s, 1H, N*H*-18); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 16.7, 17.4 (25, 26), 25.8 (15), 47.8 (1CH_2 14), 58.2 (12), 111.4 (24), 113.2 (16), 118.8 (21), 119.3 (22), 122.0 (3), 122.3 (17), 127.4 (20), 127.8 (28, 32), 128.7 (30), 128.7 (9), 128.9 (29, 31), 131.1 (9), 131.6 (6), 135.3 (27), 136.5 (19), 137.07, 137.5 (7, 11), 157.1 (5).

N-((4-chlorophenyl)(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)methyl)-2-(1H-indol-3-yl)ethanamine **(4n)**. The general method was followed using tryptamine **(5b)** (500 mg, 3.12 mmol), 4-chlorobenzaldehyde **(6e)** (439 mg, 3.12 mmol), 4-methoxy-benzylisocyanide **(7b)** (459 mg, 3.12 mmol), and azidotrimethylsilane **(8)** (360 mg, 3.12 mmol), producing 1151 mg (78%) of **4n** as an amber solid; R_f = 0.47 Hex-AcOEt (3:1 V/V); m.p. 66-68°C; FT-IR (ATR) ν_{max} 3405, 3309, 1612, 1513, 1455, 1248 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 1H, N*H*-14), 2.78-2.89 (m, 2H, CH_2-16), 2.93 (t, 2H, *J* = 6.4 Hz, CH_2-15), 3.75 (s, 3H, CH_3-27), 5.05 (s, 1H, C*H*-13), 5.26 (s, 1H, CH_2-6), 6.73 (d, 2H, *J* = 7.3 Hz, C*H*-9, 11), 6.82 (d, 2H, *J* = 7.6 Hz, C*H*-8,12), 6.96 (s, 1H, C*H*-18), 7.03 (d, 2H, *J* = 7.6 Hz, C*H*-29, 33), 7.12 (t, 1H, *J* = 7.5 Hz, C*H*-23), 7.16-7.24 (m, 3H, C*H*-30, 32, 24), 7.36 (d, 1H, *J* = 81 Hz, C*H*-25), 7.52 (d, 1H, *J* = 7.9 Hz, C*H*-22), 8.58 (s, 1H, *NH*-19); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 25.1 (16), 48.0 (15), 51.0 (6), 55.8 (27), 55.3, (13), 111.9 (25), 113.5 (17), 114.7 (*9,11*), 119.1 (22), 119.7 (23), 122.5 (24), 122.8 (18), 125.6, (21) 127.7 (7), 129.2 (29, 33) 129.3 (8, 12), 129.48 (30, 32), 134.6 (31), 136.4 (28), 136.9 (20), 155.9 (5), 160.2 (10).

N-(2-(1H-indol-3-yl)ethyl)-1-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)-2-phenylethanamine **(4o)**. The general method was followed using tryptamine **(5b)** (183 mg, 1.14 mmol), 2-phenylacetaldehyde **(6j)** (137 mg, 1.14 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (150 mg, 1.14 mmol), and azidotrimethylsolane **(8)** (132 mg, 1.14 mmol), producing 349 mg (70%) of **4o** as a yellow solid; R_f = 0.50 Hex-AcOEt (3:1 V/V); m.p. 56-57°C; FT-IR (ATR) ν_{max} 3412, 3321, 1717, 1471, 1455, 1092 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3H, CH_3 of PhCH_3), 1.84 (s, 3H, CH_3 of PhCH_3), 2.73-2.82 (m, 2H, CH_2-15), 2.82-2.98 (m, 2H, CH_2-14), 3.15 (ddd, 2H, *J* = 19.8, 13.3, 7.2, Hz, CH_2-27), 3.79 (dd, 1H, *J* = 7.7, 6.6 Hz, C*H*-12), 6.79 (d, 1H, *J* = 2.3 Hz, C*H*-17), 6.92-6.97 (m, 2H, C-17), 7.04-7.14 (m, 5H, CH_{arom}), 7.14-7.22(m, 2H, CH_{arom}), 7.32 (t, 2H, *J* = 7.9 Hz, CH_{arom}), 7.46 (d, 1H, *J* = 7.9 Hz, CH_{arom}), 8.14 (s, 1H, N*H*-18); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.7, 17.5 (25, 26), 25.9 (15); 39.5 (27); 47.0 (14); 54.8 (12), 111.4, (24); 113.5 (16); 118.8 (21); 119.4, 122.1 (22, 23); 122.2 (17); 126.9, (31); 127.5 (16); 128.5, 128.6, 128.7, 128.8, 128.9, 129.6, 130.9 (8, 9, 10, 29, 30, 32, 33); 132.0 (6) 136.0 (19); 136.5,136.6 (7, 11), 137.3 (28), 157.3 (5).

N-((4-chlorophenyl)(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)-2-(4-methoxyphenyl)ethanamine **(4p)**: The general method was followed using 4-methoxyphenethylamine **(5c)** (500 mg, 3.31 mmol), 4-chlorobenzaldehyde **(6e)** (465 mg, 3.31 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (434 mg, 3.31 mmol), and azidotrimethylsilane **(8)** (381 mg, 3.31 mmol), producing 1422 mg (96%) of **4p** as a white solid; R_f = 0.46 Hex-AcOEt (3:1 V/V); m.p. 118-119°C; FT-IR (ATR) ν_{max} 3293, 1513, 1275, 1260, 1089, 1024 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (s, 3H, CH_3 of Ph*Me*$_2$), 1.90 (, 3H, CH_3 of Ph*Me*$_2$), 2.23 (s, 1H, N*H*-13), 2.67-2.81 (m, 4H, CH_2-14, 15), 3.77 (s, 3H, CH_3-31), 4.63 (s, 1H, C*H*-12), 6.78 (d, 2H, *J* = 8.2 Hz, C*H*-17, 21), 6.93 (d, 2H, *J* = 8.3 Hz, C*H*-25, 29), 7.02-7.08 (m, 3H, C*H*-8, 26, 28), 7.16-7.23 (m, 3H, C*H*-10, 17, 21), 7.37 (t, 1H, *J* = 7.6 Hz, C*H*-9); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 16.7, 17.3 (22, 23), 35.3 (31), 48.9 (15), 55.2 (14), 57.2 (12), 113.9 (17, 21), 128. 7, 128.8 (8, 10), 128.9 (17, 21), 129.1 (25, 29),

129.5 (26, 28), 131.0 (9), 131.3 (6), 131.5 (16), 134.4 (27), 135.3, 136.0 (7, 11), 136.6 (24), 156.5 (5), 158.28 (19).

1-(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)-N-(3-methoxyphenethyl)-2-methylpropan-1-amine **(4q)**: The general method was followed using 3-methoxyphenethylamine **(5d)** (350 mg, 2.31 mmol), isobutyraldehyde **(6b)** (167 mg, 2.31 mmol), 2,6-dimethylphenyl isocyanide **(7d)** (253 mg, 2.31 mmol), and azidotrimethylsilane **(8)** (304 mg, 2.31 mmol), producing 782 mg (89%) of **4q** as a yellow oil; R_f = 0.50 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3339, 1466, 1259, 1151, 1099, 1039 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.88 (dd, 3H, *J* = 20.8, 6.7 Hz, CH_3-25, 28), 1.63 (s, 1H, N*H*-13), 1.91, 1.93 (s, 3H, CH_3 of PhMe_2), 2.01-2.11 (m, 1H, C*H*-24), 2.64-2.74 (m, 3H, CH_2-14, 15), 2.82-2.89 (m, 1H, CH_2-14), 3.39 (d, 1H, *J* = 6.3 Hz, C*H*-12), 3.77 (s, 3H, CH_3-27), 6.70-6.74 (m, 3H, C*H*-17, 19, 21), 7.14-7.22 (m, 3H, C*H*-8, 10, 20), 7.37 (t, 1H, *J* = 7.6 Hz, C*H*-9); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 17.0 (25), 17.2, 17.3 (22, 23), 19.7 (28), 30.2 (24), 36.5 (14), 47.7 (15), 54.9 (27), 57.9 (12), 111.4, 114.2, 120.8 (17, 19, 21), 128.7 (8, 10), 129.1 (20), 130.6 (9), 131.8 (6), 135.4, 135.6 (7, 11), 141.0 (16), 156.9 (18), 159.5 (5).

N-((1-(tert-butyl)-1H-tetrazol-5-yl)methyl)-2-(3,4-dimethoxyphenyl)ethanamine **(4r)**: The general method was followed using homoveratrylamine **(5a)** (300 mg, 1.66 mmol), paraformaldehyde **(6k)** (50 mg, 1.66 mmol), *t*-butyl isocyanide **(7c)** (138 mg, 1.66 mmol), and azidotrimethylsilane **(8)** (191 mg, 1.66 mmol), was stirred overnight under inert atmosphere (N_2) at room temperature, producing 423 mg (80%) of **4r** as a yellow oil; R_f = 0.61 Hex-AcOEt (3:1 V/V); FT-IR (ATR) ν_{max} 3322, 1514, 1463, 1260, 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.17 (m, 1H, N*H*-9), 1.70 (s, 9H, CH_3 -7, 18, 19), 2.76-2.80 (m, 2H, CH_2-11), 2.89-2.95 (m, 2H, CH_2-10), 3.86 (t, 6H, *J* = 4.8 Hz, CH_3-21, 23), 4.15 (d, 2H, *J* = 4.5 Hz, CH_2-8), 6.71-6.75 (m, 2H, *CH*-13, 17), 6.77-6.81 (m, 1H, C*H*-16); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 29.2 (7, 18, 19), 35.5 (11), 44.0 (8), 50.4 (10), 55.7, 55.7 (21, 23), 61.1 (6), 111.4, 111.9 (13, 16), 120.4 (17), 131.9 (12), 147.4, 148,8 (14, 15), 152,7 (5).

Acknowledgements

Financial support from CONACYT (Project 166747 CB-2011-01) and post-doctoral (Dr. Alejandro Islas Jácome (CVU 176745, 290662_UG, 290735_UG) and doctoral (Luis Edilberto Cárdenas Galindo, CVU 225689, 209242) and (Carlos Jesús Cortes García, CVU 230777, 209054) fellowships are gratefully acknowledged.

References

1. García, G.; Rodríguez-Puyol, M.; Alajarín, R.; Serrano, I.; Sánchez-Alonso, P.; Griera, M.; Vaquero, J.; Rodríguez-Puyol, D.; Alvarez-Builla, J.; Díez-Marques, M. *J. Med. Chem.* **2009**, *52,* 7220-7227.
2. Herr, R. J. *Bioorg. Med. Chem.* **2002,** *10,* 3379-3393.
3. a) Chu, S. S. *Drugs Future* **1985**, *10*, 632-635; b) Cannon, J. R.; Eacho, P. I. *Biochem. J.* **1991**, *280*, 387-391.
4. Davulcu, A.; Mc Leod, D.; Li, J.; Katipally, K.; Littke, A.; Doubleday, W.; Xu, Z.; McConlogue, C.; Lai, C.; Gleeson, M.; Schwinden, M.; Parsons, R. *J. Org. Chem.* **2009**, *74*, 4068-4079.
5. Koldovskii, G. I.; Kharbash, R. B. *Russ. J. Org. Chem.* **2003**, *39*, 453-470.
6. a) *For review see:* Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240; b) Amantini, D.; Beleggia, R.; Fringelli, F.; Pizzo, F.; Vaccaro, F. *J. Org. Chem.* **2004**, *69*, 2896-2898; c) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945-7950; d) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2003**, *125*, 9983-9987; e) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984-7989. f) Keith, J. M. *J. Org. Chem.* **2006**, *71*, 9540-9543; g) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525-2527. h) Athanassopoulos, C. M.; Garnelis, T.; Vahliotis, D.; Papaioannou, D. *Org. Lett.* **2005**, *7*, 561-564; i) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 7413-7417; j) Shie, J.; Fang, J. *J. Org. Chem.* **2007**, *72*, 3141-3144.
7. Aldhoun, M.; Massi, A.; Dondoni, A. *J. Org. Chem.* **2008**, *73*, 9565-9575.
8. a) Hajra, S.; Sinha, D.; Bhowmick, M. *J. Org. Chem.* **2007**, *72*, 1852-1855; b) Borah, P.; Naidu, P. S.; Buhyan, P. J. *Tetrahedron Lett.* **2012**, *53*, 5034-5037; c) El Kaim, L.; Grimaud, L.; Patil, P. *Org. Lett.* **2011**, *13*, 1261-1263.
9. Nixey, T.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 6833-6835.
10. Kazemizadeh, A. R.; Hajaliakbari, N.; Hajian, R.; Shajari, N.; Ramazani, A. *Helv. Chim. Acta* **2012**, *95*, 594-597.
11. a) *For Review see:* El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153-2171; a) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681-3684; b) El Kaim, L.; Grimaud, L.; Purumandla, S. R. *Synlett*. **2012**, *23*, 295-297; c) Mayer, J.; Umkehrer, M.; Kalinski, C.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2005**, *46*, 7393-7396; (d) Dömling, A.; Beck, B.; Magnin-Lachaux, M. *Tetrahedron Lett.* **2006**, *47*, 4289-4291.
12. Achatz, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6360-6362.
13. Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett*. **2008**, *49*, 149-152.
14. a) Gunawan, S.; Nichol, G.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1664-1667; b) Gunawan, S.; Ayaz, M.; Moliner, F. D.; Frett, B.; Kaiser, C.; Patrick, N.; Xu, X.; Hulme, C. *Tetrahedron Lett.* **2012**, *68*, 5606-5611; c) Gunawan, S.; Keck, K.; Laetsch, A.; Hulme, C. *Mol. Divers.* **2012**, *16*, 601-606.
15. a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210; b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133-1144; (c) Ramón, D, J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634; d) Pan, S. C.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3622-3625.
16. Umkehrer, M.; Kolb, J.; Burdack, C.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2004**, *45*, 6421-6424.
17. Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett.* **2000**, *41*, 8729-8733.
18. Kalinski, C.; Umkehrer, M.; Gonnard, S.; Jager, N.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 2041-2044.
19. Bienaymé, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735-2738.
20. a) Schaffer, E, S.; Höfner, G.; Wanner, K. T. *Bioorg. Med. Chem.* **2011**, *19*, 6492-6504; b) Gunawan, S.; Petit, J.; Hulme, C. *Comb. Sci.* **2012**, *14*, 160-163; c) *Ref. 13.*
21. *See refs. 8a, 10, 11a and 12 for 1,5 dipolar electrocyclization*.