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Visible Light Photoredox-Catalyzed Coupling Reaction of Azoles with α-Carbamoylsulfides

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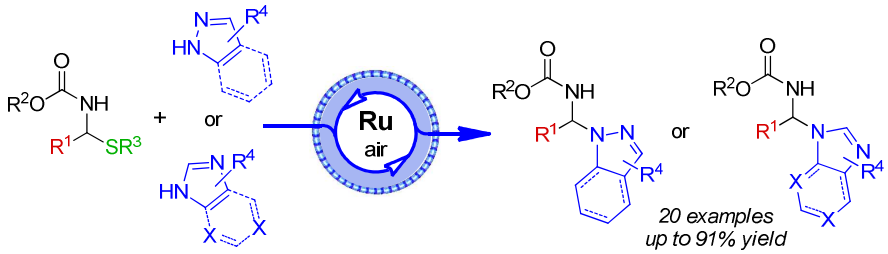
ABSTRACT

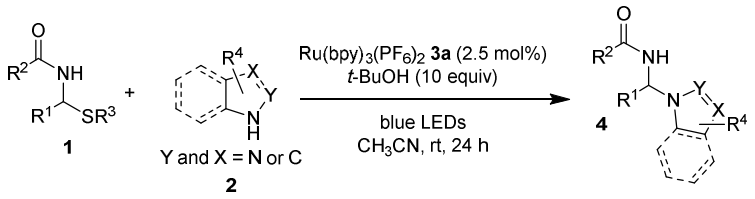


A simple straightforward strategy for the synthesis of *N*-substituted azoles is reported, which involves visible light photoredox-catalyzed coupling reaction of azoles with *α*-carbamoylsulfides. A variety of heterocyclic units, including pyrazoles, benzopyrazoles, benzoimidazoles and purines can be efficiently incorporated under mild reaction conditions in respectable yields.

INTRODUCTION

The five-membered heterocycles containing nitrogen has attracted significant interest in organic and medicinal chemistry over the past several decades. Scaffolds containing a pyrazole[1] or imidazole[2] are

found in a number of pharmaceutically and biologically active important molecules. Therefore, the development of efficient synthetic methods of these heterocycles is highly demanded. Among various methods available,[3-6] the incorporation of these valuables azoles into a α position of amines is certainly one of the most simple and direct approach. However, despite a wide variety of easily available five-membered heterocycles, such strategies have been mentioned in literature only briefly.[7] Recently, we have reported an efficient visible-light photoredox[8] catalyzed addition of various aryl and heteroaryl to α-amidosulfides[9a-e] as *N*-carbamoylimine precursors[9] leading to the rapid generation of a range of functionalized *N*-protected aryl or heteroarylamines.[10,11] In line of this work,[10,12] we envisioned that this method could be utilized to incorporate a wide range of aromatic 5-membered azacyclic units. This would lead to the formation of 2-aminomethyl-azoles which are present in various bioactive molecules.[13] We report herein an efficient visible-light photoredox catalyzed *N*-alkylation of azoles and fused azoles **2** into α-amidosulfides **1** leading to the rapid and efficient generation of a range of functionalized 2-aminomethyl-azoles **4** (Scheme 1).



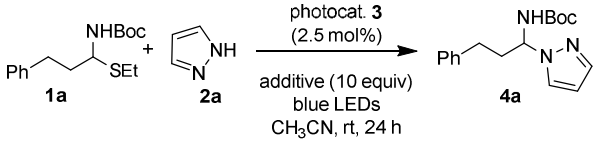
Scheme 1. Photoredox-Catalyzed Synthesis of N-Alkyl-Substituted azoles

RESULTS AND DISCUSSION

We have already reported that the reaction of pyrazole (**2a**) and *tert*-butyl-(1-(ethylthio)-3-phenylpropyl)carbamate (**1a**) in the presence of 2.5 mol % $Ru(bpy)_3(PF_6)_2$ photocatalyst **4a** under visible light irradiation (5W blue LEDs) in dichloromethane/t-BuOH (8:2, v/v) at room temperature yielded the desired product **4a** in 70% yield after 24 h.[10] Although in the previous article, mainly electron rich aromatic were examined, due to our interest in oxidative activation of C-S bond adjacent to

a nitrogen,[9c,10] we re-examined the photoredox *N*-alkylation reaction to expand their synthetic utility and gain additional insight into this visible-light photredox process. Performance of the other photoredox-catalyst, such as $Ru(bpy)_3Cl_2$, $Ru(bpz)_3Cl$ and eosin (Table 1 entries 2-4),[14] was inferior to that of $Ru(bpy)_3(PF_6)_2$. Yields were lower in the absence of *t*-BuOH (entry 7) or with hexafluoroisopropanol or EtOH as the co-solvent (entries 8 and 9).[15] As already observed by us the concentration of **1a** in the reaction is very important, the use of 0.5 M in MeCN being the best concentration for a good yield. Any change in this concentration led to a drop of the yield (entries 5 and 6 *vs*. 1). The reaction did not proceed at all in strict oxygen-free conditions (entry 10). In contrast, the yield of the product was increased to 88% (entry 11) when the reaction was carried out in presence of air (open to air, without bubbling air). Moreover, no reaction proceeds in anaerobic condition, only starting material was revovered (entry 16). These results indicated that the ruthenium complex undergoes oxidative quenching of its excited state with oxygen to give the strongly oxidizing $Ru(bpy)_3^{3+}$.[8] Other oxidative quenchers such as $BrCCl_3$[11] and methyl viologen were evaluated (entries 12 and 13) the conclusion was that the oxygen is superior to others.

Table 1. Optimization of Reaction Conditions for the Synthesis of α-Carbamoylpyrazoles.[a]



entry	**3**	additive	yield (%)[b]
1	$Ru(bpy)_3(PF_6)_2$ (**3a**)	*t*-BuOH	70
2	$Ru(bpy)_3Cl_2$ (**3b**)	*t*-BuOH	28
3	$Ru(bpz)_3Cl_2$ (**3c**)	*t*-BuOH	28
4	Eosin Y (**3d**)	*t*-BuOH	41[c]
5	**3a**	*t*-BuOH	45[d]
6	**3a**	*t*-BuOH	50[e]
7	**3a**		28[e]

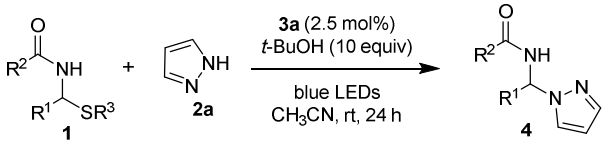
8	**3a**	HFIP	50
9	**3a**	EtOH	trace[f]
10	**3a**	*t*-BuOH	trace[g]
11	**3a**	*t*-BuOH	88[h]
12	**3a**	*t*-BuOH	19[i]
13	**3a**	*t*-BuOH	19[j]
14		*t*-BuOH	0[k]
15	**3a**	*t*-BuOH	0[k,l]
16	**3a**	*t*-BuOH	0[m]

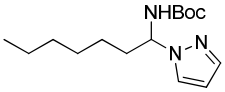
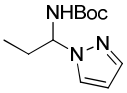
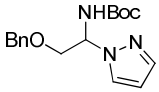
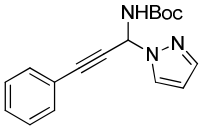
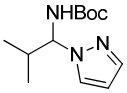
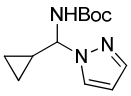
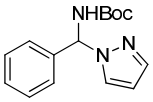
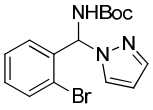
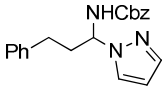
[a]General conditions: **1** (0.10 mmol), pyrazole **2a** (0.15 mmol), **3** (0.025 equiv), additive (10 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields referred to chromatographically pure product. [c]Irradiated with green LEDs. [d] MeCN (1 mL). [e] MeCN (2 mL). [f] α-carbamoylether was isolated as major product. [g] Oxygen-free conditions. [h] With air. [i]$BrCCl_3$ (0.025 mmol) was used as oxidative quencher. [j]Methyl viologen (0.025 mmol) was used as oxidative quencher. [k]Starting material was recovered. [l]Without any irradiation. [m]Under free oxygen.

Then, with the optimized reaction conditions in hand, we examined the scope and limitations of the photoredox-catalyzed *N*-alkylation reaction. As shown in Table 2, various α-carbamoylsulfides **1** were explored by using pyrazole (**2a**) as the reactant. The yields of *N*-alkylated products **4** resulting from aliphatic α-carbamoylsulfides **1** were generally moderate to excellent. The photocatalytic system also proved to be efficient for various linear aliphatic α-carbamoylsulfides **1b-1d** leading to the coupling products (**4b-4d**, entries 1-3) in good to excellent yields. We were pleased to find that the presence of functional groups such as benzyl ether (**4d,** entry 3) and alkyne (**4e**, entry 4)[16] was tolerated. The reaction between α-carbamoylsulfides derived from β-branched aldehydes **1f** and **1g** with pyrazole **2a** under the same conditions afforded moderate to good yields of corresponding *N*-alkylated products **4f** and **4g** (entries 5-6). The replacement of the Boc group **1a** with a Cbz group **1i** has no influence on the efficiency of the amidoalkylation (entry 9). In addition, the catalytic process can be applied to an aromatic α-amidosulfide such as **1h**, although the yield was slightly lower (entry 7). However, when the reaction was carried out with 5 mol% of $Ru(bpy)_3(PF_6)_2$ **3a** under otherwise identical conditions, the

expected *N*-alkylated products **4h** and **4i** were isolated in better yields (entries 7 and 8).

Table 2. Reactions of Various α-Carbamoylsulfides **1** with Pyrazole **2a**.[a]



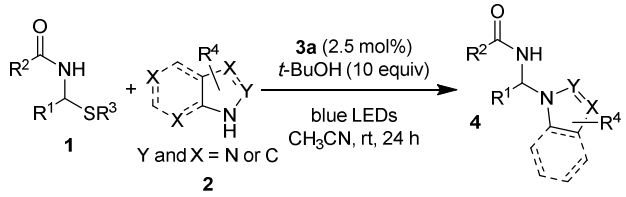
entry	R^1	Product	**4**	yield (%)[b]
1	C_6H_{13}		**4b**	87
2	C_2H_5		**4c**	61
3	C_8H_9O		**4d**	58
4	C_8H_5		**4e**	47[c]
5	C_3H_7		**4f**	75
6	C_3H_5		**4g**	41
7	C_6H_5		**4h**	45(60)[c]
8	C_6H_5		**4i**	66[c]
9	C_8H_9		**4j**	85

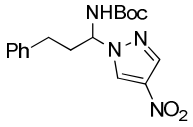
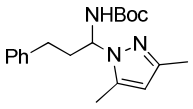
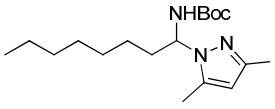
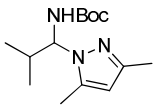
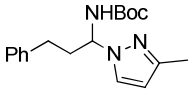
[a] Reaction conditions: **1** (0.10 mmol), pyrazole **2a** (0.15 mmol), **3a** (0.025 equiv), *t*-BuOH (10.0 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields referred to chromatographically pure product. [c]With 5 mol% of **3a**.

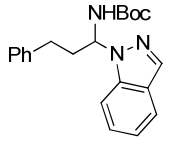
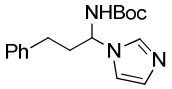
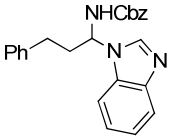
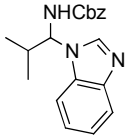
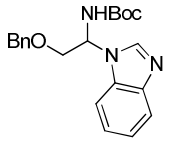
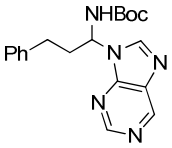
We next examined the coupling reaction of several azoles as well as fused azoles **2**. As shown in

Table 3, the presence of an electron-donating group and an electron-withdrawing group on the pyrazole ring **2b-2d** were found to be suitable substrates giving the corresponding *N*-alkyalted products **4k-4o** (entries 1-5) in good yields. Interestingly, when the 3-methylpyrazole **2d** was employed, the photocatalyzed *N*-alkylation reaction led only to the formation of the less congested regioisomer **4o** (entry 5). Similarly, the reaction of aryl-fused pyrazoles such as benzopyrazole **2e** went very smoothly affording **4p** in excellent yield (91% yield, entry 6). Unsubstituted imidazole **2f** provided the corresponding coupling adducts **4q** in a low yield, even with 5 mol% of **3a** (entries 7). On the other hand, when the benzoimidazole **2h** was the nucleophile in the reaction, *N*-alkylated products (**4r-4t**) were isolated in much better yields (entries 8-10). Most remarkably, the coupling reaction worked well with purine to afford an efficient access to azacyclic purine aza-nucleosides **4u** (entry 11).[7a]

Table 3. Reactions of α-Carbamoylsulfides **1** with Various Azoles **2**.[a]



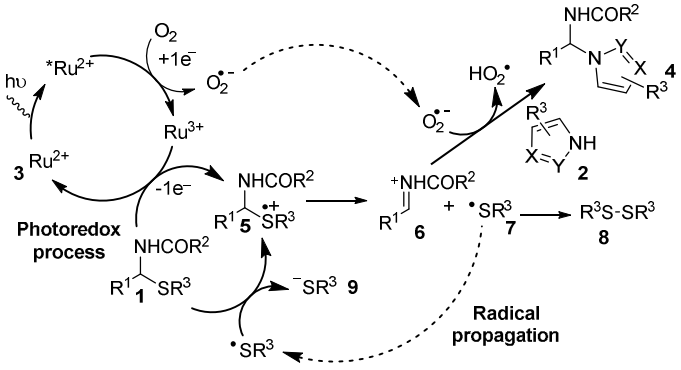
entry	R^1	Product	**4**	yield (%)[b]
1	C_8H_9		**4k**	66
2	C_8H_9		**4l**	79
3	C_7H_{15}		**4m**	59
4	C_8H_9		**4n**	75
5	C_3H_7		**4o**	86

6	C_8H_9		**4p**	91
7	C_8H_9		**4q**	21[c]
8	C_8H_9		**4r**	79
9	C_3H_7		**4s**	67
10	C_8H_9O		**4t**	74
11	C_8H_9		**4u**	81

[a] Reaction conditions: **1** (0.10 mmol), pyrazole **2a** (0.15 mmol), **3a** (0.025 equiv), *t*-BuOH (10.0 equiv) in MeCN (0.5 mL) irradiated at rt for 24 h. [b]Yields referred to chromatographically pure product. [c]With 5 mol% of **3a**.

The following control experiments were conducted to gain some mechanistic insight. No reaction took place in the absence of light and/or photocatalyst. Moreover, the formation of **4** was inhibited in the presence of radical scavengers such as TEMPO and galvinoxyl suggesting that a radical/cationic process is involved in this reaction. On the basis of the above results as well as other reports, a plausible reaction mechanism is shown in Scheme 5. Based on the literature[8,17,18] and our previous study, [10] we propose a plausible catalytic cycle for the present *N*-alkylation reaction as depicted in Scheme 2. First, Ru^{2+} is excited to $^*Ru^{2+}$ under blue Leds irradiation. Then, this excited state undergoes an oxidative quenching with oxygen molecule to give Ru^{3+} and superoxide radical anion ($O_2^{\bullet-}$). This strong oxidant Ru^{3+} is prone to activate α-carbamoylsulfides **1** through an additional single-electron oxidation step

causing the generation of radical cation **5,** and regenerating the ground-state Ru^{2+} **3**. The resulting radical cation **5** may undergo a fragmentation to cleave the labile N-S bond and give the *N*-carbamoyl iminium **6** as well as thiyl radical **7** Unfortunately, all attempts to prove the formation of this radical was unsuccessful.[19] In parallel, the thiyl radical **7** is then proposed to dimerize to form disulfide **8**. A small amount of disulfide was isolated from this reaction, confirming our assumption.[10] However, an alternative pathway involving the conversion of α-carbamoylsulfides **1** into radical cation **5** by radical chain propagation cannot be excluded at the current stage.[8,20] Indeed, when we irradiated **1a** in presence of **2a** with blue LEDs for 1 h, the corresponding **6a** was isolated in 26 % yield. While an increase in yield (41 %) was obtained when **1a** was stirred under dark conditions for 23 h after 1 h irradiation (see the supporting information). According to these experiments, the both mechanisms may proceed simultaneously.



Scheme 2. Plausible reaction mechanism

CONCLUSION

In summary, we have developed an efficient photoredox-catalyzed coupling strategy for the construction of *N*-substituted azoles from readily available α-amidosulfides. This protocol features mild conditions, a relatively broad scope, and high atom-economy in generating an array of 2-aminomethyl-azoles with high efficiency. Further investigations are underway to probe the mechanism and to extend the scope of the *N*-alkylation.

EXPERIMENTAL SECTION

Materials and General methods. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. NMR spectra (^{1}H, ^{13}C) were recorded with 500 and 300 MHz spectrometers. Flash column chromatography was carried out using 40-63 μm particle sized silica gel. Preparative thin layer chromatography (prep TLC) was performed using silica gel 60 F254 plates. Visualization was accomplished by irradiation with a UV light at 254 nm. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode. Infrared spectra were taken using solids or neat oils on a diamond surface, and the results are given in cm^{-1}. All reactions were carried out under argon atmosphere in oven dried glassware with magnetic stirring. Reagents were obtained from commercial supplier and used without further purification unless otherwise noted. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Visible light irradiations were performed with a Flexled INSPIRE LED lamp (3.6 W; λ = 465 nm). $Ru(bpy)_3(PF_6)_2$ was purchased from Sigma Aldrich. All other commercially available reagents and solvents were used without further purification. The α-amidosulfides **1** were prepared according to literature procedure.[7b,c]

General Procedure: A flame-dried test tube, flushed with Air, was charged with the corresponding α-amidosulfide **1** (0.1 mmol, 1.0 equiv) and dissolved in MeCN (0.5 mL) and *t*-BuOH (0.1 mL, 10 equiv). $Ru(bpy)_3(PF_6)_2$ **3a** (2.2 mg, 2.50 mol%) then the corresponding azole **2** (0.15 mmol, 1.50 equiv) was then added. The resultant reaction mixture was irradiated with blue LEDs during 24 h. Then, the reaction mixture was directly purified by flash chromatography on silica gel (*n*-Heptane/EtOAc) to afford the corresponding pure compound **4a-4u**.

***Tert*-Butyl (3-phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (4a).**[10] Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC:

heptane/ethyl acetate 7/3, to afford 26.6 mg of a colourless solid, 88% yield. MP**:** 86–97°C. IR (cm^{-1}): 3249, 2973, 1698, 1529, 1446, 1407, 1366, 1294, 1239, 1148, 1095, 1047, 1010, 990, 958, 863, 804, 761, 698. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.63 (s, 1H), 7.57 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.26 (s, 1H), 5.84 (d, *J* = 9.2 Hz, 1H), 5.77 (m, 1H), 2.54-2.51 (m, 3H), 2.43-2.36 (m, 1H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 140.3, 140.2, 130.0, 128.6 (× 2), 128.5 (× 2), 126.3, 104.9, 80.3, 66.4, 36.0, 31.5, 28.3 (× 3). HRMS (ESI TOF): m/z = 324.1702 $[M+Na]^+$, $C_{17}H_{23}N_3O_2Na$ requires 324.1688.

***Tert*-Butyl (1-(1H-pyrazol-1-yl)heptyl)carbamate (4b)**. Reaction on 32 mg (0.092 mmol) of tert-butyl (1-(phenylthio)heptyl)carbamate **(1b)**. Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 7/3, to afford 24.3 mg of a colourless solid, 87% yield. MP: 60–61°C. IR (cm^{-1}): 3213, 2930, 1702, 1537, 1448, 1404, 1390, 1363, 1299, 1280, 1248, 1158, 1088, 1046, 1000, 869, 760, 747, 686. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.48 (s, 2H), 6.13 (s, 1H), 5.72 (br s, 1H), 5.52 (br s, 1H), 2.12 (br s, 1H), 1.98 (br s, 1H), 1.33 (s, 9H), 1.28-1.08 (m, 8H), 0.78 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 140.0, 129.6, 104.7, 80.2, 67.2, 34.7, 31.6, 28.6, 28.3 (× 3), 25.3, 22.5, 14.0. HRMS (ESI TOF): m/z = 304.2004 $[M+Na]^+$, $C_{15}H_{27}N_3O_2Na$ requires 304.2001.

***Tert*-Butyl (1-(1H-pyrazol-1-yl)propyl)carbamate (4c)**. Reaction on 21.9 mg (0.099 mmol) of tert-butyl (2-methyl-1-(phenylthio)propyl)carbamate **(1c)**. Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 9/1, to afford 13.8 mg of a colourless solid, 61% yield. MP: 75–76°C. IR (cm^{-1}): 3208, 2973, 1714, 1699, 1543, 1366, 1302, 1288, 1247, 1163, 1097, 1042, 1004, 827, 764, 742. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.58 (s, 2H), 6.23 (s, 1H), 5.74–5.66 (m, 2H), 2.23–1.99 (m, 2H), 1.42 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 140.0, 129.7, 104.7, 80.2, 68.5, 28.2 (× 3), 28.0, 9.8. HRMS (ESI TOF): m/z = 226.1552 $[M+H]^+$, $C_{11}H_{20}N_3O_2$ requires 226.1556.

***Tert*-Butyl (2-(benzyloxy)-1-(1H-pyrazol-1-yl)ethyl)carbamate (4d)**. Reaction on 31.1 mg (0.099 mmol) of tert-butyl (2-(benzyloxy)-1-(ethylthio)ethyl)carbamate (**1d)**. Eluent for the preparative TLC:

heptane/ethyl acetate 7/3, to afford 18.5 mg of a colourless solid, 58% yield. MP: 83–84°C. IR (cm^{-1}): 3219, 2969, 2931, 2891, 1698, 1525, 1369, 1308, 1241, 1155, 1134, 1087, 1042, 1027, 957, 757, 737, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.64 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.39–7.28 (m, 3H), 7.26–7.24 (m, 2H), 6.29 (t, J = 2.0 Hz, 1H), 6.02 (m, 1H), 5.86 (d br, J = 8.5 Hz, 1H), 4.48 (s, 2H), 4.00–3.89 (m, 2H), 1.45 (s, 9H) . ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.6, 140.0, 137.4, 129.2, 128.5 (× 2), 127.9, 127.7 (× 2), 105.2, 80.6, 73.4, 70.5, 66.3, 28.2 (× 3). HRMS (ESI TOF): m/z = 318.1804 $[M+H]^+$, $C_{17}H_{24}N_3O_3$ requires 318.1818

***Tert*-Butyl (2-(benzyloxy)-1-(1H-pyrazol-1-yl)ethyl)carbamate (4e)**. Reaction on 29.1 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylprop-2-yn-1-yl)carbamate (**1e**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3, to afford 14 mg of white foam, 47% yield. IR (cm^{-1}): 3241, 2978, 2240, 1705, 1512, 1492, 1444, 1394, 1368, 1324, 1247, 1155, 1085, 1046, 1027, 1009, 994, 966, 918, 862, 804, 756, 691. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.70 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.47–7.42 (m, 2H), 7.34-7.27 (m, 3H), 6.85 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 1.8 Hz, 1H), 5.94 (d , J = 9.2 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 140.9, 132.2 (x 2), 129.4, 128.7, 128.5 (x 2), 121.3, 106.1 (x 2), 86.0, 82.6, 59.2, 29.9, 28.2 (x 3). HRMS (ESI TOF): m/z = 320.1381 $[M+Na]^+$, $C_{17}H_{19}N_3O_2Na$ requires 320.1375. m/z = 126.1552 $[M+H]^+$, $C_{12}H_{20}N_3O_2$ requires 126.1556

***Tert*-Butyl (2-methyl-1-(1H-pyrazol-1-yl)propyl)carbamate (4f)**. Reaction on 22.1 mg (0.099 mmol) of tert-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 7/3, to afford 13.7 mg of a colourless solid, 57% yield. MP: 116-117°C. IR (cm^{-1}): 3223, 2974, 1703, 1537, 1392, 1366, 1300, 1248, 1157, 1088, 1041, 1017, 939, 876, 853, 810, 754, 701. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.55 (s, 1H), 7.51 (s, 1H), 6.21 (s, 1H), 5.52 (d, J = 7.7 Hz, 1H), 5.37 (t, J = 9.0 Hz, 1H), 2.38 (h, J = 6.5 Hz, 1H), 1.40 (s, 9H), 1.06 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.2, 140.0, 130.0, 104.4, 80.1, 72.8, 33.1, 28.2 (× 3), 18.8, 18.6. HRMS (ESI TOF): m/z = 240.1715 $[M+H]^+$, $C_{12}H_{22}N_3O_2$ requires 240.1712 and m/z = 262.1534 $[M+Na]^+$, $C_{12}H_{21}N_3O_2Na$ requires 262.1531

***Tert*-butyl (cyclopropyl(1H-pyrazol-1-yl)methyl)carbamate (4g)**. Reaction on 21.3 mg (0.099 mmol) of tert-butyl (cyclopropyl(ethylthio)methyl)carbamate **(1g)**. Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 9/1, to afford 9.8 mg of a colourless solid, 41% yield. MP: 85-86°C. IR (cm^{-1}): 3343, 3006, 2932, 1690, 1528, 1309, 1251, 1235, 1152, 1021, 758. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.59 (s, 1H), 7.56 (s, 1H), 6.25 (t, J = 2.0 Hz, 3H), 5.75 (m, 1H), 5.20 (t, J = 8.5 Hz, 1H), 1.64 (m, 1H), 1.43 (s, 9H), 0.75–0.35 (m, 2H) . ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.9, 139.8, 128.8, 104.9, 80.4, 71.0, 28.3 (× 3), 15.9, 3.5 (× 2). HRMS (ESI TOF): m/z = 260.1373 $[M+Na]^+$, $C_{12}H_{19}N_3O_2Na$ requires 260.1375.

***Tert*-Butyl (phenyl(1H-pyrazol-1-yl)methyl)carbamate (4h).** Reaction on 26.7 mg (0.099 mmol) of tert-butyl ((ethylthio)(phenyl)methyl)carbamate **(1h)**. Eluent for the preparative TLC: heptane/ethyl acetate 7/3, to afford 16.3 mg of a colourless solid, 60% yield. MP: 125-126°C. IR (cm^{-1}): 3251, 2968, 1702, 1530, 1390, 1365, 1329, 1269, 1242, 1176, 1154, 1046, 1009, 918, 868, 817, 765. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.67 (s br, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.40-7.33 (m, 3H), 7.20-7.18 (m, 2H), 7.15 (d br, J = 8.7 Hz, 1H), 6.33 (t, J = 2.0 Hz, 1H), 6.03 (d br, J = 8.6 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.6, 140.4, 138.2, 129.4, 128.8 (× 2), 128.7, 126.2 (× 2), 105.4, 80.8, 69.2, 28.3 (× 3). HRMS (ESI TOF): m/z = 296.1362 $[M+Na]^+$, $C_{15}H_{19}N_3O_2Na$ requires 296.1375.

***tert*-butyl ((2-bromophenyl)(1H-pyrazol-1-yl)methyl)carbamate (4i)**. Reaction on 34.6 mg (0.100 mmol) of tert-butyl ((2-bromophenyl)(ethylthio)methyl)carbamate (**1i)**. Eluent for the preparative TLC: heptane/ethyl acetate 2/8, to afford 23.2 mg of a white foam, 66% yield. **IR** (cm^{-1}): 2926, 1702, 1509, 1367, 1248, 1153, 1027, 754. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.73-7.66 (m, 1H), 7.64-7.55 (m, 1H), 7.36-7.26 (m, 2H), 7.24-7.15 (m, 2H), 6.34-6.26 (m, 1H), 5.91-5.64 (m, 1H), 3.85 (s, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 140.6, 137.4, 133.5, 130.4, 128.1, 128.0, 125.0, 112.4, 111.8, 105.7, 102.4, 56.0, 28.3 (x 3). HRMS (ESI TOF): m/z = 374.0470 $[M+Na]^+$, $C_{15}H_{18}BrN_3O_2Na$ requires 374.0480.

Benzyl (3-phenyl-1-(1H-pyrazol-1-yl)propyl)carbamate (4j). Reaction on 33 mg (0.100 mmol) of

benzyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1j**). Eluent for the preparative TLC: heptane/ethyl acetate 7/3, to afford 28.6 mg of a colourless oil, 85% yield. IR (cm^{-1}): 3302, 3029, 1703, 1529, 1497, 1231, 1043, 1029, 748, 696. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.65 (s, 1H), 7.60 (s, 1H), 7.40–7.20 (m, 8H), 7.14–7.11 (m, 2H), 6.41 (d br, J = 9.2 Hz, 1H), 6.28 (s, 1H), 5.81 (t, J = 8.1 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 5.00 (d, J = 12.3 Hz, 1H), 2.63–2.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.5, 140.4, 140.1, 136.0, 130.1, 128.6 (× 2), 128.5 (× 2), 128.4 (× 2), 128.2, 128.1, 126.3, 126.1, 105.0, 67.1, 66.8, 35.8, 31.4. HRMS (ESI TOF): m/z = 336.1703 $[M+H]^+$, $C_{20}H_{22}N_3O_2$ requires 336.1712.

***Tert*-Butyl (1-(4-nitro-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (4k)**. Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: heptane/ethyl acetate 6/4, to afford 22.9 mg of a colourless solid, 66% yield. MP: 140–141°C. IR (cm^{-1}): 3333, 3142, 2980, 1689, 1524, 1512, 1315, 1289, 1274, 1154, 861, 817, 752, 705. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.29 (s br, 1H), 8.15 (s, 1H), 7.36-7.23 (m, 3H), 7.16-7.13 (m, 2H), 5.73-5.57 (m, 2H), 2.67-2.32 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.3, 139.3, 136.4, 135.3, 128.8 (× 2), 128.3 (× 2), 126.7 (x 2), 81.4, 68.2, 35.1, 31.3, 28.2 (× 3). HRMS (ESI TOF): m/z = 381.1337 $[M+Cl]^-$, $C_{17}H_{22}N_4O_4Cl$ requires 381.1330.

***Tert*-Butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (4l)**. Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: heptane/ethyl acetate 6/4, to afford 26.1 mg of a colourless solid, 79% yield. MP: 121–122°C. IR (cm^{-1}): 3187, 2981, 1703, 1538, 1454, 1273, 1243, 1156, 1054, 1031, 779, 767, 717, 694. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32–7.13 (m, 5H), 6.10 (d br, J = 9.2 Hz, 1H), 5.77 (s, 1H), 5.70 (m, 1H), 2.52–2.33 (m, 4H), 2.27 (s, 3H), 2.24 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 148.4, 140.7, 139.6, 128.5 (× 2), 128.4 (× 2), 126.1, 104.7, 79.0, 62.2, 36.4, 31.5, 28.3 (× 3), 13.7, 10.7. HRMS (ESI TOF): m/z = 330.2169 $[M+H]^+$, $C_{19}H_{28}N_3O_2$ requires 330.2182.

***Tert*-Butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)octyl)carbamate (4m)**. Reaction on 28.9 mg (0.099

mmol) of tert-butyl (1-(phenylthio)octyl)carbamate **(1k)**. Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 7/3, to afford 29 mg of oil, 59% yield. IR (cm^{-1}): 3190, 2927, 2857, 1705, 1556, 1459, 1365, 1350, 1290, 1273, 1246, 1178, 1048, 1001, 873, 780, 753. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.74 (s, 1H), 5.71-5.59 (m, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 2.16-1.88 (m, 2H), 1.41 (s, 9H), 1.34-0.99 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 148.2, 134.4, 104.4, 79.8, 62.8, 35.3, 31.6, 29.0, 28.7, 28.2 (x3), 25.2, 22.5, 13.9, 13.6, 10.7. HRMS (ESI TOF): m/z = 324.2646 $[M+H]^+$, $C_{18}H_{34}N_3O_2$ requires 324.2651.

***Tert*-butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-methylpropyl)carbamate (4n)**. Reaction on 22.1 mg (0.099 mmol) of tert-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 7/3, to afford 20.1 mg of a white foam, 75% yield. IR (cm^{-1}): 3196, 2977, 1699, 1539, 1475, 1459, 1390, 1362, 1294, 1247, 1166, 1041, 1010, 950, 881, 858, 845, 779, 738. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.73 (s, 1H), 5.70 (s, 1H), 5.27 (t, *J* = 9.9 Hz, 1H), 2.42-2.26 (m, 4H), 2.22 (s, 3H), 1.40 (s, 9H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.3, 148.3, 139.8, 104.4, 79.9, 68.6, 33.9, 28.4 (x3), 19.2, 18.7, 13.8, 11.0. HRMS (ESI TOF): m/z = 268.2031 $[M+H]^+$, $C_{14}H_{26}N_3O_2$ requires 268.2025.

***Tert*-Butyl (1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-phenylpropyl)carbamate (4o)**. Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: heptane/ethyl acetate 6/4, to afford 27.2 mg of a white foam, 86% yield. IR (cm^{-1}): 3214, 3028, 2977, 2931, 1709, 1521, 1497, 1454, 1391, 1366, 1327, 1292, 1272, 1245, 1162, 1048, 1028, 998, 911, 868, 752, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.47-7.40 (m, 1H), 7.28-7.24 (m, 2H), 7.20-7.15 (m, 1H), 7.12-7.09 (m, 2H), 5.98-5.96 (m, 1H), 5.82-5.75 (m, 1H), 5.63-5.56 (m, 1H), 2.56-2.40 (m, 3H), 2.29 (s, 3H), 2.25 (m, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 149.5, 139.5, 130.9, 128.6 (x 2), 128.5, 126.3, 104.9, 104.5, 66.3, 62.5, 36.1, 31.6, 28.4 (x3), 13.9, 10.8. HRMS (ESI TOF): m/z = 316.2018 $[M+H]^+$, $C_{18}H_{26}N_3O_2$ requires 316.2025.

***Tert*-Butyl (1-(1H-indazol-1-yl)-3-phenylpropyl)carbamate (4p)**. Reaction on 50 mg (0.10 mmol) of

tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: heptane/ethyl acetate 7/3, to afford 32 mg of a colourless solid, 91% yield. MP: 129–130°C. IR (cm^{-1}): 3194, 3027, 2972, 1710, 1544, 1366, 1287, 1263, 1250, 1156, 1121, 1045, 1028, 1010, 911, 853, 790, 761, 734, 702, 657. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (s br, 1H), 7.79 (dd, J = 8.8 and 0.9 Hz, 1H), 7.72 (dt, J = 8.4 and 1.0 Hz, 1H), 7.38–7.20 (m, 4H), 7.16–7.11 (m, 3H), 6.49 (d br, J = 9.0 Hz, 1H), 6.07 (m, 1H), 2.72–2.48 (m, 4H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6, 141.3, 139.5, 132.5, 128.7 (× 2), 128.4 (× 2), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0, 31.7, 28.2 (× 3). HRMS (ESI TOF): m/z = 352.2014 $[M+H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

***Tert*-Butyl (1-(1H-imidazol-1-yl)-3-phenylpropyl)carbamate (4q).** Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: pure ethyl acetate, to afford 6.3 mg of a colourless solid, 21% yield. MP: 158–159°C. IR (cm^{-1}): 3181, 2972, 2936, 1702, 1284, 1254, 1218, 1159, 1073, 1047, 1025, 768, 755, 739, 701, 660. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.63 (s br, 1H), 7.26 7.12 (m, 3H), 7.06 6.96 (m, 4H), 5.68 (br s, 1H), 5.35 (br s, 1H), 2.56 (t, J = 7.6 Hz, 2H), 2.24 (m, 2H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.4, 139.5, 135.9, 129.2, 128.7 (× 2), 128.4 (× 2), 126.6, 116.3, 81.0, 63.2, 36.5, 31.6, 28.3 (× 3). HRMS (ESI TOF): m/z = 302.1860 $[M+H]^+$, $C_{17}H_{24}N_3O_2$ requires 302.1869.

***tert*-Butyl (1-(1H-benzo[d]imidazol-1-yl)-3-phenylpropyl)carbamate (4r).**[10] Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate (**1a**). Eluent for the preparative TLC: heptane/ethyl acetate 2/8, to afford 27.6 mg of a colourless oil, 79% yield. IR (cm^{-1}): 2978, 1706, 1492, 1455, 1366, 1250, 1156, 1047, 1026, 741, 698. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.01 (s br, 1H), 7.80 (s, 1H), 7.51 (br s, 1H), 7.28-7.19 (m, 5H), 7.11-7.09 (m, 2H), 5.99 (br s, 1H), 5.81 (br s, 1H), 2.65 (m, 2H), 2.49 (m, 2H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.7, 143.6, 141.3, 139.5, 132.5, 128.7 (× 2), 128.4 (× 2), 126.6, 123.2, 122.6, 120.3, 110.8, 80.8, 62.4, 36.0, 31.7, 28.2 (× 3). HRMS (ESI TOF): m/z = 352.2010 $[M+H]^+$, $C_{21}H_{26}N_3O_2$ requires 352.2025.

***Tert*-butyl (1-(1H-benzo[d]imidazol-1-yl)-2-methylpropyl)carbamate (4s).** Reaction on 22.1 mg

(0.100 mmol) of tert-butyl (2-methyl-1-(phenylthio)propyl)carbamate (**1f**). Eluent for the flash column chomatorgraphy: heptane/ethyl acetate 2/8, to afford 19.5 mg of a white foam, 67% yield. IR (cm^{-1}): 2976, 1707, 1491, 1457, 1392, 1367, 1310, 1282, 1219, 1158, 1043, 1011, 848, 772, 742. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09-8.00 (m, 1H), 7.86-7.78 (m, 1H), 7.59-7.47 (m, 1H), 7.35-7.24 (m, 2H), 5.86-5.31 (m, 2H), 2.60-2.34 (m, 1H), 1.38 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.8, 143.9, 141.6, 132.8, 123.1, 122.4, 120.4, 110.7 (x 2), 68.8, 32.6, 28.2 (x3), 19.0, 18.9. HRMS (ESI TOF): m/z = 290.1865 $[M+H]^+$, $C_{16}H_{24}N_3O_2$ requires 290.1869.

Tert-butyl (1-(1H-benzo[d]imidazol-1-yl)-2-(benzyloxy)ethyl)carbamate (4t). Reaction on 31.1 mg (0.100 mmol) of tert-butyl (2-(benzyloxy)-1-(ethylthio)ethyl)carbamate (**1d)**. Eluent for the preparative TLC: heptane/ethyl acetate 2/8, to afford 27.3 mg of a colourless solid, 74% yield. MP: 83–84°C. IR (cm^{-1}): 3219, 2969, 2931, 2891, 1698, 1525, 1369, 1308, 1241, 1155, 1134, 1087, 1042, 1027, 957, 757, 737, 699. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.24 (br s, 1H), 7.81-7.77 (m, 1H), 7.59 (br s, 1H), 7.30-7.17 (m, 7H), 6.20-6.05 (m, 1H), 5.87(d, *J* = 8.7 Hz, 1H), 4.47 (s, 2H), 3.92-3.75 (m, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 154.5, 143.4, 141.7, 136.7, 133.0, 128.8 (x 2), 128.4 (x 2), 128.1 (x 2), 123.3, 122.6, 120.3, 110.6, 74.0, 70.6, 61.2, 28.3 (x 3). HRMS (ESI TOF): m/z = 368.1964 $[M+H]^+$, $C_{21}H_{26}N_3O_3$ requires 368.1974.

Tert-butyl (3-phenyl-1-(9H-purin-9-yl)propyl)carbamate (4s). Reaction on 29.5 mg (0.100 mmol) of tert-butyl (1-(ethylthio)-3-phenylpropyl)carbamate **(1a)**. Eluent for the preparative TLC: heptane/ethyl acetate 6/4, to afford 28.6 mg of a white foam, 81% yield. IR (cm^{-1}): 2977, 1711, 1595, 1494, 1455, 1392, 1368, 1343, 1299, 1250, 1158, 1049, 909, 850, 794, 736, 700. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.15 (s, 1H), 8.97 (s, 1H), 8.11 (s, 1H), 7.33-7.27 (m, 1H), 7.26-7.16 (m, 2H), 7.14-7.05 (m, 2H), 6.05-5.88 (m, 2H), 2.86-2.53 (m, 4H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 152.3, 150.9, 148.8, 145.3, 139.3, 128.7 (x2), 128.3 (x2), 126.6, 63.8, 60.5, 34.6, 31.7, 28.2 (x3), 26.2, 21.2. HRMS (ESI TOF): m/z = 354.1928 $[M+H]^+$, $C_{19}H_{24}N_5O_2$ requires 354.1930.

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NOTES

The authors declare no competing financial interest.

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SUPPORTING INFORMATION

Experimental details, characterization of new compounds, selected NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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