The Study on Synthesis of Some New 1,2,3-Triazolylurea and Carbonyl Amide Derivatives

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The study on syntheses of some N-substituted-N′-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]-urea **6a-e** and N-substituted-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]carbonyl amide **6f-l** derivatives were reported in this paper. The yielded products **6a-l** were confirmed by elemental analyses, NMR, MS and IR spectra.

Keywords: Synthesis; Urea; Carbamide; 5-Methyl-1-(4-chlorophenyl)-1,2,3-triazole; N-substituted-N′-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]-urea derivatives; N-Substituted-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]carbonyl amide derivatives; Curtius rearrangement.

INTRODUCTION

Some urea (carbamide) derivatives are very good effective herbicides[1,2] in agriculture. Certain compounds having a 1,2,3-triazole nucleus have been reported as antibacterial, antifungal, antiviral, anti-inflammatory and analgesic.[3] Recently some new 1,2,3-triazole derivatives have been synthesized that inhibits tumor proliferation, invasion, metastasis[4] and are useful in treating CRF (corticotropin releasing factor)-related disorders, particularly anxiety, depression or other psychiatric, neurological disorders as well as treatment of immunology, cardiovascular or heart-related diseases, colonic hypersensitivity, associability with psychopathology disturbances and stress.[5] For this reason, synthesis of several new carbamide derivatives containing a 1,2,3-triazole nucleus in a molecule is very interesting. The title compounds were prepared according to the following method.

EXPERIMENTAL

All melting points are uncorrected and determined on an XT_4-100x microscopic melting point apparatus. IR spectra were obtained in KBr discs on a Shimadzu IR-435 spectrometer. MS were performed on a HP-5988A spectrometer (EI at 70 eV). ^{1}H NMR spectroscopy ($CDCl_3$ or DMSO-d_6) was recorded on an Avance DRX 200 NMR instrument with TMS as an internal standard. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer.

Thionyl chloride was redistilled (bp 79 °C). 5-Methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carboxylic acid **3** was prepared following methods in the literature.[3]

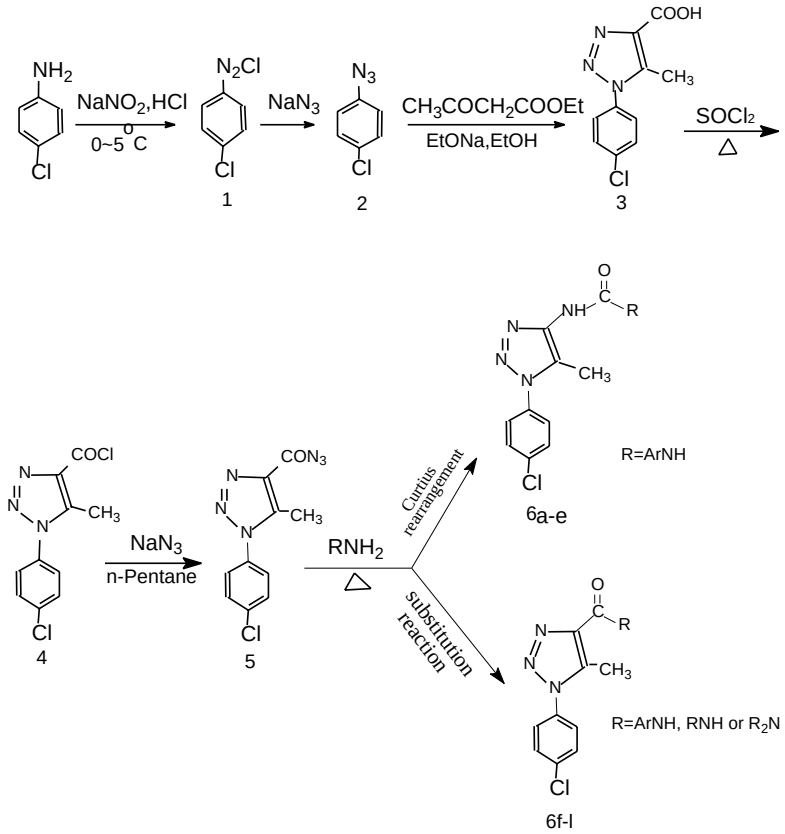
The preparation of 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carbonyl chloride 4

Place a mixture of 49.14 g (30 mL, 0.413 mole) of redistilled thionyl chloride and 10 g (0.042 mole) of compound **3** in a 100 mL round bottomed flask; heat and shake the mixture on a water bath for 2 hours. Reflux for 2 hours, distil excess thionyl chloride under reduced pressure and cool to room temperature. A white solid is obtained and recrystallized with anhydrous diethyl ether. The yield of **4** is a white crystalline solid, m.p. 149-150 °C, 9.1 g (85%). IR υ_{max}: 3067, 3097 (Ar-H), 1760 (C=O), 1548, 1498 (s, Ar), 1274 (C=N-N), 977.5 (w, -N-N=N-), 464.4 (m, $\overset{O}{\underset{C-Cl}{\|}}$) cm^{-1}. ^{1}H NMR δ_H: 7.568-7.611 (d, 2H, J = 8.6 Hz, Ph-H), 7.399-7.442 (d, 2H, J = 8.6 Hz, Ph-H); 2.593 (s, 3H, CH_3-) ppm. MS *m/z* (%): 255 (M^+, 9%), 227 (10), 220 (12), 199 (11), 192 (27), 164 (37), 154 (26), 152 (86), 128 (12), 113 (31), 111 (100), 75 (96), 63 (19).

The preparation of 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carbonyl azide 5

Stir a suspended mixture of compound **4** 9 g (0.035 mole), 50 mL n-pentane and sodium azide 3.4 g (0.052 mole) in a 100 mL round bottomed flask until compound **4** has disappeared (track by TLC) at room temperature. The suspended mixture was filtered and crude solid products

Scheme I The synthesis route of title compounds



were dissolved with acetone in order to remove less soluble impurities and then recrystallized. A white solid is obtained. The yield of **5** is a white crystalline solid, m.p. 129-130 °C (dec.), 7.9 g (86%). IR υ_{max}: 3067, 3098 (Ar-H), 2132, 2167 (m, $-\overset{O}{\overset{\|}{C}}-\ddot{N}=N\equiv N \longleftrightarrow -\overset{O}{\overset{\|}{C}}-\ddot{N}-\ddot{N}\equiv N$), 1696 (s, C=O), 1559, 1499 (s, Ar), 1262 (C=N-N), 1217 (s, $-\overset{O}{\overset{\|}{C}}-N$), 975.0 (s, -N-N=N-) cm^{-1}. ^1H NMR δ_H: 7.568-7.611 (d, 2H, J = 8.6 Hz, Ph-H), 7.405-7.462 (d, 2H, J = 8.6 Hz, Ph-H); 2.640 (s, 3H, $-CH_3$) ppm. MS *m/z* (%): 262 (M^+, 4%), 234 (1), 220 (2), 192 (2), 180 (14), 178 (43), 165 (14), 163 (39), 154 (12), 152 (36), 139 (10), 137 (31), 128 (4), 113 (29), 111 (100), 75 (76), 63 (13).

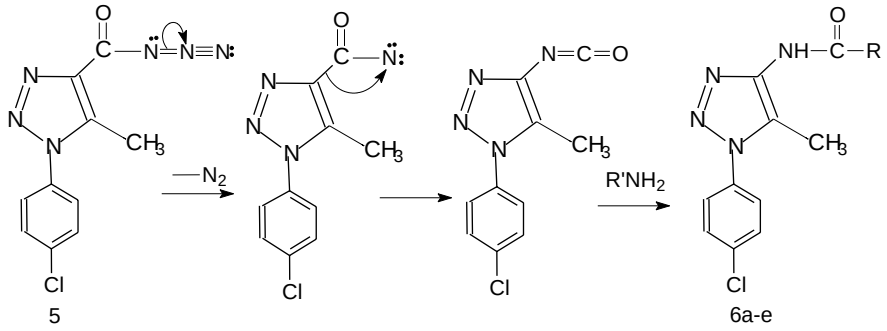
General procedure of preparation of N-substituted-N′-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]urea derivatives 6a-l

A solution of the mixture of 1.9 mmole 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carbonyl azide **5** and 1.9 mmole amino group derivatives in 5-10 mL DMF was heated under reflux (range of 80~100 °C) until compound **5** had disappeared. After the reaction mixture was cooled and 5-10 mL water were added, the solid residue was separated by column chromatography ($CH_3CO_2CH_2CH_3$:petroleum ether = 1:3) to afford **6a-l**.

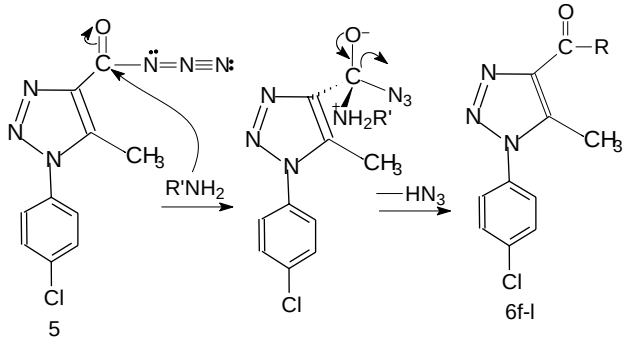
RESULTS AND DISCUSSION

Some new N-substituted-N′-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]-urea derivatives **6a-e** have been synthesized by the Curtius rearrangement of 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carbonyl azide **5** and the addition of its products isocyanates with various amino group derivatives.[6] Some new N-substituted-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]carbonyl amides **6f-l** have been synthesized by the reaction of 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-carbonyl azide **5** with various amino group derivatives. We isolated products **6a-e** and **6f-l** when most of these reactions yielded the products under reaction conditions. We claim that the reaction mechanism is the following formation under the neutral reaction conditions. The high electronegativity of the substitute group on the aromatic cycle decreases the electron density on the amino group nitrogen atom; thus aromatic ammine is unsuitable to attack the carbonyl of compound **5**. The nucleophilicity of amino group derivatives is weak or the obstruction of space is very large, the reaction products are **6a-e** by the Curtius rearrangement of **5**. The nucleophilicity of amino group derivatives is strong; reaction products are **6f-l** by the substitution of **5**.

Scheme II The reaction mechanism of title compounds **6a-e**



Scheme III The reaction mechanism of title compounds **6f-l**



The reaction of 3-BrC_6H_4-NH_2 and 4-BrC_6H_4-NH_2 with azide **5** produces **6c**, **6j** and **6d**, **6k**.

The structure of these compounds was characterized with ^{1}H NMR, IR and MS spectroscopy and results are given in Tables 2, 3 and 4. The IR spectra data of compound **6a-e** characteristic peaks at 3185-3202, 3265-3270 and 1670-1692 cm^{-1} could be found. These peaks could be assigned to NH and $\nu_{C=O}$. The vibration bands of N-N=N were in the region of 972-979 cm^{-1}. The IR spectra data of compound **6f-l** show

Table 1. Structures, Yields and Melting Points of Alkyl\aryl N-[5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-Yl]-carbamic Acid Derivatives **6a-l**

Compound[a]	R	Yield (%)	M.p. (°C)
6a	α-$C_{10}H_7$-NH-	90	254-255
6b	β-$C_{10}H_7$-NH-	60	244-245
6c	3-BrC_6H_4-NH-	49	200-201
6d	4-BrC_6H_4-NH-	24	252-253
6e	2,5-$Cl_2C_6H_3$-NH-	78	186-187
6f	$(CH_3CH_2)_2$N-	95	102-103
6g	$(CH_3CH_2CH_2)_2$N-	96	104-105
6h	$(CH_3)_3$C-NH-	95	137-138
6i	C_6H_5-NH-	97	202-203
6j	3-BrC_6H_4-NH-	21	191-192
6k	4-BrC_6H_4-NH-	56	200-202
6l	4-CH_3O-C_6H_4-NH-	87	202-203

[a] Satisfactory microanalyses were obtained for all the compounds

Table 2. IR Spectral Data for Compounds **6a-l**

Compound	IR (cm^{-1}) (KBr disc)
6a	3265, 3185, 3095, 3065, 2918, 1670, 1647, 1613, 1564, 1499, 1264, 1236, 1092, 1007, 972, 833, 788, 762, 700
6b	3267, 3187, 3100, 3049, 2918, 1690, 1611, 1585, 1561, 1503, 1253, 1215, 1095, 1009, 979, 833, 746, 706
6c	3294, 3234, 3100, 3047, 2917, 1718, 1594, 1548, 1498, 1481, 1257, 1230, 1096, 1009, 978, 829, 766, 676, 614
6d	3275, 3201, 3101, 3064, 2925, 1701, 1612, 1556, 1501, 1291, 1251, 1215, 1094, 1007, 976, 828, 752, 705
6e	3270, 3202, 3101, 3061, 2924, 1692, 1615, 1585, 1535, 1504, 1257, 1215, 1094, 1007, 978, 834, 772, 710
6f	3066, 2985, 2966, 2934, 1609, 1544, 1502, 1484, 1458, 1267, 1207, 1093, 1006, 979, 839, 775, 700
6g	3076, 2966, 2932, 2869, 1616, 1556, 1500, 1468, 1431, 1243, 1094, 1005, 977, 835, 751, 706
6h	3100, 3078, 2970, 2928, 1667, 1572, 1505, 1455, 1268, 1217, 1091, 1007, 982, 834, 745, 708
6I	3100, 3054, 2972, 2925, 1673, 1597, 1527, 1495, 1440, 1037, 1272, 1242, 1095, 997, 829, 757, 694
6j	3103, 3075, 2924, 2854, 1675, 1588, 1521, 1495, 1419, 1270, 1240, 1161, 1092, 1068, 984, 830, 779
6k	3383, 3100, 2925, 1684, 1590, 1568, 1522, 1497, 1421, 1300, 1237, 1091, 1068, 1004, 978, 833, 811
6l	3100, 3003, 2953, 2931, 1669, 1612, 1572, 1515, 1497, 1255, 1231, 1177, 1090, 971, 831

Table 3. ^{1}H NMR Spectral Data for Compounds

Compound	^{1}H NMR δ (ppm)
6a	($CDCl_3$) 8.613 (b, 1H, NH), 7.442-7.550 (q, 4H, p-C_6H_4Cl), 7.442-8.274 (m, 7H, α-$C_{10}H_7$), 7.450 (b, 1H, NH), 2.398 (s, 3H, CH_3)
6b	(DMSO-d_6) 9.074 (b, 1H, NH), 8.581 (b, 1H, NH), 7.677-7.836 (q, 4H, p-C_6H_4Cl), 7.322-8.048 (m,7H, β-$C_{10}H_7$), 2.256 (s, 3H, CH_3)
6c	(DMSO-d_6) 9.054 (b, 1H, NH), 8.064 (b, 1H, NH), 7.573-7.617 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.426-7.470 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.202-7.617 (m, 4H, m-C_6H_4Br), 2.691 (s, 3H, CH_3)
6d	(DMSO-d_6) 9.021 (b, 1H, NH), 8.566 (b, 1H, NH), 7.229-7.694 (q, 4H, p-C_6H_4Cl), 7.229-7.694 (q, 4H, p-C_6H_4Br), 2.246 (s, 3H, CH_3)
6e	(DMSO-d_6) 9.438 (b, 1H, NH), 8.930 (b, 1H, NH), 7.505-7.549 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.106-7.144 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.704, 8.306 (s, 3H, 2, 5-$Cl_2C_6H_3$), 2.278 (s, 3H, CH_3)
6f	($CDCl_3$) 7.534-7.578 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.396-7.440 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 3.805-3.909, 3.522-3.628 (q, 4H, *J* = 7Hz, 2-CH_{2-}), 1.234-1.306, 1.306-1.385 (t, 6H, *J* = 7Hz, 2-CH_3), 2.534 (s, 3H, CH_3)
6g	($CDCl_3$) 7.532-7.576 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.397-7.441 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 3.435-3.512, 3.741-3.818 (t, 4H, *J* = 7Hz, 2-CH_{2-}), 1.656-1.816 (m, 4H, *J* = 7Hz, 2-CH_{2-}), 0.867-1.017 (m, 6H, *J* = 7 Hz,2-CH_3), 2.524 (s, 3H, CH_3)
6h	($CDCl_3$) 7.535-7.579 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.374-7.418 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.163 (b, 1H, NH), 2.620 (s, 3H, CH_3)
6i	($CDCl_3$) 9.059 (b, 1H, NH), 7.571-7.614 (d, 2H, *J* = 8.6 Hz, p-C_6H_4Cl), 7.357-7.398 (d, 2H, *J* = 8.6 Hz, p-C_6H_4Cl), 7.128-7.739 (m, 5H, -C_6H_5), 2.696 (s, 3H, CH_3)
6j	($CDCl_3$) 7.277-7.272 (d, 1H, *J* = 2 Hz, m-C_6H_4Br), 7.063 (s, 1H, NH), 6.985-7.204 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 6.838-6.914 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 6.573-6.900 (m, 3H, m-C_6H_4Br), 2.691 (s, 3H, CH_3)
6k	($CDCl_3$) 10.070 (b, 1H, NH), 7.835-7.879 (d, 2H, *J* = 8.6 Hz, p-C_6H_4Cl), 7.730 (s, 4H, p-C_6H_4Br), 7.504-7.548 (d, 2H, *J* = 8.6 Hz, p-C_6H_4Cl), 2.572 (s, 3H, CH_3)
6l	($CDCl_3$) 8.961 (b, 1H, NH), 7.563-7.608 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.432-7.477 (d, 2H, *J* = 8.8 Hz, p-C_6H_4Cl), 7.608-7.654 (d, 2H, *J* = 9 Hz, p-$C_6H_4OCH_3$), 6.916-6.961 (d, 2H, *J* = 9 Hz, p-$C_6H_4OCH_3$), 3.838 (s, 3H, -CH_3), 2.697 (s, 3H, CH_3)

Table 4. MS Spectral Data for Compounds **6a-l**

No	M^+	*m/z* (%)
6a	377(3)	362(1) 349(1) 314(1) 312(4) 237(1) 235(4) 221(2) 208(9) 192(7) 181(9) 179(22) 171(11) 163(13) 154(30) 152(84) 143(80) 138(35) 127(21) 111(100) 102(9) 75(83)
6b	377(3)	362(2) 349(1) 313(1) 312(1) 237(1) 235(2) 221(3) 208(6) 197(4) 181(10) 179(23) 169(62) 163(9) 154(24) 152(72) 143(100) 138(27) 127(26) 111(77) 102(9) 75(56)
6c	405(1.7)	407(1.5) 368(2) 326(1) 264(2) 255(2) 236(3) 234(2) 227(9) 208(5) 199(34) 197(37) 181(17) 179(45) 173(39) 171(52) 165(13) 163(13) 154(25) 152(75) 145(96) 138(31) 131(9) 111(90) 102(8) 75(60) 55(57) 44(100)
6d	405(1)	407(1.3) 379(1) 331(1) 252(1) 235(1) 234(1) 225(1) 208(5) 197(22) 181(17) 179(42) 173(37) 171(53) 163(11) 154(28) 152(86) 145(100) 138(35) 127(4) 111(91) 102(7) 75(77)
6e	395(1)	360(1) 345(1) 332(1) 297(1) 234(1) 219(1) 208(4) 206(4) 189(18) 181(22) 179(60) 171(9) 163(48) 161(57) 154(29) 152(87) 145(96) 138(45) 124(26) 111(100) 102(7) 91(25) 75(86)
6f	292(1)	221(1) 219(2) 212(5) 207(3) 195(2) 194(5) 181(2) 179(3) 169(2) 167(4) 163(3) 154(6) 152(11) 145(4) 139(5) 135(7) 121(14) 113(15) 111(42) 97(20) 91(63) 69(48) 44(100)
6g	320(1)	305(1) 291(9) 263(2) 235(17) 222(8) 220(23) 207(1) 194(9) 193(10) 192(13) 180(2) 178(5) 166(8) 164(19) 154(14) 152(45) 138(4) 128(7) 111(45) 100(100) 75(33) 43(66)
6h	292(1)	277(18) 249(6) 235(2) 222(4) 220(10) 208(10) 207(7) 192(19) 191(11) 181(4) 179(7) 173(4) 167(12) 164(39) 154(13) 152(41) 145(11) 138(13) 127(9) 111(42) 75(50) 57(100)
6i	312(28)	283(1) 269(1) 255(3) 241(3) 234(1) 214(3) 205(1) 194(17) 192(53) 181(4) 179(4) 164(45) 152(35) 146(5) 138(18) 129(20) 127(32) 113(31) 111(100) 93(44) 77(44) 75(72) 65(30)
6j	390(16)	392(23) 363(1) 349(1) 347(1) 321(2) 294(2) 268(2) 247(9) 236(5) 219(5) 194(25) 192(72) 171(9) 164(56) 152(39) 146(6) 143(3) 138(19) 127(45) 111(100) 91(29) 75(84) 63(33)
6k	390(45)	392(60) 335(2) 321(3) 294(3) 268(2) 247(9) 236(7) 219(8) 194(22) 192(59) 171(15) 164(50) 152(46) 146(12) 143(9) 138(23) 127(25) 111(100) 91(25) 75(45) 63(19)
6l	342(46)	311(1) 285(3) 271(8) 251(4) 244(5) 236(2) 219(2) 207(1) 194(9) 192(28) 181(9) 179(9) 164(46) 155(31) 153(100) 140(16) 138(45) 134(16) 128(9) 122(38) 111(96) 108(27) 95(21) 75(59)

characteristic peaks at 3100-3103 and 1609-1675 cm^{-1} could be found. These peaks could be assigned to NH and $\nu_{C=O}$. The vibration bands of N-N=N were in the region of 971-997 cm^{-1}.

Comparing the ^1H NMR spectra of **5** with **6**, we could see that after the Curtius rearrangement to **6a-e** the most noticeable change is that the signals of amino protons at δ 8.613-9.430, 7.450-8.930 ppm appeared. The chemical shift of the triazole ring methyl group shows in the range δ 2.256-2.620 ppm, whereas the aromatic protons resonate at δ 7.229-8.930 ppm. We could see that after the Curtius rearrangement to **6f-l** the most noticeable change is that the signals of amino protons at δ 7.163-9.059 ppm appeared. The chemical shift of the triazole ring methyl group shows in the range δ 2.256-2.620 ppm, whereas the aromatic protons resonate at δ 6.961-8.064 ppm.

We investigated the MS spectra of **6a-l** and the results showed that compounds **6a-l** had weak molecular ion peak; their base peak ions were 111 (4-Clphenyl), 57 (t-Bu), 143 (naphthyloxy). Analyzing the fragments from the subsequent cleavage of the molecular ions, we found that the MS spectra of **6a-l** exhibited some important ion peaks at *m/z* 208 (4-9), 181 (9-22), 179 (22-60), 154 (24-30).

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