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Facile syntheses of 3-halo and mixed 3,5-dihalo analogues of *N*-acetyl-L-tyrosine via sulfonic acid-catalysed regioselective monohalogenation

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ABSTRACT

The combination of catalytic amounts of *p*-toluenesulfonic acid and 1 equiv of *N*-halosuccinimide afforded highly selective ring-halogenation of *N*-acetyl-L-tyrosine, furnishing either *N*-acetyl-3-halo-L-tyrosine analogues or mixed 3,5-dihalo derivatives in a one-pot reaction with excellent yields at room temperature.

3-Halo-L-tyrosines, constituents in marine metabolites such as geodiamolides A–F,[1] are also amino acid residues of L-thyronine analogues, which have been shown to exhibit thyroxine antagonist properties.[2] Examples of syntheses of ring-halogenated tyrosines involving direct electrophilic halogenation of L-tyrosine[3] or its *N*-acetyl analogue[4] are few and specific for each halo-analogue, and offer no unified methodology to synthesise systematically any variants of mono, di and mixed dihalo-L-tyrosines in a one-pot reaction. *N*-Acetyl-3,5-dichloro-L-tyrosine was synthesised via acetylation of 3,5-dichloro-L-tyrosine, made by dichlorination of L-tyrosine.[5] Dibromination was achieved with bromine in acetic acid, furnishing *N*-acetyl-3,5-dibromo-L-tyrosine after acetylation.[6] Di-iodination, involving H_2O_2 and iodine and then acetylation gave *N*-acetyl-3,5-diiodo-L-tyrosine.[7]

The lack of a systematic methodology for the syntheses of 3-halo, 3,5-dihalo and mixed 3,5-dihalo-L-tyrosines, and coupled with our goal to synthesise halogenated variants of L-thyronine for biological studies, have prompted us to search for a facile, mild and chemically inexpensive regioselective halogenation methodology to affect monohalogenation of *N*-acetyl-L-tyrosine. The principal problem of ring-halogenation of the phenol ring of tyrosine is its high reactivity, and hence the control of mono versus dihalogenation. Previous examples of phenol monobromination involved various organo bromide salts and *N*-bromosuccinimide (NBS).[8] With NBS as the bromonium ion source, catalytic reagents employed to affect selective monobromination have included SiO_2,[9a] HZSM-5,[9b] $HBF_4{\cdot}Et_2O$,[9c] TBAB,[9d] SO_3H-functionalised silica,[9e] and ammonium acetate.[9f] For monoiodination, the combination of iodine and catalytic amounts of cerium ammonium nitrate (CAN) afforded *ortho*-iodination.[10]

We report herein a regioselective halogenation methodology for syntheses of 3-halo and mixed-3,5-dihalo analogues of *N*-acetyl-L-tyrosine using a combination of *N*-halosuccinimide and catalytic amounts of *p*-toluenesulfonic acid (TsOH) in solvents such as acetonitrile, 1,4-dioxane and ethyl acetate at room temperature. This combination of *N*-halosuccinimide and catalytic amounts of TsOH had been used previously in electrophilic halogenation of polyalkylbenzenes.[11] With TsOH as catalyst, ring-halogenations of polyalkylbenzenes proceeded with enhanced reactivity. In contrast to the classical view of ring-halogenations of phenols (such as tribromination of phenol in aqueous solution and selective monobromination in non-polar CCl_4 or CS_2), the combination of *N*-halosuccinimide and TsOH, which had previously afforded enhanced halonium ion reactivity with polyalkylbenzenes, gave herein, high regioselectivity towards halogenation of *N*-acetyl-L-tyrosine.

Using 1 equiv of TsOH and *N*-chlorosuccinimide (NCS) in 1,4-dioxane, *N*-acetyl-L-tyrosine (**1**) was converted at room temperature into *N*-acetyl-3-chloro-L-tyrosine (**2a**) in 90% yield and 100% selectivity (Table 1).[12,13] The same reaction in acetonitrile gave **2a** in 94% yield and with 100% selectivity. Ring chlorination of **1** in 1,4-dioxane or acetonitrile with NCS, in the absence of TsOH, gave **2a** in 26% and 22% yields (100% selectivity in both cases), respectively.

Using NBS, which was previously found to be more reactive than NCS with polyalkylbenzenes,[11] ring bromination of tyrosine represents a challenge; minimising ring dibromination while enhancing monobromination selectivity. With 1 equiv of NBS in 1,4-dioxane, *N*-acetyl-3-bromo-L-tyrosine (**2b**) was obtained in 91% yield and 96% selectivity using 1 equiv of TsOH (Table 1).[14] In acetonitrile, **2b** was obtained in 90% yield and 95% selectivity with 1 equiv each of TsOH and NBS at room temperature. On the other hand, the combination of 1 equiv each of TsOH and NBS in less polar solvents, THF and ethyl acetate, afforded **2b** in 88% (93% selectivity) and 93% yields (96% selectivity), respectively. Without TsOH, bromination in 1,4-dioxane furnished **2b** and *N*-acetyl-3,5-dibromo-L-tyrosine (**3b**) in yields of 53% and 39%, respectively. In acetonitrile at room temperature and without TsOH, **2b** and **3b** were obtained in yields of 49% and 38%,

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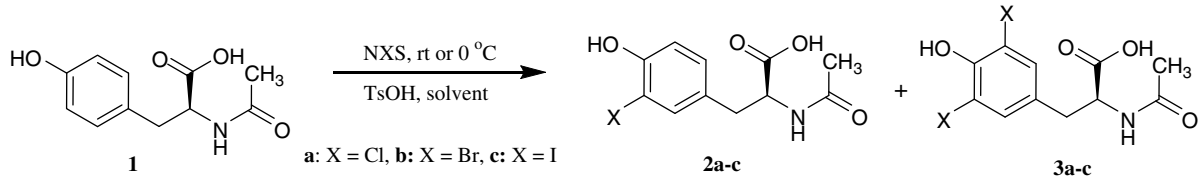
Table 1
Effects of TsOH and temperature on the selectivity of monohalogenation of **1** in various solvents[a]



Entry	Product	Solvent	Equivalents of TsOH	Temperature	Time (h)	% Product ratio[b]		
						1	3-	3,5-
1		1,4-Dioxane	0	rt	18	74	26	0
2		1,4-Dioxane	1	rt	18	10	90	0
3		CH_3CN	0	rt	18	78	22	0
4		CH_3CN	1	rt	18	5	95	0
5		CH_3CN	1	rt	6	6	94	0
6		CH_3CN	1	0 °C	6	5	95	0
7		CH_3CN	1[c]	rt	6	4	96	0
8		1,4-Dioxane	0	rt	18	8	53	39
9		1,4-Dioxane	1	rt	18	5	91	4
10		THF	0	rt	18	11	60	29
11		THF	1	rt	18	5	88	7
12		EtOAc	0	rt	18	13	52	35
13		EtOAc	1	rt	18	3	93	4
14		CH_3COOH	0	rt	18	13	77	10
15		CH_3COOH	0	15 °C to rt	18	2	92	6
16		CH_3COOH	1	15 °C to rt	18	3	94	3
17		CH_3CN	0	rt	18	13	49	38
18		CH_3CN	1	rt	18	2	96	2
19		CH_3CN	1	rt	6	5	90	5
20		CH_3CN	1	0 °C	6	4	91	5
21		CH_3CN	1[c]	rt	6	8	64	28
22		1,4-Dioxane	0	rt	6	11	67	22
23		1,4-Dioxane	1	rt	6	37	63	0
24		CH_3CN	0	rt	6	16	57	27
25		CH_3CN	1	rt	6	3	97	0
26		CH_3CN	1	rt	18	5	95	0
27		CH_3CN	1	0 °C	6	27	69	4
28		CH_3CN	1[c]	rt	6	18	59	23

[a] Reaction conditions: TsOH (1 mmol) was added to the stirred solution containing compound **1** (1 mmol), maintained at 0 °C or room temperature. After 5 min, 1 equiv of *N*-halosuccinimide was added and the mixture was stirred for either 6 or 18 h.
[b] Product mixtures were converted to methyl esters and analysed by GC.
[c] TsOH (1 equiv to **1**) was added 15 min later to the reaction mixture containing compound **1** and *N*-halosuccinimide.

respectively, and in THF and ethyl acetate, the yields of **3b** were 29% and 35%, respectively.

The reaction of **1** in 1,4-dioxane at room temperature with 1 equiv of TsOH and NIS afforded *N*-acetyl-3-iodo-L-tyrosine (**2c**) in 63% yield and 100% selectivity (Table 1). In acetonitrile, iodination of **1** at room temperature gave **2c** in 97% yield and 100% selectivity (90% isolated yield).[15] In the absence of TsOH, iodination of **1** furnished both **2c** and *N*-acetyl-3,5-diiodo-L-tyrosine (**3c**). Thus, in 1,4-dioxane and acetonitrile the yields of **2c** were 67% and 57%, while the yields of **3c** were 22% and 27%, respectively. With the exception of monobromination, monochlorination and monoiodination of the ring of tyrosine proceeded with more enhanced yields and selectivities in acetonitrile than in 1,4-dioxane. Given that the previous finding showed ring bromination enhancement in acetonitrile with activated anisoles, it was therefore expected that ring monohalogenation of tyrosine would fare worse in this solvent.[16] The findings herein seem to show otherwise, as observed with monochlorination and monoiodination, and also the indifference of monobromination yields to non-polar and polar solvents.

The effect of TsOH on the ring-halogenation of tyrosine was investigated by changing the order of the addition of TsOH.[12] In the above-discussed reactions, TsOH was added prior to the addition of *N*-halosuccinimide. Reversing the order of TsOH addition, 15 min after the addition of *N*-halosuccinimide, the yields and the selectivities of **2b–c** were reduced. While at the same time, the yields of the dihalo adducts (**3b** and **3c**) were increased. Thus iodination of **1** with NIS, followed by TsOH addition, gave a yield of 59% and 72% selectivity for **2c** and 23% yield for the diiodo adduct (**3c**). Bromination with NBS with delayed TsOH addition afforded **2b** in a yield of 64% and 70% selectivity along with a 28% yield of the dibromo adduct (**3b**). For chlorination, the change in the order of TsOH addition did not affect the yield or selectivity of **2a**.

The effect of low temperature (0 °C) on monohalogenation of **1** was also investigated. As shown in Table 1, lowering the temperature of the chlorination reaction to 0 °C did not affect the yield of **2a** significantly compared to the same reaction conducted at room temperature. Bromination of **1** at ice-bath temperature did not show any significant effect on the yield of **2b**. For iodination, on the other hand, lowering the temperature reduced the yield of **2c** (from 97% to 69%) while at the same time increasing slightly the production of **3c**.

Varying the amounts of TsOH was also investigated. As shown in Table 2, the optimum conditions for chlorination is at 0.1 equiv of TsOH (**2a**: 90% isolated yield). For bromination, 0.1 equiv of TsOH also gave the highest yield of **2b** (94% isolated yield). With iodination, however, reducing the amount of TsOH did not improve the yield of **2c**, but instead led to a decline in the yield of **2c** and an increase in the amount of the unreacted starting material (Table 2, entry 3). For the highest yield of **2c** (90% isolated yield), the

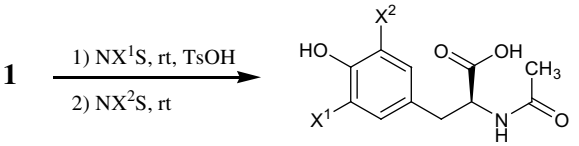
Table 2
Effects of varying the amounts of TsOH on the regioselective halogenations of **1**[a]

Entry	NXS	% Product ratio[b]								
		1% TsOH			10% TsOH			50% TsOH		
		1	3-	3,5-	**1**	3-	3,5-	**1**	3-	3,5-
1	NCS	5	95	—	5	95	—	9	91	—
2	NBS	1	96	3	1	96	3	3	95	2
3	NIS	11	84	5	4	95	1	2	97	1

[a] Reaction conditions: TsOH (0.01–0.5 mmol) was added to the stirring solution containing **1** (1 mmol). After 5 min, 1 equiv of *N*-halosuccinimide was added and the reaction mixture was stirred for 6 h at room temperature.
[b] Product mixtures were converted into methyl esters and analysed by GC–MS.

optimum conditions appear to be the use of 1 equiv of TsOH relative to both NIS and the starting substrate **1**.

Given that dihalogenation is best achieved in the absence of TsOH, a useful route for the synthesis of *N*-acetyl-3,5-dihalo-L-tyrosine (compounds **3a–c**) is at hand. The synthesis of **3a** was achieved in 91% yield by reacting **1** with 2.2 equiv of NCS in acetonitrile at room temperature for 18 h.[17] For **3b**, 2.0 equiv of NBS was reacted with **1** in acetonitrile at room temperature for 18 h to furnish **3b** in 99% yield (95% isolated yield).[18] X-ray crystal structures of both **3a** and **3b** showed an *S*-configuration about the methine α-carbon of tyrosine.[19] In addition, the specific optical rotation values of **3a** and **3b** matched those of the literature.[4b,6,17,18] With **3c**, the absence of TsOH in the reaction mixture and using 2.2 equiv of NIS to 1 equiv of **1** in acetonitrile at room temperature gave only a 74% yield. However, the addition of 1 equiv of TsOH to the same reaction mixture and under identical conditions enhanced the yield of **3c** to 92% (isolated: 85%).[20]



X^1, X^2 = **a**: Cl, I; **b**: Br, I; **c**: Br, Cl **4a-c**

The high regioselectivity of halogenations of **1**, enhanced by the addition of 0.1–1 equiv of TsOH, permits the systematic synthesis of mixed 3,5-dihalo analogues of *N*-acetyl-L-tyrosine. Thus, *N*-acetyl-3-chloro-5-iodo-L-tyrosine (**4a**) was obtained in 99% yield (73% isolated yield) from a one-pot reaction mixture initially containing 0.1 equiv each of TsOH, 1.1 equiv of NCS and **1**, which was allowed to be stirred in acetonitrile at room temperature followed by the addition of 1.5 equiv of NIS.[21] For *N*-acetyl-3-bromo-5-iodo-L-tyrosine (**4b**), the synthesis was conducted in the same manner with bromination (1 equiv of NBS and 15 mol % TsOH) implemented first for 18 h at room temperature followed by iodination (1.5 equiv of NIS).[22] This one-pot bromination–iodination combination reaction furnished **4b** in 92% yield (82% isolated yield). Using the same solvent and room temperature conditions as previously applied to **4a** and **4b**, *N*-acetyl-3-bromo-5-chloro-L-tyrosine (**4c**) was obtained from the one-pot reaction in 98% yield (95% isolated yield) with the combination sequence of chlorination (0.1 equiv of TsOH and 1.1 equiv of NCS) and bromination (1.1 equiv of NBS).[23]

The finding that the addition of TsOH prior to the addition of *N*-halosuccinimide enhances the selectivity for monohalogenation of the phenol ring of L-tyrosine has led to the development of a simple methodology for monohalogenation of the ring of *N*-acetyl-L-tyrosine. The versatility of this methodology has permitted the syntheses of either 3,5-dihalo or mixed 3,5-dihalo analogues of *N*-acetyl-L-tyrosine in a one-pot sequence. The role of TsOH in the halogenation enhancement is yet to be determined. However, given the importance of the sequence of the addition of TsOH in the reaction, we speculate that TsOH might depress the formation of the phenolate form of the phenol ring of L-tyrosine and thereby diminish halogenation via the phenolic anion. Studies are underway to further probe the versatility of this methodology to phenols and other related systems and the results will be reported in due course.

Acknowledgements

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12. *Typical preparation of N-acetyl-3-halo-L-tyrosine*: To a stirring solution of *N*-acetyl-L-tyrosine (1 mmol) in 20 mL of solvent, TsOH was added and, after 5 min, 1 equiv of *N*-halosuccinimide was added in one portion. The reaction was left to stir at room temperature for 6–18 h. For the work up, the organic solution was diluted with ethyl acetate and washed three times with a 5% aqueous solution of $Na_2S_2O_3$, followed by three washes with water and lastly with brine. After evaporation of the solvents under vacuum, the solid was subjected to silica gel chromatography or converted to the corresponding methyl ester for GC–MS analysis.
13. *Compound* **2a**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.51 (d, *J* = 8 Hz, 1H), 7.23 (d, *J* = 2 Hz, 1H), 7.06 (dd, *J* = 2 and 8 Hz, 1H), 6.93 (d, *J* = 8 Hz, 1H), 4.75–4.68 (m, 1H), 3.15–3.09 (m, 1H), 2.97–2.89 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 173.0, 171.1, 152.7, 131.5, 130.5, 129.8, 120.7, 117.5, 54.5, 37.0, 22.6; IR (KBr): 3349, 1732, 1628, 1613 1424, 1334, 1227 cm^{-1}; GC/MS (methyl ester), (EI) *m*/*z* (rel int.): 273 (0.4, $(M+2)^+$), 271 (1, M^+), 214 (34, $((M+2)-H_2NCOCH_3)^+$), 212 (100, $(M-H_2NCOCH_3)^+$), 183 (10, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 181 (31, $(M-H_2NCOCH_3-OCH_3)^+$), 172 (6), 170 (18), 143 (24), 141 (70), 107 (9), 99 (8), 88 (44), 77 (21), 60 (11), 51 (11), 43 (41), 32 (7).
14. *Compound* **2b**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.32 (d, *J* = 7 Hz, 1H), 7.25 (d, *J* = 2 Hz, 1H), 6.96 (dd, *J* = 2 and 8 Hz, 1H), 6.78 (d, *J* = 8 Hz, 1H), 4.58–4.51 (m, 1H), 3.00–2.94 (m, 1H), 2.81–2.74 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 173.1, 170.8, 153.7, 134.5, 130.9, 130.5, 117.1, 110.0, 54.5, 36.9, 22.6; IR (KBr): 3349, 1726, 1632, 1612, 1422, 1341, 1221 cm^{-1}; GC/MS (methyl ester), (EI) *m*/*z* (rel int.): 317 (2, $(M+2)^+$), 315 (2, M^+), 258 (98, $((M+2)-H_2NCOCH_3)^+$), 256 (100, $(M-H_2NCOCH_3)^+$), 227 (22, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 225 (22, $(M-H_2NCOCH_3-OCH_3)^+$), 216 (12), 214 (14), 187 (55), 185 (56), 146 (4), 135 (12), 118 (5), 107 (10), 99 (9), 88 (45), 77 (21), 60 (11), 51 (11), 43 (39), 33 (3).
15. *Compound* **2c**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.47 (d, *J* = 2 Hz, 1H), 7.44 (s, 1H, N–H), 6.98 (dd, *J* = 2 and 8 Hz, 1H), 6.73 (d, *J* = 8 Hz, 1H), 4.57–4.50 (m, 1H), 2.99–2.92 (m, 1H), 2.79–2.72 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 173.2, 171.4, 156.4, 140.7, 131.3, 131.5, 115.6, 84.3, 54.5, 36.7, 22.7; IR (KBr): 3356, 1709, 1630, 1604, 1416, 1344, 1221 cm^{-1}; GC/MS (methyl ester), (EI) *m*/*z* (rel int.): 363 (2, M^+), 304 (100, $(M-H_2NCOCH_3)^+$), 273 (14,

($M-H_2NCOCH_3-OCH_3)^+$), 262 (9), 233 (47), 178 (2), 146 (3), 135 (5), 118 (2), 106 (11), 88 (18), 77 (7), 60 (5), 51 (5), 43 (19).

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17. *Compound* **3a**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.42 (d, J = 6 Hz, 1H), 7.24 (s, 2H), 4.74–4.67 (m, 1H), 3.15–3.09 (dd, J = 5 and 14 Hz, 1H), 2.97–2.90 (dd, J = 8 and 14 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.8, 170.5, 148.7, 131.5, 130.2, 125.1, 54.1, 36.8, 22.58; IR (KBr): 3554, 3392, 3353, 1717, 1659, 1610, 1416, 1333, 1228 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 307 (3, $(M+2)^+$), 305 (3, M^+), 248 (65, $((M+2)-H_2NCOCH_3)^+$), 256 (100, $(M-H_2NCOCH_3)^+$), 217 (21, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 215 (32, $(M-H_2NCOCH_3-OCH_3)^+$), 206 (14), 204 (22), 177 (23), 175 (35), 169 (5), 141 (9), 111 (9), 99 (13), 88 (86), 75 (14), 60 (43), 43 (54) 33 (5); $[\alpha]_D^{25}$ found: +83 (c 0.353, 1,4-dioxane), reported:[4b] +83.
18. *Compound* **3b**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.47 (d, 1H), 7.44 (s, 2H), 4.73–4.66 (m, 1H), 3.16–3.09 (dd, J = 5 and 14 Hz, 1H), 2.97–2.90 (dd, J = 8 and 14 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.8, 170.6, 150.3, 134.0, 132.9, 111.3, 54.2, 36.6, 22.6; IR (KBr): 3555, 3397, 3358, 1722, 1655, 1612, 1408, 1318, 1224 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 397 (1, $(M+4)^+$), 395 (3, $(M+2)^+$), 393 (1, M^+), 338 (52, $((M+4)-H_2NCOCH_3)^+$), 336 (100, $((M+2)-H_2NCOCH_3)^+$), 334 (55, $(M-H_2NCOCH_3)^+$), 307 (10, $((M+4)-H_2NCOCH_3-OCH_3)^+$), 305 (18, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 303 (10, $(M-H_2NCOCH_3-OCH_3)^+$), 296 (5), 294 (13), 292 (6), 267 (16), 265 (31), 263 (16), 226/224 (2), 215 (6) 213 (7), 187 (5) 185 (8), 157/155 (4), 133 (5), 131 (6), 99 (12), 88 (86), 77 (12), 60 (36); $[\alpha]_D^{25}$ found: +33.5 (c 0.183, CH_3OH), reported:[6] +34.5.
19. Manuscript in preparation. Crystal structures of **3a** and **3b** were determined by Professor Miriam Rossi, Department of Chemistry, Vassar College, USA, and Dr. Franco Caruso, ICB-CNR, Ple. Aldo Moro 5, Rome Italy.
20. *Compound* **3c**: ^{1}H NMR (300 MHz, acetone-d_6): δ 9.9 (s, br, 1H), 7.63 (s, 2H), 7.34 (d, J = 8 Hz, 1H), 4.70–4.67 (m, 1H), 3.17–3.05 (dd, J = 5 and 14 Hz, 1H), 2.94–2.87 (dd, J = 8 and 14 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.8, 170.4, 154.8, 141.3, 134.5, 84.3, 54.1, 36.1, 22.6; IR (KBr): 3467, 3377, 3344, 1709, 1653, 1615, 1404, 1310, 1246 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 489 (1, M^+), 430 (100, $(M-H_2NCOCH_3)^+$), 399 (9, $(M-H_2NCOCH_3-OCH_3)^+$), 359 (30), 232 (7), 105 (7), 88 (24), 77 (7), 60 (8), 43 (23), 32 (25).
21. *Compound* **4a**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.48 (d, J = 2 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.17 (d, J = 2 Hz, 1H), 4.59–4.52 (m, 1H), 3.01–2.94 (m, 1H), 2.82–2.75 (m, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.8, 170.5, 151.8, 139.7, 133.0, 131.6, 120.1, 85.6, 54.2, 36.4, 22.6; IR (KBr): 3344, 1712, 1631, 1613, 1408, 1319, 1243 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 397 (2, M^+), 340 (34, $((M+2)-H_2NCOCH_3)^+$), 338 (100, $(M-H_2NCOCH_3)^+$), 309 (4, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 307 (14, $(M-H_2NCOCH_3-OCH_3)^+$), 298 (4), 296 (11), 269 (9), 267 (26), 169 (4), 140 (8), 105 (5), 88 (42), 76 (5), 60 (17), 43 (38), 32 (15).
22. *Compound* **4b**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.67 (dd, J = 2 and 7 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.44 (s, 1H), 4.74–4.65 (m, 1H), 3.15–3.08 (m, 1H), 2.98–2.91 (m, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.8, 170.5, 152.5, 140.4, 134.8, 133.7, 85.5, 54.2, 36.3, 22.6; IR: (KBr): 3343, 1709, 1655, 1626, 1407, 1312, 1245 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 443 (2, $(M+2)^+$), 441 (2, M^+), 384 (99, $((M+2)-H_2NCOCH_3)^+$), 382 (100, $(M-H_2NCOCH_3)^+$), 353 (12, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 351 (13, $(M-H_2NCOCH_3-OCH_3)^+$), 342 (10), 340 (11), 313 (32), 311 (33), 258/256 (5), 185 (10), 133/131 (7), 105 (15), 88 (85), 77 (18), 60 (29) 43 (77), 33 (6).
23. *Compound* **4c**: ^{1}H NMR (300 MHz, acetone-d_6): δ 7.20 (s, 1H), 7.16 (d, J = 2 Hz, 1H), 7.05 (d, J = 2 Hz, 1H), 4.48–4.44 (m, 1H), 2.92–2.85 (m, 1H), 2.73–2.66 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 172.0, 170.0, 148.8, 132.7, 131.5, 130.2, 121.2, 110.8, 53.3, 35.9, 21.9; IR: (KBr): 3396, 1708, 1650, 1626, 1411, 1321, 1242 cm^{-1}; GC/MS (methyl ester), (EI) m/z (rel int.): 351 (2, $(M+2)^+$), 349 (2, M^+), 294 (21, $((M+4)-H_2NCOCH_3)^+$), 292 (100, $((M+2)-H_2NCOCH_3)^+$), 290 (72, $(M-H_2NCOCH_3)^+$), 263 (5, $((M+4)-H_2NCOCH_3-OCH_3)^+$), 261 (23, $((M+2)-H_2NCOCH_3-OCH_3)^+$), 259 (17, $(M-H_2NCOCH_3-OCH_3)^+$), 252 (3). 250 (15), 248 (12), 223 (8), 221 (32), 219 (27), 207 (5), 180 (3), 169 (9), 155 (3), 141 (7), 131 (6), 111 (4), 99 (12), 88 (82), 77 (13), 75 (13), 60 (37), 43 (64), 32 (28).