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A rapid microwave-assisted procedure for easy access to N_x polydentate ligands for potential application in α -RIT.

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Abstract: Heterocycles bearing a hydrazine moiety react with bisaldehydes or bisketones to afford new N_x polydentate ligands suitable for α -radioimmunotherapy. We developed a fast and efficient method using microwave-assisted technology to obtain chelators with variable size and number of coordination centres which were fully characterized. The complexation efficiency with astatine will be assessed.

Key words: Astatine, radioimmunotherapy, pyrimidinone, triazinone, chelating agent.

Radioimmunotherapy (RIT) is a developing and promising technique for the treatment of small tumors.¹⁻³ It consists of injecting patients with a radiopharmaceutical able to target and selectively destroy tumour cells. The radionuclides usually used are α or β^- emitters with a short half-life, attached to a vector (antibody or hapten) through a bifunctional chelating agent.⁴⁻⁶ In order to minimize irradiation of healthy tissue whilst delivering radionuclides to tumors, the metal complex between chelating agent and radionuclide has to be stable in human serum.

Among the potential radionuclides, ²¹¹At has attracted interest as a prospective candidate for α -radioimmunotherapy applications due to its adequate physicochemical characteristics: α -emitter with a half-life of 7.2 h, the emission of high energy α particles (6.8 MeV), and ability to deposit large amounts of energy in a microvolume.⁷ Astatine is also an x-ray emitter allowing external imaging of the radiopharmaceutical distribution. Nevertheless, the chemistry of astatine remains in its infancy due to the absence of a stable isotope. The current approach for labelling biomolecules with ²¹¹At rests on covalent attachment to a carbon atom.⁸ Unfortunately,

a significant number of studies have shown that astatinated radiopharmaceuticals can be stable to *in vitro* conditions, but generally more unstable *in vivo*.^{9,11} Nevertheless, clinical studies are in progress in United State and in Sweden.^{12,13} Although it is clear that much of the chemistry ascribed to halogens is applicable, the chemical similarity between astatine and its nearest halogen neighbour, iodine, is not always obvious. The general trend in the periodic system suggests that astatine is more metallic in character than iodine. Indeed, it has been reported that astatine presents a metal-like behaviour when existing under the oxidation states +I and +III as At^+ and AtO^+ species.^{14,15} Different groups have reported the formation of coordination complexes between AtO^+ and N⁻ or S⁻ containing organic chelating agents.¹⁶⁻¹⁸ The stability of these complexes is however not sufficient to use this chelation approach in RIT.

These considerations brought us to develop new N_x polydentate ligands with variable size and number of coordination centres. At the same time as a fundamental, theoretical and pragmatic study around element astatine, we led here a purely empirical approach. This paper reports the synthesis of chelating agents **L**₁₋₈ containing heterocyclic rings (Figure 1). Our expertise in the synthesis of heterocycles led us to this choice of ligands. They present a semi-rigid scaffold due to partial conjugation between the linker and heterocycle. This characteristic is essential to preorganization, an important ligand property.^{19,20} The degree of freedom is minimized, so that the structure of the chelate before complexation is similar to that in the complex. Preorganization provides high thermodynamic stability as well as increased kinetic inertness of the metal complex.

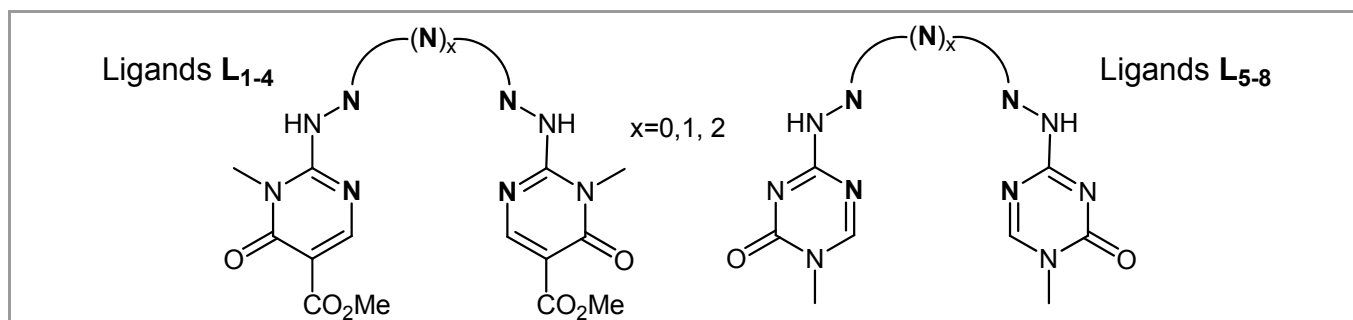
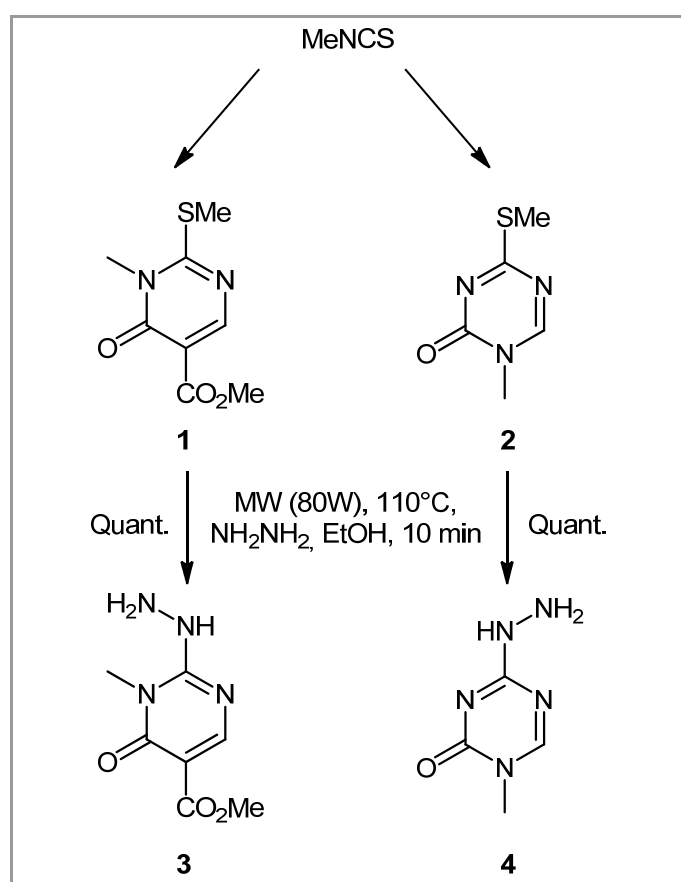


Figure 1 Polydentate chelators prepared in the study

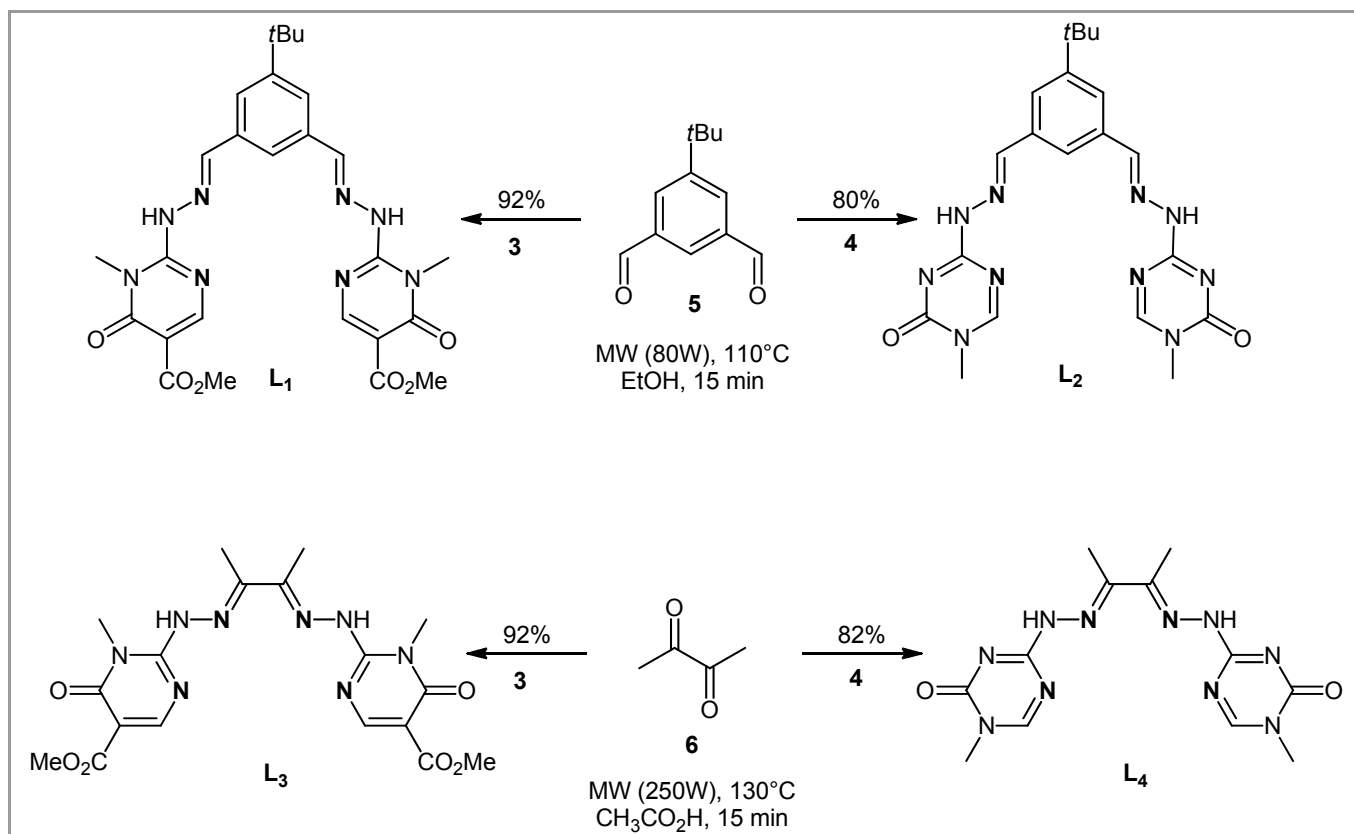
Commercially available methylisothiocyanate was used as the starting reagent for the synthesis of chelating agents **L**₁₋₈. The key step in this synthetic process was the preparation of the two corresponding hydrazino-heterocyclic rings **3** and **4** (Scheme 1). The intermediary pyrimidinone **1** and triazinone **2** were obtained in high yields according to our previously described methodology.^{21,22} Nucleophilic displacement of the methylsulfanyl group of **1** and **2** with hydrazine was carried out using ethanol as solvent to afford 2-hydrazonopyrimidine **3** and 2-hydrazonotriazine **4**.²³ The reaction was performed under microwave irradiation in order to minimize reaction time and secondary reactions. Indeed, with pyrimidinone **1**, at room temperature and after 20 h, a by-product (20%) resulting from double attack of hydrazine onto two heterocycles, was observed.

Finally, the heterocyclic rings **3** and **4** were converted to the new polydentate ligands **L**₁₋₈ with 4 to 6 coordination centres (N₄, N₅ and N₆) by a double imination reaction with dialdehydes **5,8** or diketones **6,7**.²⁴ These carbonyl compounds were commercially available except **5**. This latter compound was prepared by initial reduction (using BH₃.THF) of 5-*tert*-butylisophthalic acid to give the corresponding diol, which was subsequently oxidized (PCC/CH₂Cl₂) into the dialdehyde.²⁵

To prepare N₄ tetradentate ligands **L**₁₋₄, two equivalents of heterocyclic ring **3** or **4** were reacted with 1,3-bis(formyl)-5-*tert*-butylbenzene **5** or butane-2,3-dione **6** (Scheme 2). The syntheses were performed under microwave irradiation at 110°C in ethanol for dialdehyde **5** and at 130°C in acetic acid for diketone **6** and afforded the N₄ ligands in high yields.²⁴ Microwave irradiation significantly improved yields and condensation reaction kinetics compared to conventional thermal protocol.

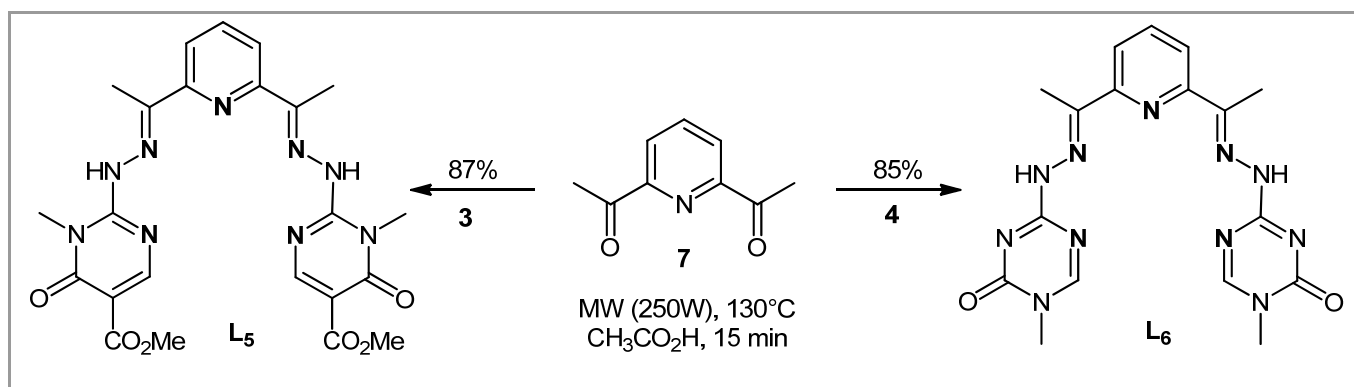


Scheme 1 Synthetic route to heterocycles **3** and **4**



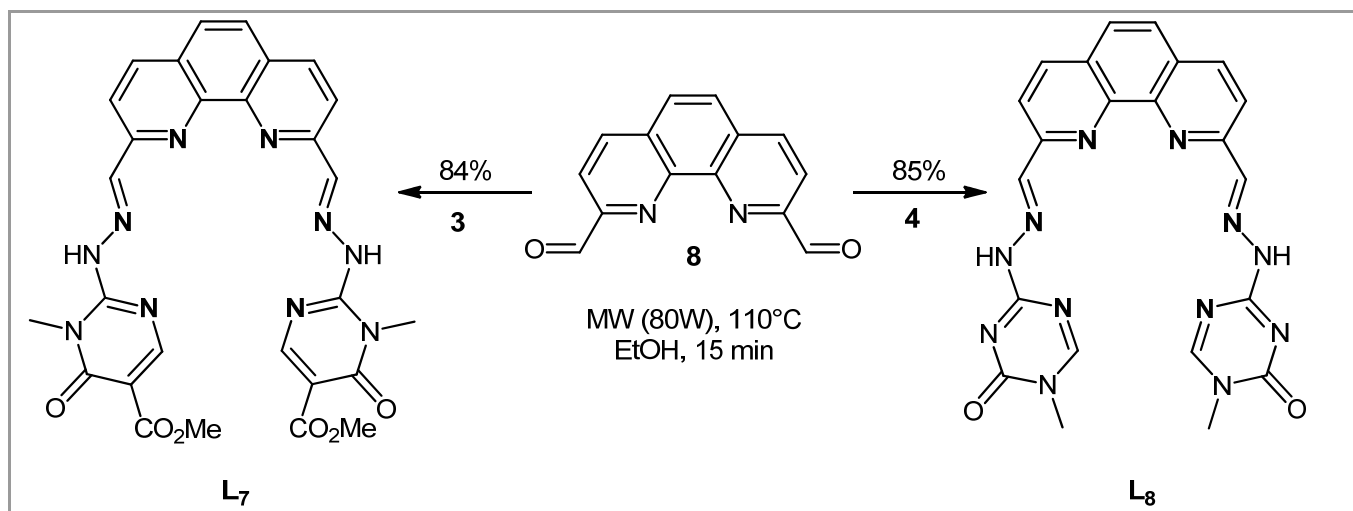
Scheme 2 Tetradentate ligands L_{1-4} with pyrimidinone and triazinone scaffolds.

N_5 pentadentate ligands were prepared in a similar way (scheme 3). Reaction of heterocyclic ring **3** or **4** with diacetylpyrimidine **7** led to the formation of ligands L_5 and L_6 in high yields.



Scheme 3 Pentadentate ligands L_5 and L_6 with pyrimidinone and triazinone scaffolds

Finally, N_6 hexadentate ligands L_7 and L_8 were analogously prepared by condensation of 2,9-diformylphenanthroline **8** and pyrimidine **3** or triazine **4** (Scheme 4). These N_6 ligands possess the rigidity imposed by the central phenanthroline ring and the flexibility of the heterocyclic arms.



Scheme 4 Hexadentate ligands **L₇** and **L₈** with pyrimidinone and triazinone scaffolds

All new ligands **L₁₋₈** were isolated with a high degree of purity by simple filtration after microwave heating in glass vial. Their structure was determined unequivocally by complementary $^1\text{H}/^{13}\text{C}$ -2D NMR techniques (COSY, HMQC and HMBC).²⁶

In conclusion, the synthesis of N_x polydentate ligands (N_4 , N_5 and N_6) was efficiently and simply performed by use of microwave-assisted technology. These chelators were prepared in 50-80% overall yield from methylisothiocyanate. The described way of synthesis will be

easily adaptable to various starting heterocyclic structures. Study of the complexing ability of these new chelating agents toward astatine, suitable for α -radioimmunotherapy, is under progress. According to the results of this study we envision the synthesis of various analogues of ligands **L₁₋₈** in order to adjust their structure (size, nature, number of coordination centers and heterocyclic ring) to finally find out the ligand which would be best suited for astatine.

Acknowledgment

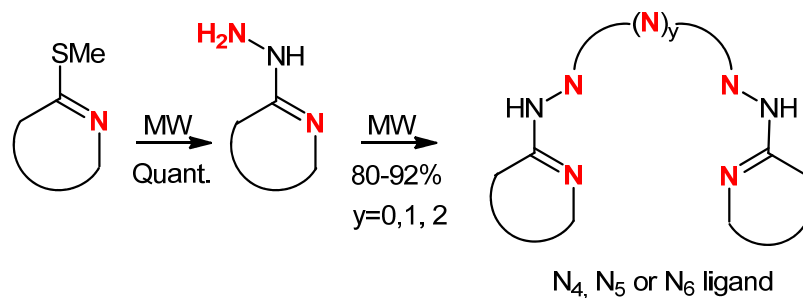
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- (24) General procedure for ligands **L**₁₋₈: to a 10 mL microwave reaction vessel was placed heterocyclic ring **3** or **4** (0.5 mmol) and dialdehyde **5** or **8** or diketone **6** or **7** (0.25 mmol) in methanol for **L**_{1,2,7,8} (4 mL) or in acetic acid for **L**₃₋₆ (4 mL). The vial was heated (internal temperature measured by fibre-optic) in a microwave synthesizer (MultiSYNTH[®], Milestone S.r.l.) to 110°C (2 min (110 W) ramp + 15 min irradiation (80 W)) for **L**_{1,2,7,8} or to 130°C (2 min (300 W) ramp + 15 min irradiation (250 W)) for **L**₃₋₆. The solvent was removed under vacuum and the solid residue was washed with diethyl ether. The product was filtered and dried under vacuum to afford ligands **L**₁₋₈.
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- (26) Spectroscopic data of ligands **L**₁₋₈: **L**₁: Mp: 243-244°C. IR (KBr): 3245, 1733, 1628, 1480, 1193, 1147 cm⁻¹. ¹H RMN (TFA) δ 1.23 (s, 9H, C(CH₃)₃), 3.61 (s, 6H, NCH₃), 3.87 (s, 6H, OCH₃), 7.78 (s, 2H, H_{ar}), 8.02 (s, 1H, H_{ar}), 8.52 (s, 2H, CH), 8.59 (s, 2H, CH_{pyr}); ¹³C RMN (TFA) δ 27.3, 28.4, 33.4, 52.1, 106.5, 122.4, 130.3, 145.6, 148.9, 153.8, 155.7, 156.4, 162.7; MS (maldi) *m/z*: 551.42 [M+H]⁺, 573.31 [M+Na]⁺. **L**₂: Mp: 245-247°C. IR (KBr): 3302, 1674, 1493, 1429, 1303, 1193 cm⁻¹. ¹H RMN (TFA) δ 1.37 (s, 9H, C(CH₃)₃), 3.68 (s, 6H, NCH₃), 8.12 (s, 2H, H_{ar}), 8.30 (s, 1H, H_{ar}), 8.50 (s, 2H, CH), 8.52 (s, 2H, CH_{tri}); ¹³C RMN (TFA) δ 28.5, 33.6, 33.7, 125.7, 130.1, 130.9, 146.3, 153.9, 154.4, 157.0, 161.3; MS (CI-) *m/z*: 436.2 [M]⁺. **L**₃: Mp: 197-199°C. IR (KBr): 3304, 1723, 1652, 1480, 1189, 1149 cm⁻¹. ¹H RMN (TFA) δ 2.40 (s, 6H, CH₃), 3.66 (s, 6H, NCH₃), 3.87 (s, 6H, OCH₃), 8.57 (s, 2H, CH_{pyr}); ¹³C RMN (TFA) δ 10.7, 27.5, 52.3, 108.4, 145.0, 149.8, 155.1, 160.1, 162.3; MS (CI+) *m/z*: 447.3 [M+H]⁺. **L**₄: Mp: > 250°C. IR (KBr): 3434, 3071, 1691, 1622, 1494, 1291 cm⁻¹. ¹H RMN (TFA) δ 2.52 (s, 6H, CH₃), 3.61 (s, 6H, NCH₃), 8.53 (s, 2H, CH_{tri}); ¹³C RMN (TFA) δ 10.7, 33.9, 146.4, 155.8, 161.0, 162.2; MS (CI+) *m/z*: 333.0 [M+H]⁺. **L**₅: Mp: 247-249°C. IR (KBr): 3216, 1734, 1627, 1481, 1189, 1148 cm⁻¹. ¹H RMN (TFA) δ 2.73 (s, 6H, CH₃), 3.75 (s, 6H, NCH₃), 3.95 (s, 6H, OCH₃), 8.45 (d, 2H, *J* = 8.0 Hz, H_{ar}), 8.64 (s, 1H, H_{pyr}), 8.81 (t, 1H, *J* = 8.0 Hz, H_{ar}); ¹³C RMN (TFA) δ 12.8, 27.9, 52.2, 104.9, 126.4, 146.3, 146.5, 148.1, 150.1, 154.1, 157.7, 163.4; MS (maldi) *m/z*: 524.52 [M+H]⁺, 546.33 [M+Na]⁺. **L**₆: Mp: 211-213°C. IR (KBr): 3220, 1634, 1489, 1303, 1187 cm⁻¹. ¹H RMN (TFA) δ 2.74 (s, 6H, CH₃), 3.66 (s, 6H, NCH₃), 8.55 (d, 2H, *J* = 8.0 Hz, H_{ar}), 8.65 (s, 1H, H_{tri}), 8.85 (t, 1H, *J* = 8.0 Hz, H_{ar}); ¹³C RMN (TFA) δ 12.4, 34.0, 126.9, 145.0, 146.1, 148.6, 150.9, 157.5, 162.9; MS (CI-) *m/z*: 409.2 [M]⁺. **L**₇: Mp: > 250°C. IR (KBr): 1733, 1627, 1495, 1191, 1146 cm⁻¹. ¹H RMN (TFA) δ 3.66 (s, 6H, NCH₃), 3.86 (s, 6H, OCH₃), 8.18 (s, 2H, H_{ar}), 8.69 (s, 2H, H_{pyr}), 8.72 (d, 2H, *J* = 8.5 Hz, H_{ar}), 8.84 (d, 2H, *J* = 8.5 Hz, H_{ar}), 9.15 (s, 2H, CH); ¹³C RMN (TFA) δ 28.7, 53.2, 107.8, 123.7, 129.0, 131.9, 137.5, 143.2, 146.4, 147.7, 150.0, 150.9, 151.0, 163.4; MS (maldi) *m/z*: 597.41 [M+H]⁺, 619.22 [M+Na]⁺. **L**₈: Mp: > 250°C. IR (KBr): 3212, 1623, 14932, 1306, 1186 cm⁻¹. ¹H RMN (TFA) δ 3.69 (s, 6H, NCH₃), 8.27 (s, 2H, H_{ar}), 8.69 (s, 2H, H_{ar}), 8.61 (s, 2H, H_{tri}), 8.89 (d, 2H, *J* = 8.6 Hz, H_{ar}), 9.06 (s, 2H, CH), 9.29 (d, 2H, *J* = 8.6 Hz, H_{ar}); ¹³C RMN (TFA) δ 33.9, 123.2, 128.0, 130.9, 136.3, 141.8, 147.1, 147.3, 149.7, 156.1, 162.7; MS (CI-) *m/z*: 482.2 [M]⁺.

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