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Short communication

Synthesis and evaluation of spectroscopic properties of newly synthesized push–pull 6-amino-8-styryl purines

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ABSTRACT

New 6-amino-8-styryl purines were synthesized using direct C–H bond functionalization. These push–pull compounds showed strong fluorescence, high quantum yields and a noteworthy fluorosolvatochromism. Deprotected purines **7a**–**c** are promising targets for incorporation into nucleic acids as they are still fluorescent in aqueous media.

1. Introduction

Over the past decade, fluorescence spectroscopy has gained considerable attention because of its wide range of applications. Notably, fluorescent molecules are known for their use in bioimaging, sensing, following chemical interactions of biomolecules or monitoring the delivery of therapeutics [1–3]. The photophysical properties of nucleosides have been studied lately as the purine scaffold exhibits promising fluorescent properties [4–10]. Indeed, nucleoside derivatives find applications in biological imaging of live cells [11,12], in DNA detection [13,14] or as fluorescent probes [15]. As such, developing new fluorescent purines fulfilling the standards of an ideal fluorophore and thus displaying high quantum yield combined with large Stokes shift is of great interest. Indeed, extending the π-conjugation usually results in a bathochromic shift of absorption and emission wavelengths and an increased quantum yield. Also, the fluorescent properties can be enhanced using push–pull structures which skeleton is composed of a conjugated π-electron system substituted by an electron withdrawing group and an electron donor one. In this context, we envisioned the synthesis of new push–pull purines bearing an amino substituent on the position 6 as the electron donor moiety and a π-conjugated styryl linker on the position 8, substituted with an electron withdrawing group in the para position of the phenyl ring. Although a styryl spacer has already been used in the examination of the fluorescent properties of caffeine or guanosine respectively bearing an oxo or a free amino group on position 6, the combination of both an *N*,*N*′-substituted amino group and a styryl group on the purine ring has never been reported.[11,15–17] Moreover, examination of the fluorescence properties of these compounds in water was not investigated.

Given that we have recently developed methods for the C–H bond direct functionalization of azoles [18,19], including purines [20], we applied these conditions for the synthesis of our molecules thereby optimizing the number of steps and providing an easy and rapid access to these potential fluorescent compounds. Herein, we disclose the synthesis and the investigation of photophysical properties of new push–pull 6-amino-8-styryl purines in organic solvents and water. The impact of the different substituents is discussed.

2. Experimental

2.1. General experimental methods

Commercially available reagents and solvents were used without further purification unless otherwise stated. Yields refer to

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isolated and purified products. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) visualized under UV light. Column chromatography was performed on silica gel 60, 40–63 μm. Chemical shifts of ^{1}H NMR and ^{13}C NMR were reported in ppm (δ units) and residual non deuterated solvent was used as internal reference. The following abbreviations were used to designate the multiplicities : s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, m = multiplet. Microwave irradiation was performed on CEM Explorer (CEM Corporation). Temperature measurement of the reaction mixture within the Discovery series was achieved by an IR sensor. The method was set with maximum power of 150 W, with maximum pressure of 17 bar and used without powermax. Reaction times refer to the hold time at the desired set temperature. Reaction cooling was performed by compressed air after the heating period was over. UV–vis experiments were monitored on a Cary Series UV–vis spectrophotometer (Agilent Technologies). Fluorescence spectra were recorded on a Cary Eclipse fluorescence spectrophotometer (Agilent Technologies) at room temperature. Measurements were performed with solutions of OD < 0.1 to avoid re-absorption of the emitted light, and data were corrected with a blank and from the variations of the detector with the emitted wavelength. Fluorescence quantum yield were measured according to Williams comparative method using quinine sulfate in 1 M H_2SO_4 as reference. [21] Absorption and fluorescence spectra were recorded for four solutions of increasing concentrations with an absorbance comprised between 0.01 and 0.1 to avoid re-absorption phenomenon. Electrospray ionization mass spectrometry (ESI-MS) was performed at the Institut Curie and HRMS were performed at the Small Molecule Mass Spectrometry platform of IMAGIF (ICSN, Gif-Sur-Yvette, France).

2.2. Chemical

*N*9-protected purines **1** and **4** were prepared according to the literature [22,23]. 8-styrylpurines **2a**–**b** and **5a**–**b** were synthetized through our formerly developed direct alkenylation method [20]. 6-aminopurines **3a**–**h** and **6a**–**c** were obtained following our previously described procedure under Buchwald-Hartwig-inspired palladium cross-coupling conditions [24]. Purines **7a**–**c** were deprotected under acidic conditions [25].

2.2.1. 9-benzyl-6-chloro-9H-purine (**1**)

White solid (51%) : ^{1}H NMR (300 MHz, $CDCl_3$) 8.80 (s, 1H), 8.10 (s, 1H), 7.37–7.33 (m, 5H), 5.46 (s, 2H). Spectroscopic data were in agreement with those reported in the literature [22].

2.2.2. (E)-9-benzyl-6-chloro-8-(4-(trifluoromethyl)styryl)-9H-purine (**2a**)

White solid (60%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.16 (d, J = 15 Hz, 1H), 7.67–7.59 (m, 4H), 7.40–7.33 (m, 3H), 7.23 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 15.9 Hz, 1H), 5.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 153.2, 151.8, 149.7, 139.3, 138.4, 135.1, 131.8, 131.7, 129.4, 128.8, 127.9, 127.0, 126.11, 126.06, 114.4, 46.4. MS (ES+) m/z (%) : 437.2 (80) $[M + Na]^+$. HRMS (ESI) calcd for $C_{21}H_{15}ClF_3N_4$ $[(M + H)^+]$ 415.0937, found 415.0945.

2.2.3. (E)-4-(2-(9-benzyl-6-chloro-9H-purin-8-yl)vinyl) benzonitrile (**2b**)

Beige solid (56%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.13 (d, J = 15.9 Hz, 1H), 7.70–7.58 (m, 4H), 7.40–7.35 (m, 3H), 7.22 (d, J = 6.8 Hz, 2H), 7.09 (d, J = 15.8 Hz, 1H), 5.62 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 152.8, 151.9, 149.9, 139.3, 138.6, 135.1, 132.8, 131.7, 129.5, 128.8, 128.1, 126.9, 118.5, 115.4, 113.1, 46.4. MS (ES+) m/z (%) : 394.3 (100) $[M + Na]^+$. HRMS (ESI) calcd for $C_{21}H_{15}ClN_5$ $[(M + H)^+]$ 372.1016, found 372.1009.

2.2.4. (E)-4-(2-(9-benzyl-6-((4-methoxybenzyl)amino)-9H-purin-8-yl)vinyl)benzonitrile (**3a**)

Yellow solid (67%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.71 (d, J = 15.9 Hz, 1H), 7.62–7.46 (m, 4H), 7.36–7.28 (m, 5H), 7.20 (d, J = 6.8 Hz, 2H), 7.01 (d, J = 15.8 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 6.35 (bs, 1H), 5.51 (s, 2H), 4.81 (bs, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.2, 153.5, 147.3, 140.0, 136.0, 134.3, 132.7, 130.5, 129.2, 128.3, 127.6, 126.8, 119.9, 118.7, 116.6, 114.1, 112.1, 55.4, 45.8, 44.2. MS (ES+) m/z (%) : 473.3 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{29}H_{25}N_6O$ $[(M + H)^+]$ 473.2090, found 473.2094.

2.2.5. (E)-9-benzyl-N-(4-methoxybenzyl)-8-(4-(trifluoromethyl) styryl)-9H-purin-6-amine (**3b**)

Yellow solid (68%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.75 (d, J = 15.9 Hz, 1H), 7.61–7.50 (m, 4H), 7.37–7.29 (m, 5H), 7.22 (d, J = 6.5 Hz, 2H), 7.01 (d, J = 15.9 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.24 (bs, 1H), 5.52 (s, 2H), 4.83 (bs, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.2, 153.4, 147.6, 139.1, 136.1, 134.9, 130.6, 129.3, 128.2, 127.3, 126.8, 125.8, 122.2, 119.9, 115.7, 114.1, 55.3, 45.7, 44.3. MS (ES+) m/z (%) : 516.5 (80) $[M + H]^+$. HRMS (ESI) calcd for $C_{29}H_{25}F_3N_5O$ $[(M + H)^+]$ 516.2011, found 516.1995.

2.2.6. (E)-4-(2-(9-benzyl-6-(pyrrolidin-1-yl)-9H-purin-8-yl)vinyl) benzonitrile (**3c**)

Yellow solid (99%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.73 (d, J = 15.8 Hz, 1H), 7.64–7.51 (m, 4H), 7.36–7.27 (m, 3H), 7.18 (d, J = 6.5 Hz, 2H), 7.03 (d, J = 15.8 Hz, 1H), 5.52 (s, 2H), 4.28 (bs, 2H), 3.82 (bs, 2H), 2.07 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 152.8, 151.6, 146.0, 140.5, 136.3, 133.2, 132.6, 129.1, 128.1, 127.5, 126.7, 120.8, 118.8, 117.1, 111.8, 49.2 45.5, 30.2. MS (ES+) m/z (%) : 407.4 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{25}H_{23}N_6$ $[(M + H)^+]$ 407.1984, found 407.1978.

2.2.7. (E)-9-benzyl-6-(pyrrolidin-1-yl)-8-(4-(trifluoromethyl) styryl)-9H-purine (**3d**)

Yellow solid (84%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.76 (d, J = 15.8 Hz, 1H), 7.62–7.53 (m, 4H), 7.35–7.28 (m, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 15.8 Hz, 1H), 5.52 (s, 2H), 4.29 (bs, 2H), 3.82 (bs, 2H), 2.07 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.8, 151.6, 146.4, 139.6, 136.4, 133.9, 130.7, 130.2, 129.1, 128.1, 127.3, 126.8, 125.8, 120.7, 116.2, 49.1, 45.6, 30.2. MS (ES+) m/z (%) : 450.5 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{25}H_{23}F_3N_5$ $[(M + H)^+]$ 450.1906, found 450.1912.

2.2.8. (E)-4-(2-(9-benzyl-6-((2-methoxyethyl)amino)-9H-purin-8-yl)vinyl)benzonitrile (**3e**)

Yellow solid (95%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.78 (d, J = 15.9 Hz, 1H), 7.66–7.51 (m, 4H), 7.36–7.29 (m, 3H), 7.20 (d, J = 6.8 Hz, 2H), 7.03 (d, J = 15.9 Hz, 1H), 6.15 (bs, 1H), 5.52 (s, 2H), 3.91 (bs, 2H), 3.67 (*t*, J = 5.1 Hz, 2H), 3.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.3, 150.6, 147.3, 140.1, 136.1, 134.2, 132.6, 129.2, 128.2, 127.6, 126.8, 120.2, 118.7, 116.7, 112.1, 71.3, 58.9, 45.7, 29.8. MS (ES+) m/z (%) : 411.4 (100) $[M + H]^+$. HRMS (ESI) calcd for $C_{24}H_{23}N_6O$ $[(M + H)^+]$ 411.1933, found 411.1933.

2.2.9. (E)-9-benzyl-N-(2-methoxyethyl)-8-(4-(trifluoromethyl) styryl)-9H-purin-6-amine (**3f**)

Yellow solid (62%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.80 (d, J = 15.9 Hz, 1H), 7.62–7.53 (m, 4H), 7.36–7.28 (m, 3H), 7.20 (d, J = 7.0 Hz, 2H), 7.01 (d, J = 15.9 Hz, 1H), 6.24 (bs, 1H), 5.52 (s, 2H), 3.92 (bs, 2H), 3.67 (*t*, J = 4.9 Hz, 2H), 3.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 153.2, 147.6, 139.2, 136.1, 134.9, 130.9, 130.5, 129.2,