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2,6-Diphenylthiazolo[3,2-*b*][1,2,4]triazoles as telomeric G-quadruplex stabilizers

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ABSTRACT

The design and synthesis of 2,6-diphenylthiazolo[3,2-*b*][1,2,4]triazoles characterized by a large aromatic building block bearing cationic side chains are reported. These molecules are evaluated as telomeric G-quadruplex stabilizers and for their selectivity towards duplex DNA by competition experiments. Two compounds (**14a**, **19**) were found active with high selectivity for telomeric G-quadruplex over duplex DNA.

Telomeres are guanine-rich DNA sequences located at the end of eukaryotic chromosomes, which protect them from fusion and degradation.[1] Human somatic cells undergo erosion of telomeres after each cell division,[2] leading to replicative senescence and apoptosis.[3] In contrast, most cancer cells are able to maintain telomere length either by the activity of telomerase or by recombination between telomeres (alternative lengthening of telomeres).[4] Almost two decades ago, it was shown that the telomeric G-overhang is able to fold into G-quadruplex structures, leading to inhibition of telomerase activity.[5] The telomeric G-quadruplex building blocks (called G-quartets) are based on stacked associations of hoogsteen bonded guanines, forming square aromatic surfaces whose dimensions are larger than the duplex DNA. This difference constitutes the basis for designing selective telomeric G-quadruplex ligands that are capable of stabilizing them so as to inhibit telomerase activity and reverse tumor cell immortalization.[6,7] Indeed, prolonged treatment of various tumor cell lines with telomeric G-quadruplex ligands has been shown to provoke a telomerase-like inhibition phenotype (including telomere shortening, delayed growth inhibition and senescence induction), but also telomere uncapping (including apoptosis, telomere fusion, anaphase bridges, G-overhang degradation and DNA damage to telomeres).[8,9]

So far, several telomeric G-quadruplex interacting ligands have been described (Scheme 1), such as acridine **1**,[10] anthraquinone **2**,[6] perylene **3**,[11] and dibenzophenanthroline **4**,[12] (for a recent review see Ref. 13). Most of them include a large aromatic core suitable for π-π stacking interaction with terminal G-tetrads and possess cationic side chains able to engage electrostatic bonds with DNA phosphates.

Previous studies from our laboratory focused on the synthesis and intercalative properties of a 2-phenyl-6-thiazolyl[3,2-*b*][1,2,4]triazole (PETT).[14] Because Hoechst 33258 was shown to present G-quadruplex binding properties[15] and displayed some scaffold similarities with PETT, we planned to develop new molecules based on this bicyclic condensed system (Scheme 2), presenting these features. It confers a crescent shape to the extended aromatic structure and above all, cationic chains substituting two lateral phenyl rings.

We present here the synthesis of a series of 2,6-diphenylthiazolo[3,2-*b*][1,2,4]triazoles **12a**,**b**, **13a**,**b**, **14a**,**b**, **15–19** and the ability of some of them to stabilize telomeric G-quadruplex.

The synthesis of substituted 2,6-diphenylthiazolo[3,2-*b*][1,2,4]triazoles was performed from ethyl 4-hydroxybenzoate. The thiazolo[3,2-*b*][1,2,4]triazole scaffold was prepared as

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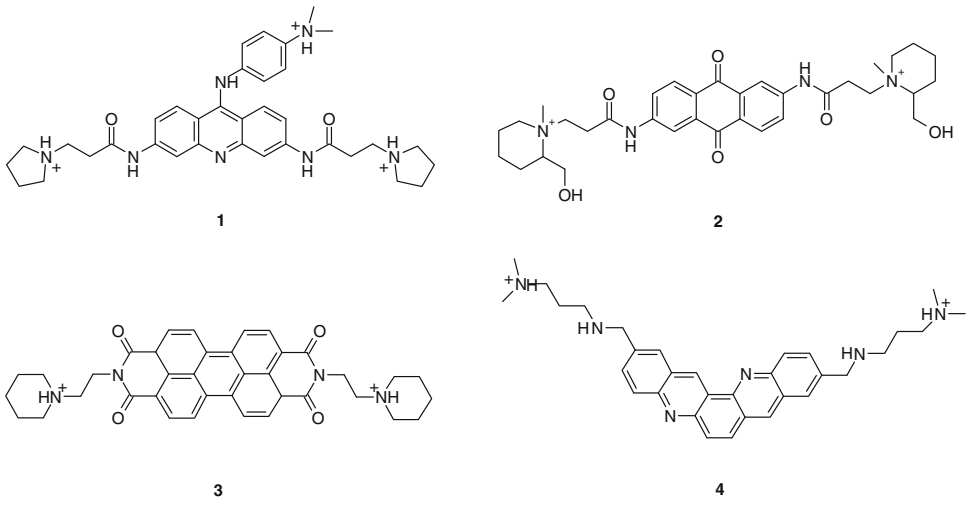
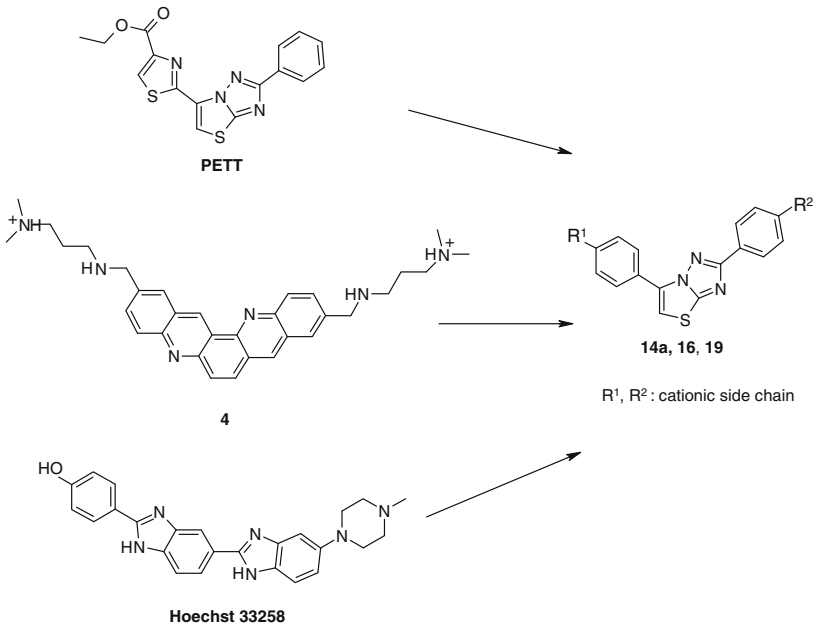
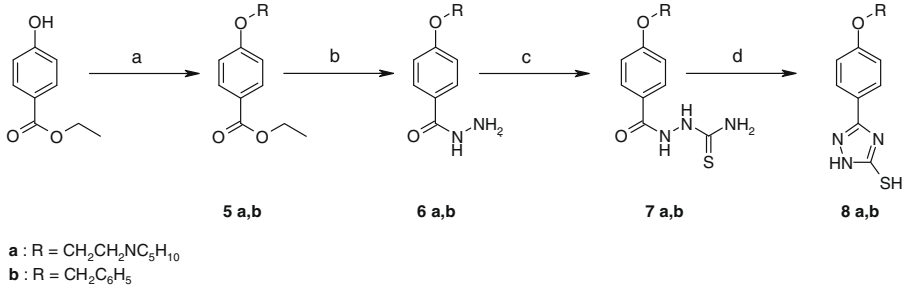


Scheme 1. Structure of some telomeric G-quadruplex ligands.



Scheme 2. Drug design of 2,6-diphenylthiazolo[3,2-*b*][1,2,4]triazoles.



Scheme 3. Reagents and conditions: (a) 1-(2-Chloroethyl)piperidine or benzyl bromide (1.2 equiv), K_2CO_3 (3.2 equiv), DMF, 80 °C, 12 h, 95%; (b) NH_2NH_2,H_2O (2.5 equiv), EtOH, reflux, 72 h, 82–88%; (c) NH_4SCN (2.5 equiv), 1 N HCl (2.5 equiv), EtOH, reflux, 60 h, 86%; (d) (i) 1% NaOH (2 equiv), 90 °C, 12 h, (ii) 1 N HCl (pH 6), 71–91%.

previously described,[16,17] using appropriate 3-mercapto-5-aryl-[1,2,4]-triazoles and α-bromoketones. The O-alkylated 3-mercapto-5-aryl-[1,2,4]-triazoles **8a**,**b** were obtained (Scheme 3) by O-alkylation of ethyl 4-hydroxybenzoate followed by the reaction of hydrazine monohydrate on ester (hydrazides **6a**,**b**); subsequent addition of ammonium thiocyanate in acidic conditions gave thiosemicarbazides **7a**,**b**. Cyclization in alkaline medium led to 3-mercapto-5-aryl-[1,2,4]-triazoles **8a**,**b** at very high yields.