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Translating G-quadruplex ligands from bench to bedside: a Stephen Neidle's legacy

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Abstract.

DNA and RNA G-quadruplexes (G4s) are alternative nucleic acid structures that can fold from thousands of guanine (G)-rich sequences in the genome and transcriptome of human cells. Invaluable information about the prevalence and functional relevance of G4s has been gained using G4-specific small molecules (or G4 ligands): cell-based ligand perturbation experiments have indeed provided readouts that were astutely exploited to gain accurate and reliable insights into G4 biology. As a consequence, these investigations have opened the way towards using G4 ligands as drug candidates to fight against genetic diseases, chiefly cancers. This quite active field of research, at the crossroads between chemical biology and medicinal chemistry, thus entirely relies on specific G4 ligands. The greatest contribution to the G4 ligand field is undoubtedly to be attributed to Prof. Stephen Neidle (London, UK). He was indeed the first to design and synthesize G4-interacting compounds, fully characterize their interaction with their G4 targets, and study them in cells with an eye towards benefiting from the central position of G4s in cellular biology to use them as new targets for therapeutic intervention. This review provides an overview of the developments that the G4 ligand field has experienced since the initial impetus provided by Prof. Neidle in 1997, and depicts the trajectories taken by some of them to become ever smarter molecular tools (chemical biology) or drug candidates under clinical assessment (medicinal chemistry).

Keywords: G-quadruplex; Ligands; Molecular tools; Clinical trials

Introduction.

The first time I read the name of Stephen Neidle was in the Michael J. Waring's benchmark review titled "*DNA modification and cancer*", which described the state of the art of drug-DNA interactions as it was in 1981.(1) The Neidle's work in question was illuminating as it provided a direct visualization of the way a 3,6-diaminoacridine (or proflavine) intercalated between two G≡C base pairs by X-ray crystallography.(2) Everything that will subsequently make the Neidle's career so successful was already in there: a small organic molecule interacting with DNA, or ligand (he has now >300 ligands in his name in the G4 ligand database, G4LDB),(3) the structure of a DNA/ligand complex solved by crystallography (he has now >100 structures deposited in the RCSB PDB), an eye already turned to the possible biological applications and therapeutic consequences of such an interaction (one of his lead compounds, QN-302, is now going through a phase I clinical trial). A perfect balance between medicinal chemistry and chemical biology.

Undoubtedly, his research had the strongest impact on the field of G-quadruplex (G4) nucleic acids,(4,5) both G4 DNA(6,7) and RNA.(8-10) His cumulative experience in designing, synthesizing and studying DNA ligands has rapidly—and ideally—positioned himself to launch the very first investigations on small molecules selective for G4 (or G4 ligands). Roughly a decade after Laurence Hurley rightly surmised about the potential of G4s as targets for drug design,(11) Neidle and Hurley published in 1997 in *J. Med. Chem.* a seminal article (now cumulating >700 citations) on the very first prototype of a G4 ligand, a 2,6-diaminoanthraquinone able to stabilize the telomeric G4 and, in doing so, inhibit the telomerase enzyme through an original mechanism.(12) This article (whose basis is to be found, according to legend, in.. a Swiss pub), was not *per se* the very first article reporting on interactions between a G4 and a small molecule, as Dipankar Sen and Richard Shafer described such an interaction in 1996;(13,14) however, this was the first article reporting on the possible therapeutic use of G4 ligands, and on the connection between a biologically relevant G4 (telomeric G4), a cancer-specific enzyme (telomerase) and a potential drug candidate (G4 ligand). From this landmark article, an impressive number of studies were launched to uncover ever more efficient ligands (that is, displaying both high affinity and selectivity for G4s).

There would be no point into trying to describe here the hundreds of ligands published over the past 27 years given their huge number and chemical diversity (>4000 G4LDB entries, several excellent reviews have been recently published on this topic),(15-19) nor to list the

different Neidle's contributions in an exhaustive manner (*vide supra*). Conversely, describing the trajectories that some molecules took following the initial Neidle/Hurley's impetus (Figure 1), to become key players in the G4 field might illuminate the intellectual and experimental processes that led to the level of G4 ligand scientific maturity as we know it today. As further discussed below, this evolution has led to the validation by use of a handful of ligands only, chief among them pyridostatin and PhenDC3 (*vide infra*) as prototypical chemical biology tools, and QN-302 and CX-5461 whose design resulted from medicinal chemistry campaigns.

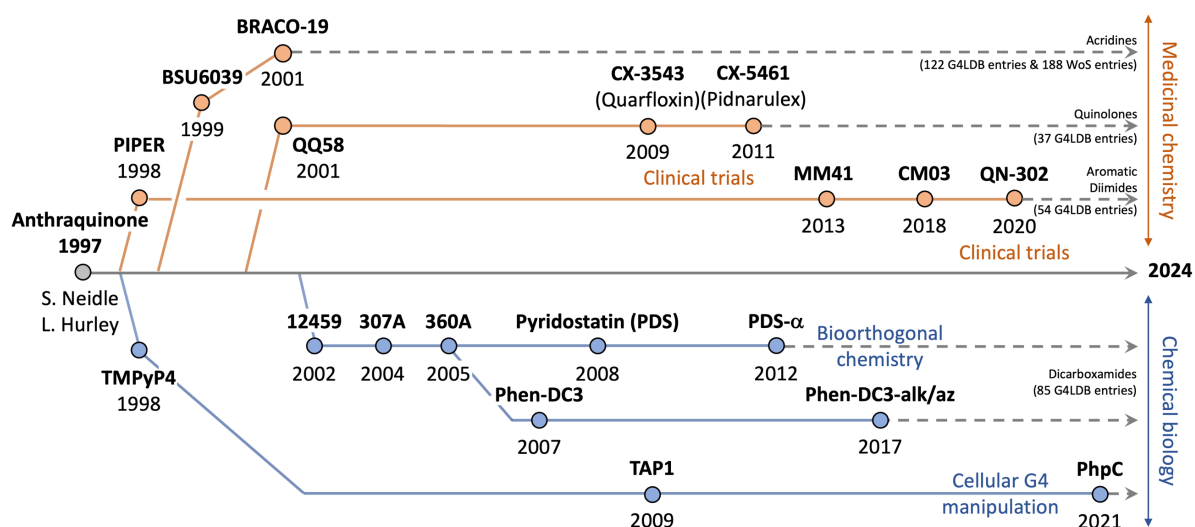


Figure 1. Tree structure showing the trajectories (from 1997 to 2024) taken by the most representative G4 ligands, which have led to investigations that are still ongoing (grey dashed arrows). These ligands are being used as molecular tools for applications in either medicinal chemistry (in orange, ending up with a series of clinical trials for Quarflorin, Pidnarulex and QN-302) and chemical biology (in blue, including bioorthogonal investigations and G4 manipulation at the cellular level). G4LDB: G4 ligand database; WoS: Web Of Science.

How has the field of quadruplex ligands fared since 1997?(20)

The answer to this question is undoubtedly “very good”! With more than 4000 G4LDB entries,(3) and roughly 200 articles/year (PubMed) published in the last couple of years, this field is quite active. While most if not all ligands developed so far intend to be used for therapeutic interventions in different areas (cancers,(17,21) neuropathologies,(22,23) viral infection,(24) etc.), a distinction can nevertheless be made between ligands that have pushed the understanding of G4 biology forwards, thereby abiding by the definition of chemical biology, and those whose applications in preclinical/clinical stages is now becoming a reality, thereby abiding by the definition of medicinal chemistry.

Chemical biology: the term ‘chemical biology’ was first coined by Linus Pauling in 1954;(25) since then, the definition has constantly evolved towards a functional approach in which chemicals are used as positive and/or negative modulators of biological systems to gain a deeper understanding of cell circuitries.(26,27) In the G4 field, chemical biology thus aims at using ligands to uncover the cellular pathways in which G4s play key regulatory roles. The success of this approach relies on both the G4 selectivity of the ligands used but also on their modularity: indeed, monitoring the cellular outcomes triggered upon ligand titration is an efficient way to gain insights into the G4-associated pathways, but it remains an overall analysis. It must be completed by a more detailed analysis in which a chemical manipulation of the ligand once in its cellular binding sites (so called bioorthogonal chemistry, defined as chemical reactions performed in biological environments without affecting biomolecules or interfering with biochemical processes) provides finer mechanistic details. This corresponds to the definition of molecular tools, and the recent developments of *in situ* click chemistry was a key asset for achieving this challenge.(28)

Pyridostatin (PDS, Figure 2) is an excellent example of G4 molecular tool, and certainly the most used ligands nowadays. While it may be hazardous to retrace the origin of a molecular design for others, that of PDS most likely originates in the successful development of pyridodicarboxamide (PDC) ligands, which themselves thrived from a series of bisquinolinium compounds developed as from 2002.(29,30) A private/public consortium steered by Jean-Francois Riou indeed identified a series of 1,3,5-triazines able to inhibit the telomerase enzyme by sequestering its substrate, the telomeric overhang, under a G4 structure that is not coped with by the enzyme efficiently.(29,31,32) Among these triazines, the compound 12459 was the most active (high G4 affinity evaluated by FRET-melting, excellent selectivity over duplex-DNA, and potent inhibitory effect on telomerase evaluated by TRAP assay). However, the known fragility of triazine cores in physiological conditions led the authors to change it for a pyridine, thus giving rise to the PDC series, whose leading compounds were first the asymmetrical 307A(33) and then, the symmetrical 360A.(34) The G4-interacting properties of 360A were excellent, established thanks to a wide selection of *in vitro* techniques (FRET-melting, SPR, ITC and G4-FID assays). It efficiently targets telomeres, as demonstrated by both its cellular localization using the radioactive ³H-360A and its ability to alter telomere biology (displacing telomere-binding proteins such as TRF1, TRF2 and POT1 and triggering telomeric DNA damage).(35)

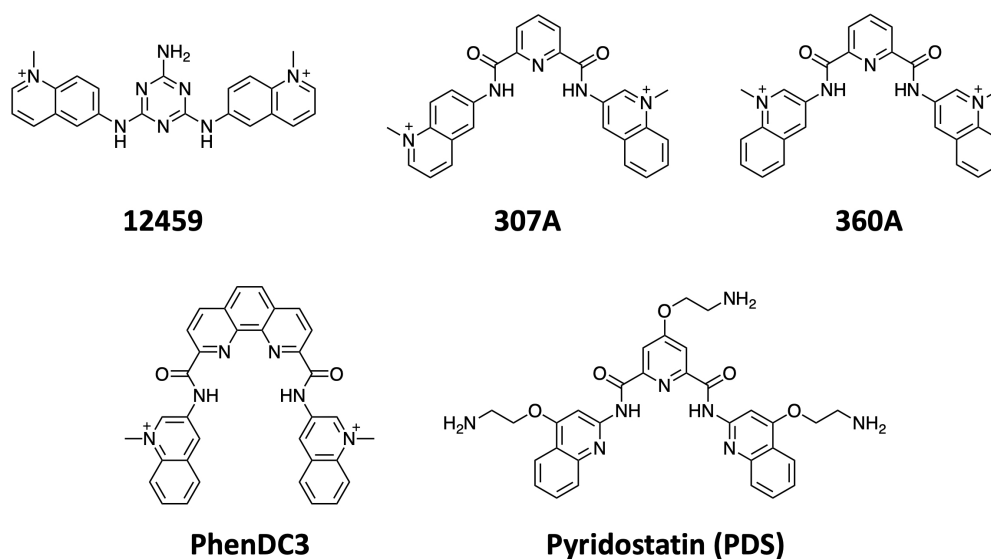


Figure 2. Chemical biology molecular tools: the dicarboxamide family

From there, two different strategies were followed to keep on improving the PDC properties: on one side, Marie-Paule Teulade-Fichou changed the pyridine core for a phenanthroline, which led to PhenDC3.(36) The structural organization of this molecule optimizes the overlap between the ligand and the accessible G-quartet of a G4, reaching a still unbeaten level of G4 affinity. On the other side, Riou and Shankar Balasubramanian changed the quinolinium arm for a 2-aminoethoxy-quinolin arm, pH-responsive and engageable in hydrogen bonds, which led to PDS.(37) Both strategies were successful as PhenDC3 and PDS display excellent affinity and selectivity for G4s, and are among the most studied and used G4 ligands to date. However, notable differences can be noted: in spite of comparable G4-interacting properties *in vitro*, the cellular properties of PhenDC3 and PDS differ because, while both ligands are toxic to cancer cells, the mechanism underlying their activity is different. The effects of PDS mainly originate in its ability to create DNA damage by physically trapping topoisomerase 2 (Top2) at G4 sites:(38) the resulting ternary complexes PDS/G4/Top2 is stable enough to hamper the motion of polymerases along the their duplex substrates, the collision leading to lethal double-strand breaks (DSBs). PhenDC3 does not trap Top2 neither trigger DNA damage; the reason for such a difference remains unknown at present. The cellular activity of PhenDC3 results from a combination of inhibitory effects, including that of telomerase (its localization at telomeres was demonstrated by nanoSIMS using Br-PhenDC3)(39) and of G4-helicases, which results in replication stress and genetic instability.(40)

Beyond the cellular investigations of their own properties, 360A, PhenDC3 and PDS have proven invaluable chemical biology tools for better understanding G4 biology, as demonstrated by both the versatility and scope of applications that their derivatives found. For instance, biotinylated PDS was used as a molecular bait for G4 capture and isolation experiments by affinity precipitation(41) while biotinylated 360A was involved in SELEX experiments.(42) These three compounds were conjugated to fluorophores (BODIPY for 360A and PhenDC3,(43,44) silicon-rhodamine for PDS)(45) to be used as G4-specific dyes in cells (fixed cells for 360A and PhenDC3, live cells for PDS). Bioorthogonal investigations were conducted with clickable analogues: PDS- α allowed for the very first visualization of G4s in human cells by *in situ* clicked with AF594-azide;(46) PhenDC3-alk and PhenDC3-az were used to track G4s in fixed cancer cells once being conjugated with a Cy5 probe;(47) and PDC-4,3-Alk was used either pre-clicked or *in situ* clicked with 5-BrdU-N₃ for being immunodetected by G4-GIS (G4-ligand guided immunofluorescence staining).(48) Proteomics were also performed using clickable and photoactivatable PDS derivatives: the development of both G4-LIMCAP (for G4 Ligand-mediated cross-linking and pull-down)(49) and CMPP (for co-binding-mediated protein profiling)(50) relied on PDB-DA-A, and photoPDS, respectively, which were used to identify G4-binding proteins in human cancer cells. These are just a few examples of multipurpose applications that are made possible using versatile molecular tools, and the 360A, PhenDC3 and PDS derivatives have achieved outstanding results in this field.

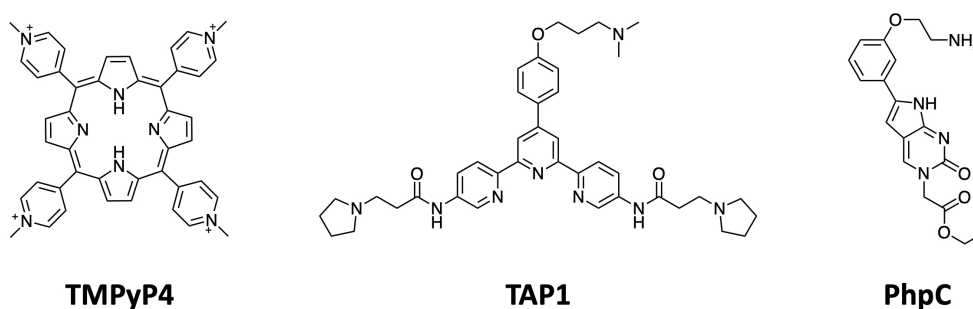


Figure 3. Chemical biology molecular tools: the G4-unfolder family

Finally, for fully abiding by the law of chemical biology, the involvement of G4 in cellular pathways should be ascertained on the basis of opposite outcomes monitored upon either positive (stabilization) or negative modulation (destabilization) of G4s by *ad hoc* molecular effectors. Although relevant, this approach was quite difficult to implement in the G4 field,

mostly because of the lack of reliable G4-destabilizing molecules.(51) Quite surprisingly, the development of such molecular tools arose out of the study of a ligand that has long been regarded as a benchmark G4 stabilizer, TMPyP4 (Figure 3), before being recognized as a troublesome ligand interacting with any DNA secondary structure thanks to efficient—but indiscriminate—electrostatic interactions. Hurley first identified TMPyP4 as a promising ligand and subsequently thoroughly investigated its effect on tumor cells.(52,53) One of his articles, published in 2002, is rightfully recognized as a reference in the field, providing the demonstration that a G4 located in the promoter region of a gene (*c-Myc*) might be targeted by a ligand (TMPyP4) to gain control over its expression.(54) However, only a year later, the first report on its G4 destabilizing properties (or, better put, on its higher affinity for the G4-prone sequence in its random-coiled conformation) was published by Michael Fry (co-authoring Hurley).(55) The consequences were two-fold: on one side, this prompted researchers to launch a series of investigations aiming at better understanding and controlling the TMPyP4's G4-interacting properties (which resulted in dozens of porphyrinic derivatives);(16) on the other side, this served as a demonstration that a small molecule could indeed disrupt a G4 structure and consequently as a basis for investigations aiming at uncovering more efficient (and selective) molecular G4 unfolders. The first step in this direction was taken with a terpyridine derivative (TAP1) published by Balasubramanian in 2009,(56) followed by a series of interesting prototypes(57) including the promising G-clamp analogue phenylpyrrolocytosine, known as PhpC,(58) whose ability to disrupt G4 structures was demonstrated both *in vitro* and in human cells.(59) It has to be noted that the quite paradoxical properties of TMPyP4 (stabilization *versus* destabilization) were found to be strongly dependent on the experimental conditions used, notably the excess of ligand (with respect to DNA) used during the experiments, which makes its use rather difficult to control. It has to be also noted that a single study has been reported to date in which the cellular consequences of G4 stabilization (PDS) *versus* destabilization (PhpC) were directly compared, which revealed both the extent and complexity of the involvement of G4s in multilevel and intricate regulatory networks.(60)

Medicinal chemistry: besides these chemical manipulations at the cellular level that ultimately aim at gaining deep insights into the roles that G4s play in cell circuitries, G4 ligands were also used for therapeutic purposes. According to John Neumeyer, citing Alfred Burger, medicinal

chemistry consists in “vary(ing) patiently the chemical structures of physiologically active compounds until a useful drug could be evolved as a tool in medicine”.(61) With hundreds of ligands developed so far, most if not all being declined in dozens of derivatives, a whole range of research activity in the G4 field complies with the definition of medicinal chemistry.

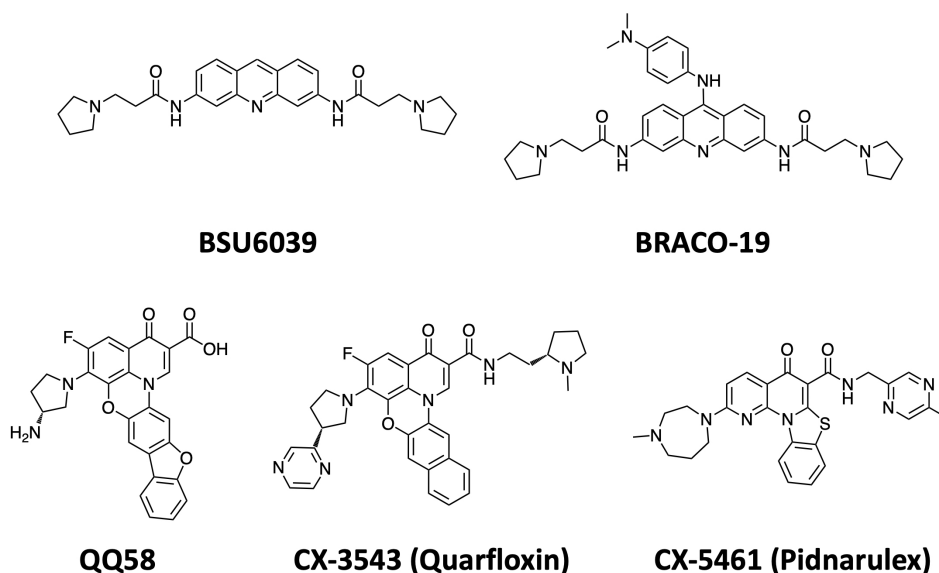


Figure 4. Medicinal chemistry molecular tools: the acridine (upper panel) and quinolone (lower panel) families

Shortly after its inception in 1997, the field of G4 ligands was fueled by Neidle on one side, who decided to change the initial 2,6-diaminoanthraquinone core for 3,6-disubstituted (BSU6039) and then 3,6,9-trisubstituted acridine core (BRACO-19),(62-64) (Figure 4) and Hurley on the other side, who divided his efforts between porphyrins (*vide supra*) and condensed polyaromatic ligands (the perylene-based PIPER, the quinolone QQ58). Neidle’s approach was driven by a crystal structure obtained with BSU6039(65) who provided fine details about how *i-* the acridine core lays atop the accessible G-quartet of a G4, *ii-* its flexible arms fit well within the entrance of 2 of the G4 grooves, and *iii-* secondary interactions between the ligand’s core and the surrounding loops further stabilizes the resulting DNA/ligand complex. This structure left open the possibility of strengthening the ligand binding by adding an additional arm on the central ring (9-position) of the acridine, to act as an extra anchor site within the third G4 groove. This led to the design of the trisubstituted BRACO-19,(66) and the crystal structure of its complex with G4 subsequently obtained confirmed that BRACO-19 is ideally designed to fit snugly within the G4 ligand binding site,

structurally defined by the space between the G-quartet, grooves and loops.(67) From a medicinal chemistry point of view, this crystal structure also explained why none of the many BRACO-19 derivatives outperformed the parent compound in terms of G4 binding. The antiproliferative activity of BRACO-19 against cancer cell proliferation *in vitro* were remarkable, acting by a multilevel mode of action including telomerase downregulation, but its translation to animal models (xenografted mice) revealed some limitations in terms of both availability and stability.(68-70) A derivative named AS1410,(71) developed in collaboration with Antisoma PLC., was designed to circumvent these issues, but its preclinical studies were stopped due to an elevated off-target toxicity.

In parallel to these efforts, Hurley bet on other series of well-established DNA interacting motifs to create new ligands, the fluoroquinolone on one side and the perylenetetracarboxylic diimide (PDI) on the other side. Fluoroquinolones were known to act as Top2 poisons, thanks to their efficient DNA-intercalating properties. Hurley decided to extend their aromatic surface to optimize G-quartet interactions, and changed the fluoroquinolone core for a quinobenzophenoxazine core, found to have lower Top2 poisoning activity and higher G4-stabilizing and telomerase inhibiting properties.(72) The lead compound, QQ58,(73) displayed quite interesting properties but was not pushed forward because Cylene Pharmaceuticals bet on 2 other derivatives, Quarfloxin (CX-3543)(74) and then Pidnarulex (CX-5461),(75) which were soon enrolled in clinical trials (Figure 4). Quarfloxin was initially thought to target c-Myc G4 but its mechanism of action was revisited because the engagement of c-Myc G4 was unclear: instead, it was shown to mostly interact with ribosomal DNA (rDNA) G4s, where it precluded the binding of the G4-affinic protein nucleolin and inhibited the processivity of RNA polymerase I (RNA Pol I), in charge of the production of ribosomal RNA (rRNA). Quarfloxin enters clinical trials in 2005 (patients with advanced solid tumors, NCT00955786; with low-to-intermediate grade neuroendocrine carcinoma, NCT00780663; with relapsed B-cell chronic lymphocytic leukemia, NCT00485966) but these studies were stopped because it was found not active enough to warrant further investigations. Cylene Pharmaceuticals then focused on Pidnarulex, which was structurally optimized to inhibit RNA Pol I. Dozens of studies from different labs provided a corpus of results from which a multiple mechanism of action can be inferred: Pidnarulex stabilizes G4s and from there, triggers a series of G4-mediated cellular events including DNA damage (that has been exploited in chemically induced synthetic lethality cocktails)(76) and Top2 inhibition (the enzyme being physically trapped at ligand-

stabilized G4 sites).(38,77,78) Pidnarulex enters clinical trials in 2013 (patients with advanced haematologic malignancies, ACTRN12613001061729; with metastatic prostate cancer in combination with Talazoparib, NCT05425862) but the responses obtained were partial, along with serious concerns about phototoxicity issues. These responses were later found to be correlated with genetic predisposition to DNA repair deficiencies: on this basis, another trial was launched in 2021 selecting patients with BRCA1/2, PALB2 or homologous recombination (HR) deficiencies (NCT02719977(79) and NCT04890613, ongoing). However, it was recently reported that caution must be exercised when using Pidnarulex, owing to its high mutagenic potential, further highlighting the need for deciphering the mechanism(s) underlying its therapeutic activity.(80)

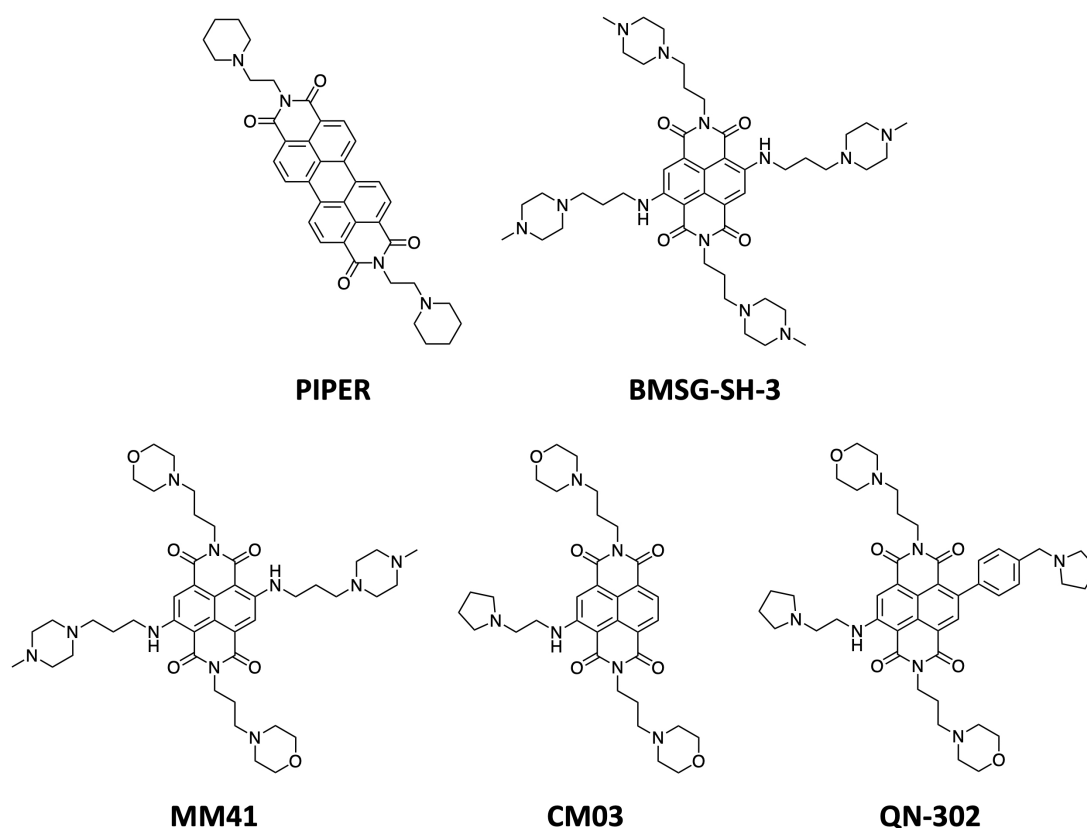


Figure 5. Medicinal chemistry molecular tools: the aromatic diimide family

The other thread of Hurley's research focused on perylene-based PIPER (Figure 5).(81) This molecule was found quite effective *in vitro* but its ability to self-aggregate, along with its rather limited water solubility, somehow hampered its further use.(82,83) However, the corresponding but smaller naphthalenetetracarboxylic diimide (or naphthalenediimide, NDI)

core, circumvented most of the limitations of PIPER. Indeed, the several generation of NDIs, initially investigated by Manlio Palumbo(84) and developed by Neidle,(85) then by several research groups in Italy, chief among them Mauro Freccero(86) and Sara Richter,(87) shine by their modularity: NDI can have 2 to 4 amine-containing arms (symmetrical, or not) and their core can be extended in order to fully control not only their G4-interacting properties but also their water solubility, self-aggregation propensity and spectroscopic properties. Neidle notably designed and optimized a series of NDIs and assessed their anticancer activity against a panel of cancer cell lines. One of his first hits was a tetra-substituted NDI referred to as MM41 (Figure 5).(88) Its design resulted from an attempt to decrease the cationic charges of the very first prototype of G4-binding NDI BMSG-SH-3,(85,89) by changing two of the four N-methyl-piperazine sidearms with less basic morpholino sidearms. MM41 was found active against both cultured pancreatic ductal adenocarcinoma (PDAC) cell proliferation (MIA PaCa-2 cells, IC₅₀ value of *ca.* 10 nM) and corresponding xenografts, through a mechanism involving the down-regulation of a series of cancer-related genes, notably *Bcl2* and *KRAS*, likely upon interaction with their promoter G4s.(90) The crystal structure of the human telomeric G4/MM41 complex indicated that the fourth sidearms minimally participated to ligand binding;(88) removing it led to the second hit, a three-armed NDI referred to as CM03.(91) This NDI displayed slightly better antiproliferative activity against cultured cancer cells than CM03 and was used *in vivo* against both models of PDAC and gemcitabine-resistant cancer cell lines.(92) A transcriptome-wide (RNA-seq) analysis indicated that CM03 massively downregulates the expression of genes (*ca.* 600 genes), notably that of numerous PDAC-related genes (*ca.* 60 genes, including *MAPK11* for instance), by interacting with the G4s found in their sequences. A further optimization of its G4 affinity by adding a fourth sidearm comprising a phenyl unit able to stack atop the terminal G-quartet resulted in the third hit, named QN-302 (formerly reported as SOP1812).(93-95) It was found to be 10-fold more active *in vitro* than CM03 (with an IC₅₀ value of *ca.* 1 nM) and of superior potency in animal models of PDAC. This improved properties were ascribed to its better G4-interacting properties, originating in both the stacking properties of the phenyl unit of this additional arm and the protrusion of its pyrrolidino tail further into the fourth G4 groove. A comparison of RNA-seq data obtained with CM03 and QN-302 indicated that both compounds affected the same pathways, although to a greater extent for QN-302, with a subset of genes (*ca.* 80 genes) found to be specifically down-regulated by QN-302.(96) Among the most down-regulated genes was

S100P, which is strategically interesting as it is known to be up-regulated in PDAC and thus, considered to be a valuable target for therapeutic intervention. QN-302 was selected by Qualigen Therapeutics as a clinical candidate and recently (in Nov. 2023) engaged in a phase I clinical trial (patients with advanced or metastatic solid tumors, NCT06086522). It is to date the most advanced G4-targeting agent under clinical assessment.

Conclusion.

“Straight roads do not make skillful drivers” (from ‘The fifth mountain’, P. Coelho, 1996). The path followed by G4 ligands from their inception in 1997 to their current state of maturity in 2024 was anything but straight. There were turns and U-turns, cross-roads and dead-ends, acceleration and deceleration, which made this field sometimes daunting but always fascinating for the intrepid drivers. Stephen Neidle was one of them and for sure among of the most skillful ones. He not only developed the different families of G4 ligands described above and provided a detailed structural basis for their interaction with their G4 targets, he was also involved in the study of many other ligands (*e.g.*, berberine(97) and cryptolepine(98) derivatives, bistriazole-(99) and diarylurea-based(100) ligands, to name but a few). He also play the most active role in accelerating the translation from *in vitro* studies to cell-based assays and xenograft models, till his recent achievement in having one of his compounds now under clinical evaluation in humans. His endless energy and scientific curiosity drove the community forward for decades, and the community will never be grateful enough for his contributions. To do everything possible to keep on advancing the field of G4 ligands is the best way we have of thanking him for his unwavering dedication.



Graphic for the Table of Content

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