Details of the research work duly signed by the applicant, for which the Sun Pharma Science Foundation Research Award is claimed, including references and illustrations (not to exceed 6000 words).

Modulating the Structure and Function of Non-canonical Nucleic Acids for Anticancer and Antimicrobial Therapies

Nucleic acids, apart from the right-handed double-helical structure, can adopt various non-canonical secondary structures; among which G-quadruplexes and i-motifs are well-studied. G-quadruplex (G4) and i-motif (iM) are four-stranded non-canonical nucleic acid secondary structures formed from guanine (G)-rich and cytosine (C)-rich sequences, respectively. Majority of these secondary motif forming sequences are prevalent within the regulatory regions of the genome, particularly within the promoter region of various genes (*c-MYC, VEGF, BCL-2, KRAS, c-KIT, etc*) and in the telomeres, suggesting their role in gene regulation (Figure 1).[1]

G-quadruplexes are mostly believed as a repressor of gene expression whereas stabilization of i-motifs is mainly associated with transcriptional activation. The contradictory biological role of i-motifs and G-quadruplexes is coordinated in living cells by the simultaneous or mutually exclusive formation of these structures. Therefore, targeting G-quadruplex or i-motif with small molecules may lead to prospective cure for cancer and other genetic diseases. Hence these non-canonical DNAs are potential targets for drug design and modulation of gene expression.

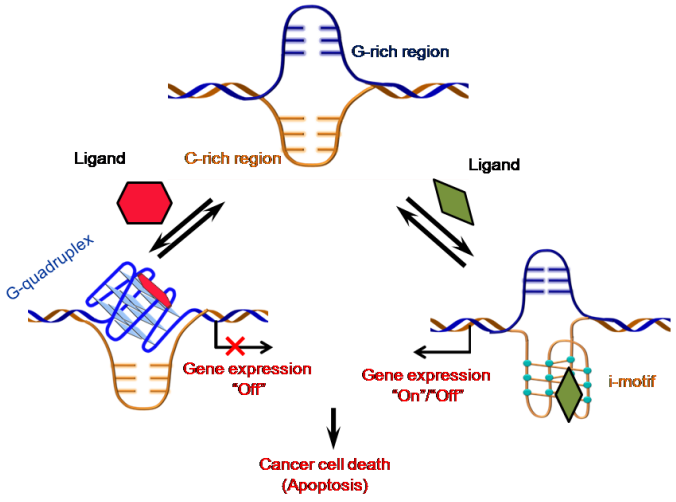


Figure 1. Regulation of gene expression by G4 and i-motif.

(A) Regulation of gene expression by targeting G-quadruplexes and i-motifs for cancer therapy: Till date a wide range of G-quadruplex binding molecules,[3] as well as a few i-motif binding compounds are reported in the literature[4]. With the genome largely existing in a duplex structure, it is of utmost importance that a ligand should specifically bind towards a particular G-quadruplex or i-motif structures and show little or no interactions with double helical DNA. Additionally, it is desirable for the ligands to have amenable properties, like stability under

physiological conditions, low toxicity and specific interaction with a particular quadruplex/i-motif topology in biological system. This would provide a good basis for a therapeutic window, where the molecules interact with the target DNA secondary structures without too many undesirable side effects.

Dr. Dash and her group used both rational design and target-guided synthetic methods to design novel molecular probes for understanding the structure and functional role of nucleic acid secondary structures in cellular system.

(1) Rational design of ligands: Prof. Dash and her group has used copper (I) catalyzed Huisgen1,3-dipolar cycloaddition (CuAAC) to synthesize a series of compounds (1-15) as selective G-quadruplex/ i-motif DNA binders (Figure 2). They have employed click chemistry to functionalize different heteroaromatic moieties with appropriate side chains to generate triazole ring systems that display efficient binding abilities for DNA quadruplexes of different topologies and show significant biological activities in cellular systems.

Her group has designed novel molecular probes like nucleosides, peptidomimetics and heteroaromatic ligands that exhibit high binding affinity for the different G-quadruplexes or i-motif structures (*c-MYC* G-4, *c-KIT1* G-4, *hTELO* G4, *BCL2* iM, etc.) and inhibit cellular proliferation in cancer cell lines.[5-18] Different biological analysis like dual luciferase assay, Western Blot analysis and qRT-PCR established that these ligands repress the respective gene expression by promoter G-quadruplex stabilization. They also reported a peptidomimetic moiety that shows high selectivity for i-motifs and upregulates *BCL2* gene expression by targeting *BCL2* promoter i-motifs, exhibiting significant antiproliferative activities in different cancer cells.[19] In 2020, Dash et al. reported another prolinamide-derived peptidomimetic ligand PBP2 (10) that binds selectively to G-quadruplex structures and could induce synthetic lethality in MCF7 breast cancer cells by repressing both *c-MYC* and *BCL2* gene expressions.[13] These ligands could be useful for clinical studies on cancer therapeutics.

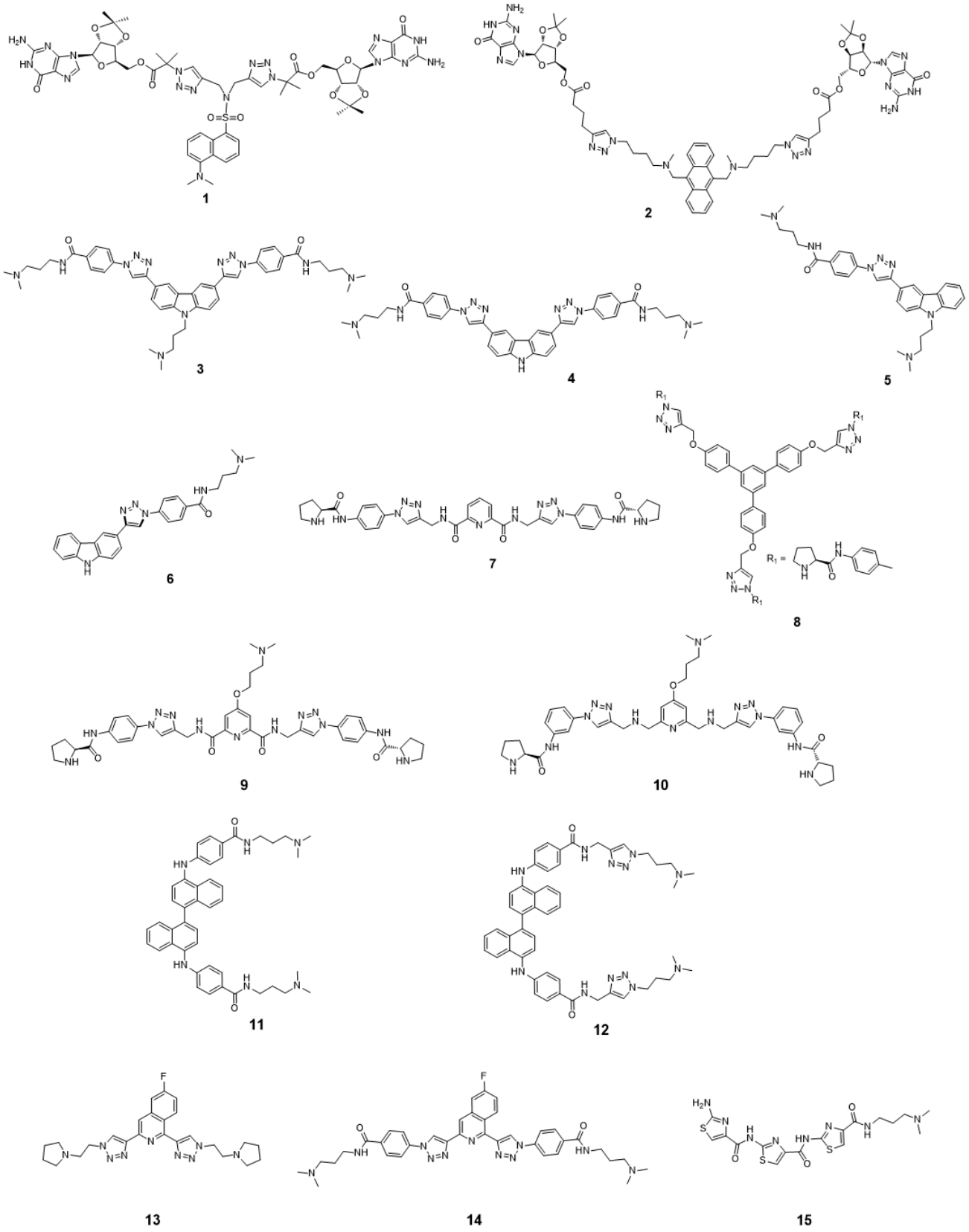


Figure 2. Structure of ligands (1-15).

Synthesis of PNA mimics: PNAs are synthetic analogues of natural nucleic acids that can undergo complementary base pairing with themselves as well as DNA or RNA by Watson–Crick base pairing. These molecules can be used for sequence specific targeting of biologically relevant genes, contributing towards genomic alterations. However, the major limitation of PNAs is their poor cellular permeability and water insolubility due to formation of a globular structure. Chemical modification of PNAs can abrogate these inherent shortcomings of PNAs making these molecules as powerful candidates for anticancer therapeutics. Prof. Dash and her group synthesized PNA-like scaffolds by incorporating five-membered thiazole rings as modified bases instead of nucleobases and studied their subsequent effects on gene regulation by biophysical and in vitro assays.[20] A thiazole-modified PNA trimer Thz-3 (25) selectively binds and stabilizes c-MYC G4 DNA over other G4s and duplex DNA. Furthermore, the PNA trimer easily permeates the cellular membrane and suppresses c-MYC mRNA expression in HeLa cells by targeting the promoter G4 (Figure 3).

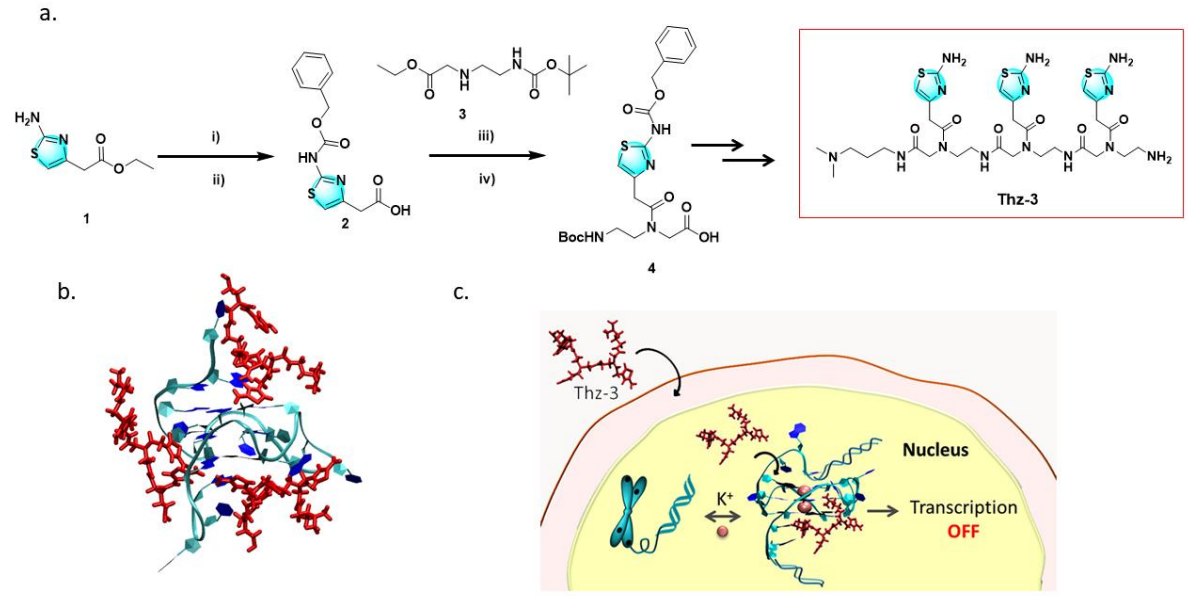


Figure 3. PNA mimics targeting c-MYC G-quadruplex

(2) Target-guided synthesis of selective ligands: Dash and co-workers also used target guided combinatorial methods like kinetically controlled in-situ cycloaddition and thermodynamically controlled dynamic combinatorial chemistry (DCC) using DNA-linked gold coated magnetic nanoparticles for synthesizing selective ligands (16-23) specific for a particular G-quadruplex or i-motif structure (Figure 4).

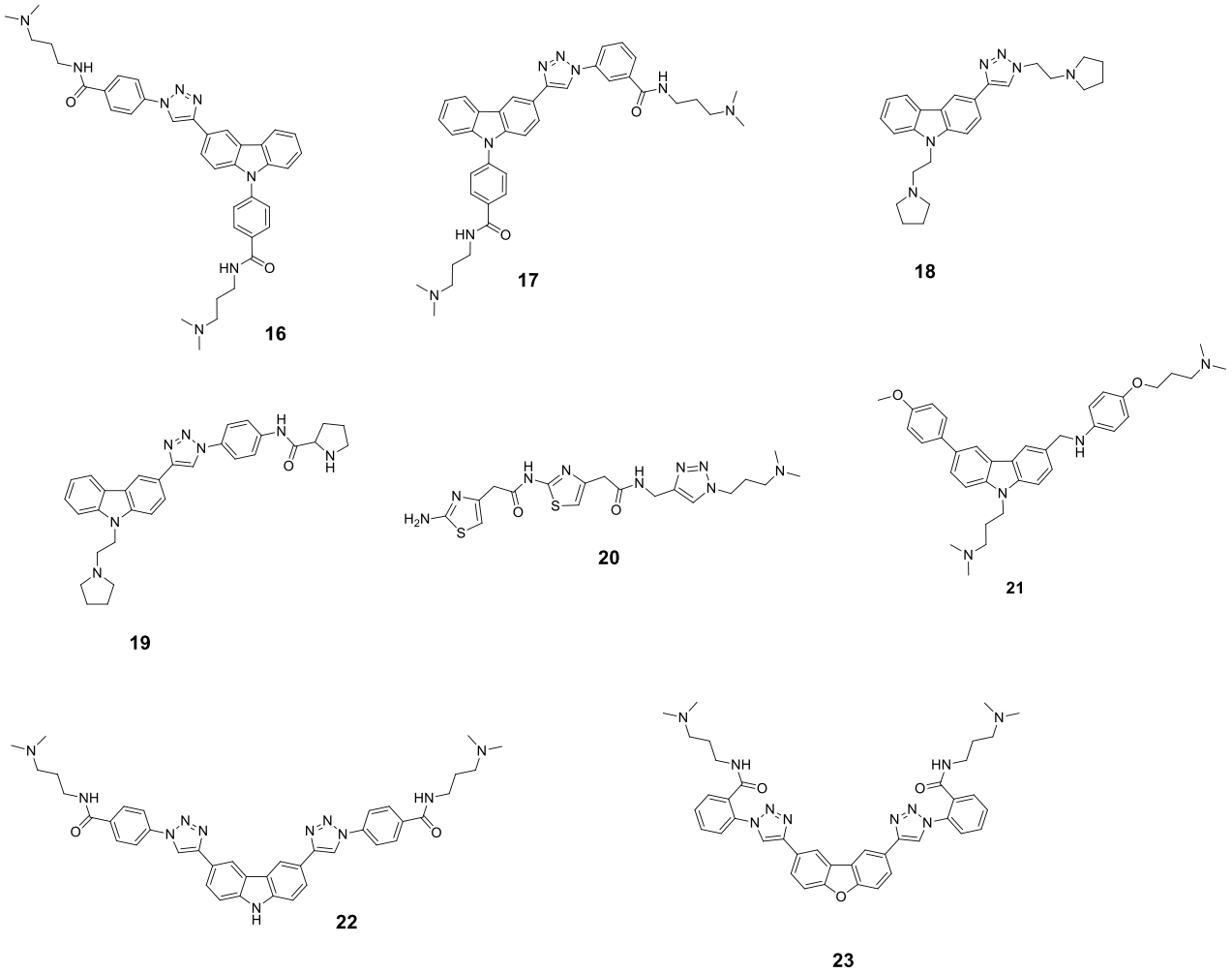


Figure 4. Structure of ligands (16-23).

Dr. Dash and her team introduced an innovative approach for the target guided synthesis (TGS) of G-quadruplex ligands in which Cu free in-situ click reaction, using DNA as a nano-template, has been employed[21] (Figure 5). The DNA nano-template has been devised by immobilizing *c-MYC* G-quadruplex gold coated magnetic nanoparticles. The DNA nano-template facilitates the cycloaddition of azide and carbazole-alkyne fragments, generating selective high affinity quadruplex ligands. The generated ligands can easily be isolated by magnetic decantation and the G-quadruplex nano-template can be easily recovered and recycled. This approach has also been used to develop specific ligands for G-quadruplex (16,17) or i-motif (18, 19) structures.[19]

The design and synthesis of ligands capable of binding to i-motifs are challenging due to the pH-dependent structural complexity of i-motif DNAs. In this regard, target guided synthesis (TGS) appears to be a promising methodology for the discovery of specific and high-affinity i-motif ligands. Dash et al. have used *c-MYC* and *BCL2* i-motifs as the templates to generate selective ligands from a pool of reactive azide–alkyne building blocks. Thiolated DNA targets are immobilized on the surface of gold-coated iron nanoparticles to enable efficient isolation of the newly generated ligands from the solution mixture by simple magnetic decantation. The in-situ cycloaddition provided triazole leads (18 and 19) for *c-MYC* and *BCL2* i-motif DNA. *In vitro* cellular studies revealed that the *c-MYC* i-motif lead 18 downregulates

the *c-MYC* gene expression whereas the *BCL2* i-motif lead 18 upregulates the *BCL2* gene expression.[19]

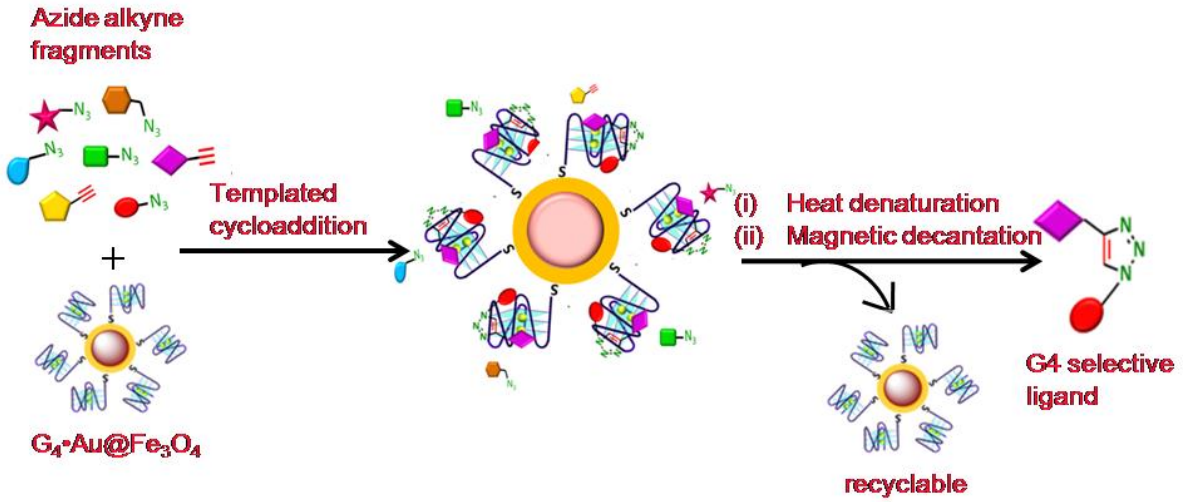


Figure 5. Target guided approach for the synthesis of selective G4 ligands

Apart from generating selective ligands for non-canonical DNA structures like G-quadruplex and i-motif by TGS approach, this methodology has also been used to design ligands specific for TAR RNA.[22] Human immunodeficiency virus type-1 (HIV-1) contains a cis-acting regulatory element called TAR RNA that can form a stable hairpin structure. This highly conserved element binds to the trans-activator protein Tat and facilitates viral replication in its latent state.[23] The inhibition of Tat–TAR interactions by selectively targeting TAR RNA can, therefore, be used as an anti-HIV therapeutic strategy. Biotin-tagged TAR RNA has been used to assemble its own ligands from a pool of reactive azide and alkyne building blocks. The hit triazole-linked thiazole peptidomimetic products have been isolated from the biotin-tagged target templates using streptavidin beads. The major triazole lead 20 generated by the TAR RNA presumably binds to the hairpin structure, showing specificity for TAR RNA over TAR DNA and effectively inhibits Tat–TAR RNA interactions.

In another study, a nanotemplate-guided Dynamic Combinatorial Chemical method has been employed to generate specific carbazole derived ligands for the *c-MYC* promoter G-quadruplex.[24] The gold-coated magnetic nanoparticle-conjugated G-quadruplex DNA has been used as the template for the dynamic selection of ligands from a pool of carbazole aldehyde and amine building blocks. The lead compound 21 selectively binds to *c-MYC* G4 DNA over dsDNA, suppressing the expression of *c-MYC* gene. Moreover, the ligand **21** can enter the nucleus and induce DNA damage in cancer cells.

(3) A pull-down screening assay to identify potent anticancer agents: Prof. Dash and her team has developed a simple, high-throughput, and reliable screening method to identify selective ligands for a particular G-quadruplex topology from a series of small molecules[25] (Figure 6). In this method, G-quadruplex linked magnetic gold nanoparticles (NP) have been used which could efficiently select high affinity binder for the G4 from a pool of ligands. Unbound ligands were eliminated by simple magnetic decantation. These DNA linked nanoparticles are easily synthesizable and can be reused; making it a cheap screening method.

In addition, this technique is applicable to any ligands independent of their solubility, UV absorbance, and intrinsic fluorescence properties, allowing quick screening of large compound libraries. Initially, the group optimized this competitive screening method with known G4 ligands and then used a new series of G-quadruplex interactive bis-triazolyl ligands (22 and 23) to identify the most potent binders for *c-MYC* and *BCL2* G-quadruplexes. The ligands, thus identified, show specific binding ability for distinct G4-DNAs in the cellular system and exert significant anticancer activities.

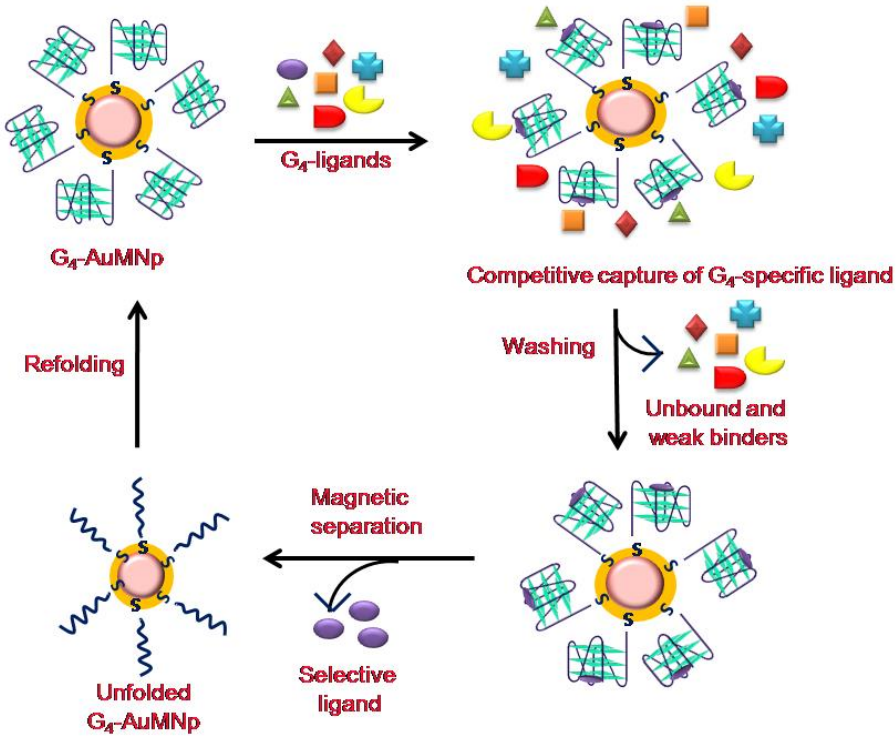


Figure 6. G4-AuMNps-mediated pull-down-based screening assay.

(4) Bio-orthogonal synthesis of ligands within cellular systems: Recently, Dash and co-workers demonstrated that DNA G4s can promote macrocyclization-like challenging reactions, enabling the synthesis of molecules specifically designed for modulating gene function (Figure 7).[26] The planar G-quartets present within DNA G4s provided a size complementary reaction platform for the macrocyclization of bifunctional azide and alkyne fragments from a pool of reacting fragments. G-quadruplexes were grafted on magnetic nanoparticles for easy identification of the best binder from the reaction mixture. The peptidomimetic macrocyclic ligand M1 (24) exhibited excellent binding affinity for G-quadruplexes. They also demonstrated that the bio-orthogonal in situ click reaction using bifunctional azide and alkyne fragments enabled selective and controlled synthesis of macrocyclic ligands within living cells without interfering with the DNA G-quadruplex biomolecules. The macrocyle along with its unreacted azide exhibited excellent downregulation of oncogene expression in cancer cells. This approach combining the unique properties of DNA G4s and the selective synthesis enabled by biorthogonal chemistry provides new avenues for designing and optimizing anticancer drugs with enhanced efficacy and specificity.

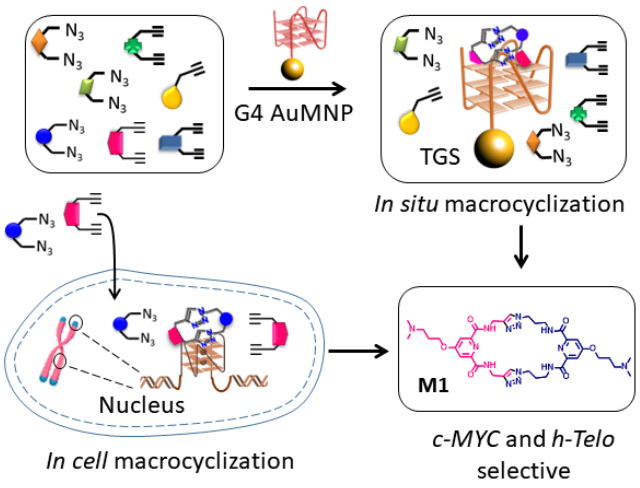


Figure 7. Target guided Bio-orthogonal synthesis of ligands within cellular systems

(B) Targeting non-canonical nucleic acids to combat antimicrobial resistance: Antibiotic resistance poses a significant global health threat, necessitating innovative strategies to combat multidrug-resistant bacterial infections. In this context, Dash and group introduced a novel approach to counter antibiotic resistance by stabilizing G-quadruplex structures within the open reading frames of key resistance-associated genes in the pathogenic bacteria *Streptococcus pneumoniae*.[27] They synthesized a bis-anthracene derivative An4 (26) that significantly reduced ciprofloxacin resistance in multidrug-resistant bacterial strains by 12.5-fold through enhanced drug retention and downregulation of drug efflux gene expression (Figure 8). This study presents a pioneering strategy to combat antibiotic resistance by genetically reducing drug efflux pump expression through G-quadruplex stabilization, offering promising avenues for addressing antibiotic resistance.

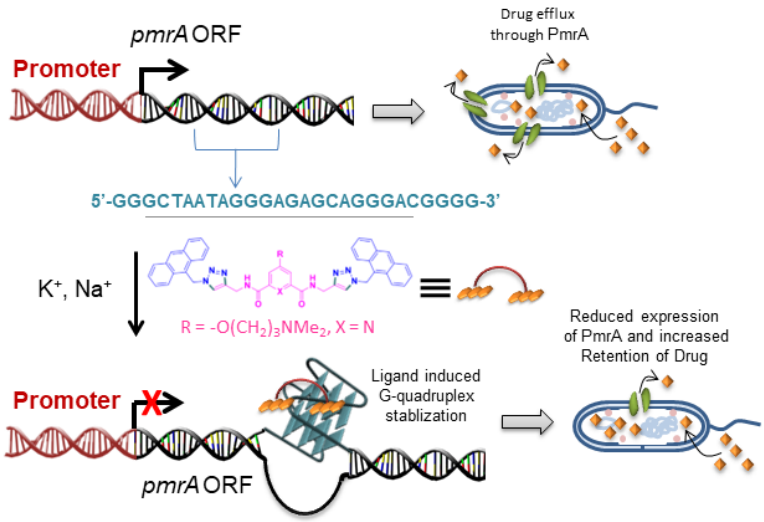


Figure 8. G4 binding inhibitor combats drug resistance in *S. pneumoniae*

(C) Small molecule-DNA based biomolecular devices: DNA secondary structures are not only useful for biomedical applications but also exhibit profound applications in the field of bio-nanotechnology. Both G-quadruplex and i-motif structures have emerged as versatile scaffolds to fabricate different programmable nanostructures. In Prof. Dash's group, they have used DNA secondary structures and their components to construct bio-nanowires, logic gates and enzyme regulated DNA based devices, transmembrane ion channels that have potential applications in sensing and therapeutics (Figure 9). DNA secondary structure interacting ligands 27, 28 have been used for detection and induction of nanoarchitectures of human telomeric quadruplex[28].

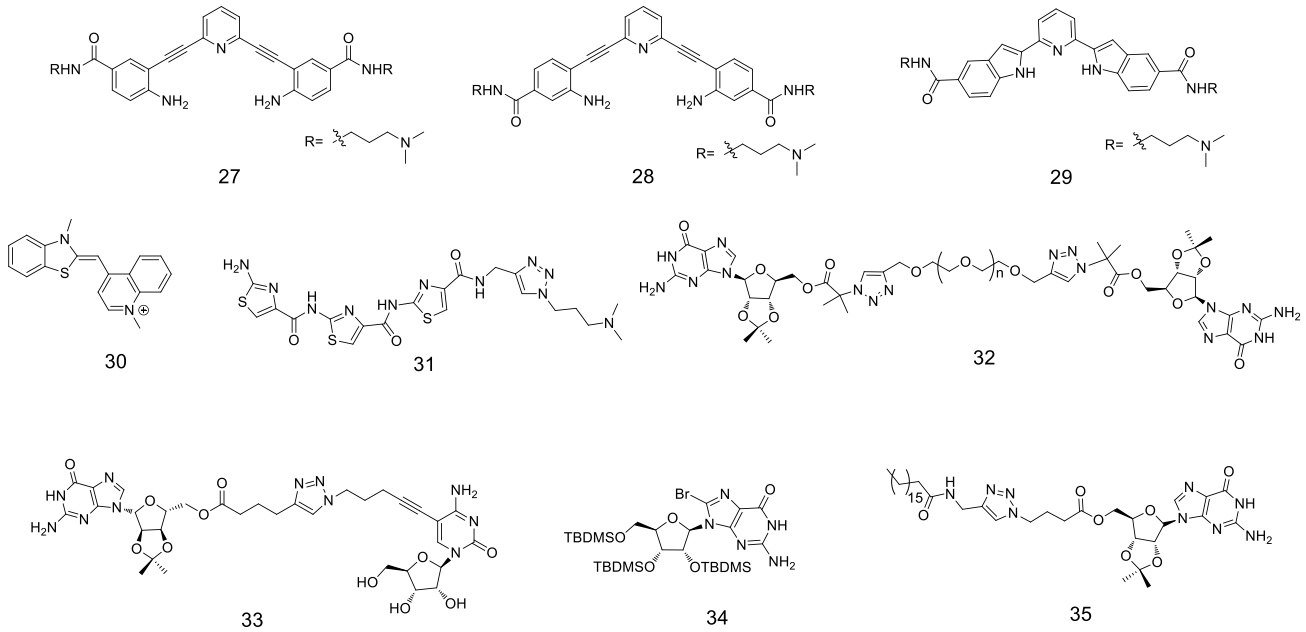


Figure 9. Structure of ligands 27 – 35.

(1) Nucleic acid-based logic devices: G-quadruplex-small molecule interactions have also been used to fabricate DNA logic gates with pH as an external modulator.[29] They demonstrated by fluorescence spectroscopic study that the fluorescence intensity of a mixture of bis-indole based G4 ligand (29) and *c-KIT2* G-quadruplex DNA increases with increase in pH and decreases with a decrease in pH. Using another 'turn-on' quadruplex binding ligand thiazole orange (30), a variety of logic operations (XNOR, NOR, AND, NAND and NOT) have been devised based on the interactions of the small molecules (29 and 30) among themselves and with the *c-KIT2* promoter quadruplex sequence with pH as an external modulator. In another study, they synthesized a carbazole probe 4 that exhibits distinct turn-on fluorescence responses upon interaction with *h-TELO* and nuclease enzymes (DNase I and nuclease S1)[30]. This differential fluorescence behavior of ligand-stabilized *h-TELO* in the presence of different nucleases has been used to construct a sensor device to detect the activity of DNase I as well as performing various logic operations, which may be useful for designing intelligent biomolecular machines (Figure 10).

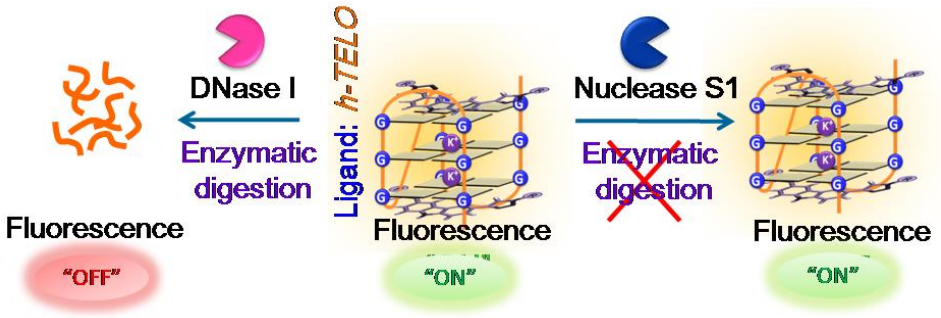


Figure 10. Differential activity of enzymes on ligand bound DNA.

Recently, in 2024, Dash and co-workers developed pH-responsive logic devices using HIV-1 TAR hairpins in combination with a thiazole peptide (31) that exhibits turn-on fluorescence upon interacting with TAR RNA or DNA. The pH alteration leads to conformational changes of the hairpin structure, enabling the construction of a multi-reset reusable logic system which could be developed for *in vitro* sensing of the HIV-1 viral RNA[31].

(2) Ion channels: The development of artificial ion channels that can mimic the fundamental functions of the natural ones would be of great importance to biological research. Dash et al. synthesized bis-guanosine derivatives 32 with covalent spacers that can self-assemble in the lipid bilayer to form channel like structures and can modulate the traffic of various ions (Na^+, K^+ and Cs^+) across the phospholipid bilayer (Figure 11A)[32,33]. In another study, they constructed an artificial transmembrane ion channel using a self-complementary G-C bis-nucleoside by one-pot modular azide-alkyne cycloaddition (Figure 11B).[34] Her group has also reported the self-assembly of a lipophilic tert-butyldimethylsilyl (TBDMS) protected bromo guanosine derivative G1 (34) that can form discrete transmembrane ion channels specific for K^+. These also exhibit strong birefringence upon exposure to polarized light, which can be used in different applications like data storage, development of optical devices and bio-imaging[35]. In a pioneering work, her group demonstrated that a lipophilic guanosine (MG) (35) non-covalently stabilizes a quadruplex and promotes its insertion within lipid bilayer. The resulting DNA ionophore selectively transports K^+ ions across cellular membranes (Figure 11C)[36].

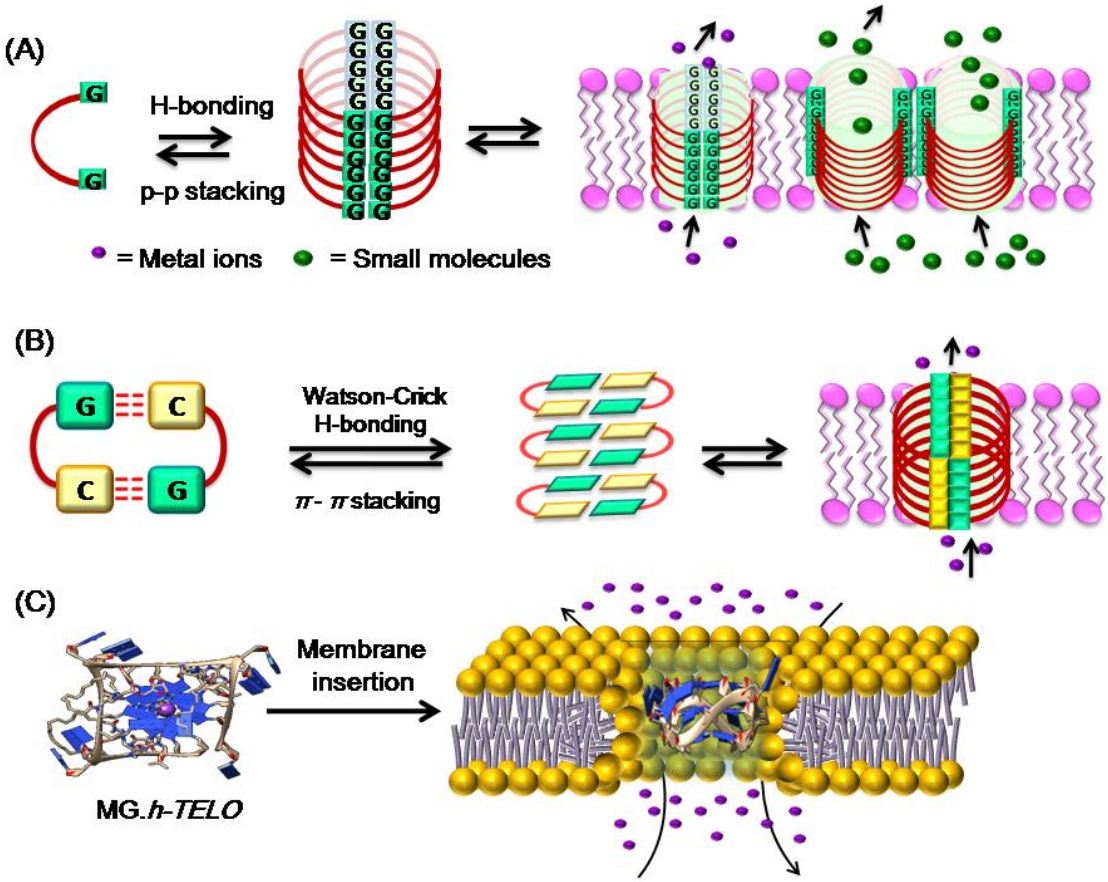


Figure 11. Artificial ion channels based on nucleoside derivatives.

Very recently, Prof. Dash and her group synthesized a thiazole-based DNA binding peptide mimic TBP2 (36) which exhibits the unique ability to form self-assembled nanostructures in lipid microenvironments and effectively transports K^+ and Na^+ ions across model lipid bilayer membranes. Moreover, TBP2 inhibits cancer cell growth by modulating intracellular ion concentrations and G-quadruplex-mediated transcriptional regulation of oncogenes[37] (Figure 12).

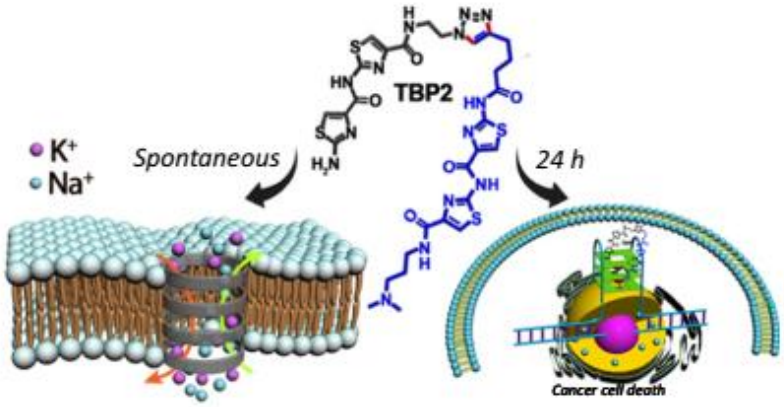


Figure 12. Peptidomimetic channel TBP2 forming gated ion channels and inducing cell death

(3) Hydrogel: Prof. Dash also used G-quartet, basic building of G-quadruplexes as a molecular template to design hydrogels with various biomedical applications. They developed a novel G-quartet hydrogel construct, prepared from guanosine and phenylboronic acid in the presence of K^+ and Pb^{2+} ions[38] (Figure 13A). The K^+ stabilized hydrogel binds to iron (III)-hemin and shows DNAzyme like peroxidase activity, catalyzing oxidation of 3,3,5,5'-tetramethylbenzidine (TMB) in the presence of H_2O_2. Furthermore, the conformation of the G-quartet assemblies in the hydrogel can be altered by varying the K^+ and Pb^{2+} ions and this conformational switching has been used to devise a molecular logic gate for sensing of toxic Pb^{2+} ions. Recently. it was demonstrated that the guanosine hydrogels can facilitates the macrocyclization of bis-azide and bis-alkyne fragments. The resulting macrocycle enhances viscoelastic properties, and strengthens the hydrogel network. This approach holds potential for synthesizing drugs *in situ* and delivering them in a stimuli-responsive manner.[39,40] In another study, cytidine nucleoside, boronic acids have been used to prepare hydrogel in the presence of Ag^+ ions[41,42] (Figures 13B). These hydrogels, presumably formed by an i-motif like arrangement of cytidine and its boronate ester analogues, possess excellent thixotropic and self-healing properties. Moreover, these hydrogels show potent antibacterial activities against various Gram-negative bacteria[41] and antileishmanial activities[42]. These hydrogels could therefore find promising applications in combating microbial skin infections by topical treatment.

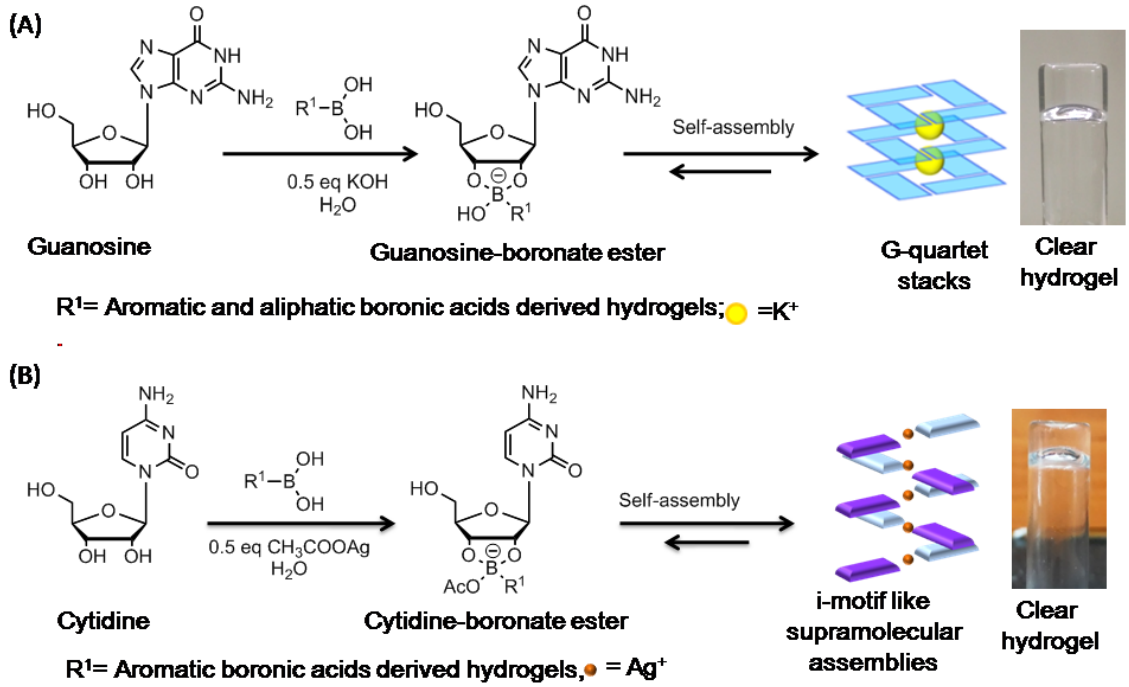
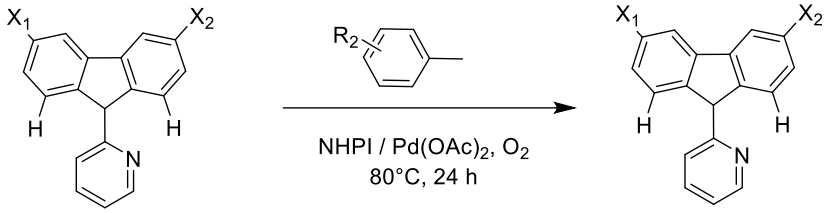


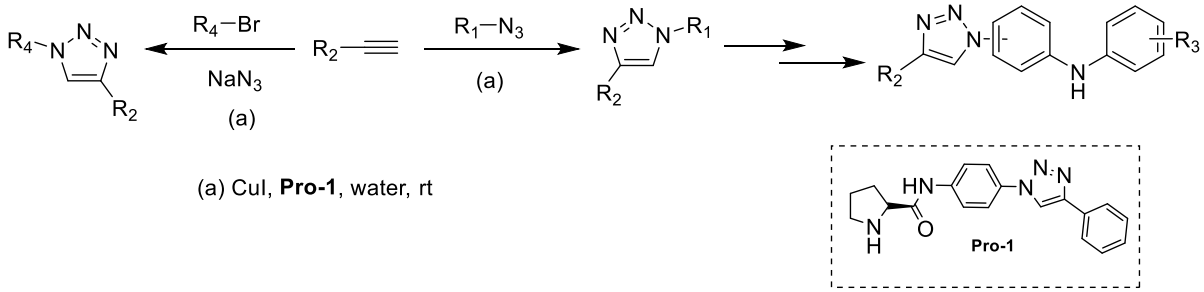
Figure 13. Nucleoside derived supramolecular hydrogels.

(D) Synthesis of biologically active compounds: The most significant contributions of Prof. Dash in this area are development of new approaches for the development of naturally occurring alkaloids, and other natural products. These methods may find industrial applications for the synthesis of natural products and complex organic molecules.
Some of the contributions of Prof. Dash in this field are as follows.

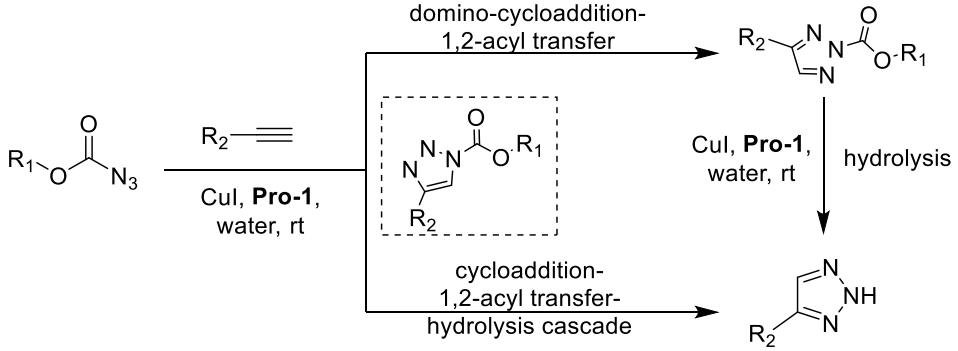
1. A palladium-catalyzed monoacylation of carbazoles using toluene derivatives, in presence of NHPI as the cocatalyst and oxygen as the oxidant has been delineated. The acylation of monosubstituted N-pyridylcarbazoles using aldehydes, takes place regioselectively at the C-8 position. This highly site-selective acylation proceeds through a radical process.[43]



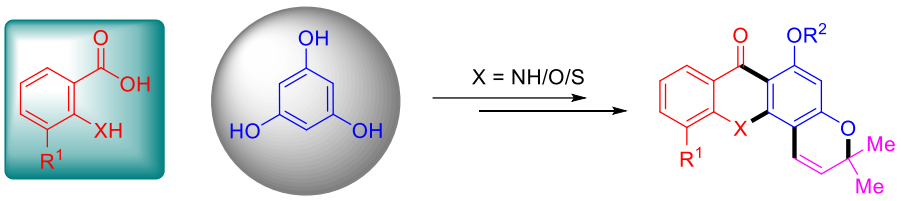
2. Cycloaddition of a wide range of azides with terminal alkynes using catalytic CuI and a prolinamide ligand (Pro-I) in aqueous media under aerobic conditions, leading to triazoles formation, has been achieved. The synthetic utility of the method is demonstrated by the synthesis of pharmacologically relevant triazolyl diaryl amines via a Cu(I) catalyzed relay cycloaddition and Ullmann coupling sequence.[44]



3. A cascade sequence involving [3+2] cycloaddition, 1,2-acyl migration and hydrolysis yielding 2H-1,2,3-triazoles via the regioselective formation of N^2 -carboxyalkylated triazoles, has been achieved in aqueous media. The reaction proceeds in presence of a CuI–prolinamide catalyst system, where prolinamide promotes the novel organocatalytic 1,2-acyl migration as well as hydrolysis of the resulting N^2 -carboxyalkylated triazoles.[45]



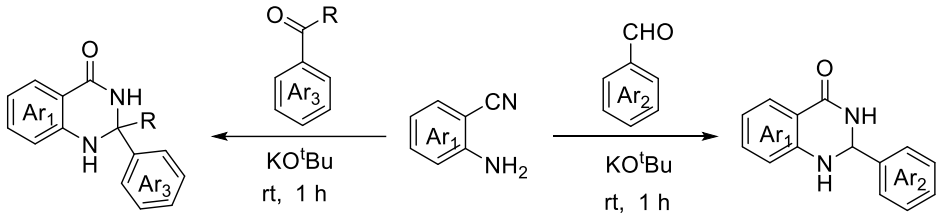
4. The tetracyclic acridone alkaloids acronycines, noracronycines, atalaphyllidine and 5-hydroxynoracronycine are synthesized from commercially available anthranilic acid and phenol derivatives via condensation reaction and regioselective annulation in excellent overall yields and in minimal steps. Moreover, the present strategy has been showcased in the synthesis of oxa and thia analogues of acronycine alkaloid.[46]



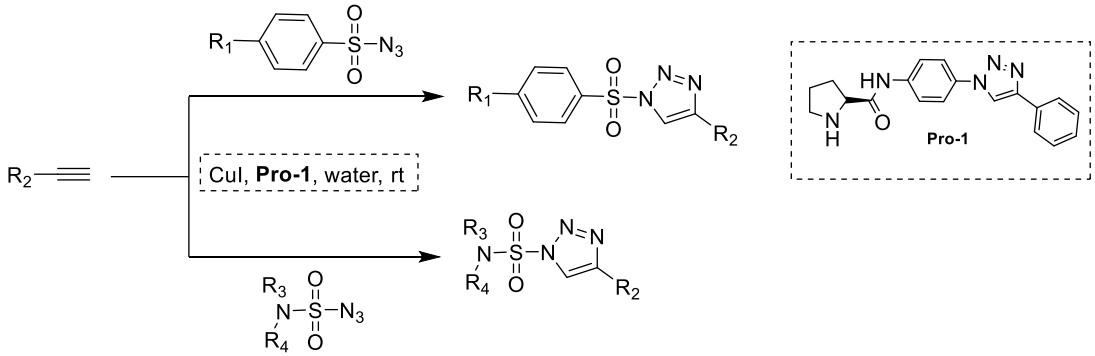
- *simple and scalable synthetic pathway*
- *regioslective annulation*
- *synthesis of tetracyclic acridone alkloids*
- *excellent yields*
- *synthesis of oxa and thia analogues of acridone alkaloids*

X = NMe, R^1 = H, R^2 = Me; Acronycine
X = NMe, R^1 = H, R^2 = H; Noracronycine
X = NH, R^1 = OH, R^2 = H; Atalaphyllidine
X = NMe, R^1 = OH, R^2 = H; 5-hydroxynoracronycine

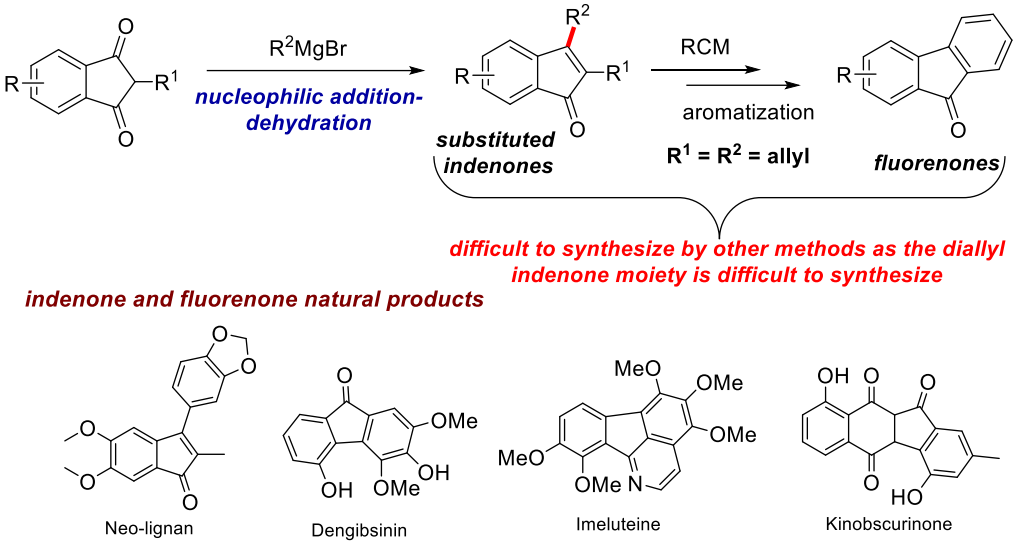
5. An efficient synthetic protocol to access heterocyclic dihydroquinazolinones by a transition-metal free process, involving the reaction of 2-aminobenzonitriles with aldehydes in the presence of KO^{t}Bu has been achieved. Following a radical pathway, the reaction is feasible at room temperature, features a broad substrate scope and tolerance to a wide range of functional groups.[47]



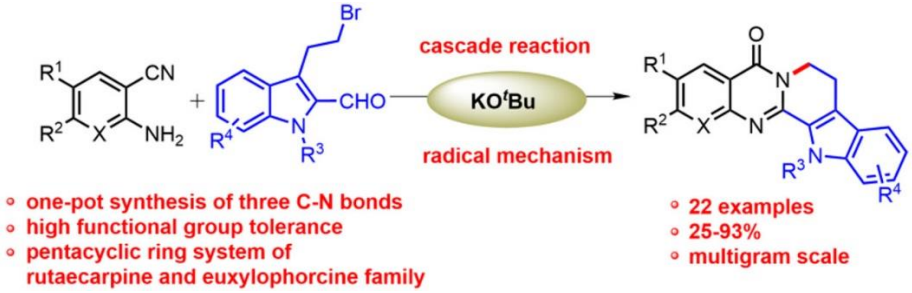
6. A Cu(I) catalyzed method using a prolinamide ligand that selectively generates N-sulfonyl and sulfamoyltriazoles in aqueous media by inhibiting the cleavage of the N1–N2 bond of 5-cuprated triazole intermediates, has been delineated. The method is mild and tolerant to air, moisture and a wide range of functional groups, thereby providing easy access to a variety of triazole products.[48]



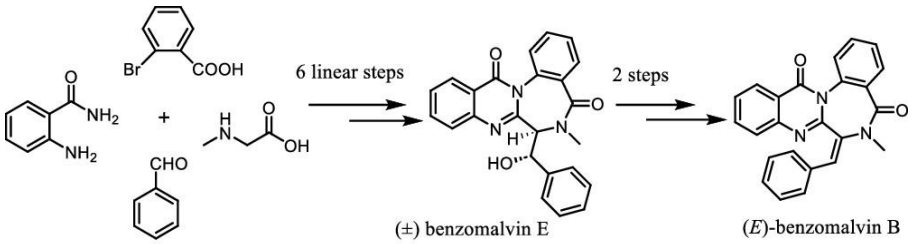
7. An efficient, one-step method has been used to access substituted indenones derivatives and natural products such as neo-lignan and isoampelopsin D, in a regiospecific manner by Grignard addition to indene-1,3-dione. Additionally, the synthesized diallyl indenones serve as RCM precursors, yielding substituted fluorenone derivatives via RCM-aromatization sequence.[49]



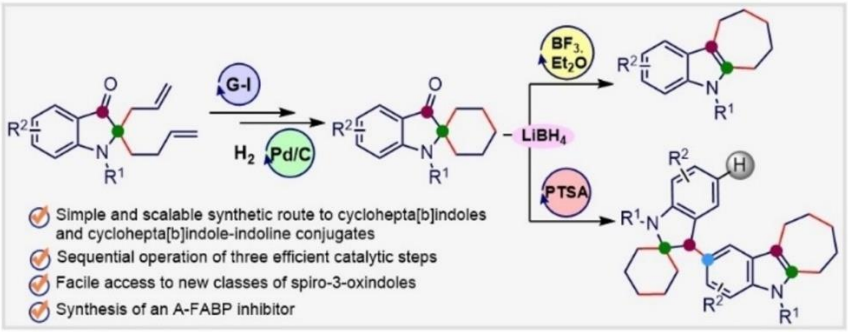
8. An innovative, cost-efficient method was introduced to synthesize biologically relevant analogs of rutaecarpine alkaloids via a single-step cascade reaction. Using 2-aminobenzonitriles and substituted indole-2-carbaldehydes with KOtBu as a base, the pentacyclic core is efficiently formed, integrating a sequential cascade process encompassing dihydroquinazolinone ring formation, oxidation, and cyclization within a single reaction vessel. This method can be successfully applied on a larger scale, making it economically viable.[50]



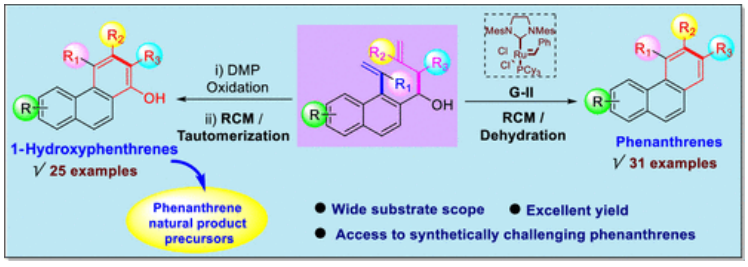
9. Dash and group demonstrated the first total synthesis of (±) benzomalvin E, featuring a quinazolino moiety with a 6–6–6–7-fused tetracyclic skeleton containing three nitrogen atoms. The key transformation involves Cu-catalyzed intramolecular C–N arylation of quinazolinone, leading to a sclerotigenin analogue that undergoes nucleophilic addition with benzaldehyde, enabling the synthesis of (±) benzomalvin E in six linear steps with a 33% overall yield. The (±) benzomalvin E's structure was validated by 2-D NMR and single crystal XRD analysis and was further transformed into (*E*)-benzomalvin B.[51]



10. Dash and group introduced an innovative sequential catalytic assembly for synthesizing cyclohepta[*b*]indoles, an A-FABP inhibitor prevalent in natural products and pharmaceuticals, from readily available isatin derivatives. The process involves three catalytic sequences: ring-closing metathesis, catalytic hydrogenation, and acid-catalyzed ring expansion. The synthesis involves ring closing metathesis and catalytic hydrogenation of the 2,2-dialkene-3-oxindole derivatives, leading to a novel class of saturated and unsaturated spirocyclic 3-oxindoles which further undergo acid-catalyzed ring expansion to provide a facile access to both cyclohepta[*b*]indoles and cyclohepta[*b*]indole-indoline derivatives.[52]



11. They also developed an efficient synthetic strategy for phenanthrenes and 1-hydroxyphenanthrenes through aromatization-assisted ring-closing metathesis (RCM). It involves vinylation of 1-bromo-2-naphthaldehyde derivatives, Barbier allylation, and subsequent one-pot RCM/dehydration of the diene precursors to yield phenanthrene derivatives. Further, the corresponding keto analogues of diene precursors produce 1-hydroxyphenanthrenes through RCM and aromatization-driven keto–enol tautomerism. This pathway enables rapid access to a diverse array of functionalized phenanthrenes and 1-hydroxyphenanthrenes, including synthetically challenging derivatives containing both –OH and –OMe groups via the sequential construction of the terminal phenanthrene ring.[53]



Conclusion

Non-canonical nucleic acids have emerged as attractive targets as well as tools in anticancer and antimicrobial drug development. Prof. Dash has employed various chemical approaches for designing and synthesizing selective ligands against a particular G-quadruplex or i-motif structure. Recently reported molecules can further be explored for preclinical and clinical trials and may be used as potential therapeutic candidates for the treatment of human cancers and other diseases. She has also demonstrated these non-canonical nucleic acids as novel targets in microbes to combat antimicrobial resistance. In addition, she has revealed the potential of these noncanonical nucleic acid structures to design nanoscale structures and devices which may found profound applications in bio-sensing, molecular computing and therapeutic applications. Although there is much to be understood about these non-canonical nucleic acid structures, the successful design of molecular probes and G-quadruplex based functional nanostructures by Prof. Dash will undoubtedly lead to many new opportunities and innovative applications for developing next generation therapeutics and nanodevices in the field of pharmaceutical sciences.

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