Contribution To Expanding the Genetic Alphabet, Genetic Code and SNPs Genotyping for Personalized Medicine: Click Chemistry and Sonogashira Coupling As Key Synthetic Protocols Adopted In All

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Subhendu Sekhar Bag was born at Tikarpara, Bankura, West Bengal, India and received his MSc (1st class) and PhD degrees in chemistry from IIT Kharagpur, in 1998 and 2005, respectively. After postdoctoral research (JST and JSPS) he started his independent career at the Department of Chemistry, IIT Guwahati, India, in 2008 and became an Associate Professor in 2013. He served as a Lead Guest Editor of *Journal of Nucleic Acids* and is serving as an editorial board member of *Biological and Biomedical Reports*, *STM Journals*, and *World Research Journal of Chemistry*. His research group is actively involved in designing unnatural-fluorescent nucleobase pairs which could drive the synthesis of unnatural proteins containing their designer amino acids. "Click-chemistry" is being utilized as a key step for synthesis in this research.

Pablo Barrio studied chemistry at the University of Oviedo, obtaining his PhD under the supervision of Prof. Barluenga. Later, he joined the Carreira group at ETH and then the Fustero group at the University of Valencia. He is focused on two topics: the asymmetric synthesis of benzo-fused carbo- and heterocycles and the chiral Brønsted acid catalysed allylboration reaction. He is also interested in the use of terphenyls in medicinal chemistry. In addition, he has carried out stays at Trinity College (Dublin), MPI (Muelheim) and Gakushuin University (Tokyo); part of this work was carried out at the latter.

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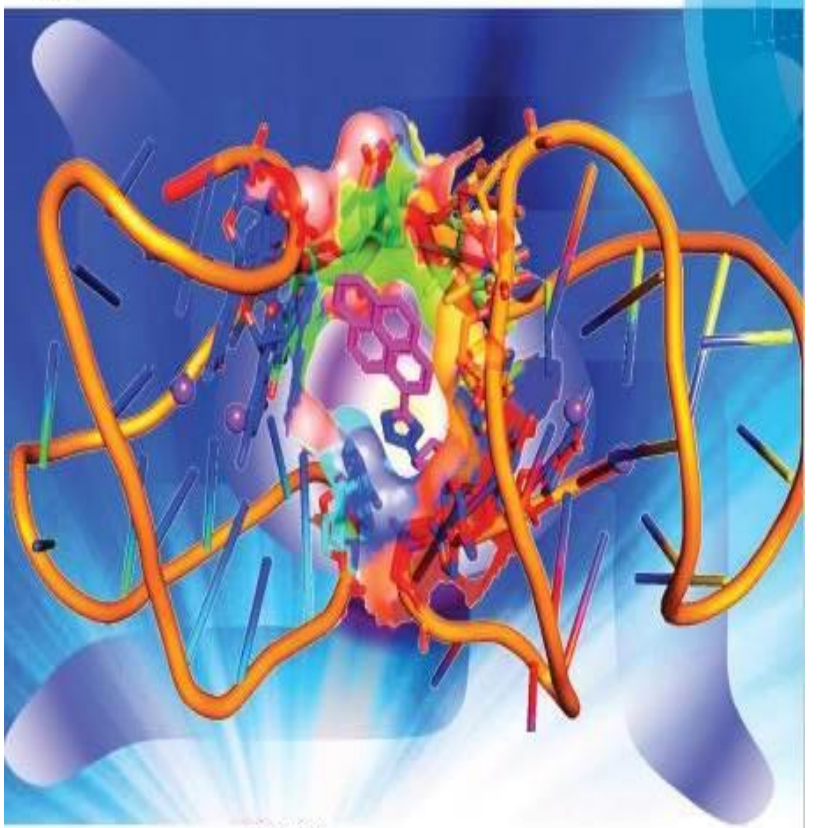


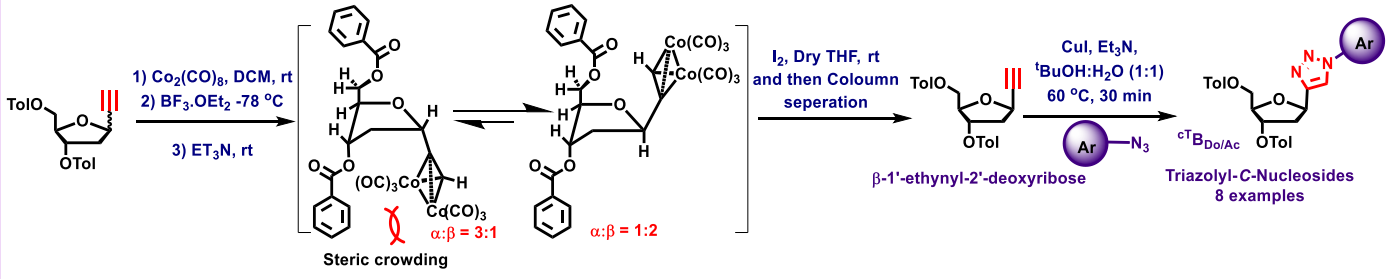
ISSN 1477-0520

COMMUNICATION
Subhendu Sekhar Bag et al.
Tetrazolylpyrene unnatural nucleoside as a human telomeric multimeric G-quadruplex selective switch-on fluorescent sensor

Contributions to Expanding the Genetic Alphabets

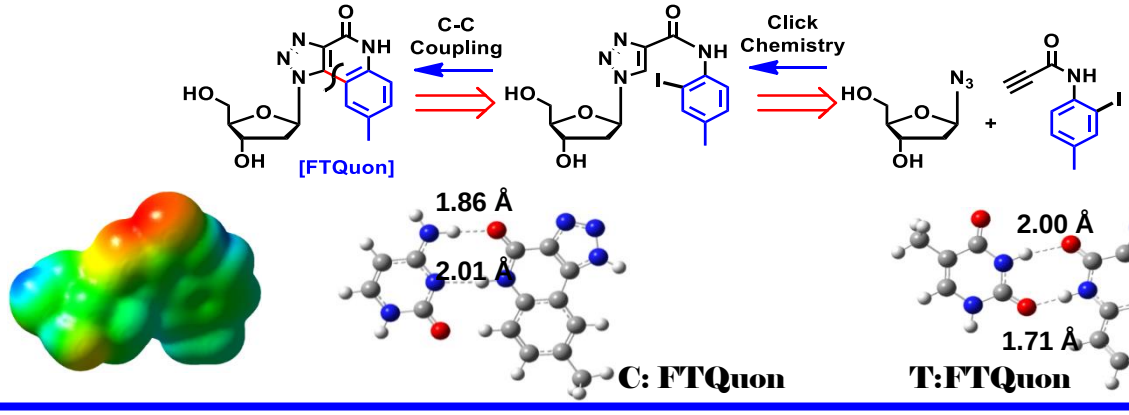
Triazolyl *C*-Nucleosides: Synthesis and Photophysical Properties

[Bag *et al. Tetrahedron*, 2019, *75*, *3024*]



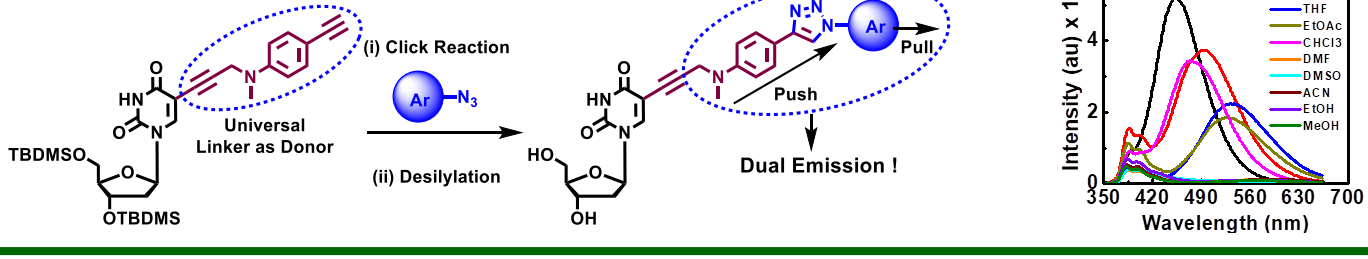
Design of a Fused Triazolyl 2-Quinolinone Unnatural Nucleoside *via* a Tandem CuAAC-Ullmann Coupling Reaction and Study of Photophysical Property

[Bag *et al. Tetrahedron*, 2018, *74*, 2218.]



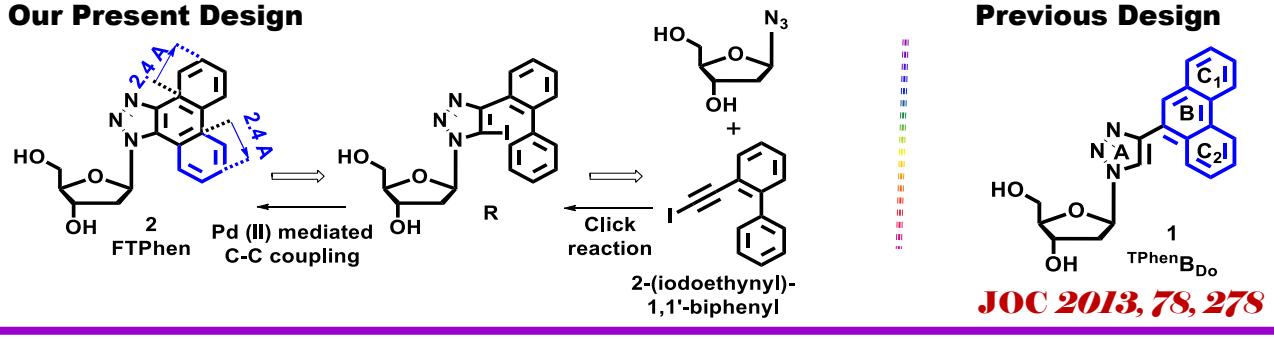
Design of "Click" Fluorescent Labelled 2′-deoxyuridinesvia C5-Propynylaminomethylphenyl acetylene as a Universal Linker: Synthesis, Photophysical Property and Interaction with BSA

[Bag *et al. JOC*, 2018, *83*, 7606]



Design, Synthesis and Photophysical Property of a Doubly Widened Fused- Triazolyl-Phenanthrene Unnatural Nucleoside

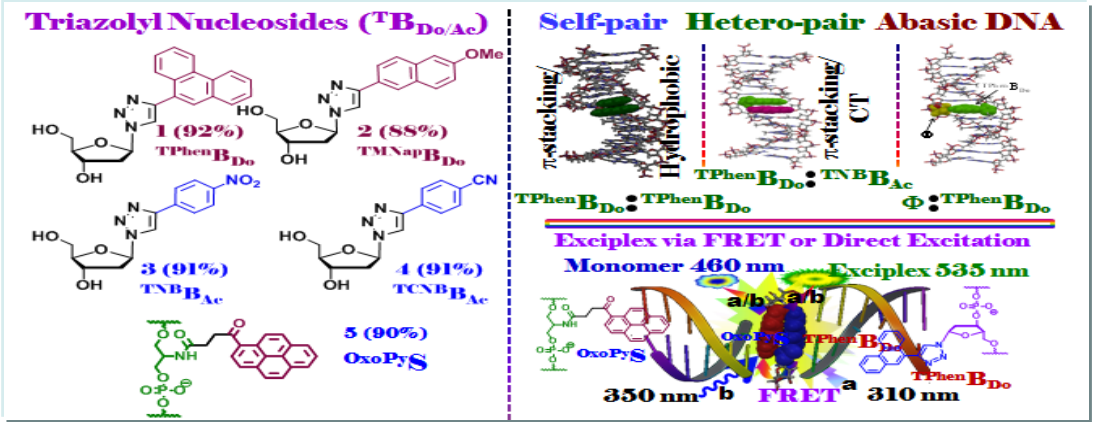
[Bag *et al. Chemistry Select* 2017, *2*, 3577]



Contributions to Expanding the Genetic Alphabets

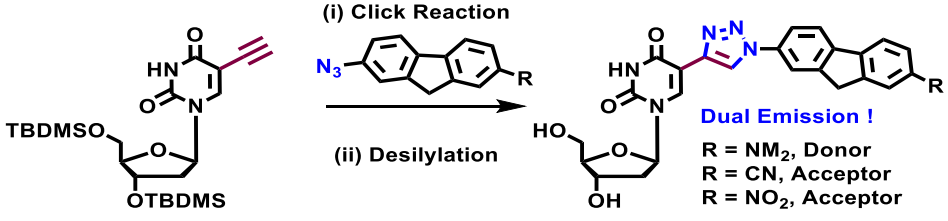
Triazolyl-Donor/Acceptor Unnatural Nucleosides and Oligonucleotide Probes

[Bag *et al. Curr. Protoc. Nucleic Acid Chem.* 2015, *58*:1.32.1-1.32.27.; *Org. Biomol. Chem.* 2016, *14*, 5088]



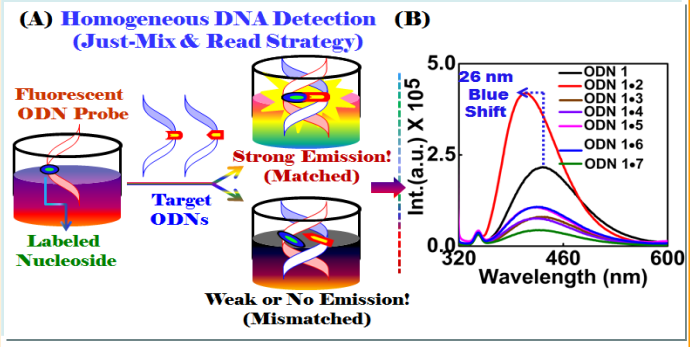
Triazolyl Fluorene labeled Donor/Acceptor nucleoside with Dual emission

[Bag et al. *Communicated*]



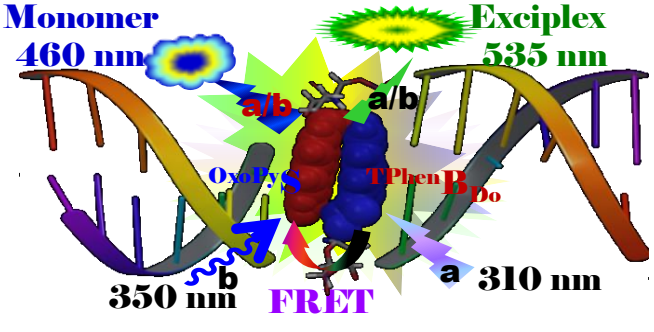
Wavelength Shifting Oligonucleotide Probe for DNA Detection

[Bag *et al. Bioorg. Med. Chem. Lett.* 2014, *24*, 4678.]



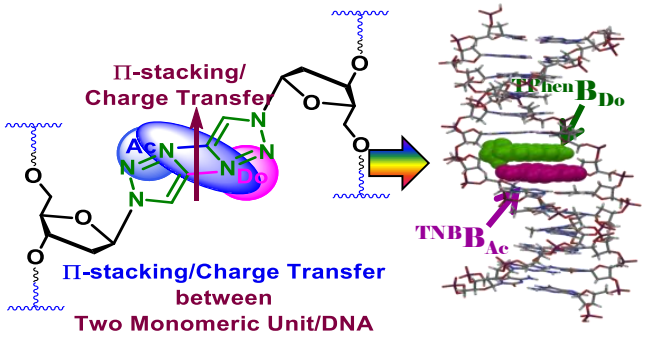
Dual Door Entry to Exciplex Emission

[Bag *et al. Chem. Commun.* 2014, *50*, 829.]



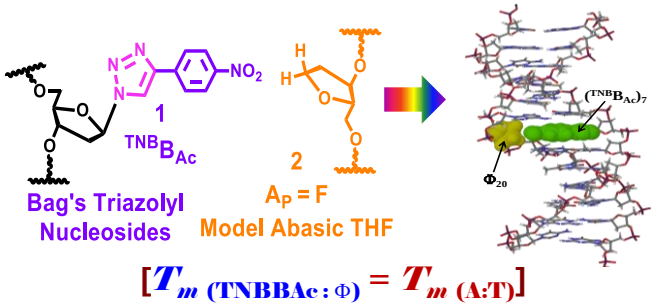
Charge Transfer Complexation Mediated Duplex Stabilization

[Bag *et al. J. Org. Chem.* 2013, *78*, 278.]



Triazolyl Nitrobenzene Nucleoside Stabilizes an Abasic Site

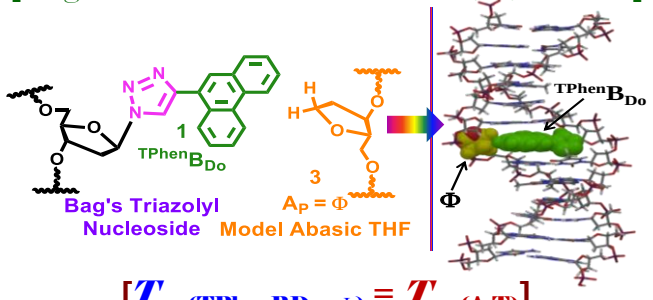
[Bag *et al. To be* Communicated.]



Contributions to Expanding the Genetic Alphabets

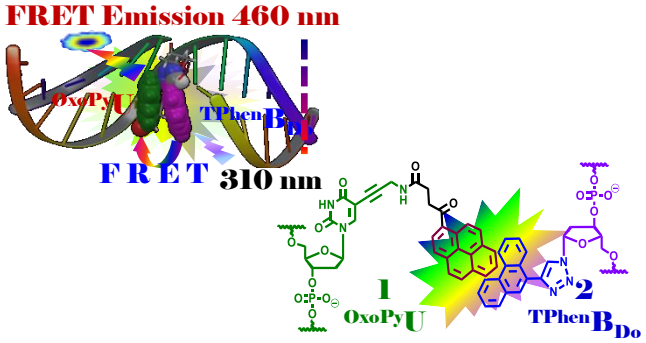
Unnatural Triazolyl Phenanthrene Nucleoside Efficiently Stabilizes an Abasic Site

[Bag *et al. RSC Advances* 2013, *3*, 21352.]



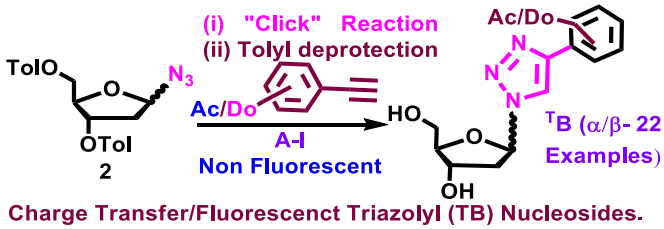
$[T_m$ (TPhenBDo : Φ) = T_m (A:T)]

Hybridization Accompanying FRET Event [Bag *et al. J. Photochem. Photobiol. B: Biology* 2016, *162*, 669.]



Triazolyl *N*-Nucleosides-Synthesis and Photophysical Properties

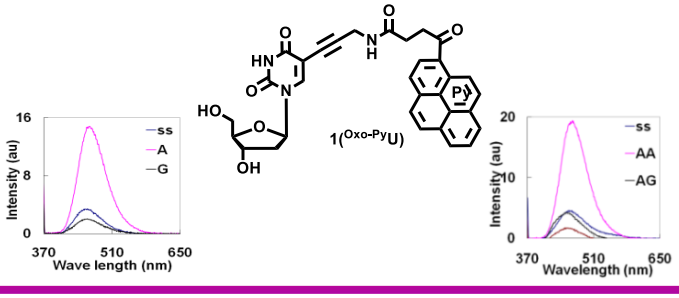
[Bag *et al. Org. Biomol. Chem.* 2016, *14*, 5088]



Charge Transfer/Fluorescenct Triazolyl (TB) Nucleosides.

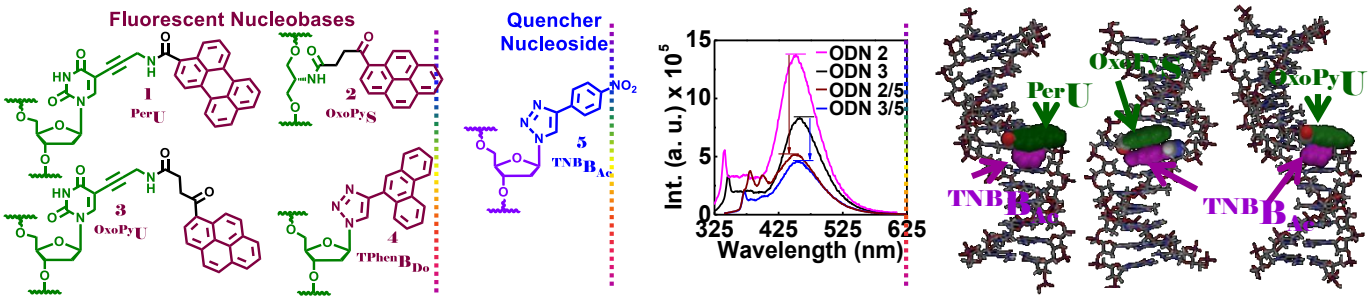
Detection of "A" and Consecutive "AA" Base of a Target ODN

[Bag *et al. Bioorg. Med. Chem. Lett.* 2010, *20*, 3227.]



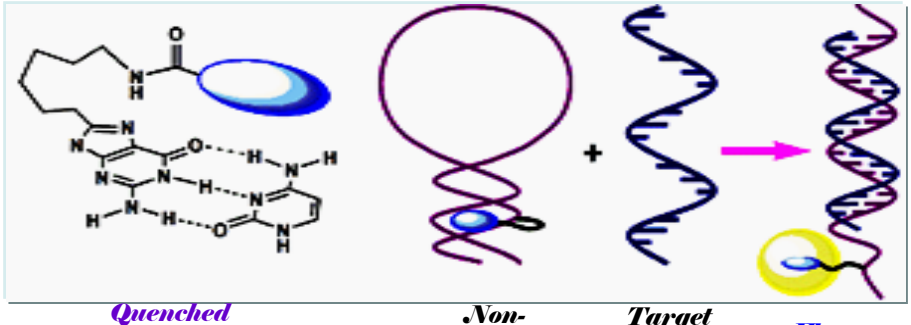
Triazolyl Nitrobenzene Nucleoside as Potent Quencher as Natural Guanosine

[Bag *et al.* To be Communicated]



Ends Free Molecular Beacon

[Bag *et al. Bioorg. Med. Chem. Lett.* 2009, *19*, 6392.]

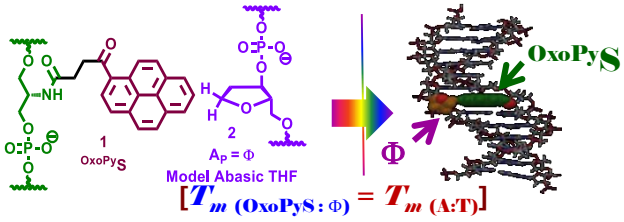


Quenched by G-C Pair *Non-Fluorescent* *Target ODN* *Fluorescent*

Contributions to Expanding the Genetic Alphabets

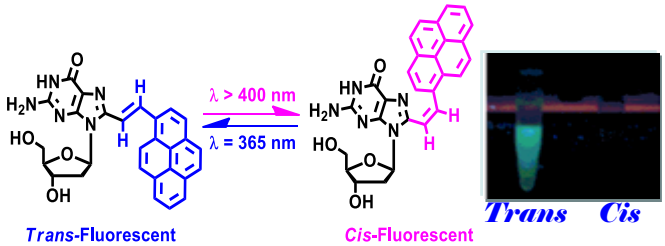
Stabilization of an Abasic Site Paired Against Non-Nucleosidic Base Surrogate

[Bag *et al.* To be Communicated.]

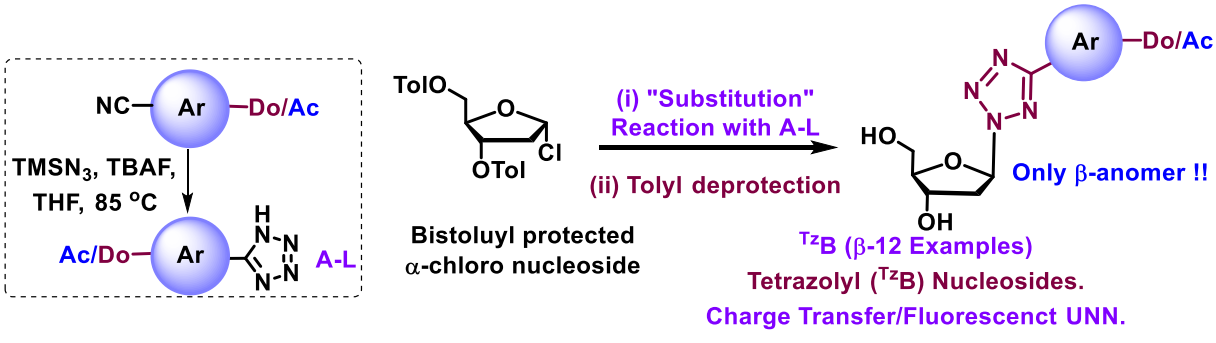


Photochromic Vinylpyrene 2'-deoxyguanosine

[Bag *et al. Tet. Lett.* 2009, *50*, 1403.]



Stereoselective and Regioselective Synthesis of Donor/Acceptor Tetrazolyl Nucleosides [Bag *et al. Bioorg. Med. Chem. Lett.* 2016, *26*, 2044]

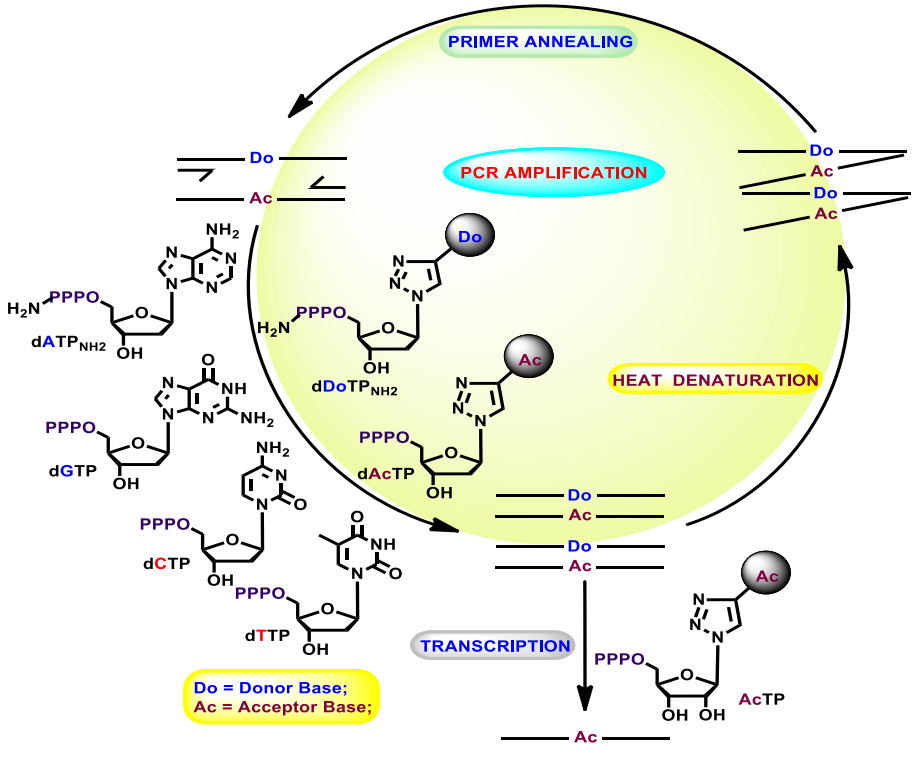


Expansion of the Genetic Alphabet: Unnatural Nucleobases and their Applications

[Bag *et al. Journal of Nucleic Acids* 2012, Article ID 718582, 2 pages (Editorial).]

Current Focus

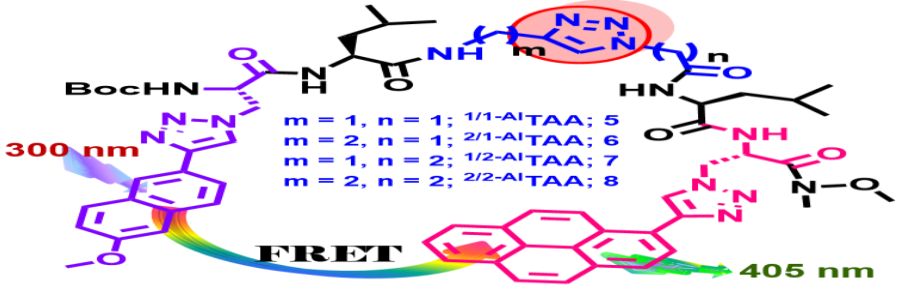
Amplification of Unnatural Triazolyl/Tetrazolyl/Fused Triazolyl Donor-Acceptor Base Pair by PCR and *in vitro* Transcription



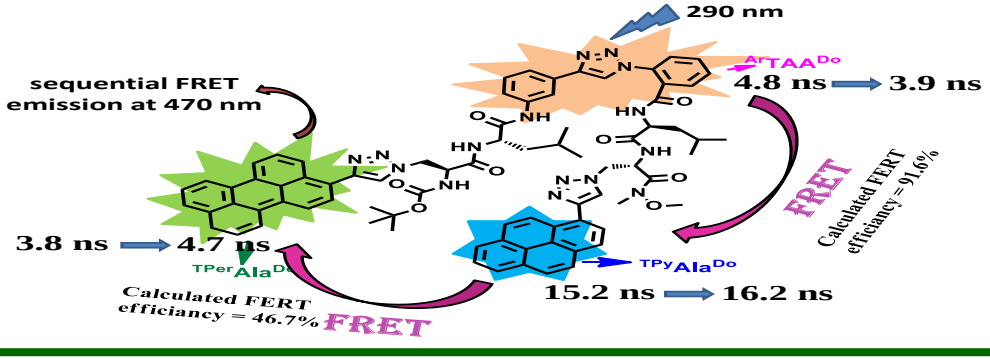
Contributions to Expanding the Genetic Codes

FRET Events in Fluorescent Pentapeptides Containing Aliphatic Triazolo Amino Acid Scaffolds: Role of Spacer Lengths

[Bag *et al. J. Photochem. Photobiol. A: Chem.* 2019, *378*, 171]

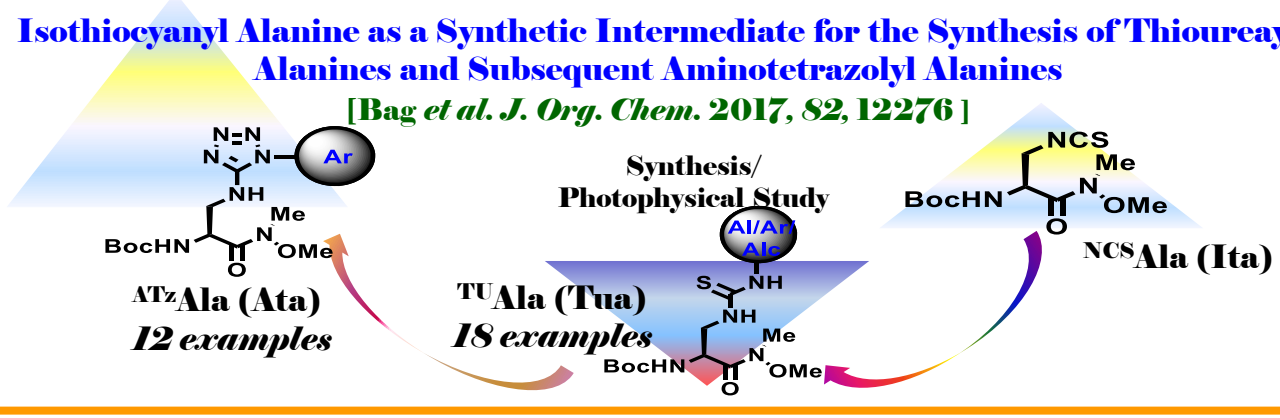


FRET Relay in an o,m-Aromatic Amino Acid Scaffolded Trichromophoric β-Turn Pentapeptide [Bag *et al.* Chem. Commun. 2018, *54*, 9765]



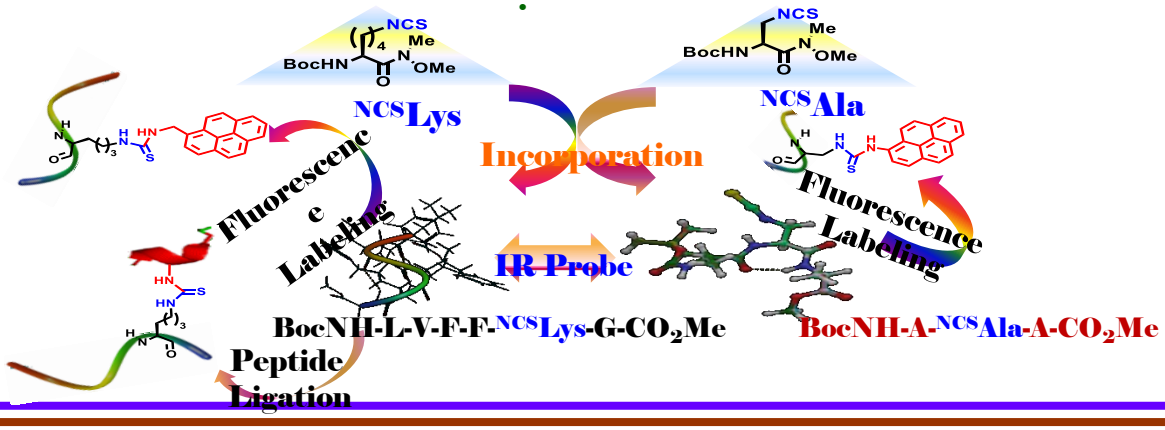
Isothiocyanyl Alanine as a Synthetic Intermediate for the Synthesis of Thioureayl Alanines and Subsequent Aminotetrazolyl Alanines

[Bag *et al. J. Org. Chem.* 2017, *82*, 12276]



Multipurpose Isothiocyanyl Alanine/Lysine: Use as Solvatochromic IR Probes and in Site Specific Labeling/Ligation of Short Peptides

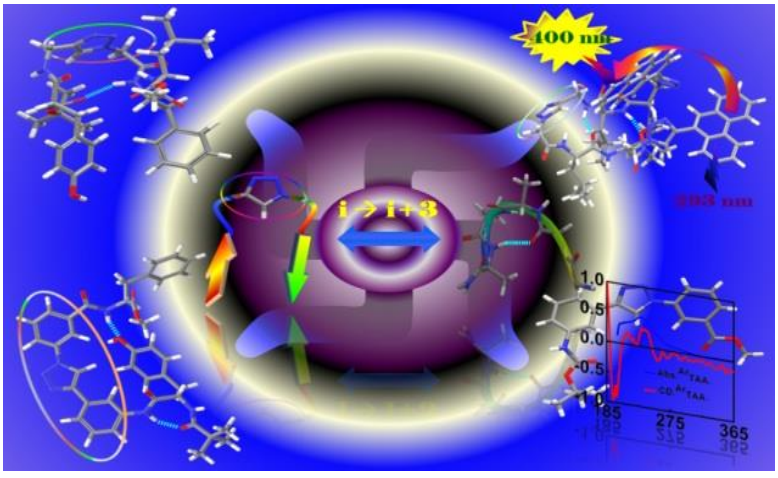
[Bag *et al. Bioorg. Med. Chem. Lett.* 2018, *28*, 1404]



Contributions to Expanding the Genetic Codes

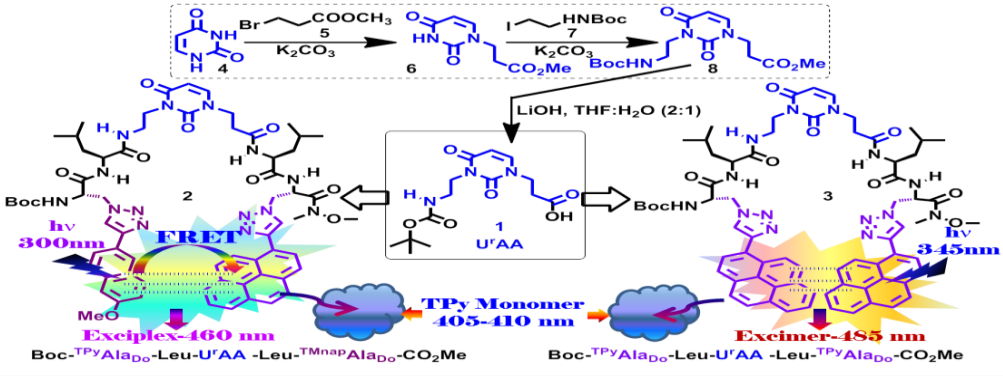
Unnatural Amino Acid as a Molecular Scaffold for Novel β-turn Peptidomimetics

[Bag *et al. Chem. Commun.* 2015, *51*, 5242 ;Emerging Investigators Issue.]



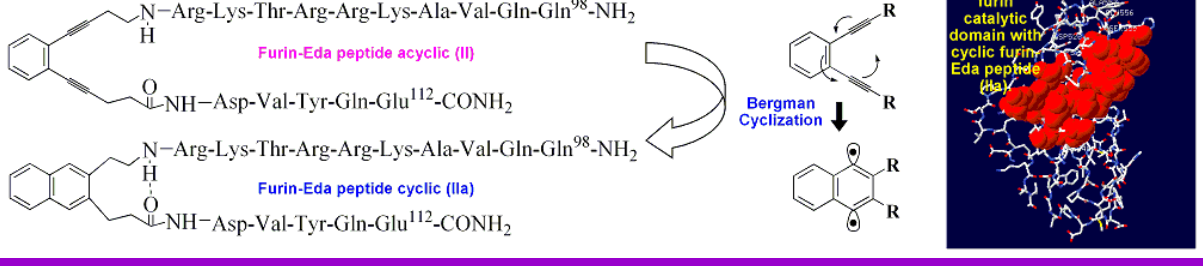
Uracil Amino Acids Scaffold for β-Turn Peptidomimetics

[Bag *et al. Bioorg. Med. Chem. Lett.* 2017, 27, 5387.]



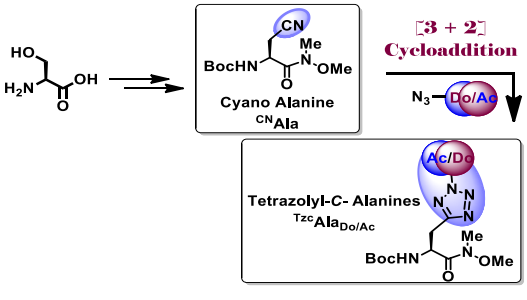
A Novel Enediynyl Peptide Inhibitor of Furin

[Bag & Basak *et al., PLoS One* 2009, *4(11)*, No pp.]



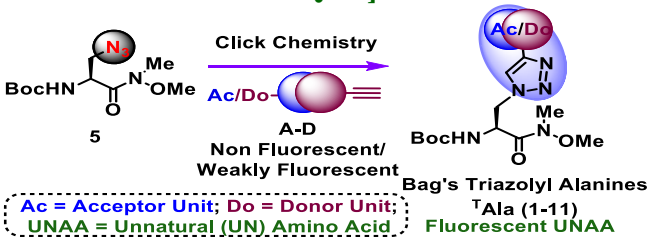
Tetrazolyl-*C*-Unnatural Amino Acids : Synthesis and Photophysical Properties

[Bag *et al.* Ongoing Project.]



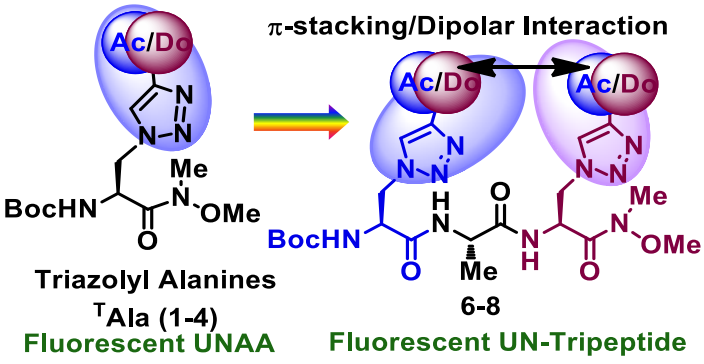
Triazolyl-Unnatural Amino Acids : Synthesis and Photophysical Properties

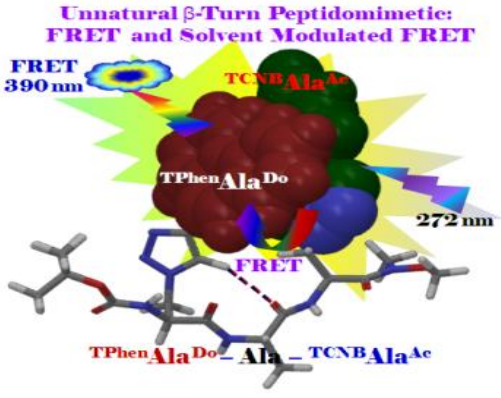
[Bag *et al. Bioorg. Med. Chem.* 2016, *24*, 3579.]



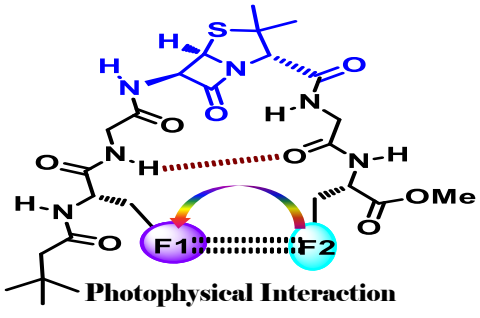
Contributions to Expanding the Genetic Codes

FRET Event in β-Turn Conformation [Bag *et al. Chem. Commun.* 2014, *50*, 433.]

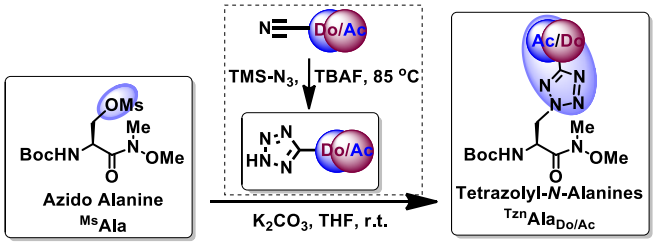




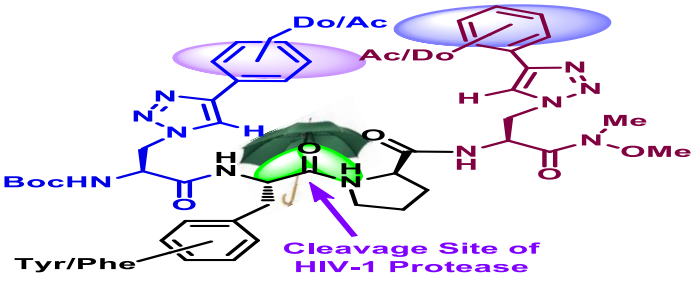
β-Lactam Based Peptidomimetics
[Bag *et al.* Ongoing Project.]



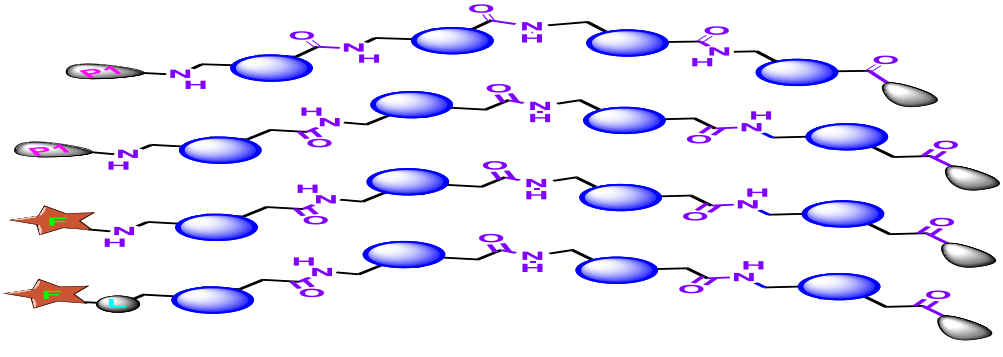
Tetrazolyl-*N*-Unnatural Amino Acids : Synthesis and Photophysical Properties
[Bag *et al.* Ongoing Project.]



β-Turn Peptidomimetics: Umbrella Cover- HIV-I Protease Inhibition
[Bag *et al.* To be Communicated.]



Polyamides of Constrained Molecular Scaffold as Distamycin Analogues
[Bag *et al.* To be Communicated.]

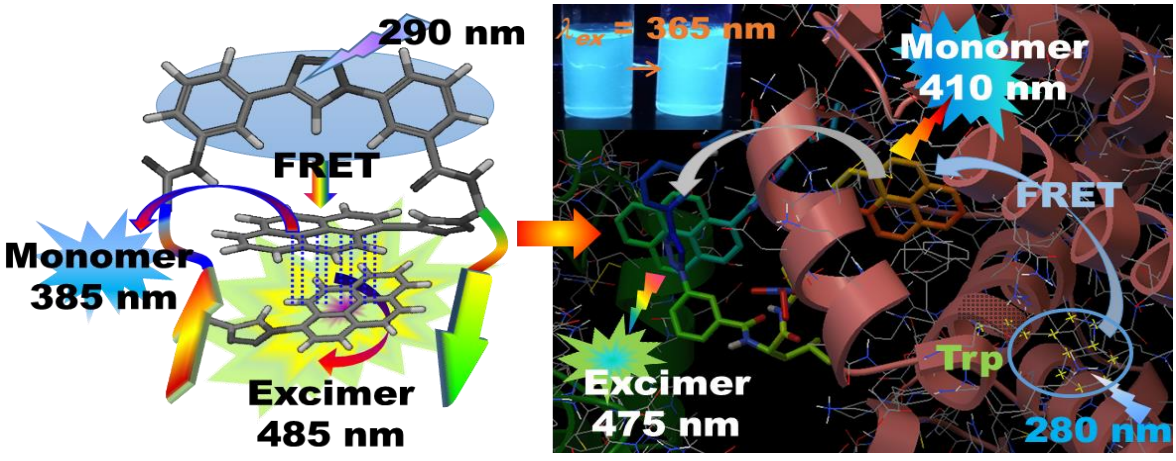


P1, P2: Protective Groups;
F: Fluorophore;
L: Linker/Part of F

Contributions to Expanding the Genetic Codes

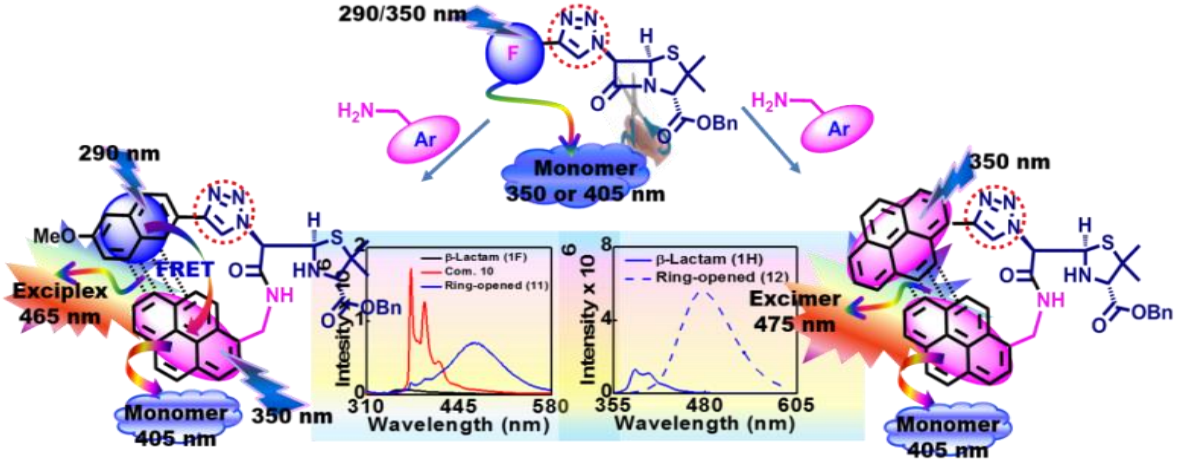
Aromatic Triazolo-Amino Acids Scaffolded Trichromophoric β-sheet Pentapeptide- Dual Path to Excimer Emission

[Bag *et al. RSC Advances* 2016, *6*, 72654.]



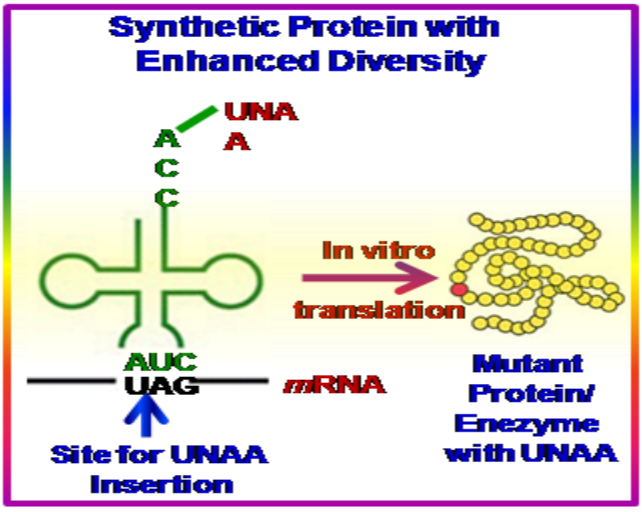
Monitoring Chemical Cleavage of Triazolyl β-Lactams by Fluorescence

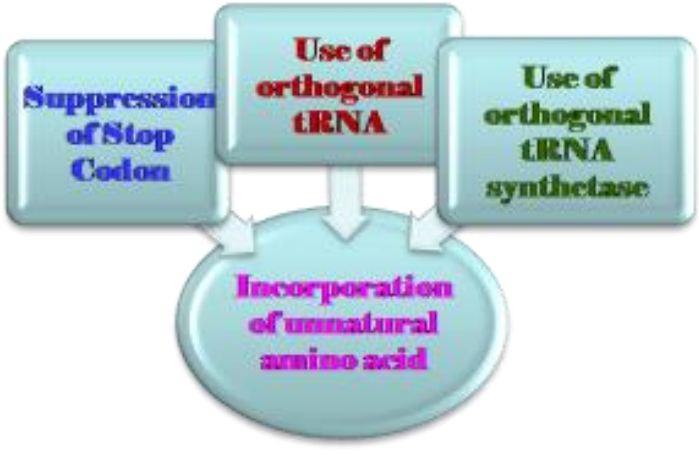
[Bag *et al. J. Phochem.Photobiol. A:Chemistry 2018, 353, 464.*]



Current Focus:

Incorporation of Triazolyl/Tetrazolyl/Other Unnatural Amino Acids into Proteins by Nonsense Suppression Codon Method

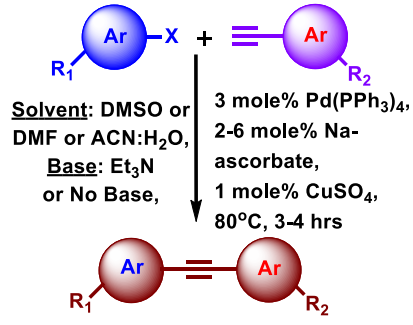




Contributions to Synthetic Methodology / Physical Organic Chemistry

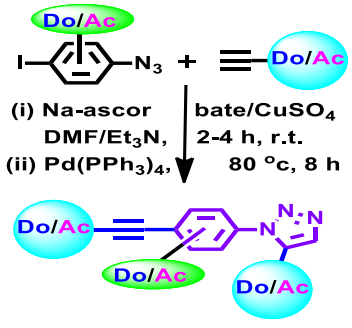
Click-Reagent Version of Sonogashira Coupling

[Bag *et al. J. Org. Chem.* 2011, *76*, 2332.]



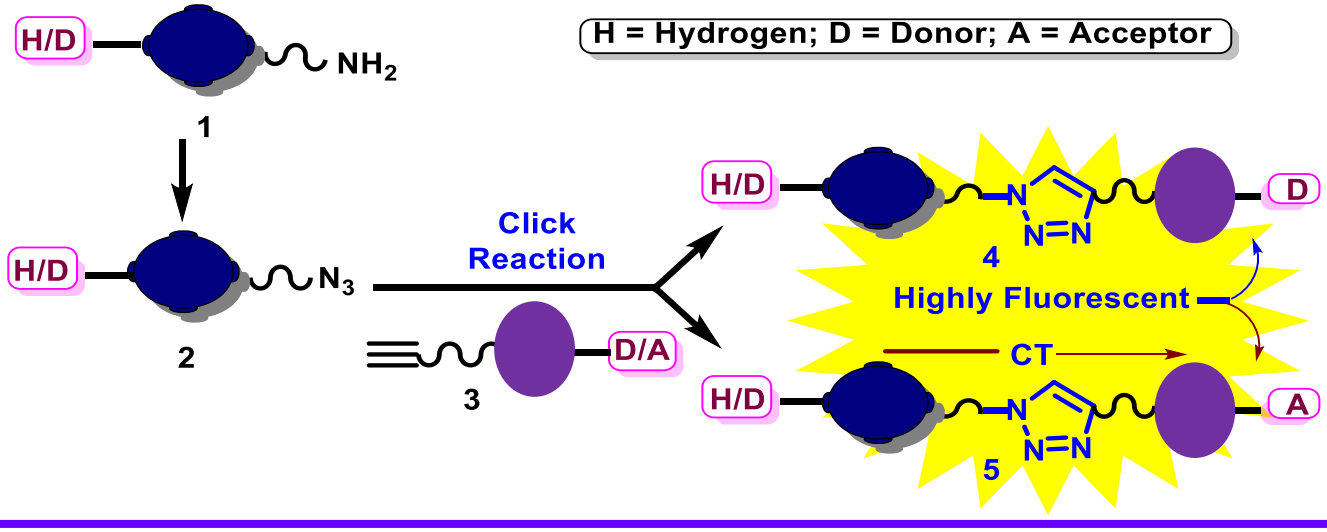
One PotClick and Sonogashira Coupling

[Bag *et al.* To be Communicated.]



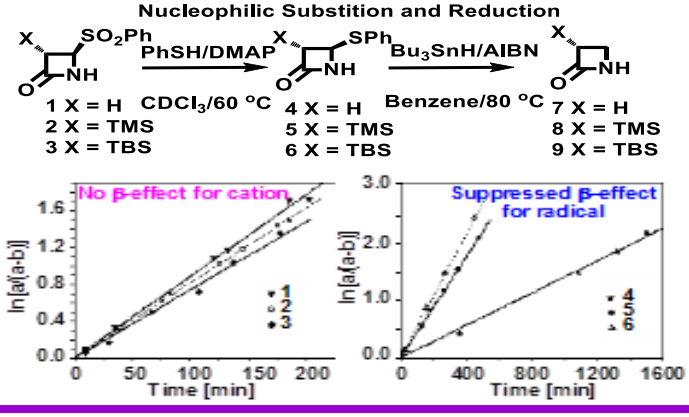
Installation/Modulation of the Emission Response via Click Reaction

[Bag *et al. J. Org. Chem.* 2011, *76*, 3348.]



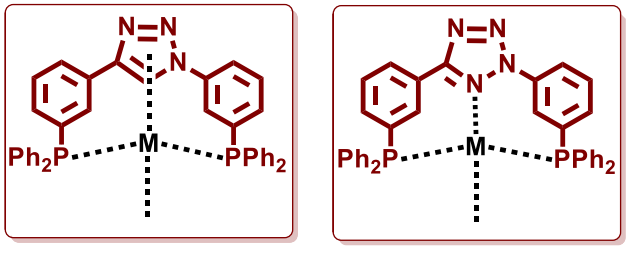
Suppressed β-Effect of Silicon : The Role of Antiaromaticity

[Bag *et al. Org. Lett.* 2009, *11*, 5722.]



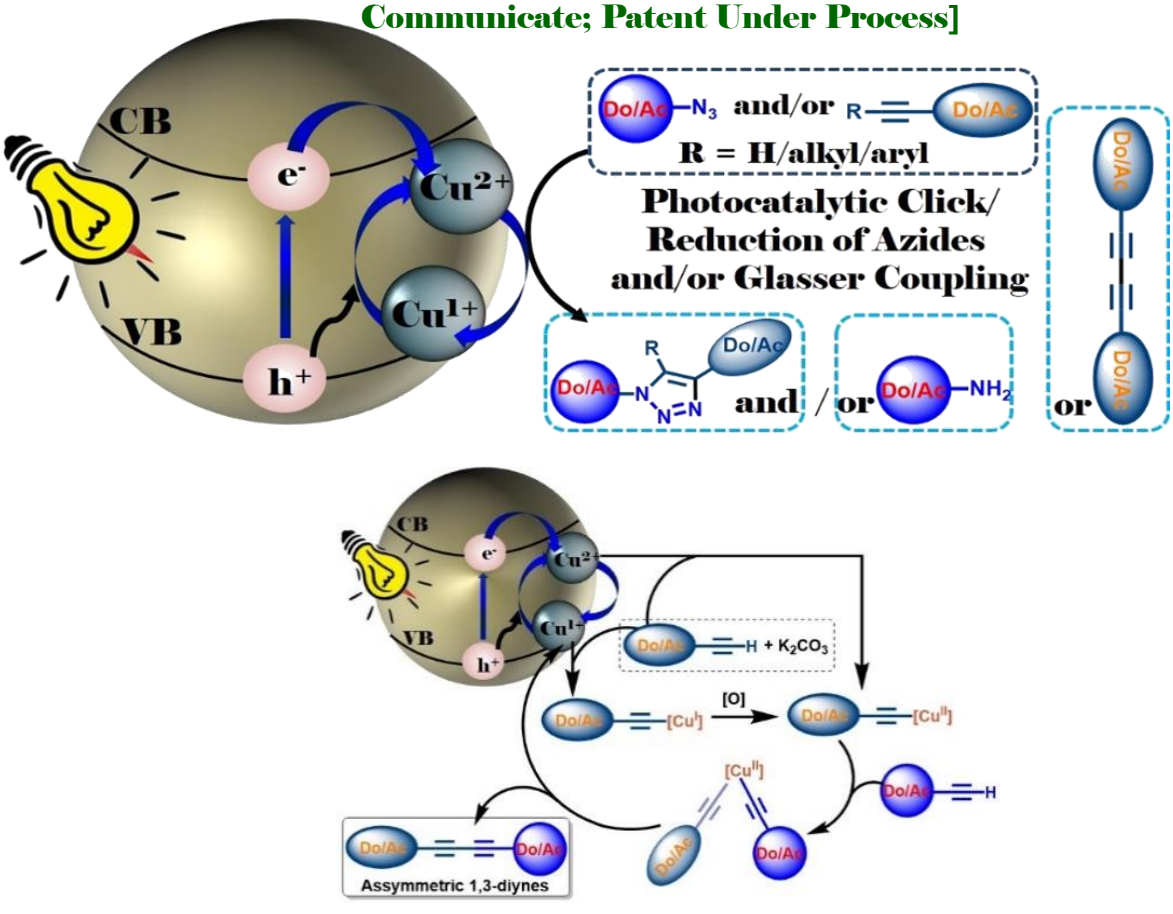
Triazolo/Tetrazolo Atropomers as Catalyst for Asymmetric Synthesis

[Bag *et al.* Ongoing Project.]

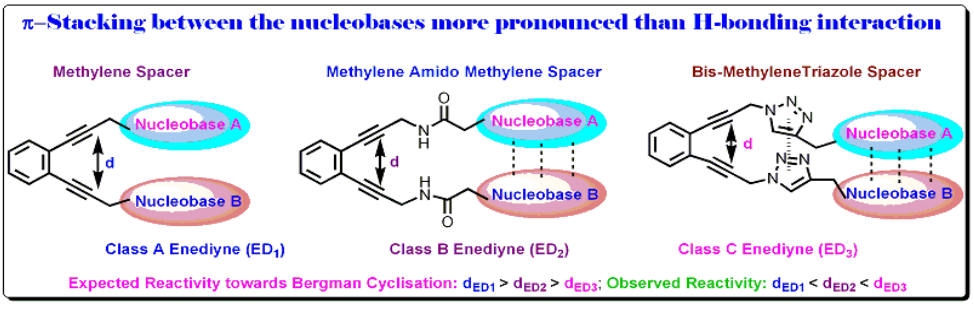


Contributions to Synthetic Methodology / Physical Organic Chemistry

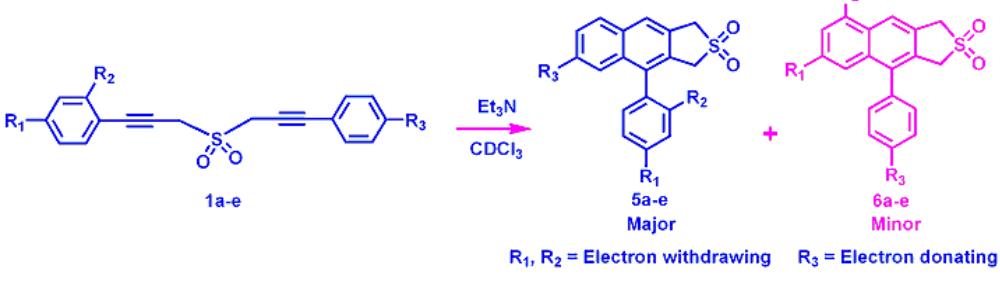
Photocatalytic Click Reaction and Glaser Coupling Using a Smart and Multitalented Nanocomposite Photocatalyst [Bag *et al. To be* Communicate; Patent Under Process]



Reactivity of Enediyne-Nucleobase Hybrids: Effect of Intramolecular π-Stacking [Bag & Basak *et al.*, *Tetrahedron* 2012, *68*, 8600.]

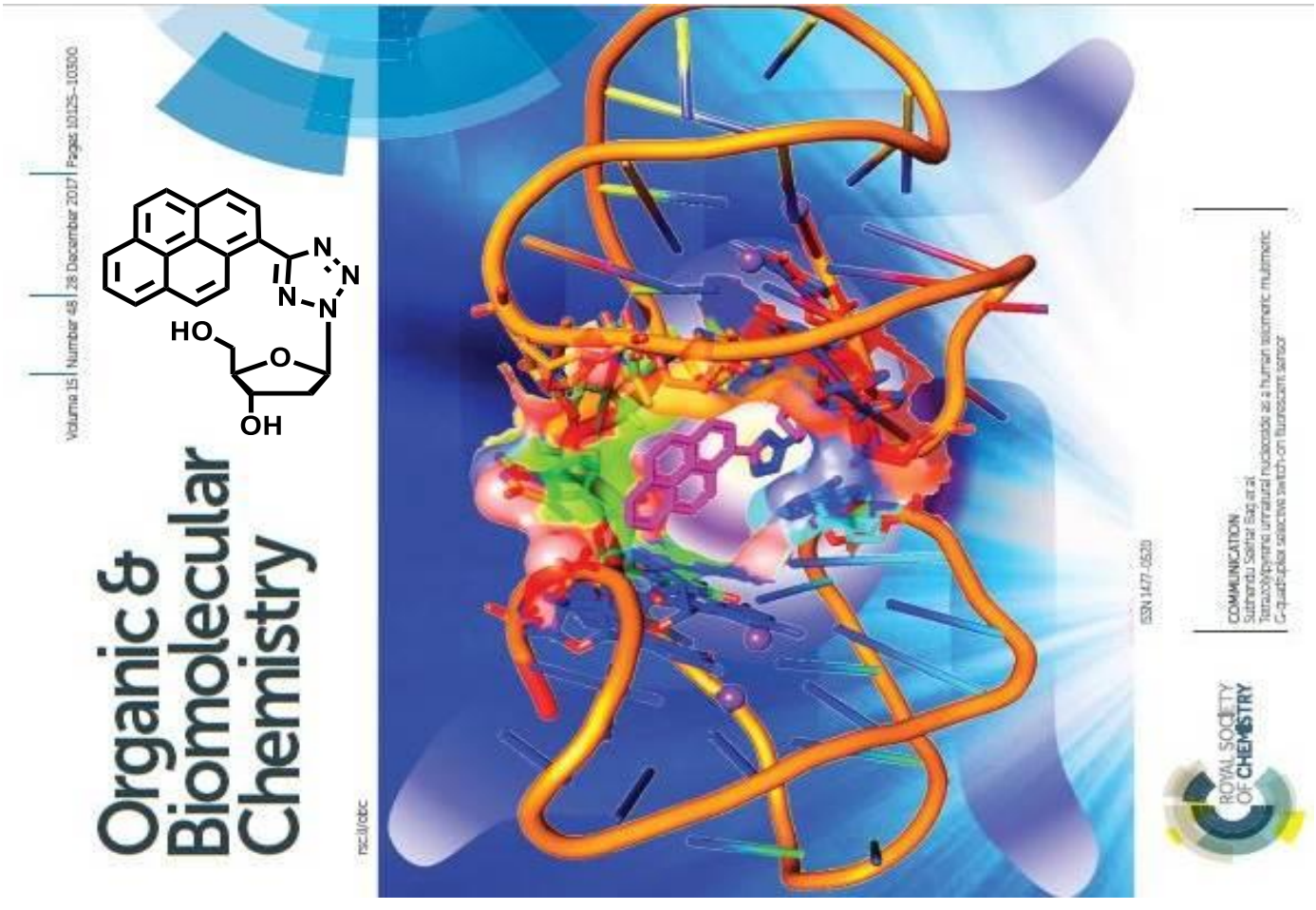


Selectivity in Garratt–Braverman Cyclization [Bag & Basak *et al.*, *Org. Lett.* 2011, *13*, 888.]

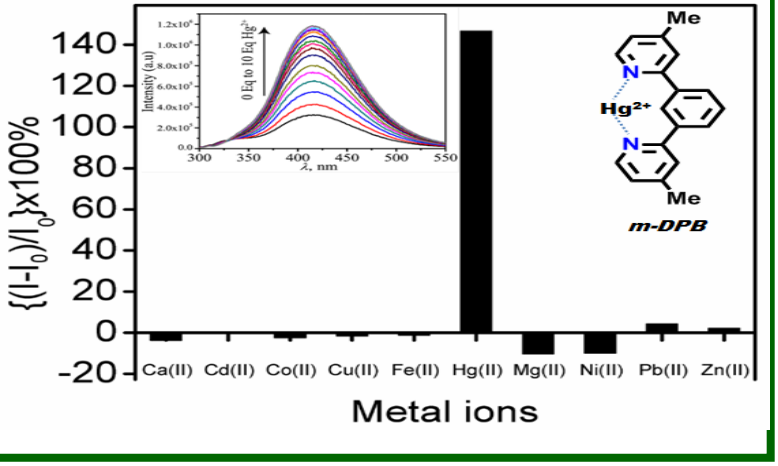


Contributions to Biochemical Sensor / Few Other Independent Works

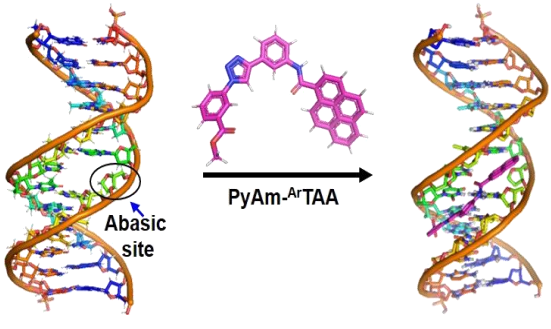
Specific Detection of Multimeric G-Quadruplex DNA with Unnatural Fluorescent Nucleoside [Bag *et al. Org. Biomol. Chem.* 2017, *15*, 10145 (Outside Front Cover Page).]



Fluorometric sensing of Hg^{2+} ion with light-up probe Bis-Pyridobenzene [Bag *et al. Sensors & Actuators: B. Chemical* 2017, *238*, 903.]



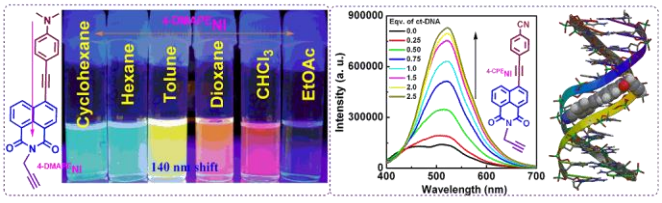
Label-free Sensing of Abasic DNA using Pyrenylamido Triazolyl Aromatic Amino Acid Scaffold as AIE probe [Bag *et al. J. Photochem. Photobiol .A.* 2020, *388*, 112186]



Contributions to Biochemical Sensor / Few Other Independent Works

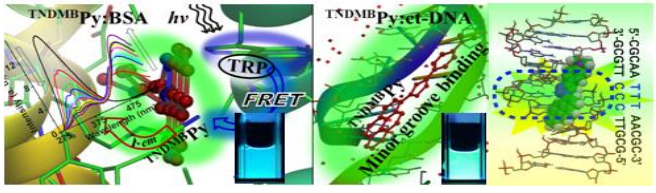
Fluorescence Switch-on Sensing of Calf Thymus (ct)-DNA

[Bag *et al.* Bioorg. Med. Chem. Lett. 2013, *23*, 96.]



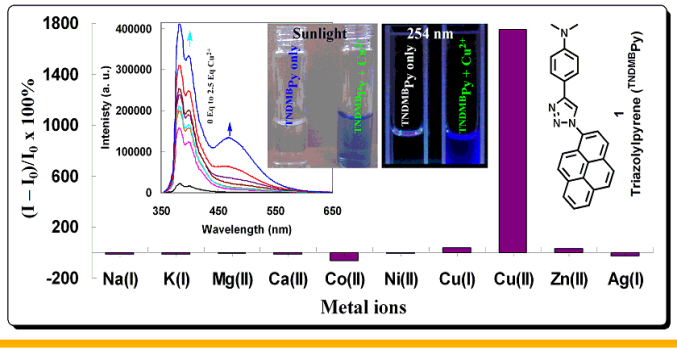
Sensing Biomolecules and Label Free Mismatched DNA Detection

[Bag *et al. Tet. Lett.* 2013, *54*, 2627.]



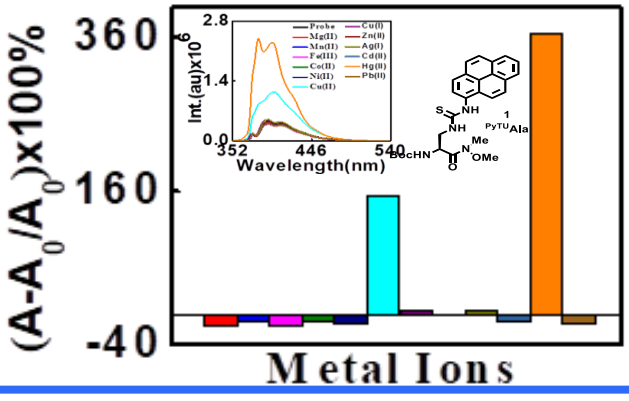
Fluorometric sensing of Cu^{2+} ion with light-up probe $^{TNDMB}Py$

[Bag *et al. Tet. Lett.* 2012, *53*, 5875.]



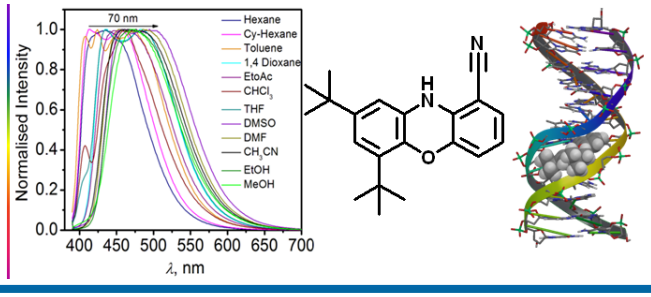
Fluorometric Sensing of Hg^{2+}/Cu^{2+} ion with ^{TuPy}Ala

[Bag *et al.* Chemistry Select, 2018, 3, 11758]



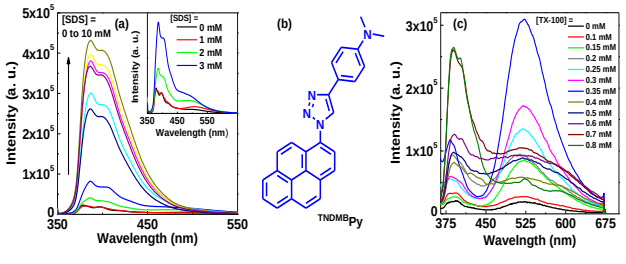
Fluorescent Cyanophenoxazine & Light-up Sensing of ct-DNA

[Bag *et al. RSC Adv.* 2013, *3*, 5374.]



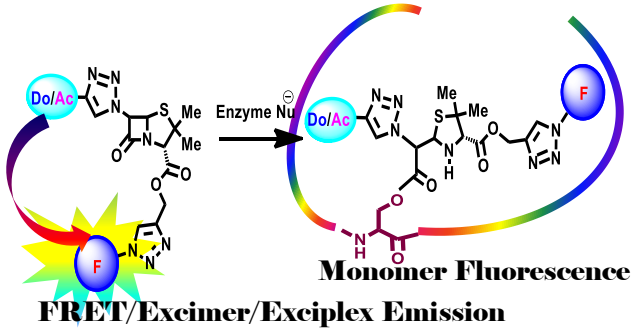
Sensing of Micellar Microenvironment with Dual Fluorescent Probe $^{TNDMB}Py$

[Bag et al. *J. Fluorescence* 2013, *23*, 929.]



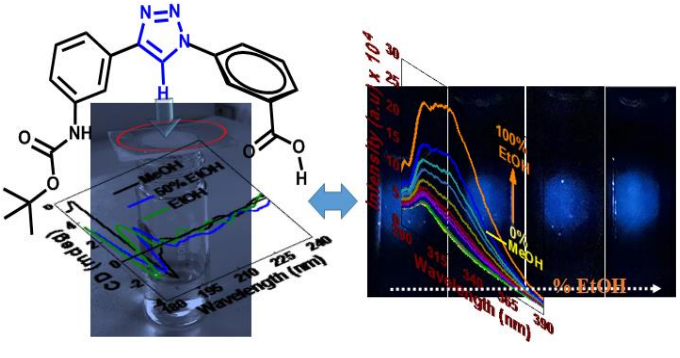
Monitoring Enzymatic Cleavage of Triazolyl β-Lactams by Fluorescence

[Bag *et al.* Ongoing Project.]



Aromatic Triazolyl Amino Acid Scaffold as Ethanol Sensor

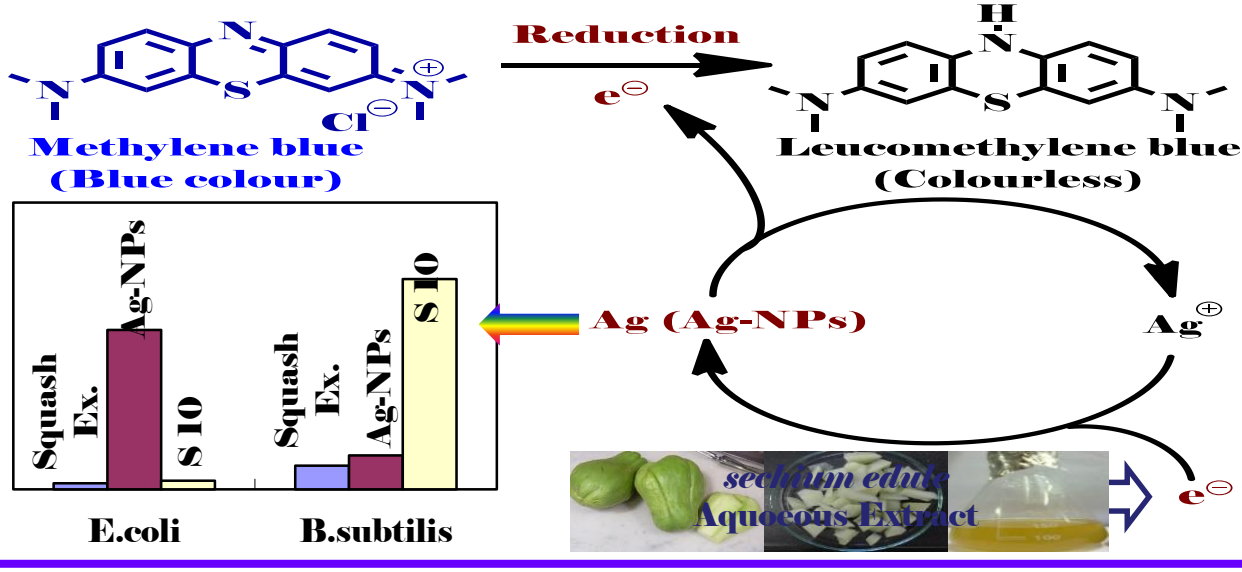
[Bag *et al. New J. Chem.* 2017, 41, 13391]



Contributions to Biochemical Sensor / Few Other Independent Works

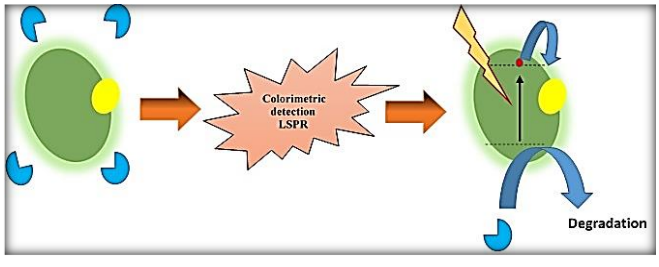
Green Synthesis of Silver Nanoparticle Using *Sechium edule* Aqueous Extract and Study of Antimicrobial and Catalytic Activity

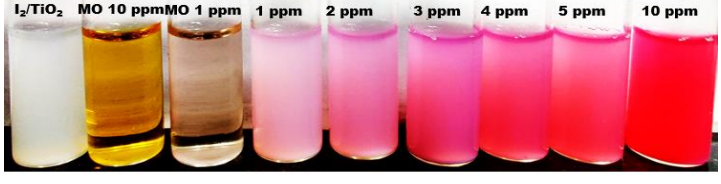
[Bag et al., *Curr. Nanomater 2018, 3, 140-146*]



Rapid "sense and shoot": In-situ colorimetric sensing and degradation of biological and organic species in aqueous environment

[Bag et al., (Under Preparation)]

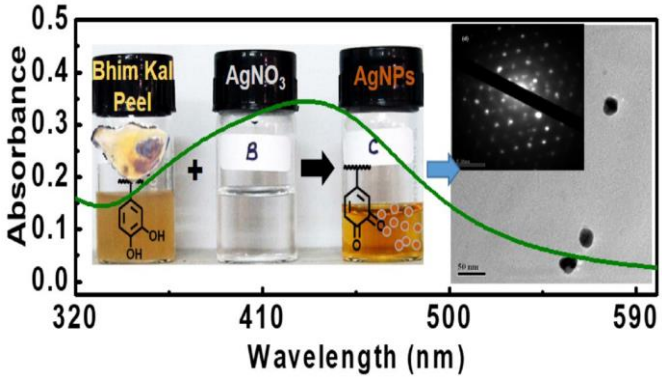




Methylene Blue Sensing by I_2/TiO_2 Nanoparticles

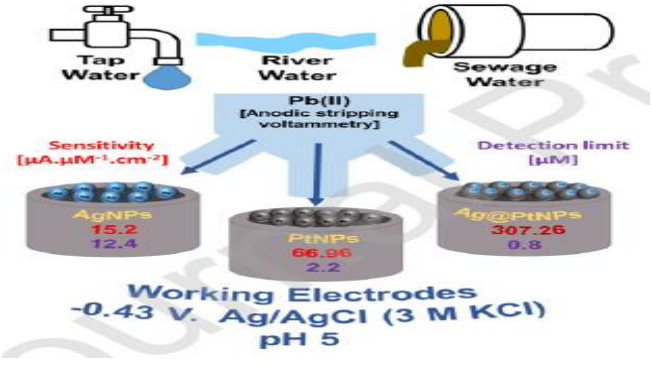
Biomimetic Synthesis of Silver Nanoparticles Using Bhimkol Peel Extract as Biological Waste: Its Antibacterial Activity and Role of Ripen Stage of the Peel

Bag et al. Curr. Nanomater., 2020, (In Print)



Synthesis of Highly Structured Spherical Ag@Pt Core-shell NPs using Bio-analytes for Electrocatalytic Pb(II) Sensing

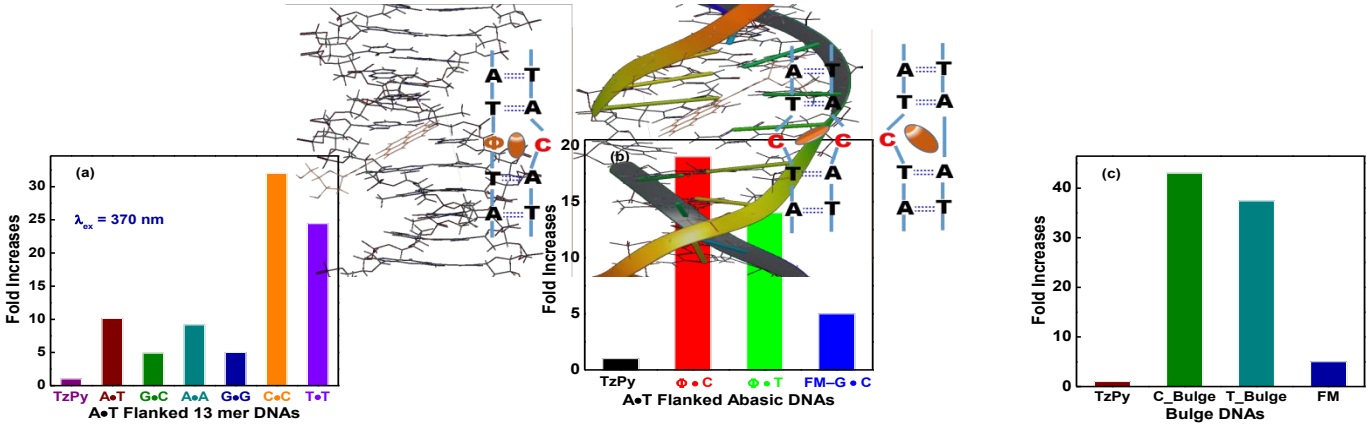
Bag et al. *Sens. Actuat. B* 2020, *XX, XX (In Print)*



Contributions to Biochemical Sensor / Few Other Independent Works

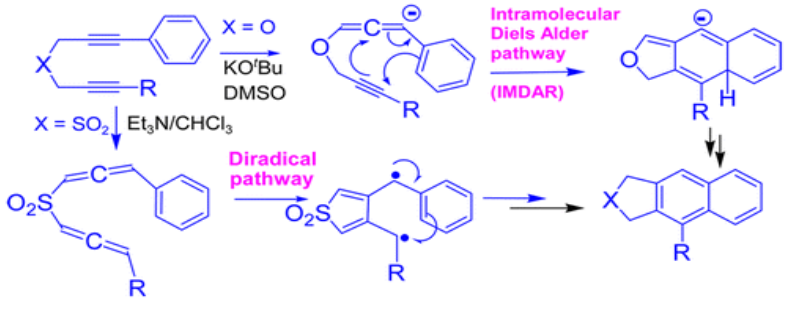
Label Free Mismatched, Abasic and Bulge DNA Detection

[Bag *et al. J. Photochem. Photobiol. B* 2017, *173*, 165]

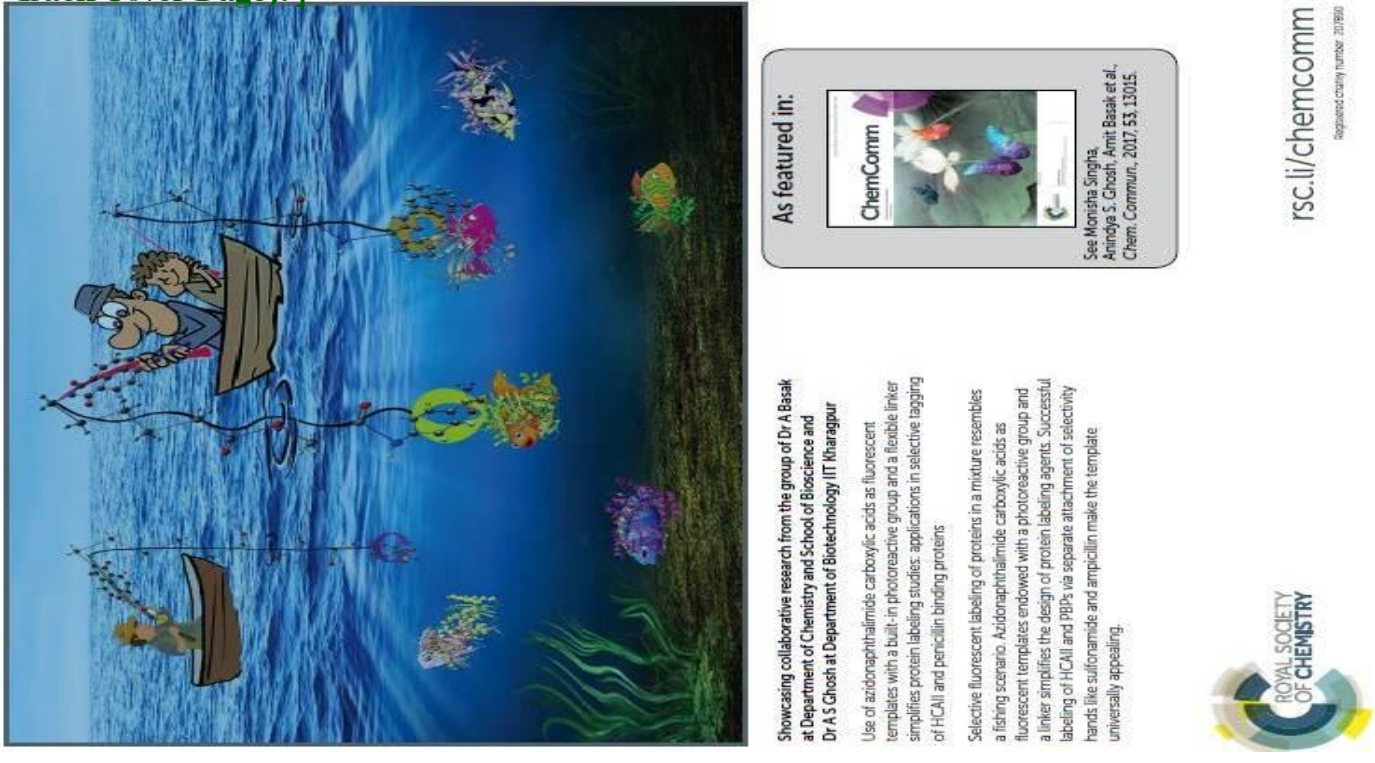


Collaborative Work: Mechanistic Studies on Garratt-Braverman Cyclization

[Das, Joyee; Bag,* Subhendu Sekhar; Basak*, Amit, *J. Org. Chem.* 2016, *81*, 4623.]



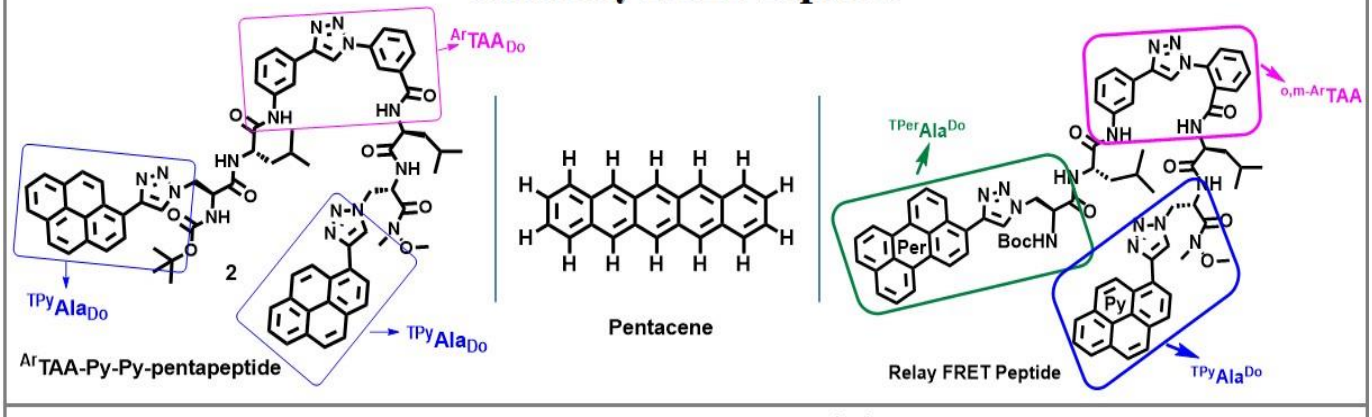
Collaborative Work: Selective Tagging of HCAII and Penicillin Binding Proteins with Azido Naphthalimide Carboxylic Acids [*Chem. Commun.* 2017, *53*, 13015 (Outside Back Cover Page).]

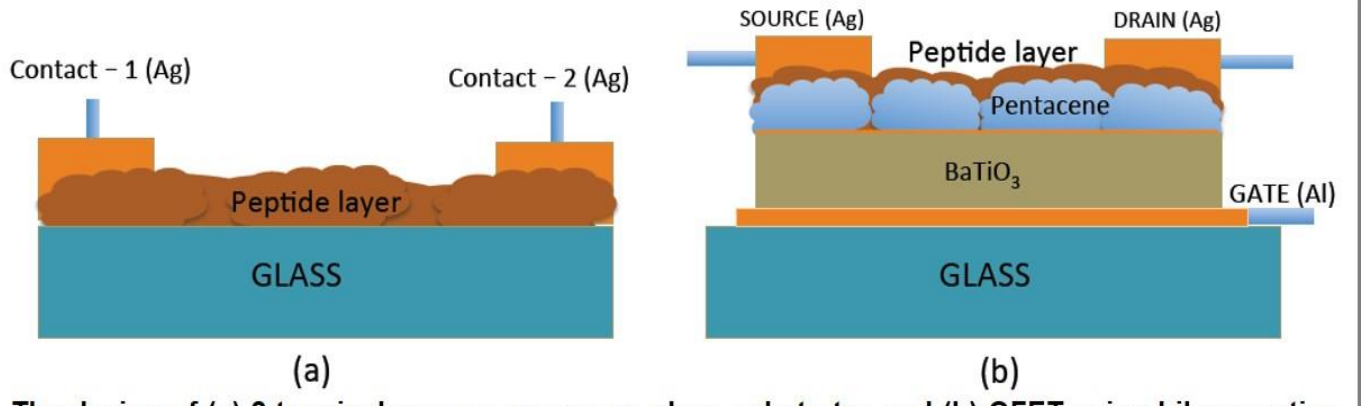


Sensing of Gaseous Ethanol and Blood Protein in Solution With Peptide Based OFET Sensor

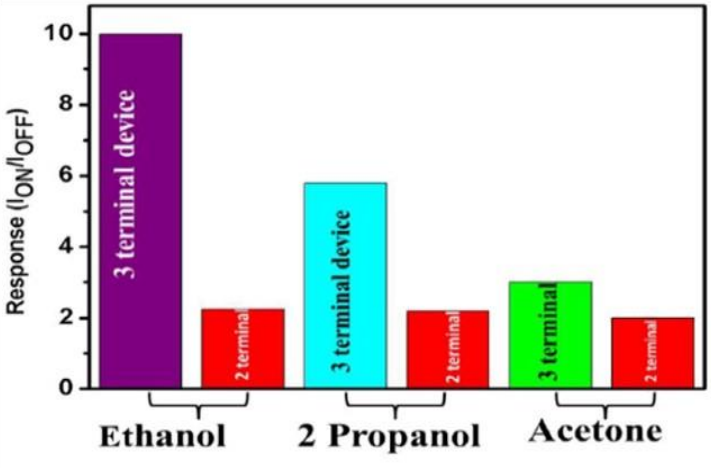
Bag & Goswami et al. (Patent in Process)

Device Fabrication with Synthesised fluorescent Unnatural Peptide-^{Ar}TAA-Py-Py and Relay FRET Peptides





The design of (a) 2-terminal sensors grown on glass substrates and (b) OFET using bilayer active channel comprising ^{Ar}TAA_Py-Py Pentapeptide and pentacene. $BaTiO_3$ is used as dielectric layer.



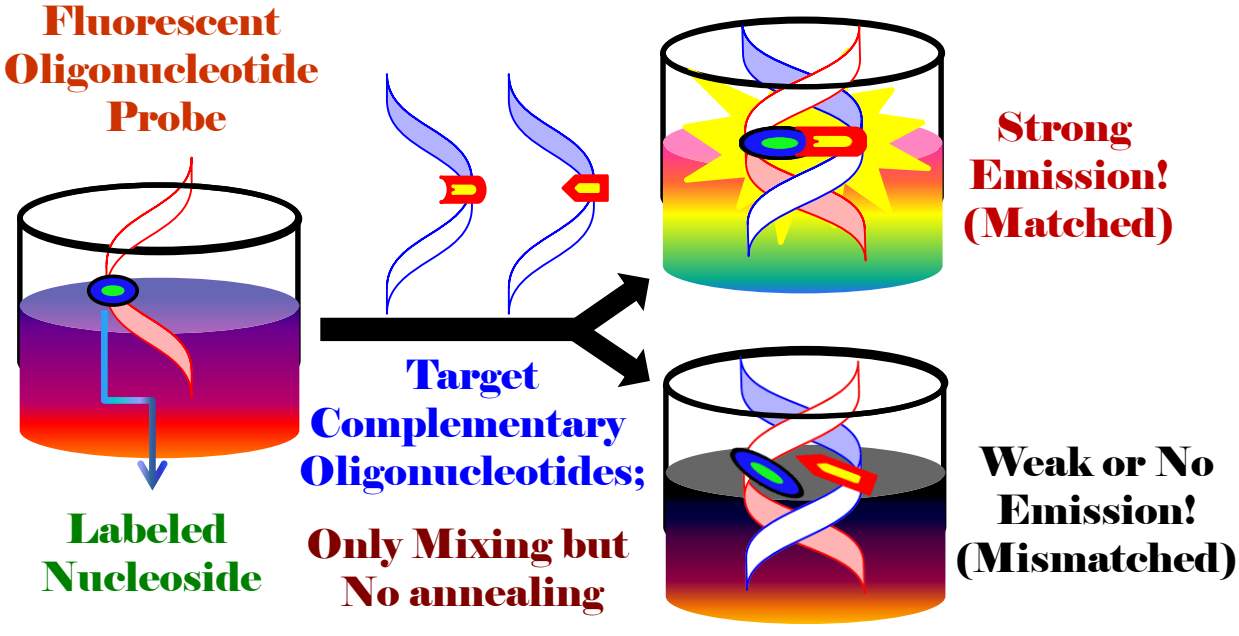
	Ethanol		Isopropanol		Acetone	
	2 Terminal	3 Terminal	2 Terminal	3 Terminal	2 Terminal	3 Terminal
Responsibility Time (in Sec.)	3 S	2.5 S	3 S	3 S	7 S	4 S
Recovery Time (in Sec.)	3 S	2.4 S	3.5 S	28 S	13 S	4 S

Response and recovery of 2-terminal and OFET based sensors

Contributions to Genotyping Single Nucleotide Polymorphism (SNPs) for Personalized Medicine

Contributions to Genotyping Single Nucleotide Polymorphism (SNPs) for Personalized Medicine

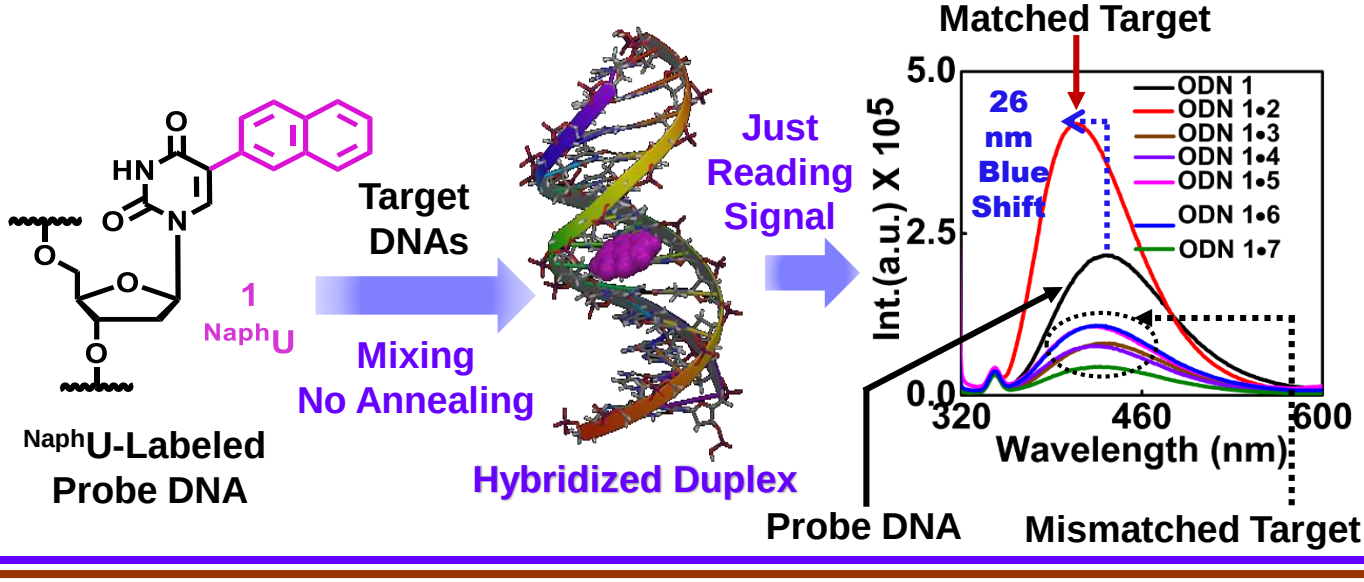
"Just Mix & Read" Strategy for Homogeneous Genotyping SNPs: The Designing Concept



Representaive Publications: (a) *J. Photochem. Photobiol. A. Chem.* **2020,** *388*, 112186**.** (b) *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3227. (c) *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4678. (d) *Org. Biomol. Chem.* **2017**, *15,* 10145 **[Cover page feature: Outside Front Cover]**. (e) *J. Photochem. Photobiol. B* **2017**, *173*, 165. (f) *RSC Adv.* **2013**, *3, 21352*. (g) *Tetrahedron Lett.* **2013**, *54*, 2627. (h) *J. Photochem. Photobiol. B:* **2016**, *162*, 669. (i) *J. Org. Chem.* **2018**, *83*, 7606. (j) John Wiley & Sons (**2016**). (ISBN: 978-1-118-17586-6). (k) *Tetrahedron Letters 50*, **2009,** 1403. *(l) Tetrahedron* **2009,** *65*, 934. **(m)** *Tetrahedron*, **2008,** *64*, 3578.

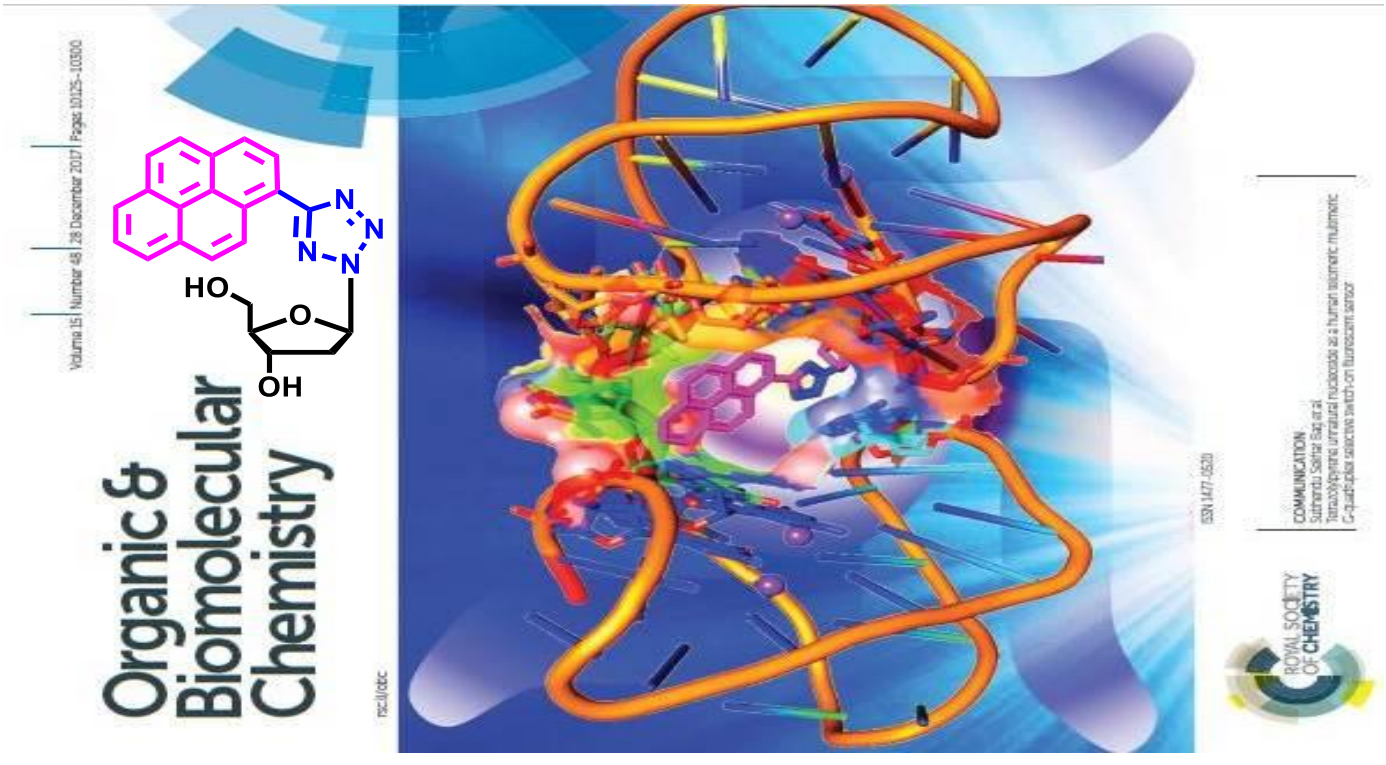
Wavelength Shifting Oligonucleotide Probe for DNA Detection

[Bag *et al. Bioorg. Med. Chem. Lett.* 2014, *24*, 4678.]



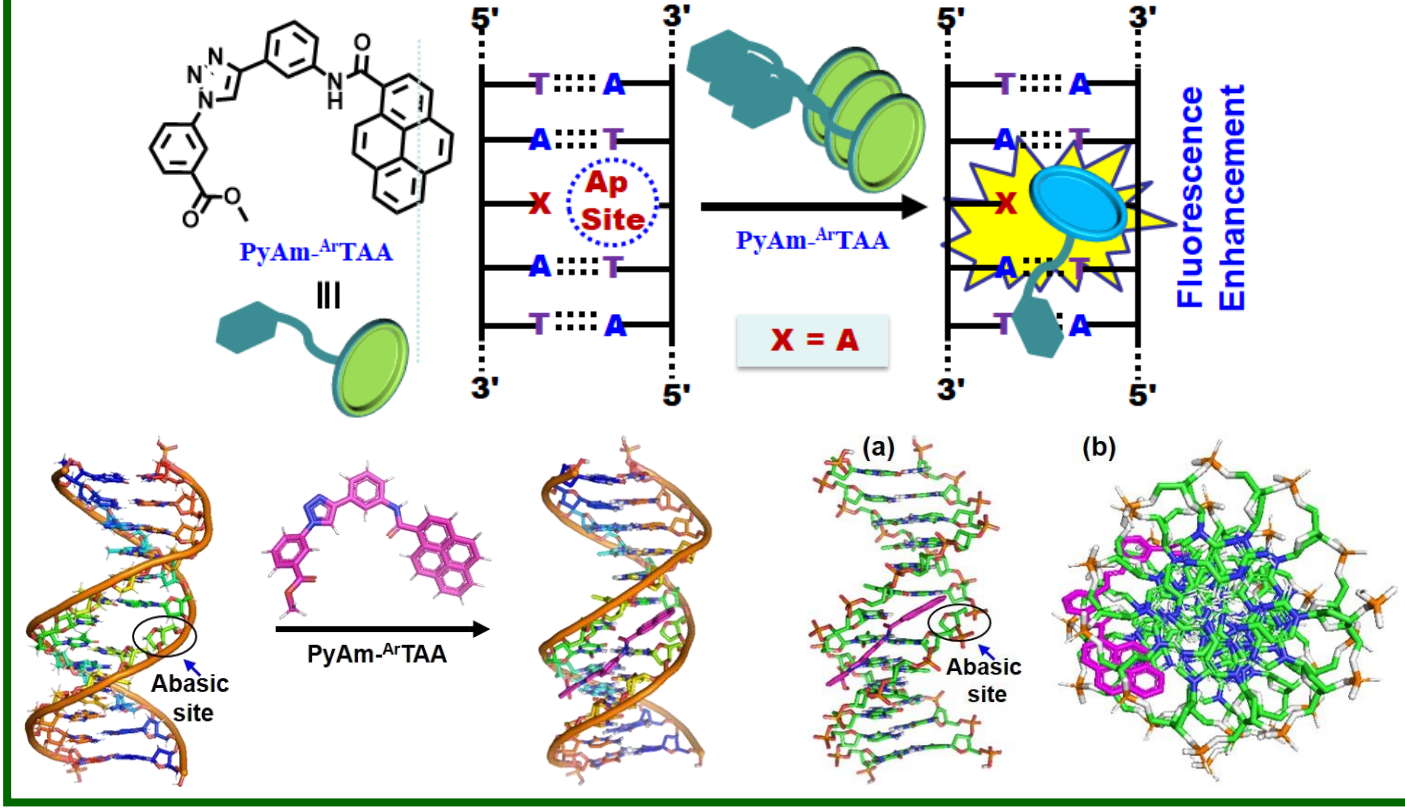
Specific Detection of Multimeric G-Quadruplex DNA with Unnatural Fluorescent Nucleoside

[Bag *et al. Org. Biomol. Chem.* 2017, *15*, 10145 (Outside Front Cover Page)]



Label-free Sensing of Abasic DNA using Pyrenylamido Triazolyl Aromatic Amino Acid Scaffold as AIE probe

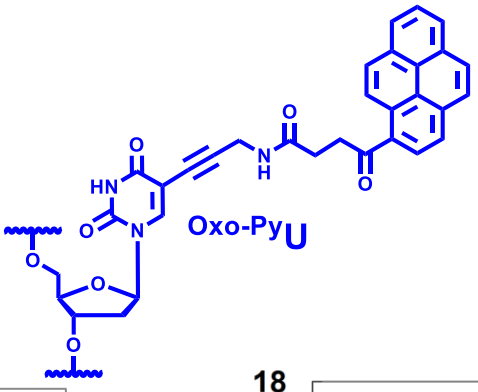
[Bag *et al. J. Photochem. Photobiol. A. Chem.* 2020, 388, 112186]

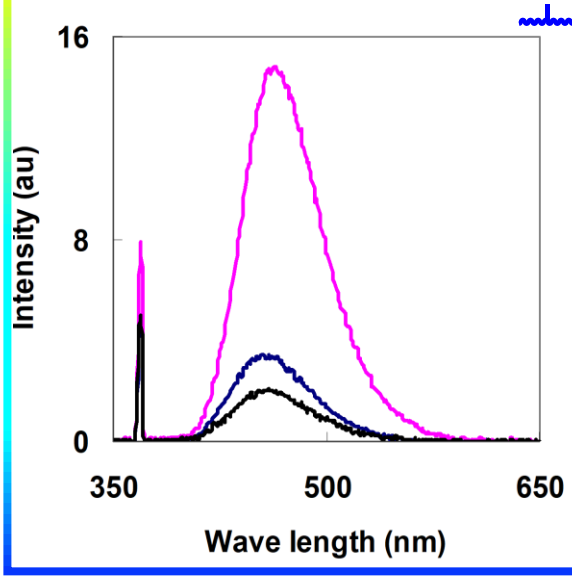


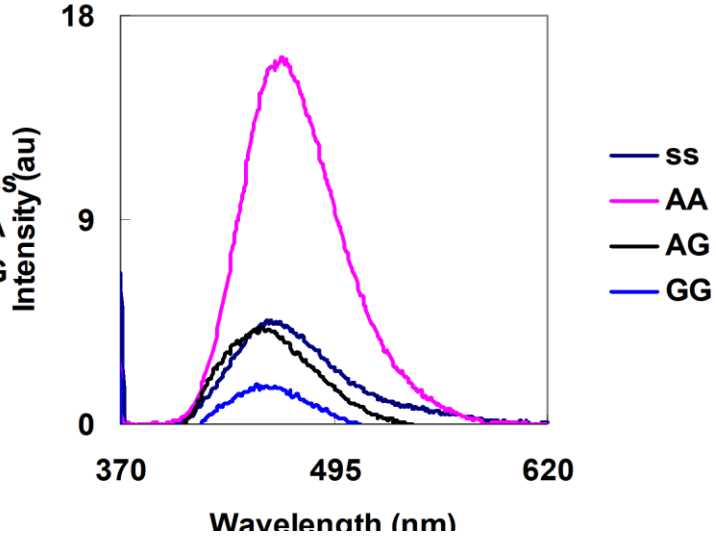
Doubly Labeled DNA Probe: Detection of "A" and Consecutive "AA" Base of a Target ODN

[Bag *et al. Bioorg. Med. Chem. Lett.* 2010, *20*, 3227.]

ODNs	Sequences	ODNs	Sequences
ODN 1 ODN 2	5'-d(CGCAAT$^{Oxo\text{-}Py}$UTAACGC)-3' 5'-d(GCGTTA N ATTGCG)-3' [N = A, G, T]	ODN 3 ODN 4	5'-d(CGCAAT$^{Oxo\text{-}Py}$U$^{Oxo\text{-}Py}$UTAACGC)-3' 5'-d(GCGTTA NNAA ATTGCG)-3' [N = AA, GG, TT]

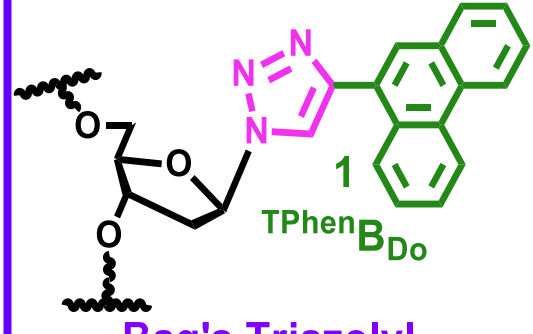




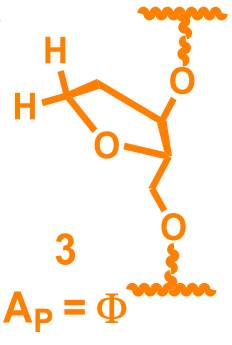


Fluorimetric Sensing of Abasic DNA Lesion with Unnatural Triazolyl Phenanthrene Nucleoside Labeled DNA Probe

[Bag *et al. RSC Advances* 2013, *3*, 21352.]

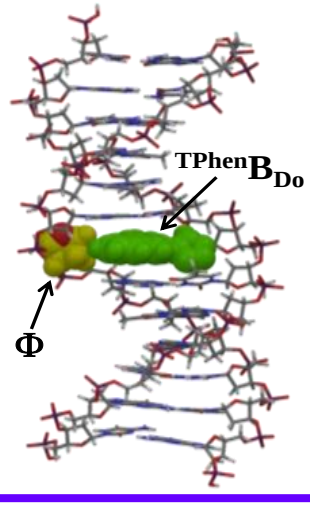


Bag's Triazolyl Nucleoside



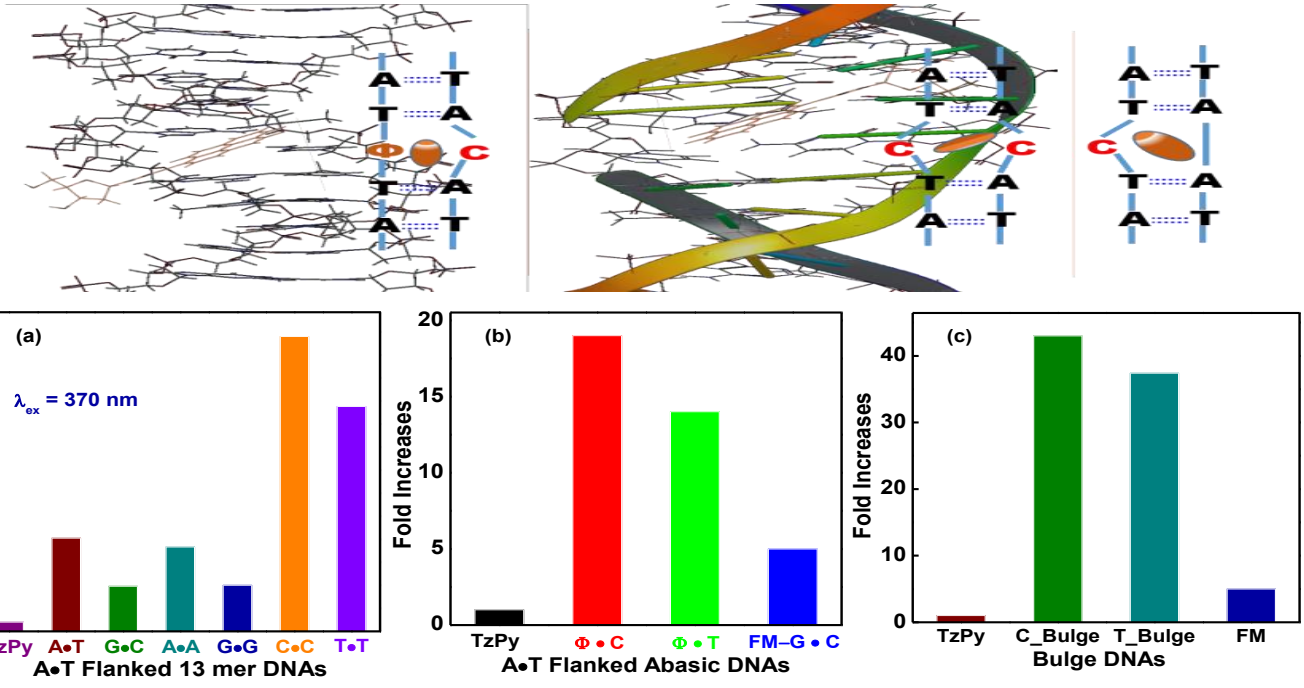
Model Abasic THF

[T_m (TPhenBDo : Φ) = T_m (A:T)]



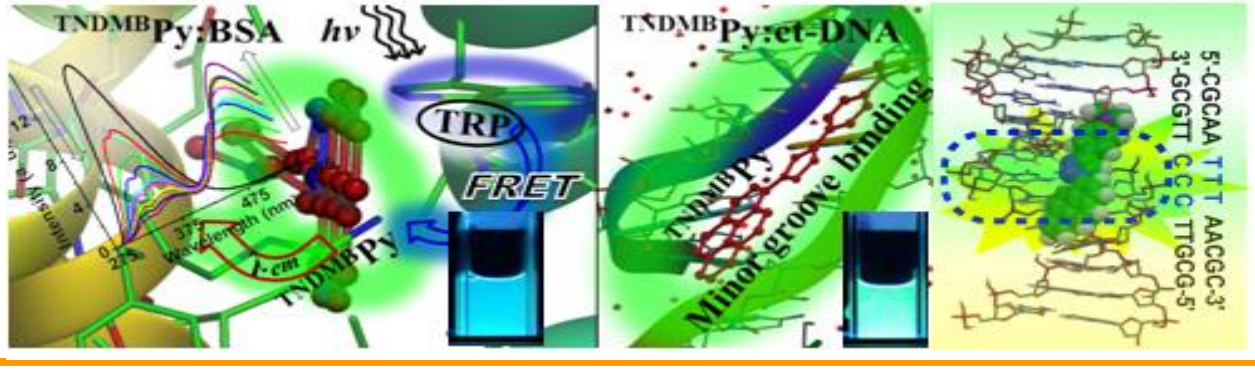
Label Free Detection of Mismatched, Abasic and Bulge DNA Lesions Using A Fluorescent Unnatural Nucleoside

[Bag *et al. J. Photochem. Photobiol. B* 2017, *173*, 165]



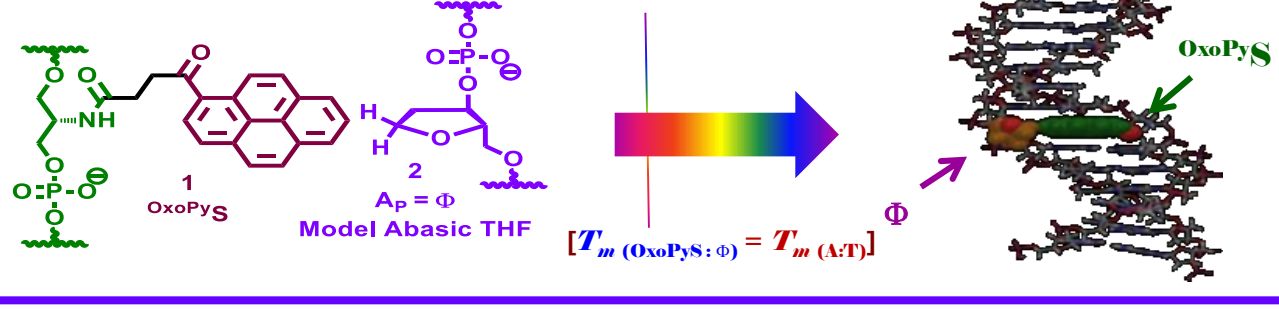
Label Free Mismatched DNA and BSA Protein Detection

[Bag *et al. Tet. Lett.* 2013, *54*, 2627.]



Stabilization of an Abasic Site Paired Against Non-Nucleosidic Base Surrogate

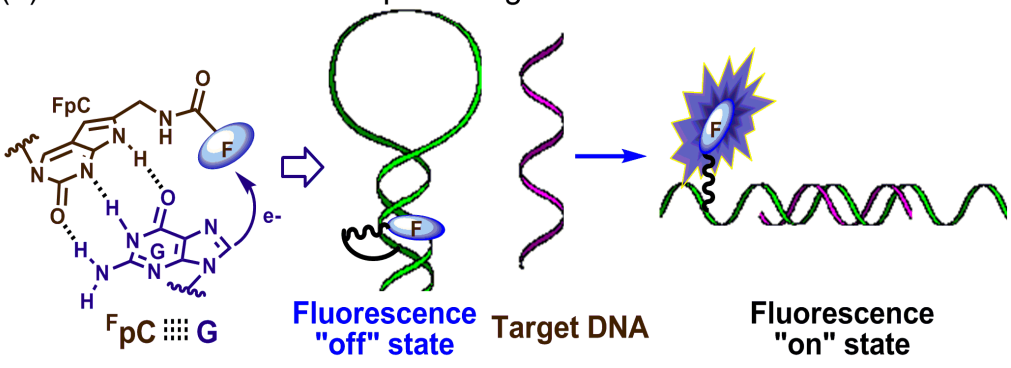
[Bag *et al.* To be Communicated.]

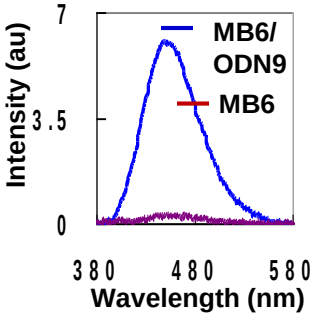


2nd Generation Ends-free-self-quenched MB Probes: Genotyping SNPs Irrespective of Sequences and The Stem Length

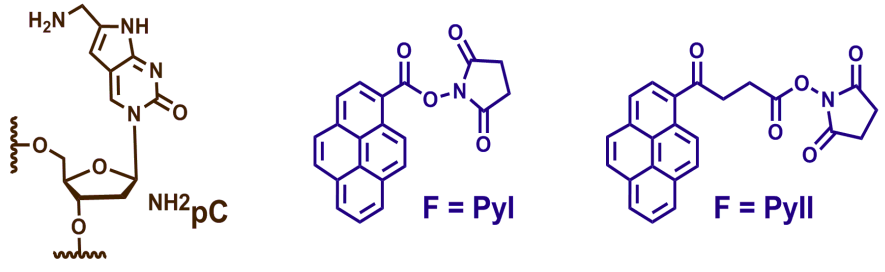
[Bag and Saito *et al. Tetrahedron* 2009, 65, 934.]

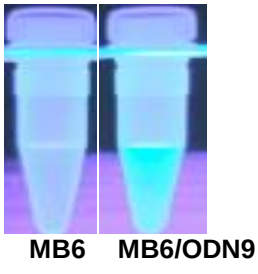
(a) Mode of fluorescence quenching and mechanism of action:





(b) Chemical structures of the fluorophore and pyrrolocytidine:

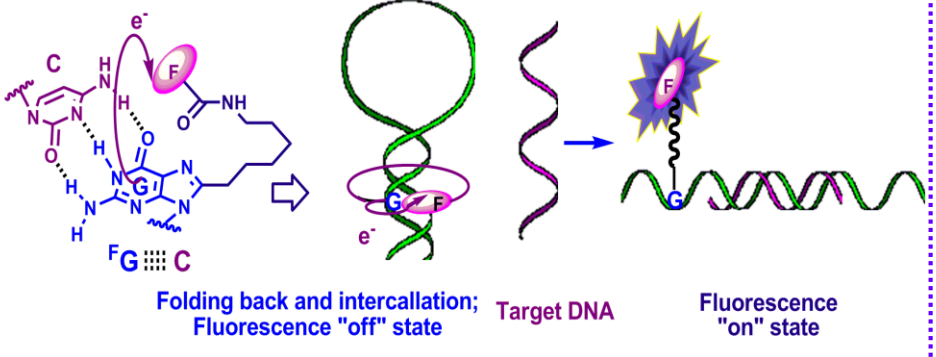




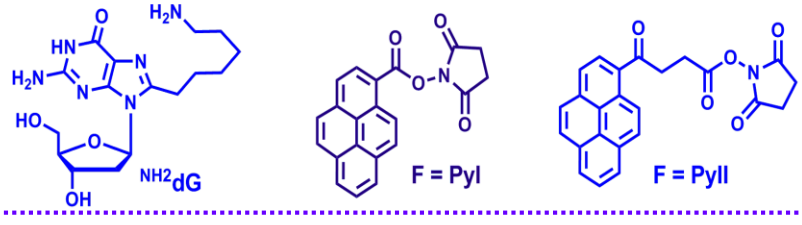
3rd Generation Self-quenched MBs with Ultimate Simplicity: Folding Back And Intercallation Assisted Genotyping SNPs

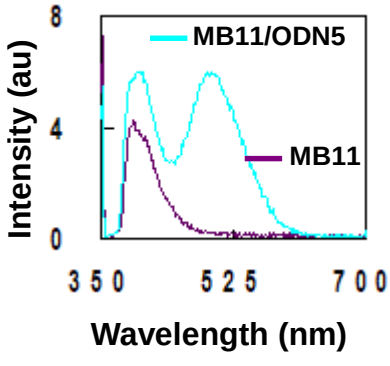
[Bag and Saito *et al. Tetrahedron Letters* 2009, *50*, 1403.]

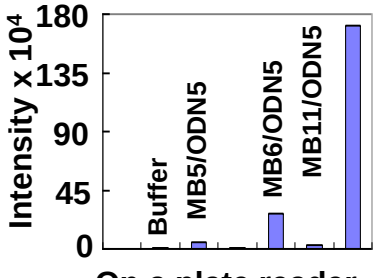
(a) Mode of fluorescence quenching and mechanism of action:



(b) Chemical structure of the fluorophores and C8-alkylamino-dG:



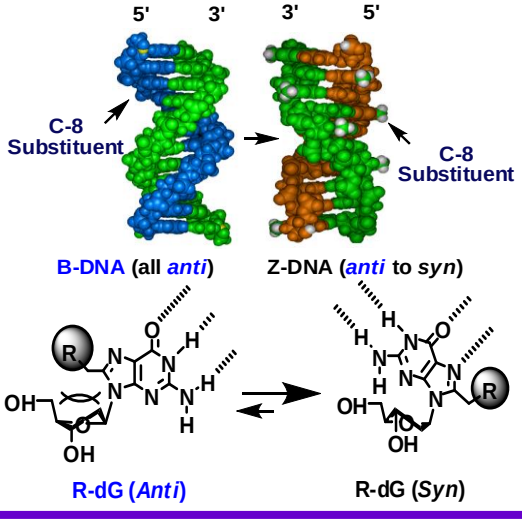


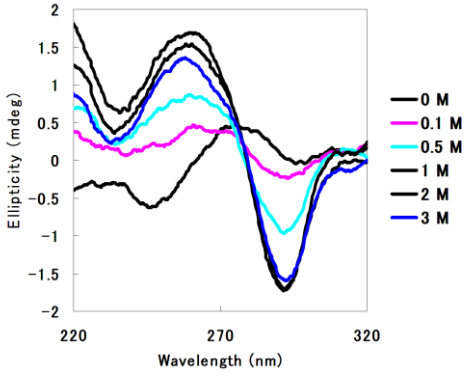


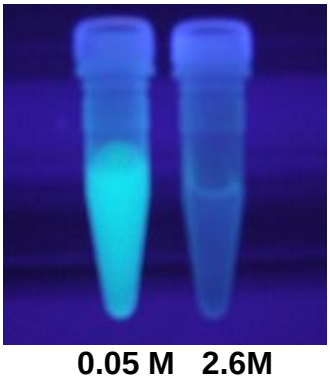
On a plate reader
λ_{ex} = 355 nm;
λ_{em} = 460/535 nm

dG with C8-Alkylamino Group as Universal Linker : Fluorometric Sensing of the B–Z DNA Transition

[Bag & Saito *et al*., *Tetrahedron*, 2008, *64*, 3578.]

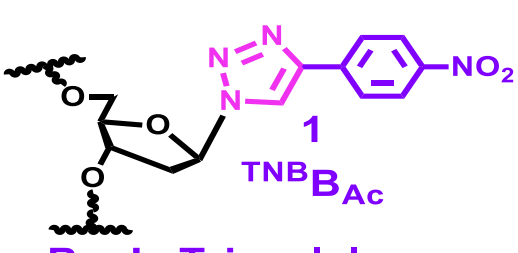




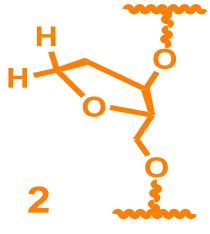


Detection of an Abasic Site with Unnatural Triazolyl Nitrobenzene Nucleoside

[Bag *et al. Under Revision, (DNA Repair)*]



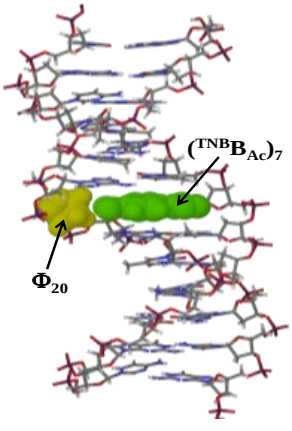
Bag's Triazolyl Nucleosides



A_P = F

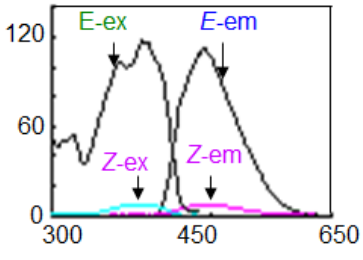
Model Abasic THF

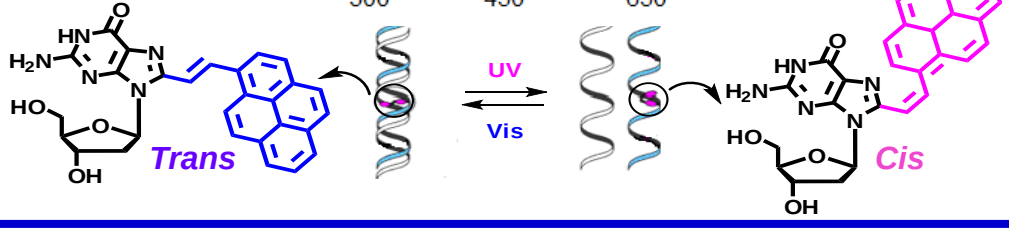
$[T_m$ (TNBBAc : Φ) = T_m (A:T)$]$

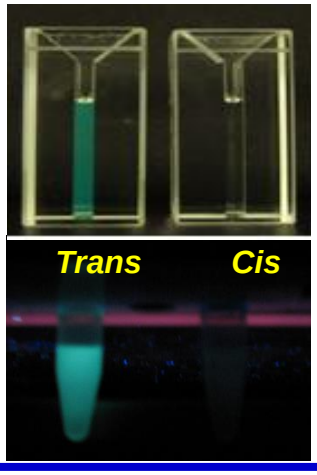


Fluorescent Photoswitchable Nucleoside: Photoregulation of DNA Hybridization

[Bag & Saito *et al*., *Tetrahedron Letters* 2009, *50*, 1403.]

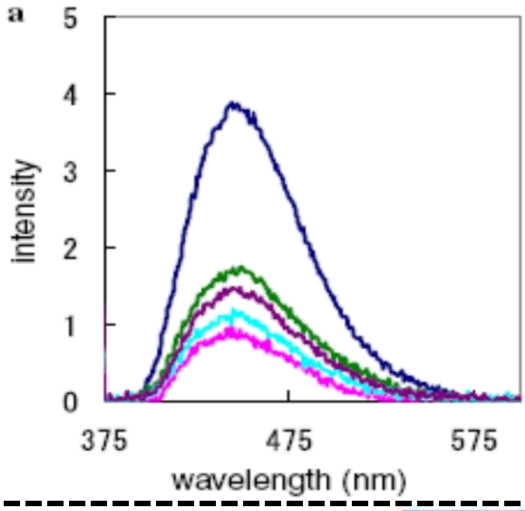






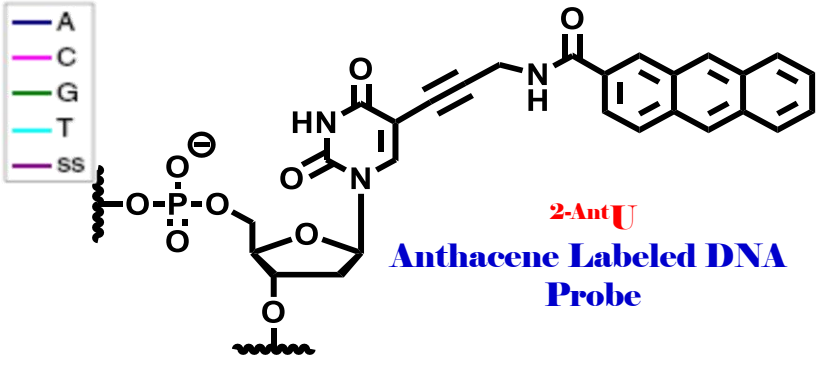
Anthracene-DNA Probe: *abl/bcr* Cancer Gene Detection

[Bag & Saito *et al*., *Bioorg. Med. Chem.*, 2008, *16*, 107]



5'-dCGCAAC $^{2\text{-Ant}}$U CAACGC)-3'

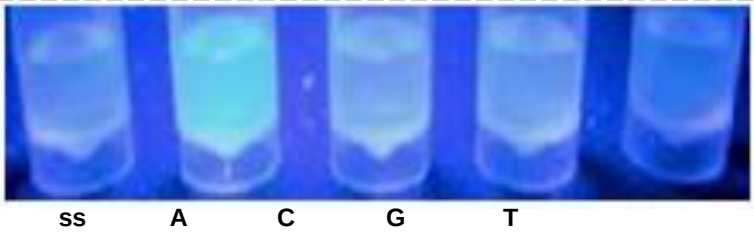
5'-d(CGCAAC N CAACGC)-3' [N = A, G, C, T]



$^{2\text{-Ant}}$U

Anthacene Labeled DNA Probe

Illuminated at 365 nm



***abl* gene sequence**

5'-NH_2-C_{12}-TGAAGGGCT$^{2\text{-Ant}}$UCTTCCAGATA-3'

3'-ACTTCCCGA N GAAGGTCTAT-5'

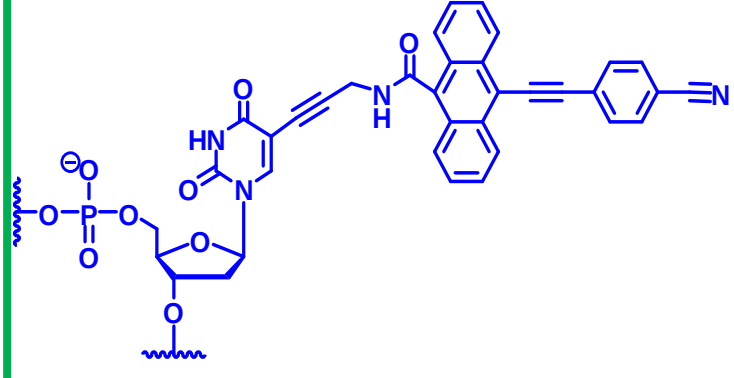
(N = A, C, G, or T)

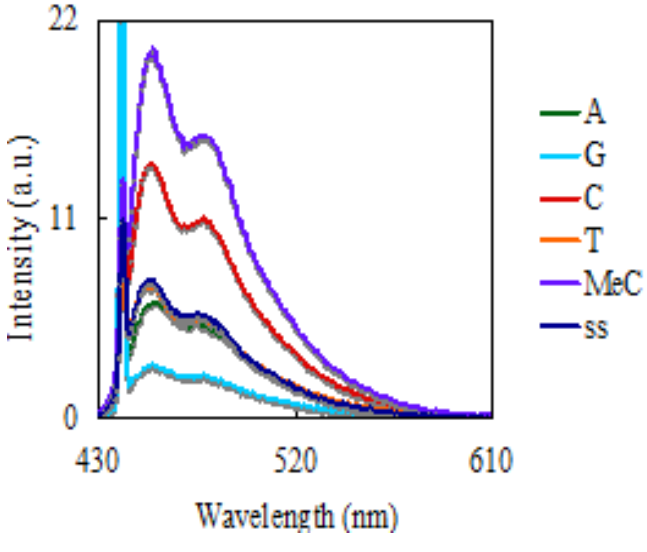
Fluorescent Oligonucleotide Probe for the Detection of T/C Mismatch and Distinction of ^{Me}C From C

[Bag et al. *(To Be Communicated)*]

ODN 1 5'-d(CGCAAT$^{9\text{-CN-Ant}}$UTAACGC)-3'

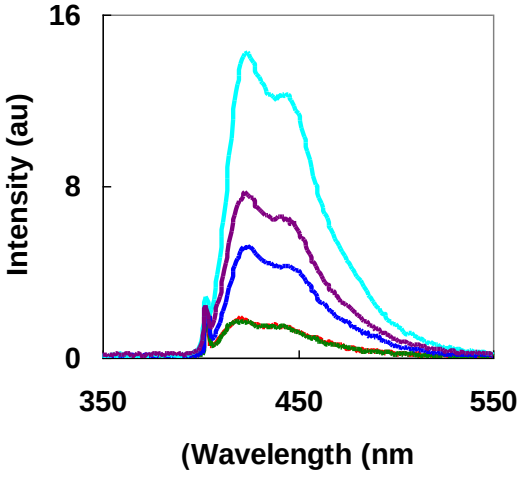
ODN 2 5'-d(GCGTTANATTGCC)-3' [N = A, G, C, T, ^{Me}C]

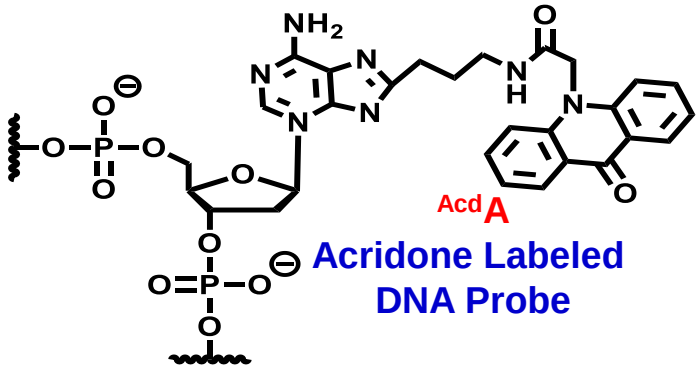




Acridone Labeled DNA Probe for the Detection of SNPs via a Switch-on Fluorescence Response

[Bag & Saito *et al*., *Chem. Lett.*, 2006, *35*, 1182]



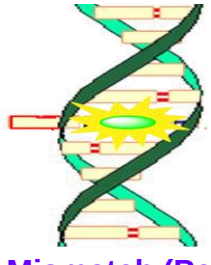


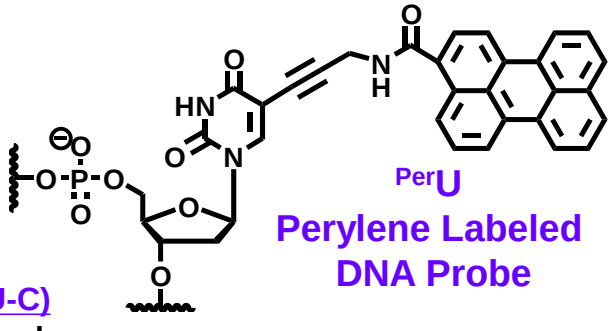
5'-d(CGCAAT ^{Acd}A TAACGC)-3'
5'-d(CGCAAT N TAACGC)-3' [N = A, G, C, T]

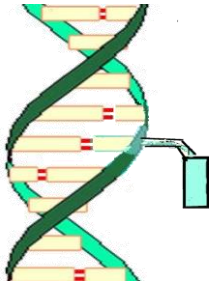
Perylene Labeled Probe : Concept for T/C SNP Genotyping

[Bag & Saito *et al*., *Bioorg. Med. Chem. Lett.*, 2006, *16*, 6338]

OUR CONCEPT







Mismatch (PerU-C)

- Rotation of glycosyl bond
- Per involves in tercalative stacking into Major Groove
- Facing Hydrophobic environment→ Strong Fluorescence

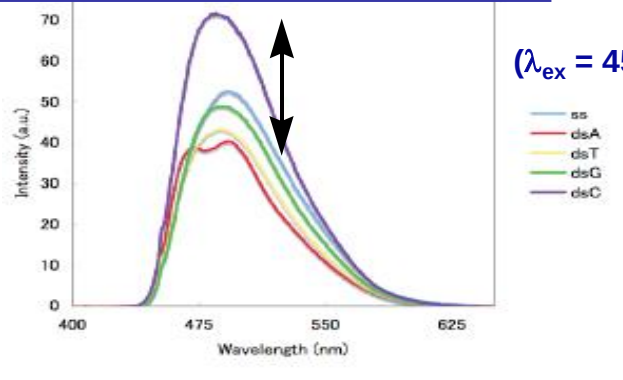
Match (PerU-A)

- Per extrudes outside of Major Groove;
- Facing Polar aqueous environment→ Weak Fluorescence

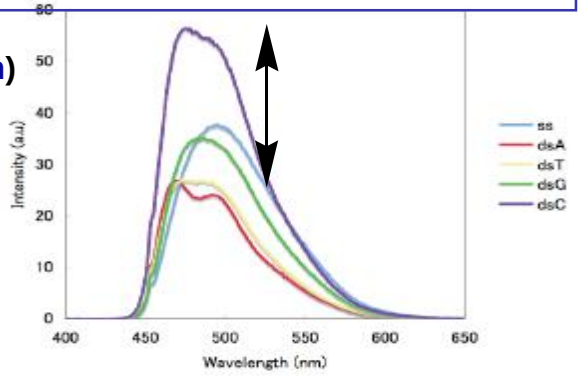
Result

A/T-rich: 5'-d(CGCAAT ^{Per}U TAACGC)-3'
5'-d(GCGTTA N ATTGCG)-3'

G/C-rich: 5'-d(CGCAAC ^{Per}U CAACGC)-3'
5'-d(GCGTTG N GTTGCG)-3'



(λ_{ex} = 452 nm)

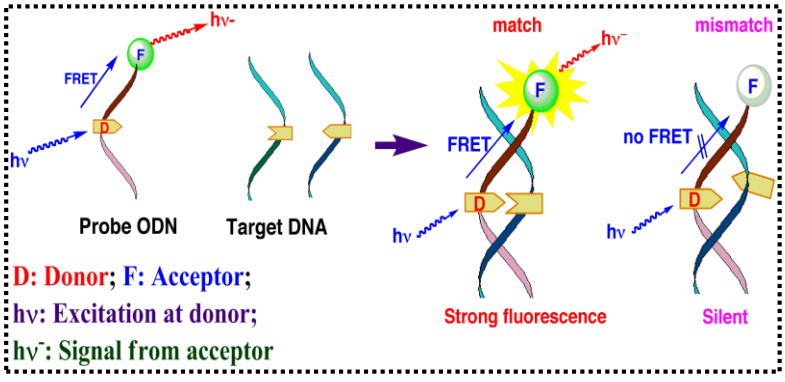


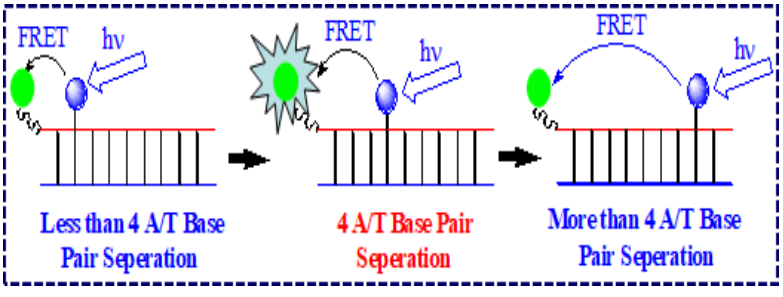
Fluorescence Response Upon hybridisation

FRET Based Strategy for DNA Sequence Analysis

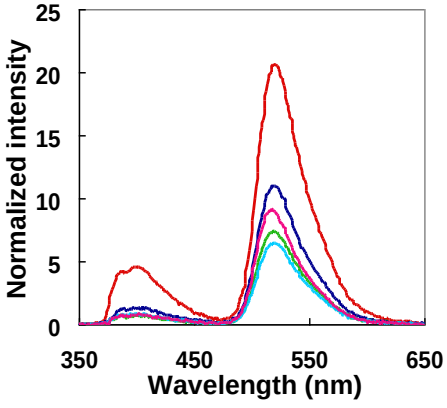
[Bag & Saito *et al.*, *Chem. Commun.*, 2007, *21*, 2133.]

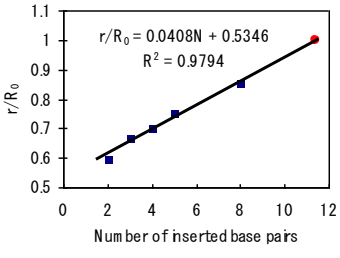
The Concept





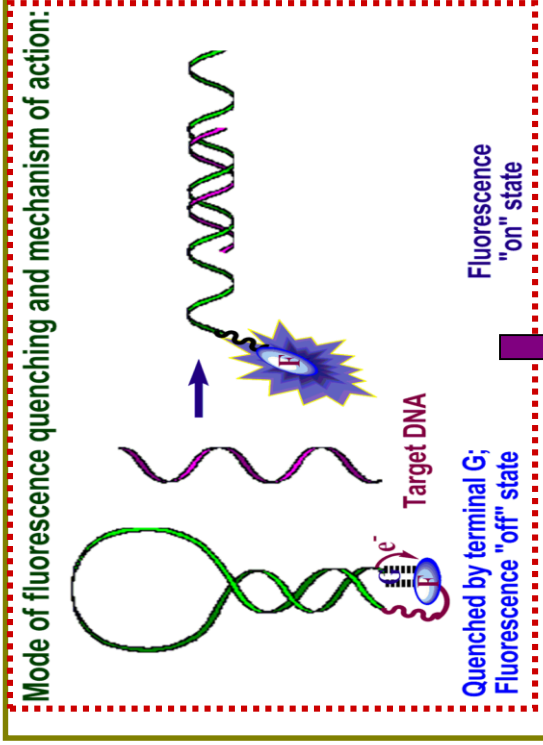
5'-d(F-AAAT^{Py}UTAACGCACACG)-3'

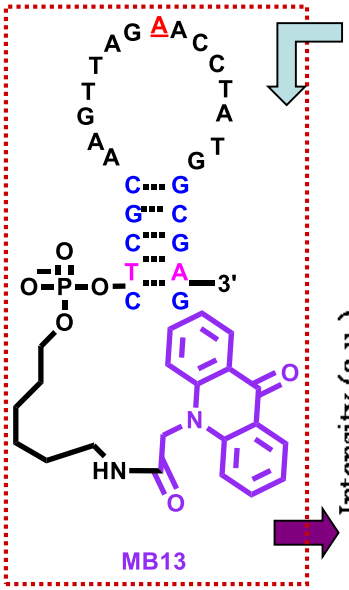


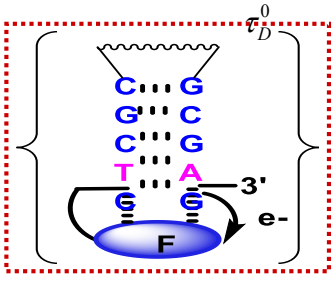


FRET efficiency and the selectivity decreased as distance increased by more than four A/T base pairs.

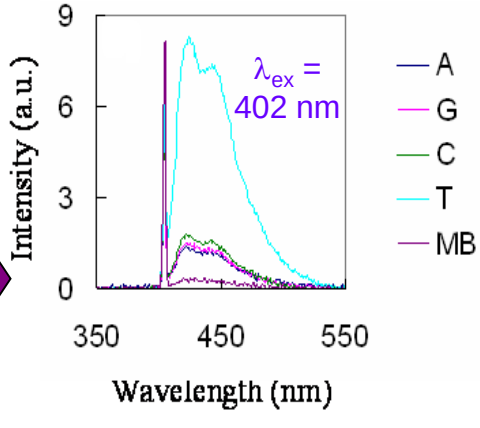
1st Generation G-quenched MB Probe: On/Off Sensing of Target DNA Sequences and SNPs Typing [Bag & Saito *et al.*, *Chem. Commun.*, 2007, *43*, 4492 (Chemical Biology Research Article 2007, 12.)]







Stem with Terminal G/C



FINAL CONCLUSION and FUTURE SCOPE

GENOMIC RESEARCH FOR THE FUTURE: PERSONALISED MEDICINE

Personalized Medicine:

Simply, it can be defined as the use of information from a patient's genotype to:

- **initiate a preventative measure against the development of a disease or condition, and**
- **select the most appropriate therapy for a disease or condition that is particularly suited to that patient.**

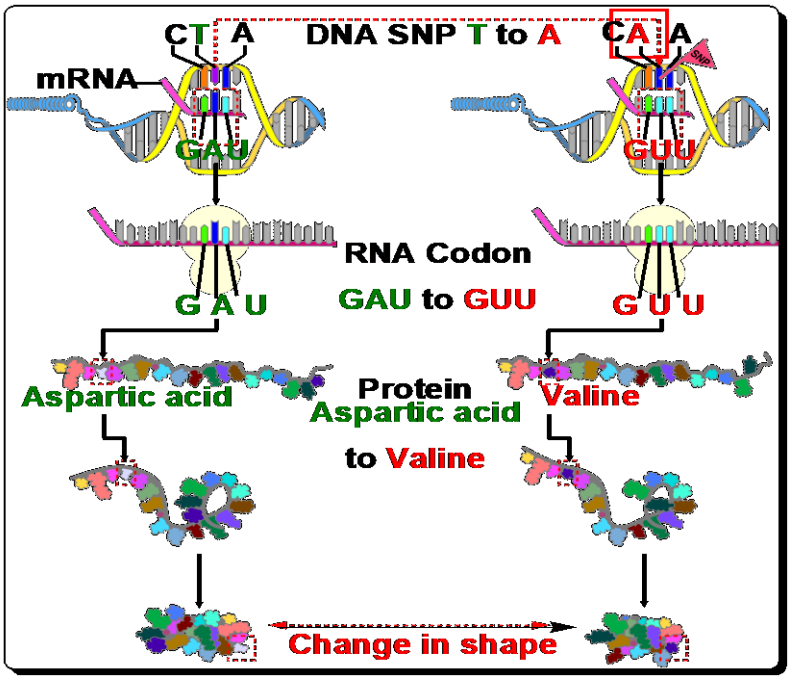
Single Nucleotide Polymorphisms (SNPs) and Personalised Medicine (PM):

Tiny variation (0.1 %) in DNA makes a person unique and SNPs explain:-

- **Person's uniqueness in physical appearance**
- **Disease susceptibility**
- **Different response to a specific drug treatment**
- **Different side effects in response to the same drug**
- **Proteins-drug/DNA-drug interaction**
- **SNPs occur in coding regions→ could alter the protein → could influence a person's health.**
- **SNP Profiles may help to identify Cancer Genes**
- **Role of SNPs to calculate risk factors with cancer**
- **Scientists think "SNP is the key enabler in the realization of the concept of personalized medicine".**

One Example : Effect of SNPs In the Coding Regions:

Harmful Changes in Protein: Mutations-→Sickle cell anemia. Hemoglobin beta gene→Hemoglobin molecule not carry oxygen



Thus, SNPs are the attractive target for better understanding the genetic basis of complex diseases, and to realize the potential of pharmacogenetics.

Therefore, the first Step of the Concept of Personalised Medicine (PM) is to

- **Identify, catalogue mapping and Profile making of all SNPs in the human genome.**
- **Indentification of genetic differences between people that predict susceptibility to diseases or affect to a drug response**
- **Saliva samples of a person is tested and the results are interpreted as genetic association with risk or without risk**

So, the development of simple, easy, cost effective and Unique SNPs typing protocols/chemistry/platforms is highly desirable to realise the Concept of Personalised Medicine (PM) .

Our Efforts: We have developed several conceptual probes/techniques and were able to use them for gene detection successfully. In this way development of simple technology might able to help in detection of all the SNPs of Human genome.

- Thus, ongoing, novel, easy and high throughput detection techniques, microarray, expectedly would allow to us detect SNPs in large scale and thereby we will be able to make SNPs profile of a person.

- This will allow physicians to compare with the global mutations repository and to diagnose a particular disease associated with a mutation.

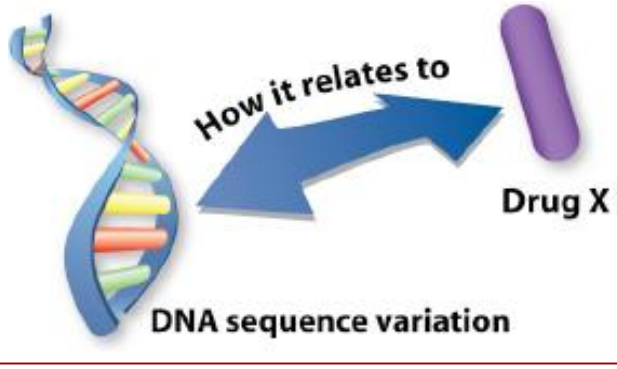
- Identifying genetic susceptibility to disease

- Allow to study pharmacogenomics to revolutionize the practice of medicine by individualisation of treatment through the use of novel diagnostic tools.

- Pharmacogenomics would reduce the trial-and-error approach of treatment and thereby limit the exposure of patients to drugs that are not effective or are toxic for them or have serious, side effects.

Thus, our continuous efforts blended with pharmacogenomics would allow us, one day, to fix the disease at the Genetic level and to provide tailor medical treatment (Personalised Medicine) to the individuals with all round positive health impact.

Our ongoing Drug design and development project along with study of Drug -DNA/Drug-Protein interaction and the above knowledge would help in designing genetically effective Personalised Drugs.



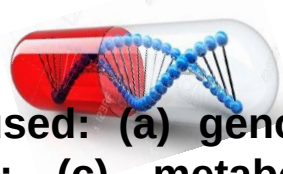
The Positive Health Impact: Promises of Personalized Medicine

Traditional Medicine:

- **Protocol: Doctors used: (a) Family History, (b) Socioeconomic circumstances, (c) Environmental factors, (d) "one-drug-fits-all" model.**

- **Results: Symptomatic treatment, Trial & error medication, less guaranteed effectiveness, More side effect.**

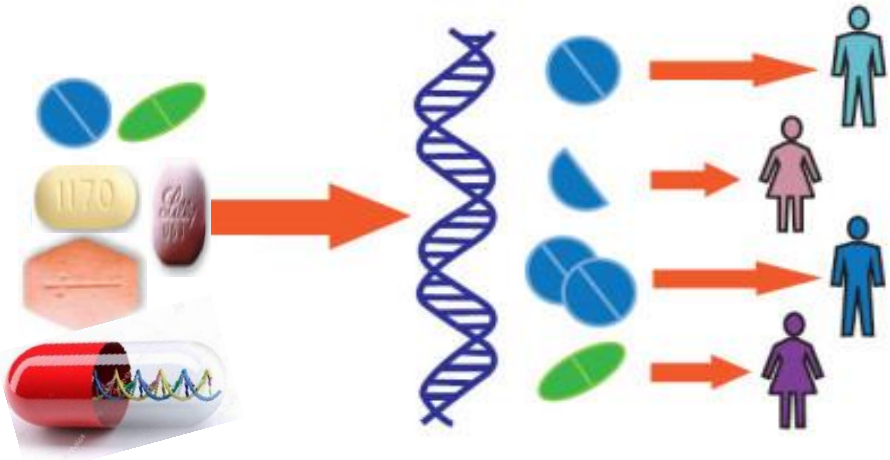
Personalised Medicine (PM):



- **Protocol: doctors used: (a) genomic/genetic testing; (b) proteomic profiling; (c) metabolomic analysis (study metabolites), (d) 'the right drug for the right patient at the right dose and time' model.**

- **Results: Positive Health Impact and the Promises of Personalised Medicine (PM):**
  - **PM seeks to address all the shortcomings of conventional medicine (CM)**
  - **Better Diagnoses and Earlier Interventions**
  - **More Efficient Drug Development**
  - **More Effective Therapies: In addition to all benefits, testing will help to predict the best dosing schedule or combination of drugs for a particular patient.**
  - **No side effect**

Traditional Medicine



Personalised Medicine (PM):

CURRENT/FUTURE FOCUS

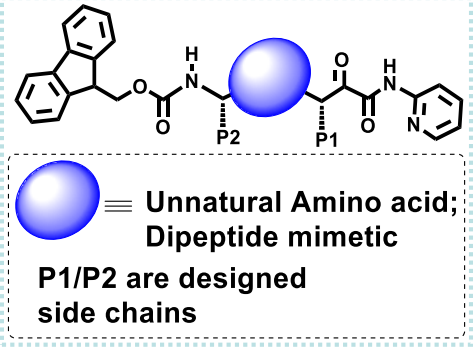
Translation of an Expanded Genetic Alphabet Into an Expanded Genetic Code; Personalized Medicine and Development of Nucleoside/Peptidomitic Drug Inhibitors For COVID-19/AIDS

CURRENT/FUTURE FOCUS

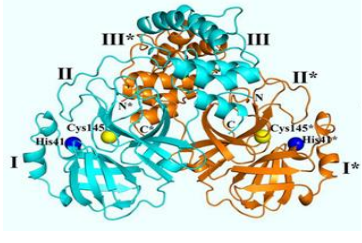
Translation of an Expanded Genetic Alphabet Into an Expanded Genetic Code; Personalized Medicine and Development of Nucleoside/Peptidomitic Drug Inhibitors For COVID-19/AIDS

Design of Unnatural Triazolyl Amino Acid Scaffold Based Peptidomimetic Inhibitor of SARS-CoV-2 M^{pro}

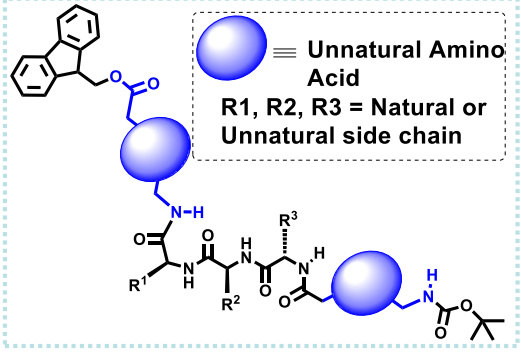
SARS-CoV-2 (2019-nCoV) coronavirus is posing dangers worldwide at the very moment. Currently, the clinical treatment of the disease, CoVID-19 is mainly symptomatic combined with repurposing of already marketed antiviral drugs. Therefore, there remains an urgent need and challenges to save the human life worldwide by developing specific antiviral therapeutics and vaccines against SARS-CoV-2. Inhibition of HIV-protease-I was a successful strategy for the treatment of HIV. On the same line, the main protease of SARS-CoV-2 can be regarded as promising target for antiviral drug. The appearance of recent crystal structure of that main protease enables to design specific inhibitory drug candidates. As the activity of the protease is inhibited, the viral replication would stop.



SARS-CoV-2 M^{pro} Inhibitor α-keto-amide mimetic



3D structure of SARS-CoV-2 M^{pro}



SARS-CoV M^{pro}s Inhibitor Analogue of inhibitor N3

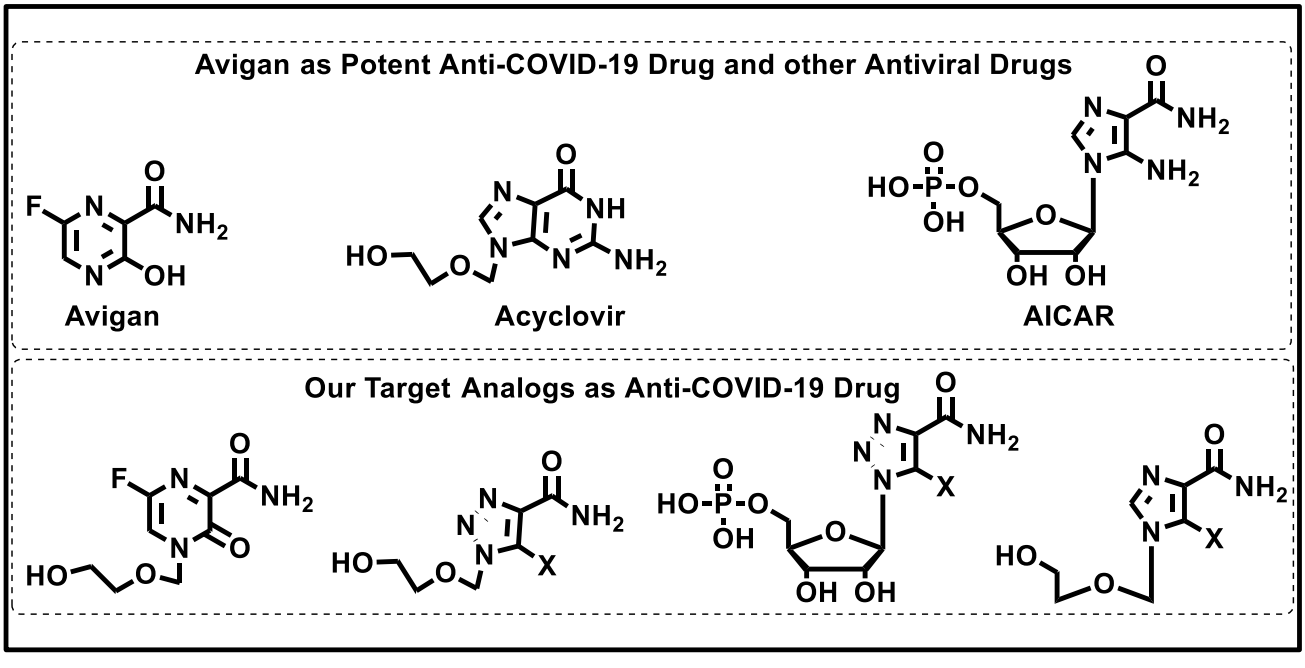
As a continuation of our research on unnatural amino acid and β-turn/sheet peptidomimetics, we recently devoted ourselves in synthesising potent peptidomimetic inhibitor of coronavirus main protease and thus decided to contribute to the society. The design involves the utilisation of our already reported dipeptide mimetic amino acid scaffold in both the cases. We propose that the variation of P1/P2 would lead to potent α-keto amide inhibitor. On the same line we expect that the designed N-3 analogue could be a better candidate for inhibiting **SARS-CoV M^{pro}s**

CURRENT/FUTURE FOCUS

Design of Avigan Analog and Sugar Modified Natural/ Unnatural Nucleobase Analog as Antiviral Drug for COVID-19

[Bag and Saito et al.]

SARS-CoV-2 (2019-nCoV) coronavirus is posing dangers worldwide at the very moment. Currently, the clinical treatment of the disease, CoVID-19, is mainly symptomatic combined with the repurposing of already marketed antiviral drugs. Therefore, there remains an urgent need and challenge to save human life worldwide by developing specific antiviral therapeutics and vaccines against SARS-CoV-2. The approved influenza drug, Favipiravir (Avigan) selectively inhibits the RNA polymerase of the influenza virus, an enzyme required for viral replication once human host cells are infected. COVID-19 also uses this enzyme to replicate and is classified in to the same type of single-stranded RNA virus like influenza. Recently, Avigan is used as the only drug to help tackle the spread of the COVID-19 pandemic in Japan, and the Government of Japan came forward to help other countries by providing this drug. The structures of Avigan and the other two antiviral drugs and the target analogs are given below.

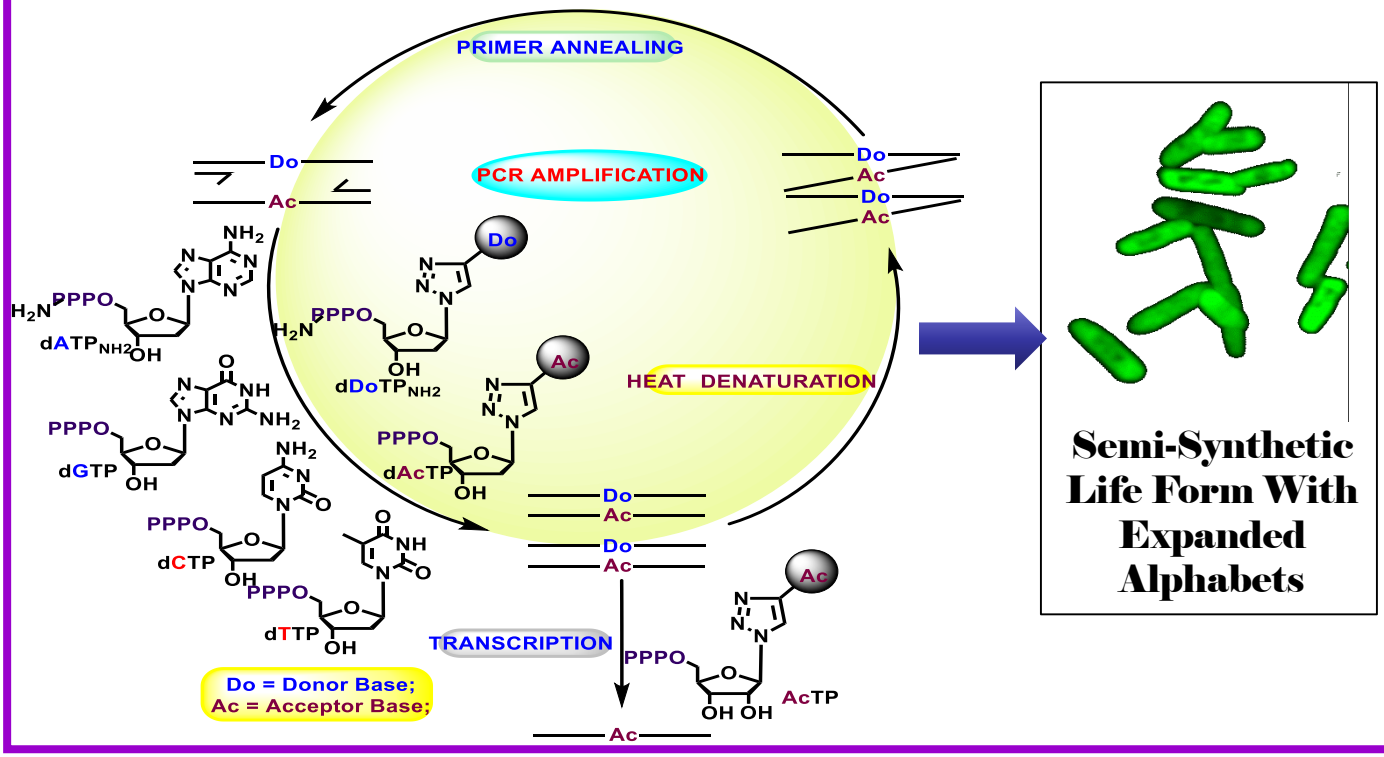


In this crisis and as a continuation of the research efforts for the synthesis of novel nucleosides, Dr. Bag has recently involved in collaborative work with Prof. Isao Saito, Kyoto University, Japan, for developing antiviral nucleosides such as Avigan and AICAR analogs. Considering the effectiveness of Avigan against Coronavirus and the side effects of other nucleoside based drugs, they came up with target designed analogs. Their preliminary model study suggested replacing the ribose by linear alcohol as in acyclovir. Furthermore, the triazole containing bases shows strong interaction and binding effect reflecting their activity to stop the extension of RNA of the virus. This collaborative work would yield a highly effective COVID-19 drug.

CURRENT/FUTURE FOCUS

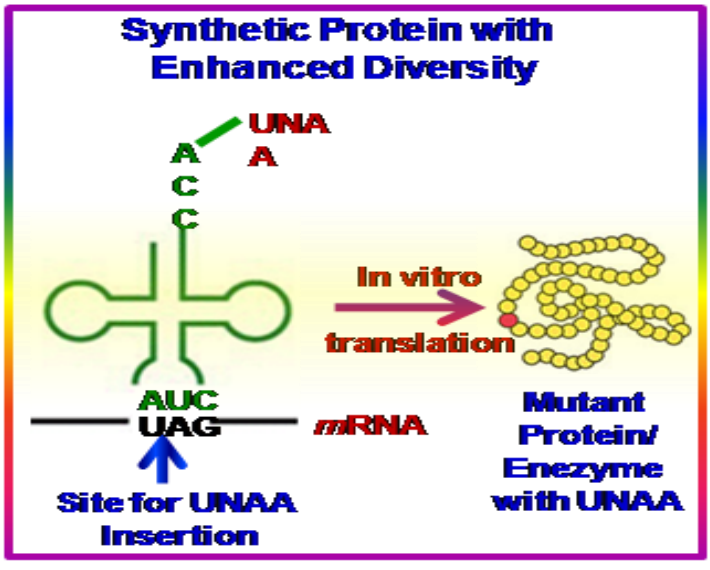
Translation of an Expanded Genetic Alphabet Into an Expanded Genetic Code; Development of Nucleoside/Peptidomitic Drug Inhibitors For COVID-19/AIDS and Personalized Medicine

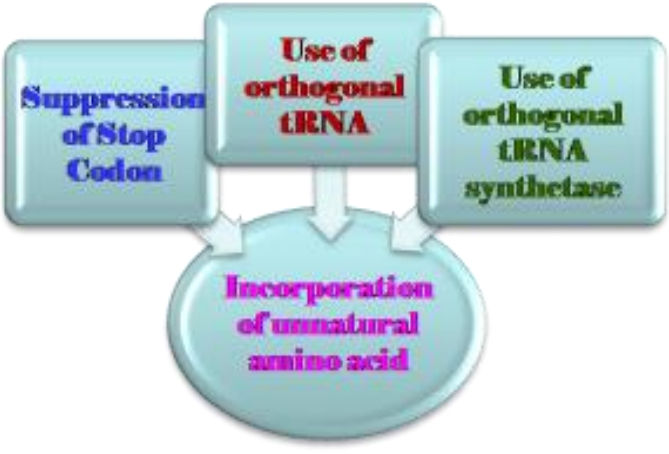
Unnatural DNA Bases into Gene: Organism with Unnatural Functional DNA



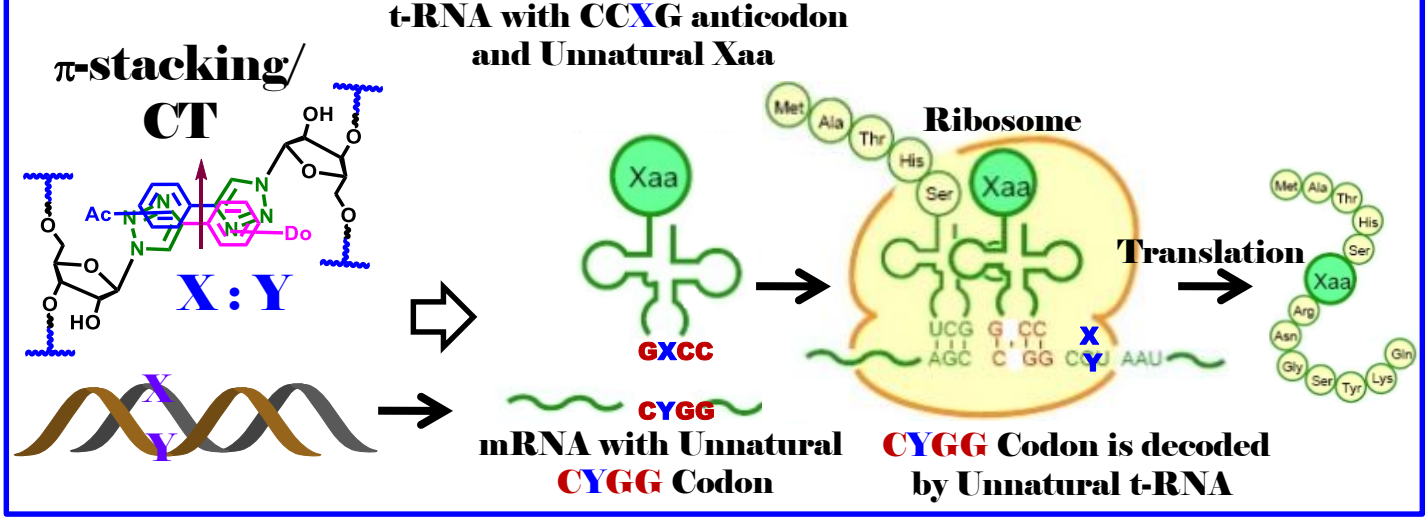
Current/Future Focus

Unnatural Amino Acids into Proteins by Nonsense Suppression Codon Method: Organism with Unnatural Functional Proteins



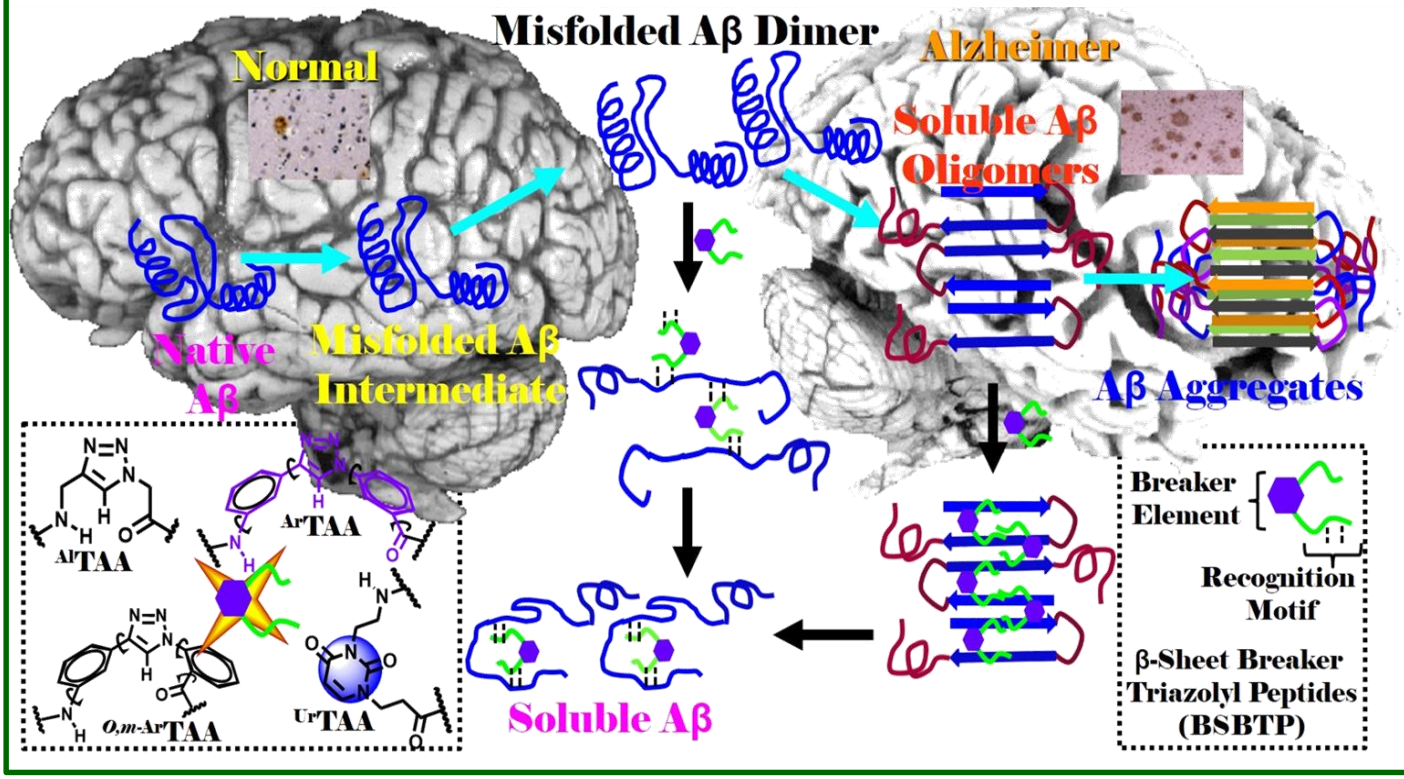


Translation of an Expanded Genetic Alphabet Into an Expanded Genetic Code: Semi-synthetic Life Form Fully Armed and Operational

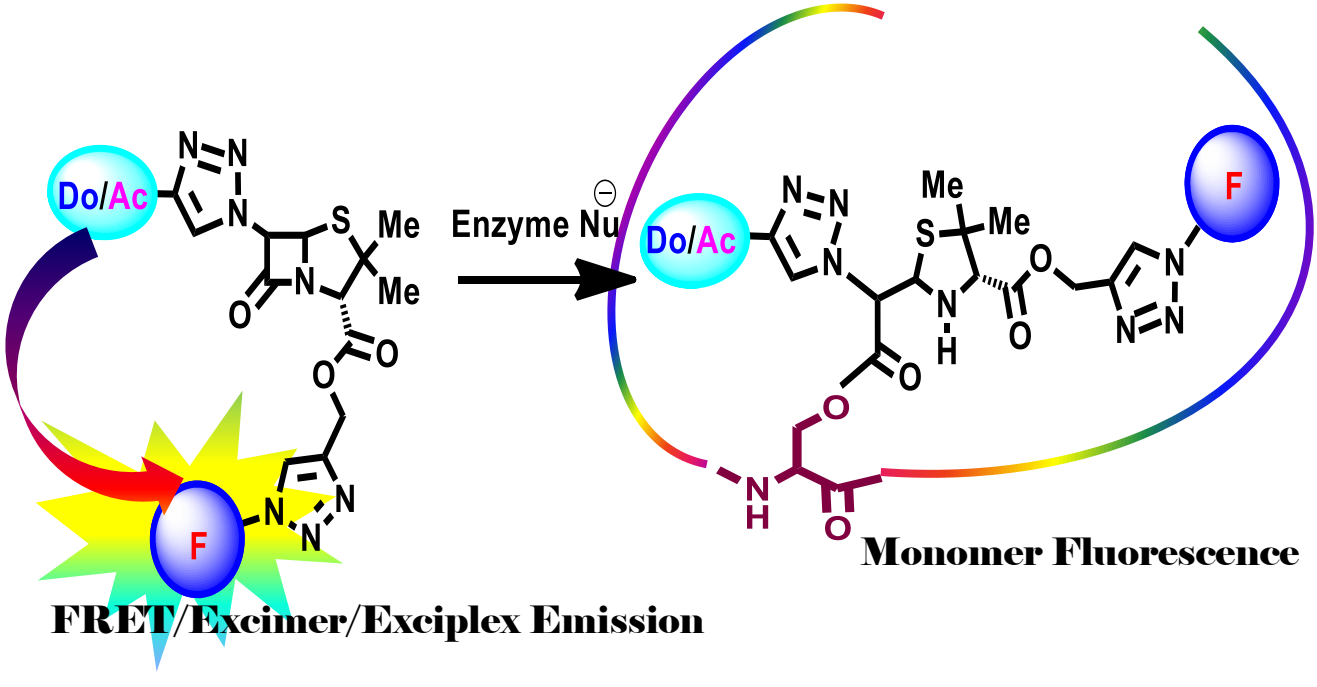


Current/Future Focus

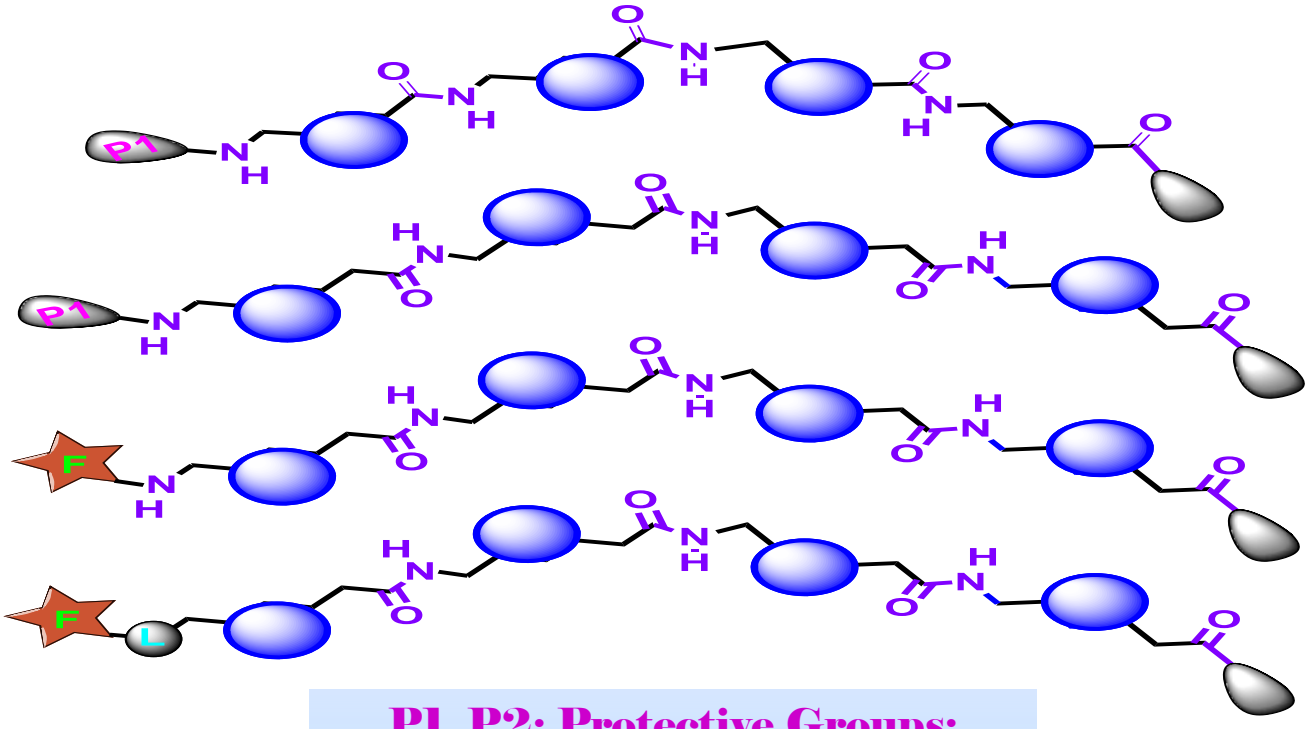
Hope for Alzheimer's patients:Possible Treatment withβ-Sheet Breaker Peptide Drugs



Hope for Antibiotics: Monitoring Enzymatic Cleavage of Triazolyl β-Lactams by Fluorescence

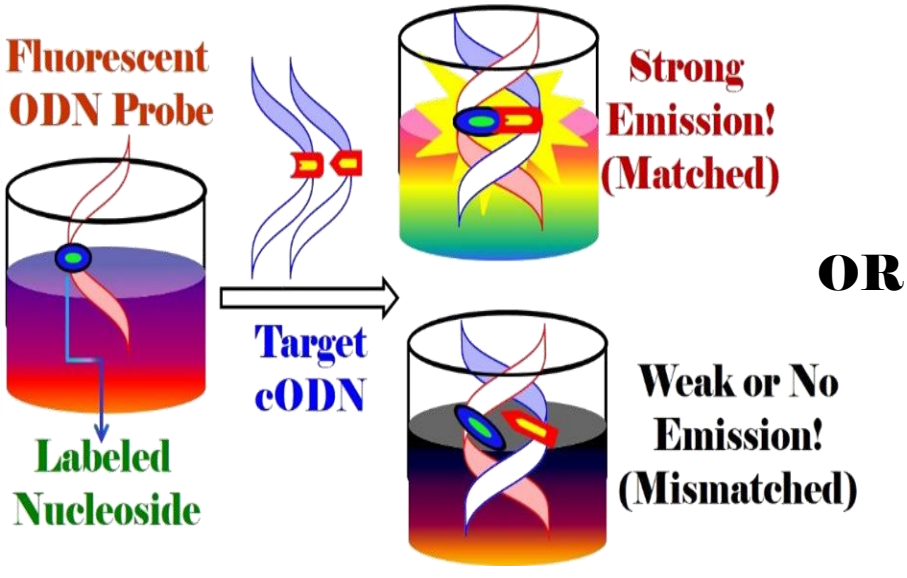


Polyamides of Constrained Molecular Scaffold as Distamycin Analogues to Combat Tumours



P1, P2: Protective Groups;
F: Fluorophore;
L: Linker/Part of F

Labelled/Label Free Detection of SARS-COV-2, EGFR, CRC Gene Mutations and Multimeric G-Quadruplex DNA



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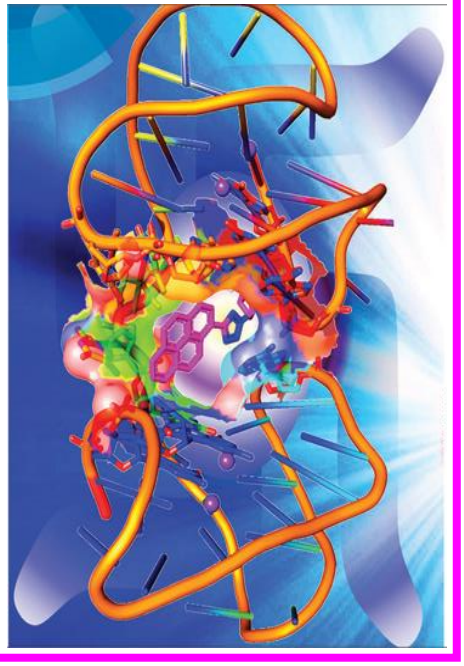


GENOMIC RESEARCH FOR THE FUTURE: PERSONALISED MEDICINE

Personalized Medicine:

Simply, it can be defined as the use of information from a patient's genotype to:

- **initiate a preventative measure against the development of a disease or condition, and**
- **select the most appropriate therapy for a disease or condition that is particularly suited to that patient.**

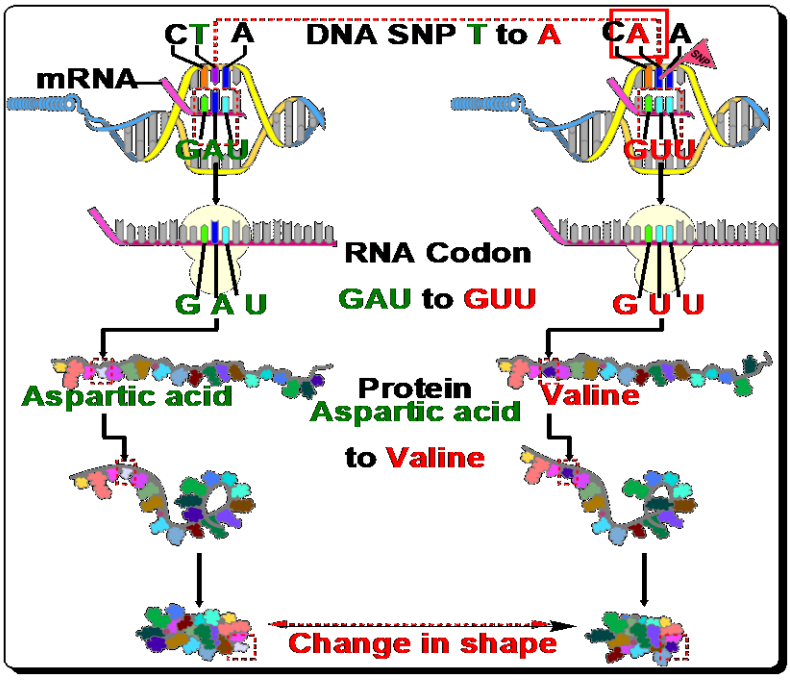
Single Nucleotide Polymorphisms (SNPs) and Personalised Medicine (PM):

Tiny variation (0.1 %) in DNA makes a person unique and SNPs explain:-

- **Person's uniqueness in physical appearance**
- **Disease susceptibility**
- **Different response to a specific drug treatment**
- **Different side effects in response to the same drug**
- **Proteins-drug/DNA-drug interaction**
- **SNPs occur in coding regions→ could alter the protein → could influence a person's health.**
- **SNP Profiles may help to identify Cancer Genes**
- **Role of SNPs to calculate risk factors with cancer**
- **Scientists think "SNP is the key enabler in the realization of the concept of personalized medicine".**

One Example : Effect of SNPs In the Coding Regions:

Harmful Changes in Protein: Mutations-→Sickle cell anemia. Hemoglobin beta gene→Hemoglobin molecule not carry oxygen



Thus, SNPs are the attractive target for better understanding the genetic basis of complex diseases, and to realize the potential of pharmacogenetics.

Therefore, the first Step of the Concept of Personalised Medicine (PM) is to

- **Identify, catalogue mapping and Profile making of all SNPs in the human genome.**
- **Indentification of genetic differences between people that predict susceptibility to diseases or affect to a drug response**
- **Saliva samples of a person is tested and the results are interpreted as genetic association with risk or without risk**

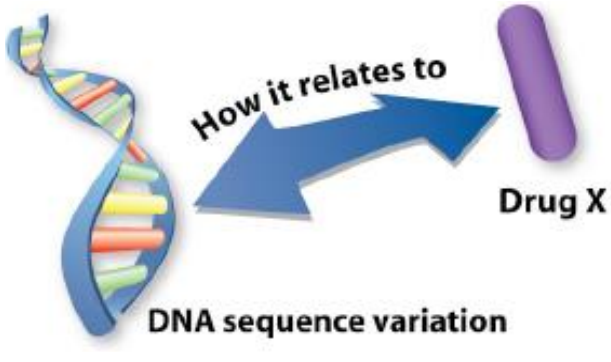
So, the development of simple, easy, cost effective and Unique SNPs typing protocols/chemistry/platforms is highly desirable to realize the Concept of Personalised Medicine (PM) .

Our Efforts: We have developed several conceptual probes/techniques and were able to use them for gene detection successfully. In this way development of simple technology might able to help in detection of all the SNPs of Human genome.

- Thus, ongoing, novel, easy and high throughput detection techniques, microarray, expectedly would allow to us detect SNPs in large scale and thereby we will be able to make SNPs profile of a person.
- This will allow physicians to compare with the global mutations repository and to diagnose a particular disease associated with a mutation.
- Identifying genetic susceptibility to disease
- Allow to study pharmacogenomics to revolutionize the practice of medicine by individualization of treatment through the use of novel diagnostic tools.
- Pharmacogenomics would reduce the trial-and-error approach of treatment and thereby limit the exposure of patients to drugs that are not effective or are toxic for them or have serious, side effects.

Thus, our continuous efforts blended with pharmacogenomics would allow us, one day, to fix the disease at the Genetic level and to provide tailor medical treatment (Personalised Medicine) to the individuals with all round positive health impact.

Our ongoing Drug design and development project along with study of Drug -DNA/Drug-Protein interaction and the above knowledge would help in designing genetically effective Personalized Drugs.



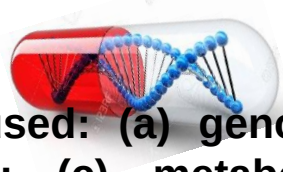
The Positive Health Impact: Promises of Personalized Medicine

Traditional Medicine:

- **Protocol: Doctors used: (a) Family History, (b) Socioeconomic circumstances, (c) Environmental factors, (d) "one-drug-fits-all" model.**

- **Results: Symptomatic treatment, Trial & error medication, less guaranteed effectiveness, More side effect.**

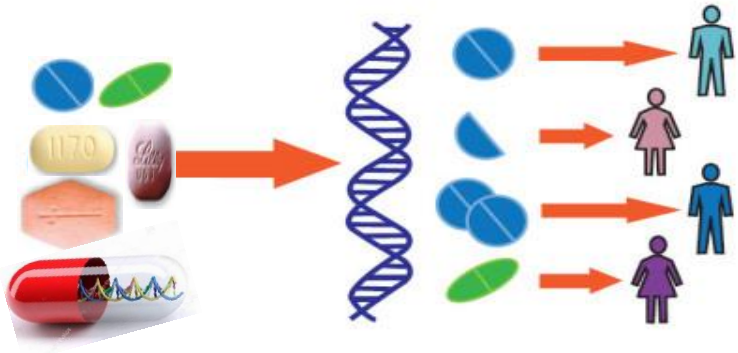
Personalised Medicine (PM):



- **Protocol: doctors used: (a) genomic/genetic testing; (b) proteomic profiling; (c) metabolomic analysis (study metabolites), (d) 'the right drug for the right patient at the right dose and time' model.**

- **Results: Positive Health Impact and the Promises of Personalised Medicine (PM):**
  - **PM seeks to address all the shortcomings of conventional medicine (CM)**
  - **Better Diagnoses and Earlier Interventions**
  - **More Efficient Drug Development**
  - **More Effective Therapies: In addition to all benefits, testing will help to predict the best dosing schedule or combination of drugs for a particular patient.**
  - **No side effect**

Traditional Medicine



Personalised Medicine (PM):