CURRICULUM VITAE

Dr. M. P. NARASIMHA RAO, Ph.D.
Department of Chemistry& Biochemistry,
University of Notre Dame,
Notre Dame, IN. USA.
Mobile : +1(413)362-6707
Email : pmeka@nd.edu, raop110@yahoo.com

Current Position

University of Notre Dame, Notre Dame
Postdoctoral Research Associate Nov 2017- tilldate

Education

Ph.D. (2008-2014) Organic and Medicinal Chemistry,
MCP Division, CSIR-IICT, Hyderabad, India-500007.
Thesis Title: "Synthesis and biological evaluation *β*-carboline-benzimidazole, imidazothiadiazole and indole-indolinone conjugates as potential anticancer agents."

M. S (2003-2005) Organic Chemistry, Sri Venkateswara University, Tirupati, India.

B. S (2000-2003) Major: Chemistry, Sri Venkateswara University, Tirupati, India.

Research Experience

Nov 2017- till date **Postdoctoral Research Associate**
Advisor: Prof. Brian Blagg
Dept. of Chemistry & biochemistry, University of Notre Dame,
- Notre Dame, IN, USA.

Sep 2015- Nov 2017 **Postdoctoral Research Associate**
Advisor: Prof. Jeanne Hardy
Dept. of Chemistry, University of Massachusetts, Amherst MA.

Mar 2008- Mar 2014 **Doctoral research**
Advisor: Dr. Ahmed Kamal, FRSC, MCP-Division, CSIR-IICT, Hyderabad, India-500007.

Industrial Experience

Mar 2014 - Sep 2015 **Senior Research Associate**
GVK Biosciences Pvt. Ltd. IDA Nacharam, Hyderabad, India.

Jul 2005 - Feb 2008 **Senior Chemist**
Dr. A.V. Ramarao Research foundation Pvt. Ltd.
IDA Nacharam, Hyderabad, India.

Awards

2015 Manning Inventor Fellowship
University of Massachusetts, Amherst, MA, USA.

2008 - 2010 Junior Research Fellowship, CSIR-UGC, Govt. of India.

2010 - 2014 Senior Research Fellowship, CSIR-UGC, Govt. of India.

Publications & Patents:

14. FUROXAN-BASED COMPOUNDS AND USES THEREOF
MP Narasimharao, Jeanne Hardy.
US Patent WO2019140194 (A1), 2019.

13. *"Synthesis and Biological Evaluation of Imidazo [2,1-b][1,3,4]thiadiazole linked Oxindole Conjugates as Tubulin Polymerization Inhibitors and apoptosis induces". Ahmed Kamal*,* **M. P. Narasimha Rao**, *P. Sowjanya, P. Swapna, Vijaykumar D. Nimbarte, M. Kishore, K. Jeshma and Nishant Jain.* (***Bio Organic chemistry***., **2018**, 76, 420-436).

12. *"Telomerase inhibition and human telomeric G-quadruplex DNA stabilization by a β-carboline–benzimidazole derivative at low concentration". Kranthikumar Yadav,*[b], **Penchala Narasimha Rao Meka**,[c] *Sudeshna Sadhu,*[a] *Sravanthi Devi Guggilapu,*[d] *Jeshma* Kovvuri,[c] *Ahmed Kamal,*[c,d] *Ragampeta Srinivas,*[b] *Panuganti Devayani,*[a] *Nagendra Babu Bathini,*[d] *Narayana Nagesh* *[a] (***ACS Biochemistry*** **2017**, *56*, 4392- 4404)

11. "*Synthesis of β-carboline-benzimidazole conjugates using lanthanum nitrate as a catalyst and their biological evaluation*". *Ahmed Kamal*,* **M. P. Narasimha Rao**, *P. Swapna, Vunnam Srinivasulu, Chandrakant Bagul, Anver Basha Shaik, Kishore Mullagiri, Jeshma Kovvuri, Vangala Santhosh Reddy, K. Vidyasagar and Narayana Nagesh* (***Org. Biomol. Chem***., **2014**, *12*, 2370-2387).

10. *"Synthesis and Biological Evaluation of Imidazo [2,1-b][1,3,4]thiadiazole linked oxindole Conjugates as Potent Tubulin Polymerization Inhibitors". Ahmed Kamal*,* **M. P. Narasimha Rao**, *Pompi Das, P. Swapna, Sowjanya Polepalli, Vijaykumar D. Nimbarte, Kishore Mullagiri, Jeshma Kovvuri and Nishant Jain.* (***ChemMedChem.***, **2014**, *9*, 1463-1475).

9. *"Synthesis of imidazothiadiazole–benzimidazole conjugates as mitochondrial apoptosis inducers". Ahmed Kamal*, Swapna Ponnampalli, M. V. P. S. Vishnuvardhan,* **M. P. Narasimha Rao**, *Kishore Mullagiri, V Lakshma Nayak and Bagul Chandrakant*. (***Med. Chem. Commun.***, **2014**, 5, 1644-1650).

8. *"Palladium-Catalyzed Aryl C-H Activation and Tandem ortho Hydroxylation/Alkoxylation of 2-Aryl Benzimidazoles: Cytotoxicity and DNA-Binding Studies". Ahmed Kamal*, Vunnam Srinivasulu, Manda Sathish, Yellaiah Tangella, V. Lakshma Nayak,* **M. P. Narasimha Rao**, *Nagula Shankaraiah, and Narayana Nagesh.* (***Asian J. Org. Chem***. **2014**, 3, 68-76).

7. *"Synthesis and Biological Evaluation of Imidazopyridine–Oxindole Conjugates as Microtubule-Targeting Agents". Ahmed Kamal*, Vangala Santhosh Reddy, Santosh Karnewar, Sumit S. Chourasiya, Anver Basha Shaik, G. Bharath Kumar, Chandan Kishor, M. Kashi Reddy,* **M. P. Narasimha Rao**, *Ananthamurthy Nagabhushana, Kallaganti V. S. Ramakrishna, Anthony Addlagatta and Srigiridhar Kotamraju.* (***ChemMedChem***, **2013**, *8*, 2015-2025).

6. *"Synthesis, biological evaluation of new oxazolidino-sulfonamides as potential antimicrobial agents". Ahmed Kamal*, P. Swapna, Rajesh V.C.R.N.C. Shetti, Anver Basha Shaik,* **M. P. Narasimha Rao**, *Soma Gupta*. (***European Journal of Medicinal Chemistry***, **2013**, *62*, 661-669).

5. *"Anti-tubercular agents. Part 7: A new class of diarylpyrrole-oxazolidinone conjugates as antimycobacterial agents". Ahmed Kamal*, P. Swapna, Rajesh V.C.R.N.C. Shetti,* **M. P. Narasimha Rao**, *Inshad Ali Khan, Sandeep Sharma, Nitin Pal Kalia, Sunil Kumar, Bagul Chandrakant.* (***European Journal of Medicinal Chemistry***, **2013**, *64*, 239-251).

4. *"Carbazole–pyrrolo[2,1-c][1,4]benzodiazepine conjugates: design, synthesis, and biological evaluation". Ahmed Kamal*, Rajesh V. C. R. N. C. Shetti, M. Janaki Ramaiah, P. Swapna, A. Mallareddy,* **M. P. Narasimha Rao**, *G. Narahari Sastry and Manika Pal-Bhadra*. **(*Med. Chem. Commun.*, 2011**, 2, 780-788).

3. *"Synthess and Biological Evaluation of Imidazo [2,1-b][1,3,4]thiadiazole- benzimidazole Conjugates as Tubulin Polymerization Inhibitors and apoptosis inducing agents".* **M. P. Narasimha Rao**, *P. Swapna, Sowjanya Polepalli, Jeshma Kovvuri, Nishant Jain and Ahmed Kamal*,* (***Med. Chem. Commun.***, Under revision).

2. *"Synthesis and Biological Evaluation of Indole-indolin-2-one conjugates as Potential Microtubule targeting agents".* **M. P. Narasimha Rao**, *P. Swapna, Sowjanya Polepalli, Jeshma Kovvuri, Nishant Jain and Ahmed Kamal*,* (Manuscript under preperation).

1. *"Potent, selective caspase-6 inhibitors engage caspase-6 active and allosteric sites".* **Penchala Narasimha Rao Meka**, *Kevin B. Dagbay, Yifei Pei, Elih M. Velazquez-Delgado and Jeanne Hardy**(Manuscript under preparation).

Conferences & Poster presentations:

- Symposium on "Organic Synthesis and Human Well Being: Emerging Opportunities and Challenges" (OSHWB) 1-4th August 2010, IICT, Hyderabad, India.
- 12th CRSI National Symposium in Chemistry & 4th CRSI-RSC Symposium in Chemistry. 4-7 of February, 2010 at NIPER & IICT, Hyderabad, India.
- Second RSC Medchem Congress-2013, Indian Institute of Chemical Technology (IICT) Tarnaka, Hyderabad-500007, India.

Technical Skills:

- Expertise in carrying out various organic reactions including air and moisture sensitive reagents/reactions such as DIBAL, n-BuLi, LDA, LAH, $AlCl_3$, Pd/C, Na metal, Raney Nickle, Grignard reactions, Diazo methane reactions, Pd catalysed reactions swern oxidation etc.,
- Expertise in design and execute multi-step synthesis of targeted bioactive molecules
- Excellent skills in purification of organic compounds using recrystallization, distillation and Column chromatography as well as preparative TLC techniques.

- Hands on experience with the instruments like Smart/Combi flash chromatography, NMR, Polari meter, LC-MS, UV-Visible, IR, and Fluorescence Spectrophotometers.
- Working experience with MTT assay, Topoisomerase studies, tubulin assay, cell cycle analysis, DNA binding studies and western blotting.
- Conversant with commonly used computer software: MS-Office, Adobe Photoshop, Chem Office, Pymol, Reaxys, Sci-Finder and Capable of preparation of lab reports and manuscripts for publication.
- Maintain good interpersonal relationships with capable of performing collaborative and independent work and identifying research problems and solving them independently.

Personal details: Male, Indian, married, Born on April 25th, 1980.

References:

1. **Brian S. J Blagg**
   Charles Huisking Professor; Director, Warren Family Research Center for Drug Discovery and Development,
   305G McCourtney Hall
   University of Notre Dame, Notre Dame
   IN,46556 USA.
   Phone: 574-631-6877
   E-mail: bblagg@nd.edu

2. **Jeanne A. Hardy**
   Associate professor of chemistry
   745A LGRT B
   710 North Pleasant Street,
   University of Massachusetts, Amherst
   MA 01003-9336, USA.
   Phone: (413) 545-3486
   Fax: (413) 545-4490
   E-mail: hardy@chem.umass.edu

3. **Dr. Narayana Nagesh,** Ph.D.
   Senior Principal Scientist
   CSIR-Center for Cellular and Molecular Biology (CCMB)
   Hyderabad-500007, India
   Tel: +91-040-27192559/27192631
   E-mail: nagesh@ccmb.res.in

RESEARCH SUMMERY

Postdoctoral Research work:

I am working on the design of the new compounds that modulate the protein folding, synthesizing desired compounds and evaluating their biological activity, the title of the project is chaperone therapeutics for the treatment of DPN. Heat shock protein 90 (Hsp 90) and Hsp 70 with small molecule compounds may improve proteostatic neurodegeneration diseases by enhancing the clearance of neurotoxic protein aggregates. However, our group has identified that pharmacologically targeting molecular chaperones has therapeutic value in treating peripheral neuropathies whose etiology is independent of proteostasis and developed novologues as small molecule inhibitors of the Hsp 90C-terminaldomain that circurmvent limitations that have confounded the clinical aspects of HSp 90 as a therapeutic target.

My previous Postdoctoral research work was carried under the supervision of Prof. Jeanne Hardy at Chemistry department in the University of Massachusetts Amherst, MA. During my postdoctoral research, I have worked on the project *"Development of Caspase-6 protease inhibitors"*.

Caspases, a family of cysteine proteases, are playing essential roles in apoptosis, Inflammation and neurodegeneration Caspase-6 cleaves many proteins involved in neurodegeneration: tau, amyloid precursor protein (APP), Huntington protein (HTT). In post-mortem brains of Alzheimer's patients, the tau found in neurofibrillary tangles has all been cleaved by caspase-6. Inhibiting caspase-6 activity should limit tau aggregation and prevents its impact on development and onset of AD.

Prof. Hardy's group performed a screening of 359,000 compounds at the Broad Institute to identify casp-6 specific and selective inhibitors. From this screen, we identified 3 candidate lead compounds that showed the request selectivity over other caspases: a bis-*N*-oxide, a piperazine and a sugar-like compound. We ultimately selected compound A (bis-*N*-oxide) as our lead, due to it having the more potency and its unparalleled selectivity. To date, the best selectivity of any reported casp-6 inhibitor is 10-fold selectivity for casp-6 over the most closely related caspases, casp-3 and casp-7. In contrast, compound A exhibits 360-fold selectivity for casp-6 over casp-7 and 7,500-fold selective for casp-6 over casp-3. Compound A reacts to form a covalent adduct, but is not generally reactive, showing no modification of the other seven other caspases or with cysteine-containing proteins generally. Compound-A has an IC_{50} against

casp-6 of 3 μM and also inhibits casp-6 in neuronal cell lines with an IC_{50} of 20 μM to improve the potency I have designed and synthesized a library of more than 80 analogs, some of which sowed unprecedented selectivity towards caspase-6 with nano-molar activity. (Patent filed and manuscript under preparation). For the IP issues, I am not able to show the structures of the compounds.

Summary of Research Work in Ph. D.:

My doctoral research was carried out at Dr. Ahmed Kamal research lab in CSIR-IICT, during my doctoral research, I have designed and synthesized a library of biologically active *β*-carboline-benzimidazole, imidazothiadiazole-oxindole/benzimidazole and indole-indolinone conjugates targeting micro-tubule polymerization, DNA-intercalation and DNA-topoisomerase-I and evaluated their anticancer activities followed by studies to elucidate the mechanism of action.

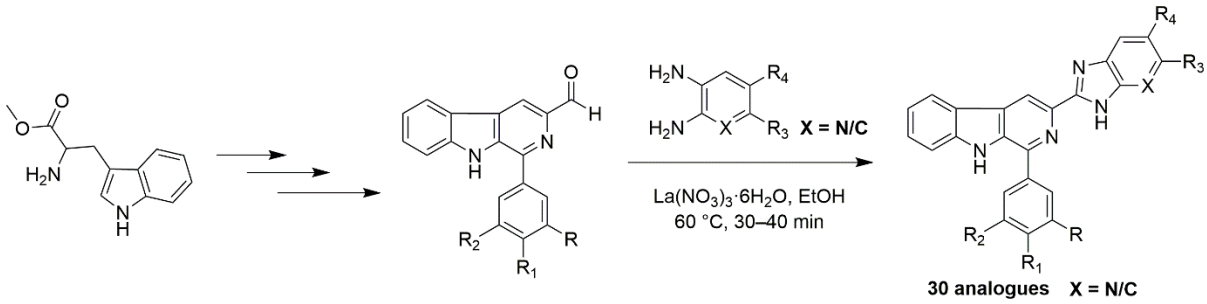
I developed some novel methodologies.

I also involved in many projects like CSIR-IICT and IIIM-Jammu under the Dept. of Science and Technology India program for the *"Development of new antitubercular agents"*. CSIR-IICT and Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Mumbai, for the *"Development of new anticancer leads"*. Industrial collaboration research project between CSIR-IICT-Ranbaxy Pvt.Ltd. research project "*Synthesis and Process development of anti-cancer agents Erlotinib and Gefitinib".*

1. A series of *β*-carboline-benzimidazole conjugates bearing a substituted benzimidazole and aryl ring at C3 and C1 respectively were designed and synthesized. The key step for their preparation involves condensation of substituted *o*-phenylenediamines with 1-(substituted phenyl)-9H-pyrido[3,4-*b*]indole-3-carbaldehyde using $La(NO_3)_3.6H_2O$ as a catalyst and evaluated their cytotoxic potential. Amongst them conjugates **5a**, **5d**, **5h** and **5r** showed significantly enhanced cytotoxic activity in comparison to the previously reported *β*-carboline derivatives (GI_{50} values range from 0.3-7.1 μM in most of the human cancer cell-lines). To substantiate the cytotoxic activity and as well to understand the nature of interaction by these conjugates with DNA; UV-Visible, CD, DNA photocleavage and inhibition of DNA topoisomerase I (topo-I) studies were performed. These conjugates (**5a**, **5d**, **5h** and **5r)** were effective in cleaving the pBR322 plasmid DNA in the presence of UV light and inhibiting the topo-I. The mode of binding of these new conjugates with DNA was also examined by using both biophysical as well as molecular docking studies, which supported their multiple mode of

interaction with DNA. In addition, SAR associated with positions 1 and 3 substituents of these conjugates was also clearly addressed. Moreover, an *in-silico* study of these *β*-carboline-benzimidazole conjugates reveal that they possess drug-like properties.

To further investigate the mechanism of action, we selected the most active compounds in this series and evaluated their mode of action. **5a** showed maximum ΔT_m, indicating its ability to effectively stabilize telomeric G-quadruplex DNA. Additionally, **5a** is efficient in inhibiting the cell cycle at subG1 phase leading to induction of apoptosis. Fluorescence microscopy studies demonstrate that **5a** derivative has potential to induce apoptosis. Further, **5a** is capable of stabilizing G-quadruplex DNA and inhibit DNA synthesis. Above all, it is evident that telomerase activity was reduced in cancer cells upon **5a** treatment. From this project, I got 2 publications.

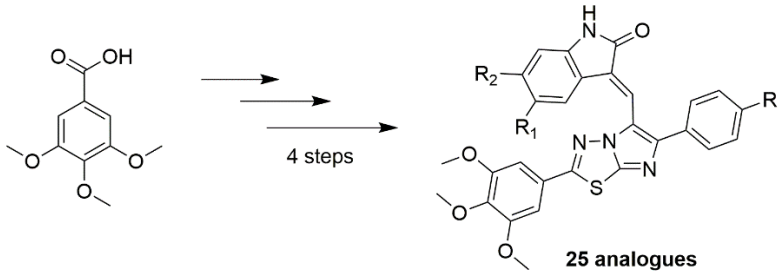


i) Synthesis of *β*-carboline-benzimidazole conjugates using lanthanum nitrate as a catalyst and their biological evaluation. **(*Org. Biomol. Chem*., 2014,** *12*, 2370-2387 and back cover page).

ii) Telomerase inhibition and human telomeric G-quadruplex DNA stabilization by a β-carboline–benzimidazole derivative at low concentration. **(*ACS Biochemistry* DOI:** 10.1021/acs.biochem.7b00008**)**

2. A series of imidazo[2,1-*b*][1,3,4]thiadiazole linked oxindole conjugates comprising of A, B, C and D ring system were synthesized and investigated for antiproliferative activity in different human cancer cell lines through various substitutions at ring C and D. Among them conjugates **7**, **11** and **15** exhibited potent antiproliferative activity; were evaluated for cell cycle, tubulin polymerization assay. Conjugates **7**, **11** and **15** treatments resulted in accumulation of cells in G2/M phase, inhibition of tubulin assembly and increase in cyclin B1 protein levels. Conjugate **7** displayed potent cytotoxicity with an IC_{50} values of 1.1- 1.6 μM and inhibit tubulin polymerization with an IC_{50} (0.15μM) value lower than that of combretastatin A-4 (1.16μM).

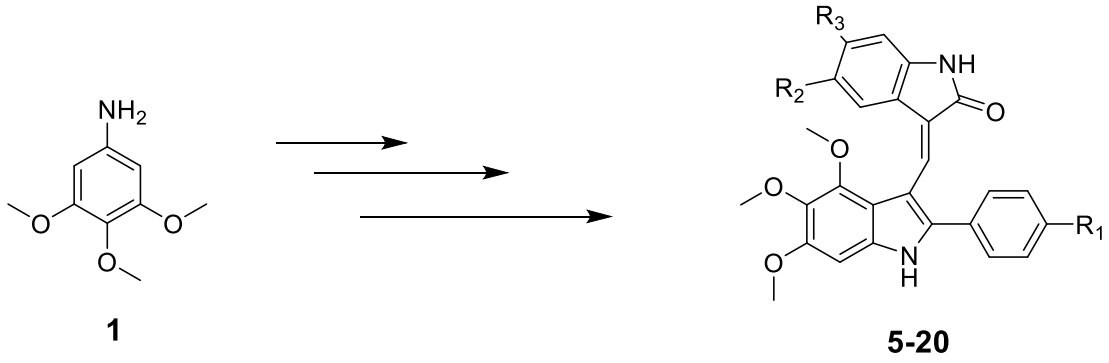
Docking studies reveal that the conjugates **7** and **11** bind with αAsn101, βThr179 and βCys241 in the colchicine-binding site of tubulin.



i). Synthesis and Biological Evaluation of Imidazo [2,1-*b*][1,3,4]thiadiazole linked oxindole Conjugates as Potent Tubulin Polymerization Inhibitors. (***ChemMedChem***., **2014**, *9*, 1463-1475)

3. The microtubule has become an important target for the design of new antimitotic anticancer agents. Drugs that inhibit microtubule polymerization are effective in the treatment of lung, breast, ovarian and other cancers. However, occurrence of peripheral neuropathy is a major complication in the development of microtubule depolymerization agents as drugs.[18] Therefore discovery of new molecules to overcome neuropathies are of immediate requirement. There has been considerable interest in the discovery and development of small molecules that affect tubulin polymerization. However, the success of tubulin polymerization inhibitors as anticancer agents has stimulated significant interest in the identification of new compounds that may be more potent or more selective in targeted tissues or tumors. Some of the potent hybrid molecules have been recently developed as new anticancer agents are by the combination of different pharmacophores.[19] These biologically active conjugates further encouraged us to synthesize some newer conjugates that are likely to enhance the anticancer activity. In this context, we have designed and synthesized a new class of indole-indolinone conjugates and evaluated for their cytotoxic potential and their effect on tubulin polymerization. All the synthesized compounds (**5-20**) were evaluated for cytotoxicity in selected human cancer cell lines of breast, kidney, lung and colon by using MTT assay. The results shown that all the synthesized conjugates (**5-20**) showed moderate to good cytotoxic activity with IC_{50} values ranging from 0.56 to 20.12μM. Amongst these conjugates, **8, 9, 10** and 1**2** showed significant cytotoxicity with IC_{50} values ranging from 0.86 to 8.06 μM against breast (MCF-7), kidney (ACHN), colon (HT-29) and lung (A549) cancer cell lines. Keeping the 4,5,6-trimethoxy indole moiety as a core (or) unchanged, we varied the substituents on the phenyl ring at C2 position of the indole and also on the indolin-2-one ring. The conjugates **10** and **12** having chloro at C4 of phenyl ring and indolin-2-one ring (**10**), chloro group at C4′ of indolin-2-one ring shown

potent cytotoxic activity with IC_{50} values ranging from 0.56 to 2.12 µM in the tested human cancer cell lines. Whereas the conjugates **8** and **9** having fluoro at C4 of phenyl ring and chloro group at C5´ (**8**), C6´ (**9**) of indolin-2-onering also exhibits better cytotoxicity with IC_{50} values ranging from 1.52 to 2.36 µM in the tested human cancer cell lines. The conjugates **16** and **17** having methoxy group at C4 of the phenyl and flouro (**16**), chloro (**17**) at C5´of the indoline-2-one also exhibited moderate cytotoxicity with IC_{50} values ranging from 1.95 to 4.62 µM against ACHN and MCF-7 cell lines. The cytotoxic activity of these indole-indolinone conjugates compared with CA4. Interestingly, conjugates **10** showed more cytotoxic activity against MCF-7 cell line than the CA4. To evaluate the mechanism of action, we also performed other cell-based assays which supports the tubulin polymerization inhibition mechanism.



i). Synthesis and Biological Evaluation of Indole-indolin-2-one conjugates as Potential Microtubule targeting agents. **(manuscript under correction)**

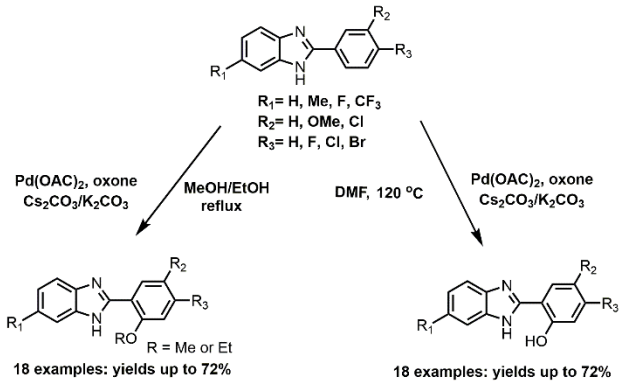
Some of the Papers from other collaborated projects during the Ph.D.

4. Palladium-Catalyzed Aryl C-H Activation and Tandem ortho Hydroxylation/Alkoxylation of 2-Aryl Benzimidazoles: Cytotoxicity and DNA-Binding Studies.

***(Asian J. Org. Chem*. 2014**, 3, 68 -76)

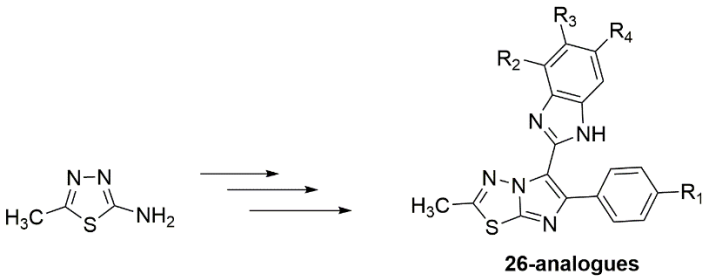
An efficient regio-selective aryl C-H activation and tandem o-hydroxylation method for 2-arylbenzimidazoles has been developed by using a $Pd(OAc)_2$ /oxone/Cs_2CO_3 catalytic system.This reaction was successfully optimized by using various catalysts, oxidants, bases, and solvents to achieve the desired products in good yields. Further, preliminary mechanistic studies were conducted to examine the source of oxygen for this transformation. Gratifyingly, this catalytic system is also suitable for the introduction of various alkoxy groups, and delivered the products in good yields. The synthesized compounds were evaluated for their cytotoxic activity in selected human cancer cell lines. Some of the representative compounds (1f, 2f, 3f and 4f) have significant IC_{50} values ranging from 1-10 µM. Structure-activity relationship

studies indicate that in these compounds the ethoxy substituent is probably responsible for the improved activity. In addition, the DNA-binding potential of these compounds was also investigated by UV/vis, fluorescence, and circular dichroism spectroscopy.



5. Synthesis of imidazothiadiazole–benzimidazole conjugates as mitochondrial apoptosis inducers. (***Med. Chem. Commun.***, **2014**, 5, 1644-1650)

A series of imidazothiadiazole–benzimidazole conjugates (3a–z) were synthesized and evaluated for their cytotoxic activity against a set of four selected human cancer cell lines.



Amongst them, compounds 3b and 3y exhibited significant anti-proliferative activity in ME-180 (cervical) cell line. Flow cytometric analysis showed that these two compounds arrested the cell cycle in the G0/G1 phase leading to the loss of mitochondrial membrane potential followed by apoptotic cell death. Further, Hoechst 33258 staining, DNA fragmentation assay, Annexin V staining assay and caspase-3 also suggested that 3b and 3y induced cell death by apoptosis. Docking studies revealed that compound 3b binds to the Gly142, Phe101, Asn140 and Arg143 on B-cell lymphoma 2 (Bcl-2) proteins and inhibition of Bcl-2 protein could be the possible mechanism of action for these compounds.

6. Synthesis and Biological Evaluation of Imidazopyridine-Oxindole Conjugates as Microtubule-Targeting Agents. (***ChemMedChem.*, 2013**, 8, 2015-2025)

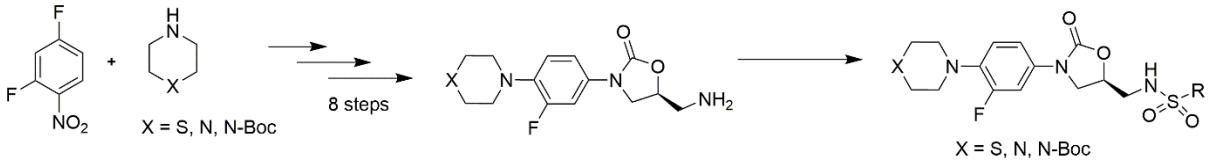
A library of imidazopyridine–oxindole conjugates was synthesised and investigated for anticancer activity against various human cancer cell lines. Some of the tested compounds, such as 10a, 10e, 10f, and 10k, exhibited promising antiproliferative activity with GI_{50} values

ranging from 0.17 to 9.31μM. Flow cytometric analysis showed that MCF-7 cells treated by these compounds arrested in the G2 /M phase of the cell cycle in a concentration-dependent manner. More particularly, compound 10f displayed a remarkable inhibitory effect on tubulin polymerisation. All the compounds depolarised mitochondrial membrane potential and caused apoptosis. These results are further supported by the decreased phosphorylation of Akt at Ser473. Studies on embryonic development revealed that the lead compounds 10f and 10k caused delay in the development of zebra fish embryos. Docking of compound 10f with tubulin protein suggested that the imidazo[1,2-a]pyridine moiety occupies the colchicine binding site of tubulin.

20 analogues

7. Synthesis, biological evaluation of new oxazolidino-sulfonamides as potential antimicrobial agents. (***European Journal of Medicinal Chemistry***, **2013**, *62*, 661-669)

A number of linezolid-like oxazolidino-sulfonamides (7a-y and 8a-b) were designed and synthesized with a view to develop antimicrobial agents with improved properties. Most of the synthesized compounds showed good to moderate activity against a panel of standard Gram-positive and Gram-negative bacteria and fungal strains. The compounds 7i and 7v exhibited significant activity, with a MIC value of 2.0-6.0 mg/mL against a panel of Gram-positive and Gram-negative bacteria. These compounds also showed activity against *Candida albicans*, with a MIC value of 4.0 mg/mL. A correlation of the antimicrobial activity with calculated lipophilicity values (C logP) is also presented.



27 analogues

8. Carbazole–pyrrolo[2,1-c][1,4]benzodiazepine conjugates: design, synthesis, and biological evaluation. (***Med. Chem. Commun.***, **2011**, 2, 780-788)

A series of carbazole–pyrrolobenzodiazepine conjugates (4a–g and 5a–f) have been designed, and synthesized as anticancer agents. These compounds are prepared by linking the C8-position

of DC-81 with a carbazole moiety through simple alkane spacers as well as piperazine side-armed alkane spacers in good yields. The DNA binding ability of these conjugates has been determined by thermal denaturation studies and also supported by molecular docking studies. These conjugates showed potent anticancer activity with GI50 ranging from 5.27–0.01 mM. The FACS analysis and BrdU assay of selected conjugates (4c, 4f, 5a and 5f) on MCF-7 cell lines disclosed the increased G1 cell cycle arrest and one of the conjugates 5f has exhibited significant anticancer activity. The analysis of the intrinsic factors involved in causing the G1 arrest in MCF-7 cell lines by 5f conjugate has been demonstrated on the proteins which play a vital role in G1 arrest followed by apoptosis (Cyclin D1, CDK4, c-Jun, JunB, CREB, p53, JNK1/2, procaspase-7, cleaved PARP, pRb, and *BAX*). Thus, these PBD conjugates (5f) have promising potency for combating human carcinoma.