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MY TWENTY YEARS WITH POLYAROMATIC COMPOUNDS

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Abstract:
We have developed synthetic methods for the preparation of new classes of anticancer agents starting from polyaromatic compounds.In this perspective, we describe some of our research on polyaromatic compounds that have find attention to the scientific community.

Introduction:
During the selection of the chemistry honors students at the Bejoy Narayan College, Itachuna, Hooghly, West Bengal, India, the interviewer faculty members had asked me to explain them the reasons I would pursue a career as a chemist. My response was that I want to become a research scientist. The interviewer started smiling. They told me whether I know the difficulty in becoming a researcher and the sacrifices I have to make in my life. Although I was not sure about the exact difficulties and challenges, I knew it would be a very hard choice. I answered to my two interviewer and others who were present in the room I would do well in research and you can follow me in the future. I had a dream from my childhood that I would conduct research on cancer areas that are not explored well and/or controversial. This feeling helped me to undertake unusual research: synthesis and biological evaluation of polyaromatic compounds as anticancer agents. The two professors (Professor P. K. Ghosh and Professor J. Nath) at the Bejoy Narayan College I mentioned above are really become very pleased to know my whole career path. Their blessings are priceless and I will continue to adore them because they never neglected my feelings what I said to them at the age of 17.

Significance:
DNA is the principal target for numerous small molecules. Organic molecules that bind to DNA constitute a classic class of molecules in anticancer therapy.[1]However, DNA binding is not only the criteriato develop anticancer molecules. An interaction with DNA is often necessary to maintainreasonable cytotoxic effects. DNA intercalators are characterized by the insertion of planar aromatic orheteroaromatic systems in between DNA base pairs.[2] Molecules like anthracene, acridines and ellipticines havegood DNA intercalator properties due to their topoisomerase inhibition activities.[3]Hydrogen bonding andstacking are important in the stabilization of the compound-DNA complex. Polycyclic aromatic compounds and their derivatives have received significant attention from chemists, pharmacologists and

biologists.[4]However, an insignificant amount ofresearch is focused on the use of compounds related to polycyclic aromatic compounds asanticancer molecules.[5]Bair *et al.* demonstrated a correlation between antitumor activity and the nature of the polyaromatic compounds.[6]Despite their efforts, a conclusive correlation between the abilityof these molecules to bind to DNA and their cytotoxic activity could not be determined. This study culminated in the development of a few benzylicaminopropanediols from a structure-activity relationship work. These amino propanediols interacted with DNA by intercalation and they acted as a topoisomerase II inhibitors. Clinicalstudies on the lead molecules were not successful due to CNS and neurologicaltoxicity. Naphthalimides, amonafide and mitonafide were selected for clinicaltrials based on their sufficient activity due to intercalation, but their clinical results were weak. Naphthalene ring was changed to anthracene in order to determine the role of the chromophore. The resulting product, azonafide proved to be effective in increasing cellular cytotoxicity over naphthalene-related compounds.[7]Azonafides molecules which demonstrated similar mechanistic characteristics when compared with common DMA intercalators, do not localize in the cell nucleus. This was an interesting finding. Other crucial differences with existing DNAintercalators, for example clinically usefulmitoxantrone[8,9], were the lack of inhibition of topoisomerase II enzymes at equivalent molar cytotoxic concentrations.

Based upon a series of scientific literature myths that polyaromatic compounds are carcinogenic and mutagenic, a scientist at the beginning of his/her career may not pursue research on them with the hope that novel anticancer agents can be derived from these types of molecules. These two properties are highly contradictory: The first well-established science describes polayaromatic compounds as cancer promoter. The second issue whether they can be used for the development of molecules that can inhibit the growth of cancer cells or even cure the disease. It is obvious that the second issue is very complicated. It is a highly questionable approach to develop polyaromatic compounds as anticancer molecules. Being an aspiring scientist at the University of Texas M. D. Anderson Cancer Center, Houston, USA, I undertook the challenge in 1995 with the background information that mustards, carbazoles and anthracenes are active anticancer agents, yet many of them are highly toxic.[10]The concept was further strengthened that scientist mainly focus interaction of DNA and RNA interaction with organic drug candidates. Highly hydrophobic and lipophilic polyaromatic compounds can also demonstrate interaction with various lipids present in the cell membrane as well as with cell nucleus.[11, 12]One can think something special, but realization of the special ideas need implementations. Based upon some literature background, we undertook a program of synthesis and evaluating of novel polyaromaticcompounds as anticanceragents in 1995. This work has given us publications, patents, grants as well as recognition.

Results:

An analysis of chrysene derivatives *in vitro* against a panel of human tumor cell lines was performed.[12]During the course of the investigation, a number of new synthetic methods for the preparation of polyaromatic amines were developed. Synthesis of this type of compound required different types of amines (6-aminochrysene, 2-amniochrysene, dibenzofluorene, flurorene, 9-aminophenanthrene, 3-amino-(9,10)-dihydrophenanthrene and 9-aminophenanthridine) as the starting compounds. A facile aromatic nitrationreaction of an aromatic compound by bismuth nitrate using solid support was developed.[13]Thisversatile method was applied for the preparation of several aromatic nitro compounds in an excellentyield. In

contrast to other methods, bismuth nitrate-induced nitration of aromatic substrates was highlyefficient, regioselective and environmentally friendly.New methods for thereduction of polycyclic aromatic nitro compounds with samarium and indium to the corresponding amines were developed in good yield[14]. The amine was then converted to several diamides and diamies. The compounds were tested against several cancer cell lines *in vitro* using cisplatin as the control. Some of the chrysene derivatives demonstrated significant
cytotoxic activity against a broad spectrum of tumor cell lines. Some general conclusions can be drawn from these results: (1) In general, the 2-and 6-chrysene derivatives demonstrated equal cytotoxicity; (2) Amide compounds with a terminal piperizine heterocyclic rings were more effective than those with a piperidine terminal ring; (3) the amino derivatives demonstrated enhancement of cytotoxic activity. However, two compounds were found to be extremely active against the seven cell lines tested (IC50 values -0.5-2.5 uM). They were more potent than cisplatin *in vitro*. The in vitro activity was close to adriamycin. The antitumor activity was then evaluated against a number of human tumors implanted in nude mice. Both solid tumors and hematologic malignant tumors were tested. The lead compound demonstrated good activity against both a human ovarian tumor (SKOV-3) and a human colon adenocarcinoma (HT- 29). This compound was also submitted to NCI for evaluation in their Developmental Therapeutics Program and it passed the initial screen for relative activity against the human tumor cell line. Complete inhibition of cell growth was produced against four of six human colon cell lines and
against three of eight melanoma cell lines. When the COMPARE algorithm was used to try to discern the potential mechanism of action of this molecule, NCI reported that the mechanism of cytotoxicity of this compound did not match that of standard cytotoxic compounds. Thus, the lead molecule may have a unique mechanism of action that would require further research to elucidate. Using the results of the three 60-cell panel runs the drug evaluation group of the NCI inserted the data in the program "COMPARE" aimed at detecting mechanisms of action of lead compounds.

Interestingly, the active chrysene compounds had not demonstrated mutagenic properties.Importantly, apoptotic pathways through caspase-3 activation played a crucial role in inducing cell death in human leukemia Jurkat T cells by several of these compounds that contain chrysene as their aromatic ring system.[12]No effect was demonstrated in a normal non-transformed line of human natural killer cells. In addition, these compounds were relatively non-toxic to mice and non-mutagenic when tested in bacterial systems. These results provide evidence for the potential chemotherapeutic use of chrysene-related compounds. Based on the results, it was alsoexpected that phenanthrene and dihyrophenanthrene compounds may not demonstrate anycarcinogenic and mutagenic properties. This conclusion was proved to be true. These compounds demonstrated activity against human colon and leukemia cancer cells by arresting cell division at the G2/M cell cycle checkpoint. This target is considered to be of considerable therapeutic interest.

The high degree of caspase-3 activation, PARP cleavage and DNA-damage demonstratedby the TUNEL assay as a result of exposure of lead compounds clearly suggested apoptotic pathwayis involved in resulting cell death. One of the most striking findings was the absence of effect ofcompound against a non-transformed, natural killer cell line. This further supported the probability thatthe effect of this compound against leukemic Jurkat T cells targets some aspect of tumor cellphysiology. There was no significantly detectable increase in caspase-3 activation at

very lowerconcentration of the amide types of compound. This finding suggests that alternate pathways exist for inducing celldamage, such as, direct interaction with the cells' surfaces for amides.

This study required a few specific molecules in order to determine the effects of structures. Specifically, we developed new oxidation method[15], dimerization of ester[16], reductive cyclization reaction[17]for the preparation of new compounds of polyaromatic nature. Functionalization of some of these molecules proved difficult to achieve an identical goal as described above. The work on polyaromatic compounds prompted us to prepare these new chemical entities and consequently, new method development was necessary. Our synthetic chemistry expertise was highly necessary to prepare new polyaromatic structures with unique features. Some of the compounds resulted in from this study showed important properties for further elaboration not only in synthetic chemistry, but also to study their biochemical mechanism of actions.[18]

Conclusion:

In contrast to literature, our research group demonstrated the preparation of several polyaromatic compounds that exhibited reasonable *in vitro* and *in vivo* activity against a number of tumor cell lines with unique mechanism of actions. Notable the lead compounds had no effects on normal cells. Results described herein were very useful to study the synthesis, biological evaluation and mechanism of action of new polyaromatic compounds. This field of research was regarded as risky in 1995. However, systematic studies with available knowledge were very helpful in the identification of novel polyaromatic molecules that showed anticancer activities. In addition, several new reactions and regents were developed during the course of this investigation. We are pursuing this subject extensively.

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References:

1. (a) Ohara, K., Smietana, M., Restouin, A., Mollard, S., Borg, J-P., Collette, Y. and Vasseur, J-J.;Amine-Guanidine Switch: A Promising Approach to Improve DNA Binding and AntiproliferativeActivities., J. Med. Chem. 50: 6465-6475, 2007. (b) Demeunynck, M., Baily, C., Wilson, W. D.; DNAand RNA Binders. Wiley-VCH; Weinheim, 2002. (c) Dervan, P. B.; Molecular Recognition of DNA bySmall Molecules, Bioorg. Med. Chem. 9: 2215-2235, 2001.

2. (a) Lerman, L S.; Structure of DNA-AcridineComplex., Proc. Natl. Acad. Sci. USA 49: 94-102, 1963.(b) Lerman, L. S.; Structural Considerations in Interaction of DNA and Acridines., J. Mol. Biol. 3: 18-30,1961.

3. (a) Martinez, R., Chacon-Garcia, L.; The Search of DNA-intercalators as Antitumoral Drugs. What ItWorked and What It Did Not Work. Curr. Med. Chem. 12: 127-151, 2005. (b) Brana, M. F., Cacho, M.,Gradillas, A. de Pascual-Teresa, B., Ramos, A.; Intercalators as Anticancer Drugs., Curr. Pharm. Des.7: 1745-1780, 2001. (c) Malone, H., Atassi, G.; DNA Topoisomerase Targeting Drugs: Mechanism ofAction and Perspectives., Anticancer Drugs 8: 811-822, 1997. (d) Baird, W. M. and Ralston, S. L;Carcinogenic Polycyclic Aromatic Hydrocarbons. In Chemical Carcinogens and Anticarcinogens,Pergamon, Eds Bowden, G. T., Fischer, S. M.; 12: 171-200, 1997. (e) Grover, P. L. and Hall, M.;Polycyclic Aromatic Hydrocarbons: Metabolism, Activation and Tumour Initiation. In ChemicalCarcinogenesis and Mutagenesis, Springer-Verlag, 1: 327-372, 1990. (f) Di Raddo, P. and Chan, T. H.;Reactions of the K-region Epoxides of Polycyclic Aromatic Hydrocarbons with Phosphodiesters. APotential Detoxification Reaction. J. Org. Chem. 47: 1427-31,1982.

4. (a) Harvey, R. G.; Polycyclic Aromatic Hydrocarbons., Wiley-VCH, 1997. (b) Rice, J. E. and Cai, ZW.,An IntramolecularArene-Triflate Coupling Reaction for the Regiospecific Synthesis of SubstitutedBenzofluoranthenes., J. Med. Chem. 58: 1415-1424, 1993. (c) Rice, J. E., Czech, A., Hussain, N. andLa Voie, E. J.; Synthesis of Fluorinated Derivatives of Benzo[k]fluoranthene and lndeno[1,2,3-cd]pyreneand 8,9-Dihydro-8,9-epoxybenzo[k]fluoranthene., J. Org. Chem. 53: 1775-1779, 1988. (d) Lee, H. andHarvey,R. G.; New Synthetic Approaches to Cyclopenta[a]phenanthrenes and their CarcinogenicDerivatives., J. Org. Chem. 53: 4253-4256, 1988. (e) Chung, Y.-S., Kruk, H., Barizo, O. M., Katz, M.and Lee-Ruff, E.; Syntheses of Cyclopentene-Fused Polynuclear Aromatic Hydrocarbons., J. Org.Chem. 52: 1284-1288, 1987. (f) Harvey, R. G., Polycyclic Hydrocarbons and Carcinogenesis; AmericanChemical Society. Washington, DC, 1985. (g) Clar, E., Polycyclic Hydrocarbons; Academic Press; NewYork, 1964. (h) Banik, B. K., Mukhopadhyay, C. and Becker, F. F. An Expeditious One Pot Synthesis of dibenzo[a,g]fluorene, Synth. Comm. 31: 2399-2403, 2001.

5. (a) Resfina, A., Chiacchio, M. A., Corsaro, A., De Clercq, E., lannazzo, D., Mastino, A., IsoxazolidinylPolycyclicAromatic Hydrocarbons: Potential DMA Intercalators., J. Med. Chem. 49: 709-715, 2006. (b) Kamal, A. ,Ramesh, G., Srinivas, O., Ramalu, P.; Synthesis and Antitumor Activity of Pyrene-linked pyrrolo[2,1-c][1,4]benzodiazopine Hybrids., Bioorg. Med. Chem. Lett. 14: 471-474, 2004. (c) Dorr, R.T., Liddil, J.D., Sami, S. M., Remers, W., Hersh, E. M., Alberts, D. S.; Preclinical Antitumor Activity of the AzonafideSeries of Anthracene-based DNA Intercalators. Anti-Cancer Drugs. 12: 213-220, 2001. (d) lyengar, B.S., Dorr, R. T., Alberts, D. S., Solyom, A. M., Krutzsch, M., Remers, W. A., 1,4-DisubstitutedAnthracene Antitumor Agents., J. Med. Chem. 40: 3734-3738, 1997. (e) Wunz, T. P., Craven, M. T.,Karol, M. D., Hill, G. C., Remers, W. A.; DNA-Binding by Antitumor Anthracene Derivatives., J. Med.Chem. 33:1549-1553, 1990.

6. (a) Bair, K. W., Andrews, C. W., Tuttle, R. L, Knick, V. C., Cory, M. and McKee, D. D.; 2-(Arylmethyl)amino-2methyl-1,3-propanediol DNA Intercalators. An Examination of the Effects ofAromatic Ring Variation on Antitumor Activity and DNA Binding., J. Med. Chem. 34: 1983-1990, 1991.(b) Bair, K. W., Tuttle, R. I., Knick, V. C., Cory, M. and McKee, D. D.; (l-Pyrenylmethyl)amino Alcohols,a New Class of Antitumor DNA Intercalators. Discovery and Initial Amine Side Chain Structure-ActivityStudies., J. Med. Chem. 33: 2385-2393,1990. Also

see: (a) Malviya, V. K., Liu, P. Y., Alberts, D. S., Surwit, E. A., Craig, J. B. and Hanningan, E. V.;Evaluation of Amonafide in Cervical Cancer Phase II., Am. J. Clin. Oncol. 15: 41-44, 1992. (b) Resell,R., Carles, J., Abad, A., Ribelles, N., Barnadas, A., Benavides, A. and Martin, M.; Phase I Study ofMitonafide in 120 h Continuous Infusion in Non Small Cell Lung Cancer., Invest. New Drugs 10: 171-175,1992; (c) Sami, S. M., Dorr, R. T., Alberts, D. S. and Remers, W. A.; 2-Substituted 1,2-Dihydro-3Hdibenz[de,h]isoquinoline-1,3-diones. A New Class of Anti-tumor Agent., J. Med. Chem. 36: 765-770,1993. (d) Sami, S. M., Dorr, R. T., Solyion, A. M., Alberts, D. S. and Remers, W. A.; Amino-Substituted2-[2/-(Dimethylamino)ethyl]-1,2-Dihydro-3H-dibenz[de,h]isoquinoline-1,3-diones. Synthesis, Anti-tumorActivity and Quantitative Structure-Activity Relationship., J. Med. Chem. 38: 983-993,1995.

7. Fukushima, T., Kawai, Y., Nakayama, T., Yamaguchi, T., Yoshida, A., Urasaki, Y., Imamura, S.,Kamiya, K., Tsutani, H., Ueda, T. and Nakamura, T.; Superior Cytotoxic Potency of MitoxantroneinInteraction with DNA: Comparison with that of Daunorubicin.,Oncol. Res. 8: 95-100, 1996.

8. (a) Venitt, S., Crofton-Sleigh, C., Agbandje, M., Jenkins, T. C., Neidle, S.; Anthracene-9,10-diones asPotential Anticancer Agents: Bacterial Mutation Studies of Amido-Substituted Derivatives Reveal anUnexpected Lack of Mutagenicity., J. Med. Chem. 41: 3748-3752, 1998. (b) Perni, R. B., Wentland, M.P., Huang, J. I., Powles, R. G., Aldous, S., Klinbeil, K. M. Peverley, A. D., Robinson, R. G., Corbett, T.H., Jones, J. L., Mattes, K. C., Rake, J. B., Coughlin, S. A.; Synthesis and Antitumor Activity of 4-Aminomethylthioxanthenone and 5-Aminomethylbenzothiopyranoindazole Derivatives., J. Med. Chem.41: 3645-3654, 1998. (c) Perry, P. J., Gowan, S. M.; Reszka, A. P. Polucci, P., Jenkins, T. C.;KellandL. R.; Neidle, S.; 1,4 and 2,6-Disubstituted Amidoanthracene-9,10-dione Derivatives as Inhibitors ofHuman Telomerase., J. Med. Chem. 41: 3253-3260, 1998. (d) Cherubim, P., Deady L. W., Dorkos, M.,Qazi, N. H., Baguley, B. C. and Denny, W. A.; Synthesis and Biological Evaluation of Phenanthrene-Derived Carboxamides as Cytotoxic Agents., Anti-cancer Drug Design 8: 429-438, 1993. (e) Lee, H.H., Palmer, B. D., Boyd, M., Baguley, B. C. and Denny, W. A.; Potential Antitumor Agents. 64.Synthesis and Antitumor Evaluation of Dibenzo[1,4]dioxin-1-carboxamides: a New Class of WeaklyBinding DMA-Intercalating Agents., J. Med. Chem. 35: 258-266, 1992. (f) Agbandje, M., Jenkins, T. C.,McKenna, R., Reszka, A. P., and Neidle, S.; Anthrecene-9,10-diones as Potential Anticancer Agents.Synthesis, DNA-Binding, and Biological Studies on a Series of 2,6-Disubstituted Derivatives., J. Med.Chem. 35: 1418, 1992. (g) Denny, W. A., Rewcastle, G. W. and Ganguley, B. C.; Potential AntitumorAgents. 59. Structure-Activity Relationships for 2-Phenylbenzimidazole-4-carboxamides, a New Classof Minimal DNA-lntercalating Agents Which May Not Act via Topoisomerase II., J. Med. Chem. 33: 814-819, 1990. (h) Wright, S. E., Mines, L. H. and White, J. C.; Effects of the Lipophilic Anticancer DrugTeniposide (VM-26) on Membrane Transport., Chem.-Biol. Interact. 75(1): 31-48, 1990 (i) Palmer, B.D., Rewcastle, G. W., Atwell, G. J., Baguley, B. C., Denny, W. A.; Potential Antitumor Agents. 54.Chromophore Requirements for in vivo Antitumor Activity Among the General Class of Linear TricyclicCarboxamides., J. Med. Chem. 31: 707-712, 1988. (j) Nicolay, K., Sautereau, A. M., Tocanne, J. F.,Brasseur, R., Huart, P., Ruysschaert, J. M. and De Kruijff, B.; A Comparative Model Membrane Studyon Structural Effects of Membrane-Active Positively Charged Antitumor Drugs., Biochim. Biophys. Acta,940: 197-208, 1988. For an excellent recent paper, see: Gomez-Monterrey, I., Campiglia, P.,Carotenuto, A., Califano, D., Pisano, C., Vesci,

L., Lama, T., Bertamino, A., Sala, M., MazzelladiBosco, M., Grieco, P. and Novellino, E., Design, Synthesis and Cytotoxic Evaluation of a New Seriesof 3-Substituted Spiro[(dihydropyrazine-2,5-dione)-6,3'-(2',3'-dihydrothieno[2,3-b]naphtho-4',9'-dione)]Derivatives., J. Med. Chem. 50: 1787-1798, 2007.

9. (a) Motohashi, N., Kurihara, T., Satoh, K., Sakagami, H., Mucsi, I., Pusztai, R., Szabo, M. and Molnar,J.; Antitumor Activity of Benzo[a]phenothiazines., Anticancer Res. 19: 1837-1842, 1999 (b) Chen, Y. H.andHuestis, W. H., Role of Membrane Lipid Distribution in Chlorpromazine-lnduced Shape Change ofHuman Erythrocytes., Biochim. Biophys. Acta, 1323: 299-309, 1997. (c) Tritton, T. R.; Cell SurfaceAction of Adriamycin, Pharmacol. Ther., 49: 293-309, 1991. (d) Tritton, T. R.; Cell Surface Action ofAdriamycin, Pharmacol. Ther., 49: 293-309, 1991. (e) Tritton, T. R.; Cell Surface Action of Adriamycin,Pharmacol. Ther., 49: 293-309, 1991. (f) Aki, H. and Yamamoto, M., BiothermodynamicCharacterization of Erythrocyte Hemolysis Induced by Phenothiazine Derivatives and Anti-InflammatoryDrugs.,Biochem. Pharm. 39: 396-398, 1990. (g) Sweet, W. D., Wood, W. G. and Schroeder, F.;Charged Anesthetics Selectively Alter Plasma Membrane Order., Biochemistry, 26: 2828-2835, 1987(h)Born, G. V. and Housely, G. M.; Effects of Modification of the Membranes of Intact Erythrocytes onthe Anti-Haemolytic Action of Chlorpromazine. Br. J. Pharm., 79: 481-487, 1983 (i) Tritton, T. R. andYee, G.; The Anticancer Agent Adriamycin can be Actively Cytotoxic Without Entering Cells., Science217: 248-250, 1982. (j) Horie, T., Sugiyama, Y., Awazu, S. and Hanano, M.; The Correlation BetweenDrug Binding to the Human Erythrocyte and its Hemolytic Activity., J. Pharm. Dyn., 4: 116-122, 1981.

10. (a) Becker, F. F. and Banik, B. K.; Polycyclic Aromatic Compounds as Anticancer Agents: Synthesisand Biological Evaluation of Some Chrysene Derivatives., Bioorg. Med. Chem. Lett., 8: 2877-2880,1998. (b) Banik, B. K. and Becker, F. F.; Synthesis, Electrophilic Substitution and Structure-ActivityRelationship Studies of Polycyclic Aromatic Compounds for the Development of Anticancer Agents.,Curr. Med. Chem. 8: 1513-1533, 2001. (c) Banik, B. K. and Becker, F. F.; PolycylicAromaticCompounds as Anticancer Agents: Structure-Activity Relationships of New Chrysene and PyreneDerivatives.,Bioorg. Med. Chem. 9: 593-605, 2001. Also see: Becker, F. F. and Banik, B. K. AntitumorChrysene Compounds., US Patent, 6,015,811, 2000. For the synthesis and biological evaluation ofdibenzofluorenes, see: Becker, F. F.; Mukhopadhyay, C., Hackfeld, L, Banik, I. and Banik, B. K.;Polycyclic Aromatic Compounds as Anticancer Agents: Synthesis and Biological Evaluation ofDibenzofluorene Derivatives., Bioorg. Med. Chem., 8: 2693-2699, 2000. Also see: Becker, F. F. andBanik, B. K.; Antitumor Dibenzofluorene Compounds., US Patent, 6,184,224, 2001. Also see:(a) Banik, B. K., Banik, I. and Becker, F. F. Stereocontrolled Synthesis of Anticancer Beta-Lactams viathe Staudinger Reaction., Bioorg. Med. Chem., 13: 3611-3622, 2005. (b) Banik, B. K. and Becker, F.F.; Banik, I.; Synthesis of Anticancer (3-Lactams: Mechanism of Action.,Bioorg. Med. Chem., 12: 2523-2528, 2004. (c) Banik, B. K. Ed. In (3-Lactams: Synthesis, Stereochemistry, Synthons and BiologicalEvaluation, Cur. Med. Chem. 2004, Volume 11.

12. Landis-Piwowar, K. R., Chen, D., Cui, Q. C., Minic, V., Becker, F. F., Banik, B. K. and Ping Dou, Q.;International. J. Mol. Med., 17: 931-935, 2006.

13. (a) Bose, A., Sanjoto, W. P., Villarreal, S., Aguilar, H., Banik, B. K.; Tetrahedron Lett. 48: 3945-3947,2007. (b) Banik, B. K.; Samajdar, S.; Banik, I.; Ng, S.; Hann, J. Montmorillonite Impregnated withBismuth Nitrate: Microwave-Assisted Facile Nitration of (3-Lactams., Heterocycles, 61: 97-100, 2003.(c) Samajdar, S., Becker, F. F. and Banik, B. K., Surface-Mediated Highly Efficient RegioselectiveNitration of Aromatic Compounds by Bismuth Nitrate, Tetrahedron Lett., 41: 8017-8020, 2000. The PIhas demonstrated the versatility of bismuth salts-catalyzed reactions. For example, see: (a) Banik, B.K.; Reddy, A.; Datta, A., Mukhopadhyay, C. Microwave-Induced Bismuth Nitrate-catalyzed Synthesis ofDihydropyrimidones via Biginelli Condensation, Tetrahedron Lett., 48: 7392-7394, 2007. (b) Banik, B.K.; Cardona, M. Bismuth Nitrate Catalyzed Novel Synthesis of Pyrrole-substituted Indolinones,Tetrahedron Lett., 47: 7385-7387, 2006 (c) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. AStraightforward Highly Efficient Paal-Knorr Synthesis ofPyrroles, Tetrahedron Lett., 46: 2643-2646,2005. (d) Thompson-ISIR Web of Science Data Base has identified our work on bismuth-catalyzedreaction as the Fast Breaking paper in the field of chemistry in 2004. ACS has highlighted Pi's work inChemical Engineering News, April 07, 2003, p 28-30. (e) Srivastava, N.; Banik, B. K. Bismuth Nitrate-Catalyzed Versatile Michael Reactions., J. Org. Chem., 68: 2109-2112, 2003. (f) Srivastava, N.;Dasgupta, S. K.; Banik, B. K. A Remarkable Bismuth Nitrate-Catalyzed Protection of CarbonylCompounds., Tetrahedron Lett. 44:1191-1193, 2003.

14. (a) Basu, M. K., Becker, F. F. and Banik, B. K., Ultrasound-Promoted Highly Efficient Reduction ofAromatic Nitro Compounds to the Aromatic Amines by Samarium/Ammonium Chloride., TetrahedronLett., 41: 6551-6554, 2000. (b) Banik, B. K., Suhendra, M., Banik, I. and Becker, F. F.,Indium/Ammonium Chloride Mediated Selective Reduction of Aromatic Nitro Compounds: PracticalSynthesis of 6-Aminochrysene., Synth. Commun., 30: 3745-3754, 2000. (c) Banik, B. K.,Mukhopadhyay, C., Venkatraman, M. S. and Becker, F. F. A Facile Reduction of Aromatic NitroCompounds to Aromatic Amines by Samarium and Iodine, Tetrahedron Lett., 39: 7343-7346, 1998. Forreduction of the aromatic nitro group and rearrangement with indium-induced reaction, see: Banik,B.K., Samajdar, S.; Banik, I. A Facile Synthesis of Oxazines by Indium-induced Reduction-Rearrangement of the Nitro (3-Lactams, Tetrahedron Lett., 44: 1699-1701, 2003.

15. (a) Banik, B. K., Ghatak, A., Mukhopadhyay, C. and Becker, F. F., Sodium Bismuthate MediatedOxidation Study of Hydrofluorenes., J. Chem. Res. 108-109, 2000. (b) Banik, B. K.; Venkatraman, M.S.; Mukhopadhyay, C.; Becker, F. F. Benzylic Oxidation by Sodium Bismuthate in Acetic Acid: A SimpleMethod for the Synthesis of Polycyclic Aromatic Ketones., Tetrahedron Lett., 39: 7247-7250, 1998.

16. Banik, B. K., Venkatraman, M. S., Banik, I. and Basu, M. K., Samarium-Induced ReductiveDimerization of Methyl Cinnamate: Synthesis of 2, 8-Diaminochrysene., Tetrahedron Lett. 45: 4737-4740, 2004.

17. Banik, B. K., Banik, I., Hackfeld, L, Becker, F. F. Indium-Induced Reductive Cyclization: Synthesis ofBiologically Active Heterocyclic Compounds.,Heterocycles, 56: 467-470, 2001.

18. Tse, C., Xiang, R. H., Bracht, T., and Naylor, S. L. Human Semaphorin 3B (SEMA3B) Located atChromosome 3p21.3 Suppresses Tumor Formation in an Adenocarcinoma Cell Line., Cancer Res., 6:542-546, 2002. Xiang, R., Davalos, A. R., Hensel, C. H., Zhou, X. J., Tse, C., and Naylor, S. L.Semaphorin 3F Gene from Human 3p21.3 Suppresses Tumor Formation in Nude Mice., Cancer Res.,62: 2637-2643, 2002.

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