International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 03 Issue: 09 | Sept -2019 ISSN: 2590-1892

Anew Drug Design strategy in the light of Molecular Hybridization Concept

Subhasis Basu, Department Of Chemistry, Visva-Bharati University

Abstract
Molecular hybridization of nucleic acids is the process in which two single-stranded nucleic acid molecules with complementary base sequences form a double-stranded nucleic acid molecule. Nucleic acid hybridization technology is a fundamental tool in molecular biology, and has been applied in various fields such as detection of gene expression, screening specific clone from cDNA or genomic library, determining the location of a gene in chromosome and diagnosis of diseases.

Cage like property for eg graphene or glue like bio material from spider of even polymer can bind rapid growth of cell for its binding nature at micro level or can trap bacterial or viral growth by trapping within Net like structure. The idea of Quantum Dots may be implied to identify such net as drug to separate from diseases infected Zone. Some time electrification or by application of Radioactivity through this net may reduce harmful diseases spreading.

Molecular hybridization: a useful tool in the design of new generation drug prototypes using the sequencing of Nucleic acids for a particular patient.Molecular hybridization is a new concept in drug design and development based on the combination of pharmacophore moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in compounds presenting modified selectivity profile, different and/or dual modes of action and reduced undesired side effects. So, in this paper, we described several examples of different strategies for drug design, discovery and pharmacy modulation focused on new innovative hybrid compounds presenting analgesic, anti-inflammatory, platelet anti-aggregating, anti-infectious, anticancer, cardio- and neuroactive properties.

By this molecular hybridization concept in the field of genetic engineering and as well as molecular biology, formation of a partially or wh olly complementary nucleic acid duplex as association of
single strands, usually between DNA and RNA s trands or previously unassociated DNA strands, but alsobetween RNA strands; used to detect and isolate specific sequences, measure homology, o r define other characteristicsof one or both strand s. If we can detect the particular cause of critical disease like Parkinson, Cancer or AIDS for a particular patient. We can synthesis the new drug design for that patient to treat them for complete cure in this molecular hybridisation concept. So this is a new generation concept for developing drug as well as the cause of the particular diseases for a particular patient. Not only that by fusing more than one drugs structure components by Molecular hybridisation concept we can make a single drug for a patient with multiple affected diseases using computer simulation more modern method in the field of medicinal chemistry. The idea will show us to find the way of sustainable health and immortality in future, based on Drug design Expert System.

Keywords: Molecular hybridization, Drug design, Hybrid compounds, Pharmacophoric group combination, DNA and RNA Sequencing, Drug design Expert System.

Contents:

A. INTRODUCTION:

Over the last decade the registration of pharmaceuticals for the treatment of new pathologies or that represent therapeutic innovations or known illnesses, mostly infectious and with high social – economic impact , such as neurogenerative diseases and cancer, has suffered a continuous decrease, contrasting with the growing of technological and scientific advances pursuing the improvement of the quality of life. Reappearing diseases such as tuberculosis, hanseniasis, smallpox, schistosomiasis, infectious diseases associated to resistant microorganisms, such as malaria, still incurable new virus and tropical diseases, besides cancer, neurodegenerative and autoimmune diseases, still represent a big challenge for the pharmaceutical sector and demand a continuous effort to the development of new therapeutic tools: more efficient, selective and economically accessible

In this paradoxical context, the Pharmaceutical Industry has invested heavily in the development of new techniques of diagnosis, investigation and creation of chemical libraries with high molecular diversity, based on combinatorial chemistry, computer-aided drug design (CADD), simulation and prediction of physicochemical and structural properties associated to drug-receptor interactions (QSAR), automatized processes of pharmacological screening (High Throughput Screening – HTS), new methods of *in vitro* and *in vivo* pharmacological evaluation, based on the advances of the molecular biology, genomics and biotechnological approaches [1-3].

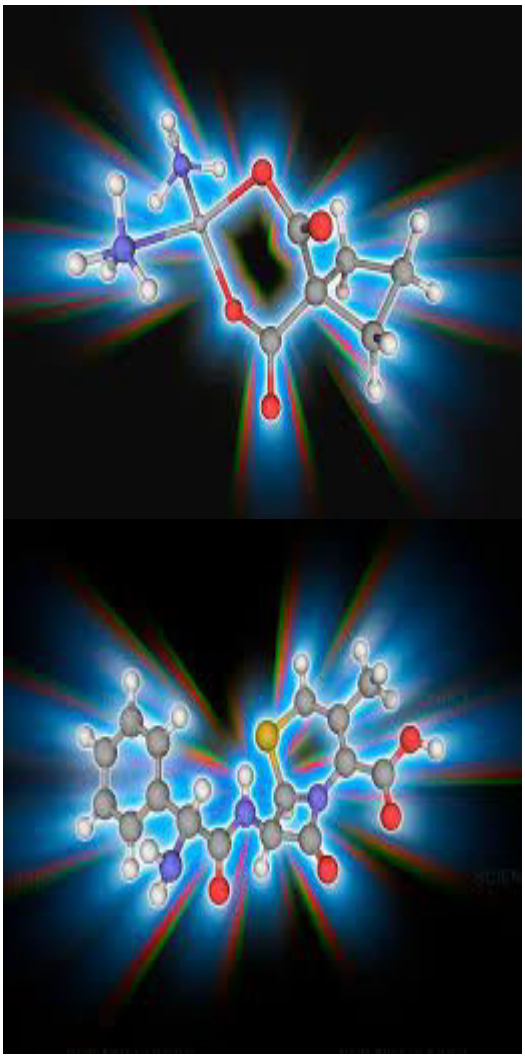
Recently, the natural products chemistry has been returning to a prominent position in the prospection of bioactive compounds, justifying the new investments in research from the pharmaceutical sector pursuing new pharmaceuticals, especially the ones whose origin is vegetal, marine or from microorganisms. The enormous chemical diversity of the secondary metabolites still challenges and inspires the synthetic and medicinal chemistry for their molecular complexity and diversity, working as role templates for the discovery of new drugs and the planning of new synthetic and semisynthetic derivatives [3-8].

On the other hand, the result of all effort was not yet able of promoting the quick access to massive quantities of new bioactive chemical entries (BioNCEs). Furnishing the expectation of high efficiency and productivity, which has not happened yet, since the number of new registered pharmaceuticals has been decreasing significantly year after year [4-5].The rational planning of new synthetic prototypes has been using a series of methods of structural modification that aim, *apriori*, at the generation of new compounds presentingoptimized pharmacodynamics and pharmacokinetic properties, exploring bioactive substances' fragments (Fragment-Based Drug Design) [9], active metabolites of drugs [10], bioisosterism [11], selective optimization of side effects of drugs [12] and drug lamentation [13]. No doubt the whole idea is based on Drug design expert system, as described in the next topic.

B. Drug Design Expert System:

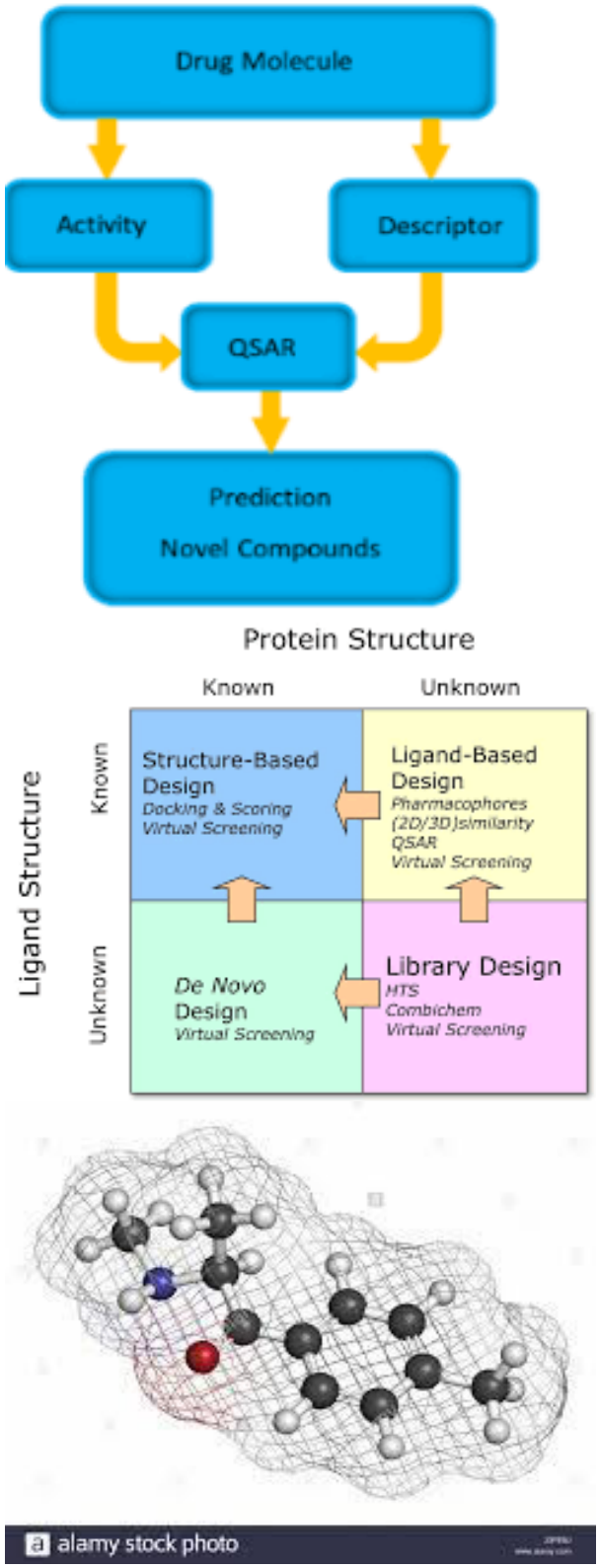
Drug Design Expert System or protocol is mainly based on the following two flowchart systems as follows.

Cage like property for eg graphene or glue like bio material from spider of even polymer can bind rapid growth of cell for its binding nature at micro level or can trap bacterial or viral growth by trapping within Net like structure. The idea of Quantum Dots may be implied to identify such net as drug to separate from diseases infected Zone. Some time electrification or by application of Radioactivity through this net may reduce harmful diseases spreading.



Cage like trapping and also electrification or Application of Radio activity in the cage..

Drug design strategy.



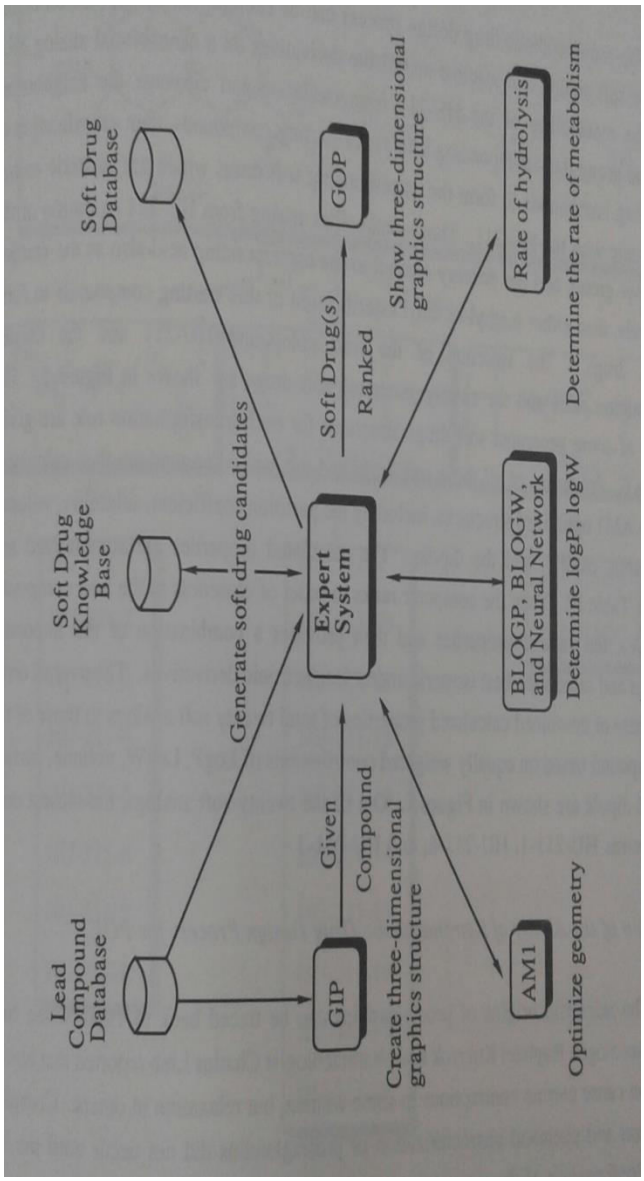


Fig. (B2). Architecture of Soft design System.

C. Molecular Hybridization of Nucleic acids

• Molecular hybridization of nucleic acids is the process in which two single-stranded nucleic acid molecules with complementary base sequences form a double-stranded nucleic acid molecule. Nucleic acid hybridization technology is a fundamental tool in molecular biology, and has been applied in various fields such as detection of gene expression, screening specific clone from cDNA or genomic library, determining the location of a gene in chromosome and diagnosis of diseases.

1. Principles Of Nucleic Acid Hybridization

The technique of nucleic acid hybridization is established and developed on the basis of the denaturation and renaturation of nucleic acids. Hydrogen bonds in double- stranded nucleic acids can be disrupted by some physicochemical elements, and two strands of nucleic acids are separated into single strand.

2. Hybridization DNA from source "Y" TACTCGACAGGCTAG
CTGATGGTCATGAGCTGTCCGATCGATCA
T DNA from source "X"
TACTCGACAGGCTAG Hybridization

3. If different single-stranded DNA molecules, or DNA and RNA molecules, or RNA molecules are mixed together in a solution, and the renaturation is allowed to occur under proper conditions, single- stranded DNA or RNA will bind with each other to form a local or whole molecule of double-stranded structure as long as the single-stranded molecules are complementary, no matter what kind of sources they come from.

4. Nucleic acid hybridization as a technique involves using a labelled nucleic acid probe, which is a known DNA or RNA fragment, to bind with the target nucleic acids, which is usually a poorly understood, heterogeneous population of nucleic acids. A probe labelled with detectable tracer is the prerequisite for determining a specific DNA sequence or gene in a sample or genomic DNA by nucleic acid hybridization.

5. The target nucleic acids to be analysed are usually denatured, and then mixed with the labelled probe in the hybridization system. The

probe will bind to the segment of nucleic acid with complementary sequence under proper conditions. The hybridization can be identified by the detection of the tracer labelling the probe. Thus the existence or the expression of specific gene can be determined.

6. Preparation And Labelling Of Nucleic Acid

7. Preparation of probes • Probes may be single-stranded or double- stranded molecules, but the working probe must be single-stranded molecules. The probes used in hybridization of nucleic acids include oligonucleotide(15-50 nucleotides), genomic DNA fragment, cDNA fragment and RNA.

8. Oligonucleotide probes are short single-stranded DNA fragments designed with a specific sequence complementary to the given region of the target DNA. They are usually synthesized in vitro.

9. Genomic DNA probes can be prepared from the cloned DNA fragment in plasmid. • cDNA probes can be prepared from the cloned cDNA in plasmid, or amplified directly from mRNA by RT-PCR. • RNA probes are usually transcribed in vitro from a cloned cDNA in a proper vector. The size of genomic DNA probes, cDNA probes and RNA probes may be 0.1 kb to 1 kb.

10. Labelling of probes • Probe is usually labelled with a detectable tracer, which is either isotopic or non- isotopic. The purified oligonucleotide is labelled in vitro by using a suitable enzyme to add the labelled nucleotide to the end of the oligonucleotide.

11. For the preparation of the labeled RNA probes, RNA probes are usually synthesized by RNA polymerase in the presence of ATP, GTP, CTP and the labelled UTP, with specific fragment of a gene or cDNA in a proper vector as template. RNA probes can then be generated and be labeled at the same time.

12. Genomic DNA probes and cDNA probes are usually labelled in the process of DNA synthesis in vitro. In the reaction of DNA synthesis with a DNA probe as template, if a labelled-dNTP, which can be incorporated into newly-synthesized DNA chain, is added as a substrate, the labelled DNA probe will be formed.

13. There are different, sensitive detecting methods for each of the labels used in nucleic acid hybridization. After hybridization, the location and the quantity of the hybrid molecules can be determined. The labels in common use include radioactive (32 P and 35 S) and nonradioactive (digoxigenin, biotin, fluorescein) substances which are used to label dNTP.

14. Hybridization Of Nucleic Acids

15. Southern blot hybridization • Southern blot hybridization is an assay for sample DNA by DNA-DNA hybridization which detects target DNA fragments that have been size-fractionated by gel electrophoresis (Figure 4-1). In Southern blot hybridization, the target DNA is digested with restriction endonucleases, size-fractionated by agarose gel electrophoresis, denatured and transferred to a nitrocellulose or nylon membrane for hybridization.

16. DNA fragments are negatively charged because of the phosphate groups so to migrate towards the positive electrode, and sieved through the porous gel during the electrophoresis. Shorter DNA fragments move faster than longer ones. For fragments between 0.1 and 20kb in length, the migration speed depends on the length of fragment. Thus, fragments in this size range are fractionated by size in a conventional agarose gel electrophoresis system.

17. Following electrophoresis, the sample DNA fragments are denatured in strong alkali, such as NaOH. Then, the denatured DNA fragments are transferred to a nitrocellulose or nylon membrane and become immobilized on the membrane.

Subsequently, the immobilized single- stranded target DNA sequences are allowed to interact with labelled single- stranded probe DNA.

18. The probe will bind only to complementary DNA sequences in the target DNA to form a target-probe heteroduplex. As the positions of the immobilized single- stranded target DNA fragments on membrane are faithful records of the sieve separation achieved by agarose electrophoresis, they can be related back to the original gel to estimate their size.

19. Figure 4-1 Southern blot hybridization detects target DNA fragments that have been size-fractionated by gel electrophoresis

20. Southern blot hybridization technique is widely applied in researches since its invention. It could be applied for analysis of gene expression, screening of recombinant plasmids, analysis of gene mutation, and identification of the existence of a given DNA such as DNA from pathogenic microorganism. It could also be used to detect deletion of gene by restrictions mapping.

21. Hybridization • The bases in DNA will only pair in very specific ways: G with C and A with T • In short DNA sequences, imprecise base pairing will not be tolerated • Long sequences can tolerate some mispairing only if hydrogen bonding of the majority of bases in a sequence exceeds the energy required to overcome mispaired bases • The source of any single strand of DNA is irrelevant, merely the sequence is important, thus complimentary DNA from different sources can form a double helix • This phenomenon of base pairing of single stranded DNA strands to form a double helix is called hybridization as it may be used to make hybrid DNA composed of strands from different sources

23. Because DNA sequences will seek out and hybridize with other sequences with which they base pair in a specific way much information can be gained about unknown DNA using single stranded DNA of known sequence • Short sequences of single stranded DNA can be used as "probes" to detect the presence of their complementary sequence in any number of applications including: – Southern blots – Northern blots (in which RNA is probed) – In situ hybridization – Dot blots . . . • In addition, the renaturation, or hybridization, of DNA in solution can tell much about the nature of organism's genomes

D.MOLECULAR HYBRIDIZATION AS A TOOL IN THE PLANNING OF NEW LIGANDS AND PROTOTYPES

The molecular hybridization (MH) is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophore sub-unities in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-unities, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates.

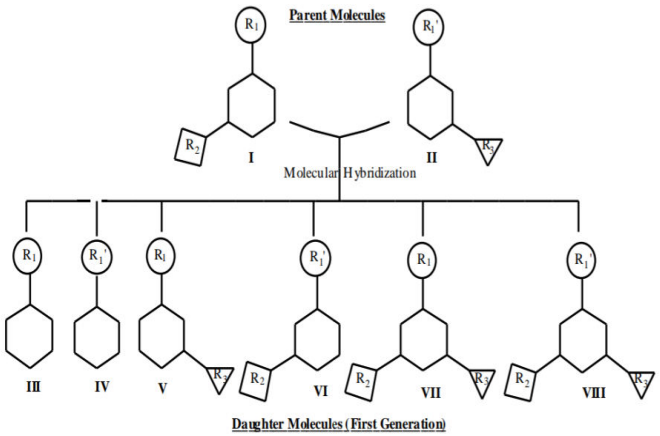


Fig. (1). Proposal of chemical evolution by combination of different structural sub-unities of parent molecules

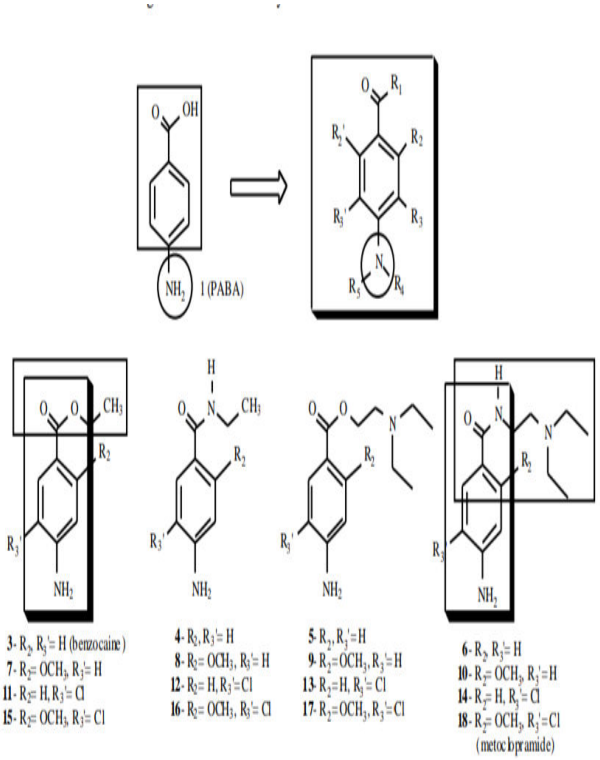


Fig. (2). Chemical library built with the PABA basic structure (**1**).

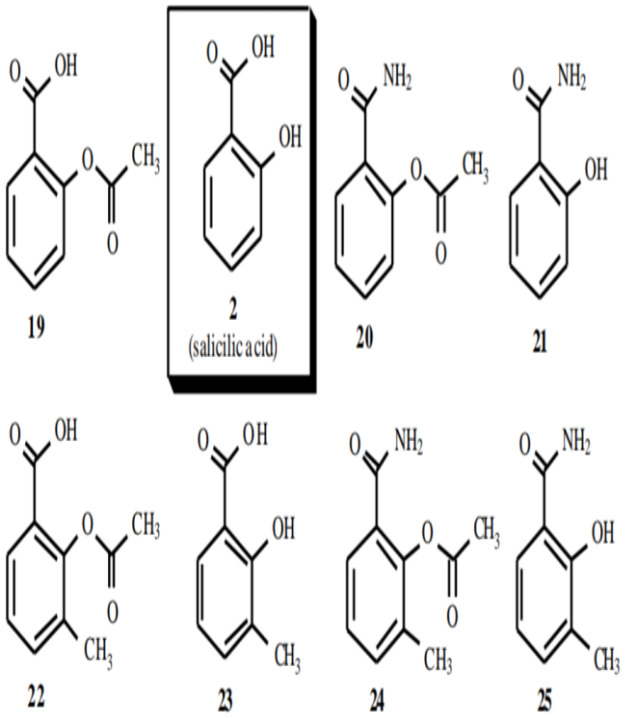


Fig. (3). Chemical library built with the basic structure of the salicylic acid (**2**).

E. CARDIOACTIVE AGENTS

Selective -adrenergic receptor antagonists are the most clinically used therapeutic class for the treatment of hypertension and angina pectoris [15]. Most of the available drugs of this class contain an 3-aryloxy-2-propanolamine structural sub-unity with an isopropyl or *t*-butyl substituent attached to the N atom, as represented by classical α-blocker agent propranolol (**26**) (Fig. (**4**)) [16]. Alternatively, these cardiovascular dysfunctions could be treated by the use of verapamil-analogue calcium antagonists as zatebradine (**27**), a benzazepinone derivative with vasodilator and bradycardic properties [17]. Collaborators [18] exploited the MH as strategy in the design of new cardio active hybrid molecules (28-33), in which aryl alkyl sub-unity of lateral chain of 27 was replaced by the2-hydroxy-3-aryloxypropylaminegroup(A), a particular structural sub unity of β-BLOCKERS(Figure-4). The pharmacological results showed that all the synthesized hybrid compounds 28-33 represented a bradycardic profile, as well as the prototype compound(27), besides vasorelaxant property of (-)-(*S*)-**30** (IC_{50} = 20 μM), probably due to its calcium antagonist effect evidenced by the inhibition of the aortic smooth muscle contraction induced by 80 mM of potassium chloride. However, despite the inclusion of 3-aryloxy-2-propanolamine (A) did not change the magnitude of the cardiovascular effects, all the hybrids **28-33** were better than the prototype **27** , considering the negative inotropic activity. It was shown that the association of the pharmacophore moiety of the lead-compound propranolol (**26**) to the zatebradine (**27**) core produced new derivatives with high affinity and selectivity for $_1$-adrenergic receptors. The compound (+)-(*R*)-**30** was the most potent of this series, revealing distinct activity profiles for both enantiomers, *R* enantiomer demonstrates affinity for $_1$-adrenergic receptors (pIC_{50} = 7.39), while *S* enantiomer showed specificity for relaxing smooth muscle vases, though in smaller extension [18].

[19]. These results indicated an evolution on the therapeutic application of this new class of

hybrid compounds in comparison to the sartans, since the original antihypertensive properties were assured, added to the benefits from the NO production in the cardiovascular system.

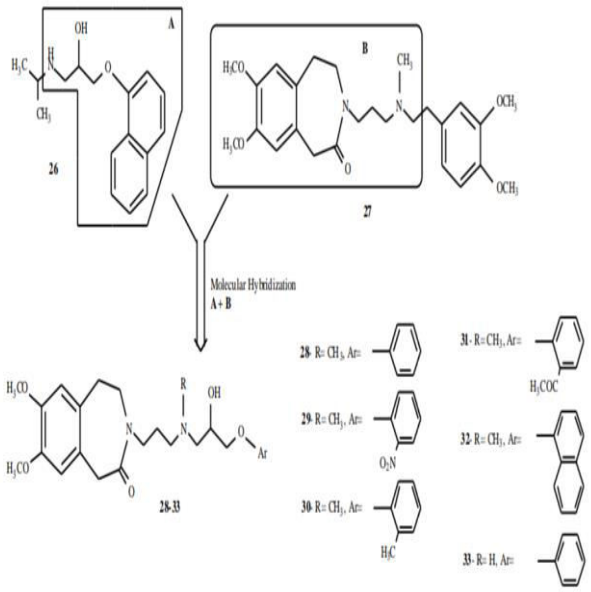


Fig. (4). Hybrid cardio active compounds planned out of propranolol (**26**) and zatebradine (**27**).

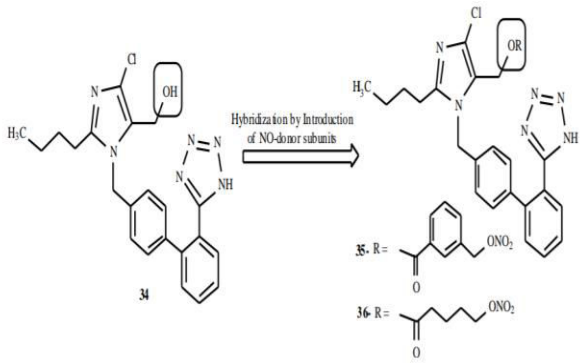


Fig. (5). Design of new hybrids **35** and **36** planned from the association of NO donor moieties to the antihypertensive drug losartan (**34**).

Fig. (6). Design of antiarrhythmic/antioxidant hybrids (**40-49**) based on the structure ofα-tocopherol (**37**), lidocaine (**38**) and procainamide (**39**).

F. ANTI-TUMORAL AGENTS

Anew research [26] proposed the synthesis of hybrids of the geldanamycine (GDM, **51**) with estradiol (**52**, Fig. (**7**)), aiming at obtaining molecules capable of causing the specific degradation of proteins, such as ligands of estradiol receptors (ER) and of the transaminase of the HER2 membrane, which are highly expressed in several types of breast cancer. The appropriate intervention on these proteins could lead to the delay of the cellular growing and/or apoptosis [27].

The ansamicines inhibit this process and induce the degradation of Hsp90 substrates [26]. The fusion between the structures of the estradiol (**52**) and GDM (**51**) should lead to new hybrid ligands that maintain the activities of both original ligands. In order to do that, a way of gathering these two structural templates in the hybrid targets **53-56** (Fig. (**7**)) was investigated, exploring the C-16 position of the estradiol, whose relative stereochemistry should be avoid steric effects over the pharmacophore hydroxyl group at C-17. In relation to the GDM (**51**), prior studies revealed that the methoxy attached carbon of benzoquinone system could act as Michael acceptor when facing amines or other bio nucleophilic species, supporting the structural design that considered the connection of a spacer unit presenting a terminal primary amino group, stereo selectively placed at C-16 of the estradiol (**52**), with this electrophilic site of GDM (**51**) (Fig. (**7**)) [26].

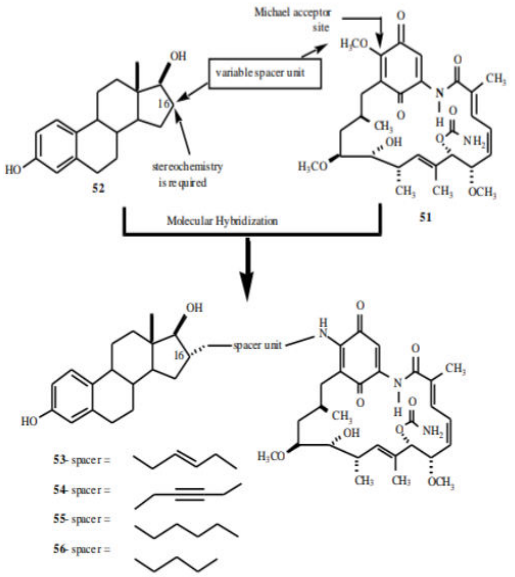


Fig. (7). Design of hybrids of the gendanamycin (**51**) and estradiol (**52**).

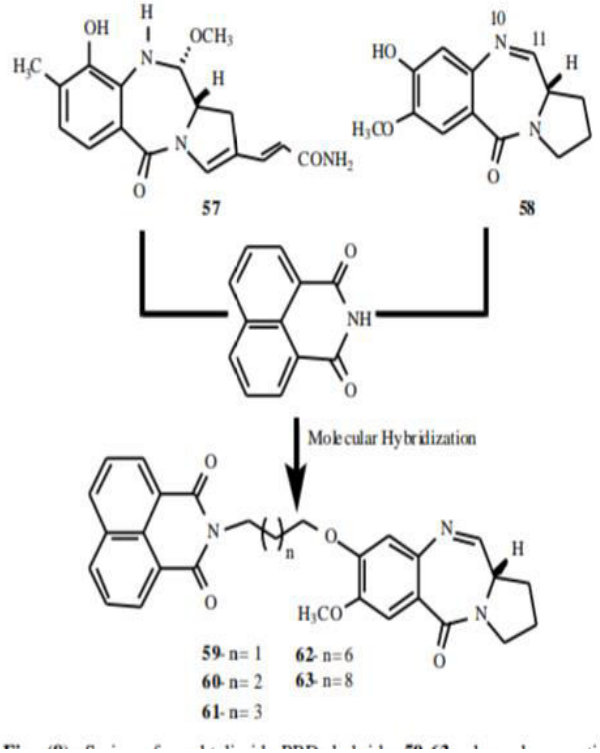
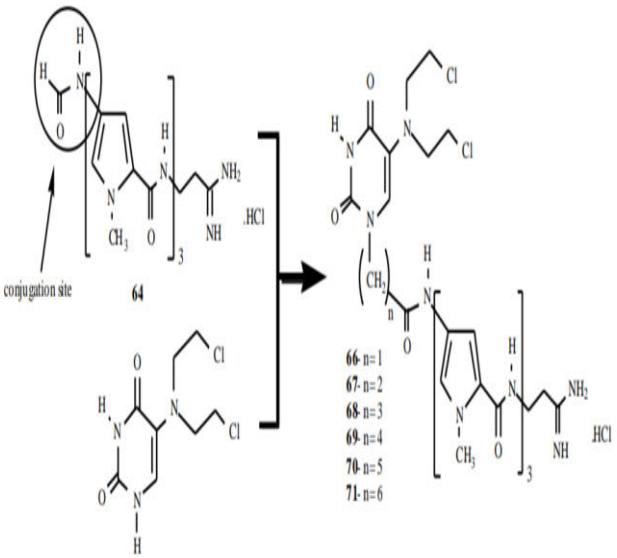


Fig. (8). Series of naphtalimide-PBD hybrids **59-63** planned as anti-tumoral agents.

The PBDs' mechanism of action is based on the nucleophilic attack of the guanine amino group to the iminic C-11 of **58** the system (or N-10-C-11 carbinolamine equivalent of **57,** Fig. (**8**)), creating adducts covalently bound to DNAsequences, being able to act not only as anti-tumoral agents but also as genes regulators and probes of the DNA structure. By exploring the naphtalimide derivative, which is a DNA intercalant agent and a potent anti-tumoral, Kamal and collaborators [28] synthesized the series of naphtalimide-PDB hybrids **59-63** (Fig. (**8**)) as drug candidates that combined the properties of DNA intercalating agent and ligand, and could present an improved anti-tumoral activity.(n = 2) over colon and renal tumour lines (log LC_{50} = -4.34 and -4.57, respectively) and **61** (n = 3) over colon and melanoma tumour cells (log LC_{50} = -4.41 and -4.43, respectively), indicating that the combination of intercalating and covalent bonding properties to the DNA in a single chemical entity represents a new approach in the development of new anti-tumoral agents [28]



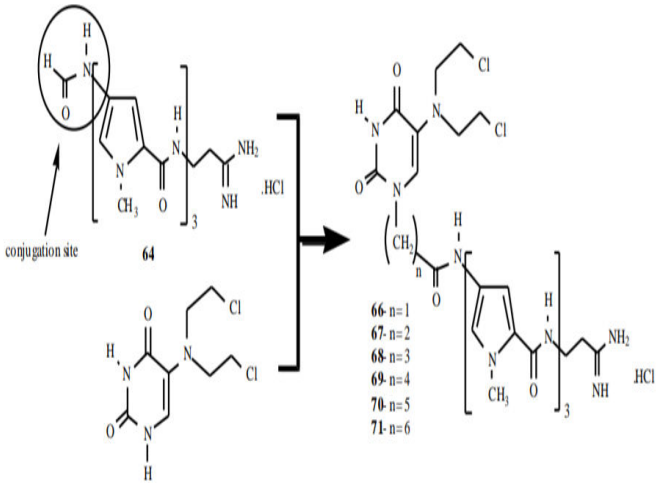


Fig. (9). Hybrids of the anti-tumoral distamicine-A (**64**) and uramustine (**65**).

Researchers [29] explored the structures of distamicine-A (**64**) and uramustine (**65**, Fig. (**9**)), a uracil mustard with strong DNA alkylating activity, to synthesize hybrid anti-tumoral agents. The result of the conjugation of the pharmacophore sub-unities of **64** and **65** , connected through polyethylene chains with diverse sizes, were six new hybrid compounds (**66-71**) with superior antitumor activity than distamicine-A (IC_{50}> 100 µM) and uramustine (IC_{50} = 5.1 µM) tested isolate against the human leukaemia K562 line.The compounds **66** (IC_{50} = 4.06 µM), **67** (IC_{50} = 2.54 µM) and **68** (IC_{50} = 7.26 µM), presenting short spacer unities (1 to 3 carbons), showed similar moderate anti-tumoral profile, which could be improved at least twenty times by the increase of thespacer chain (**69**, IC_{50} = 0.11 µM, n= 4; **70**, IC_{50} = 0.14 µM, n= 5; **71,** IC_{50}= 0.07 µM, n= 6, Fig. (**9**)). It was observed that the most potent cytotoxic hybrid derivative 71 presented a cytotoxic activity >1000 times superior to the distamicine-A (**64**) in the same experimental conditions [29].

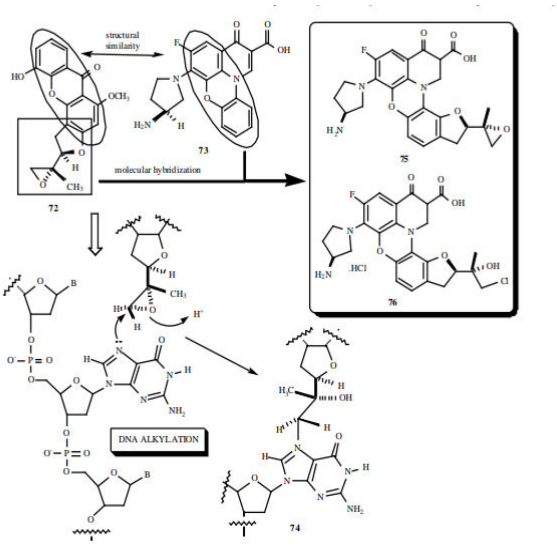
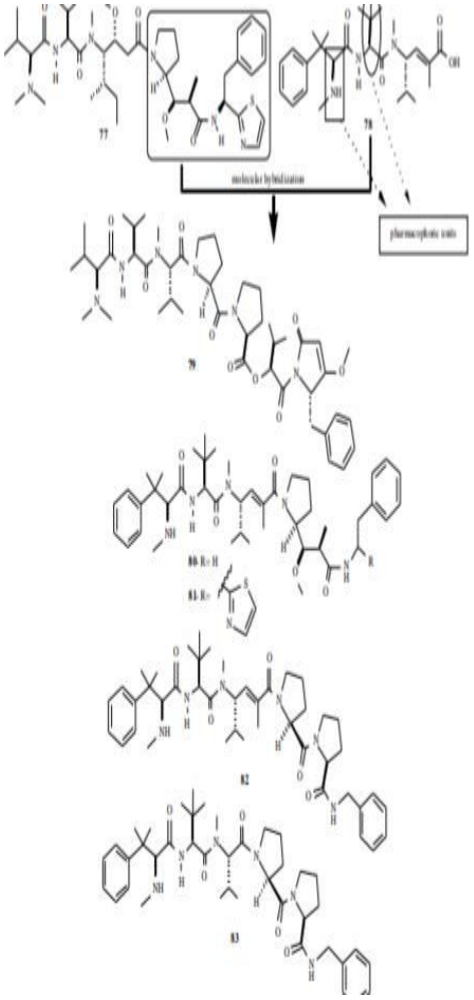


Fig. (10). Psorospermine (**72**), A-62176 (**73**), DNA alkylation adduct (**74**) formed through the nucleophilic attack of a guanine sub-unity to the oxirane ringof **72** and the molecular hybrids **75** and **7** Other approaches on the planning of anti-tumoral agents have been based on the election of the topoisomerase II as target for DNA intercalating cytotoxic agents. This enzyme catalyses changes in the DNA topology, promoting important functions

In the DNA metabolism and in the structure of the chromosomes. Psorospermine (**72**), a natural antibiotic isolated from the shells of *Psorospermum febrifuge* and A-62176 (**73**, Fig.

(**10**)),



(11). Molecular hybridization of the antitumor agents dolastatin (**77**) and taltobulin (**78**) as a tool for the design of the new analogues **79-83**.

Another example of rational planning of anti-tumoral drug candidates by molecular hybridization was related by scientists [31], who elected agents that act in the same biochemical pathway that taxanes and vinca alkaloids, useful drugs to the treatment of several cancer types. The mechanism of action of these two drugs involves the interference in the microtubules dynamics, which are proteins constituted by and b-tubulin heterodimers, preventing the chromosomal separation in the mitotic process and causing apoptosis. The dolastatin 10 (**77**) and taltobulin (HTI-286, **78**) (Fig. (**11**)) are peptide inhibitors of the tubulin polymerization, currently under clinical phase evaluation, which were elected as prototypes for the design of a new structural architecture, combining the common scaffold of analogs of **78** with structural carboxydipeptidyl sub-unity of dolastatin 10 (**77**). Previous structure-activity relationship (SAR) studies of taltobulin analogs had established some critical pharmacophorical sub-unities, such as the basic methylamine group and the demand of a bulky substituent group bound to the b-carbon of the amino acidic sub-unity of **77** (Fig. (**11**)), which were maintained in the design of the taltobulin/dolastatin hybrids **79-83** [31].

The hybrids **79-82** showed activities in resistant tumoral cellular lines, comparable to the taltobulin (**78**, IC_{50} = 0.96 nM, KB-3-1; 2.3 nM, KB-8-5 and 77 nM, KB-V1), highlighting theresults in cells KB-3-1 and KB-8-5 (**79**, IC_{50} = 0.84 and 2.2 nM; **80,** IC_{50}= 0.75 and 4.1 nM and **81,** IC_{50}= 0.90 and 5.1 nM,respectively). However, all were less active than **77** (IC_{50} = 0.073nM, KB-3-1; 0.34 nM, KB-8-5 and 43 nM, KB-V1). Besides that, **80** and **81** showed better resistance to the P-glycoprotein thanthe dolastatin 10 (**77**), as evidenced by the fraction KB-V1/KB-3-1 2 to 3 times smaller, but still greater than **77** (KB-V1/KB-3-1= 80). These two tumoral lines express a P-glycoprotein carrier and the susceptibility to the connection of this protein is related to the increase of the resistance to the treatment by multi-target drugs. On the other hand, the inferior vinylogue derivative **83** showed to be 3-4 times more potent than **78, 79** and **82** against KB-3-1 cells (IC_{50} = 0.25 nM). Nevertheless, likewise the other hybrids and the dilatations, the compound **83** presented a pronounced susceptibility for the binding to theP-glycoprotein (KB-V1/KB-3-1 > 12000) in comparison with **78.** Besides the cytotoxic activity in KB cells, all the newhybrid analogs inhibited the tubulin polymerization by 56-69% (at 0.3 µM concentration), presenting superior antitumor profile than that observed for the lead-compounds **77** (78%) and78 (88%) [31].

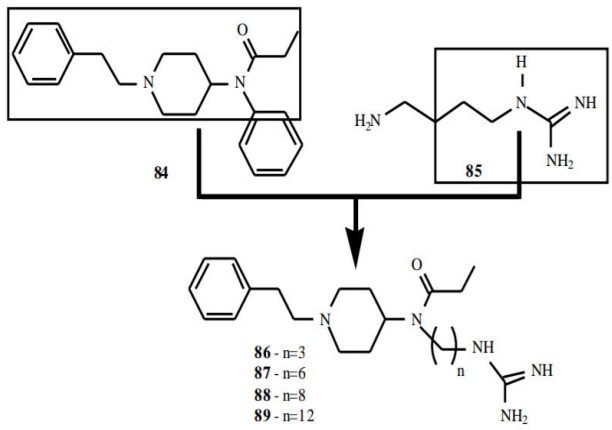


Fig. (12). Fentanyl-guanidine hybrids **86-89** planned as I_2-IBS / opioid ligands.

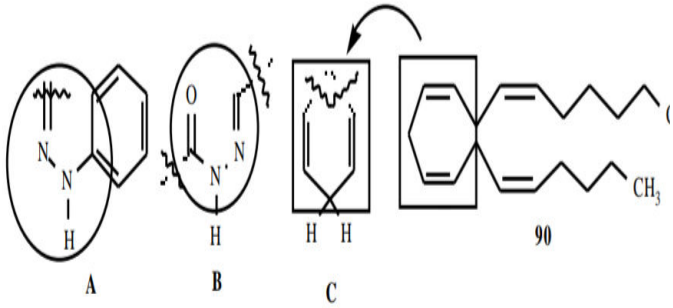


Fig. (13). Aryl- (**A**) and acyl-hydrazine (**B**) sub-unities mimicking the bis-allyl fragment (**C**) present in the arachidonic acid (**9**)

G. SIMILAR DESIGN DISEASE AGENTS

Just like as discussed in the previous section for example CARDIOACTIVE AGENTS,

ANTI-TUMORAL AGENTS we can similarly develop the design the drug structure like

ANALGESIC, ANTI-INFLAMMATORY AND ANTITHRO-MBOTIC AGENTS

ANTI-INFECTIOUS AGENTS,ANTIDIABETIC AND NEUROACTIVE AGENTS etc.

H. CONSIDERATIONS

In this article we tried to demonstrate the versatility of the molecular hybridization approach as structural modification strategy useful in the design of new optimized ligands and prototypes with new molecular architectures. New chemical classes were discovered coming from the combination of pharmacophore sub-unities of known prototypes, resulting frequently, in more potent and selective hybrid derivatives. In some cases, this strategy was exploited for the modulation of undesirable secondary effects and, in other ones, it was used to combine two distinct pharmacological profile in only one molecule, characterizing new potential dual-acting drugs, able of reproducing the effect of associations of more than one therapeutic agent. The molecular hybridization strategy is particularly interesting for the development of new prototypes for the treatment of physiopathology whose treatment is under research by scientists.

I. REFERENCES

1. Van Hijfte, L.; Marcinia, G.; Froloff, N. *J. Chromatogr. B,***1999**, *725*, 3; Dias, R. L. A.; Corrêa, A. G. *Quim. Nova***2001**, *24* , 236; Amaral, P. A.; Neves, G.; Farias, F.; Eifler-Lima, V. L. *Braz. J. Pharm. Sci.***2003**, *39* , 351.
2. Liljefors, T.; Petterson, I. Em *A textbook of drug design anddevelopment*; Krogsgaard-Larsen, P.; Liljefors, T.; Madsen, U., eds.;Harwood Academic Publishers: Amsterdan, 1996, cap. 3.; Högberg, T.; Norinder, U. Em *A textbook of drug design and development*; Krogsgaard-Larsen, P.; Liljefors, T.; Madsen, U., eds.; Harwood Academic Publishers: Amsterdan, 1996, cap. 4.

3. Wermuth, C. G. *The Practice of Medicinal Chemistry*, Elsevier Academic Press: London, **2004**.
4. Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.***2003**, *66*, 1022.
5. Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.***1997**, *60*, 52.
6. Tulp, M.; Bohlin, L. *Trends Pharmacol. Sci.***2002**, *23*, 225.

7. Cragg, G, M.; Newman, D. J. *Exp. Opin. Invest. Drugs***2000**, *9*, 1.
8. Cragg, G. M.; Newman, D. J. *Ann. Appl. Biol.***2003**, *143*, 127.
9. Erlanson, D. A.; McDowell, R. S.; O'Brien, T. *J. Med. Chem.***2004**, *47*, 3463.
10. Bisi, A.; Rampa, A.; Budriesi, R.; Gobbi, S.; Belluti, F.; Ioan, P.; Valoti, E.; Chiarini, A.; Valenti, P. *Bioorg. Med. Chem.***2003**, *11*, 1353.
11. Breschi, M. C.; Calderone, V.; Digiacomo, M.; Martelli, A.; Martinotti, E.; Minutolo, F.; Rapposelli, S.; Balsamo, A. *J. Med. Chem.***2004**, *47* , 5597.
12. Burnier, M.; Brunner, H. R. *Lancet***2000,***355*, 637.
13. Hornig, B.; Kohler, C.; Schlink, D.; Tatge, H.; Drexler, H. *Hypertension***2003**,*41*, 1092.
14. Abadir, P. M.; Carey, R. M.; Siragy, H. M. *Hypertension***2003**, *42*, 600.
15. Kullo, I. J.; Edwards, W. D.; Schwartz, R. S. *Ann. Intern. Med.***1998**, *129*, 1050.
16. Bandyopadhyay, D.; Chattopadhyay, A.; Ghosh, G.; Datta, A. G. *Curr.Med. Chem.* **2004**, *1* , 369.
17. Koufaki, M.; Calogeropoulou, T.; Rekka, E.; Chryselis, M.; Papazafiri, P.; Gaitanaki, C.; Makriyannis, A. *Bioorg. Med. Chem.***2003**, *11*, 5209.
18 Kuduk, S. D.; Zheng, F. F.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *Bioorg. Med. Chem. Lett.***1999**, *9*, 1233.
19. Huang, P. S.; Oliff, A. *Curr. Opin. Genet. Dev.***2001**, *11*, 104.
20. Kamal, A.; Reddy, B. S. N.; Reddy, G. S. K.; Ramesh, G. *Bioorg. Med.Chem. Lett.* **2002**, *1* , 1933.

BIOGRAPHIES:

Subhasis Basu

M. Sc(First Class) in Chemistry from The University Of Madras,
Master Of Science from Heriot Watt University, Honorary D. Sc from Ballsbridge University, Fellow of Indian Chemical Society, Member Of Royal Society Of Chemistry, Associate Members Of IChemE, IIChE. Worked as Ex-Assistant Professor, Faculty, Scholar(Associate) in the different Institutions, Presently working as Registered Research Scholar, Department Of Chemistry, Visva Bharati University.