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Review Paper

An overview of arene–arene interactions and application of uni-molecular models for their understanding[†]

Kamlakar Avasthi* and Amar Kumar

Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow, 226001, India
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Abstract: Interactions involving arene moieties are ubiquitous in nature and play an important role in variety of processes such as molecular recognition, crystal engineering, drug-receptor interactions, drug development etc. Understanding the nature of this weak but important noncovalent interaction will not only help us to get an insight of working of bio-macromolecules like DNA and proteins, but also help us to understand functioning of drug molecules inside the body since a majority of drug molecules contain one or another arene moiety. In addition to these it will also help in the development of new technologies such as organic semiconducting materials. One major problem in the understanding of these weak interactions is that these are easily overwhelmed by the presence of other much stronger interactions such as classical hydrogen bonding (involving two hetero atoms) etc. which makes it very difficult to decipher their exact contribution. Therefore, to overcome this problem several molecular models have been developed in the literature where these interactions can be studied in simpler and more controlled environment usually in the absence of stronger noncovalent interactions. The purpose of this review is to present the reader an overview of arene interactions and to focus on the different strategies used to develop new models for studying arene interactions especially the uni-molecular flexible models. Proper understanding of these interaction should be of immense value to chemist, medicinal chemist, biologist and supramolecular chemist and to all those interested in interface areas of chemistry and biology.

1. Introduction

Atoms and molecules can interact together leading to the formation of another molecule, by covalent interactions, or a molecular cluster, by noncovalent interactions. A covalent bond is formed when partially occupied orbitals of the interacting atoms overlap and a pair of electrons are shared by these atoms. Covalent bonds are shorter than 2 Å. In case of noncovalent interactions no such sharing of electrons takes place and these interactions act at distances of several angstroms. Noncovalent interactions were first recognized by J. D. van der Waals in the nineteenth century (1). Since then it has

Corresponding Author* E-mail: kavasthi@rediffmail.com
[†]CDRI communication no. 8312

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now been recognized that noncovalent interactions are involved in a vast number of phenomena related to the whole realm of molecular and macromolecular science such as molecular recognition, drug receptor interactions, solvent effect in reactions and the ability of geckos to climb rapidly up smooth vertical surfaces, even flat glass (2). Weak noncovalent interactions like stacking interactions (arene/ arene-arene/ π–π interactions) unlike their conventional counterparts (e.g. classical hydrogen bonding which are well characterized) or other un-conventional counterparts where H is attached to C atom instead of N/O or S atoms, are not well understood. Due to their weak nature they are usually difficult to observe in presence of stronger forces such as classical hydrogen bonding (involving two hetero atoms like O/N/S) and thus they are difficult to study both theoretically and experimentally (2,3). These forces often work together and their collective effect brings a profound change in molecular structure (conformation) as well as in supramolecular structure. In nature, where functions of bio-macromolecules like proteins, enzymes, DNA, etc., which are directly related to their structure, these weak forces play a very important role since easy formation as well as easy decomposition of molecular structures are required. These forces are sensitive to the environmental conditions and a slight change of conditions like temperature, pH etc., can bring about a significant change in conformation and hence function.

Interactions involving two or more aromatic residues are known as π–π interactions. These are among the most important but least understood of the noncovalent interactions. These interactions, though modest in energy, play a crucial role in such diverse areas as protein folding, base-to-base stacking in DNA/RNA, host-guest binding in supramolecular assemblies, crystal engineering, drug-receptor interactions and other molecular recognition processes. Since the seminal paper of Hunter on π–π interactions in 1990 (4) this area has seen increased activity and several reviews and books have appeared in the literature (5) which have highlighted different aspects of arene interactions. Recent studies have provided new insight into the driving forces, stability and selectivity of these interactions (6). The purpose of this review is to present a general overview of π–π interactions, its importance in biological and non-biological processes and to focus on the different strategies used to develop new models for studying arene interactions. The main emphasis is, however, on the uni-molecular (molecular) systems especially, where solid state structures are also known by X-ray crystallography, since bimolecular systems have been generally well covered in earlier reviews by Hunter (5h) and others (5d, 5f). C–H…π interactions involving at least one arene system will also be not discussed here as excellent reviews are available on this relatively well developed theme (5k, 5l). Main advantages of uni-molecular (molecular) systems are convenient synthesis, ^{1}H NMR and crystallographic studies. Another important advantage is that these models can be studied both at molecular and supramolecular level with ease. For example if linker between two arenes is positioned at proper place resulting system may be studied at molecular level by ^{1}H NMR spectroscopy. If a good crystal is available same study could easily be extended to supramolecular level. Intramolecular folding indicated by ^{1}H NMR spectroscopy, if strong, may show up in solid state by X-ray crystallography. Such two studies together on any system give formidable information about arene interactions compared to any other methodology. Once a good model is

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developed it can be easily applied to variety of other arene residues and substituents effect. Intramolecular arene interactions are especially important for understanding of DNA/RNA structures and protein folding. Once they are understood in depth it should be possible to apply them for drug development where they are essentially intermolecular.

2. The nature and geometry of arene–arene interaction.

The attraction between two aromatic residues present in the same or different molecules is known as arene–arene interaction or π–π interaction. The π–π interactions are weak in strength with the energy ranging from 0-50 kJ/mol (7). There are four types of π–π interaction geometries, face-to-face, edge-to-face, parallel displaced and Y-shaped (**Figure 1**) (4, 5b, 5c). Typical centroid to centroid distance for two interacting arenes in intermolecular mode is more than 3.6 Å (5h, and 5i). Another criterion of minimum distance for parallel offset arene interaction is that it is 0.4 Å longer than the sum of van der Waals radii of involved atoms (5f). Edge-to-face and parallel-displaced geometries are the most common geometries found in structural chemistry (8). Computational studies on benzene dimer showed that the edge-to-face and parallel-displaced geometries are nearly iso-energetic with binding energy of about 2 kcal/mol (9a, 9b). Face-to-face stacked geometry is commonly observed with donor–acceptor pairs. The benzene-perfluorobenzene interaction is an excellent example of this type of aromatic interaction and has been calculated to provide -15.5 kJ/mol stability (9c). In addition, there are also continuums of intermediate geometries (10a-c). Different computational techniques used for studying non-covalent interactions, including π–π interactions have been reviewed recently (9d).

There are four basic packing types for aromatic compounds reported in literature (**Figure 2**) (11). In simple herringbone structure, the nearest neighbours are non parallel. In sandwich-herringbone packing, the herringbone motif is made up of sandwich-like diads. In the third type, called β, the main interactions are between parallel translated molecules. The fourth type, called γ is characterised by 'graphitic' planes.

The nature of arene–arene interaction is still not well understood (5g, 8). Arene interactions have been proposed to consist of van der Waals, hydrophobic and electrostatic forces, however, contribution and magnitude of each of these components may vary from case to case and is a matter of many investigations. Hunter and Sanders (1990) proposed an electrostatic model to explain the strong geometrical requirements for interactions between aromatic molecules (4). They considered the σ-framework and the π-electrons separately and demonstrated that net favorable π–π interactions are actually the result of σ–π attractions that overcome π–repulsions. By using an idealized π–system, some general rules for predicting the geometry of favorable π–π interactions were derived. The electrostatic component has been proposed to arise from the interactions of the quadrupole moments of the aromatic rings. Though, benzene has no net dipole, it has an unequal distribution of charge, with greater electron-density on above and below the faces of the ring and reduced electron-density on the edge, which gives rise to the quadrupole moment. The edge-to-face and parallel-displaced geometries are stabilized due to electrostatic σ–π attraction while the face-to-face geometry is destabilized due to π–π repulsion (**Figure 3**). Generally, electron

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withdrawing groups in aromatic rings reinforce while electron donating groups weaken π–π interactions. Presence of heteroatom in aromatic ring also reinforces the π–π interactions.

For example, highly accurate quantum chemical computations revealed that benzene–pyridine and pyridine dimer bind more strongly than the benzene dimer in several configurations, and in contrast to the benzene dimer, parallel-displaced configurations can be significantly preferred over T-shaped configurations (12).

Recently, it has been found from the survey of crystallographic data stored in Cambridge Crystallographic Database that the stacking interactions in crystals of simple aromatic hydrocarbons become important only for molecules with more than three rings (13). Whereas for crystals of nitrogen substituted heterocyclic aromatic molecule, the stacking interactions become important for doubly substituted single ring molecules itself. Generally speaking, the stacking is reinforced with the increasing number of nitrogen in the ring (13a, 13b). Substitution of the hydrogen atom of an aromatic hydrocarbon by an electron withdrawing atom like F, Cl etc. or an electron withdrawing group like NO_2 reinforces the stacking interactions (13a). In a recent article (2011) however, such view of substituents effect on stacking interactions has been challenged by Wheeler (6). According to him the substituents effect can be better described as arising from local, direct interactions of the substituent with the proximal vertex of the other ring. Thus substituent effects in stacking interactions are additive, regardless of whether the substituents are on the same or opposite rings. Moreover, according to him, substituents effect are also insensitive to the introduction of heteroatom on distant parts of either stacked ring. Apparently all this refers to intermolecular interactions.

3. Importance of arene–arene interactions

3.1 Arene–arene interactions in biological systems

Arene–arene interactions are ubiquitous in nature. They are believed to provide stability to duplex DNA (14), they have been proposed to contribute to the unique properties of thermophilic proteins (15), they may play a role in aggregation of amyloid β in Alzheimer's disease (16), and they are common motifs in bio-molecular recognition.

3.1.1 Stabilization of DNA structure

DNA is a polynucleotide. The nucleotides of DNA are made from purine or pyrimidine rings (aromatic nitrogenous bases). Within the DNA molecule, the aromatic rings are lying nearly perpendicular to the length of the DNA strand (**Figure 4**). The faces of these rings are arranged parallel to each other with the distance of 3.4 Å (B-DNA), allowing the two adjacent bases to participate in π–π interaction. Though a π–π interaction is much weaker than a covalent bond, the sum of all π–π interactions within the double-stranded DNA molecule creates a large net stabilizing energy (17).

3.1.2 Protein folding

Protein folding is a process by which a polypeptide folds into its characteristic and functional 3D-structure to from a random coil. The π–π interactions, in addition to hydrogen bond play important role in protein folding. Burley and Petsko through a X-ray crystallographic study involving 34 high-resolution protein structures, analyzed the frequency of aromatic pairs and their interaction geometry (distance and dihedral

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angle) and concluded that around 60 % of aromatic side chains of phenylalanine, tyrosine, and tryptophan were involved in arene interactions (18). Aromatic rings separated by distances ranging from 4.5 to 7 Å and dihedral angles near 90° were found to be the most common. Pair-wise non bonded potential energy calculations indicated that 54 % of the aromatic interactions are attractive by 1-2 kcal/ mol. McGaughey, *et al.* extended the analysis to a larger sample of proteins and suggested that the parallel-displaced geometry was a preferred orientation (19). Remarkably, none of these two studies described the face-to-face geometry.

In another study of a larger database of 52 proteins, Hunter, *et al.* examined the orientational preferences of phenylalanine side chains in proteins using crystallographically derived atomic coordinates (20). They observed that these interacting pairs are found in a wide range of T-shaped (edge-to-face) and parallel-displaced (offset-stacked) arrangements, but they are scattered over a wide variety of conformational space with no strongly preferred single orientation.

Aromatic-aromatic interactions between phenylalanine side chains in peptides have been probed by the structure determination in crystals of three peptides: Boc-Val-Ala-Phe-Aib- Val-Ala-Phe-Aib-OMe, (I); Boc-Val-Ala-Phe-Aib-Val-Ala-Phe-Aib-Val-Ala-Phe-Aib-OMe, (II); Boc-Aib-Ala-Phe-Aib-Phe-Ala-Val-Aib-OMe, (III) (21). X-ray diffraction studies reveal that all three peptides adopt helical conformations in the solid state with the Phe side chains projecting outward. Inter-helix association in the crystals is promoted by Phe-Phe interactions. A total of 15 unique aromatic pairs have been characterized in the three independent crystal structures. The distances between the centroids of aromatic pair ranges from 5.11 to 6.86 Å, while the distance of closest approach of ring carbon atoms ranges from 3.27 to 4.59 Å. T-shaped and parallel-displaced arrangements of aromatic pairs were observed, in addition to several examples of inclined arrangements.

Aromatic π–π interactions not only determine biological structures but also modulate the physical properties of residues at enzyme active sites. In CuII-containing redox metalloproteins, the stacking of a CuII-coordinated His imidazole with a Phe side chain in the second coordination sphere affects the properties of the imidazole ring, such as its pKa value, the reduction potential E_m of the metal center, and the electron-transfer (ET) properties of the protein (22). Intramolecular stacking between a phenyl ring and the pyridine ring of a nicotinamide derivative increases the basicity of the pyridine N atom by about 0.5 pKa units (23).

Amyloids are extracellular or intracellular proteinaceous deposits exhibiting cross β-sheet structure. The amyloid formation leads to several neurodegenerative diseases like Alzheimer's disease, Parkinson's disease etc. The mechanism of amyloid formation is not fully understood. Analyses of a variety of short functional fragments from unrelated amyloid-forming proteins, a remarkable occurrence of aromatic residues was observed. The finding of aromatic residues in a diverse fragment raised the possibility that π–π interactions might play a significant role in the molecular recognition and self-assembly processes that lead to amyloid formation (16).

The X-ray structure of a 12-mer peptide having polypeptide sequence KFFEAAAKKFFE revealed that the polypeptides formed anti-parallel β-sheets in

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a cross-β arrangement. The anti-parallel β-sheets were zipped together by means of π–π interactions between adjacent phenylalanine rings and salt-bridges between charge pairs (glutamic acid–lysine), thus controlling and stabilizing the structure (**Figure 5**). These interactions are likely to be important in the formation and stability of other amyloid fibrils (24a). Bradford *et al.* in 2008 reported amyloid-like behavior of amphiphilic foldamers in aqueous solution (24b). These amphiphilic foldamers exhibited spectral characteristics consistent with folding in the pleated, stacked geometry characteristic of foldamers.

3.2 Arene-arene interactions in structure based drug design

The drug design based on knowledge of the three dimensional structure of the biological target (receptor) obtained through methods such as X-ray crystallography or NMR spectroscopy is known as structure-based drug design (or direct drug design). Most of the drugs produce their effect only after binding with its receptor. Most of the receptors are proteins but sometimes it may be a nucleic acid (particularly DNA). A drug generally, binds to its receptor through non-covalent interactions. The π–π interaction, in addition to H-bonding, is one of the most important non-covalent interactions involved in binding of drug with receptor as majority of the drugs are aromatic and the concentration of aromatic amino acid residue is particularly high in the cavity of receptor. Thus, proper understanding of π–π interaction is needed for structure based drug design (5a, 5g). Aricept (E2020, **1**) is a drug developed to treat symptoms of Alzheimer's disease. The X-ray crystallographic analysis of the complex of Aricept (E2020) with the enzyme acetyl cholinesterase revealed π–π, OH…π, and cation–π interactions as major forces that stabilize the association (**Figure 6**) (25).

DNA is a target for drug design to prevent cell replication. The π–π interaction plays a pivotal role in intercalation of drugs into DNA. The intercalation prevents DNA replication by inhibiting topoisomerase enzyme. The DNA intercalators contain aromatic residue which intercalate between DNA base pairs and the intercalator-DNA complex is stabilized by π–π interaction between aromatic residue of intercalator and nitrogenous bases of DNA. For example, daunomycin (**2**, **Figure 7**) is a chemotherapeutic of anthracycline family which has been used since 40 years for the treatment of specific type of leukemia (acute myeloid leukemia and acute lymphocytic leukemia). Structural study showed that it bound to the DNA preferentially via intercalation between GC base pairs in triplet sequences composed of two adjacent GC and CG followed by AT base pairs (**Figure 7**) (26a). DFT calculation showed that the complex gained 2/3 of its overall stability from π–π stacking interactions (26b).

The anti cancer drug 1843U89 (**3**) binds the active site of thymidylatesynthase and inhibits the transformation of dUMP to dTMP which is essential for the production of DNA. X-Ray structure of ternary complex revealed that the drug interacted with active site and dUMP through π–π interactions (**Figure 8**) (27).

3.3 Arene–arene interactions in organic synthesis

Arene interactions can play a significant role in organic synthesis (28). These interactions have been proposed to influence the yield and/or selectivity of different reaction types: intra- and intermolecular photochemical reactions (29), allylic oxidations (30),

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ruthenium-catalyzed transfer hydrogenations (31), titanium-catalyzed oxidations of sulfides (32) and others (33).

Asymmetric di-hydroxylation of styrene (**4**) with optically active diamine (**5**) gave corresponding *R* diol (**6**) in 83% yield and 96% ee (**Figure 9**) (34). The reason for enantioselectivity was favorable π–π interaction between the substrate and naphthyl group; exposing the *si* face to hydroxylation and shielding the *re* face for the attack.

McIntosh *et al.* found that the benzylation of naphthyl cyclohexane (**8**) gave corresponding benzylated (**9**) product with >98% de. The de was attributed to the π–π interactions which in turn established an anti-gauche orientation for the enolate dianion (**Figure 10**) (35).

Metal free Friedel-Crafts alkylation of substituted pyrrole (**10**) with cinnamaldehyde (**11**) in the presence of imidazolidinone catalyst (**12**) gave alkylated product **13 (Figure 11**) in 97% ee. It was suggested that π–shielding of the cinnamaldehyde derived iminium ion (**14**) contributed to facial selectivity (36).

The *exo*/*endo* ratio in epoxidation of compound **15** (**Figure 12**) was significantly affected by the nature of the substituent present in phenyl ring. The proportion of *endo* product (**17**) increased with the increasing electron withdrawing tendency of the substituent. This result was rationalized by considering that the transition state (**18**) for *endo* product was stabilized by π–π interaction between phenyl ring of m-CPBA and substrate, and the stability of the transition state (**18**) was further enhanced by increasing electron withdrawing substituents (37).

In asymmetric allylation of aromatic and heteroaromatic aldehydes (**19**) reaction rates were enhanced and enantioselectivity were observed for electron-deficient benzaldehydes, in comparison to phenyl or electron-donor-substituted aldehydes, when performing the reaction with a methoxynaphthalene bearing isoquinoline N-oxide catalyst, **21** (38). This suggests for a role of arene–arene interactions between the reacting aldehyde and the catalyst. Additionally, the loss of selectivity when exchanging the solvent from dichloromethane to acetonitrile supports the role of aromatic interactions in the transformation. Enantioselectivity was further enhanced using an electron-rich trimethoxyphenyl N-oxide catalyst (**Figure 13a**).

Arene–arene interactions have also been proposed to influence the stereo chemical outcome in the synthesis of aromatic propargylamines (**27**, **Figure 13b**) (39). A chiral CuI complex with a pyridine bis(oxazoline) ligand (**26**) was found to catalyze the reaction of aromatic aldehydes (**23**) with amines (**24**) and alkynes (**25**) to give propargylamines with high yield and enantio-selectivity. In the postulated transition state, the ligand complexes the substrate in a manner which enables two edge-to-face and one aromatic stacking interaction, thus blocking one face from the attack of the copper acetylide.

4. Models used for studying arene–arene interactions.

Due to the weak nature of aromatic interactions it is very difficult to study these types of interactions both experimentally and theoretically. In biological systems where other stronger interactions like classical hydrogen bonding coexists with these weak interactions it is not possible to

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study the role played by these interactions. Thus, small molecule model systems have been developed to study arene–arene interactions in simpler and more controlled environments. This has been documented in several reviews (5a, 40). The model systems are classified as either bi-molecular or uni-molecular systems, where the arene interactions are inter- or intramolecular.

4.1 Bimolecular model systems.

In these models, in order to study interactions involving two aromatic rings, a variety of structures have been designed such as cyclophanes (40, 41), molecular clefts (42), molecular tweezers (43-47), molecular clips (48) etc. which acts as hosts to different aromatic guests. In addition to these structures simple spacers have also been used connecting two aromatic residues to act as molecular tweezers for complexing aromatic chromophores. For example bisfunctional derivatives **28** (**Figure 14**) with an acetylenic linker based on caffeine (or 7-methyl theophylline) showed an increase in association constant relative to simple caffeine derivatives when complexed with planar aromatic guests such as 2,6-dihydroxy-benzoate and 1,3-dihydroxy-2-naphthoate (43).

These model systems have proven to be useful method of investigating the nature and significance of aromatic interactions as molecular recognition elements in biological and non-biological systems. As stated earlier such models (bimolecular) are well covered in Hunter's (5d) and other reviews (5e, 5h) and will not be discussed further. It is mentioned here due to its historical importance and features like flexibility in linker and a bicyclic arene core which is related to purine/theophylline or caffeine molecules of significant biological importance and many uni-molecular models which are discussed in next section are based on such arenes.

4.2 Uni-molecular/molecular model systems.

These models have both the interacting arene residues in the same molecule. These systems can, in principle, provide better control over the arene–arene geometry and can be studied in a wide range of solvent environment. Survey of the literature shows that various type of molecular models with varying degree of flexibility have been developed for the study of intramolecular π–π interactions. In this review we have tried to classify them on the basis of number of atoms between the arene moieties.

4.2.1 Models in which the two arene moieties are separated by three atom *propylene* linker.

The *trimethylene* linker and other linkers related to it in which the two arene moieties are separated by three atoms are perhaps the most common linkers used in the study of arene interactions. Here in this section and its subsection we try to present some examples from the literature where this linker is used as such or modified to suit the study of intramolecular π–π interactions. We have not strictly restricted ourselves to *trimethylene* linkers only as in some of these studies other linkers (e.g. *ethylene*, *butylene* etc.) are also used for the sake of completeness of the studies.

4.2.1.1 Fully flexible models in which the two arene moieties are separated by three atoms.

4.2.1.1.1 Leonard/propylene linker models.

One of the earliest attempts to study intramolecular rarene-arene interactions in a systematic way was reported by Browne *et*

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al. in 1968. Browne *et al.* pioneered the use of *polymethylene* linker, especially a *trimethylene* linker for studying stacking interactions among nucleic acid bases. (**29**, **Figure 15**) (49a). One of the major advantages of using flexible models based on *polymethylene* linker is that flexible systems can relax into the optimum geometry for aromatic π–π interaction and therefore provide a better opportunity to characterize the geometrical preferences caused by these interactions.

Nucleic acid bases containing purines and pyrimidines are stacked one above the other in nucleic acids with a distance of about 3.4 Å between adjacent bases. The use of *trimethylene* linker is based on the fact that it gives a desired distance of around 3.4 Å if two aromatic systems are stacked when connected by it. This linker at the same time does not dictate stacking, as in the absence of stacking interactions the molecule may remain open. They synthesized a series of twelve di-nucleotide analogs in which the bases are connected by a *trimethylene* chain, B-$(CH_2)_3$-B′, where B and B′ are 9-substituted adenine or guanine or 1-substituted cytosine, thymine or uracil residues (**Figure 16**). These compounds were studied optically at concentrations low enough to preclude formation of intermolecular complexes so that the perturbations associated with the 1:1 interaction of a pair of bases could be characterized, namely by UV spectra in aqueous solution at room temperature and by emission spectra in 1:1 ethylene-glycol-water glass in the vicinity of 77º K. In the series of B-$(CH_2)_3$-B′ the order of interaction in neutral aqueous solution is purine-purine > purine-pyrimidine > pyrimidine-pyrimidine as judged by hypochromism (decrease in integrated UV absorption intensity of B-C_n-B′ compared with equimolar B-$(CH_2)_2$-CH_3 and B′-$(CH_2)_2$-CH_3). The length of *polymethylene* chain was also changed to C_2 and C_6. In a series of 9,9′-polymethylene-bis(adenines) the order of interaction deduced from hypochromism and emission studies was n = 3 > 2 & 6. Reduced interaction at n = 2 reflected the impossibility of this molecule assuming folded, parallel-plane conformation which would allow maximal interaction as in Ad-C_3-Ad. An entropy effect was probably responsible for decreased interaction in the n = 6 compound relative to n = 3 (49a). The orientation effect studies were done by Leonard and Ito by synthesizing six different trimethylene-bis(adenine) isomers having different positions of attachment to the terminal adenines and therefore having differently oriented ring- axis permissible in their stacked conformations, in order to determine stacking interactions between two parallel adenine rings oriented at different axis angles toward each other (**Figure 17**) (49b). The percent hypochromism '*H*' for the long wavelength UV absorption band for each of these compounds has been determined by comparison of the UV spectrum of trimethylene-bis-adenine in aqueous solution with the composite spectrum of the two half molecules, the appropriate propyl-adenines. The '*% H*' follows a dependence upon the folded conformations available to the individual trimethylene-bis(adenines). Later on, Leonard (1979) reviewed such work on *trimethylene* bridged flexible diaryl compounds showing stacking interactions in solution, however, no X-ray structure of any compound with one *trimethylene* linker was mentioned (49c).

4.2.1.1.2 Miscellaneous *trimethylene* linker models.

Bis(theophyllin-8-yl)propane (**33**, **Figure 18**) is normally considered as the first *trimethylene* linker compound to show

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intramolecular folding in solid state though with extensive hydrogen bonding (50). Here it is important to mention that this compound belongs to biologically important xanthine class which is well known for face-to-face intermolecular interaction in solid by X-ray crystallography (51). It is important to mention that arene residue of this compound is similar to one mentioned in bimolecular model **28**.

Bis-thymine (**34**, **Figure 18**) is another compound which shows intramolecular folding in solid by X-ray structure though again with extensive H-bonding (52). Compound **35** (**Figure 18**) shows intramolecular interactions by UV studies (53), however, **35** (**Figure 18**) and its methyl iodide salt failed to show any intramolecular folding when studied by X-ray crystallography (54, 55). Avasthi *et al.* reported X-ray crystal structure of 1,3-bis(8-chlorotheophyllin-7-yl)propane (**36**) which is closely related to **33**, as far as arene core and linker are concerned, but does not have ionizable protons, without any intramolecular folding (**Figure 19**) (56). Moreover, **36** has no disorder in the *propylene* linker unlike **33** which has disorder in its linker. It is important to mention that in compounds **32**, **34** and **36** the *propylene* linker is between two N atoms while in **33** it is positioned between two C atoms and in **35** it is between one N and one C atom.

It is interesting to mention that finally, after about 30 years of Browne's study, compound **32** (**Figure 20**) was shown to have a folded conformation in solid state by X-ray crystallography (57).

4.2.1.1.3 *Propylene/Leonard* linker models based on pyrazolo[3,4-*d*]pyrimidine core.

Since 1995, research group at CDRI, Lucknow has been working on pyrazolo[3,4-*d*]pyrimidine (**PP**) core based poly-methylene, especially *trimethylene* linker compounds, in a systematic way, for investigating the conformation directing role of arene–arene interactions. **PP** system (**37**), which is isomeric with biologically important purine system (**38**) of DNA, the best known example of stacking interaction, was selected due to our experience in its chemistry and ease of handling (different activity of two methanesulfanyl groups, solubility, crystallization, isolation and characterization of isomeric products etc.) (58a-d). The first question we asked if **PP** core based *trimethylene* linker compound (**39**) can show intramolecular folding due to intramolecular π–π interaction in solution by ^{1}H NMR and second if yes, is it strong enough to survive in solid state? Thus, in 1995 we reported, for the first time, the use of **PP** ring system (**37**) which is isomeric with biologically significant purine (**38**) system for studying aromatic π–π interaction. All the three expected isomeric dimers (**39-41**, **Figure 21**) were easily isolated by column chromatography and characterized (59a). Formation of three isomeric compounds raised another important question of the effect of position of linker on intramolecular π–π interaction. Interestingly, only one compound (**39**) formed in about 50 % showed unusual up-field shift for 6-methanesulfanyl protons in its ^{1}H NMR indicating intramolecular *folding* (59a). The most important feature of these new fully flexible models is that they do not have any strong ionizing groups such as OH, NH, NH_2, SH etc., capable of forming classical H-bonding. This strategy was devised so that contribution of weaker arene–arene interactions towards conformation control, if any, could be determined without interference of stronger conventional H-bonding.

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This unusual *folding* was indeed due to intramolecular π–π interaction was easily confirmed by X-ray crystallographic studies (59b). The X-ray crystal structure revealed that **39** was *folded* at the centre of the *trimethylene* bridge to form an unusual *U-motif* and the two **PP** rings were nearly planar with an angle between the least-squares planes of 13.2° (ORTEP diagram shown in **Figure 22**) (59b). The centroids of two partially overlapping six member pyrimidine rings are represented as X1A and X1B and the distance between two centroids X1A and X1B is 3.71 Å which confirms that the two aromatic moieties are stacked due to intramolecular π–π interaction. The distance between two N atoms bearing linker is 3.28 Å which is much less than 4.9 Å seen in fully extended theophylline *trimethylene* linker compound (**36**). Vogtle refers to singly linked molecules that adopt π–stacked conformations as ‘‘*protophanes*’’ (59c).

Robustness of the unusual *U-motif* formed due to intramolecular stacking in **39** was further confirmed in over a dozen compounds having various substituents at 4 and 6 positions (60). For instance, intramolecular stacking between the two pyrazolo[3,4-*d*]pyrimidine moieties remain intact when 4-methylsulfanyl groups are replaced by bulky isopropxy groups (**42**, **Fig 23**), thus showing tolerance for bulkiness of the substituents (60c).

Surprisingly, the symmetrical cyano compound (**43**) is devoid of intramolecular π–π interactions and shows open conformation (**Figure 24**) (60f). This is surprising because literature studies indicate that electron withdrawing substituents increase the propensity of intramolecular stacking interactions, however, more work is needed before any conclusion can be drawn.

Surprisingly, positional isomer **40** isolated as co-product with **39**, did not show intramolecular stacking either by ^{1}H NMR data analysis in solution (59), or by X-ray crystallography (**Figure 25**) in solid (61). Thus, indicating that proper positioning of the *trimethylene* linker to achieve proper orientation of two involved arenes was crucial and mere presence of a *trimethylene* linker between two arene systems is not enough to show intramolecular stacking. Careful examination of structure of **40** revealed presence of weak intramolecular CH…N interaction (61).

Avasthi *et al.* later on reported synthesis (62) and X-ray structures of **45** (63) derived from **39** via intermediate **44** (**Figure 26**). Proton NMR data analysis of this compound like earlier compound **39** indicated intramolecular stacking (62). Formation of the unusual *U-motif* due to intramolecular stacking was also confirmed by X-ray crystallography.

Significance of *trimethylene* linker for facilitating intramolecular stacking, from crystal engineering point of view was further highlighted by the fact that **46**, a higher homolog of **45**, did not show any intramolecular stacking by ^{1}H NMR data analysis (64) and in fact an *extended* conformation was observed by X-ray crystallography (**Figure 27**).

To probe the generality of **PP** core to study arene interactions, studies were undertaken on dissymmetric **PP** core based polymethylene linker compounds. Thus, compound **47** showed *folded* conformation in solution as well as in solid state due to π–π interaction while its positional isomer **48** was open in solution (65).

Since use of the *propylene* linker for studying intramolecular stacking interactions between nucleic acid bases was

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pioneered by Leonard in 1968 and our success in utilizing it successfully in many compounds with **PP** system has prompted us to propose the name *Leonard* linker for *propylene* linker in 2005 (60c). Importance of the *propylene* linker compounds containing 4 bonds between two N atoms of bases can be easily appreciated by realizing that two adjacent bases in DNA with a noncovalent separation of about 3.4 Å involves 11 bonds of covalent linker (involving sugar and phosphate).

Recently, ^{1}H NMR, CD and X-ray crystallographic study on related **PP** core based *polymethylene* compounds (**49-50**, **Figure 29**) has been reported by another research group. These compounds were folded in solution by ^{1}H NMR and CD studies, however, X-ray crystallography of one *propylene* linker compound, **49a** showed an *open* conformation (**Figure 41**) (66). Interestingly, reasons for the absence of intramolecular stacking in **49a** were not discussed. It is important to mention that compound **49a** does not have two methanesulfanyl groups at 6-position present in our **PP** based compound **39** (**Figure 21**).

Key data of some important compounds in *folded*/*open* conformation are shown in **Table 1**. This also gives an idea as how conformation changes in response to different substituents. The first compound **36** is based on purine system, which is isomeric with **PP** system, and is used as reference compound as it is in open conformation and shows maximum distance between two N atoms bearing *propylene* linker. The **Table 1** has three *propylene* linker compounds based on **PP** core of which two are symmetrical and one is dissymmetrical. Important thing about these three compounds is the fact that distance between two N atoms connecting linker is < 4 Å which is much less than 4.91 Å of reference compound **36**.

Perusal of data in **Table 1** reveals interesting findings which are listed below.

1. Intramolecular distance between two centroids of six member pyrimidine rings of folded compounds (**39**, **42**, **45** and **47**) varies in the range of 3.69-4.10 Å.
2. The distance between two N atoms bearing *propylene* linker in *folded* compounds (**39**, **42**, **45** and **47**) varies in narrow range of 3.24-3.50 Å as compared to 4.91 Å in fully *extended*/*open* compound **36**.
3. The angle between the least square planes of arenes in *folded* compounds (**39**, **42**, **45** and **47**) is fairly constant (11.62-14.99).
4. The angle at central C of *propylene* linker also remains fairly constant in both *folded* and *open* compounds indicating absence of any strain due to π–π interaction.
5. The dramatic effect of the position of linker is demonstrated by unique pair of two isomeric compounds (**39** and **40**), symmetrical **39** is *folded* while dissymmetrical **40** is *open*.
6. Dramatic effect due to displacement of two methanesulfanyl groups at 4-position in *folded* **39** by cyano groups results in the formation of new compound **43** which is *open* due to absence of intramolecular arene interaction. Interestingly, both compounds (**39** and **43**) are *folded* in solution by ^{1}H NMR analysis.
7. Finally, all *folded* compounds show similar conformation in other words unusual *U-motif* described earlier is quite robust.

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4.2.1.1.4 *Butylidene* linker model with *three* atoms in linker.

In this section, now for the sake of continuity with our **PP** core based *propylene* linker work, we will describe our work on *butylidene* linker. Main similarity between these two linkers is that both have three atoms in linker. This linker also like *propylene* linker does not dictate intramolecular folding/stacking, thus in absence of intramolecular arene interaction molecule may remain in extended conformation. During the course of our earlier work it was realized that in many cases *propylene* linker compounds with different arene systems (e.g. purine) showing intramolecular folding by ^{1}H NMR in solution failed to give X-ray diffraction quality crystals. This forced us to look for another linker closely related to *propylene* linker and *butylidene* linker appeared to be a reasonable choice. Enforcing rigidity by putting one extra methylene unit at the central carbon of *propylene* linker reduces overall flexibility of *butylidene* linker. This decrease in total number of conformations (as compared to the fully flexible *propylene* linker) will hopefully facilitate the crystallization process. Thus, the first compound synthesized with *butylidene* linker was *butylidene* linker analog (**51**, **Figure 30**) of the first *propylene* linker dimer (**39**) of **PP**. The solid state conformation of the new *butylidene* linker compound **50** shows that important features such as orientation and distances between the two rings are quite comparable with that of compound **39** (67). Most significant feature of this linker is the demonstration of folded conformation for isomeric purine *butylidene* linker compound (**52**). Our earlier efforts in isolating corresponding purine compound with *propylene* linker were not successful (68).

In conclusion, the scope of **PP** core for studying arene interactions in flexible linker compounds has been considerably increased by providing an alternative for truly flexible *propylene* linker with less mobile *butylidene* linker.

4.2.1.1.5 Itahara model.

Similar *polymethylene* linkers have been utilized by Itahara to investigate stacking interactions between various purine, pyrimidine and xanthine bases in solution by ^{1}H NMR. Some of the systems (**53-57**, **Figure 31**) studied by Itahara are shown below (69, 70, 71). The N^6-methylation was found to increase the population of intermolecular aggregates in the buffer solution at pD 7.0 and had an additive effect on aggregation which was interpreted due to hydrophobic effect of the N^6-methyl groups. The aggregation of **53a** and **53b (Figure 31**) was found to depend on the length of the *polymethylene* chains (71). A relationship between the chemical shifts of adenine and xanthine ring protons of 7-[-(6-aminopurin-9-yl)alkyl]-1,3-dimethylxanthines (**56**) and the number of carbons (n = 2-10) in their *polymethylene* chains has been compared with that of 1-[-(6-aminopurin-9-yl)alkyl]-3,7-dimethylxanthines (**57**) in the buffer solutions at pD 7.0, 1.0 and 13.0 and in organic solvents. The relationship of **56** is clearly distinct from that of **57**. The concentration dependence and the effects of temperature on the chemical shifts of **56** and **57** have also been investigated. While the upfield shifts of the ring protons of **56** and **57** in the buffer solutions at pD 7.0 and 13.0 are explained in terms of stacking interactions between adenine and xanthine rings.

4.2.1.1.6 Gellman model.

Hydrophobic effect has a significant influence on aromatic interactions since

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water molecules prefer to interact among themselves rather than with aromatic surfaces. Newcomb and Gellman carried out a series of experiments to investigate this effect for two covalently tethered aromatic groups. A comparison of the stacking tendencies of phenyl, naphthyl and heterocyclic (adenine) rings in aqueous solution was carried out using ^{1}H NMR spectroscopy to study the conformational properties of carboxylate derivatives **58**-**65** (**Figure 32**) (72). The results are most consistent with the alignment of partial positive and negative charges on neighboring groups as the main force influencing the stacking interactions.

Naphthyl units connected by a flexible linker were prepared to further probe hydrophobic collapse. The three atom linker previously used forced a near parallel arrangement, but the four atom linker in **64** allowed different approaches of the aromatic moieties. An X-ray crystal structure of **64** showed an edge-to-face arrangement of the naphthyl rings and ^{1}H NMR experiments showed that the naphthyl rings are in close proximity in aqueous solution. The chemical shift differences between **64** and **65** in benzene were very similar to those in water, which suggests that the hydrophobic effect have little influence on the folding of this molecule. An excellent review has appeared recently, where along with this some other models are discussed in detail (72c).

4.2.1.1.7 Kollman model.

To understand the driving forces of aromatic stacking interactions in water, Pang *et al.* (1999) performed conformational searches, molecular dynamics simulations, potential of mean force (PMF) and free energy perturbation (FEP) calculations, syntheses and ^{1}H NMR studies on sodium 2,2-bis(indol-1-yl-methyl)acetate (**66**) (73). The conformational searches on **66** revealed that the *isobutyric acid* linker allowed the molecule to adopt the tilted T-shaped stacked, off-center stacked, face-to-face stacked, and non-stacked conformations in a vacuum (**Figure 33**). The PMF and FEP calculations suggested that the most thermodynamically stable conformers in water were the tilted T-shaped stacked and non-stacked conformers. The ^{1}H NMR result of **65** in D_2O and DMSO-d_6 at 22 °C revealed that both the tilted T-shaped stacked and nonstacked conformers were populated in D_2O and DMSO-d_6. Furthermore, population of the tilted T-shaped stacked conformation was greater in D_2O than in DMSO-d_6. These results, therefore, suggested that the hydrophobic effect played an important role in the stacking interaction of **66** in water. In this study it was concluded that indole was not a good system for studying intramolecular arene interaction.

4.2.1.2 Semi-rigid models in which the two arene moieties are separated by *three* atoms.

In addition to these flexible three carbon (C3) linkers other models having semi rigid scaffolds have been developed to study interactions involving aromatic rings in which the flexibility of linker has been curtailed which significantly decreases the total number of conformational structures thereby facilitating the two aromatic units to stay close to each other for a longer period of time. In this context, two models have been discussed i.e., the cyclohexane model and the *butylidene* model. The cyclohexane model developed by Williams *et al.*, has the *trimethylene* linker unit as a part of the cyclohexane ring.

4.2.1.2.1 Williams model based on cyclohexyl scaffold.

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Williams *et al.* undertook a computational study of the substituted *cis*-1,3-diphenylcyclohexanes (**67a-c**) (**Figure 34**) to suggest novel experimental models for the investigation of arene–arene interactions (74). Energy minima were located for diaxial conformers (a) in which aryl rings are coplanar and π–stacked and (b) in which aryl rings adopt an edge-to-face or intermediate conformation. The average distance (centre to centre) of 4.4 Å, outside the van der Waals contact distance of 3.4 Å and the minimum inter-ring distance of 3.5 Å was obtained for all diaxial conformers considered in this study. In all cases the results (a) showed good agreement with literature data on related experiments and (b) demonstrated the dominance of arene-arene electrostatic contributions to conformational energy over the negligible orbital mixing and charge transfer interactions.

4.2.1.3 Rigid models in which the two arene moieties are separated by *three* atoms of naphthyl scaffold.

In addition to these flexible and semi rigid scaffolds, some rigid scaffolds have also been developed to study interactions involving aromatic rings in which the trimethylene linker is a part of a rigid structure such as an aromatic ring. The following two model illustrates this point.

4.2.1.3.1 Cozzi model with mono cyclic arenes.

Cozzi *et al.* in 1992 developed 1,8-diaryl naphthalene based model **68** (**Figure 35a**) for studying the nature of arene–arene interaction (75a). Semi-empirical calculation showed that the phenyl rings were perpendicular to naphthalene. At room temperature all the compounds showed distinct signals in ^{1}H NMR for o/o′, m/m′ which was consistent with the restricted rotation of the phenyl groups. From the line shape analysis using different temperature NMR technique the barrier to rotation for the phenyl ring was determined. Barrier to rotation was found to increase with the increasing electron withdrawing tendency of the substituents. From this study they concluded that the nature of arene–arene interaction between two phenyl rings was electrostatic type and not charge-transfer type. The main drawback of this model was that the distance between point of attachment of two phenyl rings to naphthalene system was quite small (2.8 Å) that due to steric effect they have no option but to adopt a stacked conformation. To overcome this draw back the same group after 16 years synthesized 1,8-diaryl biphenylenes (**69** and **70**) in which the distance between two aryl rings was in the range of the distance required for arene interaction (**Figure 35b**). Barrier to rotation was found to increase with the increasing electron withdrawing tendency of the substituents in **69** while opposite result was found in **70** (75b).

4.2.1.3.2 Tumambac model bi- and tricyclic arenes.

Tumambac and Wolf have reported the preparation of highly congested 1,8-diacridylnaphthalene **71** for metal-ion-selective and enantioselective sensing using fluorescence spectroscopy (76). As a consequence of the bulkiness of the co-facial acridyl moieties, no sign of rotation about the chiral acridylnaphthalene axis of **71**, i.e., *syn*/*anti*-interconversion, has been observed even at very high temperature. Incorporation of significantly smaller substituents such as pyridyl or quinolyl rings into the peri-positions of naphthalene affords diheteroarylnaphthalenes **72** exhibiting a wide range of conformational stability.

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4.2.2 Models in which the two arene moieties are separated by flexible linker of *four* atoms.

Chloroquine is a well known drug for treatment of malaria and its mode of action involves binding to the nucleic acids. It is believed that arene interaction between the aromatic system of chloroquine and the nucleotide bases plays an important role in this process. Several models involving quinoline nucleus for studying stacking interactions between the aminoquinoline ring of the antimalarial chloroquine and the purine bases have been synthesized by Bolte *et al*. (77) in which the quinoline linked to the purine base (adenine and guanine) by a trimethylene chain (**Fig 37**, **73-77**). It is reported in these studies that adenine and guanine exhibit equal affinity for the quinoline nucleus as reflected by very close hypochromism values observed for the two models at all temperatures studied. In another study Bolte *et al.* showed that when chloro is removed (**74**) or is substituted by bromo (**75**) the stacking propensity with the purine base decreases (77d). This indicates towards the special role of chloro substituent. Nucleic acid base thymine linked by a *trimethylene* chain have been shown to interact with proflavine face-to-face in dilute aqueous solution (**Fig. 37**, **78**) (78). PUVA therapy, a photochemotherapy employing psoralen and UVA, has been used for a long time in the treatment of a number of skin disorders, such as psoriases, vitiligo, mycosis fungoides, chronic leukemia, and so on. In this, formation of an intercalated complex between psoralens and DNA is an important step, which markedly affects the successive covalent photobinding to the macromolecule. In order to investigate these processes, some of synthetic models related to DNA-intercalating molecules were prepared. Decout *et al.* prepared a series of psoralen-O-$(CH_2)_3$-adenine (**79**, **Figure 38**) and 8-methoxy-psoralenadenine (**80**, **Figure 38**) and showed that *polymethylene* bridges allow intramolecular ring-ring stacking between the two aromatic units (79). The model **75** showed the highest value of hypochromism indicating most efficient ring-ring stacking between the two aromatic units linked by four atoms. Compound **80b** showed much stronger fluorescence than all other compounds **80a**, **80c-d** indicating that the complexes adopt different preferred geometries according to chain length. No X-ray crystallographic studies were reported on these compounds.

4.2.3 Models in which the two arene moieties are separated by semi rigid linker having *six*/*seven* atoms.

4.2.3.1 Model based on triptycene.

Gung *et al.* prepared a series of triptycene-derived compounds for studying arene–arene interactions in the parallel-displaced orientation (**Figure 39a** and **39b**) (80a). Here the two interacting arene moieties are essentially separated by six atoms of which three atoms are part of a special tetracyclic scaffold (triptycene) which brings the interacting arene moieties close to each other facilitating the arene interaction. The extent of arene–arene interaction was determined by measuring *syn*/*anti* ratio using low temperature ^{1}H NMR study. This study revealed that the interactions between the arenes bearing electron–donating groups (EDG) **81** (**Figure 39a**) were either negligible or slightly repulsive, while the interactions between arenes bearing electron-withdrawing groups (EWG) were attractive. Intermediate free energy values were obtained for those compounds bearing arenes with one EDG and one EWG. For studying the stacking interactions between a benzene ring and a heterocyclic ring (pyridine or pyrimidine) Gung *et al.* used a

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series of similar triptycene-derived scaffolds **82** (**Figure 39b**) (80b).

Compared to the corresponding control compounds where a benzene ring was in the position of the heterocycle, higher attractive interactions were observed as indicated by the higher *syn/anti* ratios. The greatest attractive interactions were observed between a pyrimidine ring and *N*,*N*-dimethylamino-benzene, consistent with a predominant donor–acceptor interaction.

4.2.3.2 Molecular balance model.

Carroll *et al.* developed molecular balance **83-85** (**Figure 40**) to study the face-to-face arene–arene interactions (81). In this model the two arene moieties are effectively separated by *seven* atoms. These *seven* atoms are part of a special scaffold which allows limited flexibility to the interacting arene moieties and thus allowing them to interact more favorably. Thus arene interactions could be observed for benzenoid compounds which normally are known to exist in open conformation in fully flexible polymethylene linkers (82). The balance adopted distinct *folded* and *unfolded* conformations due to restricted rotation about a C_{aryl}-N_{imide} bond. Molecular modeling studies predicted that the benzene ring of the phenyl ether arm was perfectly positioned in the *folded*-conformer to form an effective offset face-to-face interaction with the arene shelf and the phenyl ether arm could not adopt an edge-to-face geometry in the *folded*-conformer because it was held too closely. The strength of the face-to-face π–π interaction was assessed by measuring the ratio of *folded* to *unfolded* conformers by ^{1}H NMR. The measured *folded*/*unfolded* ratios of balances **83-85** in $CDCl_3$ showed a strong correlation between the size of the arene shelf, which is consistent with the presence of an arene–arene interaction. Balances **83** and **84** with the arene of larger surface area displayed higher degrees of folding with *folded/unfolded* ratios of 0.56 and 0.42 respectively. The smaller benzene shelf of balance **85** is too small to form π–π interactions with the phenyl arm and thus had a significantly lower *folded/unfolded* ratio of 0.11.

4.2.3.3 Model based on pyrene with flexible linkers of more than *seven* atoms.

Zachariasse *et al*. reported synthesis of a large series of α,ω-bis(2-pyrenyl-carboxy)alkanes (**86a-p**, **Figure 41**) (83). Here, the two interacting arene moieties are separated by *seven* or more atoms. These atoms form a part of a flexible chain. Evidence for intramolecular pyrene dimers was obtained by ^{1}H NMR spectra showing shielding of all the aromatic protons with respect to model; 2-substituted pyrene. The dimers (**86g-p**, **Figure 41**) showed a symmetrical sandwich structure, whereas, the dimers (**86a-f**, **Figure 41**) attributed geometry in which the pyrenyl moieties were shifted along their long axis. Intramolecular aromatic π–π stacking was also reported in closely related compound, **87 (Figure 41)** (84).

4.2.3.4 Model based on electron donor–acceptor concept with flexible linker of *seven* atoms

Herrandon *et al.* investigated intramolecular interactions between different aromatic groups in a series of di-esters consisting of two aromatic groups linked by a *2-methyl-1,3-propanedioxy* spacer by ^{1}H NMR study (**Figure 42**) (85). This spacer permitted *U-shaped* conformations which placed the two terminal aromatic groups close together, parallel in a face-to-face arrangement. For the symmetrical di-esters **88** and **89** neither the chemical shifts of the aromatic group

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protons nor the vicinal coupling constants measured in the spacer provided any evidence for a high fraction of *U-shaped* conformers. In both the cases, the conformational distribution of the spacer was similar to that found for **93**, indicating that the planar aromatic groups in **88** and **89** experienced no significant mutual attractive interactions.

In contrast, substantial up-field shifts were observed in the resonance frequencies of all aromatic protons in the anthracenyl and 3,5-dinitrophenyl groups of the unsymmetrical di-ester **90** relative to those for the aromatic protons of the respective monoesters **91**, **92** and symmetrical di-esters **88** and **89**. Analysis of the temperature dependence of the vicinal coupling constants indicated highly populated *gauche* states of the two central C-C bonds of the spacer chain, consistent with a total fraction of U-shaped conformers of about 80% at ambient temperature. From the analysis of NOE experiments dinitrophenyl ring in **90** was found to be centered almost directly above the central ring of the anthracenyl group with a distance of 3.1 Å between the central point of the dinitrophenyl ring and the anthracenyl plane, and an angle of about 20° between the para axes of the two aromatic groups. The stabilization of the *U-shaped* conformers in **90** was rationalized in terms of quadrupole interactions between the two aromatic groups. The quadrupole moments associated with the two aromatic groups in **90** had opposite sign, resulting in a significant attractive interaction when the groups were oriented face-to-face. For the symmetrical di-esters (**88** and **89**) the interacting aromatic groups had identical quadrupole moments and the interaction was repulsive in the face-to-face arrangement.

4.2.3.5 Chong model.

Recently, Chong *et al*. developed a molecular balance for studying face-to-face arene–arene interactions in solution and solid state (**Figure 43**) (86). The balance had a large central 1,4,5,8-naphthalene diimide surface that formed intramolecular arene–arene interactions with two pendent arms. The molecular balance could exist in *syn* and *anti* forms. In *syn* form only one arm was involved in stacking with one surface of 1,4,5,8-naphthalene diimide while in *anti* form both the arms were involved. *Syn* and *anti* forms were not readily inter-convertible in solution and their concentration can be determined by ^{1}H NMR. Thus, *anti/syn* ratio was taken as a criterion for measuring the strength of arene–arene interactions. *Anti/syn* ratio was found to increase with the increasing surface area of Ar-group, indicating that the strength of arene–arene interactions increased with the increasing surface area of the interacting aromatic groups.

4.2.4 *Ethylene* linker models.

After demonstrating the potential of **PP** core in *propylene* and *butylidene* linker models we decided to apply **PP** system to *ethylene* linker and to check if system is good enough to show *syn* conformation in *ethylene* linker models. In very recent communication, we showed that weak arene interactions are capable of controlling conformation even in dissymmetrical 1,2-diarylethanes in which one arene residue is based on **PP** core, both in solution and in the solid state. Thus, first *ethylene* linker compound (**98**) was prepared by the reaction of 1-bromoethyl-4,6-dimethylsulfanyl-pyrazolo[3,4-*d*]pyrimidine with commercial phthalazinone. The compound, **98** was isolated as only product and no O-alkylated product was obtained. ^{1}H NMR of the compound, **98** showed intramolecular *folding* which was also confirmed by X-ray crystallography (**Figure**

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44) (87). It is important to mention that except presence of intramolecular π–π interaction there is no other intramolecular interaction like CH…π or S…arene interaction. The distance between centroids of two six member rings is 4.28 Å which is slightly more than uppermost value of the range (3.71-4.10 Å, **Table 1**) seen in *propylene* linker models. Furthermore, the distance between two N atoms bearing linker is 2.95 Å which is less than sum of the van der Waals radii of two involved N atoms.

5. Conclusion and future developments:

Present review gives an account of what has been done in the area of development of molecular models for better understanding of arene interaction during last two decades, highlighting again that nature of the arene interaction is indeed quite complex. The major problem is that of transferability i.e. understanding gained from one model cannot be easily applied to new model. While solution studies on different conformations (e.g. *folded*/*open*) by spectroscopic techniques give lot of information from molecular recognition point of view, solid state studies on different conformations (e.g. *folded*/*open*) give precise geometry and is important not only from molecular recognition point of view but must for crystal engineering point of view. Even though large amount of research has been done on arene interaction in last two decades our ability to use them effectively in a predictable way in a new situation remains unsatisfactory. Predictable use of arene interactions is highly desirable for molecular recognition, crystal engineering, drug-development and protein folding studies. Current limitations in understanding of arene interactions clearly shows that much more research needs to be done in future for their fruitful utilization in times to come. Development of more unbiased molecular models looks to be one promising area for future research. Size and electronic effects of different substituents on intramolecular interactions has both expected and un-expected outcome. When a substituent is not involved in strong intermolecular interaction its effect on intramolecular conformation is easy to predict, however, in other situations when substituent can get involved in strong intermolecular interactions, its effect on intramolecular conformation due to arene interaction becomes unpredictable. Since 1,2-diphenylethane, 1,3-diphenylpropane and 1,4-diphenylbutane are open in the solid state, in our opinion, the phenyl moiety is not a good system for studying intramolecular arene interactions in such unbiased flexible models (87). Similarly, models based on semi-rigid and rigid scaffolds may give somewhat biased information as compared to fully flexible *propylene* linker models. Comparison of the results on same arene core with *propylene*, *butylidene* and *ethylene* linker models, as exemplified in this review with **PP** core, may give valuable insights for better understanding of subtle effects of different substituents on the arene interactions. Our work with unbiased linkers also opens new avenue for conformational control due to arene interactions in flexible compounds having two heterocycles (same/different).

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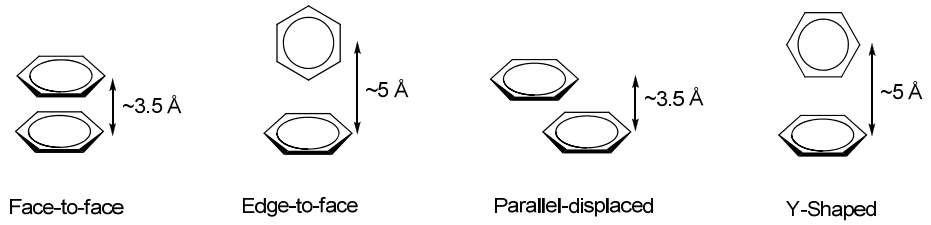

Figure 1. Four types of π–π interaction geometries (4, 5b, 5c)

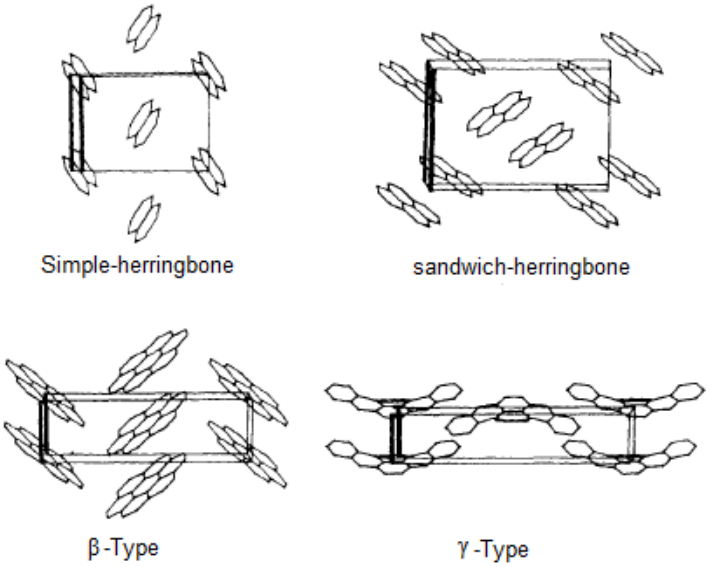

Figure 2. Four basic packing types for aromatic compounds (11)

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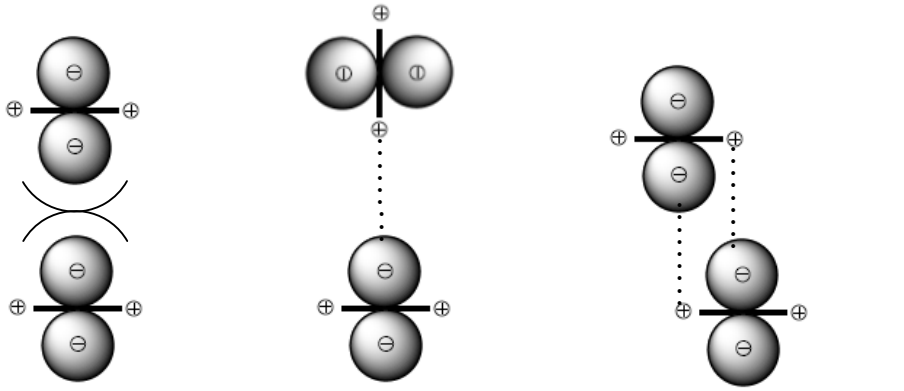

Figure 3. Electrostatic interaction between σ and π-systems of aromatic molecules (4)

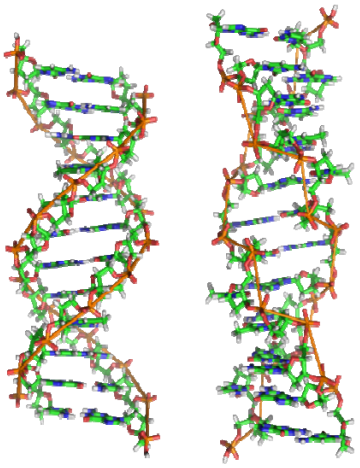

Figure 4. Base pair stacking in B and Z forms of DNA

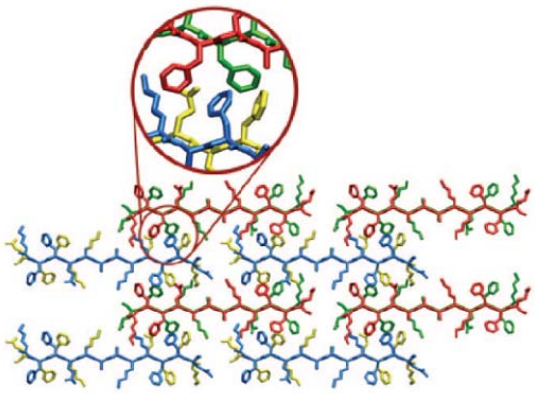

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Figure 5. Crystal packing of 12-mer amyloid showing importance of π–π staking in stabilizing crystal structure (24a)

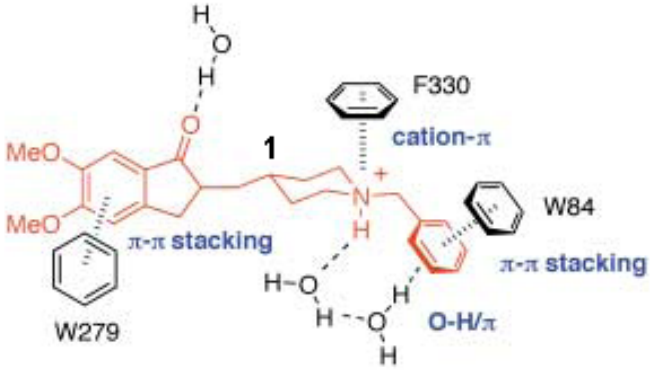

Figure 6. Binding mode of the anti-Alzheimer drug E2020 within the active site of acetyl cholinesterase from Torpedo californica (25)

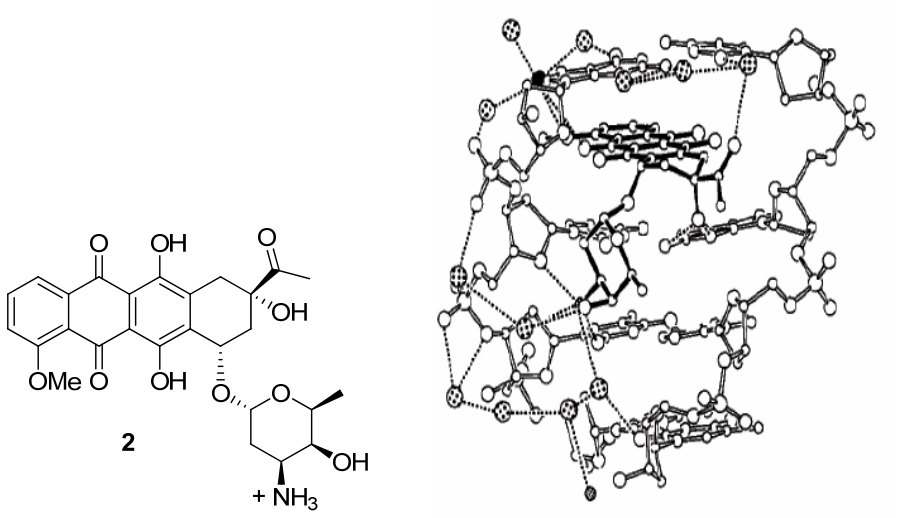

Figure 7. Daunomycin (**2**) and Daunomycin-DNA complex d (CGATGC) (26a)

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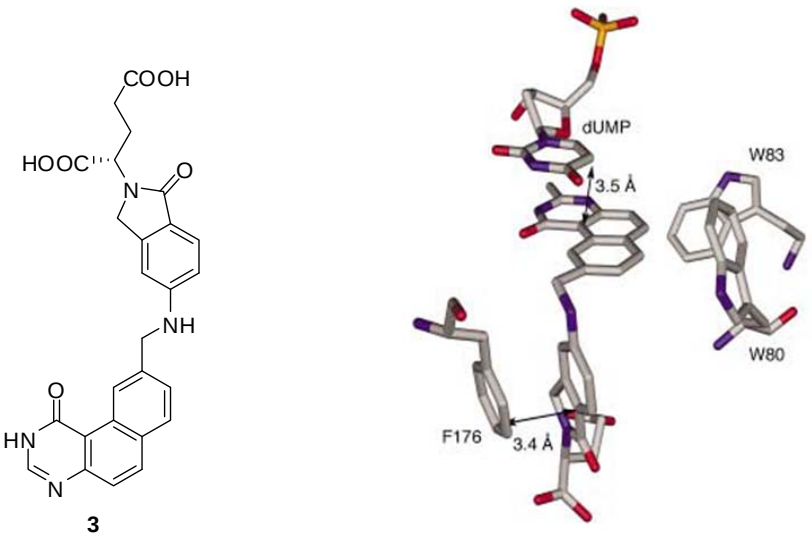

Figure 8. Arene–arene Interaction between dUMP and the anticancer drug 1843U89 bound at the active site of thymidylate Synthase (27)

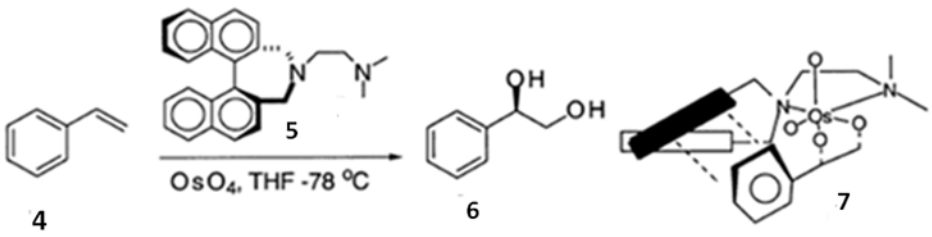

Figure 9. Enatioselective dihydroxylation of styrene (34)

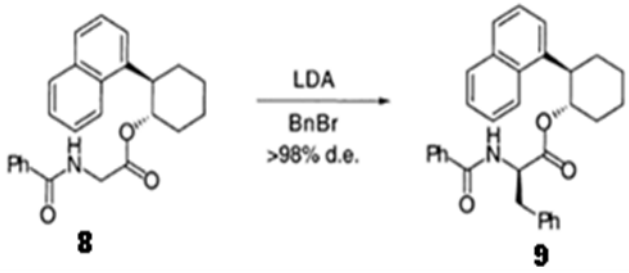

Figure 10. Diestereoselective benzylation (35)

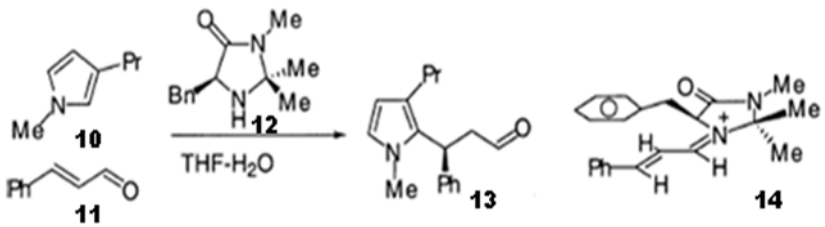

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Figure 11. Enantioselective metal free Friedel-Crafts alkylation of substituted pyrrole (36)

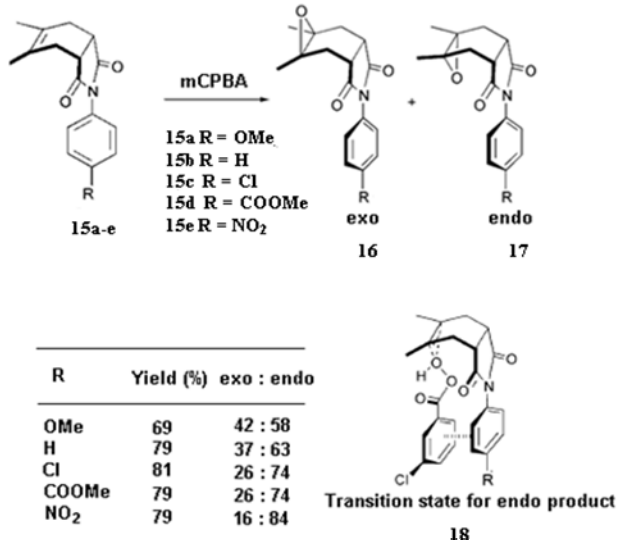

Figure 12. Stereoselective epoxidation (37)

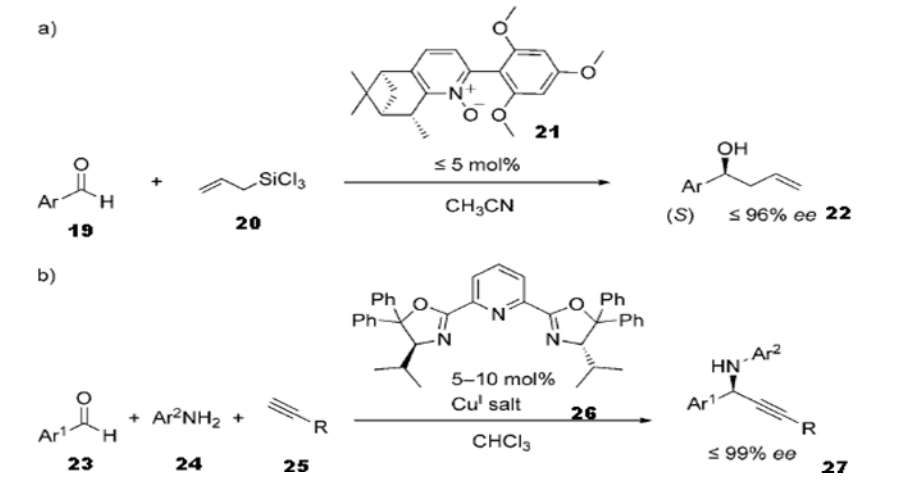

Figure 13. (a) allylation of aromatic aldehydes with chiral pyridine- type N-oxides (38)
(b) for the three-component synthesis of propargylamines (39)

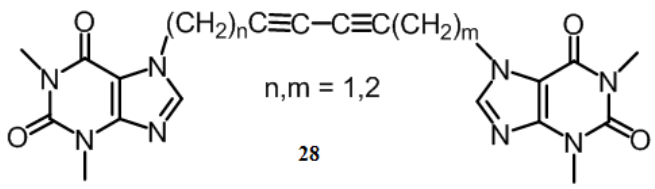

Figure 14. Whitlock's molecular tweezers (43)

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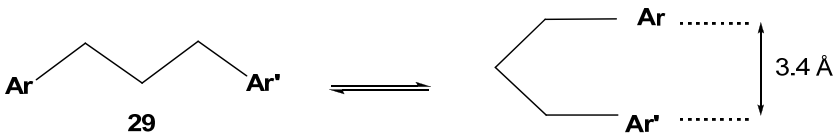

Open conformation Closed conformation

Where Ar and Ar′ are 9-substituted adenine or guanine or 1-substituted cytosine, thymine or uracil residues

Figure 15. Browne *et al.* model

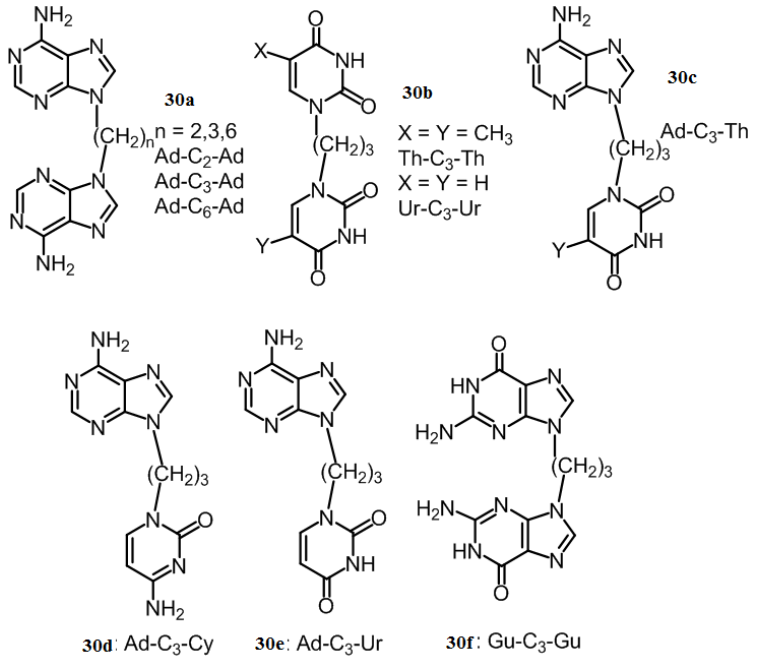

Figure 16. Dinucleotide analogs connected by *polymethylene*/*trimethylene* linker

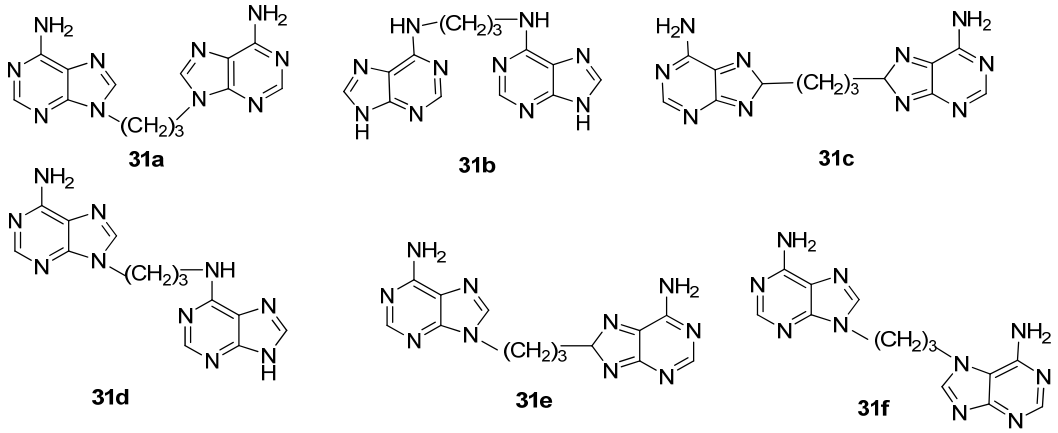

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Figure 17. Dimers of adenine linked through different positions to study orientation effect on stacking.

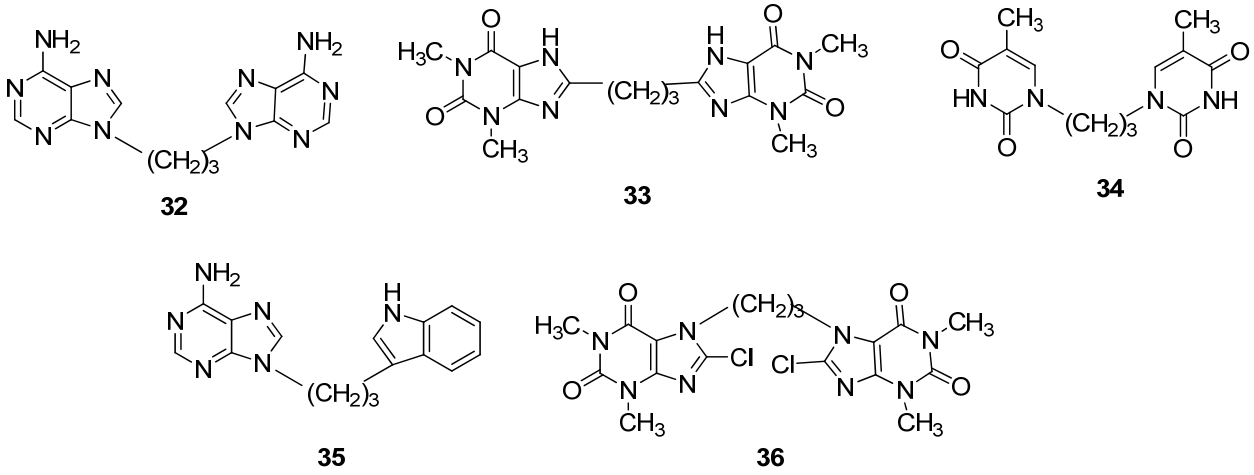

Figure 18. Different *trimethylene* linker compounds in the literature.

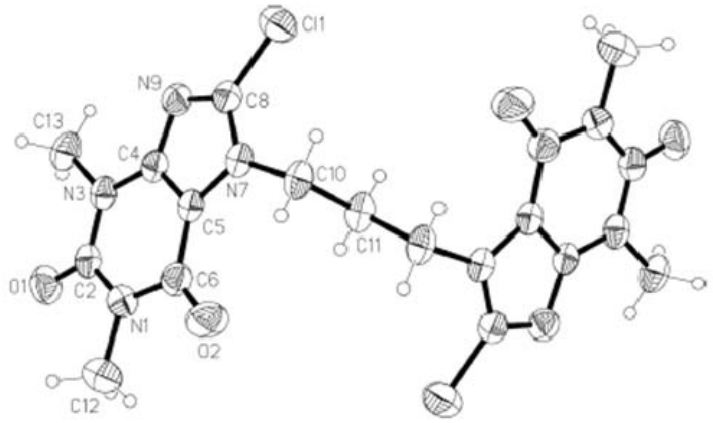

Figure 19. ORTEP diagram of **36** showing open conformation (56)

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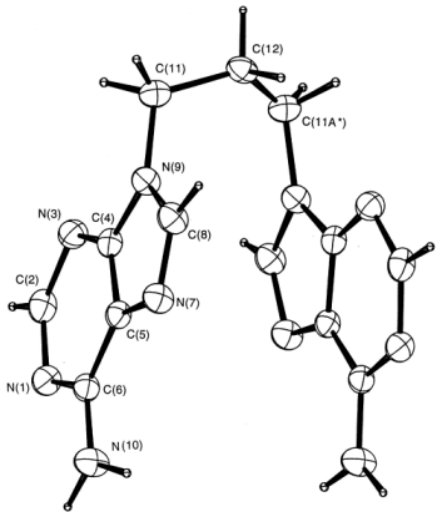

Figure 20. ORTEP diagram of **32** (57)

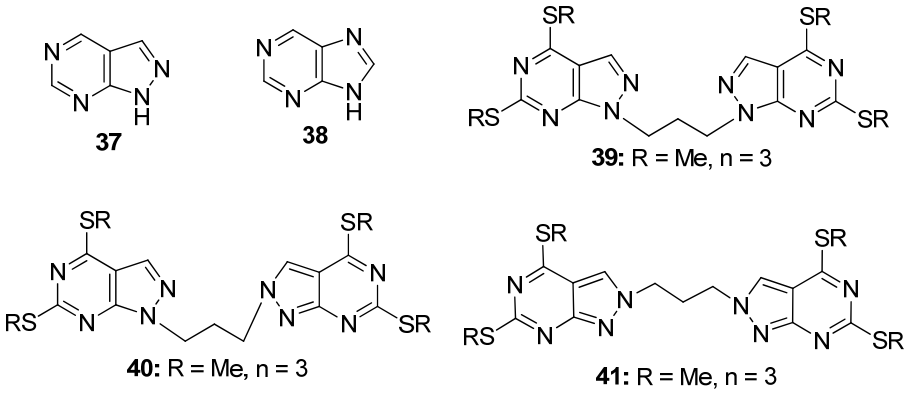

Figure 21. Pyrazolo[3,4-*d*]pyrimidine based *trimethylene* linker compounds

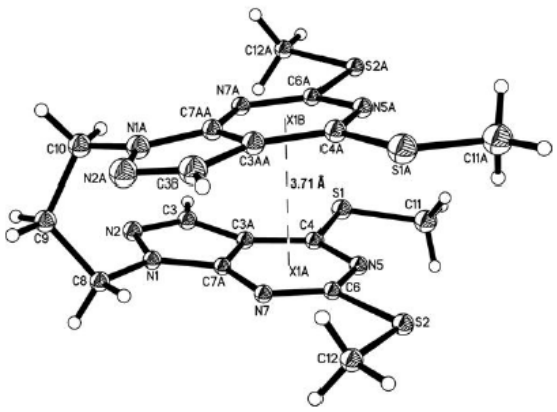

Figure 22. ORTEP diagram of **39** with atomic numbering scheme (59b)

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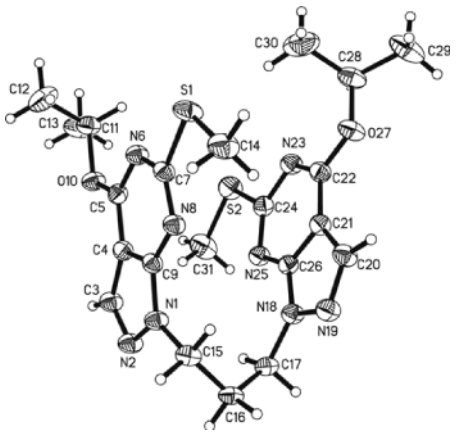

Figure 23. ORTEP diagram of **42** (at 30% probability level) with atomic labeling scheme (60c)

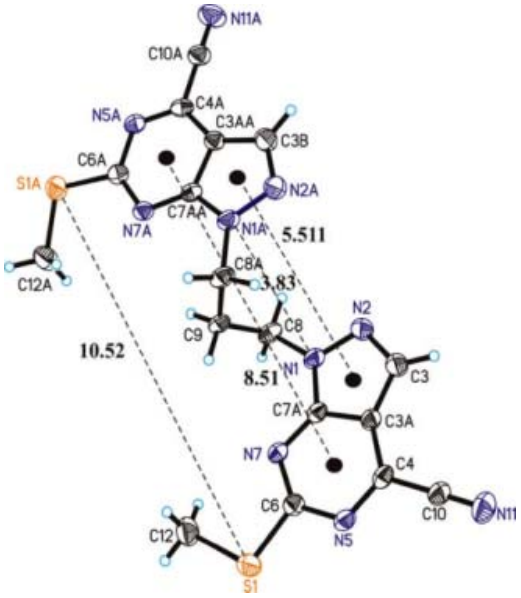

Figure 24: ORTEP diagram of **43** with atomic numbering scheme (60f).

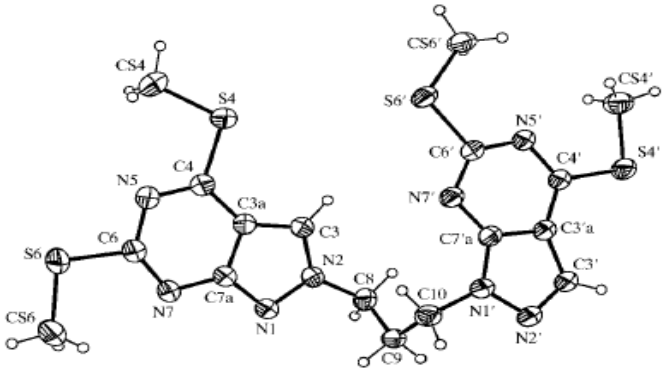

Figure 25. ORTEP diagram of **40** showing open conformation (61)

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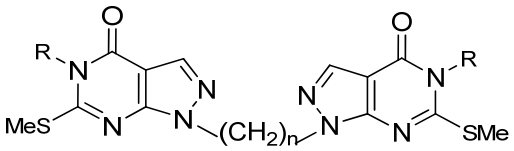


44: R = H, n = 3
45: R = Me, n = 3
46: R = Me, n = 4

Figure 26. Pyrazolo[3,4-*d*]pyrimidone compounds derived from **39**

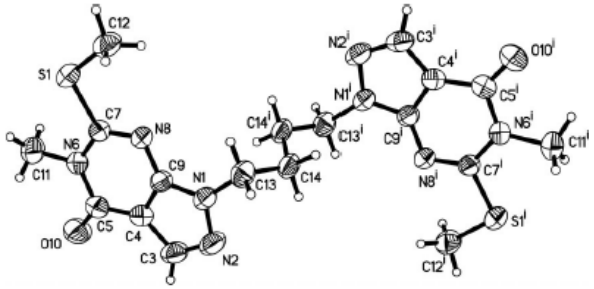
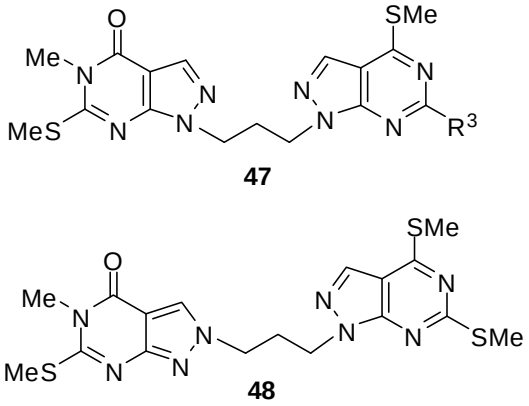


Figure 27. Displacement ellipsoid plot (50% probability), showing the molecular structure of **46** with the atomic labeling scheme (64)



47

48

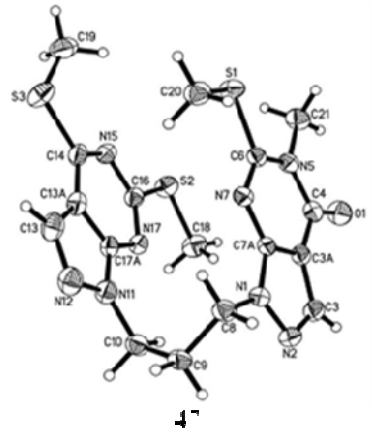


Figure 28. ORTEP Diagram of 47 (at 30% probability level) with atomic labeling scheme (65).

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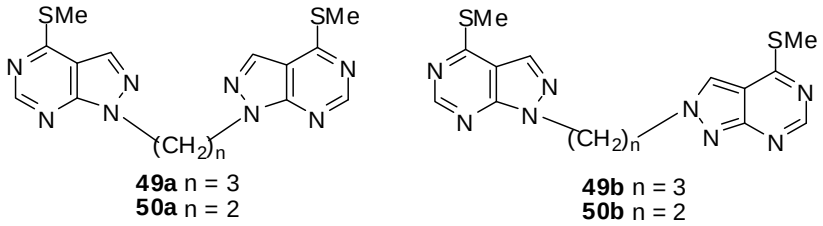

Figure 29. 4-Methylsulfany-lpyrazolo[3,4-*d*]pyrimidine based *ethylene* and *propylene* linker compounds (66).

Table 1. Important geometrical data obtained from X-ray crystallographic studies of *propylene* linker compounds based on pyrazolo[3,4-*d*]pyrimidine and isomeric purine systems.

Compound No.	Distance between two N atoms connecting linker (Å)	Intramolecular π-π stacking distance between two centroids of pyrimidine ring (Å)	Angle between the least square planes (°)	Angle at central C of *propylene* linker (°)	Folded or open	Reference
36	4.91	8.60	78.51	112.3	Open	56
39	**3.28**	3.71	13.2	114.11	**Folded**	59
40	3.96	7.29	9.3	114.87	Open	61
42	**3.24**	3.69	14.99	114.43	**Folded**	60c
43	3.88	8.51	0.36	115.02	Open	60f
45	**3.35**	3.77	12.48	115.16	**Folded**	63
47	**3.50**	4.10	11.62	114.87	**Folded**	65
49a	3.69	8.32	3.78	115.60	Open	66

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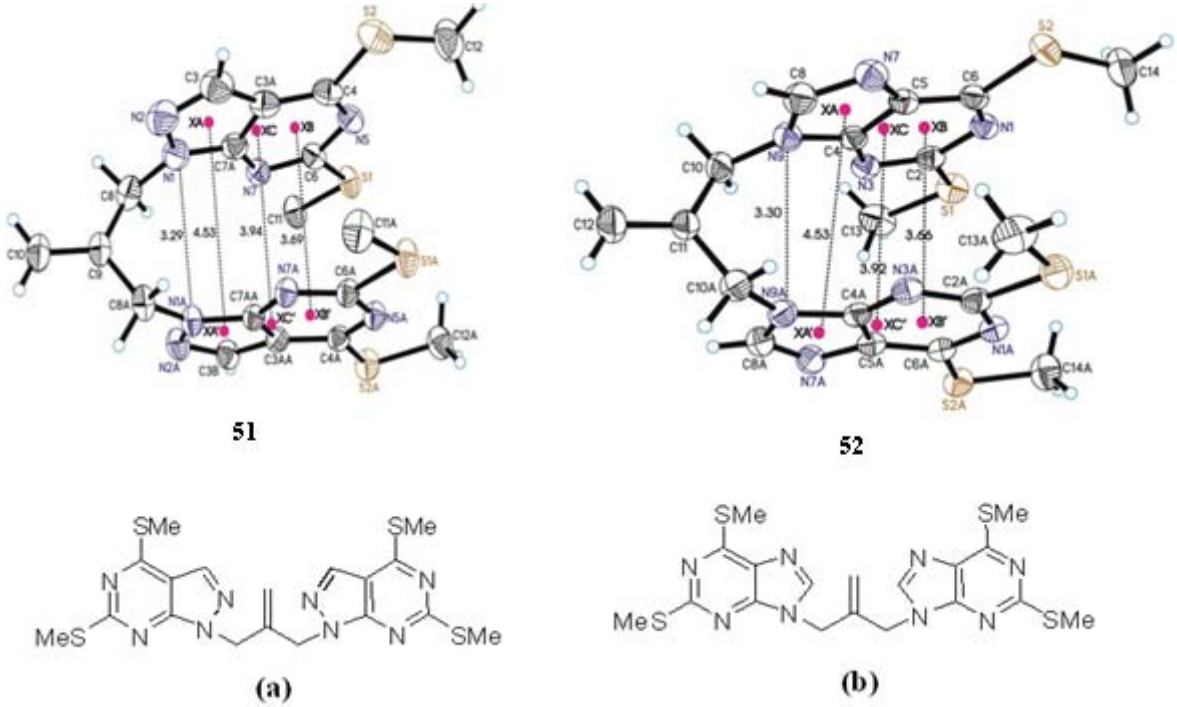

Figure 30. (a) Pyrazolo[3,4-*d*]pyrimidine based *butylidene* linker compound, **51**; (b) Purine based *butylidene* linker compound **52** (67)

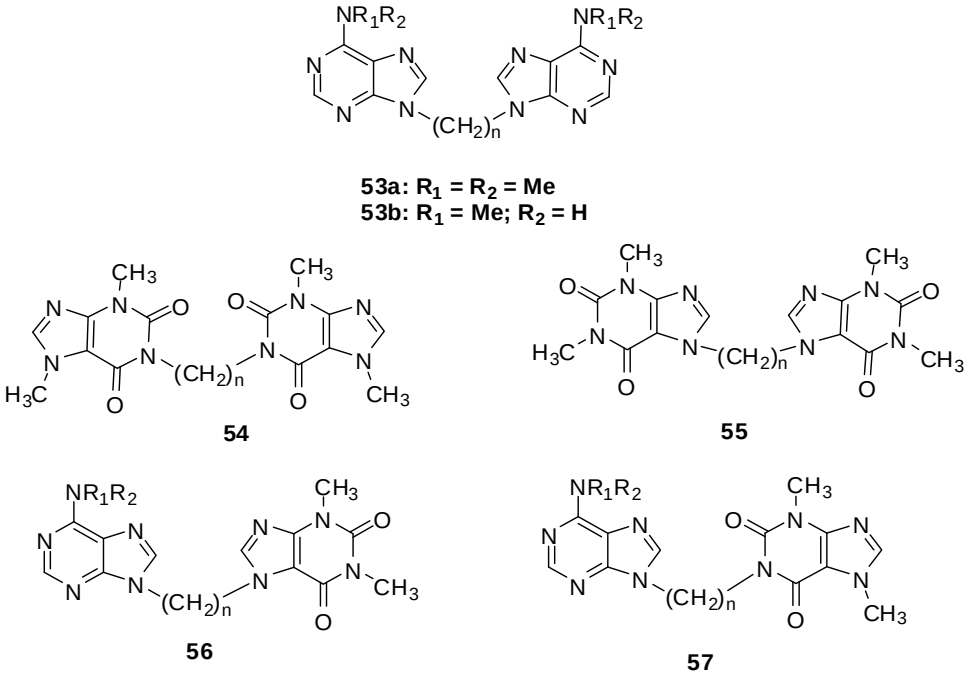

Figure 31. *Polymethylene* linker compounds of purine and xanthine bases used by Itahara

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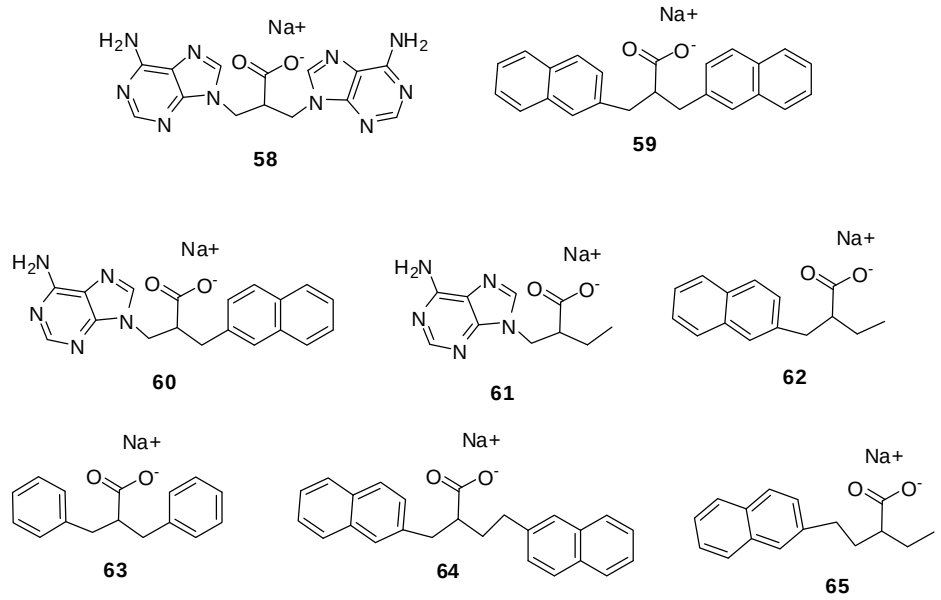

Figure 32. Compounds used to probe intramolecular aromatic interactions in water (72)

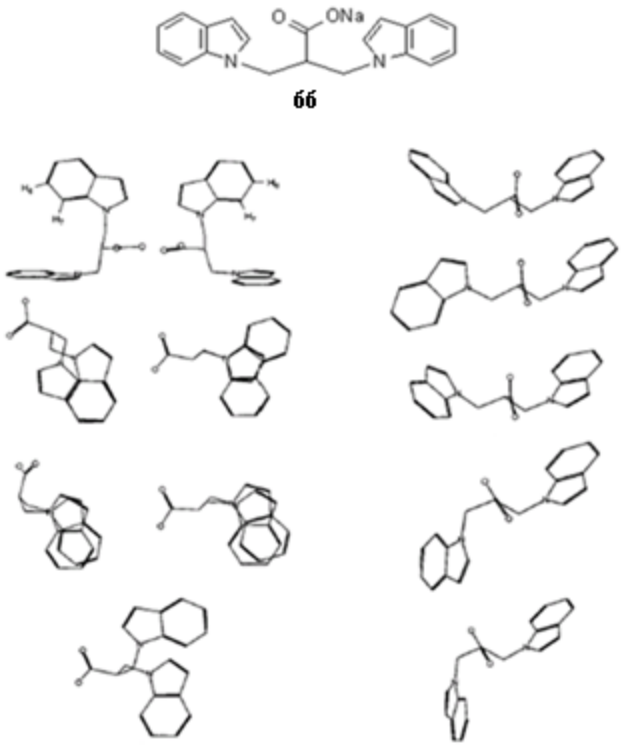

Figure 33. Conformations of **66** identified from the conformational search (73)

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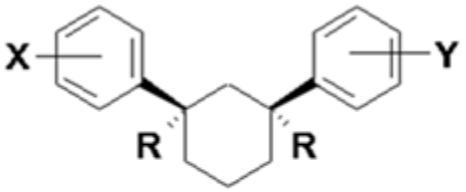
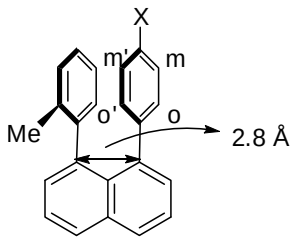


67a: R = H; X,Y = p-(H, NO_2, NH_2, etc.)
67b: R = H; X,Y = m- (H, NO_2, NH_2, etc.)
67c: R = Me; X,Y = p-(H, NO_2, NH_2, etc.)

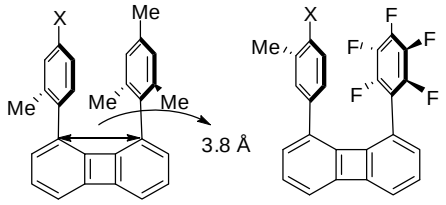
Figure 34. Cyclohexyl based models



68

X = H, Me, OMe, Cl, NO_2, COOMe

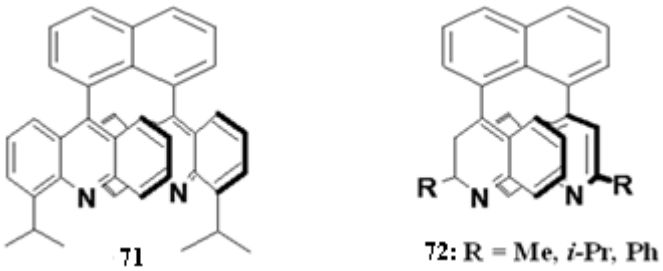
Figure 35a. Substituted 1,8-diarylnaphthalenes (75a)



69 **70**

X = Cl, H, OMe

Figure. 35b. Substituted 1,8-diarylbiphenylene (75b)



71 **72:** R = Me, *i*-Pr, Ph

Figure 36. Naphthyl based model having bi- and tricyclic arenes (76)

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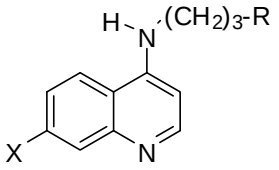
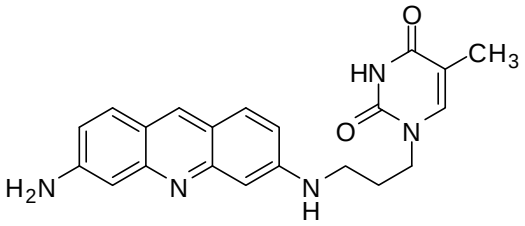
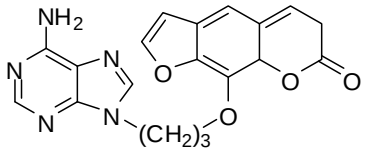


	X	R
73:	Cl	9- Adenine
74:	H	9- Adenine
75:	Br	9- Adenine
76:	Cl	9- Guanine
77:	H	9- Guanine



78

Figure 37. (a) *Polymethylene* linked quinoline compound (77) (b) *polymethylene* linked proflavine compounds (78)



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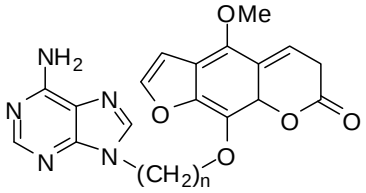

80a-d: n = 2,3,5,6

Figure 38. *Polymethylene* linked psoralen compounds (79)

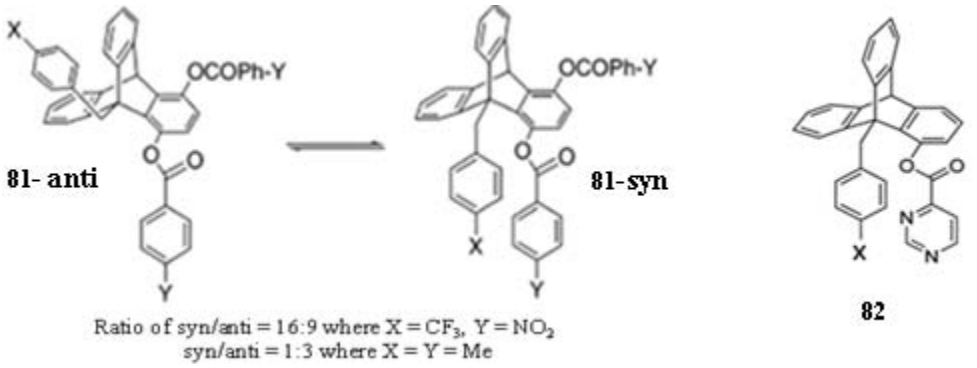

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Figure 39a. Triptycene based models for studying arene interaction between (a) benzenoid systems, **81** (80a); (**b**) between benezenoid and heterocycles **82** (80b)

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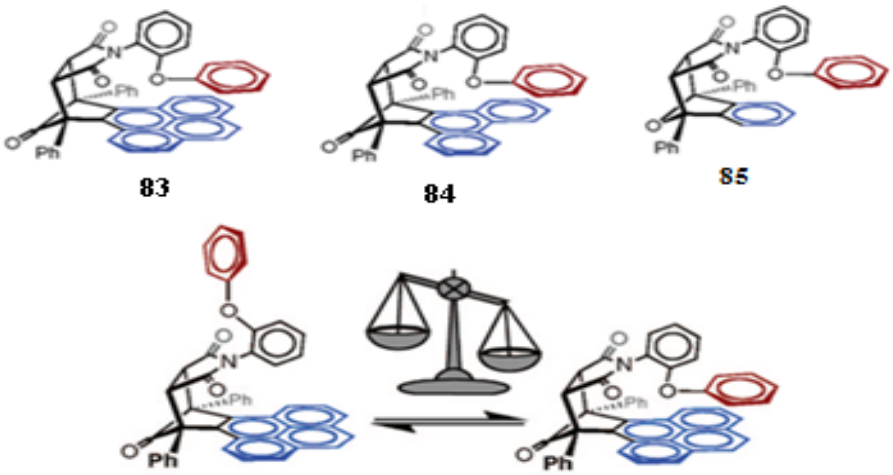

Figure 40. Carroll *et al.* model (81)

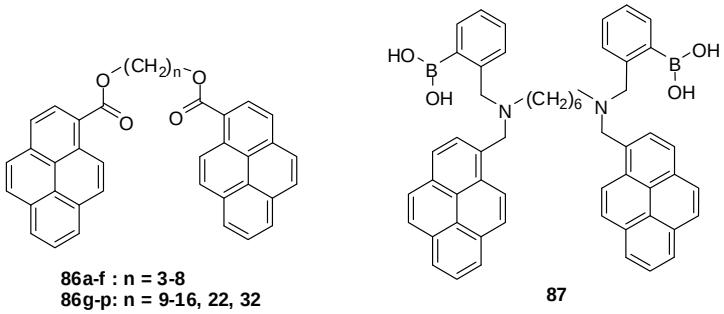

Figure 41. *Polymethylene* linked pyrenyl compounds (83, 84)

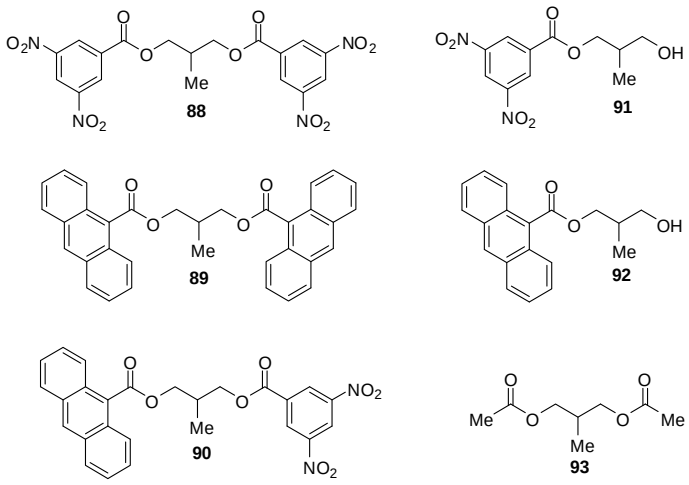

Figure 42. *2-Methyl-1,3-propanedioxy* spacer based diesters and monoesters (85)

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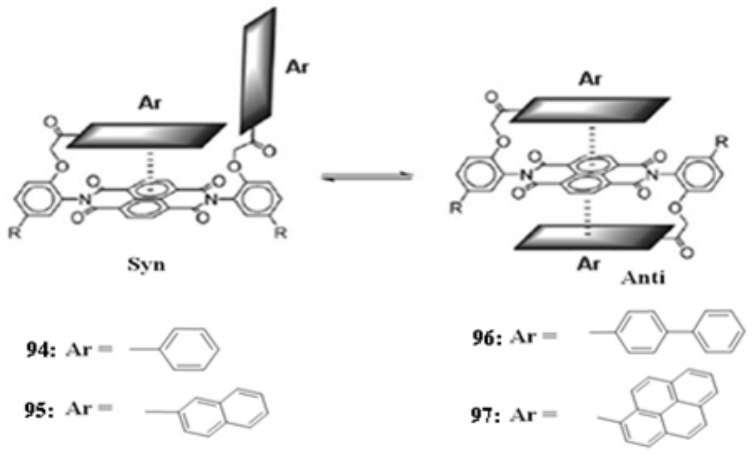

Figure 43. Chong *et al.* molecular balance for studying face-to-face arene–arene interactions (86)

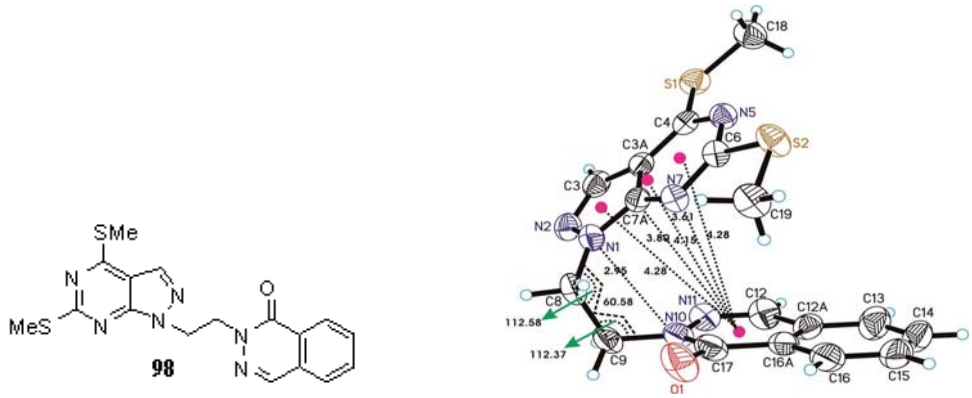

Figure 44. Pyrazolo[3,4-*d*]pyrimidine based dissymmetric *ethylene* linker compound **98** (87)

6. References

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