Medicinal chemistry of acridine and its analogues

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'Acridine' along with its functional analogue 'Acridone' is the most privileged pharmacophore in medicinal chemistry with diverse applications ranging from DNA intercalators, endonuclease mimics, ratiometric selective ion sensors, and P-glycoprotein inhibitors in countering the multi-drug resistance, enzyme inhibitors, and reversals of neurodegenerative disorders. Their interaction with DNA and ability of selectively identifying numerous biologically useful ions has cemented exploitability of the acridone nucleus in modern day therapeutics. Additionally, most derivatives and salts of acridine are planar, crystalline, and stable displaying a strong fluorescence which, when coupled with their marked bio selectivity and low cytotoxicity, enables the studying and monitoring of several biochemical, metabolic, and pharmacological processes. In this review, a detailed picture covering the important therapeutic aspects of the acridone nucleus and its functional analogues is discussed.

1. Introduction

Complexation of actinomycin D (1, Chart 1) with deoxyribonucleic acid (DNA) has been known since the 1950s¹ but identification of the intercalation phenomenon by stacking the flat polyaromatic motif-containing drug in between successive base pairs in the DNA helix in the late 1960s² led to the development of a new class of therapeutics. Then, contemporary developments led to the discovery of daunorubicin³ (2, Chart 1) and doxorubicin⁴ (3, Chart 1) in the early 1970s. A high binding specificity⁵ and efficacy⁶ of these drugs led to systematic studies for optimizing characteristic physicochemical parameters associated with acridine-based drugs and validating the mechanism responsible for their intercalation behavior.⁷

Subsequent investigations revealed that stacking interactions between the ligand molecule and DNA base pairs in the form of π - π interactions,⁸ charge transfer,⁹ and dipole induced dipole interactions¹⁰ result in substantial entropy changes¹¹ which are the principal driving forces for this exceptional occurrence. Other important considerations are size, cross sectional thickness of the ligand,¹² and the presence of side chains.¹³ The availability of a charged or an uncharged 'N' atom in the core moiety¹⁴ assists the ligand to bind to the hydrophilic outer core of DNA before sliding into the hydrophobic space between adjacent base pairs at the cost of entropy lost during the desolvation of DNA.¹⁵ The requirement of side chains is, however, relaxed in fused three ring systems like proflavine, which bind reversibly to DNA.¹⁶

Additionally, a cross sectional thickness of about 3.5 Å, which is characteristic for most poly-aromatics, is optimum for intercalation to the DNA. Structural optimization investigations coupled with clinical success of amsacrine (4, Chart 1) in 1978 as the first synthetic DNA intercalating agent led to the introduction of the acridine/acridone moiety¹⁷ to the DNA intercalating drug discovery, which was only popular for use as pigments, dyestuffs, and anti-infective agents until the end of the 20th century. This laid a foundation for the development of numerous mainstream therapeutics with acridine or its functional analogues: acridone or tacrine, as their integral part.¹⁸ Besides, numerous acridine/acridone containing alkaloids possessing myriad biological activities are extracted from natural sources.¹⁹ These natural sources, identified as microbes (source of inubosins),²⁰ marine sponges (source of nordercitin, dercitamine, dercitamide, and cyclodercitin),²¹ tree barks (source of acronycine),²² and fruit extracts,²³ act as reservoirs for the extraction of acridine-based alkaloids and have been successfully employed for the treatment of various diseases.²⁴ In addition, successful investigations on acridine alkaloids from the *Rutaceae* family have had their anti-herbicidal activity validated by blocking both photosystems I and II of the herb's photosynthetic pathway.²⁵ Several acridone-based insect antifeedant alkaloids were also reported which exhibited substantial activities against the fungus, *Cladosporium cucumerinum* and *Bacillus subtilis*.²⁶ Matasyoh *et al.* 2011, reported larvicidal activity of acridone alkaloids obtained from the rutaceae family against *Anopheles gambiae* acridone. The reported alkaloids produced 80–100% mortality in the larvae population.²⁷ dos Santos *et al.* 2009, evaluated the bioactivity of acridone alkaloids isolated from *Swinglea glutinosa* (Bl.) Merr. against *Leishmania donovani* L82, chloroquine-sensitive *Plasmodium falciparum* 3D7, and

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Chart 1 Classical DNA intercalators.

Trypanosoma brucei rhodesiense STIB900. The test acridone alkaloids also displayed significantly higher cytotoxicity towards cancer cells.²⁸ Wang *et al.* 2014, investigated another set of acridone alkaloids obtained from the rutaceae family for their cytotoxicity profile against prostate cancer cell lines PC-3M and Lymph Node Carcinoma of Prostate, LNCaP; and their antimalarial activities against *Plasmodium falciparum* 3D7, and Dd2.²⁹ With IC₅₀ in a nano molar range, the test alkaloids produced substantial results against both the cancer cell lines and malarial strains.²⁹ Weniger *et al.* 2001, introduced prenylated acridone alkaloids extracted from the stem bark of *Swinglea glutinosa*, and tested their potency against chloroquine-sensitive and resistant *Plasmodium falciparum* strains. These alkaloids also displayed a minimal cytotoxicity as examined with HeLa cells.³⁰ Therefore, owing to their innumerable biological applications, the medicinal chemistry of acridines needs to be acknowledged for the development of next generation therapeutics.

2. Biological activity of acridine

2.1 Acridines in anticancer therapy: DNA intercalators

2.1.1 Structure–activity relationships for DNA intercalating acridines. The first report on the validation of intercalation

behaviors of acridines was communicated in 1961 (ref. 31) followed by another report in 1962 demonstrating the structure of a DNA–acridine complex.³² These reports concluded that intercalation results in a loss of the structure and stability of DNA by unwinding and lengthening its size³³ and a decrease of the linear charge density,³⁴ an extensively exploited characteristic used to develop novel anticancer therapeutics. However, the ability to intercalate does not solely validate their biological activity. Primarily, anticancer potency, and also a number of other factors like topoisomerase and telomerase inhibition, initiation of ROS mediated oxidative stress, arresting of the cell cycle, and interaction with P-glycoprotein, also come into play which makes the acridine/acridone moiety a privileged scaffold for anticancer chemotherapy. Quantification of structure activity relationships (SAR) of acridines for screening potential antitumor candidates based on DNA intercalation profiles increased in pace from the early 1970s. SAR investigations on 9-anilinoaridines towards DNA binding done mainly for the L1210 leukemia system presented interesting findings for validating the acridine nucleus as a core scaffold for antitumor drug discovery. Earlier reports on the 4'-(acridin-9-ylamino)alkanesulfonanilides ring confirmed the necessity of electron-donor substituents

(6a–6b, Chart 2) and a high electron density at the 6' position for a marked antileukemic activity. These investigations also put a limit on the maximum number of substituents (*i.e.*, three) with an appropriate size being as large as an iodine atom and smaller than an isopropyl group.³⁵ An *in vivo* investigation on these compounds further validated that a 4-CH₃ substituent on the acridine ring (7a, Chart 2) seems to promote drug translocation conceivably by sterically deterring binding to accessible but undesired sites. Similarly, the test of a drug with a free –NH₂ group on the acridine ring system was found to be unharmonious against the s.c. implanted tumor. Contrarily, drugs with an acetyl or monomethyl protected –NH₂ group can inhibit s.c. implanted tumors³⁶ (7b–7d, Chart 2). SAR analysis made further revelations on substituted acridines concerning the number of substituents which the core scaffold could bear for an optimum activity. Reportedly, increasing the number of substituents disturbs the crucial lipophilic–hydrophilic balance of a drug. Activity was found to diminish for acridine variants appended with both 4-CH₃ and 3-NH₂ (6c, Chart 2), NHCOCH₃ (6d and 6e, Chart 2) or NO₂ (6f and 6g, Chart 2) substituents. The behav-

iors of test variants with 3,6-disubstituted functionalities having variable electronic character advocated a limited site bulk tolerance. However, the asymmetrically 3,5-disubstituted analogues, specifically the 3-NH₂–5-CH₃–3''-OCH₃ variant with an optimum dose requirement of qd 1–5, 1.25 mg kg^{–1} per day was found to be the most consistent finding among these series of compounds.³⁷ Further analysis for an enhanced site binding was made by appending the alkanesulfonamide chain of 4'-(9-acridinylamino)alkanesulfonamides with additional basic functionality: [–NHSO₂(CH₂)_nNH₃⁺; –NHSO₂–(CH₂)_nNHC(=NH₂)NH₂⁺] which provided the compounds (7e–7g, Chart 2) with an augmented activity and an improved log P_o value.³⁸ For a better understanding of the relevance of sulfonamide anion in the antileukemic (L1210) 4'-(9-acridinylamino)methanesulfonamides, test compounds with a –NHSO₂CH₃ group replaced with a –COOH have been studied inferring that antitumor activity is retained for the carboxylate functionality appended at the 1' position only (8a and 8b, Chart 2). The activity was only permissible for 1'-COOH and 1'-(CH₂)₂COOH analogues whereas the analogue 1' and 3'-CH₂COOH (8c and 8d, Chart 2) was found to be

6. 4-(acridin-9-ylamino)methanesulfonamide

- 6a. 2' = halogens, –NH₂, –OCH₃, –CH₃
 6b. 3' = –NH₂, –NHSO₂CH₃, –OH, NO₂
 6c. 3 = –NH₂, 4 = –CH₃
 6d. 3 = –NHCOCH₃, 3' = –CH₃
 6e. 3 = –NHCOCH₃, 5 = –CH₃
 6f. 3 = –NO₂, 5 = –CH₃
 6g. 3 = NO₂, 5, 6 = –(CH₃)₂, 3' = OCH₃

7. 4-(acridin-9-ylamino)alkanesulfonamide

- 7a. R = CH₃, 4-CH₃
 7b. R = CH₃, 3-NHCOCH₃
 7c. R = CH₃, 3-NHCH₃
 7d. R = CH₃, 3-N(CH₃)COCH₃
 7e. 3 = NO₂, R = (CH₂)₂NHCOCH₂NH₂
 7d. 3 = CH₃, R = –N(CH₃)COCH₃
 7f. 3 = CH₃, R = (CH₂)₄NH₂
 7g. 3 = NO₂, R = (CH₂)₅NHC(=NH)NH₂

8. Anilinoacridines

- 8a. 1' = COOH, 2' = CH₃, 3' = H
 8b. 1' = COOH, 2' = NO₂, 3' = H
 8c. 1' = CH₂COOH, 2', 3' = H
 8d. 1', 2' = H, 3' = CH₂COOH
 8e. 1' = –NH(CH₂)_{5,3,2}CH₃, –NHCH₂CH₃, –NH₂, –N(CH₃)₂, 2', 3' = H
 8f. 1' = H, 2' = –NH₂, –NHCH₃, 3' = H
 8g. 1' = H, 2' = H, 3' = –NHSO₂CH₃, –NHCOCH₃

Chart 2 Quantification of structure activity relationship on the intercalation behavior of 9-anilinoacridine.

inactive. These reports validated the effect of 1' substituents on the 9-anilino substituted acridine ring on its antitumor activity.³⁹ The later reports employed a drug competition assay of a test compound with fluorochrome ethidium for binding into accessible DNA sites. A fluorescence quenching was apparent for the DNA-ethidium complex due to the displacement of bound ethidium by the test compound. Further, through quantification measurements it was shown that the drug-DNA binding was improved by the presence of an electron donor substituent at 1' and 2' positions (8e and 8f, Chart 2) of the 9-anilinoacridine whereas, it was lowered by a substituent at the 3' position due to steric inhibition for entry of the acridine nucleus into an intercalation site. However, the presence of $-\text{NHSO}_2\text{CH}_3$ or $-\text{NHCOCH}_3$ substituents at the same position (8g, Chart 2) participates in H-bond formation which couples with several other stereochemical aspects eventually assuring selectivity of binding of the test drug to poly[d(G-C)] and poly[d(A-T)] sequence of DNA.⁴⁰

An appraisal of the candidature of acridine-based DNA intercalators saw a rise from the 1980s with the identification of 9-aminoacridine-4-carboxamides as a new class of antitumor agents. This class of compounds possesses an exceptional stability and water solubility coupled with a substantial antitumor activity both *in vivo* and *in vitro*. The intercalation behavior of these compounds was apparent but its corrobora-

tion with antitumor activity was more rational depending on numerous factors: separation distance, positioning, and pK values of the two cationic centers. The presence of a charged functionality (9c, Chart 3) lowered the *in vivo* activity and diminished the *in vitro* potency compared to compounds 9a and 9b. For compounds 9d and 9e that have varying degrees of amine, an unpredictable level of potency followed but these compounds retained their *in vivo* activity. Alternately, the presence of weakly basic groups to the side chain in compounds 9f, 9g, and 9h presented a stumpy *in vitro* potency that also proved indolent *in vivo*. SAR investigations for substitution at positions 5–8 were optimized by using a variety of substituents. Interestingly, the physicochemical propensity and antitumor potency of such molecules varied more favorably with their position than with the nature of the substituent groups. Substitution at the 5th position was found to have a profound effect (10b, Chart 3) on the *in vitro* and *in vivo* antileukemic activity, whereas, an enhanced selectivity toward the HCT-8 human colon carcinoma line compared to the L1210 mouse leukemia line *in vitro* has been noted for the 7 and 8 substituted test compounds⁴¹ (10c, Chart 3). Progressive reports indicated that both 5 and 7-substituted compounds intercalated equally well to DNA though the *in vivo* antitumor activity was only characteristic for the 5-substituted compounds. Especially, molecules bearing electron-

Chart 3 Quantification of structure activity relationship on the intercalation behavior of 9-aminoacridine-4-carboxamide.

withdrawing substituents warranted acridine neutrality at the physiological pH, a characteristic not favoring cytotoxicity or selective antitumor activity of weakly basic derivatives which exist primarily as efficiently distributed monocations with little activity^{42,43} (**10d–10e**, Chart 3). Interestingly, varying the

nature of the linker at the 4-position caused a substantial effect on the kinetic stability of the DNA–drug complex. Precisely, the presence of a sulfonamide substituent destabilizes this DNA–drug complex. This effect, however, reversed on replacing sulfonamide with a –CONH group (**11a–11c**, Chart 3).

Chart 4 Quantification of structure activity relationship on the intercalation behavior of some bis-acridines with an aliphatic linker.

2.1.2 Structure–activity relationships for DNA intercalating bis-acridines. The advantages of acridine/acridone as a useful nucleus in medicinal chemistry subsequently led to novel designs and development of its bis- and tris-analogues for delivering superior effects to targeted therapy compared to the mono-analogues. Initial reports for bis-acridines were made in the 1980s by King *et al.* 1982, with a unique series of bis-acridines (12, Chart 4) in which the two intercalating chromophores were spaced by symmetrical amide-linked chains with variable lengths and conformational flexibility. Their various spectrophotometric and viscometric investigations confirmed that connecting chain inflexibility was a deciding factor in determining the mono- vs. bis-intercalation mechanism indicating that the conformationally rigid bis-acridines with a small spacer length (12a–12b, Chart 4) formed the monointercalates whereas, conversely, the large spacer length in 12c with a superior conformational flexibility favored the formation of bis-intercalates.⁴⁴ The DNA binding physiognomies of a mono-, di-, and trimeric compounds of the efficient 9-aminoacridine were also scrutinized. Appending the acridine scaffold along the length of the main chain made of carboxyamidoalkyl groups effected the mono, bis-, and tris-intercalation. Quantification of the DNA unwinding angle obtained from a closed circular DNA revealed that the trimeric derivative (15, Chart 4) behaves as a tris-intercalating agent. However, increasing the appendage from bis- to trisled to a poor increase in DNA binding affinity due to a large structural constraint presented by the trimeric drug for binding to DNA. These investigations also revealed the criticality of the spacer chain for designing highly efficient DNA poly-intercalating agents.⁴⁵ SAR analysis of the substituted bis-(acridine-4-carboxamides) for their DNA intercalation potency has been corroborated by Sharma *et al.* 2003, where it was validated that the 5-substitution (16a–16e, Chart 4) favors the activity of the drug while substitution was not acceptable at the 6-position (16f–16g, Chart 4).⁴⁶ Further, 9-Cl and 9-NH₂ substituted 7-methoxyacridines reportedly showed efficient *in vitro* antiproliferative activities against *Leishmania infantum* (17, Chart 4). However, the antileishmanial potency of the test compounds depended on the nature of the substituent at both 7- and 9-positions and the length of the linker connecting the adjacent acridine rings. The test compounds showed a multitarget mode of action on *Leishmania promastigotes* by targeting the DNA metabolism and other biochemical pathways, which included protein and lipid metabolism.⁴⁷ Another magnificent bis-intercalator design has been presented by Antonini *et al.* 2003, by developing two classes of bis-acridine-4-carboxamides 18a and 18b with a linker between the 4,4' positions and 18c and 18d with a linker between the 1,1' positions and their potency as DNA-binding and potential antitumor agents was checked by gel-electrophoresis and fluorometric techniques. The results presented some outstanding observations. Molecules 18 intercalated DNA very effectively with their bis-derivatives having considerably higher AT-preferential DNA-affinity than their parent monomers. Additionally, the potency of these

compounds was found to be quite sensitive with respect to the nature of the linker connecting the parent chromophore and the 7,7'-substituents.⁴⁸

Takenaka *et al.* 1990, reported the introduction of a heterocycle containing a redox active moiety like methylviologen between the parent intercalating acridone rings to design bis-intercalating mediators with non-covalent, reversible, labelling properties for electroanalytical detection of DNA. The evaluation of a duplex unwinding angle of 28° for the compound 19a and the validation of a typical bis-intercalation behavior of the complete intercalation of the uncharged parent scaffolds in 19a also convinces a full interaction of the doubly charged viologen spacer along the length of a DNA groove.⁴⁹ Annan *et al.* 1992, reported a novel series of DNA bis-intercalators with rigid and extended pyridine spacers of varying lengths appended between the two adjacent acridine nuclei (19b, Chart 5). Compound 19b, after intercalating into the linear DNA strand, induces its cross-linking as concluded from the unwinding and folding of linear DNA. Upon ligation and removal of the compound, 19b instigates superhelical circles, catenanes, and knots that act as markers of the bis-intercalator. The significance of compound 19b is because of its applicability as a probe for the spatial organization of DNA, particularly near replication sites or near a site of recombination or topoisomerase action where two participating DNA duplexes must be in juxtaposition.⁵⁰ Zhao *et al.* 2013, designed and developed potential DNA bis-intercalators (20, Chart 5) with two glucuronic acid spacers linked to the parent scaffold by ethylenediamine. The *in vivo* investigations with Calf Thymus DNA (CT-DNA) showed that compound 20 with a remarkable key selection vector (KSV) value interacted very strongly to CT-DNA compared to quinolone, purine, or indole chromophores.⁵¹

Extensive investigations on structure–activity analysis of the acridine nucleus and its functional analogues resulted in the development of numerous therapeutics aiming on a range of molecular targets particularly related to cancer development and progression. Chart 6 demonstrates the most recent reports focusing on the inhibition of these oncological targets.

2.2 Acridine-based hybrids molecules

2.2.1 DNA intercalating acridine–porphyrin hybrids for photodynamic therapy. Mehta *et al.* 1993, introduced novel acridone-based structurally modified porphyrin ring systems as photosensitizing probes for photodynamic therapy (PDT) of malignant cancers without altering the intercalation tendency of the acridone ring or the photosensitizing ability of the porphyrin ring system. PDT selectively targets malignant tumor cells by activating the photosensitizer on exposure to a selective wavelength, thereby producing a reactive species that causes irreversible damage to the cancerous cells.⁶³ Selectivity of the PDT therapy, however, depends on accumulation of the photosensitizer in the tumor tissues as well as its photochemical efficiency. Reportedly, for molecule 21, an

Chart 5 Quantification of structure activity relationship on the intercalation behavior of some bis-acridines with a cyclic/aromatic linker.

efficient energy transfer from the acridone moiety to the porphyrin ring system requires an appropriate spacer length, which could allow conformational flexibility in the molecule. A highly efficient energy transfer has been observed for **21b–21d** ($n = 2$ to 5) compared to **21a** ($n = 2$) and **21e** ($n = 6$). Nuclease activities of the hybrid molecules **21a–21e**, Chart 7; suggested that intercalation and photosensitization could be clubbed together to provide an improved nuclease activity.⁶⁴ Ishikawa *et al.* 2001, synthesized positively charged porphyrins appended with an acridine nucleus through a diamino alkyl linkage. The resulting compounds presented a superior photocleavage activity of pUC18 plasmid DNA with a strong candidature presented by the compound accompanying the hexamethylene ($n = 6$) chain (**22e**, Chart 7). Various physical experiments with CT-DNA confirmed the binding ability of the hybrids, which also associated quantitatively with the photocleavage activity. Titration experiments also verified a repudiated intercalative binding of the porphyrin ring in CT-DNA as indicated by the nonexistence of a remarkable red shift of the Soret maxima of the hybrids.

Investigations through circular dichroism (CD) validated intercalation through the acridine ring and interaction of the porphyrin nucleus with the minor DNA groove as indicated by the presence of two negative peaks at 275 nm and at 285–290 nm in the UV range, respectively. However, the length of the linker only affected the approach of the porphyrin moiety to the DNA minor groove.⁶⁵ Intercalation behavior of the cationic porphyrin–acridine hybrids also extended to meso-substituted pyridine, imidazole, and pyrazole rings (**23**, Chart 7). Interaction of hybrid compounds with the DNA duplex was primarily through intercalation and groove binding whereas, conversely, the interaction with DNA quadruplex was stringently through stacking. Test compounds with two meso-substituted diazolium rings (**23e** and **23g**, Chart 7) were

found to exhibit a higher binding affinity towards the minor groove of DNA duplex and quadruplex compared to their mono- (**23b** and **23c**, Chart 7) and tri-substituted (**23h**, **23i**, and **23j**, Chart 7) counterparts.⁶⁶

2.2.2 DNA intercalating acridine–lexitropsin conjugates.

Early 1990s saw an advent of another class of DNA binding ligands: combilexins that are DNA ligands bestowed with a sequence-specific minor groove binding property pooled with an intercalating chromophore, which stabilizes the DNA complex and can impede the functioning of topoisomerases. Plouvier *et al.* 1994, discovered the first combilexin class of molecules by examining the antitumor property and DNA-binding characteristics of a conjugate of thiazole–lexitropsin with an anilinoacridine chromophore giving a hybrid molecule ThiaNetGA. It interacts with DNA *via* a bimodal process involving minor groove binding of the lexitropsin moiety and intercalation of the acridine scaffold (**24**, **25**, and **26**, Chart 8). The *in vitro* and *in vivo* experiments rationalize the non-toxicity of this conjugate, which shows only a modest antitumor activity against P388 leukemia cells. A detailed *in vitro* and physical analysis made it ostensible that the biological efficacy of the hybrid is due to its binding to DNA and other nuclear constituents and, additionally, the involvement of topoisomerases as the perspective target of the hybrid cannot be ignored.⁶⁷

Housiaux *et al.* 1996, attempted to reconnoiter the nature of the complex formed between a novel amsacrine-4-carboxamide-netropsin combilexin and DNA. Various complementary methods of spectroscopy that included absorption, circular and electric linear dichroism, viscometry and foot printing compiled structural and kinetic data. Investigations revealed that the conjugate slips through the DNA double helix in order to intercalate the acridine chromophore in its structure thereby positioning the netropsin nucleus and the

Sr No	Molecule	Activity	Ref.
1		Arresting of G0/ G1 phase of cell cycle	Zhou <i>et al.</i> 2018 (ref 52)
2		Topoisomerase II inhibitor	Li <i>et al.</i> 2017 (ref 53)
3		MDR modulation	Murahari <i>et al.</i> 2017 (ref 54)
4		G-quadruplex alkylation	Hazemi <i>et al.</i> 2018 (ref 55)
5		dual TOPO & HDAC inhibitors	Chen <i>et al.</i> 2018 (ref 56)
6		Impair BVDV replication/ targeting RdRp	Loddo <i>et al.</i> 2018 (ref 57)
7		Antiproliferative activity	Ismail <i>et al.</i> 2015 (ref 58)
8		Anticancer activity	Salem <i>et al.</i> 2017 (ref 59)
9		Hepatocellular carcinoma treatment	Zhang <i>et al.</i> 2017 (ref 60)
10		Antiproliferative activity	Felip-leon <i>et al.</i> 2018 (ref 61)
11		Anticancer activity	Chagas <i>et al.</i> 2016 (ref 62)

Chart 6 Recently reported biologically active molecules based on acridine/acridone nucleus.

methanesulfonanilino (27, 28, Chart 8) group inside the minor and major grooves of the double helix respectively. The conjugate however, preserves the AT selectivity deliberated by the netropsin moiety. Stopped-flow measurements appraised this threading-type of intercalation phenomenon and it complimented with characteristic structural features of the antitumor antibiotics pluramycin and nogalamycin. This magnificent design of DNA-threading combilexins offers an insight to the original route for the advancement of sequence-specific ligands proficient in establishing stable complexes with DNA.⁶⁸ Mc. Connaughie *et al.* 1995, used a DNA template-directed approach to design prototype DNA-binding combilexins. The structure of these innovative hybrids was infused with a 1,3-diarylthiazene linker moiety appended to the intercalating acridine chromophore by a substituted thiazole residue (27, Chart 8). The 9-arylacridine moiety, which assists in bifunctional interactions with the double-stranded DNA comprising the intercalation and minor groove-binding processes, also bestows an unrestricted rotation to the hybrid. Physical investigations in the form of fluorescence quenching and thermal denaturation with CTDNA and comparison of the inferences with proflavine indicated an enhanced DNA binding affinity for the test hybrids compared to the either molecular components. Interestingly, the AT-preferential binding properties of the parent difunctionalized 1,3-diarylthiazene residues was retained in the hybrid molecules despite the weak GC-preferential binding nature of the acridine moiety, however, the binding was impeded at a pH 7 indicating the prominence of a protonated derivative of the acridine nucleus. Conversely, the binding preference of the hybrid to GC-rich DNA sequences improved in the presence of strong basic groups (27d, 27e, and 27f, Chart 8). *In vitro* cytotoxicity analysis on the hybrid molecules with L1210 mouse leukemia and A2780 cancer cell lines validated the DNA binding potency of conjugate molecules, which was reportedly ten to forty times higher than the individual acridine or thiazene molecules.⁶⁹ Murahari *et al.* 2017, reported hybrid molecules comprising acridones and substituted pyrimidines as the next generation anticancer therapeutics that target malign cells through multiple mechanisms. *In vivo* investigations on these compounds validated the anticancer candidature of 28a, 28c, and 28f, $R_1 = -CH_3$ (Chart 9) against MCF7, MDA-MB-231, and A549 cell lines. Titration experiments and gel electrophoresis recognized the DNA intercalation profile of the active compounds. Additionally, *in vitro* enzyme immunoassays validate the Akt kinase activity and apoptosis induction in the target cells with a significant ability to modulate multidrug resistance (MDR) concomitant with ABCC1/MRP1. Cytotoxicity profiles of compounds 28e and 28g, $R_1 = -CH_2CH_3$ (Chart 9) were quite satisfactory against of both sensitive and resistant types of lung cancer cell lines. Compound 28e displayed negligible signs of clinical toxicity even at a higher dose of 5000 mg kg⁻¹ revealing that the hybrid systems of acridone with substituted pyrimidines could be a fruitful combination for the development of lead anticancer molecules.⁷⁰

Chart 7 Acridone-porphyrin hybrids.

2.2.3 Acridine-purine/pyrimidine conjugates as endonuclease mimics. Fkyerat *et al.* 1993,⁷¹ designed a series of molecules acting as nuclease enzyme mimics (32a-32e, Chart 9) to selectively identify and cleave DNA at apurinic sites. The unique design of these molecules integrates diverse components for explicit actions which includes a DNA intercalator, a nucleic base (purine here) for abasic site identification, and a linker capable of both binding and cleavage functions. The ¹H NMR experiments denied intramolecular ring stacking between the base and the intercalator but all the molecules were found to bind effectively to CTDNA with significant binding constants ranging from 10^4 to 10^6 M⁻¹. The test compounds induced single strand breaks in the de-purinated

pBR322 plasmid DNA, a happening for which compound 32e presented the strongest candidature even at ultra-low concentrations.

High recognition selectivity coupled with significant cleavage efficiency allows the usage of 32e as an effective alternate to the natural nuclease for *in vitro* cleavage of de-purinated DNA.⁷¹ Fkyerat *et al.* 1993, proposed that one of the two amine functionalities present in the mimic is protonated at physiological pH raising the mimic's affinity towards DNA by interacting with the phosphate backbone. The other amine, with a lower pK, reacts as a free base to promote hydrogen-abstraction thereby facilitating β -elimination of the phosphate. Replacement of the linker's -NH₂ group with -CONH₂

Chart 8 DNA threading combilexin molecules.

functionality in the mimic optimized the effect of amine functionality in its linker chain (29, Chart 9). Hybrids 29 and 31 acted as functional analogues of 32e with an incipient nuclease mimic proficiency. Experimental analysis indicated that the much anticipated DNA cleaving profile was achieved by all the hybrids, but more significant results were obtained with compounds 30 and 31 which vary only at the position of -NH₂ and -CONH₂ functionality in the linker chain and displayed a similar affinity and cleaving propensity against DNA. Mechanistically, it has been proposed that for mimics 29 and 30 the nitrogen atoms from -NH₂ and -CONH₂ groups present in the linker come in juxtaposition to the detachable hydrogen at the abasic site thereby effecting an 'endonucleases-like' DNA slicing.⁷² Martelli *et al.* 2002, designed site-specific DNA damaging agents for creating multiple damaged sites in close proximity to the abasic site by appending the endonuclease mimics (Chart 9) with a DNA damaging agent, phenanthroline or *p*-nitrobenzamide, at the acridone scaffold (33, 34, 35, and 36, Chart 10). Test molecule 35 with *n* = 4 and 6 was found to influence photocleavage of DNA upon illumination with a mechanism of action analogous to that of the artificial endonucleases 30 and 31. Side chains of intercalated acridine in molecules 35a and 35b hap-

pen to be located in the minor groove of DNA. Test molecule 36 which substantially affected the cleavage of DNA at the base opposite to the abasic site was another significant finding.⁷³

2.2.4 Acridine-peptide conjugates for targeting G-quadruplex. Carlson *et al.* 2000, developed a unique library of acridine-peptide conjugates by solid phase synthesis out of which the hybrid molecule (38, Chart 11) was reported⁷⁴ as a functional analogue of SN16713 (37, Chart 11) which is known to bind to the DNA duplex at GC rich sequence and TAR RNA region of HIV *via* intercalation.⁷⁵

This innovation received much attention⁷⁶⁻⁷⁹ and led to development of peptide nucleic acid oligomers (PNA) with a unique characteristic of binding sequence complementary targets in duplex DNA (39, Chart 11) with an extraordinary affinity and sequence specificity by helix incursion forming triplex P-loop complexes.⁸⁰ Reports have recommended that the acridine-peptide acid hybrid (40, Chart 11) steadied on the terminal G quartet by π - π interactions. The amidoalkylamino appendages at positions 3 and 6 in molecule 40 interacted with the two widest grooves and the two terminal pyrrolidine rings on these appendages and reportedly indulged in hydrophobic interactions with the sides of the grooves. These

Chart 9 Acridone–purine/pyrimidines hybrids as mimics of endonuclease enzyme.

investigations supported another similar to the pyrrolidine rings⁸¹ in molecule **40**, where the peptides on either side of the acridone scaffold interacted with two different grooves. Ladame *et al.* 2002 and 2004, developed a high-yielding, new method for the solid-phase synthesis of 3,6-bispeptide-acridone conjugates (**41** and **42**, Chart 11) involving the preliminary coupling of bi-functionalized acridone (**41**, Chart 11) to a resin-bound peptide which is “resin-(val-lys-lys-arg-NH₂)₂” followed by an on-bead site-site reaction to couple the second peptide. This method yields ultrapure and symmetrical bispeptides (**42**, Chart 11) for selective binding to a telomeric G-quadruplex DNA.⁸² Contemporary developments in the design of acridone/acridine–peptide hybrids led to the design of 3,6-bis-peptide acridine/acridone hybrids for a selective inter-

action with G-quadruplex DNA (**44–47**, Chart 12). Investigations validated a peptide sequence dependence for the hybrid to display its interactive physiognomies with the quadruplex. Best results were obtained with the hybrid's highest discrimination being obtained with hybrids **45** and **47c** that displayed a selectivity of >50-fold specificity with the quadruplex. Further insights through molecular modeling studies revealed that the human telomeric quadruplex DNA could freely house tetrapeptides, especially those on hybrid **47c** thereby leading to stabilization of the hybrid-quadruplex by non-bonded interactions in TTA loop pockets of the quadruplex. These revelations validated the G-quadruplex targeting strategy as an encouraging approach for discriminating between quadruplex and duplex DNA.⁸³ The high applicability of the

Chart 10 Acridone-purine hybrids for multiply photocleavage of DNA.

acridone-peptide hybrids led Redman *et al.* 2009, to reveal a new series of trisubstituted acridine-peptide conjugates based on molecule **40**, Chart 11 by replacing the -NMe₂ appendage with a peptide linked to the ring through a -C=O group. The resulting molecules (**43**, Chart 12) displayed an exceptional capacity to identify and differentiate between DNA quadruplexes derived from the human telomere. Reportedly, the hybrid-quadruplex affinity varied with the sequence of amino acids in a peptide chain and the position of substitution on the parent ring with an optimum limit in the range 1–5 nM.⁸⁴

2.2.5 Anticancer acridine-metal complexes. The platinum-acridine anticancer agent [PtCl(ethane-1,2-diamine)(*N*-(2-(acridin-9-ylamino)ethyl)-*N*-methylpropionimidamide, acridinium cation)](NO₃)₂ (**48**, Chart 13) was studied along with the clinical drug cisplatin for its activity and cytotoxicity against three cell lines of chemoresistant non-small cell lung cancer (NSCLC). The hybrid displayed a multifold cytotoxicity augmentation at nanomolar inhibitory concentrations

against NCI-H1435, NCI-H460, and NCI-H522 compared to cisplatin. Real time impedance evaluations verified changes in the morphology of the target cells and their adhesion with the test drug, thus validating that at equitoxic concentrations, the hybrid kills NCI-H460 cells much more proficiently compared to cisplatin. Interestingly, flow cytometric examinations on NCI-H460 cells established the S phase arrest of target cells treated with the hybrid compared to cisplatin where the cells advance towards the G2/M phase of the cell cycle. Additionally, NCI-H460 cells treated with the hybrid at IC₉₀ molar concentration for a span of 48 hours (ref. 85) displayed a substantial inhibition of DNA replication in 3/4th of the viable cells. Shionoya *et al.* 1994, designed a zinc(II) complex of acridine-pendant cyclen, (**49**, Chart 13) as a novel multipoint nucleobase receptor hybrid in aqueous solution at physiological pH. The strong acidity of Zn(II) in compound **49** ensures the water at the fifth coordination site. Investigations for the interaction of hybrid **49** with nucleosides by potentiometric pH titration, NMR, IR, UV-vis, and fluorescence spectroscopy

Chart 11 Acridine-peptide hybrids.

revealed the effects of the acridine functionality.⁸⁶ Reportedly, a binuclear Zn(II) complex of hybrid **50**, Chart 13; vigorously catalyzed the intramolecular transphosphorylation of RNA. The mechanistic elucidation revealed cooperation between the two Zn(II) ions thereby triggering weak, but effective binding interactions of the substrate to the peptide catalyst **50**. A noteworthy activity for hydrolytic cleavage of plasmid DNA with a lucid confirmation of cooperativity between the two Zn(II) centers⁸⁷ supported the mechanism of action for hybrid **50**.

The hybrid molecules of acridine with 5 and 6 membered cyclic imides (**Ia-e**, **IIa-e**, and **IIIa-e**, Chart 14) with their *in vitro* screening against five human cancer cell lines *viz.* ovary (PA-1), lung (NCl H-522), breast (T47D), liver (Hep G2), and colon (HCT-15) were found to have a remarkable inhibitory potential. The contribution of cyclic imides towards inhibition profiles of these hybrids is still vague; however, they

subsidize a pertinent *clogP* value to the molecule. Investigations revealed an *IC*₅₀ value: 6.56 μ M, 8 μ M, 5.4 μ M, 10 μ M, and 7.1 μ M for the compounds **1b**, **IIb**, **IIc**, **IId**, and **IIIId**, Chart 14, respectively, against some specific human cancer cell lines. A very favorable lipophilic index supported the candidature of these conjugates, which is an added advantage for the development of anticancer leads based on cyclic imide-acridine hybrids.⁸⁸ Serafim *et al.* 2018, developed novel compounds containing the 2-amino-cycloalkylthiophene and acridine moieties (**IV** and **V**, Chart 14). With a negligible cytotoxicity against the human erythrocyte, these hybrids interacted with DNA⁸⁹ with a binding constant of 10^4 M⁻¹. Joubert *et al.* 2014, investigated *in vitro* biological activities of 9-aminoacridine-artemisinin hybrid compounds (**VI**, Chart 14). The hybrids were found to be around tenfold active against the HeLa cells, gametocytocidal strain (NF54), and chloroquine resistant (Dd2) strains of *Plasmodium*

Chart 12 Acridine-peptide hybrids for selective identification and discrimination of G-quadruplexes.

falciparum. The hybrids also restrained the apoptosis of HepG2 and SH-SY5Y.⁹⁰ Another important derivative of

2-aminoacetamido-10-(3,5-dimethoxy)-benzyl-9(10*H*)-acridone hydrochloride **VII**, Chart 14; is likely to have a persuasive antitumor activity. The activity of the derivative **VII** on CCRF-CEM leukemia cells led to the quantification and determination of the changes in *N*-glycosylation. The analysis of *N*-glycans from whole cell lysates and cell membranes was made using an isomer-sensitive chip-based porous graphitized carbon nano-LC/MS method. Therapeutic potency of the derivative **VII** depended on regulating hypoglycosylation, thereby validating its use as a potential biomarker for monitoring toxicity and antitumor activity.⁹¹ A special series of nitric oxide donating acridone-carboxamide hybrids **VIII-a** to **VIII-f**, Chart 14, were designed to be appraised for *in vitro* cytotoxicity against different sensitive and resistant cancer cell lines. Interestingly, the cell lines administered with hybrids **VIII-c**, **VIII-f**, and **VIII-d** showed an exogenous release of nitric oxide thereby improving the accretion of doxorubicin in resistant cancer cell lines upon co-administering with doxorubicin, thus validating the efflux pump targeted approach⁹² of hybrid **VIII**. Chattopadhyay *et al.* 2013, developed novel hybrids of pterocarpan with acridone capable of binding DNA through the minor groove. These hybrids could better act as bioanalytes for DNA sensing analysis. Notably, the hybrid molecule **IX**, Chart 14 was the first hybrid molecule for selective identification of the nucleic acids.⁹³

Chart 13 Acridine-metal complexes.

Chart 14 Recently reported acridine/acridone hybrids.

2.3 Acridines based probes for biomolecules and selective ion sensing and monitoring of metabolic events

Reportedly, acridones appended with a suitable substituent at N-10 position upon interacting with ATP/ADP in HEPES buffer at the physiological pH of 7.2 displayed substantial

fluorescence vicissitudes. Since ATP is regarded as the “energy currency,” ADP is a small part of this spent currency; therefore, the selectivity and binding efficiency of these acridone-based fluorescent molecular probes with ATP/ADP are highly desirable for monitoring various metabolic processes involving both. Singh *et al.* 2011, designed acridone-

Chart 15 a–c. Acridone-based molecular probes for sensing of biologically important molecules and ions.

based fluorescent probes for *in vivo* quantitative estimation of adenosine triphosphate⁹⁴ (ATP) (51 and 52, Chart 15a) and adenosine diphosphate⁹⁵ (ADP) (53 and 54, Chart 15a) generated during the Krebs cycle in mitochondria. Changes in absorption spectra of the fluorophore corresponded to an explicit amount of ATP/ADP produced/consumed in a particular step of the glycolytic pathway. Further confirmation for the feasibility of compound-ATP/ADP interaction was confirmed by mass spectral analysis and Benesi–Hildebrand plots which established a 1:1 stoichiometry for the interaction. Using these probes, a successful monitoring of the various steps of glycolysis coupled with ATP/ADP inter-conversion, the oxidative breakdown of pyruvate in mitochondria, and the consumption/production of ATP/ADP at each step, was quantified. Like adenosine phosphates, the H_2PO_4^- ion and HSO_4^-

ion are also involved in several biological processes. H_2PO_4^- ion plays a significant role in signal transduction, energy storage of metabolism, and most importantly, it forms the backbone of DNA and RNA.⁹⁶ Amphiphilic HSO_4^- ion on the other hand dissociate into noxious SO_4^- at basic pH causing irritation in skin and eyes.⁹⁷ Zhang *et al.* 2013,⁹⁸ developed tweezer-like fluorescent probes (55 and 56, Chart 15a) appended on acridine fluorophore with anion binding properties acting as ratiometric sensors for the $\text{H}_2\text{PO}_4^-/\text{HSO}_4^-$ ions.

Various physical investigations in the form of absorption spectra, ^1H NMR and HRMS, indicated that the molecule 55a with both benzimidazolium and urea functionalities as the intended binding sites, presented a better anion sensing activity than sensors 55b and 56 containing only one type of

binding site in the form of benzimidazolium cation and urea, respectively. Interestingly, the molecule 55a presented a superior dual-responsive selective fluorescent sensing performance for H_2PO_4^- ion *via* a fluorescent bathochromic-shift and, correspondingly, for HSO_4^- ion *via* fluorescence quenching. A synergistic binding effect of benzimidazolium and urea moieties explained the exceptional selectivity of the sensor 55a for both H_2PO_4^- and HSO_4^- ions. Additionally, the $-\text{OH}$ group in H_2PO_4^- and HSO_4^- ions and the N atom of acridine in sensor 55a were found to be involved in hydrogen bonding which also contributed to enhancing and improving its anion binding efficiency.⁹⁸ The ratiometric sensing strategy instigated by synergistic binding by benzimidazolium and urea functionalities inspired the synthesis of molecules 57 and 58, Chart 15, as highly selective ratiometric fluorescent sensors for H_2PO_4^- ion *via* the anion-mediated dimer formation of the fluorophore. Compound 57 displayed a better anion binding potency towards H_2PO_4^- ion due to the synergistic binding effect of benzimidazolium and urea moieties.⁹⁹ Cu^{2+} ion is the third most abundant essential metal ion which is present in the human body and is known to play vital physiological functions.¹⁰⁰ Any dysregulation of optimum Cu^{2+} levels in the body results in serious implications in the form of diseases like Menkes and Wilson,¹⁰¹ Prion disease,¹⁰² Parkinson's,¹⁰³ and Alzheimer's.¹⁰⁴ It has been recently reported that by instigating oncogenic BRAF mutations, Cu^{2+} ions could regulate the growth of tumor cells.¹⁰⁵ Its trace detection in biological systems is therefore highly desirable. Dai *et al.* 2018, performed a single step synthesis of N,N' -(acridine-3,6-diyl)dipicolinamide (59, Chart 15) for selective and efficient detection of Cu^{2+} ions in HEPES buffer. The binding model for sensor 59 was explored by performing ^1H -NMR investigations, density function theory (DFT) calculations, and ESI mass spectral analysis which revealed the participation of 'N' atoms of pyridine and amide functionality in binding with Cu^{2+} ion in a 2:2 stoichiometry. The *in vivo* analysis verified a low toxicity and a better acceptability profile for sensor 59 in the biological systems.¹⁰⁶ Another important ion of interest the CN^- ion which is extremely toxic to mammals and a powerful asphyxiant which restricts oxygen consumption in tissues by impairing the functioning of cytochrome oxidase enzyme and causes instant death.¹⁰⁷ Yet, according to the 1996 World Health Organization (WHO) report, CN^- concentrations less than 1.9 μM are tolerable in drinking water.¹⁰⁸ It is therefore highly desirable to have selective ion sensing probes for quantification of CN^- ions in the test samples. A range of laboratory procedures could establish laboratory diagnosis of cyanide toxicity but scarce probes are available for quantification of minute but toxic CN^- ion concentrations. Yang *et al.* 2006, designed a novel ion selective ratiometric chemosensor for detection and quantification of CN^- ions in aqueous medium at μM concentrations (60, Chart 15b). The sensing of CN^- ions by this probe is centered upon an irreversible nucleophilic addition of cyanide to the 9-position of the acridinium ion in 1:1 stoichiometry (61, Chart 15b) thereby reducing the fluorescence

intensity of the probe accompanied by a noticeable color change (62, Chart 15b). Probe 60 displays a remarkable selectivity for CN^- ions in an aqueous medium over the other anions. Additionally, the sensitivity of both this fluorescence- and colorimetric-based assay was below the 1.9 μM mark as suggested by the 1996 World Health Organization (WHO) report as the maximum permissible CN^- ion concentration in potable water.¹⁰⁹

The molecular identification of amino acids and their derivatives has been an exciting venture in molecular sensing chemistry.¹¹⁰ The popularity of amino acids sensing molecular probes is chiefly because the amino acids are principal components of proteins and enzymes in living systems. In addition, amino acids are endowed with nifty capacities to form complexes with host molecules through several types of intermolecular interactions.^{111,112} The ammonium and carboxylate functionalities that are an integral part of every amino acid are projected to bind to the host molecules chiefly *via* hydrogen bonding and electrostatic interactions. Additionally, the side chain of an amino acid appended on the α -carbon is also able to make complexes with the receptor molecules *via* electrostatic interactions, van der Waals forces, hydrophobic interactions, and p-p stacking interactions. This ingenious ability of amino acids could be utilized to design functional probes for their selective sensing. Sirikulkajorn *et al.* 2009, designed novel derivatives of acridine and acridinium compounds with thiourea binding sites (63, 64, 65, and 66, Chart 15b). The binding parameters for these functional molecular probes were studied for amino acids: L-Trp, L-Phe, L-Leu, L-Ala and L-Gly, in their zwitter ion form, by using ^1H NMR spectroscopy, UV-visible spectroscopy, and fluorescence spectrophotometry techniques. It was validated that the major interactions affecting the interactions between the thiourea binding site and the carboxylate group of the zwitter ion of the corresponding amino acid were the hydrogen bonding interactions with a stoichiometry of 1:1 for all the sensors. Binding was weaker for uncharged sensor molecules 63 and 65 whereas the cyclic charged sensor molecule 64 displayed a significant binding capacity, especially for L-tryptophan (L-Trp) compared to the acyclic charged sensor molecule 66. This observation was due to the presence of a charge on the acridine moiety leading to electrostatic $\text{RCOO}^-\cdots\text{H}\cdots\text{N}^+$ interactions between the positively charged acridinium ion and the negatively charged carboxylate ion of the amino acid zwitter ion. Interestingly, the polyglycol moiety in the cyclic uncharged sensor molecule 63 provided a hydrophobic cavity for binding L-Trp resulting in a sturdier binding potency¹¹³ compared to the acyclic uncharged sensor molecule 65. Charged and uncharged reactive oxygen species are other important objects in biological systems. These are associated with the development of oxidative stress that is a key reason towards the progression of severe diseases and ageing.¹¹⁴ However, the utility of reactive oxygen species has also been extended towards the development of antitumor therapeutics.¹¹⁵ Trace detection and quantification of reactive oxygen species is therefore highly anticipated. Hu

et al. 2008, prepared vicinal diaminobenzoacridine (67, Chart 15b) as a highly effective fluorescent probe, which works on photoelectron transfer (PET) mechanism, for estimating trace amounts of nitric oxide radical (NO[•]) in human serum samples. Determination of the radical in a biological sample was done by coupling a flow injection with spectrofluorimetry to obtain a highly precise system with a linear calibration range of 1.1×10^{-7} to 5.0×10^{-6} M and a detection limit of 3.1×10^{-8} M under optimum conditions. Additionally, the test sensor 67 was found to be biologically unharmed and, being fluorescent, it was employable for visualizing the intracellular NO[•] by using a confocal laser scanning microscope.¹¹⁶ Soh *et al.* 2001, discovered another fluorescent probe composed of 2,2,6,6-tetramethylpiperidine-noxyl (TEMPO) appended with acridine and N-dithiocarbonylsarcosine (DTCS)-Fe(II) complex (68, Chart 15b) working on the 'spin exchange' concept in order to quantify the production of nitric oxide (NO). On incubating the non-fluorescent acridine-TEMPO probe with DTCS-Fe(II) complex in a buffer solution, the nitroxide radical (NO[•]) in the acridine-TEMPO interacted with the Fe(II) ion through redox interactions, thereby recovering fluorescence associated with the acridine scaffold. With a detection limit of less than 100 nM this probe could also be used for the quantification of the NO[•] radical by adding a NO releasing reagent which decreased the fluorescence of the probe due to an irreversible binding of NO to the Fe(II) and interestingly, the amount of

NO radical released directly corresponded to a decrease in fluorescence due to this interaction.¹¹⁷

Wu *et al.* 2008, designed acridine-based fluorescent probes for the quantitative trace estimation of DNA. The molecule N-((N-(2-dimethylamino)ethyl)acridine-4-carboxamide)-alanine (N-(ACR-4-CA)-ALA) (70, Chart 15c) was found to bind with DNA and that DNA had the ability to quench the fluorescence of the N-(ACR-4-CA)-ALA moiety of the probe 70 ($\lambda_{\text{ex}} = 260$ nm, $\lambda_{\text{em}} = 451$ nm). Interestingly, the quenched fluorescence intensity was proportional to the concentration of DNA with a detection limit of 9.1 ng ml^{-1} for fsDNA and 8.7 ng ml^{-1} for ctDNA, respectively.¹¹⁸ Adhikari *et al.* 2015, developed an acridone-based highly selective cell-permeable turn-on fluorescence probe (71, Chart 15c) for sensing Zn²⁺ ions in living systems. The probe exhibits yellow fluorescence at 560 nm in dry methanol/DMSO up to a 100 μM detection limit for Zn²⁺ ion which, at higher Zn²⁺ ion concentrations in dry methanol, produces a red colored, solid polymeric complex having a strong emission peak at 605 nm. This occurrence is also pertinent at a 50 μM concentration of Zn²⁺ ion concentration in water. However, the reported lowest detection limit of 71 was 0.1 nM. Interestingly, probe 71 was also functional for bioimaging of Zn²⁺ ions in human MCF 7 breast cancer cells and HeLa cells.¹¹⁹ Liang *et al.* 2016, developed a novel fluorescent probe (72, Chart 15b) as a highly selective fluorescent probe for HOCl estimation endowed with an extremely fast (within 5 s) and sensitive response. Probe 72 displays

Chart 16 Acridine-based compounds to combat Alzheimer's disease.

exceptional properties like pH-independence, tolerance to photobleaching during excitation laser irradiation, and high HOCl selectivity, which makes it a robust sensor for various biological applications.¹²⁰ Li *et al.* 2014, designed first ever probes 73 and 74, Chart 15c as enantioselective fluorescent malate ion sensors for CH₃CN. The enantioselective sensing properties of these probes was quantified with a 400 MHz NMR spectrometer using probe 73 as a chiral solvating agent. The proposed modes of sensing validated the formation of hydrogen bonds between the hydroxyl group of D-malate ion with the oxygen atoms of 73 and 74 in agreement with orientation of the carboxylate anion in MA (malate) combined with the NH group. The spectra for 73 in DMSO-d₆ solution in the absence and in the presence of 1.0 equiv. D- or L-MA (malate ion) indicated that the methylene protons next to chiral center of 73 displayed a greater effect with malate ions than another methylene group.¹²¹

2.4 Acridine and analogues as neuroprotective agents

2.4.1 Treatment of Alzheimer's disease. The viability of acridone derivatives for treatment of Alzheimer's disease is the most recently revealed application of this magnificent moiety. Alzheimer's is a neurodegenerative disease which occurs due to under-production of the neurotransmitter acetylcholine esterase.¹²² 1,2,3,4-Tetrahydroacridine (tacrine) and

its derivative, 9-amino-1,2,3,4-tetrahydroacridine (75, Chart 16), earlier used as an analeptic agent, was the first drug that was later publicized to have resilience against the activity of anticholinesterase.¹²³ Later, in the search for more efficient inhibitors of acetylcholine esterase, substituted analogues of tacrine were developed with the synthesis of 9-amino-1,2,3,4-tetrahydroacridin-1-ols (76a–76, Chart 16). Various *in vitro* analysis and *in vivo* mouse-modelling experiments predicted an anti-Alzheimer's activity. Compounds 76a and 76b were the lead compounds that notably reversed the critical syndrome associated with the disease. With an (IC₅₀ = 0.070 and 0.30 μM for compounds 76a and 76b, respectively, these leads also exhibited a substantial *in vitro* inhibition of the uptake of radiolabeled noradrenaline and dopamine.¹²⁴ McKenna investigated acetylcholinesterase and butyrylcholinesterase inhibition potency and neuronal uptake of 5-HT (serotonin) and noradrenaline of novel acridine analogues (77–81, Chart 16). Notably, variation in the size of the carbocyclic ring of 1,2,3,4-tetrahydroacridine presented a different potency against cholinesterase enzymes (77, Chart 16). Introduction of an additional ring (78 and 79, Chart 16) amplified the activity of these compounds by a massive 100–400 fold and enhanced their selectivity for acetylcholinesterase (AChE) over butyrylcholinesterase (BChE). Compounds 80 and 81 also exhibited a promising potency.¹²⁵ To further define structural requirements for optimal binding to the AChE

Chart 17 Multimeric quinacrine conjugate, inhibitor of β -amyloid fibril formation.

Chart 18 Acridone/1,2,3,4-tetrahydroacridine tagged triazole linked inhibitors of AChE activity.

peripheral site, dimeric acetylcholinesterase (AChE) inhibitor compounds appended with a single or bis-tacrine unit were designed (82 to 85, Chart 16). By varying the nature of the basic amine appended as peripheral site ligands, an improvement in inhibitory potency and selectivity were apparent. The IC_{50} concentration of these derivatives against AChE varied

as the nature of the appended ligand as: dimethylamine (84) > 4-aminopyridine (83) > 4-aminoquinoline (85) > tacrine/1,2,3,4-tetrahydroacridine¹²⁶ (75).

Formation of β -amyloid peptide plaques and their accumulation in the brain regulate the pathogenesis of Alzheimer's disease. Dolphin *et al.* 2008, scrutinized

Chart 19 Piperidine linked acridine derivatives as inhibitors of Alzheimer's linked β -amyloid peptide and prion protein expression.

quinacrine derivatives mounted on a cyclic polypeptide through oxime linkages and investigated their potency against the formation of β -amyloid fibrils. *In vitro* analysis indicate that the multimeric compound **86**, Chart 17, inhibits the A β fibril formation with an IC_{50} value of $2 \pm 10 \mu\text{M}$ unlike its nonactive monomeric analogue **87**, Chart 17. Therefore, assembling multiple copies of acridine moieties to a central scaffold could provide novel strategies for enabling multiple interactions with the target.¹²⁷

Mohammadi-Khanaposhtani *et al.* 2015, performed QSAR analysis for the identification of novel acridone-1,2,4-oxadiazole-1,2,3-triazole and acridone-1,2,4-benzyl-1,2,3-triazole hybrids. The molecules **88b** and **89g**, Chart 18; displayed pertinent activities against antiacetylcholinesterase enzyme with an $\text{IC}_{50} = 11.55 \mu\text{M}$ and $\text{IC}_{50} = 7.31 \mu\text{M}$, respectively. The results corroborated with the molecular docking investigations thus confirming a dual binding site inhibitory profile for the test compounds.^{128,129} Najafi *et al.* 2017, designed a new series of 1,2,3,4-tetrahydroacridine-1,2,3-triazole hybrids which were likely to be dual inhibitors of cholinesterase (**90a–90o**, Chart 18). The test compounds presented decent *in vitro* inhibitory activities toward both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)

enzymes. With an $\text{IC}_{50} = 0.521 \mu\text{M}$, compound **90l** was found to be the strongest candidate against AChE whereas the compound **90j** with an $\text{IC}_{50} = 0.055 \mu\text{M}$ displayed the most superior anti-BChE activity. *In vivo* studies on compound **90l** confirmed the reversal of the Alzheimer related symptoms resulting from scopolamine-induced memory impairment. Additionally, physical investigations in the form of molecular modeling and kinetic studies on compounds **90l** and **90j** validated their simultaneous binding to the peripheral anionic site (PAS) and catalytic sites (CS) of AChE and BChE.¹³⁰ Wu *et al.* 2018, reported novel hybrids taking a tacrine/1,2,3,4-tetrahydroacridine scaffold which is a functional analogue of acridine. The resulting tacrine-1,2,3-triazole compounds (**92a–92k**, Chart 18) were appraised for their inhibitory potency against acetylcholinesterase (AChE) and horse serum butyrylcholinesterase (BChE). The best candidate screened among the test compounds was **91b**, which presented a robust inhibitory potential against AChE and BChE enzymes with an IC_{50} value of $4.89 \mu\text{M}$ and $3.61 \mu\text{M}$, respectively. Mechanistic insights revealed the sensitivity of quinoline substituents at the C-1 position of the 1,2,3-triazole ring and its participation in π - π interactions with the residues Trp286 (hAChE), Ser287 (hBChE), and Pro285 (hBChE) in the

Chart 20 a. and b. Acridine-based anti-prion compounds.

peripheral anionic site (PAS) region. On the other hand, the acridine ring was found to be involved in the π - π interaction with Trp86 (hAChE) and Trp82 (hBChE) in the catalytic active site (CAS) region.¹³¹

2.4.2 Treatment of prion disease. Csuk *et al.* 2009, designed a series of piperidine linked dimeric acridine hybrid compounds (92a–92r, Chart 19) which were reported to interfere in the protein association of prion- and Alzheimer-

specific proteins and β -amyloid peptides using a screening system based on flow cytometry analysis utilizing the sophisticated fluorescence-activated cell sorting (FACS) assay. Hybrid 92i was best suited for inhibiting the activity of β -amyloid peptides whereas hybrid 92g had a strong affinity for interfering with the expression of prion protein. Nevertheless, most compounds in this hybrid library displayed substantial anti-prion activities.¹³² The prominence of piperidine

spacer tagged to an acridine nucleus in the design of anti-Alzheimer's therapeutics was further supported by the development of a novel series of 1,2,3,4-tetrahydroacridine/acridine monomers tethered with piperazine linkers (**93** and **94**, Chart 19). With a submolar IC_{50} against cholinesterases molecular docking investigations revealed that these hybrids were found to be extremely effective predominantly against human acetylcholinesterase (hAChE) and human butyrylcholinesterase (hBChE) hence acting as dual binding site inhibitors.¹³³ Another major development in the design of piperidine trussed acridine hybrids occurred in the form of molecules **95a–95m**, Chart 19. The therapeutic propensity of these hybrids has been checked *in vivo* by adopting behavioral models of amnesia, which include step down passive avoidance and elevated plus maze assays. *In vitro* analysis of AChE analytes from brain homogenate of the test mice revealed hybrid **95c** with $IC_{50} = 0.33 \mu\text{M}$ as the most potential candidate. The *in vitro* biochemical assays for the investigation of various oxidative stress metabolites, including plasma nitrite, thiobarbituric acid reactive substances, catalase, superoxide dismutase, and glutathione, acknowledged the management of scopolamine-induced oxidative stress¹³⁴ by compounds **95**.

Quinacrine (**96**, Chart 20) earlier used as an antimalarial drug¹³⁵ was in later years found to inhibit the beta-structure-rich insoluble conformer of prion protein (PrP^{Sc}) which is the ingredient in prion related disorders.¹³⁶ This led to the design and development of anti-prion drugs based on an acridine nucleus and was inspired from the quinacrine design. A novel series of quinacrine analogues based on the acridine scaffold were introduced by Thi *et al.* 2008, (**97–100**, Chart 20) having basic appendages of pyridinyl, phenyl, morpholinyl, and piperidinyl tagged at the 9-amino substituent of acridine nucleus. The anti-prion activity of these compounds was checked using four different cell models persistently infected with scrapie prion strains (ScN2a, N167, Ch2) or a human disease prion strain (F3). With a sub-micromolar EC_{50} value in the range 0.1–0.7 μM , compounds **98e** and **98f** were the most potent candidates with all cell models. These compounds were also able to overcome PrP^{Sc} at non-toxic concentrations of 1.2–2.5 μM .¹³⁷ These investigations cemented the position of the acridine nucleus in anti-prion therapy. Normal prion proteins transform to a misfolded conformational isoform, which is implicated in the form of several human transmissible neurodegenerative conditions like the Creutzfeldt-Jakob disease. For developing therapeutics against this infrequent phenomenon, Dollinger *et al.* 2006, designed a novel class of hybrids incorporating structural analogues of quinacrine and imipramine (**101a–101r**, Chart 20). *In vitro* analysis validated the candidature of **101b** as the most promising anti-prion lead.¹³⁸ For further refining the anti-prion activity of quinacrine, May *et al.* 2003, designed quinacrine-based bis-acridines with an aim to observe a synergistic effect against prion protein (PrP) corresponding to the two quinacrine residues. The results were not as expected although this report revealed a high binding affinity for bis-

acridines with nearly a 10-fold increase in the anti-prion potency as compared to quinacrine (**102**, **103**, **104**, Chart 20). Interestingly, the merging of acridine and iminodibenzyl moieties to get hybrids **101a–101f** created additive anti-prion effects in ScN2a cells with **101a** as another potential candidate with a 20-times increase in anti-prion potency.¹³⁹ A further confirmation of a bivalent approach as a feasible tactic to appraise the design of anti-prion chemical probes was made by Bongarzone *et al.* 2010, by introducing a 2,5-diamino-1,4-benzoquinones linker tethered between the two active anti-prion nuclei (**105** and **106**, Chart 20b). Compound **106** with a 6-chloro-1,2,3,4-tetrahydroacridine motif and with an $EC_{50} = 0.17 \mu\text{M}$ exhibited a remarkable anti-prion activity. Notably, with a low toxicity, the compound **106** was observed to contrast the formation of prion fibrils and oxidative stress (Chart 21).¹⁴⁰

2.5 Acridine interactions with P-glycoprotein: modulation of efflux/influx pumps

P-Glycoprotein is a transmembrane efflux pump whose cellular functioning is regulated by ATP and MDR1 gene in humans.¹⁴⁹ It is associated with the typical phenomenon of multidrug resistance¹⁵⁰ which has rendered many clinical drugs counterproductive¹⁵¹ resulting in a huge loss of capital and resources to overcome this critical occurrence.¹⁵² Numerous strategies have been adopted¹⁵³ starting from nanotherapy^{154–158} to critical designing and development of biologically interactive scaffolds^{159–163} yet, no major breakthrough has been witnessed until now. Multidrug resistance (MDR) arbitrated by MDR1 P-glycoprotein (P-gp) overexpression is therefore a main barrier to transporter-mediated chemotherapy in cancer patients. Taking acridine as the central scaffold, Gopinath *et al.* 2008, developed chemosensitizers, which are proxies that upsurge the sensitivity of MDR cells to the toxic influence of formerly less effective drugs. N10-Substituted-2-chloroacridone compounds reported as chemosensitizers (**107a–107p**, Chart 22a) were checked for their capability to escalate uptake of the drug vinblastine (VLB) in MDR KBChR-8-5 cells. Notably, a 25–30 fold reversal of resistance of KBChR-8-5 cells to VLB was observed in the presence of test compounds **107i**, **107m**, **107n**, **107o**, and **107p**. *In vitro* efflux investigations indicated that the test compounds considerably restricted the efflux of VLB thereby proposing that there may be competition for P-gp.¹⁶⁴ Singh *et al.* 2009 and 2010, scrutinized sensibly designed acridone products for their influence on Rhodamine6G (R6G) influx/efflux in the fungal cells of CAI4 strain of *Candida albicans* (**108a–108e**, Chart 22a). Compound **108e** gave the most significant results by inhibiting the growth of fungal cells by a cell rupturing mechanism. Furthermore, the influx and efflux of R6G in the fungal cells increased¹⁶⁵ in the presence of **108e**. These experimental investigations were supported by theoretical molecular docking investigations and revealed that the introduction of $-\text{COOH}$, $-\text{Cl}$ substituent at the C-4 position of the acridone scaffold in compounds

Chart 21 Recently reported hybrid compounds with anti-prion/anti-Alzheimer's activity.

109a–f, Chart 22a enhanced their interactions with components of the efflux pump. The –COOH group at C-4 interacted with P-gp and Mg²⁺ while the –Cl substituent at C-4 displayed interactions with ATP and Mg²⁺. The *in vivo* investigations and *in vitro* efflux/influx assays supported the applicability of **109e** with the –COOH functional group at the C-4 position of

acridone as the most suitable MDR modulator.¹⁶⁶ Boumendjel *et al.* 2007, performed experiments on human wild type (R482) transfected with breast cancer resistance proteins (BCRP, ABCG2) for which only a few inhibitors were known. Out of the series of new compounds **110a–e** and **111a–d**, the strongest candidature against the mitoxantrone

Chart 22 a. and b. Acridine and analogues as MDR modulators.

efflux was presented by compound **110e** with an $IC_{50} = 0.77 \mu M$, superior to the reference inhibitor GF120918.¹⁶⁷ Kumar *et al.* 2015, developed a series of N10-substituted acridone compounds (**112a–l**, **113**, **114a–b**, and **115a–b**, Chart 22a) and 2-(9-oxoacridin-10(9H)-yl)-N-phenyl acetamide derivatives (**116a–o**, Chart 22) and through various *in vitro* investigations envisaged their multi-drug resistance (MDR) modulation and anticancer potential. *In vitro* cytotoxicity analysis for compounds against human colon adenocarcinoma (HT-29), human cervical epithelioid carcinoma (HeLa), human breast adenocarcinoma (MCF-7), and human small cell lung carcinoma (A-549) cell lines by MTT assay validated substantial *in vitro* activities for compounds **112l** and **116l** against most cell lines. The multi-drug resistance modulation (MDR) potency of these compounds was examined *in silico* thereby presenting a clear picture of the interactions of compounds **112f**, **112g**, **112k**, **112l**, **114**, **115**, **116k**, and **116l** in the active site of P-glycoprotein (P-gp) and projecting a dual action inhibition through anti-cancer activity and MDR modulation.^{168,169}

Krishnegowda *et al.* 2002, examined the activity of 2-methoxy N10-substituted acridone **117a–o**, Chart 22b to establish a structure–activity relation analysis for the length of linkers connecting the acridine nucleus with N10-substituents. The capability of the test compounds to increase the uptake of vinblastine (VLB) in MDR KBCh^R-8-5 cells was scrutinized and the results screened compounds **117i**, **117f** and **117o** as potential leads. The *in vivo* analysis of compounds **117a–o** for regulating steady state accretion of VLB, a substrate for efflux mediated by P-glycoprotein (P-gp) on the MDR cell line KBChR-8-5, indicated a substantial inhibition of VLB efflux indicating a competition for P-gp between VLB and compounds under investigation. The cytotoxicity analysis presented a true picture about the role of linker chain length as an increase in chain length¹⁷⁰ augmented antiproliferative activity. Substitution of the $-OCH_3$ group from position 2 (**117a–o**, Chart 22b) to the new position 4 to get compounds **119a–o** was done as an attempt to validate SAR analysis for the position of the substituent on the acridone nucleus. A shift in the position of a substituent made a significant effect on cytotoxicity and anti-MDR activity for the test compounds.¹⁷¹ Prasad *et al.* 2008 and 2011, quantified the effect of a halogen substitution on the overall activity of N10-substituted acridones by developing a set of halogenated derivatives from the series **117a–o** to obtain a new series **118a–o**, Chart 22b. *In vitro* analysis in comparison with reference drugs doxorubicin (DX) and C1311 against several cancer cell lines of SW 1573, SW 1573 2R 160, human embryo kidney cells HEK 293, HEK 293 MRP4, HEK 293 MRP5i, human promyelocytic leukemia sensitive cell line HL-60, vincristine resistant HL-60/VINC, and doxorubicin resistant HL-60/DX validated the activity of the test molecules. Compound **118h** with chloride substitution and the fluoride substituted **118o** were screened to be the most potential lead signifying a possible and positive advancement towards the development of novel anti-MDR agents.^{172,173} Horton *et al.* 1997, intro-

duced bis-acridones tethered *via* a propyl or butyl linker (**120**, Chart 22b) as potential MDR modulators. Reportedly, the potency of compound **120** {1,3-bis(9-oxoacridin-10-yl)-propane} was found to be quite tremendous. A significant 9-fold rise in the steady state accretion of vinblastine (VLB) in the multidrug-resistant cell line KB8-5 was observed with 1 μM of compound **120**. Interestingly, compound **120** showed no signs of toxicity up to 3 μM concentration and an entire reversal of VLB resistance in KB8-5 cells could be observed at this dose. However, the effect of compound **120** on the cells reversed promptly from the moment of its removal from extracellular environment. Remarkably, the steady state accumulation of compound **120** and its rate of efflux in drug sensitive KB3-1 and drug-resistant KB8-5 cells displayed a parallel relationship confirming an inefficient transport by P-gp.¹⁷⁴ Kelly *et al.* 2009, introduced a novel derivative: (3-chloro-6-(2-diethylamino-ethoxy)-10-(2-diethylamino-ethyl)acridone) (**121**, Chart 22b) which presented exceptional synergistic properties with verapamil, chloroquine, and amodiaquine against quinoline resistance as well as quinoline-sensitive parasites. The integral acridone core promotes π – π stacking for binding to haem, the N-appendage provides a hydrogen bond acceptor needed for the chemosensitization function, and the C6-substituent expedites accumulation in the digestive vacuole (DV) *via* acid trapping. Compound **121** also results in an apparently mechanistically distinct synergism with quinine and with piperazine with an intrinsic potency and resistance-counteracting functions.¹⁷⁵

Antonini *et al.* 1999, presented a series of DNA-intercalating antitumor agents: (amino)alkyl-substituted 2,3-dihydro1H,7H-pyrimido[5,6,1-de]acridine-1,3,7-triones (**122a–i**, Chart 22b). *In vitro* analysis of these derivatives were performed on eight multidrug-resistant tumor cell lines which included human colon adenocarcinoma: HT29, LoVo sensitive and LoVo/Dx (doxorubicin-resistant) and human ovarian carcinoma: A2780 sensitive, A2780cisR (cisplatin-resistant), CH1, CH1cisR (cisplatin-resistant), and SKOV-3 cells. Compounds **122a**, **122i**, and **122g** were reported as the most potential candidates that gave desirable results in terms of cytotoxicity, lipophilicity, and tumor inhibition profile in MDR cell lines.¹⁷⁶ Kelly *et al.* 2007, while working on the MDR modulating drugs against *Plasmodium falciparum*, designed another series of novel N-substituted acridones tethered with an alkyl side chain appended to a tertiary amine group (**123**, Chart 22b). These test compounds synergistically raised the sensitivity of quinolone-based antimalarials: desethylchloroquine and quinine in chloroquine resistant parasite Dd2. Apparently, these novel acridone chemosensitizers were reported to compete for the chloroquine binding site in *P. falciparum* CQ resistance transporter (PfCRT) and substantially diminished the efflux of chloroquine from the food vacuole. Derivatives with $n > 4$ being weakly basic might diffuse across the biological membranes in the parasite in a unionized form and upon entering the acidic food vacuole may get protonated, thereby altering the pH of the environment and eventually interfering with the efflux of chloroquine and

restoring the efficacy of CQ and other quinoline antimalarials. These observations confirmed the validity of compounds 123 as novel pharmacophores for advancing chemosensitization based MDR modulators against *P. falciparum*.¹⁷⁷

3. Conclusion

The acridone nucleus endowed with numerous features like planar structure, fluorescent behavior, and DNA intercalation properties is a privileged synthon for the development of modern therapeutics. Its compatibility with biological systems and ability to interact with biomolecules of interest therefore make the acridone nucleus a useful moiety in the development of target-based drug delivery therapy for preparing hit to lead molecules.

Conflicts of interest

The authors have no conflicts of interest.

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