1.1. INTRODUCTION

“Privileged structure” in the year 1988 this term was first uncovered by Evans\(^1\) for heterocyclic 1,4-benzodiazepine-2-one, who defined it as “a single molecular framework able to provide ligands for diverse receptors.” This noticeable finding lead towards higher hit rate for some specific structural libraries of organic compounds than typical high-throughput screening results. The concept of privileged structure has widely been used for the discovery of novel biologically active molecules during the past two decades.

![Figure 1.1 Some examples of privileged structure containing drugs in market](image-url)
Over the past 15 years the privileged structure concept has found to be fruitful approach for the discovery of novel biologically active molecules. Privileged structures are those molecular scaffolds having dynamic binding properties, so as single scaffold capably provide a range of different biological targets through modification of functional groups for potent and selective ligands. In addition, these typically exhibit good drug-like properties, resulting in more drug-like compound libraries and leads. The utility of this approach is evidently shown by the numerous libraries that have been designed and constructed on such scaffolds. Privileged structure containing important drugs that are present currently in the market are shown in fig. 1.1.

From the time when privileged structure term was introduced to now a number of substructural frameworks have been implied as privileged structures, these include diphenylmethane derivatives, phenylsubstituted monocycles such as biphenyls, benzylpiperidines piperazines, 1,4-dihydropyridines, fused [7-6] ring systems such as benzothiazepines, benzodiazepines, fused [6-6] ring systems such as chromones, quinoxalines/quinazolines, 2-benzoxazolones, benzopyrans, pyranocoumarin, 1,4-dihydropyridine, and fused [5-6] ring systems such as benzimidazoles, indoles, spiro phenylpiperidines.

1.2. MAJOR CLASSES OF PRIVILEGED STRUCTURES AND ORGANISATION OF THE PRESENT REVIEW

- Fused [6-6] Ring Systems
  - Pyranocoumarins:
- Chromones:
- Coumarins:
- **Naphthalenes:**
  - Quinoxalines:
  - Quinazolines:
  - Quinazolinones:
  
  ➢ **Fused [5-6] Ring Systems**
  - Benzothiazoles
  - **Benzothiophenes**
  - **Indoles:**
    - Imidazopyridine:
  
  ➢ **Fused [7-6] Ring Systems**
  - 1,4-Benzodiazepin-2-ones:
  - 1,4-Benzodiazepin-2,5-diones and Pyrrolo[2,1-c][1,4]benzodiazepin-5,11-diones:
  - 1,5-Benzothiazepin-4-ones

  ➢ **Aryl-Substituted Monocycles**
  - Biaryls as a privileged scaffold:
  - Arylpiperazines:
  - Arylpiperidines:
  - Dihydropyridines:
  - Dihydropyrimidones:
  - **Arylidene Thiazolidines:**

These four main classes will be discussed in detail hereafter in the present review:

✔ Naphthalenes:
Benzothiophenes
Indoles:
Arylidene Thiazolidine:

1.2.1. Naphthalenes as privileged structure

Rasha et al\(^{15}\) synthesized compound 1 via aldol condensation of 2-acetyl (5,6,7,8-tetrahydro-naphthalene) with 1-naphthaldehyde followed by reacting with thiourea in 1\% ethanolic sodium hydroxide. Compound 9 recorded IC\(^{50}\) value at 5.07 \(\mu\)g/ml in the Caco-2 cell line, which is a continuous cell of heterogeneous human epithelial colorectal adenocarcinoma. Pradidphol N et al\(^{16}\) described the anticancer activity of new naphthamides. Compounds 10 and 12 showed the most potent inhibition against KB cells. They evidenced from decatenation assay that compounds 11 and 12 at 20 \(\mu\)M can inhibit hTopoIIa activity. They also reported docking experiments that revealed the same trend as the cytotoxicity and decatenation assay (fig 1.2).

![Figure 1.2](image_url)
Kerang Wang et al\textsuperscript{17} synthesized a series of novel naphthalimide derivatives with various hydroxyl alkyl amine chains through condensation and substitution reactions. They showed that compounds 13a-e as the DNA intercalator exhibited middle binding affinities with Ct-DNA. Compound 13c possessed potential application as DNA staining agent. Compound 13c and 13e exhibited potent anticancer activities against Bel-7402 cell line with IC\textsubscript{50} values of 5.57 and 9.17 µM, respectively. Upadhayaya R S\textsuperscript{18} have designed and synthesized naphthalene based molecules that were evaluated for their antimycobacterial activity against drug sensitive Mycobacterium tuberculosis H37Rv in vitro at single-dose concentration (6.25 µg/mL). Minimum inhibitory concentration of compounds 14-17 was found to be 6.25 mg/mL. They also showed molecular modeling and docking studies of designed compounds and found hydrogen bonding with Glu-61, Tyr-64 and Asn-190 amino acid residues at the putative binding site of ATP synthase, these interfaces were articulated as shown by TMC207 and Mefloquine, where hydrogen bonding was found with Glu-61 and Tyr-64 respectively (fig 1.3).
Evelia R *et al*\(^{19}\) reported the synthesis of naphthalene, di- and tetra-hydronaphtalene derivatives as restricted analogues of isoCA-4 and their anticancer properties. This group observed high cell growth inhibition against four tumour cell lines at a nanomolar level with dihydronaphthalenes 18a, b, and c; tetrahydronaphtalene 19 and naphtalene 20. These compounds exhibited a significant inhibitory activity toward tubulin polymerization (IC\(_{50} = 2-3 \, \mu M\)), comparable to that of isoCA-4. They showed that the effect of the lead compounds 18b and 20 on the cancer cells was associated with cell cycle arrest in the G2/M phase. Verma M *et al*\(^{20}\) published the synthesis of amine substituted naphthalimide analogues and there in vitro antitumour activities against 60 tumour cell lines at a single dose concentration of 10 \(\mu M\). Compound 21 exhibited significant growth inhibition and was proved to be fivefold more active than standard antitumour drug 5-fluorouracil (5-FU) with TGI and MG-MID GI\(_{50}\) values of 38.71 and 5.05 respectively. ct-DNA binding studies of this compound revealed strong interacting properties. In this study, Wei A *et al*\(^{21}\) described synthesis of novel naphthalene compounds and screening for their antidepressant-like activities in vitro and in vivo. Their values for two descriptors (ClogP, tPSA) of the bloodbrain barrier (BBB) were calculated for early assessment of the central nervous system (CNS) drug-likeness. Many of their compounds demonstrated potential protective effects on corticosterone-induced lesion of PC12 cells although they cannot repair the irreversible oxidant injury to PC12 cells by hydrogen peroxide. During their study they found the in vitro cytotoxicity data on HEK293 and L02 cells that suggested compound
22 to be a promising antidepressant candidate for subsequent investigation (fig 1.4).

Liwei Z et al\textsuperscript{22} reported Selenium analogues of two known sulfur compounds their anticancer activities. The primary results showed that most compounds had moderate anticancer activities with IC\textsubscript{50} values between $10^{-6}$ and $10^{-5}$ M. Another selenium analogue 23 showed the highest activity with the IC\textsubscript{50} values around 5.3 µM against K562 and MCF-7 cell lines. Pandya A B et al\textsuperscript{23} reported a facile route for the synthesis of 2-(5-substituted-1H-pyrazol-3-yl) naphthalen-1-ol which was employed for the anti-inflammatory activity. Further they evaluated compounds for in-vivo anti-inflammatory activity by acute carrageenan induced paw edema standard method in rats. Comparatively the standard drug Indomethacin showed 31.03\% inhibition of rat paw edema volume. From the obtained results, they concluded that compound 24 exhibited maximum activity. Kamal A et
al\textsuperscript{24-27} synthesized a library of new aryl-substituted naphthalene C8-linked pyrrolo[2,1-c][1,4]benzodiazepine (PBD) conjugates with various linker architectures and evaluated for their anticancer activity against a panel of 11 human cancer cell lines. They reported that thermal denaturation studies showed effective DNA binding capacity relative to DC-81 and induction of G0/G1-phase arrest. Also cause an increase in the levels of p53 and caspase-9 proteins, followed by apoptotic cell death. These PBD conjugates 25 and 26 showed significant anticancer activity, with GI50 values ranging from 0.01 to 3.41 µM, in comparison with some previously reported PBD conjugates such as phosphonatelinked PBD conjugates (GI50 values in the 0.17–30.50 µM range), 1,2,3-triazole-linked PBD conjugates (GI50 values in the 0.13–30.50 µM range), and triazolobenzothiadiazine linked PBD conjugates (GI50 values in the 0.22–30.30 µM range) (fig 1.5).

![Chemical structures](image-url)
Two novel functionalized endoperoxide-forming naphthalene derivatives DMNOH (27) and DMNether (28) of different polarity have been described by Damir P et al.\textsuperscript{28} which enable better flexibility for the incorporation of such photo-reactive derivatives in carrier materials of various properties. Further, they presented formation of bifunctional derivatives as a new concept to enable synergistic effects of multiple cooperating singlet oxygen binding sites which could also improve their reactivity as anticancer and antibiotic agents. They studied successful penetration of endoperoxide loaded polymer nanoparticles into human cancer cells and found promising results on cytocidal and cytostatic effects (fig 1.5).

![Figure 1.6](image_url)

The process for synthesizing naftopidil\textsuperscript{29, 30} (29) comprises of reacting 1-naphthol and epichlorohydrin in aqueous sodium hydroxide to get 1-(1-naphthyloxy)-2,3-epoxypropane followed by reaction with 1-(2-methoxyphenyl)piperazine. Naftopidil\textsuperscript{31} showed similar in vitro growth-inhibitory effects on all cell lines and an increase in G1 cell-cycle arrest. In vivo tumorigenic studies reveal significant reduction of ACHN tumor weight, Ki-67 index and microvessel density (MVD) in naftopidil-treated mice. Studies in mouse xenograft models showed a significant MVD reduction in naftopidil-treated excised human RCC.
Studies on growth-inhibitory effects of naftopidil suggest it may be a novel anticancer agent and a potential preventive option for RCC (fig 1.6). Lokhande M N et al\textsuperscript{32} demonstrated the strategy for asymmetric synthesis of (R)/(S)-propranolol, (R)/(S)-naftopidil and (R)-monobutyrin with spiroketal formation by desymmetrization, used Mitsunobu reaction for epoxide and ether formation with Steglich esterification and CAN (cerium ammonium nitrate) mediated ketal deprotection as key steps in the synthesis followed by regioselective ring opening of epoxide.

Hiroyoshi H et al reported results of an study that calmodulin antagonists such as N-(6-aminohexyl)-5-chloro-l-naphthalenesulfonamide (31) may selectively block the phase of the cell cycle (G1/S boundary phase) in a manner similar to that found with excess thymidine treatment (thymidine inhibit cell proliferation through inhibition of DNA synthesis. They showed that at 25 picoMolar concentration of compound 31 arrests cell cycle growth at the G1/S boundary phase. They also suggested that initiation of DNA synthesis
requires Ca2' or calmodulin or both. The naphthalene sulfonamide calmodulin antagonists, (31) and N-(4-aminobutyl)-5-chloro-2-naphthalenesulfonamide (33), both induce limited myeloid differentiation of the human promyelocytic cell line, HL-60. In addition, these inhibitors augment the differentiation observed when HL-60 cells are induced with retinole acid, dimethyl sulfoxide, or dibutyryl cyclic adenosine monophosphate. This study examined the response of HL-60 cells to the naphthalene sulfonamide calmodulin antagonists (30-33), which may also antagonize the action of protein kinase C. This study correlated the myeloid differentiation of HL-60 cells induced by naphthalene sulfonamides with calmodulin and protein kinase C inhibition potential in vitro (fig 1.7).

![Chemical structures](image)

**Figure 1.8**

Ethiraj K R et al synthesized Methoxy-substituted chalcones from 2-naphtylethanone and aromatic aldehydes via simple synthetic protocol. The in vitro cytotoxicity activities of the compounds were
found to possess significant cytotoxic activity against three human cancer cell lines, *viz.* HeLa, HCT15, A549. Chromatin condensation studies revealed the apoptotic nature of the compounds. They found compounds 34 and 35 as the best. In this study Kim D H and group\textsuperscript{41} investigated the effects of a novel analogue of resveratrol, HS-1793 (37), on the expression of HIF-1α and vascular endothelial growth factor (VEGF) in PC-3 human prostate cancer cells and found that HS-1793, a novel analogue of resveratrol, may be a new potent chemopreventive agent against human prostate cancer cells. Another study by Kim J \textit{et al}\textsuperscript{42} on HS-1793 using MCF-7 (wild-type p53) and MDA-MB-231 (mutant p53) human breast cancer cells revealed that the compound inhibited cell growth and induced apoptotic cell death in a concentration-dependent manner and induced G2/M arrest in the cell cycle progression in both types of cells\textsuperscript{43} (fig 1.8).

![Figure 1.9](image)

Mooney Á \textit{et al}\textsuperscript{44} reported study of N-(6-ferrocenyl-2-naphthoyl) dipeptide ethyl esters (38) that showed potent nanomolar activity in the H1299 NSCLC and Sk-Mel-28 malignant melanoma cell lines. Durrant J D \textit{et al}\textsuperscript{45} presented some new low-micromolar inhibitors (39) that bind to a newly revealed cleft which represents a putative drug-like site
might play a role in the favourable binding of these novel TbREL1 inhibitors (fig 1.9).

Nafcillin sodium (40) is a beta-lactam antibiotic of the class penicillin. It is used to treat infections caused by Gram-positive bacteria, particularly, species staphylococci species that are resistant to other penicillins. Nafcillin is considered to be therapeutically equivalent to oxacillin.46

![Chemical structure of Nafcillin sodium](image)

**Figure 1.10**

Rao K V V P et al17 reported a convenient method for the preparation of Nafcillin Sodium, a penicillin antibacterial agent, with high purity. The procedure involves the acylation of 6-aminopenicillanic acid with 2-ethoxy-1-naphthoyl chloride in the presence of triethylamine (fig 1.10).
Privileged scaffolds in medicinal chemistry: At a glance

Naftifine\(^\text{48}\) (41) is an antifungal drug used for the treatment of tinea pedis, tinea cruris, and tinea corporis. Its mechanism of action possibly involve selectively blocking sterol biosynthesis via inhibition of the squalene 2,3-epoxidase enzyme. Synthetic route comprises of preparing Schiffs base followed by reduction with NaBH\(_4\) to give amine, which was then reductively methylated by means of CH\(_2\)O and excess NaBH\(_4\).\(^\text{49}\) Another method was disclosed in the patent CN 103664631 A. Sanphui P et at\(^\text{50}\) reported molecules (42, 43) that show significant protection of neuronal cells against trophic support deprivation. Importantly, these are not toxic to normal cells and effective in low doses (fig 1.11).

Terbinafine hydrochloride\(^\text{51}\) (44) is a synthetic allylamine antifungal which is highly hydrophobic in nature and tends to accumulate in skin, nails, and fatty tissues. Alami M et al\(^\text{52}\) described a Two-Step Synthesis of Terbinafine as shown in fig. 1.12. Another process was reported by Kim G et al\(^\text{53, 54}\) where they projected Palladium coupling for the 1,3-diyne synthesis, stereospecific
Aluminium Hydride reduction to \((E)\)-1,3-enyne and sulfonate-secondary amine coupling to get Terbinafine.

\[
\begin{align*}
\text{Aluminium Hydride} & \rightarrow \text{(E)-1,3-Enyne} & \text{Sulfonate} & \rightarrow \text{Secondary Amine} \\
& \rightarrow \text{Terbinafine}
\end{align*}
\]

Tolnaftate\textsuperscript{55, 56} (42) is a synthetic thiocarbamate used to treat fungal conditions such as jock itch, athlete's foot and ringworm. The synthesis of tolnaftate comprises of three-step process starting by reacting 2-napthol with a base, to deprotonate the acidic hydrogen, followed by reacting with an intermediate formed from N-methyl-\(m\)-toluidine with \(CS_2\) and \(CH_3Br\). Displacement of the \(-SCH_3\) group resulted in the formation of final product (fig 1.13).

Richardson T I \textit{et al}\textsuperscript{57} synthesized phenoxy naphthalene derivatives (43) and showed that all compounds in the study bound to
ERα with good to excellent affinity (Ki = 1.89–0.09 nM) and range from good to moderate to non-selective for ERα over ERβ (0.8- to 33-fold). Wallace O B et al\textsuperscript{58} prepared a new series of constrained naphthalene-based SERMs (44). In this study they worked out over the side chain arrangement in the compounds and their binding effects over major cancer cell lines viz. MCF-7, Ishikawa (fig 1.13).

1.2.2 Benzothiophenes as privileged structure

Richardson T I et al\textsuperscript{57} also studied for Binding affinity (Ki), functional activity (Ishikawa antagonist IC50 and efficacy and agonist efficacy), in vivo rat uterine antagonist potency (ED50), E2 ratio for some benzothiophene derivatives (45) but unfortunately results were not much satisfactory. Chou Y et al\textsuperscript{59} reported Compound (46) by high throughput screening as a novel, potent, non-amidine factor Xa inhibitor with good selectivity against thrombin and trypsin. Lugar III C W et al\textsuperscript{60} evaluated a series of equine Estrogen (47) and showed that structure–activity studies with β-nor-6- thiaequilenin analogues of 17α-dihydroequilenin indicate that the orientation of the C-17 hydroxy group plays a more significant role than the C/D ring juncture with respect to determining affinity to the receptor. The uterine profile of the thiaequilenins 47a and 47b is encouraging and suggests that this structural platform may be useful for the design of tissue selective estrogens or SERMs (fig 1.14).
Wallace O B et al\textsuperscript{58} synthesized series of benzothiophene derivatives (48) and reported over the activity impact of spatial relationship between the side chain and ligand core. Compounds where the side chain is forced into the same plane as the backbone display significantly weaker antagonistic effects (markedly in the Ishikawa cell line) compared to the related structures where the side chain is pseudo-orthogonal to the core. This is presumably due to induction of differential receptor conformations by the ligand, which in turn leads to differential recruitment of coactivators and corepressors. Ferreira I C F R et al\textsuperscript{61} synthesized diarylamines in the 2,3,5-trimethylbenzo[b]thiophene series (49) bearing different substituents by applying the palladium-catalyzed C–N coupling methodology. The diarylamine skeleton and the different substituents for e.g. H, 1-OMe, 2-OMe, F etc. proved to be important for activity, changing selectivities and MICs, when compared with the functionalized benzo[b]thiophene for e.g. Br and NH\textsubscript{2} (fig 1.15).
Yang C et al\textsuperscript{62} synthesized benzothiophenes that contained a piperazine side chain (50) and described their binding affinities for estrogen receptors. These compounds were found to have high binding affinity and selectivity for ER \( \alpha \). It is also a potent agonist in bone tissue and an antagonist in uterus (fig 1.15).

Brunton S A et al\textsuperscript{63} reported biaryl substituted 1,4-diaminocyclohexanamides of 3-chlorobenzo thiophene-2-carboxylic acid as picomolar modulators of Hedgehog protein function. Preliminary SAR studies of the biaryl substituent led to a picomolar compound with in vivo activity of 51 has potential as a novel therapy for stroke and other neurological disorders. Bastian J A et al\textsuperscript{64} published the preparation and biological evaluation of benzo[b]thiophene diamines as thrombin inhibitors possessing conformationally restricted C-4" linkers. They showed that compared to the parent compounds i.e. the unsaturated derivatives that exhibited a modest twofold increase in thrombin inhibitory activity, whereas the more lipophilic carbocyclic ring containing analogues 51a and b affected an eightfold better profile. Sall D J et al\textsuperscript{65} studied the potential interaction of C-3" substituents of benzo[b]thiophene and found that
incorporation of small hydrophobic substituents (i.e. Br and Me) increase the potency of the parent compound by 8-fold (fig 1.16).

Nguyen T T B et al\textsuperscript{66} prepared novel series of combretastatin A-4 heterocyclic analogues with benzothiophene, attached at the C2 position and evaluated for their abilities to inhibit tubulin assembly: they reported a compound having a benzothiophene, showed an activity similar to those of colchicine or deoxypodophyllotoxine. They evaluated antiproliferative and antimitotic properties of this compound (54) against keratinocyte cancer cell lines and found that their compound had a major impact on the microtubule network in SKv-a and HaCaT cells. Pinto E et al\textsuperscript{67} evaluated the antifungal activity of several di(hetero)arylamine derivatives of the benzo[b]thiophene system against clinically relevant Candida, Aspergillus, and dermatophyte species. Their most active compound 55 showed a broad spectrum of activity (against all tested fungal strains, including
fluconazole-resistant fungi), with particularly low MICs for dermatophytes. Mourey R J et al.\textsuperscript{68} described the pharmacologic properties of a benzothiophene MK2 inhibitor (56) which is a potent freely reversible ATP-competitive compound. It inhibits MK2 activity having \( K_i \) value of 3 nM, found to be fairly selective against 200 human kinases (fig 1.17).

![Figure 1.17](image1.png)

Grese T A et al.\textsuperscript{69} have demonstrated that the 6-hydroxy and the 4\textquotesingle- hydroxy substituents of raloxifene are important for receptor binding and \textit{in vitro} activity. They showed that increased steric bulk at the 4\textquotesingle- position leads to increased uterine stimulation \textit{in vivo}, and additional substitution of the 2-aryl moiety is tolerated while additional substitution at the 4-, 5-, or 7-position of the benzothiophene results in reduced biological activity (fig 1.17).

![Figure 1.18](image2.png)
Liu H et al\textsuperscript{70} showed binding potency of a new SERM, 4′F-DMA (58), towards ER\textsubscript{α} and ER\textsubscript{β} with similarities to both raloxifene and DMA. They observed no estrogenic activity and 4′FDMA was seen to be antiproliferative in MCF-7 cells in response to estradiol treatment. More importantly 4′F-DMA was resistant to oxidation to quinoids in rat hepatocytes and in liver microsomes. Romagnoli R et al\textsuperscript{71} synthesized and evaluated benzoheterocyclic moieties and tethered to an alpha-bromo acrylic moiety acting as alkylating moiety. They found that compounds (59) were having potential antiproliferative activity against L1210 and K562 cells and some of them were found 70-fold more active than the bis-pyrrole counterpart against L1210 cell line. Papadopoulou M V et al\textsuperscript{72} identified 3-nitrotiazole-based heteroarylamides/sulphonamides as potent in vitro antichagasic drugs in which chlorothiophene-sulfonamides, benzothiopheneamides (17, 18) and the benzothiazole-amide 19 were active against T. cruzi at nM concentrations, being up to 14-fold more potent than Bnz (fig 1.18).

![Chemical Structures](image)

61a: $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{F}, R_2 = \text{OH}$
61b: $R_1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{F}, R_2 = \text{H}$
61c: $R_1 = \text{CH}_2\text{CH}_2\text{F}, R_2 = \text{H}$

Figure 1.19
Lee K C et al\textsuperscript{73} synthesized three fluoroalkylated derivatives (61a-c) of raloxifene with the formation of benzo[b]thiophene and a substituted phenyl group (ring C) using a Stille reaction as key step in the synthesis. The in vitro binding affinities of the substituted raloxifenes 61a-c were higher than the affinity of raloxifene itself (25%). Queiroz M R P et al\textsuperscript{74} prepared ortho-Chlorodiarylamines in the 2,3,7-trimethylbenzo[b]thiophene series by C–N palladium-catalyzed cross-coupling using P(t-Bu)\textsubscript{3} as ligand and NaOt-Bu as base. They reported that the thienocarboline (62) showed lower MICs for \textit{B. cereus} and for \textit{C. albicans} than the corresponding thienocarbazole but for \textit{B. subtilis} both present the same MIC (fig 1.19).

1.2.3. Indole based privileged scaffolds

Indole is present in a large number of important compounds occurring naturally or synthetically. Natural occurance could be of plants of marine type. They vary in colour and odour from simple alkylindoles to complicated indole derivatives. The compounds 3-(3'-indoyl) propionic acid, indole-3-pyruvic acid, and the 1-, 2-, and 5-methylindole-3-acetic acids possess activities similar to each other (Fig 1.20).
1.2.3.1. Natural products and alkaloids containing an Indole nucleus

Serotonin\textsuperscript{75} (67), a neurotransmitter, is a chemical created by the bilateral animals responsible to maintain mood balance, regulate aging, learning and memory. Serotonin levels and signalling alterations shown to regulate bone mass in mice and humans\textsuperscript{76}. Serotonin is biosynthesized in the body from tryptophan (63) which is a monoamine alkaloid, also believed to play as neuromodulator (fig 20). The potential anticancer properties of indole derivatives present in many plants and fungus are largely unexplored. One important bioactive molecule present in cruciferous vegetables is Indole 3-carbinol (I3C; 71) and known for prevention of some cancers for e.g. breast, prostate, colorectal and trans-placental cancer\textsuperscript{77-83}. Gastric acid converted I3C to 3, 3'-diindolylmethane (DIM, 72), a biologically active dimer, which participates in nuclear processes within the cell. Anticancer properties of I3C/DIM could be attributed via changes in cell cycle progression, apoptosis and DNA repair\textsuperscript{84, 85} (Fig 1.21).
Another alkaloid is evodiamine\textsuperscript{86} (73) isolated from *Evodiae fructus*. Its fruits are popularly used for the treatment of headaches and abdominal pain in China. This is also active against Alzheimer’s disease, obesity and cardiovascular diseases. In 2010 Shittu H. et al\textsuperscript{87} reported about increased glucose uptake capability of akuammicine (74) in fully differentiated 3T3-L1 adipocytes. This alkaloid is isolated from seeds of *Picralima nitida* (Apocynaceae) and is useful in the management of type2 diabetes (fig 1.21).

Vincristine\textsuperscript{88} (75) and Vinblastine\textsuperscript{89} (76), a well-known medications containing indole nucleus, used to treat a number of types of cancer. It works by inhibiting mitosis and cell cycle arrest. A monoterpene indole alkaloid named Vincamine\textsuperscript{90} (77) which is also a marketed drug works as peripheral vasodilator to increases flow of blood to the brain. Vincamine is which is found in the leaves of Vinca minor. Reserpine\textsuperscript{91} (78) is an antihypertensive and antipsychotic drug used to treat high blood pressure and psychotic symptoms (fig 1.22).
Yohimbine\textsuperscript{92} (79) derived from the bark of the tree named \textit{Pausinystalia yohimbe} found in Central Africa and is used for the treatment of erectile dysfunction. Vindesine\textsuperscript{93} (80) and Mitraphylline\textsuperscript{94} (81) act as anti-mitotic and apoptosis inducing chemotherapeutic agent respectively, used to treat many types of cancers, including lung cancer, breast cancer, lymphoma, leukaemia and melanoma (fig 1.23).

\textbf{1.2.3.2. Marine Product Containing Indole Nucleus}
aplysinopsins (82) are indole containing natural products, isolated from corals and sponges, geographically distributed in Indonasia, Pacific and Mediterranean regions. These natural products have found extensive attention of chemists as potential medicines. They show antimicrobial, anti-plasmodial and cytotoxic activities and are modulated as neurotransmitters so that to act as serotonin receptors modulators. South Pacific marine sponges Rhopaloeides odorabile and Hyrtios sp. produce bromoindole derivatives viz. 6-bromoindole-3-carbaldehyde, N-methyl-5,6-dibromotryptamine, 5,6-dibromotryptamine (83-85).

These play propitious role in cosmetics and pharmaceutical industry because of their antioxidant properties and anticancer, anti-inflammatory and anti-PLA2 potentials respectively. (fig 1.24)
Fascaplysin, a sponge-derived bis-indole alkaloid shows a wide spectrum of bioactivities viz. anti-HIV-1-RTase, p56 tyrosine kinase inhibition, antiproliferative, antifungal, anti-angiogenic and as DNA intercalator. An alkaloid, called 3-((6-methylpyrazin-2-yl)methyl)-1H-indole, has been isolated from actinomycete *Serinicoccus profundi* sp. nov., and other marine compounds (Fig 1.25) displayed weak antimicrobial activity without affecting normal human liver cell line.

### 1.2.3.3. Synthetic Bioactive Molecules Containing Indole Nucleus
Beckers, T. et al\textsuperscript{99} reported that the 2-arylidindoles (86a and b) and indolyl-3-glyoxamide (87) are highly active against various tumors, including paclitaxel resistant tumors too.

![Chemical structures of 2-arylidindoles and indolyl-3-glyoxamide](image)

**Figure 1.26**

Natural product combretastatin A-4 based 2,3-diarylindoles, also called as heterocombretastatins 88 were prepared by Medarde \textit{et al}\textsuperscript{100} who reported them as antineoplastic agents. Von Angerer\textsuperscript{101} and his group synthesized analogues of formyl indolo isoquinoline as 2-phenyldindoles and showed that compound 89 completely block microtubule assembly at 40 $\mu$M concentration (fig 1.26).
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Figure 1.27

The tubulin polymerization inhibitory activity of 2-aryl-3-arylcarbonylindoles 90 and 2,3-diarylindoles 91 was reported by Flynn et al in 2002\textsuperscript{102}. Hudson, A.L et al showed that β-carbolines (92) represent a novel class of imidazoline-2 ligands with indole moiety\textsuperscript{103}. Bos, M. et al\textsuperscript{104}, reported the synthesis and activity of 5-hydroxytryptamine 2c (5-HT2c) agonist 93 based on the pyrazino[1,2-a]indoles. Husbands, S.M et al\textsuperscript{105} demonstrated that 1,2,3,4-tetrahydro-β-carboline (THBC) bind at imidazoline-2 receptors with high affinity. Escude, C. et al\textsuperscript{106} reported compounds with the benzopyrido[4,3-] indole class 94 also act as DNA intercalaters. Campbell J.A.et al\textsuperscript{107} performed 3-arylmethylation of indoles having a 6-methylsulfonyl moiety in one-pot. His group while working on anti-inflammatory program directed compound 95 as potent and selective cyclooxygenase-2 (COX-2) inhibitor (fig 1.27).

Famitinib (96) is a tyrosine kinase inhibitor and is well absorbed and extensively metabolized in cancer patients. Research studies reveal that many of faminitib metabolites are important for bioactivation of various cellular enzymes.\textsuperscript{108} Perchellet J P et al\textsuperscript{109}
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synthesized novel 6,7-annulated-4-substituted indole derivatives (97), by combining 6,7-indolyne cycloaddition and cross-coupling reactions conditioning Suzuki-Miyaura and Buchwald-Hartwig coupling, his group found these compounds are effective against murine L1210 leukemic tumor cell proliferation in vitro. In 2007 Zhang, Q and his group\textsuperscript{110} synthesized a series of tubulin polymerization inhibitors containing indole and 1,2,4-triazole rings (98). They showed that compounds unveiled potent tubulin polymerization inhibitory activity with cytotoxic activity against MDR cancer cell lines. Inhibitor-protein interactions were demonstrated using molecular docking and dynamics simulation. Functionalization of 1-benzyl-3-[4-aryl-1-piperazinyl]carbonyl-1H-indoles (99) by the Pessoa-Mahana and his group showed potential as new class of bioactive ligands at D4 receptors.\textsuperscript{111} A series spiro-2-[3’-(2’-phenyl)-3H-indolyl]-1-aryl-3-phenylaziridines (100) synthesized by Sharma et al. found to display tremendous antibacterial activity against a series of Gram+ve and Gram-ve bacterial strains. Via SAR studies they showed that there exists a linear correlation between percentage activity index and molecular refractive index.\textsuperscript{112} Hosseinnia, R et al\textsuperscript{113} reported efficient and versatile protocol to functionalize indole-substituted chromene derivatives (101) via multicomponent reaction. This ultrasound induced reaction offered better yields and reaction times than the conventional method. They showed that compounds of this series found excellent antibacterial activity against Micrococcus luteus (fig 28). Akkoc group\textsuperscript{114} synthesized a series of 3-[4-substitutedpiperazin-1-yl)methyl]-1H-indole derivatives via Mannich reaction and studied cytotoxicity of compounds on 3 cell lines. The results revealed
variable IC50 values and demonstrated the importance of substitution at the N-4 position of piperazine (fig 1.28).

Singh P et al\textsuperscript{115} synthesized hybrids of indole and barbituric acids as anticancer agents (103) They evaluated their molecules over a panel of 60 human cancer cell lines and found out two significant molecules as COX-2 inhibitors. Doris Kaufmann et al\textsuperscript{116} published in 2007 the synthesis of 2-phenylindole-3-carbaldehyde (104) and reported their antimitotic activities in human breast cancer cells. These compounds as tubulin polymerization inhibitors arrested the cell cycle in G2/M phase that probably leads to cell death. Jacquemard Ulrich et al\textsuperscript{117} synthesized pyridine derivatives of mono- and bis-indoles (105,
that show properties of CDK inhibitors and cytotoxic agents. These researchers concluded the most motivating molecule as orthodox DNA minor groove binder then identified and characterized three CDK1 inhibitors that exhibit selectivity over GSK-3. Similarly, Nassar, E et al\textsuperscript{118} also reported some pyridine, and pyrimidine derivatives (107) connected to indole via aldol condensation of 3-indolaldehyde and 4-methoxyacetophenone followed by cyclization of pyridine over α-β unsaturated ketone and found to have good antitumor and antimicrobial activities (fig 1.29).

Five years back, Ahmed Kamal et al\textsuperscript{119} synthesized 3,3-diindolyl oxyindoles (108) and evaluated for anticancer activity. Indole α-methylene-γ-lactones (109) reported by Ding et al\textsuperscript{120} showed potency as AKT-m TOR signaling pathway kinase inhibitors. Yu-Shan Wu et al\textsuperscript{121} evaluated hydroxylated and O-demethylated, phase I metabolites of 6-methoxy-3-(3′,4′,5′-trimethoxy-benzoyl)-1H-indole, a potent antitumor agent (110). They found these metabolites active...
against various cancer cell lines at nanomolar to picomolar concentrations in the KB, H460, and HT-29 cell lines (fig 1.30).

Urgaonkar S et al\textsuperscript{122} published anti-malarial activity of 2-amino-3-hydroxyindoles (111). They efficiently synthesized its analogues with good yields and established the extraordinary use of TBDMSNH\textsubscript{2}. Ryu C K et al\textsuperscript{123} in 2009 synthesized 1H-pyrrolo[3,2-g]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1H-benzo[f]indoles (112) and evaluated their antifungal activities against pathogenic fungi (fig 1.30).
### 1.2.3.4. INDOLE CONTAINING SOME MARKETTED DRUGS

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Indication</strong></th>
<th><strong>Chemical Structure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan&lt;sup&gt;124&lt;/sup&gt;</td>
<td>Migraine, headaches</td>
<td><img src="image" alt="Sumatriptan" /></td>
</tr>
<tr>
<td>Ondasetron&lt;sup&gt;125&lt;/sup&gt;</td>
<td>Nausea and vomiting caused by cancer chemotherapy</td>
<td><img src="image" alt="Ondasetron" /></td>
</tr>
<tr>
<td>Alosetron&lt;sup&gt;126&lt;/sup&gt;</td>
<td>Severe diarrhea-predominant, irritable bowel syndrome</td>
<td><img src="image" alt="Alosetron" /></td>
</tr>
<tr>
<td>Roxindole&lt;sup&gt;127&lt;/sup&gt;</td>
<td>Anti-depressant and anxiolytic effects</td>
<td><img src="image" alt="Roxindole" /></td>
</tr>
<tr>
<td>Delavirdine&lt;sup&gt;128&lt;/sup&gt;</td>
<td>Anti-HIV</td>
<td><img src="image" alt="Delavirdine" /></td>
</tr>
<tr>
<td>Vinorelbine&lt;sup&gt;129&lt;/sup&gt;</td>
<td>Anticancer</td>
<td><img src="image" alt="Vinorelbine" /></td>
</tr>
<tr>
<td>Perindopril&lt;sup&gt;130&lt;/sup&gt;</td>
<td>Antihypertensive</td>
<td><img src="image" alt="Perindopril" /></td>
</tr>
<tr>
<td>Atevirdine&lt;sup&gt;131&lt;/sup&gt;</td>
<td>Anti-HIV</td>
<td><img src="image" alt="Atevirdine" /></td>
</tr>
<tr>
<td>Pindolol&lt;sup&gt;132&lt;/sup&gt;</td>
<td>Antihypertensive</td>
<td><img src="image" alt="Pindolol" /></td>
</tr>
</tbody>
</table>
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Arbidol,\textsuperscript{133} Antiviral

Binedaline,\textsuperscript{134} Antidepressant

Zafirlukast,\textsuperscript{135} Anti-Asthmatic

Cediranib\textsuperscript{136} Anticancer

Amedalin\textsuperscript{137} Antidepressant

Bucindolol\textsuperscript{138} β-Blockers

Panobinostat\textsuperscript{139} Anti-leukamic

Oxypertine\textsuperscript{140} Antipsychotic

Apaziquone\textsuperscript{141} Anticancer

Siramesine\textsuperscript{142} Antidepressant

Tropisetron\textsuperscript{143} Antiemetic

Indalpine\textsuperscript{144} Antidepressant
1.2.4. Thaizolidines as privileged structure:

In their effort to develop selective sphingosine kinase-2 (SphK2) inhibitors as pharmacological tools Liu A K et al$^{151}$ synthesized 3-(2-amino-ethyl)-5-[3-(4-butoxyl-phenyl)-propylidene]-thiazolidine-2,4-dione (K145). They found K145 is a selective SphK2 inhibitor. K145 also pointedly inhibited U937 tumor growth in nude mice both via intraperitoneal or oral administration, indicating in vivo efficacy of K145 as a potential lead anticancer agent. Önen F E et al$^{152}$ synthesized thiazolidine based compounds (113) and evaluated them as potent thymidylate synthase X inhibitors. They evaluated the catalytic activity of the enzyme in the presence of these molecules which revealed ThyX inhibitors with submicromolar concentrations could lead to effective potential biomedical interest. Gududuru V et al$^{153}$ after a study in 2005 concluded that 2-aryltiazolidine-4-carboxylic acid amides (114)
represent a new class of agents for prostate cancer agents. Their compounds induced apoptosis in prostate cancer cells. Gouveia F L et al\textsuperscript{154} in their study demonstrated enrichment of antimicrobial activity by replacement of thiocarbonyl instead of carbonyl in thiazolidine ring. They synthesized 5-arylidene-4-thioxo-thiazolidine-2-ones (115) and identified them as having multidrug-resistant antibacterial properties (fig 1.31).

Figure 1.31

In another work, Bozdag\textsuperscript{7}-Dundar O et al\textsuperscript{155} synthesized chromonyl-2,4-thiazolidinediones (116) derivatives to evaluate them as aldose reductase inhibitors. They reported that compound (117) to be the most active with IC50 value of 0.261, 0.021 \( \mu \)M. Mohan, R., et al\textsuperscript{156} published the findings obtained in his study that indicated that 2,4-thiazolidinedione group could be utilised to inhibit HDAC having potential for lead optimization (119) via derivatization of most active compound (118). Onen-Bayram et al\textsuperscript{157} identified potent cytotoxic thiazolidine compound via chemogenomics strategy as an apoptosis-inducing agent. They initiated by testing their compound on breast, endometrial, liver, and colon cancer cell lines and found (120) with IC50 upto 5 \( \mu \)M. Via Cell cycle analysis with ALC67 on liver cells they revealed that SubG1/G1 arrest. They also demonstrated involvement of caspase-9 in apoptotic pathway (fig 1.32).
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Figure 1.32

Lu Y et al\textsuperscript{158} reported synthesis of 2-arylthiazolidine-4-carboxylic acid amide (ATCAA) and their antiproliferative activity against melanoma and prostate cancer cells. The best selectivity and growth-inhibition activity was shown by Compound 121 against B16-F1, A375, and WM-164 (melanoma cell lines) whereas compounds 122 and 123 showed potency against DU 145, PC-3, LNCaP, and PPC-1 (prostate cancer). This group showed the dose dependent tumor growth inhibition in nude mice bearing A375 melanoma tumors via in vivo studies upto 10 mg/kg dose. Havrylyuk D et al\textsuperscript{159} synthesized novel 5-pyrazoline substituted 4-thiazolidinones and evaluated for in vitro anticancer activity. This group found that derivatives 124 and 125 demonstrated a particular sensitivity profile toward the leukemia subpanel cell lines with GI50 value ranging between 2.12-4.58 µM and 1.64-3.20 µM respectively. By hybridization of two diverse bioactive molecules Romagnoli R et al\textsuperscript{160} synthesized N-3-substituted-5-arylidene thiazolidine-2,4-dione derivatives (126) that contained a bromoacryloylamido moiety at p or m to the phenyl group of the arylidene portion. They observed suppressed proliferation of human myeloid leukaemia HL-60 and U937 cells. They concluded that compounds induced apoptotic cell death via caspase activation. Ha Y
M et al\textsuperscript{161} synthesized a series of novel thiazolidine derivatives of which (Z)-5-(4-hydroxybenzyliidene)thiazolidine-2,4-dione (127) (IC50 13.36 \(\mu\)M) and (Z)-5-(3-hydroxy-4-methoxybenzyliidene)thiazolidine-2,4-dione (128) (IC50 9.87 \(\mu\)M) showed much greater tyrosinase inhibitory activities. Kinetic studies revealed that 127 and 128 are competitive inhibitors of mushroom tyrosinase (fig 1.33).

Liu K et al\textsuperscript{162} published the synthesis and evaluation of a series of 2,5-disubstituted-thiazolidine-2,4-diones as potential anticancer agents by inhibiting Raf kinase inhibitor. They identified compound 129 as having improved anti-proliferative activities in U937, M12 and DU145 cancer cells via cell cycle arrest in S phase. Zheng C et al\textsuperscript{163} reported synthesis of 5-aryloxypyrazoles as antibacterial agents and found active against Grampositive bacteria \textit{Staphylococcus aureus} 4220, compound 130 found to be the most potent at MIC = 1 \(\mu\)g/mL against the multidrug-resistant strains. They also showed that the compounds tested did not affect cell viability on the Human cervical (HeLa) cells at their MICs. Mendonça E A M et al\textsuperscript{164} synthesized (5Z)-[5-acridin-9-ylmethylene-3-(4-methyl-benzyl)-thiazolidine-2,4-dione],
(131), for the purpose of developing more effective and less toxic anticancer drugs (fig 1.34).

Joseph A et al\(^\text{165}\) developed a series of novel 5-alkyl/aryl thiadiazole substituted thiazolidin-4-ones to be screened for in vitro anti-proliferative activity in MCF-7 cell line via MTT assay. His group showed that the compound of this series possesses an \(IC_{50}\) less than 150\(\mu\text{mol L}^{-1}\). They found, 2-(2-nitrophenyl)- 3-(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one (132), 2-(3-fluorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one (133), and 2-(4-chlorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-thiazolidin-4-one (134) to be the most active derivatives among the tested compounds with \(IC_{50}\) values of 46.34, 66.84, and 60.71 \(\mu\text{mol L}^{-1}\), respectively (fig 1.35).

Bertamino A et al\(^\text{166}\) reported that derivative 5-bromo-3’-(cyclohexane carbonyl)-1-methyl-2-oxospiro[indoline-3,2’-thiazolidine] (135) in the series synthesized by his group emerged as the most potent compound which showed to inhibit p53–MDM2
interaction at 5 μM in vitro. They confirmed the interactions between 135 and Trp23 and Phe19 clefts via docking studies (fig 1.35).

Thiazolidinedione (TZD) derivatives, also called glitazones, were developed in the early 1980s as drugs for type 2 diabetes. Among them, troglitazone, rosiglitazone, and pioglitazone were in the late 1990s. These drugs are known to act by binding to PPARs (fig 1.36).

![Figure 1.36](image)

Later, Troglitazone was withdrawn from the market due to severe liver toxicity in several patients. Rosiglitazone and pioglitazone are currently in clinical use. Recently, several studies have demonstrated compounds containing scaffolds similar to TZD exhibit inhibitory effects against PTP1B and other enzymes (fig 1.36).

1.3. CONCLUSION

In conclusion we have hereby reviewed and reproduced some privileged scaffolds containing molecules as well as some marketed drugs. The research on ‘privileged structures’ is of great importance in the field of medicinal chemistry. This area has been successfully explored for many target classes. This is proved to be an effective approach towards the discovery and optimization of novel bioactive molecules which permits the identification of greater numbers of bioactive compounds.
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