2. LITERATURE REVIEW

GAPS - AIM AND OBJECTIVES

2. Literature Review - Gaps - Aim and Objectives

2.1. Role of natural products in drug discovery

Natural Products has always inspired the scientific community for the discovery of newer drugs and therapeutic agents. Amongst the 38 drugs approved by USFDA in 2019, 8 drugs were either natural products/ inspired analogues (**Fig. 2.1**) [1]. Among these drugs, imipenem and cilastatin were marketed earlier, however, these drugs are approved as a new combination forms with relebactum, that is indicated for the complicated urinary tract and intra-abdominal infections.

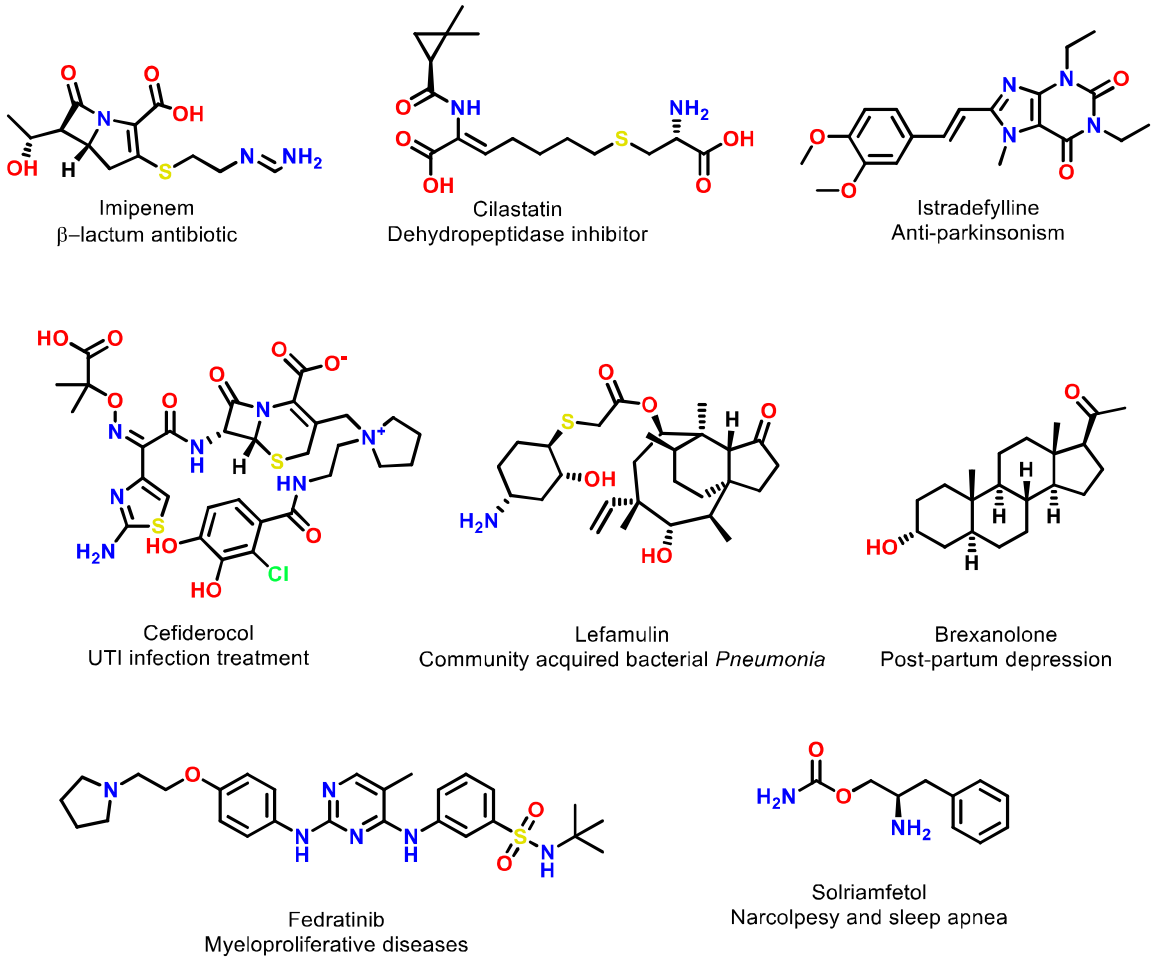


Fig. 2.1. USFDA approved natural product/inspired drugs in 2019 (with their clinical condition)

Plant-derived natural products are characterized by their wide structural diversity and low toxicity. Along with this, natural sources are included in the routine life of individuals as food, hence they act as larger sources of various bioactive natural products. In earlier times, the drug discovery from natural sources mainly relied on the trial-and-error method. However, the current scenario offers an advantage in terms of integrating sophisticated

techniques such as molecular modelling, high throughput screening, LC-MS/MS etc with the knowledge of various ancient documents that records the clinical uses of several plants with their indications. Thus drug development can be fastened with the help of such integrated and interdisciplinary approaches [2,3].

Chemical/structural modification of natural products also plays a major role in the drug discovery process. For instance, orlistat is a structural modification of lipstatin, derived from the *Streptomyces toxytricini* [4]. Similarly, chemical modification of cinchona alkaloids has resulted in the formation of oxautin-1 as an autophagy inhibitor [5]. There are many such examples wherein natural products have been used as leads for discovery of drugs/drug canddiadtes.

Overall, medicinal plants and their derived natural products have played a crucial role in drug discovery and development.

2.2. Plant-derived PL inhibitors

Due to the large potential and availability of traditional knowledge of the plant products for the management of obesity condition, more research has focussed on the identification of PL inhibitors from the plant sources. Traditionally these plants are used as crude extracts/mixtures, however, as a part of drug discovery programmes, investigation of bioactive natural products from these plant sources provides an exciting opportunity for the development of newer PL inhibitors.

The exhaustive research in the area of plant-derived PL inhibitors has resulted in the identification of a wide range of scaffolds, that are mainly classified as polyphenols, saponins, triterpenes, alkaloids, etc [6–11].

2.2.1. Polyphenols

Polyphenols is a general term for polyhydroxy phenolic compounds. They are widely found in vegetables, fruits and various medicinal plants. They have numerous pharmacological activities such as antioxidant, hypolipidemic, antiviral etc and are known to inhibit enzymes. Among the naturally derived PL inhibitors, polyphenols contribute a major share and are classified into various classes such as flavonoids, stilbenes, benzofurans etc. (**Fig. 2.2**) [12].

2.2.1.1. Flavonoids

Flavonoids consist of a C_6-C_3-C_6 structural backbone, in which the two C_6 units (Ring A and Ring B) are phenolic in nature and are linked to a chromane ring (Ring C). These flavonoids are further divided into various classes depending on the hydroxylation and oxidation pattern in the chromane ring (**Fig. 2.2**) [13].

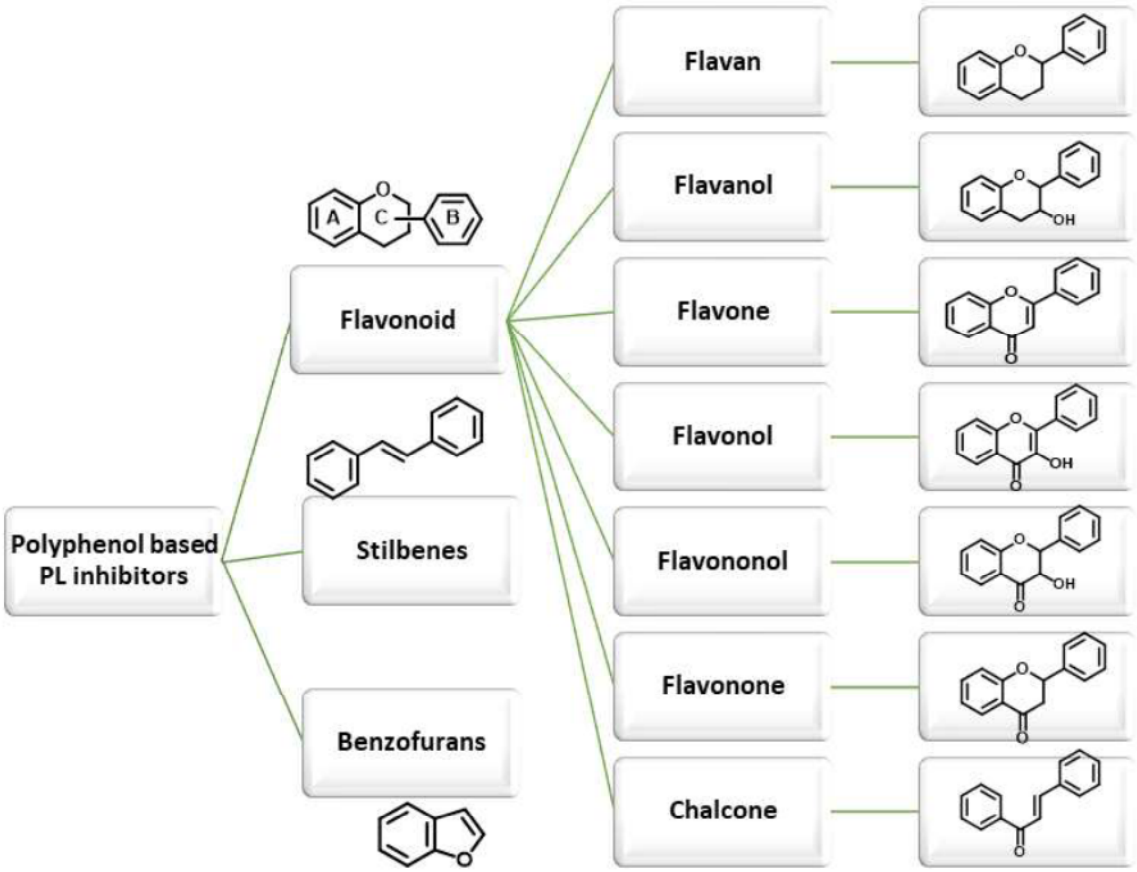


Fig. 2.2. General classification of polyphenol-based PL inhibitors

Polyphenols isolated from the tea varieties have been widely explored for the PL inhibitory potential. More than six varieties of tea species have been explored for their antiobesity effects *via* PL inhibition [2,14–18]. Numerous galloylated and non-galloylated natural products have been reported, wherein the increment in the esterification has resulted in the enhancement of PL inhibitory potential (**Table 2.1, Fig. 2.3**).

Table 2.1. Polyphenols reported from tea with PL inhibitory activity

Compound	IC_{50}	Ref.
(−) Catechin 3-*O*-gallate	0.543 μM	[18]
(−) Epiafzelechin 3- *O* -gallate	2.582 μM	[18]
(−) Epicatechin (4β→8) (−)-epigallocatechin 3- *O*-gallate	0.147 μM	[18]
(−) Epicatechin 3- *O* -(3′- *O* -methyl) gallate	0.680 μM	[18]
(−) Epicatechin 3- *O* -gallate	0.452 μM,	[18]
	2.37 μM	[19]
	13.00 μM	[20]
(−) Epicatechin 3- *O* -gallate (4β→8)-(−)-epigallocatechin 3- *O* -gallate	0.846 μM	[18]
−) Epigallocatechin	128 μM	[19]
(−) Epigallocatechin (4β→8)- (−)-epicatechin 3- *O* -gallate	0.913 μM	[18]
(−) Epigallocatechin 3,5-di- *O* -gallate	0.098 μM	[18]
(−) Epigallocatechin 3- *O* -gallate	0.349 μM,	[18]
	0.177 μM	[19]
(−) Epigallocatechin 3- *O* -gallate (4β→8)- (−)-epicatechin 3- *O*-gallate	0.612 μM	[18]
(−) Epigallocatechin 3- *O* -p-coumaroate	0.885 μM	[18]
−) Gallocatechin 3,5- di- *O* -gallate	0.213 μM	[18]
(−) Gallocatechin 3- *O*-gallate	0.437 μM	[18]
(+) Catechin (4R-8)- (−)-epigallocatechin	7.912 μM	[18]
(+) Gallocatechin (4R-8)-(−)-epicatechin	2.862 μM	[18]
8-C-ascorbyl(−)-epigallocatechin	0.646 μM	[18]
8-C-ascorbyl(−)-epigallocatechin 3- *O*-gallate	0.791 μM	[18]
Procyanidin B-2	7.958 μM	[18]
Procyanidin B-3	2.941 μM	[18]
Prodelphinidin A-2 3′- *O* -gallate	0.171 μM	[18]
Prodelphinidin B-2	2.951 μM	[18]
Prodelphinidin B-2 3,3′- di- *O* -gallate	0.107 μM	[18]
Prodelphinidin B-2 3′- *O* -gallate	1.969 μM	[18]
Prodelphinidin B-4	6.230 μM	[18]
Prodelphinidin B-4 3′- *O* -gallate	0.223 μM	[18]
Prodelphinidin B-5 3,3′- di- *O* -gallate	0.558 μM	[18]
Theaflavin	0.106 μM,	[18]
	1.203 μM	[19]
Theaflavin 3,3′-di- *O*-gallate	0.092 μM,	[18]
	0.364 μM	[19]
Theaflavin 3′- *O* -gallate	0.112 μM,	[18]
	0.447 μM	[19]
Theaflavin 3- *O* -gallate	0.514 μM	[19]

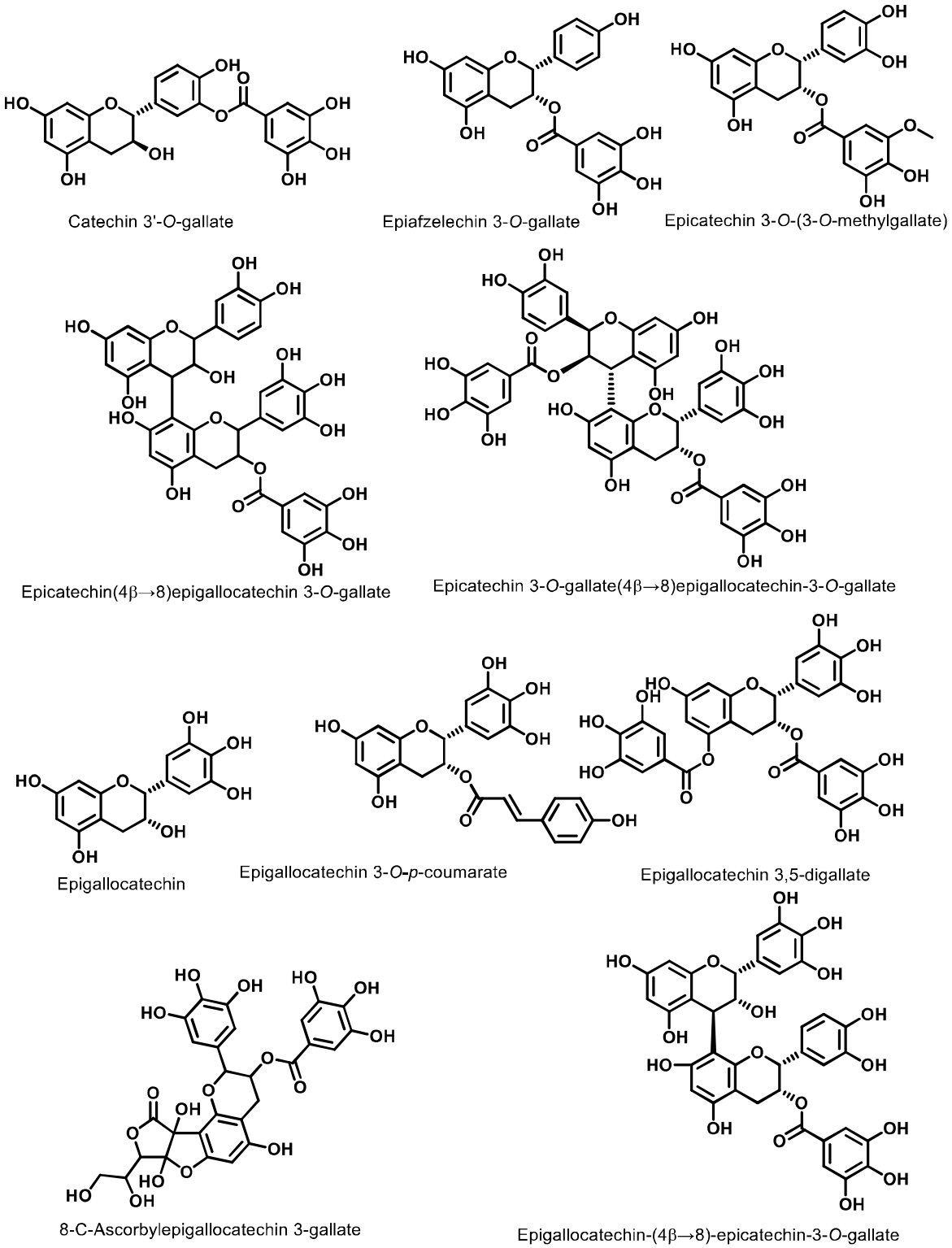


Fig. 2.3. Chemical structures of polyphenols isolated from tea

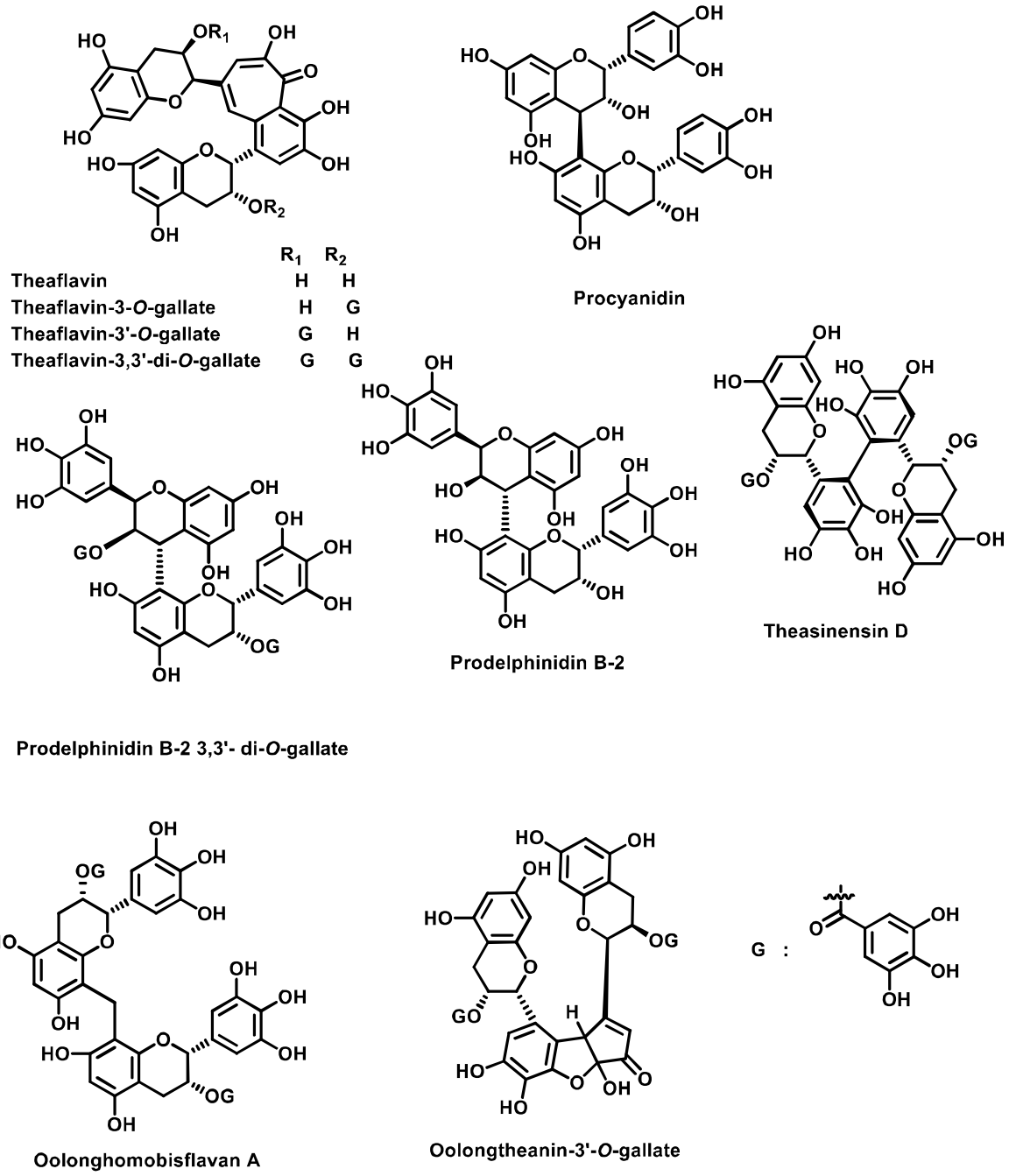


Fig. 2.3 Chemical structures of polyphenols isolated from tea. ……*contd*

Polyphenols from other plant species have also been explored. However, they exhibited a lesser PL inhibitory potential than the tea polyphenols (**Table 2.2, Fig. 2.4**).

Table 2.2. Polyphenols reported from various plants with PL inhibitory activity

Compound	**IC_{50} (μM)**
Eremochloa ophiuroides [21]	
Derhamnosylmaysin	25.9
Chrysoeriol 6-*C*-β-D-boivinopyranoside	50.5
Isoorientin	44.6
Orientin	31.6
Methyl chlorogenate	33.6
Licochalcone A	103
Chamaecrista nomame [20]	
Luteolin	7.1
Intsia palembanica [22]	
Myricetin	337.5
Fustin	13.7
Quercetin	421.1
Citrus reticulata [23]	
Neohesperidin	75.3
Hesperidin	52.4
Nelumbo nucifera [24]	
Quercetin-3-*O*-β-D arabinopyranosyl-(1→2)-β-D-galactopyranoside	66.86
Quercetin-3-*O*-β-D-glucuronide	135.01
Kaempferol-3-*O*-β-D glucuronide	94.00
Glycyrrhiza glabra [25]	
Isoliquiritigenin	7.3
3,3′,4,4′tetrahydroxy-2-methoxychalcone	35.5
Cassia siamea [25]	
Bianthraquinone	41.8

From the above literature, it is clear that the ***galloyl esters exerted a potential PL inhibition than the non-gallolyated analogues***. Further, the ***degree of increments in the galloyl substitution results in enhancement of PL inhibition potential***.

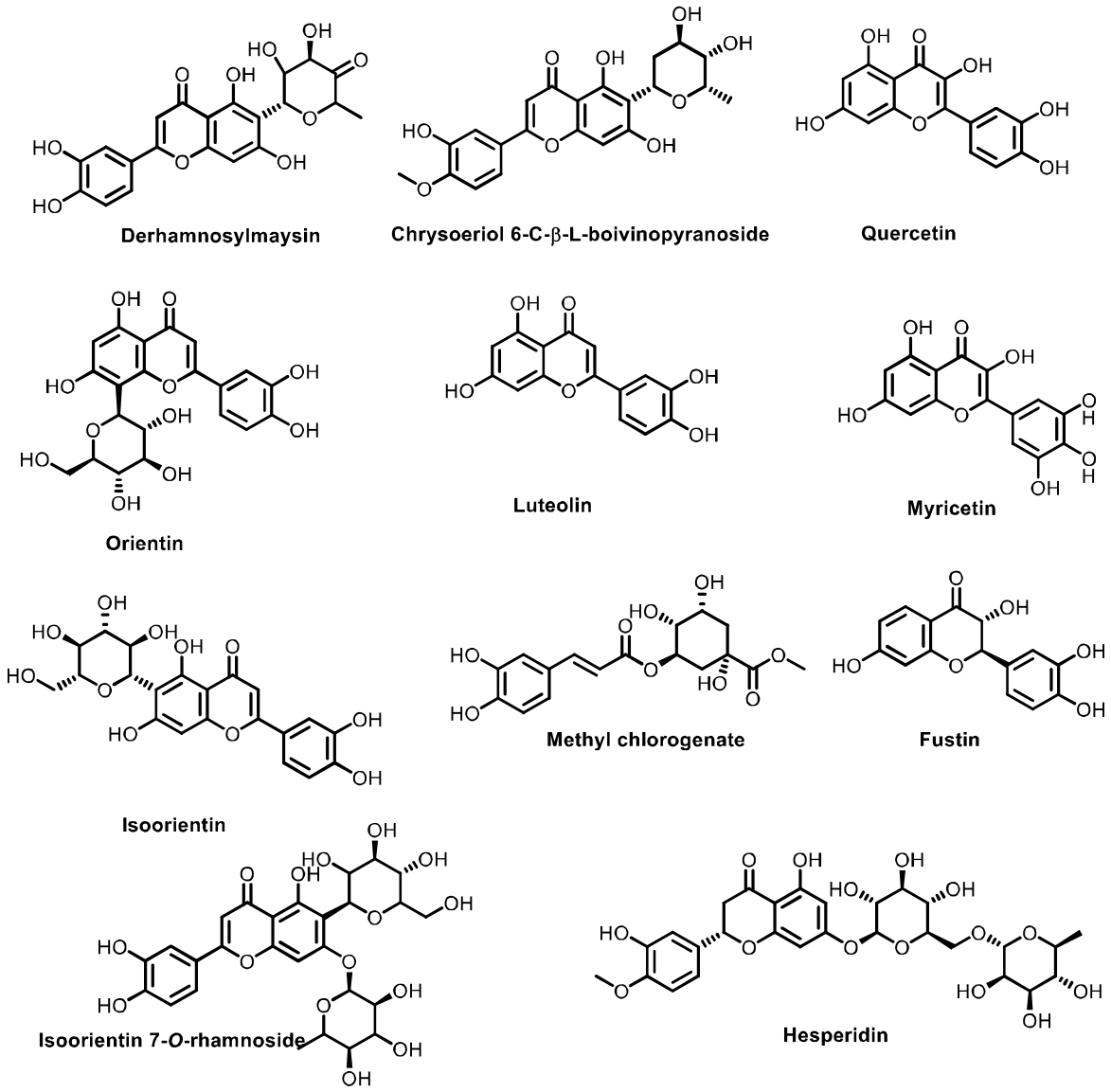


Fig. 2.4 Chemical structures of polyphenols isolated from various plants

Apart from these glycosides, various polyphenols were reported with prenyl/ geranyl attachments (**Table 2.3, Fig. 2.5**). It is interesting to note that, ***the presence of prenyl or geranyl substitution resulted in increased PL inhibitory potential.***

Table 2.3. Prenyl/ geranyl substituted polyphenols with PL inhibitory activity

Compound	IC_{50}
Artocarpus nitidus* and *A. hypargeus [26,27]	
Norartocarpin	1.8 μM
Brosimone I	3.4 μM
Hypargyflavone A	2.3 μM
Morus alba [28]	
Morusalnol A	0.71 μM
Cudrania tricuspidate [29,30]	
Cudraflavanone A	6.5 μM
Cudraflavanone D	9.0 μM
8-Prenyl naringenin	76.9 μM
Cudracuspiflavanone A	54.8 μM

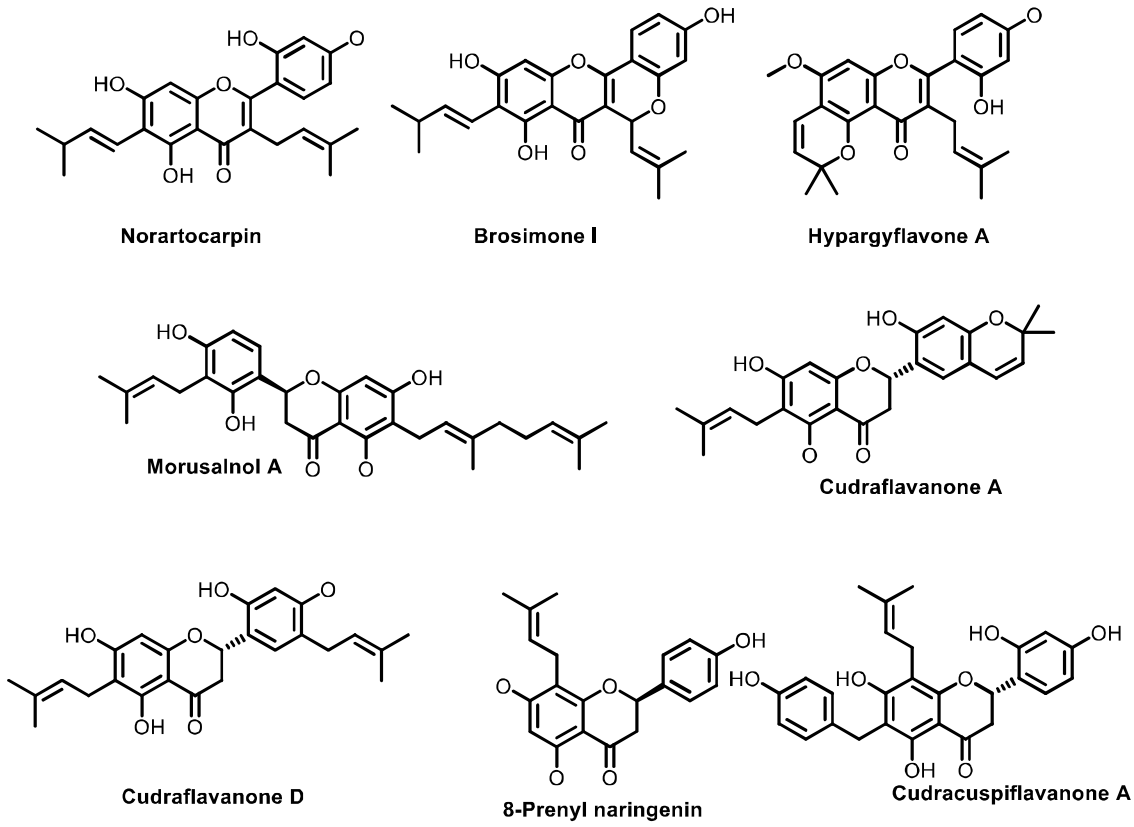


Fig. 2.5. Chemical structures of polyphenols containing prenyl/geranyl substitutions

2.2.1.2. Stilbenes

Stilbene (1,2-diphenylethylene) is

shining. Stilbenes are structurally characterized by the presence of a 1,2-diphenylethylene nucleus with hydroxyl groups substituted on the aromatic rings [31]. Few stilbene natural products have been reported for their PL inhibition potential and are summarised in **Table 2.4** and **Fig. 2.6**

Table 2.4. Stilbene based PL inhibitors

Compound	IC_{50}
Vitis vinifera [32]	
trans-Resveratrol	> 200 μM
trans-Piceid	76.1 μM
cis-Piceid	121.5 μM
Morus alba [28]	
Morusibene A	0.85 μM
Dioscorea opposita [33]	
3,3',5-trihydroxy-2'-methoxybibenzyl	8.77 μM
Tristin	13.50 μM

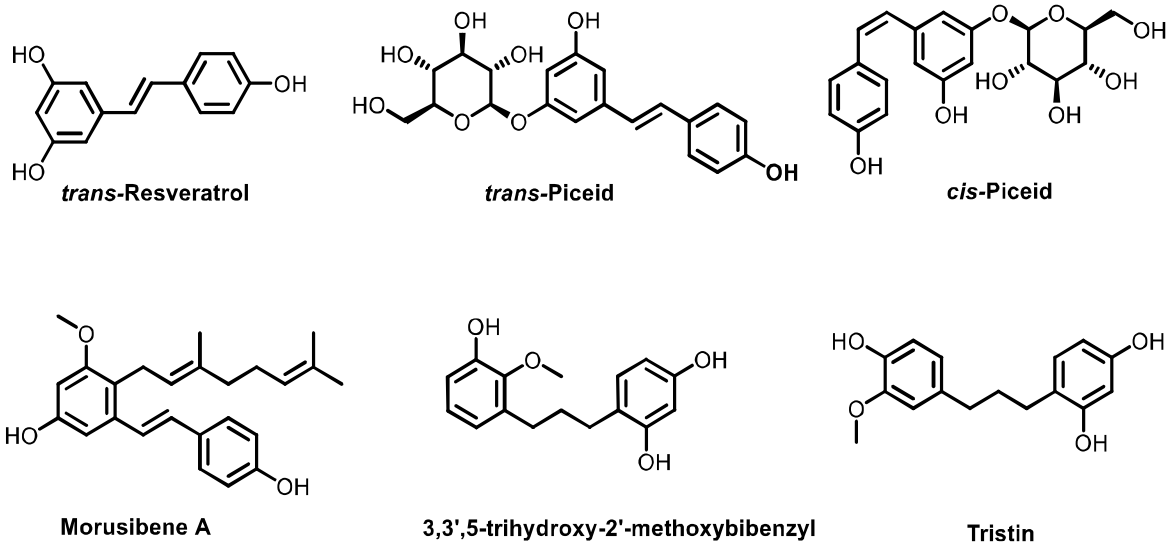


Fig. 2.6. Chemical structures of stilbene type polyphenols having PL inhibition potential

2.2.1.3. Benzofurans

Numerous benzofuran analogues have been evaluated for their PL inhibition. However, the majority of PL inhibitory benzofurans have been limited to *Morus alba* and *Shorea roxburghii* [28,34]. These natural products exerted a moderate to potent PL inhibitory activities ry potential than the unsubstituted analogues (**Fig 2.7**).

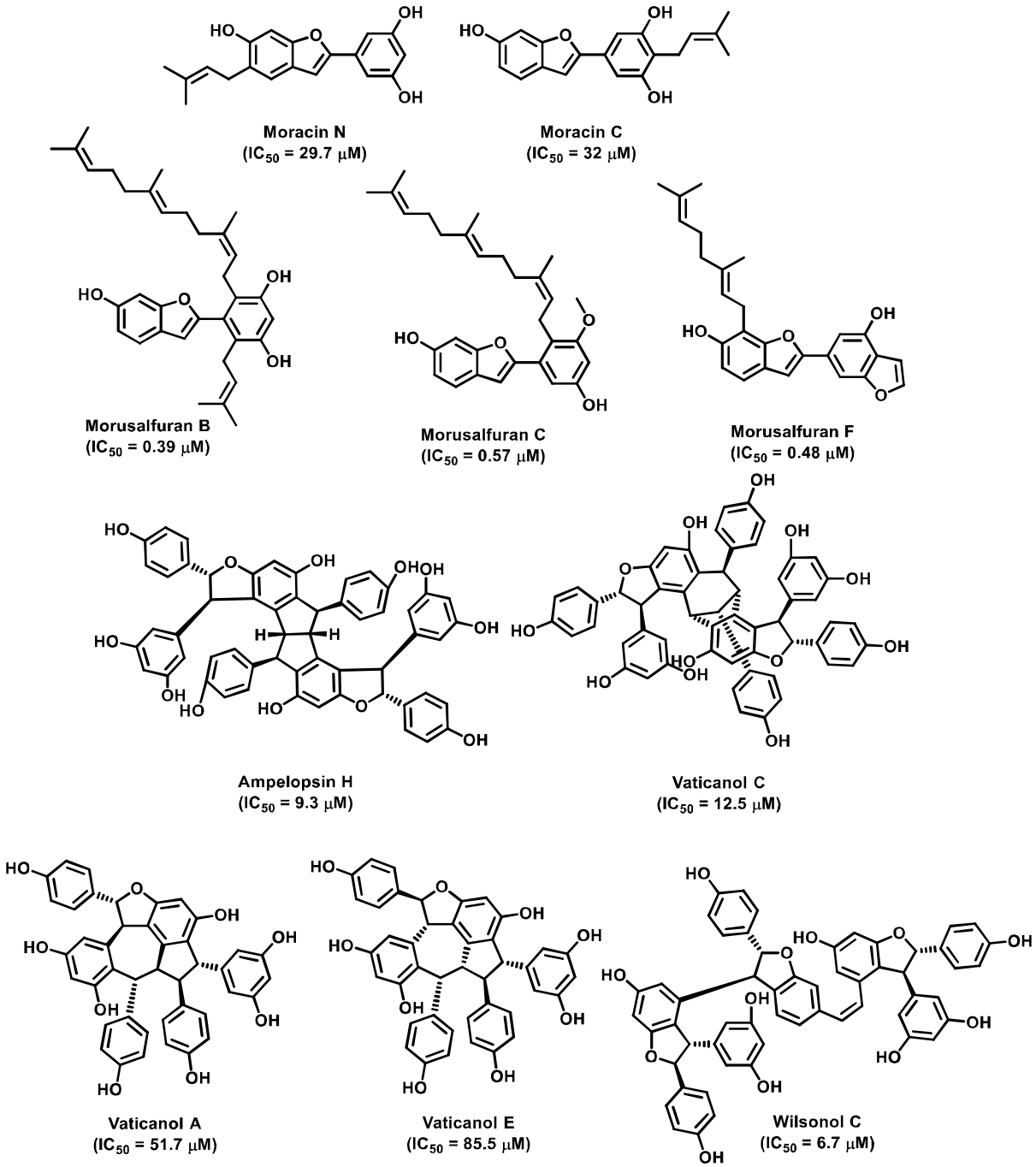


Fig. 2.7. Chemical structures of benzofuran type polyphenols with PL inhibition activity

2.2.2. Saponins

Saponins are a heterogeneous group of glycosides that are widely distributed in plants of agricultural importance, particularly legumes. In the area of PL inhibition, saponins contribute to the second most explored class of natural products with over 200 saponins that have been evaluated for their PL inhibitory activity [9,11]. However, a majority of the saponins have been found to exhibit moderate to poor PL inhibition. A summary of various saponins and their activity are represented in **Table 2.5** and **Fig. 2.8**.

Table 2.5. Saponin based PL inhibitors

Compound	**IC_{50}**	**Compound**	**IC_{50}**
Platycodon grandiflorum [35,36]		***Bellis perennis*** [37]	
Prosapogenin D	1.3 mM	Perennisaponin H	137 µM
Platycodin A	*204 µM	Perennisaponin I	147 µM
Platycodin C	*208 µM	Perennisaponin J	148 µM
Deapioplatycodin D	*259 µM	Perennisaponin L	81.4 µM
Acanthopanax senticosus [38]		***Dioscorea nipponica*** [39]	
Silphioside F	0.22 mM	Prosapogenin A	2.48 µM
Copteroside B	0.25 mM	Dioscin	20 µg/mL
Gypsogenin 3-*O*-β-D-glucuronide	0.29 mM	Diosgenin	28 µg/mL
Sapindus rarak [40]		Gracillin	29 µg/mL
Rarasaponin I	131 µM	***Gypsophila oldhamiana*** [41]	
Rarasaponin II	172 µM	Gypsosaponin A	*522 µM
Rarasaponin III	576 µM	Gypsosaponin B	*327 µM
Raraoside A	151 µM	Gypsosaponin C	*876 µM
Ilex paraguariensis [42]		Alisol F 24-acetate	45.5 µM
Matesaponin I	*53.2 µM	3-*O-trans-p*-coumaroyl actinidic acid	14.95 µM
Nudicaucin C	*65 µM		

*The IC_{50} values were calculated as approximate from the % inhibition reported in the literature

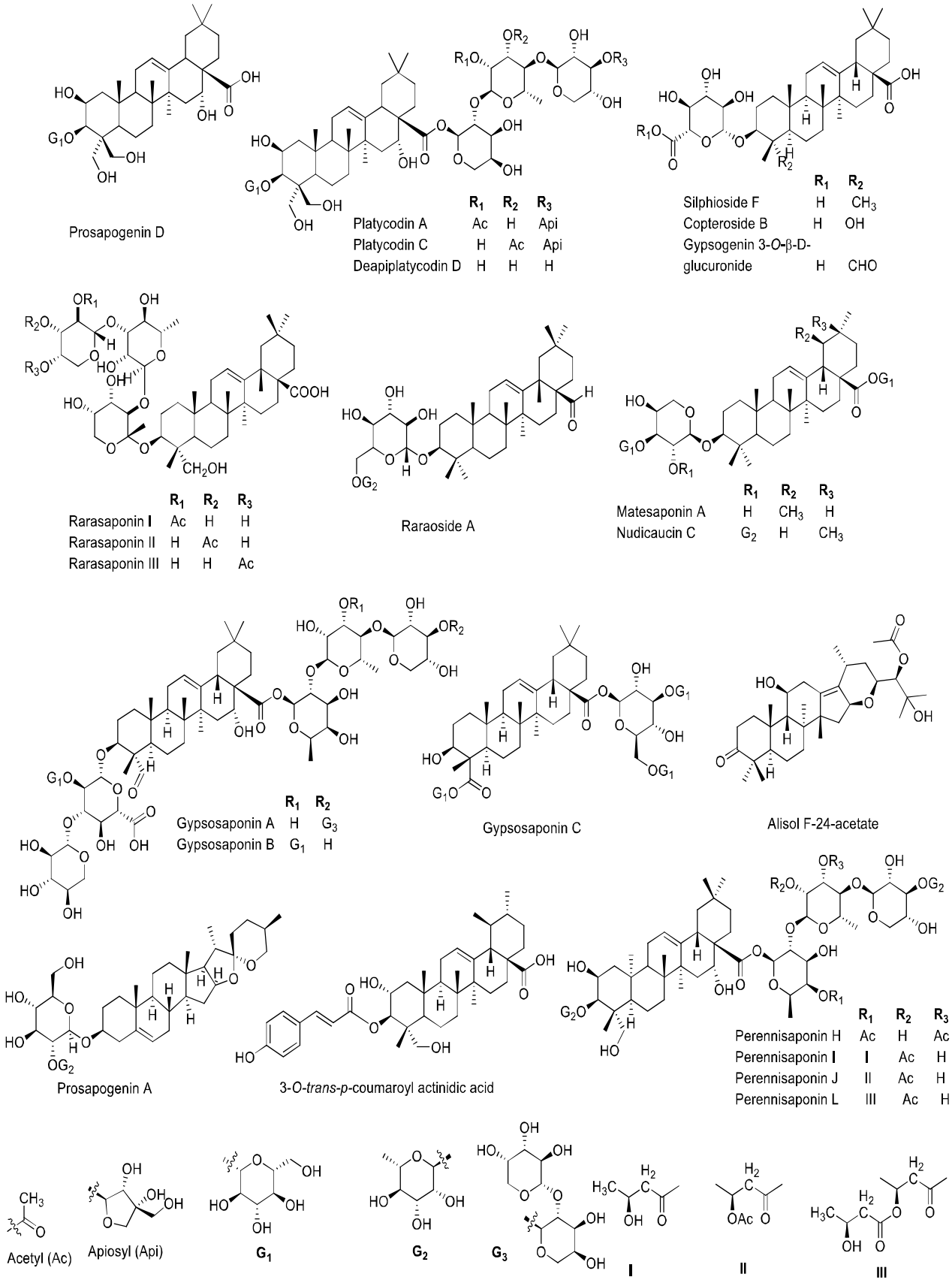


Fig. 2.8. Chemical structures of various saponins with PL inhibitory activity

2.2.3. Alkaloids

Alkaloids are cyclic organic natural products containing nitrogen in a negative oxidation state, which are of limited distribution among living organisms [43]. Meissner proposed alkaloids as *"plant-derived substance that react like alkalis"*. A few alkaloids are only explored for PL inhibition, and are summarised in **Table 2.6** and **Fig. 2.9** Further, these alkaloids belong to various subclasses, *viz.* pyrroles, benzylisoquinolines, carbazoles and bisindoles.

Table 2.6. Alkaloid based PL inhibitors

Compound	Activity (IC_{50})	Compound	Activity (IC_{50})
N. nucifera [44]		***Murraya koenigii*** [45]	
Liriodenine	> 100 µM	Mahanimbin	17.9 µM
Oleracein E	> 100 µM	Koenimbine	168.6 µM
***Berberis* sp.** [46]		Koenigicine	428.6 µM
Dihydroberberine	23.7µM	Clausazoline K	>500 µM
Berberine	314.5 µM	***Tabernaemontana divaricata*** [47]	
P.somniferum [48]		Conophylline	3.36 µM
Papaverine	106.6 µM		

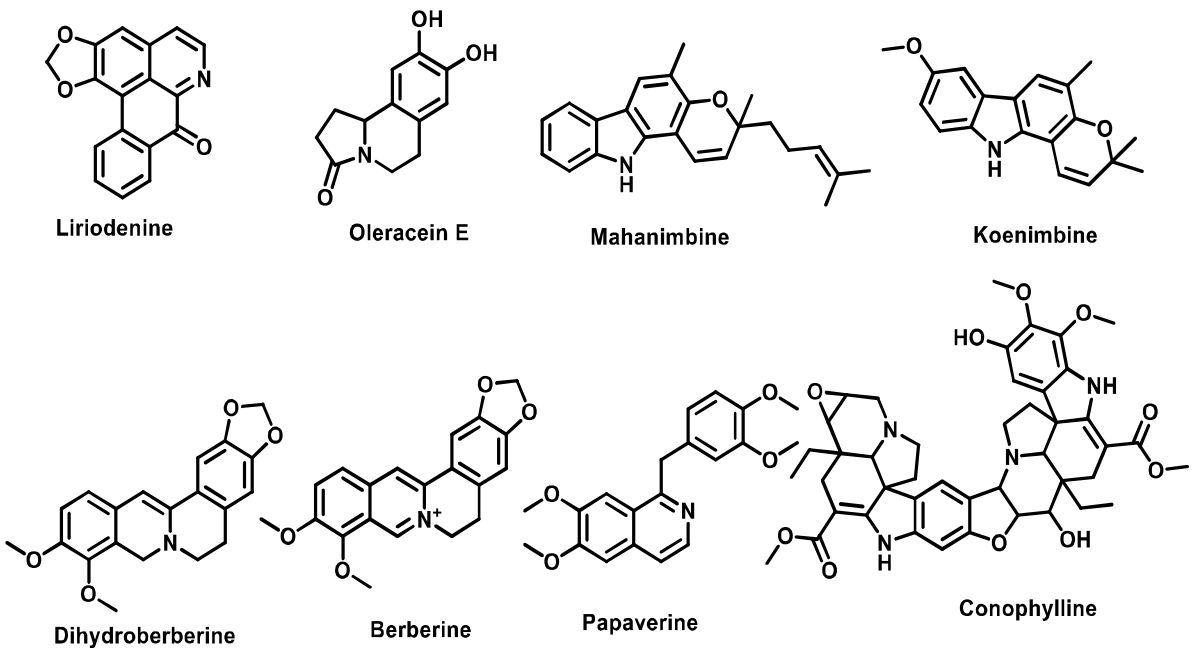


Fig. 2.9. Chemical structures of various alkaloids with PL inhibitory activity

2.2.4. Terpenoids

The term "Terpen" (English, "terpene") is attributed to Kekule, who coined it to describe $C_{10}H_{18}$ hydrocarbons occurring in turpentine (German, "Terpentin") oil. Terpenoids are the diverse class of naturally occurring organic natural products derived from the 5-carbon precursor, isoprene [49,50]. Numerous agents from these class are reported for their PL inhibition, however, they exhibit a moderate to poor PL inhibitory potential **Table 2.7** and **Fig. 2.10**.

Table 2.7. Terpenoid based PL inhibitors

Compound	Activity (IC_{50})	Compound	Activity (IC_{50})
Gardenia jasminoides [51]		***Actinidia arguta*** [52]	
Crocin	2.76 mM	3-O-*trans*-p-coumaroyl actinidic acid	14.95 µM
Crocetin	6.40 mM	Ursolic acid	15.83 µM
Ginkgo biloba [53]		23-hydroxyursolic acid	41.67 µM
Ginkgolides A	53.95 mM	Corosolic acid	20.42 µM
Ginkgolides B	211.79 mM	Asiatic acid	76.45 µM
Bilobalide	184.18 mM	Betulinic acid	21.10µM

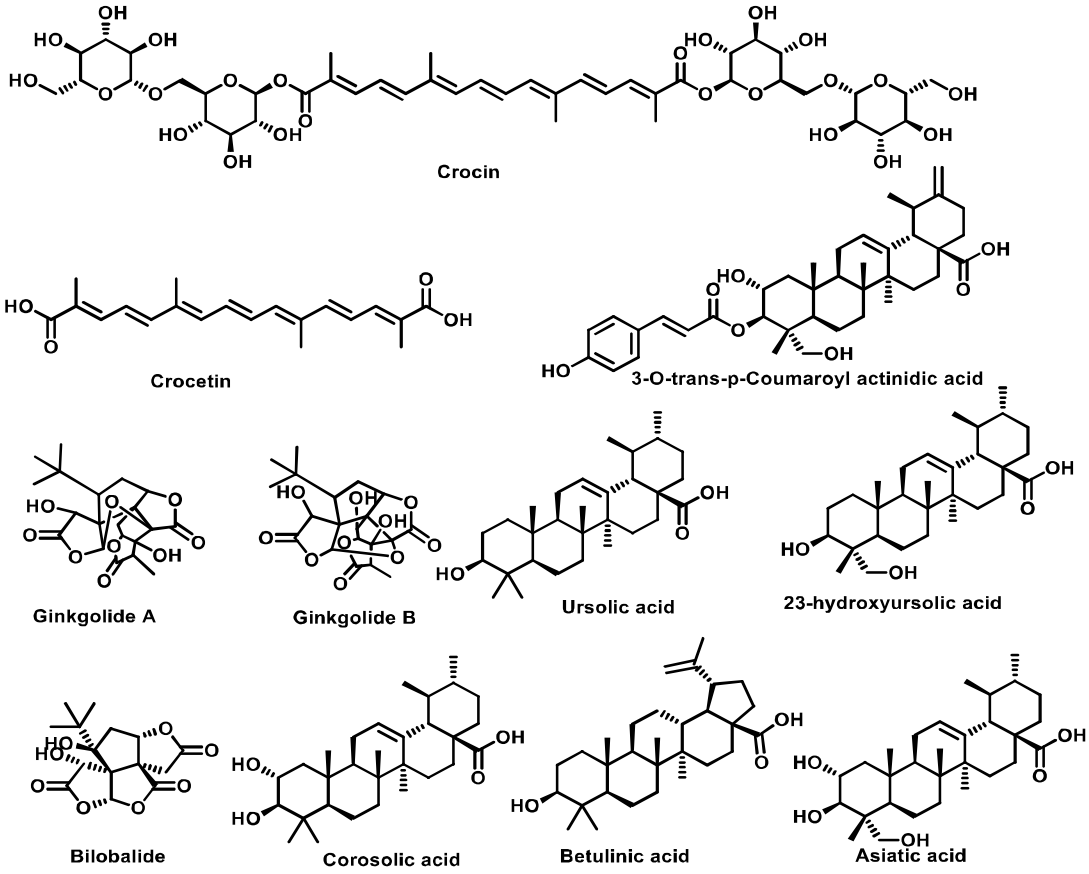


Fig. 2.10. Chemical structures of various terpenoids with PL inhibitory activity

2.3. Microbial source derived PL inhibitors

In the continued search of effective antiobesity agents, several natural products from microorganisms (bacterial, fungal and marine species) have been screened for the identification of potent PL inhibitors. Among the microbial-derived analogues exerting PL inhibitory properties, β-lactones (2-oxetanones) have gained much attention due to their widespread occurrence, biological activities and their synthetic utility. Numerous lactone type analogues, namely ebelactones, panclicins and vibralactones isolated from the *Streptomyces* and *Boreostereum* species contribute the major [54–57] share (**Fig. 2.11**).

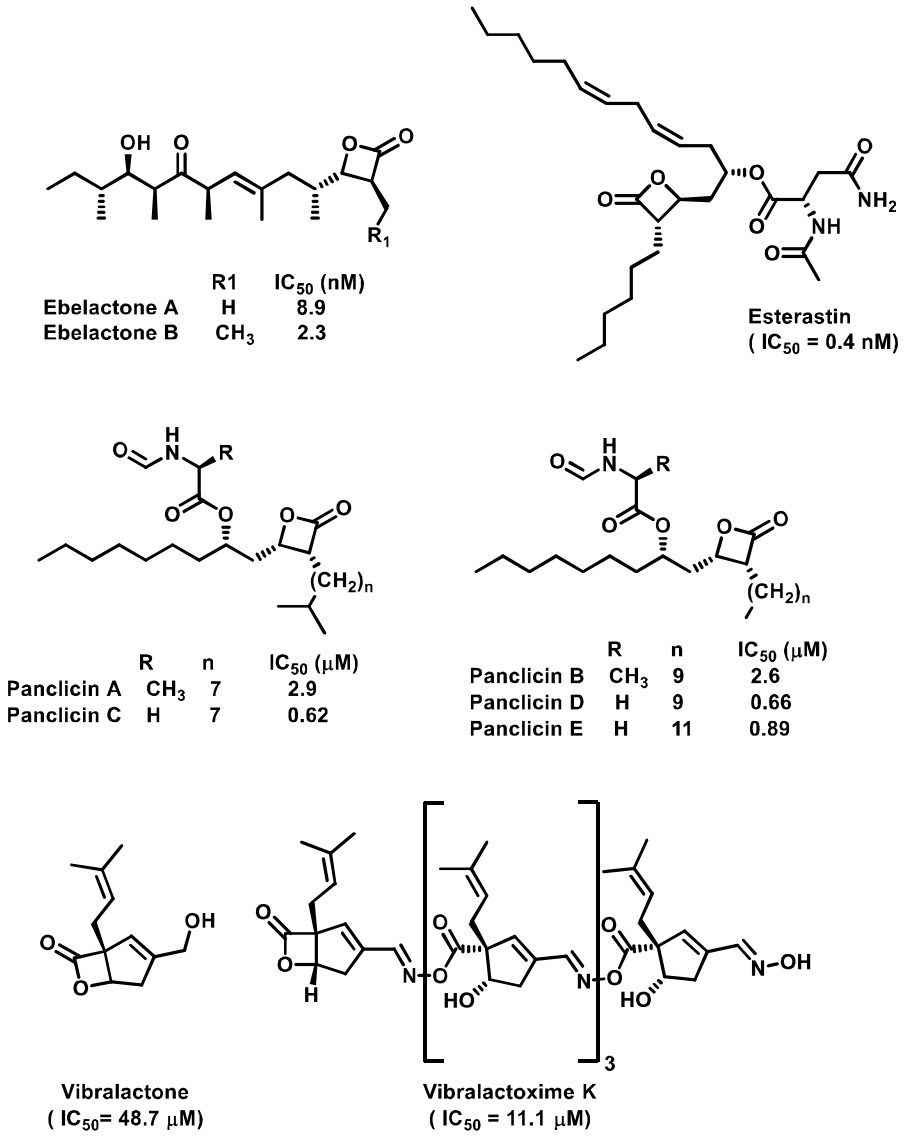


Fig. 2.11. Chemical structures of various β-lactone containing microbial metabolites with PL inhibitory activity

Orlistat, a commercially available PL inhibitor possessing the lactone ring, has further inspired the researchers to explore the microbial flora for the discovery of effective anti- -lactone, that opened a new arena for the search of such kind of natural products [6]. Orlistat is the hydrogenated form of lipstatin, isolated from *S. toxytricini* in 1987 [58]. Interestingly, lactone analogues exert a potent PL inhibition activity. Among these analogues, Esterastin, a closely related analogue of orlistat exerted PL inhibitory activity in nM range (IC_{50} = 0.4 nM).

Apart from these analogues, numerous analogues of monascus pigment having moderate PL-inhibitory activities have also reported [59,60]. Monascus pigments have been used for many years as a natural food colourant and health food in East Asia. Amongst the 50 produced pigments, aromatic and non-polar aliphatic L-, D-amino acids containing analogues exhibited the moderate PL inhibition potential (**Fig. 2.12**).

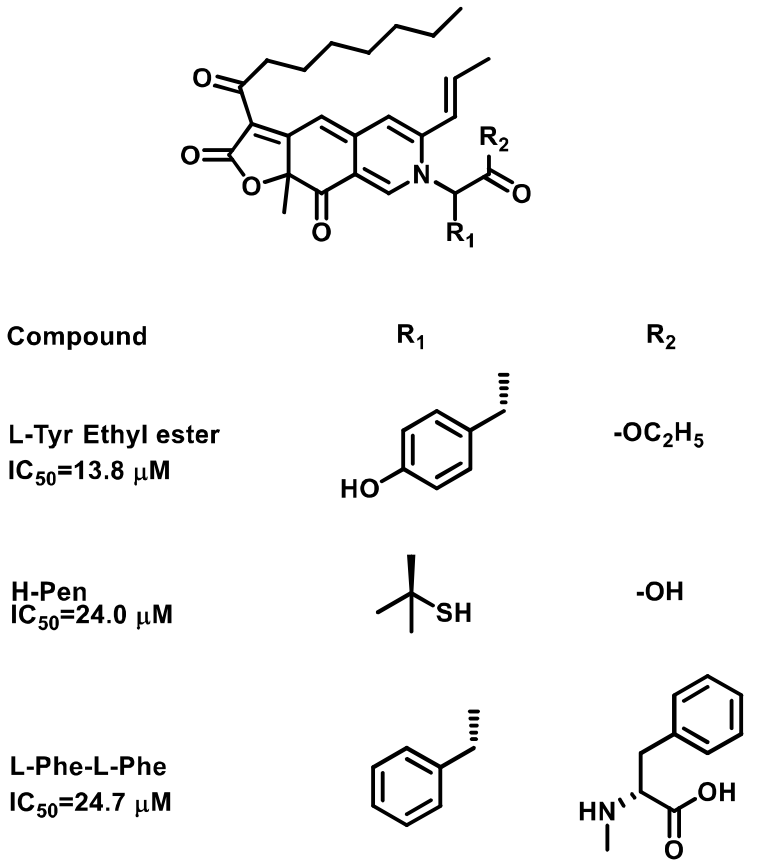


Fig. 2.12. Various monascus pigments and their PL inhibitory activity

PL inhibitory potential of numerous fungal endophytes has also been reported. A study reported by Mahiti Gupta *et al.* [61], evaluated 70 fungal endophytes for their anti-obesity potential *via* PL inhibition. Ethyl acetate extract of culture filtrate (#57 TBBLAM) exerted

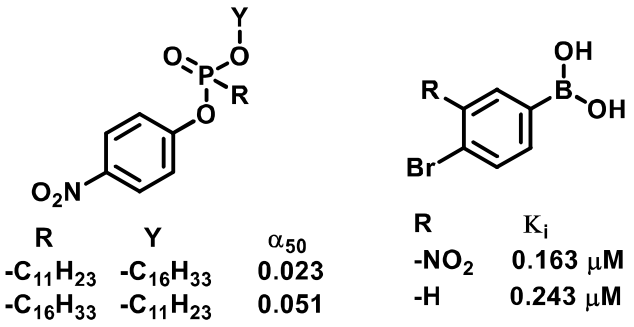
a comparable inhibitory potential (IC_{50} = 3.69 µg/mL) to that of orlistat (IC_{50} = 2.73 µg/mL). In another report, 27 endophytes from *V. odorata* were isolated and evaluated for their PL inhibitory potential [62]. Among the screened endophytes, VOLF4 (*Aspergillus* sp.) exerted promising PL inhibitory activity (IC_{50} < 3.8 µg/mL), while 7 extracts displayed an IC_{50} lesser than 10 µg/mL.

2.4. Synthetic PL inhibitors

Commonly employed strategy for synthetic PL inhibitors is mainly based on the structure of the natural substrate of PL, *i.e.* triglycerides or its related backbones such as 1,3-diaminopropan-2-ol, 2-amino alcohol, glycerol and 2-methyl glycerol, that forms a triglyceride kind of molecule. Moreover, to make a stable interaction and proper orientation with the active sites of PL, two essential structural features required are, (i) nucleophilic moiety, that is able to react with the active-site serine oxygen; (ii) lipophilic part which in connection with hydrophilic fragment ensures its aggregation at the phase boundary. These analogues have been further modified to more stable and/or hindered ester or amide or ether linkage with numerous hydrophobic functionalities being attached [6,25].

Due to the similarity in the charge distribution and geometry of transition state during carboxyl ester hydrolysis, phosphonates esters have been reported to be efficient PL inhibitors (**Fig. 2.13**). These kind of analogues exert their activity by the formation of a covalent bond between the phosphorus atom in phosphonates and the nucleophilic oxygen atom of serine. The first report on the PL inhibitory potential of phosphonates is available in the case of *O*-ethyl-*O*-(*p*-nitrophenyl) n-hexylphosphonate, that inhibited lipases from *Candida antarctica* and *Rhizomucor miehei.* The PL inhibitory efficiency of phosphonates depends on the alkyl chain length, the nature of the leaving group, and the influence of the ester substituent etc. Replacement of ester functionality with phosphonates has also been reported for the potential PL inhibitions [63,64].

PL inhibitory potential of phenylboronic acid has been also explored previously (**Fig. 2.13**). The presence of empty *p*-orbital on boron facilitates its interaction with the nucleophilic group of PL, resulting in its inhibitory property. The 3-nitro-4-bromobenzene and 4-bromobenzene derivatives possessed potent PL inhibitory activity of 0.163 and 0.243 µM [65].



R	Y	α_{50}
$-C_{11}H_{23}$	$-C_{16}H_{33}$	0.023
$-C_{16}H_{33}$	$-C_{11}H_{23}$	0.051

R	K_i
$-NO_2$	0.163 μM
-H	0.243 μM

Fig. 2.13. Boronic acids and phosphonates based PL inhibitors

Various other synthetic pharmacophores explored for their PL inhibition includes oxadiazole, chalcones, benzylisoquinolines, bisbenzimidazoles and triazoles etc.

Vanessa point *et al*, designed and synthesized 5-methoxy-*N*-3-phenyl substituted-1,3,4-oxadiazol-2(3H)-ones and screened for the reactivity and selectivity towards PL inhibition. These analogues exhibited inhibition in the range of 10.71- 85.1 % at X_i value of 100 and 35.8 - 87.5 % at X_i value of 400 [66]. Later in 2016, they designed and synthesized a new series of ten 5-alkoxy-N-3-(3-phenoxyphenyl)-1,3,4-oxadiazol-2(3H)-one derivative (RmPPOX) [67]. These analogues were further found to be selective and potent inhibitors of mammalian digestive lipases (**Fig. 2.14**) and were found to strongly discriminate classical PL (poorly inhibition) from gastric lipase (fully inhibition).

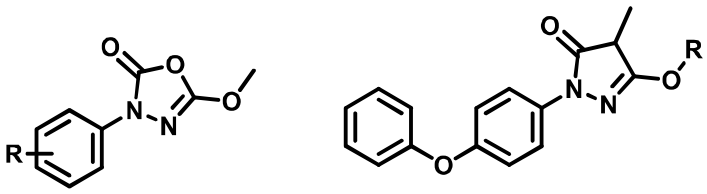


Fig. 2.14. 5-Methoxy-*N*-3-phenyl substituted-1,3,4-oxadiazol-2(3H)-ones and 5-Alkoxy-*N*-3-(3-phenoxyphenyl)-1,3,4-oxadiazol-2(3H)-one based PL inhibitors

Tian Feng *et al*, designed and synthesized a series of benzyltetrahydroisoquinoline analogues (**Fig. 2.15**) through Bischler-Napieralski cyclization [68]. The *in vitro* PL inhibitory activity was assessed and the screened analogues exhibited significant PL inhibitory activity ranging from 10.28 - 39.46 μM.

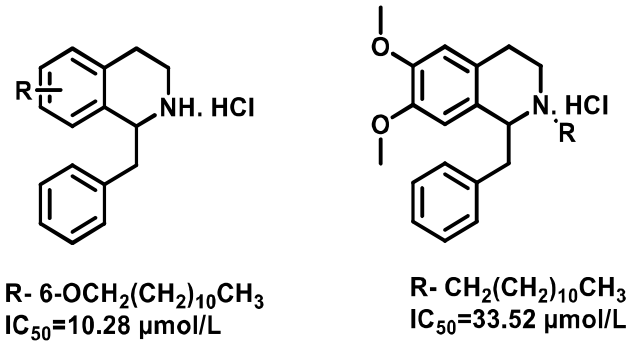


Fig. 2.15. Benzyltetrahydroisoquinoline type based PL inhibitors

Emre Mentese *et al*, synthesized benzimidazole based PL inhibitors using iminoester hydrochlorides of phenylacetic acid and 4,5-dichloro-1,2-phenylenediamine under microwave irradiation. Among the screened analogues, maximum PL inhibitory potential of 170 µg/mL (IC_{50}) was obtained. Later in 2014, using pharmacophore hybrid-based approach, a new series of bisbenzimidazole and perimidine hybrid analogues were synthesized by the same group. The resultant analogues exhibited a potent PL inhibitory activity (IC_{50} = 0.26 and 0.20 µg/mL). Similarly, in 2015, a new series of fluorine-containing benzimidazoles and bisbenzimidazoles were synthesized by the reaction of *o*-phenylenediamines with iminoester hydrochlorides in methanol under microwave irradiation. The study resulted in potent analogue with PL inhibitory activity of 2.01 µg/mL and 1.50 µg/mL (IC_{50}). In 2016, a new series of 2-substituted quinazolin-4(3H)-one- coumarin hybrid analogues were synthesized and screened for their PL inhibition properties. Among the synthesized analogues, N'-{2-[2-(3,4-dichlorobenzyl)-4-oxoquinazolin-3(4H)-yl]acetyl}-2-oxo-2H-chromene-3-carbohydrazide and N'-{2-[2-(4-bromobenzyl)-4-oxoquinazolin-3(4H)-yl]acetyl}-2-oxo-2H-chromene-3-carbohydrazide exhibited a strong PL inhibitions (IC_{50} values 3.52 and 2.85 µM, respectively) [69–72]. Coumarin-Triazole hybrid analogues were also evaluated for the PL inhibition by the above group. The synthesized analogues exhibited a potential PL inhibition (IC_{50} value ranges from 1.80 to 5.76 µM) (**Fig. 2.16**).

Sridhar *et al*, designed and synthesized numerous carbazole oxoacetamide PL inhibitors wherein the carbazole scaffold was inspired from conophylline alkaloid isolated from *Tabernaemontana divaricata*. The study resulted in a potent analogue with an IC_{50} of 6.31 µM [73]. Later, based on the structural hopping approach, carbazole nucleus was replaced with an indole nucleus, and the study further resulted in the potent analogues than the parent (IC_{50} = 4.53 µM) [74]. Further, incorporation of essential structural features such as

long-chain functionalities (prenyl/geranyl), denser aromatic groups (indole) resulted in a potent activity for the indole-oxoacetamide analogues (IC_{50} = 1.68 µM) [75] (**Fig. 2.17**).

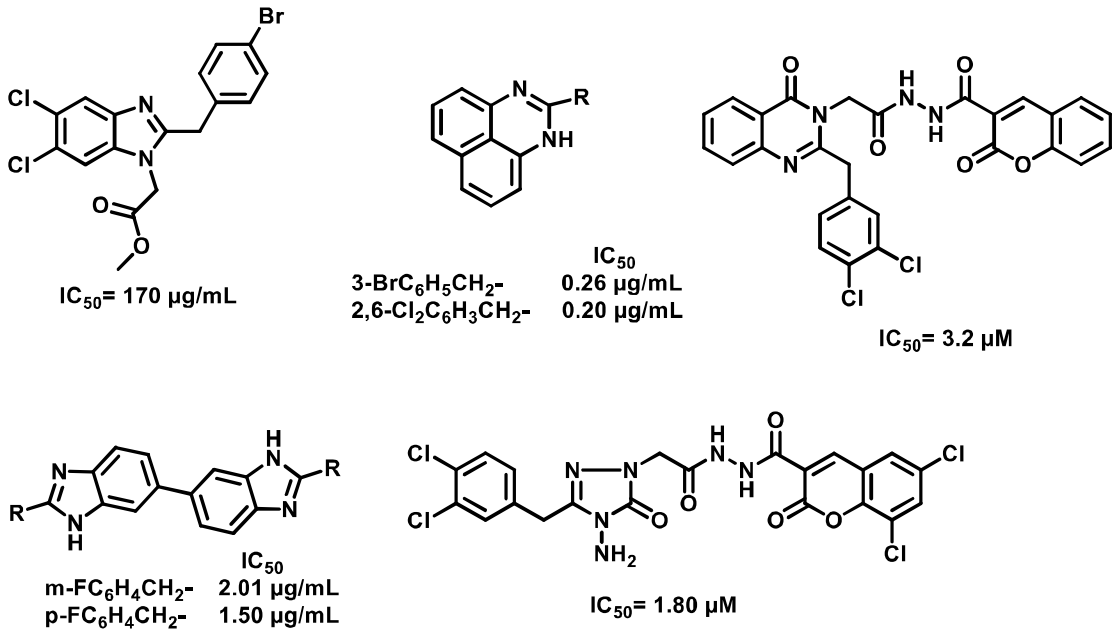


Fig. 2.16. Benzimidazole, benzimidazole with perimidine, bisbenzimidazole, quinazoline-coumarin and triazole-coumarin hybrid analogues based PL inhibitors

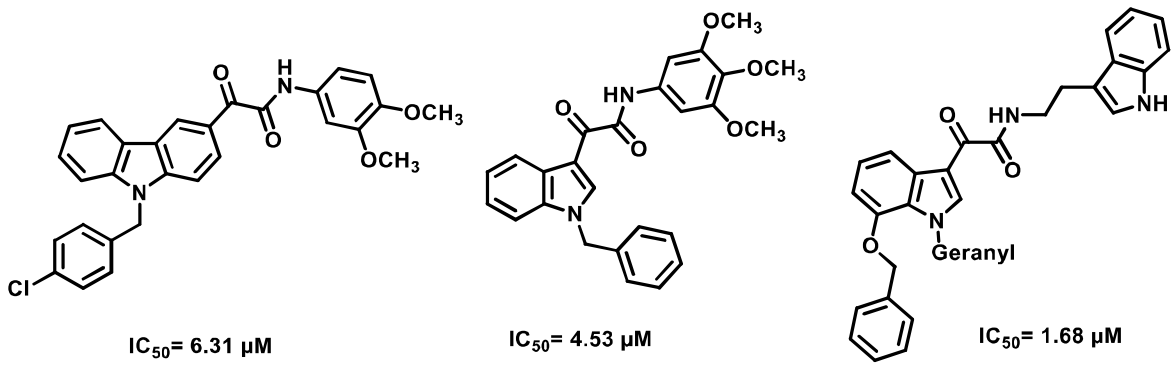


Fig. 2.17. Carbazolyl/indolyl oxoacetamide based PL inhibitors

The effects of five-membered heterocycles on the PL inhibition have also been reported in the literature. For instance, PL inhibitory potential of a thiazolidinedione and rhodanine scaffolds have been explored. Amide bonds present in these analogues are expected to interact with the nucleophilic Ser 152. To provide the hydrophobic interactions with the active site amino acids, numerous hydrophobic residues have been attached to these 5 membered scaffolds. The study resulted in the potent PL inhibitors with IC_{50} = 4.81 and 5.16 µM, respectively from thiazolidinedione and rhodanine scaffolds (**Fig. 2.18**).

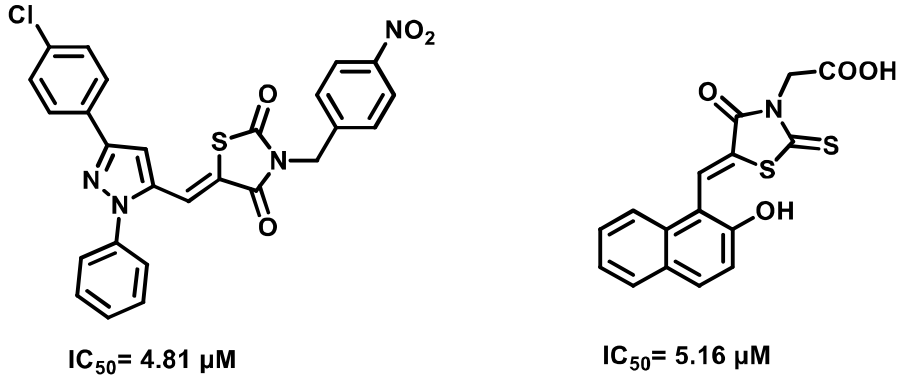


Fig. 2.18. Thiazolidinedione and rhodanine based PL inhibitors

2.5. Gaps in existing research

Due to the large imbalance between the energy intake and expenditure associated with the sedentary life, obesity prevalence is increasing in a pandemic proportion. Although diet management and exercise are considered as a key tool for the prevention of obesity, adherence to these strategies seems to be difficult to the obese population. Thus, numerous pharmacotherapies are used for the management of obesity and its associated conditions. In the current scenario, only few drugs are available clinically but with unclear understanding of their long term safety. Among the numerous targets explored for obesity management, inhibition of PL is considered as one of the most promising target due to the non-involvement of systemic effects.

Orlistat is the only USFDA approved PL inhibitory drug for the long-term management of obesity. The most commonly reported adverse effects of orlistat includes gastrointestinal effects like bloating, steatorrhea, faecal incontinence and oily stools [76]. However, In April 2011, the consumer advocacy group and drug safety watchdog Public Citizen sent a letter to FDA requesting the ban of orlistat, citing liver toxicity as well as evidence from the FDA adverse reaction files that included 47 cases of acute pancreatitis and 73 cases of kidney stones [77]. These events highlight the necessity for the development of safer and effective anti-obesity drugs acting *via* PL inhibition.

A wide array of pharmacological activities of the natural products have always inspired the scientific community for the identification of newer drugs/drug candidates. Traditionally, many medicinal plants are used in the treatment of metabolic disorders. Hence, exploration of various natural products derived from plant and microbial sources etc., has resulted in the discovery of numerous PL inhibitors. Although these natural products are comprised of huge chemical diversity, they do not possess a comparable activity to that of orlistat.

Further, the isolation of these natural products has been carried out in a predative manner, without focussing on their PL inhibitory activity. Also, most of these compounds do not fulfil the essential structural criteria for the PL inhibition, that might also be one of the reason for their moderate PL inhibition potential.

The ongoing research in the area of synthetic PL inhibitors mainly involves the combination of two active pharmacophores into a single chemical entity. Only a few reports are available wherein a combination of traditional knowledge in adjunct with the newer methods (*in silico* approach followed by synthetic methodology) are used for the identification of potent PL inhibitors. These adjunctive strategies may be helpful for the identification and or synthesis of potential PL inhibitors.

2.6. Aim

Considering the potential gaps in the existing research, the present thesis aims at ***"the discovery of potent natural product-based pancreatic lipase inhibitory lead and its inspired analogues"*** and would involve a wide array of studies that include information from the traditional medicine, natural product isolation, molecular modelling, synthesis, *in-vitro* and *in-vivo* studies.

2.7. Objectives

i. To prepare extracts from the selected Indian medicinal plants and to determine their *in-vitro* inhibitory activity against pancreatic lipase
ii. To perform bioassay guided fractionation of the most potent extract followed by purification and characterization of the isolated compound(s)
iii. To evaluate the isolated compound(s) for *in-vitro* pancreatic lipase inhibition and to identify the structural features required for activity using *in silico* studies
iv. To synthesize, characterize and evaluate pancreatic lipase inhibitory activity of various synthetic analogues of the natural product lead
v. To evaluate the *in-vivo* efficacy of the most potent synthetic analogue(s) using High Fat Diet (HFD) fed mice model

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