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Abstract: The tetralone and tetralone derivatives, as crucial structural scaffolds of potential novel drugs targeted at multiple biological end-points, are normally found in several natural compounds and also, it can be used as parental scaffold and/or intermediate for the synthesis of a series of pharmacologically active compounds with a broad-spectrum of bioactivities including antibacterial, antitumor, CNS effect and so on. Meanwhile, SAR information of its analogues has drawn attentions among medicinal chemists, which could contribute to the further research related to tetralone derivatives aimed at multiple targets. This review encompasses pharmacological activities, SAR analysis and docking study of tetralone and its derivatives, expecting to provide a general retrospect and prospect on tetralone derivatives.

Abbreviations

Abbreviation	Full Name
A1	Adenosine1
A2	Adenosine A2
ABC	ATP binding cassettes
AChE	Acetylcholine (Ach) enzyme
AD	Alzheimer's disease
CNS	Central nervous system
atRA	All-trans retinoic acid
COLO205	Human colon cancer cells
CRC	Colorectal cancer
CYP24	24-Hydroxylase
CYP24A1	25-hydroxyvitamin D3-24-hydroxylase
CYPs	Cytochromes P450s
DPPH	2,2-diphenyl-1-picrylhydrazyl
HCC	Hepatocellular carcinoma cells
HCC827	Lung adenocarcinoma
HCV	Hepatitis C Virus
HepG2	Hepatocellular carcinoma
IOP	Intraocular pressure
KM12	KM12-SM Cell Line
LPS	Lipopolysaccharide
MAO-A	Monoamine oxidases A
MAO-B	Monoamine oxidases B
MCF10A	Normal epithelial breast cells
MCF-7	Michigan cancer foundation-7
MD-AMB-231 cancer	Triple-negative breast
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistantStaphylococcusaureus
MTPA esters	α-methoxy-αD-trifluoromethylphenylacetic acid (MTPA) esters
PET	Positron emission tomography
PPAR-c	Peroxisome proliferator-activated receptor-c
ROS	Reactive oxygen species
RSA	Radical scavenging activity
RT-PCR	Real time polymerase chain reaction study
SAR	Structure-activity relationship
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
TET	Tetracycline
5-HT	5-Hydroxytryptamine

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1. Introduction

Tetralones, a wide collection of aromatic bicyclic compounds bearing moiety of 3,4-dihydro-1H-naphthalen-1-ones or 3,4-dihydro-1H-naphthalen-2-ones (Fig.1), have been studied because of their chemical characteristics and potential as lead compounds in pharmaceutical industry. Since the early 20th century and even before, chemists worldwide have been interested in the isolation, synthesis, structural modification of tetralone and tetralone derivatives because of their importance in the synthesis of bioactive compounds such as steroids, prostaglandin analogs, dyes, heterocycles and pharmaceuticals and novel drug candidates [1-6]. Take sertraline for example, one kind of selective serotonin reuptake inhibitor (SSRI) drug in the therapy of depression, 1-tetralone plays an important role as the starting material [7]. Levobunol (Table 8), a nonselective beta-adrenoceptor antagonist developed based on tetralone scaffold, has the ability to lower the level of IOP and FDA has approved its clinical usage in the treatment of patients with eye diseases such as chronic open-angle glaucoma or ocular hypertension [8]. Tetralone derivatives, including natural and synthetic tetralone derivatives, demonstrated a broad spectrum of biological activities. This review is a compendious and full-scaled account focusing on the bioactivities of tetralones as anti-cancer, antibacterial, anti-viral agents and protein inhibitors. The SAR and docking analysis of tetralone derivatives were also summarized as a complement to their bioactivities in order to provide more useful information with researchers in the design and synthesis of potential target compounds. It is noteworthy that there are fewer existing reviews regarding tetralone derivatives, while the similar reviews mainly focus on their chemical properties [9-11], where the bioactivities and SAR study are still lack of discussion. This review also gives a summarization on the application of tetralone nucleus as intermediate and material in medicinal chemistry. Besides, the application of tetralone scaffold in the construction of fluorescence probes was summarized as well so as to explore its application in detecting a variety of analysts in medicine, environment and food industry rapidly and precisely.

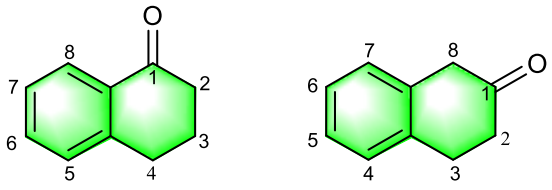

Fig.1. Structures of 1-tetralone and 2-tetralone.

2. Synthesis strategy of tetralones

Although tetralone derivatives are widely distributed in medicinal plants, the inconvenient extraction and isolation method could pose a challenge to their extensive usage. Chemists worldwide have conducted in-depth research on the synthesis of tetralone compounds in view of its importance in various industries. This section aims to give a brief summarization of the advances in the synthetic strategy of tetralones. There are mainly two kinds of tetralone congeners, which are 1-tetralone and 2-tetralone, respectively. The following three points could be summarized from relevant literatures for the synthesis of 1-tetralone. 1) the synthetic routes to 1-tetralone are still limited, mainly focus on intramolecular Friedel-Crafts reaction [12-14]; 2) In general, most 1-tetralones are synthesized through the oxidation reaction of corresponding tetralin derivatives, by directly reacting with oxidants such as PCC or indirectly reacting with oxygen in the presence of catalyst, such as Cr, Cu, Mn, Ru [15-17]; 3)1-tetralones could also be yielded from tetralinol via oxidation reaction [18-20].

Being one kind of useful aromatic bicyclic ketones, 2-tetralones (beta-tetralones) have an important role to play in pharmaceutical application because they are normally highly reactive moiety in chemical reaction and appropriate natural precursors. Compared to 1-tetralones, the 2-tetralones are more unaffordable because they are usually difficult to be synthesized (low reaction yield) and stored (strict storage conditions) [21]. The biological activities of 2-tetralones have engaged the interest of chemists and also stimulated the research regarding to their preparation. To date, the preparation methodologies of 2-tetralones mainly focused on 3 parts: (1) the expansion of 1-indanone ring [22-24]; (2) transformations in compounds containing a pre-formed tetraline ring [25]; (3) the direct construction of tetraline ring starting from monocyclic aromatic precursors [16,26-28].

The industrial production system of tetralones has been highly well-established today and the annual demand of 1-tetralone is more than 1 billion U.S. dollars throughout the world. There are a variety of commercially available tetralone derivatives in the market, which could be readily used

as chemical starting material and intermediates in chemical and pharmaceutical industries.

3. Pharmacological activity of tetralone derivatives

A wide variety of pharmacological activities regarding to tetralone derivatives have been reported including anti-tumor, CNS effect, antibacterial and so on.

3.1 Pharmacological profile of natural tetralone derivatives

A series of natural tetralone derivatives are widely distributed in a certain variety of medicinal plants, such as *Juglans mandshurica*, *New Caledonian Zygogynum species*, *Juglans species* and etc. These tetralone derivatives exhibit multiple bioactivities including antifungal, antimicrobial and anticancer activities, which are summarized as follows (Table 1).

Laurent et al. isolated **1** (Fig. 2) as a new phenolic tetralone obtained from *Humicola grisea Traaen* [29], and **1** could inhibit the growth of KB cell lines, exemplified by the IC_{50} values ranged from 1 to 5 ppm. Verified by MTPA esters, **1** also has an absolute configuration bearing three chiral centers (10R, 3S, 4S) and this feature contributes to its application in synthesizing various diastereomers, although a low molecular weight may cause some limitations in the total synthesis to a certain degree. Scytalone (**2**) (Fig. 2) was firstly identified by Li group and 3 (Fig. 2) was firstly reported by Gremaud et al. [30][31]. Medina and colleagues also isolated these two bioactive compounds from red alga *Asparagopsis taxiformis-Falkenbergia* stage [32]. Antimicrobial assay exhibited that both compounds were inactive against MRSA and *E. coli*. However, being considered as intermediates or side products in DHN type melanin biosynthesis of fungal sources tetralone derivatives, **3** and **4** (Fig. 2) have thus been regarded as chemotaxonomic markers. A new *α*-tetralone derivative **5** (Fig. 2) was obtained from *Arisaema erubescens* by Wang et al. for the first time [30]. Compound **5** showed antifungal activity, exhibiting inhibition activity against *F. oxysporium* and *R. solani* with EC_{50} values lower than 2576.6 μM, whereas no inhibition activity was observed for **5** on species *C. gloeosporioides*, *X. oryzae* and *M. oryzae*. Additionally, compound **5** exhibited high cytotoxicity against a series of tumor cell lines, with IC_{50} values > 100.0 μM. Allouche et al. isolated and characterized four phenyl-3-tetralones (**6**, **7**, **8** and **9**) (Fig.

2) from five different *Caledonian Zygogynum* species [33] Agonists to PPAR-c normally have therapeutic value in the treatment of diseases including diabetes and cancer [34]. Potent binding affinity on PPAR-c has been observed on compounds **6**, **7**, **8** and **9** (Ki = 5.8, 17.9, 4.9 and 4.7 μM, respectively); also the potent cytotoxic activity against KB cancer cell lines of these compounds was found as well. Besides, **6**-**9** exhibited more potent inhibitory activity on KB cancer cell line compared to taxotere. Two new tetralones, compound **10** and compound **11** (Fig. 2), were isolated from *Z. calothyrsum* [35]. Both of them exhibited potent cytotoxicity against COLO205, with GI_{50} of 17.0, and 11.0 μM, respectively; also the cytotoxicity versus KM12 was also high, with GI_{50} of 14.0 μM for **10** and 17.0 μM for **11**. Two novel tetralone compounds named Juglanstetralone A (**12**) and Juglanstetralone B (**13**) (Fig. 2), were isolated from *Juglans mandshurica* by Guo and colleagues [36]. Compound **12** showed potent cytotoxicity on BGC-823 cell lines (IC_{50} = 503.4 μM), whereas no similar effect was found on compound **13**. Compound **14** (Fig. 2) was obtained from pericarps of the Juglans species by Liu et al [37], which exhibited potent growth inhibition on the protein tyrosine phosphatase 1B and could be further used in the insulin receptor's dephosphorylation. Therefore, **14** could be regarded as potential therapeutic agents intervening diseases such as type-2 diabetes and obesity. Besides, compound (**15**) (Fig. 2) exhibited medium antibacterial activity on *S. aureus* and methicillin-resistant *S. aureus* with IC_{50}/MIC of 4.96/10.00 mg/mL and 3.46/5.00 mg/mL, respectively. Two new tetralone derivatives **16** and **17** (Fig. 2), with a caffeoyl unit attached to a tetralone glycoside, were isolated from the leaves of *Cyclocarya paliurus* for the first time [38]. A series of radical scavenging assay was conducted to evaluate the antioxidant activities of compound **16** and the results showed that **16** exhibited moderate DPPH radical scavenging rate (IC_{50} = 57.5 μM), superoxide scavenging activity (IC_{50} = 61.2 μM), while the result of hydroxyl radical scavenging rate was weak (2.0-16.0 μM). It is postulated that phenolic hydroxyl groups accounted for the high antioxidant activity. Very few *α*-ditetralony glucosides have been reported, although α-teralonyl was found to be rich in natural plants. **18** (Fig. 2) as a new *α*-diteralonyl glucoside, bearing two *α*-tetralonyl glucoside moiety, was first isolated from EtOH extract of *J. mandshurica* [39]. Weak cytotoxic activity was observed on A549 and HeLa cell lines, (IC_{50} value = 73.7 μM and 85.10 μM, respectively). From the stem and bark, two known tetralones **19** and **20** (Fig. 2) were isolated and identified from *Diospyros shimbaensis* [40]. Compound **19** showed low toxicity (IC_{50} > 520.0 μM) against the MDA-MB-231 ER cancer cell

line. In antioxidant activity assay, the potent DPPH scavenging effectiveness of the isolated compound **20** could be attributed to strong intramolecular chelation involving the phenolic hydrogen. However, the RSA value of **19** was relatively higher than **20**, and their conformation and configuration may account for the observed difference by affecting the ability to access the centre of DPPH radical. Four compounds (**21**, **22**, **23** and **24**) bearing tetralone moiety were obtained from *Carya illinoinensis* [41]. The isolated compounds were evaluated for AChE inhibition activity and inhibition of AChE to prevent degradation of acetylcholine is a potential therapeutic intervention in management of neurodegenerative diseases such as Alzheimer's disease. Compound **24** (Fig. 2) was evaluated to be the most potent (IC_{50} = 101.48 μg/mL) compared to compounds **21** and **22** and **23** with IC_{50} at 273.38 μg/mL, 192.70 μg/mL and 197.70 μg/mL, respectively. Sun et al. isolated compound **25** (Fig. 2) from the Endophytic Fungus *Coniothyrium sp* and strong antifungal activity against M. violaceum and B. cinerea have been observed [42]. The radii of the zones of inhibition were obtained through agar diffusion assays. Five tetralones (**26**, **27**, **28**, **29** and **30**) were isolated from *Juglans mandshurica* [43], and further investigations on their bioactivities showed that tetralones **26**, **27** and **28** could inhibit the proliferation of NCI-H1975 cells in a selective manner.

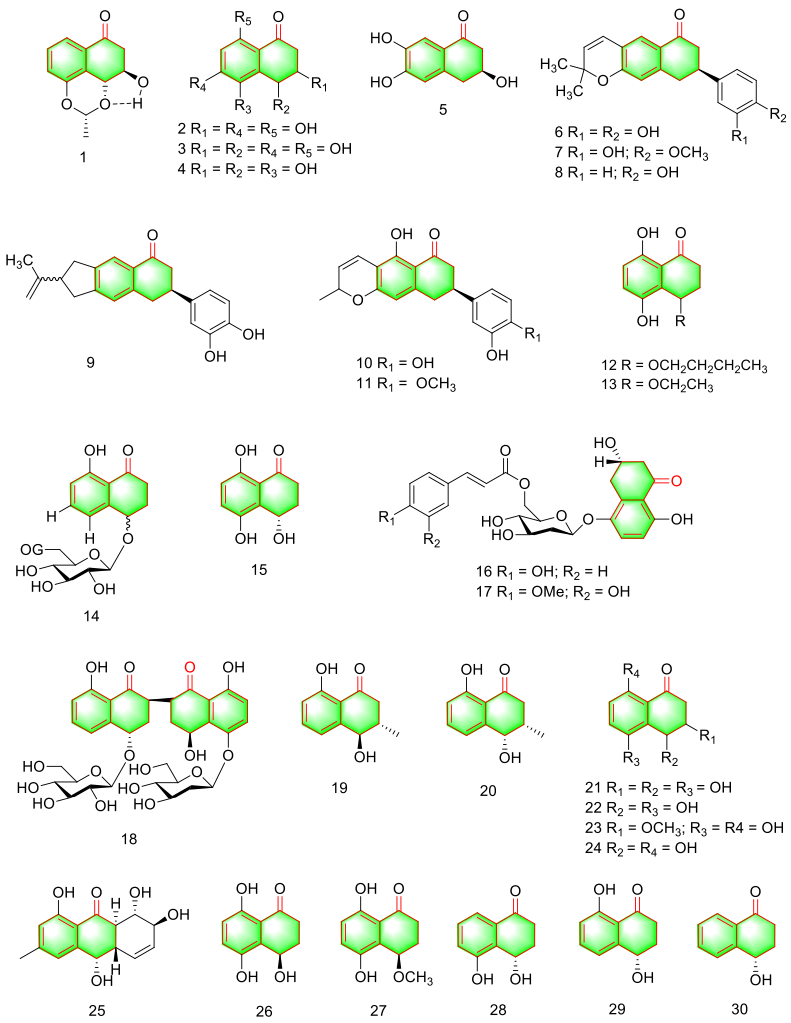

Fig. 2. Natural tetralone derivatives with pharmacological activities.

3.2 Pharmacological activities of synthetic tetralone derivatives

3.2.1 Anticancer activity

Since tumor today still constitutes the leading causes of death, researchers worldwide have been paying much attention on the development of antitumor agents with more therapeutic values and less side effects. A variety of tetralone derivatives with potential antitumor activity have been reported.

3.2.1.1 P450 inhibitors

Cytochromes P450s (CYPs), a superfamily of enzymes that catalyze the metabolism of drugs and some of the most clinically crucial CYPs isoforms are found to play an important role in cancer therapies [44]. For example, the cytochrome P450 component CYP24A1, as an enzyme that

accelerate metabolism of calcitriol and derivatives [45], could be regarded as a biomarker in the treatment of colorectal cancer due to the fact that its expression and concentration normally increases significantly during colorectal carcinogenesis; also CYPs inhibitors are crucial in the treatment of renal, lung, breast and prostate cancers by enhancing the levels of endogenous calcitriol and vitamin D analogues [46]. Several novel tetralone derivatives have been synthesized and investigated by researchers so as to find potential leads for selective P450 inhibitors (Table 2).

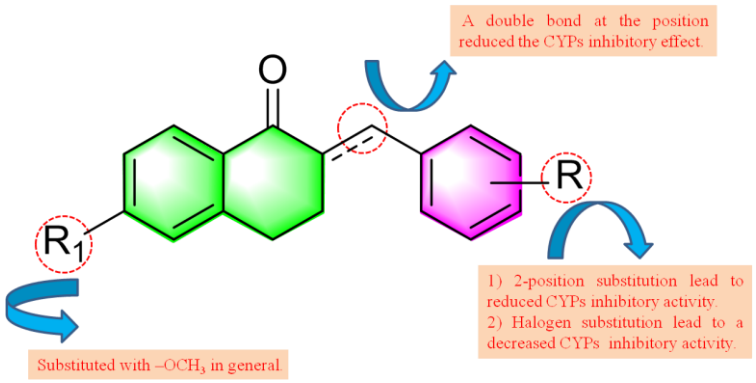

Fig. 3. SAR of tetralone derivatives with anticancer activities.

For human males, prostate cancer remains the major cause of cancer death and therapeutic intervention has been proved to be quite necessary for this disease. Differentiation therapy has been developed as a useful therapy strategy for prostate cancer in recent years and some pro-differentiating agents such as vitamin D3 (and their analogues) have thus been developed [47, 48]. 1,25$(OH)_2$D3 (calcitriol) as the most active metabolite of vitamin D3, have been regarded as an pro-differentiating and antiproliferative, agent in differentiation therapy [49]. However, the usage of calcitriol and its derivatives as differentiating agents is quite limited in differentiation therapy of cancer because 24-hydroxylase (CYP24) has the ability to quickly metabolize the calcitriol into less active metabolites [50]. As a result, CYP24 inhibitors could lead to enhanced differentiating capabilities via inhibiting the activity of CYP24 and increasing the levels of active metabolite of vitamin D3. The synthesis of novel tetralone derivatives and evaluation of their inhibitory activity against kidney mitochondrial CYP24 was reported by Yee et al. [51]. The results showed the 2-benzyltetralone derivatives **31** (Fig. 6) exhibited promising inhibitory activity (IC_{50}= 0.90 μM), which could be used as a lead compound for developing novel CYP24 inhibitors. The SAR demonstrated that the inhibitory activity of benzylidene derivatives was less potent than benzyl derivatives. The flexibility at C2 position of benzylidene and benzyl derivatives is crucial

for the synthesized inhibitors to interact with the active site of enzyme. For 2-benzyltetralone derivatives, alkyl and aryl substituent at the 2-benzyl position contributes to good biological activity, while the reduced activity could be observed when the 4-benzyl position was substituted with aryl. According to observed statistics, introducing more substantial group such as *N*, *N*-dimethyl was not tolerated. A slight preference was observed that a 6-OCH_3 rather than a 6-OH replacement in the naphthalene ring leads to better bioactivities.

1,25$(OH)_2$D3 could exert pro-differentiating and anti-proliferative activities on prostate cancer cells both *in vitro* and *in vivo* [52,53]. The combinational use of 1, 25$(OH)_2$D3 with different CYP24 inhibitors has become a more useful combination therapy of androgen-independent prostate cancer with better cell inhibitory effect. The same research group synthesized compound **32** (Fig. 6) as a CYP24 inhibitor and evaluated for its anticancer effects *in vitro* [54]. Of those, compound **32** could exhibit potent inhibition on Vitamin D3 metabolizing enzymes (IC_{50} = 3.50 M). The combination use of 10.0 M tetralone derivative and 10.00 nM 1,25$(OH)_2$D3 resulted in a more than 25% growth inhibition activity in DU-145 cell line, which was in accordance with an enhanced levels of $p21^{waf1/cip1}$ and GADD45 mRNA, two biomarkers which are related to the growth-inhibitory effects in calcitriol-sensitive cell lines.

Combination therapy of 1, 25-D3 and targeted CYP24 inhibitors also exhibited excellent therapy effect in treating colorectal cancer (CRC). Kósa and co-workers synthesized a few tetralone compounds potentially to exert inhibition activity on CYP24A1 [55], among all the compounds, **33** (Fig. 6) had inhibitory potential with a quite low cytotoxity on CRC. Potent anti-proliferative activity could be observed on caco-2 cell lines when combining the use of 1, 25-D3 (a different type of calcitriol) and KD-35, while the administration of 1, 25-D3 alone was almost ineffective. After incubation of 2.0 μM KD-35 and 200.0 μM of 1, 25-D3, cell number showed a decrease of 35.81% relatively to the control, compared to 1, 25-D3 alone, although no apparent difference was observed between the level of CYP24A1 mRNA expressed either in the presence of various concentrations of **33** or in the untreated controls. The mechanism of enzyme inhibitory effect of tetralones is speculated to be achieved through hydrophobic interactions, such as hydrogen bonds, between the inhibitors and the specific enzyme, which is a flexible mechanism with significant

selectivity.

Aboraia et al. synthesized a class of 2-substituted benzylidene- and benzyl- derivatives based on tetralone scaffold and investigated their inhibitory activity against CYP24A1 hydroxylase [56]. Compound **34** (IC_{50}=1.9×10^3 μM) (Fig. 6) showed optimal activity compared with ketoconazole (IC_{50} = 0.5×10^3 μM). Compound **35** (Fig. 6) was an instance of selective CYP27A1 inhibitors, with an IC_{50} value of 59.00 nM, the number of which was much lower than that of CYP24A1 (IC_{50} = 16.3×10^3 μM). Compound **36** (Fig. 6) exhibited weak inhibitory activity against the wild type CYP24A1 (IC_{50} = 25.60 ×10^3 μM), while an increase in the inhibitory activity towards L148F and M416T mutants was observed. The enhanced binding affinity **36** could be attributed to the π-π interaction between the phenylalanine side chain and the aromatic ring of the tetralone scaffold. From the SAR perspective, inhibitors with an addition of double bond at the attachment position between the tetralone moiety and benzyl ring resulted in a reduced inhibitory effect, which could be attributed to the enhanced conjugation effect of the double bond with phenyl group, thereby decreasing the conformational flexibility of the structure. However, decreased inhibitory activity would be observed when 2-position was substituted with phenyl group. Compounds containing fluorine groups could increase the cell-membrane penetrating capacity and the bioavailability, thereby increasing the bioactivity.

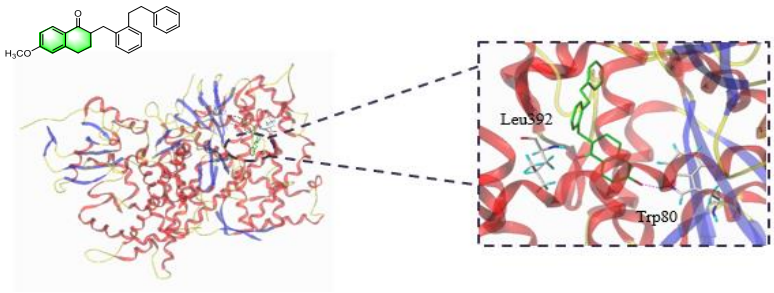

Fig. 4. Docking of **36** into the 'mutated' L148F CYP24A1 homology model enzyme cavity accomplished by SYBYL-X.

At Cardiff [57], a variety of 2-benzyl substituted tetralone derivatives against liver microsomal retinoic acid metabolizing enzymes were reported for the first time. Among all the compounds, **37** and **38** (Fig. 6) were potent enzyme inhibitors (IC_{50} = 0.50 and 0.80 μM) with ketoconazole as reference in the liver microsomal assay, while in the MCF-7 cell assay, compound **39** and

compound **40** (Fig. 6) with unsaturated benzylidene were found to exhibit stronger CYP26A1 inhibitory activity than others (IC_{50} = 7.00 and 5.00 μM), and the effectiveness of them was almost the same with that of liarozole (IC_{50} = 7.00 μM). Human CYP26A1 was used as model to conduct Flex[30] docking studies (Fig. 5), and the results showed that, similarly to atRA, all the tetralone derivatives positioned in a hydrophobic tunnel with the interaction at the enzyme active site, although additional interactions including hydrophobic interactions, coordinate binding and hydrogen bonding were noted in **39** and **40** as well, which could provide an explanation to the enhanced activity of the compounds (Table 1).

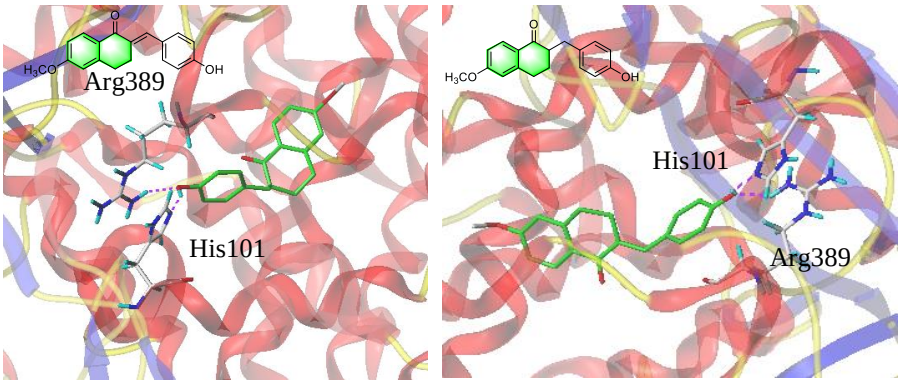

Fig. 5. Docking of **39** and **40** and the active site of CYP26A1 accomplished by SYBYL-X.

3.2.1.2 Other synthetic anticancer agents

A variety of tetralone derivatives were designed and synthesized to exhibit antiproliferative effect on different cancer cell lines. Wen and teammates investigated the anticancer effects of **41** (Fig. 6) in hepatocellular carcinoma (HCC) cells [58]. The result showed that, in the nude mice assay, the administration of **41** significantly inhibited the growth and cell proliferation of HepG2 cells without obvious side-effects on the index of body and organ including liver and spleen. Furthermore, the positive staining ratio of some key mediators including p-Akt, NF-κB, MMP9 and MMP2 in HCC cell proliferation and metastasis became much lower, at 2.91 %, 35.47%, 7.64% and 9.69 %, respectively.

Hallgas et al. reported a class of novel bicyclic, *α,β*-unsaturated ketones with anti-proliferative activity on cancer cell lines [59]. A remarkable antiproliferative activity was observed for the compound **42**, **43**, **44** (Fig. 6) investigated in A431 cell line (IC_{50} < 10.0 μM), while molecules including compounds **45**, **46** (IC_{50} > 20.0 μM) (Fig.6) displayed weaker biological effectiveness.

SAR showed that the incorporation of heteroatom in the aryliden ring would not affect anti-proliferative activity. Halogen substitution such as chlor- and fluoro- generally lead to a decreased activity in the biological potency derivatives,, but introducing Br- at 4 position result in inactive compounds. Structural modifications affecting the skeleton of the fused ring system or aryliden substitution normally result in a negative impact on the bioactivity of the compound, while modifications with 4-OCH_3 group and the pyridyl groups represented typical exception.

Zhu and colleagues studied the antitumor activity of multiple 4,4-dimethyl-tetralone derivatives in depth [60]. The in vitro cytotoxicity assay showed that compounds **47**, **48** and **49** (Fig. 6) exhibited potent anticancer activity on almost all the tested cancer cell lines. Theoretical calculation and analysis were conducted to investigate the difference in antitumor activity between **49** and its corresponding monosubstituted compounds **50** and **51** (Fig. 6). HOMO and LUMO orbitals are two frontier orbitals with different electron-donating activity, the property which could significantly influence the structure-relationship activity of specific compounds [61]. The frontier molecular orbitals calculation and analysis showed that compound **49**, owning higher negative electrostatic potential at the portion of R group, possessed higher dipole moment (9.48 D) than **50** (9.01 D), and **51** (5.23 D) and the distribution of electron could be responsible for the observed difference in terms of antitumor activity (Table 2).

Chalcone is a key structural moiety with broad-spectrum biological activities and many anticancer agents have been developed based on this backbone [62]. However, few chalcones containing the same crucial moieties of tetralone have been reported in the past decade according to the published literature [63]. Wang et al. firstly reported a cluster of indolyl-tetralone chalcones as new leading structures to develop novel anticancer drugs [64]. In A549 cells, compound **52** (Fig. 6) displayed potent cytotoxicity (EC_{50} = 0.55 μM), while no cytotoxicity was observed in the normal lung epithelial cells when the concentrations ranged between 0.01 and 10.00 μM. Compound **53** (Fig. 6) dose-dependently decreased the viability of A549 cell line with an EC_{50} of 0.11 μM, exhibiting a excellent cytotoxicity. The SAR could be concluded that fluorine substitution of tetralone backbone at 7 position normally results in an increased effectiveness (> 4-fold difference), while a bromine replacement had the contrary effect. Additionally, mono-methoxy

substituted compounds such as **52** (EC_{50} = 0.55 μM) exhibited a better biological activity compared with derivatives with di-methoxy groups, such as **54** and **55** (Fig. 6).

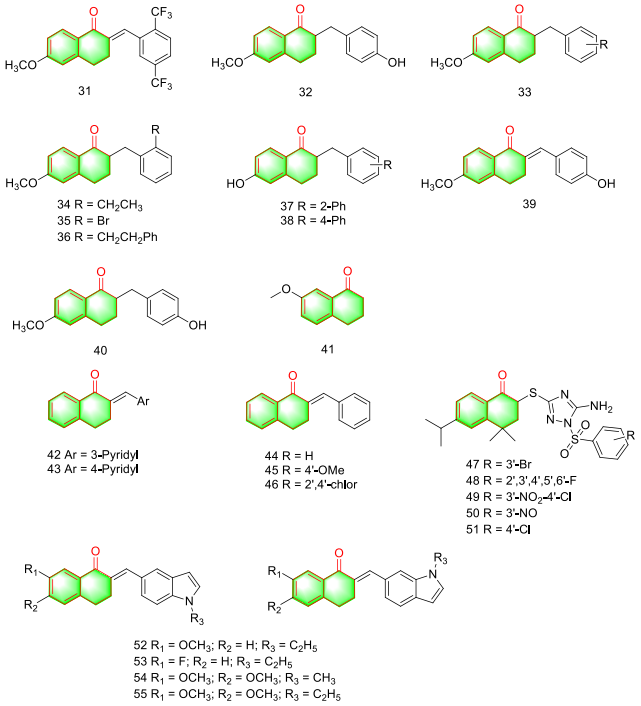

Fig. 6. Synthetic tetralone derivatives with anticancer activities.

3.2.2 CNS agents of synthetic tetralone derivatives

CNS disorders represent a series of diseases whose symptoms contain cognitive impairment and maniac or depressive behavior and millions of people around the world are suffering from this kind of diseases every year [65]. The complex pathogenesis of CNS disorders account for the high investment but low returns of CNS agents. Multiple tetralone derivatives have been found to exhibit CNS effect including anti-depression, anti-parkinson, anti-schizophrenia, anti-alzheimer and neuroprotective effect. A variety of compounds have thus been developed aimed at various targets including 5-HT, Ache, MAO-A/B and etc.

3.2.2.1 MAO-A/B inhibitors

Belonging to the protein family of flavin-containing amine oxidoreductases, monoamine oxidases (MAO-A and MAO-B) as a family of enzymes that catalyze the oxidation of monoamines on the outer membranes of mitochondria, play a crucial role in the metabolism of monoamine neurotransmitters such as serotonin, norepinephrine and dopamine, thereby regulating their concentrations in the brain [66,67]. Inhibitors of MAOs have been proved to have great

therapeutic value in the therapy of neuropsychiatric and neurodegenerative disorders [68]. MAO-A isomer mainly regulates the breakdown of serotonin in the human central system [69], and inhibitors of the enzyme have been employed as antidepressant and anxiolytic agent [70], while MAO-B isomer, with a higher concentration and activity in the brain than MAO-A [71], could affect region in Parkinson's disease and also metabolize dopamine in the CNS with aging. A series of MAO inhibitors based on tetralone scaffolds have been developed and most of them demonstrated more potent MAO-B inhibition than that of MAO-A isomer, although the selectivity of MAO inhibitors mainly depends on the substitution and functional groups of tetralone moiety. Some selective MAO-A inhibitors and dual-target-directed MAO-A/B inhibitors are also summarized as follows (Table 3).

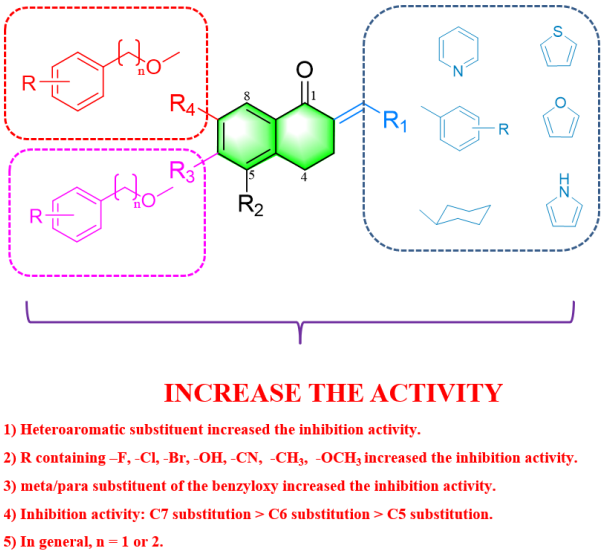

Fig. 7. SAR of tetralone derivatives with MAO inhibitory activity.

Earlier study has shown that chromone is a crucial parental backbone to synthesize MAO inhibitors [72]. Similarly to chromone moiety from perspective of chemical structure, *α*-tetralone derivatives with potential MAO inhibitory activity have been synthesized and investigated by Legoabe and co-workers and all the 1-tetralone derivatives had potent biological activity to inhibit the human MAO-A and B [73], especially MAO-B isomer ($IC_{50} < 7.8\times10^{-4}$ μM). Compound **56** (Fig. 10) displayed the strongest inhibitory activity on MAO-B ($IC_{50} = 4.5\times10^{-3}$ μM), with almost 300-fold selectivity for MAO-B more than MAO-A, whereas **57** (Fig. 10) was the most potent MAO-A inhibitor ($IC_{50} = 2.4\times10^{-4}$ μM), showing an approximately 3-folds selectivity for MAO-A compared to MAO-B. The SAR indicated that C6 substitution of the 1-tetralone moiety is a

requirement and the order of effectiveness of C6- substitutes follows benzyloxy > phenylethoxy > phenylpropoxy substituent for MAO-A inhibition activity, and alkyl and halogen substituent are more favorable on the *meta* and *para* positions of the benzyloxy.

Further study was conducted on the 1-tetralone by the same research group [74]. Several C7-substituted 1-tetralone derivatives as novel MAO inhibitors have been developed. Compared with C6-substituted 1-tetralone, 1-tetralone moiety with arylalkyloxy substitution on C7 resulted in better both MAO-A and MAO-B inhibitory activity, with IC_{50} values ranged from 8.9×10^{-4} μM to 7.4×10^{-1} μM. Compound **58** (Fig. 10) as the most selective MAO-B inhibitor ($IC_{50}=3.8 \times 10^{-3}$ μM, could be regarded as one of the potential drug candidates for treating Parkinson's disease. Compound **59** (Fig. 10) displayed a dual-target-directed manner, with IC_{50} of 0.010 μM for MAO-A and 1.2×10^{-3} μM for MAO-B, respectively, this unique property endowed it the ability to treat either motor or depression symptom accompanied with Parkinson's disease. Compound **60** (Fig. 10), a potent and reversible MAO-A inhibitor (IC_{50} = 0.366 μM), reversibility owned better drug safety in clinical use. Molecular docking studies of compound **60** could be concluded that Van der Waals interactions would be more important than hydrogen bonding in terms of the inhibitor stabilization (Fig. 8). As for **60**, the principal Van der Waals interactions between it and MAO-B occur with Tyr-326 also contributing significantly to inhibitor stabilization. SAR could be concluded that C7 replacement is crucial for MAO-B inhibition activity and a benzyloxy replacement on C7 results in more selective MAO-B inhibitors, followed by phenylethoxy and phenylpropoxy substitution. No obvious relationship between the position of the substituent of the benzyloxy ring and MAO-B inhibition potency exists, although when alkyl substituted on the meta and para position of benzyloxy ring could enhance MAO-B inhibition potency; also the correlations between the nature of the substituent on the benzyloxy ring and MAO-B inhibition potency was not apparent, although high potency inhibitors were found in molecules bearing electron withdrawing groups as substitution including F, Cl, Br, CN, CF_3 and so on (Table 3).

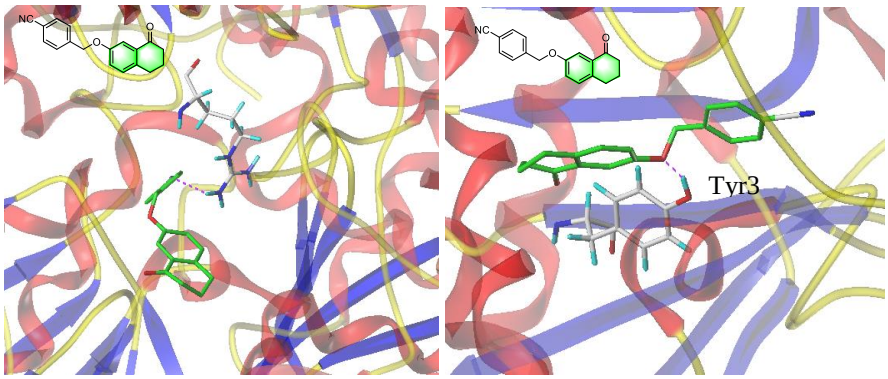

Fig. 8. Docking of **60** and the active site of MAO-A and MAO-B accomplished by SYBYL-X.

Amakali and colleagues introduced multiple heterocycles such as pyridine, furan, pyrrole, thiophene into tetralone phenyl ring to synthesize a series of 2-heteroarylidene substituted compounds based 1-tetralone backbone [75]. Compound **61** (Fig. 10) was a highly selective MAO-A inhibitor (IC_{50} = 1.37 μM) with no inhibitory activity on MAO-B. **62** (Fig. 10) was the most potent MAO-B inhibitor of all the phenyl substituted derivatives (IC_{50} = 0.71 μM). Some preliminary SAR may be derived: (1) 2-Chloro-3-pyridine and phenyl substitution benefited MAO-A inhibition activity; (2) For MAO-B inhibitors, thiophene substituted compounds showed better activity than pyridine substituted compounds; (3) Non-aromatic cyclohexyl substituents could contribute to relatively potent MAO-B inhibition. (5) The effect of different substituents on MAO-B inhibition potency in decreased order follows: cyclohexyl, phenyl > thiophene > pyridine, furane, pyrrole, cyclopentyl; (6) -OCH_3 replacement on the phenyl ring of tetralone moiety is advantageous of MAO inhibition activity.

A variety of benzylidene derivatives were investigated by Amakali et al. as potential MAO inhibitors and the results showed that almost all the derivatives exhibited higher potency inhibition for MAO-B over MAO-A isomer, suggesting that they are selective MAO-B inhibitors [76]. Only two derivatives (**63** and **64**) possessed IC_{50} values lower than 1.000 μM for MAO-A inhibition. Compound **63** (IC_{50} = 0.754 μM) displayed the highest MAO-A inhibition activity within this series, while **64** (IC_{50} = 0.006 μM) was the most potent MAO-B inhibitor, with lazabemide used as reference (IC_{50} = 0.091 μM). SAR could be concluded that the 2-benzylidene-1-tetralone substituent on A- and B-rings are decisive for high potency inhibition. Besides, a substituent on the B-ring could significantly enhance MAO-B inhibition, even when the A-ring is unsubstituted, while addition of an appropriate substituent on the A-ring, such as the 7-hydroxy group, yields

higher potency inhibition compared to derivatives substituted on the B-ring alone. Hydroxy and methoxy substitution of the A-ring on the other hand result in high potency MAO-B inhibitors, whereas amino substitution has the exact opposite effect.

Cloete et al. reported several 1-tetralone derivatives and evaluated their bioactivities [77]. Almost all the synthesized compounds selectively displayed more potent MAO-B inhibitory effect compared to MAO-A isoform (SI values > 1.8), while compounds **65** and **66** (Fig. 10) were two good examples which exhibited strong inhibition potency on MAO-A with IC_{50} values ranged from 0.623 μM to 0.575 μM. Particularly, **67** (Fig. 10) was not only a high-potency MAO-A inhibitor, with a more than 108-fold potency than toloxatone (IC_{50} = 3.920 μM), but also the strongest MAO-B inhibitor (IC_{50} = 0.0011 μM), with lazabemide used as reference (IC_{50} = 0.091 μM). SAR analysis showed that the position of substitution on tetralone moiety could affect the activity significantly, in comparison with C6 and C5 substitution, C7 substitution leads to better MAO-B inhibitors capable to accommodate the active site of the enzyme and form more productive interactions. Additional van der Waals interactions could be formed by adding a Cl to the side chain and this modification could enhance MAO-B inhibition potency. SAR could be concluded that (1) Substitution especially benzyloxy substitution on C7 leads to the best inhibitory activity for both isomers, followed by the C6 and C5 substitution. (2) Electron withdrawing groups such as F, Cl, Br, I, CH_3, CN and CF_3 substituted on benzyloxy ring increases MAO inhibitory activity of the inhibitors. (3) Phenylpropoxy substituted on the position 6 yield compound with better activity than benzyloxy substituted on the same position, while the benzyloxy moiety is preferable to C7 position.

3.2.2.2 5-HT2A and D2 receptors

Schizophrenia, a severe and devastating psychiatric disorders, now become one of the hot spots of CNS research [78]. D2-like and 5-HT2A receptors have been regarded as targets of developing antipsychotic drugs [79]. In 1950s, a huge advancement in the therapy of schizophrenia was conducted by introducing the butyrophenone haloperidol into the clinic [80]. Haloperidol, however, proved to be ineffective for treating negative symptoms of schizophrenia as well as neurocognitive deficits. In 2007, Torrado et al. synthesized aminobutyrophenones **68** and **69** (Fig.

10) and both compounds exhibited potent affinity for the 5-HT2A receptors, i.e. Ki = 1.6 for 5-HT2A, Ki = 2.7×10^{-3} μM for 5-HT2C [81]. Compound S38 was also the most selective for the serotonin 5-HT2A receptor subtype (Ki =0.15 μM). Both of the compounds were potent D2 receptor antagonists as well, although the Ki values of them were higher than those as 5-HT2A receptors. SAR could be concluded that the binding affinity of the acceptors would not be remarkably influenced by the methoxy groups substituted on the tetralone ring, while the substitution on aromatic ring is a prerequisite for the affinity for serotonin and dopamine receptors. Therefore, in order to find extra binding interactions (hydrogen or ionic bonding interactions) with the target, chemical modification strategies including adding various substituent such as alkyl or aryl groups have been developed in the lead structure.

Researchers have focused on modulating the butyrophenone system via the combination of antagonism of 5-HT2 and D2 receptors in a single molecule. Carro et al. reported a cluster of α-tetralone derivatives with strong binding affinities for both D2 and 5-HT2 receptors [82]. Compound **70** (Fig. 10) displayed a potent binding affinity, with pKi values of 7.80 for 5-HT2A and 7.76 for D2 receptors respectively, indicating a typical antipsychotic behavior. Compound **71** substituted with an amino group at 7 position of tetralone moiety led to a potent 5-HT2A/ D2 affinity, exhibiting an 8.30-fold pKi value for both receptors compared to **70**. The presence of the amino-containing groups such as -NH_2 group may account for the difference in binding affinity, as additional interaction could be established between the acceptor and the binding site of receptors. SAR could be concluded that the effect of C7 substitution with nitro group or amino moiety on tetralone core could be illustrated by better binding affinities for receptors including serotonin, rather than dopamine receptor. Besides, the introduction of 6-fluorobenzisoxazolyl piperidine could be a better choice to 5-HT2A and D2 receptor's binding affinities than those bearing 2-methoxyphenyl piperidine groups (Table 4).

3.2.2.3 Adenosine receptors

Adenosine, a neuro- and homeostatic modulator, has a large amount of effects to exert in human body [83], and the receptors of which (A1 and A2A) have been regarded as potential targets for novel drugs development related to neurological disorders [84,85]. Rensburg et al. synthesized a

cluster of benzylidene-1-tetralone derivatives with antagonism for the AR [86], radioligand binding assays were conducted to evaluate the preferential structural characteristics necessary for A1/A2A AR affinity. Compounds **72**, **73**, **74** and **75** (Fig. 10) were regarded as potential drug candidates of A1 and A2A AR antagonists with high potency and selectivity for treating neurodegenerative disorders. Within them, **75** possessed the highest A2A AR affinity (A2A Ki = 1.62×10^{3} μM, SI = 7), SAR derived from this series suggested that structural modifications at both rings could affect AR affinity (Fig. 9). Ring A with -OCH_3 substituted yielded low binding affinity of A1 and A2A AR, while -OH replacement on phenyl ring enhanced A1 AR affinity and selectivity. In addition, replacement on the phenyl ring with a 2-amino-pyridine ring would be beneficial to the affinity and selectivity of the A2A AR (Table 5).

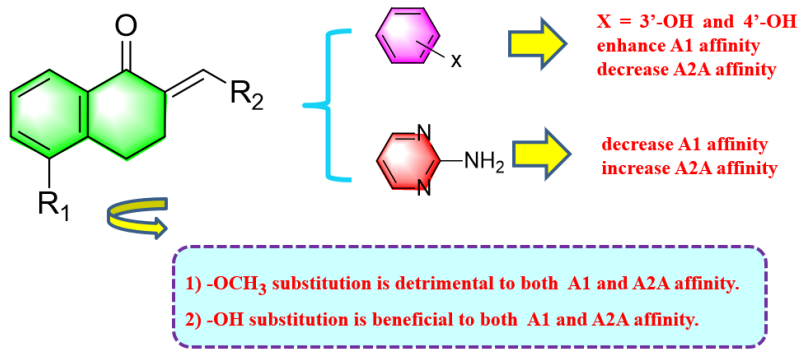

Fig. 9. SAR of tetralone derivatives with adenosine affinity.

76 as the most selective A1 AR antagonist (binding affinity of A1 and/or A2A AR <10.0 μM) was synthesized by Rensburg and co-workers [87]. The substitution of -OCH_3 on C5 of ring A led to a complete loss of both A1 and A2A AR affinities. However, ring B substitution (including -H, -OH and -OCH_3) was not as crucial for A1 and A2A AR affinity as ring A substitution did. -OH group substituted on C3' of ring B resulted in better A1/ A2A AR affinity compared with -OCH_3 substituted group. Compound **77** (Fig. 10) was a typical dual-targeted acceptor of the series, with high binding affinity for both receptors with Ki value lower than 10.0 μM (SI = 1).

3.2.2.4 Other inhibitors

AChE, a key enzyme in biological nerve conduction, could accelerate the progression of AD by catalyzing degradation of acetylcholine (ACh) and inducting the Aβ aggregation [88]. Researchers worldwide have paid much attention in developing selective and potent AChE inhibitors so as to

inhibit ACh degradation. Rizzo reported some specific compounds bearing tetralone backbone in molecule [89]. Among them, compounds **78** and **79** (Fig. 10), with an alkyl chain containing an amino group, had a good ability to contact the peripheral anionic site, which is located at the lip of acetylcholinesterase (AChE)'s gorge, thereby significantly inhibiting Ab aggregation induced by AChE, especially for Aβ 42 peptide, the most amyloidogenic form of amyloid accumulated and produced in the brain of Alzheimer's disease. SAR study demonstrated that methoxy replacement in position 6 with a pentyl chain (compound **78**) yielded more potent compounds with stronger inhibition activity, especially in comparison with the compound **79** (Table 7). "one-molecule, multiple-target" as a hypothesis-based multi target directed ligand (MTDL) approach was proposed by Leng et al in 2016 [90]. This approach has profound therapeutic value in AD treatment and a cluster of unsaturated tetralone derivatives have been developed based on that strategy. Potent inhibitory activity was observed of those synthesized compounds on MAO-B, AChE, and self-induced Aβ1-42 aggregation in vitro experiments. Compound **80** (Fig. 10) may be a good example of multifunctional agents for AD treatment, exhibiting privileged AChE inhibitory activity, with IC_{50} value of 0.045 μM, as well as strong MAO-B inhibition activity (IC_{50} = 0.880 μM); also compound **80** had the ability to disassemble the Aβ fibrils generated by self-induced Aβ aggregation by almost 80.0 %. It is speculated that the substitution of methyl in cyclohexanone ring of the tetralone ring system, nitro substitution on phenyl of tetralone moiety, and dimethoxy substitution at phenyl of aldehydes contributes to enhanced activities in all cases, which is reflected in compounds **80**, **81**, and **82** and these compounds showed excellent bio-activities on all test targets with multifunctional property (Table 7).

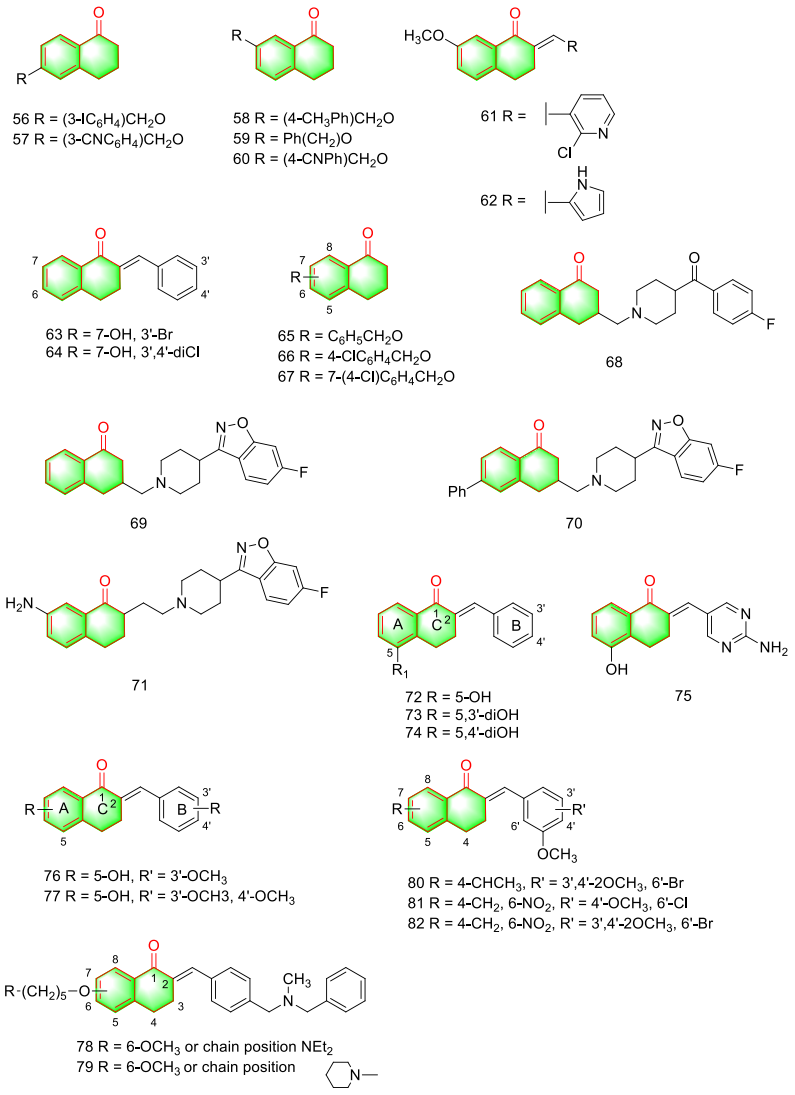

Fig. 10. Synthetic tetralone derivatives with CNS effect.

3.2.3 Antifungal activities

Fungal infections have emerged as a growing threat to human health especially for those patients who are infected with HIV and being treated with cancer chemotherapy drugs [91]. Gupta et al designed and synthesized some new antifungal agents using Claisen-Schmidt condensation reaction with suitable derivatives [92]. The newly synthesized derivatives showed antifungal activity against *Microsporum gypseum*, which could cause dermatomycoses, a type of infection difficult to treat. Among all the tested compounds, two compounds **83** and **84** (Fig. 11) were more effective than the others, with MIC value at 1.5 and 3.0 µg/mL against *Microsporum gypseum*, respectively. The SAR showed that electron withdrawing groups, such as a Cl group contributes to a better activity when it is placed in the *para* position, while the *ortho* position replaced with a Cl

group led to the same potency as Br substituted at the *para* position, moreover, the introduction of -OCH_3 group led to a decreased effectiveness. Conclusions regarding with the correlation between antifungal activity and the planarity of substituted molecules showed that the activity of compound decreased as the number of substituent increased, substitution with a bulky group significantly lower the activity of derivatives, indicating the steric hindrance may reduce the activity.

3.2.4 Antibacterial activities

Antimicrobial activities of *β*-lactam fused spiroisoxazolidine tetralones have been reported by Natarajan Arumugam et al. reported several [93]. The antibacterial and antifungal activities of the synthesized compounds were also investigated. The MICs of all the tested compounds on the mycelial of plant fungal pathogens were in a wide range of 25 to 150 μg/mL. **85** (Fig. 11) exhibited potent activity on both fungal pathogens named *F. oxysporum* (MIC = 50 μg/mL) and *M. phaseolina* (MIC = 25 μg/mL), while other compounds inhibited mycelial growth in a higher range of concentration between 50 and 150 μg/mL, with carbon used as reference.

3.2.5 Anti-inflammatory activity

Inflammation, a normal and complex physiological response of human body to a variety of foreign organism, constitutes a crucial part in the process of immune response to diverse types of infections including injury, pain, toxin, and stimuli [94]. A promising therapy strategy mainly depending on the intervention and regulation of ROS production in macrophages has been developed in the past decades. Earlier study has shown that introducing aminocyclopentyl group to 1-tetralone nucleus was beneficial to exerting the anti-inflammatory effects [95]. Inspired by that, Katila et al. designed more than thirty compounds bearing tetralone moiety via the Claisen-Schmidt reaction and investigated their inhibitory effect on LPS-induced ROS production in RAW 264.7 macrophages [96]. The most potent ROS inhibitory effect was observed on compound **86** (Fig. 11), with an IC_{50} value of 0.25 μM. SAR study indicated that 1-tetralone was proved to be a more suitable parental skeleton of potent ROS inhibitors, in comparison with indanone or chromanone skeleton. In RAW 264.7 macrophages, C6 substitution with amino on 1-tetralone moiety was greatly advantageous to the inhibitory activity of LPS-induced ROS

production.

3.2.6Antitubercular agents

Tuberculosis represents an infectious diseases which has been listed as a public health problem by WHO with a target to eliminate tuberculosis by the year of 2050 [97]. Natural tetralone derivatives such as shinanolone and hydroxymethoxy tetralone, isolated from *Euclea natalensis* and *Engelhardia roxburghiana Hay*, have been reported to have potent antimycobacterial activities [98,99], exhibiting antitubercular activity against H37Rv strain with MIC at 100.00 μg/mL and 6.25 μg/mL, respectively. Inspired by the efficacy of these natural tetralone derivatives, Chanda et al. synthesized a cluster of tetralones via Vilsmeier-Haack-Arnold reaction [100]. Most of these compounds displayed antitubercular activity against Mycobacterium tuberculosis H37Rv strain with MICs ranged from 30.00 to 500.00 μg/mL. Further modifications have been conducted on the analogue **87** so as to study SAR of the derivatives. Further investigations for acute oral toxicity have been conducted in swiss albino mice model and the most active compound **88** (MIC = 30.00 μg/mL) also had a quite high safe dose of 300.00 mg/kg (Fig. 11).

3.2.7 Antiviral activity

Manvar et al. synthesized a series of *α*-aryl-*α*-tetralones with potent antiviral activity and selectivity in-vitro against HCV replicon reporter cells [101]. There are in total 4 compounds exhibited EC_{50} values below 8.0 mM against HCV genotype 1b whereas 7 compounds displayed EC_{50} values below 5.0 mM against HCV genotype 2a. Compound **89** (Fig. 11) was found to be the most potent lead against HCV genotype 2a (EC_{50} = 1.5×10^3 μM, SI > 101.4). Compound **90** (Fig. 11) was the most potent and selective against both Huh7/Rep-Feo1b replicon reporter cells (IC_{50} =1.8 μM, SI > 111) and also Huh7.5-FGR-JC1-Rluc2A replicon reporter cells (IC_{50} = 4.3 μM, SI > 46).

3.2.8 Tetralone derivatives (α and β) as an adjuvant with therapeutic drugs to reduce drug resistance and enhance efficacy

The world has entered the post-antibiotic era and according to Higgins (2007), rather than fighting against multiple drug resistance, now it is the time to find alternatives and methods to weaken and avoid it [102]. Plants-extracted compounds have thus become a promising candidate as ATP

binding cassettes (ABC) transporter blockers to revert the resistance of multidrug. Dwivedi et al. investigated the reversal mechanism of drug resistance of compound **91** (Fig. 11) isolated from *Ammannia spp.* As well as its semi-synthetic derivatives using multidrug resistant Escherichia coli (MDREC) [103]. The results showed that the compound **91** and its semi-synthetic derivatives **92** (Fig. 11) could exert inhibition activity on multi drug resistant clinical isolates MDREC-KG4 and MDREC-KG1, multi drug resistant mutants MDREC-EM5, MDREC-EM7, with MIC value ranged from 250-1000 μg/mL. In a combination assay of these compounds with tetracycline (TET), the MIC of which reduced up to eight folds. In time kill assay, the cell viability of E. coli reduced at 4 MIC when compound **91** and its derivative **92** were used together with tetracycline, while the reduction in viability of MDREC-KG4 could be achieved at lower concentrations (1/4 MIC and 1/8 MIC) of TET. Compounds **91** and **92** could inhibit the activity of ATP dependent efflux pumps and ATPase at 25 μg/mL, and an optimal reduction in the MIC of TET could also be observed. In RT-PCR study, either the alone administration and or co-administration of compounds **91** and **92** with TET significantly down-regulated the expression of efflux pump gene (yojI) encoding multidrug ABC transporter protein.

3.2.9 Tetralone compounds as antioxidant against oxidative stress

Beteck et al. investigated other activities of various tetralone analogus such as anti-trypanosomal, antimalarial via the resazurin assay protocol and in virto pLDH assay [104]. The results showed that totally 26 compounds displayed a lower than 25.0% T.b. brucei cell viability. There are in total 12 compounds displaying strong anti-trypanosomal activity with IC_{50} values ranged from 0.4 to 6.7 μM. Of these compounds, compound **93** (Fig. 11) had low parasite viability at 0.7% and a very privileged IC_{50} value of 0.4 μM; also a micromolar activity, a low molecular weight (250 KD) and a low total polar surface area (37) were observed on the same compound, these characteristics contribute to its hit-to-lead optimization. Antimalarial activity of the tetralone derivatives was evaluated on the chloroquine-sensitive strain of Plasmodium falciparum (strain 3D7). Most compounds of this series normally showed a low cytotoxicity effect against the HeLa cell line and weak antimalarial activity against 3D7, with few compounds exhibiting HeLa cell viability below 25.0% at 20.0 μM and only seven compounds exhibited 3D7 viability less than 25.0%. SAR analysis showed that anti-trypanosomal activity could be significantly affected by the benzene ring

and the cyclohexanone ring substituted on the tetralone moiety. The introduction of -NH_2 on benzene ring attached to tetralone normally negatively affects the anti-trypanosomal activity, while substitutes such as -OH and -OCH_3 contributes to an increased anti-trypanosomal activity. In terms of anti-trypanosomal activity, six-membered heteroaromatic rings systems such as cyclohexane and cyclopentane had a better performance compared to five-membered heteroaromatic ring such as furan, thiophene, and pyrrole.

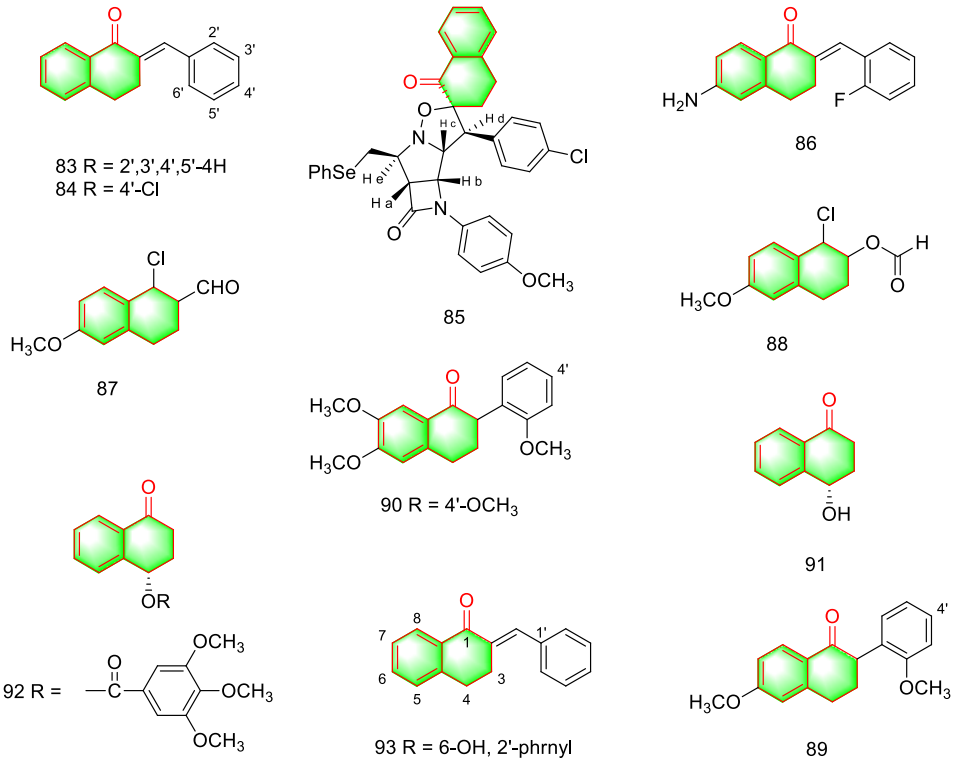

Fig. 11. Synthetic tetralone derivatives with other activities.

3.3 Application of tetralone moiety in medicinal chemistry

Bearing carbonyl moiety as the chemically reactive group, 1-tetralone and 2-tetralone could be further modified to yield compounds with bicyclic-conjugated system, which has wide application as the starting materials and intermediates in the synthesis of biologically active substances. Some FDA approved and investigational drugs containing tetralone moiety are summarized as follows (Table 8).

3.3.1 PB28 derivatives

σ1 and σ2 receptors, correspondingly over-expressed in many cancers [105], are regarded as a crucial molecular targets for developing radiotracers to imagine tumors using techniques such as positron emission tomography (PET) [106]. Bearing a tetralin and/or naphthalene moiety, *σ*-agonist PB28 (**94**) (Fig. 12) is a representative σ receptor ligands used to monitor the proliferation status of solid tumors in cancer therapies [107]. The tetralin/naphthalene nucleus is indispensable as pharmacophore of PB28, which was explored by keeping the 1-propyl-4-cyclohexylpiperazine structure and removing the hydrophobic portion, and the lack of the hydrophobic moiety led to the complete loss of the *σ* affinity activity [108]. However, the high lipophilicity of PB28 may put a limitation on its usage as a CNS radiotracer [106]. Inspired by that, Abate et al. reported a series of σ2-selective ligands with reduced lipophilic character by introducing more polar functional groups to the tetralin system [109]. Within the series, compound **95** (Fig. 12) was the best σ2 receptor agent (Ki = 5.92×10^{-3} μM), with the ability to enter into tumor cells (log $D_{7.4}$ = 2.38), indicating the potential of this compound to be a PET tracer for the imaging of σ2 receptor-overexpressing cancers; also the minimal antiproliferative activity in SK-N-SH cells (100% viability at 100 μM), and moderate activity (EC_{50} = 8.10 μM) at the P-gp efflux pump were observed on **95** as well. A series of σ2 receptor ligands were synthesized via Grignard reactions where 1-tetralone was used as the starting material [110]. Among all the compounds, the most active and selective binding affinity was observed on compound **96** (Fig. 12) (Ki = 5.30×10^{-3} μM on [^{3}H]DTG and Ki = 7.1×10^{-2} μM on [^{3}H]-(+)-pentazocine). Compound **97** (Fig. 12) represented a dual-target ligand with both 5-HT1A and σ affinity (Ki = 5.3×10^{-3} μM on [^{3}H] DTG and Ki =7.1×10^{-2} μM on [^{3}H]-(+)-pentazocine). SAR indicated that for phenylpiperazines, a slightly selective σ2 ligand or a mixed σ/5-HT1A affinity compound with a D-2 and PCP selective profile could be observed when a cyclohexyl or a benzyl group substituted on the aryl group. Besides, the chiral center of the tetralin ring requires more investigations to clarify the stereochemical properties.

3.3.2 DA agonists

The dopamine (DA) receptor as a system which has been targeted for the treatment of CNS diseases, has attracted the interest from researchers worldwide. Aminotetralin derivatives constituted one of the lead molecules which were earliest investigated for D3 activity and

7-OH-DPAT, although their binding affinity and selectivity ratio varied in different laboratories and assay conditions. Aminotetralin moiety, owning the ability to react with the agonist binding sites in DA receptor, has become an indispensable moiety in the construction of DA agonists, where the tetralones were normally used as starting materials. A large amount of work has already been conducted regarding hybrid approach by introducing different chemical groups to aminotetralin moiety, so as to develop target compounds with good selectivity. Homan et al. combined substituted benzamides to the molecules to obtain compound **98** (Fig. 12), representing a typical structure based on hybrid approach [111]. Biswas and co-workers introduced piperazine fragment to the aminotetralin moiety and compound **99** (Fig. 12) was developed as the lead compound with high D3 selectivity. Potent in vivo contralateral rotational activity in unilaterally lesioned 6-OHDA-treated rats was also observed on this compound [112], indicating it a drug with excellent blood-brain barrier crossing ability. Further study was carried out by the same group to delineate molecular determinants and developed a better selective D3 receptor. A series of optically active 5-hydroxy-tetralone derivatives were synthesized from 5-methoxy-2-tetralone [113]. Among all the compounds, compound **100**, **101** (Fig. 12) exhibited higher potency, better selectivity for D3 (Ki = 0.82 nM; D2/D3 = 31.50) and longer duration of action than others (lasted beyond 12 h at 5.00 μmol/kg) in vivo rat rotational study.

3.3.3 Compounds derived from tetralone with other medicinal properties

Potent anti-angiogenic and antitumor activity has been observed in the active heterocyclic derivatives bearing pyrazole moiety. Inspired by that, Tzanetou et al. reported a novel class of indazole by combining tetralone moiety and pharmacophore pyrazole into one molecule so as to investigate the relationship between the anti-angiogenic activities and pyrazole substituent [114]. Within the series, the tetralone-fused pyrazoles compounds **102** (IC_{50} = 1.5 μM) and **103** (IC_{50} = 5.6 μM) (Fig. 12) exhibited the most potent cytostatic properties against MCF-7 cells. Therefore, tetralone-fused pyrazoles may serve as parental scaffolds in the study of anti-angiogenic agents.

Compounds bearing heterocyclic ring systems have been verified to exhibit significant inhibitory activity towards different types of cancer disease. The fact motivated Ahmed et al. to synthesize compounds derived from 6-methoxy-1-tetralone bearing different heterocyclic ring systems such

as thiazole in one molecule [115], with target to construct new candidates with enhanced anticancer activity. Compound **104** (Fig. 12) demonstrated the best cytotoxic activity against MCF-7 cell line (IC_{50} = 0.93 μM), with Saturosporin as reference (IC_{50} = 6.08 ± 0.15 μM), while a less toxicity was observed on normal epithelial breast cells (MCF10A), indicating a very good safety profile.

Hepatitis C Virus (HCV) as a kind of virus leading to serious health disorders including cirrhosis, steatosis, hepatocellular carcinoma, has posed a huge challenge to human health [116]. More affordable antiviral drugs are still in large demand today, although many HCV inhibitors have been approved in the last 5 years. LQB-34, an anti-HCV candidate based on coumarin scaffold has been previously synthesized by Kaushik-Basu et al., where expensive multi-step synthesis was required [117]. In order to lower the cost of production, a class of 5-carba-pterocarpens as the trimmed version were synthesized by Fernandes et al. [118, 119]. Among the series, compound **105** (Fig. 12) , bearing three phenol groups, displayed the most optimal activity (EC_{50} = 5.5 μM) and the highest selectivity (SI = 20) in Huh7/Rep-Feo1b replicon reporter cells, while in Huh7.5-FGR-JC1- Rluc2A reporter cells, **106** (Fig. 12) was the lead compound with high potency and selectivity (EC_{50} = 1.5 μM, SI = 70). SAR demonstrated that phenol substitution on A- and D-ring is essential and compounds with better bioactivity can be yielded by introducing substitutions at positions 3 and 4 of the A-ring.

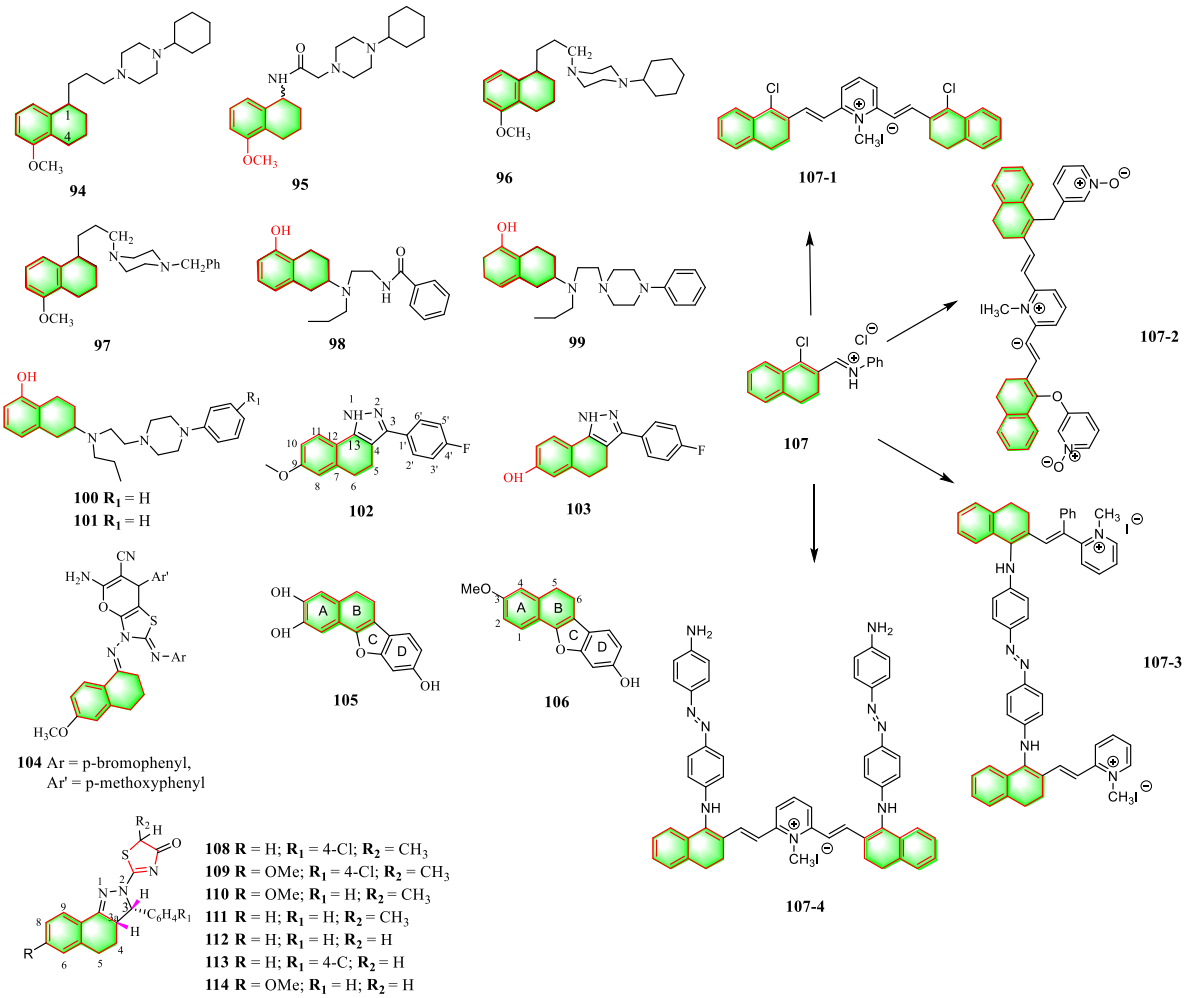

Fig. 12. Compounds derived from α/β tetralone with various activities.

Fadda et al. reported a class of novel cyanine dyes by a one-pot step reaction, where **107** (Fig. 12) was yielded as an important intermediate from 1-tetralone via Vilsmeier-Haack reaction [120]. The synthesized compounds **107**-1,2,3,4 represents four compounds derived from intermediate **107** with the strongest inhibitory activity on HepG2 and MCF-7 cell lines, while no effect was observed on the normal cells (WI-38 and Vero cells were used as reference). The structure-activity relationship showed that the introduction of azo group and phenyl rings enhanced the inhibitory activity versus HepG2 cells, since the enhanced degree of π-conjugated system attached to the pyridine rings.

There are in total seven indazolyl-thiazol-4(5H)-ones were obtained, from 2-arylidene-1-tetralones and their antibacterial and antifungal activities were evaluated as well [121]. Compounds **108** and **109** (MIC = 12.5 μg/mL) showed a good effect on S. aureus, E. coli and A. Niger (Fig. 12). Potent antibacterial activity against S. aureus and E. coli were observed on compounds **110** and **111** (MIC

= 6.25 μg/mL). Compounds **112** and **113** (Fig. 12) are good example of broad-spectrum antibacterial and antifungal agents. **114** (MIC = 12.5 μg/mL) showed privileged antifungal activities against C. albicans and A. fumigates (Fig. 12).

4. Application of tetralone moiety in fluorescent probes

Chromogenic and fluorogenic probes could be regarded as the reagents which are capable to interact with analytes (targets) accompanied by the changes of their spectroscopic (chromogenic, or luminescent including chemiluminescent) properties; according to such changes, the analytes could thus be determined [122,123]. Fluorogenic probes normally features in high sensitivity, short response time, good selectivity and convenient operation when detecting and analyzing targets; these excellent characteristics contribute to its application in food, medicine and medical analysis. Spectroscopic or signaling moiety, one of the most important parts of a specific fluorogenic probe, has the ability to determine the optical properties of the system thereby playing an important role in the analysis. Tetralone derivatives are bicyclic aromatic conjugated system and chemical modifications could be introduced to obtain new types of fluorescent dye by connecting various chemical groups on the bicyclic structure so as to form a push-pull electron system, which contributes largely to excellent optical properties. Therefore, tetralone derivatives are of great significance for the preparation of fluorescent probes.

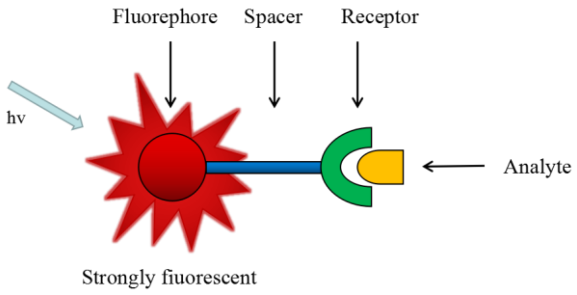

Fig. 13. Constitution of a typical fluorescent probe.

A fluorescent probe named **ADT-MAM** (Fig. 14, 19), was reported by Wu group for the first time to monitor the level of ClO^- in the biological microenvironment [124]. The probe was designed and synthesized from tetralone backbone, in which the acylhydrazone schiff base was introduced as a linker to connect the fluorescent group (DTC) and the recognition group diaminomaleonitrile. ADT-MAM, with a low detection limit of 1.57×10^2 μM, exhibited excellent properties including

large stokes shift, short response time, high selectivity and high sensitivity. It was also characterized by low toxicity and good membrane permeability in living cells. The probe itself does not have fluorescence properties, while after a rapid reaction with hypochlorite, and the diaminomaleonitrile group could depart to yield an aldehyde compound emitting intense fluorescence. The synthesis strategy could be concluded that the starting material 6-methoxytetralone was subsequently demethylated to obtain the free hydroxyl group, which underwent smile rearrangement to obtain the amino compound, followed by protection of the amino group with iodomethane, and after Vilsmeier-Haack reaction and condensation reaction the probe product ADT-MAM was finally obtained.

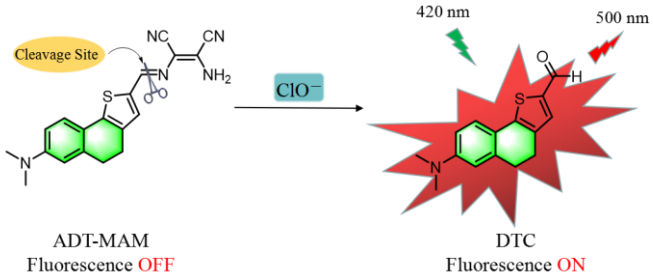

Fig. 14. Mechanism of probe **ADT-MAM**.

With Meldrum's acid as the recognition group, another fluorescent probe based on tetralone scaffold for the detection of ClO^- was also reported by the same group [125]. The probe **DDD** (Fig. 15,19) had two fluorescence emission peaks, at 555 nm and 625 nm, respectively. After the addition of ClO^-, the fluoresce intensity at 555 nm became stronger while that at 635 nm became weaker. The fluorescent probe **DDD** exhibited excellent sensitivity with a low detection limit of 0.15 M. The results of biological applications showed that the probe has low cytotoxicity, high cell membrane permeability, and good biostability, and good results were obtained for cell imaging as well as in vivo fluorescence confocal imaging of zebrafish.

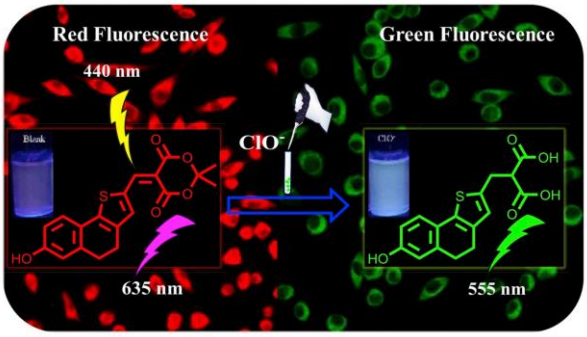

Fig. 15. Mechanism of the probe **DDD**.

The same group further investigated the tetralone backbone in depth and developed a fluorescent probe **DDTM** (Fig. 16, 19) by linking the DTC fluorescent group to reactive dicyanomethyl group and introducing a double bond into the system, the probe itself could be used to monitor pH changes in the biological systems [126]. A well-conjugated system existed within the probe to form a push-pull electron system and ICT effect could thus be observed. The probe itself has an ICT effect, and the structural change caused by the addition of OH^- leads to a compound with high fluorescence due to the inhibition of the ICT process. The fluorescence spectrum showed that at 578 nm, the fluorescence intensity of the system dose-dependently increased with pH value and a well linear relationship could be observed in the range of 9.5-10.7. The UV absorption intensity dose-dependently also increased with pH value and a good linear relationship was also observed (pH=10.5-13.5). Subsequently, after experimental analysis, the results showed that the probe DDTM has good selectivity for hydroxyl radicals. Finally, the cytotoxicity test and bioimaging results showed that the probe has the advantage of low cytotoxicity with good bioimaging effect.

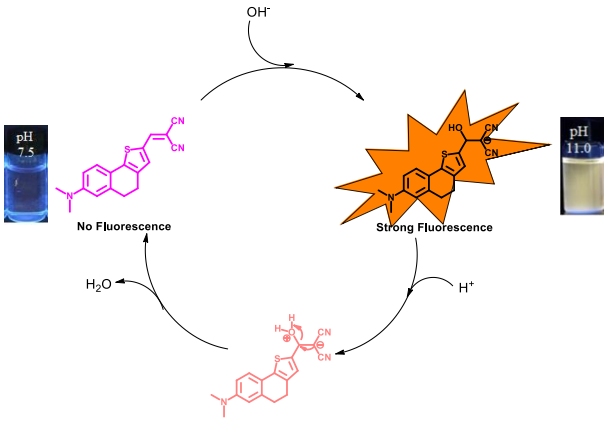

Fig. 16. Mechanism of the probe **DDTM**.

Using 6-methoxytetralone as a starting material, Chen et al. synthesized a concentration-dependent fluorescent probe owning near-infrared properties to detect thiols (Cys) in micro-environment [127]. Thiols represent biologically important molecules in human body and the fluctuations of thiol concentrations are normally associated with a wide range of diseases and it is of great importance to monitor its change in living systems. The fluorescent probe, **CHMC-thiol** (Fig. 17, 19), was consisted of a 2,4-dinitrobenzenesulfonate moiety as a high sensitivity site and a chloride fraction as the low sensitivity site with different fluorescence response patterns for different concentration ranges of thiols. At 680 nm, the probe showed a

turn-on pattern of fluorescence signal for lower concentrations of biothiols (0-50 μM), while its fluorescence signal showed a dose-dependently manner for detecting higher concentrations of thiols (50-500 μM). For low concentrations of thiols, the fluorescence turn-on mode could be attributed to the thiol-mediated departure of the 2,4-dinitrobenzenesulfonate group, while treated with high concentrations of Cys, the Cl group in CHMC- thiol was firstly substituted by the thiol group of Cys to produce a 4-sulfhydryl intermediate, followed by partial substitution of the sulfhydryl group via intramolecular SNAr substitution, leading to the formation of a 4-amino product. This difference leads to a difference in the nature of the two luminescence mechanisms.

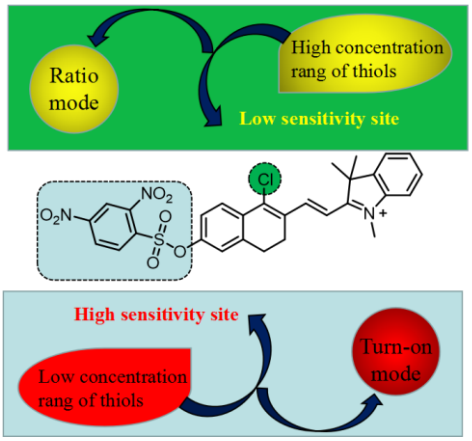

Fig. 17. Mechanism of the probe **CHMC-thiol**.

A class of **STHDP** dyes (Fig. 18, 19) were reported and 2-tetralone was used as the starting material [128]. Both in solid and solution states, p-conjugation of these dyes between the phenyl group and the phenanthridine moiety contributed to these dyes highly emissive properties. Dye 1 had two peaks, with an intense absorption band maximum at the lowest energy absorption (360 nm), while the emission maximum of dye was observed at 416 nm, and the corresponding stokes shift value was calculated to be 3894 cm^{-1}. Further introduction of electron-donating groups and electron-withdrawing groups on dye 1 was conducted to obtain better red-shifted dyes, and dye 4 was found to exhibit more red shifted absorption figure than the other dyes.

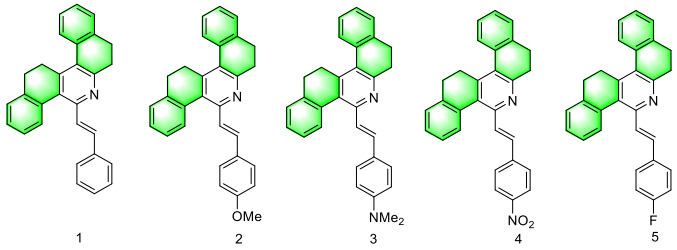

Fig. 18. Structures of a class of **STHDP** dyes.

A simple method to detect hydrazine was developed by Du et al. [129]. Fluorescent probe **DPT** (Fig. 19) with tetralone skeleton as raw material and barbituric acid as the unique recognition group was designed and synthesized. Under neutral conditions, the probe shows an excitation peak at 380 nm and an emission peak at 527 nm. When hydrazine (N_2H_4•H_2O) exists in the environment, the probe reacts with barbituric acid to obtain the compound DPT-N_2H_4, and the spectral properties show large emission signal changes and emit strong fluorescence (more than 40 times enhancement). In addition, the DPT probe has the advantages of wide pH range, low detection limit (5×10^{-8} M), wide linear response range (0-34 μM) and large Stokes shift (147 nm). It can be widely used to detect hydrazine under physiological conditions. And DPT probe has been successfully used in the imaging of hydrazine in living cells, with good biological activity.

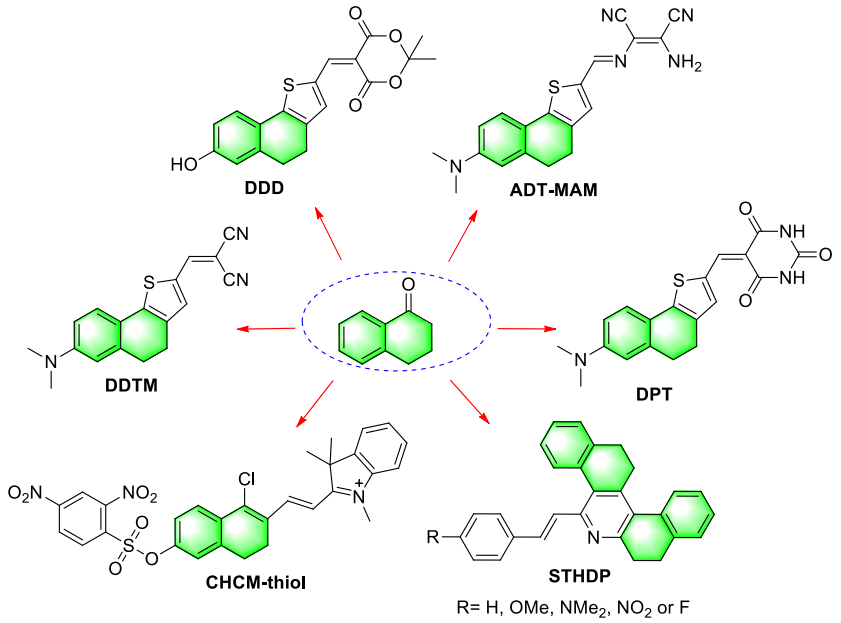

Fig. 19. Fluorescent probes based on tetralone moiety with various activities.

5. Conclusion and perspective

Bearing 3,4-dihydronaphthalene systems with different substitutes at the different positions, tetralone derivatives, as one of the most explored precursors within multiple aromatic bicyclic ketones, have exhibited immense biological significance. The recent advances from a synthetic standpoint were summarized briefly, illustrating that traditional Friedel-Crafts reaction still represents the mainstream of synthetic methods of tetralones, although several novel synthetic

strategies based on highly-effective catalysts have been developed as well. The process of tetralone derivatives development is similar to other bioactive compounds, beginning with isolation and extraction from natural plants, a series of analogues have subsequently been explored according to drug design strategy. This review article also focused on the pharmacological activities of natural and synthetic tetralone derivatives having been targeted for their antitumor, CNS effect, protein inhibitors, anti-inflammatory, antitubercular, antiviral activities, etc.

According to the existing literatures, the modification of tetralone scaffold mainly focused on three aspects: 1) 1-tetralone could be a better choice than 2-tetralone in terms of structural modification to synthesize potential target compounds, which may be attributed to the reactivity of the compounds and the affordability of the starting materials; 2) from the SAR perspective, the synthesized tetralone analogues of various pharmacological with the C2, C4, C6 and C7 position of the tetralone moiety incorporated five-membered and/or six-membered heterocyclic rings generally lead to an increase in the bioactivities because of the higher level of conjugation system; 3) tetralone scaffold is a good backbone to construct fluorescence probes with excellent optical properties and many researches regarded carbonyl group of the tetralone moiety as a reactive site to introduce functional groups and increase the level of conjugation as well as captodative effect, where Vilsmeier-Haack consistantly has a role to play in the modification.

Although most studies reported a wide range of bioactivities and pharmacological activities of tetralone derivatives both *in viro* and *in vitro*, the underlying mechanism at molecular level still lacks depth. Besides, the relationship between the pharmacological activities and the structures require further discussion and investigation, so as to lay a solid foundation to the design of novel tetralone derivatives with better effects. High-throughput screening and the use of combinatorial chemistry technologies may contribute to the discovery and design of lead compounds regarding tetralones in the future.

Declaration of competing interest

No personal or financial conflicts of interest have been found among all the authors.

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Table 1. Bioactivities and mechanisms of natural tetralone derivatives.

Compound number	Cell/animal models	Natural plants	Bioactivities and mechanisms	IC_{50} value/ inhibition value
1	KB cell lines	cultures of *Humicola grisea Traaen*	cytotoxic activity on KB cell lines	IC_{50} = 1 - 5 ppm
5	-	culture broth of the endophytic fungus *Phoma* species plant *Arisaema erubescens*	antifungal activity against *F. oxysporium* and *R. solani*	EC_{50} = 413.2 and 48.5 μg/mL
6	Human KB tumor cell line	the bark and leaves of *New Caledonian Zygogynum* species	Antiproliferative activity against KB cancer cell line	IC_{50} = 1.4 μM
11	Colon cancer cell lines COLO205 and KM12	*Z. calothyrsum*	anti-tumor activity	GI_{50} = 11.0 and 17.0 μM, respectively
12	BGC-823 cells	green walnut husks of *Juglans mandshurica*	cytotoxicity assay against BGC-823 cells	IC_{50} = 125.9 $\mu g \cdot mL^{-1}$
14	-	pericarps of the *Juglans* species	growth inhibition on the protein tyrosine phosphatase 1B	-
15	-	the fresh pericarps of Juglans sigillata (Juglandaceae)	antibacterial activity against *S. aureus* and methicillin-resistant *S. aureus*	IC_{50}/MIC = 4.96/10.00 mg/mL and 3.46/5.00 mg/mL, repectively
16	-	the leaves of *Cyclocarya paliurus*	DPPH and superoxidescavenging activity	$\mathbf{IC_{50}}$ = 57.50 and 61.20 μmol/L
18	A549 and HeLa cell lines	the husk of *J. mandshurica*	cytotoxic activity on A549 and HeLa cell lines	IC_{50} = 73.70 μM and 85.10 μM, respectively
24	-	green husk of *Carya illinoinensis*	AChE inhibition activity	IC_{50} = 101.48 mg/mL

25	-	Endophytic Fungus *Coniothyrium sp*	antifungal activity against M. violaceum and B. cinerea	-
26-28	Non-small-cell lung carcinoma (NCI-H1975) cells	the immature exocarps of *Juglans mandshurica*	Inhibition activity against non-small-cell lung carcinoma (NCI-H1975) cells,	-

Table 2. Anti-tumor activities and mechanisms of synthetic tetralone derivatives.

Compound number	Cell/animal models	Bioactivities and mechanisms	Dose/ Concentration	IC_{50} value/ inhibition value
31	-	CYP24 inhibition activity	-	IC_{50} = 0.90 μM
32	rat kidney mitochondria (male Wistar rats) and DU-145 cells	CYP24 and CYP27B1 inhibition activities	1- 100 μM	IC_{50} = 3.50 M
33	human epithelial colorectal adenocarcinoma cell line	CYP24A1 inhibition activity	0.1, 0.3, 1 and 3 mmol/L	35.81% (2.00 μmol/L)
34	wild type CYP24A1 expressing cell line	CYP24A1 inhibition activity	1×10^4 M, 1×10^5 M, 1×10^6 M, and 1×10^7 M	IC_{50} = 1.90 mM
35	wild type CYP24A1 expressing cell line	CYP27A1 and CYP24A1 inhibition activity	1×10^4 M, 1×10^5 M, 1×10^6 M, and 1×10^7 M	IC_{50} = 59.00 nM and 16.30 mM, respectively
37	rat liver microsomes and Human MCF-7 breast cancer cells	CYP26A1 inhibition activity	Microsomes, 18 μM; MCF-7 cells, 12 μM	IC_{50} = 0.50 μM
38	rat liver microsomes and Human MCF-7 breast cancer cells	CYP26A1 inhibition activity	Microsomes, 18 μM; MCF-7 cells, 12 μM	IC_{50} = 0.80 μM
41	human hepatoma cell lines (HepG2 and LO2)	anticancer effects	31.25, 62.5, 125, 250, 500, and 1,000 μM	More than 50% (500 μM)
42	A431 human epidermoid carcinoma cell line			

49	human cancer cell lines, i.e., T-24, MCF-7, HepG2, A549, and HT-29	antitumor activities against human cancer cell lines	0.8, 4, 20, 100 μM	9.89, 22.22, 26.91, 28.86 and 21.43 μM, respectively
52	lung carcinoma (A549)	antitumor activities	0, 0.1, 0.33, 1.0, 3.33 and 10 μM	More than 80% (10 μM)

Table 3. MAO inhibition activities of synthetic tetralone derivatives.

Compound number	Bioactivities and mechanisms	IC_{50} value		SI IC50 (MAO-A)/IC50(MAO-B)
		MAO-A	MAO-B	
56	MAO inhibition activity	1.29 ± 0.14 μM	0.0045 ± 0.0003 μM	287
57	MAO inhibition activity	0.024 ± 0.001 μM	0.078 ± 0.010 μM	0.3
58	MAO inhibition activity	0.741 ± 0.061 μM	0.0038 ± 0.0008 μM	195
59	MAO inhibition activity	0.010 ± 0.001 μM	0.0012 ± 0.0004 μM	8
60	MAO inhibition activity	0.366 ± 0.063 μM	0.047 ± 0.002 μM	8
61	MAO inhibition activity	1.37 ± 0.209 μM	NI	-
62	MAO inhibition activity	1.96 ± 0.064 μM	0.707 ± 0.088 μM	2.8
63	MAO inhibition activity	0.754 ± 0.053 μM	0.013 ± 0.0020 μM	58
64	MAO inhibition activity	1.79 ± 0.130 μM	0.0064 ± 0.00015 μM	280
67	MAO inhibition activity	0.036±0.0059 μM	0.0011±0.0002 μM	33

Table 4. Affinity of synthetic tetralone derivatives for 5-HT2A and D2 receptor.

Compound number	Bioactivities and mechanisms	pKi /Ki value	pKi ratio 5-HT2A/D2
68	high affinity for the 5-HT2A receptor	Ki 5-HT2A =1.6 nM	-
69	high affinity for the 5-HT2A receptor	Ki 5-HT2A = 2.7 nM	-
70	high affinity for the 5-HT2A and D2 receptor	pKi 5-HT2A =7.80; pKi D2 = 7.76	1.01
71	high affinity for the 5-HT2A and D2 receptor	pKi 5-HT2A = 8.30 pKi D2 = 7.33	1.13

Table 5. Affinity of synthetic tetralone derivatives for A1 and A2A receptors.

Compound number	Bioactivities and mechanisms	Ki value (μM)		SI (A2A/A1)
		A1	A2A	
72	high affinity for A1 and A2A receptors	>100	>100	-
73	high affinity for A1 and A2A receptors	1.62 ± 0.36	5.46 ± 0.49	3.4
74	high affinity for A1 and A2A receptors	1.64 ± 0.16	9.92 ± 1.10	6.0
75	high affinity for A1 and A2A receptors	11.4 ± 0.5	1.61 ± 0.23	0.14
76	high affinity for A1 and A2A receptors	4.343 ± 0.4174	-	-
77	high affinity for A1 and A2A receptors	6.843 ± 1.118	7.054 ± 2.752	1.03

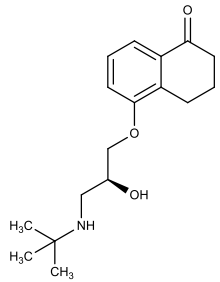
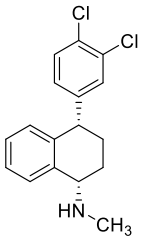
Table 6. Inhibition activity of S48 and S49 of $A\beta_{40}$ and $A\beta_{42}$ self-aggregation.

Compound number	Inhibition of AChE-induced $A\beta_{40}$ aggregation	Inhibition of $A\beta_{42}$ self-aggregation
78	42.9 ± 0.8	26.4 ± 1.1
79	48.3 ± 0.9	26.9 ± 3.4
Donepezil	22	<5
AP2238	35	<5

Table 7. IC_{50} values of S50, S51 and S52 on various enzymes.

Compound number	IC_{50} (μM)		IC_{50} BChE/IC_{50} AChE	rMAO - A IC_{50} (μM)	rMAO - A IC_{50} (μM)	IC_{50} rMAO -B/IC_{50} rMAO -A
	AChE	BuChE				
80	0.045	12.5	277.8	0.92	0.88	0.9
81	2.92	17.5	5.6	1.24	2.9	2.3
82	0.57	6.2	10.9	0.99	0.91	0.9
Donepezil	0.059	6.5	110.2	828	17.5	0.02
Tacrine	0.032	0.0059	0.2	0.047	0.12	2.5

Table 8. FDA approved and/or investigational tetralone-containing drugs.

Name	Accession Number	Groups	Chemical Formula	Indication	Structure
Levobunolol	DB01210	Approved	$C_{17}H_{25}NO_3$	lowering intraocular pressure (IOP) and may be used in patients with chronic open-angle glaucoma or ocular hypertension.	
Sertraline	DB01104	Approved	$C_{17}H_{17}Cl_2N$	a popular antidepressant medication commonly known as a selective serotonin reuptake inhibitor (SSRI)	
Estrone	DB00655	Approved		a synthetically prepared or naturally occurring steroidal estrogen