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Tetrahydropyridine: a promising heterocycle for pharmacologically active molecules

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Abstract: The tetrahydropyridine (THP) ring system has received considerable focus due to its excellent ability to act as a pharmacophore. It is recognized as a major constituent in natural alkaloids. THP derivatives have been reported for a diverse range of biological activities. Recent synthetic works contain syntheses of monosubstituted, disubstituted, trisubstituted, highly functionalized, and condensed structures. In this review, we summarize the recent literature dealing with the bioactive nature of this important heterocycle.

Key words: Functionalized tetrahydropyridine, condensed tetrahydropyridine, multicomponent reaction, antimicrobial, antiinflammatory, anticancer, tryptamine receptor agonist, muscarinic receptor agonist, enzyme inhibitors

1. Introduction

Biologically active heterocyclic compounds are abundantly found in nature.[1] Among heterocyclic compounds, pyridine and partially reduced dihydropyridine and tetrahydropyridine (THP) have emerged as excellent templates for various bioactive molecules.[2,3] Three structural isomers of THP are 1,2,3,6-tetrahydropyridine, 1,2,3,4-tetrahydropyridine, and 3,4,5,6-tetrahydropyridine. Arecoline and betanin III are the two natural biologically active THP compounds containing alkaloid and glycoside, respectively.[4–6] The most famous THP-containing neurotoxin is 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, which causes parkinsonism disease.[7,8] THP-based droperidole and tazomeline act as drugs used for the treatment of Alzheimer disease and schizophrenia.[9,10] Various THP derivatives have shown antiinflammatory,[11,12] antianginal,[13] antimicrobial,[14] antifungal,[15] antioxidant,[16] anticancer,[17] and antihypoxic[18] activities. Recently, THP derivatives have also displayed anti-Alzheimer properties.[19] Pharmacological activities of THPs are influenced greatly by the type and nature of substituents attached.[20–23] The broad spectrum of activities presented by these compounds has attracted the attention of medicinal and organic chemists. Different types of methods have been developed for the synthesis of THPs, such as [4+2] cycloaddition reactions,[24] multicomponent reactions,[25,26] radical cyclization of Baylis–Hillman adducts, aza-Morita–Baylis–Hillman reactions, and two-component reactions of aldimines and tetrahydropyrandiol.[27–29] THPs are also used in the synthesis of piperidine derivatives.[30]

In this review, THP derivatives are explored for their different pharmacological activities. Structure–activity relationship studies highlighted the important THP-derived compounds with a significant contribution towards the generation of new lead molecules that can serve as templates for future drug design and development.

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2. Activities of tetrahydropyridine derivatives

The various types of activities presented by THP-derived compounds are summarized in the following sections.

2.1. THPs as antibacterial agents

Ethyl 1-(2-chloroacetyl)-4-hydroxy-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate and their 4-O-aryl sulfonates (Figure 1, compounds **1**–**6**) were synthesized by Aridoss et al.[31] Upon evaluation for antibacterial activity compound **1** (IC_{50} = 16 μg/mL) was found to be the most active against *Enterococcus faecium* while compound **3** (IC_{90} = 16 μg/mL) showed equal activity against *E. faecium*, *E. faecalis*, and *Staphylococcus aureus.*[31] Ethyl 4-hydroxy-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate derivatives having various heterocyclic rings at the nitrogen atom via acetyl and propyl linkers also displayed antibacterial activities. Compounds having acetyl linkers were more active than those with propyl linkers. Among these derivatives, an imidazole-bearing compound (**7**) showed more prominent activity (IC_{90} = 64 μg/mL) against pathogenic resistant strains of *S. aureus*, *E. faecium*, and *E. faecalis* as compared to standard drugs linezolid and trovafloxacin.[32] Raju et al. synthesized ethyl-4-hydroxy-2,6-diaryl-5-(arylsulfonyl)-1,2,5,6-tetrahydro-3-pyridine-carboxylates by multicomponent reaction. These compounds showed excellent in vitro antimycobacterial activity (IC_{50} range =

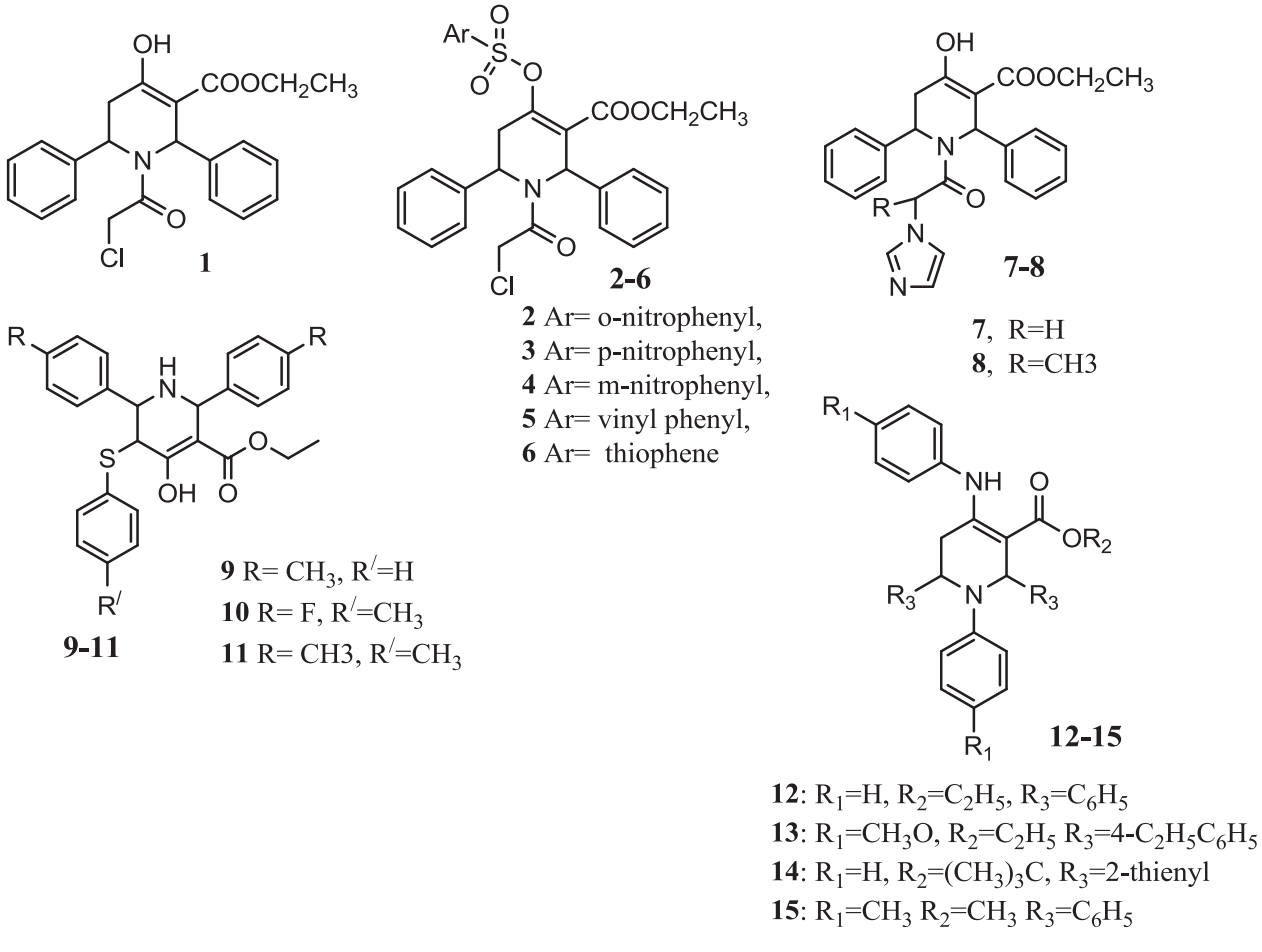

Figure 1. THP derivatives as antibacterial agents.

6.50–57.94 μM) as compared to the standard drug, pyrazinamide (IC_{50} = 50.77 μM). Among this series, compounds **9**, **10**, and **11** (IC_{50} = 6.81 μM, 6.50 μM, and 6.61 μM for **9**, **10**, and **11**, respectively) were found to be most potent. THP derivatives were also converted into pyridine derivatives that exhibited relatively higher activity.[33] Another multicomponent reaction of aromatic aldehydes, arylamines, and β-ketoester in the presence of bismuth nitrate was carried out by Yankin et al.[34] It resulted in the formation of alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-THPs-3-carboxylates. Compounds **12**, **13**, **14**, and **15** were found to be weakly active antibacterial agents (MIC = 250 μg/mL against *E. coli* and *S. aureus*) as compared to standard antibiotics.[34]

Srivastava et al.[35] synthesized another series of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine linked fluoroquinolones, in which the nitrogen of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines was attached to fluoroquinolones at position #7. Among the newly synthesized compounds, **16** (Figure 2) exhibited significant antibacterial activity (MIC = 0.12 μg/mL against *Bacillus subtilis*, *S. aureus*, and *S. epidermidis*) against susceptible as well as resistant strains of bacteria. Compound **17** was also found to be potent (MIC = 0.12 μg/mL against different strains of bacteria) and its activity was comparable to that of ciprofloxacin, gatifloxacin, and sparfloxacin.[35] Similarly, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine substituted oxazolidinones exhibited antibacterial activity against resistant strains of *S. aureus* and *E. faecalis*. The most potent compound (**18**) showed almost equivalent activity (MIC = 0.5–1.0 μg/mL against *S. aureus* and 1–2 μg/mL against *E. faecalis*, *B. pumilus*, *B. cereus*) to the antibacterial drug linezolid. Therefore, modification of the aromatic ring with unsubstituted tetrahydrothienopyridine significantly improved the antibacterial activity.[36] Anusevičius et al.[37] synthesized 1-(4-chlorophenyl)-2-methyl-4-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate. This compound was reacted with substituted hydrazines to produce THP compounds **19**, **20**, **21**, and **22**. Compounds **20**

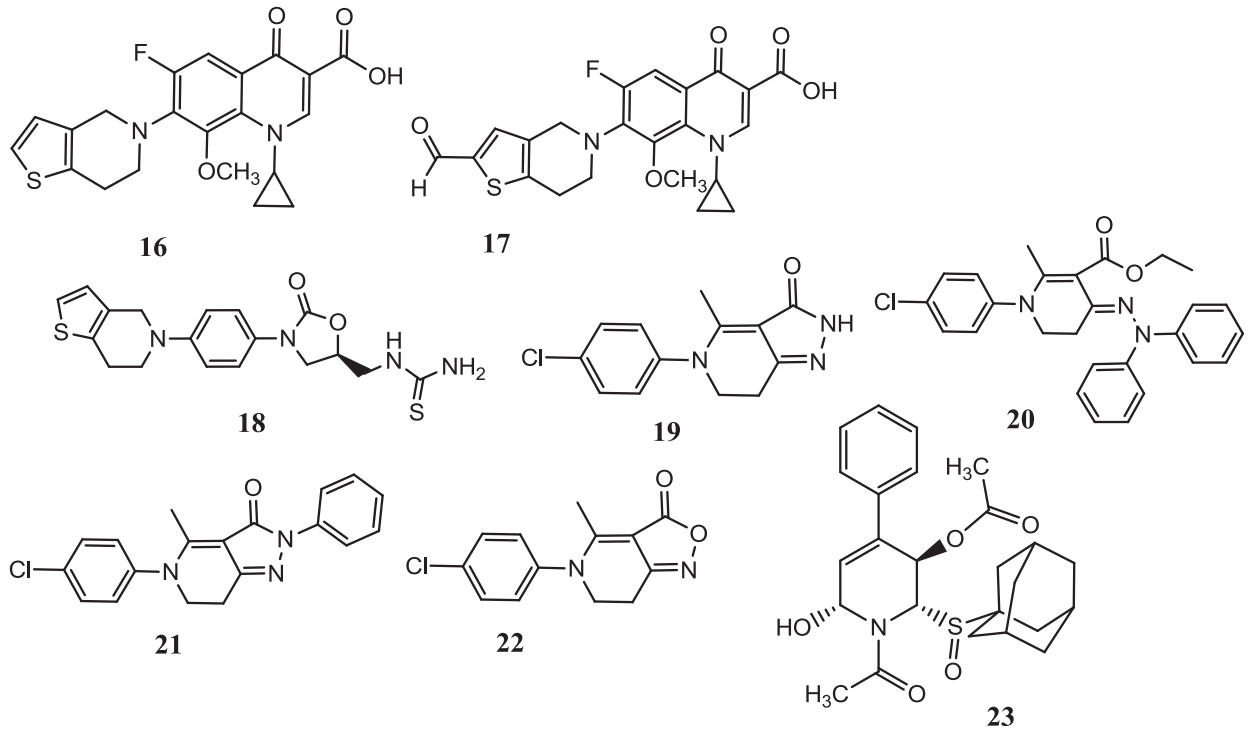

Figure 2. THP derivatives as antibacterial agents.

and **21** displayed better activity (MIC = 250 μg/cm^3) against *Pseudomonas aeruginosa* than **19** (MIC = 500 μg/cm^3).[37] Sulfoxide derivative of adamantyl THP, *N*-acetyl-2-(1-adamantyl-sulfoxo)-3-acetoxy-4-phenyl-6-hydroxy-1,2,3,6-tetrahydropyridines, was synthesized by Prachayasittikul et al.[16,38] Compound **23** presented antibacterial activity against *S. pyogenes* (IC_{50} = 256 μg/mL) and *M. catarrhalis* (IC_{50} = 256 μg/mL). The corresponding sulfide derivative of this compounds was inactive as an antimicrobial agent.

2.2. THPs as analgesic and antiinflammatory agents

1,2,3,6-Tetrahydropyridine-4-carboxamides having heteroaromatic substitution at the *N*-atom of the THP ring were synthesized Brown et al. and evaluated for in vitro transient receptor potential vanilloid (TRPV1) antagonist activity. The most potent TRPV1 antagonist (Figure 3), compound **24** (IC_{50} = 24 ± 2 nM), had a trifluoromethyl substituted pyridine ring at position #1 and trifluoromethyl sulfonyl substituted benzene ring attached to the nitrogen of the carboxamide group at position #4. It showed increased penetration into the central nervous system (CNS).[39] Pyrazole derivatives having a para amino sulfonyl or para methyl sulfonyl substituted

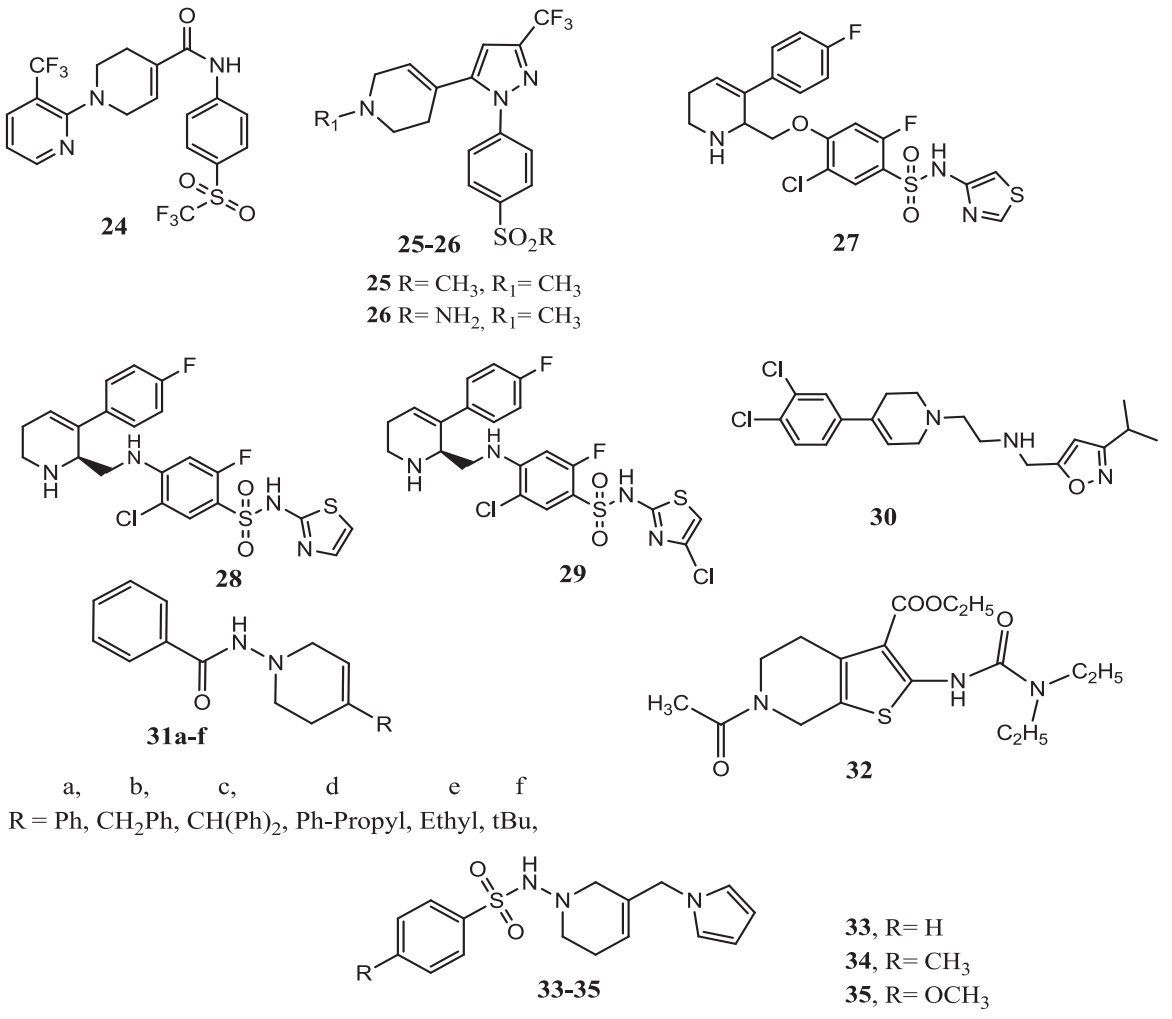

Figure 3. THP derivatives as antiinflammatory agents.

phenyl group at the nitrogen of position #1 constituted the pharmacophore for COX-2 inhibition.[40] 4-[2-(4-Methyl (amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridine derivatives were synthesized by Chowdhury et al., in which the p-tolyl group of celecoxib was replaced by the THP group. Nitric oxide donors *N*-diazen-1-ium-1,2-diolate, ethyl carboxylate, and a methyl group were attached at position #1 of the THPs. Among them, compound **26** was the most active antiinflammatory agent (ED_{50} = 61.2 mg/kg), having the methyl group attached at position #1 of the THP, as evaluated by carrageenan-induced rat foot edema model.[41] Compound **27** synthesized by Wu et al. exhibited in vitro analgesic activity (IC_{50} = 0.22 μM) by inhibiting hNav 1.7, the voltage-gated sodium channel. Structure–activity relationship studies showed that substitution on the phenyl group attached to THP and on the heterocyclic ring attached to sulfonamide did not result in significant improvement of analgesic activity but some derivatives produced comparable activity. Stereoseparation of this compound was carried out and the levo isomer of **27** exhibited better activity. Replacement of the *O*-linker with an *N*-linker produced almost equivalent activity to the starting compound, and in the *N*-linker compound, the replacement of 5-amino thiazole with 2-amino thiazole showed a prominent increase in the activity (compound **28**, *h*Nav1.7 IC_{50} = 0.031 μM). The thiazole ring was further modified to produce **29**, which was potent (*h*Nav1.7 IC_{50} = 0.011 μM) and selective and possessed good pharmacokinetic properties.[42] In acute peripheral nociception and neuropathic pain, there is involvement of T-type calcium channels and they have three isoforms: Ca_v 3.1 (α1G), Ca_v 3.2 (α1H), and Ca_v 3.3 (α1I).[43,44] Design and synthesis of new tetrahydropyridinylethylamine derivatives was carried out by Lee et al. and these compounds were evaluated for Ca_v 3.1- and Ca_v 3.2 T-type calcium channel inhibition. Compound **30**, which contains a chloro group at the meta and para positions of the 4-phenyl group, showed good blocking activity against α1G (IC_{50} = 0.80 ± 0.05 μM) and α1H (IC_{50} = 1.37 ± 0.17 μM), while the compounds in which there were unsubstituted or monosubstituted phenyl rings showed less activity. This compound also displayed prominent in vivo antinociceptive activity in a rat neuropathic pain model. It was also found to be metabolically stable and exhibited good pharmacokinetic properties.[45] Synthesis of n-benzoylamino-1,2,3,6-tetrahydropyrdines (compound **31a**–**31f**) was reported by Mochona et al., in which reaction proceeded with amination of pyridines and the resulting N-aminopyridines were reacted with suitable substituted acyl chloride to form ylides. The partial reduction of N-ylides produced substituted THPs. These compounds (**31a**–**31f**) have the potential for antiinflammatory activity.[46] 4,5,6,7-Tetrahydrothieno[2,3-*c*]pyridine derivatives were synthesized by Fujita et al. and evaluated for their ability to inhibit the production of proinflammatory mediator TNFα stimulated by lipopolysaccharide. The introduction of ester linkage at position #3 resulted in the formation of potent compounds. Compound **32** displayed prominent in vitro (IC_{50} = 6.2 μM) and in vivo activity (92.3% inhibition of edema at 50 mg/kg) as an inhibitor of production of TNFα. This compound also showed activity in an adjuvant-induced rat arthritic model.[47] Gangapuram et al. synthesized *N*-[3-(1*H*-Pyrrol-1-yl)methyl]-1,2,5,6-tetrahydropyridine-1-yl]benzamide/benzene sulfonamide and investigated it for antiinflammatory activity. Sulfonamide substituted THPs were found to be active antiinflammatory agents as determined by the inhibition of lipopolysaccharide-induced nitric oxide production. Compounds **33** (IC_{50} = 12.92 μM), **34** (IC_{50} = 14.64 μM), and **35** (IC_{50} = 19.43 μM) were the most active antiinflammatory agents. Compound **33** was also found to be an inhibitor of the release of interleukin alpha and interleukin 6.[48]

Synthesis of *N*-(substituted-phenylcarbonylamino)-4-ethyl-1,2,3,6-tetrahydropyridines (Figure 4, compounds **36a**–**36i**) as potential antiinflammatory agents was carried out by Yoon et al. by the reaction of mesitylene sulfonyl chloride with ethyl acetohydroxamate at 0 °C in the presence of triethylamine and dimethyl

formamide.[49] The THP derivatives prepared by Yoon et al. were evaluated for free radical and nitric oxide generation in C6 glioma cells activated with bacterial endotoxin lipopolysaccharide. Compound **37**, the most potent (IC_{50} = 80.97 μM) inhibitor of inducible nitric oxide synthase, contains a tertiary butyl group at position #4 of the aromatic ring. These compounds also inhibited the generation of reactive oxygen species in glioma cells, which indicates their potential to be used in neuroinflammatory diseases.[50] Nakao et al. synthesized pyridyl-pyrrole derivatives and compound **38** having a cyclic aminoalkyl group at the beta position of pyrrole showed excellent antiinflammatory (IC_{50} = 1.86 μM) activity upon evaluation as an inhibitor of lipopolysaccharide-induced production of TNFα. The activity decreased when the THP was saturated to the piperidine ring. This compound also showed prominent in vivo activity (ID_{50} = 5.89 mg/kg). Therefore, THP was found to be the optimal substituent at this position.[51] Further modification of THP showed that the alkyl group at the nitrogen of THP and at the alpha carbon produced more active compounds. The introduction of a methyl group and propyl group at the nitrogen of the THP and the methyl group at the alpha position further improve the activity. Compounds **39** (IC_{50} = 0.63 μM; ID_{50} = 1.42 mg/kg) and **40** (IC_{50} = 0.44 μM; ID_{50} = 2.79 mg/kg) were more prominent as antiinflammatory agents.[52] Further modifications of 3-pyridyl pyrrole derivatives lead to the addition of bicyclic THP at position #4 of the pyrrole ring. Compound **41** showed prominent activity (IC_{50} = 0.042 μM; ID_{50} = 1.09 mg/kg) as an inhibitor of proinflammatory mediator cytokines as compared to monocyclic THPs. Compound **41** is a racemic mixture and it was separated into its enantiomers. Compound **42**, which is *S*-enantiomer of **41**, was found to be more active (IC_{50} = 0.026 μM; ID_{50} = 0.93 mg/kg) than the *R*-enantiomer. Compound **42** also showed excellent activity as an inhibitor of different types of interleukins.[53]

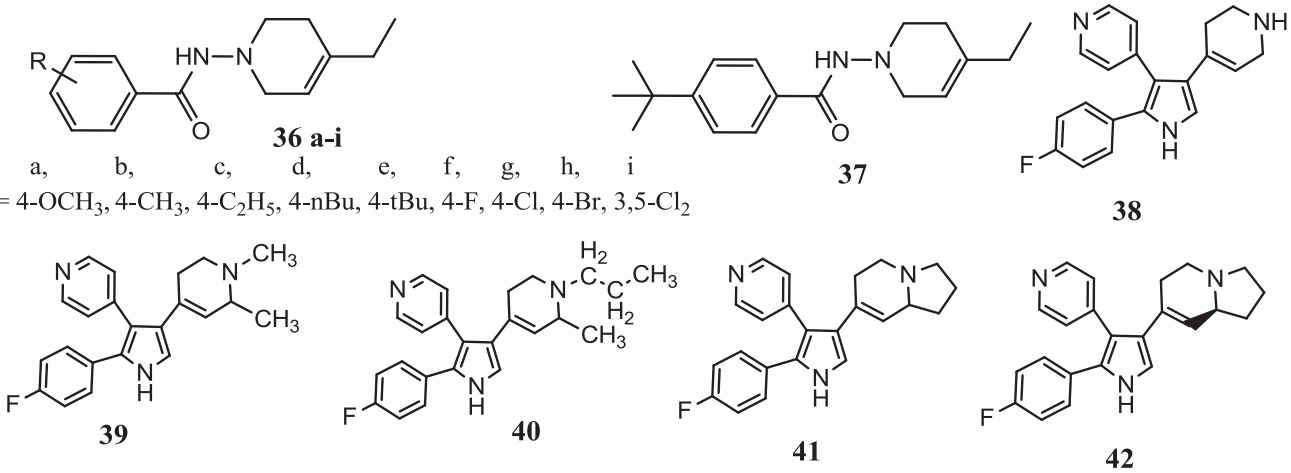

Figure 4. More THP derivatives as antiinflammatory agents.

Gwaltney et al. synthesized a series of aryltetrahydropyridine derivatives as farnesyl transferase (FT) inhibitors in which amino acids glycine, phenylalanine, and histidine were incorporated. Glycine-derived compound **43** (Figure 5) containing methyl imidazole and a benzyl group was found to be less active (FT IC_{50} = 280 nM). Phenyl alanine-derived compound **44** also showed less activity (FT IC_{50} = 240 nM and 310 nM). In the case of histidine D-isomer **46** (FT IC_{50} 1.2 nM), it exhibited more potency than L-isomer **45** (FT IC_{50} = 130 nM). This compound was less active in a cellular assay. FT inhibitors showed potential for anticancer activity.[54,55]{Gwaltney, 2003 #36;Bell, 2000 #145} 2-Alkyl-4-halo-1,2,5,6-THP (**47**) was synthesized

by León et al. by reacting homopropargyl tosylamine with different aldehydes in the presence of iron halide and dichloromethane. Evaluation of the antiproliferative activity was carried out against three different cell lines. The majority of the derivatives in this series demonstrated antiproliferative activities and colon cancer cell line WiDr was more sensitive to these compounds. The most active agent, compound **48** (GI_{50} = 3.3–6.6 μM against different cancer cell lines), contains a benzyl group and a chloro group attached to THP. This activity was assumed to be due to the unsaturation present in the THP ring because the corresponding piperidine analogs showed less activity.[17] Aeluri et al. carried out the synthesis of 1,2,3,4,6-pentasubstituted-1,2,5,6-tetrahydropyridine-3-carboxylates by multicomponent reaction in the presence of zirconium tetrachloride as the catalyst and evaluated their anticancer activity against various cancerous cell lines. Overall these compounds showed better activity against the SK-*N*-SH cell line as compared to other cell lines. The most potent THP derivatives are compounds **49** and **50** (IC_{50} = 11 ± 1.3 μM and IC_{50} 22 ± 1.3 μM for **49** and **50**, respectively, against the SK-*N*-SH cell line). Compound **49** contains a chloride atom at position #16 and position #33 while **50** is unsubstituted at this position. The other most active agent, compound **51** (IC_{50} = 58 ± 4.1 μM against the A549 cell line), contains a methoxy group at position #16 and #33.[56] Antiproliferative activity was also presented by 2-amino-3-(3,4,5-trimethoxybenzoyl)-4,5,6,7-tetrahydthieno[b]pyridines. The most potent derivative, compound **52**, showed prominent activity against the L1210 (IC_{50} = 25 nM), FM3A (IC_{50} = 46 nM), Molt/4 (IC_{50} = 45 nM), and CHO (IC_{50} = 90 nM) cancer lines. Compound **52** contains a methyl carbamate group attached to nitrogen at position #6. When the nitrogen was modified with alkyl, amides, urea, and thiourea, there was formation of less active derivatives. This compound showed cell cycle specificity and also inhibited tubulin polymerization.[57] 4-Morpholino-6-(1,2,3,6-tetrahydropyridine-4-yl)-N-(3,4,5-trimethoxyphenyl)-1,3,5-triazin-2-amine derivatives were evaluated for antiproliferative activity by using four different human cancer cell lines. The anticancer activity of these compounds ranges from 9.6 to 50 μM. Substituents on the THP strongly influenced the anticancer activity. Compound **53** was most potent against HepG2 (IC_{50} = 9.6 ± 0.4 μM), HeLa (IC_{50} = 12.3 ± 0.8 μM), A549 (IC_{50} = 10.5 ± 0.1 μM), and MCF7 (IC_{50} = 11.7 ± 0.5 μM) cell lines. It contains a nitrofuran ring at this position. Molecular docking studies showed that this compound has strong interaction (binding affinity = –7.949) with the binding site of tubulin. Substitution of a sulfonamide group or uridyl group on the THP ring produced less active or moderately active compounds.[58] Styryl derivatives (compounds **54**–**57**) of 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridines-3-carbonitriles were synthesized by Lukevics et al. and showed cytotoxic effects on tumor cells (LC_{50} = 10 μg/mL). The phenyl ring of this compound was substituted with different groups and cytotoxicity was evaluated on HT1080 and MG-22A tumor cell lines. Compounds **54** (LC_{50} = 0.8–3 μg/mL), **55** (LC_{50} = 2–5 μg/mL), **56** (LC_{50} = 2–3 μg/mL), and **57** (LC_{50} = 2–4 μg/mL) were found to be most active in this series. Disubstituted compounds showed more activity than monosubstituted but were also found to be more toxic.[59]

2.3. Tetrahydropyridines acting on 5-hydroxytryptamine (5-HT) receptors

1,4-Benzoxazepine derivatives are selective 5-HT_{1A} receptor agonists.[60] Newly synthesized 1,2,3,6-tetrahydropyridinyl-pyrimidine derivatives by Kamei et al. were evaluated for their binding properties with 5-HT_{1A}, dopamine D_2, and alpha$_1$ adrenergic receptors. These derivatives showed 5-HT_{1A} receptor affinity over the D_2 and alpha$_1$ receptors. Compound **58** (Figure 6) was most potent, having an IC_{50} value of 1.38 nM, while its regioisomer **59** was less active, having an IC_{50} value of 79.6 nM. The most active compound in this series, **60** (IC_{50} = 0.185 nM), had the methylated pyrimidine attached to the THP.[61] Conway et al. synthesized 4-aryl-

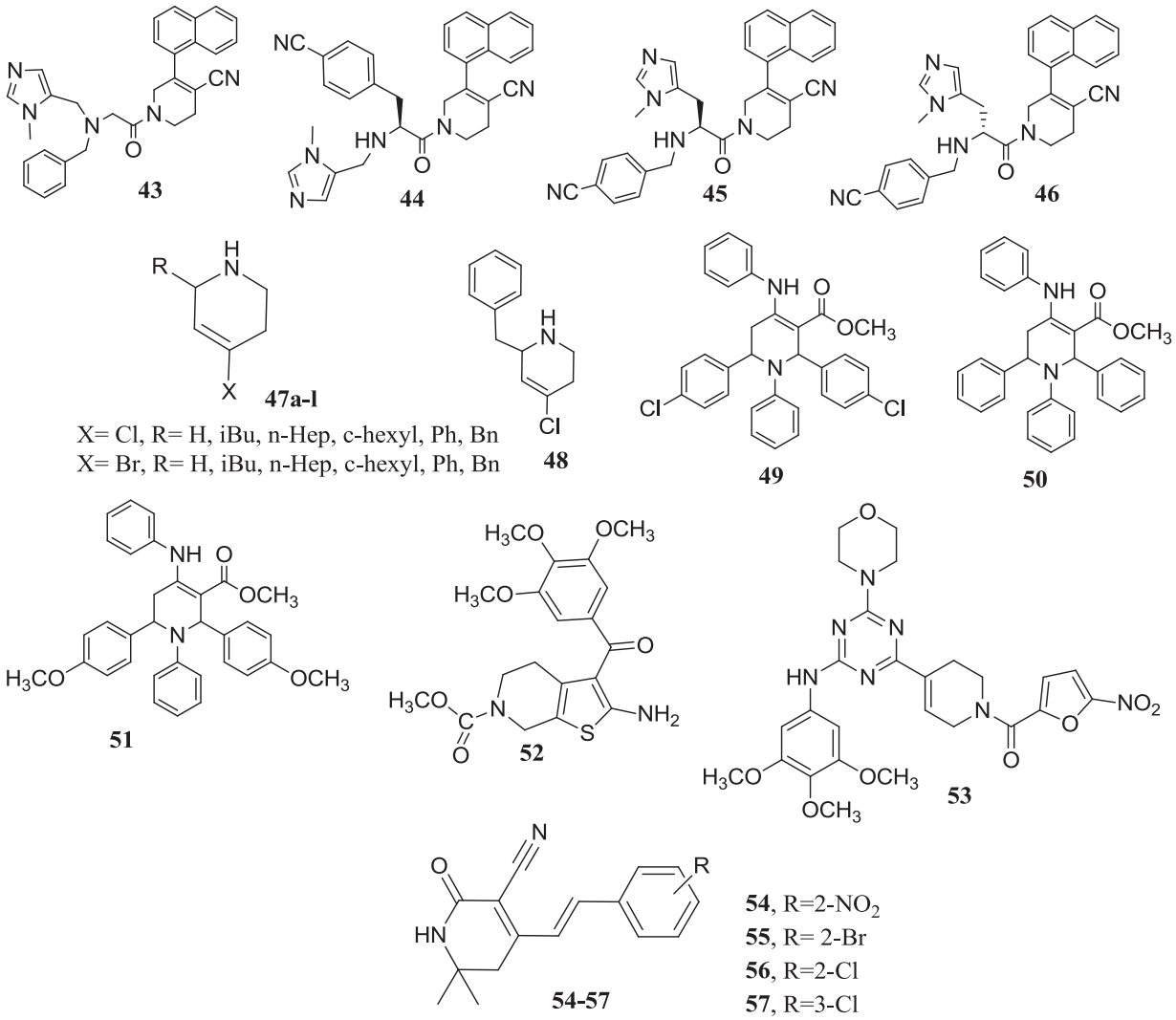

Figure 5. THP derivatives as anticancer agents.

1,2,3,6-tetrahydropyridines that exhibited agonistic activity at the 5-HT$_{2C}$ receptors as potential agents for the treatment of obesity. These compounds showed higher affinity for 5-HT$_{2C}$ than the corresponding piperidine analogues. Compound **61** was found to be the most active agonistic compound (EC_{50} = 72.3 ± 8.8 nM) and it contains a chloro group at position #3 of the phenyl group. Compound **62**, which is an indole derivative, also exhibited prominent activity (EC_{50} = 163 ± 46 nM) and has the potential for further investigation. The binding affinities of **61** and **62** are Ki = 318 ± 32 nM and 632 ± 53 nM, respectively.[62] Condensed THP derivatives tetrahydrothienopyridylbutyl-tetrahydrobenzindole synthesized by Kikuchi et al. showed more affinity towards the 5-HT$_7$ receptor. Compound **63** (pki = 8.19 ± 0.15) and compound **64** (pki = 8.01 ± 0.09) were much more potent for 5-HT$_7$ than other 5-HT receptors subtypes. The distance between tetrahydrobenzindole and tetrahydrothienopyridine is important and four carbon chain lengths were found to be optimum for selectivity to 5-HT$_7$ receptors. Further investigation showed that compound **63** is an antagonist at 5-HT$_7$ receptors.[63] 4-Phenyl-1,2,3,6-tetrahydropyridines attached with quinoxaline (compound **65**, ki = 4 ± 1) or quinoline (compound **66**, ki = 10 ± 1) exhibited affinity for 5-HT$_{1A}$ but the selectivity of quinoxaline derivatives for 5-HT$_{1A}$

was higher compared to the quinoline analogues and α_{2A} adrenoceptors.[64] 4-Substituted phenyl analogues of 4-phenyl-1,2,3,6-tetrahydropyridines showed that different electron-withdrawing and electron-donating substituents attached to the aromatic ring influenced the affinity for 5-HT$_{1A}$ receptors. The most active compound, **67**, showed higher affinity (ki = 1.10 ± 0.16) with the 5-HT$_{1A}$ receptor and it contains a methyl group at position #3 and position #5 of the phenyl ring. This may be due to the increased electron density due to the methyl group, which increases the interaction with the phenylalanine residue, or increased hydrophobic interaction of the methyl group with the valine residue in receptors of 5-HT$_1$.[65] 4-Phenyl-1,2,3,6-THP rings exhibited prominent affinity with 5-HT$_{1A}$ receptors as compared to the 4-phenyl piperazine analogues. The molecular modeling studies of this compound carried out by Dilly et al. showed that the phenyl group has a planar orientation with the THP, due to which this compound has more significant interaction with 5-HT$_{1A}$ receptors. One possible reason is the replacement of sp^3 nitrogen with sp^2 carbon, which leads to the planar orientation of the phenyl ring.[66]

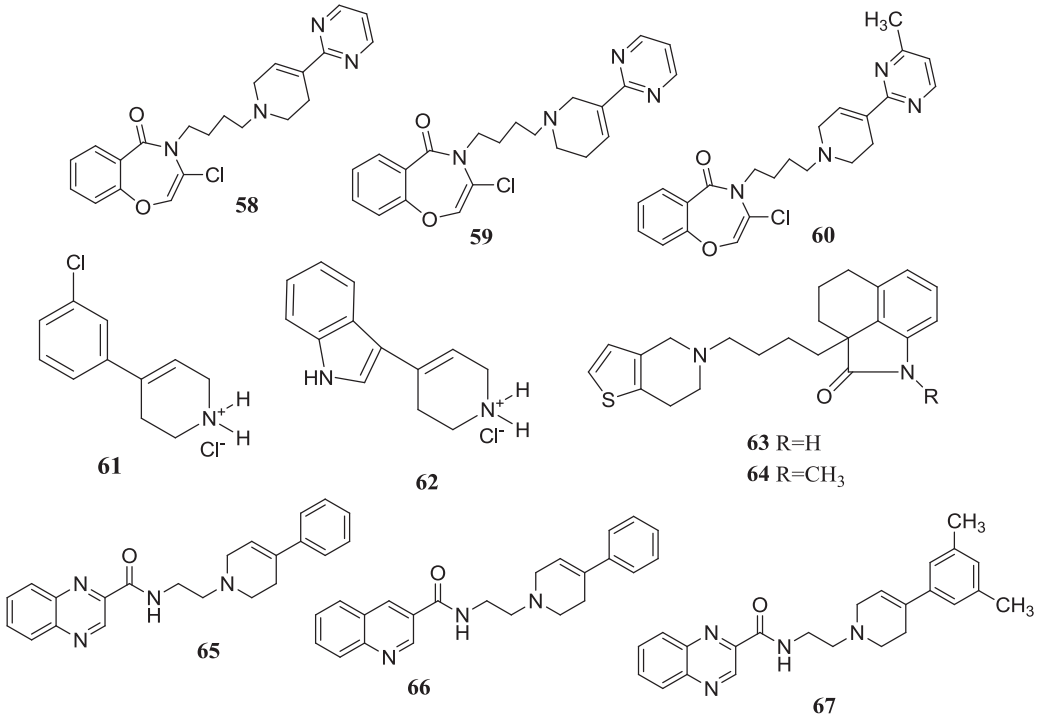

Figure 6. THP derivatives acting on tryptamine receptors.

2.4. Activity of THP derivatives at muscarinic receptors

Bivalent 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivatives were synthesized by Rajeswaran et al. using the linker groups alkoxy, thioether, and polyethylene glycol. Compound **68** (Figure 7) having alkoxy linkers exhibited high affinity (K_1 = 0.19 ± 0.004 nM) for the muscarinic receptors and contains eight methylene units. Compound **69** showed more affinity (K_1 = 0.12 ± 0.057 nM) with muscarinic receptors and it contains a 13-atom polyethylene linker chain. Compound **69** was also a potent (EC_{50} = 0.0085 ± 0.0012 μM) muscarinic agonist in nature. The agonistic activity of these compounds increases by increasing the length of the alkoxy and polyethylene glycol linking group.[67] Tetrahydropyridyl thiadiazole derivatives having an alkyl linker and

polyethylene glycol linkers were further modified by Cao et al. These compounds were not selective for a specific subtype of muscarinic receptor. Compound **70** showed affinity for M_1 ($pKi = 7.6$), M_2 ($pKi = 8.1$), M_3 ($pKi = 7.6$), and M_4 ($pKi = 8.6$) receptors. It also showed the highest activity towards M_1 ($pEC_{50} = 7.2 \pm 0.13$) receptors but was inactive towards M_3 receptors. It also showed agonistic activity towards M_2 and M_4 receptors. Therefore, **70** was expected to be effective in psychiatric disorders without producing side effects related to M_3 receptors.[68] Compound **70**, tetra(ethylene glycol)(3-methoxy-1,2,5-thiadiazole-4-yl) [3-(1-methyl-1,2,5,6-tetrahydropyrid-3-yl)-1,2,5-thiadiazol-4-yl] ether, is a muscarinic receptor agonist having selectivity for M_1 and M_2 receptors. Derivatives of this compound were synthesized by Tejada et al. using the di, tri, tetra, or penta ethylene glycol or tripropylene glycol spacer between 1,2,5,6-tetrahydropyridine and the terminal five-membered heterocyclic ring. Compound **70**, which contains a tetraethylene glycol spacer, was found to be optimum for the activity. Replacement of 1,2,5-thiadiazole with 1,2,4-thiadiazole or changing the position of the methoxy group or removal of the methoxy group resulted in the formation of compounds that showed less binding affinity for muscarinic receptors.[69] Xanomeline is a THP-containing drug and has selectivity for the M_1 receptor. It was attached to radiolabeled fluorine-18 to produce compound **71** by Kiesewetter et al. Xanomeline and fluoroxanomeline showed decreased binding in M1 and M2 knockout mice receptors. This may be due to the loss of particular subtype receptors.[70] In the new derivatives of thiadizole THPs compound **72**, which is a fluoro polyethylene glycol (PEG) derivative of thiadiazole THP, showed moderate affinity ($Ki = 48$ nM) to the M_4 receptor. Oostern et al. radiolabeled compound **72** with fluorine-18 to be used as a tracer for imaging the M_4 receptors and CNS. It was found not suitable because biodistribution studies in rodents showed the presence of polar radioactive metabolites in the CNS.[71] *N*-Alkyl/aryl substituted thiazolidinone arecoline analogues as muscarinic M_1 receptor agonists were synthesized by Sadashiva et al. Compound **73** was most potent (affinity, $Ki = 19 \pm 1.97$ μM; potency, $IC_{50} = 48 \pm 6.23$ μM) in this series and contained diphenylamine attached to the nitrogen of thiazolidinone moiety. It was also active in reversing scopolamine-induced memory loss. Derivatives presented in this series were also found to be nontoxic because no rat fatalities occurred after 1 week of administration of these drugs.[72] Anagnostaras et al. showed that 1,2,5,6-tetrahydropyridine-3-carboxylic acid ester derivatives had antagonistic activity towards muscarinic acetyl choline receptors. These compounds showed more selectivity for the M-5 receptor and this is important because antagonism at the M-1 receptor leads to cognitive deficit.[73] The most active compound, **74**, was produced by the modification of carboxylic ester at position #3. Zheng et al. showed that replacement of the ethylene linker with methylene resulted in decreased affinity for the M-5 receptor. The introduction of an electron-withdrawing or electron-donating group at position #4 of the aromatic ring also decreased the activity. Molecular docking studies showed that the binding affinity of compound **74** with the receptor was *Ki* for *h*M-5 = 2.24 μM. This compound also inhibited ($IC_{50} = 0.45$ nM) oxotremorine-evoked dopamine release from rat striatal slices.[74]

2.5. Antiplasmodial activity of THPs

Misra et al. carried out the synthesis of functionalized THPs by multicomponent reaction. These compounds displayed prominent antiplasmodial activity against the *Plasmodium falciparum* 3D7 strain. Schizontocidal activity of 100% was observed for most of the derivatives at concentrations of 10 μg/mL and 5 μg/mL. Compound **75** (Figure 8) showed 100% schizontocidal activity at 0.09 μg/mL concentration. Structure–activity relationship studies showed that replacement of methyl ester with ethyl ester decreases the antiplasmodial activity while the replacement of benzene rings at position# 2 and position #6 with thiophene or pyridyl rings

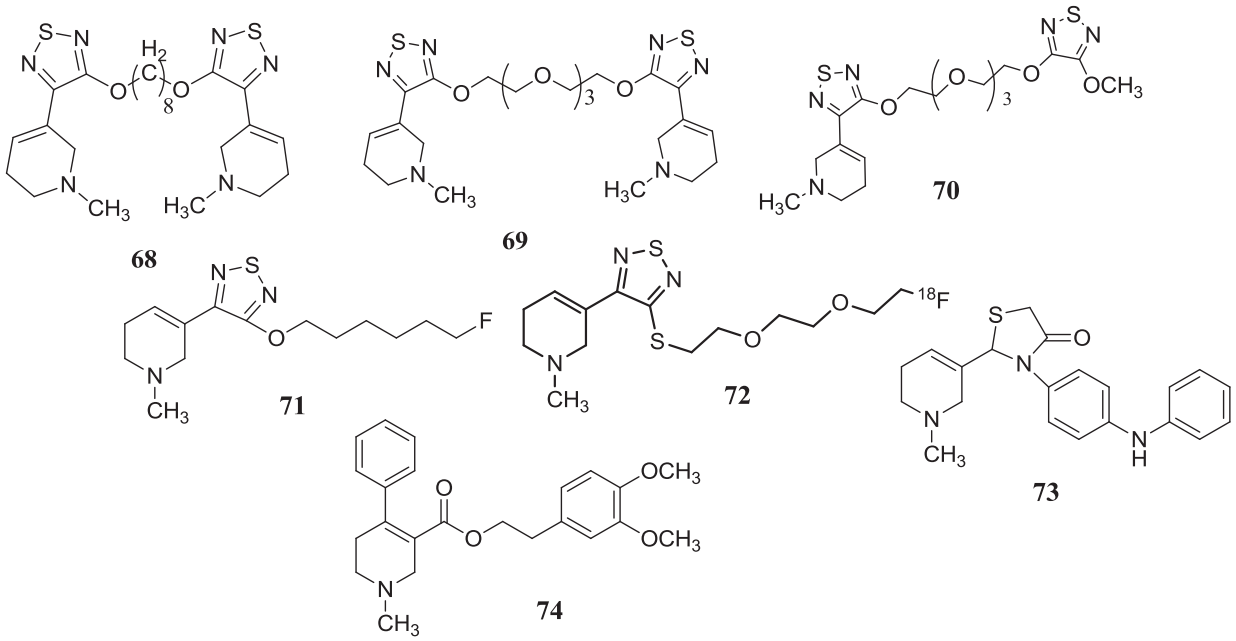

Figure 7. THP derivatives acting on muscarinic receptors.

increases the activity.[75] Such highly substituted THPs can also be synthesized using the catalyst $N,N,N^{/},N^{/}$-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly($N,N^{/}$-dibromo-N-ethyl-benzene-1,3-disulfonamide [PBBS].[76] The relationship between electronic structure and antimalarial activity of these compounds was calculated by Naranjo-Montoya et al. in order to determine the position of the active site of THP. The methods used for this analysis were simple and included the multiple linear regression method, principal component analysis, and linear discriminant analysis. Substituents on ring A, A$^{/}$, B, B$^{/}$ especially at positions #15, #32, and #29 (compound **76**) were found to be important for the activity of these compounds. In addition, it was predicted by these calculations that an electron-donating group should be added to position #16 and electron-withdrawing substituents to position #27 to produce more potent compounds.[77]

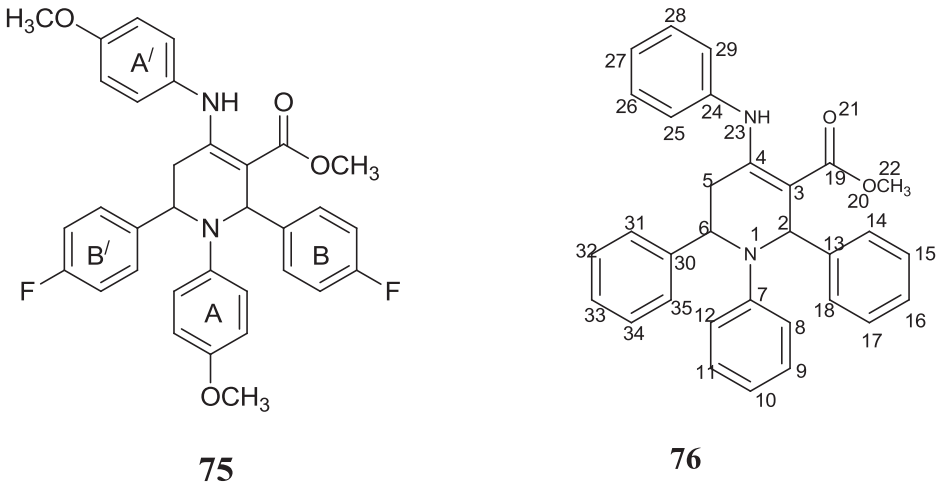

Figure 8. THP derivatives as part of antiplasmodial agents.

2.6. THPs as corticotropin-releasing inhibitors

Nakazato et al. carried out the synthesis of 4-aryl-1,2,3,6-tetrahydropyridino-pyrimidine derivatives as nonpeptide corticotropin-releasing factor inhibitors. Compounds **77** (IC_{50} = 22 nM) and **78** (IC_{50} = 10 nM) in this series were highly potent and selective inhibitors of the CRF_1 receptor (Figure 9). In the phenyl group attached to THP at position #4, 3-F and 3-Cl groups are suitable for optimal activity. Changing the position of these groups or replacement with other groups significantly lowers the activity. When the isopropyl group at the phenyl ring was replaced with methyl, a methoxy group, or a chloro group, the resultant derivative showed less activity. The methyl thio group at position #2 of compound **78** acts as a better substituent for the bromo group of compound **77**. The presence of the ethyl group is also important because the replacement of this group with others decreases the affinity for the receptor. Similarly, the modification of the methyl group also decreases the affinity of the compound with receptor.[78] Synthesis of 5-aryl-1,2,3,6-tetrahydropyridinopyrimidine derivatives was carried out by Kumagai et al. Upon evaluation for corticotropin-releasing factor (CRF_1) receptor binding affinity, compound **79** was found to be most potent (IC_{50} = 11 nM) in this series, which contains a methyl group at position #2 of the 5-aryl group of THP. Altering the position of the methyl group to position #3 or #4 or with the introduction of chlorine or fluorine at this position, less active compounds were obtained.[79]

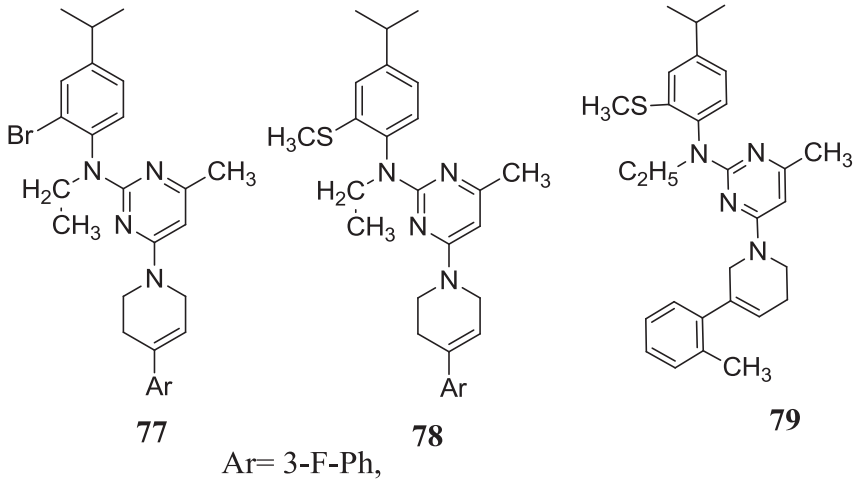

Figure 9. THP derivatives as part of corticotropin receptor antagonists.

2.7. THP derivatives as inotropic and antiarrhythmic agents

3,4-Trans-4-aryl-3-(1-pyridino)-1,2,3,4-tetrahydropyridine-6-thiolates were synthesized by Krauze et al. by one-pot condensation of an aromatic aldehyde, cyanothioacetamide, and n-acetylpyridinium chloride in the presence of piperidine. Upon evaluation of the effect on heart rate and force of contraction, no significant chronotropic activity was observed but they were active as inotropic agents. Compound **80** (Figure 10) was the most active compound (EC_{50} = 1.6 ± 0.7 μM) as a positive inotropic agent and it contains a 3-nitroaryl group at position #4 of the 1,2,3,4-tetrahydropyridines. This compound showed a hypotensive effect at higher doses (1 mg/kg) as compared to the standard drug, milrinone (0.1 mg/kg), but it was not found to be toxic at higher doses (1000 mg/kg body weight). Therefore, compound **80** has the potential for further studies.[80] Kálai et al. synthesized derivatives of amiodarone (compounds **81**–**83**) by replacing the diethyl amino ethyl side chain of phenol ether with 1,2,5,6-tetrahydropyridine nitroxide, hydroxylamine, and amine. Compound **83** showed similar inhibition

potential (IC_{50} = 2.1 ± 0.2 μM) on mitochondrial permeability transition to that of amiodarone (IC_{50} = 3.9 ± 0.8 μM) and was also found to be least toxic until 100 μM on different cell lines.[81]

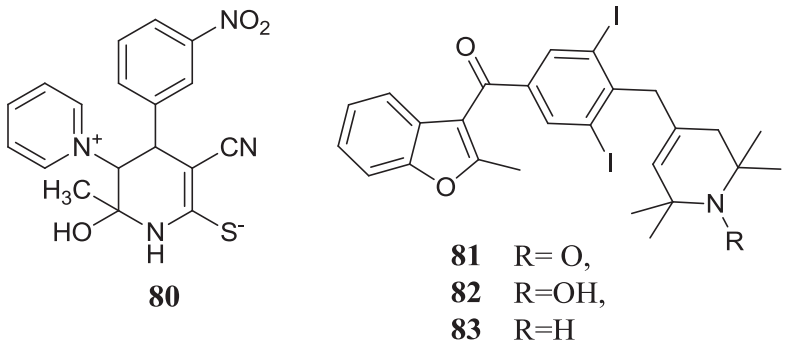

Figure 10. THP derivatives acting on the heart.

2.8. THP derivatives as poly(ADP-ribose) polymerase-1 inhibitors

PARP-1 (poly(ADP-ribose) polymerase-1), which is a chromatin base nuclear enzyme, has an important role in genomic repair.[82] Ishida et al. produced some new PARP-1 inhibitors by connecting 4-phenyl-1,2,3,6-tetrahydropyridine to the phthalazin-1(2*H*)-one, phenanthridine-6(5H)-one, and 3,5,7,8- tetrahydro-thiino[4,3-d]pyrimidine-4-one via an alkyl spacer. 4-Phenyl-1,2,3,6-tetrahydropyridine significantly contributed to the PARP-1 inhibitory activity of these compounds (Figure 11). Compound **84**, which is a pyrimidinone thiopyran analogue attached to the 4-phenyl-1,2,3,6-tetrahydropyridine via a propyl chain, showed prominent activity (IC_{50} = 8.9 nM). Compounds **85** (IC_{50} = 16 nM) and **86** (IC_{50} = 64 nM) were comparatively less active inhibitors.[83] Kálai et al. evaluated 4-carboxamido-1*H*-benzimidazoles substituted at position #2 with nitroxide, amine, or hydroxylamine precursors as PARP-1 inhibitors. Compound **87** (IC_{50} = 14 nM) having a THP ring attached to the benzimidazole was found to be the most potent compound and had a good therapeutic index. Metabolic studies of this compound showed that it is converted into nitroxide and then reduced to hydroxylamine.[84]

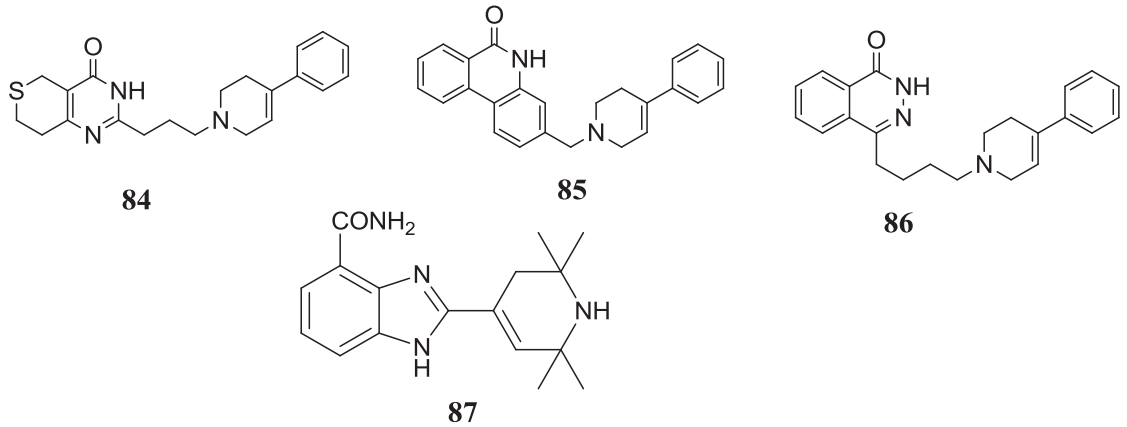

Figure 11. THP derivatives as poly(ADP-ribose) polymerase-1 inhibitors.

2.9. Insecticidal activity of THPs

The design and synthesis of novel camptothecin analogues was carried out by Liu et al. THP derivatives of camptothecin (Figure 12, compound **88**) was not a potent insecticide as it showed less mortality (14.2% after 72 h) and antifeeding activity (32.6% after 72 h) against *Mythimna separata*. Compound **89** showed increased mortality (61.8% mortality after 72 h) compared to **88**.[85] Synthesis of nitromethylene neonicotinoid derivatives containing THP was carried out by Tian et al. The final compounds, having exoether linkages, were evaluated for insecticidal activity against pea aphids. Derivatives that contained smaller groups as substituents with THP were found to be more potent. Compounds **90a**–**90h** showed mortality greater than 90% at the dose of 500 mg/L. The quantitative structure–activity relationship of these compounds showed that the volume of R_1 and R_2 substituents, hydrophobicity, and electrostatic parameters are very important determinants for the activity of these compounds.[86] Tetrahydroimidazo[1,2-a]pyridine derivatives were synthesized by aza-Diel–Alder reaction by Zhang et al. Upon evaluation of the insecticidal activity against pea aphids, most of the compounds exhibited moderate to high activities against the insect depending on the type of substituents in the benzene ring. The addition of halogen significantly increased the activity. Compounds in which the benzene ring was disubstituted were more potent. Compounds **91**, **92**, and **93** showed 100% mortality of insects at the dose of 500 mg/L.[87]

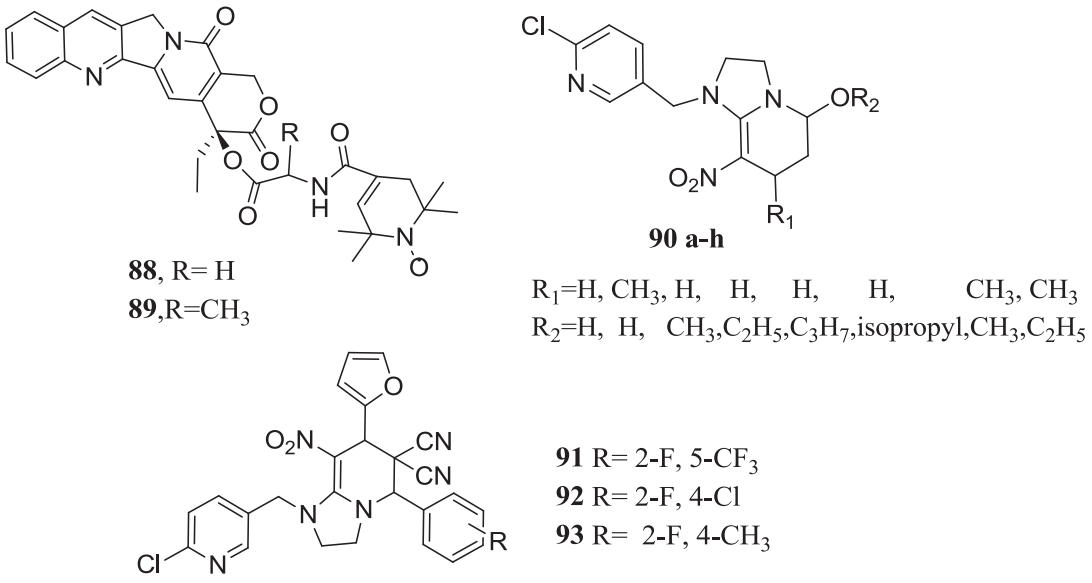

Figure 12. THP derivatives as part of insecticidal agents.

2.10. THP derivatives acting on nicotinic receptors

3-(5-Alkylamino-4-isoxazolyl)-1,2,5,6-tetrahydropyridine derived compounds synthesized by Olesen et al. were found as central nicotinic acetylcholine receptor ligands. These compounds showed selectivity for nicotinic rather than muscarinic receptors and they were more selective for the central $\alpha 4\beta 2$ receptor subtype (Figure 13, IC_{50} = 4.6 nM for the most potent compound, **94**) than the ganglionic $\alpha 3\beta 2$ subtype (IC_{50} = 48 nM for most potent compound). Position #5 of the isoxazole ring can be modified with large groups; the most active compound having propyl amine at this position appeared as an inhibitor of methyl carbachol with an IC_{50}

value of 38 nM. Replacement of the methyl group with an ethyl group at position #1 of the THP resulted in the formation of less active compounds. Similarly, position #3 of the isoxazole ring cannot bear large groups as there is a decrease in the affinity of the compound for the nicotinic receptor by the addition of a methyl group.[88]

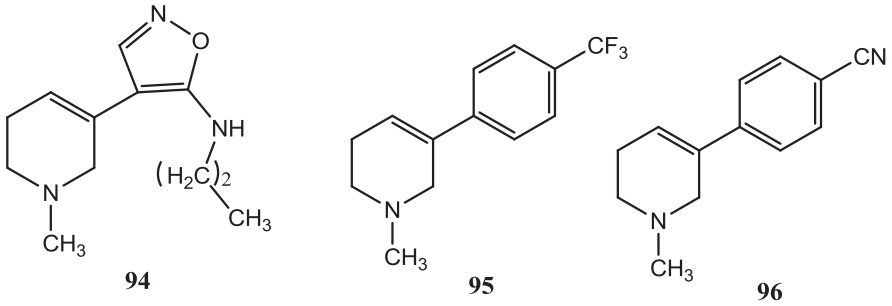

Figure 13. THP derivatives acting on nicotinic receptors and as acetyl cholinesterase inhibitors.

2.11. Acetyl cholinesterase inhibition

Synthesis of 3-aryl-*N*-methyl-1,2,5,6-tetrahydropyridine derivatives was carried out by Prasad et al. Biological evaluation as an acetyl cholinesterase inhibitor showed that the presence of trifluoromethyl (Figure 13, IC_{50} = 52 nM for compound **95**) and a cyano group (IC_{50} = 68 nM for compound **96**) at position #4 of the aromatic ring increased the activity of the compounds. These results were obtained when the activity was evaluated in human serum acetylcholinesterase. Similarly, the presence of 2-fluoro-3-chloro phenyl (IC_{50} = 170 nM) and 2-fluoro-4-biphenyl (IC_{50} = 115.6 nM) substituted aromatic rings also showed the inhibition of cholinesterase enzyme. Therefore, it can be concluded that electron-withdrawing groups increased the inhibitory activity because with electron-donating groups at this position no inhibition of acetyl cholinesterase was observed.[89]

2.12. THPs as monoamine-oxidase inhibitors

N-Substituted phenyl alkyl THPs were synthesized by Wichitnithad et al. Upon evaluation for monoamine oxidase (MAO-A and MAO-B) inhibitory activity, THP derivatives were more potent inhibitors of MAO-A than MAO-B. The introduction of substituted aromatic rings at position #1 resulted in the formation of potent compounds. Compound **97** (Figure 14), which contains a dichlorophenoxy group attached to THP through the propyl chain, was most active in this series and showed better selectivity for MAO-A (IC_{50} = 2.6 ± 0.02 nM) than MAO-B (IC_{50} = 66.4 ± 0.2 nM). It also showed noncompetitive type inhibition of MAO-A.[90] R-Nordeprenyl is a potent MAO-B inhibitor.[91] Tetrahydropyridyl carbamate derivatives of (*S*)-nordeprenyl and (*R*)-nordeprenyl were synthesized by Flaherty et al. in order to evaluate the influence of stereochemical features in interaction of these compound with MAO-A and MAO-B. The *R*-enantiomer was found to be a potent and selective inhibitor of monoamine oxidase B. This compound was also found to be nontoxic at a daily dose of 124 μmol/kg.[92]

2.13. THPs having activity on dopamine receptors

Fused furo- and pyrano-tetrahydropyrido[2,3c]coumarin derivatives (Figure 15, compounds **100** and **101**) were synthesized by Das et al. using a one-pot reaction of aromatic aldehyde, 3-aminocoumarin, and 3,4-dihydropyran

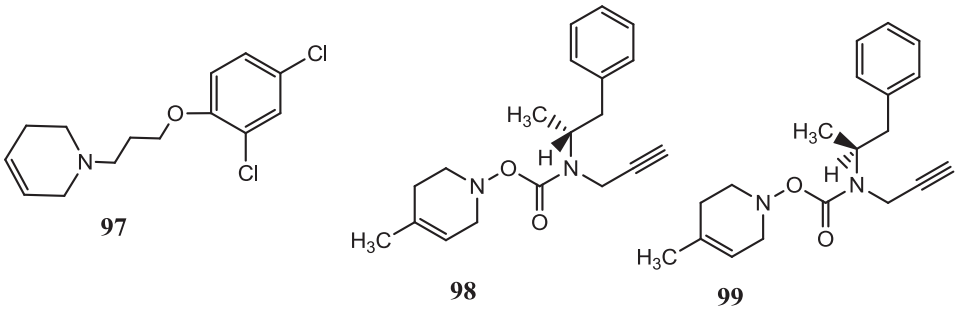

Figure 14. THP derivatives as MAO inhibitors.

by reflux in acetonitrile as a solvent. These compounds were evaluated for interaction with the dopamine D3 receptors of humans by molecular docking and some compounds showed excellent binding affinity with these receptors. The inhibition of dopamine D3 receptor is important for the treatment of schizophrenia, parkinsonism, and other neuropsychiatric disorders.[93] Löber et al. carried out the synthesis of aryl pyrazole and aryl triazole derivatives having THPs. Upon evaluation of biological activity for dopamine receptors, compounds **102** (Ki = 0.59) and **103** (Ki = 3.2) showed the maximum affinity for the D4 receptors, which is a subtype of dopamine receptors. Compound **102** exhibited a partial agonistic property against dopamine receptors.[94]

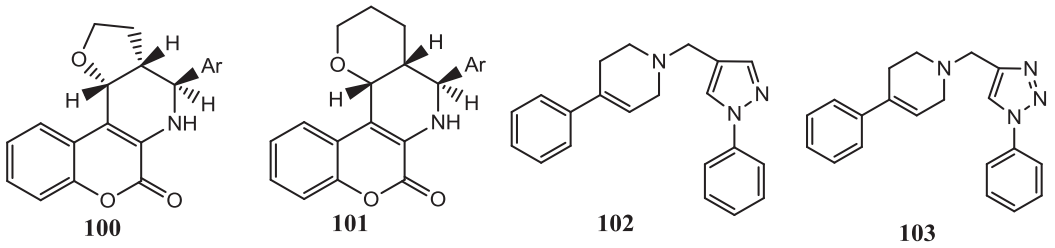

Figure 15. THP derivatives acting on dopamine receptors.

2.14. THPs as GABA inhibitors and as GABA analogues

Synthesis of tetrahydropyridine-3-carboxylate derivatives was reported by Ramachandran et al. The method was used for the synthesis of biologically active 6-substituted and 5,6-disubstituted THPs. Compound **104** (Figure 16), for example, is the chiral analogue of the C-6 substituted guvacine derivative, which is a GABA uptake inhibitor.[95] Chiral 1,2,3,6-tetrahydropyridines-4-carboxylate derivatives were synthesized as analogues of isoguvacine. The reaction takes place between amino acid-derived aldehyde and ethyl acrylate by Baylis–Hillman reaction and ring closure metathesis in the presence of Grubbs second-generation catalyst was used to form the THP rings.[96] These compounds (**105** and **106**) are the pharmacophores of GABA inhibition.[95] They have the potential to be used as anticancer, antiviral, and antidiabetic agents.[97] Ethyl 1,6-dimethyl-3-oxo-5-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (compound **107**) is a derivative of secoergoline that exhibited the inhibition of uptake of GABA (IC_{50} = 680 ± 87 μM) and glutamine (IC_{50} = 660 ± 61 μM) through cerebrocortical membranes specifically. The inhibition of uptake of GABA (IC_{50} = 3.7 ± 0.6 μM, 360 ± 8 μM) and glutamine (IC_{50} = 9 ± 0.2 nM, 591 ± 24 μM) was more effective in the presence of a known inhibitor of these neurotransmitters and took place in two phases. The inhibition of these transporters is significant for the treatment of neurological disorders such as epilepsy.[98]

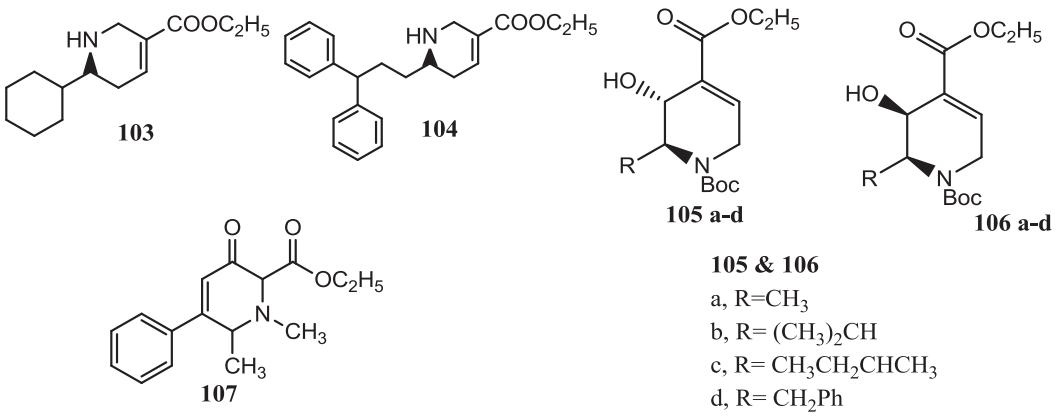

Figure 16. THP-derived compounds as GABA inhibitors.

2.15. THP as serotonin transport inhibitors

Synthesis of indole THP derivatives was carried out by Deskus et al. by reacting 5-substituted indoles with n-methyl piperidone. The binding affinity of indole THPs as serotonin transport inhibitors was evaluated. The most potent compounds (Figure 17, **108a** and **108b**) in this series contain a cyano group (IC_{50} = 19 ± 3 nM) and a nitro group (IC_{50} = 40 ± 6 nM) at position #5 of indole. Some potent compounds were produced when the THP ring was replaced with a cyclohexene ring and nitrogen was shifted out of the ring. Therefore, THP derivatives were less active as serotonin transport inhibitors.[99]

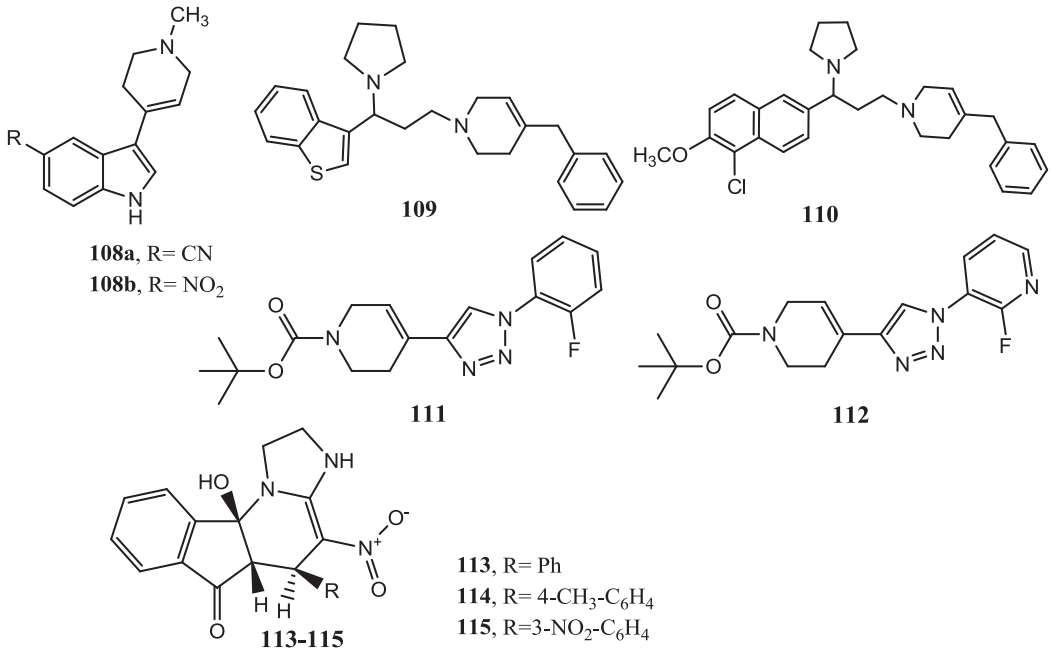

Figure 17. THP derivatives as serotonin transport inhibitors, triple reuptake inhibitors, glutamate receptor antagonists, and anti-HIV agents.

2.16. THP derivatives as triple reuptake inhibitors

Zheng et al. carried out the synthesis of a series of ara-alkyl diamine derivatives having 1,2,3,6-tetrahydropyridine rings and evaluated their activity as triple reuptake inhibitors, i.e. serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Compound **109** (Figure 17) having pyrrolidine and benzothiophine showed inhibition of three neurotransmitters (IC_{50} 5-HT = 621.3 ± 41.5 nM, IC_{50} NE = 157.3 ± 6.4 nM, IC_{50} DA = 325.4 ± 18.5 nM). Replacement of pyrrolidine with morpholine, piperidine, and piperazine produced less active compounds. Further replacement of benzothiophine with 5-chloro-6-methoxy naphthyl (compound **110**, IC_{50} 79.9%, 73.5%, 79.5% for 5-HT, NE, DA respectively at concentration of 10 μM) and 3,4-dichlorophenyl also resulted in the formation of active compounds.[100]

2.17. THPs as glutamate receptor antagonists

Ito et al. showed that 4-(1-aryltriazol-4-yl)-tetrahydropyridine derivatives possess glutamate receptor (mGluR) antagonist activity. The introduction of halogens such as a fluoro group on the benzene ring at the ortho position resulted in increased antagonistic activity. Compound **111** (IC_{50} = 6.3 ± 1.3 nM) (Figure 17) displayed prominent activity towards human glutamate subtype 1 receptors. Replacement of benzene with 3-pyridine resulted in moderate antagonistic activity. Therefore, the pyridine ring was modified by the introduction of the halogen atom and prominent increase in the antagonistic activity (compound **112**; IC_{50} = 2.6 ± 0.54 nM for $hmGluR_1$) was observed. This compound was also further modified by replacement of tertiary-butyl carbamate with tertiary-butyl acetate or tertiary-butyl groups, which resulted in less active compounds.[101]

2.18. Anti-HIV activity of THP derivatives

Mohammadi et al. synthesized new THPs, 10*b*-hydroxy-4-nitro-5-phenyl-2,3,5,5*a*-tetrahydro-1*H*-imidazo[1,2*a*] indeno[2,1*e*]pyridine-6(10*bH*)-ones, by multicomponent condensation strategy. Four components, ethylene diamine, indandione, benzaldehyde, and 1,1-bis(methylyhio)2-nitroethylene, were condensed in the ethanol as solvents. Upon evaluation for anti-HIV activity by molecular docking studies, these compounds showed encouraging binding energy with the target enzyme. The most active compound, **115** (–9.24 kcal/mol), contains a nitro substituted phenyl ring at position #5 (Figure 17). Derivative **113**, having an unsubstituted phenyl group at this position, also showed significant binding energy (–9.9 kcal/mol). Therefore, these compounds have the potential for further evaluation as HIV inibitors.[102]

2.19. Miscellaneous activities of THP derivatives

The multicomponent reaction of 5-amino-2-mercaptobeznimidazole, 5-benzylidene amino benzimidazole-2-thiole, amino aromatic aldehyde, and ethyl acetoacetate was used by Ravindernath et al. for the synthesis of benzo[d]imidazolyl THP carboxylates. These compounds exhibited antibacterial, antifungal, antioxidant, and antiinflammatory activities. Compounds **116** and **117** (**Figure 18**) were the most active antiinflammatory (volume of edema = 0.3 ± 0.028 after 3 h) and antioxidant (IC_{50} = 3.8 μM) agents, while compounds **118** (MIC = 13 μM against *E. coli*) and **119** (zone of inhibition = 30 mm against *Candida albicans*) were found to be the most potent antibacterial and antifungal agents. There was no structure–activity relationship as both electron-withdrawing and electron-donating substituents on the aromatic rings at position #2 and position #6 of the tetrahydropyridine ring demonstrated activities.[103] *N*- and *O*-acyl derivatives of 2,6-diphenyl-4-hydroxytetrahydropyridines were found to be analgesic, muscle-relaxant, and sedative as evaluated

by Soldatenkov et al. Compound **120**, which was obtained by the reaction of 2,6-diphenyl-3-carboxylate-4-oxo-piperidone with acetic anhydride, was a potent analgesic agent (time of stay on hot plate = 25 ± 8.6 s after 40 min) and it was more active than the standard drug, promedol. It was also the most active sleep-inducer (sleep = 92 ± 8 min) and a potent myorelaxant compound (time of stay on rotating rod = 2.5 ± 1.4 s).[104] *N*-Heteroarylmethyl-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid showed alpha glucosidase inhibitory activity. Structure–activity relationship studies showed that the presence of a carboxylic group at position #3, hydroxyl group at position #5, and heteroaromatic ring at position #1 is necessary for optimal activity. The most potent (IC_{50} = 2.34 μM) alpha glucosidase inhibitor was compound **121**. The derivatives in this series showed a reversible uncompetitive type of alpha glucosidase inhibition and have the potential for further modification.[105] 6-Alkyl-2,3,4,5-tetrahydropyridine derivatives were synthesized as antifungal agents by Dai et al. Alkyl chains in these compounds vary from 12-carbon to 18-carbon. Compounds having chain length of twelve and thirteen carbons did not show any antifungal activity, while significant antifungal activity was observed for compounds having chain length of fourteen to eighteen carbons. Most potent compounds had alkyl chains of sixteen and seventeen carbons. Compound **122** exhibited minimum fungicidal concentrations of 3.8 μg/mL, 7.5 μg/mL, 7.5 μg/mL, and 15 μg/mL against *Cryptococcus neoformans*, *Candida glabrata*, *Candida krusei*, and *Candida albicans*, respectively. These compounds were found to be nontoxic (tested dose = 10 μg/mL) against various cell lines.[106] Arecoline tripeptide derivatives were prepared by Marastoni et al., in which methyl 3,4-epoxypiperidine-3-carboxylate was attached to the c-terminal of the peptide chain and the n-terminal was attached to 1,2,5,6-tetrahydropyridine-3-carbonyl. The sequence of the tripeptide was valine-serine-leucine and leucine-leucine-leucine in these compounds. The derivatives in this series showed stability against plasma protease enzymes as was evident by their half-life (>360 min). Compound **123** showed more preference for tryptic type inhibition (IC_{50} = 0.31 μM), while compound **124** showed more chymotryptic type inhibition (IC_{50} = 0.77 μM). Overall, THP derivatives presented less activity as compared to aromatic derivatives in this series.[107] Densely functionalized THPs were synthesized from 1,6-dihydropyridines having a phenyl ketone group at position #3 by Watanabe et al. Compound **125** exhibited promising anti-hepatitis C virus activities (IC_{50} = 15.44 μM) in a cell culture.[108] Aryl substituted THPs showed dual agonist action against peroxisome proliferator-activated receptors alpha and gamma (PPARα/γ). Disubstituted compounds showed more potent agonistic effect on both alpha and gamma receptors as compared to the monosubstituted compounds. Compound **126** was the most potent agonist (EC_{50} = 0.064 μM, 0.661 μM for α and γ) for both alpha and gamma receptors, while **127**, the *S*-isomer, also showed prominent activity (EC_{50} = 1.73 μM, 0.639 μM for α and γ) and pharmacokinetic properties such as increased half-life and water solubility. Compound **127** also showed good glucose-lowering effect in mouse models.[109] THP derivatized compounds **128** and **129** showed prominent binding (IC_{50} = 1.2 nM, IC_{50} = 2.0 nM for **128** and **129**, respectively) with renin enzymes as determined by Remeň et al. These are the prototype achiral potent renin inhibitors. These compounds have higher pKa values as compared to corresponding piperazine derivatives. The nitrogen in tetrahydropyridine is important for renin inhibition. It is protonated and forms a bridge with aspartyl residues in the target enzyme.[110]

Condensed THPs, 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine derivatives, were reported as gamma secretase inhibitors by Takai et al. Structure–activity relationship studies showed that substitution of 1,2,4-triazole with 1,2,3-triazole, expanding the THP ring to an azepine ring, and conversion of 6-membered to 5-membered heterocycles and THP to dihydropyridine did not result in improvement of activity. The introduction

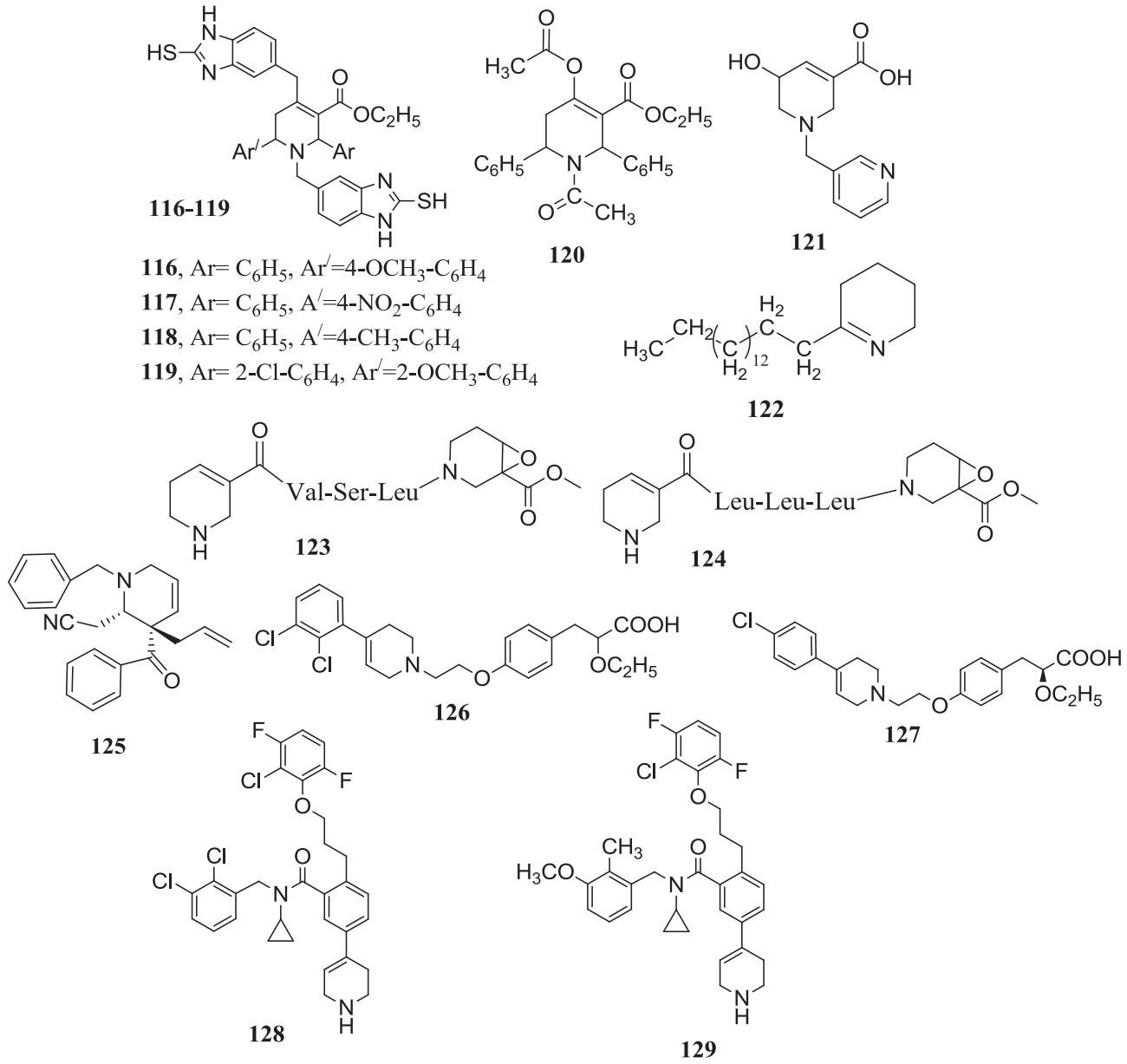

Figure 18. Pharmacologically active THP derivatives.

of lipophilic groups to this bicyclic system leads to the formation of active compounds. Compound **130** (IC_{50} Aβ_{42} = 84 nM, ligand lipophilicity efficiency = 3.6) is the most active compound, which contains trifluoromethyl and a chloro group attached to the phenyl ring (Figure 19). Stereoseparation of this compound showed that the R-isomer was more potent (Aβ_{42} = 60 nM) than the S-isomer.[111] 1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline (compound **131**) is an inhibitor of catecholamine biosynthesis. It was found to be a potent inhibitor (IC_{50} = 3 μM) of the enzyme tyrosine hydroxylase. Synthesis of two metabolites of this compound was carried out by Bringmann et al. 1-Dichloromethylene-1,2,3,4-tetrahydro-β-carbolines (**132**) was formed by the addition of potassium hydroxide in methanol to compound **131** and then heating via

reflux followed by purification and recrystallization. 2-Methyl-1-trichloromethyl-1,2,3,4-tetrahydro-β-carbolines (**133**) was produced by the methylation of compound **131** with methyl iodide. Their interaction with tyrosine hydroxylase (TH) was evaluated. Compound **133** ($IC_{50} = 3\ \mu M$) was found to be a potent inhibitor of TH while compound **132** inhibited TH at a higher concentration ($IC_{50} = 20\ \mu M$) and it enhanced the TH activity at a low concentration.[112] Almorexant is a dual orexin receptor (OX_1R and OX_2R) antagonist that contains dimethoxy substituted tetrahydroisoquinoline.[113] Pyrazolo-tetrahydropyridine as a dual orexin receptor antagonist was reported by Sifferlen et al. based upon the activity of almorexant. The structure–activity relationship of the phenyl ethyl group showed that the methyl group or trifluoromethyl group at the para position of the aromatic ring produced potent compounds. In the case of disubstituted compounds, a methyl group at the para and meta position resulted in the formation of active compounds ($hOX_1R = 7$ nM and $hOX_2R = 3$ nM for **135**). Similarly, compound **136**, which contains a trifluoromethyl group at the para and fluorine atom at meta positions, was most active in this series ($hOX_1R = 5$ nM and $hOX_2R = 4$ nM). Compounds **135** and **136** also showed activity in an in vivo sleep model.[114]

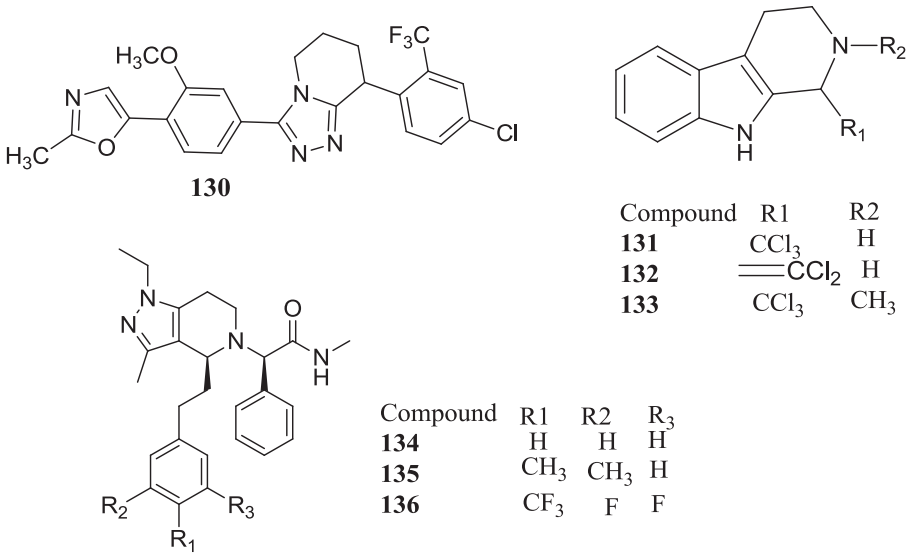

Figure 19. More pharmacologically active THP derivatives.

3. Discussion

THP is a structural part of many synthetic pharmacologically active molecules as the main pharmacophore as well as a substituent. Monosubstituted THP derivatives were found to be inhibitors of some human enzymes like MAO and proteasome. Some monosubstituted THPs having long alkyl chains showed antifungal activity. Disubstituted THP derivatives such as 3-aryl and 4-aryl derivatives showed antiinflammatory activities and also inhibited the production of proinflammatory mediators such as TNFα and interleukin. Disubstituted THP having a 1-methyl group produced activities against muscarinic and nicotinic receptors while THP having a carbamyl or aryl group produced activity against glutamate, PPAR, and corticotropin-releasing receptors. Disubstituted THP derivatives have also shown some inhibitory effects on neurotransmitters such as GABA and serotonin. 1,2,5,6-Tetrahydropyridine derivatives attached to 1,2,5-thiadiazole, particularly the dimeric compounds, exhibited agonistic properties against muscarinic receptors and derivatives having the tetraethylene glycol spacer were selective for the M_1 and M_2 subtypes of muscarinic receptors. Other

THP derivatives, 1-ethyl-4-phenyl-1,2,5,6-tetrahydropyridine-3 carboxylic acid esters, showed selectivity for M_5 receptors. The discovery of such derivatives is important for the production of compounds without producing adverse effects. Highly functionalized THP derivatives exhibited antibacterial, antifungal, antiplasmodial, antioxidant, antiinflammatory, analgesic, muscle relaxant, sedative, and anticancer activities. They have also presented activity as inotropic agents for the heart. Antibacterial activity of functionalized THP derivatives was more significant because they showed activity against different strains of pathogenic bacteria and some of them were also active against *Mycobacterium*, the causative agent of tuberculosis. THPs attached with additional aromatic and heteroaromatic rings such as imidazole-containing compounds were more prominent because they presented activity against multidrug-resistant strains of bacteria. 4-Phenyl substituted THP derivatives were found to inhibitors of the renin and PARP-1 enzymes. 4-Phenyl-1,2,3,6-tetrahydropyridine and 4-pyridyl-1,2,3,6-tetrahydropyridine attached with heterocyclic rings exhibited affinity for the 5-HT_{1A} receptors. 4-Phenyl-1,2,3,6-tetrahydropyridine, which contains halogen or some heterocyclic ring attached with a 4-phenyl group, showed more affinity for 5-HT_{2c} receptors. Condensed THPs such as tetrahydrothienopyridine derivatives showed antibacterial, anticancer, and antiinflammatory properties. Tetrahydroimidazopyridine and tetrahydroimidazoindenopyridine containing condensed THP derivatives have shown anti-HIV and insecticidal properties. Some of the condensed THP derivatives produced activities against dopamine and orexin human receptors and gamma secretase and tyrosine hydroxylase as enzyme inhibitors. THP is not a sole determinant of a particular pharmacological activity or selectivity for a particular target, but pharmacological activity is influenced by the nature and type of substituents attached to the THP. The synthesis of new THP derivatives, especially highly functionalized THP, has produced some interesting new molecules that will serve as leads for future drug discovery.

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