AUCTORES
Globalize your Research

Clinical Medical Reviews and Reports

Tiffany W. Ardley *

Open Access

Research Article

The Chemistry and Pharmacology of Tetrahydropyridines: Part 2

Shasline Gedeon, Aisha Montgomery, Madhavi Gangapuram, Kinfe K. Redda, Tiffany W. Ardley*

College of Pharmacy and Pharmaceutical Sciences, Institute of Public Health, Florida A&M University, Tallahassee, FL 32307, USA

***Corresponding Author:** Tiffany W. Ardley. College of Pharmacy and Pharmaceutical Sciences, Institute of Public Health, Florida A&M University, Tallahassee, FL 32307, USA.

Received date: November 28, 2022; **Accepted date:** December 06, 2022; **Published date:** March 20, 2023.

Citation: Shasline Gedeon, Aisha Montgomery, Madhavi Gangapuram, Kinfe K. Redda, Tiffany W. Ardley. (2023). The Chemistry and Pharmacology of Tetrahydropyridines: Part 2, *J. Clinical Medical Reviews and Reports*, 4(5) DOI: 10.31579/2690-8794/135.

Abstract

Tetrahydropyridines (THPs) have sparked notable interest as an auspicious heterocyclic moiety. Existing in distinct structural isomers including 1,2,3,4-tetrahydropyridine, 1,2,3,6-tetrahydropyridine, 2,3,4,5-tetrahydropyridine, its presence has been identified in both natural products and synthetic pharmaceutical agents. Many THP-containing compounds have been synthesized by the inspiration of known bioactive natural products and have been found to possess biologically active properties. For this reason, more innovative methods have been developed for the synthesis of substituted-tetrahydropyridine derivatives and their pharmacological activities have been determined. This review article is written to provide an overview which is a continuation of the former article by Redda et al. entitled, "The Chemistry and Pharmacology of Tetrahydropyridines". This review aims to highlight the research progress accomplished thus far and to increase the database for structure activity relationship (SAR) studies. Special attention is given to the introduction of varied substituents onto the THP ring system and its redolent effect on their pharmacological properties, specifically as anti-inflammatory and anticancer agents. Thus, the use of SAR studies of newly reported THP derivatives will help shed light on the significance of utilizing THP-containing motifs as lead compounds in drug discovery and design.

Keywords: tetrahydropyridines; synthesis; pharmacology; structure-activity relationship; cancer

Abbreviations

BBB	blood-brain barrier
Boc	tert-Butyloxycarbonyl
CN	nitrile
COX-2	cyclooxygenase 2
DMF	Dimethylformamide
ee%	percent enantiomeric excess
ERa	estrogen receptor α
ERK	extracellular signal-regulated kinase
Et	ethyl
EtOH	ethanol
Et_3N	Triethylamine
FDA	Food and Drug Association
HIV	human immunodeficiency virus

IC_{50}	Inhibitory Concentration of 50%
ID_{50}	Infectious Dose to 50 Percent of Exposed Individuals
IL	interleukin
L-NIL	l-N6-(1-imino-ethyl)-lysine
LPS	Lipopolysaccharide
MAO	monoamine oxidase
MAO-B	monoamine oxidase B
MAPK	mitogen-activated protein kinase
Me	methyl
MeOH	methanol
Mol	molar
MPP^+	1-methyl-4-phenyl pyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
MSH	mesitylenesulfonyl hydroxymate
n-Bu	Normal butyl
NO_2	Nitrogen dioxide
NS-SSA	nano-sphere silica sulfuric acid
OEt	ethoxy
OMe	methoxy
PBBS	Poly *N, N′*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide
Ph	phenyl
Raf-1	rapidly accelerated fibrosarcoma
Rt	Room temperature
SAR	Structure-activity relationship
SSRIs	selective serotonin reuptake inhibitors
TBBDA	*N, N, N′,N′*-tetrabromobenzene-1,3-disulfonamide
t-Bu	*Tert*-butyl
THF	tetrahydrofuran
THP	Tetrahydropyridine
TNFa	tumor necrosis factor-α
Ts	tosyl
mM	Micromolar

Introduction to Tetrahydropyridines

Tetrahydropyridine (THP) is a very fascinating nitrogen-containing heterocyclic moiety that has become of great interest in the medicinal and drug discovery space. This structural motif presences itself in distinct structural isomers including 1,2,3,4-tetrahydropyridine, 1,2,3,6-tetrahydropyridine, 2,3,4,5-tetrahydropyridine [1] and has been observed in both natural products and synthetic pharmaceutical agents. Betanin 1 is a natural THP-containing compound found in beets used in the food industry as a food colorant [2]. THPs have also been discovered in various alkaloids including 6-[(E)-2-(3-methoxyphenyl) ethenyl]-2,3,4,5-tetrahydropyridine 2 of Lobelia siphilitica [3] and Koreenceine B 3 in P. koreensis [4], as seen in Figure 1.

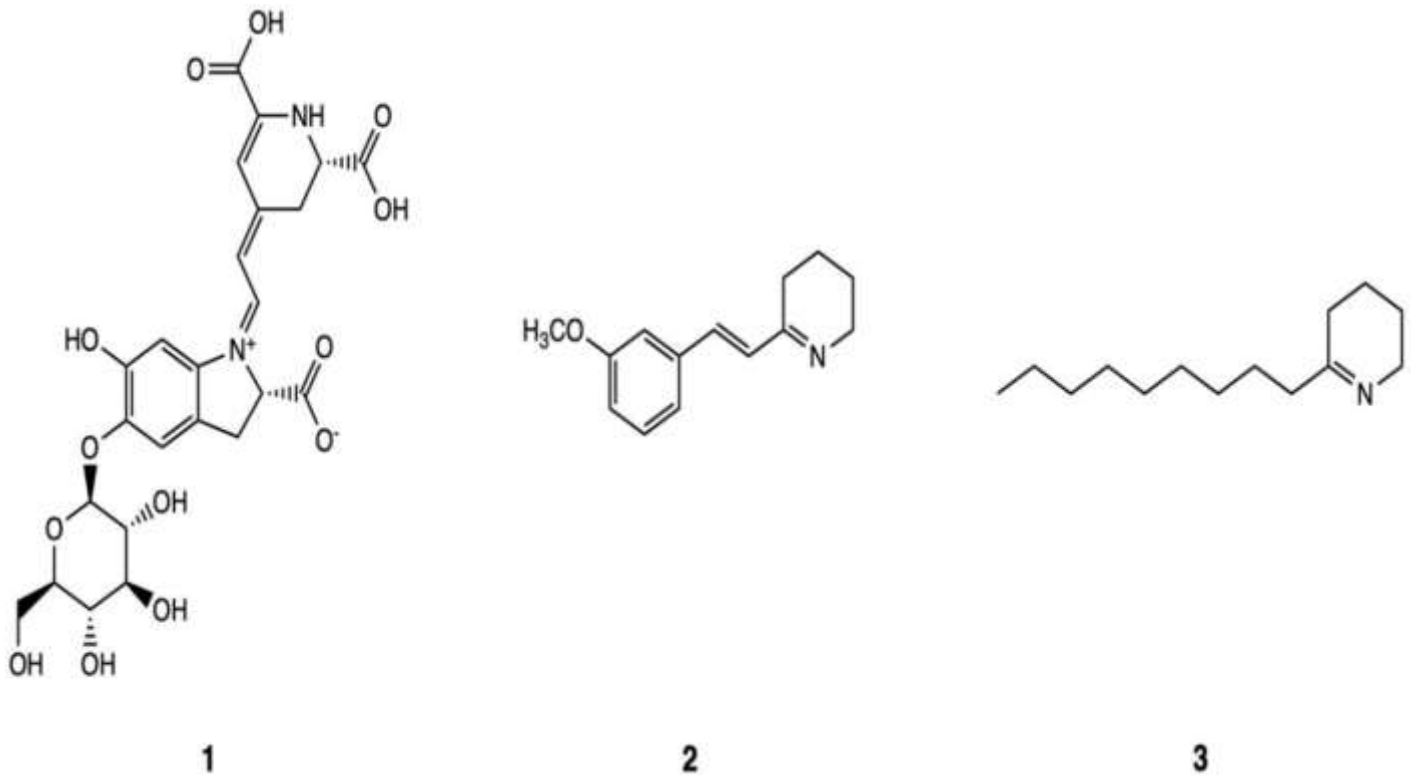


Figure 1: *Tetrahydropyridines in nature and in alkaloids.*

Additionally, many THP-containing compounds have been synthesized by the inspiration of known bioactive natural products and have been found to possess biologically active properties ranging from anti-inflammatory [5], antioxidant [6], antimicrobial [7], anticancer [8], and antifungal [9], just to name a few. There are numerous THP derivatives with a vast degree of pharmacological properties and that is greatly due to the substituents on the THP ring system. Being non-planar rings with sp3 carbon atoms, THPs are often found to be chiral molecules and in such circumstances, absolute and relative configuration of the substituents would also be pivotal in rendering biological properties [10].

Since the discovery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) 4, a compound that produces a neurotoxic metabolite responsible for irreparable Parkinsonism in humans [11], there arose interest in studying the synthesis and biological function of tetrahydropyridines. MPTP was discovered in 1982, after some people injected themselves with a substance, which at the time was known as a novel synthetic heroin. They soon developed irreversible Parkinsonism. Research studies deduced the proposed mechanism of action of MPTP to be that the powerful neurotoxic prodrug travels through the blood-brain barrier (BBB) to the substantia nigra to selectively target dopaminergic neurons, replicating the motor symptoms associated with Parkinson's Disease [12]. Upon crossing the BBB, the monoamine oxidase B (MAO-B) enzyme metabolizes MPTP by complete oxidation to yield its toxic metabolite, the 1-methyl-4-phenyl pyridinium ion (MPP+) 5 as seen in Figure 2.

Figure 2: *Oxidation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into 1-methyl-4-phenyl pyridinium ion (MPP+) by the enzyme, monoamine oxidase B.*

Permission from: [11]; He, X. J., & Nakayama, H. (2009). Neurogenesis in Neurotoxin-induced Animal Models for Parkinson's Disease—A Review of the Current Status. Journal of Toxicologic Pathology, 22(2), 101–108. https://doi.org/10.1293/tox.22.101 Copyright 2009 The Japanese Society of Toxicologic Pathology, Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License.

To date, neuroprotection research has sprout through novel synthesis of MAO-inhibitory THP-derivatives and various animal model studies, including mice, primate, zebrafish, and salamander models [13]. Tetrahydropyridines are now being studied in a much larger scope and many of their biological properties have been uncovered.

Recent Developments in THP Synthesis

Many innovative methods for the synthesis of substituted THP-derivatives have been reported. This section serves to review some of the recent developments in substituted-THP synthesis.

One-pot Synthesis

One-pot synthesis of THP derivatives has been reported as a strategy aimed to increase efficiency of a one-reactor chemical reaction. Barber et al. described a synthetic method of using a one-pot nitro-Mannich/hydroamination cascade. The first step involved an asymmetric nitro-Mannich reaction using a bifunctional organocatalyst. Then, a subsequent gold-catalyzed alkyne hydroamination, protometalation, and finally isomerization, was used to generate highly enantioselective and diastereoselective THP derivatives [14] (6a-j). All products were obtained in moderate to good yields ranging from 31-72%.

Amines containing either electron-donating or electron-withdrawing groups, aromatic aldehydes, and 1,3-dicarbonyl compounds were utilized by Ramin et al. in the presence of poly (N, N′-dibromo-N-ethyl-benzene-1,3-disulfonamide) (PBBS) and N, N, N′,N′-tetrabromobenzene-1,3-disulfonamide (TBBDA) as a catalytic source [15] in ethanol at room temperature. This reaction afforded highly substituted THP analogs (7a-l) in 54-81% yield and high purity. Another highly efficient approach for synthesizing novel THP derivatives come from employment of solid-supported catalysts, more specifically nano-sphere silica sulfuric acid (NS-SSA) [16]. According to Deraei et al., anilines, β-ketoesters, and arylaldehydes with electron-withdrawing substituents react with the NS-SSA catalyst in acetonitrile to produce substituted 1,2,3,4-THP analogs with high to excellent yields of 74-92%. Efficiency increased as Balijapalli et al. reported synthesis of THPs using metal-free catalyst reaction conditions through a tandem reaction [17]. Anilines, arylaldehydes, and β-ketoesters react with acetic acid which functions as both the solvent and the catalyst in the reaction. THP derivatives were generated in high yields of 70-96%; among them are compounds (8a-j) as seen in Figure 3.

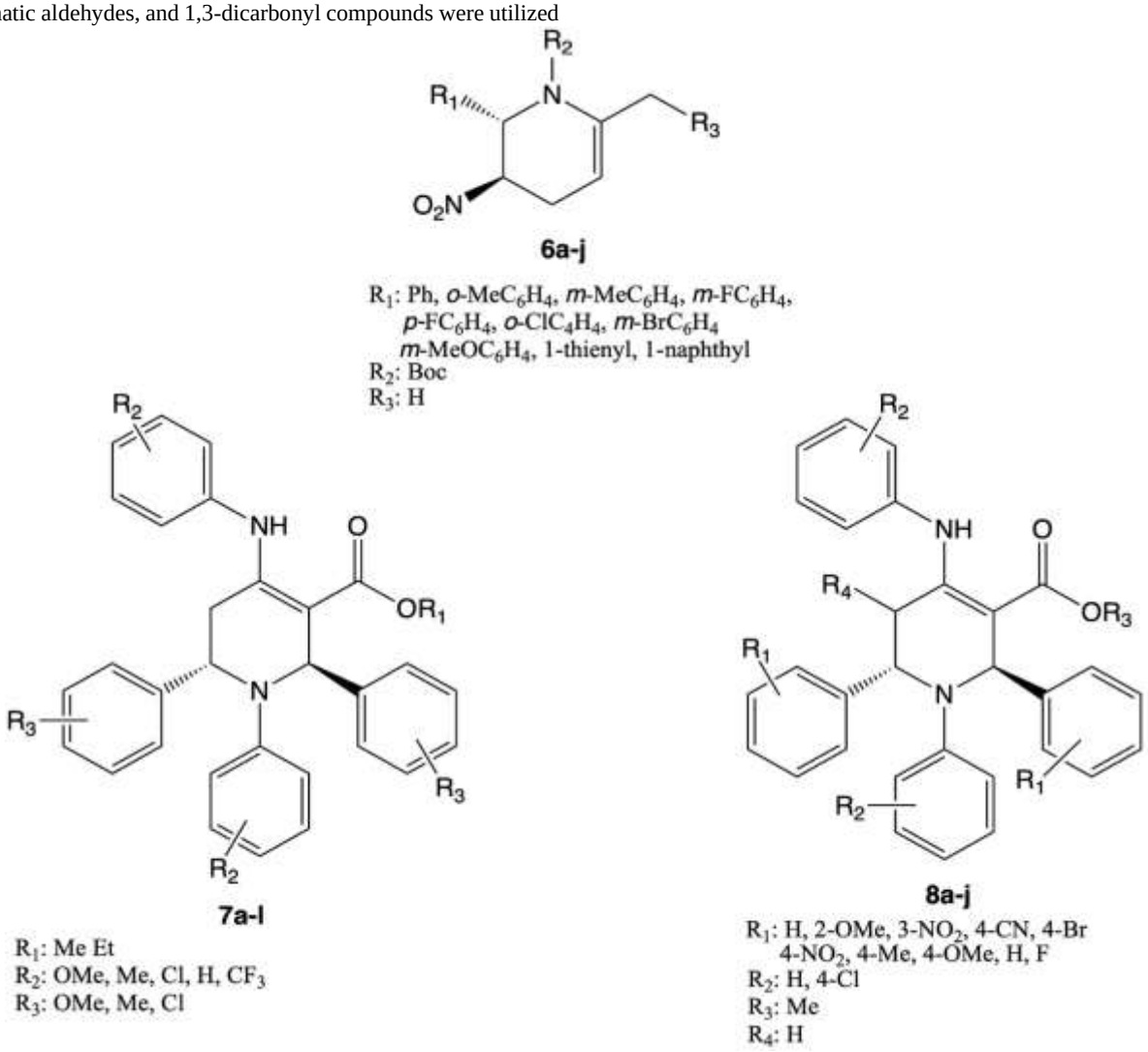


Figure 3: *THPs synthesized by way of one-pot synthesis methods.*

Cyclization Reactions

α,β-unsaturated imines and alkynes can be used to produce a resourceful reaction cascade piloting the development of highly substituted 1,2,3,6-tetrahydropyridines [18]. The rhodium(I) catalyst triggers a coupling reaction through the C–H activation of the alkyne. Electrocyclization via resonance stabilization occurs and is followed by reduction through

acid/borohydride stimulation. The desired compounds are afforded in high diastereoselectivitiy (>95%) and yields (47-95%).

From experience through previous research in phosphine-catalyzed annulation reactions, Wang et al. reported an innovative approach employing phosphine-derivative catalysis on 1-azadienes and α-substituted allene ketones to produce tetrahydropyridines [19]. The reactants undergo a [4+2]-annulation reaction to produce enantioselective target compounds (12a-j) in 46-70% yields and >97 ee% (percent enantiomeric excess) as seen in Figure 4.

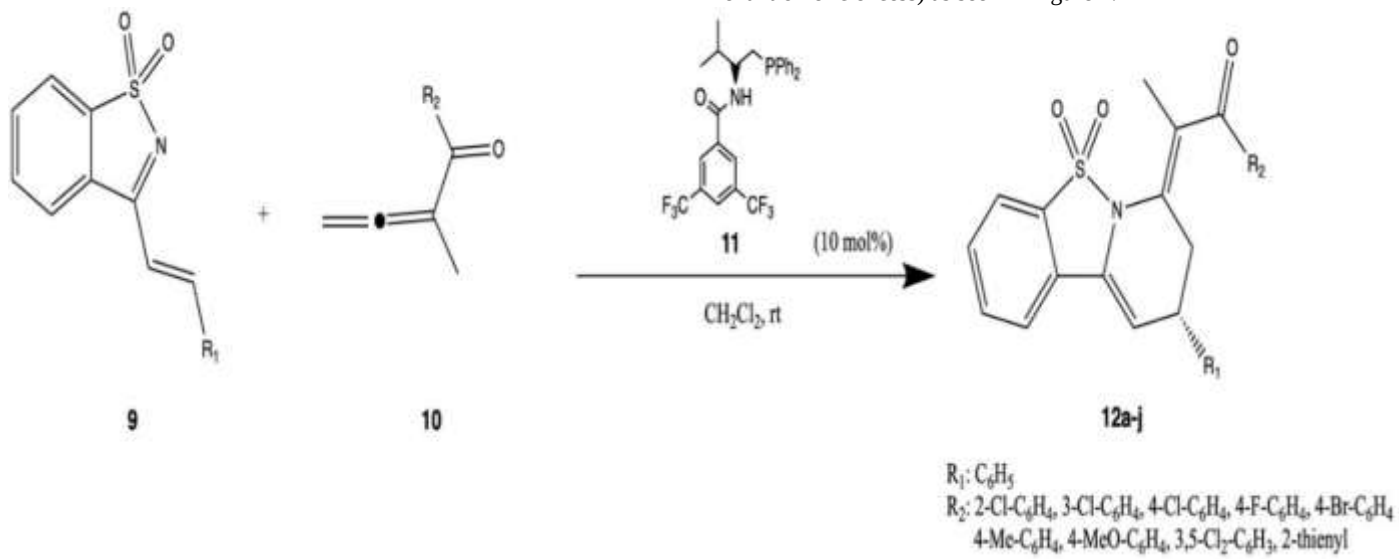


Figure 4: *A phosphine-catalyzed enantioselective [4 + 2]-annulation reaction between allene ketones and 1-azadienes to produce THP derivatives.*

Reprinted (adapted) with permission from Wang, Z., Xu, H., Su, Q., Hu, P., Shao, P.-L., et al. (2017). Enantioselective Synthesis of Tetrahydropyridines/Piperidines via Stepwise [4 + 2]/[2 + 2] Cyclizations. Organic Letters, 19(12), 3111–3114. https://doi.org/10.1021/acs.orglett.7b01221. Copyright 2017 American Chemical Society.

Palladium-catalyzed cyclization-Heck reaction can also be used to synthesize THP analogs [20]. Yan et al. recounts the formation of 3-methylene-5-phenyl-1,2,3,4-tetrahydropyridine derivatives by palladium-catalyzed cyclization-Heck reaction of allenamides and aryl halides in dioxane at 80ºC. The reactants produced moderate to good yields between 54-88%.

Tetrahydropyridines: A Pharmacological Viewpoint

The pyridine ring systems, including its partially and completely reduced ring derivatives, have made an undeniable appearance in natural products and synthetic compounds. Tetrahydropyridines bear pharmacological properties which have been reported in multifaceted scopes. THPs have been reported as dopamine-2 receptor agonists, for example, Droperidol which is used in sedation and antipsychotic, antiemetic, and migraine remedy [21-22]. THP derivatives have also been recounted for possessing antioxidant [23], antimicrobial [24], antibacterial [25], anticancer [26-27], and anti-inflammatory properties [28-29]; they exist as selective serotonin reuptake inhibitors (SSRIs) [30], acetyl cholinesterase inhibitors [31], and human immunodeficiency virus (HIV) protease inhibitors [32]. While this section serves to provide a brief overview of the pharmacological potential of THPs, Mohsin et al. provides an extensive account of the various pharmacological/biological properties related to THP derivatives [33].

Tetrahydropyridines as Anti-inflammatory Agents

Chronic inflammation of the body is a definitive cause of recurrent tissue destruction often leading to inflammation-based diseases and ailments, like osteoarthritis, rheumatoid arthritis, and even cancer. There have been great strides in the ongoing investigation into the plausibility of utilizing tetrahydropyridines as potential anti-inflammatory agents. Nakao et al. conducted research employing THP derivatives for the synthesis of proinflammatory cytokine TNFα (tumor necrosis factor-α) inhibitors as anti-inflammatory agents [34]. Because the MAPK (mitogen-activated protein kinase) pathway is a practical target for anti-inflammatory therapy, compound 13 was synthesized and exhibited good anti-inflammatory activity (IC50: 1.86µM; ID50: 5.98µM).

Ravindernath et al.'s approach to anti-inflammatory agent synthesis involved insertion of THP ring systems to enhance the pharmacological activity of benzimidazole motifs [35]. Compounds 14a-c displayed mild to moderate anti-inflammatory activity following Carrageenan-induced paw edema tests in rats, presenting decreased signs of edema progressively, up to 4 hours. Lastly, Chowdhury et al. produced novel 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2H-pyrazol-3-yl]-1,2,3,6

tetrahydropyridines to serve as cyclooxygenase-2 (COX-2) inhibitors and nitric oxide donors for anti-inflammatory treatment [36]. Focusing on the COX-2 pathway, nitric oxide donors function to inhibit platelet aggregation associated with known highly selectively COX-2 inhibitors. Compounds 15a-g delivered moderate anti-inflammatory activity as noted in Figure 5.

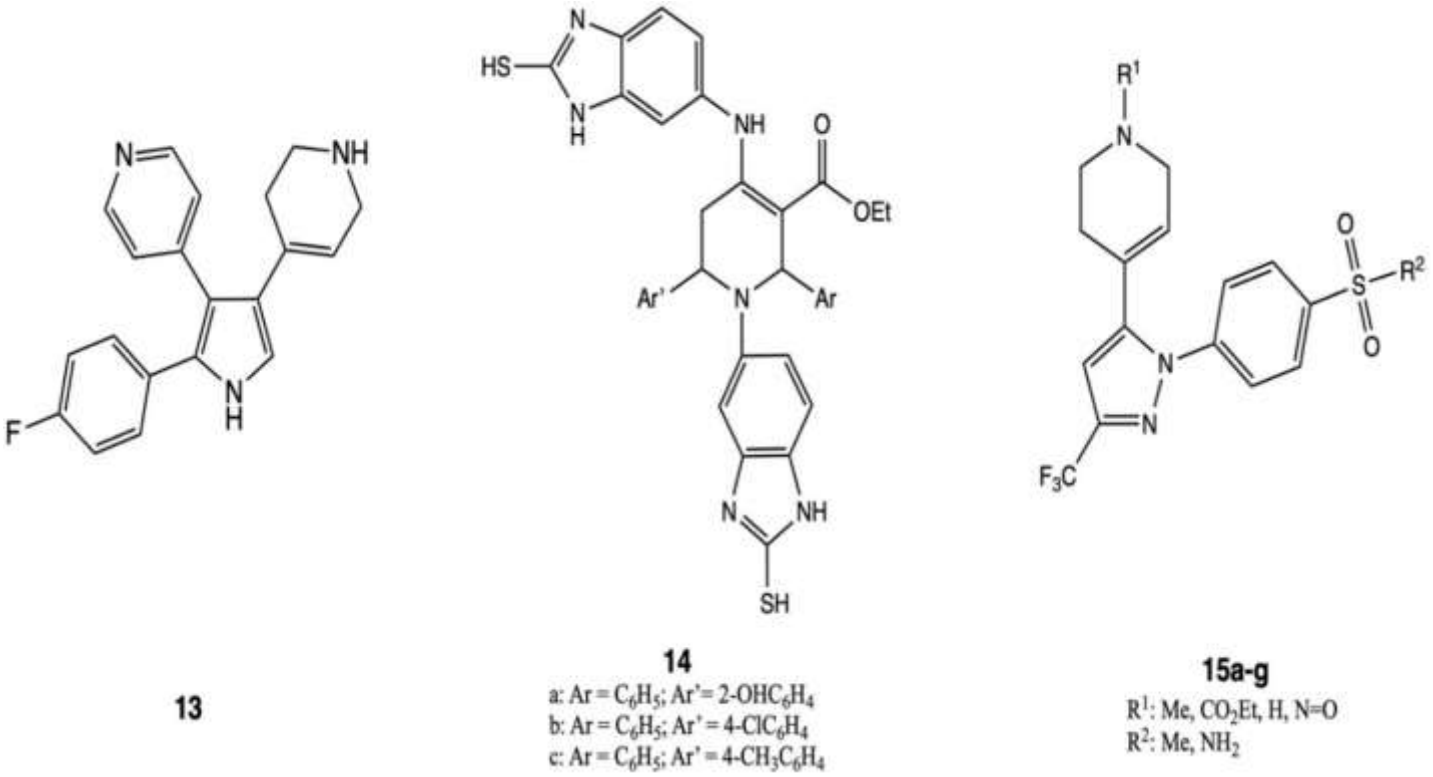


Figure 5: *THP derivatives with anti-inflammatory properties.*

Tetrahydropyridines as Anticancer Agents

Inflammation has notably been linked to cancer. As tetrahydropyridines have been incorporated into drug design as anti-inflammatory agents, ongoing investigation of THPs as anticancer agents have sprouted. Vinblastine is a THP-containing, FDA-approved chemotherapeutic drug. It is used in the treatment of Hodgkin's lymphoma, non-Hodgkin's lymphoma, breast, testicular, non-small cell lung cancer, and various other cancers [37-38]. There are very few THP-containing anticancer agents and so the search continues for more effective treatment with decreased toxic profiles and side effects. Kurtanović et al. designed and synthesized compounds as ERα antagonists, targeting the Raf-1/MAPK/ERK signal transduction pathway. Amongst them, compound 16 was tested on MCF-7 breast cancer cell lines and showed noteworthy potency (0.39±0.11 nM) as a tumor suppressor [39].

Jayashree et al. concentrated on synthesizing and testing THP chalcones for their anticancer effects. Compounds 17a-d were just a few tested against A549 (lung adenocarcinoma), HepG2 (hepatocellular liver carcinoma), HeLa (cervical cancer), HCT-116 (colon carcinoma cells), MCF-7 (breast cancer cell line), and MDA-MB-231 (breast cancer cells) cancer cells [40]. Anticancer activity was expressed in IC50 < 50µM. León et al. generated 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines and analyzed their in vitro antiproliferative activity [41]. Observations were made on human solid tumor cell lines A2780 (ovarian cancer), SW1573 (non-small cell lung cancer), and WiDr (colon cancer). Compound 18, in Figure 6, was the most potent which yielded GI50 = 3.3–6.6 µM against the tested cancer cell lines.

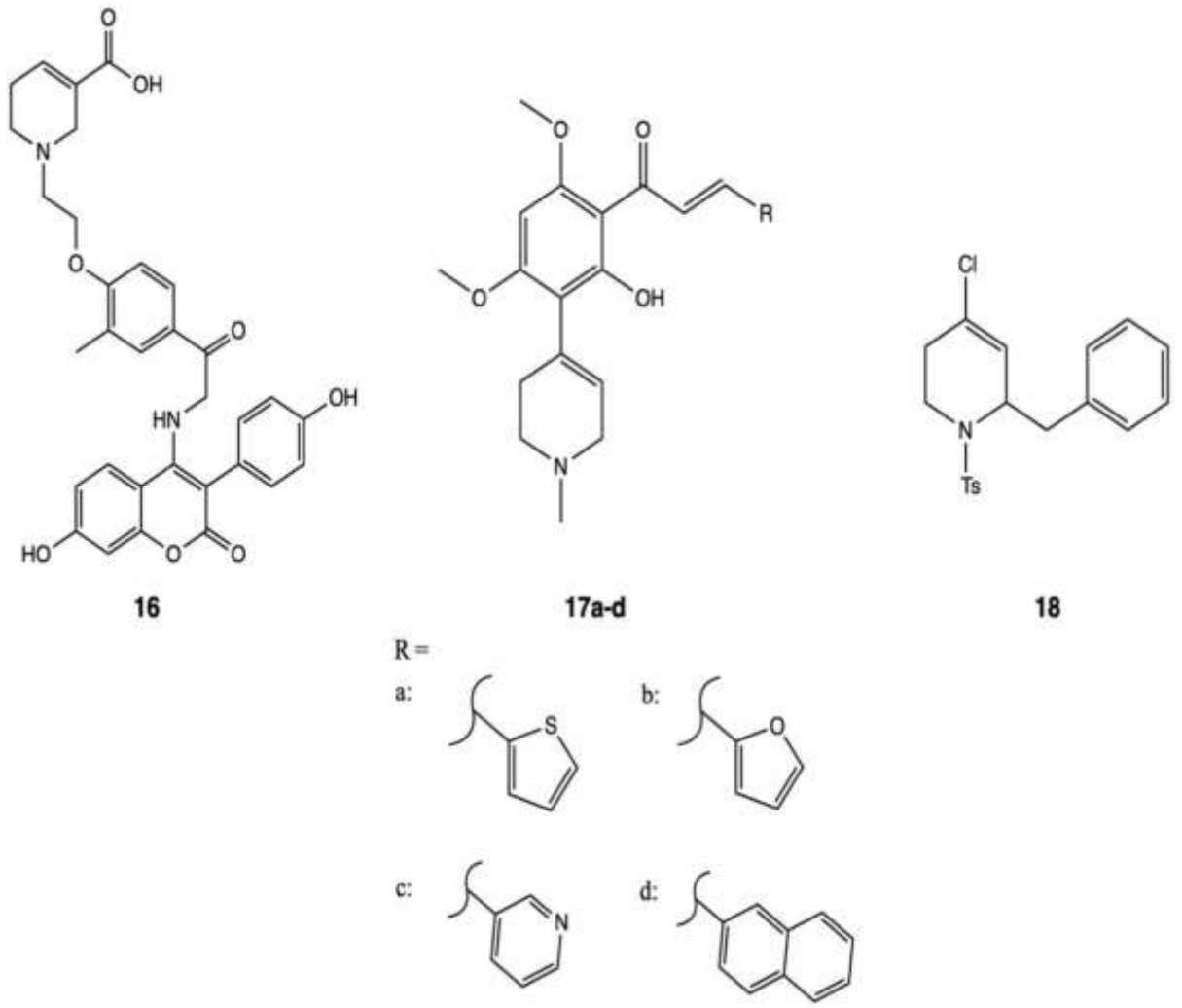


Figure 6: *THP derivatives with anticancer properties.*

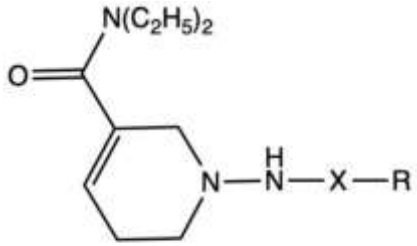
Newly Reported Tetrahydropyridines

The study of tetrahydropyridines has been a major focus in our laboratory research for many decades. As previously stated, the pharmacological properties of the THP analogs are dependent on the substituents of the THP ring. More THP derivatives have been published since the last reported in efforts to expand the database for SAR studies. Here, we present the compounds containing tetrahydropyridine ring systems that have been synthesized in our laboratories, analyzed for their pharmaceutical capabilities and medicinal applications, and reported as potential anti-inflammatory and anticancer agents.

The Chemistry

Two reaction schemes have been documented and employed as a simple method for the synthesis of substituted N-(carbonylamino)-1,2,3,6-tetrahydropyridines. Redda et al. [1] describes Figure 7 beginning with 1-chloro-2,4-dinitrobenzene and substituted pyridines refluxed in acetone. Nucleophilic aromatic substitution takes place and a 2,4-dinitrophenyl-substituted pyridinium chloride is awarded. The substituted-pyridinium chloride salt then reacted with either a benzoyl/pyridyl carbonyl or sulfonyl hydrazide in the presence of methanol and excess triethylamine at room temperature. Reflux with a p-dioxane/water mixture (4:1) promoted hydrolysis and rendered pyridinium ylides. Reduction of the ylides using sodium borohydride generated its corresponding tetrahydropyridine products. Figure 8 began with a sulfonation reaction of mesitylenesulfonyl chloride and ethylacetohydroxymate in dimethyl formamide and triethylamine that gave ethyl-O-(mesitylenesulfonyl)-acetohydroxymate. Following hydrolysis of 26 using a p-dioxane/water (4:1) mixture in 70% perchloric acid, mesitylenesulfonyl hydroxymate (MSH) formed. MSH, the aminating agent, reacted with the substituted pyridines to produce N-amino-pyridinium mesitylenesulfonate. The pyridinium salt then underwent acylation with substituted acyl chlorides in tetrahydrofuran, followed by quenching using saturated sodium bicarbonate solution to generate the ylides. The reduction of the ylides using sodium borohydride yielded its corresponding tetrahydropyridine products.

Using these synthetic methods, a plethora of novel THP derivatives have been successfully synthesized and reported. Gangapuram and Redda gave an account for the synthesis of 1-(substituted phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamides [42] as potential anti-inflammatory agents, seen in Table 1.



29a-o

Compound	R	X	Yield%
a	3-pyridyl	CO	38.5
b	4-pyridyl	CO	50.4
c	phenyl	CO	53.1
d	4 methylbenzyl	CO	38.4
e	4-flurobenzyl	CO	43.3
f	4-chlorobenzyl	CO	48.6
g	3-bromobenzyl	CO	55.3
h	4-aminobenzyl	CO	34.4
i	phenyl	SO_2	42.3
j	4-methylbenzyl	SO_2	58.0
k	4-methoxybenzyl	SO_2	49.4
l	3,4,5-trimethoxybenzyl	CO	40.7
m	4-*tert*-butybenzyl	CO	30.8
n	2-thiophene	CO	38.4
o	2-furan	CO	48.2

Table 1: *Substituents of synthesized 1-(Substituted Phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamides with percent yields.*

Compounds **29a-k** were synthesized using **Figure 7** and compounds **29l-o** were synthesized using **Figure 8**.

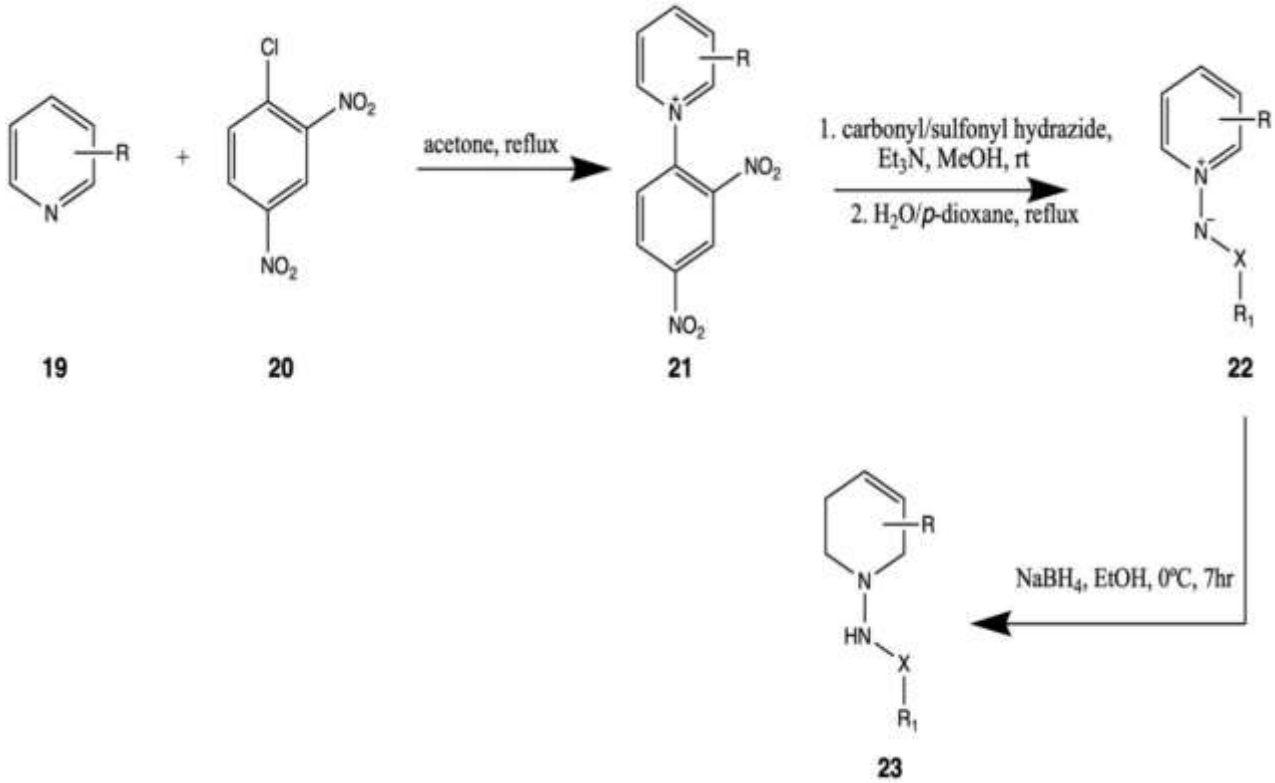


Figure 7: *Synthesis of carbonyl/sulfonylaminotetrahydropyridines using 1-chloro-2,4-dinitrobenzene. R= substituted pyridines R1: substituents of substituted carbonyl/sulfonyl hydrazides*

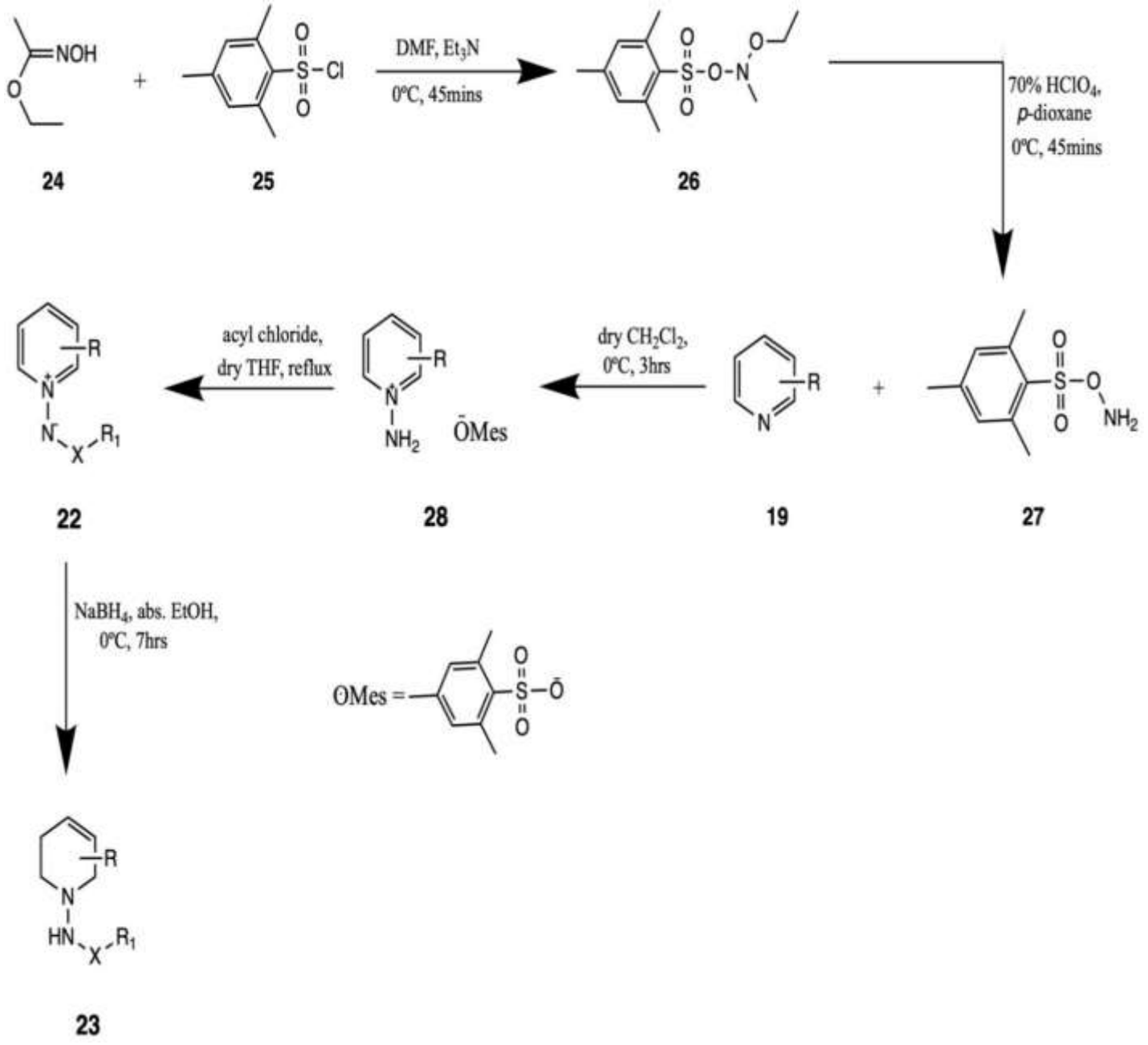


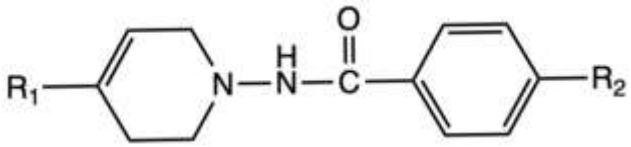
Figure 8: *Synthesis of carbonylaminotetrahydropyridines using a mesylate salt. R= substituted pyridines R1: substituents of substituted acyl chlorides*

Reprinted (adapted) with permission from Henderson, E. D., Gangapuram, M., Eyunni, S. K. V., Redda, K. K., & Wilson-Ardley, T. (2019). Design, Synthesis and Evaluation of Novel N-Substituted-[Benzoylamino]-5-Ethyl-1,2,3,6-Tetrahydropyridines as Potential Anti-Cancer Agents. Madridge Journal of Pharmaceutical Research, 3(1), 52–59. https://doi.org/10.18689/mjpr-1000109 ; Copyright: 2019 This work is licensed under a Creative Commons Attribution 4.0 International License.

N,N-Diethylnicotinamide was utilized as the substituted pyridine. Substituents from the substituted acyl chlorides are listed under the "R" group and the use of carbonyl/sulfonyl groups are listed as "X" within the table. These THP derivatives were successfully synthesized in low-to-moderate yields ranging 30.8-58.0%.

Later, Mochona and Redda successfully synthesized more novel N-benzoylamino-1,2,3,6-tetrahydropyridine derivatives [43] as potential anti-inflammatory agents, exhibited in Table 2. The THP derivatives

shown were synthesized using Figure 8. Substituents from the array of substituted pyridines and substituted acyl chlorides are listed in Table 2 as R1 and R2, respectively. The newly reported THP derivatives 30a-q were synthesized in moderate-to-good yields ranging 42-74%.

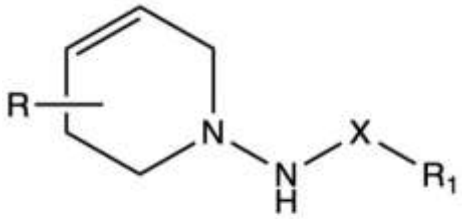


30a-q

Compound	R_1	R_2	Yield%
a	Ph	H	56
b	CH_2Ph	H	65
c	$CH(Ph)_2$	H	46
d	Ph-propyl	H	51
e	Et	H	56
f	*t*-Bu	H	72
g	H	Ph	58
h	H	*t*-Bu	62
i	H	*n*-Pr	54
j	H	*n*-Bu	46
k	H	C_4H_4* (naphtholyl-)	42
l	CH_2Ph	F	72
m	CH_2Ph	Cl	74
n	CH_2Ph	Me	68
o	CH_2Ph	Et	46
p	CH_2Ph	OMe	56
q	CH_2Ph	OEt	61

Table 2: *Substituents of synthesized N-Benzoylamino-1,2,3,6-tetrahydropyridine with percent yields.*

Similarly, Ghaffari et al. provided additional N-substituted carbonyl/sulfonylamino-1,2,3,6-tetrahydropyridines to include into the THP-derivative database [44]. Table 3 provides an outlook on those reported analogs. Figures 7 and 8 were utilized for the synthesis of these analogs. R1 specifies substituents from the substituted pyridines, R2 provides substituents from substituted acyl chlorides, and X gives carbonyl/sulfonyl addition. These THP analogs 23a-k were synthesized in fair-to-very good yields ranging from 25-83%.



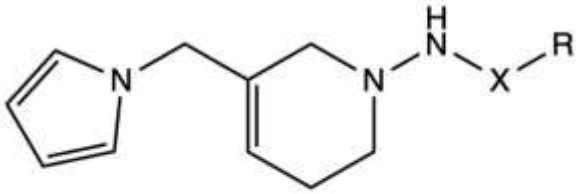
23a-k

Compound	R	R_1	X	Yield%
a	4-C_6H_5	C_6H_5	SO_2	30%
b	4-C_6H_5	2-Furyl	CO	83%
c	4-C_6H_5	2-Thiophenyl	CO	73%
d	4-C_6H_5	4-CH_3-C_6H_4	SO_2	48%
e	3-C_6H_5	4-CH_3-C_6H_4	SO_2	25%
f	3-C_6H_5	2-Furyl	CO	67%
g	3-C_6H_5	2-Thiophenyl	CO	54%
h	4-*tert*-butyl	2-Furyl	CO	80%
i	4-*tert*-butyl	2-Thiophenyl	CO	73%
j	5-ethyl	2-Furyl	CO	60%
k	5-ethyl	2-Thophenyl	CO	80%

Table3: *Substituents of synthesized N-Substituted Carbonylamino-1,2,3,6-Tetrahydropyridines with percent yields.*

Tetrahydropyridines Tested for Anti-inflammatory Properties

Twelve substituted N- [3-(1H- pyrrol-1-yl) methyl]-1,2,5,6-tetrahydropyridin-1-yl] benzamide/benzene sulfonamides were synthesized by Gangapuram et al. and evaluated for in vitro anti-inflammatory activity in murine BV-2 microglial cells. Structural modifications included a carbonyl or sulfonyl "X" group and an "R" group containing substituents with various degrees of electronic properties as seen in Table 4.



31a-l

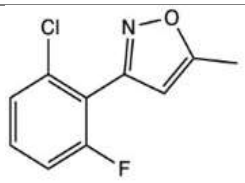
Compound	X	R	LPS-NO_2-IC_{50} (µM)	Yield%
Dexamethasone	--	--	<1.0	--
L-N6-(iminoethyl)lysine	--	--	3.16	--
a	SO_2	H	12.92	54.2%
b	SO_2	CH_3	14.64	58.5%
c	SO_2	OCH_3	19.43	65.5%
d	CO	H	>100	48.9%
e	CO	CH_3	>100	54.5%
f	CO	C_2H_5	>100	61.8%
g	CO	OCH_3	>100	57.6%
h	CO	C_4H_9	>100	56.3%
i	CO	F	>100	48.6%
j	CO	Cl	>100	52.8%
k	CO	Br	>100	60.8%
l	CO		>100	56.2%

Table 4: *Substituents and anti-inflammatory evaluations of synthesized substituted N- [3-(1H- Pyrrol-1-yl) methyl]-1,2,5,6-tetrahydropyridin-1-yl] benzamide/ benzene Sulfonamides*

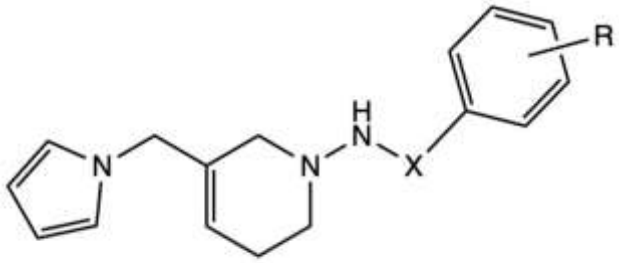
The THP derivatives were examined for nitric oxide inhibition in the lipopolysaccharide-treated microglial cells using dexamethasone and L-NIL (selective nitric oxide synthase inhibitor) as controls [45]. The most potent compound, 31a, was also assessed for interleukin (IL)-1α, IL-6, and IL-10 production and exhibited moderate anti-inflammatory activity.

Patent Submissions on Notable Tetrahydropyridines

Through diligent years of thorough research, intriguing information has been uncovered about tetrahydropyridine agents showing significant properties as anti-cancer agents. Therefore, a few patents have been published concerning novel THP compounds that have illustrated significant anticancer properties.

N-aminopyrrolylmethyltetrahydropyridines Tested for Anticancer Properties

In 2013, Florida A&M University Board of Trustees published a patent for N-aminopyrrolylmethyltetrahydropyridines means as anti-cancer agents. Redda and Gangapuram synthesized and investigated the anticancer properties of three N-aminopyrrolylmethyl-tetrahydropyridine compounds. They worked together making various modifications to the phenyl ring and a sulfonyl "X" group of their lead compound. The introduction of disparate functional groups possessing copious degrees of electronic properties led to the design of these three novel derivatives 32a-c. Following successful synthesis of these THP derivatives, they were then evaluated for their antiproliferative activity against cancer cells, specifically breast cancer cells. Antiproliferative studies were arranged against MCF-7 estrogen receptor-positive breast cancer cells, MDA-MB-231 estrogen receptor-negative breast cancer cells, and Ishikawa endometrial cancer cells. In turn, these compounds were found to be effective in inhibiting proliferative activity of the tested cancer cell lines. Cytotoxicity studies uncovered IC50 values significantly less than that of tamoxifen as seen in Table 5, warranting U.S. patent publication US8476303B2 [46].



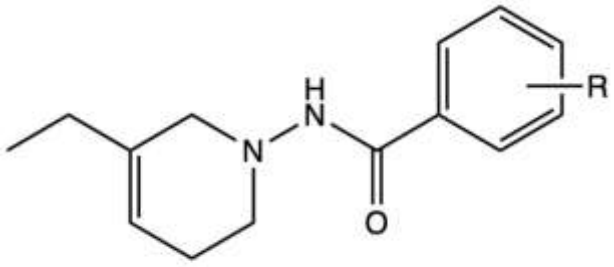
32a-c

	IC$_{50}$ µM					
Compound	**MCF-7**	**MDA-MB-231**	**Ishikawa**	**R**	**X**	**Yield %**
a	47.0	44.0	28.0	4-H	SO_2	43.9%
b	31.8	83.6	78.5	4-CH_3	SO_2	63.7%
c	49.0	53.0	53.0	4-OCH_3	SO_2	60%

Table5: *Substituents and antiproliferative data on synthesized N-Aminopyrrolylmethyltetrahydropyridines*

N-Substituted-(Benzoylamino)-5-Ethyl-1,2,3,6-Tetrahydropyridines Tested for Anticancer Properties

Henderson et al. synthesized four novel N-substituted-(benzoylamino)-5-ethyl-1,2,3,6-tetrahydropyridines which were also evaluated for their anticancer properties [47]. Structural modifications included a 5-ethyl substituent on the pyridine ring and electronically diverse substituents on the phenyl ring as seen in Table 6.



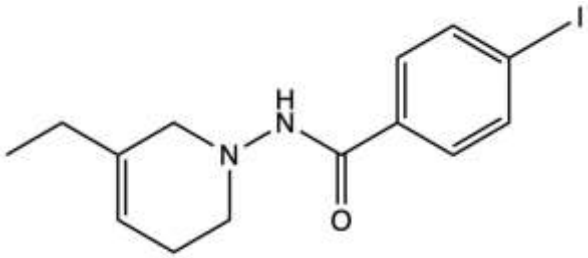
33a-d

Compound	IC$_{50}$ µM			R	Yield%
	ISHIKAWA	**MCF-7**	**MDA-MB-231**		
a	>100	81.86	>100	3,4-OCH_3	10%
b	71.88	67.19	>100	C_4H_4	20%
c	>100	82.91	>100	3,5-CF_3	36%
d	>100	>100	>100	3,5-CH_3	44%
Tamoxifen	29.89	26.97	29.40		
4-Hydroxytamoxifen	26.35	6.78	23.07		

Table 6: *Substituents and antiproliferative data on synthesized N-Substituted- [Benzoylamino]-5-Ethyl-1,2,3,6-Tetrahydropyridines*

These THP analogs were assessed for their antiproliferative properties against MCF-7 and MDA-MB-231 breast cancer cells and Ishikawa endometrial cancer cells. Studies disclosed some anticancer activity though no compound performed better than controls Tamoxifen and 4-Hydroxytamoxifen.

In continuation of this same study, Henderson et al. synthesized N-(4-iotobenzoylamino)-5-ethyl-1,2,3,6-tetrahydropyridine as a treatment for cancer. This compound was synthesized and evaluated for its anticancer properties. Structural modification included a 4-Iodo substitution on the phenyl ring as seen in Table 7.



33e

Compound	IC_{50} µM		
	ISHIKAWA	MCF-7	MDA-MB-231
33e	2.932	1.25	5.67
Tamoxifen	29.89	26.97	29.40
4-Hydroxytamoxifen	26.35	6.78	23.07

Table 7: *Substituent information and antiproliferative data on synthesized N-(4-iodobenzoylamino)-5-Ethyl-1,2,3,6-Tetrahydropyridine*

Cell viability studies were performed on this compound against the MCF-7 and MDA-MB-231 breast cancer cell lines and the Ishikawa endometrial cancer cell line to assess potential antiproliferative activity of the THP. Compound 33e displayed encouraging results as it performed better than tamoxifen and for hydroxy tamoxifen. Compound 33e produced IC50 values of 2.932, 1.25, and 5.97 for cell lines Ishikawa, MCF-7, and MDA-MB-231 respectively. Patent US20200101052A1 was published by Florida A&M University [48] in 2020.

Discussion

In short, a brief overview was given on chemical and pharmacological updates pertaining to the THP moiety. In the realm of organic chemistry, two synthetic methods have been established in our lab for the synthesis of substituted THP derivatives. One method involves the synthesis of THPs using 1-chloro-2,4-dinitrobenzene which can react with various substituted pyridines and thereafter, with substituted carbonyl or sulfonyl hydrazides. The alternative method affords THP derivatives by first synthesizing a mesylate salt to then undergo amination with substituted pyridines. These two synthetic schemes demonstrate facile approaches for THP synthesis.

Many studies have been performed over the years to increase the SAR data bank for substituted THP derivatives. THP derivatives have been synthesized and tested for potential biological activity as anti-inflammatory agents and anticancer agents. As anti-inflammatory agents, these studies have shown that THP derivatives may possess some level of anti-inflammatory properties. Other studies presented THP-containing compounds examined as anti-cancer agents. There appears to be great potential shown in this area as there has been patents filed on such THP derivatives showing their potential anti-proliferative properties compared to tamoxifen and 4-hydroxytamoxifen. In both areas of focus, the data supports the claim that biological properties may be dependent on the substitutions made on the THP ring system.

Future direction requires additional research to continue building and increasing the structural database of substituted THPs. Qualitative structure-activity relationship studies can be further utilized to discover how certain functional modifications correspond to pharmacological activity. Rational-backed structural modification will subsequently furnish more efficacious compounds with decreased toxicity and side effects.

Conclusion & Outlook

Tetrahydropyridines have become more present in the drug design stage of creating pharmacologically active molecules. THPs possess marking influence in rational-based drug discovery methods; they've radicalized both structural and ligand-based drug design strategies being that they exist as essential substituents of lead compounds and as focal structural bases for drug analogs. The presence of substituted THP moieties have been observed in numerous biologically active compounds and yet, the surface is barely scratched. Research studies convey the significance that substituents have on the THP ring system and how they affect the pharmacological characteristics of the THP-containing molecules. Many substituted THP derivatives exhibit biological activity including muscle relaxant, antibacterial, antifungal, sedative, anti-inflammatory, and anticancer. For this reason, further exploration is necessary to uncover the maximum benefits of utilizing THPs in drug discovery.

Throughout the stages of a typical inflammatory response, vascular inflammation occurs through the presence of stimulatory agents and pro-inflammatory mediators. An immune response transpires; endothelial cells recruit neutrophils and while blood cells to the injury site. Tissue damage is present and the body's macrophages and other local mediators work to restore damage done. Finally, tissue repair allows for new blood vessel formation wound healing, debris cleanup, and scar formation [49-50]. Dysregulation throughout any part of the process can lead to issues like excessive scarring or even chronic inflammation. Examination of how chronic inflammation is associated with cancer can help steer us to superior treatment options. Recent advances have been made in exploring THP derivatives as potential anti-inflammatory and anticancer agents. This review paper serves to record the advancements produced over decades of research.

Future and ongoing studies aim to focus on THP derivatives as potential anticancer agents. There are numerous routes that can be taken to accomplish this task but because THPs have been reported to possess anti-inflammatory properties and because there is a direct correlation between chronic inflammation and cancer, there exists the hypothesis that these THPs analogues may serve as potential anti-cancer agents via drug targeting within the inflammation pathway process. Drug targets are

being identified through research of the anti-inflammatory pathways as well as inflammation response mechanisms. Currently, the arachidonic acid pathway is under investigation for potential drug targets. Careful examination of the cyclooxygenase enzyme deems it a plausible drug target as literature has disclosed its role in the overproduction of harmful prostaglandin products overexpressed in both inflammation and cancer. Similarly, investigation of COX-2 has revealed its participation in tumorigenesis.

These recent discoveries are very practical for the development of powerful cancer treatment options but there is still more work to be done. The research studies presented thus far have mainly focused on breast cancer. However, this concept can be extended to other cancer types. Inflammation is not discriminatory against any specific type of cancer. In fact, inflammation is present in all different forms of cancer and so this research will benefit the advancement of therapeutic agents for the treatment of all cancers. Moreover, chronic proliferation is a rudimentary trait of cancer cells which highlights the importance of the antiproliferative studies performed. Additional studies on other biological properties of future THP derivatives can be accomplished to widen the potential therapeutic scope of the compounds. With many accessible angles left to explore, continued studies on THPs are essential to unearth their greatest potential.

Acknowledgements:

This research was also made possible by Grant Numbers U54CA233396, U54CA233444, & U54CA233465 from the National Institutes of Health (NIH), National Cancer Institute (NCI). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI. This research was also supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under the RCMI Award Number U54 MD007582. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of Interest:

The authors declare no economic interest or conflict of interest

Reference:

1. Mateeva, N. N., Winfield, L. L., & Redda, K. K. (2005). The Chemistry and Pharmacology of Tetrahydropyridines. *Current Medicinal Chemistry.* 22, 551-571.
2. Esatbeyoglu, T., Wagner, A. E., Schini-Kerth, V. B., & Rimbach, G. (2015). Betanin—A food colorant with biological activity. *Molecular Nutrition & Food Research*, *59*(1), 36–47.
3. Kesting, J. R., Tolderlund, I.-L., Pedersen, A. F., Witt, M., Jaroszewski, J. W., et al. (2009). Piperidine and Tetrahydropyridine Alkaloids from Lobelia siphilitica and Hippobroma longiflora. *Journal of Natural Products*, *72*(2), 312–315.
4. Lozano, G. L., Park, H. B., Bravo, J. I., Armstrong, E. A., Denu, J. M., et al. (2019). Bacterial Analogs of Plant Tetrahydropyridine Alkaloids Mediate Microbial Interactions in a Rhizosphere Model System. *Applied and Environmental Microbiology*, *85*(10), e03058-18.
5. Wilson, T., Onubogu, U., Kode, R., & Redda, K. (1998). *The Pharmalogical Evaluations of Some N-PyridylPhenylcarbonylaminoHydroxypropyl 1,2,3,6-Tetrahydropyridines as Potential Antiinflammtory Agents*.
6. Bharti, R., & Sharma, R. (2021). Natural acid catalyzed aqua mediated multicomponent synthesis of tetrahydropyridines and its antioxidant activities. *Materials Today: Proceedings*, *45*, 3186–3194.
7. Yankin, A. N., Nosova, N. V., Gein, V. L., & Tomilov, M. V. (2015). Multicomponent synthesis and antimicrobial activity of alkyl 4-arylamino-1,2,6-triaryl-1,2,5,6-tetrahydropyridine-3-carboxylates. *Russian Journal of General Chemistry*, *85*(4), 844–850.
8. Borman, S. (2006). Anticancer Natural Product Synthesized. *Chemical & Engineering News.* 84
9. Dai, L., Jacob, M. R., Khan, S. I., Khan, I. A., Clark, A. M., et al. (2011). Synthesis and Antifungal Activity of Natural Product-Based 6-Alkyl-2,3,4,5-tetrahydropyridines. *Journal of Natural Products*, *74*(9), 2023–2026.
10. Dudognon, Y., Rodriguez, J., Constantieux, T., Bugaut, X. (2018). Organocatalytic Enantioselective Synthesis of Tetrahydropyridines. *European Journal of Organic Chemistry*, 2018, 2432-2442.
11. He, X. J., & Nakayama, H. (2009). Neurogenesis in Neurotoxin-induced Animal Models for Parkinson's Disease—A Review of the Current Status. *Journal of Toxicologic Pathology*, *22*(2), 101–108.
12. Sian, J., Youdim, M. B. H., Riederer, P., & Gerlach, M. (1999). MPTP-Induced Parkinsonian Syndrome. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects. 6th Edition*.
13. Langston, J. W. (2017). The MPTP Story. *Journal of Parkinson's Disease*, *7*(Suppl 1), S11–S19.
14. Barber, D. M., Sanganee, H. J., & Dixon, D. J. (2012). One-Pot Catalytic Enantioselective Synthesis of Tetrahydropyridines via a Nitro-Mannich/Hydroamination Cascade. *Organic Letters*, *14*(20), 5290–5293.
15. Ramin, G.-V., & Hajar, S. (2013). Highly efficient one-pot synthesis of tetrahydropyridines. *Comptes Rendus Chimie*, *16*(11), 1047–1054.
16. Daraei, M., Zolfigol, M. A., Derakhshan-Panah, F., Shiri, M., Kruger, H. G., et al. (2015). Synthesis of tetrahydropyridines by one-pot multicomponent reaction using nano-sphere silica sulfuric acid. *Journal of the Iranian Chemical Society*, *12*(5), 855–861.
17. Balijapalli, U., Munusamy, S., Sundaramoorthy, K. N., & Iyer, S. K. (2014). Metal-Free, One-Pot, Rapid Synthesis of Tetrahydropyridines Using Acetic Acid as Solvent and Catalyst at Room Temperature. *Synthetic Communications*, *44*(7), 943–953.
18. Duttwyler, S., Lu, C., Rheingold, A. L., Bergman, R. G., & Ellman, J. A. (2012). Highly Diastereoselective Synthesis of Tetrahydropyridines by a C–H Activation–Cyclization–Reduction Cascade. *Journal of the American Chemical Society*, *134*(9), 4064–4067.
19. Wang, Z., Xu, H., Su, Q., Hu, P., Shao, P.-L., et al. (2017). Enantioselective Synthesis of Tetrahydropyridines/Piperidines via Stepwise [4 + 2]/[2 + 2] Cyclizations. *Organic Letters*, *19*(12), 3111–3114.
20. Yan, F., Liang, H., Song, J., Cui, J., Liu, Q., et al. (2017). Palladium-Catalyzed Cyclization-Heck Reaction of Allenamides: An Approach to 3-Methylene-5-phenyl-1,2,3,4-tetrahydropyridine Derivatives. *Organic Letters*, *19*(1), 86–89.
21. Vardanyan, R. S., & Hruby, V. J. (2006). 6 - Antipsychotics (Neuroleptics). In R. S. Vardanyan & V. J. Hruby (Eds.), *Synthesis of Essential Drugs* (pp. 83–101). Elsevier.
22. Vardanyan, R. (2017). *Piperidine-Based Drug Discovery.* Chapter 7 - Piperidine-Based Nonfused Biheterocycles With C–N and C–C Coupling. Elsevier.
23. Lawung, R., Prachayasittikul, S., Prachayasittikul, V., Ruchirawat, S., & Worachartcheewan, A. (2009). Activities of thiotetrahydropyridines as antioxidant and antimicrobial agents. *EXCLI Journal ; Vol. 8*, 2009.
24. Vianna, J. S., Ramis, I. B., Bierhals, D., von Groll, A., Ramos, D. F., et al. (2019). Tetrahydropyridine derivative as efflux inhibitor

in Mycobacterium abscessus. *Journal of Global Antimicrobial Resistance*, *17*, 296–299.
25. Choi, S.-H., Im, W.-B., Choi, S.-H., Cho, C.-H., Moon, H.-S., et al. (2018). *Tetrahydropyridine Derivatives and Their Use as Antibacterial Agents*.
26. Gregory, R. K., & Smith, I. E. (2000). Vinorelbine--a clinical review. *British Journal of Cancer*, *82*(12), 1907–1913.
27. Gong, J., Cho, M., Gupta, R., Synold, T. W., Frankel, P., et al. (2019). A Pilot Study of Vinorelbine Safety and Pharmacokinetics in Patients with Varying Degrees of Liver Dysfunction. *The Oncologist*, *24*(8), 1137–1145.
28. Yoon, K., Wilson, T., Williams, S., & Redda, K. (2000). Synthesis and pharmacological evaluations of N-(substituted benzoylamino)-5-carbethoxymethyl-1,2,3,6-tetrahydropyridines as potential antiinflammatory agents. *Drugs Under Experimental and Clinical Research*, *26*(3), 73–82.
29. Yoon, K. J. P., Kode, B., Bowen, L., & Redda, K. K. (2001). Synthesis of N-(substituted phenylcarbonylamino)-4-ethyl-1,2,3,6-tetrahydropyridines as potential nonsteroidal anti-inflammatory agents. *Journal of Heterocyclic Chemistry*, *38*(1), 69–76.
30. Deskus, J. A., Epperson, J. R., Sloan, C. P., Cipollina, J. A., Dextraze, P., et al. (2007). Conformationally restricted homotryptamines 3. Indole tetrahydropyridines and cyclohexenylamines as selective serotonin reuptake inhibitors. *Bioorganic & Medicinal Chemistry Letters*, *17*(11), 3099–3104.
31. Brahmachari, G., Choo, C., Ambure, P., & Roy, K. (2015). In vitro evaluation and in silico screening of synthetic acetylcholinesterase inhibitors bearing functionalized piperidine pharmacophores. *Bioorganic & Medicinal Chemistry*, *23*(15), 4567–4575.
32. Mohammadi, A. A., Taheri, S., Amouzegar, A., Ahdenov, R., Halvagar, M. R., & Sadr, A. S. (2017). Diastereoselective synthesis and molecular docking studies of novel fused tetrahydropyridine derivatives as new inhibitors of HIV protease. *Journal of Molecular Structure*, *1139*, 166–174.
33. Mohsin, N.-A., & Ahmad, M. (2018). Tetrahydropyridine: a promising heterocycle for pharmacologically active molecules. *TURKISH JOURNAL OF CHEMISTRY*, *42*(5), 1191–1216.
34. Nakao, A., Ohkawa, N., Nagasaki, T., Kagari, T., Doi, H., et al. (2009). Tetrahydropyridine derivatives with inhibitory activity on the production of proinflammatory cytokines: Part 1. *Bioorganic & Medicinal Chemistry Letters*, *19*(16), 4607–4610.
35. Ravindernath, A., & Reddy, M. S. (2017). Synthesis and evaluation of anti-inflammatory, antioxidant and antimicrobial activities of densely functionalized novel benzo [d] imidazolyl tetrahydropyridine carboxylates. *Arabian Journal of Chemistry*, *10*, S1172–S1179.
36. Chowdhury, M. A., Abdellatif, K. R. A., Dong, Y., & Knaus, E. E. (2008). Synthesis of new 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2H-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines: A search for novel nitric oxide donor anti-inflammatory agents. *Bioorganic & Medicinal Chemistry*, *16*(19), 8882–8888.
37. Sears, J. E., & Boger, D. L. (2015). Total Synthesis of Vinblastine, Related Natural Products, and Key Analogues and Development of Inspired Methodology Suitable for the Systematic Study of Their Structure–Function Properties. *Accounts of Chemical Research*, *48*(3), 653–662.
38. Silvestri, R. (2013). New Prospects for Vinblastine Analogues as Anticancer Agents. *Journal of Medicinal Chemistry*, *56*(3), 625–627.
39. Kurtanović, N., Tomašević, N., Matić, S., Mitrović, M. M., Kostić, D. A., et al. (2022). Human estrogen receptor α antagonists, part 2: Synthesis driven by rational design, in vitro antiproliferative, and in vivo anticancer evaluation of innovative coumarin-related antiestrogens as breast cancer suppressants. *European Journal of Medicinal Chemistry*, *227*, 113869.
40. Jayashree, B. S., Patel, H. H., Mathew, N. S., & Nayak, Y. (2016). Synthesis of newer piperidinyl chalcones and their anticancer activity in human cancer cell lines. *Research on Chemical Intermediates*, *42*(4), 3673–3688.
41. León, L. G., Carballo, R. M., Vega-Hernández, M. C., Martín, V. S., Padrón, J. I., et al. (2007). Antiproliferative activity of 2-alkyl-4-halopiperidines and 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines in solid tumor cell lines. *Bioorganic & Medicinal Chemistry Letters*, *17*(10), 2681–2684.
42. Gangapuram, M., & Redda, K. K. (2006). Synthesis of 1-(Substituted Phenylcarbonyl/sulfonylamino)-1,2,3,6-tetrahydropyridine-5-carboxylic acid diethylamides as Potential Anti-inflammatory Agents. *Journal of Heterocyclic Chemistry*, *43*(3), 709–718.
43. Mochona, B., & Redda, K. K. (2007). Synthesis of N-benzoylamino-1,2,3,6-tetrahydropyridine derivatives as potential anti-inflammatory agents. *Journal of Heterocyclic Chemistry*, *44*(6), 1383–1387.
44. Ghaffari, M. A., Ardley, T. W., Gangapuram, M., & Redda, K. K. (2011). Synthesis of n-substituted carbonylamino-1,2,3,6-tetrahydropyridines as potential anti-inflammatory agents. *Synthetic Communications*, *41*(7), 2615–2623.
45. Gangapuram, M., Mazzio, E., Eyunni, S., Soliman, K. F. A., & Redda, K. K. (2014). Synthesis and Biological Evaluation of Substituted N-[3-(1H-Pyrrol-1-yl)methyl]-1,2,5,6-tetrahydropyridin-1-yl]benzamide/benzene Sulfonamides as Anti-Inflammatory Agents. *Archiv Der Pharmazie*, *347*(5), 360–369.
46. Redda, K. K., & Gangapuram, M. (2013). *N-Aminopyrrolylmethyltetrahydropyridines as Anti-Cancer Agents* (Patent No. US 8,476,303B2).
47. Henderson, E. D., Gangapuram, M., Eyunni, S. K. V., Redda, K. K., & Wilson-Ardley, T. (2019). Design, Synthesis and Evaluation of Novel N-Substituted-[Benzoylamino]-5-Ethyl-1,2,3,6-Tetrahydropyridines as Potential Anti-Cancer Agents. *Madridge Journal of Pharmaceutical Research*, *3*(1), 52–59.
48. Henderson, E., Ardley, T. W., Redda, K. K., & Gangapuram, M. (2020). *USE OF N-(4-IODOBENZOYLAMINO)-5-ETHYL-1,2,3,6-TETRAHYDROPYRIDINE AS A TREATMENT FOR CANCER* (Patent No. US 10,646,479 B2).
49. Aller, M.-A., Arias, J.-L., & Arias, J. (2004). Inflammatory response phases and their hypothetical trophic meaning. *European Respiratory Journal*, *23*(2), 353–354.
50. Aller, M.A., Arias, J.L., Lorente, L., Nava, M.P., Duran, H.J., et al. (2001). Neuro-immune-endocrine functional system and vascular pathology. *Medical Hypotheses.* 57(5), 561-569.

DOI: 10.31579/2690-8794/135