Biological Forum – An International Journal **15(5a): 674-680(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Synthesis and Pharmacological Activities of Ligustrazine Derivatives: A Review

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(Received: 01 April 2023; Revised: 21 April 2023; Accepted: 06 May 2023; Published: 15 May 2023)
(Published by Research Trend)

ABSTRACT: Ligustrazine, a bioactive alkaloid extracted from Chinese herb Ligusticum chuanxiong Hort, has garnered substantial consideration in recent days because of its diverse pharmacological activities besides therapeutic potential. Developing ligustrazine derivatives can be challenging due to several factors, and there are associated challenges in the synthesis and evaluation of their pharmacological activities. This paper focuses on the synthesis, pharmacological properties, as well as therapeutic applications of ligustrazine derivatives, targeting to deliver a widespread overview of current research in this field. In conclusion, this paper consolidates current knowledge on ligustrazine derivatives, offering valuable insights into their synthesis, pharmacological activities, and therapeutic applications. The exploration of ligustrazine derivatives holds great promise for the development of innovative pharmaceuticals with enhanced therapeutic efficacy and a broader range of clinical applications.

Keywords: Ligustrazine, tetramethylpyrazine, alkylpyrazine, pharmacological activities.

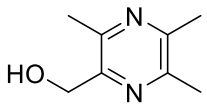
INTRODUCTION

Ligustrazine, which is also referred to as tetramethylpyrazine, is an alkylpyrazine that is isolated from Chuan Xiong, which is a dry rhizome of Chinese herb Ligusticum wallichii. This herb is extensively utilized in China for treatment of vascular illnesses such as stenocardia, coronary heart disease, and cerebral thrombosis.

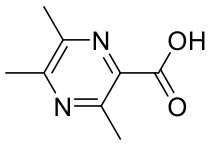
Treatment of cardiovascular and cerebrovascular disorders (CVDs) is accomplished by the utilization of its highly effective antioxidative properties (Holaso *et al.*, 2014; Rasoul *et al.*, 2014). Ligustrazine, also recognized as tetramethylpyrazine or TMP, is a kind of alkaloid. It is the primary component of chuanxiong.

Many researchers have revealed various pharmacological activities of ligustrazine, like anti-cardiovascular (Zesong *et al.*, 2004), anti-platelet (Zhang *et al.*, 2012), ischemic stroke (Li *et al.*, 2011), anti-Alzheimer's (Wu *et al.*, 2013), neuro-protective effects (Cheng *et al.*, 2007) and anti-cancer (Zou *et al.*, 2018). Since the 1980s, ligandrazine has been utilized extensively for vasodilation. (Liu *et al.*, 1990; Peng *et al.*, 1996).

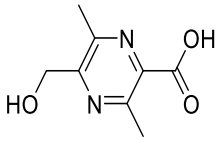
According to a number of researchers, ligustrazine possesses exceptional pharmacokinetic properties, including quick absorption, widespread dispersion, and the absence of any accumulated harmful effect. (Zeng *et al.*, 2013). A thorough examination of the urine of rats, rabbits, and humans revealed the presence of a great number of ligustrazine metabolites. (Cheng *et al.*, 2005). These metabolites include the following:



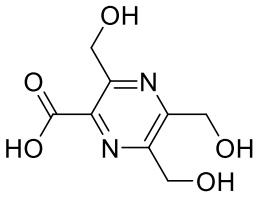
(3,5,6-trimethylpyrazin-2-yl)methanol



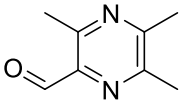
3,5,6-trimethylpyrazine-2-carboxylic acid



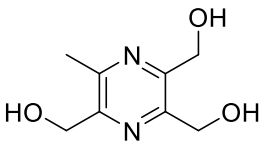
5-(hydroxymethyl)-3,6-dimethylpyrazine-2-carboxylic acid



3,5,6-tris(hydroxymethyl)pyrazine-2-carboxylic acid



3,5,6-trimethylpyrazine-2-carbaldehyde



2,3,5-trihydroxymethyl-6-methylpyrazine

There are a variety of metabolic products that have pharmacological effects that are comparable to or even superior to those of ligustrazine. For example, (3,5,6-trimethylpyrazin-2-yl)methanol has the ability to increase the clotting time from 1.63 minutes to 1.82 minutes (Chen *et al.,* 1998).

In its capacity as an antioxidant, ligustrazine has the ability to control the formation of oxidative stress and reactive oxygen species (ROS) (Jiang *et al.,* 2011; Xu *et al.,* 2015). ROS are a sort of free radicals that contain oxygen and have a high level of reactivity as compared to molecular oxygen in its ground state. ROS are characterized by the presence of unpaired electrons (Poprac *et al.,* 2017; Meyer and Barton, 2018). Redox regulation is the term utilizsed to describe regulatory systems, which are accountable for retaining equilibrium of ROS in healthy organisms (Valko *et al.,* 2007). One of the most common features of malignant cells is the presence of ROS, which is referred to as oxidative stress (Gorrini *et al.,* 2013; Valluru *et al.,* 2014). Increased oxidative stress has the potential to alter proteins, which in turn may lead to the development of Alzheimer's disease (Kell, 2010). In addition, ROS have arisen as an imperative instrument in the cardiovascular system for illness and redox signaling (Chen and Zweier, 2014). ROS plays a significant part in the growth of bacteria (Huang *et al.,* 2011) and excessive quantities of ROS may trigger inflammation (Esser *et al.,* 2012; Di *et al.,* 2012). On the basis of their pharmacological properties, the following list of ligustrazine compounds, which have the potential to treat the disorders described above, is presented.

USES IN CARDIOVASCULAR DISORDERS

It has been predicted that the incidence of heart failure would upsurge by 46% between the years 2012 and 2030, and it is expected that roughly 23.6 million individuals will pass away as a result of cardiovascular diseases in the year 2030. These diseases include such conditions as ischemic heart disease and stroke. (Mozaffarian *et al*., 2016; Sanganalmath and Bolli 2013). The most common cause of cardiovascular diseases is assumed to be atherothrombosis (Viles-Gonzalez *et al*., 2016; Yamagishi and Matsui 2010). The development of atherothrombosis is mostly influenced by the damage that occurs to endothelial cells as well as the aggregation of platelets (Zou *et al*., 2018). Additionally, ligustrazine has been shown to have effects on antifibrosis, calcium antagonists, antioxidation, and antiplatelet aggregation. Previous studies have demonstrated that it has the ability to improve microcirculation, enlarge narrow arteries, and remove blood stasis (Liu *et al*., 1990; Peng *et al*., 1996). Numerous molecular alterations of ligustrazine have been designed in order to treat cardiovascular diseases like myocardial infarction and angina. Some examples of these modifications include l ligustrazine-acylguanidine derivatives, ligustrazine-cinnamic acid derivatives, ligustrazine-piperazine derivatives, ligustrazine-amides derivatives, and ligustrazine-stilbene derivatives, among others.

Anticancer activity. Research conducted by Wang *et al*. (2010) demonstrated that ligustrazine, which is a calcium channel blocker, has the ability to boost chemosensitivity effects of drugs on human hepatocellular carcinoma BEL-7402 cells. In addition, it acts as a multidrug resistance (MDR) modulator at the same time. On the other hand, the activity of ligustrazine on tumor cells is not even close to being satisfactory. Some ligustrazine hybrids were discovered through the use of the NP hybridization technique. These hybrids include ligustrazine derivatives with curcumin, ligustrazine derivatives with terpenes, ligustrazine derivatives with cyclohexanone oxime, and many others.

Neuroprotective activity. Ligustrazine has been shown to have powerful neuroprotective effects, according to recent research (Li *et al*., 2000; Ma *et al*., 2009). As a means of further enhancing neuroprotective properties of ligustrazine, a number of novel ligustrazine derivatives, including ligustrazine-chlorooxime derivatives, ligustrazine-benzoic acid derivatives, ligustrazine-phenols derivatives, ligustrazine-nitrone derivatives, ligustrazine-vanillic acid derivatives, ligustrazine-phenolic acid derivatives, and others, were developed in accordance with combination principle in medicinal chemistry.

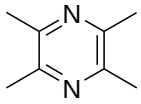
Antibacterial activity. Ligustrazine was reportedly used as an antibacterial agent in ancient China, according to research conducted by Noskin *et al*. (1999). Several ligustrazine derivatives, such as ligustrazine-oxazolidinone compounds, have been developed to research and develop novel antibacterial agents.

Linezolid is initial oxazolidinone antibacterial agent, and it has shown encouraging results in the management of numerous infections triggered by gram +ve bacteria that are resistant to multiple drugs. Oxazolidinones are a novel class of antibacterial agents. Linezolid is 1st product of this class. In latest years, a number of different structural modifications of linezolid have been carried out. Compounds that have been obtained for these alterations have demonstrated an expansion of the antibacterial spectrum and a reestablishment of sensitivity (Barbachyn and Ford 2003; Skripkin *et al*., 2008; Das *et al*., 2009). This resulted in the development and synthesis of a number of new oxazolidinone molecules (Chen *et al*., 2015). According to Pyta *et al*. (2014), the majority of the chemical exhibited powerful antibacterial activity that was comparable to that of ciprofloxacin.

Anti-inflammatory activity. It has been reported that certain ligustrazine derivatives, such as ligustrazine-rhein ether compounds, exhibit anti-inflammatory properties.

In Li *et al*. (2011) produced ligustrazine-rhein ether compounds and tested their anti-inflammatory action in mice ear edema models (Zou *et al*., 2018). It was found

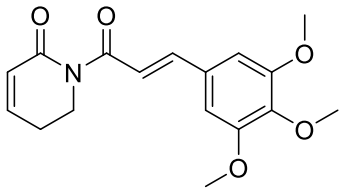
that the derivatives were effective in reducing inflammation.



Ligustrazine (Tetramethylpyrazine)

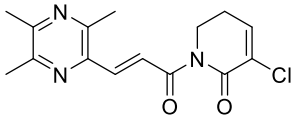
Piperlogumine and their activities

Piperlongumine, 5,6-dihydropiperlongumine, or piplartine((2E)-1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl) is the chemical formula 2(1H)-pyridinone is a physiologically active alkaloid/amide that is derived from peppers, namely from long pepper (Piper longum L.– Piperaceae). In Ayurvedic medicine, which is utilized to treat a broad variety of disorders, including tumors, long pepper is one of the elements that is utilized the most frequently. Among the pharmacological activities that have been reported for piplartine are the following: cytotoxic, genotoxic, anxiolytic, antiangiogenic, antitumor, antiplatelet aggregation, antinociceptive, antimetastatic, antidepressant, anti-atherosclerotic, antidiabetic, antibacterial, leishmanicidal, antifungal, schistosomicidal, and trypanocidal activities. Out of many pharmacological properties that piplartine possesses, the anticancer capability that it possesses is the most promising possibility. Thus, substantial researches has been conducted to study preclinical anticancer potential of piplartine. This substance is selectively cytotoxic against tumor cells through the initiation of oxidative stress; it also promotes genotoxicity; it serves as an alternate method for killing cancer cells; it has high oral bioavailability in mice; it suppresses growth of tumor in mice; and it exhibits solitary a moderate level of systemic toxicity (Bezerra *et al*., 2013).



Piperlogumine. Hybrids of Tetramethyl pyrazines with Piperlongumines

Piperlongumine (PiL) 1 raises the amount of ROS and, ideally, promotes death of malignant cells by activating a variety of distinct pathways. In addition to having a pyrazine structure that is water-soluble, ligandrazine has the ability to inhibit proliferation as well as spread of malignant cells. Aqueous solubility of compound 1 was fourteen times higher than that of the parent chemical, and it stimulated the production of ROS in colorectal cancer HCT-116 cells. In addition, the HCT-116 cells were inhibited in their proliferation, migration, invasion, and heteroadhesion by the compound 1. *In vivo* treatment with 1 has been shown to hinder growth of tumors and the spread of lung metastases, as well as to prolong survival time of tumor-bearing animals. Furthermore, the compound 1 significantly reduced the epithelial-mesenchymal transition and Wnt/β-catenin activation that was triggered by TGF-β1 in HCT-116 cells. This was achieved by decreasing the phosphorylation of Akt and GSK-3β. 1 exhibited substantial antiproliferation and antimetastasis properties when taken as a whole (Zou *et al*., 2018).



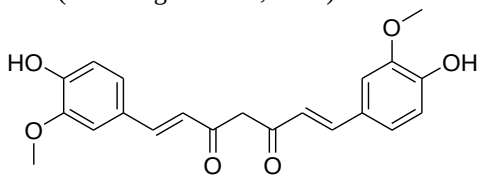
(E)-3-chloro-1-(3-(3,5,6-trimethylpyrazin-2-yl)acryloyl)-5,6-dihydropyridin-2(1H)-one

1

Curcumin

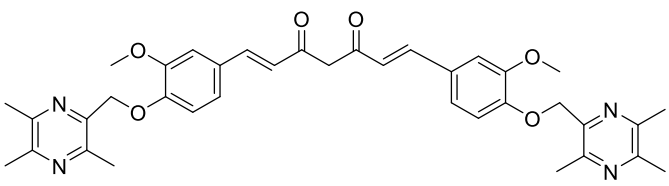
Curcumins and their activities

A polyphenolic chemical called curcumin, which is derived from the plant known as turmeric (Curcuma longa), is one of these agents which has been subject of intense research over past three to four decades because of the possibility that it can hinder growth of malignant cells (Shanmugam *et al*., 2015).



Hybrids of Tetramethyl pyrazines with Curcumins

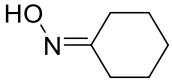
Conjugation of anti-tumor bioactive chemicals through ether or ester bonds lead to synthesis of a series of ligustrazine-curcumin derivatives. This was accomplished because of the similar antioxidant activity of the two compounds (Wang *et al*., 2012). Compound 2 demonstrated a minimal level of toxicity in vivo and was able to suppress proliferation of all cancer cells that were examined.



(1E,6E)-1,7-bis(3-methoxy-4-((3,5,6-trimethylpyrazin-2-yl)methoxy)phenyl)hepta-1,6-diene-3,5-dione

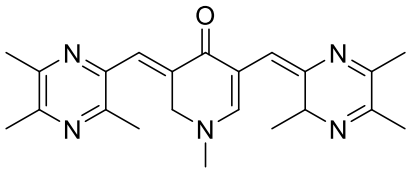
2

Cyclohexanone Oximes



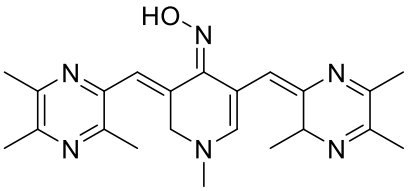
Cyclohexanone oxime

The anticancer activity of a wide variety of structurally connected α, β-unsaturated carbonyl-based compounds, including cyclohexanone, tetralone, and their oxime analogs, was demonstrated against certain tumor cell lines (Qin *et al*., 2015 and Qin *et al*., 2016). Subsequent research involves the synthesis of 34 novel ligustrazine-containing α, β-unsaturated carbonyl-based compounds as well as oximes. The goal of this research is to develop innovative multi-target medications that can be prescribed for the treatment of cancer. Compound 3b was found to be most effective anti-proliferative agent against all cancer cells, according to findings of cell viability experiments conducted on various cell lines. Compounds that possess ligustrazine moiety on both sides of linker were discovered to be effective inhibitors of EGFR. In particular, IC_{50} values for compound 3a were found to be 40 ± 20 µM, whereas compound 3b had an IC_{50} value of 20 ± 10 µM. Multidrug-resistant receptor (MDR) modulators and powerful anticancer drugs are two more applications for molecules that possess dual characteristics.



(E)-1-methyl-5-((E)-(3,5,6-trimethylpyrazin-2(3H)-ylidene)methyl)-3-((3,5,6-trimethylpyrazin-2-yl)methylene)-2,3-dihydropyridin-4(1H)-one

30 a

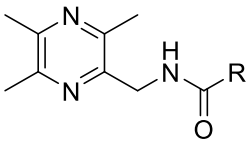


(4E,5E)-1-methyl-5-((E)-(3,5,6-trimethylpyrazin-2(3H)-ylidene)methyl)-3-((3,5,6-trimethylpyrazin-2-yl)methylene)-2,3-dihydropyridin-4(1H)-one oxime

30 b

Tetramethyl pyrazine amide derivatives

In order to improve metabolic stability, a series of innovative ligustrazine-amides were designed and synthesized. This was done since amides have a better metabolic stability than esters (Li *et al*., 2014). When it came to encouraging replication of wounded human umbilical vascular endothelial cells (HUVECs) that had been harmed by H_2O_2, the results of their protective effect on injured vascular endothelial cells indicated that certain compounds possessed extra potent activity as compared to ligustrazine. When it comes to the active compounds, compounds 4a, 4b, and 4c demonstrated the maximum potency, with EC_{50} values of 37, 70, and 55 µM, correspondingly.



Compound	R
4a	4-pyridinyl
4b	benzenemethanol, 1-acetate, α-methyl
4c	benzenemethanol, α-methyl

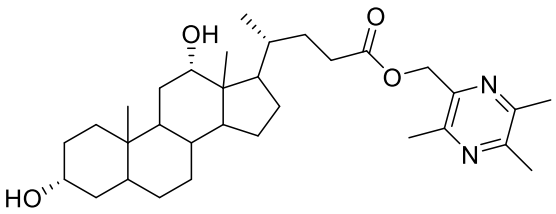
Ligustrazine terpene derivatives. Terpenoids and their derivatives were found to possess substantial selective cytotoxicity on human cancer cells, according to findings of a number of research (Schwarz *et al*., 2014). Compound 5 was one of the unique ligustrazine-triterpenes derivatives that was created as well as synthesized through the combination of bioactive ligustrazine and terpenes as anti-tumor agents (Wang *et al*., 2012). Compound 5 has shown good anticancer activity.

Furthermore, it is worth noting that the chemical 6a, which was synthesized by Xu and colleagues, had superior cytotoxic action (IC_{50} < 5.23 µM) against MCF-7, HT-29, Bel-7402, HepG2, and Hela in comparison to conventional antitumor medication cisplatin (DDP) (Xu with colleagues, 2015). In terms of selectivity for MDCK cells, the majority of the variants demonstrated superior performance. The inhibition rate of 6a against MDCK was around 26.50% when it was present at a dose of 10 µM. On other hand, the inhibition rate against human hepatoma cell HepG2 was increased to 99.87% when it was present at the same concentration.

In 2017, Xu *et al*., developed and synthesized a variety of amino acids as well as dipeptide derivatives (Xu *et al*., 2017). This was done in response to a publication that reported that addition of amino acid to betulinic acid could improve selective cytotoxicity. When compared to the positive medication cisplatin (DDP), 6b shown the highest cytotoxic activity on tumor cell lines (mean IC_{50} = 2.31 ± 0.78 mM). Conversely, it

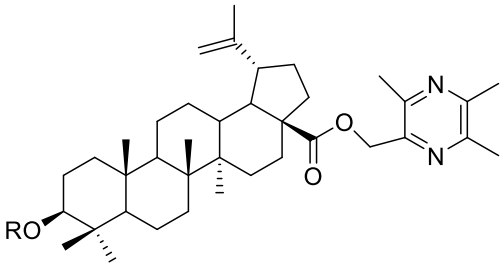
demonstrated reduced cytotoxicity on MDCK cell line compared to DDP. Additionally, 6b was found to have higher cytotoxic activity on cancer cell lines.

A novel anticancer lead molecule 7 was developed by conjugating efficient antitumor components oleanolic acid (OA) and ligustrazine together (Xu *et al*., 2014; Hou *et al*., 2015). This created a compound which was able to hinder tumor cell growth. According to Chu *et al*. (2014), many amino acids were chosen for the purpose of conjugation to the 3-hydroxy moiety of 7 through the creation of ester bonds. This was done in order to enhance the hydrophilicity and bioactivity of 7. Among the compounds that were produced, compounds 7a and 7b demonstrated much higher cytotoxicity (IC50 < 3.5 µM). It is possible that the activity could be enhanced by increasing amount of amino groups. As an example, compound 7b, which consists of two amino groups, exhibited a high level of cytotoxicity (IC_{50} < 2.5 µM) on MDCK cells as well as tumor cells.

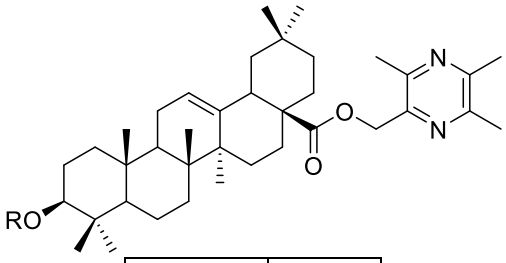


(R)-(3,5,6-trimethylpyrazin-2-yl)methyl 4-((3R,12S)-3,12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate

5



Compound	R
6a	H
6b	L-Ala-L-Sar



Compound	R
7	H
7a	Gly-H
7b	L-Lys-H

CONCLUSIONS

The use of natural ingredients is crucial to the drug discovery process. Among these natural products, ligustrazine has been utilized extensively in clinical settings because of the fact that it possesses an extensive range of high-potency antioxidant action and is hypotoxic. As the mechanism of action has been gradually recognized, ligustrazine has evolved into a topical chemical in the study that is currently being conducted.

FUTURE SCOPE

Nevertheless, because of multi-target nature of ligustrazine, the majority of ligustrazine derivatives do not possess any unique drug adaptation. This is a significant obstacle in the process of developing ligustrazine-derived drugs from the laboratory to clinical application stage. Furthermore, because ligustrazine compounds do not have a specific target, CADD as well as other methodologies have a significant challenge in terms of widespread application.

For the purpose of conducting additional research, it has been demonstrated that it is effective to be used in combination with various anticancer groups, neuroprotective groups or antioxidant activity groups, with ligustrazine in order to obtain compounds that are more powerful. Furthermore, cytotoxicity of ligustrazine derivatives is typically lesser as compared to discrete molecule. In order to achieve the goal of achieving one plus one is larger than two results, it is recommended that natural-product hybridization, pharmacophore combination, as well as a drug design strategy based on structure should be utilized extensively in the process of building new skeleton ligustrazine derivatives. This offers a shortcut to get the desired outcome. There is also the possibility of employing the prodrug method in order to extend half-time of ligustrazine derivatives. We have high hopes that ligustrazine derivatives will be able to offer fresh perspectives on the process of generating novel medications.

Acknowledgement. The authors are grateful to the Principal Prof. Anna Pratima Nikalje and Wilson College management for providing research laboratory facilities. We express a deep sense of gratitude to Dr. Abhijeet Kadam Department of Chemistry, John Wilson Education Society's, Wilson College (Autonomous), Mumbai, 400007, Maharashtra, India, for his assistance and providing the valuable suggestions and support.

Conflict of Interest. None.

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How to cite this article: Pravin Thombare, Anna Pratima Nikalje and Harichandra A. Parbat (2023). Synthesis and Pharmacological Activities of Ligustrazine Derivatives: A Review. *Biological Forum – An International Journal*, *15*(10): 674-680.