

Rowan University

Rowan Digital Works

Theses and Dissertations

2-9-2018

Semi-synthesis of a novel library of alkaloids as potential selective analgesics

Brittany M. Gallagher
Rowan University

Follow this and additional works at: <https://rdw.rowan.edu/etd>



Part of the [Chemistry Commons](#), and the [Pharmacy and Pharmaceutical Sciences Commons](#)

Recommended Citation

Gallagher, Brittany M., "Semi-synthesis of a novel library of alkaloids as potential selective analgesics" (2018). *Theses and Dissertations*. 2517.
<https://rdw.rowan.edu/etd/2517>

This Thesis is brought to you for free and open access by Rowan Digital Works. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Rowan Digital Works. For more information, please contact graduateresearch@rowan.edu.

**SEMI-SYNTHESIS OF A NOVEL LIBRARY OF ALKALOIDS AS POTENTIAL
SELECTIVE ANALGESICS**

by

Brittany M. Gallagher

A Thesis

Submitted to the
Department of Chemistry and Biochemistry
College of Science and Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
November 30, 2017

Thesis Chair: Gustavo Moura-letts, Ph.D.

© 2017 Brittany M. Gallagher

Dedication

To my parents,

I would like to dedicate this manuscript to my father, William E. Gallagher and my mother, Rosalie Gallagher. They have provided me with tremendous amounts of encouragement at every point throughout my college career. They would never allow me to give up; I would not have completed this program without their endless love and support.

Acknowledgement

To my mentor,

I would like to express my appreciation to my professor, Dr. Gustavo Moura-letts, for pushing me to be the best I could be in this field of study. During my four years in his research laboratory I have learned so much about the field of Organic Chemistry and have also learned a lot about myself in the process. Thank you so much for taking me under your wing and getting me to the point I am at today, this would have been possible without you.

Abstract

Brittany M. Gallagher
SEMI-SYNTHESIS OF A NOVEL LIBRARY OF ALKALOIDS AS POTENTIAL
SELECTIVE ANALGESICS
2017-2018
Gustavo Moura-letts, Ph.D.
Master of Science in Pharmaceutical Sciences

Semi-synthetic compounds are an important part of the therapeutic drug discovery process. The goals of the project were to synthesize different generations of matrine analogues in order to gain many opportunities to manipulate the core structure. The long-term goal was, by manipulating the structure, the possibility to increase the biological activity of the original compound while also decreasing the toxicity. The first-generation matrine analogue allows for a synthesis similar to the Striker reaction producing aminonitriles. An alkyne coupling reaction was also possible with the modification, producing propargyl-amines. Both of the reactions resulted in the addition of a triple bond substituent to the final products; increasing complexity and making the products not easily metabolized in the body, therefore able reach the target of interest. The second-generation matrine derivative was reacted with epoxides to produce amino alcohols. Aminonitriles, propargyl-amines, and amino alcohols are known to be backbones of therapeutic drug compounds. The compounds synthesized were later experimented on chronic myeloid leukemia (CML) cells, also in combination with the manufactured drug Imatinib, in order to inhibit the BCR-ABL kinase activity in the CML cell lines E255K and T315I.

Table of Contents

Abstract.....	v
List of Figures.....	viii
List of Tables	ix
Chapter 1: Matrine and Matrine Analogues.....	1
Introduction.....	1
Alkaloids.....	1
Hypothesis.....	5
Results.....	6
First-Generation Analogue.....	6
Second-Generation Analogue.....	7
Thiomatrine.....	7
Conclusion.....	7
Chapter 2: Strecker Reaction for Matrine Analogue Library.....	13
Introduction.....	13
Strecker Reaction.....	13
Amino Nitriles in Pharmacology.....	14
Our Study.....	14
Results.....	15
Conclusion.....	16

Table of Contents (continued)

Chapter 3: Alkyne Coupling for Matrine Analogue Library.....	19
Introduction.....	19
Second-Generation Modification.....	19
Our Study.....	20
Results.....	20
Conclusion.....	21
Chapter 4: Epoxide Opening for Matrine Analogue Library.....	23
Introduction.....	23
Epoxide.....	23
Our Study.....	24
Results.....	25
Conclusion.....	25
Chapter 5: Matrine Analogue Library Pharmacological Results.....	28
Introduction.....	28
Chronic Myelogenous Leukemia.....	28
Results.....	29
Structure Activity Relationship.....	30
Conclusion.....	31
Future.....	31
Experimental.....	36
References.....	38

List of Figures

Figure	Page
Figure 1. Structure of Matrine.....	9
Figure 2. First-generation Matrine Analogue.....	10
Figure 3. Second-generation matrine analogue.....	11
Figure 4. Structure of Thiomatrine	12
Figure 5. Strecker Reaction Mechanism.....	17
Figure 6. Epoxide Opening Reaction Mechanism.....	26
Figure 7. BCR-ABL Mutated Gene.....	32
Figure 8. AMA3 Compound.....	33
Figure 9. Product of Reaction 156.....	34
Figure 10. Product of Reaction 159.....	35

List of Tables

Table	Page
Table 1. First-Generation Analogue Modification Products.....	18
Table 2. Second-Generation Analogue Modifications.....	22
Table 3. Epoxide Opening Reaction Products.....	27

Chapter 1

Matrine and Matrine Analogues

Introduction

Alkaloids. Alkaloids are naturally occurring compounds produced by organisms such as bacteria, fungi, plants and animals.¹ The compounds contain basic nitrogen atoms and have neutral to weakly acidic properties; alkaloids can contain atoms such as carbon, hydrogen, nitrogen, oxygen, sulfur, chlorine, bromine, and phosphorous.¹ The compounds are used as starting points in drug discovery because of the wide range of pharmacological activities including, but not limited to, antimalarial, antiasthma, anticancer, cholinomimetic, vasodilatory, antiarrhythmic, analgesic, antibacterial, and antihyperglycemic.¹ Commonly known alkaloids include morphine, strychnine, quinine, and ephedrine.² Alkaloids can also have psychotropic and stimulant activities, recreational drugs, for example, cocaine, nicotine, and caffeine.²

Medicinal plants containing alkaloids have been used as therapeutics since around 2000 BC.³ Studies on these alkaloids began around 1804 by Friedrich Sertürner, a German chemist whom separated what he called morphium from opium.³ In German and other European languages morphium is still the term used, however was given the name morphine in the English and French language by the French physicist Joseph Louis Gay-Lussac.³ French researchers Pierre Joseph Pelletier and Joseph Bienaime Caventou discovered strychnine in the year 1818 and quinine in 1820.⁴ Other Alkaloids discovered between 1817 and 1860 included xanthine, atropine, caffeine, coniine, nicotine, colchicine, sparteine, and cocaine.⁴ A German chemist Albert Ladenburg, in 1886, created the first complete synthesis of an alkaloid.⁴ The synthesis began by reacting 2-

methylpyridine with acetaldehyde and then reducing the 2-propenyl pyridine product with sodium, otherwise known as coniine.⁵ In the 20th century spectroscopic and chromatographic methods were created which helped to quickly identify, by 2008, over 12,000 alkaloids.⁵

Matrine. Therapeutic alkaloids sophoridine, sophoranol, oxymatrine, and matrine, as well as others, are found specifically in *Sophora flavescens*, which is the dried root of the Kun Shen plant.⁶ Large doses of the plant root are needed in order to work, however the root is known to have numerous of health benefits including the treatment of skin diseases, insomnia, diarrhea, high fever, irregular heart beat, hot hands and feet, urinary tract infection, hair loss, and Hepatitis B Virus, along with various other diseases, infections, and symptoms.⁶ The alkaloid fraction of the plant root is made up of about a twenty percent combination of oxymatrine and matrine.⁶ In 1998, the Institute for Traditional Medicine introduced the fractions as a tablet under the name of Oxymatrine, also known as White Tiger; the tablet was made available to doctors to use on patients.⁷ The tablet did not have any reported side effects from use.⁷ In a clinical setting, the average dosage of the drug is 400-600 mg per day.⁷ In China, the compound is given by injection, however, in the west, the compounds are given orally because injection administration was not acceptable.⁷ The difference between receiving the medication orally rather than through injection is the oral tablet results in more of the oxymatrine converting to matrine, whereas the injection leads to higher levels of oxymatrine in the blood stream; it is not clear if one delivery method is more effective than the other.⁸ A capsule form has also been given and showed similar signs of the injected method.⁸

According to cancer specialist Chang Minyi, “*Sophora subprostrata* works through stimulating the anticancer immune mechanism of the patient and reinforcing his resistance against the growth of the tumor.”⁹ Xu Xiangru and Jiang Jikai of the Congqing University of Medical Sciences published about anticancer activity of sophora alkaloids.⁹ They discussed pharmacology studies showing the alkaloids could inhibit growth of tumor cells directly and could also affect immune functions such as turning cancer cells into normal functioning white blood cells.⁹ Xiangru and Jikai also discussed, in a clinical setting the sophora alkaloids were used successfully in treating the side effect of the decrease of white blood cells, also known as leukopenia, caused by cancer chemotherapy or radiation therapy, and for treating cancers such as leukemia, uterine cervical cancer, esophageal, and laryngeal cancer.¹⁰⁻¹¹

Matrine (Figure 1), as stated previously, is a tetracyclo-quinolizidine alkaloid obtained from the Chinese sophora *flavescens* root.¹² The herb was viewed as a medium-grade drug where both the seeds and root are considered toxic in the China Botanical Illustration, however the plant alkaloids have medicinal properties when used properly in small dosages of 3-10 grams per treatment.¹³ The compound has been used in Chinese medicine for thousands of years in the treatment of liver diseases, cardiovascular diseases, asthma, and tumors.¹³ The drug is administered mostly through injection, however can also be dispensed through tablet or capsule forms.

Matrine is also used as an analgesic or as a therapeutic against infection by pathogenic microorganisms.¹⁴ It has also been used to stimulate cell metabolism and normalize immune function.¹⁵ The mechanism of matrine is not exactly known, however, scientists believe cell arrest, inhibition of cell proliferation, and induction of apoptosis are

possible mechanisms for the anti-tumor activities seen *in vitro* and *in vivo*.¹⁵ The department of Oncology at the Hospital of Traditional Medicine conducted research to determine if using Matrine as therapy would hold anti-tumor effects on breast cancer cells, and how exactly this happened.¹⁵ The results showed death in three different types of cells, but there was less toxicity in the controlled cells.¹⁶ The possibility of down regulation of IKK β expression is the possible mechanism of action with the results shown in western blot analysis.¹⁶

Semisynthetic approaches. Prior to chemical modification techniques being developed, drugs were composed entirely of natural sources such as herbs, animal products, and inorganic material.¹⁷ Centuries later, now the active components are extracted from the natural sources, are structurally characterized, and synthesized in a laboratory.¹⁷ The laboratory semi-synthetic and total synthetic approaches can create more active, and higher tolerated drugs for consumers.¹⁷ Naturally derived compounds are semi-synthesized to increase the therapeutic properties such as metabolism rate, toxicity, and excretion.¹⁸ Anticancer compounds Topotecan and Irinotecan originate from naturally isolated Camptothecin through commercial synthesis; the drug Vinorelbine is produced from plant extracted Catharanthine for commercial production.¹⁸ Production of microbes of modified alkaloids shows possibility to speed up the semi-synthesis development of alkaloid-modified pharmaceuticals to deliver superior intermediates closer to the final products.¹⁸

Pharmacology of Matrine. There are 27 alkaloids, which have been isolated from the plant root; they are classified into groups including matrine-type alkaloids, cytosine-type alkaloids, anagyrine-type alkaloids, and lupinine-type alkaloids.¹⁹ The matrine-type

alkaloids have been identified as the bioactive component contributing to pharmacological effects on cancers, hepatitis B and C, and cardiac diseases.¹⁹ Matrine is the most active of the alkaloids and is responsible for the antitumor, anticancer, antimicrobial, anti-inflammatory, and analgesic properties.¹⁹⁻²³ In the pharmaceutical market, matrine and oxymatrine are the only two compounds required as standards of evaluation of drug quality; no less than 1.2 percent of combined content of the two compounds should be analyzed by HPLC.²⁴ Over the years, TLC, HPLC, and capillary electrophoresis have been used as methods to monitor the compounds and control the quality isolated from the plant root.²⁵ The type and size of the ring structure of the core scaffold has main impact on the therapeutic properties of the compound.²⁶ The structure of matrine contains both a nitrogen infused ring and a beta lactam ring.²⁷ Around 60 percent of small molecule drugs contain a nitrogen heterocycle.²⁸⁻³² The nitrogen heterocycle can be a structurally diverse component in therapeutics, as well as, hold responsibility as an essential factor of FDA approved pharmaceuticals.³³ The beta lactam ring is seen in present day antibiotics.³⁴ The ring results in tight bonding to the active site inhibiting enzyme activity and resulting in cell wall development.³⁵

Hypothesis

Can we perform molecular scaffold and functional group modifications towards tailoring the structure-activity relationships for Matrine.³⁷

Results

First-generation analogue. In order to begin the experiments, the first step was to open the lactam ring of the matrine in order to keep the core structure (Figure 2); this produced a methyl ester derivative and also provided an activation point for the analogue reactions. The matrine analogue reaction began with 2,940 mg of the matrine dissolved in 118.37 mL of concentrated hydrochloric acid (HCl); this reaction was refluxed for 48 hours. The solution was dried and methanolic hydrogen chloride was added to the solution, it was then stirred at room temperature while being monitored by thin layer chromatography (TLC, 10% methanol in dichloromethane). Hydrolysis of the compound was not evident by TLC, infrared spectroscopy (IR), or nuclear magnetic resonance (NMR); therefore more HCl was added and the reaction had to reflux for an additional 48 hours.

The resulting solution was dried, and rinsed with methanol three times while being dried in between. The resulting paste residue was then suspended in minimal isopropyl alcohol and diethyl ether was added while the reaction was vigorously stirring. The resulting precipitate was filtered, washed with ether, and the supernatant was dried; the process was repeated until the presentation of the matrine methyl ester was a white solid. The end product was then confirmed by ^1H NMR and ^{13}C NMR and compared to matrine's ^1H NMR and ^{13}C NMR spectra to ensure opening; the first generation matrine analogue was then used as the starting material moving forward without the need to further purify.

Second-generation analogue. The second-generation matrine analogue was a functional group modification in order to create a matrine derivative alcohol (Figure 3). The resulting alcohol derivative was more stable than the methyl ester starting material, making it easier to work with. The resulting alcohol analogue was used as the starting material for the reactions, which produced amino alcohols in the epoxide opening analogue library. An oven dried three-neck round bottom flask with a stir bar and reflux condenser was flushed with argon and charged with 141.51 mL of 1M (molar), borane-THF complex; the reaction was run under neat conditions. Matrine dihydrochloride was then added as a solid, under argon, in portions; the flask was heated and refluxed for 48 hours. The resulting reaction was quenched with methanol, underwent acid base extraction with HCl and NaOH, the aqueous layer was extracted with DCM and the product was allowed to precipitate in ethyl acetate. The resulting product was then rinsed three times with methanol and dried. The product structure was confirmed through mass spectroscopy.

Thiomatrine. The thiomatrine compound (Figure 4) was synthesized by reacting the Lawesson's reagent with matrine. The reaction was refluxed in THF and the carbonyl group was converted into the thiocarbonyl by Lawesson's reagent.

Conclusion

Semi-synthetic reactions are an important part of the therapeutic drug discovery process. Following the synthesis of the matrine generation analogues, many opportunities to manipulate the core structure with the long-term goal of increasing biological activity while decreasing toxicity were available. The first generation matrine analogue allows for a synthesis similar to the Striker reaction to occur, as well as, an alkyne coupling

reaction, adding triple bond substituents to the final product; this increases complexity and produces α -aminonitriles. The second-generation matrine analogue is easier to work with because the alcohol makes the structure less reactive than the methyl ester analogue. The second-generation matrine derivative was reacted with epoxides in order to produce amino alcohols. Both α -aminonitriles and amino alcohols are known to be backbones of therapeutic drug compounds.

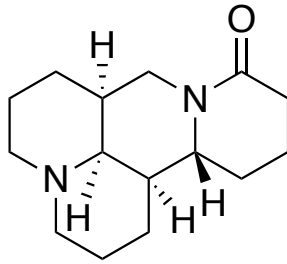


Figure 1. Structure of matrine

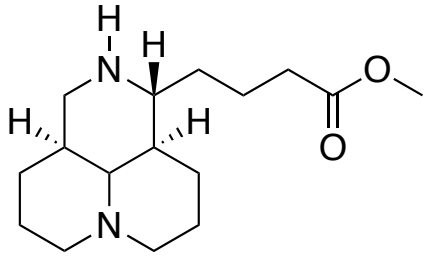


Figure 2. First-generation matrine analogue

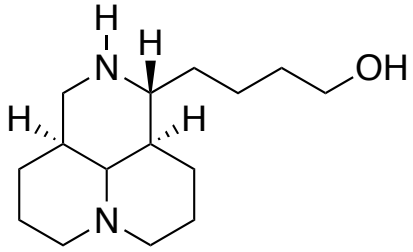


Figure 3. Second-generation matrine analogue

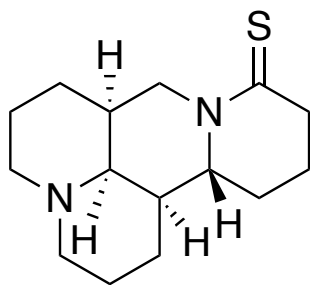


Figure 4. Structure of thiomatine

Chapter 2

Strecker Reaction for Matrine Analogue Library

Introduction

Strecker reaction. Adolph Strecker coined the Strecker amino acid synthesis (Figure 5), in 1850.³⁸ The one pot, two-step reaction is a huge advantage; the reaction is a simple and economical creation of racemic α -aminonitriles.³⁹ The synthesis also saves time and resources by avoiding the separation and purification processes, resulting in increased percent yields of the final products.⁴⁰ The components in the Strecker reaction include an aldehyde, an amine, and cyanide.⁴¹ During the Strecker reaction, the aldehyde is condensed with ammonia in the presence of cyanide in order to form an α -aminonitrile.⁴² The α -aminonitrile can then be used as an intermediate to further synthesize amino acids; the basis for proteins, peptides, and pharmaceuticals.⁴³⁻⁴⁶ A benefit of running the reaction, in such way, is the possibility of stereoselectivity.⁴⁷ There has been considerable interest in asymmetric synthesis for active α -aminonitriles; these are the key building blocks in pharmaceuticals and other approaches including biocatalytic routes, and metal catalyzed hydrogenation of enamides.⁴⁸ Asymmetric approaches are more desirable due to the use of imines followed by a nucleophilic addition of cyanide in the presence of a chiral catalyst.⁴⁹⁻⁵² In order for this direction to occur, there is the need of another donor instead of cyanide, or an iminium system instead of an imine.⁵³

Mechanism. The mechanism for the Strecker mechanism begins with the carbonyl group of the aldehyde being activated by acid; ammonia then condenses with the aldehyde to form an iminium intermediate.⁵⁴ After proton exchange, water is cleaved from the iminium ion.⁵⁴ Cyanide then adds as a nucleophile to the imine carbon, creating

an α -aminonitrile.⁵⁴ In the study, the first generation matrine analogue was used in place of ammonia.⁵⁵ Using an amine instead of ammonia changed the mechanism for the synthesis of the products.⁵⁵ Formation of an imine by reacting the aldehyde with the amine, followed by hydrocyanation is an alternate synthesis to the one pot.⁵⁵

Amino nitriles in pharmacology. The number of nitrile containing pharmaceuticals is increasing; there are over 30 drugs prescribed for a diverse range of therapeutics.⁵⁶⁻⁵⁷ In addition, more than 20 other nitrile-containing leads are in clinical development.⁵⁶⁻⁵⁷ The pattern of nitrile-containing pharmaceutical rise identifies the nitrile being a desirable pharmacophore in future drug discoveries.⁵⁸⁻⁵⁹ The functionality must be activated by an electron withdrawing group, and the electrophilic additions shown in amino nitriles, for diabetes and osteoporosis treatment, have a reversible electrophilic attack.⁵⁸⁻⁵⁹ In most cases, the nitrile group of these drugs is not metabolized by the body and is excreted without being altered.⁶⁰

Our Study

The objective of the first generation analogue synthesis was to produce semi-synthetic amino nitriles. The study began trialing different conditions to see which was able to work best for our components in order to produce the highest percent yield. Beginning with 25 mg scale reactions, a 1:1 ratio was used for starting material to aldehyde with 1 mL of cyanide (acetone cyanohydrin or hydrogen cyanide). The reactions ran under neat conditions at room temperature in a non-inert atmosphere for 24 hours. After observations were made, more small-scale reactions ran with 1-Methylpiperazine as the starting material to avoid consumption of the first generation starting material until the reaction was optimized. The ratio of aldehyde and cyanide was

increased to 2:3 respectfully; the laboratory had the most amount of sodium cyanide in stock, therefore this was the cyanide of choice moving forward, and 0.75 mL of methanol was used as the solvent. Once the reaction conditions were up to par, the reaction scale was increased to 50 mg, still using 1-Methylpiperazine as the starting material. After the reaction could be scaled up, the 50 mg reaction ran using the first generation matrine analogue. Reactions were experimented, letting the aldehyde react with the starting material for approximately 15 minutes before adding the sodium cyanide, it was determined this factor did not influence the outcome of the reaction. Finally, the reactions were scaled up to 100 mg with 3 mL of methanol solvent with the 1:2:3 equivalences of starting material to aldehyde to sodium cyanide.

Results. The variable in the reaction was our aldehyde. In order to acquire a broad-spectrum library of new compounds, both aromatic and aliphatic aldehydes were reacted. After assessing the products, it was concluded aldehydes containing carbon chains are more reactive in the formation of the amino nitriles. In the future we would like to extend the scope of the library towards determining the pharmacological properties of these scaffolds.

All of the reactions from small-scale to large-scale were monitored under thin liquid chromatography (TLC) in a chamber of 4:1 ethyl acetate to methanol. All of the products from the large-scale reactions were confirmed through ^1H NMR and ^{13}C NMR. Resulting products and yields can be observed in Table 1.

Conclusion

Pharmaceutical therapeutics containing nitriles is on the rise; this creates interest in the development of this pharmacophore in drug discovery. The information the Strecker reaction provides in addition to the use of the first-generation matrine analogue, holds all the benefits from the known reaction with the added benefits of using a nitrile already known for therapeutic effects. The determination of the results for the project concluded aldehydes containing carbon chains are more reactive in the formation of the α -aminonitriles; the longer the carbon chain, the higher of a percent yield was obtained. In the future, we aim to extend the scope of the library towards determining the pharmacological properties of these scaffolds.

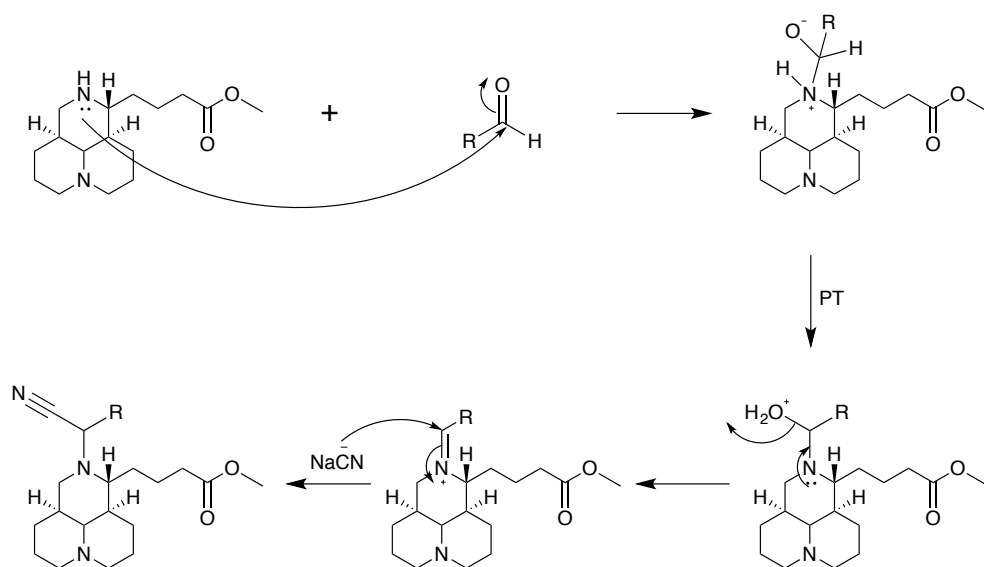


Figure 5. Strecker reaction mechanism

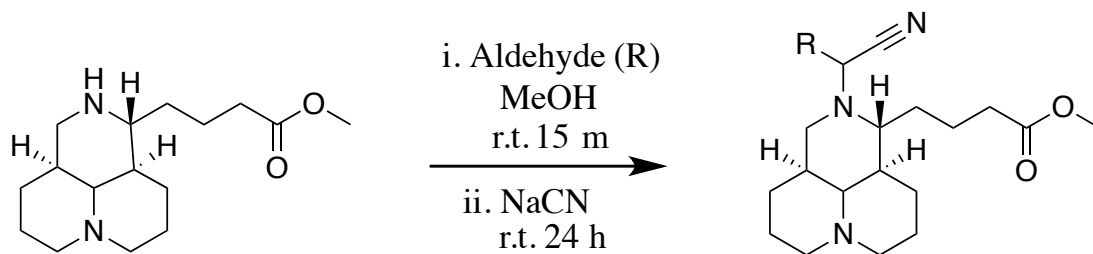


Table 1

First-Generation Analogue Modification Products

R	Percent Yield	R	Percent Yield
	75.9		41.9
	50.4		36.7
	47.6		33.1
	43.7		

Note. For all reactions: starting material was first-generation matrine analogue; 100 mg scale reactions; 1:2:3 eq of starting material, aldehyde, NaCN respectively; 3 mL of methanol; room temperature for 24 hours.

Chapter 3

Alkyne Coupling for Matrine Analogue Library

Introduction

Second-generation modification. The second-generation analogue modification was alkyne coupling reaction; during 2001 and 2002 three groups separately reported out results using this method.⁶¹ The synthesis is a multicomponent reaction involving an aldehyde, amine, and alkyne, undergoes direct dehydrative condensation, and advances using a metal catalyst.⁶¹ The reaction results in propargyl amines which are the backbone intermediates to many other compounds, including nitrogen containing active compounds, such as β -lactams, oxotremorine analogues, conformationally restricted peptides, isosteres, natural products, and therapeutic drug molecules.⁶²⁻⁶⁴ The use of alkynes is valuable in therapeutics because of the triple bond.⁶⁴ The bond makes the compound hard for the body to metabolize, thus the therapeutic will reach the target of interest.⁶⁵ Since alkynes are not metabolically liable, the potency of the drug intensifies, therefore after synthesizing the alkynes with the starting material, there is potential for an increase in the structure activity relationship (SAR) of the first-generation matrine analogue, as well as, the original matrine compound.⁶⁵

Mechanism. The alkyne coupling reaction synthesizes by the metal catalyst first activating the alkyne to make a metal acetylide.⁶⁶ The amine and aldehyde then combine to create an imine intermediate.⁶⁶ The imine then reacts with the acetylide through nucleophilic addition to form the resulting propargylamine and the metal catalyst is recovered.⁶⁶

Our Study

The alkyne coupling reaction was used as the foundation for the second-generation analogue modification. The study began with trialing different conditions to produce the highest percent yield. The 10 mg experiments were set to run overnight with various solvents; acetonitrile (ACN) 0.5 mL at 80°C and 55°C and 1 mL at 70°C, tetrahydrofuran (THF) 1.50 mL at 55°C, heptanes 0.80 mL at 55°C, and toluene 1.7-2.0 mL at 95°C. Some of these small-scale reactions were synthesized in an inert atmosphere. The first-generation matrine analogue was used as the starting material, Phenylacetylene was used as the alkyne, and while determining the best conditions, 4-Chlorobenzaldehyde remained as the consistent aldehyde. Published research papers lead to beginning with a copper catalyst because copper catalyst precursors are cheap, readily available, less toxic, and have most reactivity.⁶⁶ In the beginning stages, copper(I) iodide was the consistent catalyst. The equivalencies of the starting material, aldehyde, alkyne, and catalyst were adjusted accordingly through interpretations made during TLC analysis (chamber 4:1 ethyl acetate to methanol) of each reaction. Various metal catalysts were trialed, including copper(II) acetate, iron(III) oxide, and zinc iodide (ZnI_2), to determine which would help drive the reaction further.

Results. The reaction conditions used to scale up, to 50 mg, were determined to be 1:1:2:1 equivalence of starting material, aldehyde, alkyne, and catalyst respectfully. The solvent used moving forward was toluene (3 mL) at 100°C with zinc iodide as the catalyst, Phenylacetylene as the consistent alkyne, and various aldehydes. Both aliphatic (butyraldehyde and octylaldehyde getting below 10% yields) and aromatic aldehydes were reacted, however it was determined aromatic compounds reacted further than

aliphatic compounds. Moving forward we aim to extend the scope of the library towards determining the pharmacological properties of these scaffolds.

All of the products from the large-scale reactions were confirmed through ^1H NMR and ^{13}C NMR. The products and percent yields can be observed in Table 2.

Conclusion

The use of propargylamines is desirable in drug therapeutic discoveries. The use of the triple bond makes the compound not easily metabolized and therefore able reach the target of interest. The first-generation matrine analogue can be used as the amine starting material in order to synthesize a library of propargylamines. The observations made in the study concluded aromatic aldehydes are further reacted than aliphatic aldehydes. In the future, we aim to extend the scope of the library towards determining the pharmacological properties of these scaffolds.

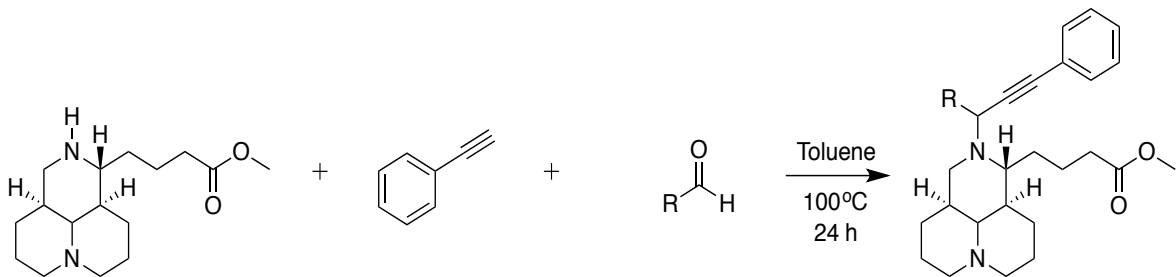


Table 2

Second-Generation Analogue Modifications

R	Percent Yield	R	Percent Yield
	98.2		76.4
	96.2		66.5
	80.3		

Note. For all reactions: starting material was the first-generation matrine analogue; the alkyne was phenylacetylene; ZnI_2 catalyst; 100 mg scale reactions; 1:1:2:1 eq of starting material, aldehyde, alkyne and catalyst respectively; 3 mL of toluene solvent; $100^\circ C$ for 24 hours.

Chapter 4

Epoxide Opening for Matrine Analogue Library

Introduction

Epoxide. An epoxide is a highly reactive, nonpolar compound due to the ring strain.⁶⁷ The bond angles of the three atoms in the ring are similar to that of an equilateral triangle; the carbon to oxygen sharp bonds result in the strain.⁶⁷ Epoxides are beneficial in synthesizing amino alcohols.⁶⁸ These alcohols can further be reacted and used as nucleophilic substitution, and the nitrogen infused ring can control the stereochemistry.⁶⁹ A benefit to synthesizing amino alcohols is chirality, this characteristic is important because it indicates optical activity, which can be used to determine different enantiomers.⁷⁰ Approximately 25 percent of drugs on the market are racemates of synthetic chiral drugs.⁷¹ A downfall to racemic compounds is the two enantiomers of a chiral drug can differ in dosage, efficacy, side effects, use, bioavailability, metabolism rate, excretion, and toxicity.⁷² The single enantiomer form has the advantage of enhanced therapeutic activity with limiting side effects and increased selectivity.⁷³

Mechanism. In the second-generation matrine analogue, the nitrogen atom in our secondary amine holds a lone pair of electrons.⁷⁴ The lone pair makes for our starting material to act as a nucleophile in the reaction scheme (Figure 6), to donate these electrons to the electrophile in order to form a chemical bond.⁷⁵ In the study, the electrophile is the epoxide; the electrons attack the least substituted carbon in the epoxide opening the ring, which allows the C-N bond to be formed in the product.⁷⁶

Our Study

During the formation of the epoxide opening analogue library, the second-generation matrine analogue was used as the nucleophile, to be reacted with various epoxides in order to produce amino alcohols.⁷⁷ The reactions ran on a 50 mg scale with about 2 mL of acetonitrile. Due to the reactions not progressing enough, the solvent was changed to 1,4-Dioxane in order to raise the temperature of the reaction. The reactions ran at 80°C (ACN) or 90°C (1,4-Dioxane) for 24 hours. The starting material was dissolved in the 2 mL of solvent and epoxide was then added at a 1:1.5 ratio respectively. The product was then compared to the starting material by TLC in a chamber of 4:1 ethyl acetate to DCM.

The product was dried and then reconstituted in diethyl ether to separate unreacted epoxide from the product. The reconstituted solution was put into a separator funnel and a small amount of 6M hydrochloric acid (HCl) was added, this was the layer the organic product diffused into. After shaking the separator funnel vigorously, the HCl layer was extracted; an acid base reaction was next generated with sodium hydroxide (NaOH) until a pH of 11 was formed, and a small amount of deionized (DI) water was then added. The new basic solution was added into a second separator funnel and the organic product was extracted three times with ethyl acetate. The organic layer was dried with sodium sulfate (Na_2SO_4) and filtered into a round bottom through gravity filtration. The round bottom was then dried and reconstituted with chloroform (CHCl_3), transferred to a tared vial, and then dried once more.

Results. The results concluded there was not a difference in yields for aromatic or aliphatic epoxides. Once our dry products were acquired, the structures were confirmed through ^1H NMR, ^{13}C NMR, and IR. The products and yields can be observed in Table 3. The study has produced a comprehensive library of matrine derived amino alcohols which allows for the efficient determination of the biological profile of the corresponding scaffold and potential development of selective therapeutics.

Conclusion

Amino alcohols are beneficial in drug therapeutics due to the chirality of the compounds. Amino alcohols have showed potential in treating diabetes, tuberculosis, as well as forming other antibiotics. This study has produce a comprehensive library of matrine amine alcohols that would allow for the efficient determination of the biological profile of the corresponding scaffold and potential development of selective therapeutics.

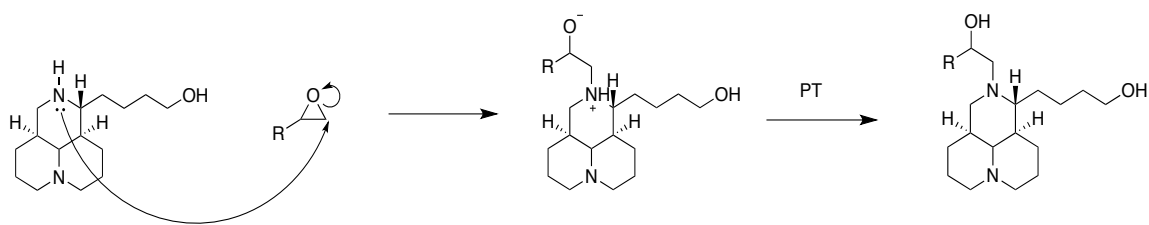


Figure 6. Epoxide opening reaction mechanism

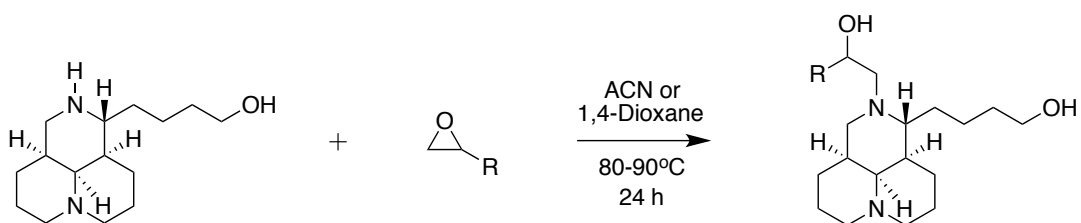


Table 3

Epoxide Opening Reaction Products

Epoxide	Percent Yield	Epoxide	Percent Yield
	53.8		43.6
	46.8		42.6
	46.3		37.6
	45.3		35.2

Note. For all reactions: The starting material was the second-generation matrine analogue; 50 mg scale reactions; 1:1.5 eq of starting material to aldehyde; 2 mL of solvent; 80°C (ACN) or 90°C (1,4-Dioxane) for 24 hours.

Chapter 5

Matrine Analogue Library Pharmacological Results

Introduction

Chronic myelogenous leukemia. Chronic myelogenous leukemia (CML) is a form of cancer, predominantly occurring in adults, which originates in blood-forming cells of bone marrow.⁷⁸⁻⁸⁰ A change occurs forming the mutated BCR-ABL gene (Figure 7) during the beginning development of the myeloid cells.⁸¹⁻⁸³ The cells begin to mature and divide without dying, crowding out other cells in the bone marrow and eventually overflow into the blood stream.⁸³ Acute leukemia can also occur from the change of the CML cells.⁸⁴⁻⁸⁵ Studies are being done on CML in laboratories, and clinical trials, to discover drugs to help fight the mutated gene and cells.⁸⁶⁻⁸⁷ Currently, Imatinib is the main source of drug choice on the market to target the BCR-ABL gene.⁸⁸ The drug is a tyrosine kinase inhibitor (TKI), which is a class of chemotherapy medication to inhibit enzyme tyrosine kinase.⁸⁹ The form of therapy allows for target treatment of certain cancers, decreasing the potential of damaging healthy cells to increase success.⁹⁰ Studies are being done to see if drugs, such as Imatinib, will give better results if combined with another form of therapy such as chemotherapy, interferon, cancer vaccines, or other potential drugs.⁹¹⁻⁹³ One study showed enhanced results when combining Imatinib with interferon; however this combination increased side effects.⁹⁴ More studies are currently running to see if the combination of dasatinib, nilotinib, cyclosporine, or hydroxychloroquine can be more beneficial when combined with various TKIs.⁹⁵⁻⁹⁸

As stated previously, *Sophora subprostrata* [sophora alkaloids] work through stimulating the anticancer immune mechanism strengthening the patients fight against the

tumor.⁹⁹ Pharmacology studies show alkaloids could inhibit growth of tumor cells directly.¹⁰¹ Recent reports claim matrine has potential to make leukemia cells transform into normal white blood cells.¹⁰² Matrine is also used as an analgesic or as a therapeutic against infection by pathogenic microorganisms; it has also been used to stimulate cell metabolism and normalize immune function.¹⁰³ The mechanism of matrine is not exactly known, however, scientists believe cell arrest, inhibition of cell proliferation, and induction of apoptosis are possible for the anti-tumor activities seen *in vitro* and *in vivo*.¹⁰⁴

Results

The first and second-generation analogues of matrine, as well as various compounds from the modification libraries were experimented to see if the compounds could be identified as inhibitors on CML cells containing the E255K and T315I BCR-ABL mutation with decreased toxicity.¹⁰⁵ The derived compounds were tested in comparison and combination to drugs known to be therapeutics to CML patients such as Imatinib.¹⁰⁶

The MTT assay showed a decrease in CML cell activity after 24 hours at 3.2 mM when exposed to matrine and the first-generation matrine analogue; thiomatrine had some effects, however not up to par with the matrine and matrine analogues.¹⁰⁷ Annexin V/PI assay was used to confirm the results of the MTT assay; survival of the CML cells were decreased at 4mM.¹⁰⁸ An analogue from the first-generation analogue library, AMA3 (Figure 8), decreased the survival percentage of the CML cell survival at 40 nM and 400 μ M. The second-generation matrine analogue did not increase apoptosis in the cell line. Two compounds of the second-generation analogue library, 156 (Figure 9) and 159

(Figure 10), were effective in the E255K cell line when combined with Imatinib.¹⁰⁸ The compounds decreased the capability of the T315I cells but were above the toxicity observed in the control, NIH3T3 and Ba/F3, lines.

Western blot analysis determined the combination treatment of 156 and Imatinib decreased the phosphorylation of Tyr⁴¹² on the BCR-ABL mutation cell lines of E255K, however this was not observed in the T315I line; this data was consistent with flow cytometric analysis.¹⁰⁹

Structure activity relationship. The known compound in the study, Imatinib, compares to the structures synthesized by all structures containing nitrogen heterocycles.^{110,111} Imatinib is the main therapeutic used in patients with CML, however the T315I cell line is resistant to the drug; this is also the cause for around 15 percent of CML patient relapses.¹¹²⁻¹¹⁵ Matrine and the first generation matrine analogue, alone, did not show much activity until 4 mM. Compound AMA3 did show cell death beginning at 40 nM. Aside from high concentrations of the synthesized compounds being used, the structures combined with Imatinib were able to increase the therapeutic effects in the cancer cell lines. Imatinib started showing some effects in P210 cell line at 1 μ M, E255K cell line at 4 μ M, and was completely resistant to T315I cells, as expected. Combining Imatinib with structure 156 increased the death rate of the cancer cell lines while allowing the healthy cells to mostly survive, however Imatinib worked better alone than with compound 159 which was more toxic.

Conclusion

Aside from the high concentrations tested thus far, there is potential for the products to work on the cell lines if the concentration can be decreased. Further analysis is needed to determine if caspase-independent apoptotic mechanism are induced due to caspase-8 and caspase-3 activation not being detectable.

Future

Compounds throughout the analogue libraries will continue to be analyzed to find an effective therapeutic for the T315I BCR-ABL mutated cells. The concentrations need to be further optimized in order to decrease the concentrations of the drug molecules in order to be considered for treatment *in vivo* studies.

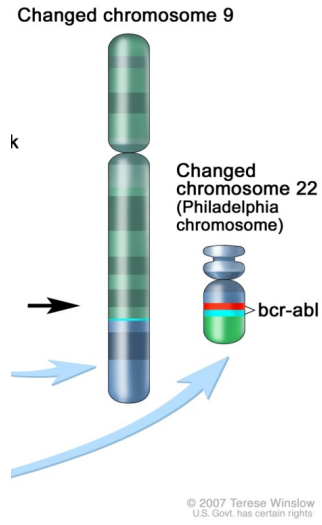


Figure 7. BCR-ABL mutated gene

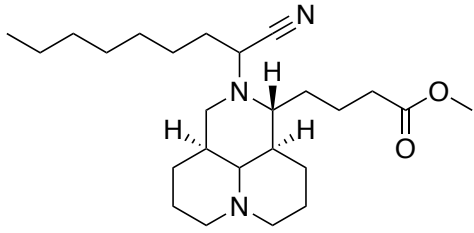


Figure 8. AMA3 compound

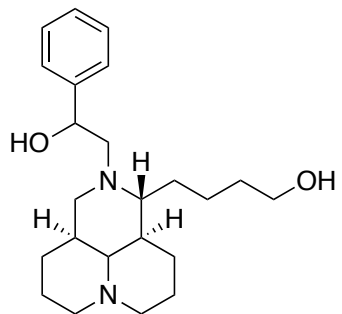


Figure 9. Product of reaction 156

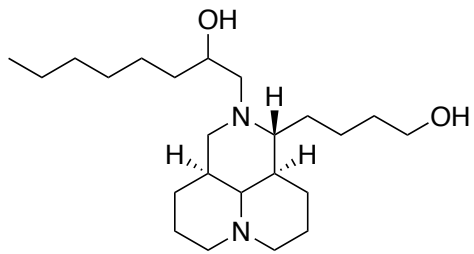


Figure 10. Product of reaction 159

Experimental

4-(2-(2-hydroxy-3-(4-methoxyphenoxy)propyl)decahydro-1*H*,4*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)butan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.02 (s, 1H), 6.89 – 6.75 (m, 3H), 4.10 – 3.84 (m, 2H), 3.73 (s, 2H), 3.59 (tt, *J* = 6.2, 4.3 Hz, 4H), 3.26 – 3.03 (m, 3H), 3.00 – 2.68 (m, 6H), 2.57 (ddd, *J* = 29.9, 12.3, 4.2 Hz, 2H), 2.04 (dt, *J* = 13.2, 2.3 Hz, 2H), 1.98 – 1.81 (m, 5H), 1.68 (dq, *J* = 13.0, 4.2 Hz, 2H), 1.67 – 1.52 (m, 2H), 1.50 (tdd, *J* = 13.0, 6.3, 3.3 Hz, 4H), 1.48 – 1.23 (m, 10H), 1.27 – 1.12 (m, 2H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 115.48, 115.47, 114.56, 71.39, 71.09, 66.24, 65.49, 64.58, 64.49, 64.05, 62.31, 62.14, 61.97, 57.62, 57.51, 57.45, 57.25, 57.23, 57.15, 57.02, 55.68, 54.26, 52.47, 51.85, 50.33, 46.22, 41.88, 41.86, 38.94, 37.21, 37.19, 37.08, 34.87, 32.86, 32.69, 32.57, 31.36, 29.66, 28.65, 28.40, 28.20, 28.15, 27.96, 27.38, 27.20, 26.78, 21.58, 21.55, 21.45, 21.38, 21.32, 21.23, 21.08, 20.83, 19.64.

4-(2-(2-(4-bromophenyl)-2-hydroxyethyl)decahydro-1*H*,4*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)butan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 (ddd, *J* = 7.9, 4.9, 2.7 Hz, 4H), 7.35 – 7.16 (m, 3H), 4.67 (dt, *J* = 10.8, 3.5 Hz, 1H), 3.66 – 3.44 (m, 7H), 3.30 – 3.00 (m, 6H), 2.86 – 2.63 (m, 9H), 2.62 – 2.51 (m, 2H), 2.30 – 2.19 (m, 1H), 2.07 – 1.91 (m, 4H), 1.86 (dddd, *J* = 18.3, 9.8, 7.8, 3.8 Hz, 8H), 1.83 – 1.63 (m, 2H), 1.68 – 1.59 (m, 2H), 1.63 – 1.50 (m, 2H), 1.48 (qd, *J* = 7.6, 7.0, 3.6 Hz, 8H), 1.47 – 1.27 (m, 7H), 1.22 (s, 1H), 1.31 – 1.10 (m, 3H).

2-(1-(4-hydroxybutyl)octahydro-1*H*,4*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-2(3*H*)-yl)cyclohexan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 3.59 (tt, *J* = 5.0, 2.5 Hz, 2H), 3.20 (dd, *J* = 13.1, 11.1 Hz, 1H), 3.08 (td, *J* = 9.5, 2.9 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.60 (dd, *J* = 11.9, 4.3 Hz, 1H), 2.09 – 1.98 (m, 1H), 2.02 – 1.82 (m, 3H), 1.78 – 1.55 (m, 2H), 1.59 – 1.43 (m, 2H), 1.35 (s, 3H), 1.46 – 1.12 (m, 4H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 64.52, 62.12, 57.62, 57.51, 51.82, 46.24, 41.92, 37.26, 32.89, 32.69, 32.62, 28.16, 26.79, 24.36, 21.55, 21.47, 21.33, 21.24.

3-(1-(4-hydroxybutyl)octahydro-1*H*,4*H*-pyrido[3,2,1-*ij*][1,6]naphthyridin-2(3*H*)-yl)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.08 – 3.93 (m, 1H), 3.60 (td, *J* = 6.2, 1.9 Hz, 6H), 3.23 (d, *J* = 12.1 Hz, 2H), 3.22 – 3.07 (m, 2H), 3.12 – 3.04 (m, 2H), 2.84 – 2.70 (m, 6H), 2.61 (dd, *J* = 11.9, 4.3 Hz, 3H), 2.14 – 1.99 (m, 4H), 2.03 – 1.90 (m, 2H), 1.94 – 1.79 (m, 8H), 1.80 – 1.39 (m, 19H), 1.43 – 1.07 (m, 22H), 0.80 (s, 1H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 134.50, 125.08, 77.22, 76.98, 72.07, 68.39, 64.48, 62.11, 57.61, 57.50, 51.87, 46.21, 44.05, 41.85, 39.63, 38.84, 37.19, 34.35, 32.72, 32.65, 32.51, 29.66, 28.15, 27.75, 27.72, 27.47, 27.22, 27.08, 26.78, 26.36, 26.12, 26.08, 21.54, 21.28, 21.22, 20.87, 19.84.

4-(2-(2-hydroxy-3-phenoxypropyl)decahydro-1H,4H-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)butan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.22 (m, 5H), 6.98 – 6.87 (m, 6H), 4.15 – 3.92 (m, 6H), 3.61 (ddd, *J* = 7.9, 6.2, 4.1 Hz, 7H), 3.29 – 3.08 (m, 5H), 2.99 (dd, *J* = 12.5, 10.3 Hz, 1H), 2.92 – 2.71 (m, 7H), 2.69 – 2.51 (m, 4H), 2.43 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.28 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.12 – 1.99 (m, 5H), 1.98 – 1.87 (m, 6H), 1.91 – 1.83 (m, 3H), 1.87 – 1.72 (m, 2H), 1.72 (dt, *J* = 8.5, 4.2 Hz, 2H), 1.71 – 1.53 (m, 6H), 1.51 (ddt, *J* = 13.8, 9.6, 5.4 Hz, 10H), 1.49 – 1.35 (m, 2H), 1.39 (s, 7H), 1.36 (s, 4H), 1.39 – 1.25 (m, 3H), 1.29 – 1.16 (m, 3H), 1.24 (s, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 129.48 , 129.40 , 120.86 , 114.53 , 76.94 , 70.54 , 70.26 , 66.12 , 65.38 , 64.58 , 64.36 , 64.04 , 62.45 , 62.22 , 62.09 , 57.59 , 57.50 , 57.48 , 57.42 , 57.26 , 57.23 , 57.16 , 57.02 , 54.23 , 52.45 , 51.93 , 51.83 , 50.20 , 46.09 , 41.69 , 38.94 , 37.04 , 36.99 , 34.90 , 32.84 , 32.63 , 32.59 , 32.34 , 31.29 , 29.69 , 28.60 , 28.33 , 28.21 , 28.10 , 27.95 , 27.39 , 27.21 , 26.76 , 21.59 , 21.51 , 21.45 , 21.39 , 21.23 , 21.19 , 21.08 , 20.80 , 19.56 .

4-(2-(2-(4-chlorophenyl)-2-hydroxyethyl)decahydro-1H,4H-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)butan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.29 (s, 1H), 7.37 – 7.18 (m, 1H), 3.71 – 3.49 (m, 3H), 3.30 – 3.05 (m, 2H), 2.94 (s, 4H), 2.88 – 2.68 (m, 3H), 2.60 (dt, *J* = 11.9, 4.7 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.99 – 1.82 (m, 3H), 1.80 – 1.44 (m, 5H), 1.39 (s, 1H), 1.27 (ttdd, *J* = 27.3, 18.1, 8.2, 4.4 Hz, 4H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 128.52 , 128.44 , 127.45 , 127.13 , 77.20 , 73.84 , 68.93 , 68.29 , 67.95 , 64.63 , 64.42 , 64.00 , 62.57 , 62.30 , 62.27 , 60.30 , 57.60 , 57.49 , 57.38 , 57.25 , 57.20 , 56.97 , 56.89 , 52.25 , 51.85 , 51.27 , 46.14 , 41.84 , 39.16 , 37.14 , 36.79 , 35.09 , 32.97 , 32.69 , 32.57 , 32.44 , 31.41 , 30.76 , 29.68 , 28.53 , 28.49 , 28.23 , 28.12 , 27.93 , 27.41 , 27.17 , 26.78 , 21.52 , 21.40 , 21.28 , 21.24 , 21.21 , 20.99 , 20.94 , 19.75 .

4-(2-(3-(furan-2-ylmethoxy)-2-hydroxypropyl)decahydro-1H,4H-pyrido[3,2,1-*ij*][1,6]naphthyridin-1-yl)butan-1-ol. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 (s, 2H), 6.35 – 6.27 (m, 4H), 4.49 (s, 1H), 4.48 (s, 3H), 3.92 – 3.80 (m, 2H), 3.60 (dd, *J* = 10.9, 4.6 Hz, 5H), 3.56 – 3.37 (m, 4H), 3.12 (t, *J* = 13.0 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.82 – 2.67 (m, 8H), 2.63 – 2.49 (m, 2H), 2.32 (dd, *J* = 13.1, 9.8 Hz, 1H), 2.18 – 2.06 (m, 1H), 2.05 – 1.88 (m, 14H), 1.92 – 1.78 (m, 4H), 1.64 (d, *J* = 10.0 Hz, 1H), 1.51 – 1.41 (m, 3H), 1.39 (s, 6H), 1.36 (d, *J* = 8.1 Hz, 3H), 1.33 – 1.16 (m, 3H), 0.83 (s, 1H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 151.65 , 142.89 , 142.72 , 116.34 , 110.23 , 109.55 , 109.40 , 109.38 , 76.79 , 72.75 , 72.33 , 70.53 , 66.55 , 65.92 , 65.25 , 65.23 , 65.01 , 64.44 , 63.93 , 62.31 , 61.82 , 61.74 , 57.44 , 57.36 , 57.32 , 57.20 , 57.16 , 54.27 , 52.45 , 51.68 , 50.17 , 45.18 , 44.28 , 38.79 , 36.86 , 34.68 , 32.58 , 32.48 , 32.19 , 31.00 , 29.66 , 28.49 , 28.11 , 27.82 , 27.31 , 27.12 , 21.51 , 21.35 , 21.32 , 21.02 , 20.99 , 20.87 , 19.46 , 1.85 .

References

- [1] Mishra, V., & Borah, D. (2006). Phytochemical and antimicrobial effects of some indigenous medicinal plants. Retrieved October 2017
- [2] Nwodo, J. N., Ibezim, A., Simoben, C. V., & Ntie-Kang, E. (2017). Exploring Cancer Therapeutics with Natural Products from African Medicinal Plants, Part II: Alkaloids, Terpenoids and Flavonoids. Retrieved October 2017
- [3] Qing, Z., Yang, P., Tang, Q., Cheng, P., Liu, X., Zheng, Y., Liu, Y., & Zeng, J (2003). Isoquinoline Alkaloids and Their Antiviral, Antibacterial, and Antifungal Activities and Structure-activity Relationship. Retrieved October 2017
- [4] Pang, J. (1999). Alkaline water used for plant protection and its preparation from traditional Chinese medicine. Retrieved October 2017
- [5] Martinez, S. M. (2006). The chemistry of alkaloids in the approach to a current social problem being drug abuse. Retrieved October 2017
- [6] S. D. (n.d.). MATRINE AND OXYMATRINE Subjects Of Chinese Research. Retrieved September, 2017, from <http://www.itmonline.org/arts/oxymatrine.htm>
- [7] Young, V. M., Forbes, M., & McNaughton, A. B. (2009). Abuse-resistant pharmaceutical formulations. Retrieved October 2017
- [8] Art of herbal remedies revealed. (2016). Retrieved September, 2017, from <http://www.chineseherbshealing.com/sophora-flavescens-root/>
- [9] Zhang, Y., Lin, Z., & Han, M. (2017). Study on the change of the content of aromatic amino acid residues in the process of malignant transformation by synchronous fluorescence spectrometry. Retrieved October 2017
- [10] Chang Minyi, *Anticancer Medicinal Herbs* (1992), Hunan Science and Technology Publishing House, Changsha.

- [11] Ningxi, Z. (2001). Study on inducing and differentiating function and mechanism of matrine on leukemia cells. *15*(1), 43-44. Retrieved September, 2017.
- [12] Ma, T., Yan, H., Shi, X., Liu, B., Ma, Z., & Zhang, X. (2009). Comprehensive evaluation of effective constituents in total alkaloids from *Sophora alopecuroides* L. and their joint action against aphids by laboratory toxicity and field efficacy. Retrieved October 2017
- [13] Zhao, L., Mao, L., Hong, G., Yang, X., & Liu, T. (2015). Design, synthesis and anticancer activity of matrine-1H-1,2,3-triazole-chalcone conjugates. *Bioorganic & Medicinal Chemistry Letters*, *25*(12), 2540-2544. doi:10.1016/j.bmcl.2015.04.051
- [14] Huang, Y., Wang, G., Zhu, J., Zhang, R., & Zhang, J. (2007). Traditional uses, phytochemistry, and pharmacological properties of *Sophora alopecuroides* L. Retrieved October 2017
- [15] Shao, H., Yang, B., Hu, R., & Wang, Y. (2013, August). Matrine effectively inhibits the proliferation of breast cancer cells through a mechanism related to the NF- κ B signaling pathway. Retrieved September, 2017, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3789031/>
- [16] Ma, D. (2006). Traditional Chinese medicine formulation for preventing and treating human papilloma virus infection and preparation method. Retrieved October 2017
- [17] Dewick, P. M. (2001). Medicinal Natural Products. Retrieved October. 2017, from https://books.google.com/books?hl=en&lr=&id=A4zptjOJfKQC&oi=fnd&pg=PA1&dq=semi%20synthetic%20approaches%20drug%20discovery&ots=whcuKZUNYl&sig=L3nmO6kCjYYGuQsKDsl dmb_wY8#v=onepage&q=semi%20synthetic%20approaches%20drug%20discovery&f=false
- [18] Ehrenworth, A. M., & Peralta-Yahya, P. (2017, February 15). Accelerating the semisynthesis of alkaloid-based drugs through metabolic engineering. Retrieved October. 2017, from <http://www.nature.com.ezproxy.rowan.edu/articles/nchembio.2308>

- [19] Zhang, B. (2003). Oxymatrine-containing bacteriostatic agent. Retrieved October 2017
- [20] Wang, X., Li, L., & Han, G. (2011). Research progress in pharmacology of matrine. Retrieved October 2017
- [21] Wu, F., Zhang, Q., & Zhang, C. (2006). Recent advances of *Sophora flavescens* applied to T cell-mediated skin diseases. Retrieved October 2017
- [22] Shao, M., & Fan, Q. (2005). New progress of antitumor research on matrine. Retrieved October 2017
- [23] Wang, W., You, R., Qin, W., Hai, L., Fang, M., Huang, G., Kang, R., Li, M., Qiao, Y., Li, J., & Li, A. (2014). Anti-tumor activities of active ingredients in Compound Kushen Injection. Retrieved October 2017
- [24] Liu, Y., Bi, T., Dai, W., Wang, G., Qian, L., Gao, Q., & Shen, G. (2001). Effects of oxymatrine on the proliferation and apoptosis of human hepatoma carcinoma cells. Retrieved October 2017
- [25] Matrine (ab142910m). (2017, September 20). Retrieved September, 2017, from <http://www.abcam.com/matrine-ab142910.html>
- [26] Lin, Z., Huang, C., Liu, X., & Jiang, J. (2010, October 31). In Vitro Anti-Tumour Activities of Quinolizidine Alkaloids Derived from *Sophora Flavescens* Ait. Retrieved October, 2017, from <http://onlinelibrary.wiley.com/store/10.1111/j.17427843.2010.00653.x/asset/j.1742-7843.2010.00653.x.pdf;jsessionid=5FD3CB9B2D524EC614470FB4D34D7CB8.f03t04?v=1&t=j9hcwkle&sbd722179e0e03ae20da2b2119ac1bf11d9801597>
- [27] Revolvly, L. (n.d.). "Strecker amino acid synthesis" on Revolvly.com. Retrieved September, 2017, from https://www.revolvly.com/main/index.php?s=Strecker amino acid synthesis&item_type=topic
- [28] Revolvly, L. (n.d.). "A3 coupling reaction" on Revolvly.com. Retrieved September, 2017, from <https://www.revolvly.com/main/index.php?s=A3 coupling reaction>

- [29] Albano, G., & Aronica, L. A. (2005). Potentiality and Synthesis of O- and N-Heterocycles: Pd-Catalyzed Cyclocarbonylative Sonogashira Coupling as a Valuable Route to Phthalans, Isochromans, and Isoindolines. Retrieved October 2017
- [30] Elbert, B. L., Farley, A. J. M., Gorman, T. W., Johnson, T. C., Genicot, C., Lallemand, B., Pasau, P., Flasz, J., Castro, J. L., MacCoss, M., Paton, R. S., Schofield, C. J., Smith, M. D., Willis, M. C., & Dixon, D. J. (2002). C-H Cyanation of 6-Ring N-Containing Heteroaromatics. Retrieved October 2017
- [31] Taib, L. A., & Al-Yamani, R. M. (2002). Synthesis of new heterocyclic nitrogen system bearing thiazolopyrazole moiety as new biocidal agents. Retrieved October 2017
- [32] Olaru, A., Vasilache, V., Danac, R., & Mangalagiu, I. I. (2005). Antimycobacterial activity of nitrogen heterocycles derivatives: 7-(pyridine-4-yl)-indolizine derivatives. Part VII8-12. Retrieved October 2017
- [33] Bandyopadhyay, D., Velazquez, J. M., & Banik, B. K. (2011, October 4). A truly green synthesis of α -aminonitriles *via* Strecker reaction. Retrieved October, 2017, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3339329/>
- [34] Gröger, H. (2003, January 22). Catalytic Enantioselective Strecker Reactions and Analogous Syntheses. Retrieved October, 2017, from <http://pubs.acs.org.ezproxy.rowan.edu/doi/pdf/10.1021/cr020038p>
- [35] Martins, P., Jesus, J., Santos, S., Raposo, L. R., Roma-Rodrigues, C., Baptista, P. V., & Fernandes, A. R. (2015, September 16). Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift towards the Use of Nanomedicine's Tool Box. Retrieved October, 2017, from www.mdpi.com/journal/molecules
- [36] Moura-Letts, G., Ph.D., (n.d.). Moura-Letts Group. Retrieved October. 2017, from <https://www.gmlresearchgroup.com/projects>
- [37] Moura-letts, Gustavo, Ph.D., Department of Chemistry and Biochemistry, Rowan University

- [38] Rakhtshah, J., & Salehzadeh, S. (2007). Molybdenum Schiff base complex supported on MNPs as an efficient and easily recyclable catalyst in three-component Strecker reaction for synthesis of α -aminonitrile derivatives. Retrieved October 2017
- [39] Corey, E. J., & Grogan, M. J. (1999, May 24). Enantioselective Synthesis of α -Amino Nitriles from N-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst. Retrieved October, 2017, from <http://pubs.acs.org/doi/abs/10.1021/o19906231>
- [40] Tadiparthi, K., Raghavendra, S., & Kamal, A. (2006). A Catalytic, One-pot and Green Synthesis of α -Amino Nitriles: Cu(BF₄)₂.x H₂O an Efficient Catalyst. Retrieved October 2017
- [41] Fleming, F. F., Yao, L., Ravikumar, P. C., Funk, L., & Shook, B. C. (2010, June 23). Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. Retrieved October, 2017, from <http://pubs.acs.org.ezproxy.rowan.edu/doi/pdf/10.1021/jm100762r>
- [42] Mas-Rosello, J., Hachisu, S., & Clayden, J. (2005). Geometry-Retentive C-Alkenylation of Lithiated α -Aminonitriles: Quaternary α -Alkenyl Amino Acids and Hydantoins. Retrieved October 2017
- [43] Kondo, M., Omori, M., Hatanaka, T., Funahashi, Y., & Nakamura, S. (2009). Catalytic Enantioselective Reaction of Allenynitriles with Imines Using Chiral Bis(imidazolines) Palladium(II) Pincer Complexes. Retrieved October 2017
- [44] Zhao, B., Lan, X., Tao, C., & Liu, X. (2010). Preparation of chiral pyridoxamine compounds as catalysts for synthesizing chiral amino acids. Retrieved October 2017
- [45] Indalkar, K. S., Khatri, C. K., & Chaturbhuj, G. U. (2009). Expedient and efficient synthesis of Strecker's α -aminonitriles catalyzed by sulfated polyborate. Retrieved October 2017
- [46] Li, P., Zhang, Y., Chen, Z., & Zhang, X. (2004). Highly efficient three-component Strecker-type reaction catalyzed by MgI₂ etherate under solvent-free conditions. Retrieved October 2017

- [47] Strecker Synthesis. (n.d.). Retrieved September, 2017, from <http://www.organic-chemistry.org/namedreactions/strecker-synthesis.shtm>
- [48] Wang, M., Li, P., & Wang, L. (2008, March 11). Silica-Immobilized NHC–CuI Complex: An Efficient and Reusable Catalyst for A3-Coupling (Aldehyde–Alkyne–Amine) under Solventless Reaction Conditions. September, 2017, <http://dx.doi.org.ezproxy.rowan.edu/10.1002/ejoc.200800006>
- [49] Lin, T., Zhang, L., Bjoerk, J., Chen, Z., Ruben, M., Barth, J. V., & Klappenberger, F. (2002). Terminal Alkyne Coupling on a Corrugated Noble Metal Surface: From Controlled Precursor Alignment to Selective Reactions. Retrieved October 2017
- [50] Sheik M. S., Aswin, K., Logaiya, K., & Sudhan, S. P. N. (2001). An efficient one-pot three-component synthesis of α -amino nitriles via Strecker reaction catalysed by bismuth(III) nitrate. Retrieved October 2017
- [51] Liu, J., & Peng, Y. (2009). Strecker reaction catalyzed by copper containing polymeric sulfonate. Retrieved October 2017
- [52] Miyagawa, S., Yoshimura, K., Yamazaki, Y., Takamatsu, N., Kuraishi, T., Aiba, S., Tokunaga, Y., & Kawasaki, T. (2004). Asymmetric Strecker Reaction Arising from the Molecular Orientation of an Achiral Imine at the Single-Crystal Face: Enantioenriched L- and D-Amino Acids. Retrieved October 2017
- [53] Kaur, P., Wever, W., Pindi, S., Milles, R., Gu, P., Shi, M., & Li, G. (2008). The GAP chemistry for chiral N-phosphonyl imine-based Strecker reaction. Retrieved October 2017
- [54] Mirza-Aghayan, M., Alvandi, F., Tavana, M. M., & Boukherroub, R. (2010). Graphite oxide catalyzed synthesis of β -amino alcohols by ring-opening of epoxides. Retrieved October 2017
- [55] Dyuschaeva, M. A. (2003). Synthesis of amino alcohol aliphatic and heterocyclic series and their derivatives. Retrieved October 2017

- [56] Maalej, E.; Chabchoub, F.; Oset-Gasque, M. J.; Esquivias-Perez, M.; Gonzalez, M. P.; Monjas, L.; Perez, C.; de los Rios, C.; Rodriguez-Franco, M. I.; Iriepa, I.; Moraleda, I.; Chioua, M.; Romero, A.; Marco-Contelles, J.; & Samadi, A. (2012). Synthesis, biological assessment, and molecular modeling of racemic 7-aryl-9,10,11,12-tetrahydro-7H-benzo[7,8]chromeno[2,3-b]quinolin-8-amines as potential drugs for the treatment of Alzheimer's disease. Retrieved October 2017
- [57] Bertuzzi, G., Fochi, M., & Franchini, M. C. (2012). Regiocontrolled 1,3-dipolar cycloadditions of nitrile imines with acetylenes and α,β -unsaturated systems: synthesis of polysubstituted and ring fused pyrazoles with pharmaceutical activity. Retrieved October 2017
- [58] MacFaul, P. A., Morley, A. D., & Crawford, J. J. (2016). A simple in vitro assay for assessing the reactivity of nitrile containing compounds. Retrieved October 2017
- [59] Gholinejad, M., Karimi, B., Aminianfar, A., & Khorasani, M. (2015, August 27). One-Pot Preparation of Propargylamines Catalyzed by Heterogeneous Copper Catalyst Supported on Periodic Mesoporous Organosilica with Ionic Liquid Framework. Retrieved September, 2017, from https://www.researchgate.net/publication/280916196_OnePot_Preparation_of_Propargylamines_Catalyzed_by_Heterogeneous_Copper_Catalyst_Supported_on_Periodic_Mesoporous_Organosilica_with_Ionic_Liquid_Framework
- [60] Hughes, T. B., & Swamidass, S. J. (2002). Deep Learning to Predict the Formation of Quinone Species in Drug Metabolism. Retrieved October 2017
- [61] Bidwell, S.; & Hratchian, H. P. (1990). Computational exploration of copper catalyzed azide-alkyne coupling reactions. Retrieved October 2017
- [62] Oulie, P., Dinoi, C., Li, C., Sournia-Saquet, A., Jacob, K., Vendier, L., & Etienne, M. (2012). CH Bond Activation of Unsaturated Hydrocarbons by a Niobium Methyl Cyclopropyl Precursor. Cyclopropyl Ring Opening and Alkyne Coupling Reaction. Retrieved October 2017
- [63] Nasrollahzadeh, M., Mohammad S. S., & Rostami-Vartooni, A. (2009). Green synthesis of CuO nanoparticles by aqueous extract of *Anthemis nobilis* flowers and their catalytic activity for the A3 coupling reaction. Retrieved October 2017

- [64] Liu, L., Tai, X., Liu, M., Li, Y., Feng, Y., & Sun, X. (2008). Supported Au/MOF-5: a highly active catalyst for three-component coupling reactions. Retrieved October 2017
- [65] Iida, A., Ueda, K., & Yamashita, M. (2010). Novel preparation of anticancer-active tricyclic compounds via alkyne coupling reaction. Retrieved October 2017
- [66] Zhang, M., Wang, L., Li, L., & Tian, A. (2003). Investigation on coupling reaction mechanism from N-(2-bromophenyl)-2,2,2-trifluoroacetamide and terminal alkyne to indol catalyzed by CuI. Retrieved October 2017
- [67] Garcia-Castro, M., Annamalai, M., Golz, C., Strohmman, C., & Kumar, K. (2014). Stereoselective Synthesis of Trisubstituted Epoxides Marks the Route to Chiral Building Blocks with Quaternary Centers. Retrieved October 2017
- [68] Ozhan K. S., Karakaplan, M., & Scopelliti, R. (2000). Synthesis and crystal structure of a chiral lactam and three amino alcohols as potential protein tyrosine phosphates 1B inhibitors. Retrieved October 2017
- [69] Ager, D. J., Prakash, I., & Schaad, D. R. (1995, November 8). 1,2-Amino Alcohols and Their Heterocyclic Derivatives as Chiral Auxiliaries in Asymmetric Synthesis. Retrieved October, 2017, from <http://pubs.acs.org.ezproxy.rowan.edu/doi/pdf/10.1021/cr9500038>
- [70] McConathy, J., Ph.D., & Owens, M. J., Ph.D. (2003, April 25). Stereochemistry in Drug Action. Retrieved October, 2017, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC353039/pdf/i1523-5998-005-02-0070.pdf>
- [71] Hutt, A. J. (2002, April). The development of single-isomer molecules: why and how. Retrieved October, 2017, from <https://www.ncbi.nlm.nih.gov/pubmed/15131488>
- [72] Aldrich, L. N., Gerlach, E. M., Helgren, T. R., Korkmaz, M. A., Oleksyuk, M., Pavlinov, I., & Xu, L. L. (1998). Stereoselective synthesis of flavonoid analogues and evaluation of biological performance diversity. Retrieved October 2017

- [73] Somina, H., Mackey, S., Lynch, V., Socol, S., Ortega, L., & Ning, Y. (2004). Synthesis, characterization and polymerization of salen iron(III) complexes. Retrieved October 2017
- [74] Dyuscbaeva, M. A. (2006). Synthesis of amino alcohol aliphatic and heterocyclic series and their derivatives. Retrieved October 2017
- [75] Dagan, A., Barzilay, C. M., & Ali, A. A. (2000). Amino-alcohol analogues and uses thereof. Retrieved October 2017
- [76] Negrisoli, G., Canevotti, R., Previtali, M., Aldini, G., Carini, M., Orioli, M., & Vistoli, G. (2017). Amino alcohol derivatives and their therapeutic activities. Retrieved October 2017
- [77] Hattori, T., Ishii, H., & Kariya, Y. (2009). Preparation of amino-alcohol using metal-supported catalyst. Retrieved October 2017
- [78] What Is Chronic Myeloid Leukemia? | Leukemia Types. (2016, February 22). Retrieved October, 2017, from <https://www.cancer.org/cancer/chronic-myeloid-leukemia/about/what-is-cml.html>
The American Cancer Society medical and editorial content team
- [79] Kim, D. U., Kim, S. H., Kim, H. T., Han, S. H., Jung, H. J., & Lee, J. Y. (2014). Method to provide information about chronic myelogenous leukemia [Machine Translation]. Retrieved October 2017
- [80] Usui, N. (2003). Correction to: JSH guideline for tumors of hematopoietic and lymphoid tissues-leukemia: 4. Chronic myelogenous leukemia (CML) /myeloproliferative neoplasms (MPN). Retrieved October 2017
- [81] Fang, Z., Jung, K. H., Yan, H. H., Kim, S. J., Son, M. K., Rumman, M., Lee, H., Kim, K. W., Yoo, H., & Hong, S. (2015). CD-200 induces apoptosis and inhibits Bcr-Abl signaling in imatinib-resistant chronic myeloid leukemia with T315I mutation. Retrieved October 2017

- [82] Liu, X., Rothe, K., Yen, R., Fruhstorfer, C., Maetzig, T., Chen, M., Forrest, D. L., Humphries, R. K., & Jiang, X. (2003). A novel AHI-1-BCR-ABL-DNM2 complex regulates leukemic properties of primitive CML cells through enhanced cellular endocytosis and ROS-mediated autophagy. Retrieved October 2017
- [83] Antoszewska-Smith, J., Pawlowska, E., & Blasiak, J. (2005). Reactive oxygen species in BCR-ABL1-expressing cells - relevance to chronic myeloid leukemia. Retrieved October 2017
- [84] Organista-Nava, J., Gomez-Gomez, Y., Illades-Aguiar, B., & Leyva-Vazquez, M. A. (2016). Regulation of the miRNA expression by TEL/AML1, BCR/ABL, MLL/AF4 and TCF3/PBX1 oncoproteins in acute lymphoblastic leukemia (review). Retrieved October 2017
- [85] Sugita, K., & Ando, K. (2007). Therapeutic agent or therapeutic method for treatment of Philadelphia chromosome positive acute lymphocytic leukemia having IKZ1 mutation containing BCR-ABL tyrosine kinase inhibitor and thalidomide derivative. Retrieved October 2017
- [86] Alberto, R. R., Yudibeth, S., Jonathan, F. M., Raul, F., Cristina, C. L., Ismael, V., Cecilia, R. M., Martiniano, B., Martinez-Archundia, M., Guadalupe, T. J., Elvia, B., & Jose, C. (2003). Design, Synthesis and Biological Evaluation of a Phenyl Butyric Acid Derivative, N-(4-chlorophenyl)-4-phenylbutanamide: A HDAC6 Inhibitor with Anti-proliferative Activity on Cervix Cancer and Leukemia Cells. Retrieved October 2017
- [87] Kaitsiotou, H., Keul, M., Hardick, J., Muehlenberg, T., Ketzer, J., Ehrt, C., Kruell, J., Medda, F., Koch, O., Giordanetto, F., Bauer, S., Rauh, D. (2002). Inhibitors to Overcome Secondary Mutations in the Stem Cell Factor Receptor KIT. Retrieved October 2017
- [88] Toman, O., Kabickova, T., Vit, O., Fiser, R., Machova Polakova, K., Zach, J., Linhartova, J., Vyoral, D., & Petrak, J. (1998). Proteomic analysis of imatinib-resistant CML-T1 cells reveals calcium homeostasis as a potential therapeutic target. Retrieved October 2017
- [89] Kinase Inhibitors. (n.d.). Retrieved October, 2017, from <http://chemoth.com/types/kinaseinhibitors>
Types of Chemotherapy Agents and Regimens

- [90] Okumu, D. O., East, M. P., Levine, M., Herring, L. E., Zhang, R., Gilbert, T. S. K., Litchfield, D. W., Zhang, Y., & Graves, L. M. (1998). BIRC6 mediates imatinib resistance independently of Mcl-1. Retrieved October 2017
- [91] Yang, T. (2005). Use of peptide biosensors for monitoring activity of kinases in chronic myelogenous leukemia. Retrieved October 2017
- [92] Zhou, H., Li, Y., Liu, B., Shan, Y., Li, Y., Zhao, L., Su, Z., & Jia, L. (2001). Downregulation of miR-224 and let-7i contribute to cell survival and chemoresistance in chronic myeloid leukemia cells by regulating ST3GAL IV expression. Retrieved October 2017
- [93] Cheloni, G., Tanturli, M., Tusa, I., De Souza, N. H., Shan, Y., Gozzini, A., Mazurier, F., Rovida, E., Li, S., & Sbarba, P. D. (2003). Targeting chronic myeloid leukemia stem cells with the hypoxia-inducible factor inhibitor acriflavine. Retrieved October 2017
- [94] Cao, Y. (2005). Quinazoline compound, and its synthesis process and application in preparing antitumor drugs. Retrieved October 2017
- [95] Darji, A. A., & Bharadia, P. D. (2016). Chronic myelogenous leukemia: a review and update of current and future therapy. Retrieved October 2017
- [96] Perazzona, B.; Lin, H.; Sun, T.; Wang, Y.; & Arlinghaus, R. (2008). Kinase domain mutants of Bcr enhance Bcr-Abl oncogenic effects. Retrieved October 2017
- [97] Helgason, G. V., Mukhopadhyay, A., Karvela, M., Salomoni, P., Calabretta, B., & Holyoake, T. L. (2000). Autophagy in Chronic Myeloid Leukaemia: Stem Cell Survival and Implication in Therapy. Retrieved October 2017
- [98] Kantarjian, H. M., Baccarani, M., Jabbour, E., Saglio, G., & Cortes, J. E. (2002). Second-Generation Tyrosine Kinase Inhibitors: The Future of Frontline CML Therapy. Retrieved October 2017
- [99] Wei, W.; Sun, P.; Yang, S.; Kang, L.; Li, Q. (2017). Indoles alkaloid and its preparation method, application in preparation of antitumor drug. Retrieved October 2017

- [100] Zhang, J., & Liu, D. (2014). *Sophora flavescens* extract used in the treatment of HPV. Retrieved October 2017
- [101] Xu, M., Yu, X., & Jin, Z. (2004). Research progress of macroporous resin separation of three *Sophora* alkaloids in *Sophora flavescens* Ait. Retrieved October 2017
- [102] Dang, Z., Jung, K., Zhu, L., Lai, W., Xie, H., Lee, K., Huang, L., & Chen, C. (2002). Identification and Synthesis of Quinolizidines with Anti-Influenza A Virus Activity. Retrieved October 2017
- [103] Duan, L., Yan, X., & Han, J. (2005). In vitro inhibitions of *Sophora* alkaloids and 4 monomer alkaloids against *Helicobacter pylori*. Retrieved October 2017
- [104] Li, H.; Tan, G.; Jiang, X.; Qiao, H.; Pan, S.; Jiang, H.; Kanwar, J. R.; & Sun, X. (2008). Therapeutic Effects of Matrine on Primary and Metastatic Breast Cancer. Retrieved October 2017
- [105] Renn, Lindsay Michelle, "Development of Novel Alkaloid Derivatives For the Treatment of Chronic Myeloid Leukemia" (2017). Theses and Dissertations. <http://rdw.rowan.edu/etd/2472>
- [106] Soverini, S., De Benedittis, C., Castagnetti, F., Gugliotta, G., Mancini, M., Bavaro, L., Polakova, K. M., Linhartova, J., Iurlo, A., Russo, D., Pane, F., Saglio, G., Rosti, G., Cavo, M., Baccarani, M., & Martinelli, G. (2010). In chronic myeloid leukemia patients on second-line tyrosine kinase inhibitor therapy, deep sequencing of BCR-ABL1 at the time of warning may allow sensitive detection of emerging drug-resistant mutants. Retrieved October 2017
- [107] Dong, Z., Gao, J., Gong, J., Li, J., Li, Y., Shen, L., & Li, J. (2009). Clinical benefit of sunitinib in gastrointestinal stromal tumors with different exon 11 mutation genotypes. Retrieved October 2017
- [108] Chen, J., Li, X., Cheng, Q., Ning, D., Ma, J., Zhang, Z., Chen, X., & Jiang, L. (2007). Effects of cyclin D1 gene silencing on cell proliferation, cell cycle, and apoptosis of hepatocellular carcinoma cells. Retrieved October 2017

- [109] Li, L., Yu, C., & Huang, H. (2004). Novel heterocyclic compounds as tyrosine kinase bcr-abl inhibitors
- [110] Lin, J., Ibrahim, P. N., Albers, A., Buell, J., Guo, Z., Pham, P., Powers, H., Shi, S., Spevak, W., Wu, G., Zhang, J., & Zhang, Y. (2012). Preparation of heterocyclic compounds and methods for kinase modulation and indications therefore. Retrieved October 2017
- [111] Sharma, V., Kamal, R., & Kumar, V. (2016). Heterocyclic Analogues as Kinase Inhibitors: A Focus Review. Retrieved October 2017
- [112] Yang, P., Gray, N. S., Miduturu, C., & Clark, M. J. (2005). Substituted heterocyclic compounds for treating or preventing viral infections. Retrieved October 2017
- [113] Min, C., Oh, B., Kim, Y., & Park, C. (2013). Preparation of heterocyclic compounds as CDK inhibitors. Retrieved October 2017
- [114] Terentjeva, S., Muceniece, D., Petushkova, J., & Lasis, V. (2000). Synthesis of novel 3-substituted benzamides related to imatinib. Retrieved October 2017
- [115] Mackinnon, A. L., & Rodriguez, M. L. (2010). Treatment of multiple myeloma with heterocyclic inhibitors of glutaminase. Retrieved October 2017