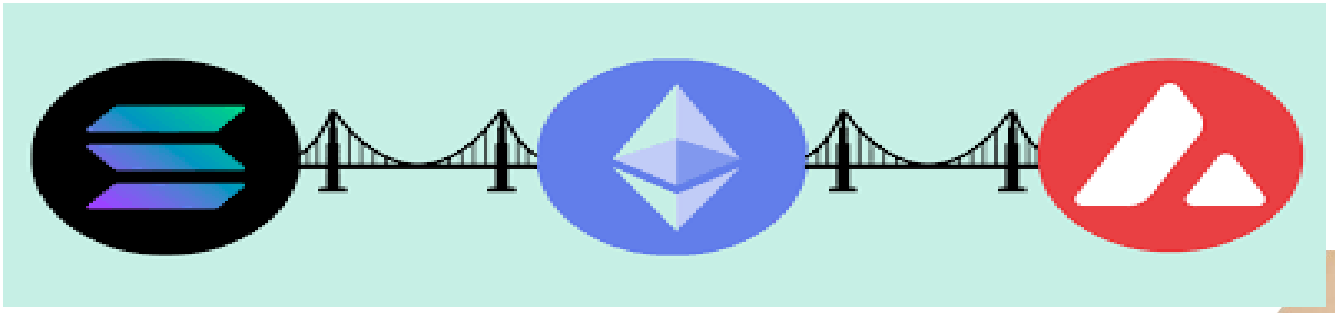

Rational Drug Design towards Sustainability !

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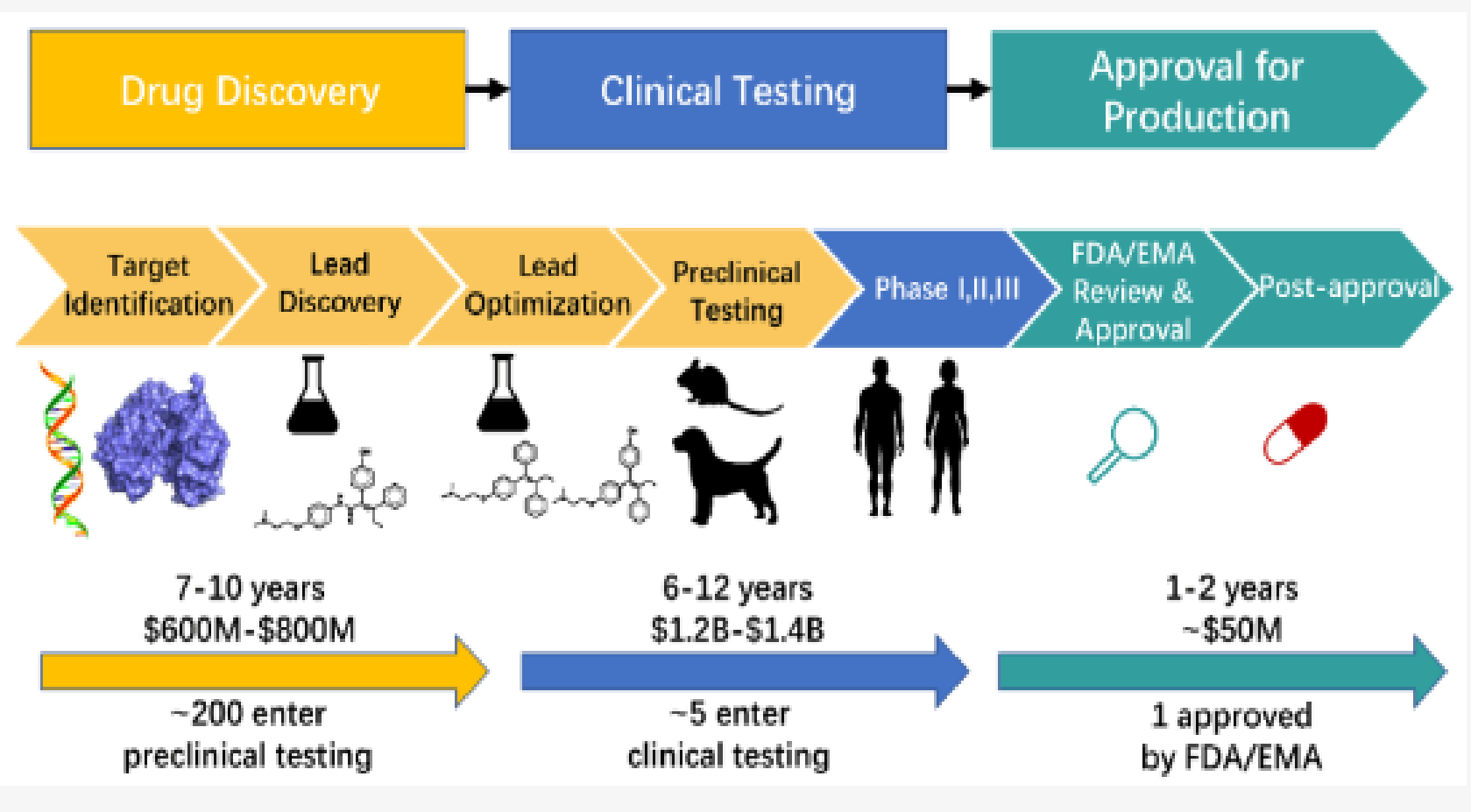
كلية الصيدلة
Faculty of Pharmacy

الجمعية العلمية لكليات الصيدلة في الوطن العربي

2007 LIMU
الجامعة الليبية الدولية
Libyan International University

The process of drug research and development.



Outline of my talk

- **Brief overview of rational drug design and green chemistry.**

1. **Traditional Drug Discovery Process**
    1. Overview of conventional drug discovery methods.
    2. Challenges and limitations in terms of environmental impact
2. **Rational Drug Design**

- **Importance of sustainability in pharmaceutical development**.
    1. Explanation of rational drug design approach.
    2. How rational drug design aims to optimize drug properties while minimizing waste and environmental impact.
    3. Examples of successful applications of rational drug design.

Traditional Drug Discovery Process

Drug Discovery (Before)
Mind drug Discovery Only!

- In the past, many medicines (and lead compounds) were isolated from plant sources.
- Since plants did not evolve with human beings in mind, the fact that they posses chemicals which results in effects on humans is incidental.

- **Finding a needle in a haystack.!!**

Challenges and limitations in terms of environmental impact.

1. Chemical Synthesis: Many drug compounds are synthesized using complex chemical reactions, which can generate hazardous waste and require large amounts of energy and resources.

2. Animal Testing: Preclinical testing often involves the use of large numbers of animals, which raises ethical concerns and can have environmental impacts related to animal husbandry and waste management.

3. Waste Disposal: Drug manufacturing processes generate significant amounts of waste, including solvents, reagents, and by-products, which must be disposed of properly to prevent environmental contamination.

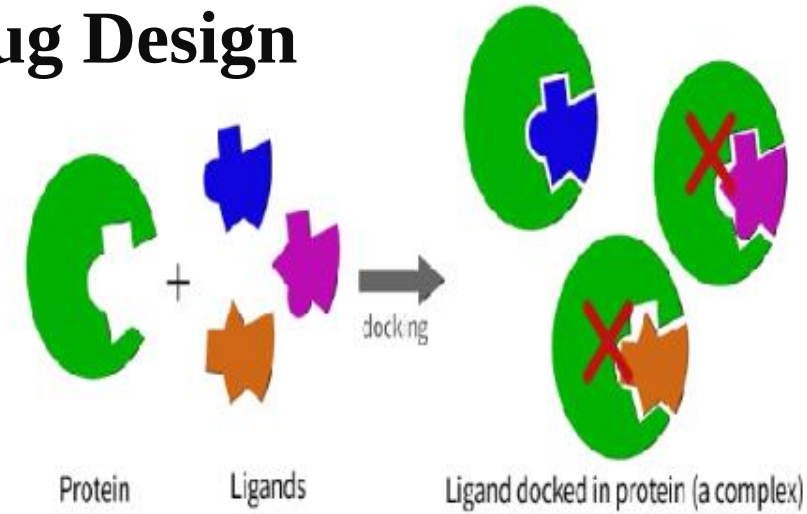
4. Energy Consumption: The drug discovery and development process requires substantial energy inputs, particularly for laboratory equipment, synthesis, and testing procedures, contributing to carbon emissions and climate change.

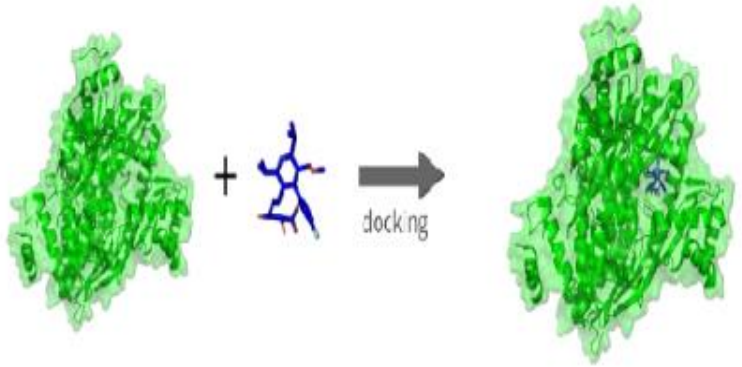
5. Resource Intensiveness: Discovering and developing a single drug candidate can require years of research, large teams of scientists, and substantial financial investments, all of which place additional strain on natural resources and ecosystems.

6. Regulatory Requirements: Regulatory requirements for drug approval often necessitate extensive testing and documentation, which can result in increased resource consumption and environmental impact.

2. Rational Drug Design

- **Definition**: Introduce rational drug design as a methodical approach to drug discovery that involves **the use of computational** and **experimental techniques** to **identify and optimize drug candidates.**



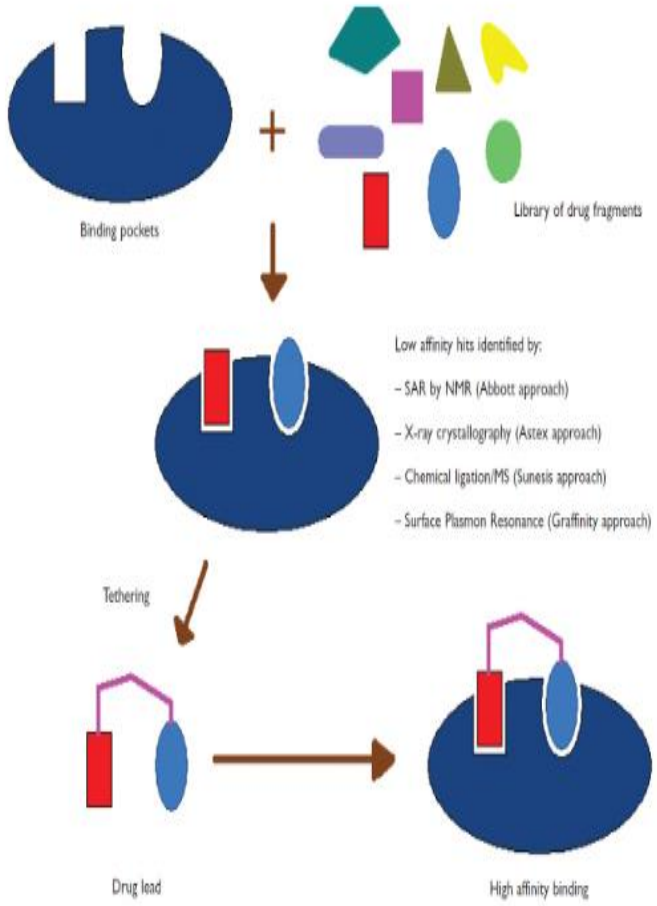


Rational Drug Design= RDD

As the demand for effective drugs has increased in the last century, **a rational drug design has begun to replace old method.**

With the progress in the field of chemistry, biology, biochemistry, pharmacology, physics and increase in computational power, drug discovery has become inter disciplinary area and entered a new phase called computer aided drug design (CADD) or

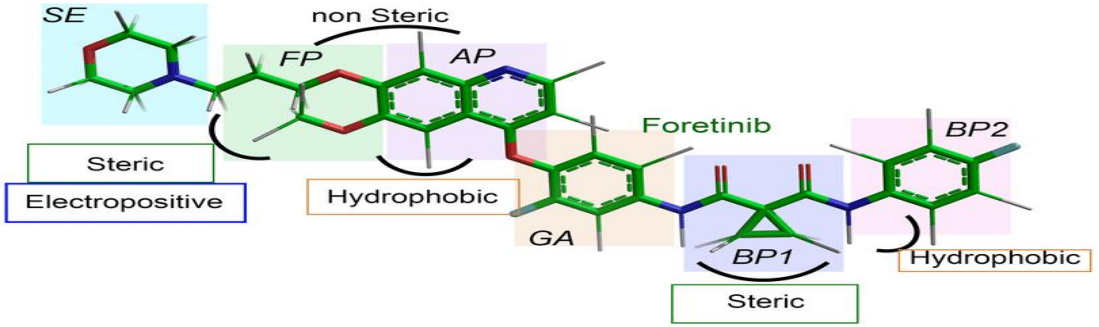
computer assisted molecular design (CAMD) (Latosińska and Latosińska 2013)



Key Components of RDD:

- Molecular modeling (MM): Use of computational tools to predict the interactions between drugs and their biological targets

- Structure-activity relationship (SAR) studies: Analysis of how chemical structure influences the activity of a drug molecule.

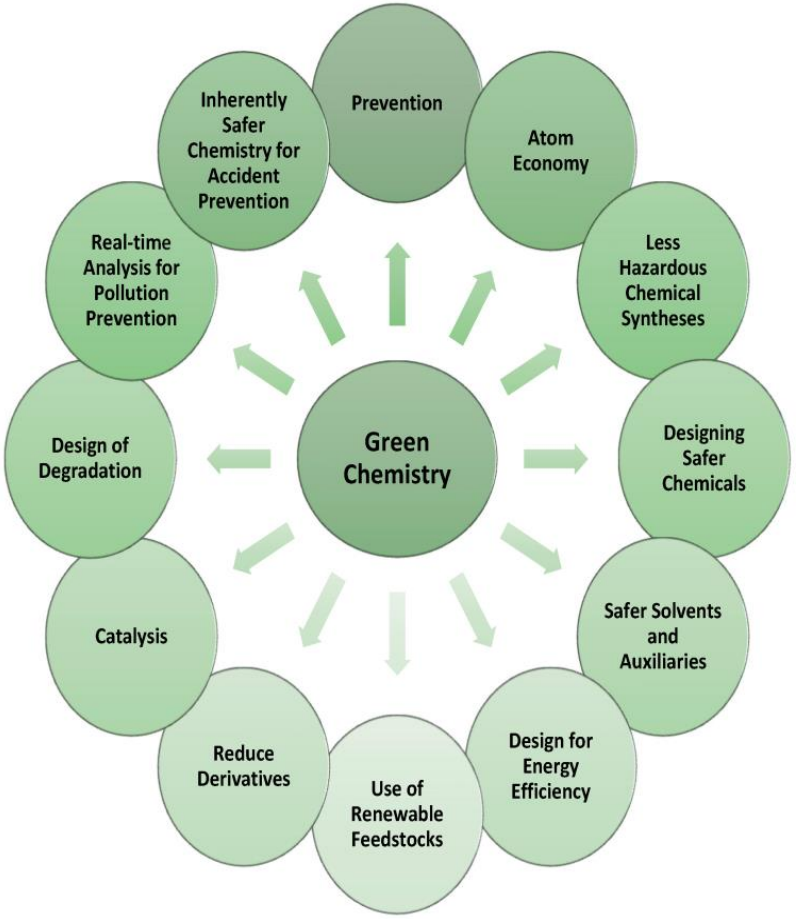


- High-throughput screening: Rapid testing of large libraries of compounds to identify potential drug candidates.

1. **Advantages**:
    1. Faster drug discovery process compared to traditional methods.
    2. Greater precision in targeting specific biological pathways.
    3. Potential for reduced costs and resource usage.
2. **Examples**:
    1. Design of HIV protease inhibitors.
    2. Development of targeted cancer therapies like imatinib (Gleevec).

Integration of Rational Drug Design and Green Chemistry

- How rational drug design principles can be aligned with green chemistry goals.
- Case studies or examples showcasing the integration of rational drug design and green chemistry.



Benefits of Sustainable Drug Development

- Environmental benefits: Reduced waste, energy consumption, and pollution.

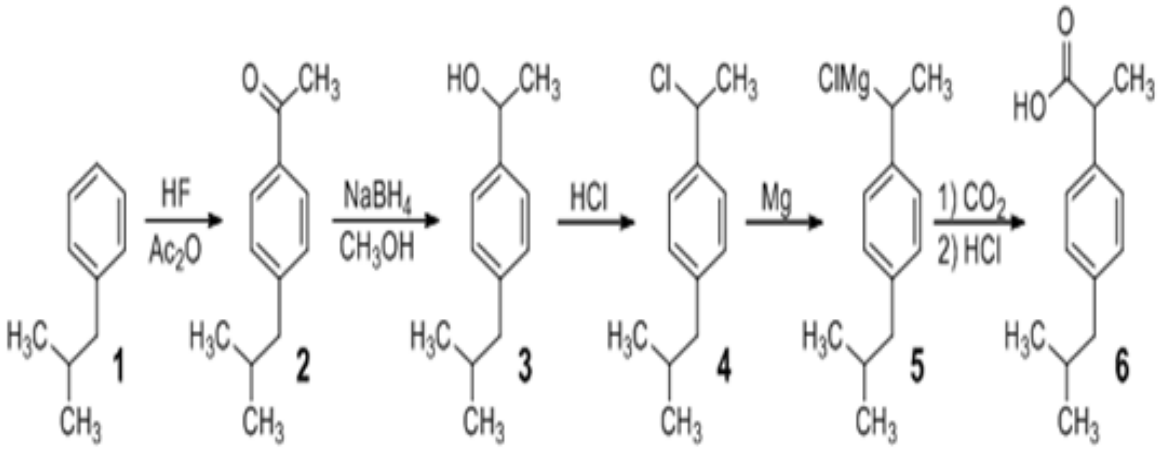
- Economic benefits: Cost savings, regulatory advantages.

- Social benefits: Improved public perception, healthier communities.

1. **Applications**:
    1. Development of greener synthetic routes for pharmaceutical intermediates.
    2. Design of environmentally friendly solvents for drug formulation.
    3. Implementation of sustainable manufacturing processes to reduce waste and energy consumption.

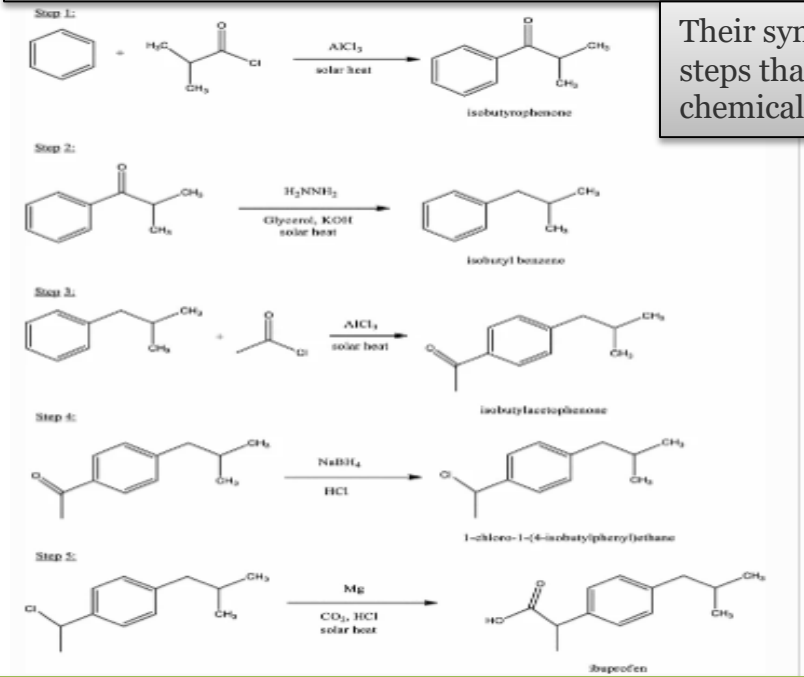
2. **Examples**:
    1. Synthesis of ibuprofen using catalytic hydrogenation instead of traditional Grignard reagents. (https://www.mdpi.com/1420-3049/26/16/4792)

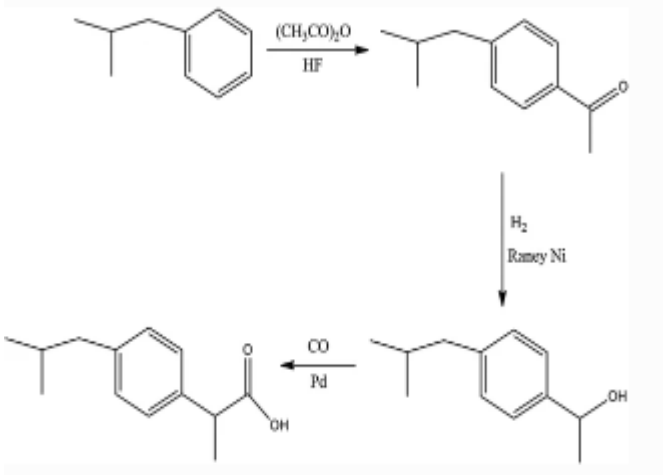
    2. Incorporation of green chemistry principles in the manufacturing of active pharmaceutical ingredients (APIs).



Boots Pure Drug Company in the 1960s

Their synthetic process involved several complicated steps that generated a considerable amount of chemical waste





The ACS Green Chemistry Institute Pharmaceutical Roundtable was formed in 2005 to encourage the incorporation of green chemistry

1992, BHC Company unveiled much more environmentally friendly and a model of "atom economy

Importance of Sustainability in Pharmaceutical Development:

1. **Environmental Impact**:
    1. Pharmaceutical manufacturing can generate significant amounts of waste and pollution.
    2. Adoption of sustainable practices can reduce carbon footprint, water usage, and air emissions.
2. **Resource Conservation**:
    1. Sustainable drug development minimizes the consumption of raw materials and energy resources.
    2. Efficient use of resources leads to cost savings and improved efficiency.
3. **Regulatory Compliance**:
    1. Regulatory agencies increasingly require pharmaceutical companies to adhere to environmental standards and guidelines.
    2. Embracing sustainability can facilitate compliance with regulations and enhance reputation.
4. **Long-Term Viability**:
    1. Sustainable practices ensure the long-term viability of the pharmaceutical industry by mitigating environmental risks and promoting responsible stewardship.
5. **Public Perception**:
    1. Consumers and stakeholders increasingly value companies that prioritize sustainability.
    2. Embracing sustainability can enhance brand reputation and foster goodwill among consumers.

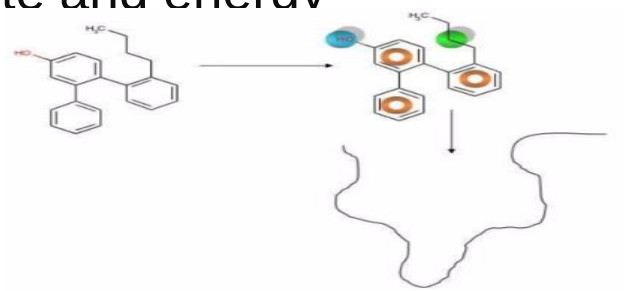
case studies

- showcasing the integration of rational drug design principles with green chemistry goals:
- demonstrate how rational drug design principles can be aligned with green chemistry goals to develop more sustainable pharmaceuticals.

1. Ligand-Based Drug Design:

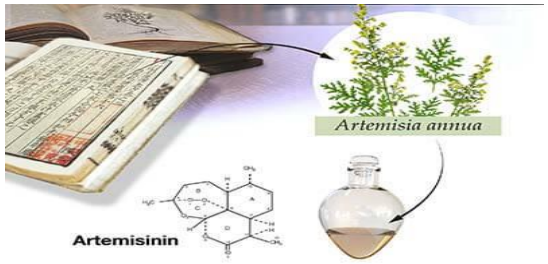
Principles:

- Ligand-based drug design involves designing molecules that bind to a specific target based on the knowledge of the target's structure and the ligand-receptor interactions.
- Green chemistry principles can be integrated by selecting ligands that are derived from renewable feedstocks and designing synthetic routes that minimize waste and energy consumption



- **Case Study:**

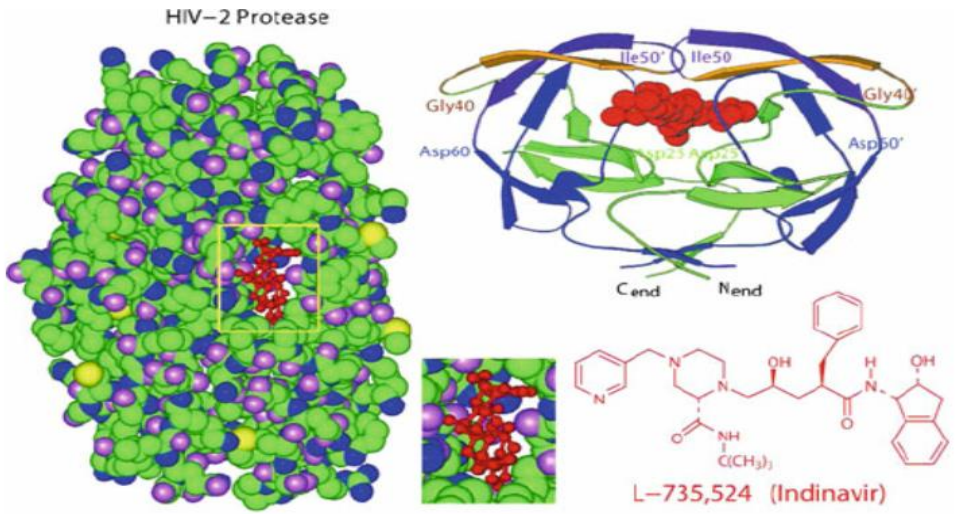
- **Artemisinin Derivatives for Malaria Treatment**: Artemisinin, derived from the sweet wormwood plant, is a potent antimalarial compound. By understanding the structure-activity relationship of artemisinin and its derivatives, researchers have designed novel derivatives with improved efficacy and reduced side effects. Synthetic routes have been optimized to use greener solvents and reduce the number of synthetic steps, resulting in a more sustainable production process.



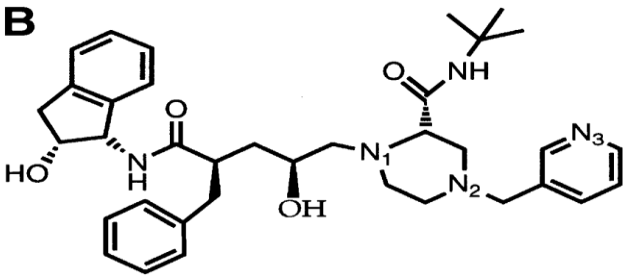
2. Structure-Based Drug Design:

Principles:

- Structure-based drug design involves designing molecules based on the three-dimensional structure of the target protein.
- Green chemistry principles can be incorporated by using computational methods to predict the environmental impact of various synthetic routes and selecting routes that minimize waste and energy usage.



Case Study:

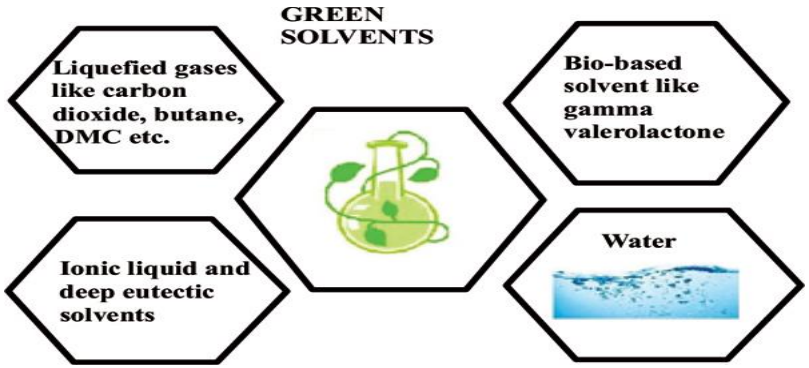


- **Design of HIV Protease Inhibitors**: HIV protease inhibitors are essential components of antiretroviral therapy for HIV/AIDS. Researchers used X-ray crystallography to determine the structure of the HIV protease enzyme and identify key binding interactions with existing inhibitors. By leveraging this structural information, they designed novel inhibitors with improved potency and selectivity. Synthetic routes were optimized to use greener reagents and minimize hazardous byproducts, resulting in a more sustainable manufacturing process.

3. Green Solvent Selection:

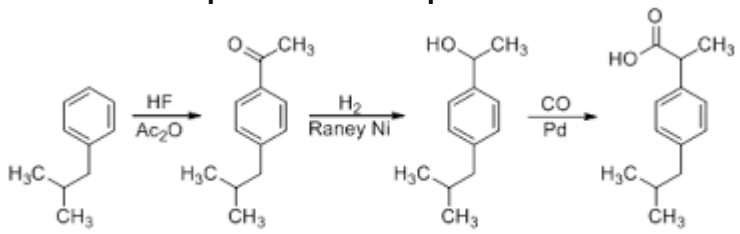
Principles:

- Green solvents are environmentally benign alternatives to traditional organic solvents, characterized by low toxicity, low volatility, and biodegradability.
- Rational drug design can incorporate green solvent selection criteria to minimize environmental impact during drug synthesis and formulation.



Case Study:

- **Synthesis of Ibuprofen**: Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID). Traditional synthesis routes for ibuprofen involve the use of **toxic solvents such as dichloromethane.** Researchers developed a greener synthesis route using catalytic hydrogenation in water as the solvent. This method eliminates the need for hazardous solvents and reduces waste, resulting in a more sustainable production process.

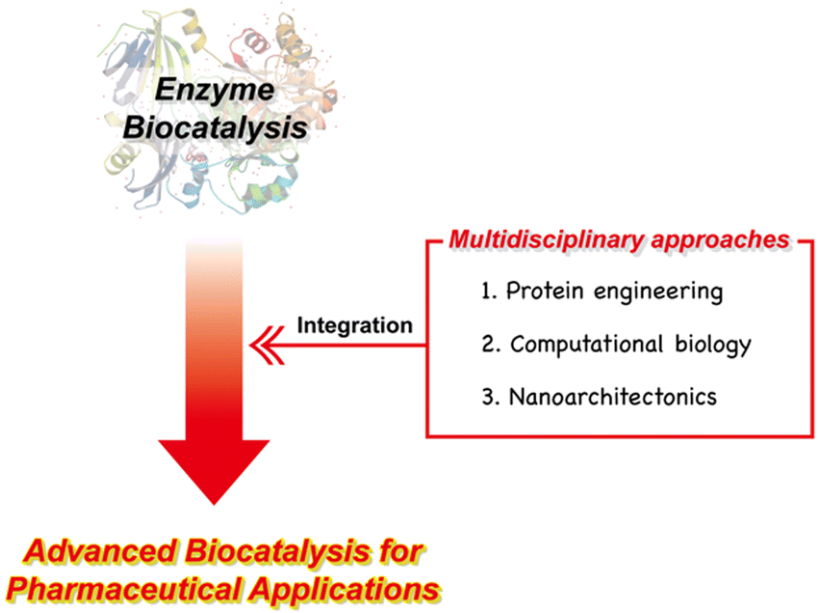


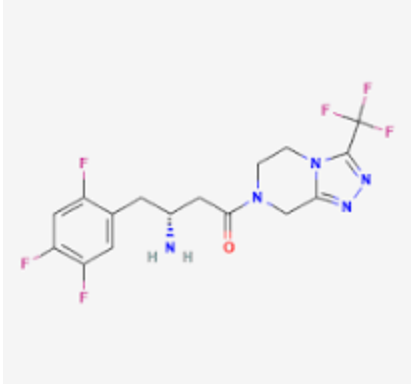
Scheme 1. BHC Company synthesis of ibuprofen

4. Biocatalysis:

Principles:

- Biocatalysis involves using enzymes or whole cells as catalysts in chemical reactions.
- Rational drug design can incorporate biocatalytic approaches to design enzymatic reactions that proceed under mild conditions and produce minimal waste.



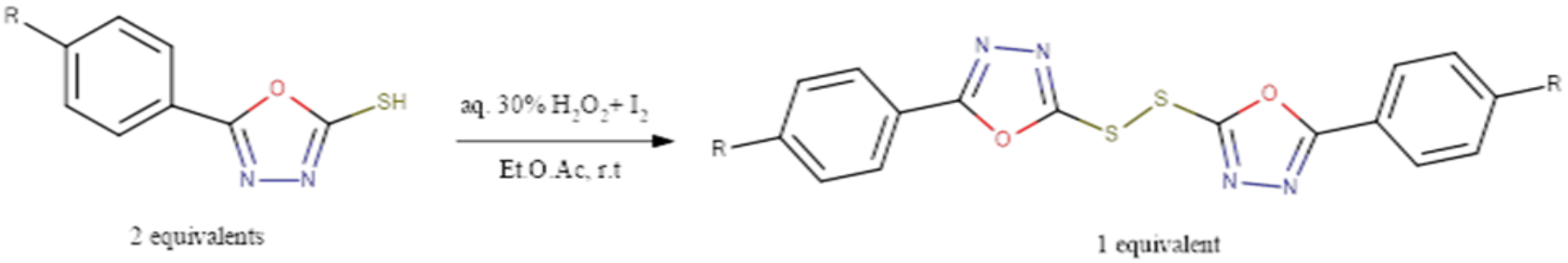


- **Case Study:**

- **Enzymatic Synthesis of Sitagliptin**: Sitagliptin is a medication used to treat type 2 diabetes. Traditional synthesis routes involve multiple steps and generate significant waste. Researchers developed an enzymatic synthesis route using a biocatalyst called transaminase. This route proceeds under mild conditions and has high selectivity, resulting in reduced waste and improved sustainability compared to traditional chemical synthesis methods.

Nohad theme's Team Work: Rational drug design towards sustainability

- **Chemical synthesis by using green chemistry** In the following two MSc' thesis (Bnar and Safa) research an eco-friendly procedure was used in order to oxidize the 1,3,4-oxadiazole-2-thiol into their corresponding di-sulfide functional groups, for this purpose hydrogen peroxide and catalytic amount of iodine was used.

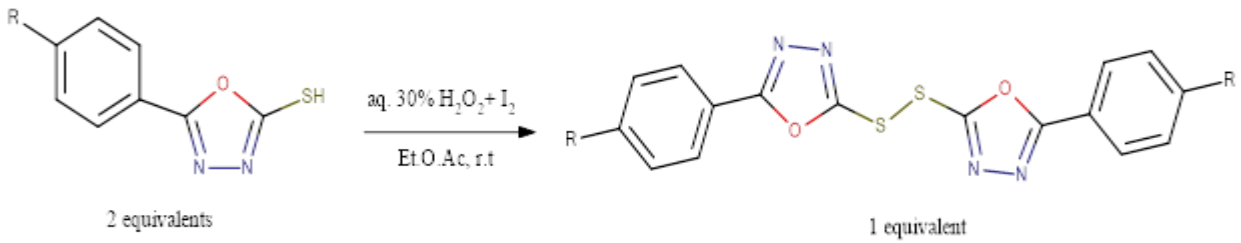


1. Bnar' MSc Thesis :

In this study we used dual strategy to design our compounds. **First**, the ligand-based design; this involved taking oxadiazole nucleus as a pharmacophore to design the rest of our compounds, and **second** strategy was the structure-based drug design, in which the active site of the target (protein) was carefully studied and the functional groups were accordingly selected and manipulated to get optimal results for later docking experiment.

The azole (-N=C-O-) groups in the 1,3,4-oxadiazole makes it a good replacement bioisoster for amides and esters, it also contributes to the increasing lipophilicity and improving pharmacokinetic parameters of molecules containing this moiety.

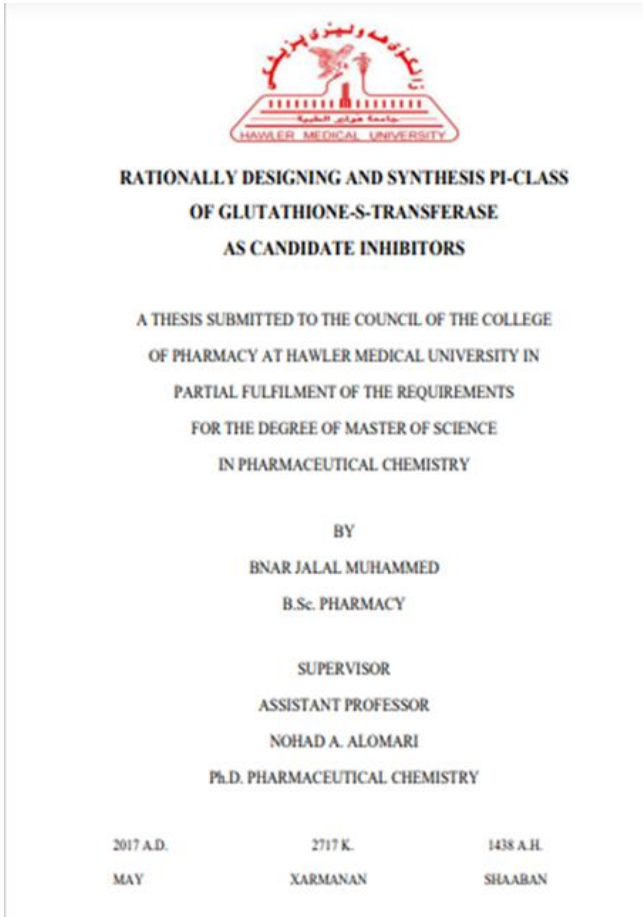
It was reported in the literature, the GSH level increases in many tumors like breast, colorectal, head, neck, and lung cancer tissues inside the tumor cells compared to normal cells (Gamcsik *et al*., 2012). Therefore the utilization of the disulfide linkers is a useful strategy to direct the anticancer therapy into the cell.



Trojan's Horse strategy

1. Using computer aided drug design had a great impact on **saving time and money in our research**, since a total of 29 compounds tested as GSTP1-1 inhibitor only 10 had affinity more than that of patent NBDHEX, and from the 10 compounds only 5 was able to act as potential inhibitor and hence were synthesized.

2. The synthesis of the compounds (5-phenyl-1,3,4-oxadiazol-2-yl)disulfanyl-1,3,4-oxadiazole) derivatives were successfully achieved and during **a short period of time (60 mins) using an eco-friendly procedure and obtaining them in (60-90) percentage of yield.**



HAWLER MEDICAL UNIVERSITY

RATIONALLY DESIGNING AND SYNTHESIS PI-CLASS OF GLUTATHIONE-S-TRANSFERASE AS CANDIDATE INHIBITORS

A THESIS SUBMITTED TO THE COUNCIL OF THE COLLEGE OF PHARMACY AT HAWLER MEDICAL UNIVERSITY IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICAL CHEMISTRY

BY

BNAR JALAL MUHAMMED

B.Sc. PHARMACY

SUPERVISOR

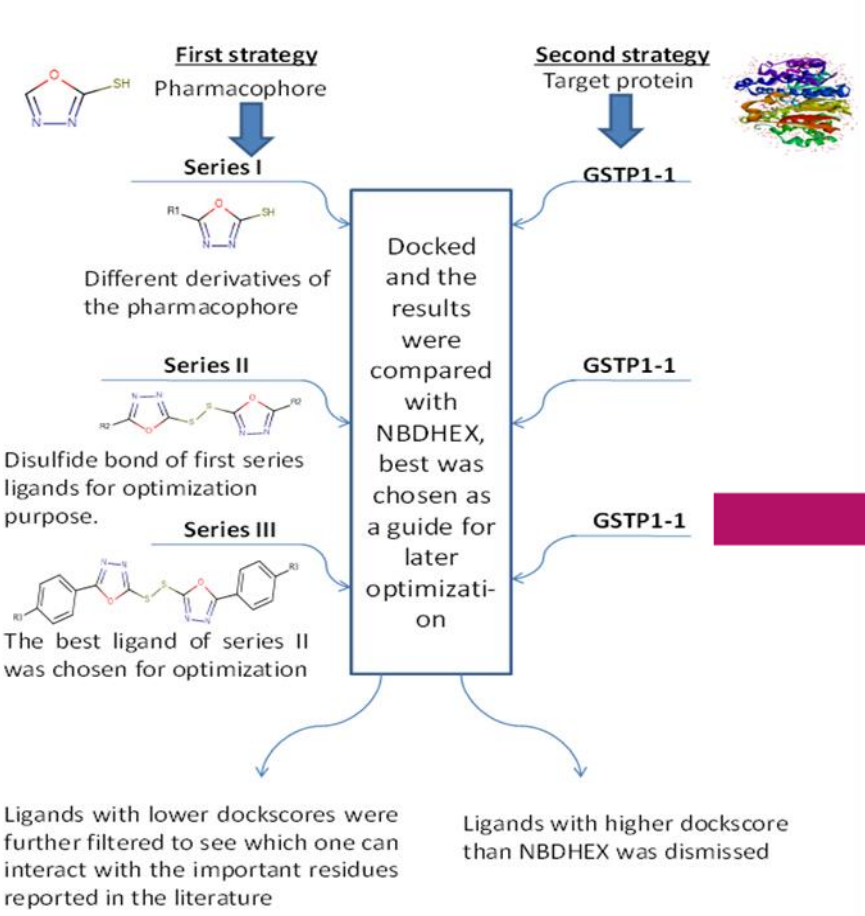
ASSISTANT PROFESSOR

NOHAD A. ALOMARI

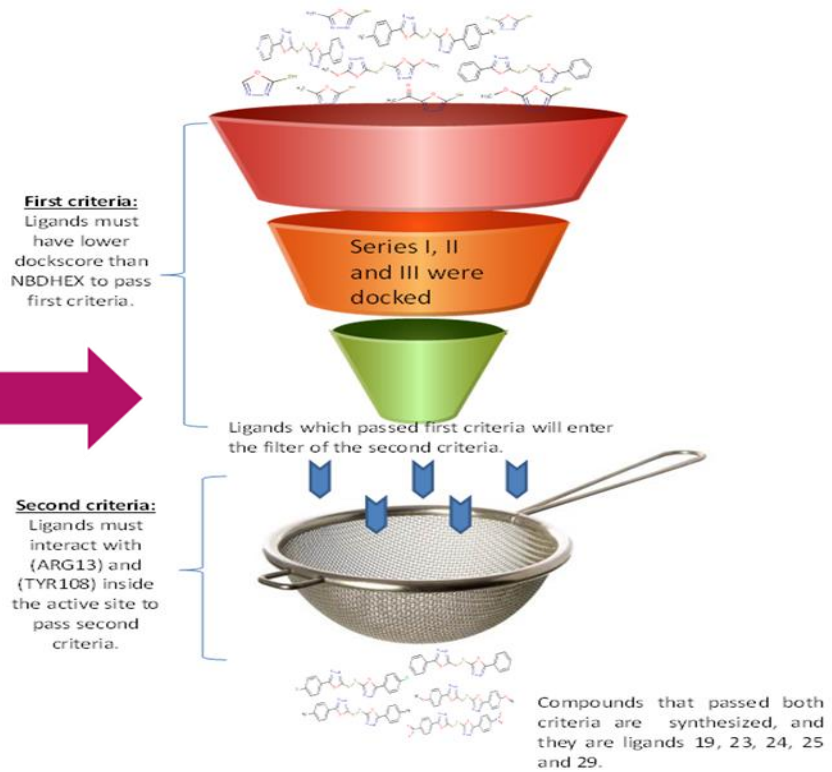
Ph.D. PHARMACEUTICAL CHEMISTRY

2017 A.D.	2717 K.	1438 A.H.
MAY	XARMANAN	SHAABAN

RDD and ecofriendly preparation



Rational drug design



R1=R2= -H, -CH_3, -OCH_3, -Cl, -NO_2, -NH_2, -OH, -COOH, - COCH3, -phenyl, -pyridine.
R3= -H, -CH_3, -OCH_3, -Cl, -NO_2, -NH_2, -OH, -COOH.

Conclusions ‘s Marks

1. Using computer aided drug design had a great impact on saving time and money in our research, since a total of 29 compounds tested as GSTP1-1 inhibitor only 10 had affinity more than that of patent NBDHEX, and from the 10 compounds only 5 was able to act as potential inhibitor and hence were synthesized.
2. The computer aided drug design enables a researcher to work at molecular level to design targeted highly **specifi**c anticancer drug.
3. The docking results revealed that the affinity and number of bonds of our compounds were much more than that of patent NBDHEX.

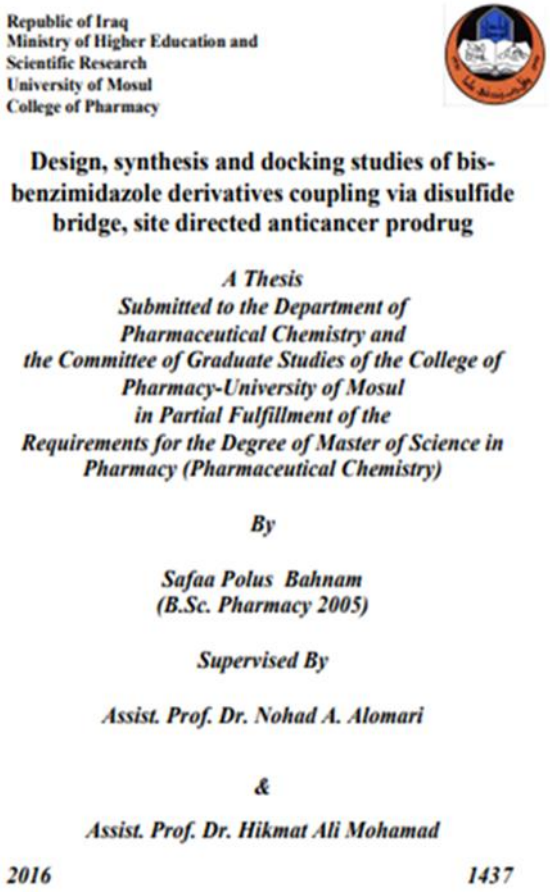
2. Safa ‘s MSc Thesis

Rational Drug Design

- The disulfide linkage is cleaved by endogenous thiols, e.g., glutathione (GSH) and thioredoxin[1]
- Glutathione (GSH) plays an important role in hypoxic state of tumors, and also the GSH is an attractive key for designing drugs that are able to target hypoxic state of tumors. The presence of cellular redox differences makes the disulfide bond useful as a potential delivery tool.
- The use of disulfide linkers is attractive by taking into account the fact that the concentration of GSH is much higher (>1,000 times) in tumor cells than that in blood plasma[4] .

Sustainability

since water is the sole byproduct, this method is environmentally friendly



Republic of Iraq
Ministry of Higher Education and
Scientific Research
University of Mosul
College of Pharmacy

Design, synthesis and docking studies of bis-benzimidazole derivatives coupling via disulfide bridge, site directed anticancer prodrug

A Thesis
Submitted to the Department of
Pharmaceutical Chemistry and
the Committee of Graduate Studies of the College of
Pharmacy-University of Mosul
in Partial Fulfillment of the
Requirements for the Degree of Master of Science in
Pharmacy (Pharmaceutical Chemistry)

By

Safaa Polus Bahnam
(B.Sc. Pharmacy 2005)

Supervised By

Assist. Prof. Dr. Nohad A. Alomari

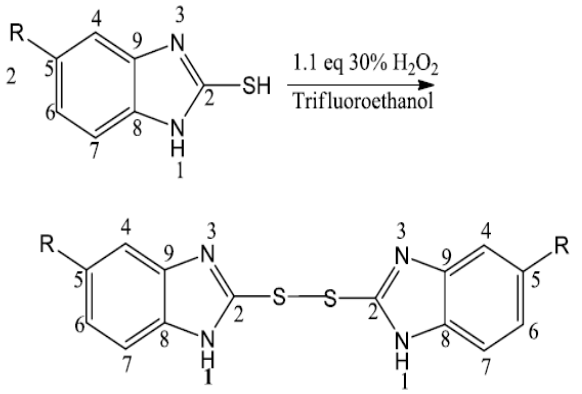
&

Assist. Prof. Dr. Hikmat Ali Mohamad

2016 *1437*

2. Safa ‘s MSc Thesis

- The performed MD(Molecular dynamics) simulation by using explicit water model was able to explore some of the real conformations of human CDK2.
- only five (A3, A9, A11, A12 and A13) managed to enter the active site of the 20ns model and form H-bonds with one or more of amino acids in hinge or linker region (GLU81, PHE82, LEU83) of the enzyme.
- **Disulfide bonds** are important functional groups for targeting glutathione-S-transferases, the use of disulfide linkers in drug design is an attractive approach because it takes into account the **fact that the concentration of glutathione is much higher (>1000 times) in tumor cells than in blood plasma** (Ojima 2008).

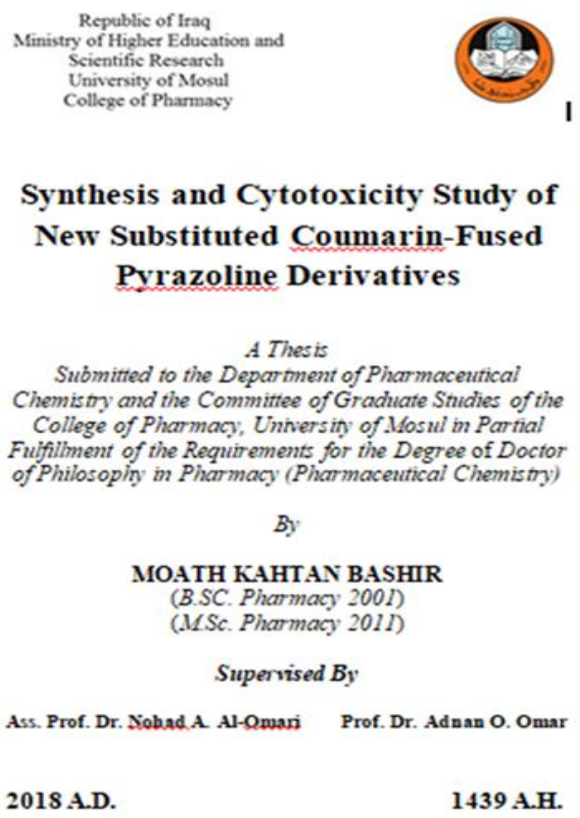


- The performed MD simulation by using explicit water model was able to explore some of the real conformations of human CDK2.
- The use of trifluoroethanol allows the use of mild conditions and affords high yields of disulfides without contamination. About 7. 30% aqueous hydrogen peroxide is inexpensive and, **since water is the sole byproduct, this method is environmentally friendly**

Moath PhD's thesis

- The advent of intermolecular cancer cell information's leads to the discovery of important anticancer drugs which **bears heterocylic residues** in its structure that resemble important biological compounds in the cell like **purine and pyrimidine** residues found in DNA and RNA; leading to block its functions and consequently cell death.

- Design,synthesis and molecular docking studies of new oxo-Benzopyranyl Pyrazoline as cycline dependent kinase inhibitors .



Republic of Iraq
Ministry of Higher Education and
Scientific Research
University of Mosul
College of Pharmacy

Synthesis and Cytotoxicity Study of New Substituted Coumarin-Fused Pyrazoline Derivatives

A Thesis
Submitted to the Department of Pharmaceutical Chemistry and the Committee of Graduate Studies of the College of Pharmacy, University of Mosul in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Pharmacy (Pharmaceutical Chemistry)

By

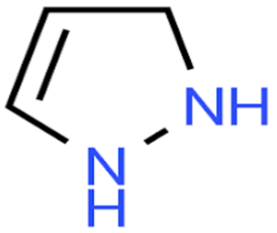
MOATH KAHTAN BASHIR
(B.SC. Pharmacy 2001)
(M.Sc. Pharmacy 2011)

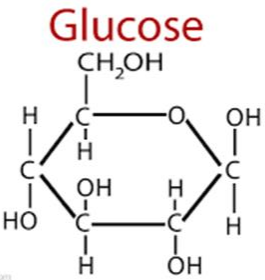
Supervised By

Ass. Prof. Dr. Nohad A. Al-Omari **Prof. Dr. Adnan O. Omar**

2018 A.D. **1439 A.H.**

- **Pyrazoline derivatives** became a motif of high interest in medicinal chemistry because of its high promising pharmacological activities especially their anticancer effect hence, **hundreds of lead compounds containing pyrazoline moiety were synthesized and tested for anti proliferative activity.**
- **glycosylation** plays an important role in protein stability, interaction, folding, cell adhesion, and even in signal transduction; hence any defect in glycosylation process was found to be related to many metabolic, neurodegenerative, and neoplastic diseases (Spiro, 2002).





Sustainability towards Patent!

(19)
جمهورية العراق
وزارة التخطيط
الجهاز المركزي للتقييس والسيطرة النوعية

براءة اختراع

(12)

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(72) اسم المخترع وعنوانه :
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3- م.م. محمد ياسين خلف / جامعة دهوك - كلية العلوم

(73) اسم صاحب البراءة : الذوات اعلاه

(74) اسم الوكيل:

(54) تسمية الأختراع:
حمايـة طريقـة تحضير المركـب
1-[p-Nitrophenyl]3-Methyl-4-oxo-benzopyranyl[4,3-c] Pyrazoline
(A3)
المضـاد للسرطان باستخدام الكيمياء الخضراء.

منحت هذه البراءة استنـادا لأحكام المـادة (21) من القانون براءة الأختراع والنماذج الصناعية رقم (65) لسنة 1970 المعدل وعلى مسؤولية المخترع.

IQ (19)
جمهورية العراق
وزارة التخطيط
الجهاز المركزي للتقييس والسيطرة النوعية

براءة اختراع (13)

(12) اللغة العربية

(11) رقم البراءة : 6864
(51) التصنيف الدولي A61K31/33
(21) رقم الطلب : 2017/546
(22) تاريخ تقديم الطلب: 2017/ 10/ 16
(52) التصنيف العراقي 6
(30) تاريخ طلب الأسبقية(33) بلد الأسبقية (31) رقم طلب الأسبقية
(45) تاريخ منح البراءة: 2021/10/24

(72) اسم المخترع وعنوانه :
1- أ.م.د.نهاد عبد الوهاب محمد | جامعة نوع | كلية الصيدلة
2-أ.د.عدنان عثمان عمر | جامعة الموصل | كلية العلوم | قسم الكيمياء
3- م.م. محمد ياسين خلف | جامعة دهوك | كلية العلوم | قسم الكيمياء

(73) اسم صاحب البراءة : الـــذوات اعـــلاه

(74) اسم الـوكيل:

(54) تسمية الأختراع:
حماية طريقة تحضير
2-Hydroxy-4-Methyl-5-0X0-Benzopyranyl[4,3-d]pyrimidine 3
المصمم باستراتيجية حصان طروادة المضاد للخلايا
السرطانية نوعي Hela ,Thp1

منحت هذه البراءة استنـادا لأحكام المـادة (21) من قـانون براءة الأختراع والنماذج الصناعية والمعلومات غير المفصح عنها والدوائر المتكاملة والاصناف النباتية رقم (65) لسنة 1970 المعدل وعلى مسؤولية المخترع.

(19)
جمهورية العراق
وزارة التخطيط
الجهاز المركزي للتقييس والسيطرة النوعية

براءة اختراع

(12)

(11) رقم البراءة : 5252
(51) التصنيف الدولي A61K31/11
(21) رقم الطلب : 2017/545
(22) تاريخ تقديم الطلب: 2017/10/16
(30) تاريخ طلب الأسبقية - بلد الأسبقية - رقم طلب الأسبقية
(52) التصنيف العراقي 6
(45) تاريخ منح البراءة: 2018/2/22

(72) اسم المخترع وعنوانه :
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2- ا.د. عدنان عثمان عمر / جامعة الموصل - كلية العلوم - قسم الكيمياء
3- م.م . محمد ياسين خلف / جامعة دهوك - كلية العلوم - قسم الكيمياء

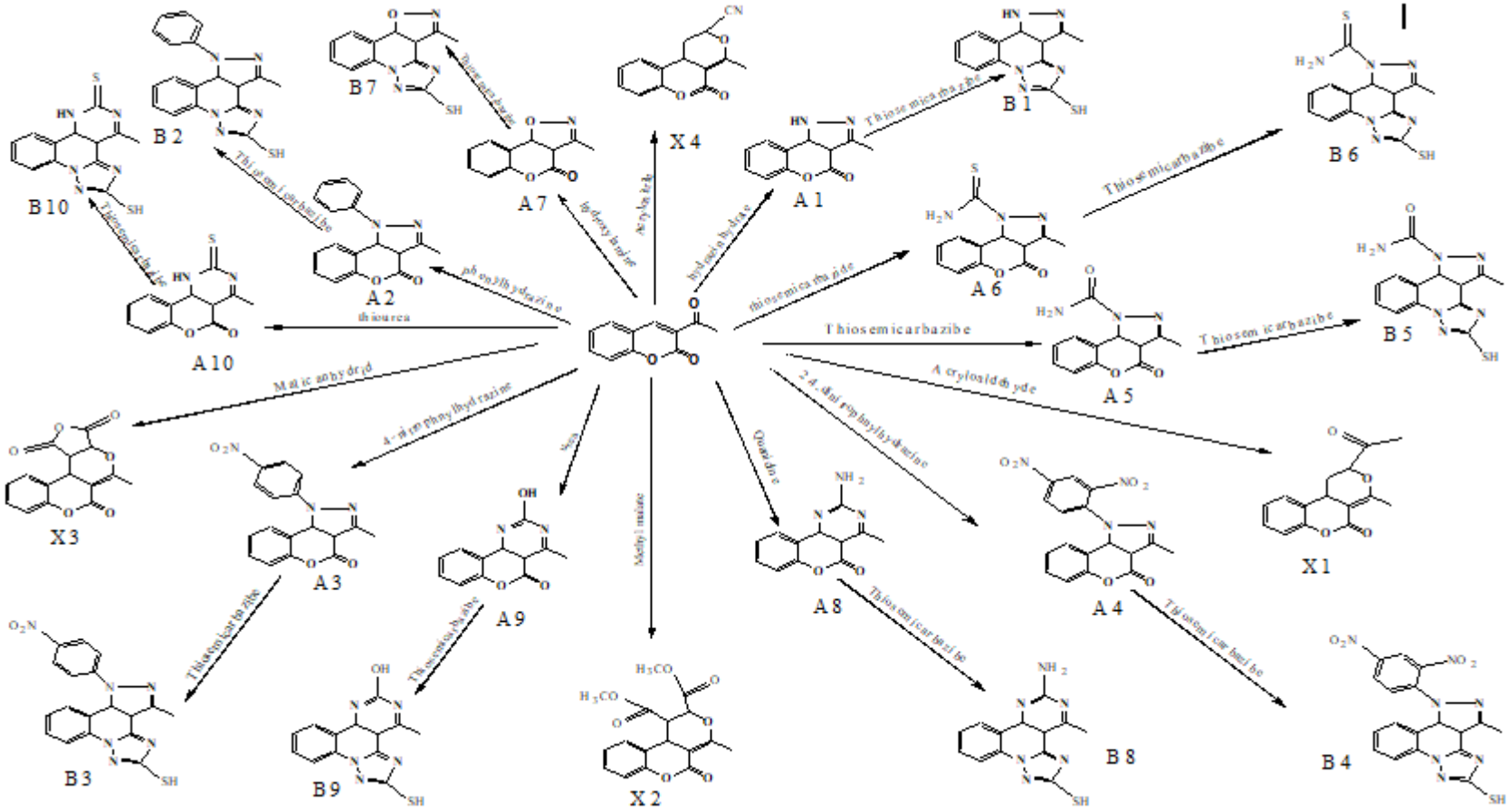
(73) اسم صاحب البراءة : الذوات اعـــلاه

(74) اسم الـوكيل:

(54) تسمية الأختراع:
تصميم وتحضير سلسلة فعالة من مشتقات ال 6-acetyle coumarine بطريقة صديقة للبيئة ودراسة فعاليتها ضد السرطانية باستخدام التلوئو البايولوجي لل ATP .

منحت هذه البراءة استنـادا لأحكام المـادة (21) من قـانون براءة الأختراع والنماذج الصناعية رقم (65) لسنة 1970 المعدل وعلى مسؤولية المخترع.

Synthesis and biological Evaluation of Some Novel New Fused Heterocycles from 3-Acetylcoumarin



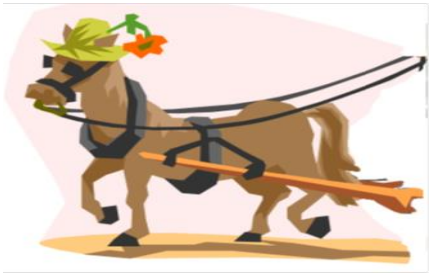
- This work involves the synthesis of some new heterocyclic compounds five and six membered such as , pyrazoline , Isoxazoline and pyrimidine fused with coumarin molecule and triazole derivatives in two main series which have been achieved starting from 3- Acetylcoumarin .

- All the compounds have been synthesized in our work prepare this compound by **ultrasonic system as a one of green chemistry**

رمز المركب	Y	درجة الانصهار (°C)	نسبة الناتج (%)		اللون
			اعتيادية	فوق الصوتية	
A1	-H	241-244	36	55	اصفر
A2	-ph	252-254	46	73	ابيض
A3	-4-$NO_2C_6H_4$	266-267	48	62	اصفر
A4	-2,4diNO_2 C_6H_3	251-253	50	53	اصفر
A5	-$CONH_2$	220-223	56	71	اصفر
A6	-$CSNH_2$	240-242	59	63	اصفر

Rational drug Discovery Driven by Medicinal chemistry !

Currently: Biology-driven drug discovery



Chemistry-driven drug discovery - back to the future?

Challenges and Future Directions

- Current challenges in implementing sustainable drug development practices.
- Opportunities for further improvement and innovation.
- Future trends in the field.

Conclusion

- Recap of key points.
- Emphasis on the importance of adopting sustainable practices in drug development.
- Call to action for the industry to prioritize sustainability.

Most Ancient City : Nineveh
Route of sustainability