Towards
unbounded
thinking.

NGU.

SCHOOL of
PHARMACY

Published International Scientific Research 2017-2021

1st edition

April 2021

NGU. SCHOOL of PHARMACY

NEWGIZA UNIVERSITY

Published Scientific Researches 2017-2021

1st edition

April 2021

SCHOOL OF PHARMACY NEWGIZA UNIVERSITY UPPER MANAGEMENT

PROF. DR. A. SAMEH FARID
Founder and President of
Newgiza University

PROF. DR. LAMIS RAGAB
Vice President of
Newgiza University

PROF. DR. MANAL MAHER
Dean of School of Pharmacy
Newgiza University

CONTENTS

STATEMENT OF THE DEAN OF SCHOOL OF PHARMACY - NEWGIZA UNIVERSITY

Education and scientific research became essential dimensions in economic and social developments. Scientific research and industry of education are found as an important component in the National Strategy for Science, Technology, and Innovation; Ministry of Higher Education and Scientific Research, Egypt, 2030.

International publishing has acquired a great importance in universities ranking. Moreover, financing research projects in any organization throughout the world depends mainly on the number of research papers internationally published by its researchers. Therefore, the Egyptian universities are encouraging their scientists and researchers to publish their work in international journals.

The Newgiza School of Pharmacy was established in August 2016 in academic collaboration with University College London (UCL). Newgiza University had the vision to build a solid foundation for the 21st century learning and research to redefine the future of Egypt through dissemination of knowledge via teaching and learning, knowledge development via scientific research activities, and application of knowledge in community service and environmental development.

Dean of school of pharmacy

Prof. Manal Maher

School of Pharmacy (SOP) Vision

NGU will create a community of interdisciplinary researchers, professors and students who foster excellence and encourage innovation. This community will spearhead academic and scientific advancement in the region and across the world by building a solid foundation for the 21st century learning.

School of Pharmacy (SOP) Mission

The BPharm (PharmD) program at NGU aims at graduating scientifically literate, research-informed, patient-centered, and socially responsible professionals who can serve the pharmaceutical needs of individuals and communities both in Egypt and abroad.

School of Pharmacy (SOP) Strategic Objectives

1. A distinct infrastructure that conforms to the international standards in education.
2. Providing world class education to the Egyptian society through partnerships with high-ranking universities (UCL) following the Egyptian and International quality education systems.
3. Preparing a distinguished pharmacy graduate in all disciplines capable of leadership, lifelong and continuing professional development.
4. Attracting students from the region and the world at large.
5. Establishing center for scientific research that contributes to the development of scientific research in Egypt and the region.
6. Serving the community and developing the environment through partnership with civil society institutions.

School of Pharmacy (SOP) Scientific Departments and Specializations

1. Department of Clinical Pharmacy
2. Department of Chemistry
   - 2.1 Department of Organic and Pharmaceutical Chemistry
   - 2.2 Department of Pharmacognosy
   - 2.3 Department of Analytical Chemistry
3. Department of Biology
   - 3.1 Department of Pharmacology and Toxicology
   - 3.2 Department of Microbiology and Immunology
   - 3.3 Department of Biochemistry
4. Department of Pharmaceutics and Industrial Pharmacy

School of Pharmacy (SOP) Scientific Research Policies

1. Developing the capabilities of the teaching staff and assistants in the field of scientific research and publishing.
2. Raising the awareness of the teaching staff and assistants with principles and ethics of scientific research.
3. Providing support to assist researchers in carrying out distinguished researches.
4. Integration with college policies in the field of education, community service, and environmental development.
5. Encouraging applied, joint researches, and research collaborations across NGU medical sector's schools that serve community needs.
6. Establishing and developing partnerships and agreements with universities and international institutions in the field of scientific research.
7. Organizing scientific conferences and symposia.
8. Preparing a research themes proposal by the heads and members of each scientific department in line with the suggested research directions.
9. Reviewing the research points proposed by the departments, arranging them according to priorities and facilities, and ensuring:
   - 9.1 The plan is flexible to match the future requirements and variables.
   - 9.2 It affords a fruitful integration between all the departments of the college and the team's work culture is taken into consideration.
10. Establishing a mechanism for implementing, following up, and updating the research plan themes of the scientific departments of the college.
11. Approving the final version of the scientific research plan from the scientific department councils and the School Council.

SCHOOL OF PHARMACY (SOP) RESEARCH DIRECTIONS

Research Direction 1. Common diseases in the Egyptian society concerning etiology, diagnosis, and management (pharmacotherapeutic & non-pharmacotherapeutic) of spreading and chronic diseases.

1.1 Cancers.
1.2 Hepatic diseases.
1.3 Metabolic disorders (Obesity and Diabetes).
1.4 Cardiovascular diseases (Hypertension).
1.5 Renal diseases.
1.6 Gastrointestinal diseases.
1.7 Infectious diseases.
1.8 Central nervous system and neurodegenerative diseases.
1.9 Musculoskeletal and autoimmune disorders.
1.10 Neurologic and psychiatric disorders.
1.11 Critical care.

Research Direction 2. Therapeutic Drug Monitoring (TDM) and disease outcome.

2.1 Therapeutic Drug Monitoring.
2.2 Drug interactions.

Research Direction 3. Personalized and precision medicines.

3.1 Pharmacogenomics.
3.1.1 Impact on disease outcome.
3.1.2 Impact on toxicity occurrence.
3.2 Nutrigenomics.
3.2.1 Impact on clinical outcome.
3.2.2 Impact on toxicity modulation.

Research Direction 4. Drug discovery.

4.1 Evaluation of new treatments of common spreading and chronic disease and minimizing possible adverse reactions.
4.2 Biopharmaceuticals (Biosimilars, Bioinformatics, Gene therapy, and recombinant DNA).
4.3 Clinical nutrition and nutraceuticals.
4.4 Herbal medicines and tissue culture.
4.5 Antibiotics resistance.
4.6 Standardization of drugs.

Research Direction 5. Drug delivery and pharmaceutical formulations and disease outcome.

5.1 Formulation and evaluation of nano-drug delivery systems.
5.2 Development and fabrication of Advanced Drug Delivery.
5.3 Targeted Drug Delivery systems.
5.4 Biopharmaceutics and Pharmacokinetics optimization.
5.5 Patient centric formulations.

Research Direction 6. Economic aspects.

Strategic Industries.

6.1.1 Agriculture wastes as sources of cellulose and green chemicals.
6.1.2 Nanotechnology Applications in the Pharmaceutical Industry.
6.1.3 Pharmaceutical Process Scale-Up.

6.2 Pharmacoeconomics.

6.2.1 Drug use evaluation.
6.2.2 Service implementation.

6.3 Water resources.

6.3.1 Development of novel nanoparticles for pharmaceutical wastewater treatment.

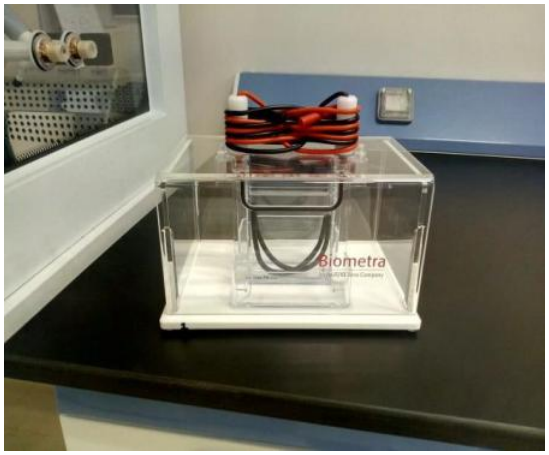
School of Pharmacy (SOP) Scientific Research Facilities and Resources

The Newgiza School of Pharmacy offers research facilities and resources needed for faculty members and teaching assistants

1. HPLC

2. UV Spectrophotometer

3. Rotary evaporator

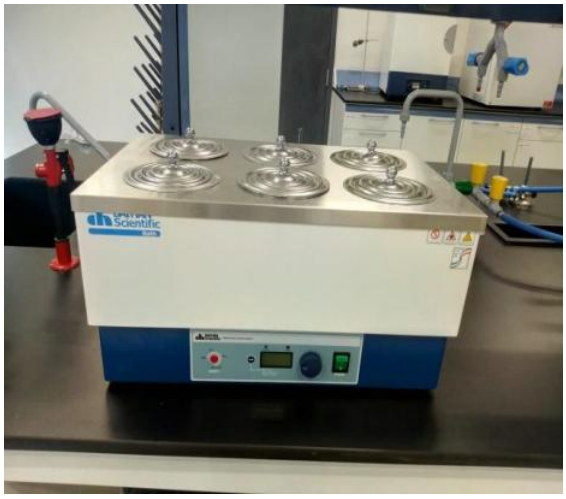


4. Electrophoresis (SDS-PAGE)

5. Colorimeter (single beam)

6. Water distillation system

7. Bath (ultrasonic)



8. Bath (water)

9. Incubator

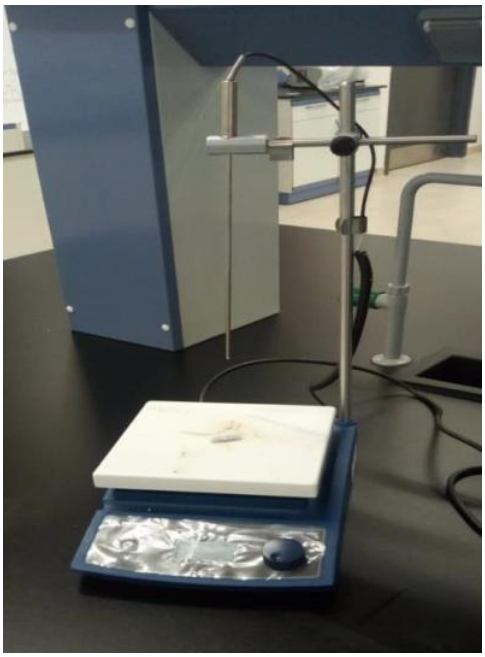
10. Oven (hot air)

11. Microfuge

12. Centrifuge (benchtop)

13. Balance (analytical - 4dp)

14. Balance (digital - 2dp)



15. Hot plate (digital - stirrers)

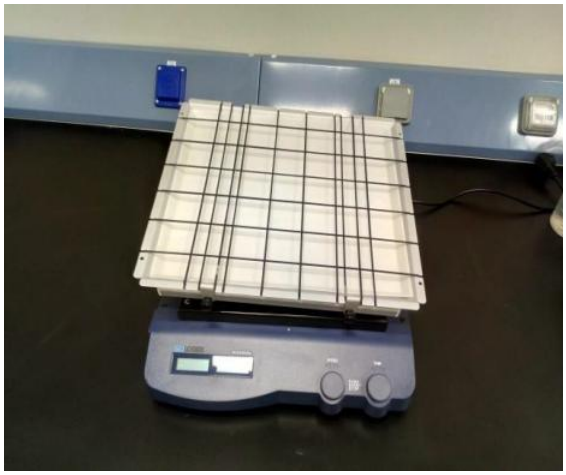
16. Hot plate (analogue - stirrers)

17. UV Lamp

18. Melting point apparatus

19. Vacuum (pump)

20. Oven (microwave)



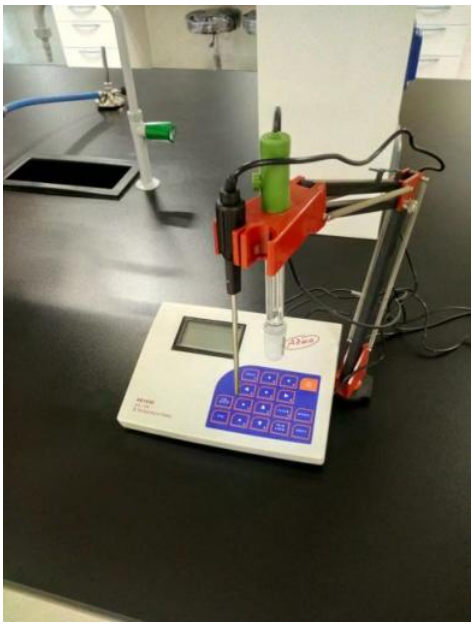
21. Rocking shaker

22. Heating block

23. Microscope

24. Recording drum

25. Conductometer



26. pH meter

27. Vortex mixer

28. Balance (with stadiometer)

29. Sphygmomanometer (BP measuring)

30. Digital automated pipettes

SCHOOL OF PHARMACY (SOP) RESEARCHERS' BIOGRAPHY

Prof. Manal Mohamed Maher Hussein, Dean of the School of Pharmacy, Newgiza University (2016 – present) and professor of microbiology and immunology. She held several positions at Faculty of Pharmacy, Cairo University including, Acting Dean (7/2014-12/2014); Vice-Dean for Education and Students Affairs (2011-2016); Coordinator of the Clinical Pharmacy Program (2009-2011). She participated in the implementation of the Clinical Pharmacy Program, until the first graduated class in 2011. Former member of the Promotion Committee of Professors and Associate Professors for Microbiology and Immunology.

Her research areas of interest are microbial resistance, fermentation technology and development of new vaccines and biotechnological products.

Dr. Manal was the PI investigator in two research projects covering the process development for the industrial production of Rifamycin B and the feasibility study for a cost-effective process for the production of Rifamycin B. Awarded a Patent No. (200312062) titled "Process for Production of Rifamycin B using improved bacterial strain".

Prof. Manal Mohammed Maher - Dean School of Pharmacy

Ahmed Sherif Attia works as a Professor of microbiology and immunology, Faculty of Pharmacy, Cairo University and has an adjunct faculty position in the School of Pharmacy, Newgiza University. He obtained his Ph.D. in molecular microbiology from the University of Texas Southwestern Medical, USA working on the molecular aspects of the microbial resistance to the complement system. Working as a postdoctoral fellow at Vanderbilt University, USA, he identified new microbial therapeutic targets and novel host antimicrobial mechanisms using cutting edge technologies. Dr. Attia's current research focuses on; i) identifying novel microbial therapeutic targets, ii) development of new vaccines and biotechnological products, and iii) discovering novel non-traditional antimicrobial agents from natural sources and through synthetic chemistry. Dr. Attia's work is highly recognized as he has been awarded several prestigious awards from both local and international entities.

Prof. Ahmed Sherif Attia – Professor of Microbiology & Immunology

Dr. Nevine is a professor of pharmaceutics and industrial pharmacy, Faculty of Pharmacy, Cairo University. Prof Nevine has a lot of international publications in the field of pharmaceutics. Her research interests include nanotechnology, controlled drug delivery systems, colon targeting, and brain targeting. Dr. Nevine is a member of the scientific committee responsible for evaluating and assessing variations (minor or major changes) for pharmaceutical products, food supplements or veterinary products at the Central Administration of Pharmaceutical Affairs (CAPA), Ministry of Health since 2010

Prof. Nevine Shawky – Professor of Pharmaceutics and Industrial Pharmacy

Dr. Rania Mohsen Abdelsalam a Professor of Pharmacology & Toxicology, Faculty of Pharmacy, Cairo University, and the head of the biology discipline at the School of Pharmacy, New Giza University. She has a solid background in the field of hepatic fibrosis, neuropharmacology and cancer she has more than 50 internationally published papers in these fields [H-index (16) and i10-index (23)]. Former member of the ethics committee (REC) in the Faculty of Pharmacy, Cairo University since 2010. She is also a member of the Central Committee for Ethics of Scientific Research, The Supreme Council of University Hospitals. Dr. Rania is the coordinator of the student support committee in School of Pharmacy, New Giza University and was the Head of the Career Center Unit (FOPCC), Faculty of Pharmacy, Cairo University.
https://scholar.google.com/citations?hl=en&user=fzq1UbcAAAAJ
https://www.researchgate.net/profile/Rania-Abd-El-Salam

Prof. Rania Mohsen – Professor of Pharmacology and Toxicology

Dr. Marwa Fouad, Professor of Pharmaceutical Chemistry. She earned her PhD from Faculty of Pharmacy, Cairo University in October 2009. She has about 65 international publications in peer reviewed journals with high impact factor. She joined Prof. Jean-Marie Pages group in UMR-MD1 Research Unit, Aix-Marseille University in France in 2013 where she worked as a postdoctoral fellow then she joined Prof. Bertrand Blankert group in Pharmaceutical analysis laboratory, Mons University in Belgium for a postdoctoral fellowship in 2014. She supervised about 50 master and PhD theses. She reviewed around 60 international publications in many international journals. She got the Award of Best International published paper in Pharmaceutical Chemistry from 3rd Scientific Conference of the Faculty of Pharmacy- Cairo University, April 2012 and 8th Scientific Conference of the Faculty of Pharmacy- Cairo University, April 2017. She also got Awards for international publications in 2011-2020 from Cairo University.
Her main research interest includes drug design, pharmaceutical synthesis and analysis, pharmacokinetics and metabolism in drug design and discovery, experimental design, molecular docking and QSAR.

Prof. Marwa Ahmed Fouad – Professor of Pharmaceutical Chemistry

Dr. Ahmed El Kerdawy former director of the Molecular Modeling Unit at the Faculty of Pharmacy, Cairo University. He earned his doctoral degree from Erlangen-Nuernberg University, Germany in Chemistry with specialization in Computer-Aided Drug Design in the Computer-Chemistry-Center (CCC) research group. His research project focused on the optimization of the current drug-design computer software, and in the same lab, he had his postdoctoral research training. Dr. El Kerdawy has a unique blend of experiences in synthetic chemistry and computer-aided drug design.
His research projects deal with using computer aided-drug design approaches for lead discovery and lead optimization for new targets for the treatment of series health problems like cancer.

A/Prof. Ahmed Elkerdawy – Ass. Professor of Pharmaceutical Chemistry

Dr. Muhammad Abdullatif is an Associate Professor of Pharmacology & Toxicology, Faculty of Pharmacy, Cairo University. Muhammed Abdullatif Saad was graduated from Faculty of Pharmacy, Cairo University in 2005. He opened his research path by targeting the disorders affecting the brain and was awarded by the 7th International Scientific Conference of Faculty of Pharmacy, Cairo University for the best Ph. D. Thesis in Pharmacology and Toxicology (2015). His post-doctoral research lane extrapolated his previous work, and he is currently involved in a research project funded by the STDF covering the development and characterization of a therapeutic vaccine intended for the treatment of multiple sclerosis. The multidisciplinary aspect of his research encompasses molecular mechanisms involved in various inflammatory disorders and diabetes. He has a deep rooting experience in teaching the preparatory course of the American Pharmacotherapy Board of Pharmacy Specialties in many institutions starting from 2010 till now. He is also a professional statistician using multiple techniques and software such as GraphPad Prism and SPSS.
Research profile
https://www.scopus.com/authid/detail.uri?authorId=55569666000

A/Prof. Muhammed Abdullatif – Ass. Professor of Pharmacology and Toxicology

Dr. Abdallah is a Lecturer of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University. He has a solid background in the field of dosage form design and is currently involved in a research project funded by the STDF covering the development and characterization of a therapeutic vaccine intended for the treatment of multiple sclerosis. The multidisciplinary aspect of his research encompasses nano-formulations, design of experiments, pharmacokinetics, and bioequivalence. Dr. Abdallah is also the director of Central Lab Unit at Faculty of Pharmacy, Cairo University and a member of stability committee offering technical consultancy to the Central Agency of Pharmaceutical Affairs at the Egyptian Ministry of Health.
Scopus Author ID: 55551799900
Researcher ID: N-4383-2017

A/Prof. Mohammed Abdullah – Ass. Professor of Pharmaceutics and Industrial Pharmacy

Dr. Sara Nageeb El-Helaly graduated from Faculty of Pharmacy, Cairo University with honors. Combining academic and professional experience, Dr. Sara worked as a teaching assistant in Faculty of Pharmacy, Cairo University as well as a community pharmacist for two years in retail pharmacies after which she managed to own and run "El-Helaly pharmacy" while completing her post-graduate studies in (brain targeting intranasal liposomal systems) from Cairo University. After acquiring her Ph.D., she opted for more academic depth, so she held a full-time position as a Lecturer in Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, besides lecturing as a part-timer in different academic institutions before settling as a full-time Associate Professor in NGU, School of Pharmacy. In parallel with academia, Dr. Sara is the chairman of the Institutional Review Board at Pharma Solutions, contract research organization, former assistant vice dean for community service and environmental development in Faculty of Pharmacy, Cairo University. She co-authored a number of publications in the field of pharmaceutical nanotechnology.

A/Prof. Sara Nageeb El-Helaly – Ass. Professor of Pharmaceutics and Industrial Pharmacy

Dr. Amr M. Saadeldeen is a lecturer of Pharmacognosy and Natural Products, and Quality Assurance Unit manager, School of Pharmacy, Newgiza University. He was graduated from Faculty of Pharmacy, Cairo University with honors. Dr. Amr completed his Ph.D. in "Biologically Guided Phytochemical Study of *Lotus polyphyllos*, Family Fabaceae" in 2014 from Helwan University. He was employed at Faculty of Pharmacy, October 6 University since 2003, as teaching assistant then worked as a lecturer of Pharmacognosy from 2014 till September 2019. Dr. Amr Saadeldeen has a solid background in the field of Quality Assurance of education. He was involved in achieving the national accreditation for Faculty of Pharmacy, October 6 University on Feb 2014 from The National Authority for Quality Assurance and Accreditation of Education (NAQAAE) as well as achieving the reaccreditation on Jul 2019 as a member of the Quality Assurance Unit team.

Dr. Amr M. Saadeldeen – Lecturer of Pharmacognosy and Natural Products

Noha El Baghdady is a Clinical Pharmacy Lecturer at New Giza University, Cairo, Egypt. She has 15 years of experience of practice, training and consultancy in the hospital and clinical pharmacy. She graduated from the Faculty of Pharmacy, Ain Shams University (2006) then got a Diploma in clinical pharmacy in 2008 and completed her Master and Doctoral degrees of Clinical Pharmacy from the same university in 2013 & 2021. Elbaghdady achieved a post-graduate Certificate in Cancer Biology and Therapeutics from Harvard Medical School in 2017. She got several scholarships from the European School of Oncology and Dubai Harvard Foundation for Medical Research.

She was a former Manager of Oncology Clinical Pharmacy and IV admixture unit at International Medical Centre, Cairo, Egypt. She participated in numerous hospital projects (Antimicrobial Stewardship, Drug formulary, and Patient education programs) Also, she was a Former instructor of Hospital Pharmacy and Oncology Clinical pharmacy at Misr International University.

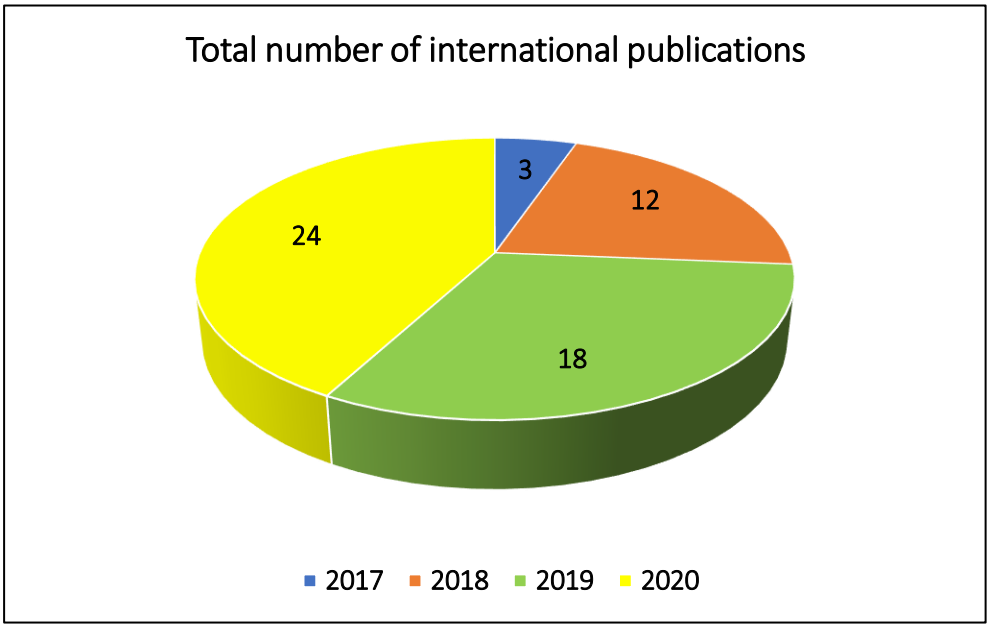
Elbaghdady has several International publications in the Oncology Clinical Research and conferences' presentations. Also, has participated as a Guest Speaker in many International conferences.

Dr. Noha S. Elbaghdady – Lecturer of Clinical Pharmacy

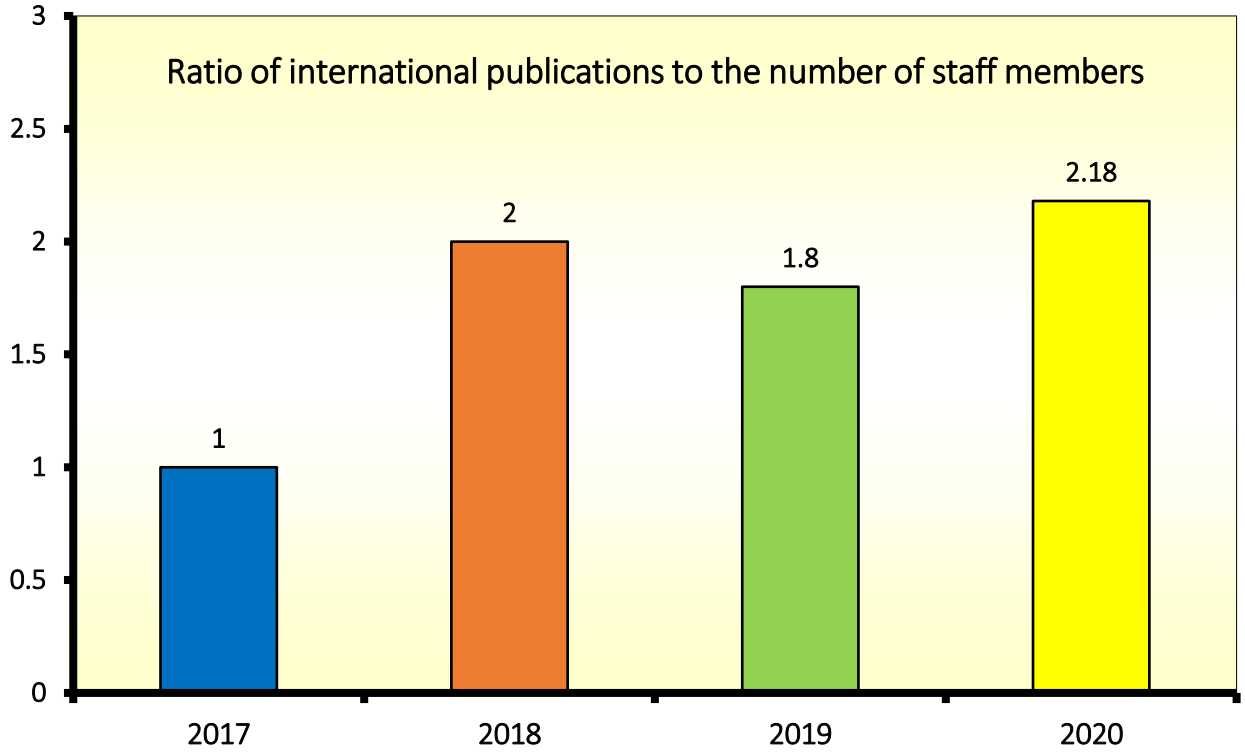
SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2017 - 2021

Sixty five (65) International publications were published with SOP/NGU affiliation throughout the period from 2017 to April 2021

Year of publication	Number of international publications
2017	3
2018	12
2019	18
2020	24
2021	8 (till April 2021)
Total international publications	65



Year of publication	Number of international publications	Number of staff members	Ratio of international publications to the number of staff members
2017	3	3	1
2018	12	6	2
2019	18	10	1.8
2020	24	11	2.18



SCHOOL OF PHARMACY (SOP) STAFF WITH HIGHEST NUMBER OF PUBLICATIONS 2020

No.	Staff members	Number of publications
1.	A/Prof. Ahmed Elkerdawy	11
2.	A/Prof. Muhammed Abdullatif	6
3.	Prof. Nevine Shawky	2
4.	Dr. Noha Salah Eldin ElBaghdady	2

SCHOOL OF PHARMACY (SOP) PUBLICATIONS WITH HIGHEST IMPACT FACTOR 2020

No.	Publications	IF
1.	• New intranasal cross-linked mosapride xyloglucan pluronics micelles (MOS-XPMs) for reflux esophagitis disease: In-vitro optimization and improved therapeutic efficacy. • Journal of Advanced Research • **Prof. Nevine Shawky**	6.992
2.	• Design, synthesis and biological evaluation of novel pyrazole sulfonamide derivatives as dual COX-2/5-LOX inhibitors. • European Journal of Medicinal Chemistry • **A/Prof. Ahmed Elkerdawy -1**	5.573
3.	• Diagnosis and Management of Hematological Adverse Events Induced by Immune Checkpoint Inhibitors: A Systematic Review. • Frontiers in Immunology • **Dr. Noha Salah Eldin ElBaghdady**	5.085
4.A.	• Design and Synthesis of some new 2,4,6-trisubstituted quinazoline EGFR inhibitors as targeted anticancer agents. • Bioorganic Chemistry • **A/Prof. Ahmed Elkerdawy -2**	4.831
4.B.	• Some 1,3,5-trisubstituted pyrazoline derivatives targeting breast cancer: Design, synthesis, cytotoxic activity, EGFR inhibition and molecular docking. • Bioorganic Chemistry • **A/Prof. Ahmed Elkerdawy -3**	4.831
5.	• A Rapid Lysostaphin Production Approach and a Convenient Novel Lysostaphin Loaded Nano-emulgel; As a Sustainable Low-Cost Methicillin-Resistant Staphylococcus aureus Combating Platform. • Biomolecules • **Prof. Manal Maher**	4.694
6.	• Aberrations of miR-126-3p, miR-181a and sirtuin1 network mediate Di-(2-ethylhexyl) phthalate-induced testicular damage in rats: The protective role of hesperidin. • Toxicology • **A/Prof. Muhammed Abdullatif -1**	4.099
7.	• Dapagliflozin improves behavioral dysfunction of Huntington's disease in rats via inhibiting apoptosis-related glycolysis. • Life Sciences • **A/Prof. Muhammed Abdullatif -2**	3.647
8.	• Mechanistic perspective of morin protection against ketoprofen-induced gastric mucosal injury: Targeting HMGB1/RAGE/NF-κB, DJ-1/Nrf2/HO-1 and PI3K/mTOR pathways. • Archives of Biochemistry and Biophysics • **A/Prof. Muhammed Abdullatif -3**	3.391
9.A.	• Targeting Receptor Tyrosine Kinase VEGFR-2 in Hepatocellular Cancer: Rational Design, Synthesis and Biological Evaluation of 1,2-Disubstituted Benzimidazoles. • Molecules • **A/Prof. Ahmed Elkerdawy -4**	3.267
9.B.	• Synthesis, Biological Evaluation and In Silico Studies of Certain Oxindole–Indole Conjugates as Anticancer CDK Inhibitors. • Molecules • **A/Prof. Ahmed Elkerdawy -5**	3.267
10.	• Neuroprotective effects of vildagliptin on drug induced Alzheimer's disease in rats with metabolic syndrome: Role of hippocampal klotho and AKT signaling pathways. • European Journal of Pharmacology • **A/Prof. Muhammed Abdullatif -4**	3.263



SOP International Publications 2021



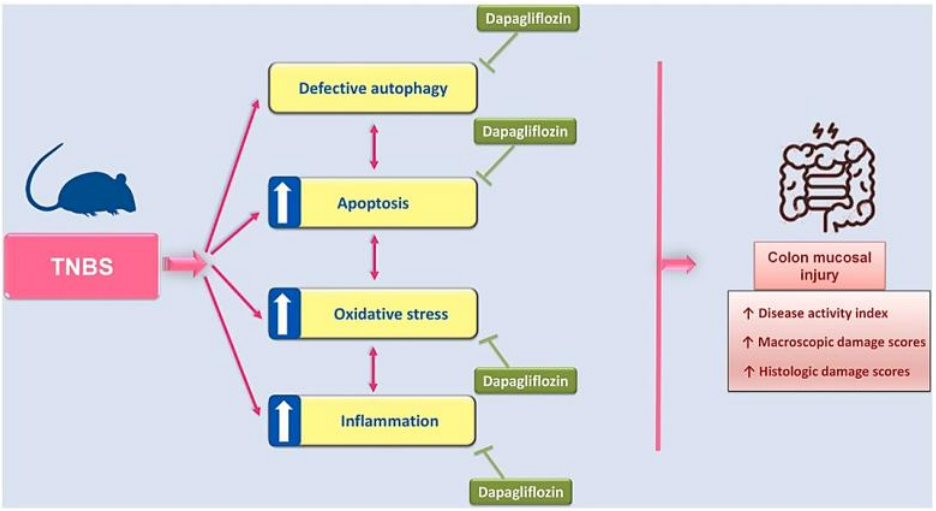
SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2021

Eight (8) International publications with SOP/NGU affiliation were published till April 2021.

1. Hany H. Arab, Muhammad Y. Al-Shorbagy, **Muhammed A. Saad**. "Activation of autophagy and suppression of apoptosis by dapagliflozin attenuates experimental inflammatory bowel disease in rats: Targeting AMPK/mTOR, HMGB1/RAGE and Nrf2/HO-1 pathways", *Chemico-Biological Interactions*, **335**, 109368, (**2021**), ISSN 0009-2797, https://doi.org/10.1016/j.cbi.2021.109368.
   IF: 3.723

Abstract

Dapagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, has featured marked anti-inflammatory effects in murine models of myocardial infarction, renal injury, and neuroinflammation. Yet, its potential impact on the pathogenesis of inflammatory bowel diseases (IBD) has not been previously investigated. The presented study aimed to explore the prospect of dapagliflozin to mitigate 2,4,6 trinitrobenzene sulfonic acid (TNBS)-induced rat colitis model which recapitulates several features of the human IBD. The molecular mechanisms pertaining to the dynamic balance between autophagy/apoptosis and colon injury were delineated, particularly, AMPK/mTOR, HMGB1/RAGE/NF-κB and Nrf2/HO-1 pathways. The colon tissues were examined using immunoblotting, ELISA, and histopathology. Dapagliflozin (0.1, 1 and 5 mg/kg; p.o.) dose-dependently mitigated colitis severity as manifested by suppression of the disease activity scores, macroscopic damage scores, colon weight/length ratio, histopathologic perturbations, and inflammatory markers. More important, dapagliflozin enhanced colonic autophagy via upregulating Beclin 1 and downregulating p62 SQSTM1 protein expression. In this context, dapagliflozin activated the AMPK/mTOR pathway by increasing the p-AMPK/AMPK and lowering the p-mTOR/mTOR ratios, thereby, favoring autophagy. Moreover, dapagliflozin dampened the colonic apoptosis via lowering the caspase-3 activity, cleaved caspase-3 expression, and Bax/Bcl-2 ratio. Furthermore, dapagliflozin attenuated the HMGB1/RAGE/NF-κB pathway via lowering HMGB1, RAGE, and p-NF-κBp65 protein expression. Regarding oxidative stress, dapagliflozin lowered the oxidative stress markers and augmented the Nrf2/HO-1 pathway. Together, the present study reveals, for the first time, the ameliorative effect of dapagliflozin against experimental colitis via augmenting colonic autophagy and curbing apoptosis through activation of AMPK/mTOR and Nrf2/HO-1 pathways and suppression of HMGB1/RAGE/NF-κB cascade.



2. **Muhammed A. Saad**, Muhammad A. Eltarzy, **Rania M. Abdel Salam**, Maha A.E. Ahmed. "Liraglutide mends cognitive impairment by averting Notch signaling pathway overexpression in a rat model of polycystic ovary syndrome", *Life Sciences,* **265**, 118731, (**2021**), ISSN 0024-3205, https://doi.org/10.1016/j.lfs.2020.118731.
IF: 3.647

Abstract

Aims

Polycystic ovary syndrome (PCOS), the rifest endocrine disorder in women, is involved in disrupting many metabolic processes. However, the impact of PCOS on cognitive deficits is still uncertain. Recently, Notch signaling pathway was identified as a key modifier in regulating the pathological process in the ovary and various neurodegenerative disorders. Liraglutide has favourable neuroprotective effects that may protect against the possible cognitive dysfunction in PCOS.

Main methods

PCOS was induced in rats by administrating Letrozole orally for 21 successive days. Then, Liraglutide (LIR) was administered intraperitoneally for 30 days. Memory was examined using Y-maze, novel object recognition (NOR), and Morris water maze (MWM) tests. Western blotting, enzyme immunoassay, and quantitative real-time PCR were used to examine Notch signaling downstream targets, as well as assessing the expression of the components of various pathways cross talked with Notch signaling in memory impairment. Furthermore, histopathological examination was performed to examine neuronal changes.

Key findings

Notch signaling was overexpressed in PCOS rats, which increased Aβ aggregation, apoptosis, and neuroinflammation. Additionally, histopathological examination showed neuronal degeneration, which was marked by diminished acetylcholine levels in the PCOS rats' hippocampi. Finally, serum levels of insulin and testosterone were elevated while estradiol was reduced. Treatment with LIR repaired Notch signaling-attributed changes and improved the PCOS-induced memory impairment in rats.

Significance

The obtained findings confirm that Notch signaling activation in the hippocampus of rats impairs cognitive functions in PCOS, which is mitigated by LIR. Therefore, LIR may offer a novel therapeutic intervention to impede PCOS-induced dementia.

3. Farag MM, Abd El Malak NS, Yehia SA, **Ahmed MA**. "Hyaluronic Acid Conjugated Metformin-Phospholipid Sonocomplex: A Biphasic Complexation Approach to Correct Hypoxic Tumour Microenvironment", *Int J Nanomedicine,* **16**, 1005-1019, (**2021**). Doi: 10.2147/IJN.S297634.
IF: 5.115

Abstract

Purpose

Development of hyaluronic acid conjugated metformin-phospholipid sonocomplexes (HA-MPS), a biphasic complexation product compiled for enhancing both the lipophilicity and targeting potential of Metformin (MET) to CD44 receptors on pancreatic cancer.

Methods

MET was chemically conjugated to hyaluronic acid (HA) via amide coupling reaction. Then, the HA conjugated MET was physically conjugated to Lipoid™S100 via ultrasound irradiation. A combined D-optimal design was implemented to statistically optimize formulation variables. The HA-MPS were characterized through solubility studies, partition coefficient, drug content uniformity, particle size and zeta potential. The optimized HA-MPS was tested via proton nuclear magnetic resonance, infrared spectroscopy to elucidate the nature of physicochemical interactions in the complex which was further scrutinized on molecular level via molecular docking and dynamic simulation.

Results

The solubility and partition studies showed a lipophilicity enhancement up to 67 folds as they adopted inverted micelles configuration based on the packing parameter hypothesis. The optimized HA-MPS showed 11.5 folds lower IC50, extra 25% reduction in oxygen consumption rate, better reduction in hypoxia-inducible factor and reactive oxygen species in MiaPaCa-2 cells.

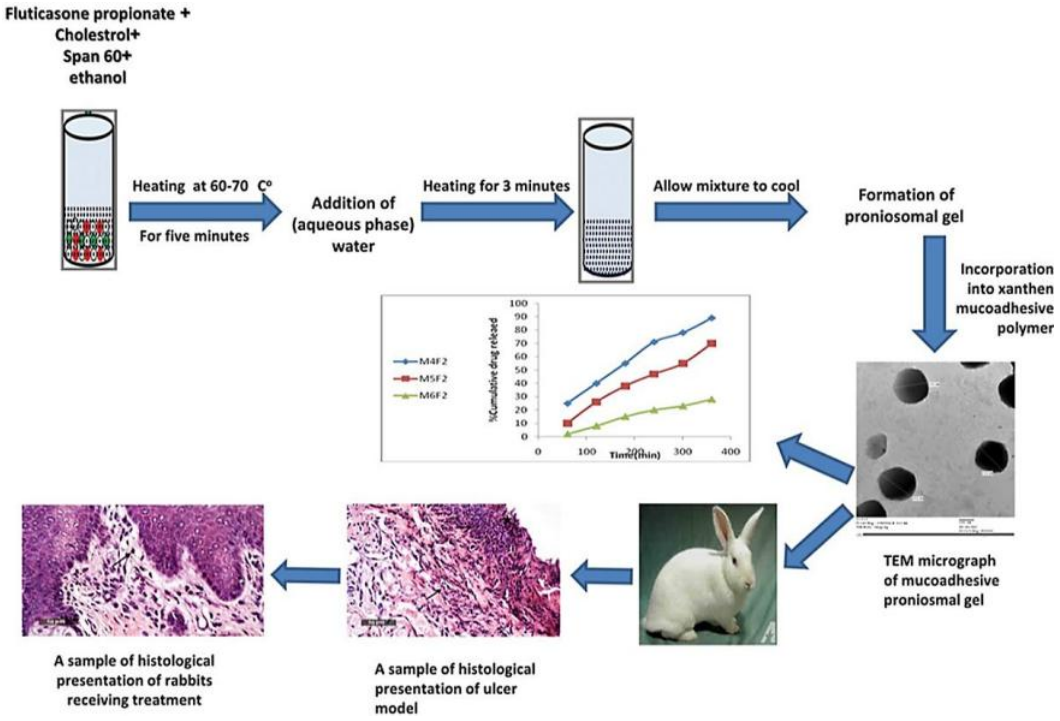
Conclusion

These results proved better internalization of MET which was reflected by abolishing hypoxic tumour microenvironment, a mainstay toward a normoxic and less resistant pancreatic cancer.

4. **Mohamed Abdallah Ahmed**, Wedian Younis Abdelgawad, Mary Kamal Gad, Magdy Ibrahim Mohamed. "A novel approach for the treatment of oral ulcerative lesion using mucoadhesive proniosome gel", *Journal of Drug Delivery Science and Technology*, 102460, (**2021**), ISSN 1773-2247, https://doi.org/10.1016/j.jddst.2021.102460.
IF: 2.734

Abstract

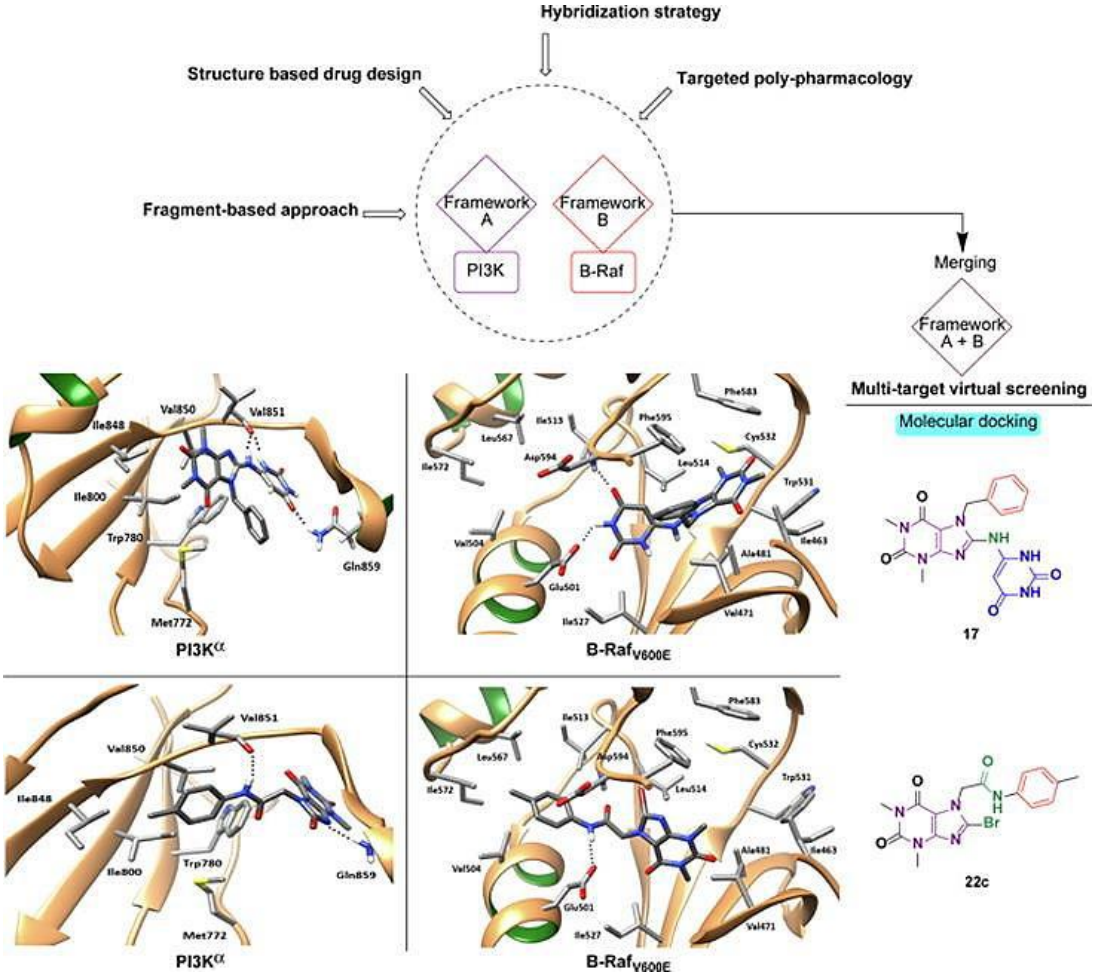
A mucoadhesive proniosome gel containing a potent corticosteroid drug (fluticasone propionate) was formulated for the local treatment of oral ulcerative lesions. The formula was made-up in an attempt to avoid the drug's severe systemic adverse effects, moreover, ensuring both efficacy and safety. Full factorial design was employed to prove the significant effect of surfactant type and cholesterol concentration on entrapment efficiency and vesicle size of the formulated proniosome gels. The optimum formula with an entrapment efficiency of 85.5 ± 2.4% was incorporated into mucoadhesive gels using different mucoadhesive polymers, namely, xanthan gum or sodium alginate. The effects of the polymer type and its concentration on the quantity of fluticasone propionate release as well as on the mucoadhesion force were studied. The optimum formula was found to possess a mucoadhesion force of 14425 ± 5.4 dyne/cm2 and maximum quantity of drug release of 89± 0.09 % which showed to follow Higuchi diffusion model of release. High-resolution transmission electron micrographs revealed that the chosen formula was smooth, homogenous and in nano size range. Cytotoxicity assay test was conducted to ensure the safety of the optimum formula. Curing of oral ulcerative lesions using an animal model was assessed and emphasized by the histopathological findings.



5. Abdalla R. Mohamed, **Ahmed M. El Kerdawy**, Riham F. George, Hanan H. Georgey, Nagwa M. Abdel Gawad. "Design, synthesis and in silico insights of new 7,8-disubstituted-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione derivatives with potent anticancer and multi-kinase inhibitory activities", *Bioorganic Chemistry*, **107**, 104569, (**2021**), ISSN 0045-2068, https://doi.org/10.1016/j.bioorg.2020.104569.
IF: 4.831

Abstract

Aiming to obtain an efficient anti-proliferative activity, structure- and ligand-based drug design approaches were expanded and utilized to design and refine a small compound library. Subsequently, thirty-two 7,8-disubstituted-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione derivatives were selected for synthesis based on the characteristic pharmacophoric features required for PI3K and B-Raf oncogenes inhibition. All the synthesized compounds were evaluated for their in vitro anticancer activity. Compounds 17 and 22c displayed an acceptable potent activity according to the DTP-NCI and were further evaluated in the NCI five doses assay. To validate our design, compounds with the highest mean growth inhibition percent were screened against the target PI3Ka and B-RafV600E to confirm their multi-kinase activity. The tested compounds showed promising multi-kinase activity. Compounds 17 and 22c anticancer effectiveness and multi-kinase activity against PI3Ka and B-RafV600E were consolidated by the inhibition of B-RafWT, EGFR and VEGFR-2 with IC50 in the sub-micromolar range. Further investigations on the most potent compounds 17 and 22c were carried out by studying their safety on normal cell line, in silico profiling and predicted ADME characteristics.



6. Eldehna WM, Al-Rashood ST, Al-Warhi T, Eskandrani RO, Alharbi A, **El Kerdawy AM**. "Novel oxindole/benzofuran hybrids as potential dual CDK2/GSK-3β inhibitors targeting breast cancer: design, synthesis, biological evaluation, and in silico studies", *J Enzyme Inhib Med Chem*, **36(1)**, 270-285, (**2021**). Doi: 10.1080/14756366.2020.1862101.
IF: 4.673

Abstract

The serine/threonine protein kinases CDK2 and GSK-3β are key oncotargets in breast cancer cell lines, therefore, in the present study three series of oxindole-benzofuran hybrids were designed and synthesised as dual CDK2/GSK-3β inhibitors targeting breast cancer (5a–g, 7a–h, and 13a–b). The N1 -unsubstituted oxindole derivatives, series 5, showed moderate to potent activity on both MCF-7 and T-47D breast cancer cell lines. Compounds 5d–f showed the most potent cytotoxic activity with IC50 of 3.41, 3.45 and 2.27 µM, respectively, on MCF-7 and of 3.82, 4.53 and 7.80 µM, respectively, on T-47D cell lines, in comparison to the used reference standard (staurosporine) IC50 of 4.81 and 4.34 µM, respectively. On the other hand, the N1 -substituted oxindole derivatives, series 7 and 13, showed moderate to weak cytotoxic activity on both breast cancer cell lines. CDK2 and GSK-3β enzyme inhibition assay of series 5 revealed that compounds 5d and 5f are showing potent dual CDK2/GSK-3β inhibitory activity with IC50 of 37.77 and 52.75 nM, respectively, on CDK2 and 32.09 and 40.13 nM, respectively, on GSK-3β. The most potent compounds 5d–f caused cell cycle arrest in the G2/M phase in MCF-7 cells inducing cell apoptosis because of the CDK2/GSK-3β inhibition. Molecular docking studies showed that the newly synthesised N1 -unsubstituted oxindole hybrids have comparable binding patterns in both CDK2 and GSK-3β. The oxindole ring is accommodated in the hinge region interacting through hydrogen bonding with the backbone CO and NH of the key amino acids Glu81 and Leu83, respectively, in CDK2 and Asp133 and Val135, respectively, in GSK-3β. Whereas, in series 7 and 13, the N1 -substitutions on the oxindole nucleus hinder the compounds from achieving these key interactions with hinge region amino acids what rationalises their moderate to low anti-proliferative activity.

7. Amer MA, Wasfi R, **Attia AS**, Ramadan MA. "Indole Derivatives Obtained from Egyptian Enterobacter sp. Soil Isolates Exhibit Antivirulence Activities against Uropathogenic Proteus mirabilis", *Antibiotics,* **10(4)**, 363, (**2021**). https://doi.org/10.3390/antibiotics10040363
IF: 3.893

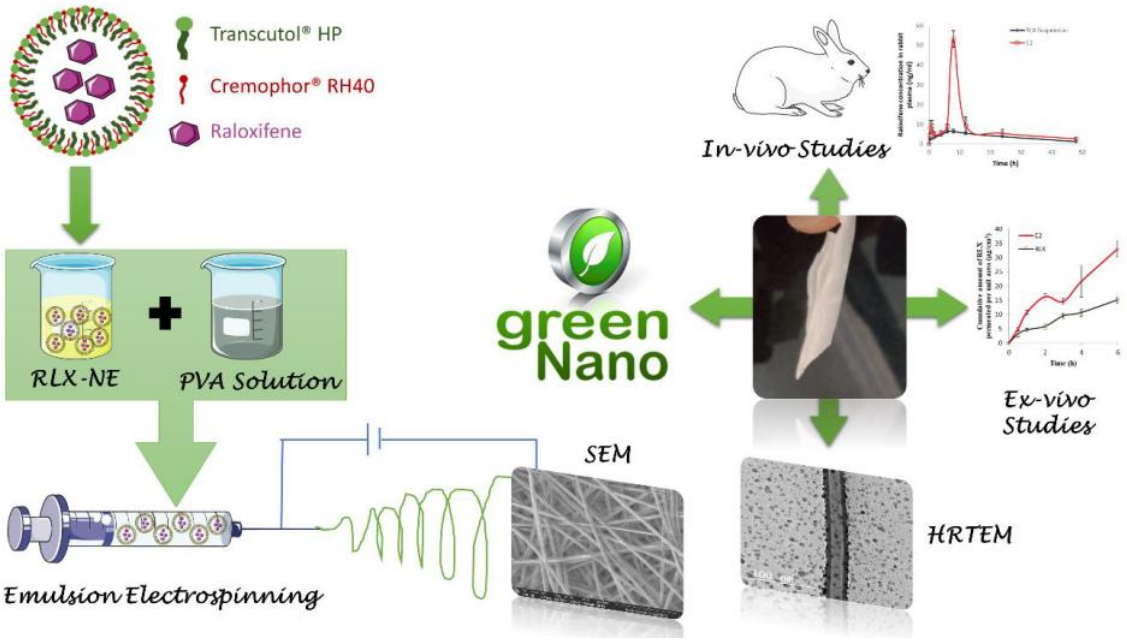
Abstract

Proteus mirabilis is a frequent cause of catheter associated urinary tract infections (CAUTIs). Several virulence factors contribute to its pathogenesis, but swarming motility, biofilm formation, and urease activity are considered the hallmarks. The increased prevalence in antibiotic resistance among uropathogens is alarming and requires searching for new treatment alternatives. With this in mind, our study aims to investigate antivirulence activity of indole derivatives against multidrug resistant P. mirabilis isolates. Ethyl acetate (EtOAc) extracts from Enterobacter sp. (rhizobacterium), isolated from Egyptian soil samples were tested for their ability to antagonize the virulence capacity and biofilm activity of P. mirabilis uropathogens. Extracts of two Enterobacter sp. isolates (coded Zch127 and Cbg70) showed the highest antivirulence activities against P. mirabilis. The two promising rhizobacteria Zch127 and Cbg70 were isolated from soil surrounding: Cucurbita pepo (Zucchini) and Brassica oleracea var. capitata L. (Cabbage), respectively. Sub-minimum inhibitory concentrations (Sub-MICs) of the two extracts showed potent antibiofilm activity with significant biofilm reduction of ten P. mirabilis clinical isolates (p-value < 0.05) in a dose-dependent manner. Interestingly, the Zch127 extract showed anti-urease, anti-swarming and anti-swimming activity against the tested strains. Indole derivatives identified represented key components of indole pyruvate, indole acetamide pathways; involved in the synthesis of indole acetic acid. Additional compounds for indole acetonitrile pathway were detected in the Zch127 extract which showed higher antivirulence activity. Accordingly, the findings of the current study model the feasibility of using these extracts as promising antivirulence agent against the P. mirabilis uropathogens and as potential therapy for treatment of urinary tract infections (UTIs).

8. **Nageeb El-Helaly, S.**; Abd-Elrasheed, E.; Salim, S.A.; Fahmy, R.H.; Salah, S.; EL-Ashmoony, M.M. "Green Nanotechnology in the Formulation of a Novel Solid Dispersed Multilayered Core-Sheath Raloxifene-Loaded Nanofibrous Buccal Film; In Vitro and In Vivo Characterization", *Pharmaceutics*, **13**, 474, (**2021**). https://doi.org/10.3390/pharmaceutics13040474
IF: 4.421

Abstract

Green nanotechnology utilizes the principles of green chemistry to formulate eco-friendly nanocarrier systems to mitigate patients and environment hazards. Raloxifene (RLX) demonstrates poor aqueous solubility (BCS class II) and low bioavailability, only 2% (extensive first-pass metabolism). The aim of this study is to enhance RLX solubility and bioavailability via development of novel solid dispersed multilayered core-sheath RLX-loaded nanofibers (RLX-NFs) without the involvement of organic solvents. A modified emulsion electrospinning technique was developed. Electrospinning of RLX-nanoemulsion (RLX-NE) with polymer solution (Poly vinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC) and Chitosan (CS)) in different volume ratios (1:9, 2:8 and 4:6) using D-optimal response surface methodology was adopted. In-vitro characterization of RLX-loaded NFs was performed; scanning electron microscope (SEM), thermal analysis, drug content, release studies and bioadhesion potential. The optimum NFs formula was evaluated for morphology using high resolution transmission electron microscopy (HRTEM), and ex-vivo drug permeation. The superiority of E2 [comprising RLX-NE and PVA (2:8)] over other NFs formulae was statistically observed with respect to Q60 (56.048%), Q240 (94.612%), fiber size (594.678 nm), mucoadhesion time 24 h, flux (5.51 µg/cm2/h) and enhancement ratio (2.12). RLX pharmacokinetics parameters were evaluated in rabbits following buccal application of NFs formula E2, relative to RLX oral dispersion. E2 showed significantly higher Cmax (53.18±4.56 ng/mL), and relative bioavailability (≈ 2.29 folds).






SOP International Publications 2020



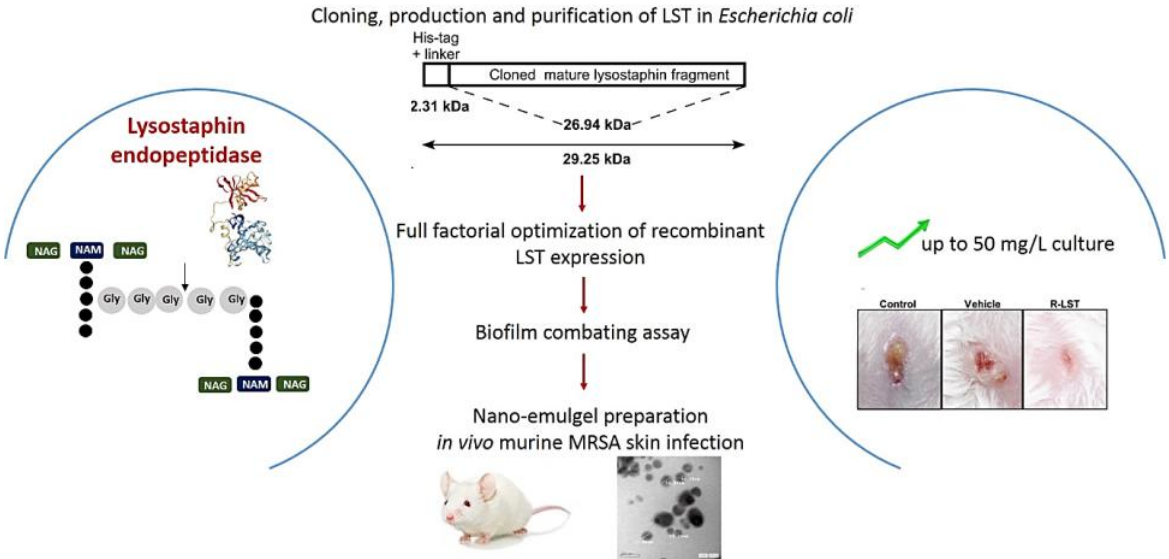

SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2020

Twenty-four (24) International publications with SOP/NGU affiliation were published in 2020.

9. Nour El-Din HT, Elhosseiny NM, El-Gendy MA, Mahmoud AA, **Hussein MMM**, Attia AS. "A Rapid Lysostaphin Production Approach and a Convenient Novel Lysostaphin Loaded Nano-emulgel; As a Sustainable Low-Cost Methicillin-Resistant Staphylococcus aureus Combating Platform", *Biomolecules*, **10(3)**, 435, (**2020**). https://doi.org/10.3390/biom10030435
IF: 4.694

Abstract

Staphylococcus aureus is a Gram-positive pathogen that is capable of infecting almost every organ in the human body. Alarmingly, the rapid emergence of methicillin-resistant S. aureus strains (MRSA) jeopardizes the available treatment options. Herein, we propose sustainable, low-cost production of recombinant lysostaphin (rLST), which is a native bacteriocin destroying the staphylococcal cell wall through its endopeptidase activity. We combined the use of E. coli BL21(DE3)/pET15b, factorial design, and simple Ni-NTA affinity chromatography to optimize rLST production. The enzyme yield was up to 50 mg/L culture, surpassing reported systems. Our rLST demonstrated superlative biofilm combating ability by inhibiting staphylococcal biofilms formation and detachment of already formed biofilms, compared to vancomycin and linezolid. Furthermore, we aimed at developing a novel rLST topical formula targeting staphylococcal skin infections. The phase inversion composition (PIC) method fulfilled this aim with its simple preparatory steps and affordable components. LST nano-emulgel (LNEG) was able to extend active LST release up to 8 h and cure skin infections in a murine skin model. We are introducing a rapid, convenient rLST production platform with an outcome of pure, active rLST incorporated into an effective LNEG formula with scaling-up potential to satisfy the needs of both research and therapeutic purposes.



10. Saad MAE, Fahmy MIM, Al-Shorbagy M, Assaf N, Hegazy AAE, El-Yamany MF. "Nateglinide Exerts Neuroprotective Effects via Downregulation of HIF-1α/TIM-3 Inflammatory Pathway and Promotion of Caveolin-1 Expression in the Rat's Hippocampus Subjected to Focal Cerebral Ischemia/Reperfusion Injury", *Inflammation,* 43(2), 401-416, (2020). Doi: 10.1007/s10753-019-01154-3.
IF: 3.212

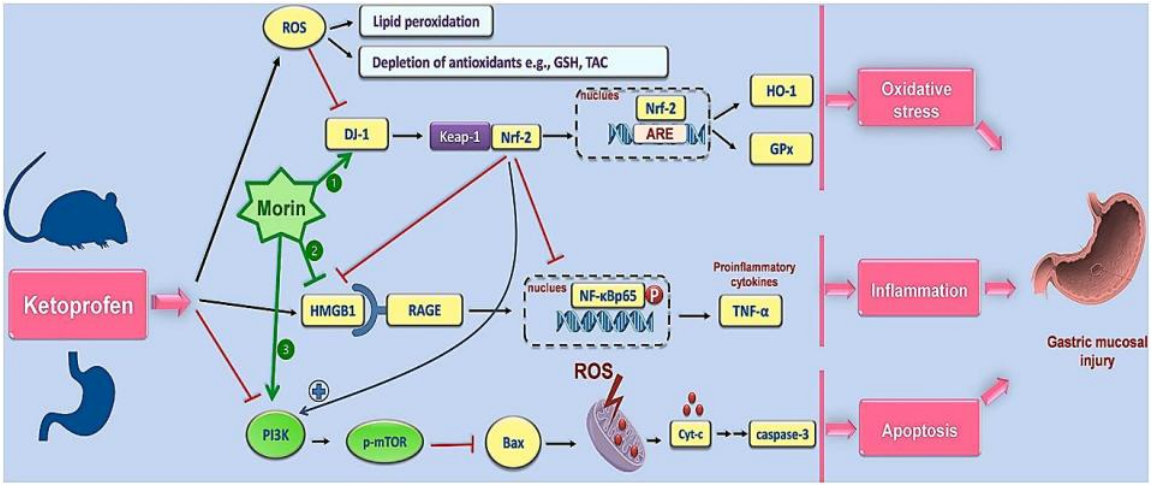
Abstract

Ischemic stroke is a major cause of death and motor disabilities all over the world. It is a muti-factorial disorder associated with inflammatory, apoptotic, and oxidative responses. Nateglinide (NAT), an insulinotropic agent used for the treatment of type 2 diabetes mellitus, recently showed potential anti-inflammatory and anti-apoptotic effects. The aim of our study was to elucidate the unique neuroprotective role of NAT in the middle cerebral artery occlusion (MCAO)-induced stroke in rats. Fifty-six male rats were divided to 4 groups (n = 14 in each group): the sham-operated group, sham receiving NAT (50 mg/kg/day, p.o) group, ischemia/reperfusion (IR) group, and IR receiving NAT group (50 mg/kg/day, p.o). MCAO caused potent deficits in motor and behavioral functions of the rats. Significant increase in inflammatory and apoptotic biomarkers has been observed in rats' hippocampi. Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway was significantly stimulated causing activation of series inflammatory biomarkers ending up neuro-inflammatory milieu. Pretreatment with NAT preserved rats' normal behavioral and motor functions. Moreover, NAT opposed the expression of hypoxia-inducible factor-1α (HIF-1α) resulting in downregulation of more inflammatory mediators namely, NF-κB, tumor necrosis factor-β (TNF-β), and the anti-survival gene PMAIP-1. NAT stimulated caveolin-1 (Cav-1) which prevented expression of oxidative biomarkers, nitric oxide (NO), and myeloperoxidase (MPO) and hamper the activation of apoptotic biomarker caspase-3. In conclusion, our work postulated that NAT exhibited its neuroprotective effects in rats with ischemic stroke via attenuation of different unique oxidative, apoptotic, and inflammatory pathways.

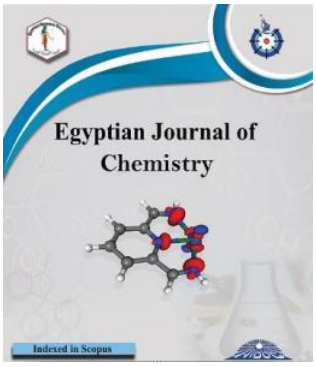
11. Hany H. Arab, **Muhammed A. Saad**, Ayman E. El-Sahar, **Muhammad Y. Al-Shorbagy**. "Mechanistic perspective of morin protection against ketoprofen-induced gastric mucosal injury: Targeting HMGB1/RAGE/NF-κB, DJ-1/Nrf2/HO-1 and PI3K/mTOR pathways", *Archives of Biochemistry and Biophysics*, **693**, 108552, (**2020**), ISSN 0003-9861, https://doi.org/10.1016/j.abb.2020.108552.
IF: 3.391

Abstract

Ketoprofen is a widely used NSAID which incurs gastric mucosal damage. The high mobility group Box 1 (HMGB1) protein is a DNA-binding protein which exerts robust inflammatory actions, however, its role in ketoprofen-induced gastric damage has not been explored. Additionally, no previous studies have linked HMGB1/RAGE/NF-κB, DJ-1/Nrf2/HO-1 and PI3K/mTOR pathways in ketoprofen-induced gastropathy. The current work aimed to explore the potential of morin, a flavonoid with marked antioxidant/anti-inflammatory actions, to protect against ketoprofen-evoked gastric damage. Moreover, the underlying mechanisms, including the impact of morin on HMGB1/RAGE/NF-κB, DJ-1/Nrf2/HO-1 and PI3K/mTOR pathways were addressed. Immunoblotting and ELISA were used to examine the expression of target signals. Morin (50 mg/kg, p. o.) attenuated the severity of gastric injury via lowering of ulceration/hemorrhage and macroscopic damage scores. Meanwhile, it attenuated the histopathologic aberrations/damage scores. In the context of inflammation, morin suppressed TNF-α and myeloperoxidase levels and enhanced IL-10. Furthermore, it inhibited HMGB1/RAGE/NF-κB pathway through downregulating HMGB1, RAGE and phospho–NF–κBp65 protein expression. Morin successfully inhibited gastric mucosal oxidative stress through lowering of lipid peroxides and boosting of reduced glutathione, glutathione peroxidase and total antioxidant capacity. It also boosted DJ-1/Nrf2/HO-1 pathway via upregulating DJ-1, Nrf2 and HO-1 protein expression. Additionally, morin counteracted the apoptotic events by downregulating the proapoptotic Bax and Bax/Bcl-2 ratio and augmenting the PI3K/mTOR pathway through upregulating PI3Kp110α and phospho-mTOR protein expression. In conclusion, the current study demonstrates, for the first time, that morin shows a promise for the management of ketoprofen-induced mucosal insult through targeting of HMGB1/RAGE/NF-κB, DJ-1/Nrf2/HO-1 and PI3K/mTOR pathways.



12. Hadir Farouk, **Muhammed A. Saad**, Sawsan S. Mahmoud, Mohammed F. El-Yamany, Ola A. Sharaf, Rania F. Ahmed, Ezz E. El-Denshary. "Effect of (+) and (-) hydroxycitric acid sterio-isomers present in natural products in counteracting insulin resistance", *Egyptian Journal of Chemistry*, **63(11)**, 4341-4354, (**2020**). DOI: 10.21608/ejchem.2020.25054.2493



Abstract

Metabolic syndrome is a cluster of cardiovascular and metabolic risk factors that include impaired glucose metabolism and obesity. The use of nutraceuticals is an ideal choice for controlling this disorder. The aim of the present study is to investigate the effect (-) hydroxycitric acid present in garcinia fruit rind and (+) hydroxycitric acid present in hibiscus calyx on metabolic syndrome and compare it to that of metformin. Metabolic syndrome was induced in rats by ingestion of high fat high fructose (HFHF) diet for 90 days. Metformin (500 mg/Kg animal b.wt.), garcinia (1000 mg/Kg animal b.wt.) and hibiscus (250 mg/Kg animal b.wt) were orally administered throughout the last 30 days of the HFHF diet regimen. Both garcinia and hibiscus were effective in reducing serum blood glucose and insulin levels. The effect of garcinia on blood glucose was comparable to that of metformin, while the effect of hibiscus on insulin and HOMA-IR was comparable to that of metformin. Both were able to reduce serum leptin level. All treated groups showed a significant decrease in total cholesterol level. Only hibiscus was able to normalize liver function while garcinia failed to reduce the elevated liver function. As a conclusion we would recommend the use of hibiscus over garcinia to overcome the adverse effects of metabolic syndrome.

13. Rasha R. Yossef, Mohamed F. Al-Yamany, **Muhammed A. Saad**, Ayman E. El-Sahar. "Neuroprotective effects of vildagliptin on drug induced Alzheimer's disease in rats with metabolic syndrome: Role of hippocampal klotho and AKT signaling pathways", *European Journal of Pharmacology*, **889**, 173612, (**2020**), ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2020.173612.
IF: 3.263

Abstract

Growing evidences suggest the presence of several similarities in the molecular mechanisms underlying the neurodegenerative diseases and metabolic abnormalities. Adults who develop Metabolic Syndrome (MS) are at a higher risk of developing Alzheimer's disease (AD). Pharmacological agents, like dipeptidyl peptidase-4 (DPP-4) inhibitors that increase the levels of glucagon like peptide 1 (GLP-1) and ameliorate symptoms of MS, have become an auspicious candidate as disease modifying agents in the treatment of AD. The present study investigates the beneficial effects of Vildagliptin, a DPP-4 inhibitor in counteracting cognitive decline in different models of dementia targeting the AKT, JAK/STAT signaling pathways and hippocampal Klotho expression, to judge the neuroprotective, anti-apoptotic and anti-inflammatory effects of the drug. Cognitive decline was induced by either administration of high fat high sugar (HFHS) diet for 45 days alone, or with oral administration of AlCl3 (100 mg/kg/day) for 60 days. Rats were orally administered Vildagliptin (10 mg/kg) for 60 days along with AlCl3 administration. Vildagliptin treatment improved spatial memory and activities in morris water maze (MWM) test and open field test respectively. Results revealed an increase of both hippocampal klotho and Bcl-2 expressions along with an increase in both AKT and ERK1/2 phosphorylation. In contrast, Vildagliptin treatment decreased hippocampal contents of inflammatory, apoptotic and oxidative stress biomarkers as TNF-α, caspase-3 and FOXO1 along with restoring metabolic abnormalities. A significant decrease in BAX expressions with JAK2/STAT3 inhibition was observed. These findings demonstrate that the neuroprotective role of vildagliptin is possibly via modulating Klotho protein together with AKT pathway.

14. Ayman E. El-Sahar, Alyasaa A. Rastanawi, Muhammed F. El-Yamany, **Muhammed A. Saad**. "Dapagliflozin improves behavioral dysfunction of Huntington's disease in rats via inhibiting apoptosis-related glycolysis", *Life Sciences*, **257**, 118076, (**2020**), ISSN 0024-3205, https://doi.org/10.1016/j.lfs.2020.118076.
IF: 3.647

Abstract

Aims

Huntington's disease is a rare neurodegenerative disorder which is associated with defected glucose metabolism with consequent behavioral disturbance including memory and locomotion. 3-nitropropionic acid (3-NP) can cause, in high single dose, an acute striatal injury/Huntington's disease. Dapagliflozin, which is one of the longest duration of action of SGLTIs family, may be able to diminish that injury and its resultant behavioral disturbances.

Material and methods

Forty rats were divided into four groups (n = 10 in each group): normal control group (CTRL), dapagliflozin (CTRL + DAPA) group, 3-nitropropionic acid (3-NP) group, and dapagliflozin plus 3-nitropropionic acid (DAPA + 3-NP) group. Behavioral tests (beam walking test, hanging wire test, limb withdrawal test, Y-maze spontaneous alteration, elevated plus maze) were performed with evaluating neurological scoring. In striatum, neurotransmitters (glutamate, aspartate, GABA, ACh and AChE activity) were measured. In addition, apoptosis and glycolysis markers (NF-κB, Cyt-c, lactate, HK-II activity, P53, calpain, PEA15 and TIGAR) were determined. Inflammation (IL-1β, IL-6, IL-8 and TNF-α) and autophagy (beclin-1, LC3 and DRAM) indicators were measured. Additionally, histopathological screening was conducted.

Key findings

3-Nitropropionic acid had the ability to perturb the neurotransmission which was reflected in impaired behavioral outcome. All of glycolysis, apoptosis and inflammation markers were elevated after 3-NP acute intoxication but autophagy parameters, except DRAM, were reduced. However, DAPA markedly reversed the abovementioned parameters.

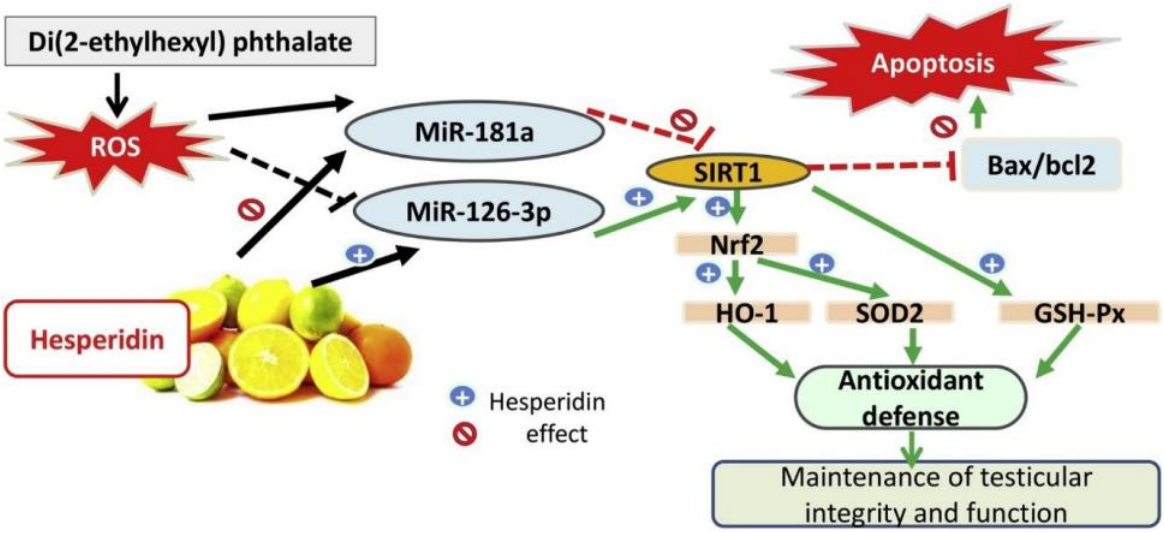
Significance

Dapagliflozin demonstrated anti-glycolytic, anti-apoptotic, anti-inflammatory and autophagic effects on 3-NP-damaged striatal cells and promoted the behavioral outcome.

15. Hebatullah S. Helmy, Mahmoud A. Senousy, Ayman E. El-Sahar, Rabab H. Sayed, **Muhammed A. Saad**, Eman M. Elbaz. "Aberrations of miR-126-3p, miR-181a and sirtuin1 network mediate Di-(2-ethylhexyl) phthalate-induced testicular damage in rats: The protective role of hesperidin", *Toxicology*, **433–434**, 152406, (**2020**), ISSN 0300-483X, https://doi.org/10.1016/j.tox.2020.152406.
IF: 4.099

Abstract

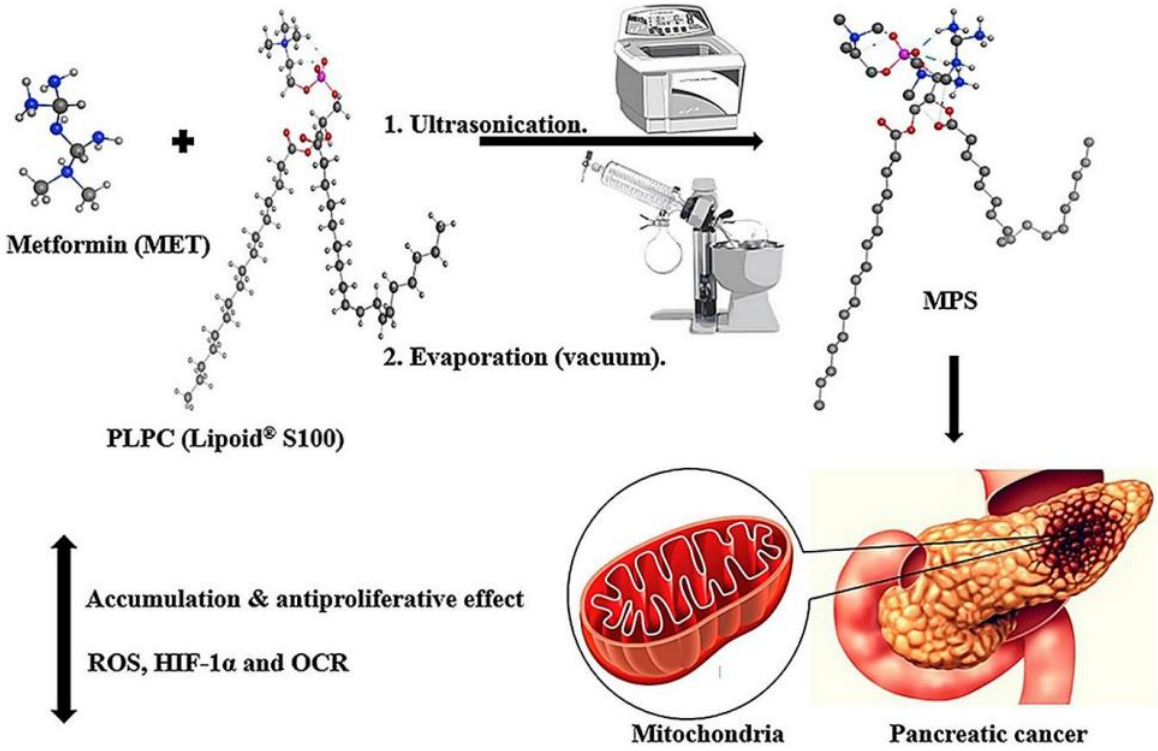
Recently, oxidative stress was implicated in the environmental contaminant Di-(2-ethylhexyl) phthalate (DEHP)-induced testicular toxicity, however the mechanism is unclear. We investigated the role of oxidative stress-responsive microRNAs in DEHP-induced aberrations and the protective effect of the citrus flavonoid, hesperidin (HSP). Male Wistar rats were randomly allocated into four groups as vehicle-treated control, DEHP-alone group (500 mg/kg/day) for 30 days, and HSP (25 or 50 mg/kg) for 60 days; testicular damage was triggered by oral administration of DEHP (500 mg/kg/day) after thirty days of oral administration of HSP (25 or 50 mg/kg). DEHP administration reduced testis weight coefficient, serum testosterone, testicular 3β-hydroxysteroid dehydrogenase and antioxidant enzyme activities, and elevated serum fatty acid-binding protein-9, testicular malondialdehyde, and Bax/Bcl2 ratio. Aberrant testicular miR-126-3p and miR-181a expression was observed, along with decreased expression of sirtuin1 (SIRT1) and its targets; nuclear factor-erythroid 2-related factor2, haeme oxygenase-1, and superoxide dismutase2. HSP administration significantly ameliorated these changes and restored testicular function in a dose-dependent manner. We highlight a novel role of oxidative stress-miR-126/miR-181a-SIRT1 network in mediating DEHP-induced changes which were reversed by the antioxidant HSP.



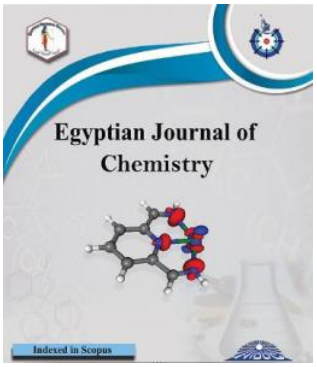
16. Michael M. Farag, Nevine S. Abd El Malak, Soad A. Yehia, **Mohammed A. Ahmed**. "Sonocomplexation as an effective tool to enhance the antitumorigenic effect of metformin: Preparation, in vitro characterization, molecular dynamic simulation & MiaPaCa-2 cell line hypoxia evaluation", *Journal of Drug Delivery Science and Technology*, **59**, 101968, (**2020**), ISSN 1773-2247, https://doi.org/10.1016/j.jddst.2020.101968.
IF: 2.734

Abstract

This study aimed to prepare metformin-phospholipid sonocomplexes (MPS) to enhance the lipophilicity, hence the permeability of this highly water-soluble drug. Metformin (MET) is an old antidiabetic drug gaining interest for being recently investigated for its antitumorigenic properties. The polarity of MET makes its cellular uptake dependent on cell membrane transporters which poses a challenging limitation to combat cancer at supraphysiological concentrations unachievable in patients. A D-optimal design was adopted to statistically optimize the formulation variables, namely phospholipid: MET ratio, sonication time and phospholipid type. MPS showed a lipophilicity enhancement up to 19 folds based on the partition coefficient comparative study with pure MET. This vast improvement was explained using the packing parameter theory as we hypothesized the self-assembly of MPS in the lipid phase in the form of inverted micelles. This was confirmed by studying MPS on the molecular level using molecular docking and molecular dynamics simulation. The optimal sonocomplex showed 3.2 folds lower IC50, reduced oxygen consumption rate (OCR), hypoxia-inducible factor (HIF-1a) and reactive oxygen species (ROS) in MiaPaCa-2 cells compared to pure MET. These results revealed the potentiality of MPS to alleviate tumor hypoxia more effectively which could be useful for resistant cancers like pancreatic ductal adenocarcinoma (PDAC).



17. Nadia G. Zaki, Walaa H. Mahmoud, **Ahmed M. El Kerdawy**, Abanoub Abdullah, Gehad G. Mohamed. "Structural Characterization, Thermal Analyses, Antiproliferative and Antimicrobial Activity of Cocaine Complexes with Mn(II) and Cu(II)", *Egyptian Journal of Chemistry*, **63(5)**, 1857-1868, (**2020**). DOI: 10.21608/ejchem.2019.16748.2019



Abstract

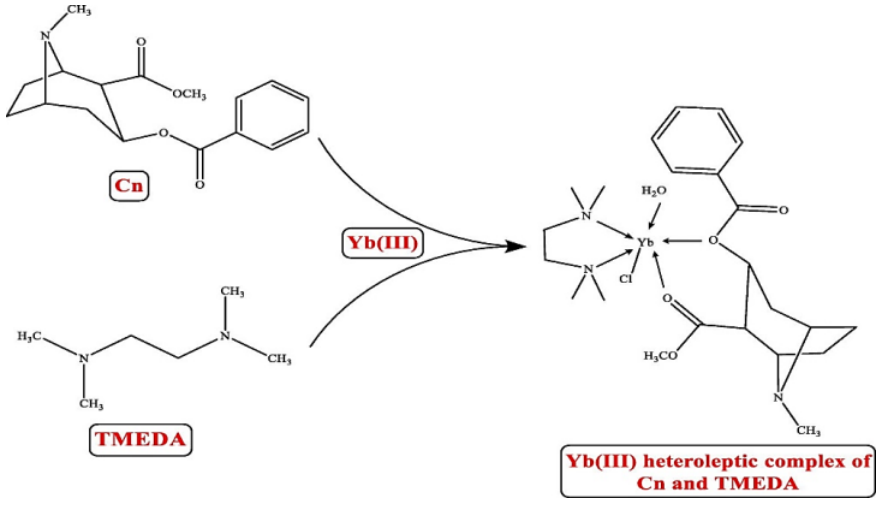
Reaction of cocaine (Cn) with Mn(II) and Cu(II) chloride salts afforded complexes of the [M(Cn)Cl(OH2)3]Cl type which were structurally characterized by elemental analysis, conductance measurements, spectroscopic methods and mass spectroscopy. Their thermal properties were studied. The in vitro antitumor activity of the newly synthesized complexes was investigated by MTT assay on MCF-7 and HepG-2 cell lines. Both complexes exhibited promising cytotoxic activity on both cell lines with high safety on normal human cells. Their antifungal activity against Aspergillus fumigatus and Candida albicans and antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Salmonella typhimurium and Escherichia coli were also included.

18. Nadia G. Zaki, Walaa H. Mahmoud, **Ahmed M. El Kerdawy**, Abanoub Mosaad Abdallah, Gehad G. Mohamed. "Heteroleptic complexes of cocaine/TMEDA with some f block metals: Synthesis, DFT studies, spectral, thermal, cytotoxicity and antimetastatic properties", *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **229**, 117938, (2020), ISSN 1386-1425, https://doi.org/10.1016/j.saa.2019.117938.
IF: 3.232

Abstract

A series of new three heteroleptic complexes of the general formula [Ln(Cn)(TMEDA)Cl(OH2)]·2Cl·xH2O, (where Ln = La(III), Er(III) and Yb(III), Cn = cocaine and TMEDA = N,N,N′,N′-tetramethylethylenediamine) were synthesized, structurally characterized by elemental analysis, spectroscopic methods, molar conductivity and mass spectrometry. Thermal properties of the synthesized complexes and their kinetic thermodynamic parameters were studied. Theoretical calculations including geometry optimization, electronic structure and electronic and thermal energies were carried out using DFT and TD-DFT calculations at B3LYP/LANL2DZ level of theory and the different quantum chemical parameters were calculated. The in vitro antiproliferative activity of the newly synthesized complexes was assessed by MTT assay on MCF-7 and HepG-2 cancer cell lines. Yb(III) complex showed promising cytotoxic activity comparable to that of cisplatin on both cell lines with minimum effect on human normal cells. Further molecular mechanistic investigations showed that Yb(III) complex is an apoptotic inducer as it raises the caspase-3 and caspase-9 cellular level in the MCF-7 cell line. Furthermore, it showed an elevating effect on the level of the tumor suppressor nuclear proteins P21 and P27 concentrations in MCF-7 cells. Moreover, Yb(III) complex hindered the cellular scavenger system of the reactive oxygen species through reducing the glutathione peroxidase (GPx) cellular level imperiling MCF-7 cells by unmanageable oxidative stress. In addition to its cytotoxic effect, Yb(III) complex showed antimetastatic properties as it decreased the cellular levels of matrix metalloproteinases MMP-3 and MMP-9. These results showed that the Yb(III) complex is a promising cytotoxic metal-based agent that exerts its action through various molecular mechanisms with minimum effects on normal cells and with additional antimetastatic properties.

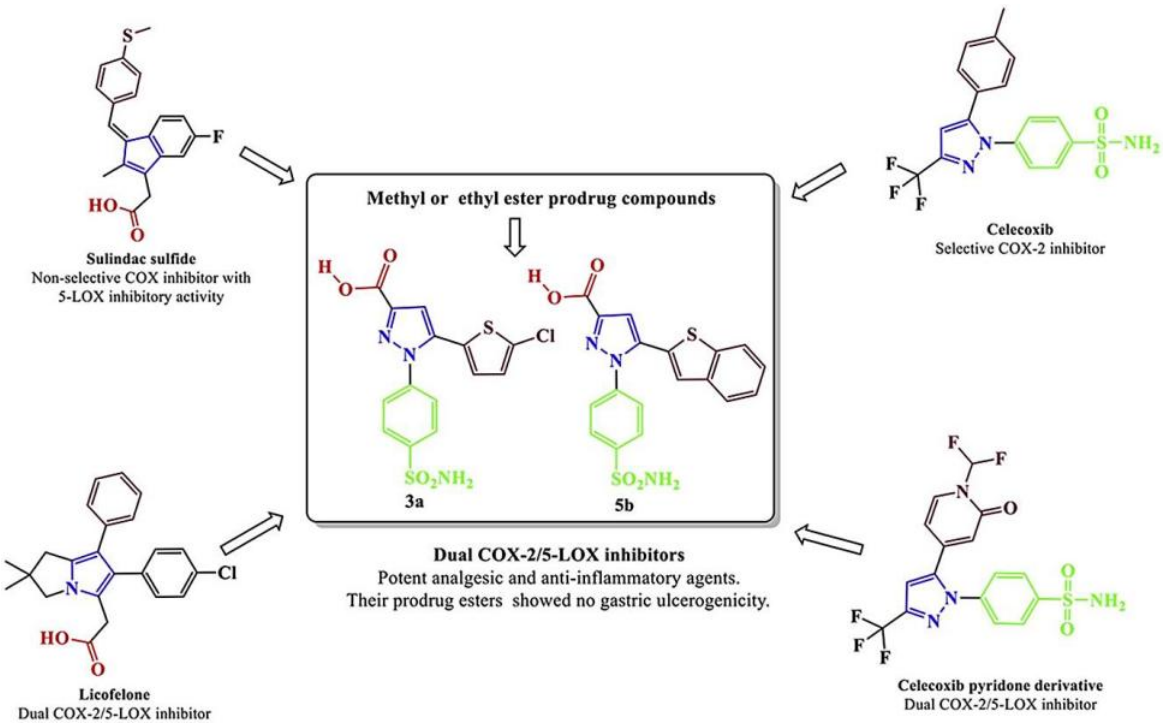
Yb(III) heteroleptic complex of Cn and TMEDA, as a representative example, was synthesized as a potent antiproliferative agent against human HepG-2 and MCF-7 cancer cells and structurally characterized by different spectral and analytical techniques such as elemental analysis, spectroscopic methods, molar conductivity, thermal analysis and DFT studies. Its antiproliferative activity was assessed by studying its cytotoxicity, antimetastatic effect, induction of apoptosis, and its influence on the expression of p21 and p27 tumor suppressor proteins and the glutathione peroxidase (GPx) activity in MCF-7 cells.



19. Ehab M. Gedawy, Asmaa E. Kassab, **Ahmed M. El Kerdawy**. "Design, synthesis and biological evaluation of novel pyrazole sulfonamide derivatives as dual COX-2/5-LOX inhibitors", *European Journal of Medicinal Chemistry*, 189, 112066, (2020), ISSN 0223-5234, https://doi.org/10.1016/j.ejmech.2020.112066.
IF: 5.573

Abstract

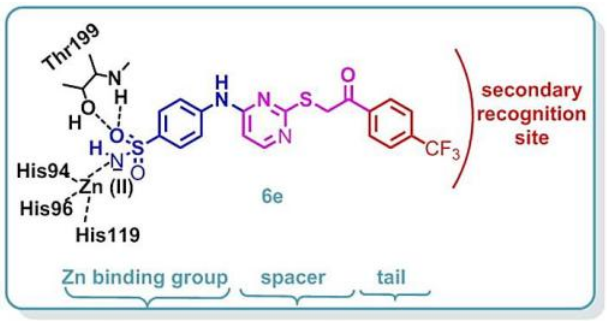
The current therapeutic demand focuses more on the discovery of safer NSAIDs rather than exploring more potent alternatives. The dual COX-2/5-LOX inhibition is a promising strategy for designing compounds with an enhanced efficacy, reduced side-effects and a broader anti-inflammatory spectrum in comparison to classical NSAIDs. In the present study, a hybridization strategy was adopted to combine the binding features of the non-selective COX inhibitor "sulindac" and the selective COX-2 inhibitor "celecoxib" which show 5-LOX inhibitory activity with that of licofelone and a celecoxib pyridone analogue which show dual COX-2/5-LOX inhibitory activity to design new series of pyrazole sulfonamide derivatives which, by design, should possess dual COX-2/5-LOX inhibitory activity. All the newly synthesized compounds were initially tested for their potential analgesic activity, then candidates that showed potential analgesic activity, were selected for the subsequent anti-inflammatory activity evaluation, as well as, ulcerogenicity testing. Moreover, in vitro assessment of their COX-1, COX-2 and 5-LOX inhibitory activities were performed. The benzothiophen-2-yl pyrazole carboxylic acid derivative 5b showed the most potent analgesic and anti-inflammatory activities surpassing that of celecoxib and indomethacin. It showed potent COX-1, COX-2 and 5-LOX inhibitory activity with IC50 of 5.40, 0.01 and 1.78 μM, respectively, showing a selectivity index of 344.56 that was much better than the used reference standards and its parent compounds, confirming its selectivity towards COX-2 over COX-1. The prodrug ester derivatives 6c and 6d showed equipotent activity to their parent compound 5b with no gastric ulcerogenicity. Molecular docking simulations confirmed that the newly synthesized compounds possess the structural features required for binding to the target enzymes COX-2 and 5-LOX.



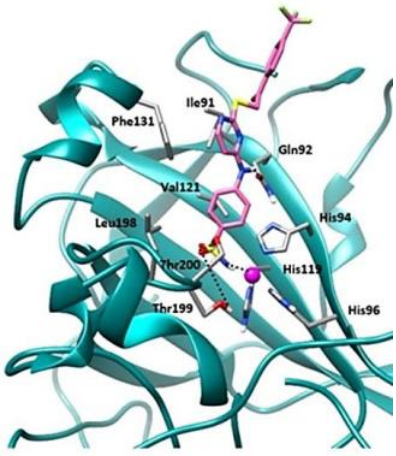
20. Heba T. Abdel-Mohsen, **Ahmed M. El Kerdawy**, Mohamed A. Omar, Emanuela Berrino, Ahmed S. Abdelsamie, Hoda I. El Diwani, Claudiu T. Supuran. "New thiopyrimidine-benzenesulfonamide conjugates as selective carbonic anhydrase II inhibitors: synthesis, in vitro biological evaluation, and molecular docking studies", *Bioorganic & Medicinal Chemistry*, **28(5)**, 115329, (**2020**), ISSN 0968-0896, https://doi.org/10.1016/j.bmc.2020.115329.
IF: 3.073

Abstract

In the present work, a new series of thiopyrimidine-benzenesulfonamide conjugates was designed, synthesized and tested as carbonic anhydrase (CA, EC 4.2.1.1) inhibitors. Our design strategy was based on the molecular hybridization of the benzenesulfonamide moiety as a zinc binding group (ZBG), an alkylated thiopyrimidine moiety as a spacer and (un)substituted phenyl moieties with various electronic and hydrophobic environments as a tail. The designed and synthesized compounds were evaluated against four human (h) CA isoforms hCA I, hCA II, hCA IX and hCA XII. Series 6 showed promising activity and selectivity toward the cytosolic isoforms hCA I and hCA II versus the membrane bound isoforms hCA IX and hCA XII. Compounds 6e and 6f showed Ki of 0.04 µM against hCA II with a selectivity of 15.8- to 980-fold towards hCA II over hCA I, hCA IX, hCA XII isoforms. Molecular docking in the hCA II active site attributed the promising inhibitory activity of series 6 to the interaction of their sulfonamide moiety with the active site Zn2+ ion as well as its hydrogen bonding with the key amino acids Thr199 and Thr200. Through hydrophobic interaction, the benzenesulfonamide and the thiopyrimidine moieties interact with the hydrophobic side chains of the amino acids Val121/Leu198 and Ile91/Phe131, respectively. These results indicated that the designed and synthesized series is an interesting scaffold that can be further optimized for the development of selective antiglaucoma drugs.



Compd	hCA II K_i (µM)	Selectivity ratio for hCA II		
		I/II	IX/II	XII/II
6e	0.04	21.8	980	22.5



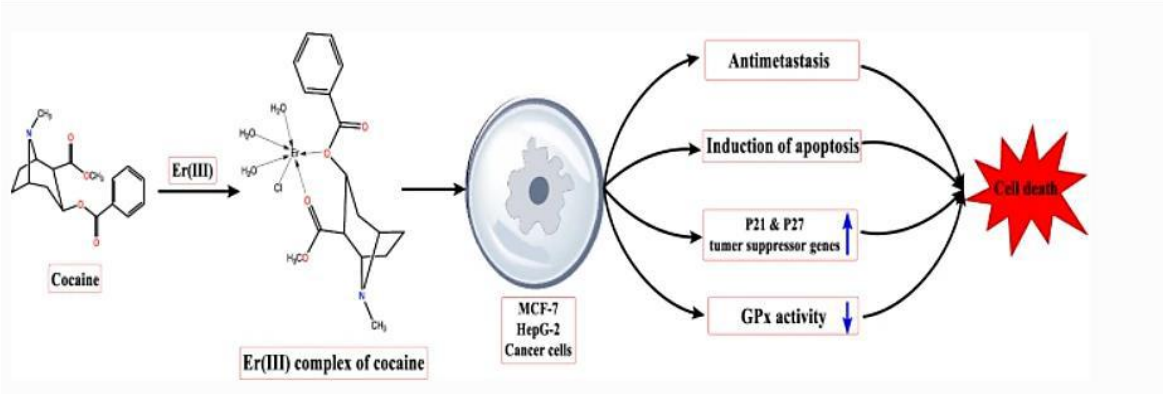
6e in CA II active site

21. Zaki, N.G., Mahmoud, W.H., **El Kerdawy, A.M.** *et al*. "Structural characterization, thermal, DFT, cytotoxicity, and antimetastatic properties of cocaine complexes with La(III), Er(III), and Yb(III)", *Res Chem Intermed,* **46**, 3193–3216, (**2020**). https://doi.org/10.1007/s11164-020-04146-3
IF: 2.262

Abstract

Reaction of cocaine (Cn) with Ln(III) chloride salts [where Ln=La(III), Er(III), and Yb(III)] afforded complexes of the [Ln(Cn)Cl(OH2)3].2Cl type which were structurally characterized by elemental analysis, conductance measurements, spectroscopic methods, and mass spectrometry. Their thermal properties and kinetic thermodynamic parameters were studied. Theoretical calculations including geometry optimization, thermal energies, and some quantum chemical parameters were carried out at DFT/B3LYP/LANL2DZ level of theory. TD-DFT calculations were also performed to assign their electronic spectra. The in vitro antitumor activity of the newly synthesized complexes was investigated by MTT assay on MCF-7 and HepG-2 cell lines. Er(III) complex exhibited promising cytotoxic activity comparable to that of cisplatin on MCF-7 cell line with high safety on normal human cells. Further molecular mechanistic investigations revealed that Er(III) complex was an apoptotic inducer as it elevated the cellular levels of caspase-3 and caspase-9 in MCF-7 cells. In addition, it displayed an elevating effect on the concentrations of the P21 and P27 tumor suppressor nuclear proteins in MCF-7 cells. Moreover, Er(III) complex hindered the cellular scavenger system of the reactive oxygen species by reducing the cellular level of glutathione peroxidase (GPx) imperiling MCF-7 cells by uncontrolled oxidative stress. Furthermore, Er(III) complex showed antimetastatic properties as it decreased the cellular levels of matrix metalloproteinases MMP-3 and MMP-9. These results concluded that the Er(III) complex is a promising anticancer metal-based agent that exerts its cytotoxic action through various molecular mechanisms with high safety on normal human cells and with additional antimetastatic properties.

Er(III)complex of Cn, as a representative example, was synthesized as a promising cytotoxic metal-based agent against human HepG-2 and MCF-7 cancer cells and structurally characterized by different spectral and analytical techniques such as elemental analysis, spectroscopic methods, molar conductivity, thermal analysis, and DFT studies. It exerts its action through various molecular mechanisms such as displaying significant antimetastatic effects by decreasing the secretion of MMP-3 and MMP-9, exhibiting remarkable induction of apoptosis by elevating the levels of caspase-3 and caspase-9proteins, inducing the expression of p21 and p27 tumor suppressor genes, and raising the glutathione peroxidase (GPx) activity.



22. Abdel-Mohsen HT, Abd El-Meguid EA, **El Kerdawy AM**, Mahmoud AEE, Ali MM. "Design, synthesis, and molecular docking of novel 2-arylbenzothiazole multiangiokinase inhibitors targeting breast cancer", *Arch Pharm (Weinheim)*, **353(4)**, e1900340, (**2020**). Doi: 10.1002/ardp.201900340.
IF: 2.590

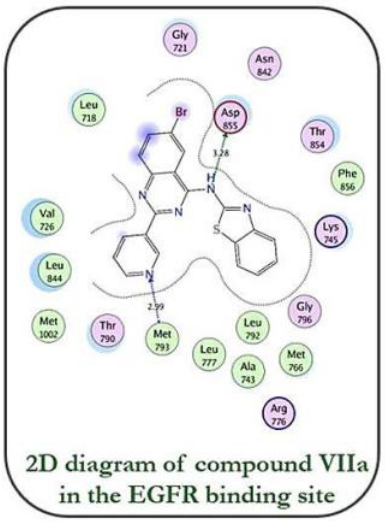
Abstract

A novel series of 2-arylbenzothiazoles 9, 10, and 12 were designed and synthesized as VEGFR-2/FGFR-1/PDGFR-β multiangiokinase inhibitors targeting breast cancer. Structural elongation of the known 2-phenylbenzothiazole scaffold (type I protein kinase inhibitor [PKI]), was carried out to afford series of type II PKIs 9, 10, and 12. Compounds 9d, 9f, 9i, and 9k exhibited potent multikinase inhibitory activity with IC50 values of 0.19, 0.18, 0.17, and 0.13 µM, respectively, against VEGFR-2; IC50 values of 0.28, 0.37, 0.19, and 0.27 µM, respectively, against FGFR-1; and IC50 values of 0.07, 0.04, 0.08, and 0.14 µM, respectively, against PDGFR-β. Moreover, the synthesized benzothiazoles demonstrated promising cytotoxic activity against the MCF-7 cell line. The most potent benzothiazoles 9d and 9i exhibited IC50 values of 7.83 and 6.58 µM, respectively, on the MCF-7 cell line in comparison to sorafenib (III), which showed IC50 = 4.33 µM. Additionally, 9d and 9i showed VEGFR-2 inhibitory activity in MCF-7 cells of 81% and 83% when compared with sorafenib (III), which showed 88% inhibition. Molecular docking of the designed compounds in the VEGFR-2 and FGFR-1 active sites showed the accommodation of the 2-phenylbenzothiazole moiety, as reported, in the hinge region of the receptor tyrosine kinase (RTK)-binding site, while the amide moiety is involved in hydrogen bond interactions with the key amino acids in the gate area; this in turn directs the aryl group to the hydrophobic allosteric back pocket of the RTKs in a type II-like binding mode. The synthesized benzothiazoles showed satisfactory ADME properties for further optimization in drug discovery.

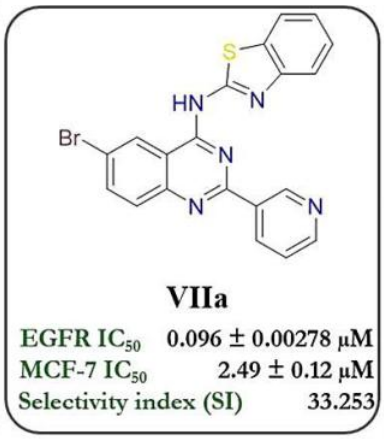
23. Heba Abdelrasheed Allam, Enayat E. Aly, Ahmed K.B.A.W. Farouk, **Ahmed M. El Kerdawy**, Essam Rashwan, Safinaz E.S. Abbass. "Design and Synthesis of some new 2,4,6-trisubstituted quinazoline EGFR inhibitors as targeted anticancer agents", *Bioorganic Chemistry*, **98**, 103726, (**2020**), ISSN 0045-2068, https://doi.org/10.1016/j.bioorg.2020.103726.
IF: 4.831

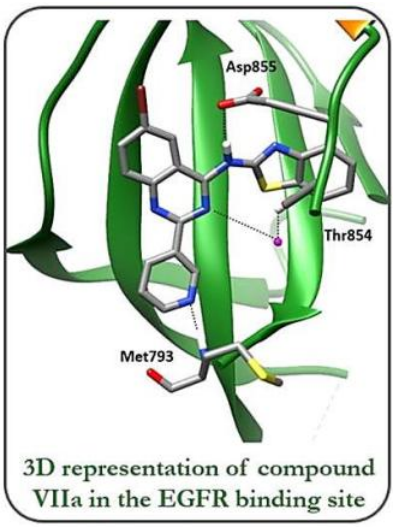
Abstract

The present study describes the synthesis of 6-bromo-2-(pyridin-3-yl)-4-substituted quinazolines starting from 4-chloro derivative VI via the reaction with either phenolic compounds to obtain VIIa-f, IXa-d, 2-amino-6-(un)substituted benzothiazole to produce VIIIa-c or hydrazine hydrate to give X. Reaction of the hydrazino functionality of X with appropriate acid anhydride, acid chloride or aldehyde affords XIa-c, XIIa-c and XIVa-i, respectively. The target compounds were screened for their efficacy as EGFR inhibitors compared to gefitinib. Compounds eliciting superior EGFR inhibitory activity were further screened for their in vitro cytotoxicity against two human cancer cell lines namely: MCF7 (breast) and A549 (lung), in addition to normal fibroblast cell WI38 relative to gefitinib as a reference. Furthermore, compounds that showed potent inhibitory activity on wild-type EGFR were screened against mutant EGFR and assayed for their cytotoxicity against mutant EGFR-expressing cell lines PC9 and HCC827. The unsubstituted benzothiazol-2-amine VIIa showing superior EGFR inhibition (IC50 = 0.096 µM) and anticancer activity against MCF-7 cell line (IC50 = 2.49 µM) was subjected to cell cycle analysis and apoptotic assay. Moreover, a molecular docking study was performed to investigate the interaction of some representive compounds with the active site of EGFR- TK.



2D diagram of compound VIIa in the EGFR binding site



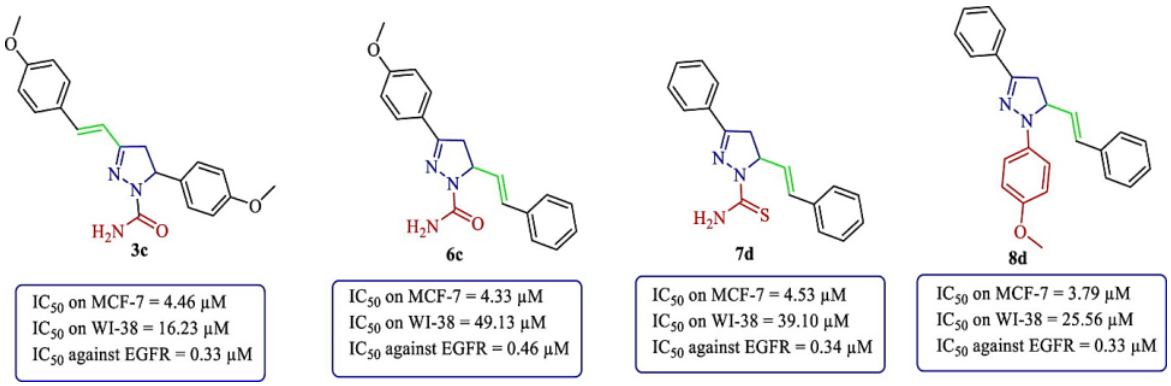


3D representation of compound VIIa in the EGFR binding site

24. Riham F. George, Manal Kandeel, Dina Y. El-Ansary, **Ahmed M. El Kerdawy**. "Some 1,3,5-trisubstituted pyrazoline derivatives targeting breast cancer: Design, synthesis, cytotoxic activity, EGFR inhibition and molecular docking", *Bioorganic Chemistry*, **99**, 103780, (**2020**), ISSN 0045-2068, https://doi.org/10.1016/j.bioorg.2020.103780.
IF: 4.831

Abstract

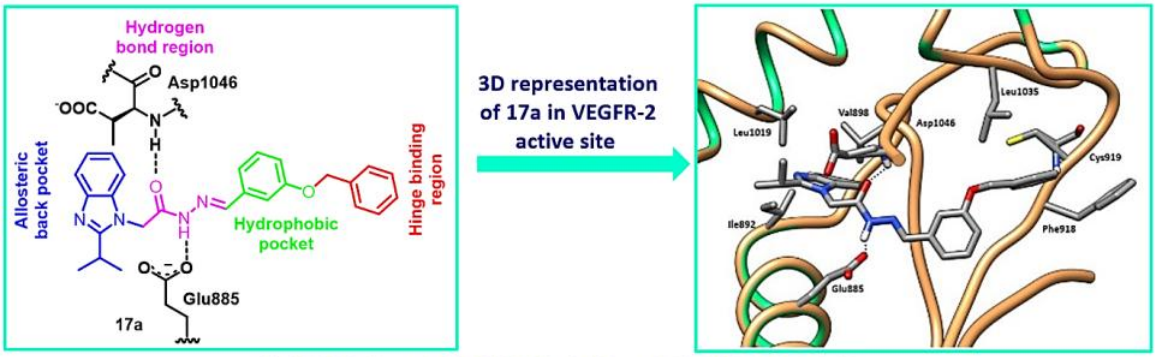
Different 1,3,5-trisubstituted pyrazoline derivatives 2a-c, 3-c, 4a-f, 6a-c, 7a-f and 8a-d were prepared via condensation reaction of the appropriate chalcone 1a-c or 5a-c with various hydrazine derivatives. All compounds were screened for their cytotoxicity against breast MCF-7 cancer cell line and the normal fibroblasts WI-38. Thirteen compounds 2a, 3a, 3c, 4a-d, 6c, 7d, 7e, 8b, 8d and 8f revealed promising cytotoxicity against MCF-7 compared to the reference standard staurosporine and they were safe to the normal fibroblasts WI-38. In addition, compounds 3c, 6c, 7d, 8b and 8d elicited higher cytotoxicity than erlotinib and exhibited promising EGFR inhibitory activity at submicromolar level comparable to that of erlotinib except for compound 8b that may exert its cytotoxicity via another mechanism besides EGFR inhibition. Molecular docking of 3c, 6c, 7d, 8b and 8d in the active site of EGFR confirmed the obtained results.



25. Abdel-Mohsen HT, Abdullaziz MA, **El Kerdawy AM**, Ragab FAF, Flanagan KJ, Mahmoud AEE, Ali MM, El Diwani HI, Senge MO. "Targeting Receptor Tyrosine Kinase VEGFR-2 in Hepatocellular Cancer: Rational Design, Synthesis and Biological Evaluation of 1,2-Disubstituted Benzimidazoles", *Molecules*, **25(4)**, 770, (**2020**). https://doi.org/10.3390/molecules25040770
IF: 3.267

Abstract

In this study, a novel series of 1,2-disubstituted benzo[d]imidazoles was rationally designed as VEGFR-2 inhibitors targeting hepatocellular carcinoma. Our design strategy is two-fold; it aimed first at studying the effect of replacing the 5-methylfuryl moiety of the well-known antiangiogenic 2-furylbenzimidazoles with an isopropyl moiety on the VEGFR-2 inhibitory activity and the cytotoxic activity. Our second objective was to further optimize the structures of the benzimidazole derivatives through elongation of the side chains at their one-position for the design of more potent type II-like VEGFR-2 inhibitors. The designed 1,2-disubstituted benzimidazoles demonstrated potent cytotoxic activity against the HepG2 cell line, reaching IC50 = 1.98 µM in comparison to sorafenib (IC50 = 10.99 µM). In addition, the synthesized compounds revealed promising VEGFR-2 inhibitory activity in the HepG2 cell line, e.g., compounds 17a and 6 showed 82% and 80% inhibition, respectively, in comparison to sorafenib (% inhibition = 92%). Studying the effect of 17a on the HepG2 cell cycle demonstrated that 17a arrested the cell cycle at the G2/M phase and induced a dose-dependent apoptotic effect. Molecular docking studies of the synthesized 1,2-disubstituted benzimidazoles in the VEGFR-2 active site displayed their ability to accomplish the essential hydrogen bonding and hydrophobic interactions for optimum inhibitory activity.

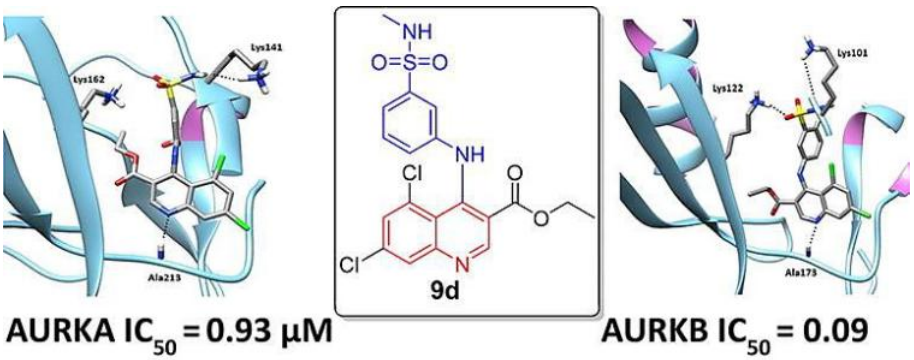


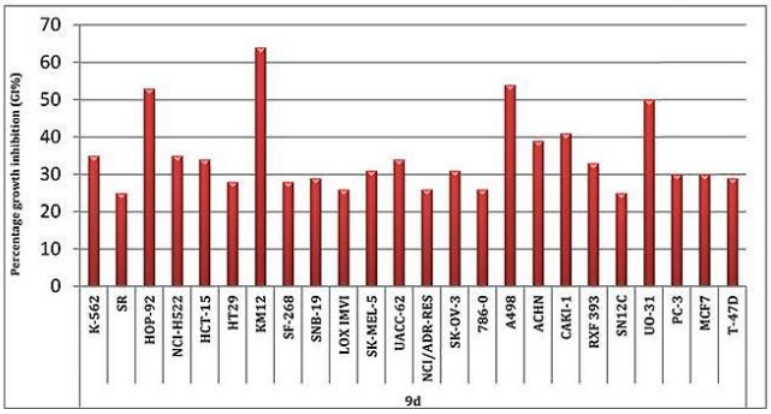
VEGFR-2: IC_{50} = 0.11 µM; FGFR-1: IC_{50} = 0.11 µM; PDGFR-β: IC_{50} = 0.05 µM; IC_{50} against HepG2 cell line = 1.98 µM; VEGFR-2 %inhibition in HepG2 cell line = 82%; 17a arrests HepG2 cell cycle at G2/M phase

26. Mohammad M. Al-Sanea, Ahmed Elkamhawy, Sora Paik, Kyeong Lee, **Ahmed M. El Kerdawy**, Bukhari Syed Nasir Abbas, Eun Joo Roh, Wagdy M. Eldehna, Heba A.H. Elshemy, Rania B Bakr, Ibrahim Ali Farahat, Abdulaziz I. Alzarea, Sami I. Alzarea, Khalid S. Alharbi, Mohamed A. Abdelgawad. "Sulfonamide-based 4-anilinoquinoline derivatives as novel dual Aurora kinase (AURKA/B) inhibitors: Synthesis, biological evaluation and in silico insights", *Bioorganic & Medicinal Chemistry*, **28(13)**, 115525, (**2020**), ISSN 0968-0896, https://doi.org/10.1016/j.bmc.2020.115525.
IF: 3.073

Abstract

Aurora kinases (AURKs) were identified as promising druggable targets for targeted cancer therapy. Aiming at the development of novel chemotype of dual AURKA/B inhibitors, herein we report the design and synthesis of three series of 4-anilinoquinoline derivatives bearing a sulfonamide moiety (5a-d, 9a-d and 11a-d). The % inhibition of AURKA/B was determined for all target quinolines, then compounds showed more than 50% inhibition on either of the enzymes, were evaluated further for their IC50 on the corresponding enzyme. In particular, compound 9d displayed potent AURKA/B inhibitory activities with IC50 of 0.93 and 0.09 µM, respectively. Also, 9d emerged as the most efficient anti-proliferative analogue in the US-NCI anticancer assay toward the NCI 60 cell lines panel, with broad spectrum activity against different cell lines from diverse cancer subpanels. Docking studies, confirmed that, the sulfonamide SO2 oxygen was involved in a hydrogen bond with Lys162 and Lys122 in AURKA and AURKB, respectively, whereas, the sulfonamide NH could catch hydrogen bond interaction with the surrounding amino acid residues Lys141, Glu260, and Asn261 in AURKA and Lys101, Glu177, and Asp234 in AURKB. Furthermore, N1 nitrogen of the quinoline scaffold formed an essential hydrogen bond with the hinge region key amino acids Ala213 and Ala173 in AURKA and AURKB, respectively.
Three series of 4-anilinoquinoline derivatives bearing a sulfonamide moiety (5a-d, 9a-d and 11a-d) were designed and synthesized as potential novel dual Aurora kinase (AURKA/B) inhibitors.

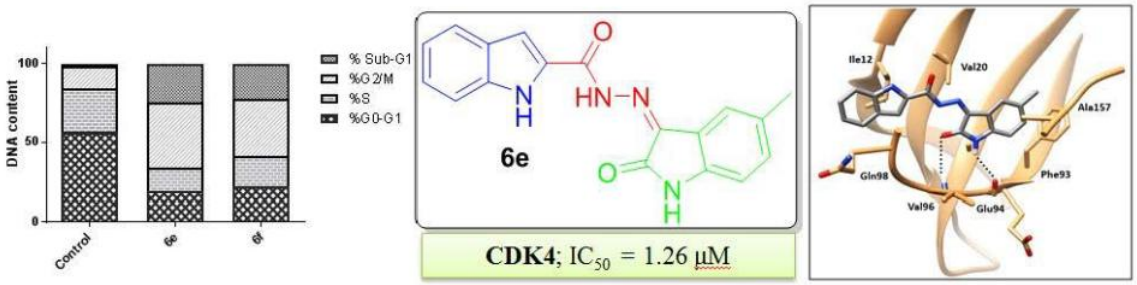




27. Al-Warhi T, **El Kerdawy AM**, Aljaeed N, Ismael OE, Ayyad RR, Eldehna WM, Abdel-Aziz HA, Al-Ansary GH. "Synthesis, Biological Evaluation and In Silico Studies of Certain Oxindole–Indole Conjugates as Anticancer CDK Inhibitors", *Molecules*, **25(9)**, 2031, (**2020**). https://doi.org/10.3390/molecules25092031
IF: 3.267

Abstract

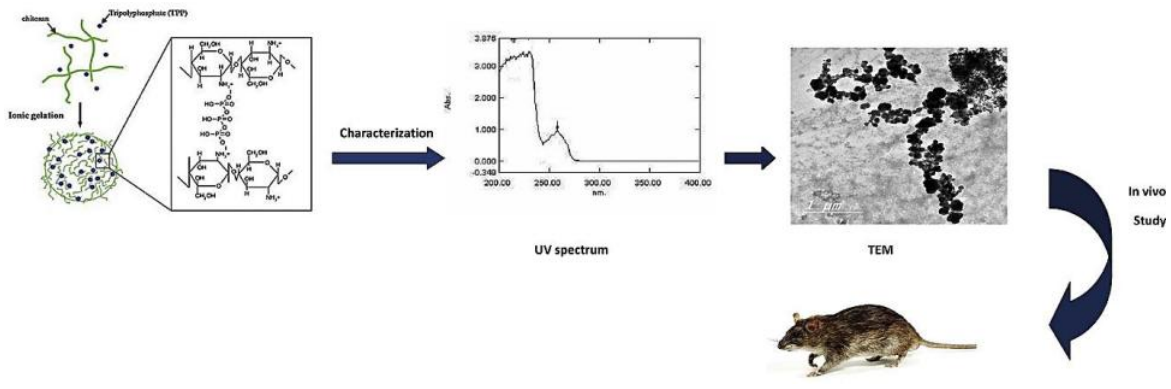
On account of their overexpression in a wide range of human malignancies, cyclin-dependent kinases (CDKs) are among the most validated cancer targets, and their inhibition has been featured as a valuable strategy for anticancer drug discovery. In this study, a hybrid pharmacophore approach was adopted to develop two series of oxindole–indole conjugates (6a–i and 9a–f) and carbocycle–indole conjugates (11a,b) as efficient antitumor agents with potential inhibitory action toward CDK4. All oxindole–indole conjugates, except 6i, 9b, and 9c efficiently affected the growth of the human breast cancer MCF-7 (IC50: 0.39 ± 0.05–21.40 ± 1.58 µM) and/or MDA-MB-231 (IC50: 1.03 ± 0.04–22.54 ± 1.67 µM) cell lines, whereas bioisosteric replacement of the oxindole nucleus with indane or tetralin rings (compounds 11a,b) diminished the anti-proliferative activity. In addition, hybrids 6e and 6f displayed effective cell cycle disturbance and proapoptotic capabilities in MCF-7 cells. Furthermore, the efficient anti-proliferative agents towards MCF-7 and/or MDA-MB-231 cell lines (6a–h, 9a, and 9e) were investigated for their potential inhibitory action toward CDK4. Hybrids 6a and 6e displayed good CDK4 inhibitory activity with IC50s equal 1.82 and 1.26 µM, respectively. The molecular docking study revealed that oxindole moiety is implicated in two H-bonding interactions via both (NH) and (C=O) groups with the key amino acids Glu94 and Val96, respectively, whereas the indole framework is stably accommodated in a hydrophobic sub-pocket establishing hydrophobic interactions with the amino acid residues of Ile12, Val20, and Gln98 lining this sub-pocket. Collectively, these results highlighted hybrids 6a and 6e as good leads for further optimization as promising antitumor drugs toward breast malignancy and CDK inhibitors.



28. Sandy N. Aziz, Alia A. Badawy, Demiana I. Nessem, **Nevine S. Abd El Malak**. "Promising nanoparticulate system for topical delivery of diphenhydramine hydrochloride: In-vitro and in-vivo evaluation", *Journal of Drug Delivery Science and Technology*, **55**, 101454, (**2020**), ISSN 1773-2247, https://doi.org/10.1016/j.jddst.2019.101454.
IF: 2.734

Abstract

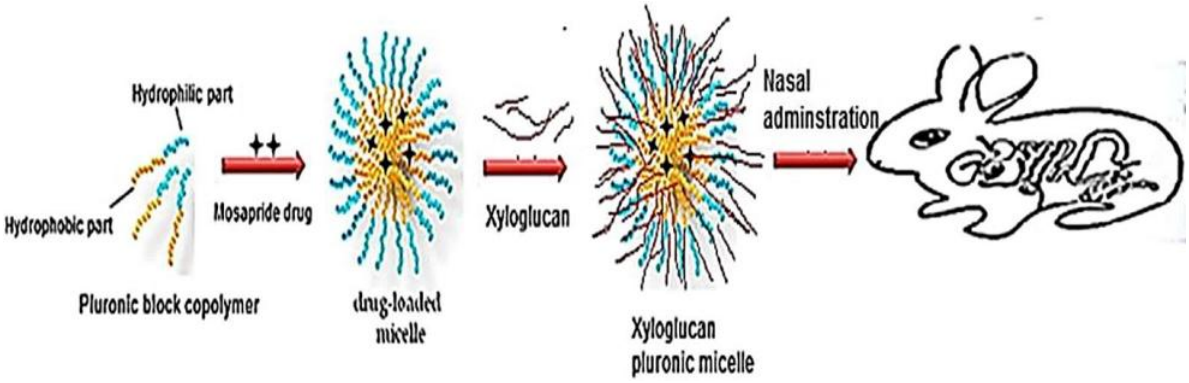
Diphenhydramine hydrochloride is a potent antihistaminic drug; its oral administration often leads to attention disturbance, CNS or anticholinergic adverse effects as dry mouth resulting in a less patient compliance with the therapy. The aim of the current study was to prepare diphenhydramine hydrochloride loaded nanoparticulate system, using chitosan as a natural polymer for topical application. Eight formulae were prepared adopting 23 factorial design. Diphenhydramine hydrochloride loaded nanoparticles were prepared by ionic gelation technique using chitosan and sodium tripolyphosphate (TPP). The formulae were evaluated regarding TEM, entrapment efficiency, particle size, zeta potential, in-vitro release, DSC, XRD, kinetics study, and in-vivo study regarding skin irritation test and histopathological examination using rats. The results revealed that the entrapment efficiency was significantly increased when increasing the chitosan concentration, the drug to polymer ratio and the chitosan to TPP (w/w) ratio. The particle size was significantly increased when increasing the chitosan concentration, the drug to polymer ratio but significantly decreased when increasing the chitosan to TPP (w/w) ratio. The zeta potential was significantly increased by increasing the chitosan concentration, the drug to polymer ratio and the chitosan to TPP (w/w) ratio. The in-vitro release study showed prolongation of drug release up to 6hrs. A comparison was made between the candidate formula (F8) (0.375% of diphenhydramine hydrochloride, drug to polymer 1:2, chitosan concentration 0.75% and chitosan to TPP (w/w) 5:1) and the marketed gel. The skin irritation test of F8 revealed its dermal safety and the statistical analysis revealed significant increase in its antihistaminic activity with reduction in the wheal area (from 150 mm2 ± 7.8 to 43.6 mm2 ± 4.9) when compared to the marketed gel (from 155 mm2 ± 6.1 to 82.1 mm2 ± 8.54). A value of r = 0.97704 suggested a good correlation between the in vitro-in vivo data of the candidate formula. The results revealed that the developed nanoparticles could have a potential for topical delivery of diphenhydramine hydrochloride.



29. Reham Waheed Hammad, Rania Abdel-Basset Sanad, **Nevine Shawky Abdelmalak**, Faisal A. Torad, Randa Latif. "New intranasal cross-linked mosapride xyloglucan pluronics micelles (MOS-XPMs) for reflux esophagitis disease: In-vitro optimization and improved therapeutic efficacy", *Journal of Advanced Research*, **23**, 83-94, (**2020**), ISSN 2090-1232, https://doi.org/10.1016/j.jare.2020.01.013.
IF: 6.992

Abstract

Mosapride belongs to class IV in Biopharmaceutics Classification System and is used in the treatment of reflux esophagitis. It exhibits poor bioavailability due to limited permeability, solubility and extensive first-pass metabolism. In this study, intranasal mosapride-loaded cross-linked xyloglucan Pluronic micelles (MOS-XPMs) was formulated and optimized to improve the low solubility & bioavailability of MOS. The solid dispersion technique using 23 full factorial design was applied. (MOS-XPMs) (F4) had the highest desirability value (0.952) and, therefore, it was selected as an optimal system. Xyloglucan cross-linked in the shell of Pluronic micelles offered improved stability and muco adhesiveness to MOS-XPMs. 1H NMR spectra ensured the cross-linking of xyloglucan with Pluronic micelle shell and micelle stabilization. A Pharmacodynamic study revealed that MOS-XPMs showed 1.5-fold increase in duodenal and cecal motility compared to MOS suspension and 1.7-fold increase compared to the oral marketed product. The new MOS-XPMs were shown to be successful at improving the therapeutic efficacy of mosapride.



30. Osman SM, Ayoub NA, Hafez SA, Ibrahim HA, El Raey MA, El-Emam SZ, Seada AA, **Saadeldeen AM.** "Aldose reductase inhibitor form Cassia glauca: A comparative study of cytotoxic activity with Ag nanoparticles (NPs) and molecular docking evaluation", *PLoS ONE*, **15(10)**, e0240856, (**2020**). https://doi.org/10.1371/journal.pone.0240856
IF: 2.740

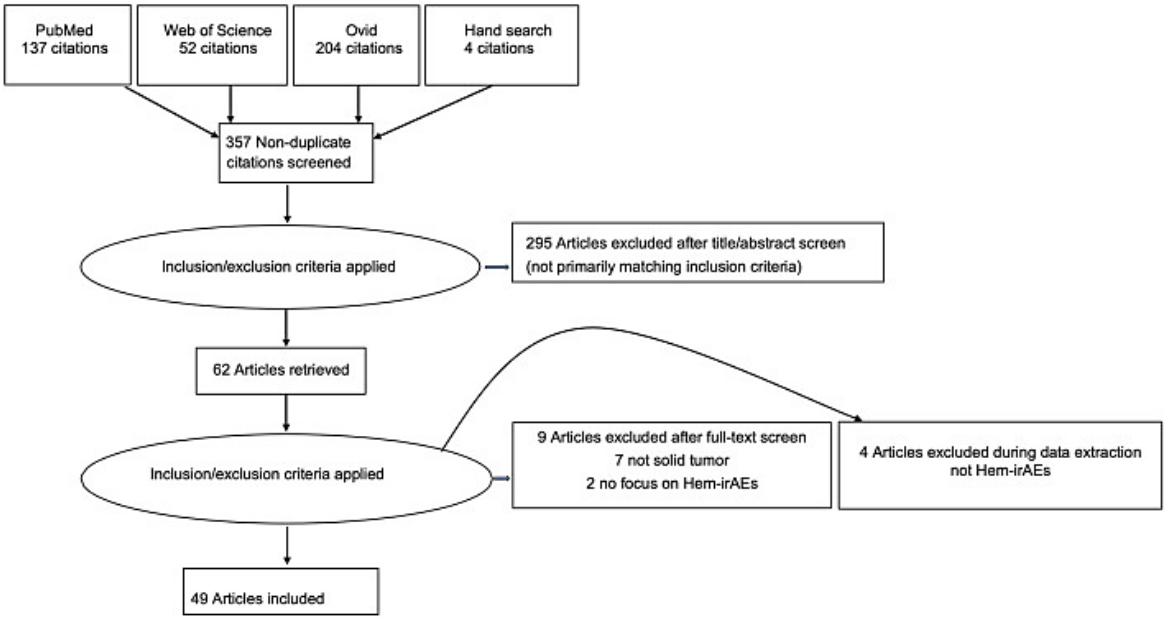
Abstract

UPLC-MS/MS profiling of *Cassia glauca* leaves extract revealed the identification of 10 flavonoids. Kaempferol 3-*O*-*β*-D-rutinoside was isolated and studied for its cytotoxic activity. It showed high cytotoxic effects against MCF-7 (IC50 of 4.6±0.038 µg/ml) and HepG-2 (IC50 of 8.2±0.024 µg/ml) cancer cell lines, compared to the leaves extracts, their Ag nanoparticles, and doxorubicin. Moreover, Kaempferol 3-*O*-*β*-D-rutinoside exerted a synergistic cytotoxic effect with doxorubicin on MCF-7 cell lines. It was discovered as kinases and aldose reductase inhibitor while rationalizing its cytotoxic activity through molecular docking study. Thus, it is expected that the cardiotoxic effects of doxorubicin can be also decreased by using Kaempferol 3-*O*-*β*-D-rutinoside due to its aldose reductase inhibitory effect. These findings suggested that Kaempferol 3-*O*-*β*-D-rutinoside could be used in combination with chemotherapeutic drugs to increase the sensitivity to their cytotoxic activity and protect against their side effects.

31. Omar NE, El-Fass KA, Abushouk AI, **Elbaghdady N**, Barakat AEM, Noreldin AE, Johar D, Yassin M, Hamad A, Elazzazy S, Dermime S. "Diagnosis and Management of Hematological Adverse Events Induced by Immune Checkpoint Inhibitors: A Systematic Review", *Front Immunol.*, **11**, 1354, (**2020**). Doi: 10.3389/fimmu.2020.01354.
IF: 5.085

Abstract

There has been less volume of literature focusing on the Immune-related Hematological Adverse Drug Events (Hem-irAEs) of Immune Checkpoint Inhibitors (ICPis) in cancer patients. Furthermore, there has been no consensus about the management of hematological toxicity from immunotherapy in the recently published practice guidelines by the European Society for Medical Oncology (ESMO). We conducted a systematic review of case reports/series to describe the diagnosis and management of potentially rare and unrecognized Hem-irAEs. We searched Medline, OVID, Web of Science for eligible articles. Data were extracted on patient characteristics, Hem-irAEs, and management strategies. We performed quality assessment using the Pierson-5 evaluation scheme and causality assessment using the Naranjo scale. Our search retrieved 49 articles that described 118 cases. The majority of patients had melanoma (57.6%) and lung cancer (26.3%). The most common Hem-irAEs reported with ICPis (such as nivolumab, ipilimumab, and pembrolizumab) were thrombocytopenia, hemolytic and aplastic anemias. Less reported adverse events included agranulocytosis and neutropenia. Steroids were commonly used to treat these adverse events with frequent success. Other used strategies included intravenous immunoglobulins (IVIG), rituximab, and transfusion of blood components. The findings of this review provide more insights into the diagnosis and management of the rarely reported Hem-irAEs of ICPis.



32. **Noha El Baghdady**, Lamia Elwakeel, Mahmoud Ellithy, Nawal Hussein, Sara Shahin, Abdel Rahman El Naggar. "Efficacy and Safety of Sorafenib Versus Supportive Care in Egyptian Advanced Hepatocellular Carcinoma Patients", *Archives of Pharmaceutical Sciences Ain Shams University*, **4(2)**, 224-236, (**2020**). DOI: 10.21608/aps.2020.45180.1043

Abstract

Objectives: Sorafenib is the standard first-line treatment for HCC. No sufficient data exists regarding its efficacy in the Egyptian population being a costly medication that is not endorsed by insurance and hence is not used in most institutions. This study aimed to evaluate the overall survival [OS], progression-free survival [PFS] and quality of life [QOL] of Egyptian HCC patients receiving sorafenib versus supportive care.

Design: A Prospective cohort observational study.

Setting: Electricity Hospital, Medical Oncology Department-Ain Shams University, and Nasser Institute for Research and Treatment, Egypt

Subjects: Fifty-five patients with HCC were eligible for enrolment in the trial. Eligible HCC patients were stratified into one of two groups based on institutions' protocols for HCC treatment. Group (1) received supportive care [n= 20] and Group (2) received sorafenib [n=35]; the patients follow up were continued for one year after diagnosis.

Main outcome measures: Patients' survival, PFS, and QOL.

Results: The one-year survival rates were 0.0% and 75.5% [p= 0.008] for group (1) versus group (2), respectively. The median PFS was 5 months and 12 months for group (1) versus group (2), respectively [p= 0.008]. The QOL of the sorafenib group was better than the supportive care group [p = 0.047]. The most common side effects with sorafenib were diarrhoea [42.8%] and hand-foot syndrome [34.2%]. In the sorafenib group, 48.57 % of the patients were requiring dose reduction.

Conclusion: Sorafenib was an effective first-line therapy in Egyptian HCC patients with a superior QOL, OS and PFS than those receiving supportive care.

SOP International Publications 2019

SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2019

Eighteen (18) International publications with SOP/NGU affiliation were published in 2019.

33. Eman M. Elbaz, Hebatullah S. Helmy, Ayman E. El-Sahar, **Muhammed A. Saad**, Rabab H. Sayed. "Lercanidipine boosts the efficacy of mesenchymal stem cell therapy in 3-NP-induced Huntington's disease model rats via modulation of the calcium/calcineurin/NFATc4 and Wnt/β-catenin signalling pathways", *Neurochemistry International*, **131**, 104548, (**2019**), ISSN 0197-0186, https://doi.org/10.1016/j.neuint.2019.104548.
IF: 3.881

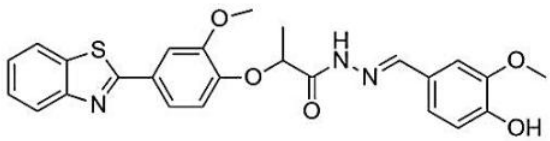
Abstract

3-Nitropropionic acid (3-NP) induces a spectrum of Huntington's disease (HD)-like neuropathologies in the rat striatum. The present study aimed to demonstrate the neuroprotective effect of lercanidipine (LER) in rats with 3-NP-induced neurotoxicity, address the possible additional protective effect of combined treatment with bone marrow-derived mesenchymal stem cells (BM-MSCs) and LER, and investigate the possible involvement of the Ca2+/calcineurin (CaN)/nuclear factor of activated T cells c4 (NFATc4) and Wnt/β-catenin signalling pathways. Rats were injected with 3-NP (10 mg/kg/day, i.p.) for two weeks and were divided into four subgroups; the first served as the control HD group, the second received a daily dose of LER (0.5 mg/kg, i.p.), the third received a single injection of BM-MSCs (1 x 106/rat, i.v.) and the last received a combination of both BM-MSCs and LER. The combined therapy improved motor and behaviour performance. Meanwhile, this treatment led to a marked reduction in striatal cytosolic Ca2+, CaN, tumour necrosis factor-alpha, and NFATc4 expression and the Bax/Bcl2 ratio. Combined therapy also increased striatal brain-derived neurotrophic factor, FOXP3, Wnt, and β-catenin protein expression. Furthermore, haematoxylin-eosin and Nissl staining revealed an amelioration of striatum tissue injury with the combined treatment. In conclusion, the current study provides evidence for a neuroprotective effect of LER and/or BM-MSCs in 3-NP-induced neurotoxicity in rats. Interestingly, combined LER/BM-MSC therapy was superior to cell therapy alone in inhibiting 3-NP-induced neurological insults via modulation of the Ca2+/CaN/NFATc4 and Wnt/β-catenin signalling pathways. LER/BM-MSC combined therapy may represent a feasible approach for improving the beneficial effects of stem cell therapy in HD.

34. Iman A.Y. Ghannam, Eman A. Abd El-Meguid, Islam H. Ali, Donia H. Sheir, **Ahmed M. El Kerdawy**. "Novel 2-arylbenzothiazole DNA gyrase inhibitors: Synthesis, antimicrobial evaluation, QSAR and molecular docking studies", *Bioorganic Chemistry*, **93**, 103373, (**2019**), ISSN 0045-2068, https://doi.org/10.1016/j.bioorg.2019.103373.
IF: 3.926

Abstract

A series of new 2-arylbenzothiazole derivatives (4, 5, 6a-j, 7a-i and 8a,b) was synthesized and tested for their antimicrobial activity against different Gram-positive, Gram-negative bacteria and yeast using ciprofloxacin and fluconazole as positive controls for the antibacterial and antifungal activities, respectively. The target compounds showed stronger inhibitory activity against Gram-negative than Gram-positive bacteria. The minimum inhibitory concentration (MIC) values were determined for those compounds showed zone of inhibition ≥ 13 mm. Based on the MIC values for the tested compounds against E. coli, compounds (4, 5, 6c, 6d, 6g, 6i, 6j, 7b, 7c, 7g and 8a) were selected and tested for their E. coli gyrase inhibitory activity. The tested compounds showed moderate inhibitory activity against E. coli gyrase. Compounds 5, 6c, 6i, 6j and 7b displayed high inhibitory activity against E. coli gyrase with IC50 values below 10 µM, however, they were less active than ciprofloxacin (E. coli gyrase IC50 = 1.14 µM). The p-hydroxy-m-methoxy benzothiazole analogue 6c was the most active tested compound (E. coli gyrase IC50 = 4.85 µM). Quantitative structure–activity relationship (QSAR) study was also implemented for the newly synthesized compounds. The QSAR study indicated that the structural feature that governs the anti-microbial activity for the newly synthesized benzothiazole derivatives is their structural hydrophilic-lipophilic balance what agrees with the chemical intuition where this balance governs their cellular absorption and so their antimicrobial activity. Molecular docking showed that the newly synthesized compounds possess the required structural feature for E. coli gyrase B inhibition through interaction with the key amino acids Asp73 and Gly77.

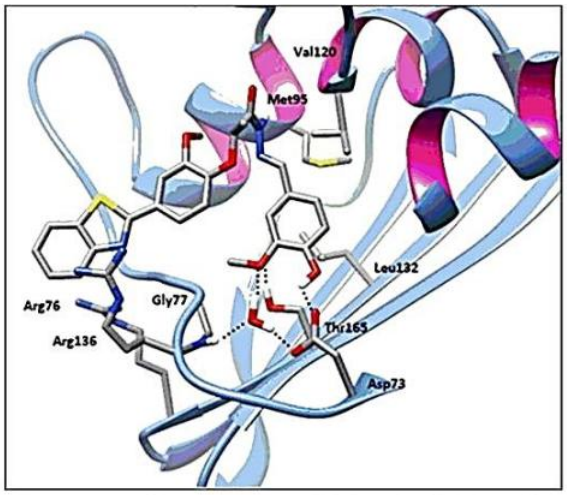


6c

E. coli DNA gyrase IC_{50} = 4.85 µM

E. faecalis, *P. aeruginosa* MIC = 1.02 µM

S. aureus, *E. coli*, *K. pneumoniae*, *C. albicans* MIC = 2.03 µM

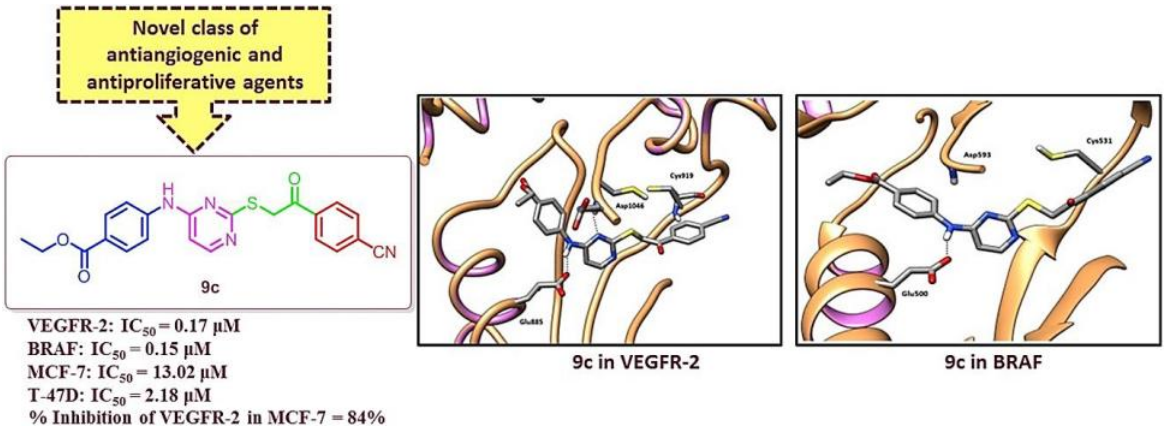


3D representation of compound 6c showing its interactions with the ATP binding site of DNA gyrase B

35. Heba T. Abdel-Mohsen, Mohamed A. Omar, **Ahmed M. El Kerdawy**, Abeer E.E. Mahmoud, Mamdouh M. Ali, Hoda I. El Diwani. "Novel potent substituted 4-amino-2-thiopyrimidines as dual VEGFR-2 and BRAF kinase inhibitors", *European Journal of Medicinal Chemistry*, **179**, 707-722, (**2019**), ISSN 0223-5234, https://doi.org/10.1016/j.ejmech.2019.06.063.
IF: 5.573

Abstract

In the present study, we report the discovery of a novel class of substituted 4-amino-2-thiopyrimidines as antiangiogenic and antiproliferative agents. Structural hybridization between 4-substituted aminopyrimidines (VEGFR-2 inhibitors) and 2-thioxopyrimidines (BRAF inhibitors) was carried out to afford substituted 4-amino-2-thiopyrimidines as type II dual VEGFR-2/BRAF inhibitors. Our design strategy was tailored such that the 4-amino-2-thiopyrimidine scaffold is to be accommodated in the central gate area of the inactive DFG-out conformation of both enzymes. On one side, the hydrophobic substituent on the 4-amino group would occupy the hydrophobic back pocket and on the other side the substituent on the sulfide moiety should extend to fit in the hinge region (front pocket). Molecular docking simulations confirmed the ability of the designed compounds to accomplish the key interactions in VEGFR-2 and BRAF active sites. Most of the synthesized substituted 4-amino-2-thiopyrimidines demonstrated potent VEGFR-2 inhibitory activity at submicromolar concentrations. Compounds 8a, 8d, 9c and 9e showed IC50 = 0.17, 0.12, 0.17 and 0.19 µM, respectively against VEGFR-2 in comparison to sorafenib (I) IC50 = 0.10 µM and regorafenib (II) IC50 = 0.005 µM. While compounds 9c, 9d and 10a showed IC50 = 0.15, 0.22 and 0.11 µM, respectively against BRAF-WT. At 10 µM concentration 9c revealed promising in vitro broad-spectrum antiproliferative activity against cancer cell lines with growth inhibition percent ranging from 10 to 90%. Moreover, compounds 7b, 8d, 9a, 9b, 9c and 9d showed potent activity against MCF7 cell line (IC50 = 17.18, 17.20, 19.98, 19.61, 13.02 and 16.54 µM, respectively). On the other hand, compounds 9c, 9d and 10d were found to be the most potent compounds against T-47D cell line (IC50 = 2.18, 8.09 and 4.36 µM, respectively).

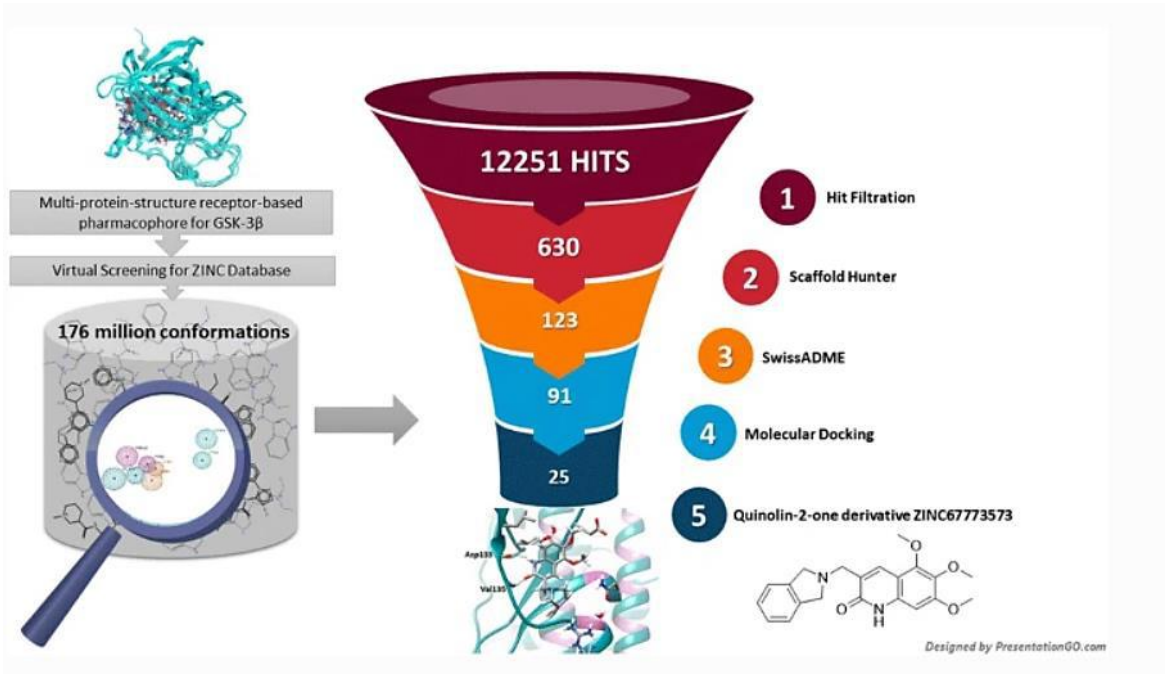


36. **El Kerdawy, A.M.**, Osman, A.A. & Zaater, M.A. "Receptor-based pharmacophore modeling, virtual screening, and molecular docking studies for the discovery of novel GSK-3β inhibitors", *J Mol Model,* **25(6)**, 171, (**2019**). https://doi.org/10.1007/s00894-019-4032-5

IF: 1.346

Abstract

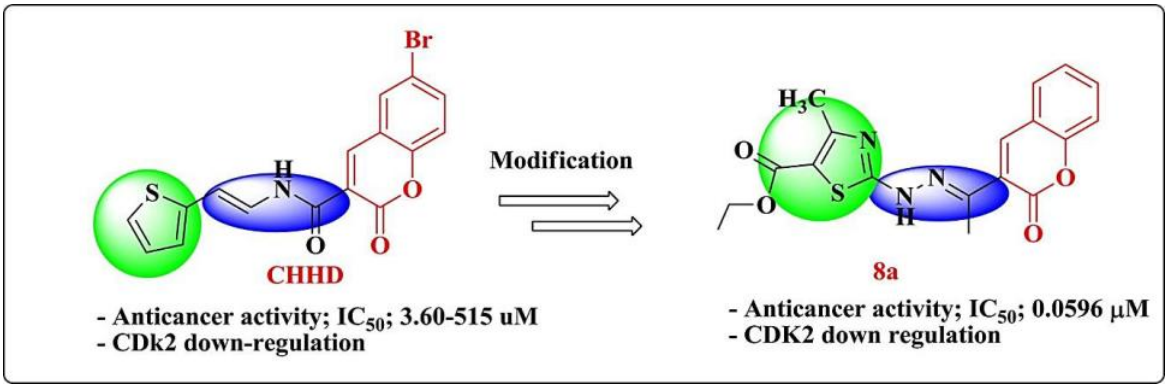
Considering the emerging importance of glycogen synthase kinase 3 beta (GSK-3β) inhibitors in treatment of Alzheimer's disease, multi-protein structure receptor-based pharmacophore modeling was adopted to generate a 3D pharmacophore model for (GSK-3β) inhibitors. The generated 3D pharmacophore was then validated using a test set of 1235 compounds. The ZINCPharmer web tool was used to virtually screen the public ZINC database using the generated 3D pharmacophore. A set of 12,251 hits was produced and then filtered according to their lead-like properties, predicted central nervous system (CNS) activity, and Pan-assay interference compounds (PAINS) fragments to 630 compounds. Scaffold Hunter was then used to cluster the filtered compounds according to their chemical structure framework. From the different clusters, 123 compounds were selected to cover the whole chemical space of the obtained hits. The SwissADME online tool was then used to filter out the compounds with undesirable pharmacokinetic properties giving a set of 91 compounds with promising predicted pharmacodynamic and pharmacokinetic properties. To confirm their binding capability to the GSK-3β binding site, molecular docking simulations were performed for the final 91 compounds in the GSK-3β binding site. Twenty-five compounds showed acceptable binding poses that bind to the key amino acids in the binding site Asp133 and Val135 with good binding scores. The quinolin-2-one derivative ZINC67773573 was found to be a promising lead for designing new GSK-3β inhibitors for Alzheimer's disease treatment.



37. Somaia S. Abd El-Karim, Yasmin M. Syam, **Ahmed M. El Kerdawy**, Tamer M. Abdelghany. "New thiazol-hydrazono-coumarin hybrids targeting human cervical cancer cells: Synthesis, CDK2 inhibition, QSAR and molecular docking studies", *Bioorganic Chemistry*, **86**, 80-96, (**2019**), ISSN 0045-2068, https://doi.org/10.1016/j.bioorg.2019.01.026.
IF: 3.926

Abstract

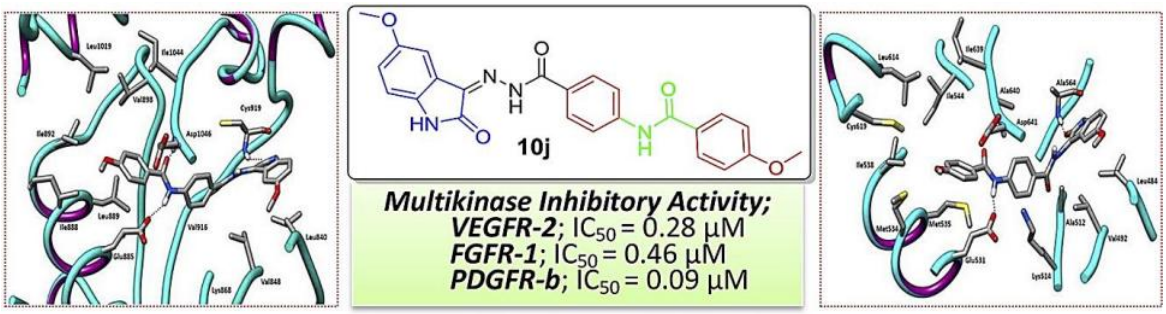
Motivated by the potential anticancer activity of both coumarin and 2-aminothiazole nuclei, a new set of thiazol-2-yl hydrazono-chromen-2-one analogs were efficiently synthesized aiming to obtain novel hybrids with potential cytotoxic activity. MTT assay investigated the significant potency of all the target compounds against the human cervical cancer cell lines (HeLa cells). Cell cycle analysis showed that the representative compound 8a led to cell cycle cessation at G0/G1 phase indicating that CDK2/E1complex could be the plausible biological target for these newly synthesized compounds. Thus, the most active compounds (7c and 8a-c) were tested for their CDK2 inhibitory activity. The biological results revealed their significant CDK2 inhibitory activity with IC50 range of 0.022–1.629 nM. Moreover, RT-PCR gene expression assay showed that compound 8a increased the levels of the nuclear CDK2 regulators P21 and P27 by 2.30 and 5.7 folds, respectively. ELISA tequnique showed also that compound 8a led to remarkable activation of caspases-9 and -3 inducing cell apoptosis. QSAR study showed that the charge distribution and molecular hydrophobicity are the structural features affecting cytotoxic activity in this series. Molecular docking study for the most potent cytotoxic compounds (7c and 8a-c) rationalized their superior CDK2 inhibitory activity through their hydrogen bonding and hydrophobic interactions with the key amino acids in the CDK2 binding site. Pharmacokinetic properties prediction of the most potent compounds showed that the newly synthesized compounds are not only with promising antitumor activity but also possess promising pharmacokinetic properties.



38. Wagdy M. Eldehna, **Ahmed M. El Kerdawy**, Ghada H. Al-Ansary, Sara T. Al-Rashood, Mamdouh M. Ali, Abeer E. Mahmoud. "Type IIA - Type IIB protein tyrosine kinase inhibitors hybridization as an efficient approach for potent multikinase inhibitor development: Design, synthesis, anti-proliferative activity, multikinase inhibitory activity and molecular modeling of novel indolinone-based ureides and amides", *European Journal of Medicinal Chemistry*, **163**, 37-53, (**2019**), ISSN 0223-5234, https://doi.org/10.1016/j.ejmech.2018.11.061.
IF: 5.573

Abstract

Pursuing on our efforts regarding development of novel multikinase inhibitors, herein we report the design and synthesis of novel 2-indolinone-based ureides 6a-u and amides 10a-j. In this work we adopt a hybridization strategy between type IIA PTK inhibitor (sorafenib) and type IIB PTK inhibitors (sunitinib and nintedanib). This was implemented via linking the indolinone core, in both sunitinib and nintedanib, which is well-fitted in the hinge region in the kinase domain front cleft and the biaryl urea extension, in sorafenib, which is accommodated in the gate area and the hydrophobic back pocket. Molecular docking of the designed hybrid compounds in VEGFR-2 and FGFR-1 active sites revealed, as planned, their ability to establish the binding interactions achieved by both original type IIA and type IIB inhibitors. The designed compounds were evaluated for their multikinase inhibitory activity towards VEGFR-2, PDGFR-b and FGFR-1 and anti-proliferative activity towards HepG2, MCF-7, A549 and A498 cancer cell lines. The ureido analogue 6u emerged as the most potent multikinase inhibitor in the ureido series with VEGFR-2, FGFR-1 and PDGFR-b IC50 of 0.18, 0.23 and 0.10 µM, respectively. Whereas, the amido congener 10j emerged as the most potent multikinase inhibitor in the amide series with VEGFR-2, FGFR-1 and PDGFR-b IC50 of 0.28, 0.46 and 0.09 µM, respectively. While, indolinone 6u was the most potent derivative towards HepG2 cells (IC50 = 2.67 ± 0.14 µM), 6r stood out as the most potent indolinone against A498 cells (IC50 = 0.78 ± 0.02 µM). Additionally, the target indolinones displayed non-significant cytotoxic impact towards human normal melanocyte (HFB4). ADME prediction study of the designed compounds showed that they are not only with promising multikinase inhibitory activity but also with favorable pharmacokinetic and drug-likeness properties. Compounds 6r and 10j are revealed to be the best compounds in terms of multikinase activity and pharmacokinetics.



39. Shendy, A.H., Eltanany, B.M., **Al-Ghobashy, M.A**. *et al*. "Coupling of GC-MS/MS to Principal Component Analysis for Assessment of Matrix Effect: Efficient Determination of Ultra-Low Levels of Pesticide Residues in Some Functional Foods", *Food Anal. Methods*, **12**, 2870–2885, (**2019**). https://doi.org/10.1007/s12161-019-01643-z
IF: 2.667

Abstract

Functional foods provide nutritional and health benefits, yet they could be contaminated with residues like pesticides and polychlorobiphenyls. These residues affect the safety, quality, and consequently the commercial value of functional foods. Therefore, the validity and efficiency of residue determination methods constitute a major analytical concern. Reduction of matrix effect (ME) has always been the golden key for guaranteed sensitivity, selectivity, and high throughput analysis. This study aims for accurate determination and streamlined quantification of 200 pesticide residues in 16 matrices. Hence, QuEChERS protocol coupled to GC-MS/MS was then employed and separations were obtained in 25 min. Dilution of the final extracts of fresh and herbal samples was carried out to achieve an acceptable balance between sensitivity and peak characteristics. Dilution factors of 1x and 5x were selected for fresh and herbal samples, respectively. Principal component analysis (PCA) was then independently applied on the digitally exported total ion chromatograms (TICs) of the studied matrices and the calculated ME%. PCA score/loading plots of TICs demonstrated the key matrix constituents that influenced the obtained trends. Similarly, three main clusters were obtained after PCA of ME% indicating a dependent relationship between matrix type and the obtained effects. Out of the obtained three clusters, an appropriate representative matrix-matched calibration (R-MMC) was selected for ME compensation. Based on the EU validation guidelines, the proposed protocol was validated at 2 and 10 µg Kg−1 with acceptable method performance. Four proficiency testing (PT) and commercial samples were successfully analyzed. The proposed protocol would help laboratories to increase sample processing capacity and to ensure the safety of functional food products. This work should serve in setting standards that warranty the quality/safety of functional foods by national regulatory authorities.

40. El-Sayed, Ghada M., **Medhat A. Al-Ghobashy**, Ali K. Attia, and Samah M. Kamal. "Nanoparticle-Enhanced Potentiometric Ion-Selective Electrodes for Therapeutic Drug Monitoring of Linezolid.", *Journal of The Electrochemical Society,* **166 (14)**, 1-9, (**2019**). DOI: 10.1149/2.1221913jes
IF: 3.721

Abstract

Nosocomial infections caused by multidrug-resistant (MDR) bacteria is treated with Linezolid (LIN) either alone or with other medications such as; Meropenem (MERO) or Theophylline (THEO). LIN has variable pharmacokinetics which makes it an ideal candidate for therapeutic drug monitoring (TDM). Ion selective electrode (ISE) is a promising tool that can be used in hospitals by medical practitioners to adjust the dose of LIN which will eventually improve the therapeutic outcomes. Four potentiometric PVC sensors were fabricated for the determination of LIN in plasma in the presence of co-administered medications (MERO and THEO). Sensor I; cationic exchanger phosphotungstate sensor covering a concentration range of 1.0×10^{-7}–1.0×10^{-4} M. while Sensor II; 2–hydroxypropyl-β-cyclodextrin (HP-βCD) sensor covered a concentration range of 1.0×10^{-9}–1.0×10^{-3} M. The last two sensors were fabricated using metal nanoparticles (NPs). Sensor III; Copper NP-incorporated HP-βCD sensor was used over a concentration range 1.0×10^{-9}–1.0×10^{-3} M, while Sensor IV; Cobalt NP-incorporated HP-βCD sensor attained the highest sensitivity of all the prepared sensors with the quantification range of 1.0×10^{-10}–1.0×10^{-4} M. Britton-Robinson buffer at pH 3.5 ± 0.5 was chosen for optimization of experimental conditions of the four sensors. The proposed sensors performance was validated according to IUPAC\FDA guidelines and was applied successfully for the determination of LIN in its pharmaceutical formulation and for TDM in incurred plasma samples. No interference was noted in the presence of (MERO) and (THEO) that are commonly co-administered with LIN as a part of the treatment protocol for healthcare-associated pneumonia (HCAP).

41. Hassan LA, **Al-Ghobashy MA**, Abbas SS. "Evaluation of the pattern and kinetics of degradation of adalimumab using a stability-indicating orthogonal testing protocol", *Biomed Chromatogr.*, **33(12)**, e4676, (**2019**). Doi: 10.1002/bmc.4676. IF: 1.728

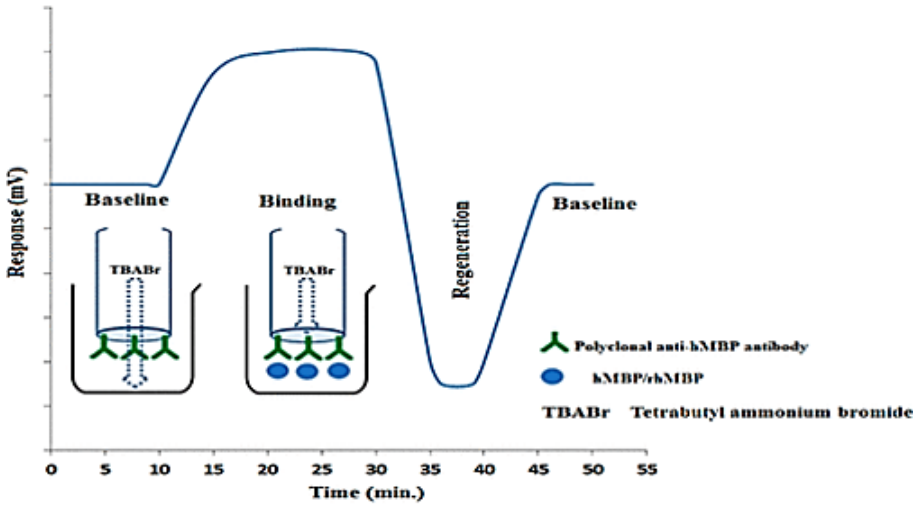
Abstract

Forced degradation studies are crucial for the evaluation of the stability and biosimilarity. Here, adalimumab was subjected to oxidation, pH, temperature, agitation and repeated freeze–thaw in order to generate all possible degradation products. An orthogonal stability-indicating testing protocol comprising SE-HPLC, RP-HPLC, TapeStation gel electrophoresis, dynamic light scattering (DLS), and functional receptor binding assay was developed and validated. The assay protocol was used for the assessment of the pattern and kinetics of aggregation/degradation of adalimumab. SE-HPLC and DLS were used to show the formation of aggregates/fragments of adalimumab under nondenaturing conditions. TapeStation electrophoresis was performed under denaturing conditions to reveal the nature of aggregates. Results of the receptor binding assay agreed to those of SE-HPLC and DLS which indicated that it can be used as an activity-indicating assay for adalimumab. RP-HPLC demonstrated excellent selectivity for adalimumab in the presence of its oxidized forms. The kinetics of degradation was studied in each case and the results showed that it followed the first-order reaction kinetics. Correlation between the results supported the quality assessment of the tested product in industrial and clinical settings. This orthogonal protocol is a useful tool in stability assessment of monoclonal antibodies and a key criterion for the biosimilarity assessment.

42. **Al-Ghobashy MA**, Nadim AH, El-Sayed GM, Nebsen M. "Label-Free Potentiometric Ion Flux Immunosensor for Determination of Recombinant Human Myelin Basic Protein: Application to Downstream Purification from Transgenic Milk", *ACS Sens.,* **4(2)**, 413-420, (**2019**). Doi: 10.1021/acssensors.8b01315.
IF: 7.333

Abstract

Recombinant human myelin basic protein (rhMBP) produced in the milk of transgenic cows was found exclusively associated with milk caseins. This hindered its direct determination without extensive sample pretreatment. Here, a label-free potentiometric immunosensor was developed and validated for the determination of rhMBP. An ion flux was generated under zero-current based on surface blocking of the polymeric membrane ion-selective electrode by anti-hMBP antibody and tetrabutylammonium bromide as a marker ion. The immunosensor was successfully employed in the quantitative determination of hMBP in the range of 0.10-20.00 µg/mL with a limit of detection of 50.00 ng/mL. The applicability of the passive ion flux immunosensor for determination of target analyte in complex matrices was investigated. Downstream purification of rhMBP from the milk of transgenic cows was achieved using cation exchange chromatography, immobilized metal affinity chromatography, and immunoaffinity chromatography. The specificity of the immunosensor along with matrix effect of milk proteins were demonstrated. Results obtained using the rhMBP immunosensor were further cross-validated using an orthogonal testing protocol assembled of RP-HPLC and SE-HPLC. It should be noted that the proposed ion flux immunosensor provided a feasible and specific tool for monitoring rhMBP concentration/purity, immunogenic activity, and stability. Such approach provides an attractive economic alternative to sophisticated biosensors required for in-process quality control of biopharmaceutical products.



43. Hassan, Lamiaa A., Sara M Shatat, Basma M Eltanany, **Medhat A Al-Ghobashy**, and Samah S Abbas. "Stability and biosimilarity assessment of infliximab using an orthogonal testing protocol and statistically-guided interpretation of peptide mapping", *Analytical methods*, **11 (25)**, 3198-3211, (**2019**). Doi: 10.1039/c9ay00903e
IF: 2.596

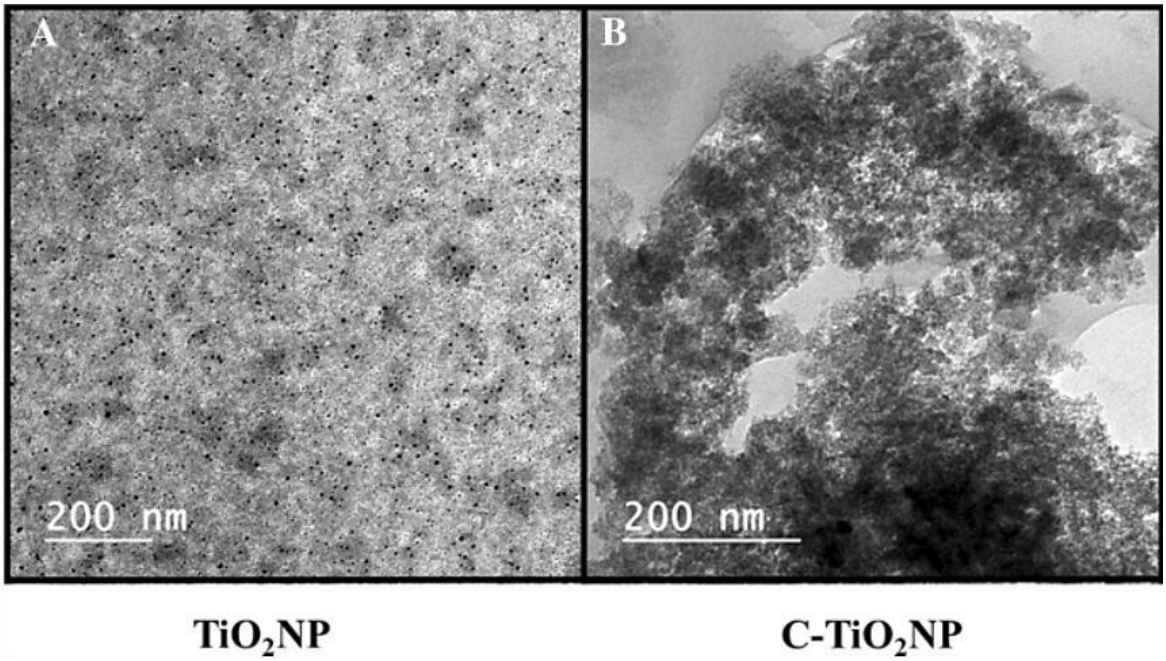
Abstract

With the growing number of biosimilars, healthcare providers opt to switch costly originator products with biosimilars. However, extensive data are required to support biosimilarity and interchangeability. In this study, factors affecting physical and chemical stability of infliximab were assessed under various stress conditions to reveal possible degradation products. A set of orthogonal stability- and purity-indicating assays involving size exclusion, reversed phase and ion exchange chromatography in addition to quantitative TapeStation gel electrophoresis, dynamic light scattering, and functional receptor binding assay was developed and used for validation. An objective, statistically-guided interpretation of peptide mapping data using principal component analysis (PM-PCA) was performed to establish a “biosimilarity fingerprint”. SE-HPLC and dynamic light scattering were used to evaluate the formation of aggregates and/or small molecular weight fragments under non-denaturing conditions. Results were correlated with those obtained under denaturing conditions using TapeStation gel electrophoresis. Results indicated that aggregates were formed via non-reducible covalent bonds. RP-HPLC showed no oxidized forms, yet the infliximab biosimilar was relatively more hydrophilic than its innovator counterpart. Ion exchange chromatography revealed slight differences in abundance of the charge variants that were not revealed using other techniques. PM-PCA and receptor binding assay showed differences, yet they were statistically non-significant (P 0.05). Results confirmed similarity in the primary structure, higher order structure and receptor-binding pattern. In-depth investigations of the critical quality attributes of infliximab along with setting up the similarity and range were required. These helped with assessment of the impact of such slight differences on the biosimilarity and interchangeability of the studied product. The developed PM-PCA along with the orthogonal assays helped locate variability that could potentially hinder both biosimilarity and interchangeability of other complex biopharmaceuticals.

44. Ibrahim, F.A., **Al-Ghobashy, M.A.** & Abo-Elmagd, I.F. "Energy-efficient carbon-doped titanium dioxide nanoparticles: synthesis, characterization, and catalytic properties under visible LED irradiation for degradation of Gemifloxacin", *SN Appl. Sci.,* **1**, 631, (**2019**). https://doi.org/10.1007/s42452-019-0644-8

Abstract

Synthesis and characterization of energy-efficient visible-light-responsive carbon-doped titanium dioxide nanoparticles (C-TiO2NP) is reported. The characterization results of C-TiO2NP using BET, TEM, DLS, and XRD indicate the following: (1) the C-TiO2NP have high surface area (77.02 m2/g), (2) size range of 5.00–10.00 nm and (3) zeta potential of 19 (pH 4.0), 4 (pH 7.0) and −21 (pH 10.0) while (4) the XRD results shows a peak pattern indicating that C-TiO2NP is mostly in the anatase phase. The photocatalytic properties of C-TiO2NP is investigated in this study using gemifloxacin antibiotic under LED in the visible region (λmax~450 nm). Results shows that C-TiO2NP have significant catalytic properties under LED visible light (up to~74% within 60 min). On the other hand, no degradation is observed for control TiO2NP using LED visible light under equivalent experimental conditions. Using control TiO2NP with H2O2 under LED visible light results in a percentage degradation of ~33.0%. Upon using C-TiO2NP with H2O2, the %degradation increases from ~33.0 to 64.0%. Although H2O2 generally enhances the activity of bare TiO2NP under UV irradiation, the %degradation under LED in the presence of C-TiO2NP and H2O2 (~64%) is smaller than that in the presence of C-TiO2NP only (~74%). Results demonstrates the applicability of C-TiO2NP as an energy-efficient and cost-effective photocatalyst under LED visible light for pharmaceutical wastewater treatment.



45. Muhammed A. Saad, Ayman E. El-Sahhar, Hany H. Arab, **Muhammad Y. Al-Shorbagy**. "Nicorandil abates arthritic perturbations induced by complete Freund's adjuvant in rats via conquering TLR4-MyD88-TRAF6 signaling pathway", *Life Sciences*, **218**, 284-291, (**2019**), ISSN 0024-3205, https://doi.org/10.1016/j.lfs.2019.01.002.
IF: 3.647

Abstract

Background and purpose

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease which poses a need to explore effective yet safe pharmacotherapeutic options. The current work aimed to study the therapeutic role of nicorandil in controlling RA.

Experimental approach

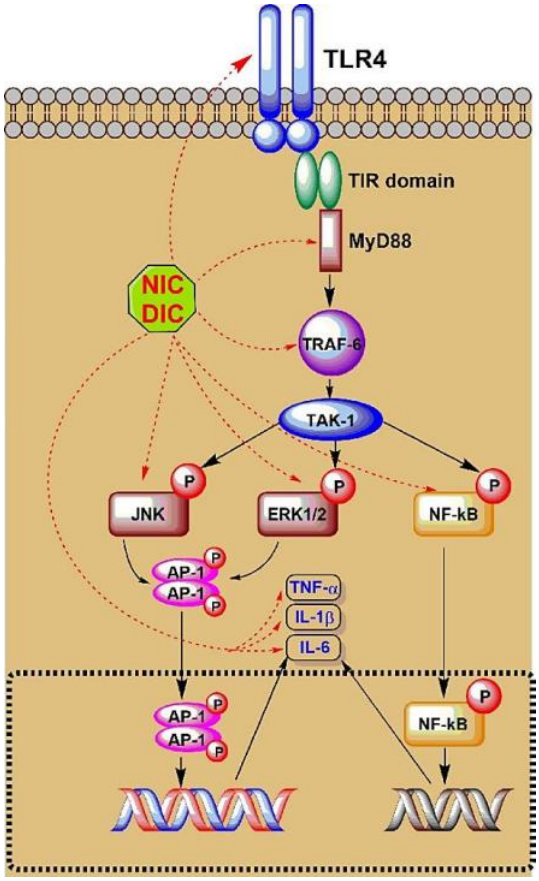
Complete Freund's adjuvant (CFA)-induced arthritis model was applied by injecting 400 μL of CFA in the right hind paw at day 0 and day 7. Four groups of rats were used as follows: normal-control (CTRL), CFA-induced arthritis (ART), CFA-induced arthritis treated with diclofenac (DIC) and CFA-induced arthritis treated with nicorandil (NIC). Both NIC and DIC were administered at day 14 for two weeks. Paw volume, knee joint diameter, pain behavior assessment as well as body weight were all periodically recorded throughout the experimental period. Following the sacrifice of animals at day 28, gene expressions of TLR-4, MyD88 and TRAF6 as well as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), nuclear factor Kappa B (NF-κB) were quantified in hind paws tissue. Finally, the serum levels of the inflammatory biomarkers (tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) together with the histopathological examination of sections in the rat hind paw were recorded.

Results

Both NIC and DIC proved promising anti-arthritic potential mediated, at least in part through switching off TLR4-MyD88-TRAF6 axis as well as downstream TRAF6 dependent activated MAP kinases and NF-κB.

Conclusion and implications

Nicorandil, via interfering with TLR4 signaling, sheds light on a potential clinical role of the drug in pursuit for safe and effective regimens for RA.



46. Radwan, A., El-Lakkany, N. M., William, S., El-Feky, G. S., **Al-Shorbagy, M. Y.**, Saleh, S., & Botros, S. A. "Novel praziquantel solid lipid nanoparticle formulation shows enhanced bioavailability and antischistosomal efficacy against murine S. mansoni infection", *Parasites Vectors*, **12(1)**, 304, (**2019**). https://doi.org/10.1186/s13071-019-3563-z

Abstract

Background

Schistosomiasis is responsible for a considerable global disease burden. This work aimed to improve the therapeutic outcome of the only available antischistosomal drug worldwide, praziquantel (PZQ), by incorporating it into a novel carrier, "solid lipid nanoparticles (SLNs)", to enhance its solubility, bioavailability and efficacy. A simple, cost-effective method was used to prepare SLN-PZQ.

Results

Compared to market PZQ (M-PZQ), SLN-PZQ was more bioavailable, as denoted by higher serum concentrations in both normal and infected mice where elevated Ka, AUC0–24, Cmax, and t1/2e with a decrease in kel were demonstrated. The AUC0–24 for SLN-PZQ in normal and Schistosoma mansoni-infected groups was almost nine- and eight-fold higher, respectively, than that for M-PZQ in corresponding groups. In normal and S. mansoni-infected mice, SLN-PZQ was detectable in serum at 24 h, while M-PZQ completely vanished 8 h post-treatment. Additionally, enhanced absorption with extended residence time was recorded for SLN-PZQ. Compared to M-PZQ, SLN-PZQ revealed superior antischistosomal activity coupled with enhanced bioavailability in all treated groups where higher percentages of worm reduction were recorded with all dosages tested. This effect was especially evident at the lower dose levels. The ED95 of SLN-PZQ was 5.29-fold lower than that of M-PZQ, with a significantly higher reduction in both the hepatic and intestinal tissue egg loads of all treated groups and almost complete disappearance of immature deposited eggs (clearly evident at the low dose levels).

Conclusions

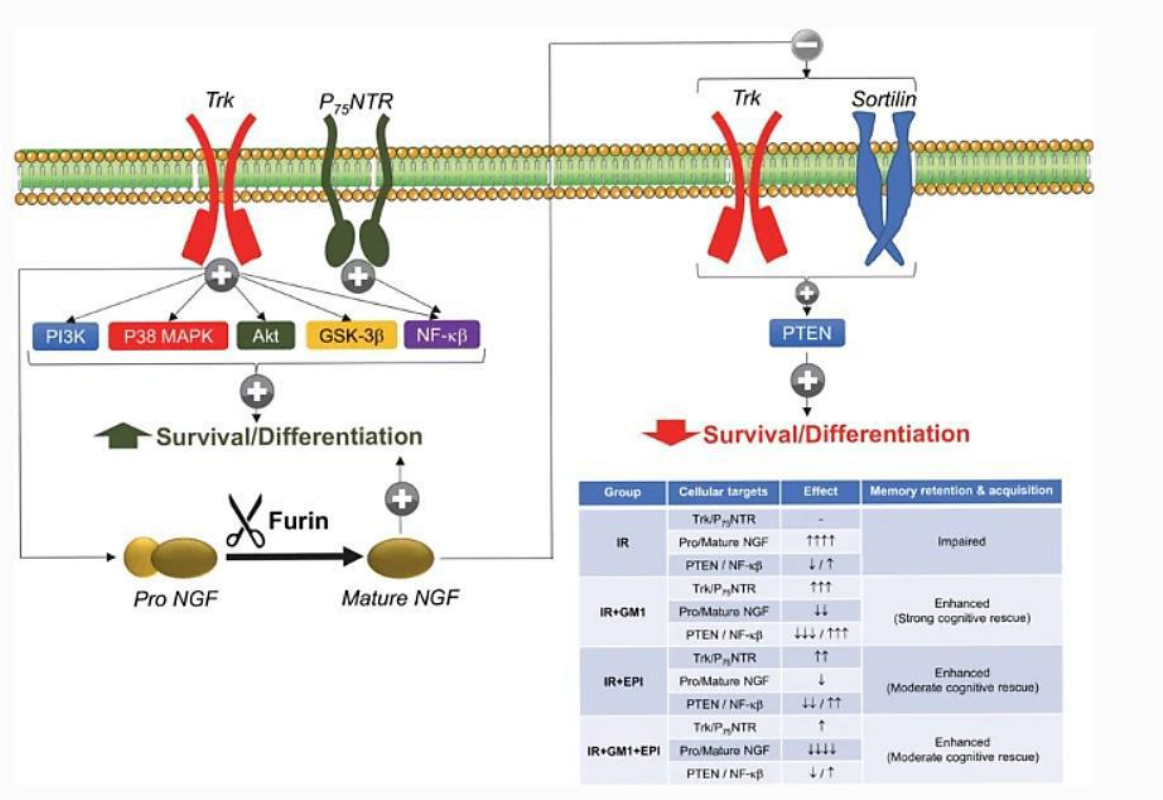
SLN-PZQ demonstrated enhanced PZQ bioavailability and antischistosomal efficacy with a safe profile despite the prolonged residence in the systemic circulation.

47. Choucry, A.M., **Al-Shorbagy, M.Y.**, Attia, A.S. *et al*. "Pharmacological Manipulation of Trk, p75NTR, and NGF Balance Restores Memory Deficit in Global Ischemia/Reperfusion Model in Rats", *J Mol Neurosci,* **68(1)**, 78–90, (**2019**). https://doi.org/10.1007/s12031-019-01284-1

IF: 2.678

Abstract

Long-term memory impairment is reported in more than 50% of cardiac arrest survivors. Monosialoganglioside (GM1) provided neuroprotection in experimental models of stroke but failed to replicate its promise clinically for unknown reasons. GM1 stimulates the release of nerve growth factor (NGF), which is synthesized as a precursor protein (pro-NGF) that either mediates apoptosis through the p75 neurotrophin receptor (p75NTR) or is cleaved by the protease furin (FUR) to yield mature NGF, the latter supporting survival through tropomyosin kinase receptor (Trk). The flavanol epicatechin (EPI) inhibits p75NTR-mediated signaling and apoptosis by pro-NGF. The aim of the current work is to test whether these two drugs affect, or communicate with, each other in the setting of CNS injuries. Using the two-vessel occlusion model of global ischemia/reperfusion (I/R), we tested if pharmacological modulation of Trk, p75NTR, and NGF balance with GM1, EPI, and their combination, can correct the memory deficit that follows this insult. Finally, we tested if FUR insufficiency and/or p75NTR-mediated apoptosis negatively affect the neurotherapeutic effect of GM1. Key proteins for Trk and p75NTR, FUR, and both forms of NGF were assessed. All treatment regiments successfully improved spatial memory retention and acquisition. A week after the insult, most Trk and p75NTR proteins were normal, but pro/mature NGF ratio remained sharply elevated and was associated with the poorest memory performance. Pharmacological correction of this balance was achieved by reinforcing Trk and p75NTR signaling. GM1 increased FUR levels, while concomitant administration of EPI weakened GM1 effect on pro-survival Trk and p75NTR mediators. GM1 neuroprotection is therefore not limited by FUR but could be dependent on p75NTR.



Group	Cellular targets	Effect	Memory retention & acquisition
IR	Trk/P75NTR	-	Impaired
	Pro/Mature NGF	↑↑↑↑	
	PTEN / NF-κβ	↓ / ↑	
IR+GM1	Trk/P75NTR	↑↑↑	Enhanced (Strong cognitive rescue)
	Pro/Mature NGF	↓↓	
	PTEN / NF-κβ	↓↓↓ / ↑↑↑	
IR+EPI	Trk/P75NTR	↑↑	Enhanced (Moderate cognitive rescue)
	Pro/Mature NGF	↓	
	PTEN / NF-κβ	↓↓ / ↑↑	
IR+GM1+EPI	Trk/P75NTR	↑	Enhanced (Moderate cognitive rescue)
	Pro/Mature NGF	↓↓↓↓	
	PTEN / NF-κβ	↓ / ↑	

48. Muhammed A. Saad, Ayman E. El-Sahhar, Hany H. Arab, **Muhammad Y. Al-Shorbagy**. "Nicorandil abates arthritic perturbations induced by complete Freund's adjuvant in rats via conquering TLR4-MyD88-TRAF6 signaling pathway", *Life Sciences*, **218**, 284-291, (**2019**), ISSN 0024-3205, https://doi.org/10.1016/j.lfs.2019.01.002.
IF: 3.647

Abstract

Background and purpose

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease which poses a need to explore effective yet safe pharmacotherapeutic options. The current work aimed to study the therapeutic role of nicorandil in controlling RA.

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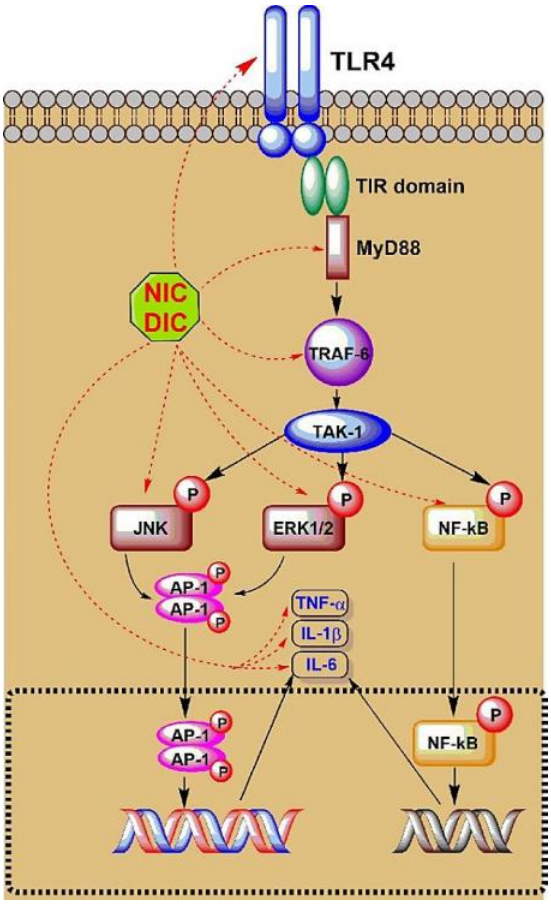
Both NIC and DIC proved promising anti-arthritic potential mediated, at least in part through switching off TLR4-MyD88-TRAF6 axis as well as downstream TRAF6 dependent activated MAP kinases and NF-κB.

Conclusion and implications

Nicorandil, via interfering with TLR4 signaling, sheds light on a potential clinical role of the drug in pursuit for safe and effective regimens for RA.



49. Hassan NF, Nada SA, Hassan A, El-Ansary MR, **Al-Shorbagy MY**, Abdelsalam RM. "Saroglitazar Deactivates the Hepatic LPS/TLR4 Signaling Pathway and Ameliorates Adipocyte Dysfunction in Rats with High-Fat Emulsion/LPS Model-Induced Non-alcoholic Steatohepatitis", *Inflammation,* **42(3)**, 1056-1070, (**2019**). Doi: 10.1007/s10753-019-00967-6.
IF: 3.212

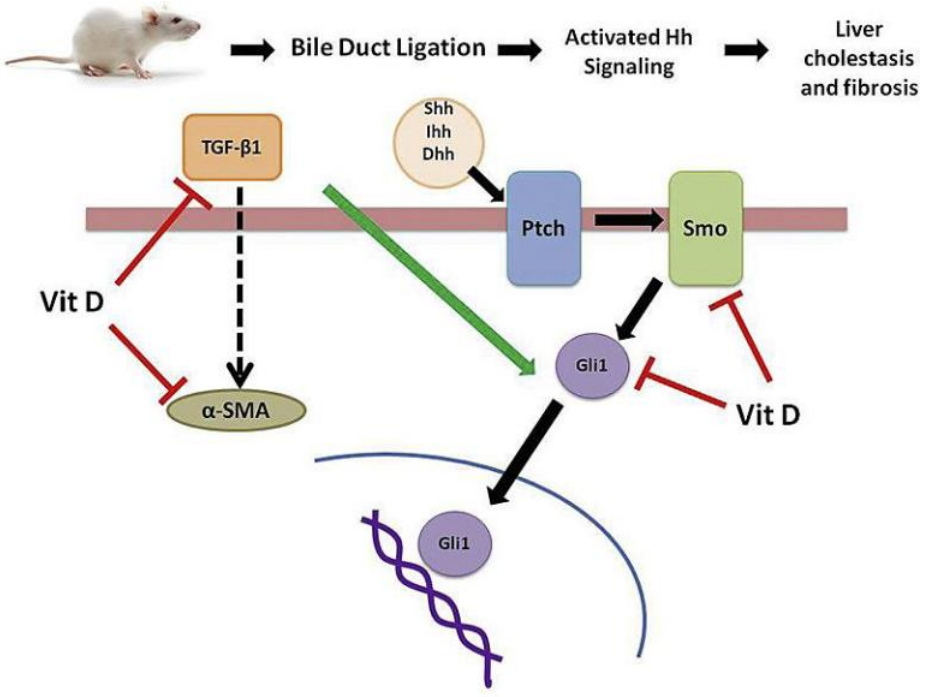
Abstract

The most epidemic liver disorder non-alcoholic steatohepatitis (NASH) is characterized by hepatic steatosis and inflammation with hepatocellular damage. Recently, it is predictable to be the extensive cause for liver transplantation. The absence of an approved therapeutic agent for NASH is the reason for investigating saroglitazar (SAR) which showed promising effects as a dual PPAR-α/γ agonist in recent studies on NASH. Here, we aimed to investigate the effect of SAR on NASH induced in rats by the administration of high-fat emulsion (HFE) and small doses of lipopolysaccharides (LPS) for 5 weeks. Rats were divided into three groups: negative control group (saline and standard rodent chow), model group (HFE(10 ml/kg/day, oral gavage) + LPS(0.5 mg/kg/week, i.p)), and SAR-treated group (HFE(10 ml/kg/day, oral gavage) + LPS(0.5 mg/kg/week, i.p.) + SAR(4 mg/kg/day, oral gavage) starting at week 3.Treatment with SAR successfully ameliorated the damaging effects of HFE with LPS, by counteracting body weight gain and biochemically by normalization of liver function parameters activity, glucose, insulin, homeostasis model of assessment (HOMA-IR) score, lipid profile levels, and histopathological examination. Significant changes in adipokine levels were perceived, resulting in a significant decline in serum leptin and tumor necrosis factor-α (TNF-α) level concurrent with adiponectin normalization. The positive effects observed for SAR on NASH are due to the downregulation of the LPS/TLR4 pathway, as indicated by the suppression of hepatic Toll-like receptor 4 (TLR4), NF-κB, TNF-α, and transforming growth factor-β1 (TGF-β1) expression. In conclusion, this work verified that SAR ameliorates NASH through deactivation of the hepatic LPS/TLR4 pathway and inhibition of adipocyte dysfunction.

50. **Noha Abdel-Rahman**, Maha H. Sharawy, Nirmeen Megahed, Mohammed S. El-Awady. "Vitamin D3 abates BDL-induced cholestasis and fibrosis in rats via regulating Hedgehog pathway", *Toxicology and Applied Pharmacology*, **380**, 114697, (**2019**), ISSN 0041-008X, https://doi.org/10.1016/j.taap.2019.114697.
IF: 3.347

Abstract

Liver cholestasis is a complex disease of broad etiologies. Hedgehog (Hh) signaling has been shown to play a pivotal role in modulating liver repair post cholestatic liver injury. We here investigated the role of vitamin D in experimental liver cholestasis induced by bile-duct ligation (BDL) in rats. Male Sprague Dawley rats underwent BDL surgery and two weeks post-surgery; vitamin D was administered daily for two weeks. Serum markers of hepatocellular integrity were measured and fibrosis was detected by measuring α-SMA and hepatic TGF-β1 as well as hepatic collagen content. Hh signaling was evaluated by measuring Smo and Gli1 levels. Histopathological examination of hepatic tissue was performed. Vitamin D alleviated obstructive cholestatic damage as illustrated by total bilirubin as well as gamma glutamyl transferase (γ-GT) serum levels. It also alleviated hepatocellular damage as suggested by reducing elevated serum aminotransferases induced by BDL. Antifibrotic activity of vitamin D was confirmed by decrease in mRNA and protein expression of α-SMA, as well as collagen content in hepatic tissue. Furthermore, vitamin D suppressed BDL-induced elevated hepatic TGF-β1 mRNA and protein levels. BDL activated Hh signaling and upregulated its upstream component smoothened (Smo) and downstream target gene Gli1. Treatment with vitamin D reduced Smo mRNA levels and suppressed hepatic Gli1 mRNA and protein levels. Molecular docking of vitamin D to Smo revealed that vitamin D binds similarly to its endogenous cholesterol ligand and blocks its activation. These results demonstrate that vitamin D mitigated cholestatic liver injury through inhibiting Hh signaling.



SOP International Publications 2018

SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2018

Twelve (12) International publications with SOP/NGU affiliation were published in 2018.

51. Marwa A. Fouad, Enas H. Tolba, Manal A. El-Shal, **Ahmed M. El Kerdawy**. "QSRR modeling for the chromatographic retention behavior of some β-lactam antibiotics using forward and firefly variable selection algorithms coupled with multiple linear regression", *Journal of Chromatography A*, **1549**, 51-62, (**2018**), ISSN 0021-9673, https://doi.org/10.1016/j.chroma.2018.03.042.
IF: 3.858

Abstract

The justified continuous emerging of new β-lactam antibiotics provokes the need for developing suitable analytical methods that accelerate and facilitate their analysis. A face central composite experimental design was adopted using different levels of phosphate buffer pH, acetonitrile percentage at zero time and after 15 min in a gradient program to obtain the optimum chromatographic conditions for the elution of 31 β-lactam antibiotics. Retention factors were used as the target property to build two QSRR models utilizing the conventional forward selection and the advanced nature-inspired firefly algorithm for descriptor selection, coupled with multiple linear regression. The obtained models showed high performance in both internal and external validation indicating their robustness and predictive ability. Williams-Hotelling test and student's t-test showed that there is no statistical significant difference between the models' results. Y-randomization validation showed that the obtained models are due to significant correlation between the selected molecular descriptors and the analytes' chromatographic retention. These results indicate that the generated FS-MLR and FFA-MLR models are showing comparable quality on both the training and validation levels. They also gave comparable information about the molecular features that influence the retention behavior of β-lactams under the current chromatographic conditions. We can conclude that in some cases simple conventional feature selection algorithm can be used to generate robust and predictive models comparable to that are generated using advanced ones.

52. Attallah, O.A., **Al-Ghobashy, M.A.**, Nebsen, M. *et al*. "Assessment of pectin-coated magnetite nanoparticles in low-energy water desalination applications", *Environ Sci Pollut Res*, **25**, 18476–18483 (**2018**). https://doi.org/10.1007/s11356-018-2060-9
IF: 2.914

Abstract

Novel magnetite nanoparticles (NPs) modified with pectin coating were fabricated, characterized, and evaluated as potential draw solute in a forward osmosis (FO) process for water desalination applications. The prepared NPs had a spherical shape with an average diameter of 200 nm and saturation magnetization of 23.13 emu/g. Thermogravimetric analysis (TGA) and FTIR spectra elucidated the successful pectin coating on magnetite surface. The potential use of the fabricated NPs in water desalination was conducted via a newly developed lab-scale FO system. Deionized water, saline water (0.2, 0.5, and 1 g% NaCl solution), and real well water (TDS=0.9 g%) were used as feed solutions. In all experiments, the water flux gradually decreased along with the extension of experimental time and NaCl rejection rate by the FO membrane was measured to be higher than 95%. Moreover, it was found that the pectin-coated magnetite NPs demonstrated to be able to draw clean water across the FO membrane from well water with a remarkable salt rejection of 97%. Thus, it is believed that the proposed FO system using pectin-coated magnetite NPs as draw solute can be a promising technique for desalination of well waters in an environmental-friendly and energy-saving manner.

53. **Medhat A. Al-Ghobashy**, Samah M. Kamal, Ghada M. El-Sayed, Ali K. Attia, Mohamed Nagy, Ahmed ElZeiny, Marwa T. Elrakaiby, Mohammed M. Nooh, Maggie Abbassi, Ramy K. Aziz. "Determination of voriconazole and co-administered drugs in plasma of pediatric cancer patients using UPLC-MS/MS: A key step towards personalized therapeutics", *Journal of Chromatography B*, **1092**, 489-498, (**2018**), ISSN 1570-0232, https://doi.org/10.1016/j.jchromb.2018.06.043.
IF: 2.813

Abstract

Untreated invasive aspergillosis results in high mortality rate in pediatric cancer patients. Voriconazole (VORI), the first line of treatment, requires strict dose monitoring because of its narrow therapeutic index and individual variation in plasma concentration levels. Commonly co-administered drugs; either Esomeprazole (ESO) or Ondansetron (OND) have reported drug-drug interaction with VORI that should adversely alter therapeutic outcomes of the latter. Although VORI, ESO and OND are co-administered to pediatric cancer patients, the combined effect of ESO and OND on the plasma concentration levels of VORI has not been fully explored. In this study, an accurate, reliable, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was developed and validated for simultaneous determination of VORI, ESO, and OND in ultra-low sample volumes (25 µL) of plasma of pediatric cancer patients. Based on the physicochemical properties of the studied drugs and internal standard, liquid-liquid extraction was successfully adopted with methyl t-butyl ether. Consistent and reproducible recovery of the three drugs and the internal standard were calculated using plasma and matrix matched samples (RE% > 72.97%, RSD < 8.29%). Chromatographic separation was carried out using UPLC with C18 column and a mobile phase of acetonitrile:water:methanol (70:25:5 V/V/V) at 0.3 mL/min. Mass spectrometric determination at positive electrospray ionization in the MRM mode was employed. The analysis was achieved within 4 min over a linear concentration range of 1.00–200.00 ng/mL for the three drugs. The assay validity was assessed as per the Food and Drug Administration guidelines for bioanalytical method validation, and satisfactory results were obtained. The accuracy and precision were within the acceptable limits for the three drugs in both quality control and incurred plasma samples. Matrix effect and process efficiency were investigated in neat solvent, post-extraction matrix, and plasma. Correlation of the plasma concentration levels of the three drugs revealed differences from the reported drug-drug interactions. This confirmed the need for simultaneous determination of VORI and co-administered drugs in order to achieve optimal therapeutic outcomes.

54. Olivia A. Attallah, **Medhat A. Al-Ghobashy**, Ahmed Taha Ayoub, Marianne Nebsen. "Magnetic molecularly imprinted polymer nanoparticles for simultaneous extraction and determination of 6-mercaptopurine and its active metabolite thioguanine in human plasma", *Journal of Chromatography A*, **1561**, 28-38, (**2018**), ISSN 0021-9673, https://doi.org/10.1016/j.chroma.2018.05.038. IF: 3.858

Abstract

Cytotoxic drugs used in cancer chemotherapy require the continuous monitoring of their plasma concentration levels for dose adjustment purposes. Such condition necessitates the presence of a sensitive technique for accurate extraction and determination of these drugs together with their active metabolites. In this study a novel solid phase extraction technique using magnetic molecularly imprinted nanoparticles (MMI-SPE) is combined with liquid chromatography tandem mass spectrometry (LC–MS/MS) to extract and determine the anti-leukemic agent; 6-mercaptopurine (6-MP) and its active metabolite thioguanine (TG) in human plasma. The magnetic molecularly imprinted nanoparticles (Fe3O4@MIP NPs) were synthesized via precipitation polymerization technique and were characterized using different characterization methods A computational approach was adopted to help in the choice of the monomer used in the fabrication process. The Fe3O4@MIPs NPs possessed a highly improved imprinting efficiency, fast adsorption kinetics following 2nd order kinetics and good adsorption capacity of 1.0 mg/g. The presented MMI-SPE provided the optimum approach in comparison to other reported ones to achieve good extraction recovery and matrix effect of trace levels of 6-MP and TG from plasma. Chromatographic separation was carried out using a validated LC–MS/MS assay and recovery, matrix effect and process efficiency were evaluated. Recovery of 6-MP and TG was in the range of 85.94–103.03%, while, matrix effect showed a mean percentage recovery of 85.94–97.62% and process efficiency of 85.54–96.18%. The proposed extraction technique is simple, effective and can be applicable to the extraction and analysis of other pharmaceutical compounds in complex matrices for therapeutic drug monitoring applications.

55. Attallah OA, **Al-Ghobashy MA**, Ayoub AT, Tuszynski JA, Nebsen M. "Computer-aided design of magnetic molecularly imprinted polymer nanoparticles for solid-phase extraction and determination of levetiracetam in human plasma", *RSC Advances*, **8(26),** 14280-92, (**2018**), https://doi.org/10.1039/C8RA02379D
IF: 3.049

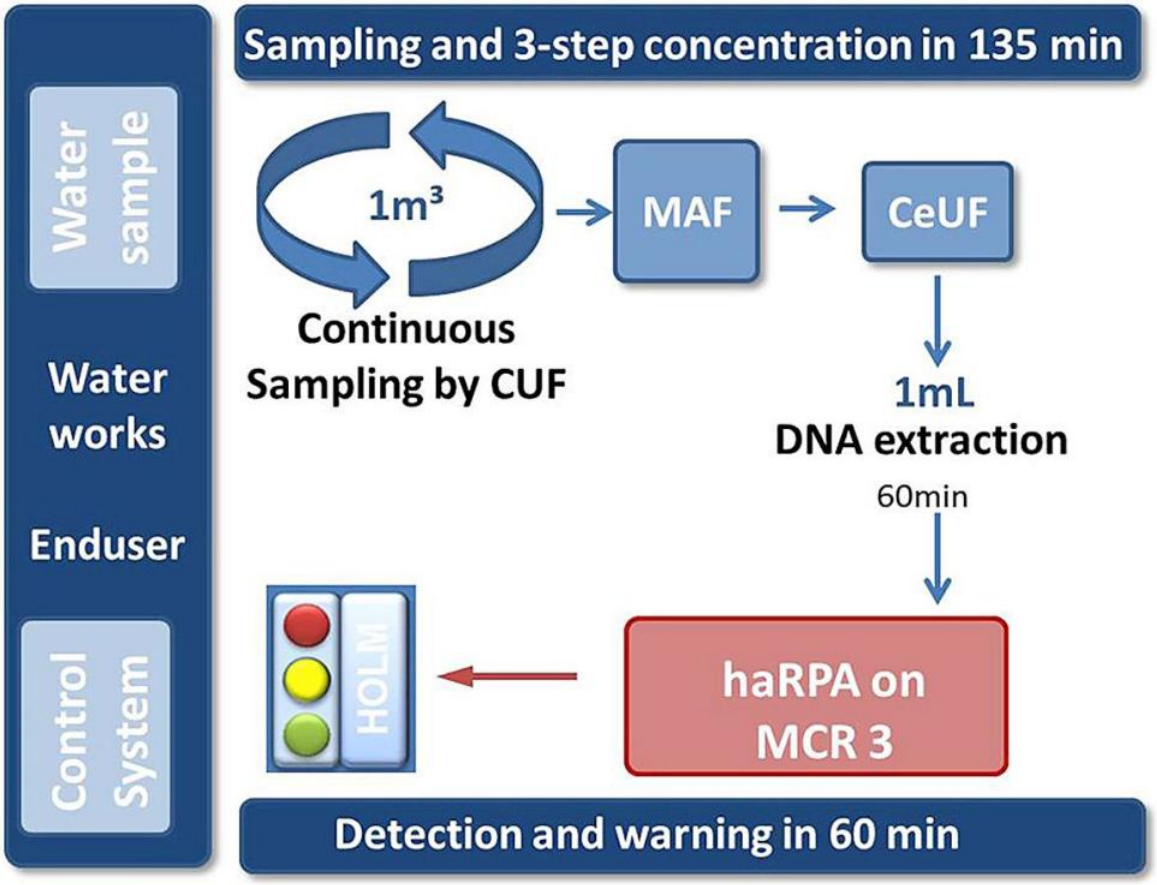
Abstract

Analytical methods should be accurate and specific to measure plasma drug concentration. Nevertheless, current sample preparation techniques suffer from limitations, including matrix interference and intensive sample preparation. In this study, a novel technique was proposed for the synthesis of a molecularly imprinted polymer (MIP) on magnetic Fe3O4 nanoparticles (NPs) with uniform core–shell structure. The Fe3O4@MIPs NPs were then applied to separate and enrich an antiepileptic drug, levetiracetam, from human plasma. A computational approach was developed to screen the functional monomers and polymerization solvents to provide a suitable design for the synthesized MIP. Different analysis techniques and re-binding experiments were performed to characterize the Fe3O4@MIP NPs, as well as to identify optimal conditions for the extraction process. Adsorption isotherms were best fitted to the Langmuir model and adsorption kinetics were modeled with pseudo-second-order kinetics. The Fe3O4@MIP NPs showed reasonable adsorption capacity and improved imprinting efficiency. A validated colorimetric assay was introduced as a comparable method to a validated HPLC assay for the quantitation of levetiracetam in plasma in the range of 10–80 µg mL−1 after extraction. The results from the HPLC and colorimetric assays showed good precision (between 1.08% and 9.87%) and recoveries (between 94% and 106%) using the Fe3O4@MIP NPs. The limit of detection and limit of quantification were estimated to be 2.58 µg mL−1 and 7.81 µg mL−1, respectively for HPLC assay and 2.32 µg mL−1 and 7.02 µg mL−1, respectively for colorimetric assay. It is believed that synthesized Fe3O4@MIP NPs as a sample clean-up technique combined with the proposed assays can be used for determination of levetiracetam in plasma.

56. Ali K. Attia, **Medhat A. Al-Ghobashy**, Ghada M. El-Sayed, Samah M. Kamal. "Voltammetric monitoring of linezolid, meropenem and theophylline in plasma", *Analytical Biochemistry*, **545**, 54-64, (**2018**), ISSN 0003-2697, https://doi.org/10.1016/j.ab.2018.01.009.
IF: 2.507

Abstract

Treatment of healthcare associated Pneumonia (HCAP) caused by Methicillin-resistant Staphylococcus aureus (MRSA) requires therapeutic protocols formed of linezolid (LIN) either alone or in combination with meropenem (MERO) and theophylline (THEO). The inter-individual pharmacokinetic variations require the development of reliable therapeutic drug monitoring (TDM) tools especially in immunocompromised patients. A sensitive square wave voltammetric sensor using multiwalled carbon nanotubes (MWCNTs) modified carbon paste electrode in Britton-Robinson buffer was developed and validated. Experimental parameters such as pH, percentage of MWCNTs, and pre-concentration time were optimized. The sensor was employed at pH 11.0 for the determination of LIN in plasma within a concentration range of 2.5 × 10−8 - 8.0 × 10−6 mol L−1without interference from co-administered medications. On the other hand, simultaneous monitoring of LIN, MERO and THEO in plasma was feasible at pH 3.0 over concentration ranges of 4.0 × 10−7- 9.0 × 10−5, 8.0 × 10−7- 9.0 × 10−5 and 8.0 × 10−7 - 9.0 × 10−5 mol L−1, respectively. The performance of the proposed sensor was validated and the applicability for TDM has been demonstrated in plasma of healthy volunteers.



57. Hoda E. Mohamed, Abeer A. Mohamed, **Medhat A. Al-Ghobashy**, Faten A. Fathalla, Samah S. Abbas. "Stability assessment of antibody-drug conjugate Trastuzumab emtansine in comparison to parent monoclonal antibody using orthogonal testing protocol", *Journal of Pharmaceutical and Biomedical Analysis*, **150**, 268-277, (**2018**), ISSN 0731-7085, https://doi.org/10.1016/j.jpba.2017.12.022.
IF: 2.983

Abstract

Antibody-drug conjugates (ADC) represent an emerging, novel class of biopharmaceuticals. The heterogeneity originating from the sophisticated structure requires orthogonal analytical techniques for quality and stability assessment of ADC to ensure safety and efficacy. In this study, the stability of Trastuzumab (recombinant humanized IgG1 mAb, targeting HER2 receptor) and its ADC with DM1 (anti-tubulin anticancer drug), Trastuzumab emtansine (T-DM1) were studied. SE-HPLC was used to monitor formation of aggregates and/or fragments of the monoclonal antibodies (mAb). Correlation with the results of reducing and non-reducing sodium dodecyl sulphate – polyacrylamide gel electrophoresis (SDS-PAGE) and dynamic light scattering (DLS) were performed to interpret the obtained results. RP-HPLC was used for assessment of the stability of DM1 in ADC while spectrophotometry was employed to determine drug antibody ratio (DAR) . The studied drugs were subjected to several stress conditions including pH, temperature, mechanical agitation and repeated freeze and thaw to generate possible degradation products and ensure suitability of the assay protocol. The degradation pattern and extent were demonstrated under the indicated stress conditions. The correlation between the results of SE-HPLC and those of SDS-PAGE and DLS ensured the validity of the orthogonal assay protocol and indicated aggregates that were not detected using SE-HPLC. Results showed clearly that T-DM1 is relatively less stable than its parent mAb. This was attributed to the presence of the drug-linker part that is attached to the mAb. RP-HPLC showed that the cytotoxic drug moiety is liable for degradation under the studied conditions resulting in alteration of DAR as well as formation of degradation products. This confirmed the need for more robust coupling chemistries for production of safe and effective ADC and highlighted the importance of orthogonal testing protocols for quality assessment. The assay protocol should be applicable for quality and stability assessment of various ADC.

58. Sara M. Shatat, Basma M. Eltanany, Abeer A. Mohamed, **Medhat A. Al-Ghobashy**, Faten A. Fathalla, Samah S. Abbas. "Coupling of on-column trypsin digestion–peptide mapping and principal component analysis for stability and biosimilarity assessment of recombinant human growth hormone", *Journal of Chromatography B*, **1072**, 105-115, (**2018**), ISSN 1570-0232, https://doi.org/10.1016/j.jchromb.2017.11.007.
IF: 2.813

Abstract

Peptide mapping (PM) is a vital technique in biopharmaceutical industry. The fingerprint obtained helps to qualitatively confirm host stability as well as verify primary structure, purity and integrity of the target protein. Yet, in-solution digestion followed by tandem mass spectrometry is not suitable as a routine quality control test. It is time consuming and requires sophisticated, expensive instruments and highly skilled operators. In an attempt to enhance the fuctionality of PM and extract multi-dimentional data about various critical quality attributes and comparability of biosimilars, coupling of PM generated using immobilized trypsin followed by HPLC-UV to principal component analysis (PCA) is proposed. Recombinant human growth hormone (rhGH); was selected as a model biopharmaceutical since it is available in the market from different manufacturers and its PM is a well-established pharmacopoeial test. Samples of different rhGH biosimilars as well as degraded samples: deamidated and oxidized were subjected to trypsin digestion followed by RP-HPLC-UV analysis. PCA of the entire chromatograms of test and reference samples was then conducted. Comparison of the scores of samples and investigation of the loadings plots clearly indicated the applicability of PM-PCA for: i) identity testing, ii) biosimilarity assessment and iii) stability evaluation. Hotelling's T2 and Q statistics were employed at 95% confidence level to measure the variation and to test the conformance of each sample to the PCA model, respectively. Coupling of PM to PCA provided a novel tool to identify peptide fragments responsible for variation between the test and reference samples as well as evaluation of the extent and relative significance of this variability. Transformation of conventional PM that is largely based on subjective visual comparison into an objective statiscally-guided analysis framework should provide a simple and economic tool to help both manufacturers and regulatory authorities in quality and biosimilarity assessment of biopharmaceuticals.

59. Ibrahim, S.M., **Al-Shorbagy, M.Y.**, Abdallah, D.M. *et al*. "Activation of α7 Nicotinic Acetylcholine Receptor Ameliorates Zymosan-Induced Acute Kidney Injury in BALB/c Mice", *Sci Rep*, **8(1)**, 16814, **(2018)**, https://doi.org/10.1038/s41598-018-35254-1
IF: 4.011

Abstract

Zymosan, a natural compound, provokes acute peritonitis and multiple organ dysfunction that affects the kidney, beside other organs via exaggerated inflammatory response. The aim of the present study is to test the role of cholinergic anti-inflammatory pathway (CAP) in alleviating acute kidney injury (AKI) induced by zymosan in BALB/c mice, using galantamine, a cholinesterase inhibitor, known to act via α7 nicotinic acetylcholine receptor (α7 nAChR) to stimulate CAP. Galantamine verified its anti-inflammatory effect by elevating acetylcholine (ACh) level, while abating the interleukin-6/ janus kinase 2 (Y1007/1008)/ signal transducer and activator of transcription 3 (Y705) (IL-6/ pY(1007/1008)-JAK2/ pY705-STAT3) inflammatory axis, with a consequent inhibition in suppressor of cytokine signaling 3 (SOCS3). This effect entails also the nuclear factor-kappa B (p65)/ high mobility group box protein-1/ (NF-κB (p65)/ HMGB-1) signaling pathway. Furthermore, the reno-curattive effect of galantamine was associated by a reduction in plasma creatinine (Cr), cystatin (Cys)-C, IL-18, and renal neutrophil gelatinase-associated lipocalin (NGAL), as well as an improved histopathological structure. Blocking the α7 nAChR by methyllycaconitine abolished the beneficial effect of galantamine to document the involvement of this receptor and the CAP in the amelioration of AKI induced by zymosan.

60. Rabab M. Ali, **Muhammad Y. Al-Shorbagy**, Maged W. Helmy, Hanan S. El-Abhar. "Role of Wnt4/β-catenin, Ang II/TGFβ, ACE2, NF-κB, and IL-18 in attenuating renal ischemia/reperfusion-induced injury in rats treated with Vit D and pioglitazone", *European Journal of Pharmacology*, **15(831)**, 68-76, (**2018**), ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2018.04.032.
IF: 3.170

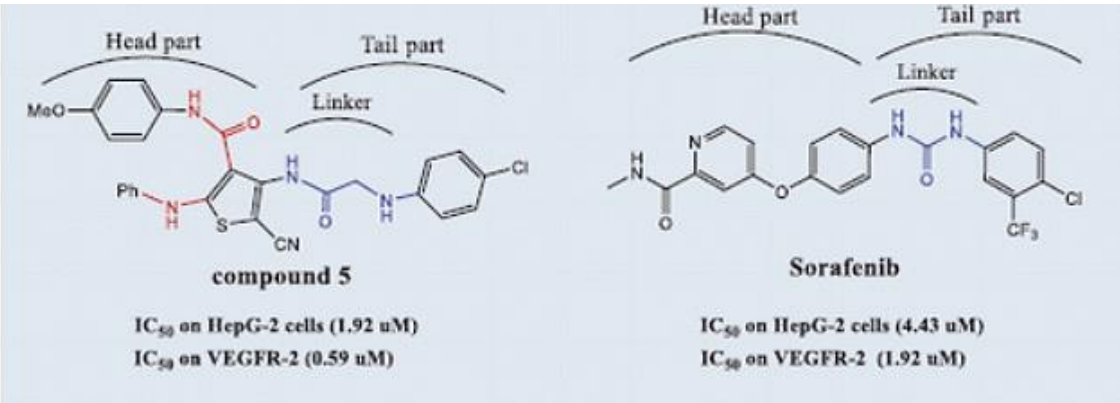
Abstract

Renal ischemia-reperfusion injury (I/RI) remains a critical clinical situation. Several evidence revealed the potential reno-protective effects of Vitamin D and/or pioglitazone, on renal I/RI. This study addresses the possible involvement of the Wnt4/β-catenin signaling, p-S536NF-κBp65, PPARγ, Ang II/TGF-β, and ACE2 as potential effectors to vitamin D and pioglitazone-mediated renoprotective effects. Two sets of Sprague-Dawley rats (n = 30 rat each), were randomized into sham, I/R, Vit D "alfacalcidol" (5 ng/kg/day), pioglitazone (5 mg/kg/day), and Vit D + pioglitazone groups. In all groups renal biochemical parameters, as well as inflammatory and structural profiles were assessed, besides the expression/contents of Wnt4/β-catenin and pS536-NF-κBp65. All treatments started 7 days before I/RI and animals were killed 24 h after I/RI in the first set, while those in the 2nd set continued their treatments for 14 days. After 24 h, all pre-treatments impeded theI/R effect on neutrophils recruitment, p-S536NF-κBp65, IL-18, NGAL, caspase-3, AngII, ACE-2, PPARγ and TGF-β, besides the expression of Wnt4 and ACE-2 with notable reflection on histological changes. Two weeks after I/RI, except a marked up regulation in Wnt4 expression and a striking elevation in the β-catenin content, the magnitude of the injurious events was relatively less pronounced, an effect that was mostly augmented by the different treatments. The current study pledges a promising and novel reno-protective role of the administration of Vit D and pioglitazone entailing a potential involvement of ICAM-1, MPO, NF-κB, Ang II, ACE2, TGFβ, and a modulation of Wnt4/β-catenin pathway.

61. Mohammed K. AbdElhameid, Madlen B. Labib, Ahmed T. Negmeldin, **Muhammad Al-Shorbagy** & Manal R. Mohammed, "Design, synthesis, and screening of ortho-amino thiophene carboxamide derivatives on hepatocellular carcinomaas VEGFR-2Inhibitors", *Journal of Enzyme Inhibition and Medicinal Chemistry*, **33(1)**, 1472-1493, (**2018**), DOI: 10.1080/14756366.2018.1503654
IF: 4.027

Abstract

In this work, design, synthesis, and screening of thiophene carboxamides 4–13 and 16–23 as dual vascular endothelial growth factor receptors (VEGFRs) and mitotic inhibitors was reported. All compounds were screened against two gastrointestinal solid cancer cells, HepG-2 and HCT-116 cell lines. The most active cytotoxic derivatives 5 and 21 displayed 2.3- and 1.7-fold higher cytotoxicity than Sorafenib against HepG-2 cells. Cell cycle and apoptosis analyses for compounds 5 and 21 showed cells accumulation in the sub-G1 phase, and cell cycle arrest at G2/M phase. The apoptotic inducing activities of compounds 5 and 21were correlated to the elevation of p53, increase in Bax/Bcl-2 ratio, and increase in caspase-3/7.Compounds 5 and 21 showed potent inhibition againstVEGFR-2 (IC50=0.59 and 1.29 µM) and β-tubulin polymerization (73% and 86% inhibition at their IC50 values).Molecular docking was performed with VEGFR-2 and tubulin binding sites to explain the displayed inhibitory activities.



62. Abd Elhameid MK, Ryad N, **Al-Shorbagy MY**, Mohammed MR, Ismail MM, El Meligie S. "Design, Synthesis and Screening of 4,6-Diaryl Pyridine and Pyrimidine Derivatives as Potential Cytotoxic Molecules", *Chem Pharm Bull*, **66(10)**, 939-952. (**2018**), Doi: 10.1248/cpb.c18-00269.
IF: 1.405

Abstract

A new series of pyridine and pyrimidine derivatives is designed and synthesized as potential antitumor molecules. The tested compounds show promising in vitro cytotoxic activity against HL-60 cell line as eight compounds: 4, 6, 11, 13, 14, 15, 18 and 21 exhibit potent cytotoxic activity in sub-micromolar concentration higher than the combretastatin A4 (CA-4). Compound 21 shows a cytotoxic activity 5-fold more potent than CA-4 on HL-60 cells. DNA-Flow cytometry cell cycle analysis and annexin-V assay on HL-60 cells show that compounds 4, 18 and 21 exhibit potent cell growth inhibition, cell cycle arrest at G2/M phase and pro-apoptotic inducing activities. The percentage inhibition assay of β-tubulin polymerization on HL-60 cells shows that the antitumor activity of the tested compounds appears to correlate well with its ability to inhibit β-tubulin polymerization. In addition, enzyme-linked immunosorbene assay (ELISA) measurement for compound 21 shows apoptotic inducing activities through significant up regulation of p53, Bax/Bcl-2 ratio and caspase-3 proteins parallel to down regulation of the level of survivin proteins.

SOP International Publications 2017

SCHOOL OF PHARMACY (SOP) INTERNATIONAL PUBLICATIONS 2017

Three (3) International publications with SOP/NGU affiliation were published in 2017.

63. Ibrahim, F.A., **Al-Ghobashy, M.A.**, Abd El-Rahman, M.K. *et al*. "Optimization and in line potentiometric monitoring of enhanced photocatalytic degradation kinetics of Gemifloxacin using TiO2 nanoparticles/H2O2". *Environ Sci Pollut Res*, **24**, 23880–23892 (**2017**). https://doi.org/10.1007/s11356-017-0045-8
IF: 2.800

Abstract

Gemifloxacin (GEM) is a broad-spectrum quinolone antibiotic. The presence of GEM residuals in industrial and hospital wastewater has been associated with genotoxicity and antibiotic resistance. In this contribution, the photodegradation of GEM using titanium dioxide nanoparticles (TiO2NPs)/H2O2 as a catalyst was optimized to eliminate residual drug and its photodegradates with antibacterial activity. A half-factorial design was implemented, investigating the effects of pH, initial concentration, H2O2 concentration, TiO2NP loading, and irradiation time. Owing to the time-dependent, multi-transformation of GEM into a wide range of structurally related photodegradation products, the monitoring of GEM throughout the experiments was achieved using both HPLC and potentiometric ion-selective electrodes (ISE). The sensor enabled in-line tracking of residual GEM in the presence of its photodegradates in real time. Results indicated that the pH, irradiation time, and GEM initial concentration were the most significant factors. At the optimum set of experimental conditions, the reaction followed first-order reaction kinetics with a mean percentage degradation of ~ 95% in less than 30 min of irradiation time and almost complete loss of antibacterial activity against Escherichia coli. The promising results demonstrated the efficiency of UV/TiO2NP/H2O2 as a photocatalyst for the breakdown of the pharmacophore of fluoroquinolones from water samples. The high selectivity, minimal solvent consumption, and lack of harmful waste generation confirmed the superiority of in-line monitoring using ISE. Optimization and in-line monitoring protocol should be applicable also at the pharmaceutical industry scale to eliminate the risk of antibiotic resistance.

64. Heba S. Abed, **Medhat A. Al-Ghobashy,** Faten A. Fathalla, Maissa Y. Salem. "Evaluation of the combined effects of pegylation and glycosylation on the stability of erythropoietin using a stability-indicating SE-HPLC", *Biologicals*, **50**, 129-136, (**2017**), ISSN 1045-1056, https://doi.org/10.1016/j.biologicals.2017.08.012.
IF: 1.872

Abstract

Recombinant human erythropoietin (rhEPO) is a commonly used biopharmaceutical for the treatment of anemia-associated disorders. Epogen; glycosylated erythropoietin (G-EPO) has short half-life and poor stability. Pegylated Epogen (Peg-G-EPO) was introduced to the market to overcome these limitations. The combined effects of pegylation and glycosylation on the stability of Peg-G-EPO was studied. Determination of Peg-G-EPO in the presence of its degradation products was achieved using SE-HPLC. The assay was validated according to ICH guidelines over concentration range of 50.00–320.00 μg/mL (r 0.9999). A mobile phase of 50 mM phosphate buffer (pH 6.5) with 300 mM sodium chloride and 20% ethanol was employed. Isocratic elution was carried out at 0.5 mL/min over run time of 30 min. Peg-G-EPO was found stable towards mechanical agitation only at low concentrations while it was stable towards repeated freeze/thaw: regardless of the concentration. Effect of temperature and pH were also investigated, and Peg-G-EPO was found stable within narrow ranges. Results indicated formation of small molecular weight and very high molecular weight aggregates that have been filtered-off the column. Although Peg-G-EPO was found relatively more stable than its non-pegylated but glycosylated version, results indicated the need for careful stability-assessment of Peg-G-EPO.

65. Moenes, Eman M., **Medhat A Al-Ghobashy**, Abeer A Mohamed, and Maissa Y Salem. "Comparative Assessment of the Effect of Glyco-engineering on the Pattern and Kinetics of Aggregate Formation of Darbepoetin Alfa using a Stability-Indicating Orthogonal Testing Protocol", *Journal of Chromatography B*, **1072**, 405-414, (**2017**), ISSN 1570-0232, doi: 10.1016/j.jchromb.2017.10.057
IF: 2.441

Abstract

Darbepoetin alfa (DA); hyper-glycosylated Erythropoietin alfa (EPO) is an essential treatment of anemia in patients with chronic kidney failure and cancer. In this study, DA and EPO were subjected to physicochemical stress factors that might be encountered during production, transport and storage (pH, temperature, agitation, repeated freeze-thaw and oxidation). An orthogonal stability-indicating assay protocol comprised of SE-HPLC, RP-HPLC, ELISA and SDS-PAGE was developed and validated to investigate the effect of further glycosylation of DA on the pattern and kinetics of degradation. Results showed a relatively higher stability and lower tendency to form high molecular weight aggregates in the case of DA when compared to EPO, under equivalent stress conditions. Dimers and aggregates were formed for both drugs across the whole pH range and following incubation at temperatures higher than 2–8°C or repeated freeze/thaw. The same observation was noted upon agitation of standard samples prepared in the formulation buffers at high speed and upon oxidation with hydrogen peroxide. The agreement between SE-HPLC, supported with spectral purity data and ELISA confirmed the specificity of both techniques for the intact drugs. Results of RP-HPLC and SDS-PAGE indicated that dimerization occurred through disulfide and bi-tyrosine covalent bonds in the case of pH and oxidation, respectively. It was evident that aggregation was significantly suppressed upon increasing the glycan size and under any of the studied stress factors loss of the glycan has not been observed. These observations supported with the slow kinetics of degradation confirmed the superiority of glyco-engineering over chemical pegylation to enhance the stability of EPO. Formation of such potentially immunogenic product-related impurities at all tested stress factors confirmed the need for orthogonal testing protocols to investigate the complex pattern of degradation of such sensitive products.

Funded Research Projects 2017-2021

FUNDED RESEARCH PROJECTS 2017 - 2021

School of Pharmacy staff has contributed in **Twelve (12)** Funded research projects since 2017

1. **ASRT**, Academy of Scientific Research and Technology, Egypt
   Ahmed S. Attia (PI)
   "The production of nanobodies using the yeast display technology as a non-conventional tool for precision medicine in infective diseases & beyond"
   December 2020 – Running

2. **ASRT**, Academy of Scientific Research and Technology, Egypt
   Grant Code: KTA-C4-4267
   Ahmed ElKerdawy
   "Towards the Establishment of a Globally Compliant Egyptian Active Pharmaceutical Ingredient Facility for Critical Diseases"
   April 2020 – Running

3. **STDF-RSG**, Science & Technology Development Fund, Egypt
   Grant Code: 34848
   Ahmed ElKerdawy
   "Development of Novel EGF Receptor Inhibitors Targeting Non-Small Cell Lung Cancer (NSCLC)"
   October 2019 – Running

4. **STDF-RSG**, Science & Technology Development Fund, Egypt
   Grant Code: 30069
   Ahmed ElKerdawy
   "Design, Synthesis, and Biological Evaluation of Novel Raf -1/VEGFR-2 Inhibitors as Antiangiogenic Agents"
   October 2019 – Running

5. **STDF-RSG**, Science & Technology Development Fund, Egypt
   Grant Code: 34859
   Ahmed ElKerdawy
   "Synthesis and biological evaluation of novel fibrates as antihyperlipidemic agents"
   October 2019 – Running

6. NCR, National Research Center, Egypt
   Project Code: 12010111
   Marwa Ahmed Fouad
   "Experimental designing for analysis and chiral separation of certain antihypertensive drugs using HPLC"
   October 2019 – Running

7. NCR, National Research Center, Egypt
   Project Code: 12010103
   Marwa Ahmed Fouad
   "Production of Certain Pharmaceutical Products based upon Nitrogen, Phosphorus, Silicon, and Selenium"
   July 2019 – Running

8. STDF, Science & Technology Development Fund, Egypt
   Ahmed Attia
   Mohamed Abdullah
   "Assessment of biosimilarity and interchangeability of locally produced biopharmaceuticals using statistically-guided orthogonal testing protocols at industrial scale"
   May 2019 – Running

9. NCR, National Research Center, Egypt
   Project Code: R110120
   Marwa Ahmed Fouad
   "Towards Discovery of Novel antibiotics: Synthesis and Biological Evaluation of New Iminophosphorane Derivatives"
   September 2018 – Running

10. Bilateral project: NRC, National Research Centre & CNR, Istituto di Chimica del Riconoscimento Molecolare
    Project code: IT II 020702
    Ahmed ElKerdawy
    "Design, Synthesis and Biological Evaluation of Novel Chalcone-based Fibrates as Novel PPAR-α Agonists"
    March 2018 – Running

11. STDF, Science & Technology Development Fund, Egypt
    Project code: STDF 15063
    Ahmed ElKerdawy
    "Development of Novel VEGF Tyrosine Kinase Receptor Antagonists Utilizing Molecular Modeling Techniques"
    March 2017 – Closed.

12. STDF, Science & Technology Development Fund, Egypt
    Medhat Al-Ghobashy (PI)
    Ahmed Attia
    Muhammad Al-Shorbagy
    Mohamed Abduallah
    "Formulation and Evaluation of Surface Functionalized Nanoparticles Enclosing Myelin Basic Protein for Treatment of Multiple Sclerosis"
    April 2016 – Closed.

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