

RASĀYAN

JOURNAL OF CHEMISTRY

(An International Quarterly Research Journal of Chemical Sciences)



Rasayan J. Chem.
ISSN (Print): 0974-1496
ISSN (Online): 0976-0083
CODEN: RJCABP

Abstracted in: Since, 2008



ELSEVIER
SCOPUS

Editorial Board

Editor-in-Chief:



Sanjay K. SHARMA, FRSC

Professor, Department of Chemistry &
Dean(Research), JECRC University, Jaipur, India

Contact: +91 9001699997

Email: editor@rasayanjournal.com

Research Interest: Green Chemistry, Organic Chemistry and Water treatment

Editorial Office:



Pratima SHARMA

Publisher and Managing Editor
RASĀYAN Journal of Chemistry
23 'Anukampa', Janakpuri, O
Stn.,Ajmer Road, Jaipur-302024 (India)

Contact: 9414202678

Email: rasayanjournal@gmail.com



CONTENTS

CURRENT ISSUE *Online First*

ARCHIVE ISSUES

DOWNLOADS

RJC CONFERENCE

SPECIAL ISSUES *Announcement*



Bassim H. Hammadi

Department of Chemical Engineering, College of Engineering,
Qatar University, P.O. Box 2713, Doha, Qatar

Contact: +97440434142

Email: b.hammadi@qu.edu.qa

Research Interest: Reaction Engineering, Adsorption Technology



Eno E. EBENSO

Professor, North-West University Gauteng, South Africa

Contact: +27825387286

Email: Eno.Ebenso@nwu.ac.za

Research Interest:



Florent ALLAIS

Director, R&D Unit of Industrial Agro-Biotechnologies URD
ABI- AgroParis Tech, Pomacle, France

Contact: +33 633 698 126

Email: Florent.allais@agroparistech.fr

Research Interest: Green Chemistry, Bio-based Polymers



Giusy LOFRANO

Department of Environment, University of Salerno, Salerno,
Italy

Contact: 0039 347 90 60 670

Email: glufrano@unisa.it

Research Interest: nanotechnologies, wastewater treatment, advanced oxidation processes



Goutam BRAHMACHARI

Professor, Chemistry Department, Visva-Bharati University,
Santiniketan-731235, India.

Contact: +91 943485744

Email: goutam.brahmachari@visva-bhartai.ac.in

Research Interest: Organic Synthesis; Green Chemistry; Natural products, Medicinal Chemistry



Hakan ARSLAN

Department of Chemistry, Faculty of
Mersin University, Mersin, TR-33343,

Contact: +90.532.7073122

Email: hakan.arslan@mersin.edu.tr

Research Interest: Coordination chemistry, Heterocyclic Chemistry Kinetic Studies, X-ray diffraction studies, Spectroscopy

SCOPUS
Indexed Since, 2008
&
UGC
Approved

2.1 ²⁰²⁰ CiteScore
45th percentile
Powered by Scopus

SJR SCImago
Journal & Country
Rank



Ishmael MASESANE

Professor, Department of Chemistry, University of Botswana,
Botswana

Contact: 26772874348

Email: MASESANE@UB.AC.BW

Research Interest: Organic synthesis, Natural product Chemistry, Medicinal Chemistry



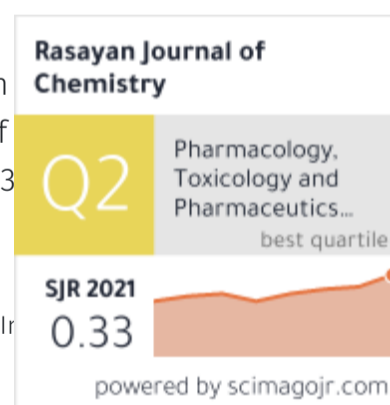
Ime Bassey OBOT

Center of Research Excellence in
Institute, King Fahd University of
(KFUPM), P.O. Box 489, Dhahran, 3

Contact: +966 13 860-8283

Email: obot@kfupm.edu.sa

Research Interest: Corrosion and Scale Inhibition, Computational Chemistry.



Marei Mailoud EL-AJAILY

University of Benghazi, Faculty of Science, Department of
Chemistry, Benghazi, Libya

Contact: 00218918315683

Email: melajaily@gmail.com

Research Interest: Mixed ligand complexes, Drugs, Applications, Corrosion inhibition, Molecular docking, DFT studies



Man SINGH

Professor and Dean, school of Chemical sciences, Gujrat
central University, Gandhinagar, Gujrat, India

Contact: +91 9408635094

Email: mansingh50@hotmail.com

Research Interest: Surface Chemistry, Physical Chemistry



This work
is
licensed
under a
[Creative Commons Attribution](#)



Mika SILLANPÄÄ



Nnabuk Okon EDDY

Department of Chemical Engineering, School of Mining, Metallurgy and Chemical Engineering, University of Johannesburg, Doornfontein 2028, South Africa

Contact: +358400205215

Email: mikaesillanpaa@gmail.com

Research Interest: Water treatment



[Pankaj KUMAR](#)

Professor and Head, Department of Chemistry, University of Energy and Petroleum studies, Dehradun, India

Contact: +917351958165

Email: pkumar@ddn.upes.ac.in

Research Interest: Biofuels and Bioenergy, Chemical sensors, Nanomaterials, Minimization of industrial wastes



[R.V. SINGH](#)

Ex Professor, Department of Chemistry, University of Rajasthan, Jaipur, India

Contact: +91 941406975

Email: vsjpr@hotmail.com

Research Interest: Inorganic Chemistry



[Soro YAYA](#)

Laboratoire des Procédés Industriels de Synthèse, de l'Environnement et des Energies Nouvelles (LAPISEN), Institut National Polytechnique (INP-HB), Yamoussoukro, BP 991 Yamoussoukro (Côte d'Ivoire)

Contact: (+225) 07 71 67 66

Email: soro_y@yahoo.fr

Research Interest: Organic synthesis, Natural Products, waste management



[V.K. GARG](#)

Professor and Dean Centre for Environmental Science and Technology School of Environment and Earth Sciences Central University of Punjab, Bathinda- 151001, India

Contact: +919812058109

Email: vinodkgarg@yahoo.com

Research Interest: Pollution Monitoring and abatement, Solid Waste Management, Radioecology

Professor, Department of Chemistry, Ahmadu Bello University, Zaria, Kaduna State, Nigeria

Contact: +2348038198753

Email: nabukeddy@yahoo.com

Research Interest: Physical Chemistry, Computational Chemistry, Nanochemistry, Industrial Chemistry, Environmental Chemistry



[Priyan PERERA](#)

Director - Center for Sustainability Department of Forestry and Environmental Science University of Sri Jayewardenepura

Contact: +94 718656457

Email: priyan@sjp.ac.lk

Research Interest: Environmental Sustainability



[Ramesh. L. GARDAS](#)

Department of Chemistry Indian Institute of Technology Madras Chennai-600 036, India

Contact: +91 9884996125

Email: gardas@iitm.ac.in

Research Interest: Physical Chemistry, Chemical Thermodynamics, Alternative Solvents



[Susheel MITTAL](#)

Senior Professor, School of Chemistry & Biochemistry, Thapar Institute of Engineering & Technology (Deemed to be University), Bhadson Road, Patiala-147004, India

Contact: +91-9815653261

Email: smittal2001@yahoo.com

Research Interest: Voltammetric Sensors, Potentiometric Sensors, Biosensors, Ambient Air Quality and Human Health



[Willian Aperador CHAPARRO](#)

School of Engineering, Universidad Militar Nueva Granada, Bogotá-111121, Colombia

Contact: + 57 3142220552

Email: william.aperador@unimilitar.edu.co

Research Interest: Materials, batteries, corrosion, coatings, tribology

Readers
around
the
world

15,953 Pageviews
Mar 9th - Apr 9th



Important Links

[Home](#)

[About us](#)

[Contact](#)

[Archive](#)

[Abstracted](#)

[Announcement](#)

[Editorial Board](#)

[Author's Guidelines](#)

[Subscription](#)

[Manuscript Submission](#)

[Current Issue](#)

About Rasayan

Rasayan J. Chem.

ISSN: 0974-1496(Print)

ISSN: 0976-0083(Online)

CODEN: RJCABP

Frequency: March, June, September & December



CONTENTS

Volume 13, Number 4, 2036-2671, October - December (2020)

[ARCHIVE ISSUES](#)

[DOWNLOADS](#)

[RJC CONFERENCE](#)

[SPECIAL ISSUES](#)

[HEAVY METALS IN HONEY PRODUCED IN SOME LOCALITIES IN KOSOVO](#)

— M. Fadil, D. Krasniqi and M. Ahmet

[ANALYSIS METHOD OF ANTI-CANCER DRUG SEMUSTINE FOR CHEMOTHERAPY BY CYCLIC VOLTAMMETRY](#)

— Deswati, Hamzar Suyani, Rahmiana Zein, Hilfi Pardi, Buchari and Henry Setiyanto

[ACUTE TOXICITY OF TEBUCONAZOLE 80%WP IN FRESHWATER FISH \(Oncorhynchus Mykiss\) FOLLOWED BY VALIDATION INCLUDING STABILITY AND DOSE VERIFICATION](#)

— T. B. Patrudu, T. Nageswara Rao and K. Raghu Babu



[CHITOSAN-STARCH FORWARD OSMOSIS MEMBRANE FOR DESALINATION OF BRACKISH WATER](#)

— Saiful, Zuliana Rahmah, Maurisa Ajrina, Marlina and Rahmi



[ISOLATION OF LIPOLYTIC BACTERIA FROM DOMESTIC WASTE COMPOST AND ITS APPLICATION TO BIODIESEL PRODUCTION](#)

— Purkan Purkan, Indah Tri Lestari, Rizky Arissirajudin, Retno Rahayu Puspita Ningsih, Wiwin Apriyani, Hamidah Nurlaila, Sri Sumarsih, Sofjan Had, Wiwin Retnowati and Seung Wook Kim



[SYNTHESIS OF EFFECTIVE ENVIRONMENTALLY FRIENDLY ADDITIVES FOR AUTOMOTIVE FUELS](#)

— L.R. Sassykova, K.A. Kadirbekov, N.K. Zhakirova, A.S. Zhumakanova, S. Sendilvelan, T. S. Abildin, A.A. Batyrbayeva, R. N. Azhigul Ponomarenko and R.G. Ryskaliyeva

[ELECTROCHEMICAL IMPEDANCE, CYCLIC VOLTAMMETRY, AND CORROSIVE BEHAVIOR IN TiO2 NANOSTRUCTURES](#)

— J. Bautista-Ruiz, W. Aperador and M.R. Joya



[PAINTING MATERIALS PRODUCTION ON THE BASIS OF PETROLEUM BITUMEN](#)

— Kulash K. Syrmanova, Aktolkyn B. Agabekova, Zhanat B. Kaldybekova, Anastassiya Y. Kovaleva and Yersultan T. Botashev

This work is licensed

[ISOTHERMS AND CAPACITY ADSORPTION OF Fe\(III\) ONTO DUCK FEATHER MODIFICATION USING CH3OH AND HCl SOLUTION](#)

— U. B. L. Utami, B. Cahyono and H. Susanto

under a Creative Commons Attribution

HYBRID POLY (O-TOLUIDINE)/MWCNT/COPPER OXIDE NANO COMPOSITE ELECTRODE FOR ELECTROCHEMICAL SUPERCAPACITOR

– [Kamal Kant Singh](#), [Ashok K. Sharma](#), [Indu Kaushal](#), [Priya Saharan](#) and [Vinit Kumar](#)

International
License.



Readers

IMPACT OF MOLECULAR INTERACTIONS ON BINARY SOLUTIONS OF 2-PROPANOL WITH METHOXY ANILINE ISOMERS AT DIFFERENT TEMPERATURES

– [G. V. Gangadhara Rao](#), [S. Suriya Shihab](#), [D. Das](#) and [Shaik. Babu](#)

around
the
world



NEW PERIPHERALLY TETRA 1-AMINO-2-NAPHTHOL-4- SULFONICACID SUBSTITUTED COBALT PHTHALOCYANINE SYNTHESIS, CHARACTERIZATION AND ELECTRO CATALYTIC STUDIES ON THE OXIDATION OF O-AMINOPHENOL

– [T. M. Sharanakumar](#), [Mounesh](#), [N. Y. Praveen Kumar](#), [K. R. Venugopala Reddy](#) and [Suresh](#)

15,965 Pageviews
Mar 9th - Apr 9th



EFFECT OF ADDITIVES ON STRUCTURE AND PROPERTIES OF ELECTRODEPOSITED NANOCRYSTALLINE COPPER

– [S. Ramalingam](#)



ORGANOCHLORINE PESTICIDES ASSESSMENT IN SEDIMENT SAMPLES FROM VAAL RIVER BY ACCELERATED SOLVENT EXTRACTION TECHNIQUE

– [Mokete J. Phele](#), [Ikechukwu P. Ejidike](#) and [Fanyana M. Mtunzi](#)



STUDIES ON NITRATE REMOVAL FROM WASTEWATER USING NANO ZINC PEROXIDE AS ADSORBENT

– [M. Nagapadma](#)



OPTIMIZATION OF HIGH-TEMPERATURE BIOETHANOL PRODUCTION FROM PINEAPPLE PEEL HYDROLYSATE USING RESPONSE SURFACE METHODOLOGY

– [H.X. Phong](#), [N.N. Thanh](#), [B.H.D. Long](#) and [P. Thanonkeo](#)



REGULARITIES OF INTERACTION OF CALCIUM CHLORIDE OF DISTILLER LIQUID WITH NATURAL SODIUM SULFATE

– [A. A. Anarbayev](#), [G. M. Ormanova](#), [B. N. Kabylbekova](#), [N. A. Vysotskaya](#) and [B. Kh. Kucharov](#)



FABRICATION OF CHITOSAN/NATURAL ZEOLITE COMPOSITE-BASED POLYMER ELECTROLYTE MEMBRANES

– [Y.A. Sihombing](#), [Susilawati](#), [S.U. Rahayu](#) and [A. Siahaan](#)



NANOCRYSTALLINE COPPER OXIDE HIGHLY DISPERSED ON MESOPOROUS ALUMINA BY INCIPIENT WETNESS IMPREGNATION METHOD: SYNTHESIS AND CHARACTERIZATION

– [M. Arul jayan](#), [S.S. Dawn](#) and [G.G. Vinoth Kumar](#)



MECHANICAL AND THERMAL PROPERTIES OF STRAINED METAL NANOPARTICLES PREPARED BY BALL MILLING METHOD

– [Purushotham Endla](#)



L-CYSTEINE HYDROCHLORIDE AS A COMPLEXING AGENT FOR THE DETERMINATION OF COBALT(II) BY SPECTROPHOTOMETRIC METHOD

– [Ashwini](#), [Gopalakrishna Bhat N.](#) and [Ronald A. Nazareth](#)



A NOVEL VALIDATION OF THE LEVOFLOXACIN DETERMINATION METHOD IN URINE (IN VITRO) USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHYUV/VIS DETECTOR

– [I. Sopyan](#), [D. Dwiputri](#) and [Mughtaridi Mughtaridi](#)



EVALUATION OF ANTIBACTERIAL AND ANTIOXIDANT ACTIVITIES OF XANTHONE ISOLATED FROM *Orophea corymbosa* LEAF

– H. P. C. A. Cane, N. Saidi, M. Mustanir, D. Darusman, R. Idroes and M. Musman



STRUCTURAL AND PHASE ANALYSIS OF PURE AND METAL ION DOPED Mn_2O_3 NANOPARTICLES PREPARED BY MICROWAVE ASSISTED SOL-GEL METHOD

– L. Jayaselvan, S. Thanka Rajan and C. Gnana Sambandam



ADSORPTIVE REMOVAL OF LEAD IONS FROM WASTEWATER USING SORBENTS DERIVED FROM *Cedrus deodara* PLANT AND ITS COMPOSITE WITH Ca-ALGINATE BEADS

– Gullapalli Sreelatha, Polavarapu Srineetha, Malireddy Venkata Sai Mohan Reddy and K. Ravindhranath



ANALYSIS OF TANNIN IN SAPODILLA FRUIT (*Manilkara zapota* (L.) VAN ROYEN)

– Baharuddin Hamzah, Sitti Rahmawati, Wayan Samuel Suwena, Muhammad Fakhrol Hardani and Ririen Hardani



DETERMINATION OF BIOLOGICAL ACTIVITY, ANTIOXIDANT ACTIVITY AND SYNTHESIS OF TRIAZOLOPYRIMIDINES

– V. P. Gilava, P. K. Patel, H. K. Ram and J. H. Chauhan



IMPROVED AND VALIDATED OF TWO SPECTROPHOTOMETRY METHOD FOR PARALLEL ASSAY OF GUAIPHENESIN, ACETAMINOPHEN AND CTM COMBINE IN SYRUP

– Muchlisyam Bachri, Masfria and Yade metri Permata



SURFACE MODIFIED MAGNETITE NANOPARTICLES: AN EFFECTIVE TOOL FOR THE SEPARATION OF TOXIC METAL IONS AND ORGANIC CONTAMINANTS FROM WASTEWATER

– A. Jangra, J. Singh, K. Rani, J. Kumar, P. Kumar and R. Kumar



DEGRADATION OF CIPROFLOXACIN USING FENTON PROCESS AND ITS EFFECT ON BIODEGRADABILITY

– V. K. Iyothirmaj, S. Mary Rebekah Sharmila and Sija Arun



ISOLATION AND CHARACTERIZATION OF PHYTOCONSTITUENTS FROM STEM OF *Elytranthe parasitica* (L.) Danser

– N. Kumar, R. Lobo and J.E. Mathew



SYNTHESIS AND DISTRIBUTIONS OF Mn^{4+} IONS IN NONMAGNETIC SiO_2

– Venkateswararao Jillepalli, Boyapati Veeranjanyulu and G. Subrahmanya Sastry



SYNTHESIS, CRYSTAL STRUCTURE AND THERMAL STUDIES OF TRIPHENYLSILANOL-PIPERAZINE ADDUCT

– M. Dinesh, V. Kavitha, G. Prabusankar, B. Babu, B. Mohanbabu, G. Donghui and P. Maadeswaran



EQUILIBRIUM STUDIES IN ADSORPTION OF HEAVY METALS USING MODIFIED GRANULAR ACTIVATED CARBON

– Y. K. Meshram, R. U. Khope and P. P. Chahande



IDENTIFICATION OF ALLELOCHEMICAL COMPOUNDS FROM EACH PART OF *Tetracera indica* (L.) MERR

– D. Guntoro, D.W. Rokhmaningsih and F.I. Nuryana



POTENTIAL BIOACTIVITIES OF ETHANOL, ETHYL ACETATE AND n-HEXANE EXTRACTS FROM PAGODA LEAVES (*Clerodendrum paniculatum* L.)

– Dewi Pertiwi, Ihsanul Hafiz and Leny



SYNTHESIS OF SPIROOXINDOLE-PYRROLIZIDINE COMPOUNDS USING Fe₃O₄-GO CATALYST AND THEIR BIOACTIVITY ASSAYS

– Mutiara Hapsari, Antonius Herry Cahyana, Syntia H. Oktavia and Agus Rimus Liandi



ADSORPTION AND CHARACTERIZATION OF Pb(II) ION ONTO POROGEN ADSORBENT MEMBRANE (CC-Pec-BADGENa): KINETIC, EQUILIBRIUM AND THERMODYNAMIC STUDIES

– B. Hastuti, D. Siswanta, Mudasir and Triyono



KINETICS OF SULFUR DIOXIDE ADSORPTION ON MODIFIED ACTIVATED COAL PRODUCED FROM PEACH SHELLS

– Aizhan Mamyrbekova, A.D. Mamitova, M.K. Kassymova, Aigul Mamyrbekova, Zh.E. Daribayev, R.E. Pralieva, M.N. Yermakhanov and G.S. Mutasheva



SYNTHESIS AND CHARACTERIZATION OF Fe₃O₄ NANOPARTICLES FROM IRON SAND WITH SONOCHEMICAL METHOD

– F. Hidayanto, H. Sutanto, P. Priyono, E. Hidayanto, A.A. Wibowo and P. Triadyaksa



FORMULATION OF THE SERUM GEL CONTAINING GREEN COFFEE BEAN (Coffea robusta L) EXTRACT AS AN ANTIOXIDANT AND TYROSINASE ENZYME INHIBITOR

– D. L. Aulifa, M. Caroline, D. Tristiyanti and A. Budiman



SYNTHESIS OF 1,1,2-TRISUBSTITUTED CYCLOPROPANE RING THROUGH CARBON-CARBON BOND NUCLEOPHILEINTERCEPTED BECKMANN FRAGMENTATION REACTION

– Nandkishor Chandan



APPLICATION OF CHEMOMETRIC METHODS FOR THE DETERMINATION OF CIPROFLOXACIN HYDROCHLORIDE AND PHENAZOPYRIDINE HYDROCHLORIDE IN THEIR PHARMACEUTICAL DOSAGE FORM

– M.M. Patel, U.H. Shah, K. Goswami, S. Bhavsar and S.G. Patel



CATALYTIC CRACKING OF VACUUM DISTILLATES ON COMPOSITE CATALYSTS

– R. Kh. Ibrasheva, V.S.Yemelyanova, L.R. Sassykova, U. N. Dzhatkambayeva, T.V. Shakiyeva, B.T. Dossumova, N.K. Zhakirova, S.Sendilvelan and T. M. Seilkhanov



OPTIMIZATION OF EXPERIMENTAL FACTORS FOR HEXAVALENT CHROMIUM REMOVAL BY DEAD BIOMASS OF WATER HYACINTH

– Sunil Kumar and Rajesh Dhankhar



IDENTIFICATION OF SECONDARY METABOLITES AND ANTIDIARRHEAL ACTIVITY OF PIRDOT LEAVES ETHANOL EXTRACT (Saurauia vulcani Korth.) FROM WEST PAKPAK, NORTH SUMATERA PROVINCE, INDONESIA

– K. Gurning, R. Boangmanalu, H.A.Simanjuntak, N. Singarimbun, R. Rahmiati and W. Lestari



SEASONAL VARIATION OF TRACE AND HEAVY METALS IN VEGETABLE PLANTS AROUND TUMMALAPALLE URANIUM MINING SITE

– S. Kulavardhana Reddy, C. Sivanandha Reddy and Gopireddy Venkata Subba Reddy



PALM SLUDGE OIL AS RAW MATERIAL OF BIODIESEL SYNTHESIS THROUGH ELECTROLYSIS PROCESS USED Ag ELECTRODE

– D. Irawan, Z. Arifin, M. Gery and M.A. Fithia



NOVEL SYNTHESIS OF 4E,10E-4-(2-PHENYLDIAZENYL)-N- ((1H-INDOLE-3-YL)METHYLENE)BENZENAMINE AND ITS APPLICATION FLUORESCENT CHEMOSENSOR FOR Ag⁺ ION, CYTOTOXICITY ACTIVITY AND DFT STUDIES

– E. Dhineshkumar, M. Iyappan and C. Anbuselvan



ADSORPTION OF AMMONIA AND METHYLENE BLUE USING COMBINATION OF COST-EFFECTIVE COCONUT HUSK ACTIVATED CARBON AND SILICA (SiO₂) AS AN ADSORBENT

– Mariana, F. Mulana, D. N. Pratama and S. Muchtar



REVIEW OF THE PROCESSING OF MINERALS AND TECHNOGENIC SULFIDE RAW MATERIAL WITH THE EXTRACTION OF METALS AND RECOVERING ELEMENTAL SULFUR BY ELECTROCHEMICAL METHODS

– A. S. Kolesnikov, V.N. Naraev, M.I. Natorhin, A.A. Saipov and O.G. Kolesnikova



PHOSPHORYLATED NATA DE PINA AS POLYMER ELECTROLYTE MEMBRANE IN FUEL CELLS

– Purnama Ningsih, Wahyuni Wulandari, Sitti Rahmawati and Anang Wahid Muhammad Diah



NICKEL-CATALYZED SUZUKI-MIYaura CROSSCOUPLING REACTIONS: ONE-POT SYNTHESIS OF 2-ARYLTHIOPHENES

– Thalishetti Krishna, Thatikonda Narendar Reddy, Eppakayala Laxminarayana and Dipak Kalita



SYNTHESIS OF BREAD FRUIT (Artocarpus communis)-BASED HYDROXYPROPYL STARCH THROUGH ETHERIFICATION USING PROPYLENE OXIDE

– Cut Fatimah Zuhra, Mimpin Ginting, Wilza Fithri Azzahra and Rini Hardiyanti



MAIN FATTY ACIDS, PHENOLIC COMPOUNDS, AND EVALUATION OF GASTROPROTECTIVE EFFECT OF MALBEC GRAPE SEEDS, A WINE INDUSTRY BY-PRODUCT

– Miki Gonzales-Uscamayta, Juana E. Chávez-Flores, Henry Obregón Tinoco, Fiorella P. Cardenas-Toro, Mario J. Simirgiotis, Jorge Borquez and Juana Robles-Caycho



5-SULFOSALICYLIC ACID (5-SSA): AN EFFICIENT ORGANOCATALYST FOR THE SYNTHESIS OF 4-METHYLCOUMARINS VIA PECHMANN CONDENSATION

– C. D. Bhenki, S. S. Karhale, K. N. Patil and V. B. Helavi



INVESTIGATION OF POLYPHENOLIC COMPOUNDS OF ?hamaenerion latifolium (L.) PLANT

– Akmaral Kozhantayeva, Sluken Rakhmadiyeva, Ozek Gulmira



CHARACTERISTIC OF GREEN SYNTHESIZED Ag NANOPARTICLE USING EXTRACT AND ESSENTIAL OIL OF Illicium verum HOOK. F. AS ANTIBACTERIAL

– Rizki Damayanti, Tamrin, Zul Alfian and Eddiyanto



WATER REMEDIATION OF CHROMIUM (VI) BASED ON SULPHURIC ACID GENERATED BIO-CHAR FROM STEMS OF Averrhoa carambola PLANT AS ADSORBENT

– Malireddy Venkata Sai Mohan Reddy, Gullapalli Sreelatha, Doddi Kishore Babu, Wondwosen Kebede Biftu and Kunta Ravindhranath



HEAVY METAL CONTAMINATIONS AND HEALTH RISK ASSESSMENT FROM FRUITS AND VEGETABLES IN BANGALORE RURAL MARKETS, KARNATAKA, INDIA

– L. Shivakumar, K. Ramakrishna Reddy and B.M.Kalshetty



ANTIHYPERGLYCEMIC ACTIVITIES ETHANOL EXTRACT OF *Musa paradisiaca* L STEMS AND DETERMINATION OF ITS ACTIVE COMPONENTS USING GC-MS

– Mayang Sari, Tamrin, Jamaran Kaban and Zul Alfian



A CORRELATION STUDY OF GROSS CALORIFIC VALUE WITH PARAMETERS OF PROXIMATE ANALYSIS OF COAL

– H. Akbar, Sumath Kumar Laha and Rakesh Saini



SOLID-PHASE EXTRACTION OF AMOXICILLIN IN AQUEOUS SYSTEM BY USING Mg-AL-OXALATE LDH AS A STATIONARY PHASE

– Dian W. Dwiasj, Mudasir Mudasir and Roto Roto



CHITOSAN-ZINC OXIDE NANOPARTICLE BASED HIGHLY SENSITIVE ELECTROCHEMICAL SENSOR FOR FORMALDEHYDE DETECTION

– Saisa, H. Agusnar, Z. Alfian and I. Nainggolan



PHYSICO-CHEMICAL AND BIOLOGICAL STUDIES ON THE COORDINATION COMPOUNDS OF N-(2-CARBAMOYL-FURANYL)-C-(3'-CARBOXY-2'- HYDROXY-PHENYL) AZETIDIN-2-ONE

– Praveen Kr. Gupta, Dinesh Kumar, Amit Kumar and Durga Dass



SYNTHESIS AND ANTI-BREAST CANCER ACTIVITIES OF ALPHA MANGOSTIN DERIVATIVES: A REVIEW

– Muhammad Fauzi and Muchtaridi Muchtaridi



ISOLATION AND CHARACTERIZATION OF STIGMASTEROL AND β -SITOSTEROL FROM WOOD BARK EXTRACT OF *Baccaurea macrocarpa* Miq. Mull. Arg

– Erwin, W.R. Pusparohmana, R.D. Safitry, E. Marlina, Usman and I.W. Kusuma



MOLECULAR MODELING, SYNTHESIS, AND QSAR OF 5-O-ACYLPINOSTROBIN DERIVATIVES AS PROMISING ANALGESIC AGENT

– Siswandono, Retno Widyowati, Andi Suryadi, Tri Widiandani and Deka Prismawan⁴



ANTIOXIDANT AND ANTIHYPERURICEMIC POTENTIALS OF RARU (*Cotylelobium melanoxylo*n Pierre) BARK

– M. Zulham Efendi Sinaga, Arida Susilowati, Firman Sebayang, Saraswati E. Br Ginting and Tati Suhartati



FLAVONOIDS CONSTITUENT ANALYSIS AND CELL CYCLE INHIBITION ACTIVITY OF ETHYLACETATE EXTRACT OF *Vernonia amygdalina* Delile. LEAVES ON LUNG CANCER CELL LINE

– P.A.Z. Hasibuan, D. Munir, D. Pertiwi, D. Satria and M.F. Lubis



INFLUENCE OF ADDITIVES ON ANTI KNOCK AND ENVIRONMENTAL PROPERTIES OF GASOLINE AND THEIR MECHANISM OF ACTION

– E.K. Kaldykozoy, B. A. Abdikerimov, G. E. Kaldygozova and E. S. Tleubay



In-silico MOLECULAR DOCKING ANALYSIS OF ANDROGRAPHOLIDE DERIVED FROM *Andrographis paniculata* AS POTENTIAL ANTI-HIV AGENT TARGETING HIV-1 REVERSE TRANSCRIPTASE

– G. Swapna, D. Rakesh and M. Estari



A NEW NATURAL PRODUCT DIKETOPIPERAZINE, ANTIBIOTICALLY ACTIVE COMPOUND FROM SYMBIOTIC FUNGUS *Purpureocillium lilacinum* ISOLATED FROM MANGROVE *Sonneratia alba*

– Robert A. Bara, Stefan Kehraus, Alexander Bogdanov, Jimmy Posangi, Fitje Losung, Ekaterina Egereva, Remy Mangindaan and Gabriele Koenig



[FLUORIDE REMOVAL FROM DRINKING WATER BY PRISTINE PUMICE AS ADSORBENT](#)

– [S. K. Singh](#), [S. Shweta](#), [Mansi Shrivastava](#) and [Shivankar Aggarwal](#)



[PHYSICOCHEMICAL ANALYSIS OF LAKE WATER USING NATURAL COAGULANTS](#)

– [S. Vanitha](#) and [N. K. Rajan](#)



[SYNTHESIS AND CHARACTERIZATIONS OF A VERSATILE SILICA INCORPORATED MAGNESIUM-ZINC OXIDE PHOTOCATALYST](#)

– [M. Athira Chandran](#), [N. Amal](#), [K. M. Sreedhar](#), [G. Sivasubramanian](#) and [K. M. Sreekanth](#)



[DESIGN OF THIOXANTHONE DERIVATIVES AS POTENTIAL TYROSINE KINASE INHIBITOR: A MOLECULAR DOCKING STUDY](#)

– [F. Hermawan](#), [I. Jumina](#) and [H.D. Pranowo](#)



[BIOACTIVE COMPOUNDS FROM MARINE SPONGE DERIVED FUNGUS *Aspergillus unguis* WR8](#)

– [D. Handayani](#), [A. Rendowati](#), [I. Aminah](#), [N. P. Ariantari](#) and [P. Proksch](#)



[RESEARCH OF HYDROCARBON COMPOSITION AND PHYSICAL AND CHEMICAL PROPERTIES OF LIGHT DISTILLATE FRACTIONS OF CASPIAN OIL](#)

– [E.K. Kaldykozov](#), [E. S. Tleubay](#), [G. E. Kaldygozova](#) and [B. A. Abdikerimov](#)



[KINETICS OF EXTRACTION OF INORGANIC CHLORIDES FROM LEAD PRODUCTION SLAGS IN THE PRESENCE OF DISTILLER LIQUID](#)

– [D. Pazylova](#), [V.M. Shevko](#), [A.S. Tleuov](#), [B.A. Lavrov](#), [N.S. Saidullayeva](#) and [A.S. Abzhanov](#)



[REMOVAL OF ALUMINUM \(III\) FROM POLLUTED WATER USING NEW EFFECTIVE BIO-SORBENTS DERIVED FROM STEMS OF *Burea monosperma* AND *Angle marmelo* PLANTS](#)

– [Polavarapu Srineetha](#), [Yeruva Alekhya Reddy](#), [Sayana Veerababu](#) and [K. Ravindhranath](#)



[GREEN SYNTHESIS OF COPPER NANOPARTICLES USING *Holoptelea integrifolia* FRUIT EXTRACT](#)

– [Anju](#), [Shruti Sharma](#), [Hari Ram Dhanetia](#) and [Alka Sharma](#)



Important Links

[Home](#)
[About us](#)
[Contact](#)
[Archive](#)
[Abstracted](#)
[Announcement](#)

[Editorial Board](#)
[Author's Guidelines](#)
[Subscription](#)
[Manuscript Submission](#)
[Current Issue](#)

About Rasayan

Rasayan J. Chem.
ISSN: 0974-1496(Print)
ISSN: 0976-0083(Online)
CODEN: RJCABP
Frequency: March, June, September & December

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/347775214>

MOLECULAR MODELING, SYNTHESIS, AND QSAR OF 5-O-ACYLPINOSTROBIN DERIVATIVES AS PROMISING ANALGESIC AGENT

Article in *Rasayan Journal of Chemistry* · December 2020

DOI: 10.31788/RJC.2020.1345749

CITATIONS

7

READS

299

5 authors, including:



Siswandono Siswodihardjo

Airlangga University

126 PUBLICATIONS 478 CITATIONS

[SEE PROFILE](#)



Retno Widyowati

Airlangga University

50 PUBLICATIONS 254 CITATIONS

[SEE PROFILE](#)



Tri Widiandani

Airlangga University

28 PUBLICATIONS 134 CITATIONS

[SEE PROFILE](#)



Deka Prismawan

Atma Jaya Catholic University of Indonesia

5 PUBLICATIONS 34 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Benzoxazinone [View project](#)



spilanthus acmella [View project](#)

MOLECULAR MODELING, SYNTHESIS, AND QSAR OF 5-O-ACYLPINOSTROBIN DERIVATIVES AS PROMISING ANALGESIC AGENT

Siswandono¹, Retno Widyowati², Andi Suryadi^{2,3}, Tri Widiandani^{1*},
and Deka Prismawan⁴

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia.

²Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia.

³Department of Pharmacy, Faculty of Sport and Health, Universitas Negeri Gorontalo, Gorontalo, 96128, Indonesia.

⁴Department of Pharmacy, School of Medicine and Health Sciences, Universitas Katolik Indonesia Atma Jaya, Jakarta, 14440, Indonesia.

*E-mail: tri-w@ff.unair.ac.id

ABSTRACT

Pain remains a major healthcare problem nowadays, despite the recent advances and knowledge about its mechanism and management. Currently marketed analgesics and NSAIDs include both non-selective COX inhibitors and selective COX-2 inhibitors exhibit several disadvantages such as increasing gastrointestinal bleeding and cardiovascular risk. We aimed to develop a potential analgesic by utilizing structural modifications on pinostrobin, which is previously known to possess anti-inflammatory properties. Schotten-Baumann esterification reaction was employed to produce four 5-O-acylpinostrobin derivatives, namely pinostrobin acetate, pinostrobin propionate, pinostrobin butyrate, and pinostrobin pentanoate, with moderate to good yields (61-84%). The acetic acid-induced writhing test using *Mus musculus* was demonstrated to evaluate the analgesic activity of the compounds. 5-O-Acylpinostrobin derivatives display some improvements in analgesic activity compared to pinostrobin itself. Pinostrobin pentanoate emerges as the most potent compound with an ED₅₀ value of 10.37 mg/kg BW. This result is consistent with the *in silico* study which we performed before the synthesis. The structural modification of pinostrobin is successful in improving the analgesic potency, resulting in pinostrobin pentanoate as the optimum compound. Furthermore, the increasing analgesic potency is in line with the increasing length of the side alkyl chain, suggesting the importance of the steric parameter in the QSAR formulation which can be invoked as a predictive tool for future optimization.

Keywords: Molecular Modeling, Synthesis, 5-O-acylpinostrobin Derivatives, Analgesic, QSAR

© RASĀYAN. All rights reserved

INTRODUCTION

Despite the increasing developments and knowledge in the past four decades about the mechanisms and management, the pain remains a major healthcare problem in the modern era. Global estimation suggests that each year, 20% of adults experience pain and another 10% of adults are diagnosed with chronic pain.¹ In general, pain is classified into either acute or chronic. Normally, acute pain is a sign of potential tissue damage, a result of accidental injury, inflammation, or surgery. While most acute pain is readily managed, however, it can progress into chronic pain if appropriate management was not provided.^{1,2} It is well established that many pathological pain states are due to the inflammatory responses in the peripheral and central nervous systems.³ Therefore, many scientific researchers also focus on inflammation since it usually involves pain and oedema as a result of the release of many pro-inflammatory mediators at the site of injury.⁴ The serious implications of pain such as depression, inability to do a normal activity, disrupted social life, and suicidal thoughts,¹ have led to an enormous discovery effort for alternative analgesics and

anti-inflammatory agents or non-steroidal anti-inflammatory drugs (NSAIDs), since many of the existing NSAIDs cause several adverse effects due to their non-selective inhibition of both cyclooxygenases (COX-1 and COX-2).⁵ COX-1 enzyme plays an important role in the synthesis of prostaglandins, key mediators which are involved in inflammation. Unfortunately, these prostaglandins also act as a gastric mucosal protective agent. Inhibition of this enzyme as part of pain management may lead to ulceration as a consequence.⁶ On the other hand, by selectively inhibiting COX-2 in pain management, the risk of upper gastrointestinal bleeding is reduced by 50-60% when compared to non-selective COX inhibition.^{7,8} However, the use of currently marketed selective COX-2 inhibitors such as rofecoxib, celecoxib, and valdecoxib increases the risk of cardiovascular events.⁹ Therefore, the development of selective COX-2 inhibitors is still of great interest to overcome the complication in pain management.

In this study, we investigated and developed an alternative analgesic, starting with pinostrobin as the lead compound. Pinostrobin is a flavonoid found as one of the major components in the rhizome of *Curcuma rotunda*.¹⁰ It is also found in *Boesenbergia pandurata* (Roxb.) Schlechter, a medicinal and culinary herb that grows abundantly in the tropical rain forest of Southeast Asia.¹¹ Several studies showed that pinostrobin possesses various pharmacological benefits, including antioxidant activity, antimicrobial activity, antifungal activity, and anti-inflammatory activity.¹² A study conducted by Gomez-Betancur *et al.* suggested that pinostrobin demonstrates analgesic and anti-inflammatory properties and might have a mechanism of action similar to NSAIDs such as ibuprofen, by inhibiting cyclooxygenase (COX).¹³ However, it displays a poor inhibitory activity against COX-1 and COX-2 at a concentration of 100 µg/mL.¹⁴ Thus, we investigated the possibility of an improved potency by performing molecular modifications, in which we employed esterification of the hydroxy group of pinostrobin using Schotten-Baumann reaction.

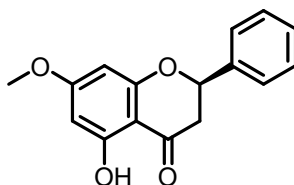


Fig.-1: The Structure of Pinostrobin

EXPERIMENTAL

Material and Methods

The molecular structure of cyclooxygenase-2 receptors with ligand diclofenac (DIF_701), PDB ID: 1PXX, can be downloaded via a protein data bank site. The 2D structure of the 5-*O*-acylpinostrobin derivatives was drawn using the ChemBioDraw Ultra version 12 (Cambridge Soft) and then copied into the ChemBio3D Ultra version 12, to create the 3D structure and measure its minimum energy using MMFF94, and then stored as .mol2.

Chemistry

General Methods. All reagents were purchased from *Sigma-Aldrich*, *Merck*, and *Dexa Medica* without purification unless otherwise stated. All solvents were reagent-grade. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60/ Kieselguhr 254 (Merck). Melting points were measured on Melt Temp Electrothermal Melting Point Apparatus, NMR spectra were recorded on JEOL ICS 400 MHz spectrometer at 25°C. Chemical shift (δ) is reported in ppm relative to the residual solvent peak using *tetramethylsilane* (TMS) as the internal standard. Mass spectra were recorded using GC/MS Agilent 6890 spectrometers. FT-IR spectra were recorded on the Perkin Elmer Spectrum One FTIR spectrophotometer.

Docking Protocol

The docking study of these compounds on the cyclooxygenase-2 receptor (1PXX) was conducted using Molegro Virtual Docker version 5.5. (CLCBio). The best docking results can be detected visually by comparing the structure of the docked molecules with the crystal structure of the reference ligand diclofenac (DIF_701) in the binding site (cavity 4). The results are presented as rerank scores. The lowest energy indicates the best binding pose between the functional group of the ligand and the amino acid residue of the

protein. The state of the environment of each compound derivative, such as hydrogen bonds, and steric interactions was determined.

Procedure for the Isolation of Pinostrobin (1)

Temu kunci (*Boesenbergia pandurata* Roxb. Schlecht) rhizomes were washed with running water, then the rhizomes were cut into small pieces and dried using the oven at 50°C. The dried rhizomes were then finely powdered, weighed, and extracted. Gradually, 2 kg of dried powder was extracted with 20 L of *n*-hexane by maceration (3 times). The solvent residue was evaporated under reduced pressure until 1/3 of the initial volume. Recrystallisation to obtain the crystalline isolate was performed by dissolving the crude in hot methanol, then it was cooled in the refrigerator for 24 hours until the crystal formed. The crystal was washed with hot methanol 4 times, then dried in the oven at 50°C to obtain pinostrobin **1**, as a white crystalline (38.7 gram, 1.94% w/w). ¹H-NMR (400 MHz, CDCl₃): 12.03 (*s*, 1 H); 7.42 (*m*, 6 H); 6.07 (*d*, *J* = 3.2, 2 H); 5.39 (*dd*, *J* = 12.8, 3.2, 1 H); 3.80 (*s*, 3 H); 3.07 (*dd*, *J* = 17.2, 12.8, 1 H); 2.81 (*dd*, *J* = 17.2, 3.2, 1 H). ¹³C-NMR (400 MHz, CDCl₃): 195.89 (C); 168.07 (C); 164.23 (C); 162.88 (C); 138.46 (C); 128.99 (CH); 126.25 (4 CH); 103.23 (C); 95.23 (C); 94.38 (CH); 79.33 (CH); 55.81 (CH₃); 43.48 (CH₂). *m/z* for (C₁₆H₁₄O₄) 270.09, found 270.1.

Procedure for the Synthesis of Pinostrobin Derivatives (GP-A).

A solution of pinostrobin **1** (11 mmol, 1.0 equiv.) in tetrahydrofuran (10 mL) was cooled down to 0°C, after which a solution of the corresponding aliphatic acyl chlorides (35 mmol, 3.2 equiv.) in tetrahydrofuran (10 mL) was added dropwise while the mixture was stirred. After that, triethylamine (62 mmol, 5.6 equiv.) was added and the mixture was stirred and let stand at room temperature for 30 minutes. Upon completion, the solvent was evaporated under reduced pressure. To the crude, hot methanol was added slowly to dissolve completely, then the solution was filtered. The filtrate was allowed to cool down to room temperature and stored in the refrigerator for 24 hours. The formed crystal was washed with methanol and filtered, then dried in an oven at 50°C.

Writhing Test Procedure

The experimental mice (*Mus musculus*) were classified into three groups consisting of the positive control group, negative control group and test group. Each group consisted of five mice. For the negative control group, each mouse was injected intraperitoneally with CMC-Na 0.5%. Sodium diclofenac was given in CMC-Na 0.5% with a given dose of 14 mg/kg BW and was used as a reference drug.¹⁵ For the test group, each mouse was injected intraperitoneally with the test compounds in CMC-Na 0.5% with three given doses of 14, 28, and 56 mg/kg BW. After 30 minutes, to all groups, each mouse was injected with a solution of acetic acid 0.6% with a dose of 10 mL/kg BW as a pain inducer. The writhing reaction was observed in each group within 30 minutes after pain induction. The percentage of pain inhibition was calculated using the following formula:

$$\% \text{ Pain Inhibition} = \frac{(W_c - W_t)}{W_c} \times 100$$

Where, *W_c* = number of writhes in the negative control group, *W_t* = number of writhes in the test group. The results of the writhing test of pinostrobin and its derivatives are shown below. The Levene statistic test was performed to examine the homogeneity between treatments (homogeneity of variance). One-way ANOVA analysis was used with a confidence level of 95% (α) = 0,05 to assess the significance of analgesic activity between the compounds. The half-maximal effective dose (ED₅₀) of each compound was calculated with probit analysis using the SPSS program.

RESULTS AND DISCUSSION

Docking

Four aliphatic acyl chlorides were selected for the esterification of pinostrobin, such as acetyl chloride, propionyl chloride, butyryl chloride, and pentanoyl chloride, to maintain the log P below five (obeying one of Lipinski's rules). Before the synthesis, we performed a docking study with the COX-2 receptor (PDB: 1PXX) using Molegro Virtual Docker v5.5 to predict the potencies of pinostrobin and its derivatives. The docking study of pinostrobin (**1**) shows two hydrogen bonds are formed between the oxygen in the carbonyl

group and *Tyr355*, and between the phenolic oxygen and *Ser353*. Besides, four steric interactions were also observed between pinostrobin and the receptor, involving three amino acids (*Leu352*, *Phe518*, *Val523*) around the substituted aromatic ring, while *Tyr355* interacts sterically with the phenolic oxygen (Fig.-2).

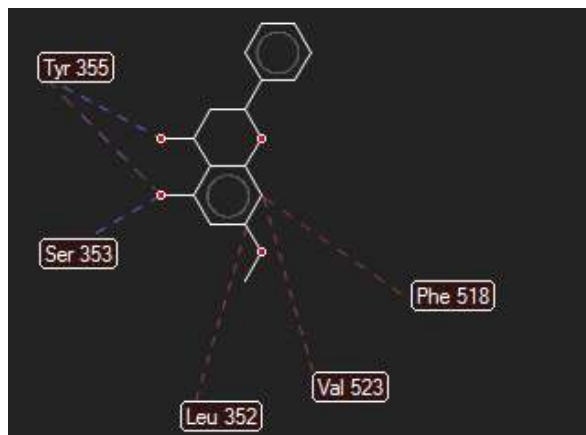


Fig.-2: The Interactions between Pinostrobin and the Receptor 1PXX as shown in the Docking Study

The hydrogen bonds and steric interactions are also found in the docking study of 5-*O*-acylpinostrobin derivatives. In pinostrobin acetate (**2**), the hydrogen bonds are present between etheric oxygen and *Tyr355*, and also between the oxygen carbonyl of the ester and *Arg120*. The steric interactions are also present involving *Ser353*, *Ala527*, *Leu352*, and *Met522*. Additionally, the docking between the other 5-*O*-acylpinostrobin derivatives, including pinostrobin propionate (**3**), pinostrobin butyrate (**4**), pinostrobin pentanoate (**5**) and the receptor shows similar hydrogen bonds and steric interaction patterns, involving *Tyr355*, *Arg120*, *Ala527*, *Leu352*, and *Met522* (figure 3). Furthermore, to predict the affinity between the compound and the receptor, we assess the value of the rerank score. Interestingly, the longer the alkyl chain of the ester, the lower the rerank score, resulting in pinostrobin pentanoate (**5**) having the optimum affinity with a rerank score of -107.59 kcal/mol compared to pinostrobin with a rerank score of -87.18 kcal/mol.

Synthesis of 5-*O*-acylpinostrobin Derivatives

With the docking information, we set out to synthesize 5-*O*-acylpinostrobin derivatives by Schotten-Baumann esterification. Pinostrobin was obtained by extraction of the dried rhizome of *Boesenbergia pandurata* (Roxb.) Schlechter, the best source for the isolation of pinostrobin.¹⁶ The Schotten-Baumann esterification reaction was performed on the phenolic group of pinostrobin, in which we reacted with the corresponding aliphatic acyl chlorides in tetrahydrofuran (THF) under basic conditions, to yield four 5-*O*-acylpinostrobin derivatives (**2-5**).

7-methoxy-4-oxo-2-phenylchroman-5-yl acetate (**2**)

This compound was synthesized according to *GP-A*, starting with acetyl chloride. The crude was purified and crystallized to afford the product as a white crystalline with 84% yield. M.p. 146-147°C. ¹H-NMR (400 MHz, CDCl₃): 7.41 (*m*, 5 H); 6.43 (*d*, *J* = 2.8, 1 H); 6.28 (*d*, *J* = 2.8, 1 H); 5.45 (*dd*, *J* = 13.6, 2.4, 1 H); 3.81 (*s*, 3 H); 3.02 (*dd*, *J* = 16.4, 13.6, 1 H); 2.74 (*dd*, *J* = 16.4, 2.4, 1 H); 2.38 (*s*, 3 H). ¹³C-NMR (400 MHz, CDCl₃): 188.93 (C); 169.69 (C); 165.59 (C); 164.34 (C); 151.94 (C); 138.48 (C); 128.98 (CH); 126.27 (4 CH); 108.03 (C); 104.88 (CH); 99.63 (CH); 79.67 (CH); 55.93 (CH₃); 45.15 (CH₂); 21.25 (CH₃). *m/z* for (C₁₈H₁₆O₅) 312.32, found 312.1.

7-methoxy-4-oxo-2-phenylchroman-5-yl propionate (**3**)

This compound was synthesized according to *GP-A*, starting with propanoyl chloride. The crude was purified and crystallized to afford the product as a white powder with a 74% yield. M.p. 121-122°C. ¹H-NMR (400 MHz, CDCl₃): 7.42 (*m*, 5 H); 6.43 (*d*, *J* = 2.8, 1 H); 6.28 (*d*, *J* = 2.8, 1 H); 5.45 (*dd*, *J* = 14.0,

2.8, 1 H); 3.81 (s, 3 H); 3.01 (dd, $J = 14.0, 16.5, 1$ H); 2.66-2.74 (m, 3 H); 1.29 (t, 3 H). ^{13}C -NMR (400 MHz, CDCl_3): 188.96 (C); 173.04 (C); 165.57 (C); 164.33 (C); 152.12 (C); 138.52 (C); 128.98 (CH); 126.25 (4 CH); 108.14 (C); 104.86 (CH); 99.58 (CH); 79.67 (CH); 55.92 (CH_3); 45.20 (CH_2); 27.74 (CH_2); 8.82 (CH_3). m/z for ($\text{C}_{19}\text{H}_{18}\text{O}_5$) 326.12, found 326.1.

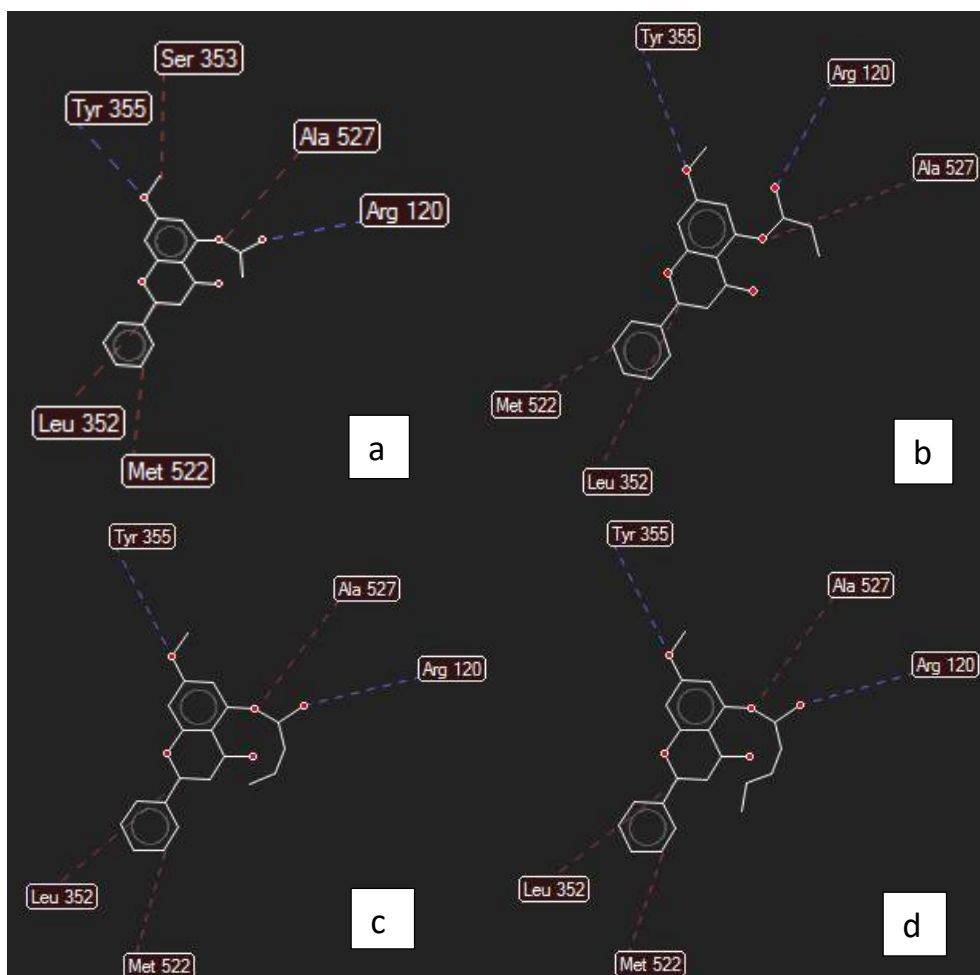


Fig.-3: The Docking Results of 5-*O*-acylpinostrobin Derivatives against COX-2 (PDB: 1PXX). (a) Pinostrobin acetate (2), (b) Pinostrobin propionate (3), (c) Pinostrobin butyrate (4), (d) Pinostrobin pentanoate (5)

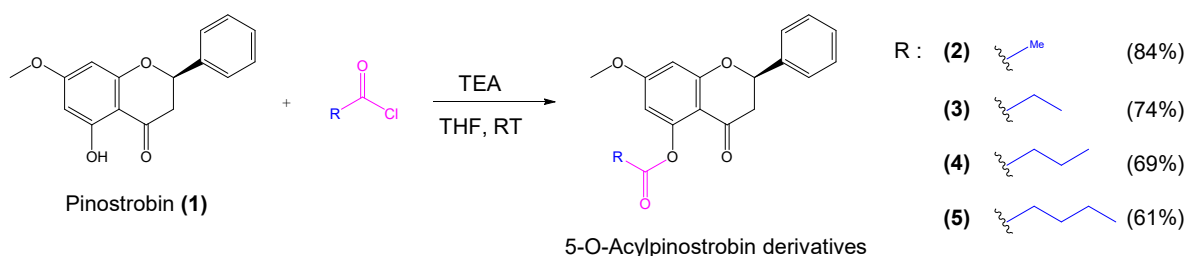


Fig.-4: Schematic Synthesis of 5-*O*-acylpinostrobin Derivatives using Schotten-Baumann Reaction

7-methoxy-4-oxo-2-phenylchroman-5-yl butyrate (4)

This compound was synthesized according to *GP-A*, starting with butyryl chloride. The crude was purified and crystallized to afford the product as a white crystalline with a 69% yield. M.p. 122-123°C. ^1H -NMR

(400 MHz, CDCl₃): 7.43 (*m*, 5 H); 6.42 (*d*, *J* = 2.4, 1 H); 6.28 (*d*, *J* = 2.4, 1 H); 5.45 (*dd*, *J* = 14.0, 3.2, 1 H); 3.81 (*s*, 3 H); 3.01 (*dd*, *J* = 16.8, 14.0, 1 H); 2.66-2.74 (*m*, 3 H); 1.81 (*m*, 2 H); 1.06 (*t*, 3 H). ¹³C-NMR (400 MHz, CDCl₃): 188.92 (C); 172.18 (C); 165.54 (C); 164.32 (C); 152.08 (C); 138.53 (C); 128.98 (CH); 126.26 (4 CH); 108.21 (C); 104.91 (CH); 99.57 (CH); 79.65 (CH); 55.92 (CH₃); 45.19 (CH₂); 36.19 (CH₂); 18.08 (CH₂); 13.87 (CH₃). *m/z* for (C₂₀H₂₀O₅) 340.13, found 340.1.

7-methoxy-4-oxo-2-phenylchroman-5-yl pentanoate (5)

This compound was synthesized according to *GP-A*, starting with pentanoyl chloride. The crude was purified and crystallized to afford the product as a white crystalline with a 61% yield. M.p. 73-74°C. ¹H-NMR (400 MHz, CDCl₃): 7.42 (*m*, 5 H); 6.43 (*d*, *J* = 2.8, 1 H); 6.27 (*d*, *J* = 2.8, 1 H); 5.45 (*dd*, *J* = 13.6, 3.2, 1 H); 3.81 (*s*, 3 H); 3.01 (*dd*, *J* = 16.8, 13.6, 1 H); 2.66-2.74 (*m*, 3 H); 1.78 (*m*, 2 H); 1.47 (*m*, 2 H); 0.97 (*t*, 3 H). ¹³C-NMR (400 MHz, CDCl₃): 188.93 (C); 172.34 (C); 165.55 (C); 164.31 (C); 152.10 (C); 138.53 (C); 128.98 (CH); 126.25 (4 CH); 108.21 (C); 104.89 (CH); 99.56 (CH); 79.65 (CH); 55.91 (CH₃); 45.20 (CH₂); 34.07 (CH₂); 26.60 (CH₂); 22.44 (CH₂); 13.93 (CH₃). *m/z* for (C₂₁H₂₂O₅) 354.15, found 354.1.

Full conversions were not achieved in the formation of 5-*O*-acylpinostrobin derivatives, despite the straightforward reaction. This can be attributed to the presence of an intramolecular hydrogen bond within pinostrobin. The position of phenolic hydrogen in the vicinity of the carbonyl oxygen might result in the formation of the hydrogen bond, thus compromising the reactivity of the hydroxy phenolic group as the nucleophile (Fig.-5).

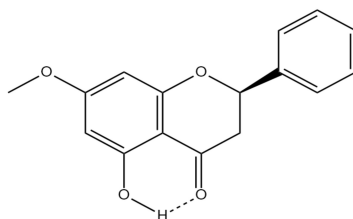


Fig.-5: Intramolecular Hydrogen Bond of Pinostrobin

Nevertheless, moderate to good yields of the compounds (**1-5**) were obtained (61-84%) after facile purification through the crystallization method. The purity of the compounds was confirmed through several methods, involving thin layer chromatography, NMR, FTIR, and mass spectroscopy, as it is critical to acquire a highly pure substance before testing it for its biological activity.¹⁷

Analgesic Evaluation

The analgesic property of pinostrobin and its derivatives was evaluated using the acetic acid-induced abdominal writhing test. This method has been widely used as a screening tool to evaluate the analgesic or anti-inflammatory properties of substances, where the pain is induced by injecting acetic acid as an irritant into the peritoneal cavity of mice (*Mus musculus*). The test animals then react by writhing, a characteristic stretching behaviour which is considered as a positive response.¹⁸⁻²⁰

Pinostrobin and its derivatives were tested in comparison with CMC-Na 0.5% as the negative control and the currently marketed analgesic drug sodium diclofenac as the positive control in a single dose. Pinostrobin and its derivatives were given in three doses (14, 28, and 56 mg/kg BW). In this method, we observed the percentage of pain inhibition of every compound which can be obtained by the following formula:

$$\% \text{ Pain Inhibition} = \frac{(W_c - W_t)}{W_c} \times 100$$

Where, *W_c* = number of writhes in the negative control group, *W_t* = number of writhes in the test group. The results of the writhing test of pinostrobin and its derivatives are shown below (Fig.-6).

The statistical analysis through the calculation of the least significant difference (LSD) shows that there is no significant difference between the analgesic activity of sodium diclofenac and **1**, **2**, **3**, and **4** compounds at dose 14 mg/kg BW. However, a significant difference is observed between sodium diclofenac and

compound **5** at the same dose. Besides, the analgesic activity between pinostrobin and its derivatives is statistically significant at the three given doses.

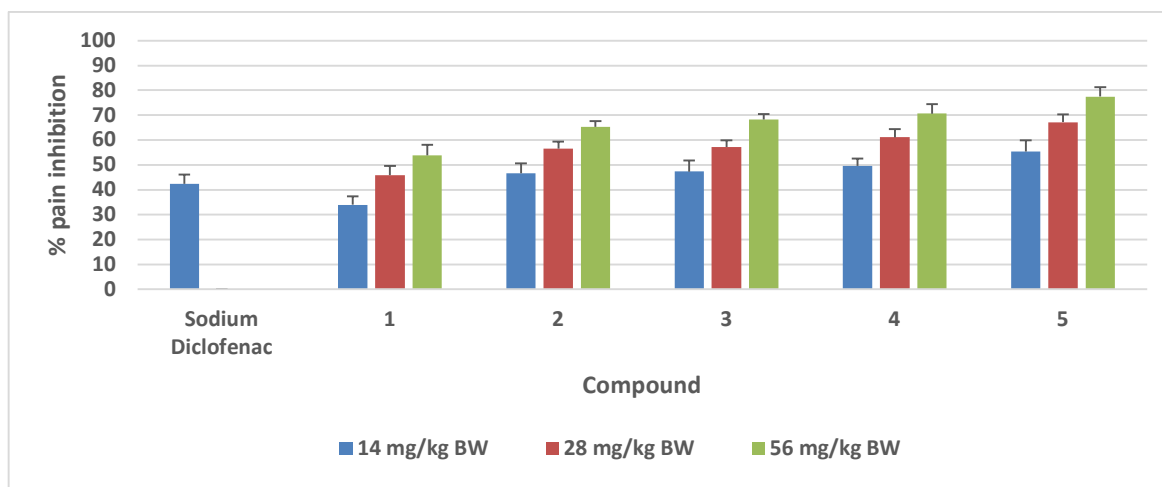


Fig.-6: The Percentage of Pain Inhibition of Pinostrobin and its Four Derivatives in Three given Doses, the Compounds were compared to Sodium Diclofenac as a Positive Control in a Single Lowest Dose

The half-maximal effective dose (ED_{50}) of each compound was determined statistically using SPSS software. ED_{50} is defined as a dose of a substance that produces a specific effect in 50% of the population under stated conditions.²¹ The ED_{50} and $\log 1/ED_{50}$ values of pinostrobin and its derivatives are shown in Table-1 below.

Table-1: Determined ED_{50} and $\log 1/ED_{50}$ Values of Pinostrobin and its Derivatives

Compound	ED_{50} (mg/kg BW)	$\log (1/ED_{50})$ (mg/kg BW)
Pinostrobin (1)	41.10	-1.61
Pinostrobin acetate (2)	17.80	-1.25
Pinostrobin propionate (3)	16.92	-1.23
Pinostrobin butyrate (4)	14.17	-1.15
Pinostrobin pentanoate (5)	10.37	-1.02

Compound **5** displays the best analgesic property with an ED_{50} value of 10.37 mg/kg BW, while pinostrobin shows a poor activity of pain inhibition with an ED_{50} value of 41.10 mg/kg BW. More importantly, the analgesic potency of 5-*O*-acylpinostrobin derivatives increases with the increasing alkyl chain length. Furthermore, we determined the quantitative structure-activity relationship (QSAR) of pinostrobin and its derivatives through the physicochemical properties, *in silico* test (rerank score), and *in vivo* test ($\log 1/ED_{50}$) are shown in Table-2 below.

Table-2: Physicochemical Properties of Pinostrobin and its Derivatives, *in silico* and *in vivo* Analgesic Activity Tests as Parameters in QSAR Determination

Compound	Log P	Log P ²	E_{total} (kcal/mol)	MR (m ³ /mol)	Rerank Score (kcal/mol)	$\log(1/ED_{50})$ (mg/kg BW)
Pinostrobin (1)	2.28	5.20	46.2108	75.29	-87.18	-1.61
Pinostrobin acetate (2)	2.26	5.11	56.8544	84.68	-90.27	-1.25
Pinostrobin propionate (3)	2.91	8.47	56.5023	89.42	-98.61	-1.23
Pinostrobin butyrate (4)	3.33	11.09	56.3453	94.02	-102.70	-1.15
Pinostrobin pentanoate (5)	3.75	14.06	56.2704	98.62	-107.59	-1.02

QSAR analysis of 5-*O*-acylpinostrobin derivatives was performed using linear and nonlinear regression analysis by SPSS software. Five QSAR equations are shown in table 3 below.

Table-3: Five QSAR Equations of 5-*O*-acylpinostrobin Derivatives involving Physicochemical Properties, *in silico* and *in vivo* Analgesic Activity Tests as Parameters

No	QSAR Equation	n	r	SE	F	Sig.
1	$\text{Log}(1/\text{ED}_{50}) = 0.272 \text{ Log P} - 2.041$	5	-0.806	0.150	5.580	0.099
2	$\text{Log}(1/\text{ED}_{50}) = 0.001 \text{ Log P}^2 + 0.268 \text{ Log P} - 2.036$	5	0.806	0.081	1.860	0.350
3	$\text{Log}(1/\text{ED}_{50}) = 0.043 E_{\text{total}} - 3.573$	5	0.894	0.114	11.944	0.041
4	$\text{Log}(1/\text{ED}_{50}) = 0.024 \text{ MR} - 3.348$	5	0.970	0.062	47.544	0.006
5	$\text{Log}(1/\text{ED}_{50}) = -0.023 \text{ RS} - 3.468$	5	0.881	0.120	10.443	0.048

In equations 1 and 2, no linear and nonlinear correlation was observed between lipophilicity (log P) of the compounds and their analgesic activity, while in equations 3, 4, and 5 there is a linear and nonlinear correlation. Equation 3 is a relationship between the electronic parameter (E_{total}) and analgesic activity of pinostrobin and its four derivatives, the higher the E_{total} of the compound, the more potent the analgesic activity. Equation 4 suggests the linear correlation between the steric property (MR) and analgesic activity of the tested compounds, the higher the value of MR, the more potent the analgesic activity. Equation 5 shows there is a linear correlation between the ligand-receptor affinity (rerank score) and the *in vivo* analgesic activity, the lower the rerank score, the lower the energy needed to stabilize the bond between the ligand and the receptor, thus the more potent the analgesic activity.

In this study, a QSAR equation involving the steric parameter is proposed as follows:

$$\text{Log}(1/\text{ED}_{50}) = 0.024 \text{ MR} - 3.348$$

(n = 5; r = 0.970; F = 47.544; sig. = 0.006; SE = 0.062)

The equation can be a reference in the prediction of the analgesic activity of 5-*O*-acylpinostrobin derivatives with different side chain by incorporating the steric parameter (MR) into the equation.

CONCLUSION

We report on a successful molecular modification of pinostrobin which resulted in an improvement of analgesic activity. Four derivatives of 5-*O*-acylpinostrobin were synthesized using a straightforward Schotten-Baumann reaction, with moderate to good yields (61-84%). The acetic acid-induced writhing test resulted in compound **5** as the most potent analgesic ($\text{ED}_{50} = 10.37 \text{ mg/kg BW}$), showing a prospect for a new drug candidate. This outcome is consistent with the *in silico* studies before the synthesis that can be utilized to predict the biological activity,²²⁻²³ in which it suggests the increasing analgesic activity as the side alkyl chain extended. Besides, a QSAR equation is proposed involving a steric parameter (MR), which constitutes a predictive tool for future optimization.

ACKNOWLEDGEMENT

This research was supported by Faculty Research Grand supported by the Faculty of Pharmacy Universitas Airlangga, Surabaya.

REFERENCES

1. (IASP) (International Association for the Study of Pain) & (EFIC) (European Federation of IASP Chapters), Unrelieved Pain is a Major Global Healthcare Problem, *Amazon*, **S3**, 1(2004),
2. B. J. Sessle, *Pain Research and Management*, **16(6)**, 416(2011), DOI:10.1155/2011/513423
3. L. R. Watkins, E. D. Milligan, and S. F. Maier, *Advances in Experimental Medicine and Biology*, **521**, 1(2003).
4. P. O. Osadebe and F. B. C. Okoye, *Journal of Ethnopharmacology*, **89(1)**,19(2003), DOI: 10.1016/S0378-8741(03)00195-8
5. C. Sostres, C. J. Gargallo, M. T. Arroyo, and A. Lanás, *Clinical Gastroenterology* **24(2)**, 121(2010).


6. J. L. Wallace, *Physiological Reviews*, **88(4)**, 1547(2008), DOI:10.1152/physrev.00004.2008
7. C. Bombardier *et al.*, *The New England Journal of Medicine*, **343**, 1520(2000), DOI: 10.1056/nejm200011233432103
8. T. J. Schnitzer *et al.*, *The Lancet*, **364**, 665(2004), DOI:10.1016/S0140-6736(04)16893-1
9. M. J. Hochmair *et al.*, *Future Oncology*, **14**, 2861(2018), DOI:10.2217/fon-2019-0346
10. Purwantiningsih, N. Jannah, and D. U. C. Rahayu, *Rasayan Journal of Chemistry*, **13(1)**, 322(2020), DOI:10.31788/RJC.2020.1315484
11. A. Chahyadi, R. Hartati, K. R. Wirasutisna, and Elfahmi, *Procedia Chemistry*, **13**, 13(2014), DOI: 10.1016/j.proche.2014.12.003
12. N. K. Patel, G. Jaiswal, and K. K. Bhutani, *Natural Product Research*, **30(18)**, 2017(2016), DOI: 10.1080/14786419.2015.1107556
13. I. Gómez-Betancur, D. Benjumea, A. Patiño, N. Jiménez, and E. Osorio, *Journal of Ethnopharmacology*, **155(3)**, 1609(2014), DOI:10.1016/j.jep.2014.08.002
14. D. Wu, M. G. Nair, and D. L. DeWitt, *Journal of Agricultural and Food Chemistry*, **50(4)**, 701(2002). DOI:10.1021/jf010963x
15. N. A. Peerzade, S. Y. Jadhav, and R. B. Bhosale, *Rasayan Journal of Chemistry*, **13(3)**, 1401(2020), DOI:10.31788/RJC.2020.1335637
16. C. Zhao *et al.*, *Separation and Purification Technology*, **133**, 168(2014), DOI: 10.1016/j.seppur.2014.06.056
17. G. F. Pauli *et al.*, *Journal of Medicinal Chemistry*, **57(22)**, 9220(2014), DOI:10.1021/jm500734a
18. S. Singh, and D. K. Majumdar, *Pharmaceutical Biology*, **33**, 188(1995), DOI: 10.3109/13880209509065361
19. A. Burke, E. Smyth, and G. A. Fitzgerald, Analgesic - Antipyretic Agents, Pharmacotherapy of Goat. in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th edition. McGraw-Hill, New York, 2006.
20. D. Mishra, G. Ghosh, P. Sudhir Kumar, and P. K. Panda, *Asian Journal of Pharmaceutical and Clinical Research*, **4**, 78(2011).
21. K. K. Rozman, J. Doull, and W. J. Hayes, Dose and Time Determining, and Other Factors Influencing, Toxicity, in *Hayes' Handbook of Pesticide Toxicology 3rd edition*, pp. 3(2010), DOI:10.1016/B978-0-12-374367-1.00001-X
22. D. Kesuma, A. L. Nasyanka, M. Rudyanto, and B. T. Purwanto, *Rasayan Journal of Chemistry*, **13(3)**, 1914(2020), DOI:10.31788/RJC.2020.1335694
23. S. Hardjono, T. Widiandani, B.T. Purwanto, A. L. Nasyanka, *Research Journal of Pharmacy and Technology*, **12(5)**, 2160(2019), DOI: 10.5958/0974-360X.2019.00359.7


[RJC-5749/2020]

Rasayan Journal of Chemistry

COUNTRY

India

 Universities and research institutions in India

 Media Ranking in India

SUBJECT AREA AND CATEGORY

Biochemistry, Genetics and Molecular Biology
└ Biochemistry

Chemical Engineering
└ Chemical Engineering (miscellaneous)

Chemistry
└ Chemistry (miscellaneous)

Energy
└ Energy (miscellaneous)

Pharmacology, Toxicology and Pharmaceutics
└ Pharmacology, Toxicology and Pharmaceutics (miscellaneous)

PUBLISHER

Rasayan Journal

H-INDEX

24

PUBLICATION TYPE

Journals

ISSN

09741496, 09760083

COVERAGE

2008-2021

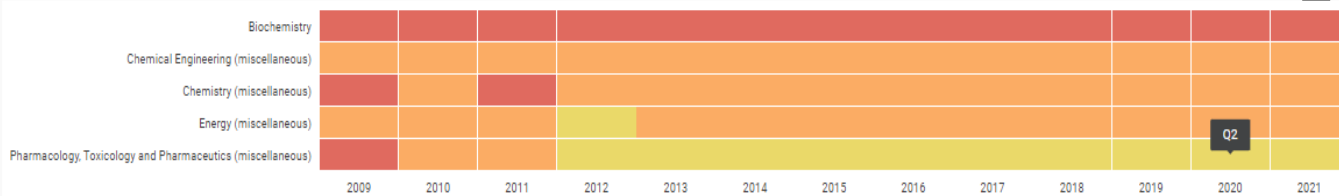
INFORMATION

[Homepage](#)

[How to publish in this journal](#)

editor@rasayanjournal.co.in

Quartiles



SJR

2012	0.210
2013	0.207
2014	0.220
2015	0.236
2016	0.250
2017	0.218
2018	0.252
2019	0.265
2020	0.281
2021	0.333

Total Documents





Source details

Rasayan Journal of Chemistry

Scopus coverage years: from 2008 to 2022

Publisher: Rasayan Journal

ISSN: 0974-1496 E-ISSN: 0976-0083

Subject area: [Pharmacology, Toxicology and Pharmaceutics: General Pharmacology, Toxicology and Pharmaceutics](#)

[Energy: General Energy](#)

[Chemistry: General Chemistry](#)

[Chemical Engineering: General Chemical Engineering](#)

[Biochemistry, Genetics and Molecular Biology: Biochemistry](#)

Source type: Journal

CiteScore 2021

2.0



SJR 2021

0.333



SNIP 2021

0.813



[View all documents >](#)

[Set document alert](#)

[Save to source list](#)

[CiteScore](#) [CiteScore rank & trend](#) [Scopus content coverage](#)

i Improved CiteScore methodology



CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. [Learn more >](#)

CiteScore 2021 ▼

$$2.0 = \frac{2,423 \text{ Citations 2018 - 2021}}{1,207 \text{ Documents 2018 - 2021}}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022 ⓘ

$$2.0 = \frac{2,828 \text{ Citations to date}}{1,405 \text{ Documents to date}}$$

Last updated on 05 March, 2023 • Updated monthly

CiteScore rank 2021 ⓘ

Category	Rank	Percentile
Pharmacology, Toxicology and Pharmaceutics	#36/74	52nd
General Pharmacology, Toxicology and Pharmaceutics		
Energy	#38/68	44th
General Energy		

[View CiteScore methodology >](#) [CiteScore FAQ >](#) [Add CiteScore to your site](#)