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(71) Applicant(s):
AL-SEHEMI, Abdullah G. [SA/SA]; Departement of Chemistry King Khalid University Abha 61413 (SA) *(for all designated states)*
CHINNAM, Sampath [IN/IN]; Department of Chemistry M.S. Ramaiah Institute of Technology (Affiliated to Visvesvaraya Technological University, Belgaum) Bengaluru 560 054, Karnataka (IN) *(for all designated states)*
PANNIPARA, Mehboobali [IN/SA]; Departement of Chemistry King Khalid University Abha 61413 (SA) *(for all designated states)*
YALLUR, Basappa C. [IN/IN]; Department of Chemistry M.S. Ramaiah Institute of Technology (Affiliated to Visvesvaraya Technological University, Belgaum) Bengaluru 560 054, Karnataka (IN) *(for all designated states)*
CHIGURUPATI, Sridevi [IN/SA]; Department of Medicinal Chemistry and Pharmacognosy College of Pharmacy Qassim University Buraydah 52571 (SA) *(for all designated states)*
GOWDA B.H., Jaswanth [IN/IN]; S/O Honnegowda B.H., Shrungarasagara Halevoor road, Huliyurdurga, Kunigal, Taluk Tumkur District 572 123, karnataka (IN) *(for all designated states)*
PAUL, Karthika [IN/IN]; Department of Pharmaceutical Analysis JSS College of Pharmacy JSS Academy of Higher Education and Research Sri Shivarathreeshwara Nagara Mysuru 570 015, Karnataka (IN) *(for all designated states)*
SHIVANNA, Chandan Ravandur [IN/IN]; Department of Pharmaceutical Analysis JSS College of Pharmacy JSS Academy of Higher Education and Research Sri Shivarathreeshwara Nagara Mysuru 570 015, Karnataka (IN) *(for all designated states)*
VARDHARAJULA, Venkata Ramaiah [IN/SA]; Department of Dental Hygiene College of Applied Health Sciences in Alrass Qassim University Al-Qassim region 51921 (SA) *(for all designated states)*

(72) Inventor(s):
AL-SEHEMI, Abdullah G.; Departement of Chemistry King Khalid University Abha 61413 (SA)
CHINNAM, Sampath; Department of Chemistry M.S. Ramaiah Institute of Technology (Affiliated to Visvesvaraya Technological University, Belgaum) Bengaluru 560 054, Karnataka (IN)
PANNIPARA, Mehboobali; Departement of Chemistry King Khalid University Abha 61413 (SA)
YALLUR, Basappa C.; Department of Chemistry M.S. Ramaiah Institute of Technology (Affiliated to Visvesvaraya Technological University, Belgaum) Bengaluru 560 054, Karnataka (IN)
CHIGURUPATI, Sridevi; Department of Medicinal Chemistry and Pharmacognosy College of Pharmacy Qassim University Buraydah 52571 (SA)
GOWDA B.H., Jaswanth; S/O Honnegowda B.H., Shrungarasagara Halevoor road, Huliyurdurga, Kunigal, Taluk Tumkur District 572 123, karnataka (IN)
PAUL, Karthika; Department of Pharmaceutical Analysis JSS College of Pharmacy JSS Academy of Higher Education and Research Sri Shivarathreeshwara Nagara Mysuru 570 015, Karnataka (IN)
SHIVANNA, Chandan Ravandur; Department of Pharmaceutical Analysis JSS College of Pharmacy JSS Academy of Higher Education and Research Sri Shivarathreeshwara Nagara Mysuru 570 015, Karnataka (IN)
VARDHARAJULA, Venkata Ramaiah; Department of Dental Hygiene College of Applied Health Sciences in Alrass Qassim University Al-Qassim region 51921 (SA)

(74) Agent(s):

KHURANA & KHURANA, ADVOCATES & IP ATTORNEYS; E-13, UPSIDC, Site-IV, Behind-Grand Venice Kasna Road, Greater Noida, National Capital Region Uttar Pradesh 201310 (IN)

(54) Title (EN): SYNTHESIS AND IN SILICO STUDIES OF NOVEL ANTI-SARS-COV SULFONAMIDES AS POTENTIAL INHIBITORS AGAINST COVID-19 PROTEIN TARGET: SARS-COV-2 MAIN PROTEASE (M PRO)

(54) Title (FR): SYNTHÈSE ET ÉTUDES IN SILICO DE NOUVEAUX SULFONAMIDES ANTI-SARS-COV EN TANT QU'INHIBITEURS POTENTIELS CONTRE UNE PROTÉINE CIBLE DE LA COVID-19 : LA PRINCIPALE PROTÉASE DU SARS-COV -2 (MPRO)

(57) Abstract:

(EN): A cluster of pneumonia cases and COVID-19 pandemic that started in Wuhan, China, was caused by novel beta coronavirus, the 2019 novel coronavirus (2019-nCoV). This has led to many number of deaths and many were infected worldwide owing to the absence of effective therapies against coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2). Viral maturation requires the activity of the main viral protease (Mpro) and thereby, inhibition stops the advancement of the disease. The current invention delivers a potential anti-viral drug candidates docked against COVID-19 protein targets: SARS-CoV-2 main protease, drug-likeness, efficacy, molecular docking, physicochemical and pharmacokinetic studies of novel synthesized sulfonamide analogues. Physicochemical and pharmacokinetic properties have been evaluated on the basis of certain parameters like Lipinski rule of 5 (RO5 rule) and ADMET (absorption, distribution, metabolism, excretion and toxicity). All the synthesized compounds follow Lipinski rule of five (RO5 rule) and the compounds followed the range of rotational bonds, hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), topological surface area (TPSA), number of violations, etc. All these compounds shown good pharmacokinetic properties, zero renal OCT2 substrate toxicity and negligible toxicity values. BOILED-egg model was carried out for evaluating the gastrointestinal absorption and brain penetration effect. Compounds 3b and 3d comes under white region of egg and exhibited good gastrointestinal absorption, whereas, 3a, 3c, 3e and 3f compounds fall under yellow region (yolk) of egg which showed good brain penetration effect. All novel sulfonamide analogues including commercially available anti-COVID-19 drugs, Hydroxychloquine and Umifenovir docked with COVID-19 protein targets, i.e., PDB: 6VWW & 6Y2E.Compound 3c when docked with PDB: 6VWW shown maximum energy of -22.06 kcal/mol with two hydrogen binding interactions which are better than marketed drugs. Similarly, compound 3a exhibited highest energy of -14.00 kcal/mol.

(FR): Un groupe de cas de pneumonie et la pandémie de COVID-19 qui a commencé à Wuhan en Chine a ont été provoqués par un nouveau bêtacoronavirus, le nouveau coronavirus apparu en 2019 (2019-nCoV). Un grand nombreux de décès et d'infections sont survenus dans le monde entier en l'absence de traitements efficaces contre le coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2). La maturation virale nécessite l'activité de la principale protéase virale (Mpro) et, par conséquent, son inhibition interrompt la progression de la maladie. La présente invention concerne des médicaments antiviraux candidats potentiels dirigés contre des protéines cibles de la COVID -19 : la principale protéase du SARS-CoV-2, ainsi que la ressemblance médicamenteuse, l'efficacité, l'amarrage moléculaire, les études physico-chimiques et pharmacocinétiques de nouveaux analogues de sulfonamide synthétisés. Les propriétés physico-chimiques et pharmacocinétiques ont été évaluées sur la base de certains paramètres de type règle des 5 de Lipinski (règle RO5) et ADMET (absorption, distribution, métabolisme, excrétion et toxicité). Tous les composés synthétisés suivent la règle des cinq de Lipinski (RO5) et les composés sont conformes en termes de liaisons de rotation, d'accepteurs de liaison hydrogène (HBA), de donneurs de liaison hydrogène (HBD), de surface topologique (TPSA), du nombre de violations, etc. Tous ces composés ont montré de bonnes propriétés pharmacocinétiques, une toxicité de substrat OCT2 rénale nulle et des valeurs de toxicité négligeables. Un modèle BOILED-egg a été réalisé pour évaluer l'absorption gastro-intestinale et l'effet de pénétration dans le cerveau. Les composés 3b et 3d se trouvent dans la région du blanc de l'œuf et présentent une bonne absorption gastro-intestinale, tandis que les composés 3a, 3c, 3e et 3f se trouvent dans la région du jaune (vitellus) de l'œuf qui a montré un bon effet de pénétration dans le cerveau. Tous les nouveaux analogues de sulfonamide, notamment les médicaments anti-COVID-19 disponibles dans le commerce, l'hydroxychloquine et l'umifénovir ont été arrimés à des protéines cibles de la COVID-19, à savoir PDB : 6 VWW : 6 Y2E. Le composé 3c lorsqu'il est arrimé à PDB : 6 VWW a montré une énergie maximale de -22,06 kcal/mol avec deux interactions de liaison à l'hydrogène qui sont meilleures que les médicaments commercialisés. De même, le composé 3a présente l'énergie la plus élevée de -14,00 kcal/mol.

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