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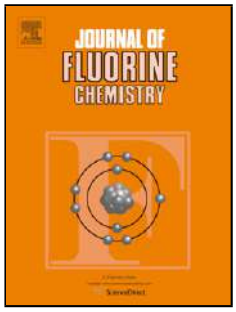

Synthesis, characterization, *in vitro* DNA photocleavage and cytotoxicity studies of 4-arylazo-1-phenyl-3-(2-thienyl)-5-hydroxy-5-trifluoromethylpyrazolines and regioisomeric 4-arylazo-1-phenyl-5(3)-(2-thienyl)-3(5)-trifluoromethylpyrazoles

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Synthesis, Characterization, *in vitro* DNA Photocleavage and Cytotoxicity studies of 4-Arylazo-1-phenyl-3-(2-thienyl)-5-hydroxy-5-trifluoromethylpyrazolines and Regioisomeric 4-Arylazo-1-phenyl-5(3)-(2-thienyl)-3(5)-trifluoromethylpyrazoles

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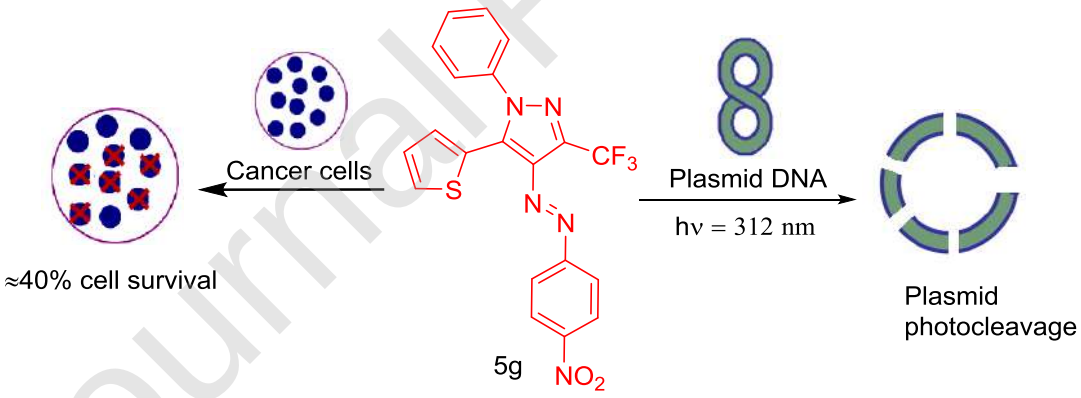
Graphical Abstract:-



Highlights

- Synthesis of 4-arylazo-1-phenyl-3-(2-thienyl)-5-hydroxy-5-trifluoromethylpyrazolines and regioisomeric 4-arylazo-1-phenyl-5(3)-(2-thienyl)-3(5)-trifluoromethylpyrazoles was accomplished.
- All the synthesized compounds were screened for their DNA photocleavage on suercoiled pBr322 plasmoid.

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ORIGINAL PAPER

Chitosan embedded with Ag/Au nanoparticles: investigation of their structural, optical and sensing properties

Meena[1,2] · Annu Sharma[1] · Rajiv Kumar[3,4] · Sita Ram[5] · Pawan K. Sharma[3]

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Abstract

Quantitative detection of hydrogen peroxide (H_2O_2) is reported by utilizing an optical sensor based on the Surface Plasmon Resonances (SPR) of Ag and Au nanoparticles embedded in chitosan, a biopolymer. Ag and Au nanoparticles, fabricated by chemical reduction approach, were incorporated individually in chitosan matrix by solution casting method. Subsequently, their presence in the host matrix was confirmed using UV-visible spectroscopy, X-Ray diffractometer (XRD), High Resolution Transmission Electron Microscopy (HRTEM) and Field Emission Scanning Electron Microscopy (FESEM) along with Energy Dispersive Analysis of X-Ray (EDAX) spectroscopy. Structural changes induced in chitosan with addition of varying concentration of Ag or Au nanoparticles were studied using Fourier transform infrared (FTIR) spectroscopy. Optical energy gap of chitosan decreased from 3.82 ± 0.28 eV to 1.84 ± 0.19 eV for Ag-chitosan nanocomposite (Nc) film containing 0.50 wt% Ag nanoparticle while to a value of 2.14 ± 0.08 eV for Au-chitosan Nc film containing 0.5 wt% of Au nanoparticle. A significant difference in position and intensity of SPR absorption band was observed as a function of variable concentration of H_2O_2. The detection limit of these optical sensors is upto 0.3 μM concentration of H_2O_2.

Keywords Nanocomposite · Chitosan · Plasmon · Absorption · Sensor

Introduction

Chitosan is a linear cationic polysaccharide derived from the deacetylation of chitin, the second most abundant polysaccharide after cellulose [1]. Though like other biopolymers chitin is biodegradable, biocompatible and non-toxic but its applications and processing are limited due to its insolubility in conventional solvents. Owing to this fact chitosan is derived by chemical/enzymatic deacetylation of chitin thus maintaining green properties of chitin [2].

Chitosan can be claimed as one of the best contenders for fabricating thin films owing to its excellent film-forming property. It contains free amino and hydroxyl groups which can be functionalized through binding with the cationic and anionic

Highlights
- Stable Ag-chitosan and Au-chitosan Nc films were fabricated.
- Optical energy gap reduces to 1.84 ± 0.19 eV and 2.14 ± 0.08 eV for Ag-chitosan Nc film and Au-chitosan Nc film respectively as compared to 3.82 ± 0.28 eV for chitosan.
- FTIR analysis confirms the strong interaction of Ag and Au nanoparticles with chitosan.
- The detection limit of these optical sensors is upto 0.3 μM concentration of H_2O_2.

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forms of noble metals and can stabilize their nanoparticles [3]. Due to these unique physico-chemical properties chitosan is finding increasing applications in the fields of biotechnology, nanotechnology, food technology, agriculture, medicine, water purification and textiles [4].

Among different nanofillers metal nanoparticles are one of the most popular nanofillers as they exhibit size and shape dependent properties, resulting in their applications in optoelectronics, catalysis, coatings and sensors [5–7]. Nanoparticles of noble metals silver (Ag) and gold (Au) display peculiar characteristics like; surface plasmon resonance (SPR) in visible region, surface enhanced Raman scattering (SERS), outstanding plasmonic activity, catalytic activity etc. [8–10]. Such features of interest of Ag and Au nanoparticles make them potential candidates for diverse technological applications such as sensors [11], optics [12], filter technology [13], photovoltaic applications [14], etc. Therefore, incorporation of Ag or Au nanoparticles in chitosan matrix is a unique way to combine the properties of both noble metal nanoparticles as well as chitosan highlighting the need for comprehensive studies on synthesis and characterization of Ag-chitosan and Au-chitosan Ncs. There are several reports pertaining to antibacterial, antifungal as well as photoresponsive properties of Ag/Au-chitosan Ncs [15–18]. However, there is still a need for in-depth investigation of optical and sensing properties of Ag-chitosan and Au-chitosan Nc films in order to explore the full potential of applications of Ag-chitosan and Au-chitosan Nc films.

Sensors play an imperative role in analyzing the environment, providing information on industrial production processes, quality management of food products and numerous other applications. They provide valuable information by interacting with various chemical components. Hydrogen peroxide (H_2O_2) is one of the analytes that is routinely being used by the medical community. H_2O_2 is being used in several fields such as water treatment plants, fumigation as well as bleaching and cleaning microcircuits [19] however, it is hazardous to environment and living organisms. Even a little concentration of H_2O_2 can harm the cellular system. Hence, detection of H_2O_2 quantity in environment, food, pharmaceutical products and particularly in clinical laboratories is of utmost importance [20].

Thus, the development of new techniques for the quantitative detection of H_2O_2 is essential. Ning et al. [21] have utilized platinum, $ZnFe_2O_4$ functionalized reduced graphene oxide based electrode for determination of H_2O_2. They observed high sensitivity and selectivity of electrode towards H_2O_2. Zhang et al. [22] have employed Au/CeO_2–chitosan composite film as electrochemical biosensors for detection of H_2O_2. However, these techniques suffer from several drawbacks such as use of highly sophisticated instruments and low selectivity/poor reproducibility. Therefore, other alternative methods are required for the determination of H_2O_2. One of the ideal candidates for the determination of H_2O_2 is SPR based optical sensor due to its high sensitivity and cost effective detection. SPR sensing is based on the principle of measurable shifts in the SPR wavelength due to its strong dependence on refractive index of surrounding medium. Noghabi et al. [23] investigated the colorimetric sensing of green synthesized Ag nanoparticles towards H_2O_2. They observed a significant change in the intensity of SPR peak with increasing concentration of H_2O_2. Mohan et al. [24] have also employed starch stabilized Ag nanoparticles for detection of H_2O_2. However, fabrication of SPR based sensor for the detection of H_2O_2 by utilizing Ag-chitosan and Au-chitosan Nc films has seldom been reported.

The present research work reports the synthesis of Ag and Au nanoparticles via chemical reduction approach and fabrication of Ag-chitosan and Au-chitosan Nc films by solution casting technique. The structural and optical properties of synthesized Nc films have been investigated and their sensitivity towards H_2O_2 has been demonstrated.

Experimental section

Reagents and materials

Silver nitrate ($AgNO_3$) (Mol. wt. = 169.87 g mol^{-1}), glycerol (Mol. wt. = 92.10 g mol^{-1}) and tri-sodium citrate dihydrate (Mol. wt. = 294.10 g mol^{-1}) were procured from Rankem. Soluble starch (Mol. wt. = 342.30 g mol^{-1}), 36% H_2O_2 (Mol. wt. = 34.01 g mol^{-1}) and acetic acid (Mol. wt. = 60 g mol^{-1}) were bought from HIMEDIA. Choloauric acid ($HAuCl_4.xH_2O$) was purchased from Molychem. Chitosan (viscosity 47.78 cp) with degree of deacetylation 96.80% was procured from Central Institute of Fisheries (CIF) Kochi, India. Analytical grade chemicals were used as received and deionized water was used to prepare all solutions.

Methods

Preparation of Ag nanoparticles

For synthesizing Ag nanoparticles, 0.1 g of soluble starch was dissolved in 25 ml of distilled water at 85 °C. Subsequently, 10 ml of freshly prepared 0.04 M $AgNO_3$ was added to 25 ml of hot aqueous solution of soluble starch under vigorous stirring under dark. Then 15 ml of 0.12 M fructose solution was added to the reactive system, which was held at 85 °C under vigorous stirring for half an hour when colour of the mixture changed to light yellow indicating the formation of Ag nanoparticles. Colour of the mixture continued to darken and finally turned brown after 1 h [10, 25, 26].

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Research paper

Tail approach synthesis of novel benzenesulfonamides incorporating 1,3,4-oxadiazole hybrids as potent inhibitor of carbonic anhydrase I, II, IX, and XII isoenzymes

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In silico enhancement of azo dye adsorption affinity for cellulose fibre through mechanistic interpretation under guidance of QSPR models using Monte Carlo method with index of ideality correlation

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ABSTRACT

Azo dyes are a group of chemical moieties joined by azo (-N=N-) group with potential usefulness in different industrial applications. But these dyes are not devoid of hazardous consequence because of poor affinity for the fibre and discharge into the water stream. The chemical aspects of 72 azo dyes towards cellulose fibre in terms of their affinity by QSPR have been explored in the present work. We have employed two approaches, namely balance of correlation without *IIC* (TF_1) and balance of correlation with *IIC* (TF_2), to generate 16 QSAR models from 8 splits. The determination coefficient of calibration and validation set was found higher when the QSPR models were developed using the index of ideality correlation (*IIC*) parameter (TF_2). The model developed with TF_2 for split 3 was considered as a prominent model because the determination coefficient of the validation set was maximum ($r^2 = 0.9468$). The applicability domain (AD) was also analysed based on 'statistical defect', d (A) for a SMILES attribute. The mechanistic interpretation was done by identifying the SMILES attributes responsible for the promoter of endpoint increase and promoter of endpoint decrease. These SMILES attributes were applied to design 15 new dyes with higher affinity for cellulose fibre.

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KEYWORDS
QSPR; azo dyes affinity; IIC; applicability domain (AD); OECD

Introduction

The use of colouring is a very sophisticated method used to change the colour features of various substrates, including cloth, paper and leather. Substances with dyeing abilities were derived from natural substances, mostly from animals or plants, before even the mid-nineteenth century [1]. But by the advent of the twentieth century, natural dyes were rendered almost obsolete by synthetic dyes. Today, nearly all commercially produced dyes and pigments are synthetic compounds, with a few inorganic pigments [2,3]. Dyes are used in almost all types of products in the market such as textiles, paper, food, packaging, plastics, lasers, biometrics, solar capture, diagnostic tools, cosmetics and household goods [4–6].

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The whole textile industry is highly dependent on the dyes, and approximately 700,000 tons of more than 100,000 dyes are produced annually for commercial purpose [7,8]. These display an enormous range of dazzling shades and good wet fastness. However, dye loss, which is mainly caused by relatively poor dye fibre fixation and the presence of unreactive hydrolysed dye, is a matter of concern as it leads to the release of dyes into the environment. Pollution of the environment resulting from the release of industrial effluents has attracted the attention of the scientific community worldwide [9]. Effluents from industries such as textiles, leather, paper and plastic contain different types of artificial dyestuffs. The groundwater quality is adversely affected by the haphazard discharge of these dyes into sewage, ponds and rivers. It has been proposed that nearly 10–15% of the total dye production is discharged into the environment through wastewater, which poses serious hazards to the flora and fauna [8]. Literature survey reveals that a few dyes can be degraded by microorganisms under anaerobic condition [10]. So, in most of cases, these dyes lead to the production of carcinogenic compounds [10,11].

Azo dyes are chemicals identified by the existence of one or more azo units (-N=N-), generally, in numbers one or four, connected to phenyl and naphthyl radicals, which are typically substituted by certain pairings of functional groups namely: amino ($-NH_2$), chlorine (-Cl), hydroxyl (-OH), methyl ($-CH_3$), nitro ($-NO_2$), sulphonic acid and sodium salts ($-SO_3Na$) [12–16]. Azo dyes constitute the biggest group of colours, as around 70% of all organic dyes products are azo dyes [17]. These are extensively consumed by the dyeing industry and are present in almost all types of dyes, such as direct, reactive, and disperse dyes [18–20]. Notwithstanding the challenge in the processing of the residues produced and the detrimental implications for their use, azo dyes, particularly sulphuric ones, are extensively employed for dyeing fabrics. This is partly because of low costs and good affinity features [21]. Levels of dye fixation can be measured in terms of the dye–fibre attractive force commonly known as 'affinity', and the design of high-affinity dyes is the need of the hour [22].

The fibre of cellulose is an incredible natural resource that has extensive uses in numerous industrial products, and particularly in textiles. In this, two glucose moieties are interconnected through a glycosidic linkage and polymer components form a hydrogen bond set-up with hydroxyl groups and ethereal oxygen. Cellulose cannot fixate ionic dyes due to a lack of ionic sites in its structure [23]. Therefore dye molecules with some special structural characteristics are required for direct dying of the cotton. Several factors such as the formation of hydrogen bonds, electrostatic fields, hydrophobicity, etc., influence the affinity between cotton and dye molecule, and therefore diverse experimental records exist in the literature [6,23–30]. For that reason, various computational approaches such as quantitative structure–property/activity relationships (QSPR/QSAR) have been extensively used to study this affinity [23,25–31].

QSAR modelling is a statistical approach correlating the structural information of chemicals with endpoints/response values (activity/property/toxicity) using chemometric techniques [32,33]. CORAL (http://www.insilico.eu/coral/) software is commonly used for the building of QSAR models in accordance with OECD principles [34,35]. It uses the SMILES notations of the molecules in the input file and extracts the best model using Monte Carlo optimization [36–38]. Many endpoints, including pharmacological and toxicological, have been modelled by this prestigious tool [39–45].

interpretation was done by identifying the SMILES attributes responsible for the promoter of endpoint increase and promoter of endpoint decrease. These SMILES attributes were applied to design 15 new dyes with higher affinity for cellulose fibre. Hence, it can be summarized that the present QSPR method enhances the azo dye adsorption affinity for cellulose fibre through mechanistic interpretation under the guidance of the QSPR model using the Monte Carlo method with index of ideality correlation.

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Author contributions

Authors have done equivalent contributions to this work.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data availability

The processed data required to reproduce these findings are available to download from supporting information.

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In-silico identification of fingerprint of pyrazolyl sulfonamide responsible for inhibition of *N*-myristoyltransferase using Monte Carlo method with index of ideality of correlation

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ABSTRACT

Human African trypanosomiasis (HAT) or sleeping sickness like infections remain a serious health concern around the globe due to unavailability of safe and potential drugs for their treatment. Moreover, developing safe, potential and highly specific target based treatments is still a challenge for present drug discovery programs. A series of pyrazole based sulfonamides are identified as an inhibitor of *Trypanosoma brucei N*-myristoyltransferase (TbNMT). In the present manuscript, we have developed robust and reliable QSAR models by using the balance of correlation method in CORAL software. The chemical structures are represented by simplified molecular input line entry system (SMILES). The significance of the index of ideality correlation (IIC) with applicability domain (AD) is also studied at depth. The models developed by considering the index of ideality of correlation (IIC) were found to statistically more significant and robust. One QSAR model with best $R^2_{calibration} = 0.8638$ for split 2 was considered as the leading model. A greater value of cRp^2 *i.e.* 0.5 for all models in Y-randomization test showed the robustness of developed models. The outliers and promoters of increase and decrease of endpoint were also extracted independently from the leading models. The mechanistic interpretation of developed models explains the role of different structural attributes in predicting the pIC_{50} of pyrazole sulfonamides extracted from the crystal structure of Leishmania major N-myristoyltransferase (NMT) along with co-crystallized myristoyl-CoA and ligands NMT106, NMT157, NMT187 and NMT236 (PDB ID: 4A2Z, 4A30, 4A32, 2WSA).

Abbreviations: HAT: Human African trypanosomiasis; IIC: Index of Ideality of Correlation; TbNMT: *Trypanosoma brucei N*-myristoyltransferase; CW: Correlation weight; OECD: Organization of Economic Co-operation and Development; QSAR: Quantitative Structure Activity Relationship; CORAL: CORrelation And Logic; AD: Applicability Domain

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Introduction

Human African trypanosomiasis (HAT) or sleeping sickness is caused by the kinetoplastid parasite *Trypanosoma brucei* and it is transmitted by the bite of an infected tsetse fly (*Glossina* genus) (Nagle et al., 2014; Njoroge et al., 2014). Mainly two species *i.e. Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* of the above protozoan parasite is responsible for the HAT disease which leads to death if not treated properly or treatment is delayed (Klug et al., 2020; Lepovitz et al., 2020; Scarim et al., 2020). The clinical features are characterized by lymphadenopathy, fever and excessive sleepiness due to encephalopathy or encephalitis (Macleod et al., 2020; Singh et al., 2019; Watson et al., 2019). This disease is progressed by two distinct stages: the hemolymphatic stage and central nervous system (CNS) involvement or meningoencephalitic stage. The first stage is initially an acute stage, starts with the proliferation of parasite in the hemolymphatic system and give rise to non-specific symptoms (Bayliss et al., 2017; Harrison et al., 2018; Klug et al., 2020; Montalvo-Quiros et al., 2015; Patrick et al., 2017). However, the second stage onsets with the migration of parasite from the hemolymphatic system to CNS and cause classical symptoms of sleeping sickness, ultimately leading to coma and death. In the present scenario, the drugs available for HAT treatment are unsafe and frequently allied with severe or life-threatening side effects such as fatal encephalopathy, agranulocytosis, drug-resistance, and myocardial damage. Mainly five drugs (suramin, pentamidine, melarsoprol, eflornithine and nifurtimox) are used to treat various stages of HAT disease (Hagen et al., 2020). For 1st stage treatment, suramin and pentamidine are used, whereas melarsoprol and eflornithine are recommended for stage 2 infection. Recently, the nifurtimox-eflornithine combination therapy (NECT) has

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A Monte Carlo method based QSPR model for prediction of reaction rate constants of hydrated electrons with organic contaminants

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A Monte Carlo method based QSPR model for prediction of reaction rate constants of hydrated electrons with organic contaminants

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ABSTRACT

The Monte Carlo algorithm was applied to formulate a robust quantitative structure–property relationship (QSPR) model to compute the reactions rate constants of hydrated electron values for a data set of 309 water contaminants containing 125 aliphatic and 184 phenyl-based chemicals. The QSPR models were computed with the hybrid optimal descriptors which were procured by combining the SMILES and hydrogen-suppressed molecular graph for both classes of compounds. Approximately 75% of the total experimental data set was randomly divided into training and invisible training sets, while approximately 25% was divided into calibration and validation sets. The authenticity and robustness of the developed QSPR models were also judged by the Index of Ideality of Correlation. In QSPR modelling of aliphatic compounds, the numerical values of r^2_{Training}, $r^2_{\text{Validation}}$, Q^2_{Training} and $Q^2_{\text{Validation}}$ were in the range of 0.852–0.905, 0.815–0.894, 0.839–0.897 and 0.737–0.867, respectively. Whereas, in the QSPR modelling of phenyl-based compounds, the numerical values of r^2_{Training}, $r^2_{\text{Validation}}$, Q^2_{Training} and $Q^2_{\text{Validation}}$ were in the range of 0.867–0.896, 0.852–0.865, 0.816–0.850 and 0.760–0.762, respectively. The structural attributes, which are promoters of log $K_{e^-_{aq}}$ increase/decrease are also extracted from the SMILES notation for mechanistic interpretation. These QSPR models can also be applied to compute the reaction rate constants of organic contaminants.

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Introduction

Currently, one notable problem is water pollution associated with contaminants released by industrial effluent wastes, leakage from water tanks, marine dumping, radioactive waste and atmospheric deposition. The quality of water is important for health in both developing and developed countries. Water pollution has a direct effect on human health, crops and the industrial sector. A literature survey shows that various methods such as chemical oxidation technologies, nanofiltration, reverse osmosis and advanced oxidation process have been used to eliminate contaminants, especially for organic compounds [1]. Biological or chemical

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results of the models were obtained using the hybrid descriptor, that is both molecular graph (HSG) and SMILES descriptor. Split 2 gave the leading model for the aliphatic data set, and in the case of phenyl-based compounds the leading model was given by split 3. The described approach provides the possibility of predictions of rate constants of hydrated electrons with new organic contaminants. The authenticity and robustness of the developed models were predicted by various statistical parameters such as r^2, *CCC*, *IIC*, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, r^2_m, CR^2_p etc. The structural attributes, which are promoters of log $K_{e^-_{aq}}$ increase or decrease, are recognized from the leading models. The present hybrid QSPR models are more robust and predictive than models reported in the literature. In the present paper, the developed QSPR models are based on molecular structures and these do not involve the use of 3D molecular descriptors, physicochemical descriptors, and/or descriptors of quantum mechanics. Hence, it can be concluded that the present QSPR method can be used to predict the log $K_{e^-_{aq}}$ of 309 water contaminants containing 125 aliphatic and 184 phenyl-based compounds using the Monte Carlo method with index of ideality correlation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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In-silico identification of fingerprint of pyrazolyl sulfonamide responsible for inhibition of *N*-myristoyltransferase using Monte Carlo method with index of ideality of correlation

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ABSTRACT

Human African trypanosomiasis (HAT) or sleeping sickness like infections remain a serious health concern around the globe due to unavailability of safe and potential drugs for their treatment. Moreover, developing safe, potential and highly specific target based treatments is still a challenge for present drug discovery programs. A series of pyrazole based sulfonamides are identified as an inhibitor of *Trypanosoma brucei N*-myristoyltransferase (TbNMT). In the present manuscript, we have developed robust and reliable QSAR models by using the balance of correlation method in CORAL software. The chemical structures are represented by simplified molecular input line entry system (SMILES). The significance of the index of ideality correlation (IIC) with applicability domain (AD) is also studied at depth. The models developed by considering the index of ideality of correlation (IIC) were found to statistically more significant and robust. One QSAR model with best $R^2_{calibration} = 0.8638$ for split 2 was considered as the leading model. A greater value of cRp^2 *i.e.* 0.5 for all models in Y-randomization test showed the robustness of developed models. The outliers and promoters of increase and decrease of endpoint were also extracted independently from the leading models. The mechanistic interpretation of developed models explains the role of different structural attributes in predicting the pIC_{50} of pyrazole sulfonamides extracted from the crystal structure of Leishmania major N-myristoyltransferase (NMT) along with co-crystallized myristoyl-CoA and ligands NMT106, NMT157, NMT187 and NMT236 (PDB ID: 4A2Z, 4A30, 4A32, 2WSA).

Abbreviations: HAT: Human African trypanosomiasis; IIC: Index of Ideality of Correlation; TbNMT: *Trypanosoma brucei N*-myristoyltransferase; CW: Correlation weight; OECD: Organization of Economic Co-operation and Development; QSAR: Quantitative Structure Activity Relationship; CORAL: CORrelation And Logic; AD: Applicability Domain

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Introduction

Human African trypanosomiasis (HAT) or sleeping sickness is caused by the kinetoplastid parasite *Trypanosoma brucei* and it is transmitted by the bite of an infected tsetse fly (*Glossina* genus) (Nagle et al., 2014; Njoroge et al., 2014). Mainly two species *i.e. Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* of the above protozoan parasite is responsible for the HAT disease which leads to death if not treated properly or treatment is delayed (Klug et al., 2020; Lepovitz et al., 2020; Scarim et al., 2020). The clinical features are characterized by lymphadenopathy, fever and excessive sleepiness due to encephalopathy or encephalitis (Macleod et al., 2020; Singh et al., 2019; Watson et al., 2019). This disease is progressed by two distinct stages: the hemolymphatic stage and central nervous system (CNS) involvement or meningoencephalitic stage. The first stage is initially an acute stage, starts with the proliferation of parasite in the hemolymphatic system and give rise to non-specific symptoms (Bayliss et al., 2017; Harrison et al., 2018; Klug et al., 2020; Montalvo-Quiros et al., 2015; Patrick et al., 2017). However, the second stage onsets with the migration of parasite from the hemolymphatic system to CNS and cause classical symptoms of sleeping sickness, ultimately leading to coma and death. In the present scenario, the drugs available for HAT treatment are unsafe and frequently allied with severe or life-threatening side effects such as fatal encephalopathy, agranulocytosis, drug-resistance, and myocardial damage. Mainly five drugs (suramin, pentamidine, melarsoprol, eflornithine and nifurtimox) are used to treat various stages of HAT disease (Hagen et al., 2020). For 1st stage treatment, suramin and pentamidine are used, whereas melarsoprol and eflornithine are recommended for stage 2 infection. Recently, the nifurtimox-eflornithine combination therapy (NECT) has

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In silico exploration of the fingerprints triggering modulation of glutaminyl cyclase inhibition for the treatment of Alzheimer's disease using SMILES based attributes in Monte Carlo optimization

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ABSTRACT

Alzheimer's disease is the most common neurodegenerative disorder and being a social burden Alzheimer's has become an economic liability on developing countries. With limited understanding regarding the cause of disease, it is commonly identified by extracellular deposit of amyloid β (Aβ) peptides as senile plaques. Pyroglutamated Aβ is identified from the brain of AD patients and constituted the majority of total Aβ present. The formation of Pyroglutamated Aβ could be hindered by the use of Glutaminyl cyclase inhibitors and could efficiently improve the symptoms of Alzheimer's. The literature revealed the competence of quantitative structure activity/property relationship studies in drug discovery. The present work explores the efficiency of Monte Carlo based QSAR modelling studies on a dataset of 125 Glutaminyl cyclase inhibitors with *pKi* taken as the endpoint for QSAR analysis. The dataset is divided into training, subtraining, calibration and validation sets resulting in the generation of five random splits. The validation is performed in accordance with the Organization of Economic Corporation and Development principles. The values of R^2, Q^2, index of ideality of correlation, concordance correlation coefficient, av. r^2_m and delta r^2_m of calibration set of the best split are found to be 0.9012, 0.8775, 0.9479, 0.9435, 0.8347 and 0.0847, respectively. The structural features responsible for increasing the inhibitory activity are identified. These structural features are added to a base compound from the dataset to design six novel molecules. These new molecules possess improved inhibitory activity as compare to the base compound. The results are further supported by docking studies.

Abbreviations: AD: Alzheimer's disease; APP: amyloid precursor protein; ASP: aspartic acid; Aβ: amyloid beta; BACE: beta site amyloid precursor protein cleaving enzyme; CCC: concordance correlation coefficient; DCW: descriptors of correlation weight; GLN: glutamine; GLU: glutamic acid; HIS: histidine; IIC: index of ideality of correlation; ILE: isoleucine; LEU: leucine; MAE: mean absolute error; OECD: organisation for economic cooperation and development; PDB: protein data bank; PHE: phenylalanine; QSAR: quantitative structure activity relationship; RMSE: root mean square error; SMILES: simplified molecular input line entry system; TRP: tryptophan; ZBG: zinc binding group

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Introduction

Alzheimer's disease (AD) is a prevalent irreversible neurological disease and according to the Brightfocus Foundation, worldwide 50 million people are suffering from Alzheimer's or neurological dementia (Alzheimer's-Disease-International, 2019). The disease is responsible for the social and economic burden. In 2018, the estimated cost of Alzheimer's and dementia care in the US was $277 billion (Alzheimer's-Association, 2018). The most common identifiable symptom of Alzheimer's is memory loss. As the disease advances from preclinical to late-stage, the symptoms encompass behavioural, cognitive, functional and complete mental decline of the patient (Kumar et al., 2015). Now a days, neuropsychiatric symptoms like depression, apathy, aggression, and psychosis are identified as main features of AD, and symptoms complexity characterize the disease progression (Lanctôt et al., 2017; Li et al., 2014). In addition to genetics, head injuries, depression, diabetes and obesity, age is the most prominent factor leading to AD (Lao et al., 2019).

Clinical diagnosis of AD includes patient history, collateral history from relatives, and clinical remarks, based on the existence of neurological and neuropsychological features. With limited understanding regarding the cause of disease, it is commonly identified by extracellular deposits of amyloid β (Aβ) peptides as senile plaques, transmission loss at synapsis, tangles formed by deposition of tau protein and degeneration of cholinergic neurons (Du et al., 2018; Verma et al.,

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hydrogen bonding with ILE 303. In GC06, the benzene group was substituted with amino group. In GC06, the coordination bond with Zinc was absent but subsequently, the benzene ring of the molecule showed π-π stacking interactions with HIS 330, TRP 329 and imidazole with PHE 325. The 5-methyl substituent of imidazole ring was seen involved in π-alkyl interactions with ILE 303. The substituted amino group showed hydrogen bonding interactions with ASP 159 and GLU 201.

Conclusion

Five different SMILES based QSAR models were developed on 125 glutaminyl cyclase inhibitors adopting logical and scientific process. The developed models were thoroughly validated, and various validation parameters were found to be within described limits. The studies pointed towards the importance of five-membered heterocyclic ring with three methylene unit spacer attached to two heavy atoms with a terminal phenyl ring. The results also demonstrated the importance of 5-methyl substituted imidazole ring and alkyl-substituted benzene ring in activity enhancement. Structural features extracted from the best QSAR model helped in designing of novel 06 glutaminyl cyclase inhibitor compounds. The newly designed compounds were found to have improved inhibitory potential. The *pKi* of compound GC05 was found to be 4.05. Docking studies further verified the results as the designed compound showed the crucial binding interactions with the residues of the active site and the binding affinity was in well correlation with the predicted inhibition potential. The results of the present study are very encouraging and would be very useful for researchers working in the field of AD treatment.

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Disclosure statement

There is no conflict of interest.

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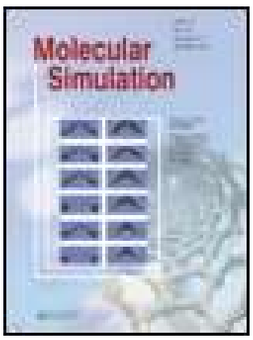

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Index of ideality of correlation and correlation contradiction index: a confluent perusal on acetylcholinesterase inhibitors

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Index of ideality of correlation and correlation contradiction index: a confluent perusal on acetylcholinesterase inhibitors

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ABSTRACT

Alzheimer's disease is one of the leading causes of disability and death in the global scenario. Acetylcholinesterase inhibitors are symptomatically involved in the therapeutic management of Alzheimer's disease. Due to the prophetic capability of SMILES-based QSAR studies, the current method explored its efficiency for designing novel inhibitors of acetylcholinesterase enzyme. Two newly introduced validation parameters (the ideality of correlation (IIC) and the correlation contradiction index (CCI)) were studied for further validating the predictive capability of developed models. The index of ideality of correlation was found to have a positive effect on models developed in comparison to models developed without IIC. The structural features accountable for intensifying the inhibitory activity were identified by performing QSAR modelling studies on 60 acetylcholinesterase inhibitors from the literature. Based on the molecular features identified designing of new molecules was accomplished and was found to have satisfactory inhibitory potential. Docking interactions of designed molecules pointed the importance of position of nitro group, aromatic ring and alkyl substitution in influencing the inhibitory activity and binding interactions. The designed compound DD2 was found to have highest inhibitory potential (4.33) and binding affinity (−11.2 kcal mol^{-1}).

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Alzheimer's disease; Acetylcholinesterase inhibitors; QSAR; Index of ideality of correlation; correlation contradiction index

1. Introduction

With over 40 million people suffering and the sixth leading cause of death, Alzheimer's disease has become the most widespread neurodegenerative disorder. It is not only a social burden but also an economic burden for developing countries. The present lifestyle has also contributed towards the growth of the disease. Regardless of extensive research over the last century the knowledge regarding the exact cause and the ways for its treatment are still incomplete [1–3]. In light of the above facts there are only four FDA-approved drugs e.g. donepezil, rivastigmine, galantamine and memantine that can only slow down the advancement of the disease. The first three drugs are Acetylcholinesterase inhibitors (AChEIs) and are based on Cholinergic hypothesis which states that the reduction in the level of acetylcholine and loss of cholinergic neurons are responsible for learning difficulties and cognitive impairment [4,5]. AChEIs causes inhibition of cholinesterase enzyme responsible for the breakdown of acetylcholine. This improves acetylcholine levels in brains and slows the memory loss.

The last few decades have witnessed a considerable increase in the use of computational methods in drug discovery and development collectively called as Rational Drug Design [6]. Reduction in laboratory and animal testing experiments are the reasons responsible for the diversion of traditional drug design to rational drug design. One of the cost-effective and predictive techniques of Rational Drug Design is Quantitative Structure Activity Relationship (QSAR). QSAR studies include the mathematical correlation of descriptors of a bioactive molecule with its activity. In QSAR-based drug designing the pharmacokinetic/toxicological parameters are appropriately correlated with potency/selectivity [7–11]. The literature revealed that SMILES-based QSAR studies have remarkable prophetic capability [12–18]. The purpose of the current work is the explanation of CORAL software as a means for QSAR modelling [19], which uses simplified molecular input line entry system (SMILES)-based optimal descriptor [20–22]. Prediction capability is the most important criterion for QSAR model development process. To determine this criterion many statistical methods have been reported in the literature. However, none of them is capable of estimating the prediction ability of QSAR model individually and all are associated with one or more drawbacks. Recently a new criterion of predictability i.e Index of ideality of correlation (IIC) has been suggested by Toropov[23–25] which is based on correlation coefficient and mean absolute error. In 2019, same authors have introduced a new criterion for prediction i.e. correlation contradiction index (CCI) [26]. It has been shown that there is good correlation between correlation coefficient of validation and CCI. In this work, comparison of IIC and CCI has been performed using a new dataset of 60 AChEIs. The further effect of IIC on CCI has also been investigated. In addition, the

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Synthesis and characterization of water-soluble chitosan derivatives: spectral, thermal and biological studies

Sohan Lal, Sanjiv Arora, Shikha Rani, Parvin Kumar, Pooja Dabas & Jaideep Malik

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Synthesis and characterization of water-soluble chitosan derivatives: spectral, thermal and biological studies

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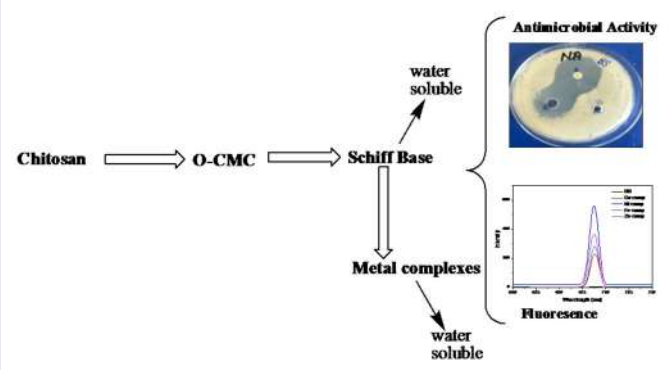
ABSTRACT

In this study, different water-soluble derivatives of chitosan were synthesized by treating chitosan with monochloroacetic acid to yield O-carboxymethyl chitosan (O-CMC) and this O-CMC treated with vanillin to form Schiff base. Metal complexes of this Schiff base were prepared with different salt of metal ions like Cu(II), Ni(II), Fe(II) and Zn(II). O-CMC and its Schiff base were characterized by FTIR, ^{1}H-NMR and all other derivatives were characterized by using FTIR, UV-visible and fluorescence spectroscopic techniques. In FTIR study, the main characteristic peaks were observed at 1744 cm^{-1} (C = O str. in O-CMC), 1666 cm^{-1} (C = N str. peak in Schiff base) and 600–640 cm^{-1} (metal-ligand str.). In ^{1}H-NMR different signals were obtained at δ 9.58 ppm due to the proton of imine group (–CH = N- in Schiff base) and signals in between δ 6.5 and 7.5 ppm due to aromatic protons. Antimicrobial activity of all these derivatives was also investigated against *Bacillus subtilis* (Gram-positive bacteria), *Escherichia coli* (Gram-negative bacteria) and *Aspergillus niger* (fungi). The result shows that Ni- and Zn-complexes of O-CMC Schiff base has almost similar activity as that of standard drug ampicillin. Thermal behavior of all these derivatives was also examined by using TG/DTG techniques.

RESEARCH HIGHLIGHTS

- Water-soluble derivatives of chitosan were synthesized (O-CMC, Schiff base and metal complexes).
- All derivatives were characterized by using different techniques (FTIR, ^{1}H-NMR).
- Thermal, spectral and antimicrobial studies were also carried out.
- All derivatives are water-soluble and thermally stable and exhibited enhanced antimicrobial activity.

GRAPHICAL ABSTRACT



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Antimicrobial activity; metal complexes; Schiff base; thermal study; water-soluble O-CMC

1. Introduction

Natural biopolymers become very popular among the peoples because they have some unique properties of biocompatibility, biodegradability, they can be extracted from natural resources like agriculture and marine food resources and with the additional benefit of their use is that they are safe for our environment. Chitin is also a natural biopolymer which has all these properties and can be obtained as waste material from the exoskeleton of crustaceans (shrimp, lobster, crab, crawfish, etc.) after food processing.[1] But chitin is not soluble as such in most of the solvents that reduce its applications so; it is converted into chitosan, which is

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which showed that Zn-metal ion binds very efficiently with Schiff base.

4.5. Antimicrobial results

The antimicrobial activity of chitosan and its different water-soluble derivatives were investigated against *B. subtilis* (Gram-positive strain), *E. coli* (Gram-negative strain) and their antifungal activity against *A.niger*. The antibacterial activities of all these compounds were calculated by measuring the zone of inhibition method against the test organisms/specimen. The tested biopolymers possessed variable antibacterial activity against *B. subtilis* with a diameter of zone of inhibitions ranging in between 10 and 32 mm (Figure 5) and against *E. coli* the diameter of zones in between 10 and 26 mm (Figure 5). Among all the tested samples, Zn-complex and Ni-complex were found to be most effective against Gram-positive and Gram-negative bacteria because their zones of inhibition had the largest diameter. The overall results of antibacterial activity showed that all the newly synthesized derivatives are more effective than chitosan against both the strains (*B. subtilis* and *E. coli*) but Zn- and Ni-complexes of Schiff base showed almost equal activity as that of standard drug ampicillin.

On the basis of very good antibacterial activity of Ni-complex and Zn-complex, further investigation was carried out to find their least but sufficient amount to show their antibacterial action in terms of MIC. For this purpose, the optical density (OD) of solution of Ni-complex and Zn-complex of different concentrations containing inocula of *B. subtilis* and *E. coli* at 600 nm was recorded by using spectrophotometer.[38] The initial concentration of metal complexes of Schiff base was prepared 2000 ppm against *B. subtilis* but the concentration of metal complex against *E. coli* was 3000 ppm and then they were decreased to get optimum result. As the concentration of metal complex solution decreased turbidity of solution increases which showed more growth of bacteria in the solution. The results showed that MIC of Ni-complex and Zn-complex against *B. subtilis* was nearby 1 mg per ml (1000 ppm) and against *E. coli* was between 1.75 mg and 2 mg per ml (1750–2000 ppm).

The antifungal activity of chitosan, O-CMC and its derivatives was tested against *A.niger* by using poisoned food method (Figure 6). In the antifungal activity, among all the tested compounds Zn and Ni metal complexes of Schiff base showed good activity with more than 0.55 inhibition against *A.niger,* whereas other tested compounds showed moderate activity. Thus, the results of antifungal activity showed that all the synthesized derivatives have moderate activity, but Schiff base and its metal complexes were found to be most active as compared to chitosan.

The mechanism of biological activity of chitosan and its derivatives can be explained as negatively charged bacterial membrane interact with the positively charged chitosan molecules and eventually the normal cell got destroyed.[39] Greater positive charge on -N in case of Schiff base of (-RC = N-) as compared to amine group of polymeric chain of chitosan (-NH_2 group) may be the reason for higher antimicrobial activity of Schiff base of chitosan. The metal complexes were more biologically active than Schiff base because the density of positive charge on -N increased after chelation of Schiff base with metal ions.[24]

5. Conclusion

The present work describes the synthesis and characterization of water-soluble derivatives of chitosan i.e., O-CMC, Schiff base of O-CMC and metal complexes of Schiff base with Cu(II), Ni(II), Fe(II) and Zn(II) ions. O-CMC was prepared by reacting chitosan with monochloroacetic acid in strong basic condition and this O-CMC was treated with vanillin to obtain Schiff base and due to the chelating property of Schiff base different metal complexes were prepared. FTIR, ^{1}H-NMR, UV-visible and fluorescence are some spectroscopic techniques which were used to confirm the structure of all these derivatives. Antimicrobial property of chitosan and its derivatives was investigated against bacteria (*B. subtilis*, *E. coli*) and fungi (*A. niger*). Analysis of results showed that Schiff base and its metal complexes have enhanced antimicrobial activities as compared to chitosan. Among these two derivatives, Zn and Ni-complexes of Schiff base have comparable antimicrobial activity to the standard drug ampicillin. Investigations were also carried out to find out MIC of these compounds by using a broth dilution method. The thermal inquiry of chitosan and its synthesized derivatives showed that they were quite thermally stable and stability of metal complexes was slightly more than Schiff base with also increased in their char yield due to the formation of their metal oxides.

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Use of Graph Based Descriptors for Determination of Structural Features Causing Modulation of Fructose-1,6-Bisphosphatase

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ABSTRACT

Fructose-1,6-bisphosphatase performs a significant function in regulating the blood glucose level in type 2 diabetes by controlling the process gluconeogenesis. In this research work optimal descriptor (graph) based quantitative structural activity relationship studies of a set of 203 fructose-1,6-bisphosphatase has been performed with the help of Monte Carlo optimization. Distribution of compounds into different sets such as training set, invisible training set, calibration set and validation sets resulted in formation of splits. Statistical parameters obtained from quantitative structural activity relationship modeling were good for various designed splits. The statistical parameters such as R^2 and Q^2 for calibration and validation sets of best split developed were found to be 0.8338, 0.7908 & 0.7920 and 0.7036 respectively. Based on the results obtained for correlation weights, different structural attributes were described as promoters and demoters of the endpoint. Further these structural attributes were used in designing of new fructose-1,6-bisphosphatase inhibitors and molecular docking study was accomplished for the determination of interactions of designed molecules with the enzyme.

Introduction

Diabetes mellitus (DM) is a disorder related to imbalance in carbohydrate, protein and fat metabolism and characterized by hyperglycemia [1]. Hyperglycemia results into microvascular and macrovascular problems such as failure of visualization, heart disease etc [2]. World Health Organization (WHO) has included diabetes in chronic diseases [3]. About 80 % of the total deaths occur due to diabetes every year [4] and the rate at which it is spreading, diabetic patients will enhance up to 300 million in 2025 [5]. Diabetes Mellitus or non-insulin-dependent diabetes mellitus (NIDDM) is regarded as the mostly widespread type of diabetes in all known forms [6]. Although various therapeutics agents are available as anti-diabetic drugs, but still many of them have a number of serious side effects. In medicinal chemistry, development of anti-diabetic drugs with less side effects and relatively low price is still a challenge [7]. From different radioisotopic analysis & some experimentation by means of ^{13}C NMR, it has been reported that the glucose (in non-absorptive state) is produced in the liver by a process known as the GNG (gluconeogenesis). In Type-2 diabetic (T2D) patients GNG flux is excessive. Hence, to maintain the level of blood glucose in T2D patients, GNG as a pharmacological target represents an attractive approach [8]. Gluconeogenesis involves a principle regulatory enzyme fructose-1,6-bisphosphatase which converts the fructose-1,6-bisphosphate into fructose-6-phosphate and an inorganic phosphate is also released with it [9].

In the modern medicine development practices, to predict the pharmacological action of novel molecules by Quantitative structure activity relationship (QSAR) is assumed as the best option [10]. The major motive of all QSAR modeling process is the development of a model which can correlate pharmacological activity of a molecule with its properties by a simple mathematical equation [11]. For QSPR/QSAR study, the CORALSEA software is one of the best

compounds are given in **Table S7** along with their structures, which are comparable with experimental data given by Dang et al. [16].

Conclusion

In current research work, three QSAR models of a dataset of 203 Fructose-1,6-bisphosphatase inhibitors using graph based optimal descriptors have been developed by CORAL. During QSAR modeling process OECD guidelines were strictly taken into consideration and developed models have good predictions regarding all the statistical parameters. Extracted structural features emphasized the importance of Morgan's extended connectivity, path lengths, vertex numbers and nearest neighboring code in modulation of FBPase inhibitory activity. Incorporation of these graph attributes in the structure of compound D155 resulted in design of novel compounds with increased activity. Further the prediction ability of best QSAR model was confirmed by higher docking score of designed molecules. The suggested novel inhibitors could be tested for their in vitro activity in the laboratory and this study will assist the researchers in further design and development of novel FBPase inhibitors.

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Conflict of Interest

There is no conflict of interest.

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Bicyclic 5-5 Systems With One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 3:0☆

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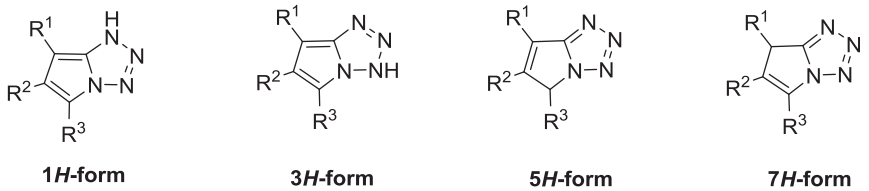
Introduction

The present chapter is an extension of review presented in CHEC-II(1996) (Chapter 11.06) which covers five-membered fused bicyclic systems with three heteroatoms in the same ring and one bridgehead nitrogen atom.[1] Some additional entries based on such fused systems appeared in the literature after the publication of CHEC-II (2015). In this chapter, some of the fused bicyclic compounds are shown which are reported in the literature in terms of scientific findings. The ring systems covered by this chapter are fused tetrazoles.

Theoretical methods

Structure and tautomerism

Various theoretical aspects related to the structure and tautomerism of pyrrolotetrazoles have been discussed in this chapter. The studies on structure and tautomerism were done using quantum-chemical methods (HF/6-31G** and DFT B3LYP/ANO-S) in the gas phase. In the case of pyrrolotetrazoles based heterocyclic systems, theoretically four neutral prototropic forms (1*H*-, 3*H*, 5*H*- and 7*H*-tautomers) are possible (Scheme 1).



Scheme 1

The four theoretically possible tautomeric forms are further categorized into two class based on the aromaticity of the pyrrole ring. In the first case, 1*H*- and 3*H*-tautomers are placed where aromaticity of half pyrrole ring remains intact. On the contrary, in the second case maintenance of aromaticity for pyrrole ring is impossible for 5*H*- and 7*H*-tautomers. The aromaticity of the pyrrole ring in both the cases is controlled solely by the proton transfer from the pyrrole ring to the tetrazole ring or vice versa (Scheme 2).

Scheme 2

☆*Change History*: April 2020. P Kumar and J Sindhu prepared the update. In the section "Energetics of Intramolecular cyclisation", the citation of Table 2 has been changed.

The annular tautomerism in pyrrolo[1,2-*d*]tetrazoles was explored for the first time by Zubarev et al. using quantum-chemical methods (HF/6-31G** and DFT B3LYP/ANO-S) (DFT calculations) in the gas phase.[2] The total energy was calculated for the four possible tautomers (*i.e.*, 1*H*-, 3*H*-, 5*H*, and 7*H*-forms) to find the stable one among them. The calculation was done using unsubstituted as well as mono-, di- and tri-substituted derivatives to explore the effect of the substituent on the stability of tautomeric forms. Both electron-donating and electron-withdrawing substituents (Me, CN and Cl) were used in various positions of the pyrrole ring help in the evaluation of the influence of electronic nature and their positions on the prototropic tautomerism of these annulated systems. The structures of all possible forms were optimized using DFT method, no negative frequencies were found and the total energies were calculated taking ZPE-corrections into account. It was observed that 5*H*-tautomer is the most stable form for unsubstituted pyrrolotetrazoles and its derivatives containing methyl substituents at the carbon atom(s) in which aromaticity of the tetrazole fragment is maintained. On the contrary, 1*H*-tautomer is the most stable form for pyrrolotetrazoles with electron-withdrawing substituents (CN or Cl) in which the pyrrole fragment is aromatic. A difference in the relative electron-accepting ability of heterocyclic half-rings may affect the stability of such tautomeric forms.

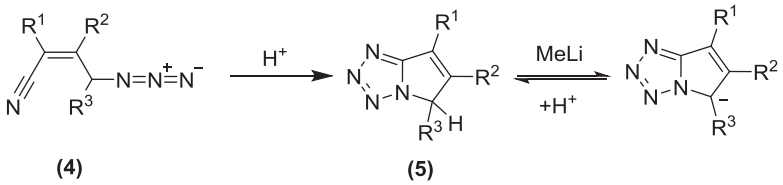
The aromaticity for various tautomeric forms (1*H*-, 3*H*-, 5*H*-, and 7*H*-forms) was calculated using various geometrical parameters (bond lengths) obtained from the optimized structure, where optimization was done using HF/6-31G** method. Pozharskii criterion, based on deviations of interatomic bond orders from the average value in each annulated heterocyclic system, was used for the determination of aromaticity of each of the above-mentioned prototropic forms (Table 1).

Table 1 Aromaticity (in percentage) of various prototropic forms of pyrrolotetrazoles calculated according to the Pozharskii criterion optimized by the HF/6-31G** method.

Form	*Aromaticity (A,%)*		*Integral aromaticity of annulated system*
	Pyrrole ring	*Tetrazole ring*	
1*H*	35	28	32
3*H*	38	32	35
5*H*	10	50	30
7*H*	12	50	31

Energetics of intramolecular cycloaddition

An attempt was made by Santelli and co-workers to study the theoretical aspect of intramolecular cycloaddition of azidoenynes and azidobutenenitriles to give 5*H*-pyrrolo[1,2-*d*]tetrazoles.[3] The theoretical calculations were done by DFT using B3LYP/6-311++G(3df,3pd) level of theory in ideal gas and H_2O as a solvent. The same level of theory was used for the transition state during the cyclisation of the parent compound. The synthesis and alkylation/acylation of 5*H*-pyrrolo[1,2-*d*]tetrazoles was reported by the cyclization of 4-azidobut-2-enenitriles in the acidic medium.[4,5] In the present chapter, the calculated thermodynamic and kinetic data concerning various steps reported by these workers have been discussed. The thermal cyclization of 4-azidobut-2-enenitriles **(4a-4f)** to **5a-5f** was weakly exergonic and explained the lack of experimental observation in neutral medium (Scheme 3, Table 2). Nevertheless, the use of H_2O as solvent facilitated this thermal cyclization.



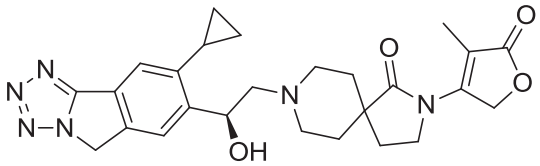
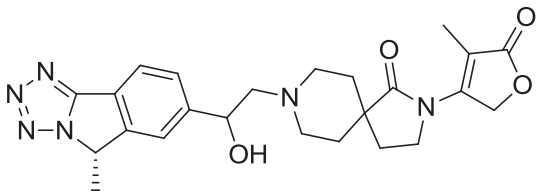
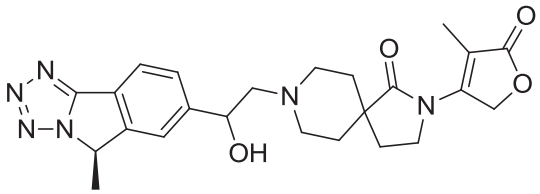
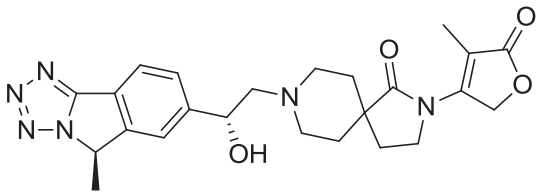
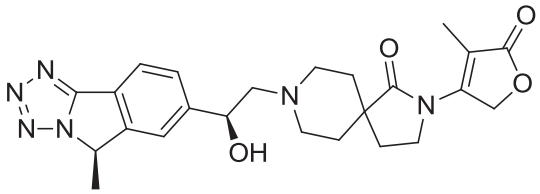
Scheme 3

Table 2 Energetics of the thermal cycloaddition of 4-azidobut-2-enenitriles (4a–4f) to 5*H*-pyrrolo[1,2-*d*]tetrazoles (5a-5f).

R		$\Delta E = E_5 - E_4$	$\Delta G = G_5 - G_4$	$\Delta E = E_5 - E_4$	$\Delta G = G_5 - G_4$
		[Kcal mol^{-1}][a]	[Kcal mol^{-1}][a]	[Kcal mol^{-1}][b]	[Kcal mol^{-1}][b]
4a→**5a**	$R^1 = R^2 = R^3 = H$	−9.66	−4.37	−13.02	−7.54
4b→**5b**	R^1 = Me, $R^2 = R^3 = H$	−11.40	−6.28	−14.55	−9.34
4c→**5c**	$R^1 = R^3 = H$, R^2 = Me	−8.87	−3.58	−12.60	−7.27
4d→**5d**	$R^1 = R^2$ = Me, $R^3 = H$	−12.69	−7.17	−16.22	−10.06
4e→**5e**	$R^1 = H$, $R^2 = R^3$ = Me	−11.07	−5.86	−14.61	−9.35
4f→**5f**	$R^1 = R^2 = R^3$ = Me	−14.48	−9.41	−17.81	−12.43

[a]Calculated in ideal gas.
[b]Calculated using H_2O as solvent.

Table 6 (Continued)

S. No	*Compound*	*Thallium Flux* IC_{50}
31j		0.082
31k		0.087
31l		0.027
31m		0.036
31n		0.029

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Quantitative structure activity relationship studies of novel hydrazone derivatives as α-amylase inhibitors with index of ideality of correlation

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Quantitative structure activity relationship studies of novel hydrazone derivatives as α-amylase inhibitors with index of ideality of correlation

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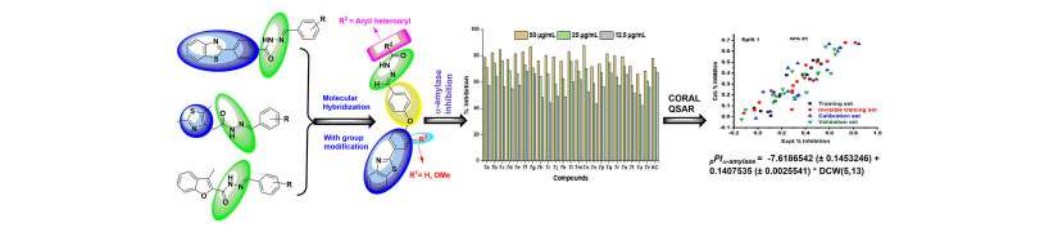
ABSTRACT

The present manuscript describes the synthesis, α-amylase inhibition, *in silico* studies and in-depth quantitative structure–activity relationship (QSAR) of a library of aroyl hydrazones based on benzothiazole skeleton. All the compounds of the developed library are characterized by various spectral techniques. α-Amylase inhibitory potential of all compounds has been explored, where compound **7n** exhibits remarkable α-amylase inhibition of 87.5% at 50 µg/mL. Robust QSAR models are made by using the balance of correlation method in CORAL software. The chemical structures at different concentration with optimal descriptors are represented by SMILES. A data set of 66 SMILES of 22 hydrazones at three distinct concentrations are prepared. The significance of the index of ideality of correlation (IIC) with applicability domain (AD) is also studied at depth. A QSAR model with best $R^2_{validation} = 0.8587$ for split 1 is considered as a leading model. The outliers and promoters of increase and decrease of endpoint are also extracted. The binding modes of the most active compound, that is, **7n** in the active site of *Aspergillus oryzae* α-amylase (**PDB ID: 7TAA**) are also explored by *in silico* molecular docking studies. Compound **7n** displays high resemblance in binding mode and pose with the standard drug acarbose. Molecular dynamics simulations performed on protein–ligand complex for 100 ns, the protein gets stabilised after 20 ns and remained below 2 Å for the remaining simulation. Moreover, the deviation observed in RMSF during simulation for each amino acid residue with respect to Cα carbon atom is insignificant.



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Abbreviations: IIC: index of ideality of correlation; CW: correlation weight; OECD: Organization of Economic Co-operation and Development; QSAR: quantitative structure–activity relationship; CORAL: CORrelation And Logic; AD: applicability domain; MD: molecular dynamics

1. Introduction

Diabetes and obesity are a cluster of metabolic disorders related to lifestyle and characterised by high blood glucose over a prolonged time. The increasing occurrence of these two disorders accelerated the discovery of new drugs. α-Amylase (EC 3.2.1.1) is an endoamylase which mainly occurs in plants, microorganism and higher organisms and belongs to 13th family of glycoside hydrolases (GH13). Its main function is to hydrolyze the α-D-(1,4)-glycosidic linkage in starch (Brayer et al., 1995; Shi et al., 2018; Souza & Magalhães, 2010) and retaining α-anomeric configuration in the products. The over-expression of α-amylase leads to hyperglycaemia which results in the development of diabetes mellitus. This feature established α-amylase as a well-known molecular target for type 2 diabetes mellitus. Marketed drugs prescribed to treat type-II diabetes mellitus are associated with numerous side effects such as diarrhoea,

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the QSAR model built by CORAL Software, AD is calculated by arranging SMILES attributes in the training and calibration sets. If a compound falls outside the range of AD, it is labelled as an outlier. In the CORAL QSAR model, the AD is defined in consonance with the distribution of SMILES characteristics in training and calibration sets as two steps:

Step 1: The definition of statistical defects ($d(F_K)$) for each of the SMILES attributes included to construct the model:

$$d(F_K) = \frac{P_T(A_K) - \mathrm{P_C(A_K)}}{N_T(A_K) + N_C(A_K)} \tag{11}$$

where $P_T(A_K)$ and $P_C(A_K)$ are probabilities of attributes A_K in training and calibration set, respectively; $N_T(A_K)$ and $N_C(A_K)$ are the frequency of attributes A_K in the training set and calibration sets, respectively.

Step 2: the calculation for all substances the statistical SMILES defect (D_j):

$$D_j = \sum_{K=1}^{NA} d(F_K) \tag{12}$$

where NA is the number of non-blocked SMILES attributes in the SMILES.

In the current statistical calculation, a compound falls in AD if

$$D_j < 2 \times \overline{\mathrm{DefectNS}} \tag{13}$$

Here, $\overline{\mathrm{DefectNS}}$ is the average of the statistical SMILES defect for the training set.

8.2. Docking studies

Marvin sketch was used for preparing the optimized 3D structure of compounds **7n**. The protein data bank was assessed for the PDB structure of α-amylase for *A. oryzae* (**PDB ID: 7TAA**) (http://www.rcsb.org/pdb). The protein was prepared by using UCSF Chimera 1.10 (Pettersen et al., 2004) in which co-crystallized ligand and solvent molecules were removed to avoid interference in binding interactions. Missing side-chain gaps were filled using Dun Brack Rotamer Library (Dunbrack, 2002). Gasteiger charges were calculated using AMBERf14SB and antechamber (Wang et al., 2006) and hydrogens were added. The docking studies were performed using Auto Dock Vina 1.1.2 (Trott & Olson, 2010). Grid center with following size center_x = 38.1433640994, center_y = 39.1685534078, center_z = 31.0477751774, size_x = 25.0, size_y = 25.0 and size_z = 25.0 was placed on the active site. The results of docking studies were analysed using Desmond interface.

8.3. MD simulations

The molecular dynamics simulation of the docked complex of 7TAA.pdb with **7n** was performed for 100 ns using Desmond module of Schrödinger 2019-4 to establish the stability of the docked complex (Guo et al., 2010). The docked poses of protein ligand complexes were used as input structures and each complex was prepared by system setup option in Desmond module. Explict solvent system with OPLS2005 force field was used for this simulation study. Orthorhombic periodic boundary condition for 10 Å buffer region was used for solvation of molecular system with crystallographic water (TIP3P) (Jorgensen et al., 1983) and the system was neutralised by adding Na^+ as counter ions. An ensemble (NPT) of Nose–Hoover thermostat (Martyna et al., 1992, 1994) and barostat was applied to maintain the constant temperature (300 K) and pressure (1 bar) of the systems, respectively. A limited memory algorithm (Broyden–Fletcher–Goldfarb–Shanno (LBFGS)) was employed with convergence threshold gradient of 1 kcal/mol/Å for energy minimization. The data were collected for every 100 ps, and the obtained trajectory was analyzed with Desmond interphase.

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Author contributions

Authors have done equivalent contributions to this work.

Disclosure statement

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CORAL: QSAR models of CB1 cannabinoid receptor inhibitors based on local and global SMILES attributes with the index of ideality of correlation and the correlation contradiction index

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ABSTRACT

Obesity has acquired notable attention due to its high occurrence and link with grievous health problems such as hypertension, diabetes and heart disease. It has been reported that the endocannabinoid system executes a pivotal part in the management of food absorption, fat augmentation, and energy balance. In the present manuscript, we report a detailed QSAR analysis for 165 CB1 cannabinoid receptor inhibitors employing the Monte Carlo optimization process incorporated within the CORAL software. Eight splits are made from the whole dataset and sixteen QSAR models are developed from these splits employing two target function TF_1 (without index of ideality of correlation) and TF_2 (with index of ideality of correlation). All the QSAR models developed with TF_2 have better predictive potential than the models developed with TF_1. The model built for split 5 using TF_2 is the leading model due to the higher value of the determination coefficient of the validation set ($R^2_{Valid} = 0.8518$). The index of ideality of correlation (IIC) improves the statistical performance of CORAL-based QSAR-models and gives statistically robust predictive models of the investigated endpoint pIC_{50}. In the present manuscript, a novel criterion "Correlation Contradiction Index (CCI)" is also applied to know its predictive potential. The absolute value of CCI for calibration set is less when QSAR models are developed employing IIC. The promoters of increase and decrease endpoint pIC_{50} are identified and these are applied to design seven new compounds. All the newly designed molecule were docked into in the active site of human cannabinoid receptor CB1 (PDB ID: 5tgz).

1. Introduction

Obesity is a worldwide health problem. In 2016, about 74 million boys and 50 million girls were overweight and obesity has greatly increased in recent decades [1]. Obesity has acquired notable attention due to its high occurrence and link with grievous health problems such as hypertension, diabetes and heart disease [2–4]. Food and Drug Administration (FDA) has approved the only one medicine, Orlistat, to treat the obesity in children and adolescents. Whereas in adults, the FDA has recommended six drugs i.e. Orlistat, Phentermine, Bupropion, Lorcaserin and Liraglutide for obesity treatment. The therapeutic potential of these drugs has been limited due to their unwanted side effects and variable efficacy [5,6]. Therefore, the novel target development for the anti-obesity drug is still a challenge to the medicinal chemist [7,8]. Literature survey reveals that the endocannabinoid system gave a new platform for anti-obesity drug development [9–13]. It has been reported that the endocannabinoid system executes a pivotal role in the management of food absorption, fat augmentation, and energy balance [14]. The hyperactivation of this endogenous signalling system appears to be firmly associated with abdominal obesity and the progress of the metabolic syndrome. The two cannabinoid receptors subtypes, CB1 and CB2, are a member of the G-protein coupled seven-transmembrane-spanning receptor family (GPCRs) [15,16]. The CB1 and CB2 receptor are expressed in the central nervous system & peripheral tissues and immune system, respectively. The CB1 receptor is presumed to be associated in the management of perception, motor activity, sensation, idea, understanding through thought, the senses, intuition resulting from the process of cognition and the suppression of transmitter release through its coupling to ions channels [17,18]. The antagonism of CB1 receptor has been discovered by the scientific community as an alluring target for obesity therapy because the specific blockage of this receptor can induce bodyweight reduction [14,15,17].

Quantitative structure-activity relationship (QSAR) is an important

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List of abbreviation

CB1	Cannabinoid Receptor-1
CCC	Concordance Correlation Coefficient
CORAL:	CORrelations And Logic
IIC	Index of Ideality Correlation
MAE	Mean Absolute Error
QSAR	Quantitative Structure Activity Relationship
SMILES	Simplified Input-Line Entry System
CCI	Correlation Contradiction Index
TF	Target fuction

part of computer-assisted drug design (CADD) and it has been effectively applied for designing of new lead molecules [19–22]. QSAR correlates the endpoints with the structural features of the molecules. Especially, the CORAL software (http://www.insilico.eu/coral) based on the Monte Carlo algorithm has been extensively used for designing the QSAR models [19,20,23–27]. In this software, the molecular attributes obtained from simplified input-line entry system (SMILES) and molecular graph have been applied to develop QSAR models. The molecular descriptor in terms of correlation weight (CW) has been calculated by CORAL software and the numerical value of CW gives a maximal value of a target function. This method is applied by the different research group for a large number of various physicochemical, biochemical, ecological, and medicinal endpoints [19,23–25]. In the last few years, the index of ideality correlation (IIC) has been calculated to judge the predictive potential of built QSAR model and it helps to predict the better model in place of various statistical parameters such as Q^2, Q^2F_1, Q^2F_2, Q^2F_3 etc [19,28–31].

In continuation to our work on QSAR [32–34] and synthesis of pharmacological active heterocyclic compounds [35–42], we herein publicize the CORAL based QSAR-models for 165 CB1 cannabinoid receptor inhibitors. In this manuscript, two new criteria Index of ideality correlation (IIC) and Correlation Contradiction Index (CCI) is also studied.

2. Materials and method

2.1. Dataset

A total of 165 CB1 cannabinoid receptor inhibitors were taken from the database https://www.ebi.ac.uk/chembl/old/(CheMBL ID are given in Supporting information) and same experimental condition was applied to measure the IC_{50} of CB1 receptor [6,17,43,44]. All IC_{50} (nM) values for CB1 cannabinoid receptor were converted into the corresponding pIC_{50} ($-logIC_{50}$) and it is taken as a dependent factor for the building of QSAR models. Eight splits were made from the whole dataset and each split was

Table 1
Percentage of the identity of splits 1–8 CB1 receptor inhibitors.

Split	SET	Split 1 (%)	Split 2 (%)	Split 3 (%)	Split 4 (%)	Split 5 (%)	Split 6 (%)	Split 7 (%)	Split 8 (%)
Split 1	Total	100	0.0	0.0	0.0	25.5	24.8	24.2	25.5
	Training	100	0.0	0.0	0.0	24.4	26.5	24.4	24.4
	Invisible training	100	0.0	0.0	0.0	26.2	24.1	24.1	26.5
	Calibration	100	0.0	0.0	0.0	26.5	24.1	23.8	26.5
	Validation	100	0.0	0.0	0.0	24.7	24.7	24.7	24.4
Split 2	Total		100	0.0	0.0	24.8	25.5	25.5	24.2
	Training		100	0.0	0.0	24.1	26.2	26.5	24.1
	Invisible training		100	0.0	0.0	26.5	24.4	24.4	24.4
	Calibration		100	0.0	0.0	24.7	24.7	24.4	24.7
	Validation		100	0.0	0.0	24.1	26.5	26.5	23.8
Split 3	Total			100	0.0	24.2	25.5	25.5	24.8
	Training			100	0.0	24.7	24.4	24.7	24.7
	Invisible training			100	0.0	23.8	26.5	26.5	24.1
	Calibration			100	0.0	24.1	26.5	26.2	24.1
	Validation			100	0.0	24.4	24.4	24.4	26.5
Split 4	Total				100	25.5	24.2	24.8	25.5
	Training				100	26.5	23.8	24.1	26.5
	Invisible training				100	24.4	24.7	24.7	24.7
	Calibration				100	24.4	24.4	26.5	24.4
	Validation				100	26.5	24.1	24.1	26.2
Split 5	Total					100	0.0	0.0	0.0
	Training					100	0.0	0.0	0.0
	Invisible training					100	0.0	0.0	0.0
	Calibration					100	0.0	0.0	0.0
	Validation					100	0.0	0.0	0.0
Split 6	Total						100	0.0	0.0
	Training						100	0.0	0.0
	Invisible training						100	0.0	0.0
	Calibration						100	0.0	0.0
	Validation						100	0.0	0.0
Split 7	Total							100	0.0
	Training							100	0.0
	Invisible training							100	0.0
	Calibration							100	0.0
	Validation							100	0.0
Split 8	Total								100
	Training								100
	Invisible training								100
	Calibration								100
	Validation								100

& editing.

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Appendix A. Supplementary data

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Cytotoxicity of quantum dots: Use of quasiSMILES in development of reliable models with index of ideality of correlation and the consensus modelling

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ABSTRACT

The assessment of cytotoxicity of quantum dots is very essential for environmental and health risk analysis. In the present work we have modelled HeLa cell cytotoxicity of sixty one CdSe quantum dots with ZnS shell as a function of its experimental conditions and molecular construction using quasiSMILES representations. The index of ideality of correlation helps in the building of ten statistically significant models having good fitting ability with value of R^2 ranging from 0.8414 to 0.9609 for the training set. The split 5 model is rated as the best model with values of R^2, Q^2_{F1}, Q^2_{F2} and Q^2_{F3} as 0.8964, 0.8267, 0.8264 and 0.8777 respectively for the calibration set. The extraction of features causing increase and decrease of cytotoxicity of quantum dots indicates importance of neutral surface charge, surface modified with protein, 72 h exposure time, combination of MTT assay with surface protein in decreasing the cytotoxicity. Amphiphilic polymer, polyol ligand with neutral charge, 0.5 – 0.6 nm quantum dot diameter with lipid ligand and unmodified positively charged surface are grouped in toxicity enhancer features. Further, consensus modelling using split 5 and 8 patterns enhances the prediction quality by increasing the R^2_{val} to 0.9361 and 0.9656 respectively.

1. Introduction

Quantum Dots (QDs) have wide range of applications in various fields like quantum computing, solar cells, laser diodes, LEDs, transistors, displays and medical imaging (Choi et al., 2018; Imamoglu, 2003; Jin et al., 2011; Kahmann et al., 2020; Reithmaier and Forchel, 2003; Sakho and Oluwafemi, 2019). Extensive work is going on to make these attractive nanomaterials applicable for pharmaceutical and medical purposes because of their potential features of greater quantum yield, broad excitation, narrow emissions and superb photostability (Bajwa et al., 2016; Reshma and Mohanan, 2019). However the increasing opportunities in biological applications for quantum dots have introduced significant concerns with respect to their toxicological effects (Hu et al., 2017).

Many reports show that many QDs are cytotoxic in nature (Shiohara et al., 2004; Rozenzhak et al., 2005; Deka et al., 2009; Lee et al., 2010; Zhang et al., 2010; Bakalova et al., 2011; Chahal et al., 2012; Yeh et al., 2013) and causes inhibition of cell development, mitochondrial dysfunction, DNA destruction, and apoptosis (Nikazar et al., 2020). The cytotoxicity is influenced by the chemical and physical properties of QDs like size, surface ligand, charge, concentration etc (Oh et al., 2016). Therefore determination of cytotoxicity of QDs is very important. To check the toxicity in vitro and in vivo is expensive and also much harmful for the animals which are being employed for testing (Erhirhie et al., 2018) but there exist no other method to easily assess the cytotoxicity of QDs till date.

Computational methods enjoy the top positions in prior determination of toxicity of chemicals (Raies and Bajic, 2016) and among these methods, quantitative structure activity relationship (QSAR) techniques are of paramount importance. In this process the endpoint of any series of structures is correlated with the chemical and physicochemical characteristics of the compounds via mathematical functions (Buglak et al., 2019; Basant et al., 2016). The era of QSAR started with the use of graph based descriptors as independent variables (Bonchev et al., 1980; Randić, 2001). Later on simplified molecular input-line entry system (SMILES) notations of the molecules has been frequently used in the creation of robust and predictive QSAR models for many endpoints including physical, chemical and biological endpoints through the

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illustrates the comparison of MAE (95 %) for individual and three consensus models for validation sets of both splits. All these outcomes suggest that the consensus model can be used for better prediction of the cytotoxicity of the quantum dots of cadmium.

4. Conclusion

This study was designed to develop the quantitative feature toxicity relationship models for the prediction of cytotoxicity of sixty one CdSe quantum dots using quasiSMILES representations. The increase in the weight of index of ideality of correlation from 0.0 to 0.2 resulted in formation of statistically reliable models with high prediction capability. Model generated with split 5 was most successful in calibration set prediction with value of prediction quality parameter Q^2_{F1} as 0.8267. Extraction of cytotoxicity modulating features pointed towards the involvement of 0.6−0.7 nm QDs diameter and its combination with polyol ligand, neutral unmodified surface, WST assay with 72 h exposure time in reducing the cytotoxicity while unmodified surface and positive surface charge with lipid were favourable for cytotoxic effects of quantum dots. Original consensus models made from ten individual models using split 5 and 8 patterns were more predictive for validation sets and the value of determination coefficient for validation sets increased to 0.9361 and 0.9656 respectively. The mean absolute error (95 %) was also reduced to 0.0815 for split 8 validation set. The resultant consensus models also possessed wider applicability domain containing all the calibration and validation set objects and can be used for prediction of cytotoxicity of QDs with reliability. This combination of index of ideality of correlation and consensus modelling can be applied for predictive and accurate modelling of different endpoints related with nano as well as other materials.

CRediT authorship contribution statement

Ashwani Kumar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing - original draft, Writing - review & editing. **Parvin Kumar:** Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.123777.

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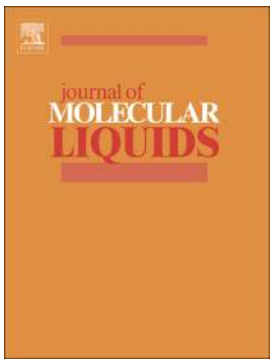

Quantitative structure toxicity analysis of ionic liquids toward acetylcholinesterase enzymes using novel QSTR models with index of ideality of correlation and correlation contradictions index

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Quantitative Structure Toxicity Analysis of Ionic Liquids toward Acetylcholinesterase Enzymes Using Novel QSTR Models with Index of Ideality of Correlation and Correlation Contradictions Index

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Abstract: Ionic liquids (ILs) have enticed the curiosity of chemists due to their vast applications in academic and industrial research. These have many advantages over other conventional solvents such as broad liquid temperature, negligible vapour pressure, non-volatility, etc. But, from an environmental point of view, these advantages can develop heterogeneous toxic results when released into the environment. It is important to predict the toxicity of ionic liquids. A useful tool for predicting ILs toxicity is the quantitative structure-toxicity relationship (QSTR). The toxicity of ionic liquids is evaluated by predicting the acetylcholinesterase (AChE, EC3.1.1.7) enzyme inhibition. In the present manuscript, an exhaustive QSTR analysis for 229 ionic liquids as an acetylcholinesterase enzyme inhibitor is described using the inbuilt Monte Carlo optimization method of CORAL software. Eleven splits are prepared and from these split, 22 QSTR models are developed using two target functions, i.e. TF_1 (without IIC) and TF_2 (with IIC). All models developed by TF_2 are robust and have better predictability. The model developed for split 1 using TF_2 is considered as the best model (R^2_{Valid} = 0.7782). In the present work, a novel parameter "Correlation Contradiction Index (CCI)" is studied to recognize its predictability. The docking simulation was also performed to understand the mechanistic interpretation. Further, the mechanistic interpretation of the best QSTR model was in good correlation with the three-dimensional studies of ligand binding. In order to see the true picture of inhibitory potential, ligand transport study of five ILs (IL015, IL040, IL116, IL156 and IL211) was studied in the tunnel leading to the active site of AChE using the services of Caver Web. Result of the transport study showed that these ILs formed a most stable complex in the active site and not in the tunnel and did not obstruct the tunnel for the accessibility of the enzyme active site for the substrate.

Keyword: QSTR, Ionic Liquids, Toxicity, Acetylcholinesterase, IIC, CCI

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CRediT author statement:

Both authors have an equal contribution.

Ashwani Kumar: Data curation, Software, Validation, Literature survey, Reviewing and Editing

Parvin Kumar: Conceptualization, Methodology, Software, Writing- original draft, Reviewing and Editing

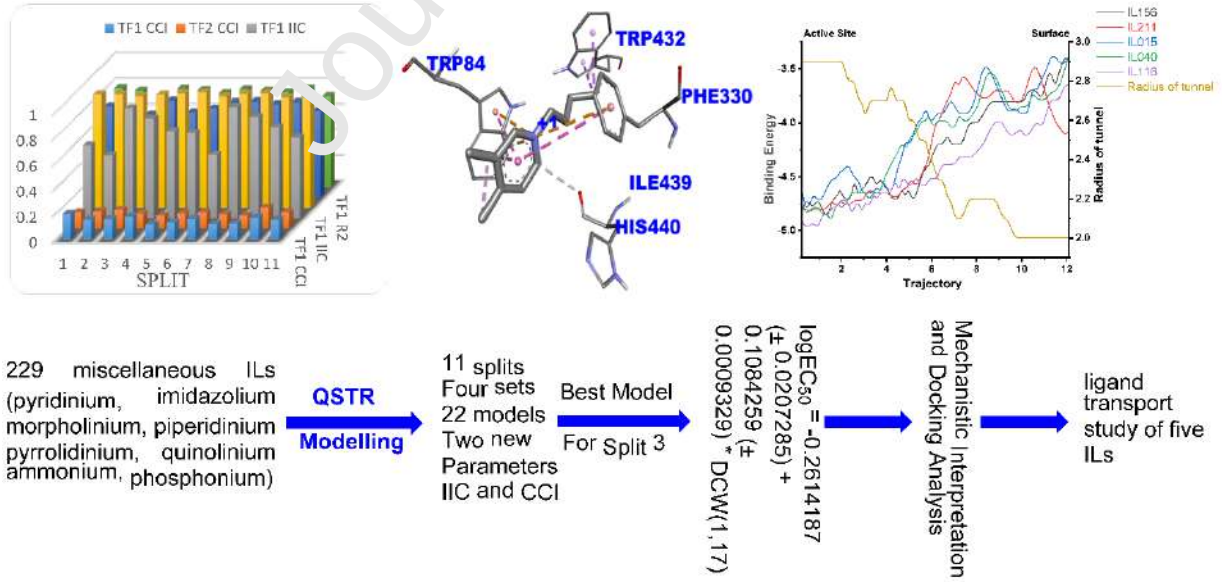
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

GRAPHICAL ABSTRACT

The Correlation Contradictions Index (CCI): Predicting the Toxicity of Ionic Liquids toward Acetylcholinesterase Enzymes Using Novel QSTR Models with Index of Ideality of Correlation

Ashwani Kumar[a], Parvin Kumar[b]*



Highlights:

- 22 QSTR models for 229 of ionic liquids are developed from 11 random splits
- Toxicity of ionic liquids are predicted toward acetylcholinesterase Enzymes
- IIC and CCI are examined as a criterion of predictive potential
- The mechanistic interpretation was confirmed by the docking studies
- Ligand transport study of five ILs was studied using the Caver Web Server

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Synthesis, Crystal structure and DFT studies of Polyfunctionalized Alkenes: A transition Metal-Free C(sp^2)-H Sulfenylation of electron deficient Alkyne

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ABSTRACT

An efficient, novel and transition metal-free protocol has been developed for the synthesis of polyfunctionalized aminothioalkenes *via* direct C–H sulfenylation of *in situ* generated enamines. The reaction was performed using a catalytic amount of inexpensive and nontoxic K_2CO_3 under mild reaction condition. All the reactions resulted in good to excellent yields. The cross-coupling reaction has been achieved by *in situ* aerobic oxidation at room temperature with good functional group tolerance. The molecular architecture and stereochemistry has been established by spectral data, X-ray single crystal diffraction studies and supported by Density Functional theory (DFT). Hirshfeld surface analysis has been used to explore the intramolecular and intermolecular interactions present in the case of **4a**. Moreover, the intramolecular hyperconjugative interactions have been investigated using natural bond orbitals (NBOs) analysis and their intensity was categorized according to their second-order stabilization energy (E(2)). The electrostatic properties such as global reactivity descriptors, local reactivity descriptors, ESP and NLO have been investigated using DFT method and B3LYP/6–311+*G*(d) level of theory.

1. Introduction

Development of novel, green and accessible procedures for the synthesis polyfunctionalized functionalities is a worthwhile contribution in organic synthesis. The progression of new C-S cross-dehydrogenative coupling (CDC) strategies attract synthetic organic chemists due to wide application of organosulfur compounds in pharmaceuticals, agrochemicals, organic dyes, and materials chemistry [1–6]. The C–H activation is a class of organic transformations [7–9], wherein the Heck reaction has established itself with high practicality [10,11]. Lately, the cross-coupling (CC) reaction of aryl halides with aryl thiols has become one of the most efficient method for C-S bond formation. A number of CDC reactions have been developed recently to form C_{sp}-C_{sp}, C_{sp}-$C_{sp}{}^2$ and $C_{sp}{}^2$-$C_{sp}{}^2$ bonds [12–19]. With the focus on emergence of "*atom-economy*" [20,21] and "*green chemistry*"[22] in organic synthesis, transition metal-free functionalization and specially, the C–C and C-X bond formation *via* C–H activation or CDC reactions has become more important.

Several CDC reaction based methodologies have been developed for thiolation/sulfenylation *via* C–H activation which, however, require synthesis of thiolation reagents initially [23–31]. Direct utilization of arylthiols as sulfenylating agent in metal-free protocols have not been explored to a significant extent. Thiolation/sulfenylation of five and six membered heterocycles has been reported using transition metal-free reagents *viz.* I_2/BSA [32], K_2CO_3/DMSO [33], I_2/DMSO [34], *N*-chlorosuccinimide [35], I_2/DMSO [36], and $KClO_3$/ethylacetate [37]. Molecular oxygen has been utilized as mild oxidant in organic synthesis by various research groups in C–H oxygenation [38], C–H amination [39] and C–H thiolation of enamines/enaminones [40,41]. To the best of our knowledge, synthesis of polyfunctionalized alkenes *via* CDC mediated sulfenylation of enamines by using environmentally benign method has not been explored yet.

The non-covalent interactions largely affect the molecular architecture by controlling the aggregation process in crystals. [42] The role of strong hydrogen bonds (O—H••••O, N—H••••H, N—H••••O etc.) is very significant in crystal packing [43]. Further, crystal pack-

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Table 1
Optimization of reaction conditions[a].

Entry	Base (equiv.)	Solvent	Time(h)	Yield(4a)
1.	–	CH_3CN	24 h	No reaction
2.	K_2CO_3 (2)	CH_3CN	24 h	42[b]
3.	K_2CO_3 (1)	CH_3CN	24 h	32[b]
4.	K_2CO_3 (4)	CH_3CN	24 h	42[b]
5.	K_2CO_3 (4)	EtOH	24 h	42[b]
6.	K_2CO_3 (4)	THF	24 h	20[b]
7.	K_2CO_3 (4)	DCM	24 h	36[b]
8.	K_2CO_3 (4)	DMF	12 h	76
9.	K_2CO_3 (4)	DMSO	09 h	83
10.	NaOH (4)	DMSO	24 h	68
11.	Cs_2CO_3 (4)	DMSO	24 h	78
12.	K_2CO_3 (4)	DMSO	24 h	No reaction[c]

[a] **Conditions: 1a** (1.0 mmol), **2a** (1.0 mmol) and **3a** (2.0 mmol), base in 5 mL of solvent at room temperature;
[b] Incomplete Reaction;
[c] reaction was attempted under N_2 atmosphere.

Table 2
Synthesis of polyfunctionalized aminothioalkenes (**4a-4i**).

Compound no	R^1	R^2	Ar	Time (h)	Yield (%)
4a	OMe	H	C_6H_5	09	83
4b	OMe	H	4-ClC_6H_4	08	82
4c	OMe	H	2-Naphtyl	12	85
4d	Cl	H	4-ClC_6H_4	10	85
4e	Br	H	4-BrC_6H_4	24	78
4f	Me	H	4-MeC_6H_4	12	86
4g	H	H	4-ClC_6H_4	12	81
4h	F	H	4-ClC_6H_4	24	80
4i	Cl	Cl	2-Naphthyl	12	82

ing in molecules devoid of these strong directional forces depends mainly upon weak interactions. The role of -CH group in self-assembly is well established and plays a significant role in crystal packing [44]. DFT based theoretical methods provide an alternative to crystallography for molecular structure prediction. The detailed exploration of structural features from optimized molecular geometry using DFT based methods is one of our interest [45]. [46]

Keeping in view the need of development of novel transition metal-free methodologies and continuing our interest in the same field [47–50], we have carried out metal free C–H sulfenylation of *in situ* prepared enamines and their detailed structural study using X-ray single crystal diffraction studies (XCDS) and DFT methods

2. Results and discussion

2.1. Chemistry

The direct sulfenylation of *in situ* generated enamine was investigated using a one-pot, three-component protocol, where dimethylacetylenedicarboxylate (**1a**), *p*-anisidine (**2a**) and thiophenol (**3a**) were used as model substrates. Firstly, a mixture of dimethylacetylenedicarboxylate (**1a**) (1.0 mmol) and *p*-anisidine (**2a**) (1.0 mmol) was stirred at room temperature in ethanol for 5 min. After the formation of enamine, as monitored by TLC using EtOAc: Pet ether (10:90, *v/v*) as solvent, ethanol was removed under reduced pressure and 2.0 mmol of thiophenol **(3a)** in 5 mL of CH_3CN was added to the reaction mixture. The contents were stirred at room temperature and the progress of the reaction was monitored using TLC for 24 h. No new product formation was observed in the reaction even after 24 h (Table 1, entry 1) (Scheme 1). The same model reaction was further explored using K_2CO_3 (2 equiv.) as a base. A new spot was observed on TLC, however, the reaction was incomplete even after 24 h. The reaction was quenched by adding ice. The reaction mixture was extracted using DCM, dried over anhyd. Na_2SO_4 and chromatographed over silica gel (230–400) using EtOAc: Pet ether (2:98, *v/v*) as eluent. The solid thus separated was characterized as dimethyl 2-((4-methoxyphenyl)amino)-3-(phenylthio)fumarate **(4a)** using ^1H NMR, ^{13}C NMR and X-ray single crystal diffraction studies (XCDS) and was obtained in 42% yield (Table 1, entry 2).

In order to develop a highly efficient and convenient methodology for the synthesis of aminothioalkenes **(4)**, the scope of the same model reaction was further explored using different concentration of base *i.e.,* 1 eq. and 4 eq. of K_2CO_3 (Table 1, entries 3 & 4). It was observed that reaction went to completion with high yield when higher concentration of base was used (Table 1, entry 4).

A variety of solvents *i.e.,* EtOH, THF, DCM, DMF and DMSO were explored in the same model reaction using K_2CO_3 (4 equiv.) as a base (Table 1, entry 5–9). In first three cases, reactions did not proceed to completion even after 24 h and gave 42%, 20% and 36% of **4a**, respectively (Table 1, entries 5–7) while in case of DMF, the reaction was complete in 12 h but gives **4a** in 76% yield (Table 1, entry 8). To our delight, the reaction carried out in DMSO at room temperature under ideal conditions resulted in 83% yield of **4a** in 9 h (Table 1, entry 9). The effect of different bases like NaOH and Cs_2CO_3 (Table 1, entries 10 & 11) was also explored. However, no significant improvement in yield and reaction time was observed in both the conditions. In order to explore the role of air, the reaction was carried out under N_2 atmosphere and no desired product **(4a)** were detected (Table 1, entry 12). It can be inferred that thiol **3a** undergoes aerobic oxidation *in situ* to disulfide. This shows that the reactions occurring *via* an aerobic oxidative cross-coupling.

It can be inferred from above results that the reaction of dimethylacetylenedicarboxylate (**1a**) (1 mmol), *p*-anisidine (**2a**) (1 mmol) and thiophenol (**3a**) (2 mmol) in presence of 4 equiv. of K_2CO_3 using DMSO as solvent is the standardized reaction condition for the synthesis of dimethyl 2-(phenyl)thio)-3-((4-methoxyphenyl)amino)fumarate **(4a)**.

The developed methodology was then extended to other substrates by carrying out reactions of dimethylacetylenedicarboxylate (**1a**) with substituted thiophenol and aniline under otherwise identical conditions (Scheme 2). All the reaction gave the corresponding polyfunctionalized alkenes in high yields in 8–24 h under similar condition **(4b-4i)**. The developed methodology failed to yield desired product when aliphatic thiol (*n*-hexanethiol) was reacted with *in situ* generated enamine under identical conditions.

We believe that the thioarylation proceeds by a nucleophilic attack of *in situ* generated enamine on diphenyldisulfide linkage followed by isomerization to give the desired product (Scheme 3). The initial formation of enamine from dialkyl acetylenedicarboxylate and aromatic amine in ethanol was followed by removal of ethanol under reduced pressure. This was followed by addition of 2 eq. of thiophenol which undergoes aerial oxidation in K_2CO_3/DMSO, followed by attack of enamine on disulphide to give the desired compound polyfunctionalized aminothioalkenes.

2.2. Molecular structure (X-ray diffraction)

The detailed molecular structure of dimethyl 2-((4-methoxyphenyl)amino)-3-(phenylthio)fumarate **(4a)** was explored using XCDS. The *trans* stereochemistry of double bond in **4a** was confirmed from the structure derived from diffraction studies (Fig. 1). The ORTEP view of the asymmetric unit along with the optimized structure of **4a** are shown in Fig. 1. The refinement details and crystallographic parameters are provided as supplementary material (Table S1). The molecule **4a** crystallises in monoclinic system within *p21/n* space group with lattice parameter a = 10.8877(2) Å, b = 20.6639(3) Å, c = 8.1934(8) Å with β= 90.502(3)° respectively.

Dimethyl 2-((4-chlorophenyl)thio)-3-((4-fluorophenyl)amino)fumarate (4 h)

Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$)δ_H 10.79 (s, 1H, NH), 7.27–7.12 (m, 6H, ArH), 7.03 (t, J = 8.5 Hz, 2H, ArH), 3.72 (s, 3H, $COOCH_3$), 3.63 (s, 3H, $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$)δ_C 170.34, 162.74, 161.03(d, $^1J_{C\text{-}F}$ = 246 Hz), 159.39, 137.01, 134.14, 131.38, 128.77, 127.72, 125.33, 116.26 (d, $^2J_{C\text{-}F}$ = 24.7 Hz), 85.57, 52.54, 52.15.

Dimethyl 2-((3,4-dichlorophenyl)amino)-3-(naphthalen-2-ylthio)fumarate(4i)

Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$)δ_H 10.95 (s, 1H, NH), 7.81–7.72 (m, 3H, ArH), 7.66 (s, 1H, ArH), 7.49–7.35 (m, 4H, ArH), 7.29 (d, J = 2.7 Hz, 1H, ArH), 7.02 (dd, J = 8.7, 2.7 Hz, 1H, ArH), 3.71 (s, 6H, 2 X $COOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$)δ_C 170.65, 163.05, 158.27, 137.49, 135.77, 133.82, 132.68, 131.82, 128.41, 127.83, 127.26, 126.50, 125.46, 124.91, 124.41, 124.12, 119.56, 87.16, 52.87, 52.45.

5.2 X-ray crystal studies

The single crystal of compound **4a** suitable for X-ray analysis was obtained by slow evaporation method using acetonitrile as solvent. Single, clear, whitish block of single crystal of **4a** suitable for X-ray was mounted on Xcalibur, Sapphire3 diffractometer using mylar loop. The data collection was done at a steady temperature of T = 298 K. The structure was solved using Olex2 [64] and the model was refined with ShelXL using full matrix least squares minimisation on F^2 [65]. The final completeness is 100% out to 29.556° in Θ. A multi-scan absorption correction was performed using CrysAlisPro 1.171.38.46 (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The absorption coefficient μ of this material is 0.205 mm^{-1} at this wavelength (λ = 0.71073 Å) and the minimum and maximum transmissions are 0.796 and 1.000. Crystal explorer 17.5 was used for Hirshfeld surface generation and 2d fingerprint analysis [66]. Crystallography data excluding structure factors has been deposited on Cambridge crystallography database with CCDC no. **1,993,445** for **4a**.

5.3 Computational details of dft studies

All DFT calculations presented in the present manuscript were performed with Gaussian 09 program package [67] using hybrid exchange correlation functional B3LYP and 6–311(+)G(d) basis set [68]. Initially, the geometry of all the polyfunctionalized aminothiols **(4a-4i)** was optimized using same level of theory. No imaginary frequencies were found for any of the structure, which indicates their stability at global minima. Density of states (DOS) were calculated using Gausssum 3.0. [69] After optimization of the molecular geometries, the global reactivity descriptors were calculated utilizing the information contained in FMO's [70,71]. The NBO calculations were performed using NBO 3.0 program implemented in Gaussian 09 W package using the same level of theory to explore the hyperconjugative interaction present in the molecule [72]. Thereafter, Fukui function were calculated from same NBO analysis at same level of theory to explore the possibility of charge transfer in polyfunctionalized aminothiols **(4a-4i)**. Avogardo 2.0 was used for the visualization of the results of DFT calculations. [73]

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2020.129089.

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REVIEW ARTICLE

A review of antimalarial activity of two or three nitrogen atoms containing heterocyclic compounds

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Abstract
Malaria, a nocuous disease, which has become a major challenge for the health resulting in deaths of millions of people around the globe. Malaria is a parasitic disease propagated by mosquitoes and infects the human beings. Several species of *Plasmodium* are responsible for this life-threatening disease and *Plasmodium falciparum* being the most virulent. In order to eradicate the malarial parasite, the researchers are making consistent efforts in synthesizing new antimalarial drug candidates by paying attention to the various drug targets. In this manuscript, the main focus is on the antimalarial activity of numerous heterocyclic compounds reported by the researchers since 2010 against the different strains of *Plasmodium*. Antimalarial activities of the two and three nitrogen-containing heterocycles along with their structure–activity relationship are described.

Keywords Malaria · *Plasmodium falciparum* · Heterocycles · Antimalarial activity · Structure–activity relationship

Introduction

Malaria, a vector-borne infectious disease, is one of the utmost annihilating diseases of the ever-changing world predominated chiefly in tropical regions (Ridley 2002). The World Health Organization evaluated 219 million malaria cases across the entire globe, an increment of 2 million from the preceding year and 435 thousand quietus at annual frequency as well as 1190 on daily occurrence, predominantly moppets (Tse et al. 2019). Six species of single-celled eukaryotic *Plasmodium* parasites are the causative agents of malaria: *P. knowlesi, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae*, and *P. falciparum*. Out of all these, *P. falciparum* is liable for ~90% of the infections (Lee et al. 2019). *Plasmodium falciparum* is the most noxious and has the highest rates of complications, mortality as well as the prevalence of erythrocytic disorders globally (Buffet et al. 2011). *Plasmodium* is an obligate intracellular parasite that requires two hosts for the completion of its life process, i.e., for sexual life cycle—an arthropod vector and asexual life cycle-human host (Jensen et al. 2020). Administration of the transmissive form i.e., the sporozite into the human skin with the assistance of the female Anopheles mosquito with an anticoagulant saliva prior to the blood meal. Sporozoites intrude the lymphoid system and get dispersed to defile the liver. In the liver, they turn out to be intracellular and escalate to embody hundreds of merozoites that are actually invasive (the pre- or exo-erythrocytic phase). Merozoites are discharged into the blood stream and assail the erythrocytes. The parasite *Plasmodium* nourishes on its host cell within an erythrocyte, thereafter proliferates to form corresponding merozoites which move out and invade novel erythrocytes, the cycle reoccurs. There is a variation in time within different species from invasion to exit, 48 h for *P. vivax* and *P. falciparum* and 72 h for *P. malariae* and *P. ovale*, the contemporaneous release of merozoites coexisting with fever peaks. Ultimately a sexual phase commences where the parasite develops intrinsically in its host cell into either a macrogametocyte i.e., a female gametocyte or a male gametocyte i.e., a microgametocyte. The reliance on the continuation of the life process is on gametocytes being carried into the feeding female mosquito's gut where twain of gametocytes flee from their host cells. Male gametocytes segregate abruptly into numerous locomotive whip-like microgametes, which can individually fecundate a female macrogamete for the formation of a zygote. The parasite

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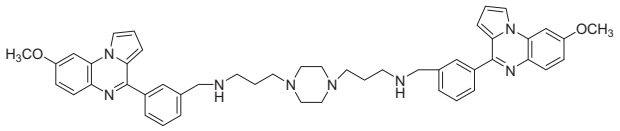
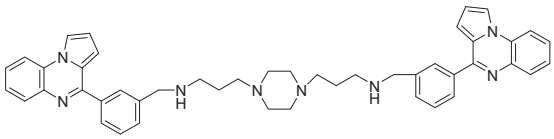
susceptibility strain as well as $IC_{50} = 0.05 \pm 0.01\ \mu M$ for chloroquine-resistant strain (Guillon et al. 2017).



IC_{50}=0.04±0.004μM (3D7strain)

(46)



IC_{50}=0.05±0.01μM (W2 strain)

(47)

Conclusion

Malaria is a disease which posed a great burden on the human beings becoming the cause of mortality of millions of people all over the world. In order to obliterate the parasite responsible for this disease and simultaneous failure of the conventional antimalarial drugs led to the modification of already available drugs as well as development of novel drugs. In this manuscript, a comprehensive review of the two and three nitrogen-containing heterocycles since 2010 has been described. Diverse heterocyclic scaffolds were utilized for the evolvement of more drugs with an enhanced bioavailability and improved physicochemical properties. The activity of numerous compounds was evaluated against various *Plasmodium falciparum* strains such as chloroquine-sensitive, chloroquine-resistant as well as multidrug-resistant strains. More and more novel compounds with an improved pharmacokinetic profile would be synthesized which would be more effective, economic as well as safe for human use. These hybrids would also possess least toxicity and a greater antimalarial potency.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Tankyrase inhibitors: emerging and promising therapeutics for cancer treatment

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Abstract

Cancer is a disease portrayed by the uncontrolled growth of irregular cells. Tankyrase, a member of poly(ADP-ribose) polymerase family, mediates Wnt signal transduction and has emerged as a new molecular target for the therapy of different kinds of cancer. Wnt/β-catenin signaling functions significantly in a wide scope of biological events, such as the upkeep of genomic stability, transcriptional control, energy metabolism, and apoptosis. ADP-ribosylation is a reversible posttranslational modification process that regulates several cellular signaling pathways in which transferase enzymes such as mono (ADP-ribosyl) and poly(ADP-ribosyl) transferases move a unit of ADP-ribose moiety from the NAD^+ co-substrate to specific amino acid side chains and/or potentially ADP-ribose units on target proteins. Recently, inhibition of tankyrase has risen as an appealing strategy for the discovery of novel anticancer drugs. The current review offers an understanding of the ongoing improvements on new lead structures as inhibitors of tankyrase and their activities. A special spotlight is set on the structure-activity relationship, molecular docking, polypharmacology profile, and binding mode at the active center.

Keywords Cancer · Tankyrase · ADP-ribosylation · Wnt/β-catenin signaling · Tankyrase inhibitors

Abbreviations

ARTD	ADP-ribose transferase
PARP	Poly(ADP-ribose)polymerase
TNKS	Tankyrase
PKA	Protein kinaseA
APC	Adenomatous polyposis coli gene
CK1	Casein kinase1
GSK3	Glycogen synthase kinase 3
TCF	T-cell factor
LEF	Lymphoid enhancer-binding factor
LRP6	Lipoprotein receptor-related protein
TRF	Telomere repeat-binding factor
MAPK	Mitogen-activated protein kinase
SAM	Sterile alpha motif
NuMA	Nuclear mitotic apparatus protein
IRAP	Insulin-responsive aminopeptidase

Introduction

The human body comprises a huge number of cells; these cells grow and divide to produce new cells as the body needs them. At that point, when cells grow old or damaged, they die and new cells replace them. The mechanism once in a while goes wrong and various cells grow uncontrolled, which prompts cancer [1]. Cancer is a deadly ailment brought about by uncontrolled cell growth and originates from the additional mass tissue known as tumor and spreads all through the circulatory system in the human body [2]. Leukemia affects the blood cells and includes them in their maturity and immaturity. Some of the tumors do not spread all through the body yet they grow wildly like benign tumors [3]. Normal cells regulate their development and kill themselves when they become unhealthy. Various organs can be influenced by cancer cells like the lungs, kidney, eyes, heart, brain, and so forth [4].

Numerous investigations have indicated that tankyrases assume a fundamental part in the development and progression of distinct types of carcinomas involving fibrosarcoma, pancreatic adenocarcinoma, ovarian cancer, glioblastoma, gastric cancer, breast cancer, and transitional cell carcinoma of the bladder. Tankyrase 1 (TNKS1) and

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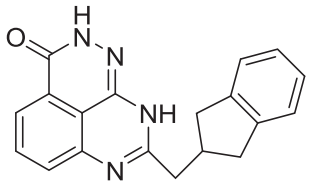
a distinct spectrum of clinical opportunity. E7499 currently completed the first period of the clinical trial [88, 89].



(91) E7449

PARP1/2 IC_{50} = 0.002μM / 0.001μM

TNKS1/2 IC_{50} = 0.05 μM / 0.12 μM

Conclusion

In humans, alteration of TNKS1 and TANK2 and distorted Wnt pathway underlies a wide array of diseases including tumor development, tumor commencement, cell senescence, cell demise, proliferation, and metastasis. In recent decades, tankyrases and the Wnt pathway have proven to be an appealing target for the discovery of anticancer drugs. The tankyrase inhibitors which focus the amino acid of the adenosine binding site along with the residues of the nicotinamide binding site show an exceptionally particular nature for tankyrase over other ARTD isoenzymes. A large number of tankyrase inhibitors that have been developed indicated structural similarity with the significant coenzyme NAD^+, which may cause toxicities due to off-target binding. High specificity is important for the novel tankyrase inhibitors to avoid the potential adverse effects. The literature review demonstrated the computational studies by using various potent compounds that help the researchers to observe a potential association between the coupling site and inhibitor molecule. It shows that the inhibitory activity of nicotinamide restricting site inhibitors can be expanded by designing new analogs that collaborate with hydrophobic amino acids Phe1188 residue of TNKS1 and Phe1035 of TNKS2. Moreover, it is also indicated that adenosine binding site restricted inhibitors form aryl interaction or π–π stacking interaction with polar amino-acids Histidine. This selective character of TNKS1 and TNKS2 inhibitors provides an excellent platform for dual-site binders. A recently established quinazoline derivative was discovered to be more potent when compared with other tankyrase inhibitors. The quinazoline moiety ties to the nicotinamide binding motif and forms hydrogen bonding with glycine and serine. The central part of the moiety constitutes a hydrogen bond with Tyrosine amino acid, while extended lateral chains form hydrogen bonding with aspartate and glycine amino residues of the protein. All these findings will give meaningful clues in the design and advancement of new specific inhibitors that can be utilized to treat different kinds of cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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BIOINFORMATICS AND STATISTICS

Construction of pioneering quantitative structure activity relationship screening models for abuse potential of designer drugs using index of ideality of correlation in monte carlo optimization

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Abstract
Drug abuse is a worldwide wide problem affecting individual, society and the environment in general and it is nothing less than the attempted ecocide. Designer drugs are the chemical substances used for recreational purposes and have addictive properties. The production of designer drugs at disturbing pace is creating difficulties for the investigators in their testing. Computational evaluation method can be an interesting approach for early checking of abusive drugs. In the present work, quantitative structure activity relationship (QSAR) models are developed for abusive potential of designer drugs using SMILES and graph based parameters. Dopamine transporter/serotonin transporter inhibition (DAT/SERT) ratio was used as endpoint and the whole data set was divided into eight non identical splits for development of the models using balance of correlation technique of Monte Carlo optimization. The internal and external cross validation results confirmed that the models created with index of ideality of correlation were reliable and robust in prediction. The developed models followed all the five principles of the Organisation for Economic Co-operation and Development. The best model split 2 possessed good fitting ability and internal as well as external predictive ability and it was used in explanation of activity trends of different classes of designer drugs.

Keywords Drug abuse · Designer drugs · DAT/SERT ratio · Quantitative structure activity relationship · Index of ideality of correlation

Introduction

Drug addiction is a major issue around the world that imposes immense social and economic pressures on people and on society at large (Han and Gu 2006). According to the World drug report 2019, approximately 35 million people are affected with illicit drug use disorders worldwide. Internationally, around 11 million people took injectable illicit drugs in 2017, of whom 1.4 million are infected with HIV and 5.6 million with hepatitis C (Hansford 2019). There is burgeoning worldwide apprehension about the synthetic analogs of controlled drugs being produced and marketed to curtail drug laws and escape prohibition. "Designer drugs" or "legal highs" are the psychotropic drugs which are purposely commercialized and delivered for recreational use by perpetuating shortcomings in current controlled substance legislation (Weaver et al. 2015). Many chemicals alluded as designer pharmaceutical products may be licensed medically in various countries, thus not meeting the standard concept of a designer drug (Luethi and Liechti 2020).

The abuse of designer drugs among youngsters is prevalent, particularly in the "rave and dance club scene" (Richter et al. 2019). Usage of "classic" designer drugs like ecstasy was record high in the 1990s but is still consumed today and that caused the development of most of the "classic" designer drugs in various countries (Langman and Snozek 2019). These drugs generate euphoria and feeling of high energy, and a tendency for socialization. Designer drugs

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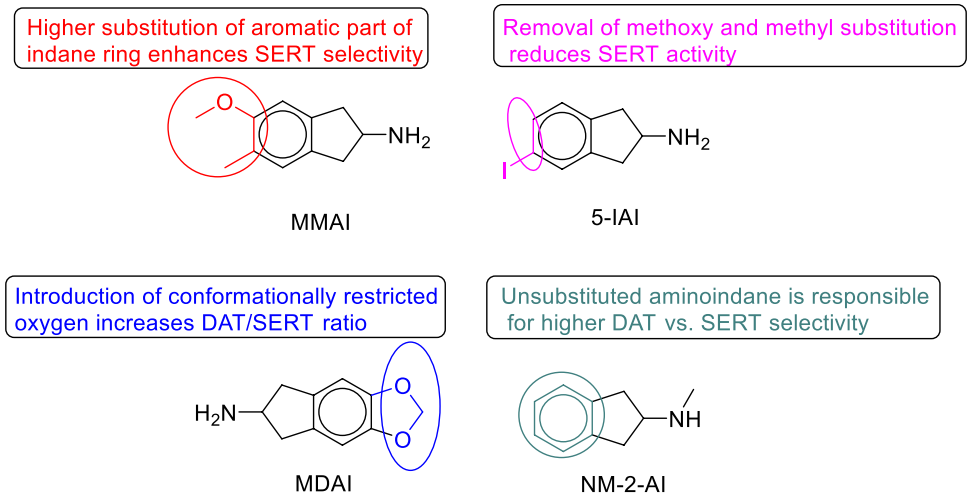

Fig. 8 Description of SAR among Aminoindanes

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

Identification of good and bad fragments of tricyclic triazinone analogues as potential PKC-θ inhibitors through SMILES–based QSAR and molecular docking

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Abstract

Based on the mechanism of action of PKC-θ, the inhibition of this enzyme is considered a potential target for the treatment of autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis. In the present study, 57 structurally diverse tricyclic triazinone analogues as potential PKC-θ inhibitors has been taken into consideration for QSAR analysis through Monte Carlo optimization. QSAR models are developed using the balance of correlation method in the CORAL software with two target functions (TF_1 and TF_2). The models constructed with IIC are found more robust and authentic. The established QSAR model with best $R^2_{calibration} = 0.9653$ for split 3 is considered the topmost model. The predictabilities of the recommended QSAR model are assessed through various statistical parameters. The outlier of each model is also identified using the applicability domain (AD). The common mechanistic interpretation of the increasing and decreasing attributes has been extracted by evaluating the correlation weights of diverse structural attributes obtained in three Monte Carlo optimization runs from two splits, i.e., split 3 and 4. In the last, the result of mechanistic interpretation is validated by performing the docking studies of compounds PKC03, PKC07, PKC16, PKC25, and PKC56 in the experimental structure of protein kinase C-θ (PDB ID: 4Q9Z). The numerical value of the correlation coefficient between calculated activity and binding affinity is found 0.9597. Hence, the developed QSAR models are descriptive and predictive in nature and the results are in sound agreement with the experimental observations.

Keywords Protein kinase C-θ · QSAR · CORAL software · IIC · Docking

Introduction

The immune system is an intricate network of biochemical aspects that warrants the integrity of the organism by attacking potential pathogens [1]. However, sometimes, our immune system overreacts and attacks at the organism itself. Therefore, the abnormalities in the immune system, mainly the over-activation of T cells, lead to autoimmune and other secondary diseases [2, 3]. It has been cited in the literature that humans and mice lacking functional regulatory T cells (Tregs) due to mutations in the Foxp3 gene give way to severe lymphoproliferative and inflammatory disease [4–8]. Considering the significant role of T lymphocytes in monitoring and facilitating different types of immune reactions, the T cells are considered major drug targets for treating immunological disorders [9]. The unsatisfactory results with various side effects of the calcineurin inhibitor drugs, such as cyclosporine A (tacrolimus), lead to the development of new immunosuppressive non-calcineurin inhibitors, especially the PKC-θ inhibitors [10].

The protein kinase C (PKC) enzyme family executes an important part in signal transduction pathways that affect cell proliferation and differentiation. The protein kinase C theta (PKC-θ) is a novel member of Ca^{2+}-independent novel PKC family and it is predominantly expressed in lymphocytes (T cells) and mast cells [11, 12]. The novel isoform PKC-θ performs a significant function in the activation and survival of T cells by transmitting the T cell receptor (TCR) signaling. Literature survey reveals that the response of PKC-θ deficient

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Comparison of the results with reported models

Literature survey reveals that only one manuscript by Lingwei et al. describing the QSAR study of 54 tricyclic triazinone analogues as potential PKC-θ inhibitors is available [45]. The comparison of the present study and the literature report is given in Table 6. Lingwei et al. have developed the QSAR models based on the CoMFA, CoMSIA, HQSAR, and 2D-QSAR study. The reported QSAR models are quite complex. The reported QSAR models are constructed with six or seven variables, i.e., multiparametric model. The numerical value of R^2 and Q^2 for the training set of reported QSAR models is higher than the present leading QSAR model. On the other hand, the actual predictive power of a QSAR model can be evaluated by the test set/calibration set. The value of the determination coefficient R^2_{cal} of the QSAR models constructed by TF_2 for split 3 is 0.9653 which is more than all the reported models. The present work describes the QSAR modeling of 57 tricyclic triazinone analogues using four splits because "QSAR is a random event" while the formerly reported models are developed only using one split. All QSAR models or present research work are statistically significant and monoparametric which makes their interpretation very easy compared with the other reported models. In the earlier report, the statistical parameters IIC, CCC, Q^2_{F2}, and Q^2_{F3} are not reported. In the present QSAR modeling, the structural attributes responsible for the increase and decrease of the endpoint are also reported.

Conclusion

The present research demonstrates the development of new robust and reliable QSAR models for tricyclic triazinone analogues as PKC-θ inhibitors based on the Monte Carlo optimization method. The SMILES were used to symbolize the chemical structures of tricyclic triazinone analogues. The QSAR models were developed using the balance of correlation method in the CORAL software with two target functions (TF_1 and TF_2). The IIC was applied to improve the robustness and predictability of the developed QSAR models with second target function (TF2). The models constructed with IIC were found more robust and authentic. The established QSAR model with best $R^2_{calibration} = 0.9653$ for split 3 was deliberated as the topmost model. The predictabilities of the recommended QSAR model were assessed through various statistical parameters such as R^2, CCC, IIC, Q^2, Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, s, MAE, F, RMSE, R^2_m, ΔR^2_m, $C_{R^2_p}$, and Y test. However, all of the established models were appropriate to predict the PKC-θ inhibition of tricyclic triazinone analogues. The outlier of each model was also identified using the applicability domain (AD). The outliers were absent in all QSAR models developed by TF_1. However, in the case of the QSAR models constructed by TF_2, the number of outliers was 10 and 9 for split 1 and split 3, respectively, while in other splits, outliers were absent. The common mechanistic interpretation of the increasing and decreasing attributes had been extracted by evaluating the correlation weights of diverse structural attributes obtained in three Monte Carlo optimization runs from two splits, i.e., split 3 and 4. In the last, the result of mechanistic interpretation was validated by performing the docking studies of compounds PKC03, PKC07, PKC16, PKC25, and PKC56 in the experimental structure of protein kinase C theta (PDB ID: 4Q9Z). The numerical value of the correlation coefficient between calculated activity and binding affinity was found 0.9597 while it was 0.9837 between experimental activity and binding affinity. Hence, the developed QSAR models were descriptive and predictive in nature and the results were in sound consensus with the experimental observations.

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Authors' contributions Authors have done equivalent contributions to this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Control of growth solution on the dimensions of gold nanorods accounted for LSPR sensitivity toward liquid ammonia sensing

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ABSTRACT

In the present study, the effect of dimensions of gold nanorods on its sensing property to detect liquid ammonia was reported. Gold nanorods with two different aspect ratios (GNR1 and GNR2) derived from different lengths and diameters were synthesized using seed-mediated growth method, and the aspect ratio was controlled by changing the silver ion concentration in growth solution. The morphological and size measurement was performed using Transmission Electron Microscopy (TEM), and the average value of aspect ratio (AR) was found to be 3.0 and 3.2 for GNR1 and GNR2, respectively. The characteristics transverse and longitudinal mode of localized surface plasmon resonance (LSPR) have been clearly depicted in UV–vis absorption spectrum of both GNR1 and GNR2. The red shift in longitudinal mode of LSPR from 718 to 732 nm has been observed for GNR with change in aspect ratio from 3.0 to 3.2, respectively. These samples of GNR were tested for liquid ammonia sensing with concentration ranging from 100 to 500 ppm. A clear cut blue shift in longitudinal mode of LSPR of prepared gold nanorod was observed. However, the GNR2 was found to be more sensitive toward liquid ammonia sensing. The origin of such blue shifting and sensitivity of longitudinal mode of LSPR of gold nanorod was explained on the basis of orientation dependence and Dipolar Exciton Coupling Model of coupled plasmon in assemblies of anisotropic plasmonic nanoparticles. With the help of this model, blue shifting in longitudinal plasmon band was correlated with the enhanced formation of H-aggregation induced by dipolar coupling of GNR clusters followed by hydrogen bonding after successive addition of ammonia solution.

1. Introduction

Over the last decades, nanometer sized structures of noble metal like silver, gold, platinum, etc. have received wide attention due to their special optical response known as surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) [1]. Generally, there is a difference in LSPR and SPR; in LSPR, the induced plasmon oscillate locally to the nanostructure upon interaction with incident electromagnetic radiation while in SPR the induced plasmon oscillate along the metal-dielectric interface [2]. Because of this aspect, the decay length of the exponentially decaying electromagnetic field is observed to be shorter in LSPR than that observed in SPR [3,4]. This decay length for plasmon resonance plays vital role and acts as the foundation for biosensing applications. This property reduces the sensitivity response arises due to interference from solution refractive index as well as pH fluctuations whilst providing increased sensitivity to refractive index changes on the surface. Therefore, directing the larger sensitivity of LSPR to molecular binding and rather than bulk effects. Among various shapes, rod like nanostructures are in a great demand due to anisotropic optical response of LSPR which can be tuned from visible to Infra-red (IR) region of electromagnetic (EM) spectrum, depending upon their aspect ratio [5–7]. The anisotropic optical response relies due to existence of two LSPR absorption band: transverse mode and longitudinal mode of resonance due to the collective oscillation of the quasi-free electrons along the long and short axes of nanorod like structure when excited by EM radiation of comparable wavelength, respectively [8]. The transverse mode is mainly a function of diameter of nanorod observed in a lower side of visible region of EM spectrum and found almost numb to the nanorod morphology. The longitudinal mode observed at higher wavelength side is a function of aspect ratio and refractive index of the surrounding medium and therefore provide tunability of plasmon resonance band covering from green to near IR of EM spectrum wavelength [9,10]. This tunable nature of LSPR benefited from anistropic geometry of noble metal nanorods provide them a wide

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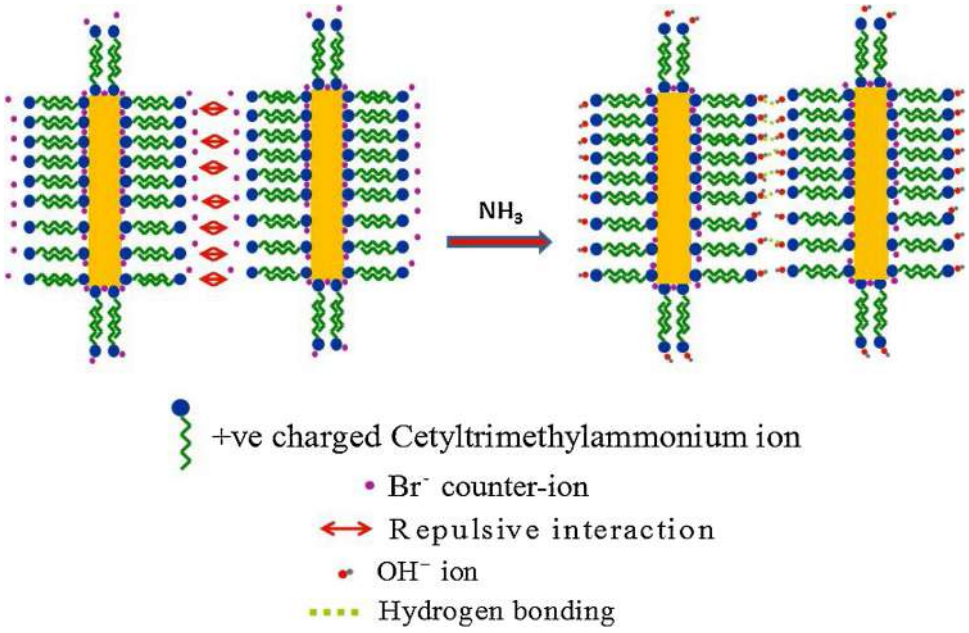

Scheme 2. Effect of ammonia addition on plasmonic coupling between H-aggregates induced by coupling orientation (c) of scheme 1 .

be more sensitive. The formation of H-aggregates is induced by the formation of microscopic dipole on the surface of GNR, which will change the energy absorption and is thus responsible for plasmon shifting and causing such sensitivity. Thus, on the basis of orientation dependence of coupled plasmon of anisotropic nanoparticles and interaction energy dependence of dipole moment in Dipolar Exciton Coupling Model, the coupling of GNR after the addition of ammonia solution is explained. For nanorod with larger length, such couplings are more, resulting in more shifting in plasmonic wavelength leading to their better sensitivity.

Ethics statement

I certify that this article has not been published previously and is not under consideration for publication elsewhere. There is no conflict of interest regarding this article. I also declare if this article will accepted in this journal, then it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the Publisher.

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Synthesis of pyrazole based novel aurone analogs and their cytotoxic activity against MCF-7 Cell line

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Synthesis of pyrazole based novel aurone analogs and their cytotoxic activity against MCF-7 Cell line

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Conclusions

The reaction is highly stereospecific and all the products obtained are geometrically pure Z-isomer obtained in higher yield. Fourteen novel aurones were synthesized and screened against MCF-7 cancer cell line for their anticancer activity. All these compounds exhibited moderate to excellent anticancer activity. Among these fourteen compounds, six compounds (**3e**, **3c**, **3i**, **3a**, **3b** and **3n**) have exhibited excellent cytotoxic efficacy against MCF-7 cell line.

Conflict of interest

The authors declare no conflict of interest.

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Synthesis of pyrazole based novel aurone analogs and their cytotoxic activity against MCF-7 Cell line

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