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A REVIEW SYNTHESIS, EVALUATION AND QSAR STUDY OF SUBSTITUTED 1, 2, 4 TRIAZOLE NUCLEUS

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ABSTRACT

Heterocyclic chemistry has now become a separate field of chemistry with long history, present society and future prospects. Synthesis of new chemical entities is major bottleneck in drug discovery. The earliest compounds known to mankind were of heterocyclic origin. Life, like ours, is totally dependent on the heterocyclic compounds heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as into the related fields such as biochemistry, polymers and material sciences Five-membered nitrogen heterocycle compounds are important structural fragments and considered as biologically active compounds, corrosion inhibitors, pesticides, dyes, acid- base indicator, and other industrial chemicals. This review article covers the latest information over active triazole derivatives having different pharmacological action such as, antiviral, anticonvulsant, anti-inflammatory, antibacterial, antifungal and antituberculosis anxiolytics, anti-convulsants, antimigraine, antihistaminics, CNS stimulants It can act as an important tool for medicinal chemists to develop newer compounds possessing triazole moiety that could be better agents in terms of efficacy and safety. QSAR relies on the basic assumption that molecules with similar physicochemical properties or structures. QSAR is a statistical model that relates a set of structural descriptor of a chemical compound to its biological compound. QSAR studies predict the biological activity, physiochemical properties of the molecules and explain the target of the molecules, which part of synthesized molecule is responsible for the activity. Prediction could reduce the requirement for lengthy and expensive animal tests QSAR study is use full for the large amount of biological target

information is the available in the microbiology. Automation of chemical synthesis and pharmacological screening has also provided a vast amount of experimental data.

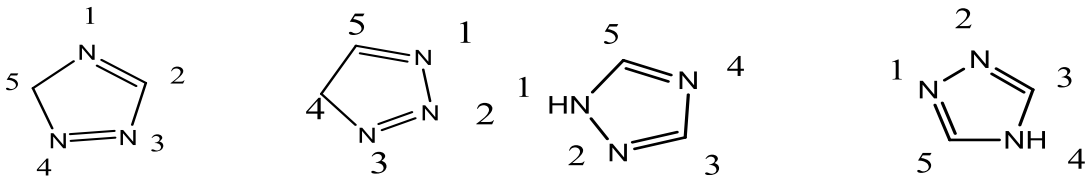
KEYWORD: Antifungal, QSAR, Antibacterial activity. Einhorn–Brunner reaction Dimroth Reaction. Pellizzari Reaction.

1. INTRODUCTION

Triazole and its derivatives have attracted considerable attention for the past few decades due to their chemotherapeutical values Different heterocyclic analogues were evaluated for their diverse biological activities. Out of them, the 1,2,4-triazole nucleus is an ubiquitous structural feature of many synthetic compounds with diversified therapeutic efficacy. A large volume of published literature over the last few decades precludes a comprehensive review. The triazole moiety seems to be very small but its broad biological profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. This article presents a comprehensive review on the pharmacological activities of some novel derivatives of the 1,2,4-triazole moiety. Heterocyclic chemistry is a separate field of organic chemistry with long history and future prospects. Life is totally dependent on the heterocyclic compounds, such as purine and pyrimidine bases (building unit of DNA and RNA).

Now a days, the heterocyclic chemistry brings reagents and synthetic methods of its own usual activity in synthesis of drugs, pesticides and detergents as well as into the correlated fields such as biochemistry, polymers Dyes [and material sciences. Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as in pharmaceuticals, herbicides, dyes, and many more compounds1. These heterocycles have great importance in drug discovery as the hetero atoms present in them make hydrogen bonds with the receptors present in the body and thus giving their significant pharmacological actions. Hetero cycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics and alkaloids, as well as in pharmaceuticals, herbicides, dyes, and many more compounds1. Out of several heterocyclic compounds, those with Nitrogen atom in their structure give promising pharmacological activities. Triazole, also known as pyrrodiazole, simplest form of the triazole family is triazole itself. is one of the classes of organic heterocyclic compounds containing a five membered diunsaturated ring structure composed of three nitrogen atoms and two carbon atoms at non-adjacent positions having molecular

formula $C_2H_3N_3$. Triazole is a white to pale yellow crystalline solid with a weak, characteristic odour, it is soluble in water and alcohol, melts at 120°C and boils at 260°C. It occurs as a pair of isomeric chemical compounds 1,2,3-triazole, and 1,2,4-triazole, and a molecular weight of 69.06 Two isomers of triazole are 1,2,4-triazole.[1] and 1,2,3-triazole[2]:):Tautomers of 1,2,4-triazoles 1,2,4-triazoles exists in two tautomeric forms. 1*H* and 4*H*-1,2,4-triazole is considered to be pharmacologically important nucleus2.[3][4]



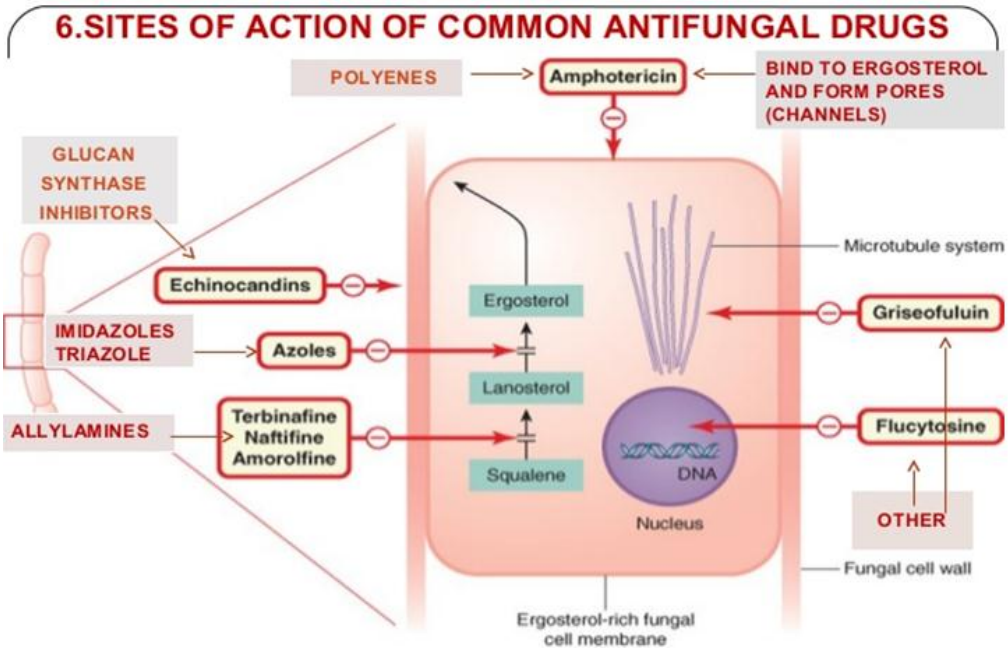
1 2 3 4

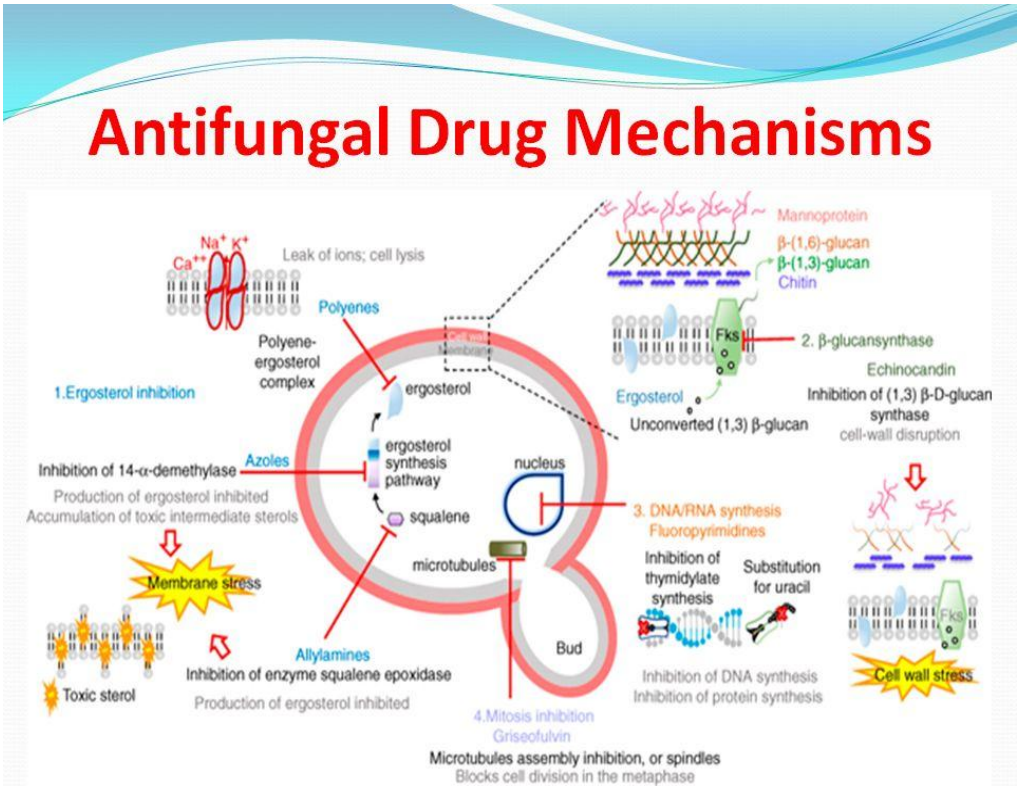
A number of 1,2,4-triazole-3-one and its heterocyclic derivatives represent an interesting class of compounds possessing a broad spectrum of biological activities like antimicrobial, anticonvulsant, and 5-HT2 antagonists. Furthermore 1, 2, 4-triazoles bearing piperazine substituent's show biological activities, such as antibacterial, antifungal and anticancer. Also, some halo phenyl ethers incorporating the 1, 2, 4-triazole nucleus possess good anticancer and analgesic activities.

1.1. Mechanism of action

Substituted 1,2,4triazole nucleus is a common example found in various marketed drug. Such as fluconazole, tetraconazole, rizatriptantriazolium, with act as antifungal agent Azole antifungal agents are use full drug and are widely used for the treatment of topic or inner mycoses in particular AIDS related mycotic pathologies. Azole derivatives block ergo-sterol biosynthesis, causing its depletion and accumulation of lanosterol and some other 14-methyl sterols. Such sterols alter membrane fluidity with concomitant reduction in the activity of membrane –associated enzyme's increased permeability and inhibition of cell growth and replication. The intermediate step of ergosterol biosynthesis is the De- methylation of lanosterol performed by 14-alfa-lanosterol de-methylase(p-450-14_{DM},CYP51) a membrane of the enzyme cytochrome P-450 dependent super family. Which catalyzes the removal of 14-alpha methyl group of lanosterol. Crossover inhibition of cpy51 in different species is assumed to cause undesirable side effect and is one of the reasons for the search of better, more selective agent. Azoles are competitive inhibitors of lanosterol 14 α-demethylase (a cytochrome P-450 enzyme), leading to a decrease in the fungal biosynthesis of ergosterol,

which is a key compound of fungal cell membranes, thereby preventing fungal growth.





2.QSAR is a statistical model that relates a set of structural descriptor of a chemical compound to its biological compound. QSAR studies predict the biological activity, physiochemical properties of the molecules and explain the target of the molecules, which part of synthesized molecule is responsible for the activity. Prediction could reduce the requirement for lengthy and expensive animal tests. Reduction of animal test reducing animal

use, obviously pain and discomfort to animal. QSAR have found wide use in correlating the bioactivity of all kinds of organic (heterocyclic) compounds with all kinds of biological entities. QSAR methods for building predictive models of the relationships between molecular structure and useful properties are becoming increasingly important. QSAR study is use full for the large amount of biological target information is the available in the microbiology. Automation of chemical synthesis and pharmacological screening has also provided a vast amount of experimental data. QSAR model for designing libraries and extracting information from molecular data base and high throughput screening experiment of animal. The ability of to predict the physiochemical, pharmacokinetic, toxicological property of these reduce the expensive late development failure.quantitative structure–activity relationship (QSAR) analysis is the most powerful method due to its high and fast throughput and good hit rate. As the first preliminary step of a QSAR model development, relevant chemogenomics data are collected from databases and the literature. Then, chemical descriptors are calculated on different levels of representation of molecular structure, ranging from 1D to *n*D, and then correlated with the biological property using machine learning techniques. Once developed and validated, QSAR models are applied to predict the biological property of novel compounds. Although the experimental testing of computational hits is not an inherent part of QSAR methodology, it is highly desired and should be performed as an ultimate validation of developed models. In this mini-review, we summarize and critically analyze the recent trends of QSAR-based VS in drug discovery and demonstrate successful applications in identifying perspective compounds with desired properties. Moreover, we provide some recommendations about the best practices for QSAR-based VS along with the future perspectives of this approach.

2.1 **QSAR** is a statistical model that relates a set of ***structural descriptors*** of a chemical compound to its biological activity. QSAR has been widely used to predict the toxicity of substances in bulk form (especially drug-like compunds) but, up to date, QSAR studies for the prediction of nanoparticle toxicity have been rarely reported.

The European system for new chemical management (REACH) promotes QSAR methods as an alternative way of toxicity testing. QSAR models are very useful in case of the classic chemicals but the concept of nano-QSAR is still under development. All chemical substances need to be tested in terms of their toxicological and environmental properties before their use There are several reasons to use QSAR Models: very fast, often free, reduce the number of

animals used in experiments The most important sources of information Alternative, fast developing applications Reduction in the time, cost and animal testing To predict biological activity and physico-chemical properties by rational means To comprehend and rationalize the mechanisms of action within a series of chemicals Savings in the cost of product development Predictions could reduce the requirement for lengthy and expensive animal tests. Reduction of animal tests, thus reducing animal use and obviously pain and discomfort to animals Other area Other areas of promoting green and greener chemistry toincrease efficiency and eliminate wastes of promoting green and greener chemistry.

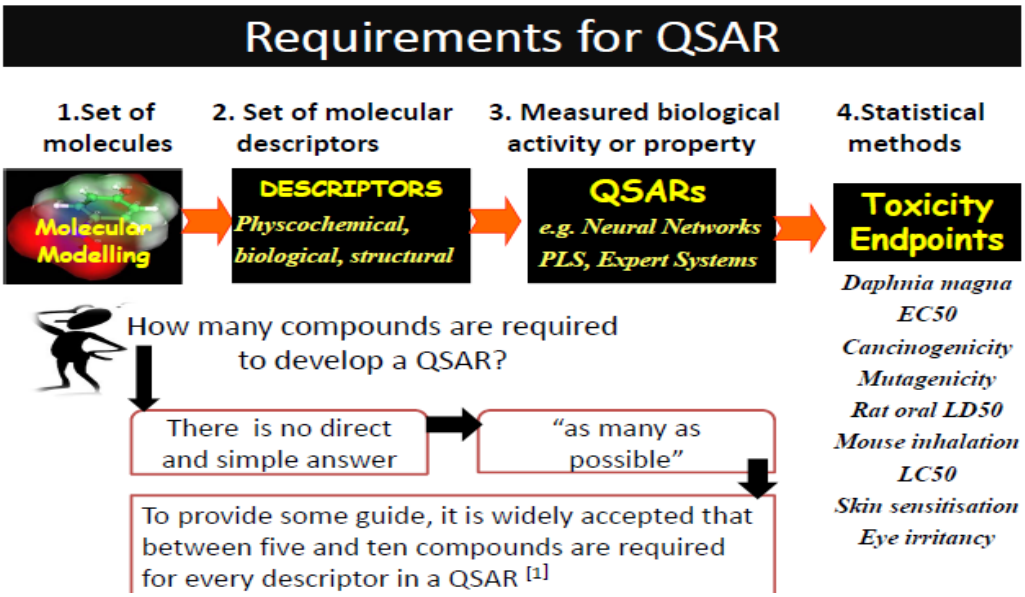


Figure-2.

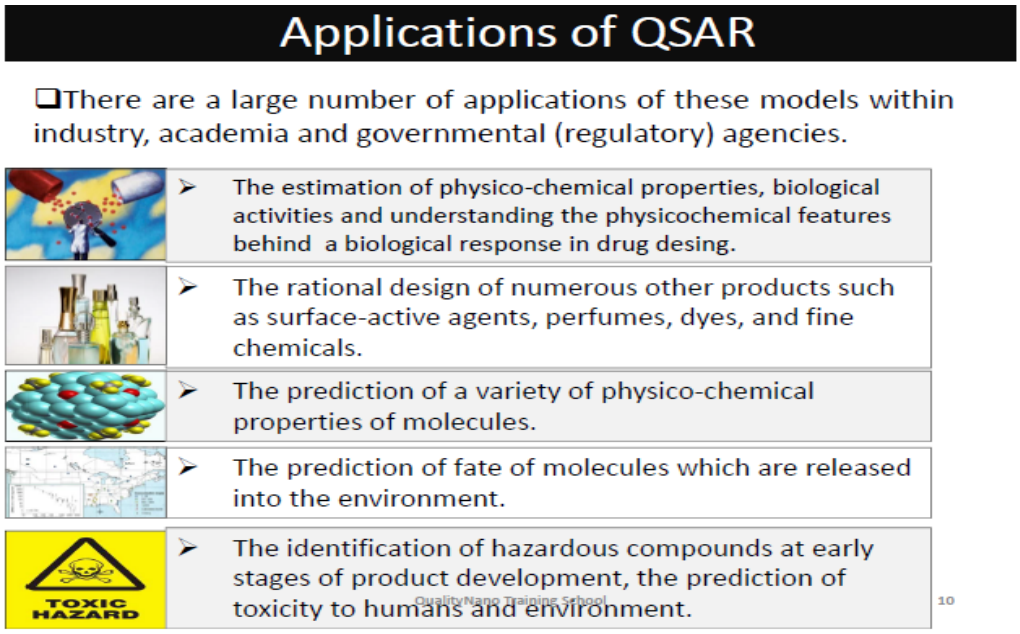


Figure 3.

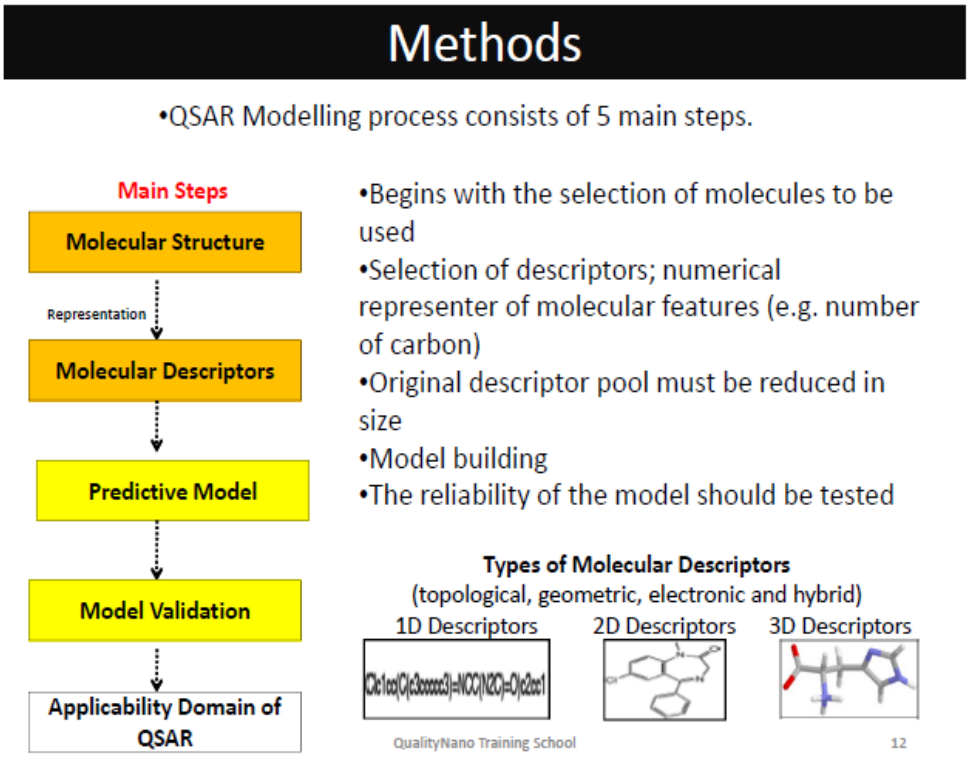


Figure 4.

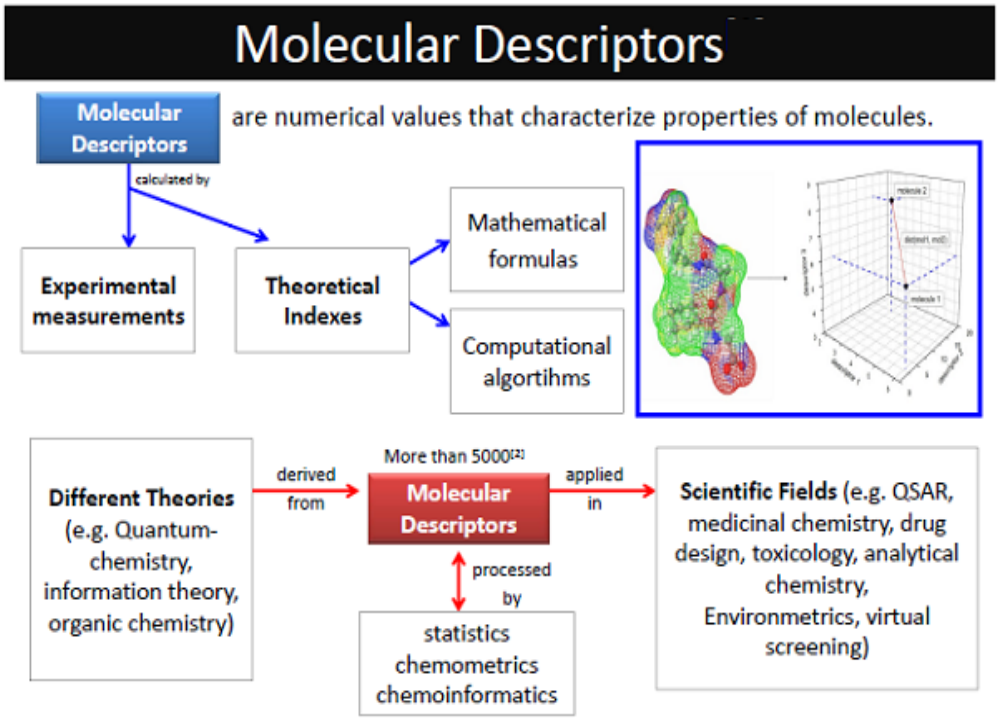
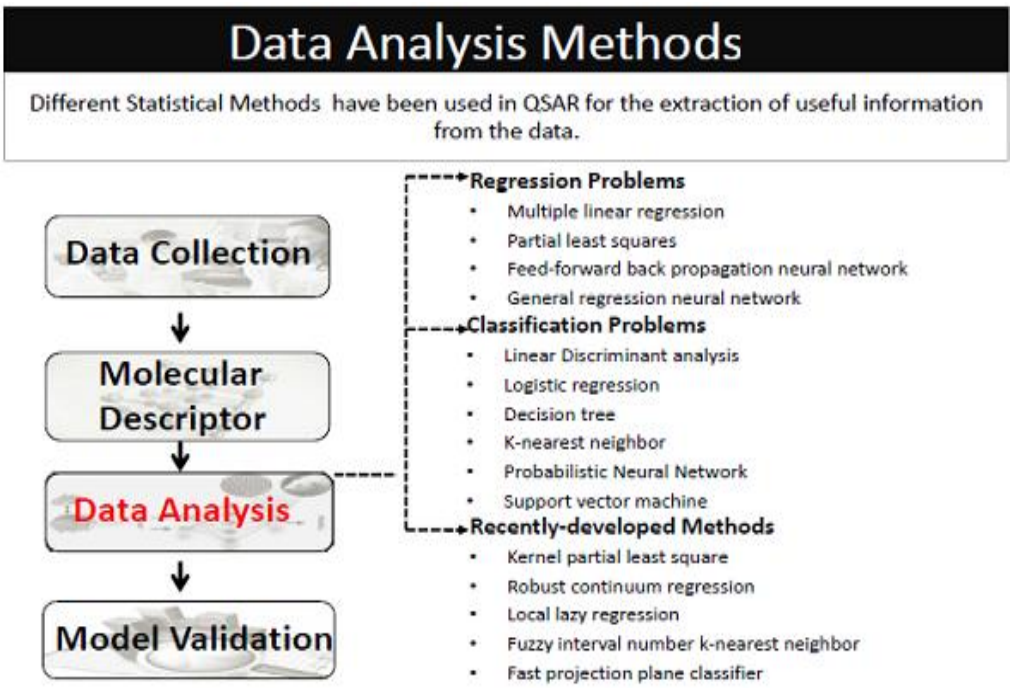


Figure 5.



2.3 Theoretical molecular descriptors

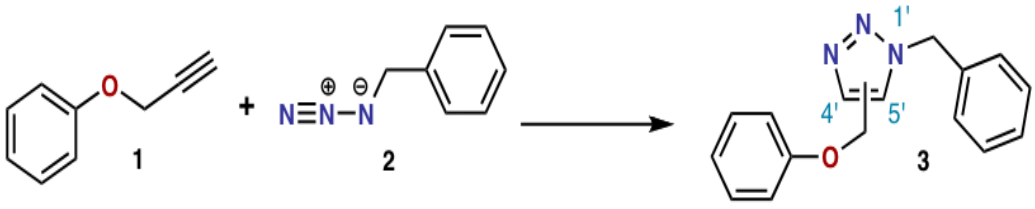
The structures of the compounds under study have been drawn in 2D ChemDraw.[18] The drawn structures were then converted into 3D modules using the default conversion procedure implemented in the CS Chem3D Ultra. The energy of these 3D-structures was minimized in the MOPAC module using the AM1 procedure for closed shell systems. All these energy minimized structures of respective compounds have been ported to DRAGON software for the computation of descriptors for the titled compounds (Table 1). This software offers several hundreds of descriptors from different perspectives corresponding to 0D-, 1D-, and 2D-descriptor modules. The outlined modules comprised of ten different classes, namely, the constitutional (CONST), the topological (TOPO), the molecular walk counts (MWC), the BCUT descriptors (BCUT), the Galvez topological charge indices (GALVEZ), the 2D autocorrelations (2D- AUTO), the functional groups (FUNC), the atom- centered fragments (ACF), the empirical descriptors (EMP), and the properties describing descriptors (PROP). For each of these classes the DRAGON software computes a large number of descriptors which are characteristic to the molecules under multi-descriptor environment. The combinatorial protocol in multiple linear regression (CP- MLR) procedure has been used in the present work for developing QSAR models. activity. A brief description of the computational procedure is given below.

2.4 Model development

The CP-MLR is a 'filter' based variable selection procedure for model development in QSAR studies.[16] Its procedural aspects and implementation are discussed in some of our recent publications. It involves selected subset regressions. In this procedure a combinatorial strategy with appropriately placed 'filters' has been interfaced with MLR to result in the extraction of diverse structure-activity models, each having unique combination of descriptors from the dataset under study. Here the 'filters' are significance evaluators of the variables in regression at different stages of model development. Of these, filter-1 is set in terms of inter- parameter correlation cutoff criteria for variables to stay as a subset (filter-1, default value 0.3 and upper limit ≤ 0.79). In this, if two variables are correlated higher than a predefined cutoff value the respective variable combination is forbidden and will be rejected. The second filter is in terms of t-values of regression coefficients of variables associated with a subset (filter- 2, default value 2.0). Here Accordingly, a filter has been set in terms of predefined threshold level of r-bar (filter-3, default value 0.71) to decide the variables' 'merit' in the model formation. Finally, to exclude false or artificial correlations, the external consistency of the variables of the model have been addressed in terms of cross- validated R^2 or Q^2 criteria from the leave-one-out (LOO) cross-validation procedure as default option (filter-4, default threshold value $0.3 \leq Q^2 \leq 1.0$). All these filters make the variable selection process efficient and lead to unique solution. The utility of a QSAR model is based on its accurate prediction ability for new compounds. A model is valid only within its training domain, and new compounds must be assessed as belonging to the domain before the model is applied. The applicability domain is assessed by the leverage values for each compound. A Williams plot (the plot of standardized residuals versus leverage values (*h*) can then be used for an immediate and simple graphical detection of both the response outliers (Y outliers) and structurally influential chemicals (X outliers) in the model. In this plot, the applicability

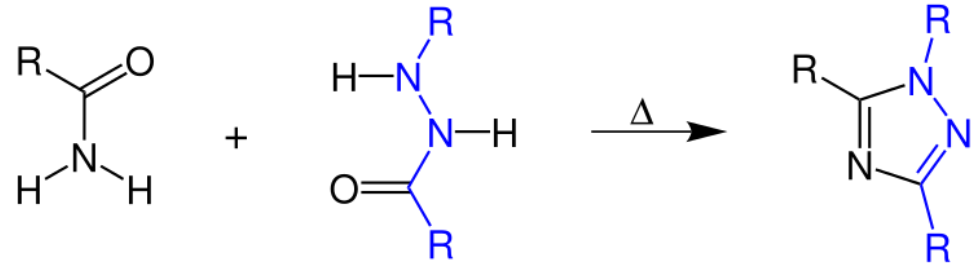
3. Synthesis of Triazole nucleus by following Name reaction reaction

1. **Azide-Alkyne Huisgen Cycloaddition** is a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a1,2,3-triazole.



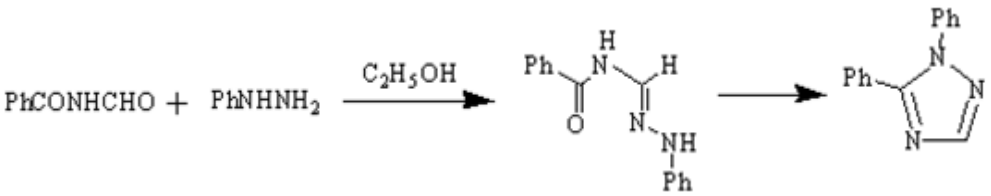
2. Pellizzari reaction

The Pellizzari reaction was discovered in 1911 by Guido Pellizzari, and is the organic reaction of an amide and a hydrazide to form a 1,2,4-triazole The product is similar to that of the Einhorn-Brunner reaction, but the mechanism itself is not regioselective.



3. Einhorn- Brunner Reaction

The synthesis of 1,2,4-triazoles by condensation between hydrazines or mono substituted hydrazine and diacylamines in the presence of weak acid is known as the Einhorn–Brunner reaction. For example: *N*-formyl benzamide and phenyl hydrazine gave 1,5-diphenyl-1,2,4-triazole3,4. *Parminder Kaur.*

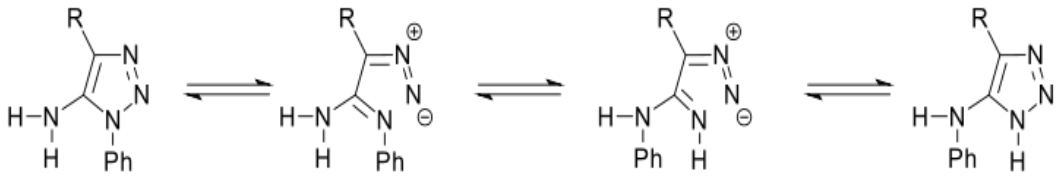


4. Dimroth rearrangement

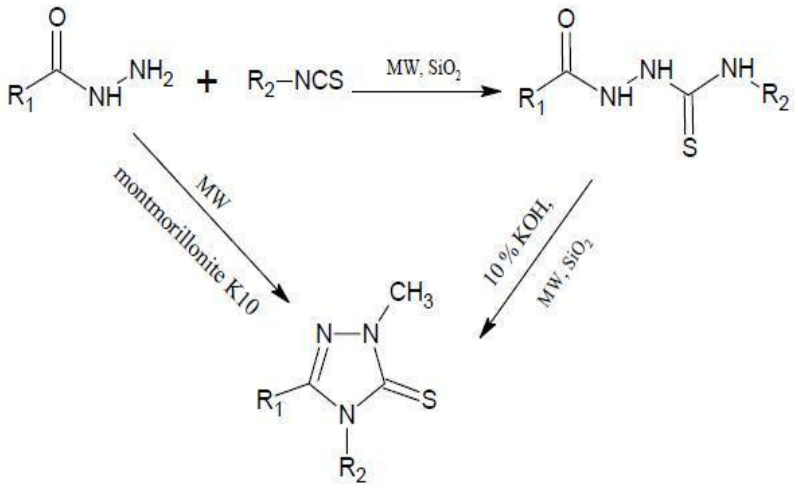
The Dimroth rearrangement is a rearrangement reaction taking place with certain 1,2,3-triazoles where endocyclic and exocyclic nitrogen atoms switch place. This organic reaction was discovered in 1909 by Otto Dimroth With R a phenyl group the reaction takes place in boiling pyridine for 24 **hours**.

3.1 Other scheme for synthesis of triazole nucleus

1. 4,5-Disubstituted-1,2,4-triazole-3-thiones have been prepared in one stage from there action of acid hydrazide with alkyl or aryl iso thiocyanate in the presence of a KOH (10%) solution on the surface of silica gel as well as on the surface of montmorillonite K10 under microwave irradiation. These triazoles have also been prepared from the reaction of 4-substituted-1-aroyl thiosemi carbazides, with a KOH (10%) solution on the surface of silica gel under microwave irradiation.

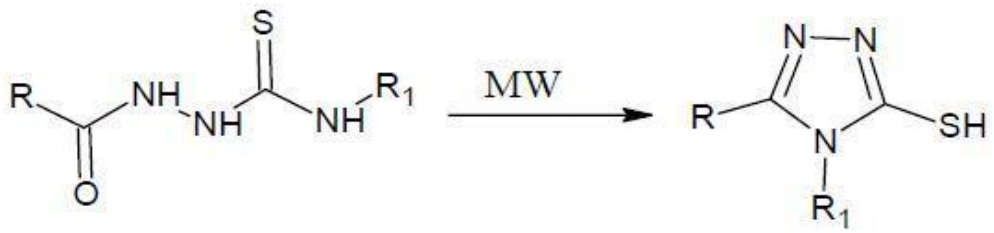


Scheme 1.



Scheme- 2.

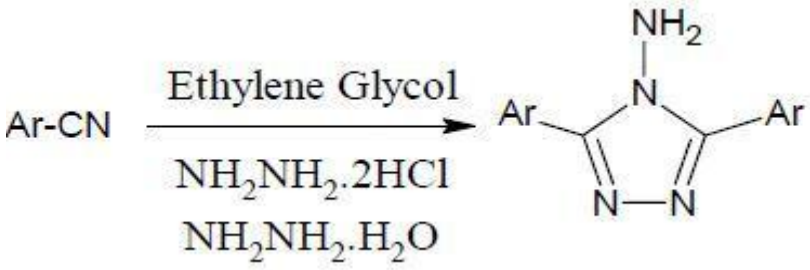
2. Zamani and Bagheri have reported different types of 4,5-disubstituted 1,2,4-triazole-3-thiones by microwave irradiation as well as by a classical method. The beneficial effect of microwave irradiation on the dehydrative cyclization of thiosemicarbazides in different reaction media is described. The results show that the effect of microwave irradiation on the reaction studied was the shortening of reaction times (from 2–9 h to 2–4 min) and a minor decrease (1–4%) of yields (Scheme 2).



R- Benzyl, 2- methyl phenyl R_1 – 2-pyridyl, 3-pyridyl, 4-pyridyl

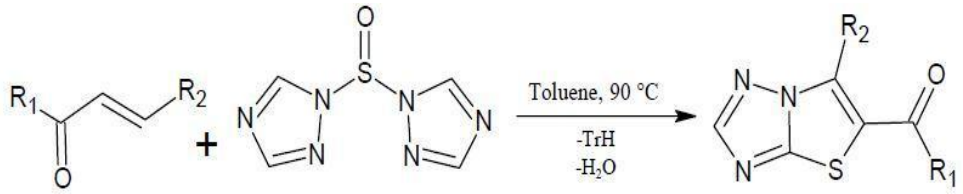
Scheme-3.

3. Bentiss et al. have synthesized 3,5-disubstituted-4-amino-1,2,4-triazoles from thereaction of aromatic nitriles with $NH_2NH_2 \cdot 2HCl$ in the presence of $NH_2NH_2 \cdot 2H_2O$ excess in ethylene glycol under microwave irradiation (Scheme 3).



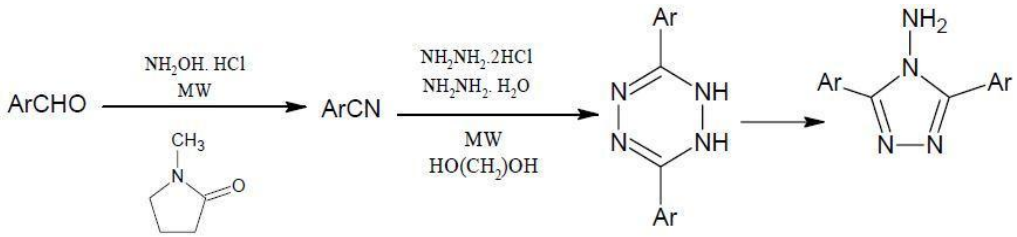
Scheme 4.

4. A novel one-step synthesis of thiazolo-[3,2-b]-1,2,4-triazoles were reported from thereaction of chalcones with bis-(1,2,4-triazolyl)-sulfoxide15 (Scheme 4).



Scheme – 5.

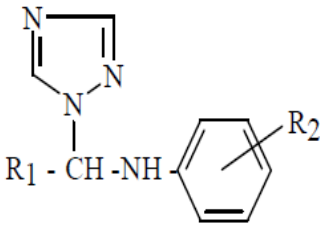
5. Symmetrical 3,5-substituted-4-amino-1,2,4-triazoles are quickly prepared from aromaticaldehydes via nitriles by two-step reactions without any separation under microwave irradiation for several minutes (Scheme 5).



4. Review of literature

1,2,4-Triazoles were known to possess important pharmacological activities such as antifungal and antiviral. Some well-known antifungal drugs (Yagisawa, 2004; Johnson et al., 1999) like fluconazole (Tsukuda et al., 1998; Narayanan et al., 1993), itraconazole (Bailey et al., 1990), ravuconazole (Roberts et al., 2000), voriconazole (Sanati et al., 1997; Perea et al., 2000; Espinel-Ingroff, 1998), ICI 153066 (Boyle et al., 1988), and posaconazole (Oakley et al., 1997) contain 1,2,4-triazole moiety. The activity of these compounds is based on the inhibition of biosynthesis of ergosterol (themajor steroid present in fungal membranes) by blocking 14-a-demethylation, which occurs with accumulation of 14-a-methyl-steroids and disruption of the fungal membranes (Vanden Bossche et al., 1993; Massa et al., 1992; Doignon and Rozes, 1992). Fluconazole also causes second bronchialarch anomalies in mice

(Tiboni, 1993). Quantitative structure activity relationship (QSAR) refers to a discipline in chemical informatics that addresses the modeling of biological activities or chemical reactivity based on the quantitative and chemical features of the molecule. QSAR relies on the basic assumption that molecules with similar physicochemical properties or structures will have similar activities (Huang et al., 2007). QSAR is one of the most important areas in chemometrics, and is used extensively in drug design and medicinalchemistry. Once a reliable QSAR model is established, we can predict the activities of molecules, and know which structural features play an important role in biological processes (Mungalpara et al., 2010; Kumar et al., 2007, 2009; Narasimhan et al., 2006).A usual QSAR method needs several steps with the help of several software packages. Hence the prediction of QSAR model is not so easy and is a time-demanding process (Berhanu et al., 2012). In the present study we used freely available tools with manual assessment for better interpretation of predicted models even though it was time demanding. Using PaDEL descriptors (Yap, 2011) all possible 2D, 3D descriptors were generated and these data are used to perform regression analysis to correlate between the biological activities. Here we have five strains of antibacterial and four strains of antifungal activity data, hence for QSAR model studies the average MIC values of respective antibacterial and antifungal activity were considered for regression analysis. This average data helped to minimize the consistency of QSAR approach to prove the relative molecular descriptors for respective activity **Vesna D et al** "QSAR of Some N1-Aryl/Heteroarylaminomethyl/ethyl-1,2,4- Triazoles Part II: Antimicrobial Activity Against *Bacillus Subtilis"* was performedusing the computer-assisted multiple regression procedure. Using the Hansch and Free Wilson approaches the activity contribution for either the aminomethyl/aminoethyl unit or the aromatic/heteroaromatic ring was determined from the correlation equation.



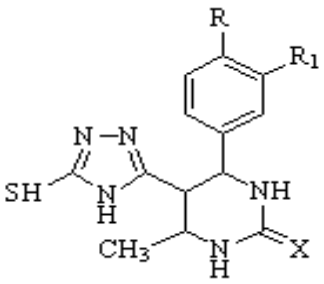
Kishore B *et al* "A Qsar Study On Pyrazole And Triazole Derivatives As Selective Canine Cox-2 Inhibitors The canine COX-2 inhibitory activity of pyrazole and triazole derivatives has been quantitatively analyzed in terms of Dragon descriptors using CP-MLR. The descriptors identified in CP-MLR analysis have highlighted the role of atomic properties in

respective lags of 2D-autocorrelations (MATS8m, GATS4v and GATS6p) and Modified Burden eigenvalues (BELp2 and BELm6), E-state topological parameter (TIE) and 3rd order mean Galvez topological charge (JGI3) to explain the canine COX-2 inhibitory actions of pyrazole and triazole.

Siva S. *et all* "Synthesis and QSAR studies of some novel disubstituted 1,2,4-triazoles as antimicrobial agents Disubstituted 1,2,4-triazoles 3a–k, 4a–k, and 6a–k have been synthesized from anthranilic acid and nicotinic acid, respectively, through a multi-step reaction sequence via their hydrazides. Synthesized compounds wereevaluated for their in vitro antimicrobial activity against twogram-positive bacteria (S. aureus and B. subtilis), threegram-negative bacteria (E. coli, S. typhi, and K. pneumonia) as well as four fungi (A. niger, A. fumigatus, A. flavus, andC. albicans). To explore computational approach, structure– activity relationships were generated statistically using thesynthesized compounds and their respective quantitative values of biological activities.

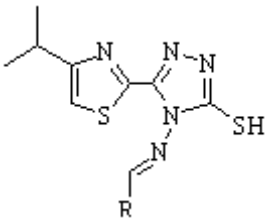
Antibacterial and Antifungal activity

B. Andrews *et al* synthesized a series of pyrimidine bearing 1,2,4-triazole[13] and evaluated for antifungal activity. Most of the compounds shown promising antifungal activity when compared with the standard drug Amphotericin-B. All these compounds were screened for antifungal activity by *Candida albicans, Penicillium sps. and Aspergillus niger.* Amphotericin-B was used as standard drug. Most of the synthesized compounds showed moderate to good inhibition at 10 µg/ml concentration. However the activity was less compared to the standard drugs53.



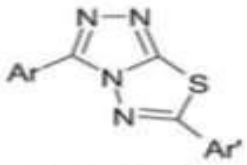
Kumar *et al* synthesized a series of 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole[16] & were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis H37Rv* strain by using broth dilution assay method which indicated that two compounds at MIC 4 □g/ml exhibited two fold enhanced potency than parent compound and the results indicated that some of them exhibited promising activities at MIC 16-16.5 □g/ml

and they deserve more consideration as potential anti-tubercular agents when compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with standard isoniazid56



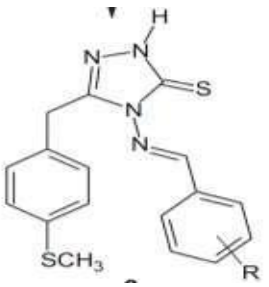
R- 4-CH3-C6H4; 4-Br-C6H4; 2-OHC6H4; Ar- 4-NO2-C6H4; 4-CH3-C6H4; 4-F-C6H4; 2-Cl-C6H4; 4-OCH3C6H4; 2,4-(OCH3)2-C6H4 3-Cl-C6H4

V. Mathew et al. (2006) synthesized some Several 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadizoles by the condensation of 4-amino-3-aryl/aralkyl substituted-5- mercapto-1,2,4-triazoles 3(a–c) with various substituted aromatic /hetero aromatic acids through a single step reaction. Synthesized triazolothiadiazoles investigated for their antibacterial, antifungal, anti-inflammatory and analgesic activities.

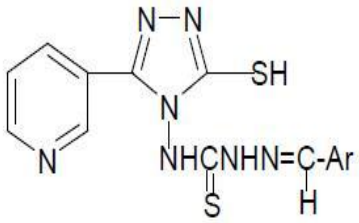


8 -11 (a-c)

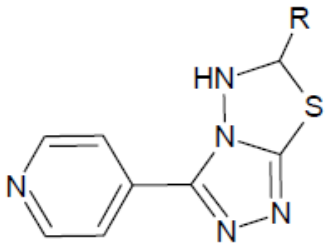
Mithun Ashok et al. (2007) synthesized Two new series of Mannich bases, namely,1-(morpholino)methyl-3-(4-methylthiobenzyl)-4-(substituted arylidene) amino-1,2,4- triazol-5-thiones 3 and 1-(N-methylpiperazino)methyl-3-(4-methyl thiobenzyl)-4-(substitutedarylidene) amino-1,2,4-triazol-5-thiones which shows antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiellapneumoniae.



Aniket Kshirsagar et all. (2009) synthesized thiosemicarbazide derivatives of 5-mercapto-3-(3'-pyridyl)-4H-1, 2, 4-triazole. The synthesized compounds were screened for antifungal activity by using cup plate agar diffusion method against *C. albicans*, antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and anticonvulsant activity by Maximum Electroshock (MES) method.

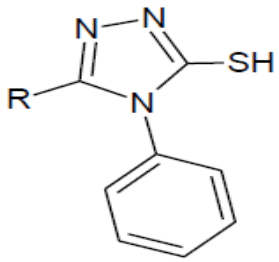


Hirpara *et all,* synthesized a series of 6-aryl-3-pyridin-4-yl-5,6-dihydro[1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazoles and investigated for antimicrobial activity, 2011 Vol 2(1) Page no 186-197



3a, R=C_6H_5

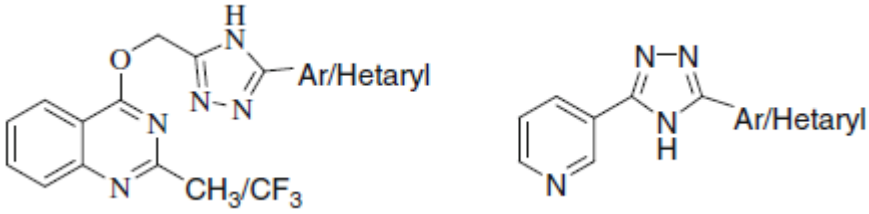
Mudasir R B et all, reported the synthesis of substituted triazoles and thiazolidinones from fatty acids and screened for antimicrobial activity.



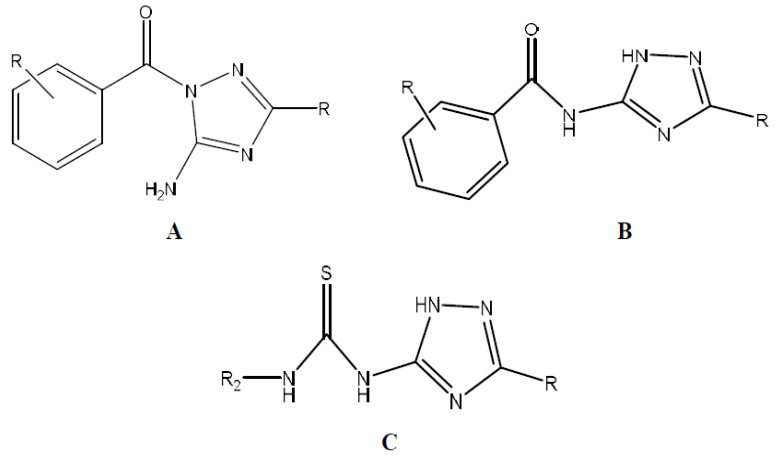
3a, R=CH_2=CH$(CH_2)_8$-

Siva S et all "Synthesis and QSAR studies of some novel disubstituted 1,2,4-triazoles as antimicrobial agents Disubstituted 1,2,4-triazoles 3a–k, 4a–k, and 6a–k have been synthesized from anthranilic acid and nicotinic acid, respectively, through a multi-step reaction sequence via their hydrazides. Synthesized compounds were evaluated for their in

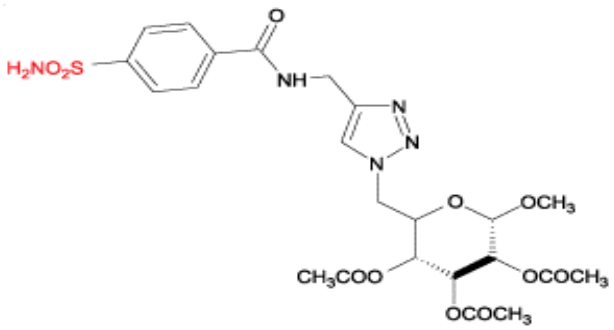
vitro antimicrobial activity against two gram-positive bacteria (S. aureus and B. subtilis), three gram-negative bacteria (E. coli, S. typhi, and K. pneumonia) as well as four fungi (A. niger, A. fumigatus, A. flavus, and C. albicans).”



El L. et all,”QSAR Study of New Compounds Based on 1,2,4-Triazole as Potential Anticancer Agents”. Pancreatic cancer is an aggressive cancer, usually with poor prognosis, as it is mostly discovered at an advanced stage of developmentwhere treatment is challenging. Using principal components analysis (PCA) of variable selection, multiple linear regression (MLR),multiple non-linear regression (MNLR) and the artificial neural network (ANN), 2D-QSAR models for the anti-pancreatic cancer activityare developed from a set of twenty three molecules of 1,2,4-triazole derivatives to build the QSAR models.

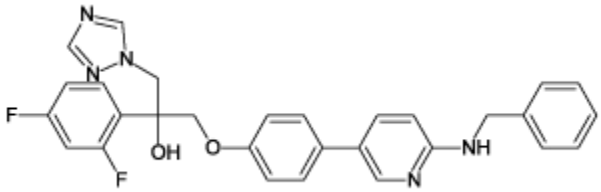


The quantitative structure–activity relationship (QSAR) demonstrated that the stereochemical diversity within the carbohydrate tails effectively interrogated the carbonic anhydrase (CA) active site topology, generating in some instances inhibitors with hCA IX selectivity, an important outcome in the quest for potential cancer therapy. Wilkinson et al. presented a new class of CA inhibitors comprising of 28 glycosyl triazole aryl suphonamide derivatives (**51**) generated through click chemistry. These compounds were assessed for their ability to inhibit three human CA (hCA) isozymes *in vitro*: cytosolic hCA I, hCA II and transmembrane tumour-associated hCA IX. A number of derivatives were found to be selective inhibitors for the cancer associated isozyme hCA IX.



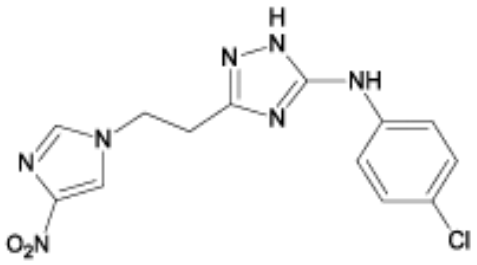
51

Liu et al. synthesised a series of 1-(substituted biaryloxy)-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl) propan-2-ol derivatives, **3**, and their antifungal activity was evaluated against eight human pathogenic fungi *in vitro*. Seventeen compounds showed activity between 4- and 64-fold higher than voriconazole against *Candida albicans*. Structure–activity relationship clearly suggested that introduction of a biaryloxy side chain greatly enhanced the antifungal activity of triazole analogues against *Candida* species.[15]



3

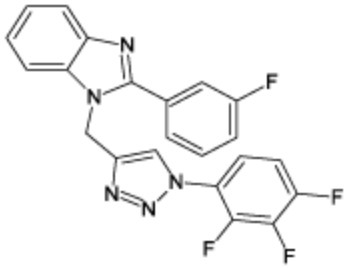
Demirayak et al. reported some 3-arylamino-5-[2-(substituted imidazole-1-yl or benzimidazol-1-yl)ethyl]-1,2,4-triazole derivatives[4] which were evaluated for antifungal activity against *Candida albicans* and *Candida glabrata* by using the tube dilution technique. The *in vitro* antifungal activity results showed that the most sensitive microorganism to the control antifungal, ketoconazol is *Candida glabrata*.



4. *N*-(4-chlorophenyl)-3-[2-(4-nitro-1*H*-imidazol-1-yl)ethyl]-1*H*-1,2,4-triazol-5-amine

Gill et al. reported some novel[1,2,3] triazoles clubbed with fluorine benzimidazole[5] series of H37Rv strain inhibitors which were found to be potentially active against *Mycobacterium*

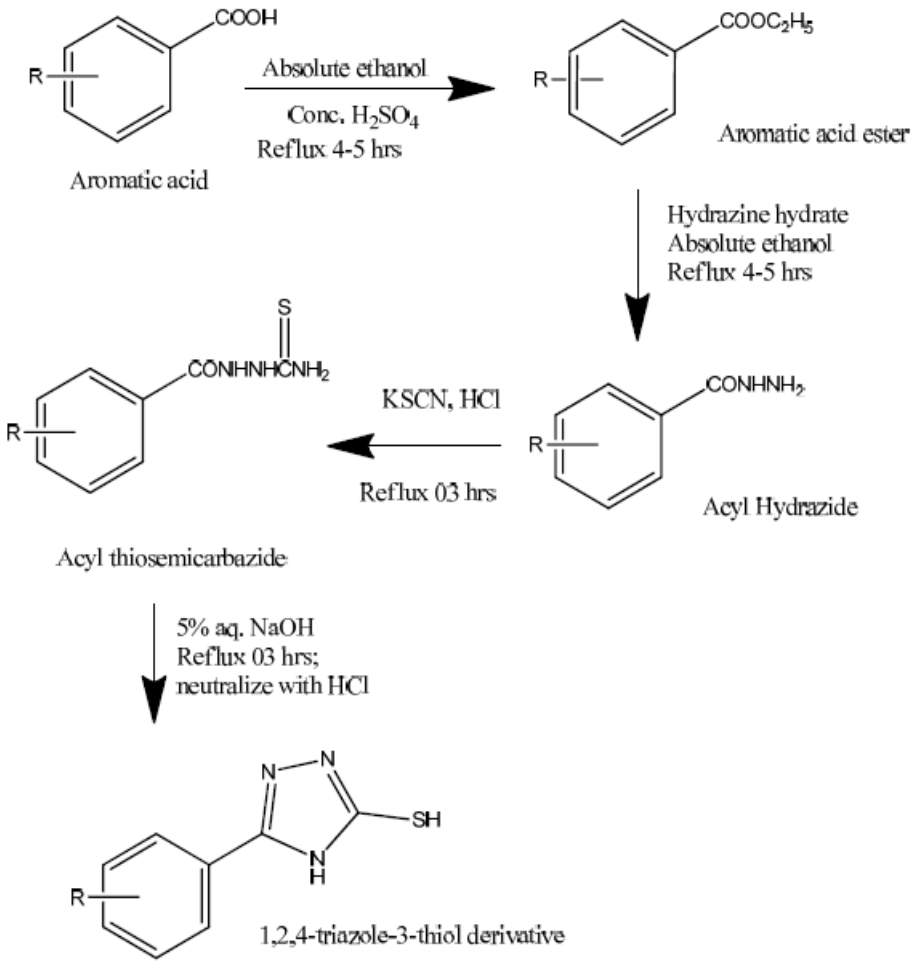
tuberculosis on the basis of promising results of preliminary antimicrobial study. Some of the derivatives under further evaluation are showing improved activity compared to rifampin.[31]



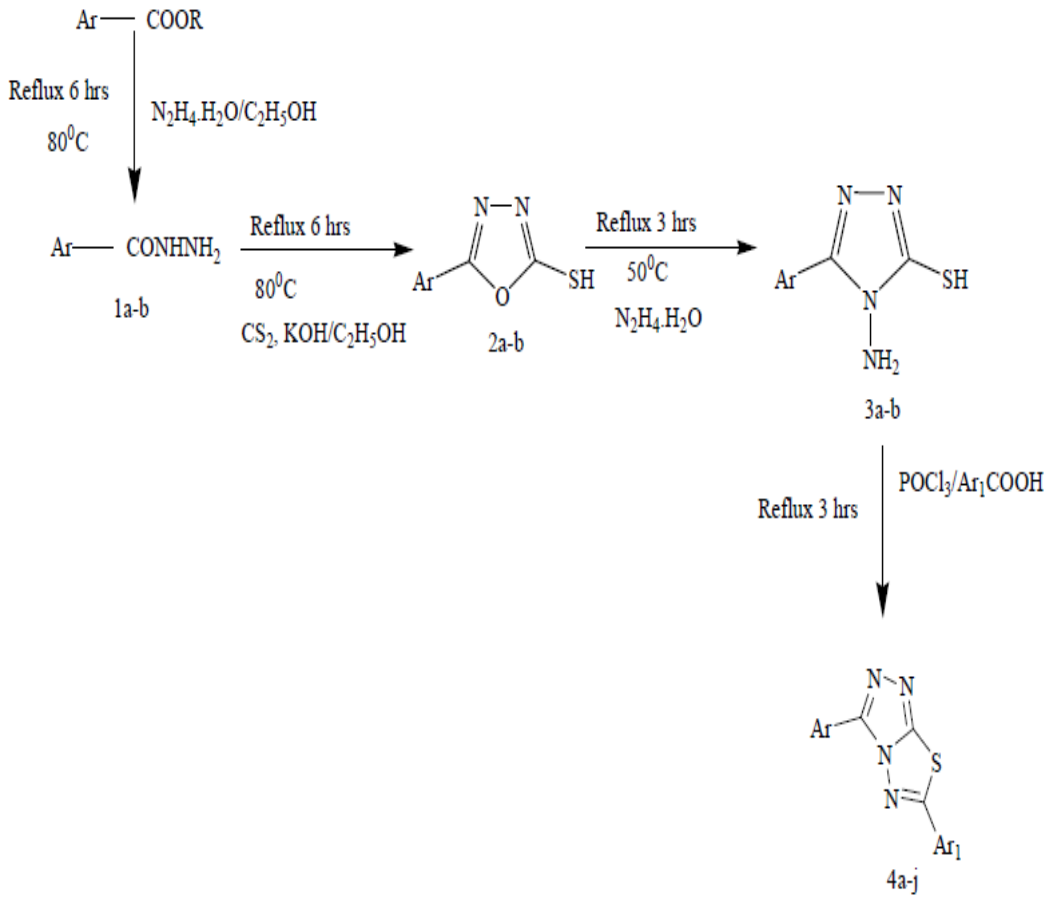
5. 2-(3-fluorophenyl)-1-{[1-(2,3,4,-trifluorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-benzimidazole

Pokrovskaya et al. investigated a series of new hybrid structures containing a fluoroquinolone (ciprofloxacin) and aminoglycoside (neomycin) antibiotics linked via 1,2,3-triazole moiety (**7**). Their antibacterial activities were determined against both Gram-negative and Gram-positive bacteria, including resistant strains each drug separately or their 1:1 mixture.

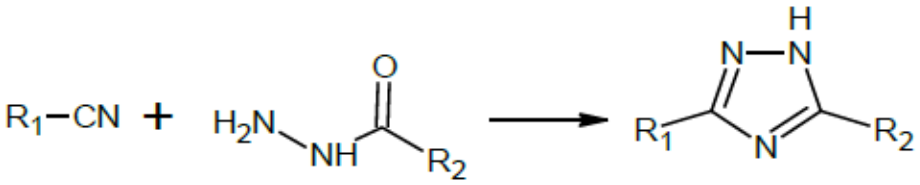
5. Experimental work



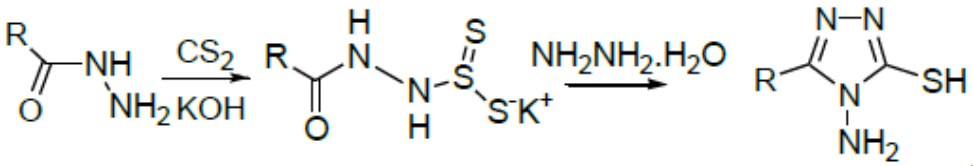
Scheme-1.



Scheme-2.



Scheme-3.



Scheme-4.

Procedeeure

1, 2, 4-triazole derivatives have been synthesized in**scheme (1)** via aromatic carboxylic acid hydrazide intermediate. The aromatic carboxylic acid is first esterified in the presence of conc. H_2SO_4 and absolute ethanol. The corresponding acid ester is then treated with 85% hydrazine hydrate in the presence of absolute ethanol as solvent that resulted in the formation

of corresponding carboxylic acid hydrazide in equimolar proportions. The resulting hydrazide is treated with Potassium thiocyanate in acidic medium which resulted in the formation of thiosemicarbazide and the yields were quantitative. Cyclization of the thiosemicarbazide in the presence of NaOH resulted in the formation of the corresponding carboxylic acid-1,2,4-triazole-3-thiol derivative.

Synthesis of aromatic acid ester

The corresponding aromatic acid (0.1 mol) wasrefluxed with absolute ethanol (0.5 mol) in presence of 1-3 ml of conc. H_2SO_4 and few porcelain pieces in a round bottom flask for 4-5 hours. After refluxing, excess ethanol was removed by heating under reduced pressure. The resultant solution was diluted with 200 ml of distilled water and neutralized with the help of a solution of sodium bicarbonate. After complete neutralization, the product (aromatic acid ester) was extracted with carbon tetrachloride (CCl_4). The CCl_4 layer, after separation was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the product.

Synthesis of acyl hydrazide

The aromatic ester (0.05 mol) prepared above is refluxedwith hydrazine hydrate (0.25 mol) in absolute ethanol for 4-5 hours. After refluxing is over, the mixture is cooled down. The cold mixture is dissolved in absolute ethanol and filtered. On cooling the filtrate white crystals of the acyl hydrazide separate out.

Synthesis of acyl thiosemicarbazide

The corresponding acyl thiosemicarbazide wasprepared by refluxing a suspension of acyl hydrazide (0.02 mole), potassium thiocyanate (0.04 mole), hydrochloric acid (10ml) and water (200 ml) for 3 hours. On cooling the mixture a white solid separated out which was filtered, dried and then re-crystallized from ethanol.

Synthesis of 5-aromatic substituted-4H-1,2,4-triazole-3-thiol

The correspondingthiosemicarbazide (0.01 mole) obtained in the previous step was refluxed in sodium hydroxide solution (5%, 50 ml) for 3 hours. After 3 hours the resulting solution was treated with activated charcoal, filtered and cooled. The filtrate was neutralized with hydrochloric acid to pH.[5-6] A solid crystalline product separated which was filtered, dried and recrystallized from dilute ethanol.

Calculation of the Molecular Descriptors

The different descriptors used in this work are calculated by ACD/ChemSketch program. Steric descriptors and thermodynamic ones are calculated using ACD/ChemSketch and ChemBioOffice.[17-18] after the energy optimization for each compound using the MM2 method (force field method with gradient setting root mean square (RMS) 0.1 kcal mol-1).[16] In this work, as shown in Table 2, 11 descriptors have been chosen to describe the target molecular structures.

Statistical Analysis

The 11 descriptors calculated for this series are used to find the relation linking the molecular structures by the biological activity (Table 2). To explain the structure activity relationship, the 11 quantitative descriptors of the1,2,4-triazole (1 to 23) compounds are studied using different statistical methods:-. PCA is a useful method in dealing with the problems of the unfavourable more descriptor/molecule ratio and collinearility. This method aims to select descriptors that are directly related to biological activity.

Experimental Data

In the present study, twenty three[23] of 1,2,4-triazole have been chosen for their anticancer activities against the human pancreatic cancer cell line (Panc-1). Experimentally, those novel hybrids of 1,2,4-triazole have been prepared by gathering the two bioactive entities 1,2,4-triazole and isothiocyanates in one compact structure for the purpose of synergism. For their experimental activity, Graph Pad Prism software (Graph Pad Software, San Diego, CA, USA) has been used to calculate the median inhibition concentration (IC50) for all compounds. Figure 1 represents the basic structure of the 1,2,4-triazole and Table 1 shows the studied substitutions of the compounds and corresponding experimental activities of pIC50 with (pIC50 = log10 IC50).The different descriptors used in this work are calculated by ACD/ChemSketch program.[3] Steric descriptors and thermodynamic ones are calculated using ACD/ChemSketch and ChemBioOffice[16-17], after the energy optimization for each compound using the MM2 method (force field method with gradient setting root mean square (RMS) 0.1 kcal mol-1) In this work, as shown in Table 2, 11 descriptors have been chosen to describe the target molecular structures. The 11 descriptors calculated for this series are used to find the relation linking the molecular structures by the biological activity (Table 2). To explain the structureactivity relationship, the 11 quantitative descriptors of the 1,2,4-triazole[1-16] compounds are studied using different statistical methods:-The principal

component analysis (PCA) has been performed using the XLSTAT software, version 2015 to predict anticancer activities pIC50. PCA is a statistical method based on minimizing all the information encoded in the structures of the compounds. In most cases of QSAR studies, the researchers confront problems such as the elimination of irrelevant information in the original descriptors matrix involved, the unfavorable ratio of the number of descriptors to that of molecules of interest, and collinearity among the descriptors used. PCA is a useful method in dealing with the problems of the unfavorable more descriptor/molecule ratio and collinearity. This method aims to select descriptors that are directly related to biological activity[18] The informationcontained in the data is listed in Tables 1 and 2.

Table 1: Compounds and Radicals under Study.[3]

	Compounds	R	R_1	R_2	pIC_{50}
A	1	C_6H_5	4-OCH_3	-	5.60
	2	Pyridine-3-yl	4-OCH_3	-	5.82
	3	Pyridine-4-yl	4-OCH_3	-	5.72
	4	C_6H_5	3,4-di(OCH_3)	-	5.13
	5	3,4,5-Tri(OCH_3)C_6H_2	3,4-di(OCH_3)	-	5.10
	6	Pyridine-3-yl	3,4-di(OCH_3)	-	5.14
	7	Pyridine-4-yl	3,4-di(OCH_3)	-	5.38
	8	C_6H_5	3,4,5-tri(OCH_3)	-	5.25
	9	3,4,5-Tri(OCH_3)C_6H_2	3,4,5-tri(OCH_3)	-	5.23
	10	Pyridine-3-yl	3,4,5-tri(OCH_3)	-	5.02
	11	Pyridine-4-yl	3,4,5-tri(OCH_3)	-	4.92
	12	4-Cl-C_6H_4-	3,4,5-tri(OCH_3)	-	5.34
B	13	4-OCH_3-C_6H_4-	4-OCH_3	-	5.88
	14	3-Cl-C_6H_4-	4-OCH_3	-	5.45
	15	4-OCH_3-C_6H_4-	3,4-di(OCH_3)	-	5.49
	16	3-Cl-C_6H_4-	3,4-di(OCH_3)	-	6.00
	17	4-OCH_3-C_6H_4-	3,4,5-tri(OCH_3)	-	5.14
C	18	3,4,5-Tri(OCH_3)-C_6H_2-	-	C_6H_5	5.37
	19	3,4,5-Tri(OCH_3)-C_6H_2-	-	C_2H_5	5.25
	20	4-OCH_3-C_6H_4-	-	C_6H_5	5.49
	21	4-OCH_3-C_6H_4-	-	C_2H_5	5.31
	22	3-Cl-C_6H_4-	-	C_6H_5	5.22
	23	3-Cl-C_6H_4-	-	C_2H_5	5.13

pIC50 = -log(IC50).

The multiple linear regression statistic techniques (MLR) are used to study the relationship between one dependent variable and several independent variables. It is a mathematical technique to minimize the difference between the actual and predicted values; - The nonlinear multiple regression statistic (NMRS) technique is a nonlinear method in which the descriptors proposed by MLR are applied in accordance to the data set (training set). In the previous works, the pre programmed function has been used:

Table 2: Dataset Used for the QSAR Analysis of the 1,2,4-Triazole Derivatives.[3]

Compounds	MW	MR	MV	Pc	n	γ	D	αe	logP	HBA	HBD
A1	82.67	244.5	294.30	605.8	1.657	52.9	1.31	32.77	3.47	5	1
A2	81.11	213.1	295.29	587.0	1.686	57.4	1.38	32.15	2.22	6	1
A3	81.11	213.1	295.29	587.0	1.686	57.4	1.38	32.15	2.22	6	1
A4	89.39	246.3	324.33	681.4	1.645	58.5	1.31	35.43	3.78	6	2
A5	87.60	234.3	328.75	660.6	1.670	63.2	1.40	34.73	4.47	5	2
A6	88.48	246.2	324.33	656.1	1.637	50.4	1.31	35.07	3.12	6	1
A7	105.92	311.1	414.41	806.8	1.596	45.1	1.33	41.99	2.57	9	1
A8	86.92	234.8	325.32	637.2	1.662	54.2	1.38	34.46	1.87	7	1
A9	86.92	234.8	325.32	637.2	1.662	54.3	1.38	34.46	1.87	7	1
A10	96.07	270.3	354.35	738.1	1.628	55.5	1.31	38.08	3.66	7	2
A11	94.28	258.3	358.77	717.3	1.650	59.4	1.38	37.37	4.34	6	2
A12	94.29	267.9	354.35	706.3	1.621	48.3	1.31	37.38	3.02	7	1
B1	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B2	111.73	332.8	444.43	857.1	1.586	43.9	1.33	44.29	2.47	10	1
B3	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B4	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
B5	98.89	277.1	388.80	735.2	1.632	49.5	1.40	39.20	3.64	7	1
B6	92.74	256.5	355.34	687.5	1.642	51.6	1.38	36.76	1.77	8	1
C1	102.75	294.3	384.38	794.8	1.615	53.1	1.30	40.73	3.534	8	2
C2	107.75	279.7	385.44	798.1	1.695	66.2	1.37	42.64	4.480	6	3
C3	91.25	257.7	337.39	711.5	1.626	58.0	1.30	36.17	3.154	6	3
C4	77.89	209.7	277.34	598.1	1.664	66.1	1.32	30.88	3.407	4	3
C5	76.11	197.7	281.76	577.3	1.696	72.7	1.42	30.17	4.092	3	3

$$Y = a + (bX1 + cX2 + dX3 + eX4 \ldots) + (fX12 + gX21 + hX32 + iX42 \ldots) \quad (1)$$

where a, b, c, d ….represent the parameters and X1, X2, X3, X4…represent the variables.

Pharmacological activities

The triazole scaffold is extremely versatile and has been featured in a number of clinically used drugs, highlighting the importance of this nucleus. The most relevant and recent studies have revealed that triazole derivatives have a broad spectrum of pharmacological activities which can be classified into the following categories

Antimicrobial activity

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including development of resistance to current antibacterial therapy and a very rapid increase of primary and opportunistic fungal infections in immune compromised patients with AIDS or undergoing anticancer therapy and organ transplants.

Systemic fungal infections are life-threatening and have become increasingly common in immuno-compromised hosts. Currently triazole drugs (fluconazole, itraconazole, voriconazole and posaconazole) are most frequently used antifungals in clinical therapy. They possess a broad spectrum of activity and reduced toxicity when compared with imidazole antifungals.

However, resistance to azoles is emerging and may pose a serious health problem in future. In addition, triazole drugs are often associated with hepatotoxicity and have a limited antifungal spectrum. Consequently, it remains attractive to develop new triazole derivatives possessing broader antifungal spectra and higher therapeutic indexes.

In vitro Antimicrobial Study

A cup plate method was employed for the *invitro* study of antibacterial and antifungal effectagainst *Bacillus subtilis, Staphylococcus aureus, Proteus mirabilis, Salmonella typhi, Candida albicans*and *Aspergillusniger*.

The antimicrobial screening was done by using agar plate diffusion method. This method depends upon the diffusion of the various samples from a cavity through the solidified agar layer of petri dish to an extent such that the growth of the added microorganism is prevented entirely in the circular area or zone around the cavity containing the sample. Using micropipette 0.5 ml of each of the seeded broth containing 10^{-5}-10^{-6}Efu/ml test organism were incubated on solidified agar and spreaded uniformly with a glass spreader. Then four

wells were cut in the agar layer of each plate with an aluminium bore of 6 mm diameter to contain 0.5 ml each of sample solution, standard drug, DMSO and methanol. The plates were incubated for 24 hours at 37^0C in case of antibacterial activity.

The antimicrobial activities of the compoundswere evaluated against six different strains of bacteria and two strains of fungi using well diffusion method and the Minimum Inhibitory Concentrations (MICs) of the compounds were determined using serial dilution method. Gentamycin was used as standard drug for antibacterial activity and Amphotericin B was used as standard drug for antifungal activity. The compounds were screened *in vitro* for antibacterial activity against E. Coli (ATCC®10536), Staphylococcus aureus (ATCC ®25923), Staphylococcus cohni (MPCST 121), Proteus vulgaris (ATCC®6380), Klebsiella pneumonia (ATCC®13883) and Pseudomonas aerugenosa (ATCC®25619). Further all the compounds were screened for antifungal activity against Aspergillusniger (ATCC® 16404) and Candida albicans (ATCC®14053). I

ANTIFUNGAL ACTIVITY

The antifungal activity determination was carried out in the same way as used in antibacterial study; only different nutrient medium was used i.e., Sabouraud-Dextrose Agar media (SDA media) instead of Nutrient agar medium which was used in antibacterial study.Minimum inhibitory concentrations of the compounds were determined as follows: Two fold dilutions (six) of the samples were carried out starting from the concentration of 0.1 – 20 mg/ml. The tubes were inoculated with a microorganism suspension at a final density of 10^5 cells/ml. The tubes were incubated at 37^0C for 24 hours. The lowest concentration of the tubes which did not show any visible growth after macroscopic evaluation was considered as the MIC of the respective compound.

RESULTS AND DISCUSSION

In this QSAR study, the collected data are first randomly divided into two parts: a learning set consisting of 19 molecules, and a test set consisting of 4 molecules used to validate the models formed; both parts are presented in Table 2. Table 3. The calculated linear correlation coefficients R of the series of descriptors are less than 0.95 ($R < 0.95$). This demonstrates the nondependence of the descriptors used to develop the models. 3.1. Principal Components Analysis (PCA).

Multiple Linear Regressions (MLR)[3]

Based on the topological descriptors selected by the PCA method, the objective is to predict quantitatively the effects of the substituents on the activity of the twenty three molecules against the human pancreatic cancer cell line, using multiple linear regression. The following equation represents the best linear QSAR model obtained using the regression linear multiple (MLR) method:

*p*IC50 = 5.42 + 0.74 × MR + 0.26 × MV - 0.23 × Pc +1.95 × logP + 2.134 × HBA + 3.80 × HBD

N = 23; R = 0.89; R2 = 0.80; Q2 = 0.51; MSE = 0.028; F = 8.03; P = 0.0012

Multiple Nonlinear Regressions (MNLR)

The statistical nonlinear regression method has been used to improve the predicted activity (pIC50) quantitatively. It has taken into account the 6 chosen descriptors. The resulting equation is:

pIC50 = 17.00557 + 0.47943 × MR + 0.11951 × MV + 0.17840 × Pc + 2.74684 × logP + 3.38813 × HBA -

2.96510 × HBD - 0.00056 ×MR^2 + 0.00002 × MV^2 + 0.00002 × Pc^2 + 0.03587 × logP^2 - 0.02738 ×

HBA^2 + 1.44924 × HBD^2

N = 23; R = 0.995; R2 = 0.992; Q2 = 0.90; MSE = 0.002

CONCLUSIONS

In this work, the QSAR regression has been investigated to predict the anticancer biological activity against the human pancreatic cancer cell line (Panc-1) of several compounds, based on the 1,2,4-triazole derivatives. The key statistical terms like R or R2 of different models obtained have been compared using different statistical tools and different descriptors, as it is shown in Table 2. A good stability and prediction ability have been exhibited by MLR, MNLR and ANN models, on the same set of descriptor. Furthermore, the obtained results from each model on this series of compounds are quite similar. None of the established models is considered better than th other. The predictive power of the model obtained has been confirmed by LOO cross-validation. A strong correlation is observed between the experimental and predicted values of the biological activities, indicating the validity and quality of the QSAR model developed in this work. Finally, based on the results obtained, the chosen descriptors are rich in information and have a great influence on the activity of the 23

studied molecules may be used with other descriptors for the development of predictive QSAR models.

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