International Journal of Current Research in Medical Sciences
ISSN: 2454-5716
www.ijcrims.com
Volume 2, Issue 6, June-2016

Original Research Article

SOI: http://s-o-i.org/1.15/ijcrms-2016-2-6-5

Quantitative Structure Activity Relationship Study of MF-63 (Phenanthrene Imidazole Series) Derivatives for mPGES-1 Inhibitory Activity

Shashank Misra[1#], Himanshu Ojha[1#], Rakesh Kumar[2], Dinesh Gupta[2] and Kulbhushan Sharma[1*]

[1]Division of Radiation Biosciences, Institute of Nuclear Medicine and Allied Sciences, Delhi -110054, India.

[2]Bioinformatics Group, International Centre for Genetic Engg. And Biotechnology, Aruna Asaf Ali Mag, New Delhi-110067, India.

*Corresponding author: **Dr. Kulbhushan Sharma,** Metabolic Cell Signaling Group Division of Radiation Biosciences, Institute of Nuclear Medicine and Allied Sciences, Delhi -110054, India.

E-mail: *kulsinmas@gmail.com*

[#] These authors contributed equally for the scientific work.

Abstract

Inhibition of COX-2 signaling has been one of the strategies to reduce occurrence and aggressiveness of many cancer types. Due to several side effects associated with the direct targeting of COX-2, inhibition of various other key players in COX-2 signaling like mPGES-1 is suggested. MF-63 is known to inhibit mPGES-1; a crucial component of COX-2 signaling. In this study, a quantitative structure activity relationship (QSAR) was performed on eighteen bioactive MF-63 (phenanthrene imidazole) derivatives. Initially 3224 molecular descriptors were obtained using DRAGON software and finally a model was developed using five of them. For variable selection, Genetic Algorithm (GA) method was used. The model was build using Partial Least Square Regression (PLSR). The most significant model generated was having correlation coefficient (r2) of 0. 9421 cross validated correlation coefficient (q2) of 0. 7888, F-test value of 81.33, r2 for external test set (pred_ r2) 0.6011, coefficient of correlation of predicted data set and (pred_r2se) 0.9706. Descriptors found suitable to construct the model included radial distribution function (RDF110u), GETAWAY descriptor (R3u), Moran Autocorrelation descriptor (MATS5v) and MoRSE descriptors (Mor28v and Mor31p). As these descriptors majorly belong to electronic and structural properties, our proposed model indicated that these properties significantly contribute towards the potency of MF-63 derivatives. The current study will aid in the future designing and development of more potent mPGES-1 inhibitors as anti-cancer agents.

Keywords: COX-2, Descriptors, Imidazole, PLSR method, QSAR.

Introduction

Cancer, a complex process defined by uncontrolled cellular growth and proliferation is a major cause of death worldwide [1]. Decades of research has demonstrated the link between COX-2 expression levels, inflammation and many cancer types. Thus, inhibition of COX-2 signaling

has been one of the strategies to reduce inflammation and occurrence and aggressiveness of cancer. Earlier inhibitors of COX like NSAID and COXIBs are reported to be associated with several side effects[2]. Even the recent therapies (siRNA, shRNA and miRNA) directed against either COX or specifically COX-2 have several snags associated. Hitherto, there has not been a single universal therapeutic strategy that has minimal COX-2 associated adverse side effects.

In addition to COX-2, there are numerous other downstream molecules such as PGE2 (microsomal PGES {mPGES1} enzyme) and EP receptors which may be targeted to minimize the damaging side effects and thus may serve as a broad spectrum, specific and long term therapeutic cure for cancers caused through COX-2/PGE2 mediated signaling (Fig. 1).

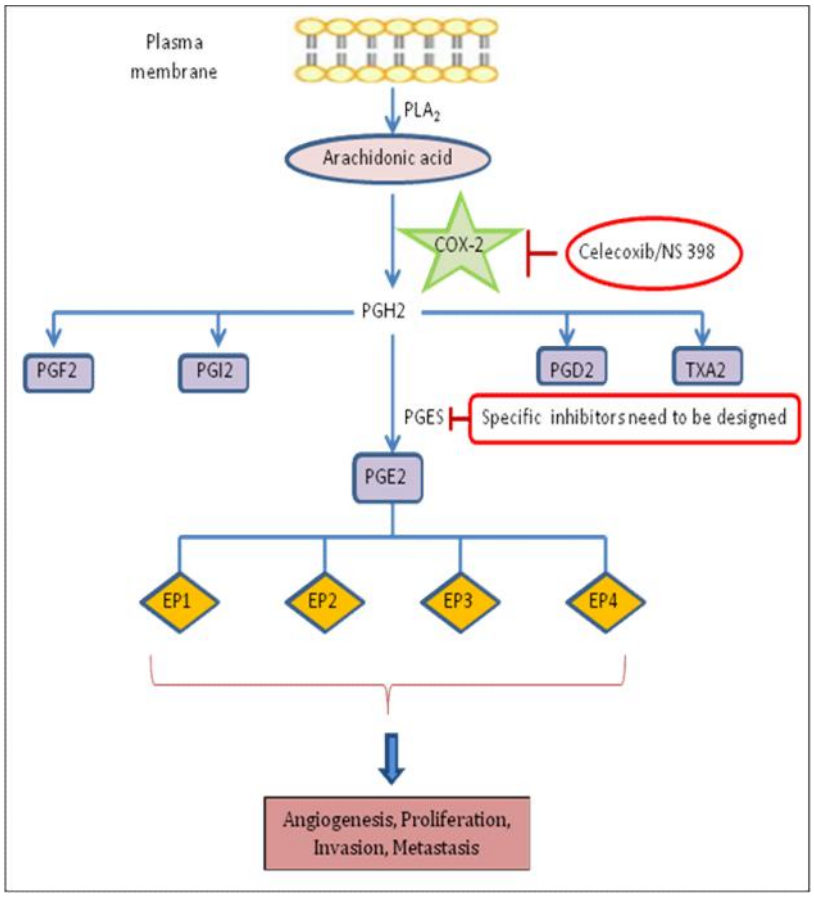


Fig. (1). COX-2 signaling pathway and cancer. The figure shows basic COX-2 signaling and its association with cancer. Targeting of various steps like formation of PGH2 using traditional COX-2 inhibitors (NSAIDs and COXIBs) and that of PGE2 formation i.e. PGES enzyme, using inhibitors like MF-63 have also been shown.

The synthesis of PGE2 is catalyzed by the presence of three specific PGE2 synthases (PGES) of which mPGES-1 expression levels have been found to be associated with various human cancer types (colon, lung, penis, stomach, head and neck) and could serve as a better therapeutic target[3-11]. Published reports of reduced clonogenic capacity of cell lines with knocked down mPGES-1 using shRNA and inhibition of xenograft tumor growth in nude mice demonstrates it as a good drug target [12].

Reduced cell proliferation, attenuated matrigel invasiveness and increased extracellular matrix adhesion has also been observed when mPGES-1 was knocked down using siRNA in Lewis lung carcinoma cells[13, 14]. The studies discussed above evidently establish the role of mPGES-1 in cancer progression in various cancer cells. The studies mentioned signifies not only the importance of mPGES-1 in the progression and maintenance of cancer but also justify the rationale for developing strategies that focus on

chemopreventive targeting of this enzyme for cancer suppression. Thus, compounds targeting mPGES-1 have received considerable attention recently and may be helpful in cancer therapy (Fig. 1)[15]. These compounds may block PGE2 production and thus COX-2 signaling. Inhibition of mPGES-1 activity by compounds of phenanthrene imidazole series like MF-63 has already been reported[16, 17]. MF-63, a JAK kinase inhibitor is a potent and selective {>1000-fold over human mPGES-2 and thromboxane synthase (TXS)} inhibitor of human mPGES-1 enzyme. High potency and selectivity has been found in cell-based assays under high plasma protein conditions. Reduced PGE2 production in LPS-stimulated human whole-blood (EC50 = 1.3 μM) without concomitant inhibition of TXB2 (EC50 > 40 μM) further demonstrate its selectivity[18]. In Guinea pigs, oral administration of MF63 suppresses PGE2 synthesis which led to efficient analgesic and antipyretic effects, with reduced PGI2 as GI toxicity usually encountered on NSAIDs treatment[19]. Bioavailability of MF-63 was also revealed in mice and rats but its mPGES-1 inhibitory activity was lacking in these species. Intravenous administration of MF-63 had a short half-life in rats and rhesus monkeys (1.5 and 1.3 h, respectively)[16]. Consequently, it becomes imperative to design new molecules of this series for improving the existing compound in terms of enhanced potency of mPGES-1 inhibition, favorable pharmacokinetic profile and reduced toxicity.

Quantitative structure activity relationships (QSAR) studies facilitates in relating the biological activities of compounds to their measurable physicochemical parameters which have major influence on the compound's activity acting as drug [20, 21]. In QSAR studies, the numerical representations of the molecular structures i.e. molecular descriptors have been stated as key players. Genetic Algorithm Partial Least Square Regression (GA-PLSR) was performed in order to investigate the correlations between the calculated molecular descriptors of MF63 {2-[6-chloro-9- 9(3 -hydroxy-3-methylbutyl)-1H-phenanthro [9, 10-d] imidazol-2-yl] benzene-1, 3-dicarbonitrile} derivatives and their experimental minimum inhibitory concentrations for mPGES-1 inhibition.

A QSAR model was build on the basis of correlation which identified various key properties. This model can be subsequently exploited to identify derivatives with superior potency and drug-likeliness by manipulating the structural features in the imidazole moiety.

Materials and Methods

Data Set

The chemical structure of the basic phenanthrene imidazole molecule has been shown in **Fig. 2.**

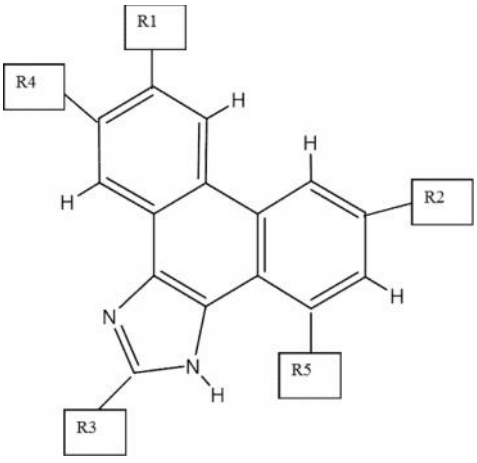
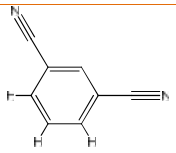
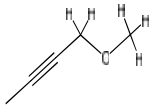
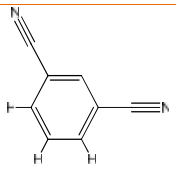
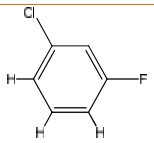
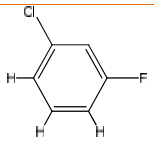
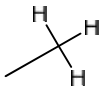
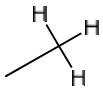
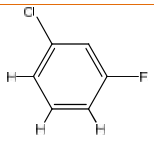
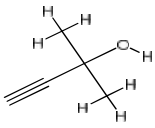
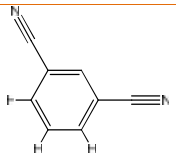
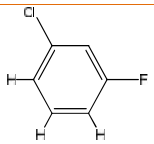
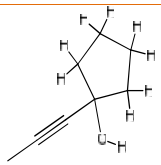
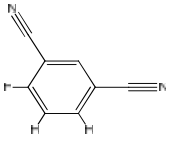
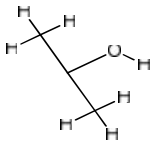
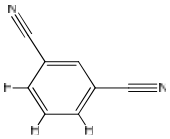
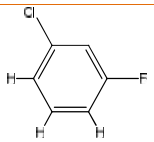
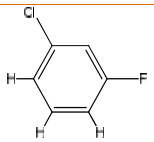
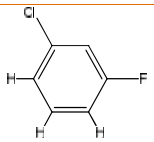
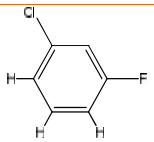
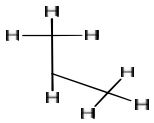
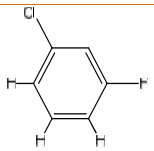
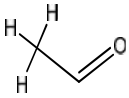
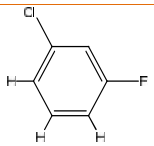
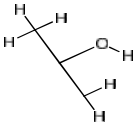
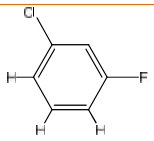
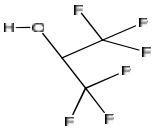
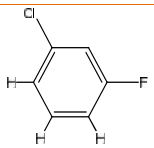
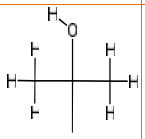
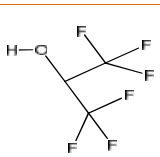
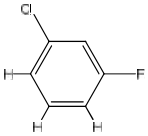


Fig. (2). Basic structure of tri substituted phenanthrene imidazole compound. The figure shows basic structure of the compound whose derivatives have been used in the study. R_1, R_2 R_3, R_4 and R_5 show the five positions where the derivatives were varied in terms of substituents.

Derivatives of the basic phenanthrene imidazole compound were imported from pubmed (http://pubchem.ncbi.nlm.nih.gov) and are enlisted in Table **1**. The chemical structure of the basic phenanthrene imidazole molecule has been shown in Fig. **2**.The mPGES-1 inhibitory activity of 18 compounds was expressed as IC_{50} values (µM) *i.e.* the effective concentration of a compound to achieve 50% inhibition of mPGES-1 enzyme activity and was used as the dependent variable in the following QSAR study. The IC_{50} values were found to vary between the highest values of 7.4 µM and the lowest value of 0.013 µM as shown in Table **1**.

Table **1:** Structure and mPGES inhibition activity of MF-63 derivatives (**1-18**) observed as IC_{50} values (µM).

Compound No.	R_1	R_2	R_3	R_4	R_5	IC_{50} (µM)
1	H	Cl		H	H	0.42
2	Cl			H	H	0.06
3	H	Cl		H	H	0.71
4	H	H		Cl	H	4.3
5				H	H	1.1
6	Cl			H	H	0.013
7	H	H		H	H	2.6
8	Cl			H	H	0.027

9	Cl			H	H	0.034
10	H	H		Br	H	7.4
11	H	H		H	Br	5
12	Br	Br		H	H	1
13	H	Br		H	H	1.1
14	Br			H	H	2
15		Br		H	H	0.33
16	Br			H	H	0.28
17	Br			H	H	0.45
18				H	H	2.3

Computation of Molecular Descriptor.

Molecular descriptors were used to represent the compound in order to build a QSAR model**.** All of the compound structures were sketched using Chem Draw Ultra 12 (Cambridge software). The compounds were used as input into DRAGON PLUS software (version 5.5, 2007) to calculate molecular descriptors. 3224 molecular descriptors including (a) 0D-constitutional descriptors; (b) 1D-functional groups counts, atom-centered fragments; (c) 2D-topological descriptors, connectivity indices, walk and path counts, 2D autocorrelations, information indices, edge adjacency indices, topological charge index, Burden eigenvalues, eigenvalue-based index; (d) 3D-Randic molecular profiles, RDF descriptors, 3D-MoRSE descriptors, geometrical descriptors, WHIM descriptors[22], GETAWAY descriptors [23]; (e) charge descriptors; and (f) molecular properties were analyzed. Detailed calculation procedure and the above mentioned descriptors can be assed in Handbook of Molecular Descriptors and references list of DRAGON package respectively[24]. Initially, 1443 molecular descriptors were obtained on the basis of exclusion of constant or near-constant and pair wise correlation variables which were further kept for sub- variable selection. Molecular descriptors with correlation coefficient >0.99 were removed.

Division of data set into Training and Test Set.

The data set was divided into training set and test sets in a 3:1 ratio randomly so as to build and validate the QSAR models, both internally and externally using VLifeMDS 4.0 software.

Feature Selection and QSAR Construction by Genetic Algorithm-Partial Least Squares (PLS) Regression Analysis.

Selection of the descriptors relevant to the bioactivity was made using Genetic algorithm (GA). GA performance controlling parameters were laid down as**:** chromosome length, 5; population size, 10; number of generations, 5000; mutation probability, 0.05.PLS analysis (popular regression technique) helps in relating the dependent variables (Y) to several independent (X) variables. PLS relates a matrix Y of dependent variables to a matrix X of molecular structure descriptors. Main aim of PLS regression is to predict the activity (Y) from (X) and to illustrate their common structure[25]. An expansion of the multiple linear regression (MLR) is PLSR. PLSR has been stated as the least restrictive of the various multivariate extensions of the multiple linear regression models. This method is utilized as an investigative analysis tool to choose suitable predictor variables and to recognize outliers before classical linear regression. In this work, GA- PLSR method from VLifeMDS software (version 4.0) was used to build the relationship between bioactivity and structural descriptors[26]. The statistical significance of the QSAR model was adjudged on the following statistical parameters: squared correlation coefficient (r^2), F-test (F-test for statistical significance of the model), cross-validated squared correlation coefficient (q^2) and predicted correlation coefficient for the external test set (pred_r^2).

Internal and external validation of GA-PLSR model.

Models were validated internally and externally using VLifeMDS 4.0 software. Finally, q^2; a value indicative of internal validation was obtained. Similarly, pred_r^2 was obtained after external validation. The pred_ r^2 value pinpoints towards the predictive power of the QSAR model for external test set.

Results and Discussion

The present study was designed to determine structural features or to quote in terms of quantitative structure activity relationship, molecular descriptors that primarily influence the IC50 values so that further potent and improved MF63 derivatives may be designed and synthesized.

QSAR Model.

Substitutions at position R1, R4 and R5 in the basic phenanthrene imidazole molecule does not

seem to significantly influence the potency (inverse of IC_{50}) as indicated from Table **1**. In contrast, position R2 and R3 seem to influence potency the most. An in-depth analysis suggested that the enhanced bulkiness of substituents at R2 position increases the potency of the compound. This is evident from the comparison of the substituents at R2 position among compounds number 4, 5 and 6. The effect is maximally observed in compound 6 and 8.

Similarly the substitution at R3 significantly influenced the potency. It may be advocated by comparing compound 1 and 3 where replacement of cyanide group with halogens decrease the potency from 0.42 to 0.71. Therefore, the relationship between R3 substitution and potency indicated that electronic properties have influence over the potency.

During the QSAR modeling, the compounds were divided into training (13) and test (5) sets through the randomized method. 1443 structural descriptors that were most relevant to the IC50 values of the compounds were calculated by DRAGON PLUS (version 5.5, 2007). These descriptors were employed as inputs for GA selection procedure.Next, PLSR was performed to obtain the equation. QSAR models were proposed on the basis of the evaluated q^2 and pred_r^2 values. A five-variable model was obtained using GA-PLSR. The corresponding regression equation generated was:

Y= -0.25RDF110u -6.14R3u +9.52MATS5v +1.71Mor28v -6.52Mor31p +11.42… (Equation 1)

where u indicates polarizability unweighted; v indicate volume and p indicate polarizability.

The important descriptors observed to influence the inhibitory activity of the compounds in our proposed model equation are (i) Moran Autocorrelation descriptor MATS5v (Moran autocorrelation-lag 5 /weighted by atomic van der Waals volumes), (ii) MoRSE descriptor Mor28v (signal 28/weighted by atomic Van der Waals volumes) (iii)MoRSE descriptor Mor31p (signal 31 /weighted by atomic polarizabilities) (iv) R3u (R autocorrelation of lag 3/ polarizability unweighted), which is a GETAWAY descriptor. The initial important descriptors are subjected to atomic volumes whereas the latter two are weighted by the atomic polarizibility. The GETAWAY (Geometry, Topology, and Atom-Weights Assembly) descriptors are defined asmolecular descriptors resulting from the Molecular Influence Matrix (MIM). MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction) are obtained from Infrared spectra simulation using a prevalent scattering function and Moran Autocorrelation descriptor is 2D Autocorrelation indices. The remaining descriptor RDF110u (Radial Distribution Function- 110 / unweighted) is a Radial distribution function.

In comparison to other descriptors this descriptor seems to least affect the inhibitory activity of compound in the equation. Our model suggests that the descriptors shown to affect the potency of MF-63 derivatives majorly belong to structural and electronic class. This further substantiates our previous observations based on the data given in Table 1. The QSAR model includes statistical parameters such as r^2 (squared correlation coefficient), q^2 (cross- validated correlation coefficient), pred_r^2 (predicted correlation coefficient for the external test set), F (Fisher ratio that reflects the ratio of the variance explained by the model and the variance due to the error in the regression). The terms r^2 se, q^2 se and pred_r^2 se are the standard errors terms for r^2, q^2 and pred_r^2.

A predictive and statistically significant QSAR model should have values of r^2 and q^2 greater than 0.6 along with high values of the F-test, pred_r^2 value>0.5 and smaller values for r^2 se, q^2 se and pred_r^2 se. Our model gave the following values: correlation coefficient r^2 (training set) = 0.9421; q^2=0.7888; F test value=81.33; r^2 se= 0.6070 and q^2 se=1.1592.

The stastical parameters such as pred_r^2= 0. 6011 and pred_r^2se = 0.9706 (test set) that are essential for determing the prediction ability of a QSAR model, was found to be satisfactory[27].

Thus, the QSAR model generated from the equation looks steady and predictive.

Table 2 displays the predicted IC50 values derived from the model.

Table **2.** Predicted and Experimental inhibitory activity data of compounds studied.

Compound	Status	Predicted IC $_{50}$(µM)	Experimental IC $_{50}$(µM)
1	Training	1.37898	0.42
2	Test	0.71832	0.06
3	Test	0.49026	0.71
4	Training	3.73657	4.3
5	Test	2.58223	1.1
6	Test	-0.86846	0.013
7	Test	3.15509	2.6
8	Training	0.39756	0.027
9	Training	0.0374	0.034
10	Training	7.35649	7.4
11	Training	5.11032	5
12	Training	1.37905	1
13	Training	0.47417	1.1
14	Training	1.49583	2
15	Training	1.18673	0.33
16	Training	0.62292	0.28
17	Training	-0.33813	0.45
18	Training	2.62748	2.3

The regression plot of the developed model has been shown in Fig. 3. The plot suggests predictability of our model in terms of the experimental IC50 and predicted IC50 values.

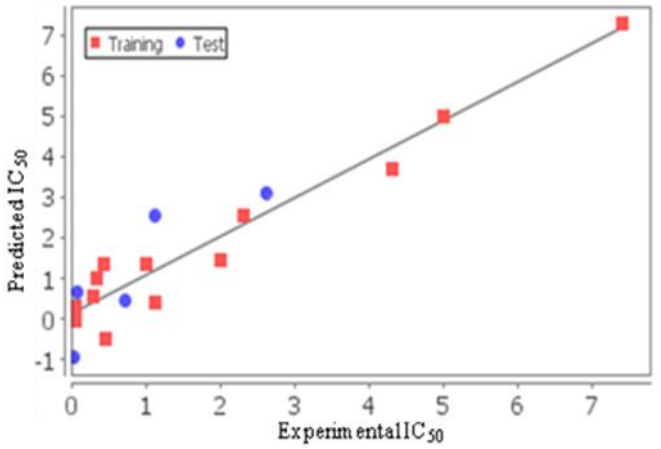


Fig. (3). Plot of experimental IC_{50} values against the calculated values of IC_{50}.

The proposed model would help in identifying the factors that controls the potency of the compounds on retrospective analyzing of the descriptors used in the model. The standardized regression coefficient value of each descriptor highlights the relative importance of the descriptors in determination of the activity of the compounds.

Conclusion

The results as discussed above connote that few molecular descriptors in the QSAR model can carve the biological activity of MF63 derivatives with the structure of mPGES-1. A penta-parametric regression equation with r^2 = 0. 9421, q^2 = 0. 7888 and pred_r^2= 0.6011 validates our model. The descriptors belonging to electronic and structural class appears to largely influence the minimum inhibitory concentration when descriptors in the proposed model are analyzed. These descriptors seem to have maximum effect on the generation of significant QSAR model. The PLSR analysis signifies a good correlation between structure and activity. Therefore, in order to obtain a more potent and specific inhibitor for mPGES-1, (IC50) of the discussed derivatives can be further developed by employing structural and electronic properties like molecular volume and polarizibility. The importance of this study could be inferred in terms of the successful prediction of the molecular properties that principally control the anti-cancer activity of these phenanthrene imidazole derivatives by QSAR method. Continuing on the same line, the predicted anti-cancer activity for recently designed phenanthrene imidazole derivatives can also be calculated in-silico which ultimately may save time and valuable resources and as a result expedite drug designing process. In order to explain diminutively, the present study facilitates **in** development of most effective biological imidazole derivatives which may serve as mPGES-1 inhibitor thus hampering COX-2 signaling and helping in the recovery from COX-2 associated cancer.

List of abbreviation

PLSR, partial linear square regression; COX, cyclooxygenase; mPGES-1, microsomal prostaglandin E synthase-1; QSAR, quantitative structure activity relationships; $IC_{50,}$ inhibitory concentration $_{50}$.

Conflict of interest

There are no conflicts of interest in the manuscript. We thank Director, INMAS and Defence Research and Development Organization for the financial support. Shashank Misra is a DST-INSPIRE fellow.

Acknowledgements

We thank Dr. Swapnil Sharma for her help in writing and editing of the manuscript. One of the authors Mr Shashank Misra wants to acknowledge DST for fellowship. The authors sincerely acknowledged the kind guidance of Dr B S Dwarakanath Sc G (Division Head) and revered Dr R P Tripathi, Outstanding Scientist and Director INMAS.

References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.
2. Green, G.A., *Understanding NSAIDs: from aspirin to COX-2.* Clin Cornerstone, 2001. **3**(5): p. 50-60.
3. Yoshimatsu, K., et al., *Inducible prostaglandin E synthase is overexpressed in non-small cell lung cancer.* Clin Cancer Res, 2001. **7**(9): p. 2669-74.
4. Yoshimatsu, K., et al., *Inducible microsomal prostaglandin E synthase is overexpressed in colorectal adenomas and cancer.* Clin Cancer Res, 2001. **7**(12): p. 3971-6.
5. Golijanin, D., et al., *Cyclooxygenase-2 and microsomal prostaglandin E synthase-1 are overexpressed in squamous cell carcinoma of the penis.* Clin Cancer Res, 2004. **10**(3): p. 1024-31.
6. van Rees, B.P., et al., *Expression of microsomal prostaglandin E synthase-1 in intestinal type gastric adenocarcinoma and in gastric cancer cell lines.* Int J Cancer, 2003. **107**(4): p. 551-6.
7. Cohen, E.G., et al., *Microsomal prostaglandin E synthase-1 is overexpressed in head and neck squamous cell carcinoma.* Clin Cancer Res, 2003. **9**(9): p. 3425-30.
8. Kletter, D., et al., *Global comparisons of lectin-glycan interactions using a database of analyzed glycan array data.* Mol Cell Proteomics, 2013. **12**(4): p. 1026-35.

9. Singh, S., et al., *Upregulation of glycans containing 3' fucose in a subset of pancreatic cancers uncovered using fusion-tagged lectins.* J Proteome Res, 2015. **14**(6): p. 2594-605.
10. Birendra, K.C., et al., *Spontaneous Regression of Refractory Diffuse Large B-Cell Lymphoma with Improvement in Immune Status with ART in a Patient with HIV: A Case Report and Literature Review.* Am J Case Rep, 2015. **16**: p. 347-52.
11. McCarter, C., et al., *Prediction of glycan motifs using quantitative analysis of multi-lectin binding: Motifs on MUC1 produced by cultured pancreatic cancer cells.* Proteomics Clin Appl, 2013. **7**(9-10): p. 632-41.
12. Hanaka, H., et al., *Microsomal prostaglandin E synthase 1 determines tumor growth in vivo of prostate and lung cancer cells.* Proc Natl Acad Sci U S A, 2009. **106**(44): p. 18757-62.
13. Kamei, D., et al., *Microsomal prostaglandin E synthase-1 in both cancer cells and hosts contributes to tumour growth, invasion and metastasis.* Biochem J, 2010. **425**(2): p. 361-71.
14. Tang, H., et al., *Glycan motif profiling reveals plasma sialyl-lewis x elevations in pancreatic cancers that are negative for sialyl-lewis A.* Mol Cell Proteomics, 2015. **14**(5): p. 1323-33.
15. Nakanishi, M., et al., *mPGES-1 as a target for cancer suppression: A comprehensive invited review "Phospholipase A2 and lipid mediators".* Biochimie, 2010. **92**(6): p. 660-4.
16. Giroux, A., et al., *Discovery of disubstituted phenanthrene imidazoles as potent, selective and orally active mPGES-1 inhibitors.* Bioorg Med Chem Lett, 2009. **19**(20): p. 5837-41.
17. Cote, B., et al., *Substituted phenanthrene imidazoles as potent, selective, and orally active mPGES-1 inhibitors.* Bioorg Med Chem Lett, 2007. **17**(24): p. 6816-20.
18. Chang, H.H. and E.J. Meuillet, *Identification and development of mPGES-1 inhibitors: where we are at?* Future Med Chem, 2011. **3**(15): p. 1909-34.
19. Xu, D., et al., *MF63 [2-(6-chloro-1H-phenanthro[9,10-d]imidazol-2-yl)-isophthalonitrile], a selective microsomal prostaglandin E synthase-1 inhibitor, relieves pyresis and pain in preclinical models of inflammation.* J Pharmacol Exp Ther, 2008. **326**(3): p. 754-63.
20. Ojha, H., et al., *Quantitative structure activity relationship study of 2,4,6-trisubstituted-s-triazine derivatives as antimalarial inhibitors of Plasmodium falciparum dihydrofolate reductase.* Chem Biol Drug Des, 2011. **77**(1): p. 57-62.
21. Karelson, M., *Molecular Descriptors in QSAR / QSPR.* Wiley Interscience: New York, USA.
22. Todeschini, R. and P. Gramatica, *New 3D molecular descriptors: the WHIM theory and QSAR applications.* Perspectives in Drug Discovery and Design, 1998. **9**(0): p. 355-380.
23. Consonni, V., R. Todeschini, and M. Pavan, *Structure/response correlations and similarity/diversity analysis by GETAWAY descriptors. 1. Theory of the novel 3D molecular descriptors.* J Chem Inf Comput Sci, 2002. **42**(3): p. 682-92.
24. Leardi, R., R. Boggia, and M. Terrile, *Genetic algorithms as a strategy for feature selection.* Journal of Chemometrics, 1992. **6**(5): p. 267-281.
25. Tobias, R.D. and *An introduction to partial least squares Regression.*
26. Singh, S., R.L. Simpson, and R.G. Bennett, *Relaxin activates peroxisome proliferator-activated receptor gamma (PPARgamma) through a pathway involving PPARgamma coactivator 1alpha (PGC1alpha).* J Biol Chem, 2015. **290**(2): p. 950-9.

27. Jain, S.K.S., Lokesh; Jain, Rahul; Yadav, Arvind K., *QSAR Analysis on 2-(4-(Piperidin-1-yl)piperidin-1-yl)-6-Substituted Thiazolo[4,5-B]Pyridines as H3 Receptor Antagonists.* Der Pharma Chemica, 2012. **4**(3): p. 1080.

Access this Article in Online	
Quick Response Code	**Website:** www.icrims.com **Subject:** Medicine

How to cite this article:
Shashank Misra, Himanshu Ojha, Rakesh Kumar, Dinesh Gupta and Kulbhushan Sharma. (2016) Quantitative Structure Activity Relationship Study of MF-63 **(**Phenanthrene Imidazole Series) Derivatives for mPGES-1 Inhibitory Activity**.** Int. J. Curr. Res. Med. Sci. 2(6): 32-42.