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ARTICLE

QSAR Screening of 5-Substituent-2(1H)-pyridone Derivatives with Improved Pharmacokinetic Parameters

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ABSTRACT

Pirfenidone is used as antifibrotic agent for treatment of liver and lung fibrosis. The pirfenidone has problem of high dose requirement, low efficacy and short half-life. The present communication deals with the quantitative structure activity relationship (QSAR) and docking analysis on the series of 5-substituent-2(1*H*)-pyridone derivatives for identification of structural features which governs the pharmacodynamic and pharmacokinetic activities of 5-substituent-2(1*H*)-pyridone derivatives as antifibrotic agents. Best QSAR model with r^2 = 0.8687 and q^2 = 0.6278, developed by multiple linear regression (MLR) method has showed that bulky substituent's which are capable imparting electron withdrawing capacity to the molecules or making electronegative potential will be increasing the antifibrotic potential of 5-substituent-2(1*H*)-pyridone derivatives. The results of docking studies proved that designing of potent molecules with improved pharmacokinetics would be possible as sites of interactions are different for antifibrotic activity (mitogen activated protein kinase p 38 gamma) and metabolism (Cytochrome P 4501A2).

KEYWORDS

Pyridone, Pirfenidone, QSAR, Metabolism, Multiple linear regression, Protein kinase.

INTRODUCTION

During reparative or reactive process, generation of excess fibrous connective tissue in an organ or tissue will occur, called as fibrosis. It will occur in many organs like lungs, skin, liver, kidney, bones, heart, shoulders, *etc*. Most of these will lead to severe conditions like surgery, organs replacement, *etc*. Renal fibrosis is indication of kidney tissue's failure to heal wounds-after chronic and sustained injury. It leads to fibrosis of glomerulus and proximal convoluted tubules (PCT) in nephron. Generation of the matrix-producing cells is an important cause of fibrosis which will be due to mesangial and fibroblast activation, tubular epithelial-mesenchymal transition *etc*. and factors that induces such a phenomenon can be called as fibrogenic factors. Amongst all, transforming growth factor-beta (TGF-β) is involved in pathogenesis of renal fibrosis. It has become more promising to identify exact cause of matrix degradation leading to tissue scaring when kidney is injured. The recent antifibrotic drug development was carried out by designing agent that will blocks fibrogenic activity of TGF-β

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signalling cascade [1]. Along with antifibrotic agents, anti-hypertensive agents, anti-inflammatory agents or steroids *etc*. are used to prevent progression of fibrosis to chronic kidney failure. The excessive accumulation of matrix outside cells will lead to renal fibrosis that can lead to end-stage renal failure. This stage will be possible to treat only with transplantation of kidney or haemodialysis [2,3]. Fibrosis can occur in either glomerulus or proximal tubular cells of kidney. The development of renal fibrosis is mainly due to activation of signalling cascades of TGF-β, present prominently in proximal tubular cells of the kidneys. An effective approach to minimize side effects and increase bio-distribution of antifibrotic agent in kidney is the development of targeted drug delivery [4]. The pirfenidone (Fig. 1) is an only pyridone derivative available, used in treatment of liver and lung fibrosis [5]. It is useful for various types of organs fibrosis as it acts on tumour necrosis factor-α, transforming growth factor-β, platelets derived growth factor and necrosis factor-jbetc. but more promising target for antifibrotic activity is TGF-β [6]. But it has few shortcomings, such as, high dose requirement, low efficacy and short half-life [7,8]. The 4-methyl group of pirfenidone was rapidly metabolized to carboxylic acid (Fig. 1), which has very less activity as compared to pirfenidone. Thus, it is possible to increase potency of antifibrosis agent by its decreasing biochemical transformations. The short half-life is due to high rate of metabolism hence its dose is also high. Thus pirfenidone will be an effective antifibrotic agent without any shortcomings by solving problem of fast metabolism at carbon 4 in pyridone ring of pirfenidone. In present communication, we have carried out 2D QSAR and docking studies to identify structural features responsible for activity and metabolism of 5-substituent-2(1H)-pyridone derivatives as antifibrotic agents. Thus it would be possible to design pyridone derivative with less metabolism without compromising antifibrotic activity.

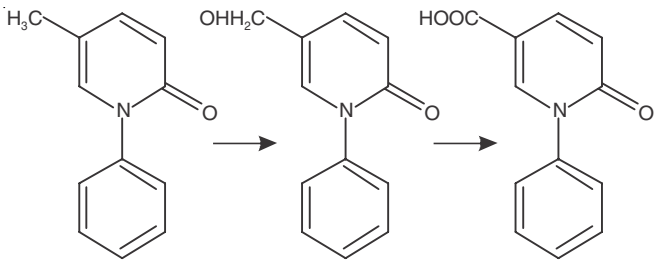


Fig. 1. Two step oxidative metabolism of pirfenidone by cytochrome P 450 1 A2

EXPERIMENTAL

Data set: The data set for the present study was taken from literature reported by Gao-Yun Hu *et al*. [9].

Ligand preparation: Molecules in the data set were build in V life MDS 4.2 molecular builder using structure of pyridone as the template. The ligand geometries were optimized by minimization using MMFF 94 as force field till a gradient of energy minimization 0.001 kcal/mol/Å was reached.

QSAR analysis: Molecules under study were randomly divided in to the test and training set using ramdom slection method. Negative logarithm of inhibitory concentration (IC_{50}) values for antifibrotic activity were utilized as dependent variable in the QSAR studies.

Full search multiple linear regression method [10-14]: Multiple linear regression (MLR) analysis was utilised to correlate the biological activity with the 2D descriptors as independent variables. MLR model generated are validated using number of parameters like r^2, q^2 and F test. Thus models having r^2 above 0.7 were used to check the external validation while F test was utilized to check the significance of the developed QSAR model. The selected models are shown in Table-1.

Activity prediction: QSAR models which are having correlation coefficient above r^2 above 0.7 were checked for their external predictivity. The observed and the predicted values for antifibrotic activity are shown in Table-2 (Fig. 2).

TABLE-2
OBSERVED AND PREDICTED ANTIFIBROTIC ACTIVITIES PYRIDONE DERIVATIVES

Compd. No.	Observed activity[a]	Predicted activity[a]	Compd. No.	Observed activity[a]	Predicted activity[a]
1a	0.80	0.99	**3a**	1.10	1.04
1b	0.91	0.84	**3b**	0.30	0.52
1c	0.97	0. 93	**3c**	0.39	0.40
1d	1.09	1.00	**3d**	0.84	0.87
1e	2.12	2.32	**4a**	0.43	0.36
1f	0.51	0.59	**4b**	0.41	0.38
2a	0.34	0.36	**4c**	0.62	0.20
2b	0.63	0.60	**4d**	0.38	0.42
2c	0.17	0.76	**4e**	1.40	1.14
2d	0.28	0.55	**4f**	0.91	0.97
2e	0.29	0.53	**4g**	0.08	0.07
2f	0.66	0.18	**4h**	3.26	3.51
2g	0.89	0.05	**5a**	0.32	0.31
2h	0.71	0.14	**5b**	2.75	2.43
2i	0.29	0.53	**5c**	2.75	2.43
2j	0.30	0.52	–	–	–

[a]Antifibrotic activity in pIC_{50} values in mM.

Docking studies [15-17]: To explore the inhibition modes as well as metabolism modes of molecules under study docking analysis were carried out using Biopredicta module of Vlife MDS 4.2. We utilized the crystal structure of cytochrome P450 1A2 (PDB ID 2HI4) for metabolism prediction and Mitogen activated protein kinase (MAPK) (PDB ID 1CM8) for activity prediction.

RESULTS AND DISCUSSION

In the present study, 21 molecules were used in the training set (first 21 molecules in Table-3) to derive QSAR models with the number of descriptors not more than two per model.

TABLE-1
SELECTED QSAR EQUATION ALONG WITH STATISTICAL PARAMETERS EMPLOYED FOR MODEL SELECTION

QSAR Model	N	r^2	q^2	F value	Pred r^2
pKi = 0.0143 + 0.0300 (± 0.0087) radius of gyration -8.9062 (± 3.3192) average positive potential	31	0.8687	0.6278	15	0.6658

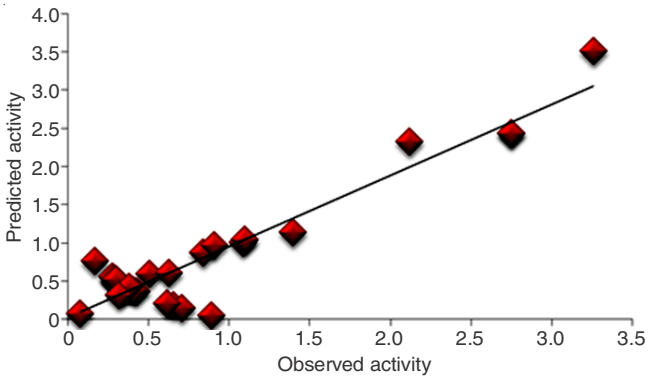
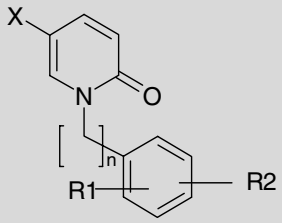


Fig. 2. Correlation plot of observed and predicted antifibrotic activities for QSAR model

TABLE-3
STRUCTURES OF 5-SUBSTITUENT-2(1H)-PYRIDONE AND 1-SUBSTITUTED PHENYL OR BENZYL-5-TRIFLUOROMETHYL-2(1H)-PYRIDONE DERIVATIVES



Compd. No.	X	n	R1	R2
1a	Cl	0	H	3-Cl
1b	Cl	0	H	4-OCH_3
1c	Cl	0	H	3-CH_3
1d	Cl	0	H	2-CH_3
1e	Cl	0	H	4-Cl
1f	CF_3	0	2-Cl	4-NO_2
2a	CF_3	1	H	4-NO_2
2b	CF_3	1	2-NO_2	H
2c	CF_3	1	2-F	H
2d	CF_3	1	H	4-OCH_3
2e	CF_3	1	2-Cl	6-Cl
2f	CF_3	1	H	4-F
2g	CF_3	1	H	3-Cl
2h	CF_3	1	H	H
2i	CF_3	0	Cl	4-NH_2
2j	CF_3	1	H	4-NH_2
3a	CF_3	1	2-NH_2	H
3b	CF_3	0	2-Cl	4-$NH(CH_2)_2O(CH_2)_2OH$
3c	CF_3	0	2-Cl	4-$NH[OH\ (CH_2)_2]_2$
3d	CF_3	0	2-Cl	4-$NH(CH_2)_2OH$
4a	CF_3	0	2-Cl	4-$NH(CH_2)_2OBu$
4b	CF_3	1	2-$NH(CH_2)_2OH$	H
4c	CF_3	1	H	4-$NH(CH_2)_2OH$
4d	CF_3	1	H	4-$NH(CH_2)_3OH$
4e	CF_3	1	H	4-$NH(CH_2)_2O(CH_2)_2OH$
4f	CF_3	0	2-Cl	4-$NHCOCH_3$
4g	CF_3	1	H	4-$NHCOCH_3$
4h	CF_3	1	2-$NHCOCH_3$	H
5a	CF_3	1	H	H
5b	CH_3	0	H	H
5c	CH_3	1	H	H

The descriptor represents the physiochemical properties of molecules are calculated and utilized for MLR studies. To evaluate the predictive ability of generated 2D-QSAR models, a test set of 10 molecules (last 10 molecules in Table-3) with regularly distributed biological activities was used (Table-2). On successful runs of multiple liner regression, different sets of equations were generated and these equations were further analyzed statistically to select the best model. As shown in Table-1, one model was selected after screening various combinations of different descriptors. The model was selected on the basis of r^2, q^2, pred r^2, F and P values (Table-1).

Interpretation of QSAR model: Model A was found best to express anti fibrotic activity as confirmed by judging internal and external predictivity and other statistical terms like the pred r and F and having r^2 0.8687 and q^2 0.6278. The contributing parameters in this model are radius of gyration and average positive potential. The radius of gyration is topological parameter signifies the size and shape of the molecule which is the distribution of atomic masses in a molecule. The radius of gyration is positively contributing towards the activity which shows that substitution of bulkier substituent's on pyridone ring can yield increase in activity also decrease the metabolic activity of the molecules due to change in the conformation and shape of the molecules. The second parameter average positive potential signifies the average of the total positive electrostatic potential on van der Waals surface area of the molecule. This descriptor is negatively contributing towards the activity so substitution of electron withdrawing groups on aryl ring can increase the activity and substitution of electron with drawing groups on the aryl ring makes the aryl ring perpendicular to pyridone ring and which is unfavourable conformation to the CYP 450 1 A2 to bind. The QSAR studies showed that bulky substituent's which are capable imparting electron withdrawing capacity to the molecules or making electronegative potential will be Increasing the antifibrotic potential of 5-substituent-2(1H)-pyridone derivatives.

Docking results: Molecular docking simulation were performed to establish mode of inhibition and probable metabolism pathway of 5-substituent-2(1H)-pyridone derivatives. As pirfenidone is inhibitor of mitogen activated protein kinase (MAPK) p 38 gamma, involved in secretion of inflammatory mediators, the X ray crystal of mitogen activated protein kinase (MAPK) p 38 gamma (PDB ID 1CM8) was utilized for identifying exact mode of action of molecules under study and on similar protein docking of pirfenidone was also carried out to compare the results of 5-substituent-2(1H)-pyridone derivatives. All the 21 derivatives were docked in similar site showed hydrogen bonding interaction with ASP1171, LYS1056, VAL1041 and hydrophobic interaction with ALA1040, ASP1115, LYS1118 and Vander Waals interactions with VAL1033, ALA1040, VAL1041, LYS1056, MET1109, GLY1157, LEU1170 and ASP1171 and pirfenidone showed interaction with hydrophobic interaction with ALA1040 and van der Waals interactions with VAL1033, ALA1040, VAL1041, LYS1056, MET1109 (Fig. 3). This indicates 5-substituent-2(1H)-pyridone derivatives are having similar mechanism of action to that of pirfenidone. To study the metabolism pattern of pirfenidone and 5-substituent-2(1H)-pyridone derivatives we utilised X ray crystal structure of cytochrome P450 1A2 (PDB ID 2HI4). The cytochrome P450 1A2 act on pirfenidone and metabolize the molecule by the oxidation of methyl group

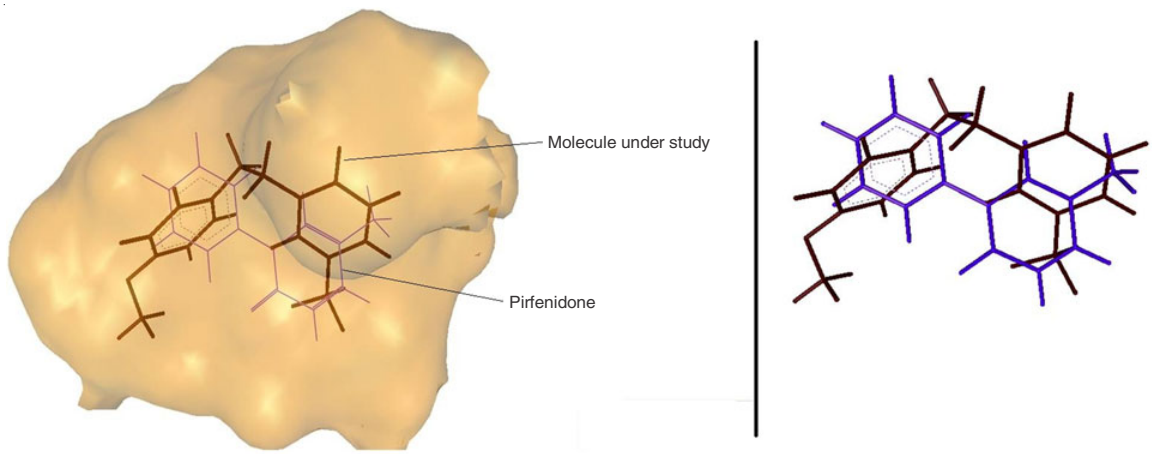


Fig. 4. Best fitted conformation of pirfenidone (pink/blue) and 5-substituent-2(1H)-pyridone (brown) in cytochrome P 450 1A2

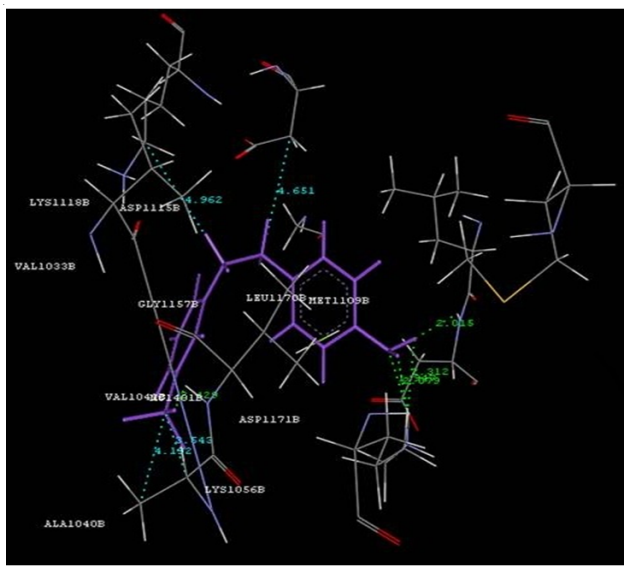


Fig. 3. Best posed 5-substituent-2(1H)-pyridone derivative docked in MAPK p 38 gamma

to acid (Fig. 1). In 5-substituent-2(1H)-pyridone derivatives, methyl group is replaced by trifluoromethyl group and substitution of electron with drawing groups on the aryl rings are present. This molecular changes makes the conformation of molecule in such way that the aryl ring and pyridone ring perpendicular to each other and this conformation of 5-substituent-2(1H)-pyridone is sterically unfavourable for binding with cytochrome P450 1A2 (Fig. 4). So 5-substituent-2(1H)-pyridone derivatives will act as good anti fibrotic agents with similar pharmacodymic properties but better pharmacokinetic profiles.

Conclusion

A computational approach involving QSAR and docking analysis was employed to identify molecular structural features required for effective antifibrotic agent for treatment and prevention of metabolism. A highly predictive QSAR model was generated based on 21 training set compounds, which showed radius of gyration and average positive potential are major contributing parameters for antifibrotic activity. The docking analysis indicated that 5-substituent-2(1H)-pyridone and pirfenidone act by the similar way but the 5-substituent-2(1H)-pyridone derivatives are having better pharmacokinetic properties. Thus, the utility of our QSAR model to predict activity of the test set compounds shows that the model is able to predict antifibrotic activity satisfactorily. Thus, the design and development of lead molecules on the basis of data obtained from this QSAR and docking analysis is likely to yield potent compounds with improved pharmacokinetics.

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