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ORIGINAL RESEARCH

New thiazolidinyl analogs containing pyridine ring: synthesis, biological evaluation and QSAR studies

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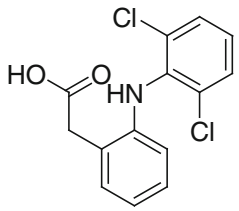
Abstract A series of pyridine derivatives of thiazolidin-4-ones (**4a–4o**) has been synthesized. Structures of these compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data. All the synthesized compounds have been evaluated for their anti-inflammatory and analgesic effects. The results showed that compound 2-[4-methylphenylimino]-5-(1*H*-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4d**), 2-(2, 4-dinitro-phenylhydrazinylidine)-5-(1*H*-pyridin-2-yl-methylidene)-1,3-thiazolidin-4-one (**4h**), and 2-[3-nitro-phenylimino]-5-(1*H*-pyridin-2-yl-methylidene)-1,3-thiazolidin-4-one (**4j**) exhibited good anti-inflammatory and analgesic activity. Compound **4h** was found to be the most active compound of the series with an interesting dual anti-inflammatory and analgesic activity. Docking simulation was performed to position synthesized compounds into the active site of COX-2. The relationships of energy-based docking score with analgesic and anti-inflammatory activities were also investigated by linear regression method. The QSAR models with R^2 of 0.621 and 0.740 were developed for analgesic and anti-inflammatory activities, respectively.

Keywords Analgesic activity · Anti-inflammatory · COX-2 inhibitors · Docking · QSAR

Introduction

Pharmacological inhibition of cyclooxygenase (COX) enzyme (EC 1.14.99.1) can provide relief from the symptoms of inflammation and pain by inhibiting the formation of important biological mediators called Eicosanoids. COX-2 is an inducible isoform that leads to inflammation. Inflammation is a multi-factorial process which reflects the response of organism to various stimuli and is related to many disorders such as arthritis, asthma, and psoriasis (Bennamane *et al.*, 2011). Classical non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, diclofenac, and flurbiprofen, non-selectively inhibit both forms of COX with gastric and renal side effects. The selective inhibition of COX-2 will provide a new generation of NSAIDs with significantly reduced side effects. Diclofenac ($C_{14}H_{11}Cl_2NO_2$) possesses wide spectrum of biological activities like anti-inflammatory, analgesic, platelet aggregation, lysosomal enzymes, and carbohydrate metabolism (Brogden *et al.*, 1980). Various dosage forms of diclofenac such as tablets, emulsions, suppositories, and injection have been prepared and characterized (Lamas *et al.*, 2010; Varshika *et al.*, 2009; Ramadan, 2012).



Diclofenac

Heterocyclic moieties, like indoles, thiazolidine-4-ones, pyrazoles, piperazines, pyridines, etc., have always got considerable attention due to their numerous pharmacological activities (Marson, 2011; Sharma *et al.*, 2010). Thiazolidin-4-one ring has attracted profound interest for their wide range of pharmacological activities, such as anticonvulsant (Siddiqui *et al.*, 2010), antimicrobial (Rajanarendar *et al.*, 2011), anti-inflammatory (Zacher *et al.*, 2008), and

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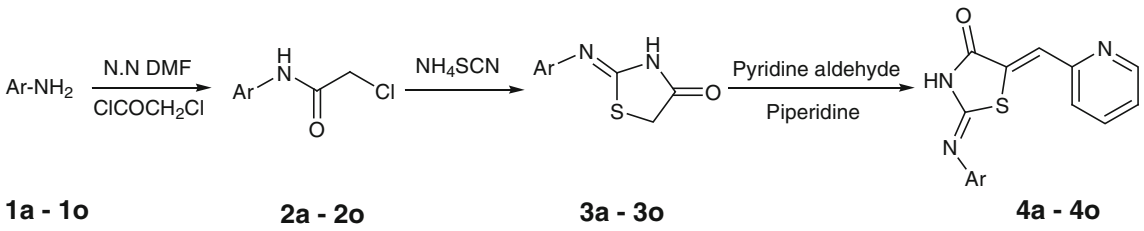


Scheme 1 Synthetic scheme

analgesic (Sharma *et al.*, 2010) activities. A number of thiazolidin-4-one derivatives have been reported to possess diversified activities (Rawal *et al.*, 2007; Rawal *et al.*, 2005; Murugesan *et al.* 2009; Sharma *et al.*, 2011; Raghubir *et al.*, 2011).

Furthermore, heterocyclic ring pyridine plays an important role in antidiabetic activity of some drugs like pioglitazone, rosiglitazone (Hosni and Abdulla, 2008). Compounds possessing pyridine ring also exhibits activities like anti-inflammatory, analgesic, antimicrobial (Ramesh *et al.*, 2008), antithyroid (Lagorce *et al.*, 1993), antiviral and anti-HIV (Balzarini *et al.*, 2005). In view of these, it was thought of interest to combine the both pharmacophoric moieties, i.e., thiazolidine-4-one and pyridine ring. A series of 2-(arylimino)-5-(pyridine-2-yl-methylidene)-1,3-thiazolidine-4-ones (**4a–4o**) were synthesized and evaluated for their potential as analgesic and anti-inflammatory agents. Docking simulations were performed by X-ray crystallographic structure of the COX-2 (PDB ID 3HS5) in complex with arachidonic acid as an inhibitor to explore the binding modes of all the synthesized compounds at the active site. In addition, we have made an attempt to integrate the power of QSAR and molecular docking by means of docking-generated energy-based score as a descriptor for building QSAR models. By this strategy, the information regarding binding mode of ligands in the active site was accumulated which would in turn assist the accurate prediction of biological activity.

Results and discussion

Chemistry

The synthesis of compounds 2-chloro-*N*-arylacetamide were carried out by reaction of appropriate substituted aromatic amine (**1a–1o**) with chloro-acetyl-chloride in presence of DMF by earlier reported method by Geronikaki *et al.*, (2007). The synthetic route of the compounds is outlined in Scheme 1. On reaction with ammonium thiocyanate in ethanol, 2-chloro-*N*-arylacetamide (**2a–2o**) yielded corresponding 2-(arylimino)-1,3-thiazolidin-4-ones (**3a–3o**). Reacting these **3a–3o** with pyridine-aldehyde and piperidine in ethanol afforded the corresponding 2-(arylimino)-5-(pyridine-2-ylmethylidene)-1,3-thiazolidin-4-ones (**4a–4o**).

The structures of the synthesized compounds were confirmed by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectral studies. The general IR spectral characters of some of the representative compounds **3a–3o**, i.e., **3a**, **3b**, and **3e** showed absorption bands ranging from 3,124 to 3,140 cm^{-1} for N–H and 1,690–1,720 cm^{-1} for C=O stretching of thiazolidinone ring. In the IR spectra of compounds **4a–4o**, the N–H and C=O stretching bands of thiazolidinone ring were observed in the range 3,031–3,140 and 1,666–1,723 cm^{-1}, respectively. The presence of the N–H stretching band in the IR spectra of **4a–4o** provided evidence that the bond between pyridine aldehyde and compounds **3a–3o** was formed at the 5-position of the thiazolidinone ring rather than at the 3-position. The absence of absorption band due to CH_2 of thiazolidinone and the presence of band in the range 1,615–1,640 cm^{-1} because of C=C absorption in the IR spectra of compounds **4a–4o** again provides confirmatory evidence for bond formation at 5-position of the thiazolidinone ring rather than at the 3-position.

The ^{1}H NMR of **3a**, **3b** and **3e** chosen as prototypes showed single N–H resonances in the δ 12.41–12.55 ppm region and singlet at δ 4.23–4.35 ppm due to CH_2 protons of thiazolidinone ring. The singlet at δ 12.21–12.82 ppm due to N–H of thiazolidinone ring in the ^{1}H NMR spectrum of **4a–4o** showed that the nitrogen still had a proton, which further supported the substitution at the 5-position. In addition, the absence of signal due to CH_2 protons of thiazolidinone ring and the presence of singlet at δ 6.78–7.95 ppm because of C=CH proton in the ^{1}H NMR spectrum of **4a–4o** confirms the replacement of proton from 5th position of compounds **3a–3o** with pyridine-2-yl-methylidene group.

Electron impact mass spectra of **3a**, **3b,** and **3e** showed an accurate molecular ion peak at *m/z* 192.62, 226.62, and 210.62, respectively, which confirmed their molecular weights. Similarly, the EIMS displayed accurate molecular ion peak at *m/z* 281, 315.24, 295.24, 295, 299, 296, 326, 386, 311, 326.64, 360.64, 309.64, 315.64, 295.24, and 360 for title compounds **4a–4o**, respectively.

Pharmacological evaluation

All the synthesized compounds **4a–4o** have been evaluated for their anti-inflammatory and analgesic activities. The evaluation of anti-inflammatory activity was carried out by the method of Joseph *et al.*, (2009) by carrageenan-induced paw edema test. The results are summarized in Table 1. Compounds **4a–4o** at 10 mg/kg body weight p.o. exhibited 26.17, 34.78, 39.67, 43.83, 34.67, 39.67, 34.78, 56.52, 39.13, 43.48, 39.67, 39.67, 26.17, 30.43, and 30.43 % anti-inflammatory activity, respectively, whereas diclofenac exhibited 43.48 % anti-inflammatory activity at 10 mg/kg body weight p.o. The results indicate that all the synthesized compounds are active as anti-inflammatory agent. Compound **4b**, **4c**, **4e**, **4f**, **4g**, **4i**, **4k**, **4l**, **4n**, and **4o** exhibited good anti-inflammatory activity, i.e., more than 30 % inhibition of inflammation, compound **4d** and **4j** exhibited anti-inflammatory activity comparable to that exhibited by diclofenac, while compound **4h** showed anti-inflammatory activity better than diclofenac.

The compounds **4a–4o** were evaluated for analgesic activity by acetic acid-induced writhing model (Kumar *et al.*, 2007) and results are summarized in Table 1. Compounds **4a–4o** at 50 mg/kg body weight p.o. exhibited 29.17, 41.67, 52.34, 43.17, 45.63, 46.16, 36.74, 68.74, 42.44, 62.34, 37.42, 51.45, 36.24, 43.56, and 28.67 % analgesic activity whereas diclofenac exhibited 60.23 % analgesic activity at 50 mg/kg body weight p.o. A look at Table 1 indicates that all the compounds exhibited analgesic activity. Compounds **4b**, **4c**, **4d**, **4e**, **4f**, **4i**, **4l**, and **4n** exhibited good analgesic activity, i.e., more than 40 % inhibition of writhing while compound **4j** and **4h** showed analgesic activity better than diclofenac.

The compound **4h**, having nitro group at position 2 and 4 of phenyl ring, was found to be the most active compound of the series with an interesting dual anti-inflammatory and analgesic activity. However, no direct correlation could be justified between the nature of functionality and the pharmacological activity of the compounds.

Molecular docking studies

Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Docking of a ligand is typically achieved by generating a number of orientation (or poses) of a ligand within the active sites, and scoring of poses to identify one or more that closely approximate the bioactive conformation determined by X-ray crystallography (Still *et al.*, 1990).

Despite the fact that pharmacological mechanism of action was not determined for the synthesized compounds, our results based upon the similarity between these molecules and previously investigated thiazolidin-4-ones derivatives strongly support the hypothesis that these compounds could act through the inhibition of Cyclooxygenase-2 (COX-2) enzyme. In the present work, docking simulations were performed on all the synthesized compounds **4a–4o** by X-ray crystallographic structure of the COX-2 (PDB code 3HS5) in complex with arachidonic acid as an inhibitor to explore the binding modes and biomolecular interactions of these compounds at the active site by means of GLIDE.

Glide searches for favorable interactions between ligand molecules and a receptor molecule. The combination of position and orientation of a ligand relative to the receptor along with its conformation is referred to as a ligand pose. Final scoring is then carried out on the energy-minimized poses.

All the synthesized thiazolidinone compounds **4a–4o** and diclofenac were embedded in the binding pocket formed by the amino acid SER53, THR212, GLU86, PHE210, and LEU294 of COX-2. The results of docking analysis, i.e., docking scores (glide score) and conformational energy of the docked pose for compounds **4a–4o** are depicted in Table 2.

All the synthesized derivatives of thiazolidin-4-ones interact actively with the COX-2 and forms hydrogen bonds with COX-2 except compound **4a**. The oxo group present at fourth position of thiazolidinone moiety of compound **4i**, **4j**, and **4l** forms a hydrogen bond (distance 2.756, 2.583, and 1.765 Å, respectively) with the residue THR212. Similarly, the oxygen of the ortho nitro group in phenyl ring of compound **4h** forms a hydrogen bond with the THR212 residue with a bond distance of 2.485 Å. The oxygen of the para nitro group in phenyl ring of compound **4k** forms a hydrogen bond (distance of 1.824 Å) with the THR212 residue bond (Fig. 1).

As shown in Table 3, compound **4h** exhibited highest value of docking score, i.e., −9.63, which was found to be comparable to that of diclofenac (−10.31), which indicates energetically favored binding of **4h** with COX-2. This is in accordance with the observation that compound **4h** was found to be the most active compound of the series with an interesting dual anti-inflammatory and analgesic activity. Similarly, the compounds **4c**, **4d**, **4f**, **4i**, **4j**, **4k**, and **4l** exhibited good value of docking score (more than −6) indicating energetically favorable binding of these compounds with COX-2.

Quantitative structure activity relationship (QSAR) studies

In recent years, in silico techniques like QSAR and molecular docking are gaining high popularity in the drug discovery

Table 1 Anti-inflammatory and analgesic activity of compounds **4a**–**4o**

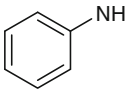
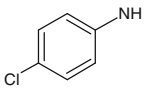
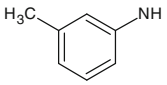
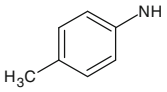
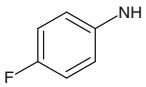
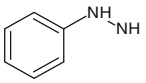
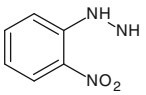
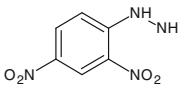
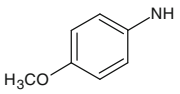
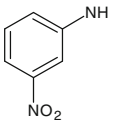
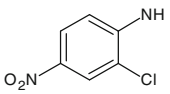
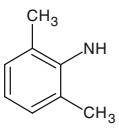
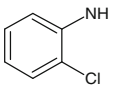
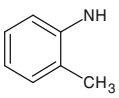
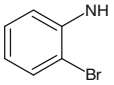
Comp.	Ar	Anti-inflammatory activity		Analgesic activity	
		Edema (ΔT)* (mm) ± SEM	Activity (%) at 120 min	Mean no of writhing ± SEM	Inhibition (%)
4a		0.17 ± 0.003	26.17	21.10 ± 0.69	29.17
4b		0.15 ± 0.009	34.78	18.17 ± 0.22	41.67
4c		0.14 ± .006	39.67	14.50 ± 0.26	52.34
4d		0.13 ± 0.007	43.83	17.29 ± 0.27	43.17
4e		0.15 ± 0.01	34.67	17.29 ± 0.27	43.17
4f		0.14 ± 0.01	39.67	16.38 ± 0.22	46.16
4g		0.15 ± 0.006	34.78	19.32 ± 0.36	36.74
4h		0.10 ± 0.014	56.52	9.35 ± 0.28	68.74
4i		0.14 ± 0.006	39.13	17.48 ± 0.31	42.44
4j		0.13 ± 0.005	43.48	11.71 ± 0.12	62.34
4k		0.14 ± 0.01	39.67	19.50 ± 0.42	37.42
4l		0.14 ± 0.003	39.67	15.29 ± 0.38	51.45
4m		0.17 ± 0.01	26.17	19.53 ± 0.42	36.24
4n		0.16 ± 0.006	30.43	17.55 ± 0.58	43.56

Table 1 continued

Comp.	Ar	Anti-inflammatory activity		Analgesic activity	
		Edema (ΔT)* (mm) ± SEM	Activity (%) at 120 min	Mean no of writhing ± SEM	Inhibition (%)
4o		0.16 ± 0.005	30.43	22.17 ± 0.42	28.67
Diclo-fenac sodium	–	0.13 ± 0.002	43.48	10.40 ± 0.14	60.23

Values are mean ± SEM from 6 animals in each group, $p < 0.05$, * $p < 0.01$, compared to control

(Schneider and Fechner, 2005). Both these methodologies allow the identification of probable lead candidates expeditiously before chemical synthesis and characterization, thereby, making the process more cost effective (Muegge and Oloff, 2006; Willet, 2006). Keeping in view the importance of docking and performance of QSAR, we integrated both approaches by docking-generated energy-based score as descriptor for QSAR modeling. The major benefit presumed by this integration would be an additional validation of the docking results by prediction of their bioactivity values by means of QSAR models. Hence, in the present work, the relationships of docking score (Table 2) with the experimentally observed analgesic and anti-inflammatory activities (Table 1) of compounds **4a–4o** were also investigated.

For proposing statistically significant models, QSAR models were generated by the technique of linear regression. All the regression analysis was performed by means of SPSS software. Predictive ability of the proposed models was evaluated by leave-one-out cross validation method (Dureja *et al.*, 2007). The criterion of squared correlation coefficient of the prediction was used to access the quality of the predictive ability of model.

Linear regression analysis has indicated that statistically significant results are obtained by docking-generated energy-based score, i.e., docking score (glide score) as descriptor. Linear regression yielded the following models for analgesic and anti-inflammatory activities:

$$\begin{aligned}&\text{Analgesic activity (percentage inhibition of writhing)}\\&= -8.114\ (\text{glide score}) - 4.868\\&n = 15;\ R^2 = 0.614;\ R^2_{\text{adj}} = 0.584;\\&F = 20.663;\ R^2(\text{CV}) = 0.622;\ \text{PRESS} = 655.9;\\&R^2_{\text{pred}} = 0.613;\ Q = 0.086 \qquad (1)\end{aligned}$$

Table 2 Ligand receptor interaction data of compounds **4a–4o**

Compound	No. of H-bond	Glide score	Conformational energy (kJ/mole)
4a	0	−5.17	−21.55
4b	1	−5.53	−31.59
4c	1	−6.12	−35.03
4d	1	−6.28	−34.88
4e	2	−5.72	−21.11
4f	1	−6.03	−33.36
4g	1	−5.52	−32.58
4h	1	−9.63	−35.80
4i	1	−6.07	−25.43
4j	1	−6.23	−35.78
4k	1	−6.22	−29.50
4l	1	−6.18	−29.48
4m	1	−5.78	−18.59
4n	1	−5.61	−32.80
4o	1	−4.96	−23.70
Diclofenac	1	−10.31	−37.40

Table 3 Experimentally observed and predicted activities of compounds **4a–4o**

Compound	Anti-inflammatory activity		Analgesic activity	
	Observed activity	Predicted activity	Observed activity	Predicted activity
4a	26.17	31.64	29.17	37.08
4b	34.78	33.89	41.67	40
4c	39.67	37.58	52.34	44.79
4d	43.83	38.59	43.17	46.09
4e	34.67	35.08	43.17	41.54
4f	39.67	37.02	46.16	44.06
4g	34.78	33.83	36.74	39.92
4h	56.52	59.55	68.74	73.27
4i	39.13	37.27	42.44	44.38
4j	43.48	38.27	62.34	45.68
4k	39.67	38.21	37.42	45.68
4l	39.67	37.96	51.45	45.28
4m	26.17	35.46	36.24	42.03
4n	30.43	34.39	43.56	40.65
4o	30.43	30.32	28.67	35.38

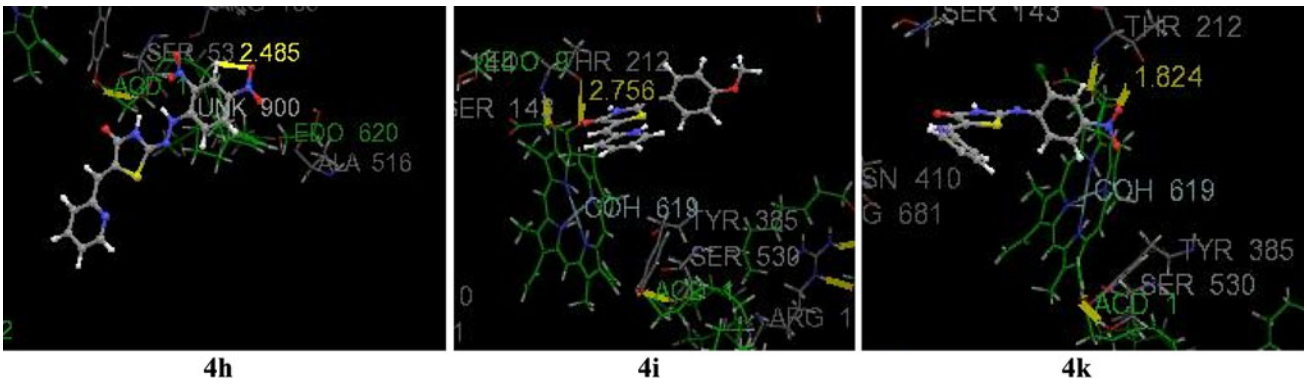


Fig. 1 Binding mode of compound **4h**, **4i**, and **4k** showing H-bonding interaction (in *yellow color*) with the COX-2 (PDB code 3HS5)

$$\begin{aligned}&\text{Anti-inflammatory activity (percentage inhibition of oedema)}\\&= -6.259\ (\text{glide score}) - 0.721\\&n = 15;\ R^2 = 0.741;\ R^2_{\text{adj}} = 0.721;\\&F = 37.098;\ R^2(\text{CV}) = 0.744;\ \text{PRESS} = 217.4;\\&R^2_{\text{pred}} = 0.74;\ Q = 0.181 \qquad (2)\end{aligned}$$

The model 1 could explain 58.4 % of variance (adjusted coefficient of variation). The leave-one-out predicted variance was found to be 62.2 %. When this model was applied for the prediction of analgesic activity, the R^2_{pred} was found to be 61.3 %. Similarly, model 2 could explain 72.1 % of variance. The leave-one-out predicted variance was found to be 74.4 %, while the model 2 was applied for prediction of anti-inflammatory activity, the R^2_{pred} was found to be 74 %.

In order to investigate the predictive power of the proposed models, we calculated Pogliani's quality factor (Q). The Pogliani's quality factor (Q) is defined as the ratio of the model represented by correlation coefficient to that of the standard error of estimation (R^2/SE) (Nikolic *et al.*, 1998). The value of Pogliani's quality factor Q is the largest for model 2, indicating that it has highest predictive power as compared to model 1.

In order to confirm our results, we have estimated analgesic and anti-inflammatory activity by means of model 1 and 2, respectively, and compared them with the experimentally observed activities. Such a comparison is shown in the Table 3 and Fig. 2. The predicted analgesic and anti-inflammatory activity by leave-one-out procedure exhibited a correlation of 0.621 and 0.740 ($n = 15$) with reported analgesic activity and anti-inflammatory activity using model 1 and 2, respectively (Fig. 2). For a reliable model, the squared predictive correlation coefficient should be >0.60 (Dureja *et al.*, 2007; Wold S, 1991). The results of this study reveal that the proposed QSAR models 1 and 2 can be used for the prediction of analgesic and anti-inflammatory activities, respectively.

Conclusion

In the present studies, a series of 2-(aryl-imino)-5-(pyridine-2-yl-methylidene)-1,3-thiazolidine-4-ones (**4a–4o**) was synthesized successfully in convenient steps in 45–93 % yields and evaluated for their potential as analgesic and anti-inflammatory agents. All the synthesised compounds exhibited anti-inflammatory and analgesic activities in vivo. Compound 2-[4-methylphenylimino]-5-(1*H*-pyridin-2-yl-methylidene)-1,3-thiazolidin-4-one (**4d**), 2-(2,4-dinitro-phenylhydrazinylidine)-5-(1*H*-pyridin-2-yl-methylidene)-1,3-thiazolidin-4-one (**4h**) and 2-[3-nitro-phenylimino]-5-(1*H*-pyridin-2-yl-methylidene)-1,3-thiazolidin-4-one (**4j**) exhibited pronounced anti-inflammatory activity comparable to the reference standard diclofenac. Compounds **4h** and **4j** also showed more analgesic activity as compared to that of diclofenac. SAR studies led to the conclusions that compounds containing Br and Cl at phenyl ring are consistently more potent and the alkyl group in phenyl ring led to the decrease in inhibitory activity if present at ortho and meta position. NO_2 group at ortho and para position of phenyl ring increases the activity; but, when it is at meta position, it decreased the activity. In addition, molecular docking studies were carried out to position all the synthesized compounds **4a–4o** and diclofenac into the active site of COX-2. All the compounds interact actively with the COX-2 and form hydrogen bonds with COX-2 except compound **4a**. Compound **4h** exhibited the highest value of docking score, which indicates energetically favored binding of **4h** with COX-2. This is in accordance with the observation that compound **4h** was also found to be the most active compound of the series with an interesting dual anti-inflammatory and analgesic activity.

Keeping in view the importance of docking and better performance of QSAR, we integrated both approaches by means of docking-generated energy-based score as descriptor for QSAR modeling. The statistically significant QSAR models with R^2 of 0.621 and 0.740 were developed. Investigations reveal significant correlation of

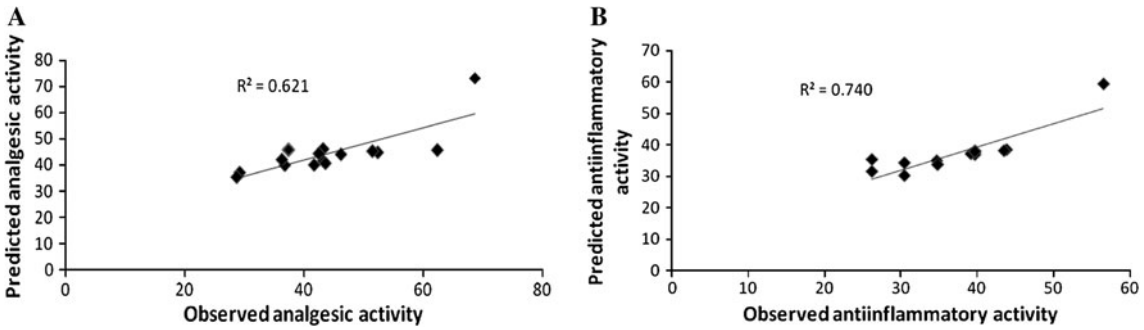


Fig. 2 Relation between observed and predicted analgesic (**a**) and anti-inflammatory (**b**) activity of compounds **4a–4o**

anti-inflammatory and analgesic activities with docking-generated energy-based score. QSAR models were generated by the technique of linear regressions. Leave-one-out cross validation methods were used to validate the reliability of model. All the proposed models possess good statistical significance. We believe that the derived QSAR models will be of interest and significance for the strategic design of more potent thiazolidin-4-ones as analgesic and anti-inflammatory agents. The statistically significant correlation between docking score and experimentally observed biological activity emphasizes on the usefulness of docking and QSAR methodology.

Materials and methods

Chemistry

All the chemicals and solvents employed in the present study were procured from Merck AG (Mumbai, India), SD Fines (Mumbai, India), and Qualigens (Navi Mumbai, India). Melting points were determined on a Lab India MR-VIS visual melting range apparatus and are uncorrected. Elemental analysis was performed on Flash 2000 CHN–S–O– analyzer (Thermo Fisher). The IR spectra were obtained on a Perkin Elmer IR spectrophotometer (Navi Mumbai, India) using potassium bromide disk. NMR spectra (Massachusetts, USA) were recorded using a Bruker 400 spectrometer (Fallanden, Switzerland) and chemical shifts are expressed as δ (ppm) with tetramethylsilane as an internal standard. Mass spectra were recorded on Waters Q-TOF micro mass spectrometer (Manchester, UK) by electron spray ionization method.

*Synthesis of 2-chloro-N-arylacetamide (**2a–2o**)*

To a solution of aromatic amine (0.01 mol) in DMF (30 ml), chloro acetyl chloride (0.01 mol) was added drop wise with constant stirring. The reaction mixture was refluxed for 2 h and cooled to room temperature. The solid mass so obtained was filtered, washed with water, dried, and purified by recrystallization from ethanol to obtain 2-chloro-*N*-arylacetamides **2a–2o**.

*Synthesis of 2-(arylimino)-1,3-thiazolidin-4-ones (**3a–3o**)*

The mixture of 2-chloro-*N*-arylacetamide (**2a–2o**) (0.05 mol) and ammonium thiocyanate (0.1 mol) in ethanol (50 ml) was refluxed for 1 h and left overnight. Solid thus obtained was separated by filtration and recrystallized from ethanol to give the corresponding 2-(arylimino)-1,3-thiazolidin-4-ones **3a–3o**.

*2-(Phenylimino)-1,3-thiazolidin-4-one (**3a**)* m.p.: 198–201; % yield: 73; IR (KBr) cm^{-1}: 3140 (N–H of thiazolidin-4-one), 3047 (C–H str. of aromatic), 1690 (C=O of thiazolidin-4-one), 1589 (C=N); ^{1}H NMR, δ ppm (DMSO-*d*6): 12.55 (1H, s, NH of thiazolidin-4-one), 7.23–7.94 (m, 9H, Ar), 4.23 (2H, s, CH_2); EI-MS *m*/*z*: 192.62 M^+; Anal. Calcd. for $C_9H_8N_2OS$ (192.23): C, 35.97; H, 2.66; N, 9.33. Found: C, 35.91; H, 2.52; N, 9.14.

*2-(4-Chlorophenylimino)-1,3-thiazolidin-4-one (**3b**)* m.p.: 221–223; % yield: 59; IR (KBr) cm^{-1}: 3134 (N–H of lactam), 3037 (C–H str. of aromatic), 1697 (C=O of thiazolidin-4-one), 1575 cm^{-1} (C=N); ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.51(1H, s, NH– thiazolidinone), 7.23–7.94 (m, 9H, Ar), 4.45 (2H, s, $–CH_2$). EI-MS: *m*/*z* 226.62 M^+; Anal. Calcd. for $C_9H_7ClN_2OS$ (226.68): C, 35.96; H, 2.32; N, 9.30. Found: C, 35.64; H, 2.46; N, 9.54.

*2-(4-Fluorophenylimino)-1,3-thiazolidin-4-one (**3e**)* m.p.: 238–239; % yield: 69; IR (KBr) cm^{-1}: 3124 (N–H of lactam), 3045 (C–H str. of aromatic), 1714 (C=O of thiazolidinone), 1575 cm^{-1} (C=N) ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.41(1H, s, NH– thiazolidinone), 7.13–7.74 (m, 9H, Ar), 4.35 (2H, s, $–CH_2$). EI-MS: *m*/*z* 210.62 M^+; Anal. Calcd. for $C_9H_7FN_2OS$ (210.22): C, 35.74; H, 2.37; N, 9.34. Found: C, 35.64; H, 2.42; N, 9.44.

*Synthesis of 2-(arylimino)-5-(pyridin-2-yl-methylidene)-1,3-thiazolidine-4-one (**4a–4o**)*

The mixture of 2-(arylimino)-1,3-thiazolidin-4-one (**3a**–**3o**) (0.01 mol), pyridine aldehyde (0.01 mol), and piperidine (few drops) was refluxed for 24 h. The mixture was then cooled and poured on to crushed ice. The solid thus obtained was separated by filtration and purified by recrystallized from rectified spirit to give corresponding 2-(arylimino)-5-(pyridin-2-yl-methylidene)-1,3-thiazolidine-4-one (**4a–4o**).

*5-(1H-pyridin-2-ylmethylidene)-2-(phenylimino)-1,3-thiazolidin-4-one (**4a**)* (m.p.: 265–267; % yield: 60; IR (KBr) cm^{-1}: 3140 (N–H of lactam), 3047 (C–H str. of aromatic), 1702 (C=O of thiazolidinone), 1625 (C=C aromatic), 1589 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.55 (1H, s, NH, thiazolidinone), 6.9 (1H, s, =CH), 7.23–7.94 (m, 9H, Ar). EI-MS: *m*/*z* 281 M^+; Anal. Calcd. for $C_{15}H_{11}N_3OS$ (281.33): C, 44.91; H, 2.71; N, 10.34. Found: C, 44.34; H, 2.56; N, 10.74.

*2[4-Chlorophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4b**)* m.p.: 232–235; % yield: 61; IR (KBr) cm^{-1}: 3138 (N–H of lactam), 3057 (C–H str. of aromatic), 1723 (C=O of thiazolidinone), 1632 (C=C aromatic), 1592 cm^{-1} (C=N), 114 cm^{-1}. ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.82 (1H, s, NH, thiazolidinone), 7.25 (1H, s, C=CH), 6.98–7.54 (m, 8H, Ar). EI-MS: *m*/*z* 315.24 M^+; Anal. Calcd. for $C_{15}H_{10}ClN_3OS$ (315.77): C, 44.34; H, 2.62; N, 10.14. Found: C, 44.64; H, 2.56; N, 10.74.

*2[3-Methylphenylimino]-5-(1H-pyridine-2-ylmethylidene)-1,3-thiazolidin-4-one (**4c**)* m.p.: 251–253; % yield: 62; IR (KBr) cm^{-1}: 3138 (N–H of lactam), 3057 (C–H str. of aromatic), 1712 (C=O of thiazolidinone), 1624 (C= aromatic), 1592 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.25 (1H, s, NH, thiazolidinone), 6.9 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar), 2.37 (3H, s, CH_3). EI-MS: *m*/*z* 295.24 M^+; Anal. Calcd. for $C_{16}H_{13}N_3OS$ (295.35): C, 52.17; H, 3.25; N, 10.17. Found: C, 52.64; H, 3.06; N, 10.74.

*2[4-Methylphenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4d**)* m.p.: 229–231; % yield: 72; IR (KBr) cm^{-1}: 3082 (N–H of lactam), 3127 (C–H str. of aromatic), 1697 (C=O of thiazolidinone), 1636 (C=C aromatic), 1605 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.25 (1H, s, NH, thiazolidinone), 6.78 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar), 2.37 (3H, s, CH_3). ^{13}C NMR δ ppm, (DMSO-*d*6): 24.3, 121.0, 122.2, 122.4, 122.7, 130.4, 130.9, 132.0, 133.8, 136.9, 137.0, 146.0, 148.9, 154.9, 168.5. EI-MS: *m*/*z* 295 M^+; Anal. Calcd. for $C_{16}H_{13}N_3OS$ (295.35): C, 52.34; H, 3.17; N, 10.36. Found: C, 52.64; H, 3.06; N, 10.75.

*2[4-Fluorophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4e**)* m.p. 276–278; % yield: 45; IR (KBr) cm^{-1}: 3074 (N–H of lactam), 3045 (C–H str. of aromatic), 1666 (C=O of thiazolidinone), 1622 (C=C aromatic), 1582 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.23 (1H, s, NH, thiazolidinone), 7.14 (1H, s, =CH), 6.82–7.44 (m, 10H, Ar). EI-MS: *m*/*z* 299 M^+; Anal. Calcd. for $C_{15}H_{10}FN_3OS$ (299.32): C, 44.41; H, 2.51; N, 10.17. Found: C, 44.12; H, 2.14; N, 10.74.

*2-(Phenylhydrazinylidine)-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4f**)* m.p. 2263–266; % yield: 93; IR (KBr) cm^{-1}: 3138 (N–H of CONH), 3057 (C–H str. of aromatic), 1694 (C=O of thiazolidinone), 1644 (C=C aromatic), 1589 cm^{-1}(C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.21 (1H, s, NH, thiazolidinone), 6.95 (1H, s, =CH), 6.98–7.94 (m, Ar, 10H), 10.2 (IH, S, NH). EI-MS: *m*/*z* 296 M^+; Anal. Calcd. for $C_{15}H_{12}N_4OS$ (296.34): C, 52.36; H, 2.95; N, 13.70. Found: C, 52.12; H, 2.64; N, 13.74.

*2[2-Nitrophenylimino]-5-(1H-pyridine-2-ylmethylidene)-1,3-thiazolidin-4-one (**4g**)* m.p.: 282–285; % yield: 79; IR (KBr) cm^{-1}: 3036 (N–H of lactam), 3047 (C–H str. of aromatic), 1714 (C=O of thiazolidinone), 1605 (C=C aromatic), 1598 (C=N), 1513, 1340 cm^{-1} (NO_2). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.35 (1H, s, NH, thiazolidinone), 6.95 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar). EI-MS: *m*/*z* 326 M^+; Anal. Calcd. for $C_{15}H_{10}N_4O_3S$ (326.32): C, 52.46; H, 2.61; N, 13.70. Found: C, 52.12; H, 2.64; N, 13.74.

*2-(2,4-Dinitrophenylhydrazinylidine)-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4h**)* m.p.: 255–257; % yield: 84; (KBr) cm^{-1}: 3138 (N–H of CONH), 3057 (C–H str. of aromatic), 1694 (C=O of thiazolidinone), 1644 (C=C aromatic), 1589 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.21 (1H, s, NH, thiazolidinone), 6.95 (1H, s, =CH), 6.98–7.94 (m, Ar, 7H), 10.2 (IH, s, NH). ^{13}C NMR δ ppm, (DMSO-*d*6): 118.4, 120.1, 120.4, 122.7, 128.6, 131.0, 132.6, 133.7, 137.0, 148.9, 149.7, 149.9, 153.4, 144.5, 167.8. EI-MS: *m*/*z* 386 M^+; Anal. Calcd. for $C_{15}H_{10}N_6O_5S$ (386.34): C, 52.56; H, 2.71; N, 20.70. Found: C, 52.12; H, 2.64; N, 20.74.

*2[4-Methoxyphenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4i**)* m.p.: 242–244; % yield: 53; IR (KBr) cm^{-1}: 3110 (N–H of lactam), 3042 (C–H str. of aromatic), 1690 (C=O of thiazolidinone), 1643 (C=C aromatic), 1590 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.25 (1H, s, NH, thiazolidinone), 6.97 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar). EI-MS: *m*/*z* 311 M^+; Anal. Calcd. for $C_{16}H_{13}N_3O_2S$ (311.35): C, 52.36; H, 3.21; N, 10.19. Found: C, 52.12; H, 3.64; N, 10.74.

*2[3-Nitrophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4j**)* m.p.: 279–281; % yield: 67; IR (KBr) cm^{-1}: 3080 (N–H of lactam), 3047 (C–H str. of aromatic), 1713 (C=O of thiazolidinone), 1622 (C=C aromatic), 1592 (C=N), 1513, 1340 cm^{-1} (NO_2).^{1}H NMR, δ ppm, (DMSO-*d*6): 12.55 (1H, s, NH, thiazolidinone), 6.95 (1H, s, =CH), 7.2–8.44 (m, 8H, Ar). ^{13}C NMR δ ppm, (DMSO-*d*6): 118.1, 119.5, 122.1, 122.4, 123.1, 124.4, 128.0, 135.4, 137.1, 139.3, 147.6, 148.4, 154.2, 154.7, 164.8. EI-MS: *m/z* 326.64 M^+; Anal. Calcd. for $C_{15}H_{10}N_4O_3S$ (326.32): C, 44.36; H, 2.51; N, 13.65. Found: C, 44.12; H, 2.64; N, 13.74.

*2[2-Chloro,4-nitrophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4k**)* m.p.: 286–288; % yield: 47; IR (KBr) cm^{-1}: 3048 (N–H of lactam), 3057 (C–H str. of aromatic), 1687 (C=O of thiazolidinone), 1618 (C=C aromatic), 1589 (C=N), 1513, 1340 cm^{-1} (NO_2). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.55 (1H, s, NH, thiazolidinone), 7.95 (1H, s, =CH), 7.5–8.4 (m, 7H, Ar). EI-MS: *m/z* 360.64 M^+; Anal. Calcd. for $C_{15}H_9ClN_4O_3S$ (360.77): C, 43.96; H, 2.21; N, 13.65. Found: C, 43.12; H, 2.34; N, 13.74.

*2[2,6-Dimethylphenylimino]-5-(1H-pyridine-2-ylmethylidene)-1,3-thiazolidin-4-one (**4l**)* m.p.: 222–225; % yield: 57; IR (KBr) cm^{-1}: 3031 (N–H of lactam), 3037 (C–H str. of aromatic), 1697 (C=O of thiazolidinone), 1635 (C=C aromatic), 1603 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.35 (1H, s, NH, thiazolidinone), 6.95 (1H, s, =CH), 6.98–7.94 (m, 7H, Ar), 2.35 (6H, s, CH_3). EI-MS: *m/z* 309.64 M^+; Anal. Calcd. for $C_{17}H_{15}N_3OS$ (309.38): C, 50.96; H, 3.71; N, 10.65. Found: C, 50.12; H, 3.34; N, 10.74.

*2[2-Chlorophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4m**)* m.p.: 261–263; % yield: 73; IR (KBr) cm^{-1}: 3078 (N–H of lactam), 3035 (C–H str. of aromatic), 1716 (C=O of thiazolidinone), 1638 (C=C aromatic), 1589 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.55 (1H, s, NH, thiazolidinone), 6.9 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar). EI-MS: *m/z* 315.64 M^+; Anal. Calcd. for $C_{15}H_{10}ClN_3OS$ (315.77): C, 43.96; H, 2.51; N, 10.25. Found: C, 43.62; H, 2.34; N, 10.54.

*2[2-Methylphenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4n**)* m.p.: 232–235; % yield: 64; IR (KBr) cm^{-1}: 3138 (N–H of lactam), 3057 (C–H str. of aromatic), 1698 (C=O of thiazolidinone), 1632 (C=C aromatic), 1592 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.55 (1H, s, NH, thiazolidinone), 6.8 (1H, s, =CH), 6.98–7.94 (m, 8H), 2.37 (6H, s, CH_3). EI-MS: *m/z* 295.24 M^+; Anal. Calcd. for $C_{16}H_{13}N_3OS$ (295.35): C, 52.36; H, 3.31; N, 10.51. Found: C, 52.62; H, 3.34; N, 10.54.

*2[4-Bromophenylimino]-5-(1H-pyridin-2-ylmethylidene)-1,3-thiazolidin-4-one (**4o**)* m.p.: 281–283; % yield: 45; IR (KBr) cm^{-1}: 3108 (N–H of lactam), 3127 (C–H str. of aromatic), 1716 (C=O of thiazolidinone), 1632 (C=C aromatic), 1592 cm^{-1} (C=N). ^{1}H NMR, δ ppm, (DMSO-*d*6): 12.35 (1H, s, NH, thiazolidinone), 6.8 (1H, s, =CH), 6.98–7.94 (m, 8H, Ar). EI-MS: *m/z* 360 M^+; Anal. Calcd. for $C_{15}H_{10}BrN_3OS$ (360.22): C, 43.36; H, 2.51; N, 10.41. Found: C, 43.62; H, 2.34; N, 10.54.

Pharmacological evaluation

Wistar rats weighing 180–250 g and Swiss albino mice weighing 25–30 g were housed in a room maintained under controlled room temperature of 22 ± 2 °C with a relative humidity 60–70 % and provided with food and water ad libitum. All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee (Registration No. 563/02/a/CPCSEA) and were in accordance with the guidelines of the CPCSEA, Ministry of Forests and Environment, Government of India. The animals were deprived of food for 24 h before experimentation, but allowed free access to water throughout.

Anti-inflammatory activity

The anti-inflammatory activity of the synthesised compounds by the carrageenan-induced paw edema test was studied according to the method by Joseph *et al.*, (2009). The animals were divided into different groups consisting of six rats each. The control group received normal saline: tween 80 (95:5), the standard group received the standard drug diclofenac sodium 10 mg/kg body weight and the test groups received the synthesised compounds at a dose of 10 mg/kg body weight. Thirty minutes after the administration of the test and standard drugs, 0.01 ml of 1 % w/v carrageenan suspension in normal saline was injected into the left hind paw (plantar region) of all the animals. The paw volume, up to the tibiotarsal articulation, was measured using a plethysmometer (Model 7140, Ugo Basile, Italy). The percentage protection of oedema (inhibition of inflammation) was calculated according to the formula, percentage anti-inflammatory activity $= 100 \times (1 - V_t/V_c)$ where V_t and V_c are the volumes of oedema for the test compounds and control groups, respectively. It is pertinent to mention here that maximum activity was obtained at 120 min, and thus the percentage inhibition was calculated at 120 min.

Analgesic activity

The analgesic activity was measured against chemical stimuli. For analgesic activity, the animals were divided into

groups consisting of six mice each. The control group received normal saline: tween 80 (95:5). The standard group received diclofenac 50 mg/kg body weight and the test groups received the synthetic compounds at a dose of 50 mg/kg body weight. Thirty minutes later, nociception was induced by an intraperitoneal (IP) injection of acetic acid (1 %), 0.1 ml/10 g. The numbers of stretching or writhing movements were recorded from 5 to 15 min. The percentage protection was calculated by the following formula:

Percentage protection = 100 − (No. of writhes in test/No. of writhes in control) × 100.

Molecular docking studies

Ligand preparation

The chemical structures of all the compounds were drawn in maestro and geometrically refined by means of LigPrep, Version 2.4, (2010) module. The simplest use of *LigPrep* produces a single, low-energy, 3D structure with correct chiralities for each successfully proposed input structure. Chiralities and original states of ionization were retained. Tautomers and conformations were generated by Monte Carlo (MCMM) method as implemented in MacroModel Version 9.8, (2010) by means of OPLS-2005 force field. All the conformers were subsequently minimized by truncated Newton conjugate gradient (TNCG) minimization up to 500 iterations. For each molecule, a set of conformers with a maximum energy difference of 30 kcal/mol relative to the global energy minimum conformer was retained. The conformational searches were done for aqueous solution using the generalized born/solvent accessible surface (GB/SA) continuum solvation model (Schneider and Fechner, 2005).

Protein preparation

The COX-2 (PDB code 3HS5) X-ray structure was accessed from the protein data bank. A typical PDB structure file consists only of heavy atoms, can contain waters, cofactors, and metal ions, and can be multimeric. The structure generally has no information on bond orders, formal atomic charges, and generally unassigned ionization and tautomeric states. Thus, the protein structures were prepared by the protein preparation wizard in Maestro. In this step, bond orders were assigned, all hydrogens in the structure were added, and the bonds to metals were deleted and the formal charge on the metal & the neighboring atoms, that were more than the 5 Å specified distance, were adjusted. Generate Het states option was used for predicting ionization and tautomeric states of the heterocyclic group at pH 7. The next stage of protein preparation was to optimize the hydrogen bond network by reorienting hydroxyl group, water molecules, and amide groups, and selecting appropriate states and orientation of the rings in the residues. The final step in the protein preparation process was to refine the structure with a restrained minimization. Their task was initiated in the Impref minimization with the 0.3 Å RMSD for the OPLS_2005 force field.

Ligand docking

Glide, Version 5.6, (2010) searches for favorable interactions between ligand molecules and the receptor protein. Grids were generated to define the binding site of the protein and generated the electrostatic grid. No constraints were included in the grid files. The shape and properties of the receptor were represented on a grid by several different sets of field, which provide progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, grids were prepared for each conformation to insure that possible actives were not missed. Ligand molecule was picked so that it can be excluded from the grid generation with van der Waals radius scaling 1.00 and partial charge cutoff of 0.25. The compounds were docked by means of Glide with standard settings in standard precision (SP) mode.

Quantitative structure activity relationship studies

QSAR models were generated by the technique of linear regressions. All the regression analyses were performed by means of SPSS software. Regression analysis by the method of maximum R^2 was used for proposing statistically significant models. Predictive ability of the proposed models was evaluated by leave-one-out cross validation methods (Dureja *et al.*, 2007). The criteria of squared correlation coefficient of the predictions were used for the quality of the predictive ability of model.

Conflict of interest The authors declare that they have no competing interests.

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