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Prediction of photosensitivity of 1,4-dihydropyridine antihypertensives by quantitative structure-property relationship

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ABSTRACT

A quantitative structure-property relationships (QSPR) model, correlating the light sensitivity against theoretical molecular descriptors, was developed for a set of 1,4-dihydropyridine calcium channel antagonist drugs. These compounds are characterized by a high tendency to degradation when exposed to light, furnishing in the most of cases a related oxidation product from aromatization of the dihydropyridinic ring. Photodegradation was forced by exposing the drugs to a Xenon lamp, in accordance with the ICH international rules, and degradation kinetics was monitored by spectrophotometry.

The photodegradation rates combined with a series of descriptors related to the chemical structures were computed by Partial Least Squares (PLS) multivariate analysis. An accurate selection of the variables, fitting at the best the PLS model, was performed. Two descriptors related to the substituent information on both the dihydropyridinic and benzenic rings and four molecular descriptors, were selected. The QSPR model was fully cross validated and then optimized with an external set of novel 1,4-dihydropyridine drugs, obtaining very satisfactory statistical results. The good agreement between predicted and measured photodegradation rate ($R^2 = 0.8727$) demonstrated the high accuracy of the QSPR model in predicting the photosensitivity of the drugs belonging to this class. The model was finally proposed as an effective tool to design new congeneric molecules characterized by high photostability.

1. Introduction

Quantitative structure-property relationships (QSPR) techniques help to establish a correlation between the molecular structures and chemical or chemical–physical properties of a congeneric series. In the last years, QSPR approach has been investigated in various fields of chemistry, biochemistry, pharmacy and environmental chemistry [1]. In the modern pharmaceutical chemistry, the prediction of required properties of new molecules plays a very important role throughout the overall drug design. The up-to-date techniques pursue this target by means of a mathematical model. A QSPR relationship can be used to identify the parameters affecting a specific property of the molecules or to predict the same property for other molecules belonging to the series [2,3].

Elaboration of a reliable and robust experimental relationship represents the real core in a QSPR analysis [4]. An empirical equation in a QSPR model is generally expressed as:

$$f(P) = \sum_{i=1,j=1}^{i=n,j=m} a_{ij}D_{ij} + b$$

where P is the property of interest; a_{ij} and b are the regression coefficients, D_{ij} are parameters characterizing each molecular structure of the series, named descriptors [5].

The selection of the descriptors represents an essential step in improving the quality of the model. This choice has become more and more demanding because of the high number of descriptors proposed in literature [6]. The most common descriptors are constitutional or topological parameters explaining the number of carbon atoms or the chemical bonds in the molecules. Another important series of chemical descriptors, namely quantum descriptors, define the electronic and geometric properties of the molecules and their interactions [5]. Recently, a quantum chemical approach has been used to determine energetic information of the molecules and, in particular, to define the minimum energy configuration [3].

In a QSPR elaboration, it is difficult to establish as well if a chemical group can lead a significant variation on the different properties in a congeneric series. Moreover, it is daring to take as a reference the data of analogue works in literature because a substituent can give an important effect into a class of compounds and have no effect in another class [4]. The continuous development of chemometric techniques has represented in the last years a very important support to the elaboration of QSPR models. Principal Component Analysis (PCA), Partial Least Squares (PLS) and Analysis of Variance (ANOVA) have proved to be very useful tools in testing a high number of variables and then in selecting those that significantly

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influence the system. This approach has permitted the building of complex QSPR models, characterized by high prediction power [7–14].

In this work, a set of nine 1,4-dihydropyridine (1,4-DHP) antihypertensive drugs, Amlodipine (AML), Felodipine (FEL), Lercanidipine (LER), Nisoldipine (NIS), Nitrendipine (NIT), Nicardipine (NIC), Nifedipine (NIF), Manidipine (MAN), Nimodipine (NIM) has been submitted to a QSPR study. 1,4-DHP drugs are calcium antagonist agents largely used in the treatment of cardiovascular disorders, above all hypertension and cardiac arrhythmias [15–18]. Unfortunately, a feature common of all compounds of this class is the high photosensitivity. Light catalyzes their oxidation to pyridine derivatives, lacking in therapeutic effect [19–23] and, in some cases, to secondary photoproducts [24–26]. Aromatization of 1,4-DHP has also attracted considerable attention recently because it has been demonstrated that metabolism of those drugs involves an analogous cytochrome P-450 catalyzed oxidation in the liver [27].

This work aims at defining a correlation between the photodegradation rate of 1,4-DHP drugs and their chemical structure by means of QSPR modeling. The successful application of the model in predicting the light sensitivity of related compounds, or in designing new congeners with a potential high photostability, represents the final target.

Contributions about the application of QSPR analysis to photodegradation studies have been published. An interesting QSPR model for predicting the photodegradation rate of chlorinated polycyclic aromatic hydrocarbons has been proposed [28]. A set of quantum chemical descriptors has been adopted to develop QSPR models for estimation of photodegradation half-lives of persistent organic pollutants [28,29]. Structural descriptors have been used to build a QSPR relationship used in the study of photolysis mechanisms [30].

Quantitative structure-activity relationship (QSAR) analysis has been applied to the 1,4-DHP class to establish the calcium channel antagonist activity as a function of some theoretically derived descriptors [31,32]. In particular, the binding of the molecules to the receptor has been expressed by topology, hydrophobicity and surface area descriptors [32].

The proposed QSPR study was supported by multivariate regression techniques, because of their ability in computing a high number of variables. In particular, a PCA elaboration followed by PLS regression was applied to both experimental and calculated data with the aim to select a number of predictors furnishing the most useful information to define a well-fitted multivariate model.

With the aim to use homogeneous results in the model building, the photodegradation process was standardized, by performing light exposure according to the international rules [33].

2. Materials and methods

2.1. Apparatus

Absorption spectra were registered on the λ range of 190–450 nm in a 10 mm quartz cell by means of a PerkinElmer Lambda 40P Spectrophotometer at the following conditions: scan rate 1 nm s^{-1}; time response 1 s; spectral band 1 nm. The software UV Winlab 2.79.01 (PerkinElmer) was used for spectral acquisition and elaboration.

Drugs photodegradation was carried out according to the "Guide for the Photostability Testing of New Drug Substances and Products" recommended by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [33].

Light exposure was performed in a light cabinet Suntest CPS+ (Heraeus, Milan, Italy), equipped with a Xenon lamp. The apparatus was fitted with an electronic device for irradiation and temperature measuring and controlling inside the box. The system was able to closely simulate sunlight and to appropriately select spectral regions by interposition of filters.

2.2. Chemicals

FEL, NIC, NIF, NIT and Cilnidipine (CIL) were purchased from Sigma–Aldrich Co. (Italy). AML (Pfizer, Italy), LER (Recordati, Italy), MAN (Chiesi, Italy), NIM (Bayer, Italy) and NIS (Bayer, Italy) were generous gifts from the respective pharmaceutical companies. Barnidipine (BAR) was extracted from the pharmaceutical specialty Libradin (Sigma–Tau, Italy). Absolute ethanol (J.T. Baker, Holland) was of spectrophotometric grade.

2.3. Standard solutions

A series of standard solutions of each analyte in ethanol was prepared and used to set up the calibration curves. These relationships were used to carry out the drug concentration. Solute concentration was within the range 5.0–50.0 μg/ml for all the compounds.

2.4. Photodegradation conditions

The drug solutions (20 μg/ml), in a quartz cuvette perfectly stoppered, were directly light irradiated in a λ range between 300 and 800 nm, by means of a glass filter, according to the ID65 standard of the ICH rules; the power was maintained to 350 W/m^2, corresponding to a light dose of 21 kJ/min m^2, at the constant temperature of 25 °C. The UV spectra, just after preparation ($t = 0$) and at the following times: 2, 5, 8, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 300 min, were recorded.

The irradiation conditions were maintained to a moderate level because of the high sensitivity of the drugs to light, allowing so to obtain a more accurate control on the photodegradation processes.

3. Descriptors

A large number of molecular descriptors in setting the calibration set were screened using multivariate techniques. PLS analysis was adopted to select the descriptors significantly correlated with the photosensitivity of the studied molecules. Six descriptors, representative of the chemical features, emerged as the most responsible for the photosensitivity of the studied drugs: molecular volume (MV), hydrophobic constant of Hansch–Fujita (π_x), polar surface area (PSA), H bond donors (HDon), H bond acceptors (HAcc) and Octanol/Water Partition Coefficient ($X \log P$).

3.1. Molecular volume (MV)

The volume of a molecule has a clearly conventional character and it is used sometimes as a molecular index in QSAR equations [34]. MV can also be employed as a measure of molecular similarity and help in understanding the steric requirements of a receptor.

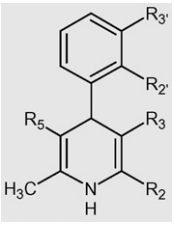
3.2. Hydrophobic constant of Hansch–Fujita (π_x)

The hydrophobic constant of Hansch–Fujita describes the contribution of a substituent to the lipophilicity of a compound and is defined as:

$$\pi_x = \log\ P(R_X) - \log\ P(R_H)$$

where R is the molecular residue and X is the substituent. $\pi_H = 0$ is the hydrophobic constant for hydrogen and it is used as referent. This predictor has a positive value if the substituent is hydrophobic

Table 1
Chemical substituents on the dihydropyridinic drugs



Drug	R_2	R_3	R_5	$R_{2'}$	$R_{3'}$
AML	$CH_2OCH_2CH_2NH_2$	$COOC_2H_5$	$COOCH_3$	Cl	H
FEL	CH_3	$COOC_2H_5$	$COOCH_3$	Cl	Cl
LER	CH_3	$COOC(CH_3)_2CH_2$ $N(CH_3)CH_2CH_2CH(Ph)_2$	$COOCH_3$	H	NO_2
MAN	CH_3	$COOCH_2CH_2$-piperazin-$CH(Ph)_2$	$COOCH_3$	H	NO_2
NIC	CH_3	$COO(CH_2)_2N(CH_3)$ CH_2Ph	$COOCH_3$	H	NO_2
NIF	CH_3	$COOCH_3$	$COOCH_3$	NO_2	H
NIM	CH_3	$COOCH_2CH_2OCH_3$	$COOCH(CH_3)_2$	H	NO_2
NIS	CH_3	$COOCH_2CH(CH_3)_2$	$COOCH_3$	NO_2	H
NIT	CH_3	$COOC_2H_5$	$COOCH_3$	H	NO_2

and a negative value if the substituent is hydrophilic [35]. This constant must be also calculated for the entire molecule because it is influenced by the overall hydrophobicity from the compound. The sum of the π_x constants of the substituents in a molecule represents the global descriptor of hydrophobicity for a molecule [36].

3.3. Polar surface area (PSA)

PSA of a molecule is used according to the approach developed by Ertl et al. [37] and it is defined as the surface sum over of polar atoms. This molecular descriptor explains the electrostatic and polarization interactions between the solute and the solvent. All the interactions are obviously weak interactions such as higher multipole, dipole and induced-dipole interactions. So, PSA can be considered an important electrostatic descriptor during a QSPR study to understand the charge distribution of the molecules and use this information to project new drugs with desired properties [34].

3.4. H bond donors (HDon) and H bond acceptors (HAcc)

Different hydrogen bond donors and acceptors are two important parameters introduced by Lipinski et al. [38] to describe molecular properties important for a drug's pharmacokinetics in the human body. The availability to form H bonds is an important parameter to define the physico-chemical properties of a drug.

3.5. Octanol/Water partition coefficient (X log P)

log *P* is a quantitative descriptor of lipophilicity and estimates the propensity of a neutral compound to differentially dissolve in two immiscible phases. It is usually referred to the octanol–water partition coefficient (*P*), expressed as logarithmic ratio. Hansch's work has started a series of studies about the biological activity varying in relation to the hydrophobic character of a molecule [39,40]. Nowadays, log *P* is commonly used in QSAR studies and drug design since it relates to drug absorption, bioavailability, metabolism, and toxicity. The calculation of the log *P* is implemented following the *X* log *P* approach developed by Wang et al. [41]. The *X* log *P* method is an atom-additive method that calculates the octanol/water partition coefficient of neutral organic molecules by summing up atom-based and substructure-based (correction factors) contributions.

3.6. Software

The theoretical descriptors from the chemical structure of the compounds were calculated by means of the Adriana.*Code* 2.0 software (Molecular Networks GmbH Computerchemie, Erlangen, Germany). This software executes the calculation of physico-chemical descriptors through empirical models for the influence of atoms in molecules and mathematical transformation techniques.

The substituent descriptors were calculated by ACD/ChemSketch 10.0 software (Advanced Chemistry Development, Inc., Toronto, Canada). This software is able to present and manipulate the molecular structure and allows to directly access the electronic substituent constants like hydrophobic constant of Hansch–Fujita and molecular volume.

PLS analysis was performed by application of the algorithms supported by the software "The Unscrambler 9.7" (Camo Process As., Oslo, Norway). This software also allowed to optimize the calibration models and develop validation procedures.

4. Results and discussion

A series of nine 1,4-DHP drugs, present in the most commercialized specialties, were collected to perform the QSPR study. Table 1 summarizes the different chemical groups in the studied drugs. Most of these drugs furnish the pyridine by-product as the only photodegradation product, according to a first-order degradation kinetics [20,42–46]. Nevertheless, after a variable time from this oxidation, secondary photoproducts come from degradation of some molecules as NIF [25], LER [47] and NIS [48].

4.1. Photodegradation kinetics

As a first step of the work, the drugs were subdued to forced photodegradation under the standard conditions reported above. The sequence of the UV spectra during light irradiation was recorded for each drug solution (20.0 μg/ml). Most of the drugs resulted completely degraded after ten minutes of light irradiation. In contrast, AML and FEL degraded at all after two hours.

A gradual decrease of the maximum peak in the zone 350–370 nm, that is a typical signal of the 1,4-DHP structure, and a contemporary increase of a new peak in the zone 260–280 nm, characteristic for the pyridinic structure, was observed for all the compounds. The residual concentration of the drugs was calculated

Table 2
Photodegradation kinetics parameters.

Drug	k	R^2	$t_{0.33}$	$\log t_{0.33}$
AML	−1.10e−05	0.9991	15 982	4.203
FEL	−1.60e−05	0.9992	11 027	4.042
LER	−9.38e−05	0.9827	608	2.783
MAN	−2.73e−04	0.9884	85	1.926
NIC	−2.08e−03	0.9985	218	2.338
NIF	−8.08e−04	0.9957	170	2.230
NIM	−9.77e−04	1.0000	30	1.474
NIS	−5.90e−03	0.9954	98	1.992
NIT	−1.49e−03	0.9963	106	2.024

t is expressed as seconds.

by using the absorbance measurement of the peaks between 350 and 370 nm, because of the insignificant absorbance of the degradation products after 330 nm. Effectively, also the main secondary photoproducts from some compounds do not have absorbance in this region [19,49].

Nevertheless, in order to obtain data as homogeneous as possible for the QSPR modeling, the spectral data used in calibration were limited to degradation equivalent to a third of the starting concentration (33.33%). Within the examined times, all the products were observed to follow a first-order kinetics. Therefore the absorbance data until the time ($t_{0.33}$) necessary to reach this degradation percentage were collected.

A good linearity was obtained by plotting the logarithm of absorbances as a function of time, in agreement with the following equation:

$$\log \%A = -kt + 2$$

where $\%A$ is the percentage of residual absorbance, k the photodegradation rate constant, t the time (s), 2 is the logarithm of starting absorbance (100%).

Table 2 summarizes the degradation kinetics parameters calculated for the drug investigated. The data were carried out from three replicate analyses for each sample and very low variance was measured in all the cases.

4.2. Selection of descriptors

QSPR modeling needed to choose the variables affecting the drugs photodegradation. The selection of the descriptors responsible of significant variations in the molecular properties represents a key step in a multivariate modeling. This choice has to be carefully performed, because excluding descriptors carrying useful information from the system may lead to misleading results in building the model. At the same time, an indiscriminate use of a higher number of predictors could increase random noise and lower the robustness of the model [50,51].

Since the number of known descriptors is very high and a full selection procedure is practically unfeasible, some methods for simplification have been developed. One of the techniques for reducing full search procedure is the multilinear regression which is based on a stepwise forward selection through extension of the correlation to new descriptors until a statistic parameter becomes better than that previously calculated one.

In the present study, PLS algorithm was applied to analyze the interactions between photosensitivity and descriptors. PLS has proved to be able in not only defining the relationship between dependent variables and predictor variables, but also reducing the number of the descriptors [14]. The root mean square error of prediction (RMSEP) was adopted as a discriminating criterion in PLS calibration and the correlation coefficient R^2 was used to evaluate the model fitting. Usually, a R^2 value higher than 0.3 can be considered statistically meaningful, a value greater than 0.5 is indicative for a good model and a value over 0.8 proves an excellent correlation.

A screening of the descriptors was made by focusing on just those describing constitutional, electrostatic and geometrical ones in consideration of the electronic and steric aspects of the aromatization reaction [52,53]. In fact, due to both technological and biological importance of 1,4-DHP oxidation, the reaction has been the subject of several studies [54–56]. The chemical–physical properties of the substituents on both the benzene and dihydropyridine moieties were particularly investigated, because they characterize the various 1,4-DHP drugs. All descriptors were calculated on the neutral species.

A series of electronic descriptors relative to the entire molecules or geometrical and hydrophobic descriptors for the chemical substituents gave significant correlation with the drug photosensitivity. In particular, by applying the PLS procedure, the molecular descriptors PSA, HDon, HAcc and $X\log P$, relative to the global chemical structures, were selected. Among the variables describing the chemical substituents, the geometrical descriptor MV and the hydrophobic descriptor $\pi_{x,}$ showed the most significant influence on photodegradation. Each drug was so described by fourteen independent descriptors.

The logarithm of the time necessary to cause a degradation of a third for each compound ($\log t_{0.33}$) was used as dependent variable. The calibration set listing the values of $\log t_{0.33}$ and the descriptors relative to all the compounds is reported in Table 3.

4.3. QSPR model

The calibration set, based on the values of $\log t_{0.33}$ (Y variable) as a function of fourteen molecular descriptors (X variables), was used to elaborate the QSPR model by means of PLS analysis.

PLS provided to perform interdependent PCA decomposition of the original data in both X and Y matrices in which new variables, called principal components or factors, were calculated as linear combinations of the old ones.

PCA transformed the original data matrix in a new matrix of scores (T) and loadings (P):

$$X = TP^T + E_X (E_X = X - X_{\text{model}})$$

$$Y = UQ^T + E_Y (E_Y = Y - Y_{\text{model}})$$

Table 3
Calibration set.

Drug	$\log t_{0.33}$	MVR_2	πR_2	MVR_3	πR_3	MVR_5	πR_5	$MVR_{2'}$	$\pi R_{2'}$	$MVR_{3'}$	$\pi R_{3'}$	HDon	HAcc	PSA	$X\log P$
AML	4.204	73.84	−0.80	67.28	0.51	50.78	−0.02	25.67	0.59	0.00	0.00	3.00	7.00	99.88	1.84
FEL	4.043	30.79	0.46	67.28	0.51	50.78	−0.02	25.67	0.59	25.67	0.59	1.00	5.00	64.63	3.73
LER	2.784	30.79	0.46	298.17	4.78	50.78	−0.02	0.00	0.00	27.06	−0.27	1.00	9.00	113.69	6.41
MAN	1.927	30.79	0.46	274.03	2.47	50.78	−0.02	0.00	0.00	27.06	−0.27	1.00	10.00	116.93	4.78
NIC	2.338	30.79	0.46	168.25	1.88	50.78	−0.02	0.00	0.00	27.06	−0.27	1.00	9.00	113.69	3.54
NIF	2.231	30.79	0.46	50.78	−0.02	50.78	−0.02	27.06	−0.27	0.00	0.00	1.00	8.00	110.45	1.95
NIM	1.475	30.79	0.46	90.15	−0.44	84.17	0.85	0.00	0.00	27.06	−0.27	1.00	9.00	119.68	2.66
NIS	1.993	30.79	0.46	100.67	1.39	50.78	−0.02	27.06	−0.27	0.00	0.00	1.00	8.00	110.45	3.03
NIT	2.025	30.79	0.46	67.28	0.51	50.78	−0.02	0.00	0.00	27.06	−0.27	1.00	8.00	110.45	2.38

Table 4
Prediction set.

		R_2		R_3		R_5		$R_{2'}$		$R_{3'}$				
Chemical substituents														
BAR		CH_3		COO-pyrrolidin-CH_2Ph		$COOCH_3$		H		NO_2				
CIL		CH_3		$COOCH_2CH_2OCH_3$		$COOCH_2CH{=}CHPh$		H		NO_2				
	$\log t_{0.33}$	MVR_2	πR_2	MVR_3	πR_3	MVR_5	πR_5	$MVR_{2'}$	$\pi R_{2'}$	$MVR_{3'}$	$\pi R_{3'}$	HDon	HAcc	PSA	$X \log P$
Predictors															
BAR	2.20	30.79	0.46	171.85	1.67	50.78	−0.02	0.00	0.00	27.06	−0.27	1.00	9.00	113.69	3.09
CIL	2.02	30.79	0.46	90.15	−0.44	136.14	2.34	0.00	0.00	27.06	−0.27	1.00	9.00	119.68	4.08

where E is the difference between the measured and calculated X and Y values.

The principal components are sorted by decreasing information content so that most of the information is preserved in the first few ones. Each principal component was extracted from the independent variables and simultaneously maximally correlated with the variance of the dependent variable [57–59].

The model was validated by fully cross procedure, adopting a leave-one-out procedure, and satisfactory statistical results were carried out. Values of 0.3984 and 0.8453 for RMSEP and R^2 were obtained, respectively, associated with an optimized number of five principal components. At this moment, the selected descriptors demonstrated to furnish useful information for the model building.

4.4. Photosensitivity prediction of external samples

An independent validation was performed by applying the defined QSPR model to two 1,4-DHP drugs external to the calibration set. The tested compounds were BAR and CIL, both drugs recently commercialized. These drugs were subdued to stress photodegradation under the same stressing conditions adopted for the calibration samples and the relative values of $t_{0.33}$ were measured. Table 4 lists the chemical substituents and the descriptor values relative to both the molecules.

When the photodegradation rate of these samples was predicted by the QSPR model, unsatisfactory statistical results were unfortunately obtained. Errors not below 8% on the $t_{0.33}$ value for BAR was carried out, but the results were particularly incorrect for CIL, whose relative errors were about 26%. The failure of the model was supposed to be caused by bad information within the data provided by the used descriptors. All the X variables do not clearly contribute useful information to build a robust model.

An optimization was so necessary so to improve as much as possible the prediction ability of the model. For this aim, the fully cross validation was coupled with the Martens' Uncertainty Test [60], which allowed the identification of perturbing samples or variables and then a further focusing of the most significant X-variables (Fig. 1). The weight of each descriptor in the model building was so considered, so that those furnishing useful information were singled out [61,62]. This procedure provided to identify the descriptors MV and π, both for the substituent R_5, as "bad-descriptors", responsible of useless or noising information. So the overall contribution of the substituent R_5 to the model was removed and the model was rebuilt on twelve descriptors.

PLS procedure carried out the following model equation:

$$\begin{aligned}\log\ t_{0.33} = {} & 8.737e-03\mathrm{MVR}_2 - 0.299\pi R_2 - 7.872e-04\mathrm{MVR}_3 \\ & +0.162\pi R_3 - 0.182\mathrm{MVR}_{2'} + 0.295\pi R_{2'} - 2.316e \\ & -02\mathrm{MVR}_{3'} + 3.743e-02\pi R_{3'} + 0.188\mathrm{HDon} \\ & -0.222\mathrm{HAcc} - 1.499e-02\mathrm{PSA} + 5.839e-03X\ \log\ P \\ & +10.773\end{aligned}$$

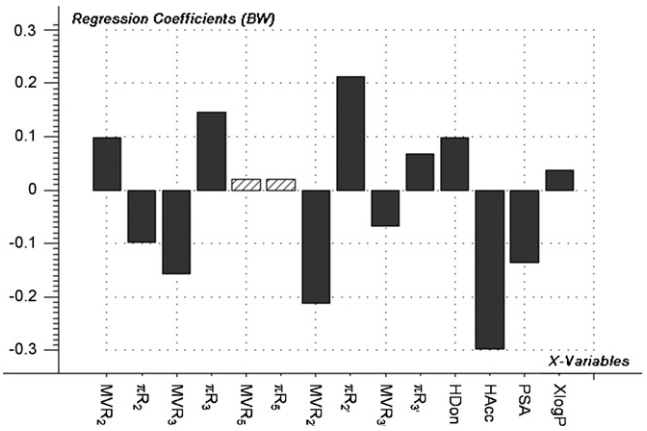


Fig. 1. Weight of the descriptors by Martens' Uncertainty Test.

When internal validation was computed on the optimized model, values of 0.3616 for RMSEP and 0.8727 for R^2, respectively, were obtained, even demonstrating an improved prediction ability of the ultimate model. Application of this model to the prediction samples gave successful results with relative errors of 2.5% and 12.62% for BAR and CIL, respectively. The measured and predicted photodegradation data of the training set were plotted in Fig. 2. The relative values for the external samples were also depicted in this graph. These results demonstrated that the optimization step notably improved the reliability and robustness of the model. The optimal number of principal components, calibrated for twelve selected descriptors, resulted equal to four, as it is evident in the graphic of Fig. 3, showing the residual variance.

Figs. 4 and 5 showed the graphical reports of "Scores" and "X- and Y-Loadings", respectively. Score graph showed the distribution of

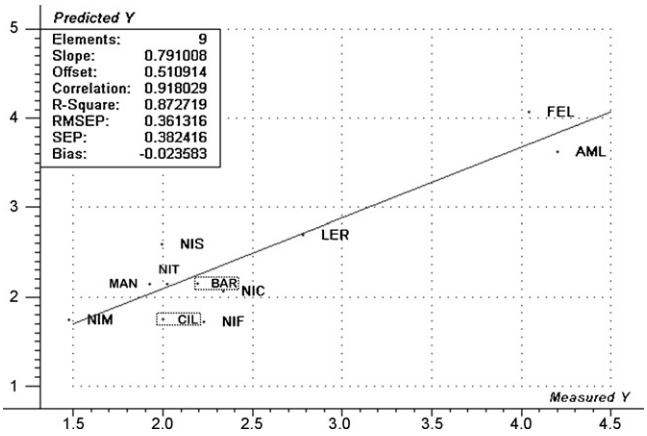


Fig. 2. Plot of predicted vs. measured photodegradation rate for 1,4-DHP drugs. The external Figure samples are marked.

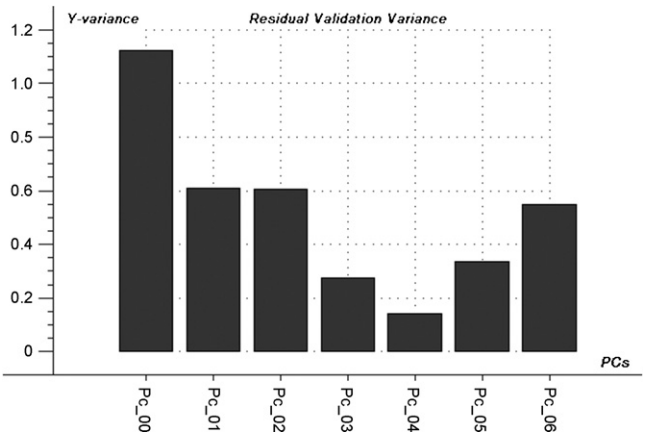


Fig. 3. Residual variance from validation of the model vs. Principal Components.

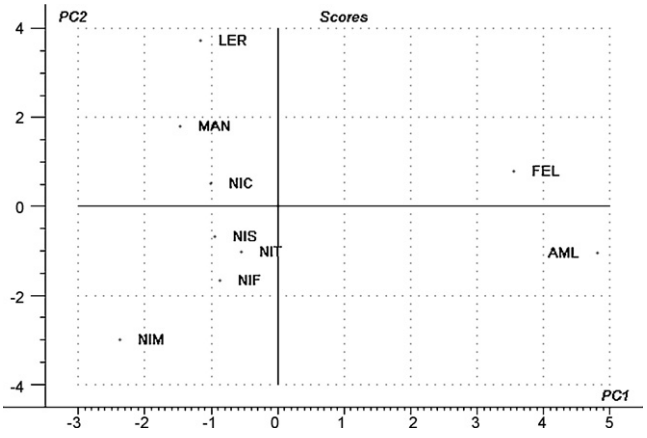


Fig. 4. Score plot of the optimized QSPR model.

the 1,4-DHP into the model space (PC1 vs. PC2), distributed according to *X* and *Y* variables. This graph helped to determine which variables were responsible for differences between samples. The drugs to the right of the score plot had a large value for variables to the right of the loading plot, and a small value for variables to the left of the loading plot; the most stable 1,4-DHP were accordingly situated in same direction of $\log t_{0.33}$.

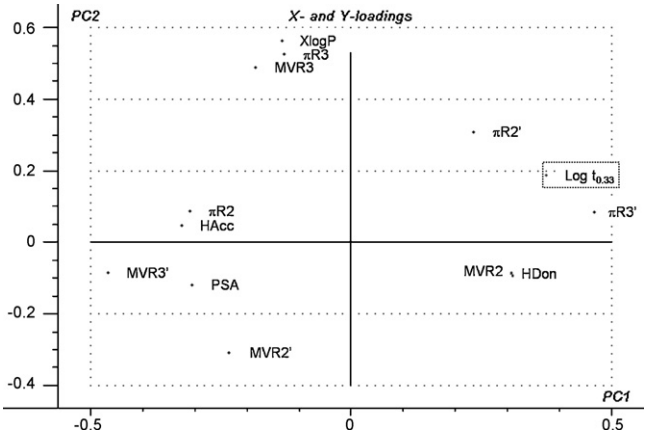


Fig. 5. X- and Y- Loading plot of the optimized QSPR model.

4.5. Design of photostable dihydropyridine molecules

The study of both model equation and validation report permitted to evaluate the weight of the used predictors on the photostability of the drugs. The molecular descriptors HAcc and PSA should be maintained low. The value of HDon has to be high, whereas the value of $X\log P$ is less influential. The substituents $R_{2'}$ and $R_{3'}$ should be small, since a low value of MV presents a discrete significance in increasing stability. At the same time, photostability is decreased if these groups have hydrophilic features. In fact, the presence of a nitro group on the 2′ position assists an intramolecular disproportionation reaction, followed by aromatization of the pyridinic ring [63]. Analogously, a low value of MV is necessary, while a hydrophobicity feature seems unimportant. On the contrary, the R_2 substituent should have large volume and hydrophilic characteristics.

5. Conclusions

In conclusion, we have built a QSPR model correlating the photostability of the 1,4-DHP drugs with global and structural fragment descriptors. The influence of different substituents on both benzene and pyridinic rings has been evaluated in terms of hydrophobic, electronic and steric parameters. The model has demonstrated a good prediction ability when applied on congeneric drugs not enclosed in the calibration modeling. The value of 0.8727 for the correlation coefficient R^2 obtained from the model validation, showed that the model has good predictive ability and robustness for estimating the photodegradation rate values of 1,4-DHP drugs. The proposed model could be applied to new compounds not covered by the original data sets. In addition, some rules have been derived from the model, which may be used by pharmaceutical chemists as a guideline on the contribution of the chemical substituents on photosensitivity of 1,4-DHP molecules. These rules could be used to identify novel 1,4-DHP structures characterized by high light stability.

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