Desirability-Based Multi-Objective QSAR in Drug Discovery

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Abstract: The adjustment of multiple criteria in hit-to-lead identification and lead optimization is a major advance in drug discovery. Thus, the development of approaches able to handle additional criteria for the early simultaneous treatment of the most important properties determining the pharmaceutical profile of a drug candidate is an emergent issue in this area. In this paper, we review a desirability-based multi-objective QSAR method allowing the joint handling of multiple properties of interest in drug discovery: the MOOP-DESIRE methodology. This methodology adapts desirability theory concepts allowing the holistic modeling of the many and conflicting biological properties determining the therapeutic utility of a drug candidate. Here we survey their suitability for key tasks involving the use of chemoinformatics methods in medicinal chemistry and drug discovery.

Keywords: MOOP-DESIRE methodology, desirability theory, multi-objective QSAR, drug discovery.

INTRODUCTION

Development of a successful drug is a complex and lengthy process, and failure at the development stage is caused by multiple factors, such as lack of efficacy, poor bioavailability, and toxicity [1]. Although "Costs of Goods" has been claimed as one of the major reasons for the end of a research & development (R&D) project [2] one cannot disregard the idea that toxicity and/or pharmacokinetics profiles of the clinical candidates are still decisive causes of failure in drug development process [3-6]. Roughly 75% of the total costs during the development of a drug is attributed to poor pharmacokinetics or to toxicity [7].

The importance and possibility of jointly considering the multiple aspects of drug action was recognized and suggested years ago by Mayer and Van de Waterbeemd [8].

As a possible way to achieve this goal, they suggest a stepwise multiple QSAR (MUQSAR) technique. In MUQSAR technique each step in drug action should be analyzed by using a quantitative method [i.e.: quantitative structure-activity/property/biotransformation/toxicity relationships (QSAR/QSPR/QSBR/QSTR)], thus permitting to fully conceive an "*overall QSAR*": *OverallQSAR* = *f*(*QSAR, QSPR, QSBR, QSTR*) [8].

Not without advising that some practical problems surely would have to be tackled, more than twenty years ago Mayer and Van de Waterbeemd were already confident about the feasibility of this approach and that the information finally obtained would worth the effort [8].

Improvement of the profile of a drug candidate requires finding the best compromise between various, often competing objectives, which shows the multi-objective nature of the drug discovery and development process. But even when a potent candidate has been identified, the pharmaceutical industry routinely has tried to optimize the remaining objectives one at a time, which often results in expensive and time-consuming cycles of trial and error [3, 6, 9].

The adjustment of the multiple criteria in hit-to-lead identification and lead optimization is considered to be a major advance in the rational drug discovery process. The aim of this paradigm shift is the prompt identification and elimination of candidate molecules that are unlikely to survive later stages of discovery and development. In turn, this new approach will reduce clinical attrition, and as a consequence, the overall cost of the process [3, 10].

All these arguments put forward the need for approaches able to early integrate drug- or lead-likeness, toxicity and bioavailability criteria in the drug discovery phase as an emergent issue [3, 6]. That is, methods that can handle additional criteria for the early simultaneous treatment of the most important properties, potency, safety, and bioavailability, determining the pharmaceutical profile of a drug candidate [11-19].

In recent years, the drug discovery/development process has been gaining in efficiency and rationality because of the continuous progress and application of chemoinformatics methods [9]. In particular, the QSAR paradigm has long been of interest in the drug design process [20].

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Yet standard chemoinformatics approaches usually ignore multiple objectives and optimize each biological property sequentially [8, 21-31]. Nevertheless, some efforts have been made recently toward unified approaches capable of modeling multiple pharmacological, pharmacokinetic, or toxicological properties onto a single QSAR equation [32-36].

Multi-objective optimization (MOOP) methods introduce a new philosophy to obtain optimality on the basis of compromises among the various objectives. These methods aim at hitting the global optimal solution by optimization of several dependent properties simultaneously. The major benefit of MOOP methods is that local optima, corresponding to one objective can be avoided by taking into account the whole spectra of objectives, thus leading to a more efficient overall process [37].

Several applications of MOOP methods in the field of drug development have appeared lately, ranging from substructure mining [38-40] to docking [41, 42], including inverse QSPR [43, 44] and QSAR [37]. Most of these MOOP applications have been based on the following approaches: weighted-sum-of-objective-functions (WSOF) and Pareto-based methods [45]. An excellent review on the subject has been published by Nicolaou *et al.* [37].

Despite the availability of numerous optimization objectives, MOOP techniques have only recently been applied to the building of QSAR models [12, 14, 46, 47]. Actually, very few reports exist of the application of MOOP methods to QSAR, and even scarcer are the reports concerning the simultaneous optimization of competing objectives directly related with the definitive pharmaceutical profile of drugs, such as therapeutic efficacy, bioavailability, and/or toxicity.

Classic QSAR approaches usually ignore the multi-objective nature of the problem focusing on the evaluation of each single property as they became available during the drug discovery process [37]. So, an approach offering a simultaneous study of several biological properties determinants for a specific therapeutic activity is considered a very attractive option in computational medicinal chemistry.

In this sense, desirability functions (DF) are well-known multi-criteria decision-making methods [48, 49]. This approach has been extensively employed in several fields [50-61]. However, despite of perfectly fit with the drug development problem, reports of computational medicinal chemistry applications are at present very limited.

In the present paper, we review a MOOP methodology based on Derringer's desirability functions [49] that allows global QSAR studies to be run jointly, considering multiple properties of interest to the drug design process as well as their suitability for key tasks involving the use of chemoinformatics methods in drug discovery.

MOOP-DESIRE METHODOLOGY

Improvement of the profile of a molecule for the drug discovery and development process requires the simultaneous optimization of several different objectives. The ideal drug should have the highest therapeutic efficacy and bioavailability, as well as the lowest toxicity.

Because of the conflicting relationship among the aforementioned properties, such a drug is almost unattainable, and if possible, it is an extremely difficult, expensive, and time-consuming task. However, finding the best compromise between such objectives is an accessible and more realistic target (see Fig. (**1**)).

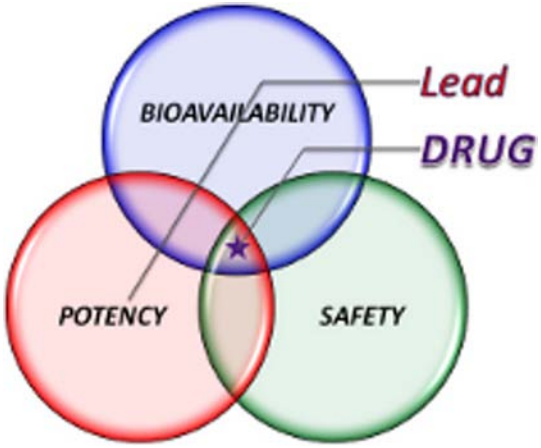


Fig. (1). Graphic representation of the compromise between therapeutic efficacy (potency), bioavailability (ADME properties) and toxicity (safety) required to reach a successful drug.

In this paper, we describe a multi-objective optimization methodology based on the desirability estimation of several interrelated responses (MOOP-DESIRE) as a tool to perform global QSAR studies, considering simultaneously the pharmacological, toxicological, and/or pharmacokinetic profiles of a set of drug candidates [13, 15]. The MOOP-DESIRE methodology is intended to find the most desirable solution that optimizes a multi-objective problem by using the Derringer's desirability function [62, 63], specifically addressed to confer rationality to the drug development process.

The process of simultaneous optimization of multiple properties of a drug candidate can be described as follows. From now on, the terms "response variable" and "independent variables" should be understood as any property to be optimized and any set of molecular descriptors (MDs) used to model each property, respectively.

Phase I: Desirability-Based multi-Objective Optimization

Prediction Model Setup

Each response variable (Y_i) is related to the n independent variables (X_n) by an unknown functional relationship, often (but not necessarily) approximated by a linear function. Each predicted response ($\hat{Y}_i$) is then estimated by a least-squares regression technique. In some cases, the developed prediction model for some responses may share the same independent variables of other response´s prediction models but with different coefficients. In this atypical case, attaining the best compromise among the responses turns out to be simpler. Actually, because of the multiplicity of factors involved in the overall

pharmaceutical profile of a molecule, one should not expect that the same subset of independent variables can optimally explain different types of biological properties (especially conflicting properties like potency and toxicity). However, in the latter case, there is still a way to maximize the desirability of several biological properties, that is, to setup a global prediction model where the predicted values of each response are fitted to a linear function using the whole subset of independent variables employed in modeling the *k* original responses. Here, the independent variables used in computing the predicted values for the original responses will remain the same. Independent variables not used in computing the predicted values for the original responses will be set to zero.

Desirability Function Selection and Evaluation

For each predicted response $\hat{Y}_i$, a desirability function d_i assigns values between 0 and 1 to the possible values of $\hat{Y}_i$. This transformed response d_i, can have many different shapes. Regardless of the shape, d_i= 0 represents a completely undesirable value of $\hat{Y}_i$, and d_i= 1 represents a completely desirable or ideal response value. The individual desirabilities are then combined using the geometric mean, which gives the overall desirability *D:*

$$D = (d_1 \times d_2 \times ... \times d_k)^{\frac{1}{k}} \quad (1)$$

with *k* denoting the number of responses.

This single value of *D* gives the overall assessment of the desirability of the combined response levels. Clearly, the range of *D* will fall in the interval [0, 1] and will increase as the balance of the properties becomes more favorable. Notice that if for any response d_i= 0, then the overall desirability is zero. Thus, the desirability maximum will be at the levels of the independent variables that simultaneously produce the maximum desirability, given the original models used for predicting each original response.

Depending on whether a particular response is to be maximized, minimized, or assigned a target value, different desirability functions can be used. Here, we used the desirability functions proposed by Derringer and Suich [49].

Let L_i, U_i, and T_i be the lower, upper, and target values, respectively, that are desired for the response $\hat{Y}_i$, with $L_i \leq T_i \leq U_i$.

If a response is of the *target* best kind, then its individual desirability function is defined as:

$$d_i = \begin{cases} \left[\frac{\hat{Y}_i - L_i}{T_i - L_i}\right]^s & \text{if} \quad L_i \leq \hat{Y}_i \leq T_i \\ \left[\frac{\hat{Y}_i - U_i}{T_i - U_i}\right]^t & \text{if} \quad T_i < \hat{Y}_i \leq U_i \\ 0 & \text{if} \quad \hat{Y}_i < L_i \quad \text{or} \quad \hat{Y}_i > U_i \end{cases} \quad (2)$$

If a response is to be maximized instead, its individual desirability function is defined as:

$$d_i = \begin{cases} 0 & \text{if} \quad \hat{Y}_i \leq L_i \\ \left[\frac{\hat{Y}_i - L_i}{T_i - L_i}\right]^s & \text{if} \quad L_i < \hat{Y}_i < T_i \\ 1 & \text{if} \quad \hat{Y}_i \geq T_i = U_i \end{cases} \quad (3)$$

In this case, T_i is interpreted as a large enough value for the response, which can be U_i.

Finally, if one wants to minimize a response, one might use:

$$d_i = \begin{cases} 1 & \text{if} \quad \hat{Y}_i \leq T_i = L_i \\ \left[\frac{\hat{Y}_i - U_i}{T_i - U_i}\right]^s & \text{if} \quad U_i < \hat{Y}_i < T_i \\ 0 & \text{if} \quad \hat{Y}_i \geq U_i \end{cases} \quad (4)$$

Here, T_i denotes a small enough value for the response, which can be L_i.

Moreover, the exponents *s* and *t* determine how important is to hit the target value T_i. For *s* =*t* = 1,the desirability function increases linearly toward T_i. Large values for *s* and *t* should be selected if it is very desirable that the value of $\hat{Y}_i$ be close to T_i or increase rapidly above L_i. On the other hand, small values of *s* and *t* should be chosen if almost any value of $\hat{Y}_i$ above L_i and below U_i are acceptable or if having values of $\hat{Y}_i$ considerably above L_i are not of critical importance [49].

In this way, one may predict the overall desirability for each drug candidate determined by *k* responses, which in turn are at the same time determined by a specific set of independent variables. However, as the Derringer's desirability function is built using the estimated responses $\hat{Y}_i$, there is no way to know how reliable the predicted *D* value of each candidate is.

To overcome this shortcoming, was proposed a statistical parameter, the *overall desirability's determination coefficient* (R^2_D), which measures the effect of the set of independent variables X_n in reduction of the uncertainty when predicting the *D* values. R^2_D is computed by using the observed D_{Yi} (calculated from Y_i) and the predicted $D_{\hat{Y}i}$ (calculated from $\hat{Y}_i$) overall desirability values instead of using directly the measured (Y_i) and predicted ($\hat{Y}_i$) response values. External and cross validations can be also implemented by using R^2_D [13].

Multi-Objective Optimization

As seen before, the desirability function condenses a multivariate optimization problem into a univariate one. Thus, the overall desirability *D* can be maximized over the independent variables domain by means of the *simplex*

method of function optimization. The final result is to find the optimal levels (or an optimal range) of the independent variables that optimize simultaneously the *k* responses determining the final quality of the product. In this way, the best possible compromise between the *k* responses is found, and consequently, the highest overall desirability for the final compound is reached (i.e., the more enviable drug candidate).

Phase II: Desirability-Based Ranking Algorithm

A ranking algorithm based on quantitative parameters estimated from the description of the cases is applied [15]. Specifically, by the application of this algorithm, it will be possible to rank drug candidates (included on the model's applicability domains) with unknown pharmaceutical profiles (like those coming from combinatorial libraries) according to their similarity with the optimal drug candidate determined by the simultaneous multi-objective optimization process previously described.

Similarity Assessment

Δ_i is the parameter used here to describe the similarity between a case *i* and the optimal case as a function of the subset of descriptive variables used for the multi-objective optimization process, which is defined as:

$$\Delta_i = \sum_{X=1}^{m} \delta_{i,X} \cdot w_X \quad (5)$$

where $\delta_{i,X}$ is the Euclidean distance between the case *i* and the optimal case, considering the parameters *X*, and w_X represents the weight or influence of the variable *X* over the global desirability *D* of the case *i*.

Desirability scaling of similarity metrics and minimization of differences between case description (Δi) and case solution (Di). The Δi values are normalized by means of the application of the Derringer desirability functions [49] to bring them to the same scale as Di. In this manner, it is possible to minimize the difference between the values of Δi and Di for every case. Specifically, the respective values of Δi are minimized by means of eq.4 in such a way that the lower values (indicative of a higher similarity with respect to the optimal case) will take the values more close to 1 and vice versa. Here, Li correspond to the lowest value of Δi (ΔiMIN) and Ui = ΔiMAX.

Next, the optimal set of weighs w_X minimizing the difference between the values of D_i and the normalized values of Δ_i for every case is found by a least-squares nonlinear data-fitting process. The weights were obtained through a nonlinear curve-fitting using the large-scale optimization algorithm [64, 65], implemented in the "*lsqcurvefit*" function of MATLAB [66].

By minimizing the differences between D_i and the normalized values of Δ_i, we achieved the highest possible degree of concordance between the description (expressed through the normalized values of Δ_i which encode the information related to the molecular structure expressed as a function of the molecular descriptors employed) and the solution of the cases (determined by the respective values of D_i, which represents the combination of the *k* properties involved on the final quality of the drug candidate). Thus, it will be possible to rank, according to Δ_i, new and pharmaceutically unknown drug candidates for whom just their molecular structure is known. In this way, it will be possible to filter and identify the most promising drug candidates, which will logically be placed first on the ordered list (the candidates with the lowest values of Δ_i and consequently the most similar ones with the optimal drug candidate determined by the desirability-based MOOP process) and to discard the candidates ordered last.

Ranking Algorithm Validation and Estimation of the Ranking Quality Index (Ψ)

A method for the validation of the ranking obtained by the use of the optimal set of weighs is proposed as well as a quantitative criterion of the quality of a ranking.

We will use some simple notations to represent ordering throughout this work. Without loss of generality, for *n* cases to be ordered, we use the actual ordering position of each case as the label to represent this case in the ordered list. For example, suppose that the label of the actual highest ranked case is *n*, the label of the actual second highest ranked case is *n* - 1, etc. We assume the examples are ordered incrementally from left to right. Then the *true-order list* is *OT* = 1, 2, 3, ...,*n*. For any ordered list generated by a ranking algorithm, it is a permutation of *OT*. We use *OR* to denote the ordered list generated by the ranking algorithm *R*. *OR* can be written as a_1, a_2, ..., a_i, where a_i is the actual ordering position of the case that is ranked *ith* in *OR*.

The ranking validation includes the following steps:

i). Order the cases in the library according to *D* in a decreasing fashion and label each case as described above (1, 2, 3, ...,*n*). This ordering corresponds to the true-order list (*OT*).

ii). Invert *OT*. This new ordering corresponds to the worst order list (*OW*).

iii). Order incrementally the cases in the library according to Δ_i and label each case as described above (a_1, a_2, ...,a_n). This ordering corresponds to the order generated by the ranking algorithm *R* (*OR*).

iv). Normalize (through eq.4) the values (labels) assigned to each case in steps 1-3 where $L_i = T_i = 1$ and U_i = the number of cases included in the library (*n*). In this way, we obtained the respective normalized order values for the true ($^{OT}d_i$) and worst ($^{OW}d_i$) order lists, as well as the order generated by the ranking algorithm *R* ($^{OR}d_i$).

v). Use the respective normalized order values to determine the difference between *OR* and *OT* ($^{OT\text{-}OR}\delta_i$)

$$^{OT-OR}\delta_i = \left| {}^{OT}d_i - {}^{OR}d_i \right| \quad (6)$$

and between *OW* and *OT* ($^{OT\text{-}OW}\delta_i$)

$$^{OT-OW}\delta_i = \left| {}^{OT}d_i - {}^{OW}d_i \right| \quad (7)$$

vi). Estimate the quality of the order generated by the ranking algorithm *R* (*OR*) by means of the ranking quality index (Ψ), which can be defined as the absolute value of the mean of $^{OT\text{-}OR}\delta_i$, for the *n* cases included in the library to be ranked:

$$\Psi = \left| \frac{\sum_{i=1}^{n} {}^{OT-OR}\delta_i}{n} \right| \quad (8)$$

After applying a correction factor $F = \frac{2}{\Psi^{OW}}$ to Ψ we obtain the corrected ranking quality index (Ψ^*):

$$\Psi^* = \left| \frac{\sum_{i=1}^{n} {}^{OT-OR}\delta_i}{n} \right| \cdot \frac{2}{\Psi^{OW}} \quad (9)$$

where Ψ^{OW} is the quality index for the worst ranking. *F* is used here to obtain a more representative indicator of the quality of a ranking and at the same time to include Ψ in the range [0, 1].

Finally, it is possible to express Ψ^* as the percentage of ranking quality ($R_{\%}$).

$$R_{\%} = (1 - \Psi^*) \cdot 100 \quad (10)$$

Fig. (**2**) summarizes schematically the use of the MOOP-DESIRE methodology as a computer-aided tool for multi-objective drug discovery.

DESIRABILITY-, WSOF-, AND PARETO-BASED MOOP METHODS

From the above detailed we can note that MOOP-DESIRE methodology like WSOF-based MOOP methods reformulates a multi-objective problem into a single one (the overall desirability). The rationale is to find a single "*best*" solution overlooking however the presence of a Pareto-front of objectives, which represents the main drawback of both methods when compared with Pareto-based methods.

Actually, the major drawback of WSOF-based methods is the selection of the most appropriate weightings because it is often not clear how the different objectives should be ranked. In addition, the method is limited in its ability to find solutions to problems involving competing objectives [37]. The MOOP-DESIRE methodology has the advantage of transforming the responses (objectives) into desirability d_i values, which are then combined into the single overall desirability *D*. So, competing objectives like potency and toxicity can be successfully handled by this method because the use of weights is avoided in the multi- to single objective problem reformulation [49].

A drawback of the Pareto-based MOOP methods is that the distribution of the Pareto-front may lead solutions to drift to more densely distributed regions of the surface and, in more extreme circumstances, lead to dictatorship conditions where a single objective dominates [37]. The use of the overall desirability values avoids this problem since they provide the overall assessment of the combined response (objective) levels.

The main drawback of the proposed MOOP-DESIRE methodology is related to the modeling technique used to fit the initial set of PMs. Since the optimization process over the independent variables domain is based on a MLR approach, neither the predicted responses nor the optimum levels of each independent variable that determines the predicted overall desirability will be reliable if the parametric assumptions inherent to regression techniques are not fulfilled [63, 67]. Specifically, the effect of potential non-linear relations between descriptors and objectives could lead to very poor predictions and consequently to very unreliable structure-desirability relationships. The combination of non-linear modeling techniques such as machine learning algorithms with evolutionary optimization methods can be a solution to this bottleneck on the application of desirability based-MOOP methods.

Although perfectible, MOOP-DESIRE methodology has been successfully applied to key drug discovery tasks, which will be summarized from now on.

MULTI-OBJECTIVE DRUG DESIGN

MOOP-DESIRE methodology has proved to be a practical tool for the theoretical design of new drug candidates with several biological properties simultaneously optimized. That is, not only to be able to translate the chemical structure into numbers to find out which are significantly related with a specific property, but in addition, to go back from these numbers to structure, or at least to some clues suggesting the structural modifications required to improve that property, or even better, more than one property at once.

Design of novel NSAIDs quinazolinones with simultaneously improved analgesic, antiinflammatory, and ulcerogenic profiles. MOOP-DESIRE methodology was applied to a library of fifteen 3-(3-methylphenyl)-2-substituted amino-*3H*-quinazolin-4-one compounds [68] in order to design novel NSAIDs quinazolinones with high analgesic (*An*) and anti-inflammatory (*Aa*) activities while keeping their ulcerogenic (*U*) ability as low as possible [13]. The use of such small and homogeneous data set is more suitable for later stages of the drug development process once identified a lead rather than for early stages. Actually, specific structural modifications can be made over the lead according to the results of the optimization process. For this, the use of clearly defined structural or physicochemical descriptors can led to interpretable structure-desirability relationships which can be used to design new candidates with an improved overall pharmaceutical profile.

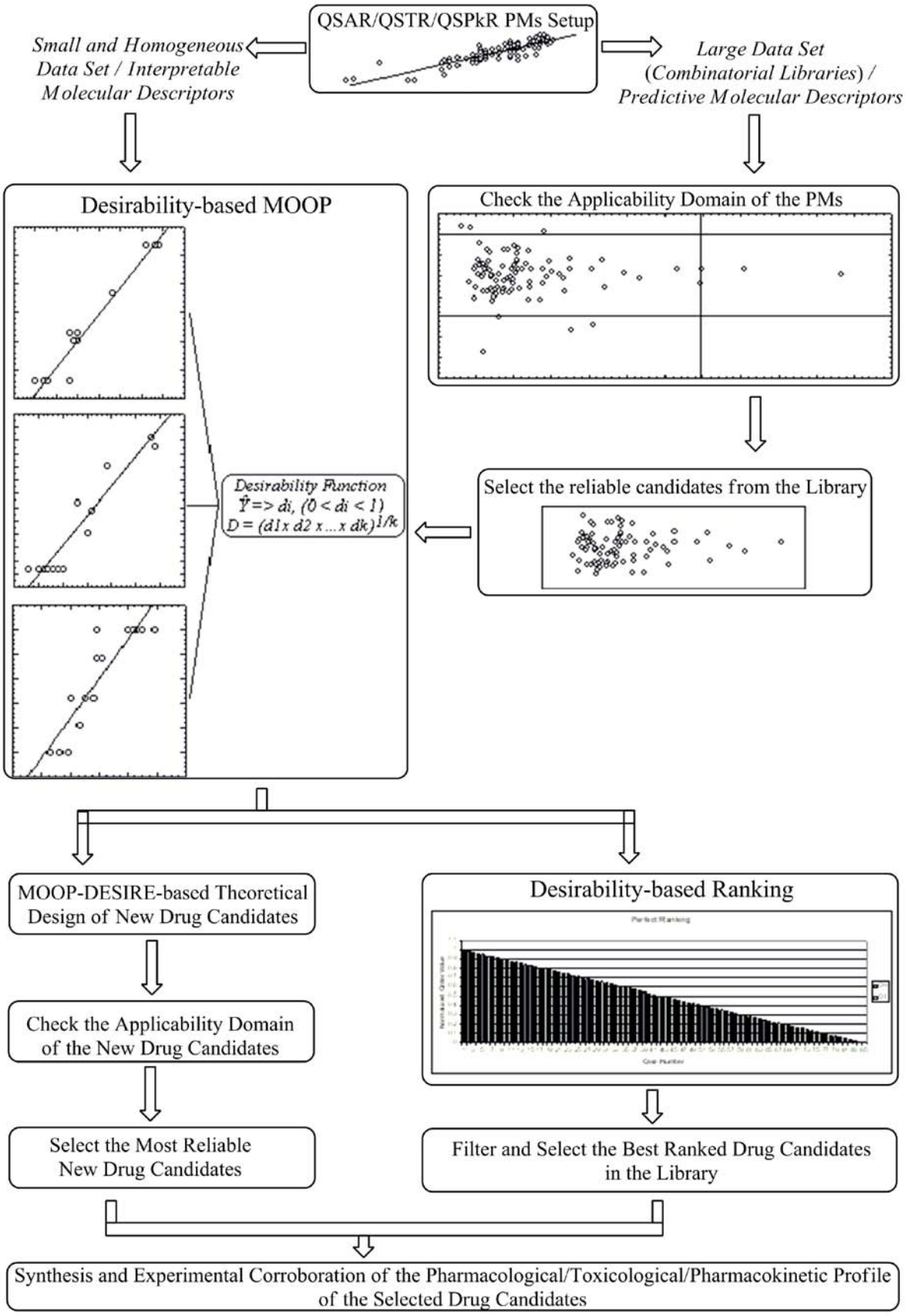


Fig. (2). MOOP-DESIRE-based rational drug discovery and development.

So, the simultaneous optimization of the analgesic, anti-inflammatory and ulcerogenic properties for the set of compounds was conducted by using as evaluation functions the best linear models relating each property to the atom centred fragments (ACF) molecular descriptors [69]. The models were good in both statistical significance and predictive ability. Good overall quality of the models is revealed by a satisfactory goodness of fit (values of the coefficient of determination (R^2) ranging from 0.803 to 0.935); as well as internal predictivity (Q^2 values between 0.713 and 0.905).

Moreover, the high Q^2_D value (0.905) provides an adequate level of reliability of the method in predicting the overall desirability *D*.

Previous to the *simplex* optimization of the overall desirability *D*, the desirability function specifications were applied to each property accordingly (see Table **1**).

Table 1. Desirability Functions Specifications. OPT: Type of Optimization Task; DES: Desirability Function Applied; L_i: Lower Bound; U_i: Upper Bound; T_i: Target; [a] Ulcerogenic Index of Aspirin Used as Ulcerogenic Reference Drug.

Response	OPT	DES	L_i	U_i	T_i
An(%)	Max.	eq.3	25	100	100
Aa(%)	Max.	eq.3	25	100	100
U	Min.	eq.4	0	1.73[a]	0

The optimization of the overall desirability was carried out to obtain the levels of the ACF descriptors that simultaneously produce the most desirable combination of all properties.

Fig. (**3**) shows the multiple response overall desirability, as well as the individual desirability functions determined by the respective pairs of predictor variables included on the three MLR models. The data reveal that a 3-(3-methylphenyl)-2-substituted amino-*3H*-quinazolin-4-one optimized candidate can have analgesic and anti-inflammatory activities of 93.43% and 82.04%, respectively, plus an ulcerogenic index of 0.44. This represents an overall desirability of 0.8; that can be attained if the quinazoline scaffold is modified with a substituent on C2 position characterized by the concurrent presence of five methyl groups (C-001 = 5) and twelve hydrogen atoms attached to a sp^3 carbon no heteroatom attached to another carbon (H-046 = 12) while avoiding the presence of heteroatoms attached to a sp^2 carbon atom linked to the aromatic side ring (C-037 = 0).

The information obtained suggest a positive role of the bulkiness of the alkyl substituents on the C-2 position of the quinazoline ring on the ulcerogenic properties while keeping or improving the analgesic and anti-inflammatory activities. The significant slope of the C-001 curve (see Fig. (**3**)) suggests that more attractive candidates could be designed with C2 substituents having more than five methyl groups. For a better understanding of this descriptor-to-chemical structure translation see Fig. (**4**).

Based on the previous analysis, a new set of nine 3-(3-methylphenyl)-2-substituted amino-*3H*-quinazolin-4-one optimized candidates was designed in which several alkyl substituents with different degree of bulkiness were linked to the C-2 position of the quinazoline ring. Chemical modifications and predicted values of the expected pharmaceutical properties are shown in Table **2**. The leverage values obtained for each new designed candidate were also considered to check whether or not each new candidate falls within the applicability domain of the original PMs.

In summary, a remarkable simultaneous improvement on the analgesic and anti-inflammatory activities plus ulcerogenic profile of the new designed candidates was obtained throughout MOOP-DESIRE methodology.

An important topic in this methodology is the space of MDs (X_1,X_2,.,X_n) used for building QSAR equations. If the equations are simple (minimal number of MDs), the MDs included on each equation are chemically and/or biophysically interpretable, and all the equations share the same or a highly similar set of MDs; the final interpretation and consequently the molecular design becomes easy and transparent, as was the case in [13]. However, on the contrary and more probable case where each property is explained as a function of multiple and hard to interpret different subsets of MDs, the final interpretation turns out to be (as best) highly complicated. This limitation was addressed by Machado *et al.* by the application of a variant of the MOOP-DESIRE methodology where the overall desirability derived from experimental property values was considered as the target response [18].

Design of selective arylpiperazine derivates for the 5-HT$_{1A}$ serotonin receptor. The purpose was to facilitate the design of new arylpiperazine anti-depressive - and/or anti-anxi ty agents [70-73] more selective for the 5-HT$_{1A}$ receptor with respect to 5-HT$_{2A}$ subtype intended to diminish the psychoactive and/or hallucinogenic adverse effects resulting from the undesired interaction with 5-HT$_{2A}$ receptor [74-78].

By using this variant the approach was reduced to a single QSAR equation independent of the number of initials responses (targets); consequently, the errors involved in the methodology could be minimized and the descriptor space to interpret was significantly reduced from ten MDs (five for each response) with the original MOOP-DESIRE methodology, to five MDs with the variant proposed. Both approaches exhibited similar predictabilities in estimating overall desirability values as well as an agreement with the available pharmacophore descriptions [79, 80].

It is important to note that the single model in the variant proposed by Machado *et al*. was dimensionally smaller but mostly composed by MDs with a difficult chemical translation/interpretation, limiting the corresponding results for molecular design. However, an elegant solution was proposed by the authors and

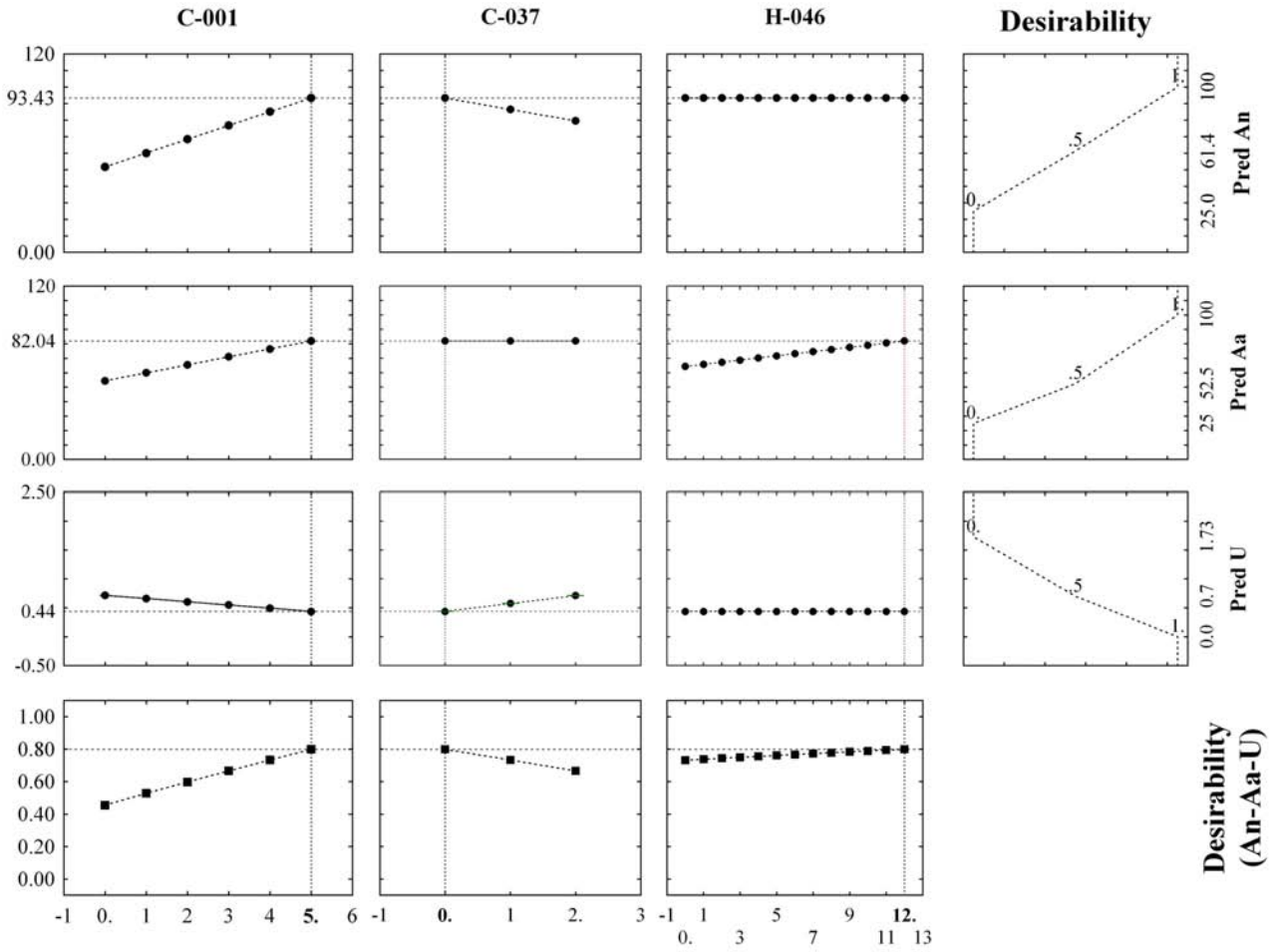


Fig. (3). Multiple response desirability function due to the analgesic activity, anti-inflammatory activity and ulcerogenic index −D(An-Aa-U) (last row), along with the individual desirability functions coming from the pairs of predictor variables included on the three MLR models(first three rows).

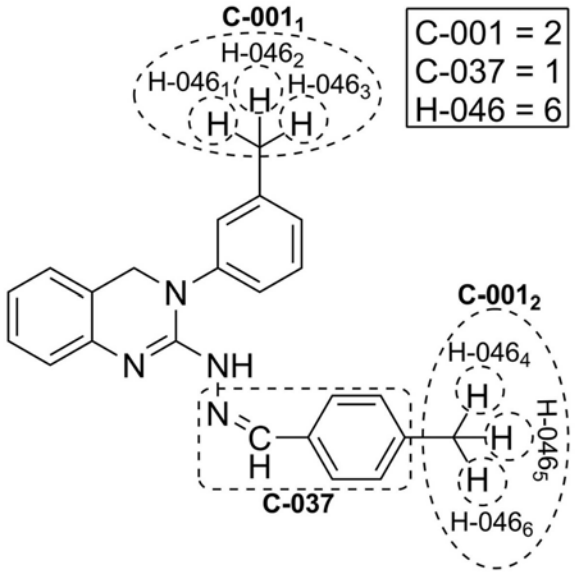
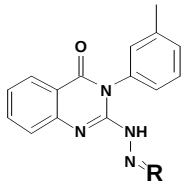


Fig. (4). Atom-Centered Fragments (ACF) descriptors for a 3-(3-methylphenyl)-2-substituted amino-3H-quinazolin-4-one compound.

Table 2. Computed ACF Descriptors (C-001, C-037 and H-046), Predicted and Leverage (h) Values for the Analgesic (An) and Anti-Inflammatory (Aa) Activities, plus the Ulcerogenic index (U) of the Nine New Designed Compounds. *Compounds out of the Predictions Model's Applicability Domain; Leverage Values Greater than a Critic Leverage (h*) are Marked in Bold.

3-(3-methylphenyl)-2-substituted amino-*3H*-quinazoline-4-one



Compound	*R*	*C-001*	*C-037*	*H-046*	An_{pred}	Aa_{pred}	U_{pred}	*h*(*An*)	*h*(*Aa*)	*h*(*U*)
ASNEW1		3	0	11	77%	70%	0.55	0.216	0.361	0.216
ASNEW2		3	0	13	77%	72%	0.55	0.216	0.496	0.216
ASNEW3		4	0	12	85%	77%	0.49	0.403	0.453	0.403
ASNEW4*		5	0	15	93%	86%	0.44	0.573	**0.614**	0.573
ASNEW5*		6	0	18	102%	96%	0.38	**0.695**	**0.724**	**0.695**
ASNEW6*		7	0	21	110%	106%	0.33	**0.777**	**0.796**	**0.777**
ASNEW7		4	0	9	85%	72%	0.49	0.403	0.401	0.403
ASNEW8		5	0	12	93%	82%	0.44	0.573	0.562	0.573
ASNEW9*		5	0	15	93%	86%	0.44	0.573	**0.614**	0.573

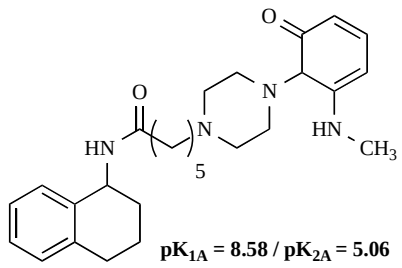
effectively applied to drug design. The solution was essentially based on the examination of the correlation matrix between "hard to interpret" MDs included in the model and ''interpretable ones'' as a way to understand predictive but hard to interpret models for future design. Results showed that model descriptors were strongly related to the principal factors involved in 5-HT receptors selectivity and affinity (flexibility, molecular weight, aromatic substructure and atom type involved in the aromatic substitution).

Specifically, higher values of desirability were related with molecules without H-donor groups or halogen atoms and with electronic density close to the benzene ortho substitution position in agreement with the principal pharmacophore aspects associated with 5-HT_{1A} receptor. This information allowed the design of a new set of 25 arylpiperazine candidates with a selective interaction profile over 5-HT_{1A} receptor. Among the 25 candidates two molecules were highlighted due to their potentially selective capabilities. These two selective candidates with 80–94% desirability values and highest differences between receptor affinities (pK_{1A} and pK_{2A}) values are shown in Fig. (**5**).

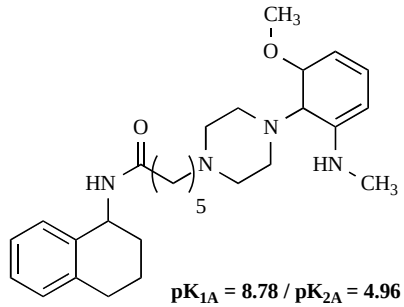
Desirability theory has been also applied, instead for multi-objective optimization, as a tool for the interpretation of multi-objective prediction models [11]. That is, instead of running a simultaneous optimization task over multiple properties of interest for drug discovery, such properties are directly combined into an overall desirability value (representing the compromise between the properties determining their pharmaceutical profile), predicted as a linear function of multiple molecular descriptors, and such a relationship is profiled in order to extract useful information on the desired trade-offs between those properties.

Extracting useful information on the desired trade-offs between binding and relative efficacy of N_6-substituted-4´-thioadenosines A_3 adenosine receptor agonists. Desirability theory was used as a tool to extract useful information on

the desired trade-offs between binding and relative efficacy of N^6-substituted-4´-thioadenosines A_3AR agonists [11]. In doing so, were used the binding affinities (K_{iA3}) and relative maximal efficacy (RE_{A3}) in the activation of the A_3AR reported by Jeong *et al.* [81] for a library of thirty two N^6-substituted-4´-thioadenosines A_3 adenosine receptor (A_3AR) agonists.



pK_{1A} = 8.58 / pK_{2A} = 5.06



pK_{1A} = 8.78 / pK_{2A} = 4.96

Fig. (5). $5HT_{1A}$ serotonin receptor selective arylpiperazine ligands designed by Machado *et al.*

Once desirability scaled both K_{iA3} and RE_{A3} responses for each compound, the corresponding overall desirability ($D_{KiA3\text{-}REA3}$) values were derived. In order to identify the factors governing the trade-offs between binding affinity and efficacy of this family of A_3AR agonists, the combined response $D_{KiA3\text{-}REA3}$ was mapped as a function of four simple 1D MDs with a direct structural and/or physiochemical explanation. The resulting model was statistically significant and predictive with values of R^2 and Q^2 about 0.8 and 0.6, respectively.

$$D_{KiA3-REA3} = 1.557(\pm 0.292) - 0.107(\pm 0.013) \times \boldsymbol{ALOGP2} + 0.203(\pm 0.033) \times \boldsymbol{nCIR} - 2.783(\pm 0.595) \times \boldsymbol{ARR} - 0.092(\pm 0.027) \times \boldsymbol{nCs} \quad (\mathbf{11})$$

According to the model regression parameters, the most influencing descriptor is the aromatic ratio (*ARR*) which is the fraction of aromatic atoms in the hydrogen suppressed molecule graph and encodes the degree of aromaticity of the molecule.

The second most influencing descriptor is the number of circuits (*nCIR*), a complexity descriptor which is related to the molecular flexibility and serves as a measure of rigidity with higher numbers of circuits corresponding to reduced flexibility. Finally, following *nCIR* in order of influence over $D_{KiA3\text{-}REA3}$ are the square of the Ghose-Crippen octanol water coefficient ((*ALOGP2*) which encodes the hydrophobic/hydrophilic character of the molecule; and *nCs*, a constitutional descriptor accounting for the number of secondary sp^3 carbon atoms in the molecule.

According to the model, a molecule with a low aromaticity degree, without secondary sp^3 carbon atoms, and containing cyclic and rigid N^6 substituents which contributes to reduce the hydrophobicity of the system could favor the balance of the binding affinity and relative efficacy profiles of N^6-substituted-4´-thioadenosine A_3AR agonists. These conclusions, although derived from a simple 1D model, were very similar to that obtained by 3D-CoMFA/CoMSIA approaches [82]. Kim and Jacobson have concluded that a bulky group, conformationally restricted, at the N^6 position of the adenine ring will increases the A_3AR binding affinity, and that a small bulky group, at this position, might be crucial for A_3AR activation.

Although useful, this information was incomplete since it is well-known that steric factors are determinant for the design of A_3AR agonists, especially for binding affinity [82]. Consequently, it is found to be important to determine the optimal size of the conformationally restricted cyclic N^6 substituent. Unfortunately, the simple inspection of the regression parameters of the PM did not offers this information. In consequence, the behavior of $D_{KiA3\text{-}REA3}$ was profiled at the mean values of the four MDs rather than looking for their optimal values (see first row in Fig. (**6**)). Accordingly, it was possible to find the levels of the MDs simultaneously producing the best possible $D_{KiA3\text{-}REA3}$ in the training set employed.

The analysis revealed that for the most favorable balance of binding affinity and agonist efficacy: the *ARR* should be not just low but near to 0.4; *ALOGP2* should be as low as possible; the number of secondary sp^3 carbon atoms should be kept around two; and *nCIR* should be not just high but close to six. At the same time, considering that the *nCIR* value of the thioadenosine nucleus is four, one can deduce that the ideal *nCIR* value of the N^6 substituent should be two. This information can be structurally translated into bicyclic N^6 type of substituents.

The inclusion in the PM of *nCIR*, instead of the number of rings in the chemical graph (*nCIC*) is also significant. Although the structural information of this pair of MDs is very similar, their graph-theoretical information is quite different. While *nCIC* encodes the number of rings, *nCIR* includes both rings and circuits (see Fig. (**7**)). So, additional information can be inferred: the bicyclic N^6 substituent should not be fused.

This result matches with previous experimental findings on the structure-activity relationship (SAR) of this family of thioadenosine derivatives [81]. The SAR obtained for this family suggests that compounds with bulky N^6 substituents lost their binding to the A_3AR. Paradoxically, among compounds showing high binding affinity at the human A_3AR, two compounds substituted with a N^6-(*trans*-2-phenylcyclopropyl) amino group were found to be full agonists at the human A_3AR. In addition, it was found that compounds with α-naphthylmethyl N^6 substituents (fused bicyclic substituents) lost their binding to the A_3AR [81].

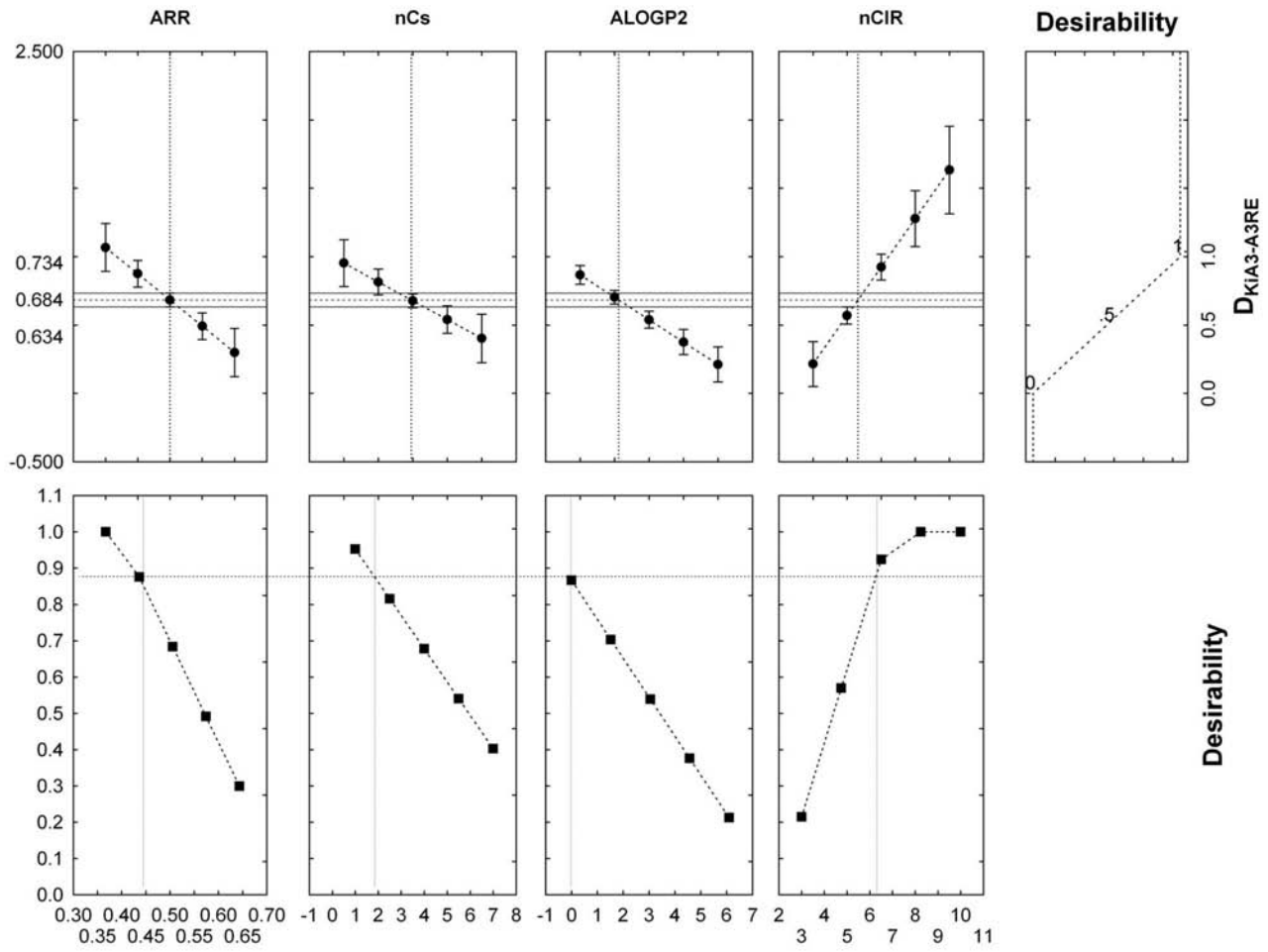


Fig. (6). Desirability profiling of the levels of the MDs that simultaneously produce the most desirable combination of binding affinity and relative efficacy of N^6-substituted-4´-thioadenosine A_3AR agonists.

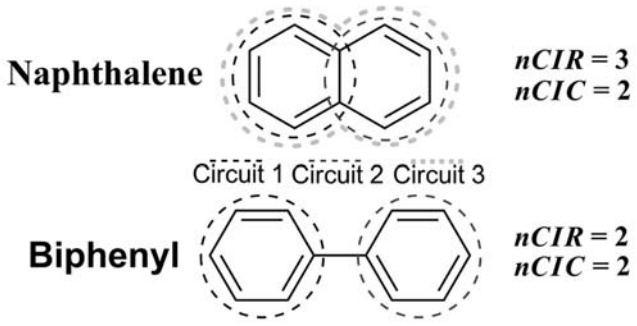


Fig. (7). Graphical illustration of the definition of nCIC and nCIR for two chemical graphs.

From the study it was also concluded that bulky N^6 substituents only affects the binding affinity, however bulky not fused bicyclic substituents such as a *trans*-2-phenylcyclopropyl group, could be beneficial for agonist efficacy without lost their binding affinity. Although that experimental study does not deal with the simultaneous analysis of both properties, their experimental findings properly matched with theoretical results.

MULTI-OBJECTIVE LIBRARY RANKING

The MOOP-DESIRE methodology can also be applied to handle larger and/or more diverse data sets, such as those frequently obtained in *High-Throughput Screening* processes, being there more appropriate for early stages of the drug development process. That is, molecules coming from large and heterogeneous data sets can be ranked and

filtered according to a certain criterion rather than applying the results of the optimization process to design new candidates. To accomplish that, one can resort to the overall desirability of each molecule as a ranking criterion or to several distance measures between the optimal values of the descriptors determined by MOOP-DESIRE and the computed values of the descriptors. In this case, it is advisable to use descriptors leading to highly predictive structure-desirability relationships rather than interpretable descriptors in order to ensure the accuracy of the predictions and therefore, an accurate assessment of the molecule's overall desirability. The suitability of the MOOP-DESIRE methodology as a multi-objective library ranking algorithm was evaluated on a library of 95 fluoroquinolones [83]. It was done with the aim of optimize simultaneously their antibacterial activity over gram-negative microorganisms (MIC) and their cytotoxic effects over mammalian cells (IC_{50}) and use these results as a pattern for a multi-objective ranking algorithm [15].

Filtering safe and potent antibacterial candidates from a heterogeneous library of antibacterial fluoroquinolones. The best linear models relating each property to the DRAGON molecular descriptors were good in both statistical significance and predictive ability, and the overall desirability function exhibits good statistical quality as indicated by the R^2_D values ~0.7. Moreover, a Q^2_D value of 0.63 provides an adequate level of reliability on the method in predicting *D*.

In order to obtain candidate(s) with high antibacterial potency (MIC) and low cytotoxicity (IC_{50}) the optimization of the overall desirability was carried out to obtain the levels of the descriptors included in the PMs that simultaneously produce the most desirable combination of the properties. Once found, the resulting optimal vector of MDs was used as a pattern to rank the library of flouroquinolones. Through a nonlinear curve-fitting process implemented in MATLAB were found the optimal set of weights w_i required to minimize the differences between descriptions (Δ_i) and solutions (D_i) in the library of compounds to rank. Next, Δ_i was used as a ranking criterion. Based on Δ_i was possible to reach a ranking of the flouroquinolones library with a corrected ranking quality index (Ψ^*) of 0.313 representing a percentage of ranking quality ($R_{\%}$) of 68.7. This ranking compared with the perfect ranking is shown in Fig. (**8**).

The quality of the ranking attained ($R_{\%}$ = 68.7) was similar to the predictability values exhibited in the PMs as well as in the MOOP process (Q^2(MIC) = 0.693, $Q^2(IC_{50})$ = 0.686, $Q^2_{D(MIC\text{-}IC50)}$ = 0.629) which indicates that the quality of both process (desirability-based MOOP and ranking) are strongly dependent of the quality of the initial set of PMs. In addition, the similarity exhibited between these values suggests that the ranking algorithm reflects the quality of the PMs and the MOOP process in which it is based.

MULTI-OBJECTIVE VIRTUAL SCREENING

Filtering the most promising candidates having the best compromise between several properties comprising the final pharmaceutical profile confers to the process of discovery and development of new drugs an elevated degree of rationality which is difficult to reach via traditional QSARs which optimize sequentially each property. The sequential optimization of the properties comprising the final pharmaceutical profile of a drug candidate implies to overlook at some stage properties equally decisive to reach a successful drug or, at least, to find only by chance a candidate with acceptable profiles of all properties simultaneously.

That is, a potent candidate once identified via QSAR has a high probability of being discarded later as a drug because of an unacceptable toxicological profile with the useless expenses of time and resources in synthesis and pharmacological assays [84]. Equally difficult is the choice of using a panel of models (*i.e.*: a parallel screening based on QSAR models to respectively map the therapeutic efficacy and toxicity) since it is not very probable to find a candidate with all the properties simultaneously optimized and if this happens the results are more by chance than fruit of a rational drug development strategy.

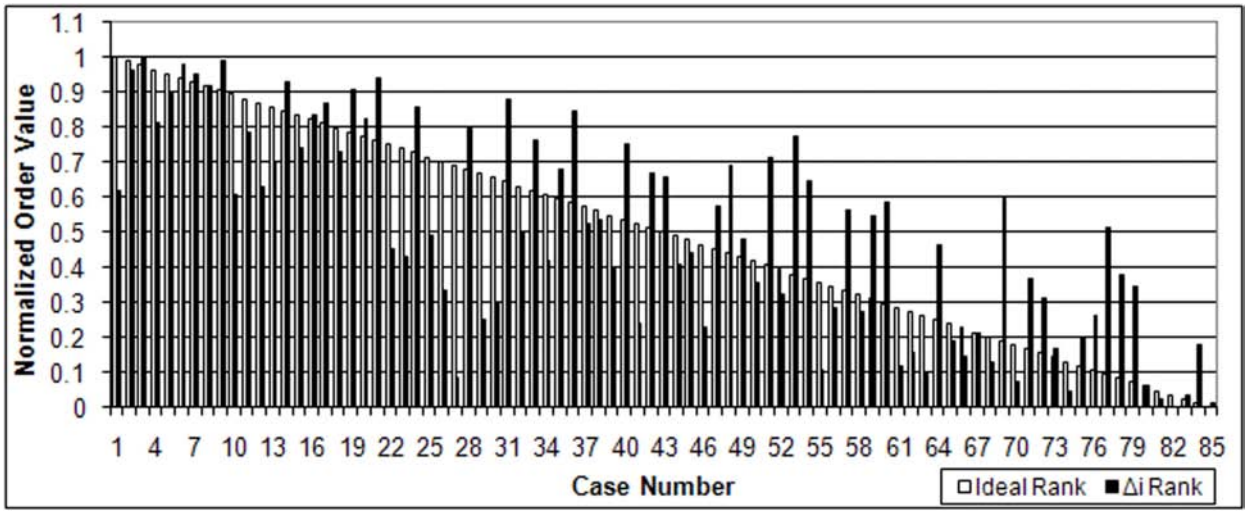


Fig. (8). Δ_i-based ranking of the fluoroquinolone library.

MOOP-DESSIRE methodology was used as a rational strategy of multi-objective virtual screening to prioritize HIV-1 non nucleoside reverse transcriptase inhibitors (NNRTIs) with acceptable trade-offs between the inhibitory efficacy and toxicity towards MT4 blood cells [19]. A retrospective analysis of the training set, based on well-known enrichment measures [85-87], was conducted allowing comparing the performance of several VS approaches. The performance of this multi-objective VS strategy to retrieve pharmaceutically acceptable NNRTI candidates from a pool of NNRTI decoys was also tested.

Prioritizing hits with appropriate trade-offs between HIV-1 reverse transcriptase inhibitor efficacy and MT4 blood cells toxicity. The main goal in a VS effort is to select a subset from a large pool of compounds (typically a compound database or a virtual library) and try to maximize the number of known actives in this subset. That is, to select the most "enriched" subset as possible.

Several enrichment metrics have been proposed in the literature to measure the enrichment ability of a VS protocol [85, 86]. In this work, we use some of the most extended.

Based on the analysis of the receiver operating characteristic (ROC) curve [86] it is possible to derive the area under the ROC curve (*ROC Metric*) [85], as well as the ratio of true positive (TP) cases and false positive (FP) cases found at the operating point of the ROC curve ($TP/FP_{ROC\text{-}OP}$) [88].

From the accumulation curve we can deduce enrichment from the area under the curve (*AUAC*) [85], from the yield of actives (*Ya*) at certain filtered fractions (*i.e.*10%), as well as from the fraction of the database that has to be screened in order to retrieve a certain percentage (100%) of the TP cases (screening percentage, $\chi_{100\%}$).

On the other hand, the enrichment factor (*EF*) takes into account the improvement of the hit rate by a VS protocol compared to a random selection.

$$EF = \frac{TP/n}{N_+/N} \quad \textbf{(12)}$$

where *TP* is the number of true positive cases retrieved, *n* the number of selected cases, *N* and N_+ are the total number of cases, and the number of positive cases in the library, respectively [85].

The suitability of a multi-objective VS approach can be checked by comparing the enrichment achieved in the screening of NNRTI candidates with a favorable pharmaceutical profile from the full set of 122 NNRTI compounds, sequentially considering the inhibitory efficacy (the predicted values of $-logIC_{50}$) and safety (the predicted values of $-logCC_{50}$) profiles in opposition to use the pharmaceutical profile information (predicted values of overall desirability $D_{IC50\text{-}CC50}$).

When the screening was conducted in a sequential manner, starting with the selection of candidates fulfilling a previously established threshold for the inhibitory efficacy and further eliminating those candidates with an unfavorable safety profile, the area of selected candidates is reduced. As a consequence, 41% of the candidates with favorable pharmaceutical profiles are mistakenly discarded (see Fig. (**9A**)). However, by considering the compromise between inhibitory efficacy and safety of the candidates through multi-objective VS ($Pred.D_{IC50\text{-}CC50} \geq 0.5$) is possible to retrieve up to 88% of the candidates with acceptable pharmaceutical profiles included on the library (see Fig. (**9B**)).

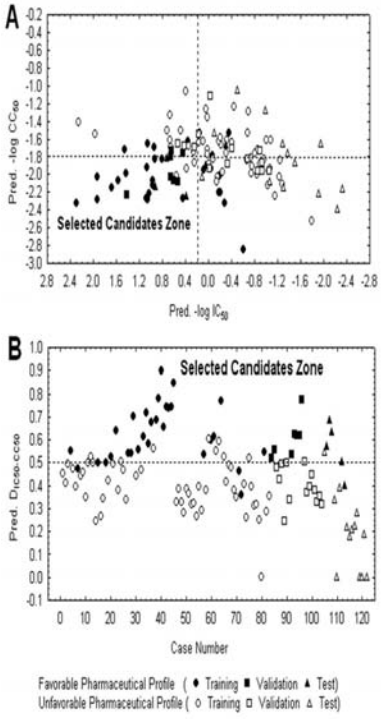


Fig. (9). Graphical representation of the results for (**A**) a sequential screening [based on the inhibitory efficacy (Pred.–logIC_{50}) and safety (Pred.–logCC_{50}) profiles], and (**B**) a multi-objective screening [based on the pharmaceutical profile (Pred.$D_{IC50-CC50}$)], of the full set of 122 NNRTI compounds.

This reveals the importance of considering multiple properties simultaneously since the sequential application of property filters could have led to the elimination of the candidate, despite it having a good balance between most of the properties [89]. The importance of achieving a balance across a range of criteria is also recognized by other groups [90].

Finally, was evaluated the ability of the multi-objective VS strategy proposed to prioritize NNRTI candidates with favorable pharmaceutical profiles ($D_{IC50\text{-}CC50} \geq 0.5$) disperse in a data set of NNRTI decoys.

NNRTI decoys are physically similar but chemically distinct from NNRTIs, so that they are unlikely to be binders of the HIV reverse transcriptase. The 12 HIV RT known ligands with favorable pharmaceutical profiles

included on the validation and test sets were used as positive cases, while 36 decoys (negative cases) for each known ligand (432 decoys in total) were randomly selected from the database of HIV RT decoys included on the directory of useful decoys (DUD) [91].

The final set of 444 compounds was ranked according to their structural similarity (Δ_i) with the previously determined optimal candidate, and the enrichment ability of this strategy was finally tested according to the well known enrichment metrics and now depicted in Table **3**.

Table 3. Enrichment Metrics for Δ_i-based Ranking of the Data Set Collected form DUD

ENRICHMENT METRICS	
ROC Curve Information	
ROC Metric	0.798
$TP/FP_{ROC\text{-}OP}$	0.833/0.215
Accumulation Curve Information	
AUAC	0.828
$\chi_{100\%}$	0.320
$Ya_{10\%}$	0.333
Enrichment Curve Information	
$EF_{10\%}$	3.364
EF_{Max}	3.592

The respective values of *AUAC* and *ROC Metric* obtained suggest that the method is able to rank a NNRTI candidate with a favorable pharmaceutical profile earlier than a NNRTI decoy with a probability around 0.8. At the same time, $TP/FP_{ROC\text{-}OP}$ informs that, to obtain the best performance is necessary to filter 23.2 % of the library, in turn leading to find 83.3% of the TP cases at a cost of only 21.5 % of FP cases, which represents a EF_{MAX} = 3.592. Furthermore, all the positive cases can be found at the first 32% of the library. On the other hand, a third of the compounds retrieved, after filtering the top 10% of the library, were NNRTI candidates with a favorable pharmaceutical profile ($Ya_{10\%}$ = 0.33), which represents an $EF_{10\%}$ = 3.364, being 10.09 the maximum possible value of *EF* for this data fraction.

So, considering the previous results, one may well expect that larger (real or virtual) libraries of molecules (always inside the applicability domain of the PMs), like combinatorial libraries, could be correctly ranked; prioritizing in this way those candidates (top ranked) with more favorable compromise between inhibitory efficacy and safety.

CONCLUDING REMARKS

In this paper, we reviewed the MOOP-DESIRE methodology, a desirability-based multi-objective QSAR method for the joint handling of multiple properties of interest in drug discovery. Their suitability for key tasks involving the use of chemoinformatics methods in medicinal chemistry and drug discovery was exposed. Overall results attained in drug design, library ranking and virtual screening tasks allows suggesting that the identification of hits with appropriate trade-offs between potency and safety, rather than fully optimized hits solely based on potency, can facilitate the hit to lead transition and increase the likelihood of the candidate to evolve into a successful drug. So, it is apparent that MOOP-DESIRE methodology can play an important role in the difficult task of reducing the size of that haystack that is the chemical space and hence speeding and rationalizing the drug discovery process.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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PATIENT CONSENT

Declared none.

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