QSAR and 3D-QSAR studies applied to compounds with anticonvulsant activity

Juan C Garro Martinez[†], Esteban G Vega-Hissi, Matías F Andrada & Mario R Estrada

[†]*Universidad Nacional de San Luis, Area de Química Física, Facultad de Química, Bioquímica y Farmacia, San Luis, Argentina*

Introduction: Quantitative structure–activity relationships (QSAR and 3D-QSAR) have been applied in the last decade to obtain a reliable statistical model for the prediction of the anticonvulsant activities of new chemical entities. However, despite the large amount of information on QSAR, no recent review has published and discussed this data in detail.

Areas covered: In this review, the authors provide a detailed discussion of QSAR studies that have been applied to compounds with anticonvulsant activity published between the years 2003 and 2013. They also evaluate the mathematical approaches and the main software used to develop the QSAR and 3D-QSAR model.

Expert opinion: QSAR methodologies continue to attract the attention of researchers and provide valuable information for the development of new potentially active compounds including those with anticonvulsant activity. This has been helped in part by improvements in the size and performance of computers; the development of specific software and the development of novel molecular descriptors, which have given rise to new and more predictive QSAR models. The extensive development of descriptors, and the way by which descriptor values are derived, have allowed the evolution of the QSAR methods. This evolution could strengthen the QSAR methods as an important tool in research and development of new and more potent anticonvulsant agents.

Keywords: anticonvulsant activity, quantitative structure–activity relationship and 3D-quantitative structure–activity relationship, review

Expert Opin. Drug Discov. [Early Online]

1. Introduction

Despite optimal use of anticonvulsant drugs, many people with seizures disorder fail to experience seizure control and others do so only at the expense of significant toxic side effects. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients [1]. The improvement of the treatment of seizure disorder over the past decade was mainly associated with the development of new anticonvulsant drugs that, taking advantage of the identification of the biological mechanisms involved, act specifically on a single target [2].

During the last years, many new anticonvulsant drugs have been developed [3-11]. In this sense, quantitative structure–activity relationship (QSAR) techniques, QSAR and 3D-QSAR, have been the most used approaches in the aided design of derivatives of known antiepileptic drugs or new compounds with this biological activity. These techniques, useful tools in molecular design and medicinal chemistry, allow the prediction of the activities of structurally diverse compounds and may assist to

10.1517/17460441.2015.968123 © 2014 Informa UK, Ltd. ISSN 1746-0441, e-ISSN 1746-045X

Article highlights.

- To date, many quantitative structure–activity relationship studies on different families of compounds with anticonvulsant activity have been developed by different research groups.
- All papers about quantitative structure–activity relationship (QSAR) and 3D-QSAR studies of compounds with known anticonvulsant activity published between the years 2003 and 2013 have been included in this review.
- The wide variety of compounds analyzed includes derivatives of urea, benzylacetamide, furanone, enaminones, sulfamides, valproic acid, imidazole, quinoxaline, benzothiazoles, and cyclopentanones.
- The molecular structure in the QSAR is encoded by means of molecular descriptors calculated from specific software such as The Dragon software.
- Several statistical approaches such as partial least-squares, multiple linear regression, principal component analysis, genetic algorithm, and ANN were utilized to select the independent variables (molecular descriptors) in the reviewed QSAR model.
- The majority of the analyzed models have a restricted field of application to a certain type of compounds.
- There is a significant interest in the discovery of new anticonvulsant drugs.
- The incessant evolution of the QSAR methodologies can collaborate in the development of new and more potent anticonvulsant agents.

This box summarizes key points contained in the article.

identify new compounds with improved activity and better profile of side effects. The combination of these techniques with traditional drug discovery methodologies increases greatly the chance of drug discovery in a sustainable and economical fashion.

The last review found in the literature about QSAR studies applied to anticonvulsant drugs was published by Hadjipavlou-Litina *et al.* in 1998 [12]. Here, we review 28 articles, published between 2003 and 2013, in which the QSAR or 3D-QSAR methods is applied to several types of compounds with known experimental anticonvulsant activity [13-40] (the years and the title of the reviewed papers are showed in **Table 1**). However, note that the papers published between the years 1999 and 2002 are not included [41-47]. We think that a summary of the publications of the last decade would provide the current information on this topic.

In the next section, we summarize the most significant data of the QSAR models in the 28 reviewed articles. We highlight the following points: i) the number and the family of compounds with anticonvulsant activity included in the total set; ii) the training and test sets composition; iii) the software used in the molecular optimization and calculation of descriptors; iv) the selection methods of molecular descriptors; v) the number of descriptors included in the model; vi) the statistic parameters; and vii) the employment of validation techniques to corroborate the predictive performance of the models.

With the purpose of standardizing the analyzed information we selected the regression coefficient (R) as the statistic parameter, which suggests the quality of training and validation of the models. Also, to unify the regression coefficient nomenclature of the training and test set, in this review, they are appointed as R_{train} and R_{test}, respectively. The regression coefficients of the cross-validation are referred as R_{loo} or R_{lmo} for leave-one-out and leave-more-out.

2. QSAR and 3D-QSAR studies

In this section, the most relevant information of the reviewed articles is summarized. The items (a), (b), (e), and (f) exposed in the previous section are listed in **Table 2**.

2.1 QSAR studies

In 2003, Sutherland *et al.* [13] developed a QSAR analysis on 94 hydantoin derivatives with measured anticonvulsant activity. The computational calculations were performed using the molecular modeling package Cerius-2 v. 4.6 [48]. A set of 127 descriptors was generated for the QSAR. The training and test sets were assembled using three different methods, 'by-activity', principal component analysis (PCA) approach, and 'distance metric' [49]. For QSARs, genetic algorithm (GA) was used for selecting subsets of 5 – 9 descriptors. Quadratic descriptors were included in one of the models (named c6q). The equation (Eq.1) for the most predictive model is:

$$\begin{aligned} ln(1/ED50) = {} & 15.6 + 0.952\,Nrot - 3.65^{3}k_{\alpha} - 9.86Q1 \\ & - 0.250PNSA3 + 129FNSA3 + 0.662\,SssCH2 \\ & - 1.79\,SdssC - 0.333PPSA3 \end{aligned} \quad (1)$$

The regression coefficients for the d8 model are 0.80 and 0.75 for the training and test sets, respectively. The molecular descriptors in this model are as follows: The geometric/structural descriptors N_{rot} = no. of rotatable bonds (excluding AT3 and AT2 terminal bonds, such as CH3 and NH2), the topological descriptors $^{3}k\alpha$ = R-modified shape index of order 3 [50-52], the electronic descriptors $Q1$ = partial charge on hydantoin ring atom 1, the hybrid descriptors PNSA3, PPSA3, and FNSA3 = charged partial surface area descriptors [53], *S*aaCH2 and SdssC = electrotopological state indices [54].

In 2004, Macchiarulo *et al.* [14] showed a QSAR study performed on a total set of 61 negative allosteric modulators of AMPA receptor, acting as anticonvulsant agents, using partial least-squares (PLS) and multiple linear regressions (MLR). All the compounds studied were constructed and optimized using the UNIVERSAL force field [55] with the Smart Minimizer protocol of Open Force Field. The QSAR analysis was performed with the QSAR+ module of Cerius-2 [48]. Thirty molecular descriptors were selected from the Cerius-2 library. Forty nine compounds were used in the training set and

Table 1. Brief information of the 28 revised papers.

Author	Year	Citations	Title
Sutherland *et al.* [13]	2003	28	Development of QSARs and classification models for anticonvulsant activity of hydantoin analogs
Macchiarulo *et al.* [14]	2004	15	QSAR study of anticonvulsant negative allosteric modulators of the AMPA receptor
Hemmateenejad *et al.* [15]	2004	9	Molecular modeling and QSAR analysis of the anticonvulsant activity of some N-phenyl-N0-(4-pyridinyl)-urea derivatives
Buchwald *et al.* [16]	2005	8	QSAR study of 2,3-benzodiazepin-4(thi)one- and 1,2-phthalazine-related negative allosteric modulators of the AMPA receptor: a structural descriptors-based reassessment
Jin *et al.* [17]	2005	4	A QSAR study for _-substituted acetamido-*N*-benzylacetamide derivatives – a novel anticonvulsant drug class
Zhang *et al.* [18]	2006	78	A novel ALL-QSAR approach: method development, applications, and virtual screening of chemical databases using validated ALL-QSAR models
Bhutoria *et al.* [19]	2006	2	A 3D-QSAR of N-substituted 4-Amino3-3-Dialkyl-2 (3H)-Furanone $GABA_A$ receptor modulators based on receptor surface analysis
Gavernet *et al.* [20]	2007	16	3D-QSAR design of novel antiepileptic sulfamides
Gunakkunru *et al.* [21]	2007	2	QSAR of riluzole series as anticonvulsants
Bhutoria *et al.* [22]	2008	0	A novel approach for the identification of selective anticonvulsants based on differential molecular properties for TBPS displacement and anticonvulsant activity: an integrated QSAR modeling
Hashemianzadeh *et al.* [23]	2008	4	DFT-based QSAR study of valproic acid and its derivatives
Sharma *et al.* [24]	2008	1	3D-QSAR studies for the binding affinity toward (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)- -propionic acid receptor
Garro Martinez *et al.* [25]	2009	9	Anticonvulsant activity of ringed enaminones: a QSAR study
Jackson *et al.* [26]	2009	7	Enaminones 8: coMFA and CoMSIA studies on some anticonvulsant enaminones
Puratchikody *et al.* [30]	2009	4	QSAR studies on antiepileptic and locomotor *in vivo* activities of 4,5-diphenyl-1H-imidazoles
Jain *et al.* [27]	2010	7	Design, synthesis, and biological evaluation of some novel benzimidazole derivatives for their potential anticonvulsant activity
Paliwal *et al.* [28]	2010	4	QSAR studies of imidazo (1,5-) quinoxalines amides, carbamates, and ureas as potent GABA modulators
Amnerkar *et al.* [29]	2010	48	Synthesis, anticonvulsant activity, and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole
Ganguly *et al.* [31]	2010	4	Comparative molecular similarity indices analysis of 1-(Naphthylalky1)-1H-imidazole analogs with antiepileptic activity
Thareja *et al.* [32]	2010	4	3D QSAR studies on 1, 3, 4-thiadiazole derivatives: an approach to design novel anticonvulsants
Najafi *et al.* [33]	2011	4	QSAR analysis of the anticonvulsant activity of some benzylacetamides based on genetic algorithm-based multiple linear regression
Garro Martinez *et al.* [34]	2011	21	QSAR study and molecular design of open-chain enaminones as anticonvulsant agents
Fegade *et al.* [35]	2011	1	QSAR analysis of some aryloxypropanolamine analogs as anticonvulsants
Jain *et al.* [36]	2012	3	Discovery of potent anticonvulsant ligands as dual NMDA and AMPA receptors antagonists by molecular modeling studies
Mozaffari *et al.* [37]	2012	2	Synthesis and evaluation of some novel methylene-bridged aryl semicarbazones as potential anticonvulsant agents
Garro Martinez *et al.* [38]	2012	1	A multivariate QSAR Study on the anticonvulsant activity of acetamido-N-benzylacetamide derivatives. influence of different molecular descriptors
Weaver *et al.* [39]	2013	0	A simple electrotopological index for QSAR correlation of physical properties with biomolecular activities
Chhajed *et al.* [40]	2013	3	Design and syntheses of some new 5-[Benzenesulphonamido]-1,3,4 –thiadiazol-2-sulphonamide as potent antiepileptic agent

ALL-QSAR: Automated lazy learning quantitative structure–activity relationship; DFT: Density functional theory; QSAR: Quantitative structure–activity relationship; TBPS: Tert-butyl-bicyclophosphorothionate.

Table 2. Summary of QSAR and 3D-QSAR models.

Author	N MD*	N Training‡	N test§	Statistic parameters
Sutherland *et al.* (2003) [13]	6	40	20	R_{train} = 0.79 R_{test} = 0.64 (model c6)
	6	40	20	R_{train} = 0.70 R_{test} = 0.61 (model d6)
	8	40	20	R_{train} = 0.80 R_{test} = 0.75 (model d8)
	6	63	31	R_{train} = 0.70 R_{test} = 0.60 (model b6)
	6	40	31	R_{train} = 0.79 R_{test} = 0.68 (model c6q)
Macchiarulo *et al.* (2004) [14]	6	49	12	R_{train} = 0.707 R_{cv} = 0.700 (PLS model)
	6	49	12	R_{train} = 0.757 R_{cv} = 0.704 (MLR model)
Hemmateenejad *et al.* (2004) [15]	2	20	-	R_{train} = 0.669 (constitutional descriptors, MLR)
	4	20	-	R_{train} = 0.924 (topological descriptors, MLR)
	2	20	-	R_{train} = 0.688 (chemical descriptors, MLR)
	2	20	-	R_{train} = 0.910 (quantum descriptors, MLR)
	3	20	-	R_{train} = 0.975 (all descriptors, MLR)
	5	20	-	R_{train} = 0.995 (PLS)
Buchwald *et al.* (2005) [16]	7	49	12	R_{train} = 0.786 R_{test} =0.730
	6	61	-	R_{train} = 0.779
Jin *et al.* (2005) [17]	7	35	-	R_{train} = 0.66 R_{loo} = 0.42 (complete data set)
	-	35	-	R_{train} = 0.77 R_{loo} = 0.63 (three outliers)
Zhang *et al.* (2006) [18]	-	39	9	R_{test} = 0.90
	-	38	10	R_{test} = 0.88
	-	40	8	R_{test} = 0.86
	-	39	9	R_{test} = 0.86
	-	37	11	R_{test} = 0.83
	-	38	10	R_{test} = 0.81
	-	36	12	R_{test} = 0.80
	-	34	14	R_{test} = 0.76
	-	32	16	R_{test} = 0.75
	-	32	16	R_{test} = 0.71
Bhutoria *et al.* (2006) [19]	-	14	5	R_{train} = 0.998 R_{loo} = 0.639 R_{lmo} = 0.943 R_{test} = 0.960
Gavernet *et al.* (2007) [20]	-	27	-	R_{train} = 0.960 R_{loo} = 0.748 (CoMFA)
	-	28	-	R_{train} = 0.897 R_{loo} = 0.708 (CoMFA)
	-	30	-	R_{train} = 0.967 R_{loo} = 0.756 (extended CoMFA, Model 1)
	-	30	-	R_{train} = 0.941 R_{loo} = 0.681 (extended CoMFA, Model 2)
Gunakkunru *et al.* (2007) [21]	-	24	-	R_{train} = 0.97 R_{loo} = 0.977
Bhutoria *et al.* (2008) [22]	4	37	8	R_{train} = 0.812 R_{loo} = 0.767 R_{test} = 0.402 (without outliers)
	4	37	8	R_{test} = 0.912 (one outlier)
	4	37	8	R_{train} = 0.795, R_{loo} = 0.742 R_{test} = 0.493 (without outliers)
	4	37	8	R_{test} = 0.910 (one outlier)
	4	37	8	R_{train} = 0.70, R_{loo} = 0.712 R_{test} = 0.514 (without outliers)
	4	37	8	R_{test} = 0.861 (one outlier)
	4	37	8	R_{train} = 0.800, R_{loo} = 0.752, R_{test} = 0.206 (without outliers)
	4	37	8	R_{test} = 0.823 (one outlier)
Hashemianzadeh *et al.* (2008) [23]	2	26	-	R_{train} = 0.543, R_{loo} = 0.183, R_{test} = 0.295 (AIM descriptors)
	2	26	-	R_{train} = 0.931, R_{loo} = 0.822, R_{test} = 0.867 (chemical descriptors)
	3	26	-	R_{train} = 0.968, R_{loo} = 0.919, R_{test} = 0.937 (quantum chemical descriptors)
	3	26	-	R_{train} = 0.968, R_{loo} = 0.919, R_{test} = 0.937 (all types of descriptors)
Sharma *et al.* (2008) [24]	-	30	5	R_{loo} = 0.766, R_{test} = 0.944 (CoMFA)
	-	30	5	R_{loo} = 0.712, R_{test} = 0.920 (CoMSIA using S,E)
	-	30	5	R_{loo} = 0.612, R_{test} = 0.855 (CoMSIA using S,E,H)
	-	30	5	R_{loo} = 0.760, R_{test} = 0.920 (CoMSIA using S,E,D,A)
	-	30	5	R_{loo} = 0.758, R_{test} = 0.919 (CoMSIA using All)

*Number of molecular descriptors.

‡Number of compounds in the training set.

§Number of compounds in the test set.

CoMFA: Comparative molecular field analysis; CoMSIA: Comparative molecular similarity indices analysis; MLR: Multiple linear regression; PLS: Partial least-squares; Rlmo: Leave-two-out; Rloo: Leave-one-out.

Table 2. Summary of QSAR and 3D-QSAR models (continued).

Author	N MD*	N Training‡	N test§	Statistic parameters
Garro Martinez *et al.* (2009) [25]	5	46	5	R_{train} = 0.870, R_{loo} = 0.835, R_{test}= 0.925
Jackson *et al.* (2009) [26]	-	26	6	R_{train} = 0.895, R_{loo} = 0.558, R_{test} =0.9697 (CoMFA)
	-	26	6	R_{train} = 0.991, R_{loo} = 0.698, R_{test} =0.9056 (CoMSIA)
	-	26	6	R_{train} = 0.939, R_{loo} = 0.688 (CoMSIA only hydrophobic field)
Puratchikody *et al.* (2009) [30]	3	19	6	R_{train} = 0.77, R_{loo} = 0.64, R_{test} = 0.75
Jain *et al.* (2010) [27]	6	23	5	R_{train} = 0.675, R_{loo} = 0.553 (without outliers)
	6	23	5	R_{train} = 0.889, R_{loo} = 0.844 (one outlier)
	5	22	5	R_{train} = 0.889, R_{loo} = 0.854
	4	22	5	R_{train} = 0.833, R_{loo} = 0.794 (without outliers)
	4	22	5	R_{train} = 0.911, R_{loo} = 0.889 (one outlier)
	4	22	5	R_{train} = 0.953, R_{loo} = 0.941 (two outliers)
	3	20	5	R_{train} = 0.923, R_{loo} = 0.909 (without outliers)
	3	20	5	R_{train} = 0.954, R_{loo} = 0.945, R_{test} =0.997 (one outlier)
Paliwal *et al.* (2010) [28]	5	34	9	R_{train} = 0.87, R_{cv} = 0.42, R_{test} =0.61 (without outliers)
	5	34	9	R_{train} = 0.87, R_{cv} = 0.81, R_{test} =0.61 (two outliers)
Amnerkar *et al.* (2010) [29]	-	29	19	R_{train} = 0.922, R_{test} = 0.811 (Model 1)
	-	29	19	R_{train} = 0.912, R_{test} = 0.811 (Model 2)
	-	29	19	R_{train} = 0.901, R_{test} = 0.802 (Model 3)
	-	29	19	R_{train} = 0.905, R_{test} = 0.807 (Model 4)
Ganguly *et al.* (2010) [31]	-	34	10	R_{train} = 0.998, R_{loo} = 0.725, R_{test}=0.667 (Model 1)
	-	34	10	R_{train} = 0.997, R_{loo} = 0.682, R_{test} =0.135 (Model 2)
	-	34	10	R_{train} = 0.995, R_{loo} = 0.661, R_{test} =0.098 (Model 3)
Najafi *et al.* (2011) [33]	6	35	-	R_{train} = 0.900, R_{loo} = 0.853 (Model 1)
	6	25	10	R_{train} = 0.893, R_{loo} = 0.823, R_{test} = 0.898 (Model 2)
Garro Martinez *et al.* (2011) [34]	5	51	5	R_{train}= 0.864, R_{loo}= 0.847, R_{test}=0.947 (MLR model)
	1	46	-	R_{train} = 0.726, R_{loo} = 0.699 (CORrelation And Logic model)
Fegade *et al.* (2011) [35]	3	27	12	R_{train} = 0.769, R_{loo} = 0.506 (Model 1)
	3	27	12	R_{train} = 0.0731 (Model 2)
	3	25	12	R_{train} = 0.828, R_{loo} = 0.565, R_{test} =0.625 (Model 3 two outliers)
Jain *et al.* (2012) [36]	3	36	12	R_{train} = 0.72, R_{loo} = 0.67, R_{test} =0.66 (2D-QSAR)
	-	36	12	R_{loo} = 0.81, R_{test} =0.83 (3D-QSAR)
Mozaffari *et al.* (2012) [37]	2	12	-	R_{train} = 0.941, R_{loo} = 0.88
Garro Martinez *et al.* (2012) [38]	4	51	7	R_{train} = 0.606, R_{loo} = 0.511, R_{test} = 0.425 (0D descriptors)
	4	51	7	R_{train} = 0.794, R_{loo} = 0.747, R_{test} = 0.761 (1D descriptors)
	4	51	7	R_{train} = 0.855, R_{loo} = 0.823, R_{test} = 0.695 (2D descriptors)
	4	51	7	R_{train} = 0.860, R_{loo} = 0.833, R_{test} = 0.903 (3D descriptors)
	2	51	7	R_{train} = 0.401, R_{loo} = 0.405, R_{test} = 0.318 (quantum descriptors)
	4	51	7	R_{train} = 0.888, R_{loo} = 0.867, R_{test} = 0.814 (All descriptors)
Weaver *et al.* (2013) [39]	1	15	-	R_{train} = 0.95
Chhajed *et al.* (2013) [40]	3	30	-	R_{train} = 0.918, R_{loo} = 0.766
	3	29	-	R_{train} = 0.931, R_{loo} = 0.806

*Number of molecular descriptors.

‡Number of compounds in the training set.

§Number of compounds in the test set.

CoMFA: Comparative molecular field analysis; CoMSIA: Comparative molecular similarity indices analysis; MLR: Multiple linear regression; PLS: Partial least-squares; Rlmo: Leave-two-out; Rloo: Leave-one-out.

12 compounds in the test set, selected by PCA. The best MLR equation (Eq.2) is:

$$\mathrm{pED50} = 5.811 - 0.125HOMO + 0.371Hbd - 0.124AlogP + 0.661I\_ssCH2 - 0.762I\_dsN + 0.483Zagrep \quad (2)$$

The regression coefficients for the training set and the cross-validation of the model are R_{train} = 0.757 and R_{cv} = 0.704, respectively. The molecular descriptors selected by the model are connected to the pharmacodynamics (I_ssCH2, I_dsN and highest occupied molecular orbital [HOMO]) and pharmacokinetic moment (Zagreb, H-bond donors, and AlogP) of the compounds.

Hemmateenejad *et al.* [15], in 2004, showed a QSAR analysis on a data set of 20 N-phenyl-N-(4-pyridinyl)-urea derivatives with anticonvulsant activity. The activity (log 1/C) data were taken from the literature [12]. The chemical structure of the molecules was drawn by the Hyperchem software [56]. The AM1 semiempirical calculation was used to optimize the 3D geometry of the molecules. Different topological and

constitutional indices were calculated for each molecule by Dragon software [57]. In addition, different quantum chemical descriptors including heat of formation, dipole moment, HOMO, and lowest unoccupied molecular orbital energy (LUMO) energies were also analyzed. An MLR-QSAR analysis using different types of molecular descriptors was performed. The regression coefficient for the best QSAR model is 0.975 (all descriptors). Then, PLS regression was used to model the structure–activity relationships (R = 0.995). The results confirmed the superiority of the results obtained by PLS relative to MLR.

In 2005, Buchwald *et al*. [16] developed a statistically more rigorous and chemically more meaningful QSAR model from the analysis of Macchiarulo *et al*. [14]. Buchwald uses MLR-based approach on the same total set of compounds (n = 61) employing new molecular descriptors for QSAR. Molecular structures were built in ChemDraw (ChemOffice Ultra 7.0; CambridgeSoft, Cambridge, MA) and optimized using semiempirical quantum chemical methods (MOPAC/AM1 with default settings) in Chem3D. The author shows a six-descriptor QSAR model using molecular descriptors that are of medicinal chemical relevance. The equation (Eq.3) of the model is:

(3)

$$\begin{aligned} ln(1/ED50) = {} & -4.358 + 0.689I\_NH \;\&\; arNH2 \\ & - 0.921i\_noOMeOPHTZ \\ & + 0.430I\_NH \;\&\; noCo - 0.821I\_pNO2 \\ & - 0.615I\_mono7,8 - 0 + 0.692logPo/w \\ & - 0.159logP2o = w \end{aligned}$$

These descriptors give about the same correlation as those used by Macchiarulo on the training set (R_{train} = 0.786 vs 0.757, n = 49); but they also perform much better on the test set (R_{test} = 0.73 vs 0.05, n = 12).

In that same year, a set of 35 benzylacetamide derivatives was employed by Jin *et al*. [17] to develop a QSAR model of the $logED_{50}$ ($-pED_{50}$) as a function of the molecular descriptors. Using the method of PLS regression in conjunction with leave-one-out cross-validation (loo), the influence of 31 topological, electronic, physicochemical, and structural properties on anticonvulsant activity was investigated. Topological indices were calculated using the TOPOLOGY program [58]. Molecular volumes based on van der Waals' volume fragmental constants were calculated using the software package QUANTA, version 4.1 [59,60]. Molecular mechanics calculations were performed using the CHARMm force field [61,62]. The equation (Eq.4) of the model with three outliers removed is:

(4)

$$\begin{aligned} -pED50 = {} & 4.60 - 0.434Wmean + 0.738rlac - 7.36qCC \\ & + 0.520q\alpha totlal + 0.285Hd\alpha + 0.163ClogP^2 \\ & - 0.272Ha\alpha \end{aligned}$$

In this equation, the descriptors are the Wiener index on distance code (Wmean), the mean information index on atomic composition (rIac), the partial charge at the C-terminal carbonyl carbon (qCC), the sum of partial charges in the α substituent ($q\alpha$total), the number of hydrogen bond donors and acceptors in the α substituent (Hdα and Haα), and the calculated value of the squared *n*-octanol/water partition coefficient. The regression analysis results in R_{train} = 0.77 and R_{cv} = 0.63.

In 2006, a novel automated lazy learning QSAR (ALL-QSAR) modeling approach was performed by Zhang *et al*. [18]. To demonstrate that ALL-QSAR can produce predictive models, they applied this method to three experimental data sets studied with alternative QSAR approaches earlier: 48 anticonvulsant agents [63]. Molecular topological descriptors were calculated with the MolConnZ program [64]. ALL-QSAR models for anticonvulsants used several training and test sets with different number of compounds. The best model used 39 compounds in the training set and 9 in the test set and presented a regression coefficient for test set of 0.90.

Gunakkunru *et al*. [21] in 2007 performed QSAR studies by stepwise MRL using steric, electronic descriptors on 24 Riluzole series, a blocker of excitatory amino acid (glutamic acid)-mediated transmission, 2-benzothiazol-amines, and 3-substituted 2-imino benzothiazolines. The results of the best-found model are R_{train} = 0.97, R_{loo} = 0.977. Descriptors used are polarizability, density, molar refractivity, molar volume, average mass, and parachor.

In 2008, Bhutoria *et al*. [22] carried out a QSAR studies on a series of 45 molecules, derivatives of butyrolactones, thiobutyrolactones, cyclopentanones, cyclohexanones, pyrrolidinones, and piperidinones with tert-butyl-bicyclophosphorothionate displacement property (IC_{50}) and anticonvulsant activity (ED_{50}) [65-70]. The models for all the compounds were generated using 3D sketcher module of Cerius2 [48]. Statistical techniques like PCA, PLS, MLR, and GA were applied to identify the structural and physicochemical requirements for anticonvulsant activity. The generated equations were statistically validated using loo cross-validation technique, randomization and prediction of activity of compounds, not used for the development of QSAR models. The best equation model has a correlation coefficient of R_{train} = 0.812, R_{loo} = 0.767, and R_{test} = 0.917 (with one outlier compound).

In the same year, Hashemianzadeh *et al*. [23] performed a QSAR study of antiepileptic drugs by mean of the quantum chemical descriptors, calculated at the level of the Density functional theory theory using 6-31G(d) basis set. A data set containing 26 valproic acid derivatives with known activity was used [71,72]. A multiparametric equation containing three descriptors with good statistical qualities was obtained by MLR and GA-MLR. Gas-phase full-geometry optimization for the investigated molecules was carried out with the Gaussian 98 [73]. The structures were optimized with Density functional theory method at the hybrid functional B3LYP (BeckeKs three-parameter [74] functional employing the Lee, Yang, and Parr correlation functional [75]). MLR and correlation analyses were carried out by the statistics software SPSS

13.0 version and Matlab 6.5 program [76]. The authors developed four models using diverse types of molecular descriptors. The best model (Eq.5) is the following:

$$pED50 = -262.746 + 0.017\,Polarizability + 13.656EPC_4 - 31.706\,EPC_5 \quad (5)$$

In the model the descriptors are as follows: P is the polarizability, EPC_4 the electrostatic potential on carbon 4, and EPC_5 the electrostatic potential on carbon 5. The model has high statistical quality, R_{train} = 0.968, R_{test} = 0.937.

In 2008, Sharma *et al.* [24] used a set of 35 triazolo [1,5-a] quinoxaline for the *(R,S)*-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic acid (AMPA) receptor [77-81] for building comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) models. The 3D-QSAR was performed using the SYBYL (Tripos Inc., USA) version 6.9 [82]. In CoMSIA calculations, physicochemical properties as steric (S), electrostatic (E), hydrophobic (H), hydrogen bond donor (D), and hydrogen bond acceptor (A) were determined for all molecules. The PLS analysis results show that the cross-validated R_{loo} is 0.766 for the CoMFA model and 0.758 for the CoMSIA model. The external validated run gives the coefficient of determination R_{test} values of 0.944 and 0.919 for CoMFA and CoMSIA, respectively.

Our research group, in 2009 [25], employed a set of 51 compounds, including classic antiepileptics and second-generation anticonvulsant drugs and compounds of the enaminone type, to develop a QSAR model, which allow the proposal of novel ringed enaminone derivatives as possible antiepileptic agents. The structures of all the compounds examined were optimized with the semiempirical method PM3 (Parametric Method-3) included in the HyperChem 6.03 software [56]. The Dragon software [57] was used to calculate 1307 theoretical molecular descriptors and the statistic calculation was performed with Matlab 7.0 software [76]. The model QSAR equation (Eq.6) is as follows:

$$-pED50 = -3.310 + 3.712BELe6 - 2.338BELp8 + 0.128RDF025v + 0.667Mor15e + 33.683R4e \quad (6)$$

The descriptors involved in this QSAR are 2D: BCUT descriptors, BELe6: lowest eigenvalue No. 6 of Burden matrix/weighted by atomic Sanderson electronegativities and BELp8: lowest eigenvalue No. 8 of Burden matrix/weighted by atomic polarizativities; 3D: RDF descriptors, RDF025v: Radial Distribution Function -2.5 weighted by atomic van der Waals volumes; 3D-MoRSE descriptors: Mor15e: 3D-MoRSE-signal 15/weighted by atomic Sanderson electronegativities; GATEWAY: R4e: R maximal autocorrelation of lag 4/weighted by atomic Sanderson electronegativities.

Other paper published in 2009 by Puratchikody [30] showed a QSAR studies on 4,5-diphenyl-1H-imidazole analogs with antiepileptic and locomotor activities. Cluster analysis and PCA were performed using statistical software package, Kyplot [83]. The structure of the various molecules was drawn and their minimum energy conformation was determined by using the consistent valence force field, one of the force fields available in Cerius2 software [48]. A total of 229 descriptors were evaluated for all the molecules. The selection of the best set of descriptors was performed by the GA technique. Data are divided into training and test sets. The three-parameter model for the antiepileptic activity fits the data well and has a good predictive capability (for training set: R_{train} = 0.77, for test set: R_{test} = 0.75). Total polar and solvent accessible surface areas of the molecule are the descriptors in the model.

Jain *et al.* studied, in 2010 [27], 28 potent $GABA_A$ receptor ligands; derivatives of benzotriazines, using a combination of various tested physicochemical, steric, electronic, and thermodynamic descriptors to determine the quantitative correlation between binding affinity and structural features. Data were analyzed with the GraphPad Prism software. The developed and validated final model showed a good correlative and predictive ability expressed by a squared correlation coefficient (R_{train}) of 0.954. The equation (Eq.7) of model is as follows:

$$pCL_i = -2.160 - 0.271CDE + 0.219\,DDE + 0.429\,PC \quad (7)$$

The equation indicated that the binding affinity, expressed as inhibition constant (K_i), is strongly dependent upon the thermodynamic properties (charge-dipole energy, dipole-dipole energy, and llipophilicity). For testing the validity of the predictive power of MLR models, the leave-one-out technique was used (R_{loo} = 0.945).

Also, in 2010, Paliwal *et al.* [28] performed a QSAR studies on imidazo(1,5-α) quinoxalines amides, carbamates, and ureas. The QSAR models have been developed by using MLR in order to identify descriptors. Leave-one-out and external validation were used to validate the developed model. All the computational studies were performed using TSAR 3.3 software. The best predictive QSAR model derived showed R_{loo} of 0.81 and predictive R_{test} of 0.61. The model reveals that multidimensional steric [verloop B_5 (subs 4)], hydrophobic [Log P (whole molecule)], electro topological [Ipso atom E state index (subs 2) and sum of E state indices (subs 4)], and hydrogen bond donor [ADME H bond donor (subs 4)] descriptors have significant impact on GABA modulator activity of the compounds.

That year Amnerkar *et al.* [29] synthesized a series of 6-substituted-[3-substituted-prop-2-eneamido]benzothiazole and 6-substituted-2-[(1-acetyl-5-substituted)-2-pyrazolin-3-yl]aminobenzothiazole, which were evaluated as potential anticonvulsant agents by mean of a 3D-QSAR analysis. The statistically significant 3D-QSAR models were generated using 29 molecules as the training set and were validated using test set of 19 compounds employing PHASE [84,85] program. The best model exhibited correlation coefficient (R_{train}) of 0.922 and test set prediction (R_{test}) of 0.814.

Najafi *et al.* in 2011 [33] developed a QSAR for predicting the anticonvulsant activity of α-substituted acetamido-N-benzylacetamide derivatives [17]. Semiempirical quantum chemical calculation method was used to find the optimum 3D geometry of the studied molecules. HyperChem software [56] was used to draw the chemical structure of the molecules. Two types of molecular descriptors calculated by Dragon [57] computer software, including the 2D autocorrelation and GETAWAY descriptors, were used to derive a quantitative relation between anticonvulsant activity and structural properties. The relevant molecular descriptors were selected by GA-MLR approach. The equation (Eq.8) of model is:

(8)

$$-pED50 = 3.0590 + 2.4863\,MATS6e + 12.4037\,H7v + 2.5769\,MATS5p - 3.6462\,ATS6e + 0.0014\,H5m$$

The values of the correlation coefficient of model are R_{train} = 0.893 and R_{test} = 0.898. Moran autocorrelation lag 6 weighted by Sanderson electronegativities (MATS6e) is the most important variable for predicting the anticonvulsant activity.

In 2011, our group [34] performed a QSAR study in order to apply for the prediction of unknown open-chain compounds. The calibration of the model was established with 51 compounds [3,86-89]. The structures of all the examined compounds are optimized with the semiempirical method PM3 (parametric method-3) included in the HyperChem 6.03 software [56]. By means of the software Dragon [57], 1307 molecular descriptors were calculated. The developed QSARs were obtained via two different modeling approaches: i) the search of molecular descriptors via multivariable linear regressions; and ii) the calculation of flexible descriptors with the CORAL (CORrelation And Logic) program. The models allowed the prediction of antiepileptic activities of 16 OCEs.

In 2011, QSAR studies were performed by Fegade *et al.* [35] on aryloxypropanolamine analogs having anticonvulsant activity using combination of various electronic, steric, thermodynamic, and topological descriptors. Training set (27 compounds) and the test set (12 compounds) were selected by considering the fact that the test set compounds represent structural diversity and a range of biological activities similar to that of training set. The QSAR computations were carried out using ChemOffice software [90]. All the molecules were drawn and converted to 3D structures in ChemDraw module. Energy minimization was performed using the MMFF94 force field [91], followed by AM-1 (Austin Model-1) Hamiltonian method, and closed-shell restricted wave function available in MOPAC. Multiple regression analysis was performed using *VALSTAT* program [92,93]. The equation (Eq.9) of model was:

(9)

$$pED50 = 3.247 + 0.064\,LUMO - 0.035\,VDE + 0.002\,CSEV$$

Model-3 shows that LUMO energy and Connolly Solvent Excluded Volume contributes positively while van der Waals energy (VDWE) contributes negatively to anticonvulsant activity. The statistic parameters of model were R_{train} = 0.828, R_{loo} = 0563, and R_{test} = 0.625.

In 2012, Jain *et al.* [36] developed 2D and 3D-QSAR models using a series of prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole as anticonvulsants [29]. All molecular modeling studies (2D and 3D) were performed using the molecular design suite (MDS) [94]. A data set of 48 compounds was used for QSAR study [29]. All QSAR studies were performed using a randomly selected training set of 36 molecules for generating 2D and 3D-QSAR models. Remaining 12 molecules were used as test set of generated QSAR models. Two hundred and thirty-nine physicochemical descriptors were calculated by QSARPlus module within VLife MDS. The 2D-QSAR model was generated by using MLR method by using V-Life MDS [94]. 3D-QSAR studies were carried out by kNN method employing Forward Stepwise Variable Selection as variable selection method. The best regression 2D-QSAR equation (Eq.10) obtained is:

(10)

$$pED50 = 0.002 - 0.062\,Roratable\ Bond\ Count - 0.004\,Mo.Wt. + 0.150\,Polarizability\ AHC$$

The descriptor polarizability atomic hybrid component plays a pivotal role in determining activity. 2D-QSAR showed a regression coefficient R_{train} = 0.72 and R_{test} = 0.66 and 3D-QSAR R_{test} = 0.83.

Also, in 2012, Mozaffari *et al.* [37] performed a QSAR study using MLR. The structures of a series of aryl semicarbazones containing a methylene bridge in their skeleton were optimized with Hyperchem using AM1 semiempirical method [56]. The resulted ligands were subjected to Dragon Software [57] for calculation of descriptors. The final MLR equation (Eq.11) is as follows:

(11)

$$p(activity) = -1.082 + 0.06T(N..Br) - 1.493\,MATS7e$$

The regression coefficient was R_{trian} = 0.941. To evaluate the predictive activity of the model, loo cross-validation internal test was used, R_{loo} = 0.88. The descriptor T(N.Br) corresponds to sum of topological distances between N and Br and is among topological descriptors. MATS7e corresponds to Moran autocorrelation -lag7/weighted by atomic Sanderson's electronegativites and is among 2D autocorrelation descriptors.

In 2012, a QSAR analysis was applied by us [38] to a library of 51 benzylacetamide derivatives with anticonvulsant activity [17]. The molecular structures of 51 compounds were optimized with the semiempirical method PM6 (parametric method-6) included in the MOPAC2009 software [95]. The optimized structures of all the examined compounds were represented by 1497 Dragon-type descriptors [57]. Using MLR, the influence of constitutional, topological, electronic, and physicochemical and quantum molecular descriptors on the activity was investigated. The validations of models was performed through the loo cross-validation technique in conjunction with external

validation. Six QSAR models were developed using diverse types of molecular descriptors. The combination of 2D and 3D descriptors produces a model of high predictive quality (R_{train} = 0.888; R_{test} = 0.814; R_{loo} = 0.867).

Weaver *et al.* in 2013 [39] used a simple electrotopological descriptor ETz as the only descriptor and developed a QSAR model to predict the anticonvulsant activity of 15 hydantoin analogs (R_{train} = 0.95). Linear regression (Eq.12) on the data of activity levels and ETz indices gives the following relationship:

$$Anticonvulsant\ Activity = -2.201 + 0.0179(ETz) \quad (12)$$

In 2013, Chhajed *et al.* performed a QSAR study on a series of thiadiazole and sulphonamide derivatives. Molecular structure was generated and optimized with CS ChemDraw Ultra 6.0 and Chem3D Ultra, respectively [40]. The relationship between response variable (as a dependent variable) and various physicochemical as well as structural descriptors (as independent variables) was established by stepwise linear multiple regression analysis using SYSTAT 10.2 and VALSTAT [92,93].

The model was developed with 29 compounds. The predicted activity shows linear relationship with activity (R_{train} = 0.931). Henry's law constant, LUMO, and VDWE have better correlation with biological activity and have low value of standard deviation. The equation was validated by leave-one-out cross-validation method (R_{loo} = 0.806) and bootstrapping method as an internal validation, which gives statistically significant values.

2.1.1 3D-QSAR studies

In 2006, Bhutoria *et al.* [19] developed a 3D-QSAR model to generate a hypothetical receptor surface model for an allosteric receptor site, 'lactone site', on the $GABA_A$ receptor. For this propose, they used a set of 19 N-substituted 4-amino-3,3-dialkyl-2 (3H)-furanone $GABA_A$ receptor modulators [96]. These molecules were divided into two sets, first, training set consisting of 14 molecules and a test set of 5 molecules. The alignment was done using the Align Module in Cerius2 [48]. The best model yielded a conventional correlation coefficient (R_{train}) of 0.998 and cross-validated R_{cv} of 0.639 and 0.943 with leave-one-out (R_{loo}) and leave-two-out (R_{lmo}) methods, respectively. In addition, external data validation with the test set was carried out, which showed very good predictive ability R_{test} = 0.960.

Gavernet *et al.* [20], in 2007, applied a 3D-QSAR method, using the CoMFA, to design new anticonvulsant sulfamides. The training set comprised 27 traditional and new-generation anticonvulsants [46,97]. The molecular modeling and comparative molecular field evaluations were performed using SYBYL version 6.6 running on a Silicon Graphics Octane workstation [97]. The regression analysis has been performed by means of PLS estimation. The regression coefficient (R_{train}) and the cross-validated (R_{loo}) of this QSAR model based on atom fit alignment are 0.960 and 0.748, respectively.

In 2009, a 3D-QSAR study CoMFA and CoMSIA on 26 structurally diverse subcutaneous pentylenetetrazol active enaminone analogs was carried out by Jackson *et al.* [26]. The molecular modeling and comparative molecular field evaluations were performed using SYBYL version 7.2 [97]. Twenty-six compounds form the training set. The 3D-QSAR models demonstrated a reliable ability to predict the CLogP of the active anticonvulsant enaminones, resulting in R_{loo} of 0.558 for CoMFA, and of 0.698 for CoMSIA.

A 3D-QSAR was performed by Ganguly in 2010 [31] on 44 structurally and functionally diverse series of 1-(Naphthylalkylimidazoles) as antiepileptic agents. The studies were carried out using the CoMSIA method by means of SYBYL 7.1n [97] molecular modeling software. A training set containing 34 molecules served to establish the models. The optimum CoMSIA model obtained for the training set was statistically significant, with cross-validated coefficient (R_{loo}) of 0.725 and conventional coefficient (R_{train}) of 0.998. The predictive capacities of the model were successfully validated by using a test set of 10 molecules that were not included in the training set. CoMSIA model (Model 1) obtained from the hydrophobic and Hbond acceptor field was found to have the best predictivity, with a predictive correlation coefficient (R_{test}) of 0.67. This model has a combination hydrophobic and H-bond acceptor fields (HA).

Thareja *et al.* in 2010 [32] carried out a 3D-QSAR study on a series of 1,3,4-thiadiazole derivatives reported as anticonvulsant. This study was performed employing self-organizing molecular field analysis (SOMFA) techniques [98] to investigate the structural requirements for the design of novel anticonvulsant. The training set comprised twenty two 1, 3, 4-thiadiazole derivatives that exhibit a potent activity in MMS test while predictive power was evaluated using a test set of 7 molecules. Physicochemical determinants of binding, such as steric and electrostatic properties, were mapped onto the molecular structures of 1, 3, 4-thiadiazole in order to interpret graphically the SOMFA results in terms of master grids showing various field contributions.

3. Conclusion

Here, we reviewed 28 articles, published in 2003 – 2013, in which the QSAR or 3D-QSAR approach is applied to compounds with experimentally assayed anticonvulsant activity. As can be seen in **Figure 1**, the interest in this topic has increased since 2008, according to the large percentage of number of papers published between the years 2008 and 2012. In these papers the PLS, MLRs, and GA are the statistic techniques mostly used for the variable selection. Analyzing the number of molecular descriptors used within the different QSAR models presented herein, we consider that several models do not meet the classical semiempirical 'rule of thumb' (at least six or seven compounds should be present by descriptor). The validation of QSAR models was performed through different approaches: i) the loo; ii) the

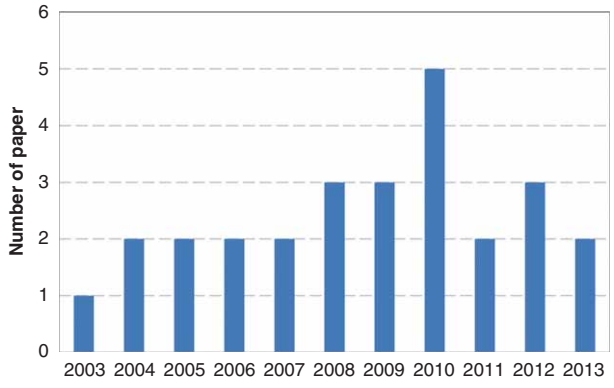

Figure 1. Number of papers published between 2003 and 2013.

leave-more-out (lmo) cross-validation procedures; and iii) a rigorous and more realistic validation procedure that involves the use of a set of molecules (test set) that do not form part of the training set. The validation statistical parameters are summarized in the **Table 2**.

Moreover, several computational programs were used to perform the geometric optimization, molecular descriptor calculations, and to develop the QSAR models. The 38% of the revised papers employed the Hyperchem and Dragon software packages to optimize the geometry and calculate the molecular descriptors. The statistic calculations were performed mostly with Matlab program (44%) **Figure 2**. The SYBYL software was mostly used to carry out the 3D-QSAR studies. We found that the QSAR models whose molecular descriptors were calculated with Dragon software present a high predictive power, probably because of the large number of molecular descriptors calculated by Dragon [57].

4. Expert opinion

The QSAR and 3D-QSAR models analyzed in this review present an excellent predictive power and could be used for the rational design of new anticonvulsant agents. However, it is important to note that the majority of the models have a restricted field of application. Despite the enormous range of compounds (derivatives of urea, benzylacetamide, furanone, enaminones, sulfamides, valproic acid, imidazole, quinoxaline, benzothiazoles, and cyclopentanones, among others) used in these studies, there is not a universal QSAR model that includes all or many of these families of compounds. In addition, in most cases, the number of compounds used to establish the structure–activity relationships is small **Table 2**. The largest number of compounds in QSAR and 3D-QSAR studies were compiled by Sutherland [13] (63 compounds) and Sharma [24] (35 compounds), respectively. It is well known that a large number of data provides much more information to the QSAR models and allows a more realistic validation.

Moreover, as mentioned above, many models do not consider the 'rule of thumb.' To the best of our knowledge, we think that a model that does not satisfy this rule results in a complex relationship with redundant information and overestimation of the statistical parameters. Thus, it can be emphasized that each model is restricted to certain type of compounds. But, it is also true that performing a large analysis is difficult, either by the scarcity and collection of experimental data or computational cost that this would require.

Even so, the QSAR and 3D-QSAR studies continue attracting more researchers and providing valuable information for the development of new potentially active compounds, not only with anticonvulsant activity but also with other biological activities. The current interest of QSAR applied to compounds with anticonvulsant activity can be noticed by the number of citations that these articles have received **Table 1**. Almost a 50% of these citations were performed between the years 2011 and 2013 and 5% belongs to the last 2 years, showing the increased and recent interest in this topic.

In addition, the increases in size and performance of computers, the development of specific software, and the novel molecular descriptors have certainly helped the rise of new QSAR models. For instance, the last version of Dragon software (version 6.0) calculates 4885 molecular descriptors and the free version e-Dragon provides > 1600 molecular descriptors. The development of molecular descriptors is a field that has been studied extensively and is still expanding. On this field, the discovery of new and more versatile descriptors provides much more structural and electronic information, which would facilitate finding the longed relationship between the molecular structure and the biological activity.

The extensive development of descriptors and the way by which descriptor values are derived have allowed the evolution of the QSAR methods. Nowadays, the QSAR can be classified in 1D-QSAR that correlates activity with global molecular properties like pKa, log P, and so on; 2D-QSAR correlating activity with structural patterns like connectivity indices, 2D pharmacophores, and so on. without taking into account the 3D representation of these properties; 3D-QSAR correlating activity with non-covalent interaction fields surrounding the molecules; 4D-QSAR additionally including ensemble of ligand configurations in 3D-QSAR; 5D-QSAR explicitly representing different induced-fit models in 4D-QSAR; and 6D-QSAR further incorporating different solvation models in 5D-QSAR. According to this evolution, it is expected that the use of QSAR methods remains an important tool in the research and development of new and more potent anticonvulsant.

We expect that current review may serve as a useful guide for new QSAR and 3D-QSAR projects involving compounds with anticonvulsive activity or any other biological activities.

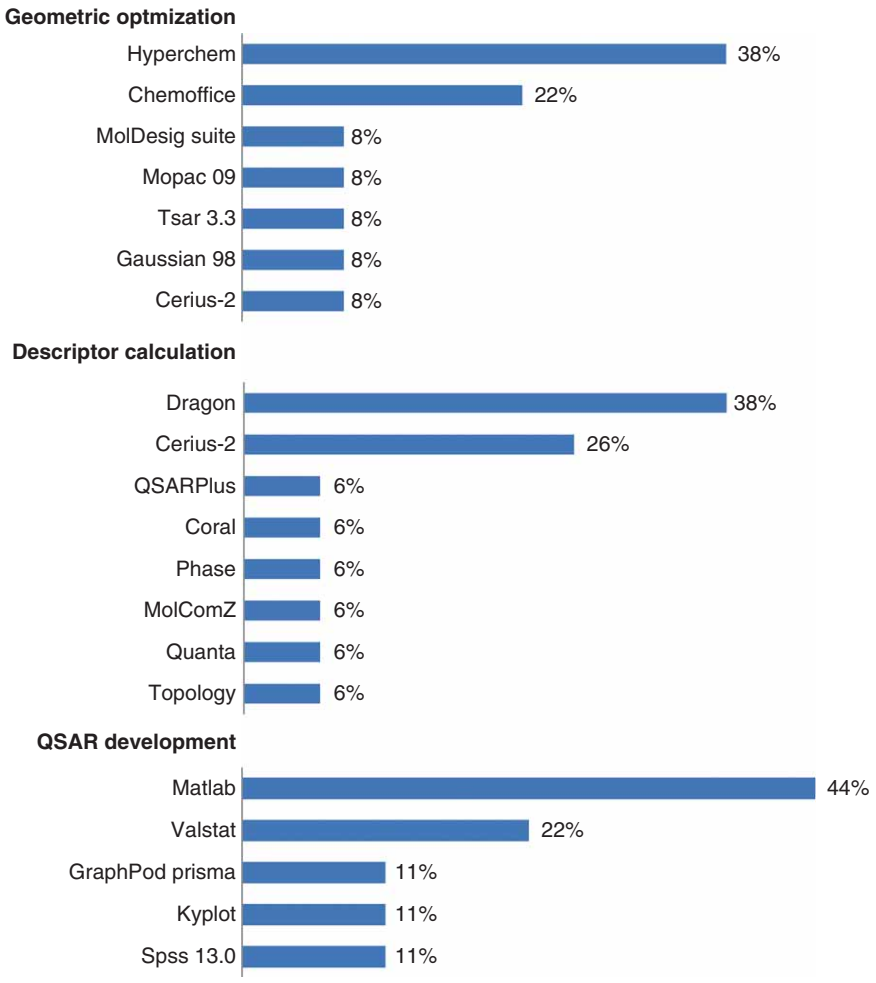

Figure 2. Computational software used to perform the geometrical optimizations, molecular descriptor calculations and development of QSAR models.

QSAR: Quantitative structure–activity relationship.

Declaration of interest

This work was supported by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) project PIP11220100100151 and Universidad Nacional de San Luis (UNSL). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Coatsworth JJ. Studies on the clinical efficacy of marketed an- tiepileptic drugs. NINDS monograph no. 12, HEW publication no. (NIH) 73-51. US Government Printing Office 1971
2. Gram L. Epilepsy care: image of the future. Epilepsia 1995;36:22-4
3. Edafiogho IO, Ananthalakshmi KV, Kombian SB. Anticonvulsant evaluation and mechanism of action of benzylamino enaminones. Bioorg Med Chem 2006;14:5266-72
4. Eddington ND, Cox DS, Khurana M, et al. Síntesis y actividad anticonvulsiva de enaminonas. Parte 7. Síntesis y evaluación anticonvulsivo de acetato de 4-[(fenil sustituido) amino]-6-metil-2-oxociclohex -3-eno-1-carboxilatos y sus derivados 5-metilciclohex-2-enona correspondientes. Eur J Med Chem 2003;38:49-64
5. Anderson AJ, Nicholson JM, Bakare O, et al. Enaminones 9. Further studies on the anticonvulsant activity and potential type IV phosphodiesterase inhibitory activity of substituted vinylic benzamides. Bioorg Med Chem 2006;14:997-1006
6. Shawali AS. Synthesis, reactions and antitumour screening of new enaminones. J Chem Res 2010;11:630-4
7. Béguin C, LeTiran A, Stables JP, et al. N-Substituted amino acid N′-benzylamides: synthesis, anticonvulsant, and metabolic activities. Bioorg Med Chem 2004;12:3079-96
8. Morieux P, Stables JP, Kohn H. Synthesis and anticonvulsant activities of N-benzyl (2R)-2-acetamido-3-oxysubstituted propionamide derivatives. Bioorg Med Chem 2008;16:8968-75
9. Salomé C, Salomé-Grosjean E, Park KD, et al. Synthesis and Anticonvulsant Activities of (R)-N-(4′-Substituted)benzyl 2-Acetamido-3-methoxypropionamides. J Med Chem 2010;53:1288-305
10. Ulloora S, Adhikari AV, Shabaraya R. Synthesis and antiepileptic studies of new imidazo[1,2-a]pyridine derivatives. Chin Chem Lett 2013;24:853-6
11. Malik S, Bahare RS, Khan SA. Design, synthesis and anticonvulsant evaluation of N-(benzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide derivatives: a hybrid pharmacophore approach. Eur J Med Chem 2013;67:1-13
12. Hadjipavlou-Litina D. Review, reevaluation, and new results in quantitative structure–activity studies of anticonvulsants. Med Res Rev 1998;18:91-119

• **The last review about quantitative structure-activity relationship (QSAR) studies on compounds with anticonvulsant activity.**

13. Sutherland JJ, Weaver DF. Development of quantitative structure-activity relationships and classification models for anticonvulsant activity of hydantoin analogues. J Chem Inf Comput Sci 2003;43:1028-36
14. Macchiarulo A, De Luca L, Costantino G, et al. A QSAR study of anticonvulsant negative allosteric modulators of the AMPA receptor. J Med Chem 2004;47:1860-3
15. Hemmateenejad B, Miri R, Tabarzad M, et al. Molecular modeling and QSAR analysis of the anticonvulsant activity of some N-phenyl-N0-(4-pyridinyl)-urea derivatives. J Mol Struc (Theochem) 2004;684:43-9
16. Buchwald P, Einstein B, Bodor N. QSAR study of 2,3-benzodiazepin-4(thi) one- and 1,2-phthalazine-related negative allosteric modulators of the AMPA receptor: a structural descriptors-based reassessment. QSAR Comb Sci 2005;24:325-31
17. Jin AY, Kohn H, Béguin C, et al. A quantitative structure-activity relationship study for α-substituted acetamido-N-benzylacetamide derivatives - A novel anticonvulsant drug class. Can J Chem 2005;83:37-45
18. Zhang S, Golbraikh A, Oloff S, et al. A novel Automated Lazy Learning QSAR (ALL-QSAR) approach: method development, applications, and virtual screening of chemical databases using validated ALL-QSAR models. J Chem Inf Model 2006;46:1984-95

•• **The most cited paper. The authors use different test sets to validate the models.**

19. Bhutoria S, Mukherjee PK, Chhabra S, et al. A 3D-QSAR of N-substituted 4-amino3-3-dialkyl-2(3H)-furanone GABA A receptor modulators based on receptor surface analysis. Lett Drug Des Discov 2006;3:1-8

• **The first 3D-QSAR analysis applied to anticonvulsant drug.**

20. Gavernet L, Dominguez Cabrera MJ, Bruno-Blanch LE, et al. 3D-QSAR design of novel antiepileptic sulfamides. Bioorg Med Chem 2007;15:1556-67
21. Gunakkunru A, Verma SM. Quantitative structure activity relationship of riluzole series as anticonvulsants. Asian J Chem 2007;19:2843-9
22. Bhutoria S, Ghoshal N. A novel approach for the identification of selective anticonvulsants based on differential molecular properties for TBPS displacement and anticonvulsant activity: an integrated QSAR modeling. QSAR Comb Sci 2008;27:876-89
23. Hashemianzadeh M, Safarpour MA, Gholamjani-Moghaddam K, et al. DFT-based QSAR study of valproic acid and its derivatives. QSAR Comb Sci 2008;27:469-74
24. Sharma RN, Thakar H, Vasu KK, et al. 3D-QSAR studies for the binding affinity toward (R,S)-2-amino-3-(3-hydroxy- 5-methylisoxazol-4-yl) - propionic acid receptor. Acta Pharm 2008;58:335-45
25. Garro Martinez JC, Duchowicz PR, Estrada MR, et al. Anticonvulsant activity of ringed enaminones: a QSAR study. QSAR Comb Sci 2009;28:1376-85
26. Jackson PL, Scott KR, Southerland WM, et al. Enaminones 8: coMFA and CoMSIA studies on some anticonvulsant enaminones. Bioorg Med Chem 2009;17:133-40
27. Jain P, Sharma PK, Rajak H, et al. Design, synthesis and biological evaluation of some novel benzimidazole derivatives for their potential anticonvulsant activity. Arch Pharm Res 2010;33:971-80
28. Paliwal SK, Singh S, Kumari S, et al. QSAR studies of imidazo (1,5-a) quinoxalines amides, carbamates and ureas as potent GABA modulators. Indian J Chem 2010;49:554-60
29. Amnerkar ND, Bhusari KP. Synthesis, anticonvulsant activity and 3D-QSAR study of some prop-2-eneamido and 1-acetyl-pyrazolin derivatives of

aminobenzothiazole. Eur J Med Chem 2010;245:149-59

30. Puratchikody A, Doble M. QSAR studies on antiepileptic and locomotor in vivo activities of 4,5-diphenyl-1H-imidazoles. Chem Biol Drug Des 2009;74:173-82
31. Ganguly S, Mishra R. Comparative molecular similarity indices analysis of 1-(Naphthylalky1)-1H- imidazole analogs with antiepileptic activity. J Young Pharm 2010;2:388-93
32. Thareja S, Aggarwal S, Verma A, et al. 3D QSAR studies on 1, 3, 4-thiadiazole derivatives: an approach to design novel anticonvulsants. Med Chem 2010;6:233-8
33. Najafi A, Ardakani SS, Marjani M. Quantitative structure-activity relationship analysis of the anticonvulsant activity of some benzylacetamides based on genetic algorithm-based multiple linear regression. Trop J Pharm Res 2011;10:483-90
34. Garro Martinez JC, Duchowicz PR, Estrada MR, et al. QSAR study and molecular design of open-chain enaminones as anticonvulsant agents. Int J Mol Sci 2011;12:9354-68
35. Fegade JD, Chaudhari RY, Patil VR. QSAR analysis of some aryloxypropanolamine analogues as anticonvulsants. Der Pharma Chemica 2011;3:96-109
36. Jain S, Bhadoriya KS, Bari SB, et al. Discovery of potent anticonvulsant ligands as dual NMDA and AMPA receptors antagonists by molecular modelling studies. Med Chem Res 2012;21:3465-84
37. Mozaffari S, Ghasemi S, Baher H, et al. Synthesis and evaluation of some novel methylene-bridged aryl semicarbazones as potential anticonvulsant agents. Med Chem Res 2012;21:3797-808
38. Garro Martinez JC, Duchowicz PR, Estrada MR, et al. A multivariate QSAR study on the anticonvulsant activity of acetamido-N-benzylacetamide derivatives. Influence of different molecular descriptors. MATCH Commun Math Comput Chem 2012;67:745-58

•• **The paper presents interesting results showing simple and predictive models.**

39. Weaver IN, Weaver DF. A simple electrotopological index for quantitative structure-activity relationship correlation of physical properties with biomolecular activities. J Math Chem 2013;51:811-16
40. Chhajed MR, Shrivastava AK, Taile VS. Design and syntheses of some new 5-[Benzenesulphonamido]-1,3,4-thiadiazol-2-sulphonamide as Potent antiepileptic agent. Macroheterocycles 2013;6:199-209
41. Shen M, LeTiran A, Xiao Y, et al. Quantitative structure-activity relationship analysis of functionalized amino acid anticonvulsant agents using k nearest neighbor and simulated annealing PLS methods. J Med Chem 2002;45:2811-23
42. Bello-Ramírez AM, Carreón-Garabito BY, Nava-Ocampo AA. Do structural properties explain the anticonvulsant activity of valproate metabolites? A QSAR analysis. Epilepsia 2002;43:475-81
43. Tarko L, Ivanciuc O. QSAR modeling of the anticonvulsant activity of phenylacetanilides with preclav (property evaluation by class variables). MATCH Commun Math Comput Chem 2001;44:201-14
44. Hou T, Xu X. Three-dimensional quantitative structure-activity relationship analyses of a series of cinnamamides. Chemometr Intell Lab Syst 2001;56:123-32
45. Netzeva T, Doytchinova I, Natcheva R. 2D and 3D QSAR analysis of some valproic acid metabolites and analogues as anticonvulsant agents. Pharm Res 2000;17:727-82
46. Tasso SM, Bruno-Blanch LE, Moon SC, et al. Pharmacophore searching and QSAR analysis in the design of anticonvulsant drugs. J Mol Struc (Theochem) 2000;504:229-40
47. Estrada E. On the topological sub-structural molecular design (TOSS-MODE) in QSPR/QSAR and drug design research. SAR QSAR Environ Res 2000;11:55-73
48. Cerius2, Version 4.6. Accelrys Inc., San Diego, CA, USA; Available from: http://www.accelrys.com
49. Everitt BS, Dunn G. Applied multivariate analysis. Oxford University Press; New York: 1992
50. Hall LH, Kier LB. The molecular connectivity chi indexes and kappa shape Indexes in structure-property modeling. In: Lipkowitz KB, Boyd DB, editors. Reviews in computational chemistry. Volume 2 Wiley; New York: 1991. p. 367-422
51. Kier LB. Shape indexes of orders one and three from molecular graphs. Quant Struct Act Relat 1986;5:1-7
52. Kier LB. Distinguishing atom differences in a molecular graph shape index. Quant Struct Act Relat 1986;5:7-12
53. Stanton DT, Jurs PC. Development and use of charged partial surface-area structural descriptors in computer-assisted quantitative structure property relationship studies. Anal Chem 1990;62:2323-9
54. Hall LH, Kier LB. Electrotopological state indexes for atom types - a novel combination of electronic, topological, and valence state information. J Chem Inf Comput Sci 1995;35:1039-45
55. Rappe AK, Casewit CJ, Colwell KS, et al. UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations. J Am Chem Soc 1992;114:10024-35
56. Hyperchem 6.03. Hypercube, Inc. Available from: http://www.hyper.com
57. Dragon 3.0 Evaluation Version. Available from: http://www.disat.unimib.it/chm
58. Gordon HL, Bikker JA. TOPOLOGY (computer program)
59. Motoc I, Marshall GR. Van der Waals volume fragmental constants. Chem Phys Lett 1985;116:415-19
60. Bondi A. Van der waals volumes and radii. J Phys Chem 1964;68:441-51
61. Brooks BR, Bruccoleri RE, Olafson BD, et al. CHARMM: a program for macromolecular energy, minimization, and dynamics calculations. J Comput Chem 1983;4:187-217
62. Momany FA, Rone R. Validation of the general purpose QUANTA 3.2/CHARMm force field. J Comput Chem 1992;13:888-900
63. Shen M, Beguin C, Golbraikh A, et al. Application of Predictive QSAR models to database mining: identification and experimental validation of novel anticonvulsant compounds. J Med Chem 2004;47:2356-64
64. Wettschereck D, Aha DW, Mohri T. A review and empirical evaluation of feature weighting methods for a class of lazy learning algorithms. Artif Intell Rev 1997;11:273-314

65. Canney DJ, Holland KD, Levine JA, et al. Synthesis and structure-activity studies of alkyl-substituted gamma-butyrolactones and gamma-thiobutyrolactones: ligands for the picrotoxin receptor. J Med Chem 1991;34:1460-7

66. Peterson EM, Xu K, Holland KD, et al. Alpha-Spirocyclopentyl- and alpha-spirocyclopropyl-gamma-butyrolactones: conformationally constrained derivatives of anticonvulsant and convulsant alpha, alpha-disubstituted gamma-butyrolactones. J Med Chem 1994;37:275-86

67. Canney DJ, Lu HF, McKeon AC, et al. Structure-activity studies of fluoroalkyl-substituted gamma-butyrolactone and gamma-thiobutyrolactone modulators of GABA(A) receptor function. Bioorg Med Chem 1998;6:43-55

68. Holland KD, Naritoku DK, McKeon AC, et al. Convulsant and anticonvulsant cyclopentanones and cyclohexanones. Mol Pharmacol 1990;37:98-103

69. Reddy PA, Hsiang BC, Latifi TN, et al. 3,3-Dialkyl- and 3-alkyl-3-benzyl-substituted 2-pyrrolidinones: a new class of anticonvulsant agents. J Med Chem 1996;39:1898-906

70. Reddy PA, Woodward KE, McIlheran SM, et al. Synthesis and anticonvulsant activities of 3,3-dialkyl- and 3-alkyl-3-benzyl-2-piperidinones (delta-valerolactams) and hexahydro-2H-azepin-2-ones (epsilon-caprolactams). J Med Chem 1997;40:44-9

71. Bojic U, Elmazar MMA, Hauck RS, et al. Further branching of valproate-related carboxylic acids reduces the teratogenic activity, but not the anticonvulsant effect. Chem Res Toxicol 1996;9:866-70

72. Palaty J, Abbott FS. Structure-activity relationships of unsaturated analogues of valproic acid. J Med Chem 1995;38:3398-406

73. Frisch MJ, Trucks GW, Schlegel HB, et al. Gaussian 98, Revision A.7. Gaussian, Inc; Pittsburgh PA: 1998

74. Becke AD. Density-functional thermochemistry. III. The role of exact exchange. J Chem Phys 1993;98:5648-52

75. Lee C, Yang W, Parr RG. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. Phys Rev B 1988;37:785-9

76. MatLab 7.0. The MathWorks Inc., Available from: http://www.mathworks.com

77. Catarzi D, Colotta V, Varano F, et al. 7-Chloro-4,5-dihydro-8-(1,2,4-triazole-4-yl)-4-oxo-1,2,4-triazolo[1,5-a] quinoxaline-2-carboxylates as novel highly selective AMPA receptor antagonists. J Med Chem 2000;43:3824-6

78. Catarzi D, Colotta V, Varano F, et al. Synthesis and biological evaluation of analogues of 7-chloro-4,5-dihydro-4-oxo-8 -(1,2,4-triazol-4-yl)-1,2,4-triazolo[1,5-a] quinox -aline-2-carboxylic acid (TQX-173) as novel selective AMPA receptor antagonists. J Med Chem 2004;47:262-72

79. Sharma RN, Thakar H, Vasu KK, et al. 3D-QSAR studies for the binding affinity toward (R,S)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic acid receptor. Acta Pharm 2008;58:335-45

80. Catarzi D, Colotta V, Varano F, et al. Synthesis, ionotropic glutamate receptor binding affinity, and structure-activity relationships of a new set of 4,5-dihydro-8-heteroaryl-4-oxo-1,2,4-triazolo[1,5-a] quinoxaline-2-carboxylates analogues of TQX-173. J Med Chem 2001;44:3157-65

81. Varano F, Catarzi D, Colotta V, et al. Synthesis and biological evaluation of a new set of pyrazolo[1,5-c]quinazoline-2-carboxylates as novel excitatory amino acid antagonists. J Med Chem 2002;45:1035-44

82. SYBYL 6.6. Tripos Inc; 1699 South Hanley Rd., St. Louis, Misourri 63144, USA: 1999

83. KyPlot 5.0. KyensLab Inc., Tokyo, Japan; Available from: http://www.kyenslab.com

84. Phase, Version 3.0.110. Schrödinger Inc; LLC, New York, USA 2008

85. Dixon SL, Smondyrev AM, Knoll EH, et al. J Comput Aided Mol Des 2006;20:647-71

86. Cox DS, Gao H, Raje S, et al. Enhancing the permeation of marker compounds and enaminone anticonvulsants across Caco-2 monolayers by modulating tight junctions using zonula occludens toxin. Eur J Pharm Biopharm 2001;52:145-50

87. Vamecq J, Lambert D, Poupaert JH, et al. Anticonvulsant activity and interactions with neuronal voltage-dependent sodium channel of analogues of ameltolide. J Med Chem 1998;41:3307-13

88. Eddington ND, Cox DS, Khurana M, et al. Synthesis and anticonvulsant activity of enaminones Part 7. Synthesis and anticonvulsant evaluation of ethyl 4-[(substituted phenyl)amino]-6-methyl-2-oxocyclohex-3-ene-1-carboxylates and their corresponding 5-methylcyclohex-2-enone derivatives. Eur J Med Chem 2003;38:49-64

89. Kombian SB, Edafiogho IO, Ananthalakshmi KV. Anticonvulsant enaminones depress excitatory synaptic transmission in the rat brain by enhancing extracellular GABA levels. Br J Pharmacol 2005;145:945-53

90. CS ChemOffice, (Evaluation version) Cambridge Soft Corporation, 100, Cambridge Park Drive, Cambridge MA, 02140 USA

91. Halgren TA, Nachbar RB. Merck molecular force field. IV. conformational energies and geometries for MMFF94. J Comput Chem 1996;17:587-615

92. SYSTAT 10.2 Systat Software, Inc. SYSTAT software Inc., San Jose, CA. Available from: http://www.systat.com

93. Gupta AK, Babu MA, Kaskhedikar SG. VALSTAT: validation program for quantitative structure activity relationship studies. Indian J Pharm Sci 2004;66:396-402

94. VLife MDS 3.5 Molecular design suite. Vlife Sciences Technologies Pvt. Ltd., Pune, India. 2008. Available from: www.vlifesciences.com

95. Stewart J. MOPAC2009. Stewart Computational Chemistry; Colorado Springs, CO, USA: Available from: http://OpenMOPAC.net

96. El Hadri A, Abouabdellah A, Thomet U, et al. N-Substituted 4-amino-3,3-dipropyl-2(3H)-furanones: new positive allosteric modulators of the GABA(A) receptor sharing electrophysiological properties with the anticonvulsant loreclezole. J Med Chem 2002;45:2824-31

97. Tasso SM, Moon SY, Bruno-Blanch LE, et al. Characterization of the anticonvulsant profile of valpromide derivatives. Bioorg Med Chem 2004;12:3857-69

98. Robinson DD, Winn PJ, Lyne PD, et al. Self-organizing molecular field analysis: a tool for structure-activity studies. J Med Chem 1999;42:573-83

Affiliation

Juan C Garro Martinez[†1,2], Esteban G Vega-Hissi[1,2], Matías F Andrada[1] & Mario R Estrada[1]
[†]Author for correspondence
[1]Universidad Nacional de San Luis, Area de Química Física, Facultad de Química, Bioquímica y Farmacia, Chacabuco 917, San Luis, 5700, Argentina
Tel: +54 2652 423789 Ext. 122;
Fax: +54 2652 423789;
E-mail: jcgarro@unsl.edu.ar
[2]Universidad Nacional de San Luis, Centro Científico Tecnológico San Luis (CCT-CONICET), Facultad de Química, Bioquímica y Farmacia, Chacabuco 917, San Luis, 5700, Argentina