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Original article

A pharmacophore model for sulphonyl-urea (-cyanoguanidine) compounds with dual action, thromboxane receptor antagonists and thromboxane synthase inhibitors

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Abstract

A 3D pharmacophore model was developed for original sulphonyl-urea (-cyanoguanidine) compounds and known molecules which behave both as thromboxane receptor antagonists and as thromboxane synthase inhibitors. Five recognition sites appear to be essential for this dual activity: two hydrogen bond acceptors, an anionic site, a hydrophobic group and an aromatic ring. Such a model could be used to design new leads possessing the same pharmacological profile and to improve the activity of our compounds.

Keywords: Pharmacophore; Thromboxane receptor antagonism; Thromboxane synthase inhibition; Sulphonyl-urea (-cyanoguanidine) ligand; *Catalyst* hypothesis

1. Introduction

Thromboxane A_2 (TXA_2), an unstable endogenous arachidonic acid metabolite, causes bronchoconstriction, vasoconstriction and platelets aggregation. It is therefore a potential therapeutic target for the treatment of several pathologies such as cardiovascular, renal and pulmonary diseases [1–3]. The first attempts to interfere with the pathological action of TXA_2 focussed on the inhibition of the thromboxane synthase enzyme (TS) catalysing TXA_2 formation. However, most thromboxane synthase inhibitors (TXSIs) proved to be poor antiplatelet agents. This lack of activity results from accumulation of PGH_2, the TXA_2 precursor, which is a TXA_2 receptor agonist [4]. This problem was overcome by designing dual agents acting as TXSIs and as TXA_2 receptor antagonists (TXRAs) [5,6]. Several compounds displaying such dual mode of action were developed (Fig. 1) [7–9].

Besides these known compounds, an original series of sulphonyl-urea and -cyanoguanidine ligands, has been reported by our group. Four of these derivatives, compounds **4**–**7** (Fig. 2), behave as both TXSIs and TXRAs (Table 1) [10–14]. Each drug was found to displace [5,6-^{3}H]SQ-29548 from TXA_2 receptors of human platelets. Moreover, these drugs completely inhibited the production of TXB_2 by human platelets at the concentration of 1 μM suggesting a thromboxane synthase inhibitory activity [10,12,13].

The aim of this study is to understand the dual mode of action of compounds **4**–**7** and to identify the essential features for TXRA/TXSI activity. In literature, only very little information about these features is available. It is only known that two features—namely a carboxylic acid group and the nitrogen atom of a pyridine ring—separated by a distance range between 8.5 and 10 Å are essential [15].

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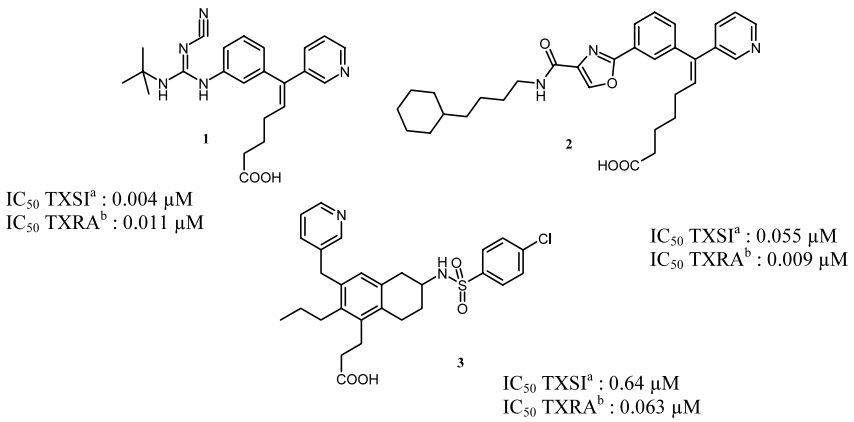


Fig. 1. Dual acting agents, TXRA and TXSI, (a) inhibition of TXB_2 formation by human gel-filtered platelets incubated with ^{14}C-arachidonic acid; (b) displacement of the high-affinity radiolabeled ligand ^{3}H-SQ-29548 from the PGH_2/TXA_2 receptor on human gel-filtered platelets.

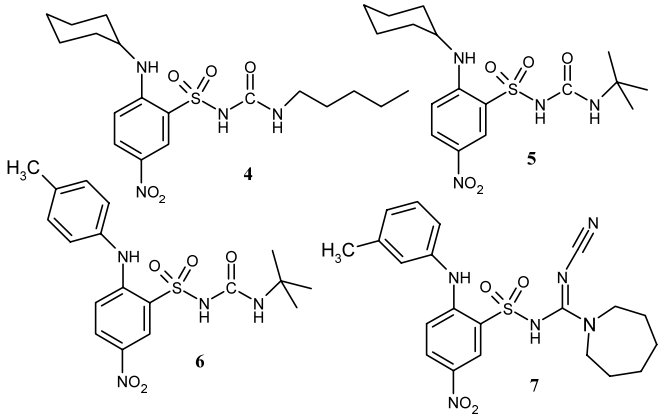


Fig. 2. Sulphonyl-urea and -cyanoguanidine compounds identified as dual acting agents.

Table 1
In vitro activity of compounds **4**–**7**

Compound	TXA_2 receptor binding [a] IC_{50} (nM)
4	1.1±0.1
5	7.8±0.7
6	1.3±0.1
7	22.1±2.0

[a] Values from Ref. [10–14].

We previously reported that the sulphonyl-urea (or -cyanoguanidine) group in compounds **4**–**7** is ionised at physiological pH ($pK_a < 7.4$) [12,16]. The ionisation site is assumed to be the nitrogen of the sulphonyl-urea, that is adjacent to two electron withdrawing groups (a sulphone and a carbonyl or cyanoguanidine group). Such a site, essential for the activity, would correspond to the carboxylic acid group of TXA_2. Indeed, replacement of the labile hydrogen by a methyl leads to compounds devoid of TXRA activity[2].

In order to extend this study, a pharmacophore model of known compounds **1**–**3** was first generated using *Catalyst* (*HipHop* module) [17]. Then compounds **4**–**7** were compared to this model to point out the common features between the molecules.

2. Method

2.1. Chemistry

Synthesis of compounds **4**, *N*-pentyl-*N′*-[(2-cyclohexylamino-5-nitrobenzene)sulphonyl]urea, **5**, *N-tert*-butyl-*N′*-[(2-cyclohexylamino-5-nitrobenzene)sulphonyl]urea, **6**, *N-tert*-butyl-*N′*-[(2-(4′-methylphenylamino)-5-nitrobenzene)sulphonyl]urea and **7**, *N*-isopropyl-*N′*-[(2-(3′-methylphenylamino)-5-nitrobenzene)sulphonyl]urea has been previously reported [12].

Briefly, the 2-chloro-5-nitroaniline is diazotised to a temperature comprised between 0 and 10 °C. The diazonium salt formed is substituted in presence of copper salts by sulphur anhydride to generate the sulphochloride which in presence of ammonia forms the corresponding 2-chloro-5-nitrobenzenesulphonamide. The chlorine is then substituted by an adequate amine. The sulphonylurea and sulphonylcyanoguanidines functions are obtained by condensation of reactive selected: isocyanates for sulphonyl-ureas or prepared (*N*-cyano-*N′*-alkyl (or aryl)carbamimidothioate of S-methyl for sulphonyl-cyanoguanidines on the sulphonamide sodium salt obtained by reaction with exactly 1 equiv. of sodium hydroxide.

[2] Results obtained from the J.M. Dogné's Ph.D. thesis, 2000, University of Liège, Belgium.

2.2. Biological assay

Biological assays of compounds **4**–**7** have been previously reported [12,13].

2.2.1. Platelet binding

The binding test realised on human washed platelets. Human platelet-rich plasma (PRP) was provided by the Belgian Red Cross. Fractions (10 mL) of this plasma were centrifuged for 10 min at $1000 \times g$ (4 °C). Freshly prepared samples of PRP (500 μL) were incubated with [5,6-^{3}H]SQ-29548 (5 nM final concentration, 100 μL) for 60 min at 25 °C. The displacement was initiated by addition of the studied ligand dissolved in the same buffer (400 μL). After incubation (30 min, 25 °C), ice-cold Tris–HCl buffer (10 mM, pH 7.4; 4 mL) was added and the sample was rapidly filtered through a glass-fibre filter (Whatman GF/C). The filters were then placed in plastic scintillation vials containing an emulsion-type scintillation mixture (4 mL) and the radioactivity was counted. The amount of [5,6-^{3}H]SQ-29548 specifically bound to the human platelet TP receptors was calculated. For the most potent drugs, three concentration–response curves were measured in triplicate using concentrations ranging from 10^{-5} to 10^{-10} M. The concentration of drug which reduced the amount of specifically bound [5,6-^{3}H]SQ-29548 by 50% (IC_{50}) was determined for each drug by non-linear regression analysis. The results are expressed as mean ± S.D.M.

2.2.2. Thromboxane synthase activity

PRP preparation is identical to that described for the platelet aggregation experiments. Each drug was dissolved in dimethylsulphoxide and diluted with a Tyrode–Hepes buffer. To 900 mL of PRP, 50 mL NaCl 0.9% and 10 mL of drug solution were added. After 6 min incubation at 37 °C under stirring (600 rpm), aggregation was induced by 40 mL sodium arachidonate (0.6 mM). After 4 min, the reaction was stopped by adding 50 mL of indomethacin (0.02 M in ethanol). The sample was immediately centrifuged ($17\,500 \times g$, for 10 s) and the supernatant was removed and frozen (−78 °C) until assayed for TXB_2. Basal and maximal production of TXB_2 was estimated in the absence and in the presence of arachidonic acid, respectively. Thromboxane synthase activity was expressed as the TXB_2 production which was measured by using a competitive enzyme immunoassay (TXB_2 EIA Kit, Cayman Chemical Company).

2.3. Conformational analysis

Conformational analysis was first performed for each compound in order to take into account their flexibility. For compounds **1** and **2**, the olefin geometry was kept in its E form, since this is related to the potency of these compounds [15,18]. For compound **3**, conformational studies were carried out on the R and S configurations because pharmacological evaluation has been done on the racemic mixture [9].

The crystal structure of compounds **1**, **4**–**7** [12,16,19,20] and the molecular mechanics optimised conformation of compounds **2** and **3** were used as a starting point for the conformational analysis.[3]

Molecular dynamics, using the *Discover3* module [21] implemented in *InsightII* [22] and the CFF91 forcefield, was first performed at 1000 K over a period of 2000 fs with a 1 fs timestep. Then, simulated annealing (down to 298 K) was carried out, followed by three sequential runs of energy minimisation using two first-order algorithms, the Steepest Descent (convergence criteria: 10 kcal mol^{-1} $Å^{-1}$) and Conjugate Gradient (0.01 kcal mol^{-1} $Å^{-1}$) and a second-order one, the Newton–Raphson (0.001 kcal mol^{-1} $Å^{-1}$). The Steepest Descent algorithm allows to quickly approximate the energetic minimum but shows an oscillatory behaviour in narrow valleys. The Conjugate Gradient method helps to precise the minimum by conjugating the search directions. Finally the Newton–Raphson algorithm considering first- and second-order derivatives was used in order to refine the search and to locate the minimum. A distance dependent dielectric constant ($1 \times r$) was chosen. For each compound, 100 conformers were generated.

2.4. Pharmacophore generation using Catalyst

Molecules with their full conformational model were submitted to the *Catalyst* hypothesis generation [17]. In this software, hypotheses approximating the pharmacophore are described as a set of features distributed within a 3D space. As there is a high structural homology among the derivatives combined with a narrow activity range, the *HipHop* method was used. It identifies common features between compounds without considering activity. Such a method was used previously for several ligand classes including 5-HT antagonists and HIV-1 protease inhibitors [23,24]. *Catalyst* takes a collection of conformational models of molecules and a selection of chemical groups,

[3] In **4** and **5**, the cyclohexyl group was ca. constrained in its stable chair conformation. Indeed, the cyclohexane adopts a puckered structure. Its most stable conformation is called the chair conformation where all the bond angles are 109.5° and all the C–H bonds are eclipsed. Its other conformation called boat is just a chair with the footrest flipped up. Although this also has bond angles of 109.5° and thus avoids any angle strain, the two hydrogens at the ends of the boat are in close contact, causing torsional strain. These flagpole hydrogens are eclipsed. This makes the boat about 5.6 kcal mol^{-1} less stable than the chair. Thus the chair predominates in liquid form although some other conformations are present because of the small activation energy.

Table 2
Parameters used for running *Catalyst* hypothesis generation

Parameters	Value of the parameter	Definition of the parameter
Principal	2 for **1**	all of the chemical features in the compound will be considered in building hypothesis space
	1 for the others	at least one mapping for each generated hypothesis will be found
MaxOmitFeat	0 for **1**	mapping of all features
	1 for the others	all but one feature must map
HyposReported	10	maximum number of hypotheses generated
Spacing	300 pm	minimum distance between actual feature locations in molecules in the training set used for identifying candidate hypotheses
Minpoints	4	minimum number of location constraints required for any hypotheses
MinSubsetPoints	4	defining the regions of hypothesis space that are most likely to be relevant to the training set
SuperpositionError	1	this option lets you adjust the R.M.S. fit of molecules to generated hypotheses. Reducing this value from one tightens the fit
Misses	1	this option means that hypotheses that fail to map completely to more than one training set compound will be disallowed
FeatureMisses	1	number of compounds allowed to not map any particular feature in a generated hypothesis
Mapping coefficient	0	this parameter controls the importance of having compounds with similar structure map to a hypothesis in a similar way
VariableWeight	0	the individual feature weights vary during the optimisation
VariableTolerance	0	the individual feature tolerance vary during the optimisation

produces a series of molecular alignments and then identifies configurations of features that are common to the set of molecules. A molecule matches these configurations if it possesses conformations and structural features that can be superimposed within a certain tolerance from the corresponding ideal locations.

In this study, the chemical features used were hydrogen bond acceptor (A), hydrogen bond donor (D), general hydrophobic (H), hydrophobic aliphatic (Z), hydrophobic aromatic (Y) and aromatic ring (R).

The A and D features are comprised of two parts: the heavy atom and the projected point of complementary site atoms. The projected points must reside outside the ligand surface. The resulting vector gives directionality to the hydrogen-bonding features.

The Z and Y features are subsets of the H class. Z includes only the centre of mass for aliphatic groups (cycloalkyl, isopropyl and methyl) and Y, only the centre of mass for aromatic groups (phenyl, indole,...).

The R feature matches five- and six-member aromatics rings. This defines two points, the ring centroid and a projected point normal to the ring plane. The projected point can map both above and below the ring.

The difference between R and Y lies in the fact that Y represents a point feature and R a feature combining a vector as well as a plane, taking into account the orientation of the aromatic moiety.

In addition to these standard features, a customised negative ionisable feature (N) involving sulphonyl-urea and -cyanoguanidine moieties was constructed in *Catalyst* because these groups were shown by previous studies to be negatively ionised at physiological pH [12,16].

In order to consider results of previous SAR studies [15], the N and A features were forced to be present in the mappings for compounds **1**, **2** and **3**. Compound **1** was taken as the reference molecule. The control parameters used for pharmacophore generation are summarised in Table 2. These are the default parameters.

3. Results and discussion

3.1. Conformational analysis

The energy range of the 100 conformers generated (ΔE; energy difference between the highest and the lowest one) and the maximum R.M.S. (a measure of the average squared position difference between 2 equiv. atoms) are depicted in Table 3 for each compound.

Fig. 3 shows some representative conformers of compounds **1** and **5**. For clarity the phenyl ring and

Table 3
ΔE and R.M.S. values for the 100 conformers generated for each compound

Compound	ΔE (kcal mol^{-1})	R.M.S. (Å)
1	9.53	4.9
2	21.70	6.0
3 (R)	16.28	4.5
3 (S)	15.89	4.0
4	12.20	4.6
5	11.9	3.3
6	7.43	3.6
7	13.32	4.6

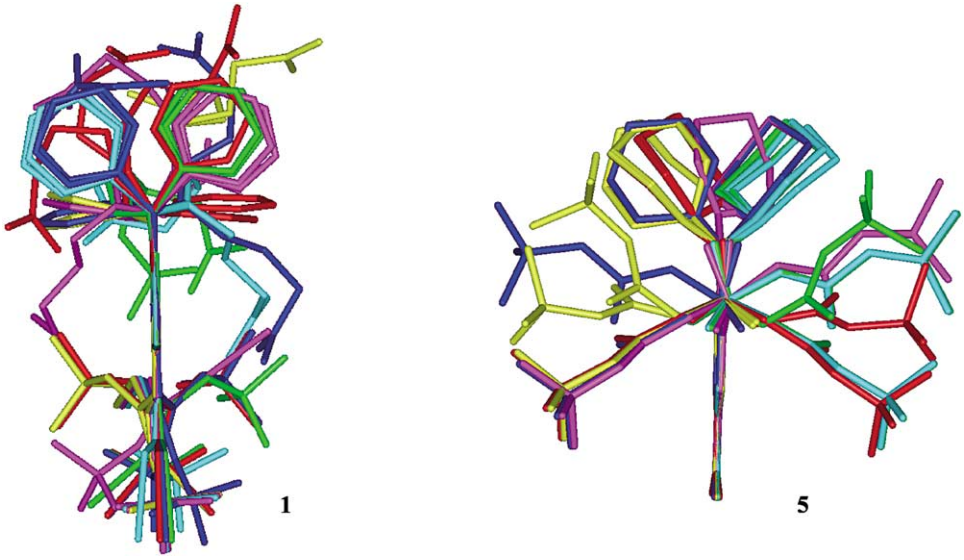


Fig. 3. Orthogonal view of some representative conformers of compounds **1** and **5**.

the nitrobenzene of all structures respectively in compounds **1** and **5** have been superimposed and the hydrogen atoms are not shown.

3.2. Pharmacophore generation using Catalyst

Compounds **1**–**3** were first superimposed. Ten five features hypotheses were obtained (Table 4). All display the same features: two H bond acceptors (A), an aromatic ring (R), a hydrophobic group (H) and a negative ionisable feature (N). The difference between each hypothesis lies on one hand in the position of the features and on the other hand in the orientation of the projected point of the H bond acceptor and the aromatic ring. We used the 'Cluster Hypothesis' function of *Catalyst* and obtained nine clusters. The hypothesis 3 and 4 are in the same cluster. The *first hypothesis* was selected for further analysis because of its best ranking. Figs. 4 and 5 show respectively the first hypothesis with mapping of compounds **1**–**3** into the five points and a 2D representation of features involved in the pharmacophore model for all compounds. For compound **3**, the R isomer allows for a better superimposition on the other molecules. The energy difference between the two isomers is about 4 kcal mol^{-1}. The fit value of R isomer is 3.25 and is higher than one of S isomer (2.87). Based on this observation, the R isomer should be more active than the S one.

As expected, the N and A classes involve respectively the carboxylic acid and the pyridine group. The distance between these two features ranges from 7.08 to 9.08 Å, in agreement with previous studies [15].

The other H bond acceptor (A) involves the cyanoguanidine, the carbonyl and the sulphone moiety respectively in compounds **1**, **2** and **3**. This point is important because substitution of the cyanoguanidine group in compound **1** for a CF_3 group is detrimental for TXRA activity (100-fold) [7].

Likewise incorporation of a CH_2 group instead of an aromatic ring (R) in compounds analogous to compound **1**, mainly reduced the TXRA activity [25].

The hydrophobic group (H) close to the H bond acceptor is more important for the TXSI activity. Indeed, replacement of the $(CH_3)_3C–NH–$ group by a NH_2 is associated with a significant decrease in activity ($\sim$100-fold) [7].

In a second step, compounds **4**–**7** were fitted into the five points pharmacophore in order to highlight their essential features for dual activity. Fig. 6 shows that *four points* are common for the seven molecules: an H bond acceptor (A), an aromatic ring (R), a negative ionisable group (N) and a hydrophobic group (H). For clarity,

Table 4
Ten hypotheses of compounds **1**, **2** and **3** and their ranking scores

Hypothesis	Feature	Rank score	Direct hit [a]	Partial hit [a]
1	NRHAA	43.0992	111	000
2	NRHAA	43.0992	111	000
3	NRHAA	42.6001	111	000
4	NRHAA	42.6001	111	000
5	NRHAA	41.7933	111	000
6	NRHAA	41.7933	111	000
7	NRHAA	41.7603	111	000
8	NRHAA	41.7603	111	000
9	NRHAA	41.7565	111	000
10	NRHAA	41.7565	111	000

[a] Direct hit, all the features of the hypothesis are mapped. Direct hit—1 means yes and 0 is no; partial hit, partial mapping of the hypothesis. Partial hit—1 means yes and 0 means no. Each number refers to a molecule.

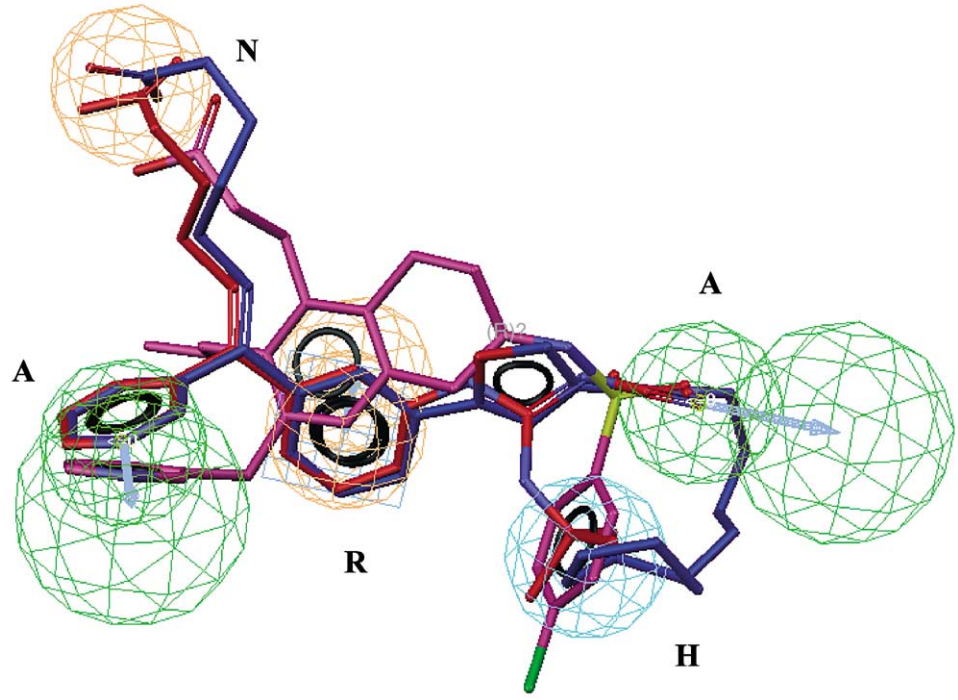
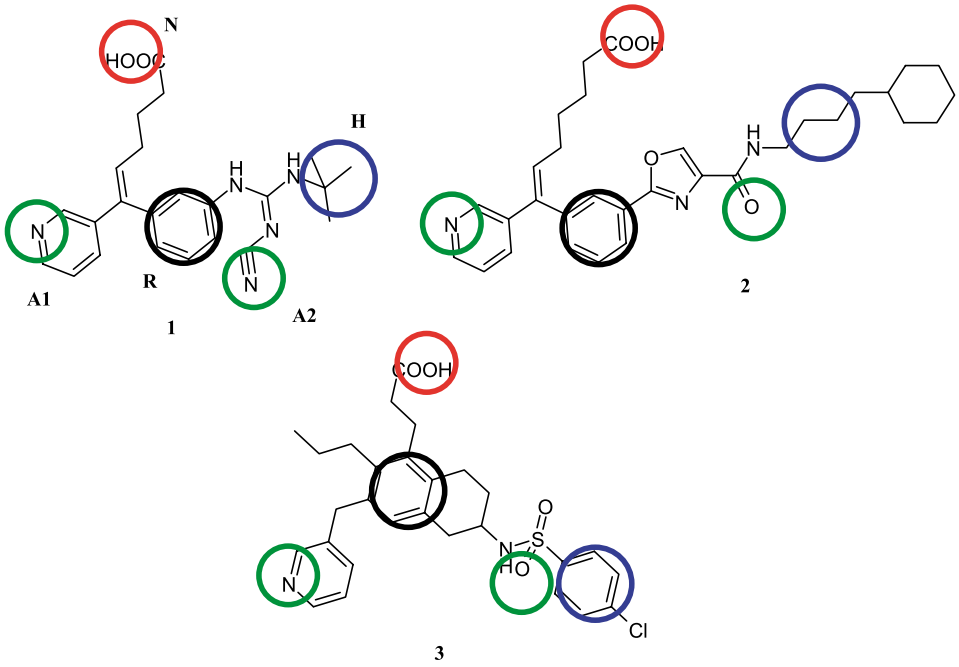


Fig. 4. Mapping of compounds **1**, **2** and **3** into the first hypothesis.



A1-N : 8.08 ±1Å **A1-R : 5.43 ±1Å** **A1-H : 9.95 ±1Å**

H-R : 5.81 ±1Å **H-A2 : 3.98 ±1Å** **A2-R : 7.54 ±1Å**

A2-N : 13.74 ±1Å **R-N : 8.57 ±1Å** **N-H : 13.82 ±1Å**

Fig. 5. A 2D representation of the features mapping on compounds **1**, **2** and **3**.

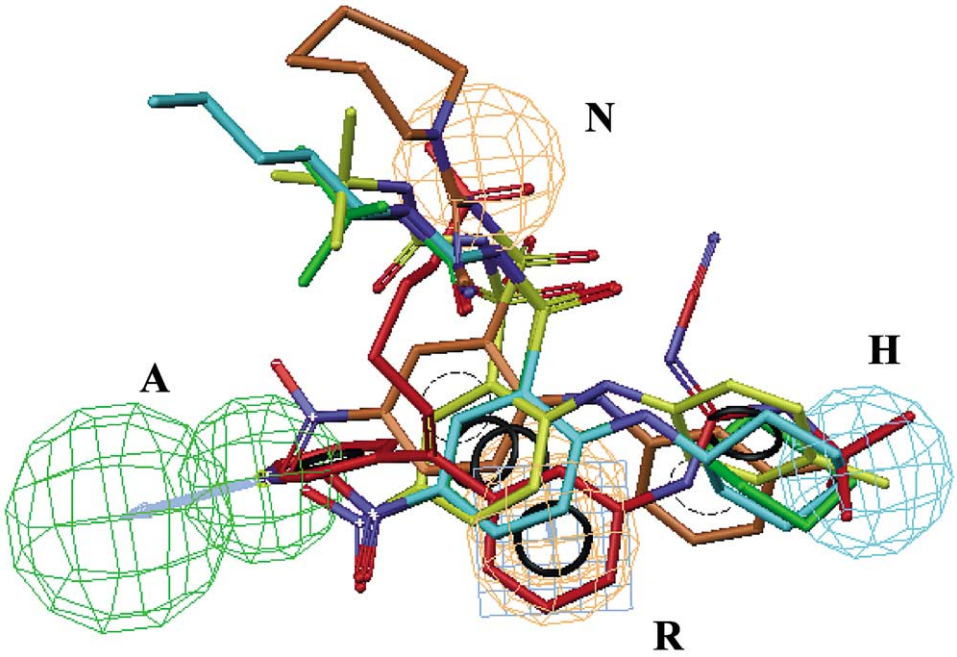


Fig. 6. The four essential features for the dual activity for the sulphonylurea family. For clarity, compounds **1** and **4**, **5**, **6**, **7** alone are superimposed.

only the superposition of compound **1** with **4**–**7** is represented with the mapped features in Fig. 6. The sulphonyl-urea (or -cyanoguanidine) group corresponds to the carboxylic acid and the nitro moiety to the pyridine group.

This observation is in agreement with other modelling studies [16] and with SAR studies. Indeed if the nitro group in compounds **4**–**7** is replaced by a CF3, a chlorine or a methyl moiety, the TXRA activity decreases.

Two other features are also assumed to be necessary for the TXRA/TXSI activity: an aromatic (R) and a hydrophobic group (H) mapping respectively the nitrobenzene and the cyclohexyl (or the toluyl) moiety. Indeed, when the cyclohexyl or the phenyl group is replaced by a C_6H_4–COOH or by a –$(CH_2)_4$–COOH, a decrease in activity is observed. Moreover, the relative position of this hydrophobic moiety is essential because when it is substituted in meta position of the nitrobenzene, the compound is less potent.

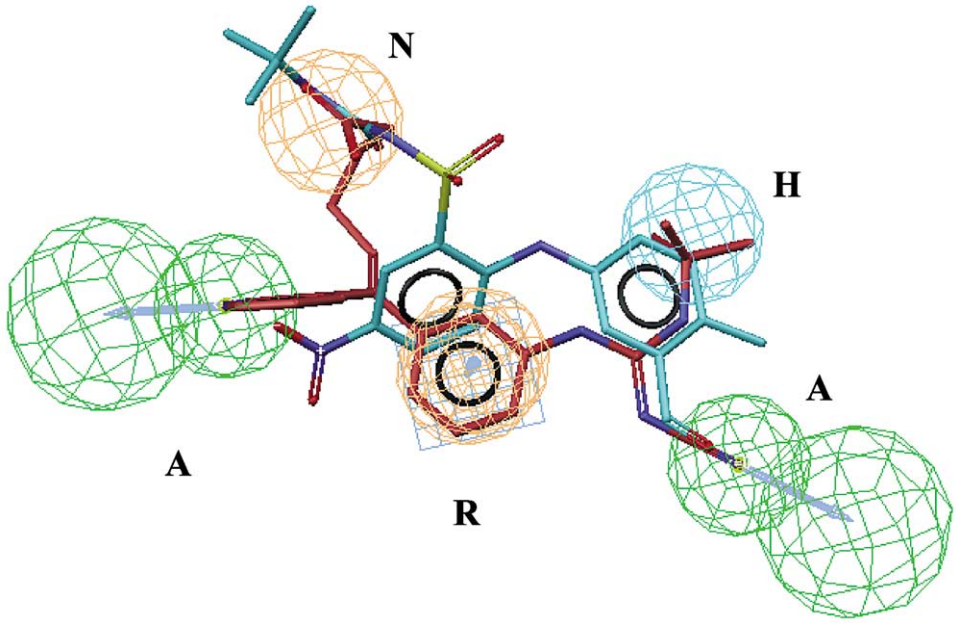


Fig. 7. Superposition of compound **1** and the proposed compound derived from **6**.

Furthermore this superimposition model (Fig. 6) can help to optimise our compounds. Indeed, compounds **1**–**3** display an H bond acceptor (A) not present in compounds **4**–**7**. Thus in order to enhance the activity of compounds **4**–**7**, it would be interesting to add an H bond acceptor, with an appropriate distance, on the cyclohexyl or the phenyl of these molecules. For example, it is proposed to add an aldehyde moiety in *ortho* position of the toluyl group in compound **6**. The mapping of this new compound superimposed with compound **1** is shown in Fig. 7. This leads to new synthesis prospects among the sulphonyl-urea series.

4. Conclusion

In order to derive the essential features to the dual activity, TXSI and TXRA, four original sulphonyl-urea (or -cyanoguanidine) were fitted into a *Catalyst* pharmacophore first established for reference dual acting agents. Modelling studies show that five points are important for such a dual activity: two H bond acceptors, an aromatic ring, a negative ionisable group and a hydrophobic group.

This model would be useful as a database query to find new structural hits with dual action. Moreover, from the superposition of the two sets of molecules, structural modifications are proposed for the sulphonylurea family in order to enhance its activity.

In the future, it would be interesting to consider if the carboxylic acid and the sulphonyl-urea groups are really negative ionisable groups or rather H bond acceptors. Indeed, as reported in the literature, the carbonyl group of the carboxylate group can be involved principally in C–H···O hydrogen bonds [26].

Moreover, as observed in several crystal structures in the CSD [27], the sulphone group can be an H bond acceptor [28] involved in NH···O [16,19,20], CH···O [29–31] or OH···O hydrogen bonds [32,33].

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