Privileged Structures: A Useful Concept for the Rational Design of New Lead Drug Candidates

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Abstract: *Privileged structures* are defined as molecular frameworks which are able of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications. In the present work, we describe some examples and applications of the usefulness of the *privileged structure* concept for the structural design of new drug candidates, by discussing the eligibility of such motifs, including the identification of the *N*-acylhydrazone template as *privileged structures*.

Key Words: Privileged structures, pharmacophoric point, rational drug design, bioactive *N*-acylhydrazones derivatives.

INTRODUCTION

Medicinal Chemistry focuses on the aspects related to the structural design, invention, discovery, identification and synthesis of therapeutically interesting compounds, *i.e.* pharmaceuticals, as well as the molecular reasons of their mechanism of action, including the understanding of the factors involved in the structure-activity relationships, absorption, distribution, metabolism, elimination and toxicity [1-2].

The molecular recognition of a drug in the biophase is resultant from intermolecular interactions with biomacromolecules, involving electrostatic forces, dispersion and hydrophobic interactions, hydrogen and covalent bonds [3-4]. The spatial arrangement of structural subunits of micromolecule, responsible for these interactions with the complementary sites of the target bioreceptor, includes the pharmacophoric requisites for its recognition, and defines qualitatively the affinity and selectivity degree of drug–bioreceptor complex [3-4].

In the recent literature, it is noticed great interest in the identification of molecular frameworks called *privileged structures*, which correspond to the minimum structural subunit, usual in several drugs or lead-compounds, able of providing ligand points for more than one type of bioreceptor [5-6]. This concept was firstly formulated by Evans [5] and improved later by Patchett and Nargund [6], who identified properties in these substructures that make their interaction with biomacromolecules easier and occasionally distinct from the ones that involve the respective endogenous ligands. Moreover, from the identification of a *privileged structure*, the desired selectivity may be modulated through supplementary molecular modifications involving other subunits or auxophoric groups. The adoption of this new concept has caused expressive impact on the development of the modern Medicinal Chemistry, as it may be noticed by the significant growing of the annual number of citations of the expression *"privileged structures"* in different databases [7] (Fig. (**1**)).

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USE OF *PRIVILEGED STRUCTURES* CONCEPT IN THE RATIONAL DESIGN OF NEW CHEMICAL LIBRARIES:

Since the 1990's, with the use of the combinatory chemistry techniques and robotized screening (*high throughput synthesis* and *high throughput screening - HTS*), the design of new chemical libraries for bioassays has become a great challenge for the medicinal chemists, leading to paradigm changes, especially in the level of research conducted in the industrial laboratories.

It is worth highlighting that, despite the substantial investment from the pharmaceutical industry sector in these new technologies, the discovery of new chemical entities (NCEs) that effectively represent an opportunity to reach the market as authentic therapeutic innovations has not fulfilled the expectations of the sector [8]. In fact, in 2005, among the 14 new medicines that came into the market, approved by the American regulating agency (FDA - *Food and Drugs Administration*), with the exception of products with diagnosis purposes, only *ca.* 50% of them had the status of authentic NCEs [9].

In this context, the pharmaceutical industrial sector involved in the research of new drugs and medicines redirected the structural design of collections of synthetic derivatives to be bioassayed by HTS, aiming at increasing the probability of obtaining new *hits* candidate to drug prototypes, which presented not only the appropriate pharmacophoric requisites, but also adequate solubility properties. The development of strategies with this purpose has been widely described in the literature and has led to the production of high impact works. Among others, we could mention the work of Lipinski and collaborators [10], who described the "rule of the five", based on the physicochemical properties of drugs and lead-compounds described in the literature. The authors postulated that an effectively promising lead-compound, must have a maximum of 5 donor points and 10 hydrogen

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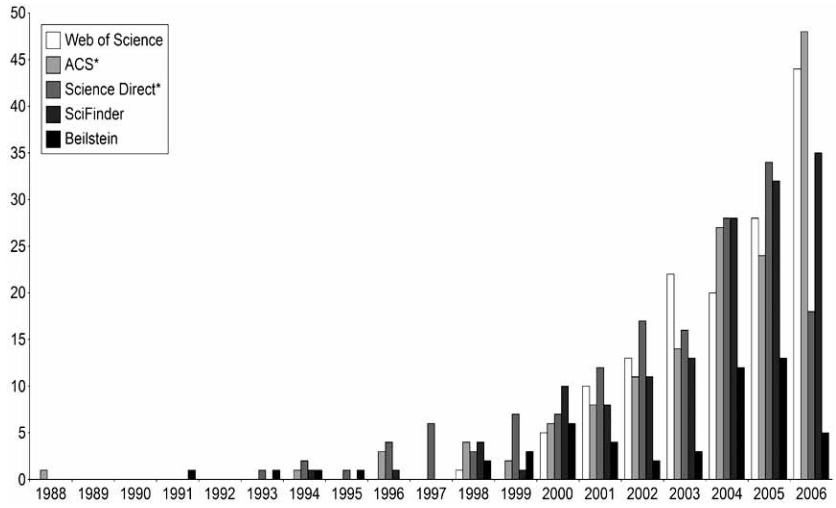

Fig. (1). Absolute number of annual citations of the term "*privileged structures*" in some bibliographic databases. The search was achieved by using the term indicated above, year by year, and starting from 1988 to 2006. The databases signed with an asterisk (*) have the search option in "*full text"*, activated in function of its availability.

bond acceptors (H-bond), molecular weight inferior to 500 atomic mass unities and calculated log P (ClogP) inferior to 5. These rules have created empiric criteria for the structural identification of new drug candidate compounds and have also shown wide applicability in the construction of chemical libraries [10].

The employment of the *privileged structures* concept in the planning of new chemical libraries [11-12] has been associated with the use of computational methods and pharmacophoric models [13-14] or with the fragmentation of bioactive molecules, prototypes or drugs, and has allowed the identification of relevant structural patterns that represent authentic biophores, providing useful frameworks to the building of new compound databases [15-20].

Schnur, Hermsmeier and Tebben [21], inventors of the *ClassPharmer* program, useful for identification of frequent (*"privileged"*) substructures in collections of bioactive molecules, recently questioned the efficacy of the election of *privileged structures* in the rational design of new compounds with selective properties against distinct biomolecular targets. These authors affirmed that just the frequency of occurrence of certain structural subunits should not be the unique criteria to ensure its condition as *privileged structures*. In this context, they explored the question of the selectivity, identified in molecular fragments generated by their program, in relation to distinct target-bioreceptor families: G-protein-coupled receptors (GPCRs), nuclear hormone receptors (NHR), serine-proteases, kinase proteins and ionic channels, recovering the original definition of Evans [5] and Patchett [6]. Furthermore, they noticed that there are high percentages of occurrence of structures called *privileged* for ionic channel ligands, among the serine-protease inhibitors (92%) (Table **1**), as well as the fact that the *privileged structures* present in the latter occurred also in high percentage (91%) in kinase inhibitors (Table **1**). On the other hand, the authors observed that the inverse did not occur, *i.e*. only 11% of the *privileged structures* identified as structural subunits present in serine-protease inhibitors integrated the structures of ionic channel ligands, and 20% of the *privileged structures* for kinase protein inhibitors were present in serine-protease inhibitors (Table **1**) [21].

Besides, the same authors verified that the GPCR ligands have wide diversity of *privileged structures* in relation to other bioreceptor families, showing that these ligands are more promiscuous and therefore present reduced selectivity

Table 1. Percentage of *Privileged Structures* Present in GPCR, Ionic Channel, NHR, Kinase-Protein and Serine-Protease Ligands*

Sub-Structures	Ligands				
	GPCRs[a]	Ionic Channels	NHR[b]	Kinase-Proteins	Serine-Proteases
GPCRs	-	26	10	11	17
Ionic channels	47	-	15	19	92
NHR	40	30	-	17	15
Kinase-proteins	48	34	16	-	20
Serine-proteases	25	11	7	91	-

*Adapted from reference [21]; [a]G-protein coupled receptors; [b]Nuclear hormonal receptors.

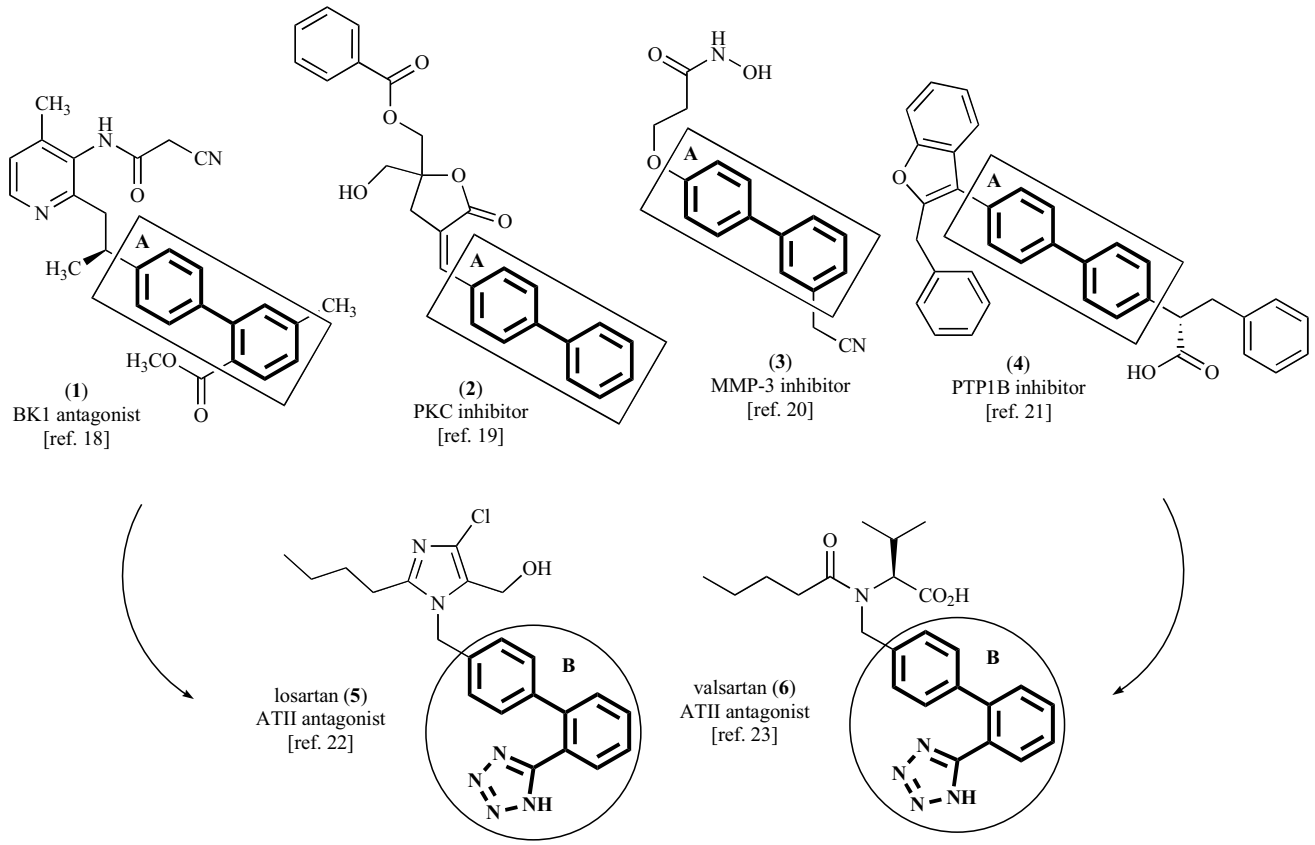

Fig. (2). *Privileged structures* of biphenyl class (A) of compounds**.** It's possible to notice the great variability of pharmacological targets to derivatives presenting biphenyl subunit (A). This profile becomes restricted to angiotensin II receptor antagonists (AT-II) with the introduction of the 2'-tetrazolobiphenyl subunit (B).

[21]. Taking as example the biphenyl substructure (A, Fig. (**2**)), classified as *privileged structure* for GPCRs [22,23], Schnur, Hermsmeier and Tebben [21] noticed that this framework is present in 5658 compounds of distinct chemical classes that act in 311 different pharmacological targets, *e.g.* bradykinin B_1 (BK_1) receptor antagonists (**1**) [24], protein kinase C (PKC) inhibitors (**2**) [25], type-3 metalloprotease inhibitors (MMP-3) (**3**) [26], protein tyrosine phosphatase 1B (PTP-1B) inhibitors (**4**) [27] (Fig. (**2**)). The *privileged* subunit 2'-tetrazolobiphenyl (B, Fig. (**2**)) was identified in 1046 compounds strictly related to the blockage of angiotensin II receptors, as illustrated by losartan (**5**) [28] and valsartan (**6**) [29] (Fig. (**2**)). These data suggest that the biphenyl privileged structure (A, Fig. (**2**)) has its molecular recognition modulated by the introduction of the tetrazole subunit [21], isosteric to the carboxylate group, conducting to the 2'-tetrazolobiphenyl pattern (B, Fig. (**2**)), just like Evans [5] and Patchett [6] preached in their original definitions of *privileged structures.*

IDENTIFICATION OF THE *PRIVILEGED STRUCTURES*

Benzodiazepines

The innovating works of Evans and colleagues [5,30-32] on the development of new non-peptidic cholecystokinin (CCK) receptor antagonists useful for the treatment of gastrointestinal disorders, such as pancreatitis and gastroesophageal reflux, aimed at obtaining new analogs of the natural product asperlicin (**7**) [33], CCK-1 receptor antagonist with IC_{50} of 1.4 μM, from the structural modification of anxiolytic benzodiazepine drugs, *e.g.* diazepam (**8**) [5,30-32]. These works culminated in the development of the devazepide (L-364,718 or MK-329) (**9**), first nonpeptidic benzodiazepine antagonist, highly selective for CCK-1 receptors, with IC_{50} of 0.8 nM, used as a pharmacological marker of this important therapeutic target. The structural planning of (**9**) involved the molecular simplification of the natural prototype (**7**), identifying the benzodiazepine (BZD) and tryptophan (Trp) subunits as pharmacophoric points essential to the molecular recognition of (**9**) by the CCK-1 receptors [5,30-32] (Fig. (**3**)).

The benzodiazepines constitute a wide class of neuroactive compounds, acting as ionic channel and G protein-coupled receptor (GPCR) ligands. As important examples of anxiolytic pharmaceuticals of this class, we can cite diazepam (**8**) and lorazepam (**10**), ligands of central gabaergic receptors [34] (Fig. (**3**) and (**4**)). In addition to the extensive number of papers describing the activity of benzodiazepine derivatives in the CCK-1 receptors [5,30-32,35-45], there are some cases in the literature in which the role of these compounds as ligands of other GPCRs is mentioned, such as κ-opioid agonists, *e.g.* tifluadom (**11**) [46], useful in the treatment of the visceral pain, the platelet activation factor (PAF) antagonists of with antithrombotic activity, as the polycyclic

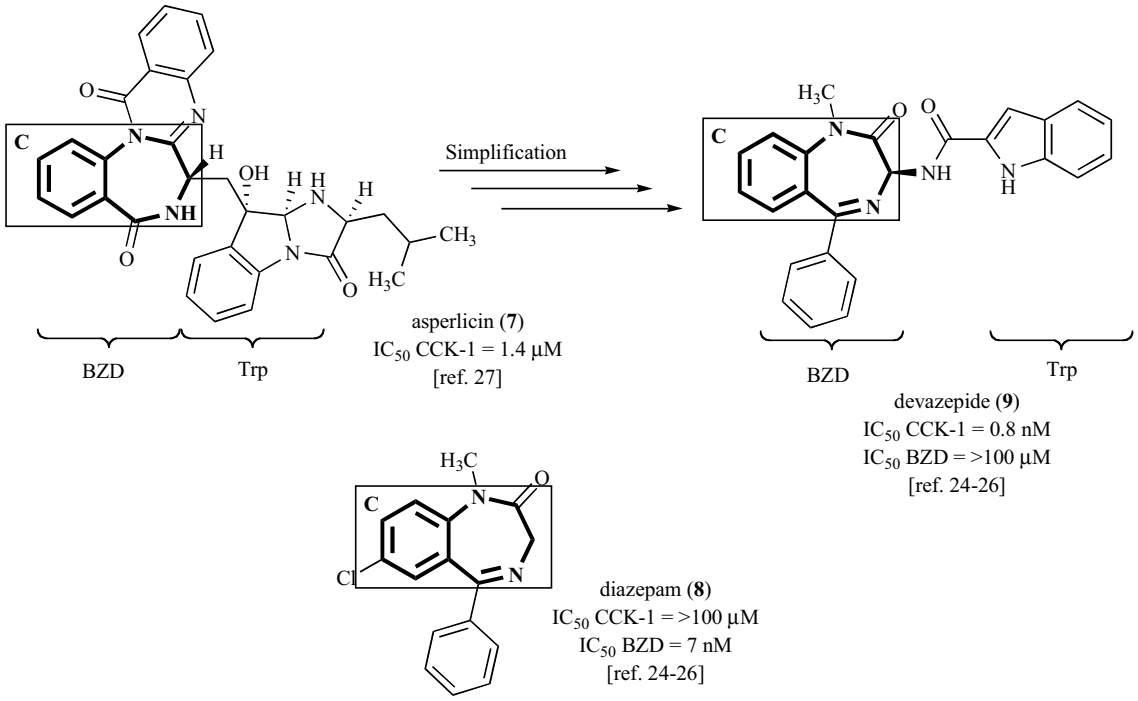

Fig. (3). Structural design of devazepide (**9**).

derivative (**12**) with IC_{50} of 7 nM [47], the neurokinine (NK)-1 receptor antagonists involved in the control of algesic and inflammatory events, *e.g.* (**13**) with pK_i of 8.0 [48] and GPIIbIIIa receptor antagonists with antithrombotic profile, *e.g.* (**14**) with IC_{50} of 11 nM [49] (Fig. (**4**)). Among the ones with enzyme inhibitor properties, it were described HIV inverse transcriptase inhibitors such as nevirapine (**15**) with IC_{50} of 84 nM [50], and RAS-farnesyltransferase inhibitors, useful for cancer treatment, exemplified by the derivative BMS-214662 (**16**) with IC_{50} of 1.4 nM [51] (Fig. (**4**)). These data characterize the benzodiazepine subunit (C, Fig. (**3**) and (**4**) as authentic *privileged structure*, able of being molecularly recognized by distinct sites of different bioreceptors.

Dihydropyridines

Another example of *privileged structure* is the dihydropyridine scaffold (D, Fig. (**5**)) usually present in calcium channel antagonist drugs, prescribed for the treatment of hypertension, as illustrated by the amlodipine (**17**) [52] and nifedipine (**18**) [53]. Appropriate structural modifications of the substituents of this *privileged structure* (D, Fig. (**5**)) provided PAF receptor antagonists, such as (**19**) [54]; A_3 adenosine receptor antagonists, useful as anti-inflammatories, exemplified by the derivative MRS 1097 (**20**) [55]; P2 purinergic receptor modulators with anti-thrombotic activity, such as MRS 2154 (**21**) [56] and α_{1A}-adrenergic antagonists, prescribed for the treatment of benign prostatic hyperplasia, illustrated by the derivative SNAP-6383 (**22**) [57], among others (Fig. (**5**)).

Spiropiperidines

Another important class of *privileged structures* is constituted of spiropiperidines (E, Fig. (**6**)), which were initially described as oxytocin receptor antagonists, useful in the prevention of preterm labor [58], and σ-opioid ligands [59], as antipsychotic drug candidates. The derivative L-366,509 (**23**) [58] (Fig. (**6**)) was able to antagonize selectively the oxytocin hormone with IC_{50} of 0.78 μM, in comparison with its action on vasopressin receptors (IC_{50} V1 = 84 μM; IC_{50} V2 = 83 μM) [58]. The selectivity of (**23**) reveals the therapeutic safety of this lead-compound, when referring to cardiovascular side effects [58]. On the other hand, the prototype L-687.384 (**24**) (Fig. (**6**)) represents an example of efficient σ-opioid ligand, with pIC_{50} of 8.42 [59].

Patchett and collaborators [60] described the discovery of the prototype MK-0667 (**25**) (Fig. (**6**)) as a growth hormone (GH) secretagogue, able of increasing the GH liberation into pituitary cell cultures with EC_{50} of 1.3 nM. This compound has also shown to be active *in vivo*, in dogs, when administered by oral route, despite possessing a peptidic subunit in its structure [60]. Additionally, MK-0667 did not alter the levels of other metabolism regulatory hormones, such as aldosterone, luteinizing hormone (LH), thyroxine and prolactin [60]. In fact, it was after the works of Patchett and colleagues that the spiropiperidines (E, Fig. (**6**)) were classified as *privileged structures*. These structural subunits are present in several other GPCR ligands, *e.g.* oxytocin and σ-opioid receptors, as well as ionic channels and diverse enzymes [6,61].

Several other bioactive spiropiperidine derivatives are related in literature, as exemplified by the derivative (**26**) (Fig. (**6**)), which present serotoninergic 5-HT_{1A} receptor antagonist (K_i = 8.3 nM) and serotonin transporter (SERT) inhibitor (K_i = 10 nM) properties, useful for the treatment of anxiety and depression [62]. The derivative RS-504393 (**27**) [63] represents an example of spiropiperidine antagonist of chemokine 2B (CCR2B) receptors, an antiinflammatory drug

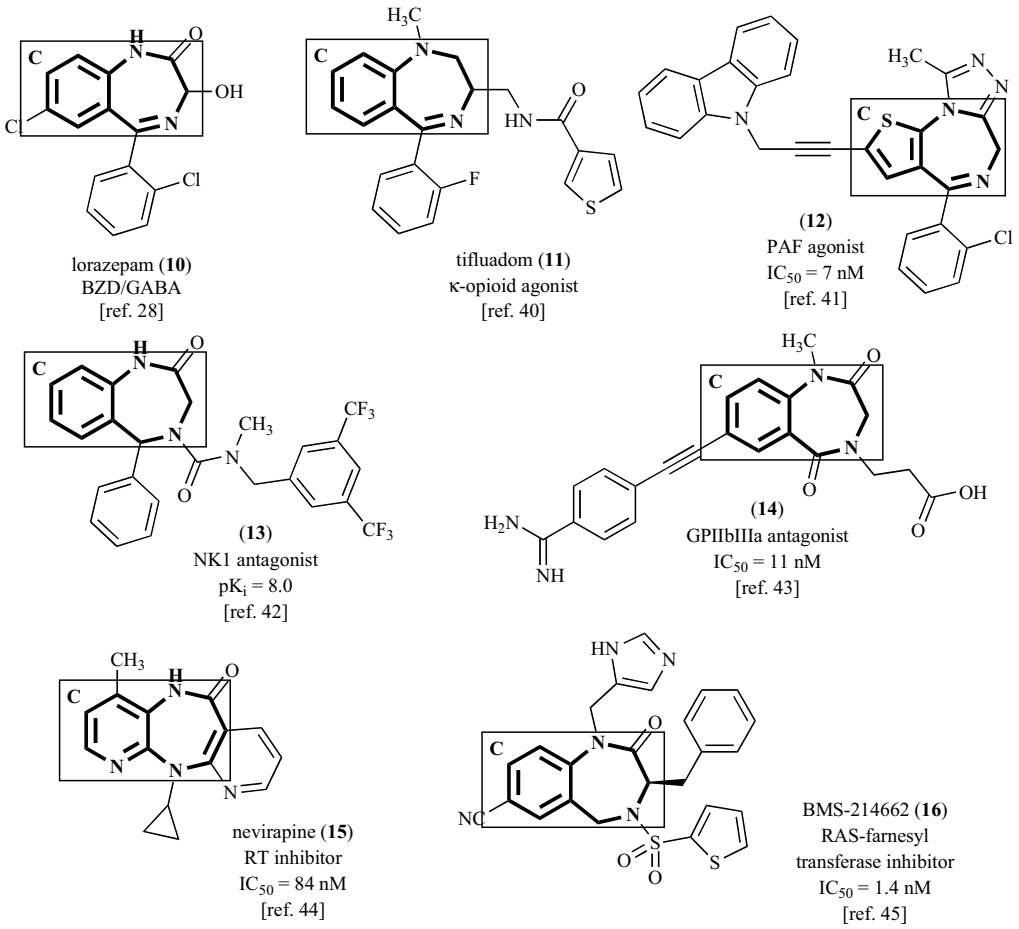

Fig. (4). Privileged structures of the benzodiazepine (C) class.

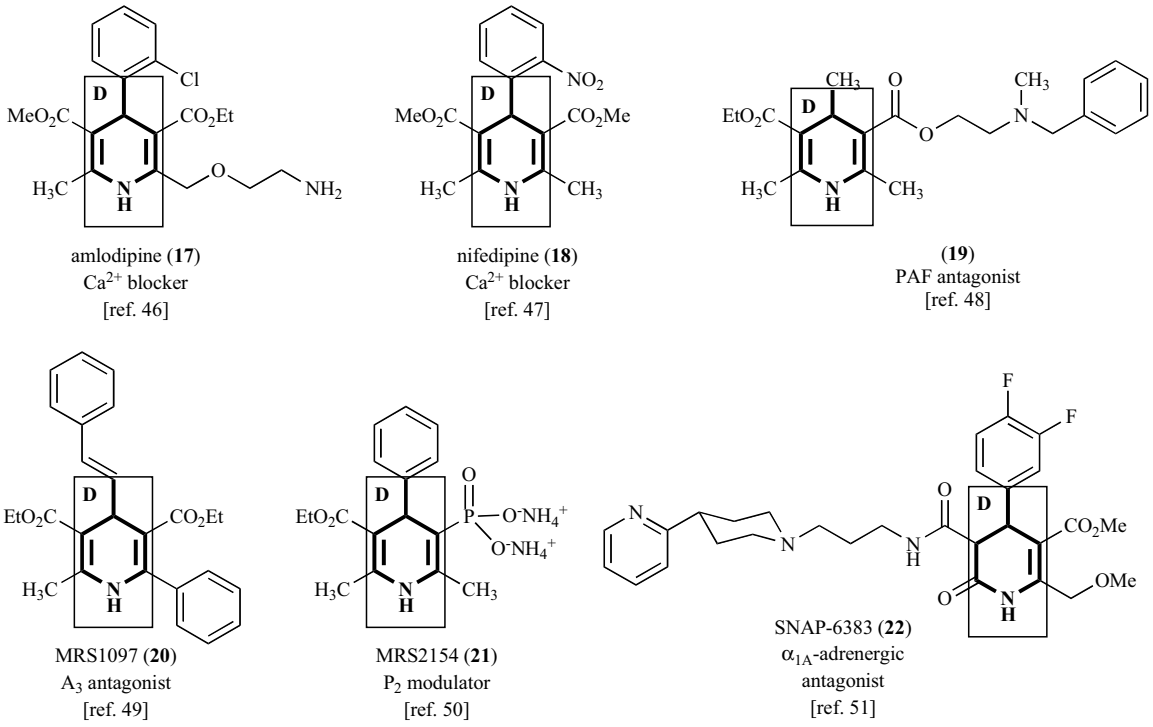

Fig. (5). Privileged structures of the dihydropyridine (D) class.

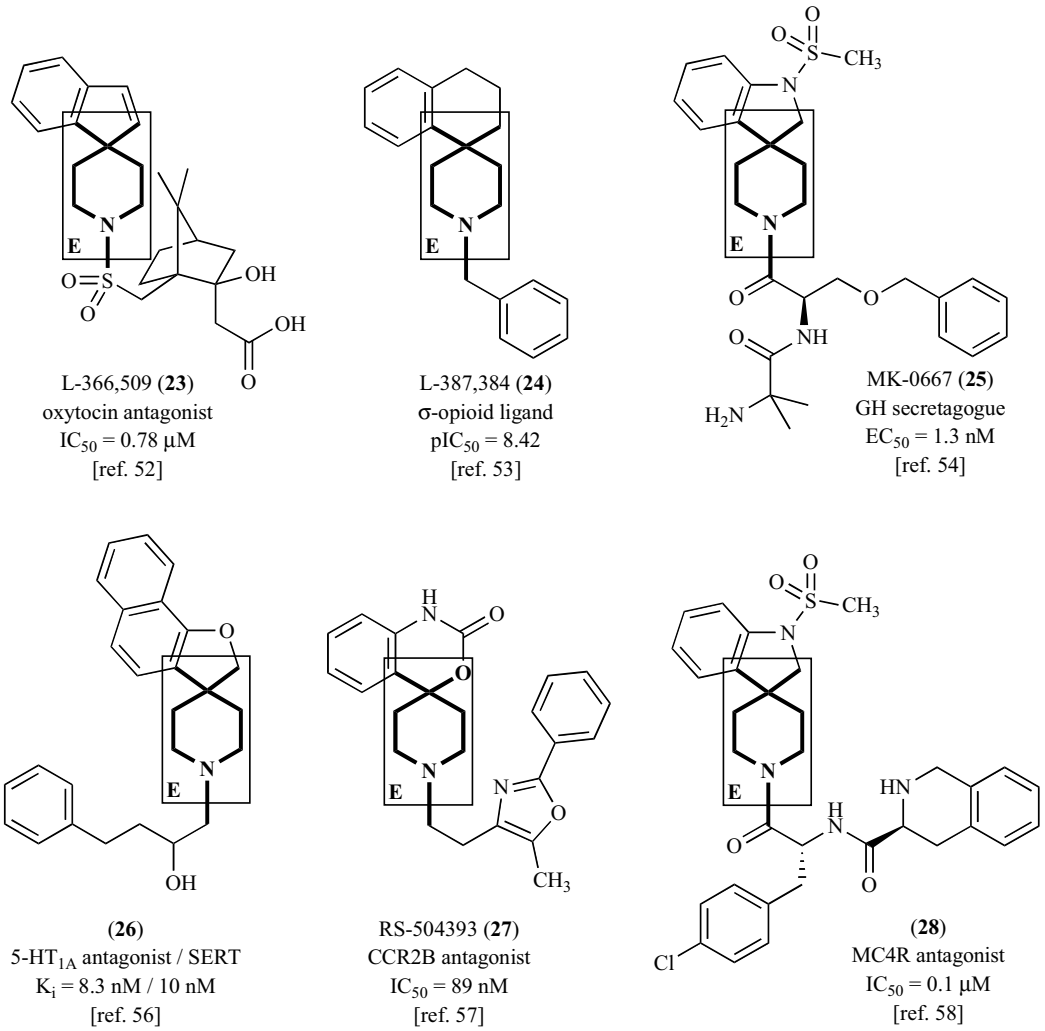

Fig. (6). Privileged structures of the spiropiperidine (E) class.

candidate, with IC_{50} of 89 nM (Fig. (**6**)), and high selectivity in comparison with other GPCRs, such as CCR1 (IC_{50} > 100000 nM), α_{1D} (IC_{50} = 460 nM) and 5-HT_{1A} (IC_{50} = 1070 nM) receptors. Among the melanocortin-4 receptor (MC4R) antagonists, it can be highlighted the spiropiperidine derivative (**28**) [64] (Fig. (**6**)), which presented an IC_{50} of 0.1 μM and potential therapeutic application in metabolic disorders.

Aminopyridazines

Aminopyridazines represent an important class of bioactive compounds, which was elected as *privileged structures* due to the presence of strategic points in the core framework, whose the adequate manipulation was able to introduce a structural diversity that allowed the building of oriented chemical libraries [65]. The works of Wermuth and colleagues explored this *privileged structure*, using the strategy of selective optimization of side activities (*SOSA*) [66-69]. This new approach consists in the structural modification of old drugs with effective pharmacological activity against new molecular targets, aiming at the optimization of these interactions, with the advantage of knowing anticipatedly the pharmacokinetic and toxicological behavior of the new drug candidate [66-69].

In this context, Wermuth and collaborators studied the optimization of the side effects of the antidepressant drug minaprine (**29**) [66], which presented reduced affinity for M_1 muscarinic receptors (K_i = 17 μM) [70-71] and for the acetylcholinesterase enzyme (AChE) (IC_{50} ~ 600 μM) [72-73]. The M_1 muscarinic ligand SR 46559A (**32**) (K_i = 3 nM) [70-71] was obtained through the transposition of the methyl group from C-3 to C-4 (**29** → **30**) of the pyridazinone ring (F, Fig. (**7**)), as well as the isosteric change of the morpholine subunit of (**30**) for a tropane ring, originating compound (**31**), and the subsequent introduction of a hydroxyl group in the ortho position of the phenyl ring of (**31**), producing the desired derivative (**32**) (Fig. (**7**)). The same molecular modification strategy was applied for obtaining the derivative (**36**), a reversible AChE inhibitor (IC_{50} = 0.01 μM) [72-73], by changing the lipophilic character of the ionizable region of (**29**), resulting in the new piperidinic isoster (**33**). Subsequent modifications in the spacer size of (**33**) led to the construction of the analogue (**34**) and, next, to (**35**), which by conformational restriction led to (**36**) (Fig. (**7**)).

Diarylheterocycles

Among the second generation of non-steroidal antiinflammatory agents, the diarylheterocyclic pattern (G, Fig.

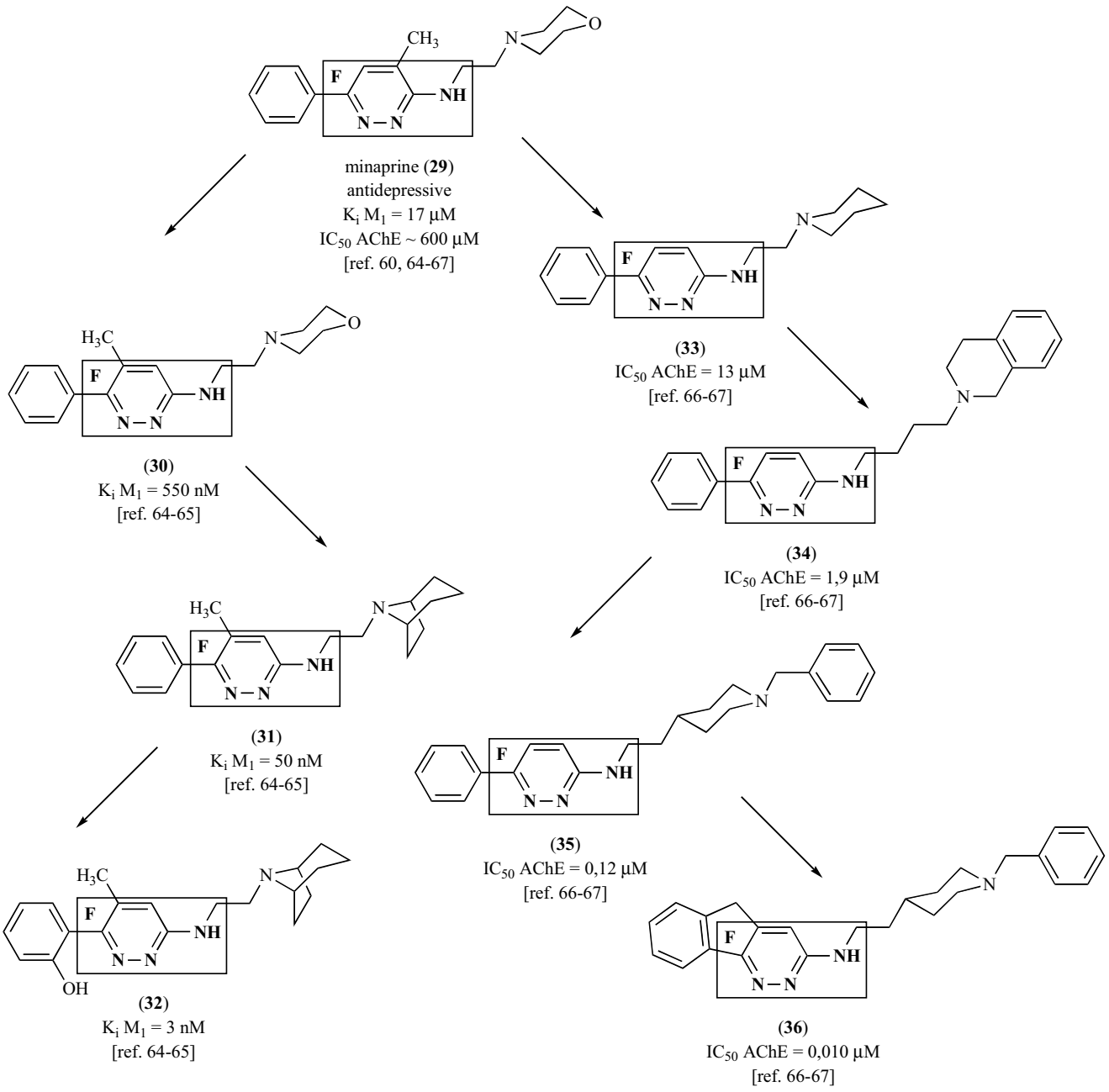

Fig. (7). Privileged structures of the aminopyridazine (F) class.

(**8**)) could be identified as *privileged structure*, being usually present in cycloxigenase-2 (COX-2) inhibitors, *e.g.* celecoxib (**37**) [74] (IC_{50} = 0.04 μM) and rofecoxib (**38**) [75] (IC_{50} = 0.02 μM); p38 mitogen activated kinase (p38 MAPK) inhibitors, *e.g.* SB-203580 (**39**) [76] (IC_{50} = 0.6 μM) and other prototypes with activity over multiple targets such as CGS-2466 (**40**), which acts as adenosine A_3 receptor antagonist, phosphodiesterase-4 (PDE-4) and p38 MAPK inhibitors [77] (Fig. (**8**)). Besides the antiinflammatory properties, these diarylheterocyclic derivatives can also act as inverse cannabinoid CB1 receptor agonists, as illustrated by rimonabant (**41**) [78] (K_i = 5.6 nM); glucagon receptor antagonists, *e.g.* (**42**) [77]; dopamine transport inhibitors, *e.g.* (**43**) [77] (Fig. (**8**)), characterizing its subunit as an authentic *privileged structure*.

IDENTIFICATION OF THE *N*-ACYLHYDRAZONE SUBUNIT (NAH) AS *PRIVILEGED STRUCTURE*

The works developed at LASSBio with *N*-acylhydrazone (NAH) derivatives, recently compiled in Fraga and Barreiro's revision [79], evidenced the *privileged structure* character of this bioactive framework. The first series of bioactive NAHs studied at LASSBio was rationally planned using Medicinal Chemistry tools concerning molecular modification, such as molecular hybridization [80], bioisosterism [81], molecular simplification [82], homologation and conformational restriction [83]. The employment of such strategies allows the rational planning of important alterations of the lipophilic character, donor/acceptor H-bonding sites, as well as in the distances and conformational orienta-

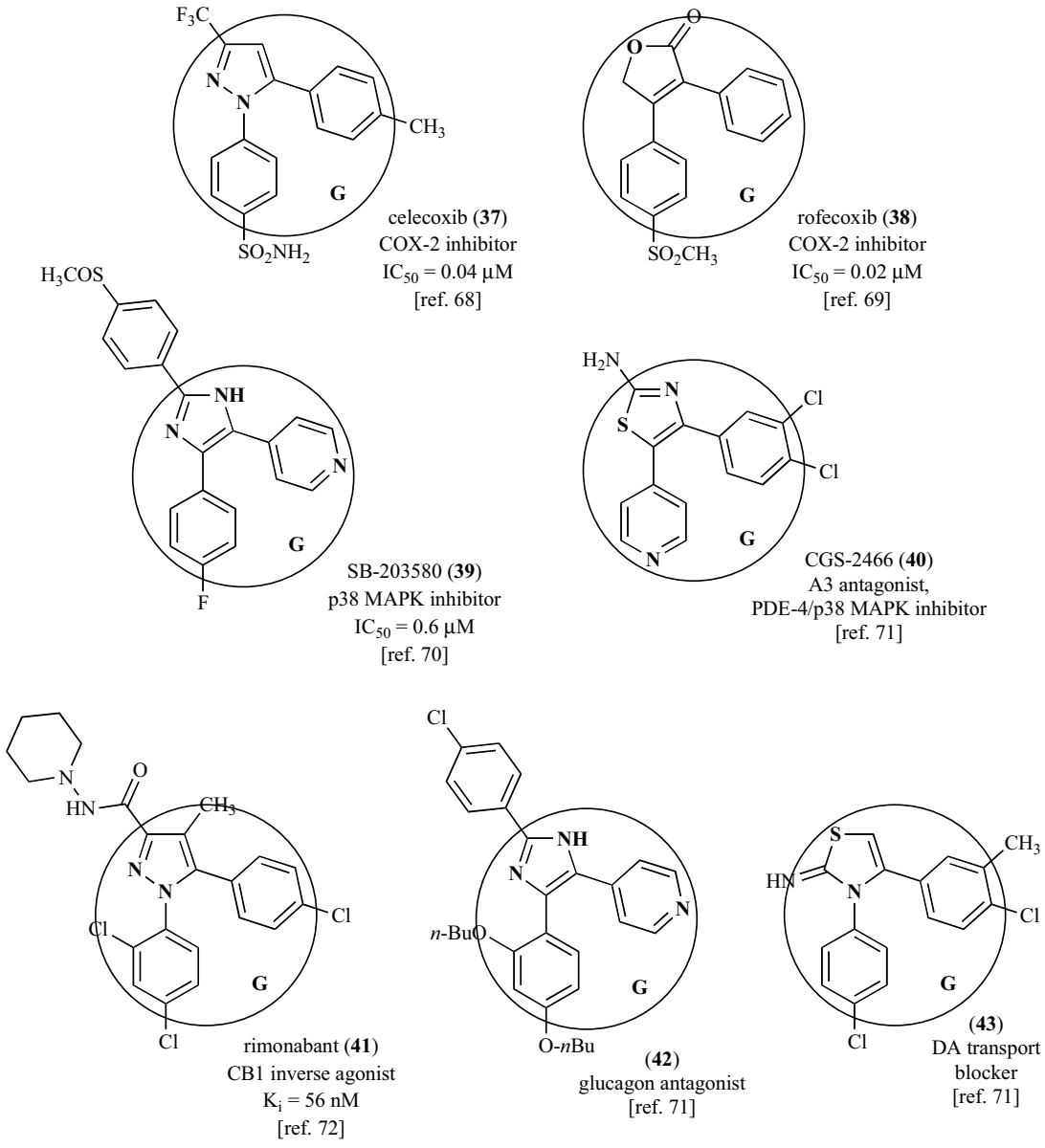

Fig. (8). Privileged structures of the diarylheterocycle (G) class.

tions of the respective pharmacophoric groups, creating a differentiation in the molecular recognition pattern of compounds of the same chemical class against different biomacromolecules, which result in distinct selectivity profiles [83].

From the molecular hybridization of two bioactive prototypes, *i.e.* BW-755c (**44**) [84] and CBS-1108 (**45**) [85], previously described as dual cyclooxygenase and 5-lipoxygenase inhibitors, the first series of analgesic and antithrombotic 4-nitropyrazole-5-hydrazone derivatives (**46**) was obtained [86-87]. Next, these compounds originated the pioneer pyrazolic NAH series (**47**) (H, Fig. (**9**)) through the classic bioisosterism among the nitro group, introduced in the series (**46**) for synthetic conveniences [86], and carboxylate moiety, besides the transposition of the hydrazone group to the carbon 4 of the N-phenylpyrazole system (Fig. (**9**)), which resulted in the obtainment of prototypes with important analgesic [88] and platelet anti-aggregating properties [89]. These results validated the structural planning of the new NAH series (**47**), demonstrating that the molecular modification strategy adopted for the optimization of the initial series (**46**) was appropriated.

The pharmacophoric character of the NAH function was investigated, through the suppression of the imine subunit of (47) (Fig. (**9**)), resulting in the respective amide derivatives (47a), which showed to be inactive in the same bioassays previously conducted. Additionally, it is essential to highlight that NAH pattern (H, Fig. (**10**)) is characterized for having different points of structural diversity, important in the building of new families of bioactive drug-candidate prototypes. Based on the bioisosterism strategies, other NAH series were synthesized and pharmacologically evaluated, in order to allow the study of the relationships between the

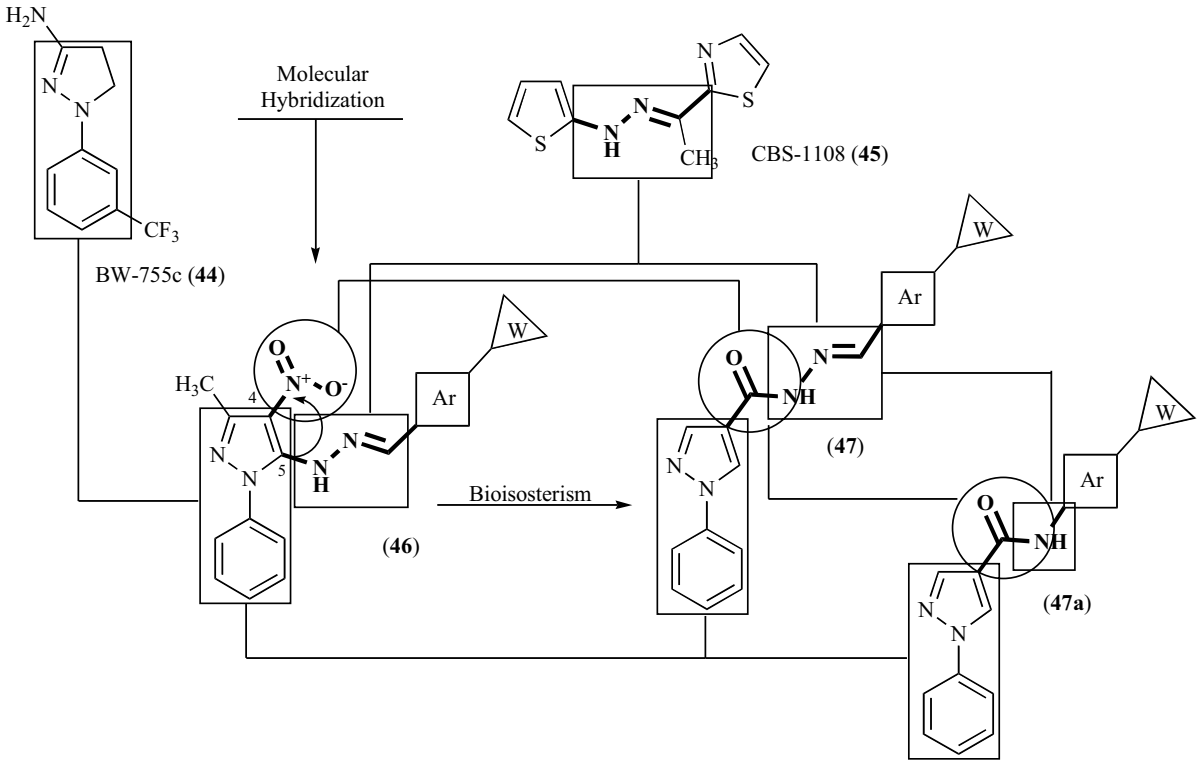

Fig. (9). Rational design of the N-acylhydrazone derivatives of series (**44**).

chemical structure and its respective analgesic, anti-inflammatory and antithrombotic activities [79].

Initially, important bioisosteric relationships were identified among the analgesic NAH derivatives LASSBio-30 (**47b**) [88], LASSBio-171 (**48**) [90], LASSBio-208 (**49**) [91] and LASSBio-349 (**50**) [92], as well as among the platelet anti-aggreganting compounds LASSBio-35 (**47c**) [89] and LASSBio-602 (**51**) [93] (Fig. (**10**)). These results suggested that modifications in the heterocyclic pattern attached to the acyl subunit did not modify drastically the pharmacological profile of the new obtained compounds. However, the manipulation of the aryl subunit attached to the imine region of NAH framework, showed to be crucial to the observed activity.

Using the message-address concept introduced by Lipkowski, Tam and Portoghese [94], it was observed that the NAH class have a differentiated pattern of pharmacological activity (*message*) when the imine region (K, Fig. (**10**)) was modified and different binding patterns (*address*) were introduced when the nature of the acyl-bound subunit (J, Fig. (**10**)) was changed. In fact, modifying rationally these two structural subunits we were able to obtain platelet anti-aggreganting compounds, illustrated by LASSBio-35 (**47c**) [89] and LASSBio-602 (**51**) [93]; peripheral analgesics, such as LASSBio-30 (**47b**) [88], LASSBio-171 (**48**) [90], LASSBio-208 (**49**) [91], LASSBio-349 (**50**) [92] and LASSBio-891 (**52**) [95] (Fig. (**10**)); central analgesics, such as LASSBio-417 (**53**) [96], based on the structure of the antipsychotic chlorpromazine (**54**), and the non-selective cannabinoid receptor ligand LASSBio-881 (**55**) [97]; cruzipain inhibitors, such as LASSBio-334 (**56**) [98], originated from the structure of the derivative ZLI48A (**57**); cardiotonic agents, such as LASSBio-294 (**58**) [99] and vasoactive derivatives, such as LASSBio-785 (**59**) [100], based on the structure of the PDE3 inhibitor, imazodan (**60**) (Fig. (**10**)).

Considering the synthetic accessibility of the NAH derivatives, it was noticed that rational modification of their sub-unities resulted in more selective compounds for certain pharmacological targets. This particular structural profile became possible to label the NAH framework as a *privileged structure*, respecting the original definition of Evans [5] and Patchett [6], considering that it is able of contributing to the molecular recognition for a wide number of biological targets, whose appropriate structural modification of their substituents.can result in selective compounds for a defined pharmacological action.

CONCLUSION

The concept of *privileged structures*, in its more strict definition, represents important tool for the identification of new structural subunits that contribute as pharmacophoric points for different pharmacologic activities [5-6]. On the previously mentioned works, the *privileged structures* represented by biphenyls, benzodiazepines, dihydropyridines, spiropiperidines, aminopyridazines, diaryl-heterocycles and NAH stood out. This new tool of understanding bioactive molecular diversity has been employed in the "colonization" of the existing *therapeutic space* for each molecular framework [100] and in association with other classical Medicinal Chemistry concepts [101] has assisted the rational design of new drug-candidate prototypes.

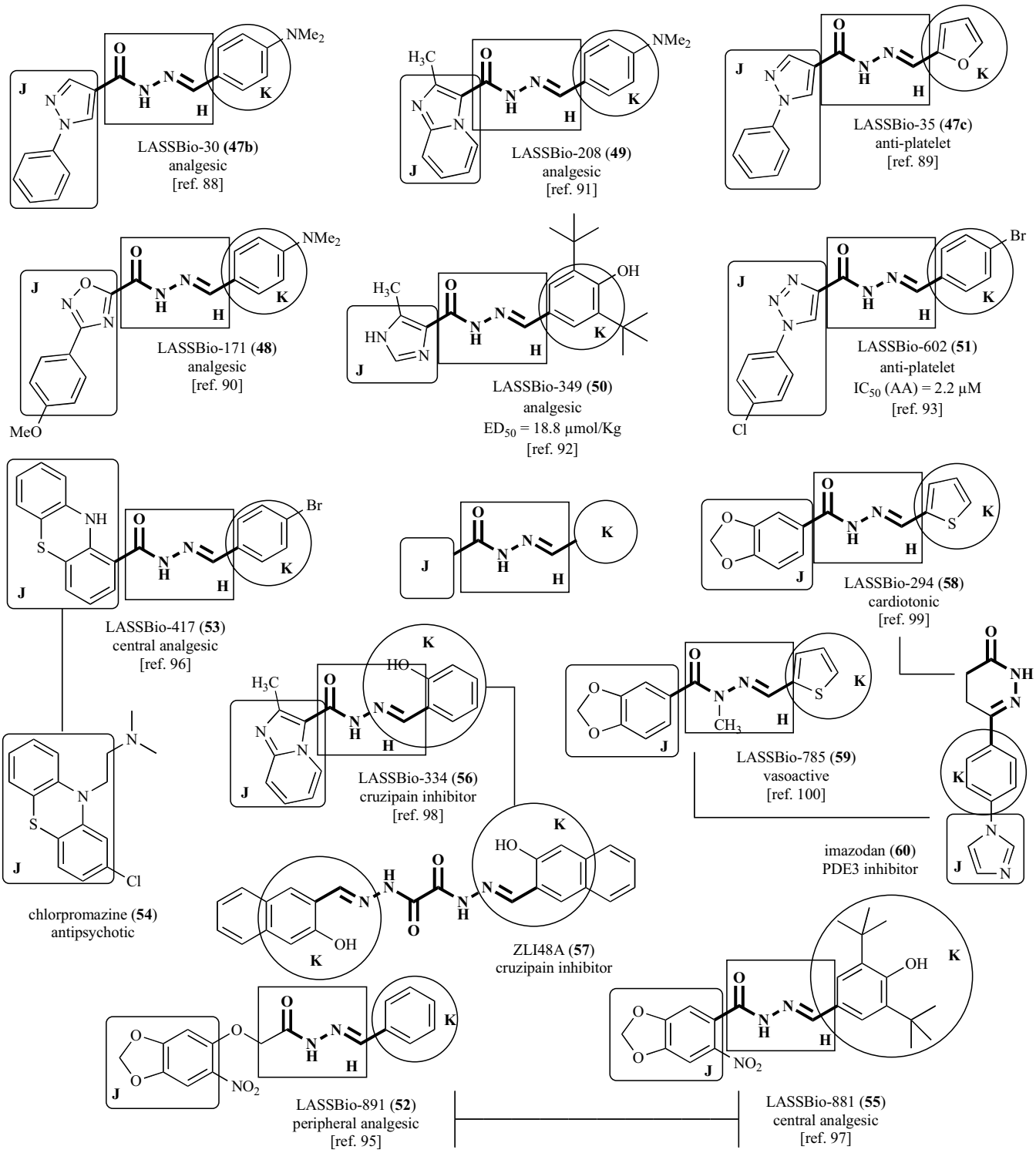

Fig. (10). Privileged structures of the N-acylhydrazone (H) class.

ACKNOWLEDGEMENTS

Thanks are due to IM-INOFAR (BR, #420.015/05-1), PRONEX-Rio (BR), CNPq (BR), FAPERJ (BR), CAPES (BR) and FUJB (BR) for the financial support and fellowships.

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Received: 07 May, 2007 **Revised: 30 May, 2007** **Accepted: 31 May, 2007**