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Review

Sigma Receptor (σR) Ligands with Antiproliferative and Anticancer Activity

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Abstract: Sigma receptor (σR) ligands have proven to be useful as cancer diagnostics and anticancer therapeutics and their ligands have been developed as molecular probes in oncology. Moreover, various σR ligands generate cancer cell death in vitro and in vivo. These σR ligands have exhibited promising results against numerous human and rodent cancers and are investigated under preclinical and clinical study trials, indicating a new category of drugs in cancer therapy.

Keywords: sigma 1 receptor antagonist; sigma 2 receptor agonist; antiproliferative activity; anticancer activity; radiolabeled and fluorescent probes; biomarkers

1. Introduction

Sigma receptors (σRs) have been recently referred in cancer pathophysiology. Initially, they were identified as opiate receptors and their description was based on the pharmacological evaluation of (±)-SKF-10,047 (*N*-allylnormetazocine), morphine and ketazocine in the chronic spinal dog model [1]. Three types of the opiate receptors were suggested and named by the corresponding greek symbol: μ for morphine, κ for ketazocine, and σ for (±)-SKF-10,047 [2,3]. Nevertheless, σRs have been classified as a distinct pharmacological receptor class and are unrelated to opioid receptors [1,4,5]. They consist of a ubiquitously expressed different binding site in the CNS and other peripheral tissues [6–9]. No endogenous ligand was known until the characterization of dimethyltryptamine (DMT) [10,11]. Steroid hormones (particularly progesterone) and sphingolipid-derived amines might also be included as endogenous ligands [12].

Originally, two types of sigma receptors (σRs) were identified, sigma 1 receptor (σ1R), which was first cloned in 1996, and sigma 2 receptor (σ2R), which has not been cloned yet [6,13–17]. One more type has been suggested, sigma 3 (σ3R), but it has not been defined adequately [18]. σ1R and σ2R have recently been involved in apoptosis (programmed cell death) [4,19–23]. σ1R and σ2R are highly expressed in cancer cells and up-regulated prior to mitosis [24,25], suggesting important cellular functions in cancer. σ1R antagonists [26–28] deactivate the receptor activity, which is anti-apoptotic and neuroprotective [4,16,19,29,30] and σ2R agonists [20–22] stimulate the receptor activity and sensitizes cancer cells for apoptosis [21,22,31]. Although there is considerable evidence of antiproliferative and cytotoxic activity for σ1R antagonists, σ2R agonists and mixed σ1R/σ2R ligands [20–23,26], the mechanism of action is still elusive.

Both σR types are overexpressed in numerous human cancer tissues, such as small- and non-small-cell lung carcinoma [24,32], large-cell carcinoma (NCI-H1299 and NCI-H838) [33], renal carcinoma [24], colon carcinoma (HCT-15 and HCT-16) [34], sarcoma [33], brain tumors (CNS U51) [35], breast cancer (MCF-7. T47D and SKBr3) and breast ductal carcinoma (T47D) [32],

melanoma (A375) [24], glioblastoma [24], adenocarcinoma (line 66), neuroblastoma (BE(2) and SK-N-SH) [24], prostate cancer (DU-145, PC3 and LnCap) [24], pancreas (MiaPaca2 and BX-PC3), liver (SKHep1), ovarian carcinoma (ICROV-1 and OVCAR-5) and leukemia (HL-60) [24]. Consequently, many pharmaceutical agents acting at the σRs have been used in the treatment of cancer and are receiving considerable attention.

A functional assay to define the agonist/antagonist behavior of σR ligands does not exist at the time of writing this review. Many σR ligands with various scaffolds have been evaluated as cytotoxic in a variety of cancer cell lines by activating caspase-dependent and caspase-independent apoptosis. This deviation in the mechanism of action can be used to define σR ligands as agonists or antagonists. More specifically, ligands that induce caspase-3 activation and cytotoxicity are commonly accepted as σR agonists, whereas compounds that do not cause caspase-3 activation and cytotoxicity are considered as antagonists [36,37].

2. Sigma Receptors (σRs)

σ1R is a polypeptide of molecular weight (MW) 29 kDa that comprises 223 amino acids and is not similar to known receptors, except for a 66.4% homology with a yeast C8-C7 sterol isomerase [6,7,9,38–42]. The σ1Rs are expressed in various tissues, and especially in the cardiac tissue and the spleen. They are widely located in the endoplasmic reticulum and the plasma membrane [6]. They are important for the modulation of cation channels (K^+, Na^+ and Ca^{2+}). σ1Rs are intracellular receptors that can translocate inside cells and act as chaperone proteins [43,44]. Chaperone proteins are responsible for the correct folding of other proteins, during their synthesis or function [45]. σ1Rs regulate Ca^{2+} signaling via the inositol triphosphate [IP3] receptor and, in particular, they ensure the Ca^{2+} signaling from endoplasmic reticulum (ER) into mitochondrion. Under cell stress conditions, the Ca^{2+} homeostasis in the ER is perturbed resulting in resistance to the potential apoptosis. Moreover, σ1Rs modulate K^+ channels in pituitary and brain cells through G protein coupling or protein-protein interactions [46]. The cell shrinkage, which is necessary for programmed cell death (apoptosis) [47–49], is mediated through K^+ loss. Moreover, σ1R is assumed to be involved in tumor genesis, as the corresponding receptor gene is a target of the oncogene c-Myc [50]. It has been shown that σ1R antagonists induce caspase-dependent apoptosis [26,51], whereas σ1R agonists prevent caspase activation [4,52]. For this reason, σ1R antagonists have antiproliferative and cytotoxic activity and the σ1R agonists are anti-apoptotic and neuroprotective [16,53].

The σ2 protein was initially characterized as the progesterone receptor membrane component 1 (PGRMC1) [54]. Even if this receptor has not been cloned yet, the corresponding gene is presumed to encode a protein of MW 21.5 kDa. In contrast to σ1Rs that dynamically translocate, σ2Rs are located in the lipid raft and are coupled with the PGRMC1 complex, EGFR, mTOR, caspases, and various ion channels [55]. σ2Rs appear to interfere in cell cycle and apoptosis by regulating the sphingolipid pathway. In particular, they produce an increase in ceramide, a sphingolipid second messenger in cell proliferation [56]. Moreover, their activation leads to high intracellular calcium concentrations that can in turn activate proteases, nucleases and other enzymes that mediate apoptosis. The σ2R is overexpressed in many tumor cell lines, thus it constitutes an attractive target for cancer diagnosis and treatment. σ2R could be used as biomarker of the tumor proliferative status, due to its high density in the proliferating tumor cells [57]. Thus, σ2R ligands could be useful for imaging cancer in vivo, using techniques such as positron emission tomography (PET) [58] or single-photon emission computerized tomography (SPECT) [59,60].

σ2R agonists and antagonists produce different effects. σ2R agonists have antiproliferative and cytotoxic activity in tumor cells in vitro as well as in vivo [61]. They provoke cell death via a multitude of distinct pathways such as caspase-dependent and -independent mechanisms [62], generation of reactive oxygen species (ROS) and autophagy [21,63]. More specifically, the caspase-dependent mechanism triggers caspase 3, 8 and 9. Another potentially exploitable fact is the interaction of σ2R ligands with p-glycoprotein (P-gp) efflux pump and their ability to decrease P-gp levels [64,65].

Nearly half of human cancers develop resistance to antineoplastic therapy due to overexpression of P-gp. Therefore, σ2R agonists can act as single antitumor agents without resistance problems or can be co-administrated with classic antineoplastic medication to reduce the Multi Drug Resistance (MDR) effect.

3. Structure Affinity Relationship of Sigma Receptors Modulators

σRs have historically invoked scientific interest due to their accommodation of different structural ligands. Consequently, a great variety of drug classes can bind to them with high affinity [66,67]. This broad structural diversity among σR ligands can be explained via a multitude of hypothesis, the most prevalent of whom suggests that the receptors possess dynamic structures, sufficiently flexible to accommodate all these structurally diverse compounds [68]. In this case, a single pharmacophore model that defines a specific three-dimensional space for pharmacophore groups may be difficult or even impossible to exist. Nevertheless, numerous two-dimensional pictorial pharmacophore models have been proposed for σR ligands.

3.1. σ-1 Selective Ligands

3.1.1. Gilligan Model

Gilligan et al. [69] identified a lead compound selective for σR (Ki = 6 nM). The lead compound **I** was analyzed into four sections, corresponding to four pharmacophore moieties, as depicted in Figure 1.

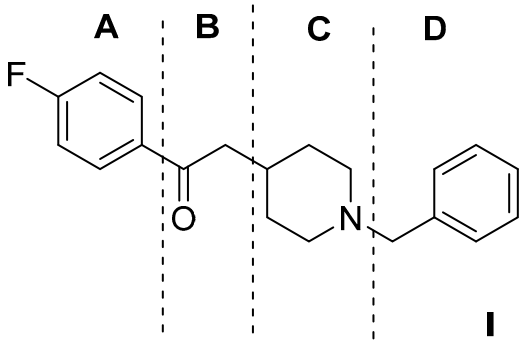

Figure 1. Gilligan model: (1) a distal aromatic ring (Region A); (2) a nitrogen heterocycle (Region C); (3) a space between the heterocycle and the distal aromatic ring (Region B); and (4) a substituent on the nitrogen heterocycle (Region D).

3.1.2. Glennon/Ablordeppey Model

This model is derived from studies that aimed at identifying a pharmacophore for the binding of benzomorphan analogs at σRs. It became immediately obvious that an intact benzomorphan moiety was not required for high-affinity binding. Compound **1** was shown to possess high affinity for σRs. Appropriate aryl substituents in the phenylethylamine portion of the molecule (including fused-ring structures) or decrease of the length of side chain by one or two methylene groups reserve high affinity (σKi < 10 nM) [70]. Both secondary and tertiary amines are potent ligands; however, one of the tertiary amine substituents could not be much larger than a methyl group [71]. Moreover, the phenylpentyl moiety, not a phenylethyl moiety, of **1**-type compounds was crucial for binding at σRs. The comparison of several phenylpentylamines **2** where $(CH_2)_n$ was varied from n = 1 to n = 4 (σKi = 2.0–2.7 nM) showed that variation of Phenyl-A to *N* chainlength had no significant impact on affinity [69,72] (Figure 2).

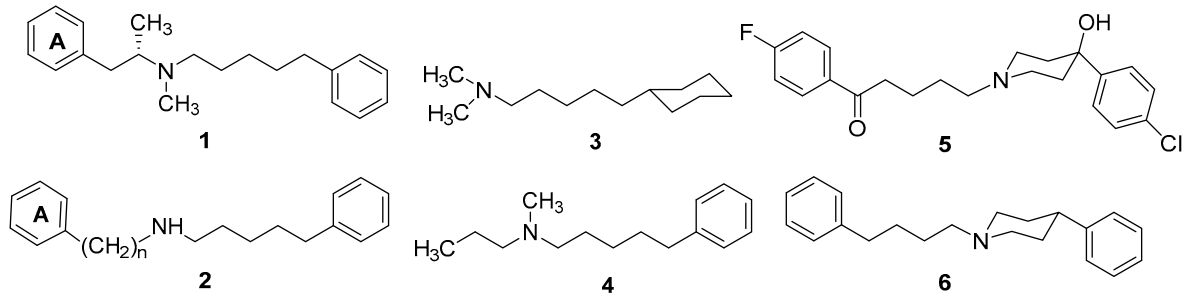

Figure 2. Structural modifications related to σ1R binding affinity.

On the other hand, either or both of the aromatic rings could be replaced by a cyclohexyl ring proving that the interaction with σRs involves a hydrophobic rather than an aromatic-type or π–π stacking interaction. Moreover, Phenyl-A could be deleted without impact on affinity; for example, derivatives **3** (σKi = 2.6 nM) and **4** (σKi = 2.4 nM) remain as potent as compound **2** [73,74]. A phenylpiperidine or phenylpiperazine ring has almost the same dimensions with a phenylethylamine and it was proven that such derivatives are also potent [75]. It was reasoned that, if the phenylpentylamine moiety is a significant pharmacophore contributor, it should be possible to extend the butyrophenone chain of haloperidol to valerophenone. Indeed, valerophenone **5** (σKi = 2.3 nM) was found to have several-fold higher affinity than haloperidol (CTKi = 10 nM). Removal of polar substituents in the phenyl ring, to afford phenylpentylamine **6**, resulted in increase of affinity (**6**; CTKi = 0.9 nM) [76]. At the time, compound **6** exhibited the highest σR affinity. The next set of experiments examined the impact of the *N*-alkyl substitution. As long as one of the *N*-alkyl substituents is a methyl group, the nature of the second substituent has limited impact on affinity, provided it is at least three carbon atoms in length. This evidence supported the hypothesis of a hydrophobic binding pocket of limited size, and that, as long as this hydrophobic binding requirement was met, derivatives presented high affinity. Further bulk substituent was probably accommodated in an associated region of bulk tolerance, and did not usually increase affinity [77] (Figure 2). All the above results were used by Glennon and Ablodeppey to propose an initial pharmacophore model for high affinity σR ligands, which is depicted in Figure 3.

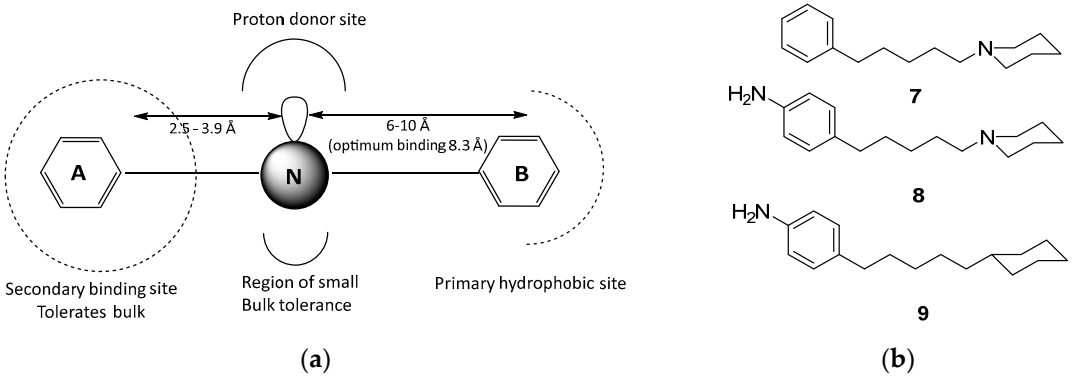

Figure 3. (**a**) Initial Glennon/Ablordeppey pharmacophore model [78]; and (**b**) structural modifications of the basic nitrogen atom.

Another question was the role of the basic nitrogen atom. Several studies had presented that σR ligands did not require a basic amine. Steroids, for instance, are σR ligands [79]. An amino group was shown to be well tolerated in the phenyl ring of derivative **7** (**8**, σKi = 38 nM). Subsequently, the piperidine amino group was deleted, giving compound **9**, which (σKi > 36,000 nM) was >50,000-fold less potent than adduct **7**. The presence and location of the basic amine proven to be important for

binding [79,80]. Various and diverse compounds have been demonstrated to be σR ligands. However, two major features have been revealed: (1) many bind with affinity only in the micromolar or very high nanomolar range; and (2) most display an aryl or hydrophobic ring separated from a basic tertiary amine by four to seven atoms. Although a five-atom linker seems optimal, compounds with longer alkyl chains might simply interact with a hydrophobic binding site on the receptor in a less efficient manner than phenyl or cyclohexyl groups. Compounds with longer chains might also fold back somewhat to be accommodated by the receptor. In any case, long chains are well tolerated.

3.2. σ-2 Selective Ligands

The synthesis of selective ligands for the σ2R versus the σ1R has always been a challenge. The fact that σ2R accommodates very different structures has made it difficult to produce a pharmacophore model for rational design of σ2R ligands [61,81].

3.2.1. Conformationally Restricted Amine Derivatives

The first class of σ2R selective ligands was the benzomorphan-7-one analogs, as illustrated in Figure 4 [82].

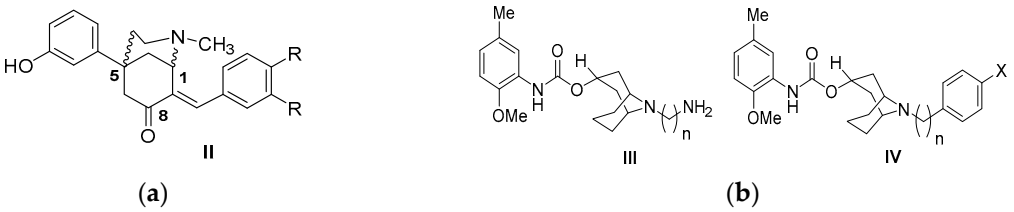

Figure 4. Conformationally restricted amine selective σ2R derivatives: (**a**) Benzomorphan-7-one analogs; and (**b**) Granatane analogs.

The most selective σ2R ligands were (+)-1*R*,5*R*-(*E*)-8-benzylidene-5-(3-hydroxyphenyl)-2-methyl-morphan-7-one (**CB-64D**, σ2Ki = 16.5 nM, σ1/σ2Ki = 185) and (+)-1*R*,5*R*-(*E*)-8-(3,4-dichlorobenzylidene)-5-(3-hydroxyphenyl)-2-methylmorphan-7-one (**CB-184**, σ2Ki = 13.4 nM, σ1/σ2Ki = 555). These benzomorphans displayed affinity for the μ opioid and σ2 receptors, because the aforementioned receptors share the same enantioselectivity. The (+)-isomers are selective for the σ2R, while the (−)-isomers have a higher binding affinity for the σ1R. This chemical category of derivatives is merged with granatane- or tropane-related bicyclo-analogs. The 9-*N* atom of the granatane ring can accommodate bulky substitutions without a significant loss of σ2R affinity and selectivity. A *N*-substitution with an additional nitrogen atom that is four or more carbon atoms apart enhances σ2R binding affinity. A *N*-aromatic substitution can also be accommodated, but is not crucial for σ2R affinity or selectivity [83–85].

3.2.2. Siramesine-Related Indole Analogs

Siramesine (Lu 28-179) was designed as a low-efficacy serotonin 5-HT1A agonist for treating depression and anxiety disorders [86], but it was later revealed that **siramesine** displayed a subnanomolar affinity for σ2R and a 140-fold selectivity for σ2R versus σ1R. This remark led to the development of a new series of siramesine analogs (σ2Ki = 0.12 nM, σ1/σ2Ki = 140) (Figure 5) [86,87]. *N*-small alkyl substitution decrease sigma affinity, while *n*-propyl, *n*-butyl groups lead to an increase of sigma binding affinity with a corresponding shift towards σ2R selectivity. The introduction of a fluorine atom or a trifluoromethyl group at the spiropiperidine benzene ring reduces σ2R affinity or selectivity. In addition, when the geometry of spiro-system changes, the affinity and selectivity towards σ2R decrease [86,87] (Figure 5).

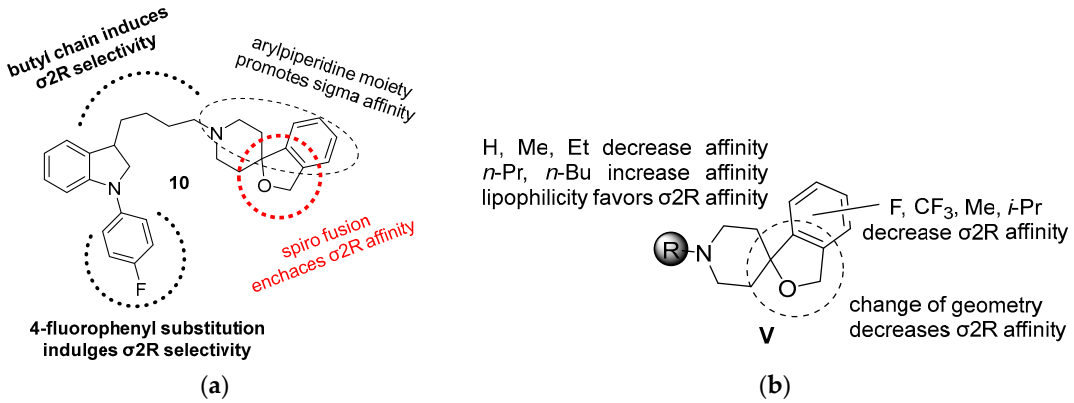

Figure 5. (**a**) Siramesine or Lu 28-179; and (**b**) structural modifications of siramesine analogs.

3.2.3. Conformationally Flexible Amine Derivatives

Benzamide highly selective σ2R derivatives are illustrated in Figure 6. These compounds were initially designed as dopamine D3 selective antagonists and partial agonists, but the structural modifications to improve the "drug-like" properties generated the aforementioned σ2R selective ligands [88,89]. The dimethoxy groups of the 6,7-dimethoxytetrahydroisoquinolines are important for maintaining a high affinity for the σ2R binding [89]. A restricted amine structure is beneficial for σ2R binding [90]. The aromatic substitution of the benzamide can tolerate large alkyl chains and an intramolecular hydrogen bond may be formed between the oxygen of the ortho-methoxy group (vide R_1, Figure 6) on the benzamide and the amide NH. This bond could be important for σ2R binding [65,91,92].

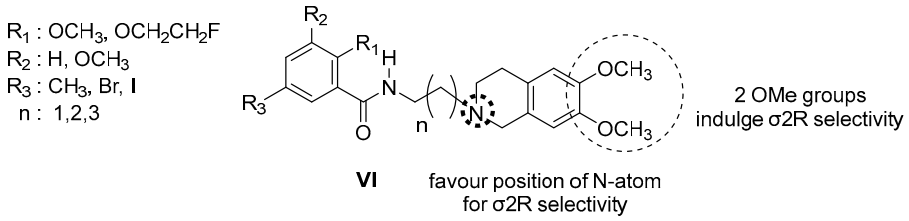

Figure 6. Conformationally flexible benzamide analogs.

Cyclohexylpiperazines and cyclohexylpiperdines have been studied for both sigma receptors, since these compounds are highly potent and nonselective σ1/2R ligands (Figure 7). The Structure–Activity Relationship of this category of compounds supported the hypothesis that the lipophilicity is correlated to the antiproliferative activity mediated by the σ2R [93]. The higher lipophilicity indulges higher affinity and efficacy.

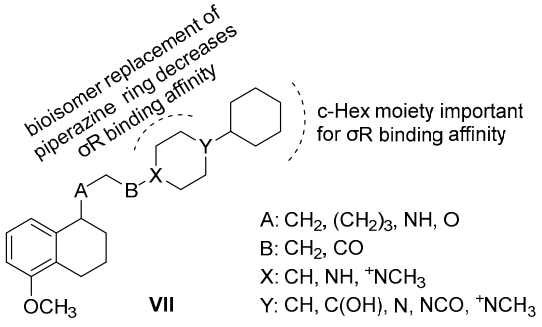

Figure 7. Cyclohexylpiperazines and cyclohexylpiperdines analogs.

In the above-mentioned model in Figure 7, *N*-cyclohexylpiperazine moiety proves to be an optimal substituent of this category of derivatives. Quaternary amines are also capable of binding to σ2R with moderate affinity and selectivity over σ1R. When a carbazole moiety replaced the 5-methoxytetraline resulted a significant decrease in σ1R binding affinity and a 273-fold selectivity for σ2R [93,94].

4. σ-Receptor (σR) Ligands in Cancer Research

σR are expressed in large quantities in the majority of cancer cell lines, suggesting that σR ligands can be used as potential tools in the treatment or diagnosis of various types of cancer [12,35,94,95].

As far as diagnosis is concerned, σR ligands can be used for diagnostic imaging using PET or SPECT. Their use as diagnostic tools is based on the aforementioned overexpression of σR in different types of cancer and as on the ability of σRs to internalize their ligands, as well. Moreover, several σR ligands contain an iodine or fluoride atom in their chemical structure, which can be easily substituted with the corresponding radioisotope [59,96–99]. Several preclinical studies evaluated the potential use of radiolabeled sigma-ligands as imaging agents in melanoma [100], breast cancer [101,102], prostate cancer [101], and lung cancer [100]. Everaert et al. highlighted that malignant melanomas can be detected in patients with 87% accuracy and 64% sensitivity at the lesion site, using a radiolabeled benzamide σ1R ligand **^{123}I-IDAB** (^{123}I-*N*-(2-diethylaminoethyl)-4-iodobenzamide) [100,102]. A preliminary clinical study showed that the σ1R ligand **^{123}I-IMBA** (^{123}I-*N*-[2-(1′-piperidinyl)-ethyl]-3-iodo-4-methoxybenzamide), is accumulated in most breast tumors in vivo due to uptake by or a high density of σRs in cancer cells, in comparison to normal tissue [102].

Leaf Huang et al. have been using selective σ1R ligands for delivering drugs to human cancer cells. Their group designed the benzamide derivative **^{125}I-IPAB** (^{125}I-(2-piperidinylaminoethyl)-4-iodobenzamide) [103,104] and incorporated it into liposomes containing doxorubicin to specifically deliver the drug to a prostate cancer cell line (DU-145) [105]. The benzamide-conjugated liposomal doxorubicin exhibited significantly higher antiproliferative activity against DU-145 cells than against non-targeted liposomal doxorubicin in vitro, and better accumulation within the tumor in vivo in a xenograft animal tumor model. Moreover, intravenous administration of the targeted liposomal doxorubicin displayed significant growth inhibition of established DU-145 tumors in nude mice, while simultaneously reducing the drug toxicity [105]. This technique was later followed by nanoparticles containing the σR ligand **^{123}I-IDAB** to target the delivery of antisense oligodeoxynucleotide and siRNA to lung cancer cells in vitro and in vivo, as well as to the B16F10 mouse melanoma lung metastasis model [106,107]. A phase II clinical trial proved that **^{123}I-BZA** (^{123}I-*N*-(2-diethylaminoethyl)-4-iodobenzamide) was useful as scintigram in diagnosis of ocular melanoma [108]. Another isomer benzamide adduct of this series of radiolabeled derivatives, which is used in the identification of melanoma metastases is **^{123}I-BZA2** (^{123}I-*N*-(2-diethylaminoethyl)-2-iodobenzamide). **^{123}I-BZA2** was studied in a multicenter Phase III clinical trial and might lead to a new treatment strategy of metastatic melanoma patients harboring melanin-positive metastases [109] (Figure 8).

Recently, various σ1R ligands have been examined for cancer chemotherapy either in conjunction with other anticancer treatments or as monotherapy. It was first shown that σ1R ligand **4-IBP** (4-(*N*-benzylpiperidin-4-yl)-4-iodobenzamide), increased the antitumor effects of temozolomide and irinotecan in vivo, a process that appears to involve the Rho guanine nucleotide dissociation inhibitor (RhoGDI) and glucosyl-ceramide synthase (GCS) [110]. It has also been demonstrated that various σ1R ligands, including current antipsychotic drugs, display antiproliferative activity with mitotic arrest in highly diffusive and migrant glioblastoma (GBM) cells in vitro. Moreover, it was observed that donepezil could provide the same additive benefit to temozolomide treatment as **4-IBP** in vivo [111]. **Rimcazole**, a σ1R ligand for the treatment of schizophrenia, was recently found to kill selectively tumor cells by a process involving HIF-1a, and has now been re-profiled for cancer chemotherapy. **Donezepil**, another σ1R ligand for the treatment of Alzheimer's disease, is being used in chemotherapy for small

cell lung cancer and as adjunctive therapy in brain tumors [112]. **Haloperidol**, known antipsychotic drug and σ1R antagonist, promotes ferroptosis in hepatocellular carcinoma cells [113].

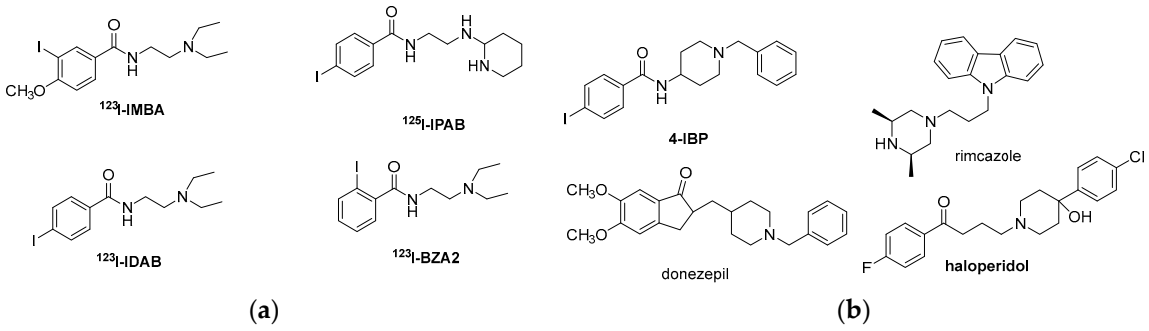

Figure 8. (**a**) Radiolabeled selective σR1 ligands that have been used in pre-clinical studies of tumor imaging; and (**b**) σR1 ligands that are being used in cancer treatment.

σ2R ligands have been used for more than 20 years as radiolabeled and fluorescent probes to provide structural information of the correspondent receptor and highlight solid tumors as biomarkers [37,114–116]. **[^{3}H]DTG** is one of the most known radioligand in the study of σ2R [114]. **[^{3}H]azido-DTG** was an important analog in the characterization of the molecular weight of σ1R and σ2R [66,114]. Various conformationally flexible benzamides (e.g., vide Figure 9, compounds **10** and **11**) are selective radiotracers for imaging the proliferative status of tumors in vivo with PET [85,115,116]. The 2-methoxy group of the previous derivatives facilitates the preparation of ^{11}C-labeladed derivatives due to alkylation of the corresponding 2-hydroxy precursors. In the next generation of radiotracers, the 2-methoxy group was replaced by the 2-fluoroethoxy moiety, because the ^{18}F-labeled tracers allow imaging studies to be conducted in due course after the radiotracer injection [117]. MicroPET imaging studies use **[^{18}F]ISO-1** in a rodent model of breast cancer and **[^{18}F]RHM-4** in a rat model of brain cancer [118]. The former is in clinical Phase I study for imaging solid tumors with PET. Different clinical trials are completed or still going on in various cancer types (primary and metastatic breast cancer, head and neck cancer, and diffuse large B-cell lymphoma) [119].

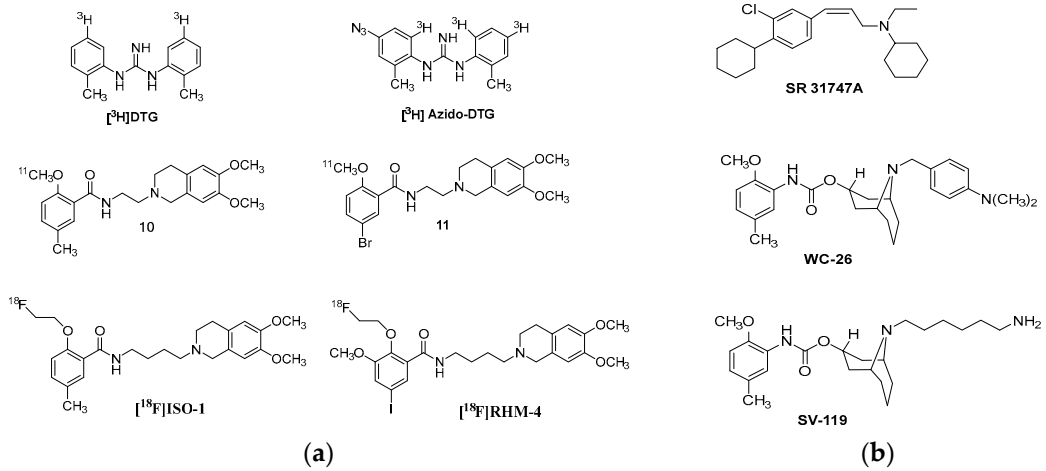

Figure 9. (**a**) Radiolabeled σ2R ligands for in vitro binding studies. ^{11}C-Labeled and ^{18}F-labeled conformational flexible benzamide analogs; (**b**) σ2R ligands for in vivo binding studies.

Several reports describe the antiproliferative and anticancer activity of σ2R ligands in variable cell lines and tumors [32,120,121] (Table 1). The last years, it has become obvious that σ2R ligands have significant role in anticancer therapy, as they provoke cancer cell death [32,121]. **Siramesine**

was active against all cancer cell lines tested. Recent experiments of **SV-119** and its congeners have been conducted in a pancreas tumor model with significant results, even though the mechanism of reaction is still elusive [122,123]. **SR31747A**, a mixed σ1/2R and human sterol isomerase binding affinity, has been tested for its anticancer activity, due to its efficacy at σRs. The significant in vitro pharmacological evaluation made **SR31747A** enter clinical trials for the treatment of androgen prostate cancer [124].

Table 1. σ2R ligands and their targets.

Origin	Species	Cell Line	σ2R Ligand
breast cancer	human	T47 D	**[^{3}H]DTG**
	human	MCF7	**[^{3}H]DTG**
	mouse	EMT-6	**[^{3}H]DTG,WC-26,SV-119**
colon cancer	human	primary tumor	**[^{3}H]DTG**
leukemia	human	Th-P1	**[^{3}H]DTG**
lung	human	NCI-H727	**[^{3}H]DTG**
melanoma	human	A375	**[^{3}H]DTG**
	human	MDA MB-435	**WC-26,SV-119**
neurologic	human	U-138MG	**[^{3}H]DTG**
	human	primary tumor	**[^{3}H]DTG**
	mouse	NB41A3	**[^{3}H]DTG**
	mouse	N1E-115	**[^{3}H]DTG**
	rat	C6	**[^{3}H]DTG**
pancreas cancer	mouse	Panc-02	**SV-119**
	human	Panc-01	**SV-119**
	human	AsPc-1	**SV-119**
	human	CFPAC	**SV-119**
prostate	human	LNCaP	**[^{3}H]DTG**
sarcoma	human	primary tumor	**[^{3}H]DTG**

Non-selective σR ligands, described as mixed σ1/2R ligands, are used in cancer diagnosis and therapy. Even though σ1R and σ2R are structurally different proteins, σ1R has been characterized as a chaperone protein [43,44] and σ2R seems to belong to a progesterone receptor complex (PGRMC1) [54], both of them share common ligands. Various publications refer to σR ligands that do not present receptor selectivity [31,125]. Cyclohexylpiperazine adducts have already been reported in the current context as non-selective σR ligands. Benzylpiperazines with σ1/2R affinity exhibit high antiproliferative activity against a wide panel of cancer cell lines [31]. Recent publications presented 1,4-benzodioxane- and 1,3-dioxolane-coupled benzylpiperazines as mixed σ1/2R ligands [126]. Moreover, the defect in binding selectivity becomes an advantage in tumor signaling. The overexpression of both σ1R and σ2R in prostate tumor and neuroblastoma [12,23,99] suggests that a dual σR radioligand might present an enhanced tumor targeting compared to a selective radioligand for a single σR subtype [127]. Another study confirms the same conclusion in radiolabeled pulmonary σR assigment [128].

5. Adamantane Derivatives with σR Binding Affinity, Antiproliferative and Anticancer Activity

Adamantane skeleton, usually characterized as "lipohilic bullet" [129], is the structural backbone of many drugs in clinical practice [130]. Various adamantane derivatives present σR binding affinity not related to antiproliferative or anticancer activity [125,131–135]. However, the following adamantane phenylalkylamines **VIII**, **IX** and **X**, as illustrated in Figure 10, exhibit σR binding affinity in combination with antiproliferative and anticancer activity [136–140].

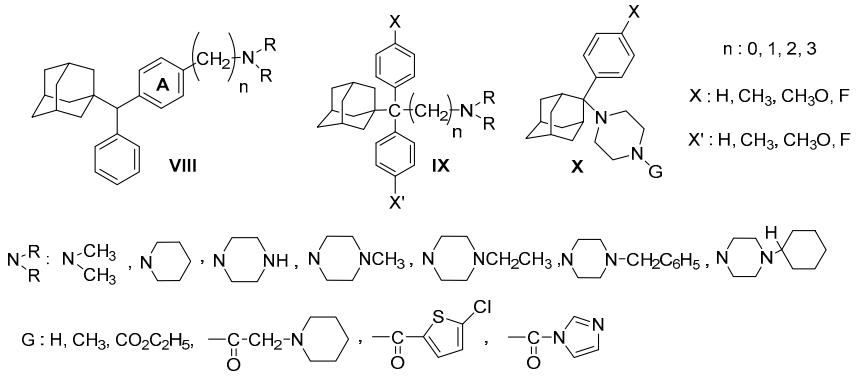

Figure 10. Adamantane derivatives with σR binding addinity and antiproliferative or anticancer activity.

The aforementioned adamantane adducts present the structural requirements for σR binding affinity (Figure 10). In the first adamantane scaffold **VIII**, benzene ring A is attached to the first piperazine nitrogen via a chain of three atoms (N, 2C) and in template **IX**, the benzene rings are linked to an amine nitrogen atom via a spacer of one, two and three methylene carbons. The substitution of the adamantane moiety has changed in 1-(2-aryl-2-adamantyl)piperazine derivatives **X**. All the above adamantane derivatives have a significant binding affinity for the σ1R and σ2R at a low nanomolecular range. Their antiproliferative activity against numerous cancer cell lines (colon, prostate, breast, ovarian, central nervous system, leukemia, pancreas, liver) was significant. These results in conjunction with their affinity for site 2 of the Na^+ channels imply that the adamantane phenylalkylamines **VIII**, **IX** and **X** have the pharmacological profile of mixed σ1/σ2R ligands [136–139].

1-Methyl-4-{3-[4-[α-(1-adamantyl)phenyl]phenyl]propyl}piperazine (**13**) presented an acceptable toxicological profile associated with an interesting antiangiogenic activity against tumors and was particularly prominent in (BxPC-3) pancreas, (DU-145 and PC3) prostate, (OVCAR-5) ovarian and (HL-60) leukemia xenografts on SCID mice [136]. 1-Methyl-4-{4-[α-(1-adamantyl) phenylmethyl]phenyl}piperazine (**12**) (σ1Ki = 3.2 nM, σ2Ki = 32 nM, σ1/σ2Ki = 11.8) was prominent in pancreas [137]. 4-[4,4-Diphenyl-4-(1-adamantyl)butyl]-1-methylpiperazine (**14**) (σ1Ki = 15 nM, σ2Ki = 60 nM, σ1/σ2Ki = 4) displays selective action against ovarian cancer on mice (IGROV-1) and presented as potent as cisplatin [138]. The above adamantane adducts were also tested with a prototypical study (formaline test) of their effect in putative neuropathic pain induced by anticancer drug Paclitaxel [28–30] and proved to be putative analgesic agents. 1-[2-(4-Fluorophenyl)-2-adamantyl]-4-(1-piperidineacetyl)piperazine (**15**) had also notable antitumor activity [139] (Figure 11).

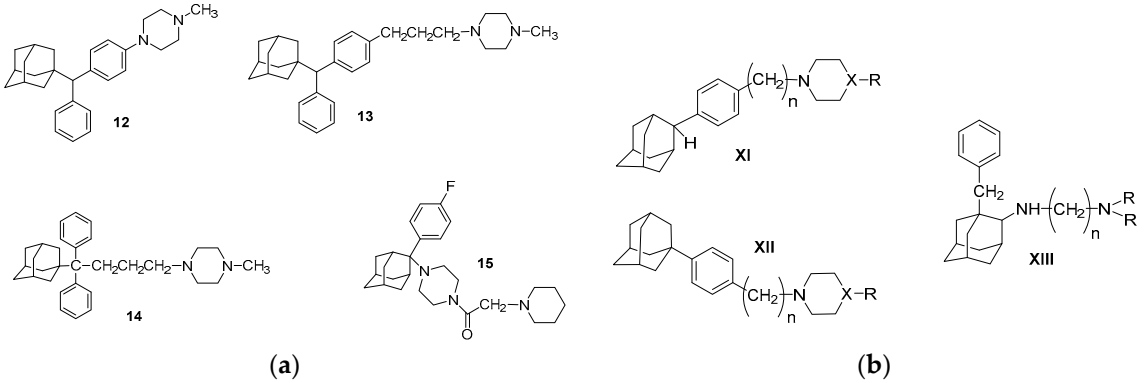

Figure 11. (**a**) Adamantane phenylalkylamines **12**–**15**; and (**b**) adamantane adducts with antiproliferative potency.

Finally, the following phenylalkylamines analogs with general type **XI** [141], **XII** [142] and **XIII** [143] have been reported for their antiproliferative activity and due to the similarities of their scaffold with compounds **VIII** and **IX**, it can be assumed that they act as σR ligands, although their binding affinities have not been investigated yet (Figure 11).

6. Conclusions

The reports described in our current review induce a new category of drugs against cancer. σRs are still poorly understood, but it has become increasingly apparent that these receptors have a significant role in cancer pathophysiology. σ1R Antagonists, σ2R agonists and mixed σ1R/σ2R ligands have antiproliferative and cytotoxic activity, even though their mechanism of action is under investigation. The fact that many σR ligands are in preclinical and clinical phase trials is a testimony of this improvement in cancer therapy.

Conflicts of Interest: The authors declare no conflict of interest.

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