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π-Cation Interactions in Molecular Recognition: Perspectives on Pharmaceuticals and Pesticides

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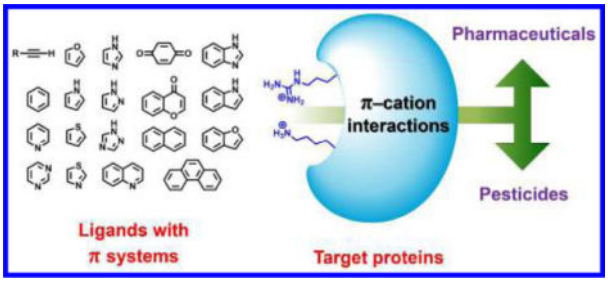
Abstract

The π-cation interaction that differs from the cation-π interaction is a valuable concept in molecular design of pharmaceuticals and pesticides. In this Perspective we present an up-to-date review (from 1995 to 2017) on bioactive molecules involving π-cation interactions with the recognition site, and categorize into systems of inhibitor-enzyme, ligand-receptor, ligand-transporter, and hapten-antibody. The concept of π-cation interactions offers use of π systems in a small molecule to enhance the binding affinity, specificity, selectivity, lipophilicity, bioavailability, and metabolic stability, which are physiochemical features desired for drugs and pesticides.

Graphical Abstract



Keywords

π-cation interaction; π-cation bond; molecular recognition; molecular design; pharmaceutical; pesticide; drug design

Introduction

Molecular recognition in biological systems relies on specific noncovalent interactions between partner molecules, including electrostatic interactions (e.g., salt bridge, hydrogen bond, and halogen bond), van der Waals interactions (e.g., dipole-dipole, dipole-induced dipole, and London dispersion forces), π-effects (cation-π, anion-π, polar-π, and π

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stacking) and hydrophobic effects. In particular, a positive charged molecule interacts with an electron-rich π system to form a strong π-effect termed the cation-π interaction or cation-π bond.[1, 2] Such an interaction is influenced by the nature of the cation and π systems, binding geometry, and solvation effects. Geometric criteria typically require a distance of ≤6 Å and an angle 60° ≤θ ≤90° between the π system and the cation center (Figure 1).[1, 2] Remarkably, the cation-π interaction comprises a substantial electrostatic characteristics, and the bonding strength is comparable to salt bridge and hydrogen bond in aqueous solutions and at physiological conditions.[3] Recent evidence indicates that the cation-π interaction is ubiquitous in nature and considerably counts on the ligand binding, which has brought attention to chemists, biologists, and material scientists.[4, 5]

Conceptually, there are two types of interactions between the π system and cationic partners depending on which one is the ligand or the ligand recognition site on a protein. In this context, cation-π interactions refer to a positive charged ligand interacting with aromatic amino acid residues (e.g., Phe, Tyr, or Trp) on target proteins. Such phenomenon has been extensively studied in the literature, as exemplified in classic cases that acetylcholine (ACh), nicotine, and muscarine with the quaternary ammonium specifically interact with Tyr and Trp residues of the mammalian acetylcholine receptors (AChRs)[6–8] (Figure 2A), and neonicotinoids selectively bind to the insect nAChR.[9, 10] Readers with interest are directed to the review articles by Dougherty et al. on the cation-π interaction[11, 12] and by Casida et al. on applications in the insecticide discovery.[13, 14] On the other hand, π-cation interactions, which were first recognized in a hapten-antibody system,[15, 16] refer to a small-molecule ligand with π systems interacting with cationic amino acid residues (e.g., protonated Arg or Lys) in target proteins (Figure 2B). Applications of the π-cation interaction concept in design of bioactive molecules, however, have not been fully exploited.

This Perspective therefore confines the scope on π-cation interactions and highlights the past development of bioactive small molecules that involve such interactions for ligand-protein recognition, primarily focusing on applications in analytical chemistry, biochemistry, medicinal chemistry, and pesticide chemistry. Some cases from our research group centering on inhibitor-enzyme and hapten-antibody interactions are elaborated. The π-cation interaction regarding protein folding, protein-protein interactions, and ligand-metal cofactor interactions is out of scope of this paper. A literature search was performed with the SciFinder database to cover a period from January 1995 to December 2017. We present our outlooks on potential applications of the π-cation interaction and bring attentions to use it as a tool in molecular design of pharmaceuticals and pesticides. The paper represents the first comprehensive review of the relevant literature on the topic of "π-cation interactions" in the past 22 years.

Inhibitor-Enzyme Interactions

Cytoplasmic enzymes without complex protein-protein or protein-membrane interactions are widely studied on the ligand-protein recognition in the literature. Glycogen synthase kinase-3β (GSK-3β), a serine/threonine protein kinase, is a therapeutic target for Alzheimer's disease, dipolar disorder, type-2 diabetes, inflammation, and many metabolic diseases. Co-crystallization of GSK-3β with an inhibitor PF-04802367 revealed that the

inhibitor binds at the ATP site of GSK-3β, where the triazole ring of PF-04802367 forms a strong π-cation interaction with Arg141 essential to its potency and selectivity.[17] *In silico* screening and synthesis led to the pyrimidin-4-one based GSK-3β inhibitors, which make π-cation interactions with Arg141 at the ATP site of GSK-3β.[18–21] Virtual screening and molecular docking also led to identification of GSK-3β inhibitors containing isoquinoline and quinazolinone scaffolds that favors π-cation interactions with Arg141 at the ATP site of GSK-3β.[22] Benzothiazinones are allosteric modulators of GSK-3β showing π-cation interactions with Lys205.[23] Aryl anilinomaleimide based inhibitors bind at the ATP site of GSK-3β and show π-cation interactions with Lys183.[24] Most recently, we applied the concept of π-cation interactions in drug design, and discovered a series of highly selective and potent GSK-3β inhibitors based on the 6-*C*-glycosylflavone scaffold.[25, 26] Comparative molecular modeling of GSK-3α/β isoforms indicated that the catechol B-ring of the 6-*C*-glycosylflavone inhibitors forms critical π-cation interactions with Lys183 at the substrate site of GSK-3β (Figure 3), but neither GSK-3α nor other 40 kinases tested, thereby achieving high GSK-3 isoform-selectivity and high kinase selectivity.[26]

Enzymes relevant to oncology are promising targets for cancer chemotherapy. Rho-associated protein kinases (ROCK1 and ROCK2) play a key role in cancer metastasis. The aminoindane triazine analogues inhibit ROCK1 in various cancer cell lines where the aminoindane moiety forms strong π-cation interactions with Lys105 of ROCK1.[27] The ROCK2 inhibitor CAY10576 showed π-cation interactions with Lys121.[28] Mitogen-activated protein kinases (MAPKs) including p38 kinases and extracellular signal-regulated kinases (ERKs) are aberrant in many tumors. The imidazolinone inhibitors form strong π-cation interactions with Lys53 of p38 kinase and Arg65 of ERK2 kinase in molecular docking studies.[29] The cyclin-dependent protein kinase-8 (CDK8) is involved in oncogenic control. The X-ray co-crystallographic analysis indicated that the aryl substituted thieno[2,3-*c*]pyridines are specific CDK8 inhibitors showing π-cation interactions with Arg356 at the ATP catalytic site.[30] The phytochemical thymoquinone forms π-cation interactions with Lys540 of the polo-box domain of polo-like kinase 1 (Plk1) responsible for anticancer activity.[31] Virtual screening of anticancer compounds also identified that many inhibitors of B-cell lymphoma extra-large proteins (Bcl-xL) show π-cation interactions between the aromatic rings of the inhibitors and the arginine residues (Arg100, Arg103, Arg132, Arg139 and Arg165) of Bcl-xL.[32] Inhibition of Poly [ADP-ribose] polymerase-1 (PARP-1) shows efficacy improvement for many cytotoxic agents in cancer therapy. Hexahydrobenzonaphthyridinones are potential anticancer agents showing favorable π-cation interactions with Arg217 and Lys242 at the catalytic site of PARP-1.[33] Ku86 enzyme and X-ray repair cross-complementing protein 4 (XRCC4) of the DNA-repair protein complex in tumors are burdens for cancer therapy. Lithospermic acid and salvianolic acid B, the traditional Chinese medicine (TCM) compounds, showed enzyme inhibitions, where the catechol ring of lithospermic acid interacts with Lys338 of Ku86 via π-cation forces,[34] while the two catechol rings of salvianolic acid B form π-cation interactions with both Lys187 and Lys190 of XRCC4.[35] Uroporphyrinogen decarboxylase (UROD) is implicated in resistance of cancer radiotherapy. The TCM compound scopolin containing the coumarin moiety forms π-cation interactions with Arg37 of UROD in molecular modeling.[36] Molecular and quantum mechanics analyses on the 5-isoxazolylbenzimidazole analogues

indicated that the binding affinity and selectivity are attributed to π-cation interactions between the aromatic moieties and Arg1173 of CREB-binding protein (CREBBP) bromodomains.[37] CREBBP associated with leukemia. The CDC25 phosphatase inhibitor IRC-083864 as a potential anticancer agent shows π-cation interactions with Arg548 of CDC25.[38]

Many antiviral and antibacterial compounds have also shown π-cation interactions with their targets. The diketo-acid compound S-1360 is a potent inhibitor of the human immunodeficiency virus type 1 (HIV-1) integrase, where the triazole ring forms π-cation interactions with Lys159 at the active site.[39] The tetrahydropyrimidine-2-one derivatives form π-cation interactions with Lys574 of glycoprotein 41 and inhibit HIV-1.[40] Molecular docking of the anti-influenza drug oseltamivir (known as Tamiflu) derivatives suggested that the aniline π system of analogues interacts with Arg152, Arg225 and Arg293 on neuraminidase of the influenza A virus (H1N1), thereby increasing the binding affinity and antiviral activities *in vitro*.[41, 42] Another class of antiviral compounds, naphthoquinones, inhibits H5N1 neuraminidase in part due to strong π-cation interactions with Arg224.[43] The phytochemical hesperetin inhibits chikungunya virus (CHIKV) activity. *In silico* study on hesperetin suggested apparent π-cation interactions with Arg70 and Arg374 in CHIKV nsP1 and nsP4 enzymes, respectively.[44] Virtual screening of the thiadiazole compounds also led to discovery of new CHIKV envelope glycoprotein inhibitors with specific π-cation interactions between Arg100 of E2 protein and Lys52 of E1 protein.[45] Baicalein is a plant-derived flavone known to show anti-dengue virus (DENV) activity. *In silico* analysis showed that baicalein forms multiple π-cation interactions with Lys42 and Lys74 in DENV NS3/NS2B protein, with Lys401 in DENV NS5 protein, and with Arg2 in DENV E protein.[46] Mechanistic investigations on the methicillin-resistant *Staphylococcus aureus* (MRSA) found that an antibiotic ceftaroline (known as Teflaro) binds at the allosteric site of penicillin binding protein 2A (PBP2A) and shows strong π-cation interactions with Lys273 and Lys316.[47] X-ray co-crystallographic analysis indicated that new β-lactamase inhibitors containing the benzoate group form π-cation interactions with Arg340 of the *Acinetobacter*-derived cephalosporinase (ADC-7) and inhibit the multidrug resistant bacterium *Acinetobacter baumannii*.[48]

Utilization of π-cation interactions has demonstrated successes in molecular design. For example, structure-based drug design led to discovery of 2,8-diazaspiro[4.5]decan-1-one analogues as new prolyl hydroxylase domain-containing protein 2 (PHD2) inhibitors for anemia treatment.[49] These analogues favor the π-cation interaction with Arg322 of PHD2 observed in the X-ray co-crystallographic complex.[49] Virtual screening of TCM for anti-aging natural products led to identification that (*S*)-tryptophan-betaxanthin and rosmarinic acid are potent agonists of NAD-dependent deacetylase sirtuin-1 (Sirt1), where their aromatic moieties form π-cation interactions with Arg274 of Sirt1 in molecular simulation studies.[50] γ-Aminobutyric acid aminotransferase (GABA-AT) regulates neurotransmission and is a therapeutic target in epileptic disorders. Aryl substituted 5,6-dihydropyrimidine-2(1*H*)-thiones are GABA-AT inhibitors and form π-cation interactions with Lys203A and Arg192A of GABA-AT.[51] Quantitative structure-activity relationship (QSAR) studies on the quinoline-4-carboxamide analogues with cytochrome P450 2C9 (CYP2C9) enzyme demonstrated that the π-cation interaction of the naphthalene moiety

with Arg108 increases the type II substrate binding affinity and prevents undesired drug-drug interactions and drug metabolism.[52] The isoflavone puerarin is a tyrosinase inhibitor forming a π-cation interaction with Arg268.[53] A synthetic aryl-copper complex [Cu(L^1)(Phen)] shows anticancer activity and proteasome inhibition, where the phenanthroline ring of the complex forms π-cation interactions with Arg125 of 20S proteasome.[54] Molecular dynamics study indicated that the phospholipase A2 (PLA2) inhibitors, PMS1062 analogues, form π-cation interactions with Arg7.[55] Studies on aryl lactosamine derivatives binding to human galectin-3 indicated that the aromatic rings show favorable π-cation interactions with Arg144 and Arg186.[56] Human macrophage migration inhibitory factor (MIF) is implicated in inflammatory and autoimmune diseases. The MIF inhibitor NVS-2 containing an anisyl group shows a π-cation interaction with Lys32 that leads to a striking increase of binding affinity.[57] Studies on 5-aminosalicylic derivatives indicated their binding to myeloperoxidase (MPO), which involves π-cation interactions with Arg239.[58] Succinate-coenzyme Q reductase (SQR) is a central enzyme in the respiratory chain and Krebs cycle, which is a target protein for pharmaceuticals and agricultural fungicides. Virtual screening and structure-based design led to discovery of many pyrazole-4-carboxamides as potent SQR inhibitors, where the pyrazole ring forms π-cation interactions with Arg46 of the C chain.[59–62]

Ligand-Receptor Interactions

Development of specific ligands to target protein receptors is continuously of great interest in drug discovery. Inspired by the classic cation-π interactions of ACh, nicotine, or muscarine with the AChRs, searching for novel aromatic ligands that specifically form π-cation interactions with cationic amino acid residues of protein receptors has been employed in the past years.

The *N*-methyl-D-aspartate (NMDA) receptor is a ligand-gated Ca^{2+} channel that mediates excitatory synaptic transmission in brains. It has been implicated in synaptic plasticity for motor and memory functions. Interestingly, a study on anesthetic aromatic compounds inhibiting the NMDA receptor indicated that the potency shows a higher linear correlation with π-cation electrostatic energy ($R^2 = 0.85$) than hydrophobicity ($R^2 = 0.30$) and molecular volume ($R^2 = 0.14$).[63] Such evidence substantiates the significance of π-cation interactions independent from hydrophobicity in molecular recognition, and implies potential in drug design. The type-3 serotonin receptor (5-HT_3R) is a pentameric ligand-gated ion channel mediating neuronal depolarization and excitation in nervous systems and is a therapeutic target for anti-emetics. The granisetron analogues are 5-HT_3R antagonists, in which the granisetron-bound crystal structure shows π-cation interactions with Arg55 of 5-HT binding protein.[64] Potassium channel subfamily K member 2 (K_{2P}2.1) is a dimeric voltage-gated ion channel essential in electrogenesis, ischemia and anesthesia. Co-crystallization of K_{2P}2.1 with two selective activators, an *N*-aryl-sulfonamide and a thiophene-carboxamide, defined a π-cation interaction with Lys271 of K_{2P}2.1 that controls binding selectivity.[65]

G protein-coupled receptors (GPCRs) are a class of transmembrane protein receptors involving tremendous cell signaling cascades, which are well-studied therapeutic targets for

human diseases. Vasopressin V1A receptor ($V_{1A}R$) is a GPCR that regulates platelet aggregation, glycogenolysis, and vascular contraction. Molecular modeling and QSAR study of 134 antagonists of $V_{1A}R$ containing benzoazepine, benzodiazepine, or 1-benzenesulfonyl-2,3-dihydro-1*H*-indole pharmacophores have demonstrated that π-cation interactions with Arg214 play an important role in the ligand binding to $V_{1A}R$ and thus contribute to the pharmacological effects.[66] Cannabinoid receptors (CB1/2) belonging to the GPCR subfamily are therapeutic targets for the treatment of neuropathic pain, glaucoma, inflammation, and cardiovascular disease. New CB2 ligands with benzimidazole and benzothiophene moieties show π-cation interactions with Lys109 responsible for the CB2 selectivity.[67]

Receptor tyrosine kinases (RTKs) are cell-surface receptors regulating diverse cellular processes and their dysfunctions have implicated in oncogenesis and cancer progression. Tropomyosin receptor kinase A (TrkA) is a RTK aberrant in different types of cancer. Salicylhydrazone analogues show TrkA inhibition in cancer cells, where the benzylidenephenyl ring of these inhibitors forms π-cation interactions with Arg673 in docking studies.[68] The biquinoline-pyridine hybrid compounds show potent inhibition against the epidermal growth factor receptor (EGFR, a RTK) and cytotoxicity against cancer cells, for which their aryl groups form π-cation interactions with Lys721 at the ATP catalytic site of EGFR.[69]

Protein receptors for protein tethering or protein-protein interactions are attractive targets for drug discovery. The urokinase receptor (uPAR), a cell membrane anchored protein, binds to protein partners and involves in plasminogen activation and cancer metastasis. Synthetic pyrrolinones inhibit uPAR against protein-protein interactions, where the π-cation interactions with Arg53 are critical as observed in the X-ray co-crystallographic structure.[70] Rational design of pro-inflammatory cytokine interleukin-2 (IL-2) inhibitors to prevent the cytokine/receptor interaction resulted in the finding that 2-methyl-1*H*-indole derivatives show strong binding affinity to IL-2 via π-cation interactions with Arg38.[71]

Ligand-Transporter Interactions

The π-cation interaction has also been found between aromatic ligands and protein transporters. The cytotoxic flavonoid derivative 3d binds with human serum albumin (HSA), by which its π-cation interactions with Lys199, Arg218, and Arg222 in HSA are critical for drug deposition and delivery.[72] The two antidiabetics, glipizide and gliclazide, bind HSA through π-cation interactions with Lys190 and Arg410, respectively.[73] Some imidazolium and pyridinium based antimicrobials show π-cation interactions with Lys195 and Arg257 of HSA.[74]

Hapten-Antibody Interactions

In the past years, the π-cation interaction between aromatic haptens and antibodies has been applied in immunoassay development for environmental management, food safety and human health relevance. The ample utilities of such methods are applicable to biomedical and agricultural areas.

Polycyclic aromatic hydrocarbons (PAHs) are pollutants derived from incomplete combustion of organic substance such as biofuel, fossil fuel, wood, cigarette, and charcoal-broiled meat. Some PAHs such as benzo[a]pyrene (BaP) are carcinogenic, mutagenic, and immunosuppressive. In our early work to develop sensitive immunoassays for detection of PAHs, we reported that the monoclonal antibody 4D5 can recognize a wide range of PAHs including BaP.[15] Mutagenesis and molecular modeling studies demonstrated that the aromatic π system of BaP forms strong interactions with LysL89 and ArgH95 at the binding site of the antibody 4D5 (Figure 2B).[16] To the best of our knowledge, the study[16] provided the first evidence with a mechanistic basis on π-cation interactions in hapten-antibody recognition, which stimulates active researches on PAHs immunoassay development and application in the following years. New PAH hapten derivatives, for example, were designed to produce monoclonal antibody B[a]P-13 with different immunospecificity.[75] The fluorescence line-narrowing spectroscopy has been used for specific analyses of complex PAHs cross-reacted with monoclonal antibodies.[76] Most recently, we engineered a ring-hydroxylating dioxygenase mutant for the catabolism of BaP by which the molecular mechanisms are involved in the π-cation and π-π stacking interactions.[77]

Polychlorinated biphenyls (PCBs) are ubiquitous, persistent and toxic organic pollutants in the environment. We found that PCBs specifically bind to the monoclonal antibody S2B1, where the PCB phenyl ring plays a pivotal role in π-cation interactions with ArgL46 at the active binding site.[78–80]

Future Perspectives

Taking advantage of π-cation interactions as a molecular design tool can improve many key features of bioactive chemicals: (1) binding affinity, (2) specificity and selectivity, (3) lipophilicity and bioavailability, and (4) metabolic stability. As elaborated above, the concept of π-cation interactions has been adopted by chemists in drug and pesticide discovery and environmental management (Table 1 and Figure 4). However, in the field of pesticides (including growth regulators), the community has not paid adequate attention as only four relevant papers on the development of SQR inhibitors[59–62] were found in the past 22 years.

The π-cation interaction is universal in biology and would have an ample application in diverse areas. Pharmaceuticals and pesticides, although aiming at different markets, are developed in a similar process. In the early stages of R&D, both are involved in target protein identification, bioassay screening, hit-to-lead, and lead optimization. In terms of target proteins, humans, plants, insects, nematodes, fungi, and bacteria share a number of homologous proteins such as cytoplasmic enzymes, GPCRs, ion channels, signaling receptors, and carrier proteins.[81, 82] Indeed, many drugs and pesticides show similar chemical structures and biological functions.[83] The concept of designing bioactive molecules to target human proteins in neurological system, cellular respiratory chain, and fatty acid/amino acid biosynthesis is applicable to relevant target proteins in pest insects or weeds.

Modern drug or pesticide discovery begins with the screening of synthetic or natural chemical libraries by means of either *in vitro* bioassay or *in silico* approach against target

proteins. Pre-selection of those chemicals with aromatic rings in consideration of π-cation interactions could plausibly increase screening hits and facilitate hit-to-lead process. Biopesticides are an emerging field of agricultural chemistry.[84] Many natural products such as phytochemicals and TCM are known to their conjugated π systems in chemical structures and have shown successes in drug discovery.[85] Prioritization of those aromatic natural products in screening might lead to promising biopesticides.

Regarding the process of molecular design and optimization, both pharmaceuticals and pesticides need to achieve high specificity and selectivity to minimize human and environmental toxicities and adverse effects. The illustrated cases here have underscored the advantage of π-cation interactions for the improvement of ligand-binding affinity and specificity. To design and optimize structures, the relative strength of π-cation interactions for the ligands can be estimated by simulation of the binding free energy. Moreover, lipophilicity is an important physicochemical parameter in chemical optimization.[86] Application of π-cation interactions in drug/pesticide design not only offers the use of aromatic π systems in a small molecule for selective, specific and high affinity molecular recognition by the target protein, but also allows appropriate adjustment of ligand bioavailability (e.g., lipophilicity, p*K*a, and solubility), transport, distribution, and metabolism. Pesticides are often used for contact management such as seed treatment and aerial application, which requires effective chemical absorption into pests. A moderate lipophilicity is therefore desirable for pesticide absorption.

Overall, the π-cation interaction is common in molecular recognition. It is a rational and feasible concept for molecular design. In the past decade, there have been some applications of π-cation interactions, but the value is still underappreciated. We believe this Perspective would shed light upon continued studies in the field of pharmaceuticals and offer new insights to the agrochemical community.

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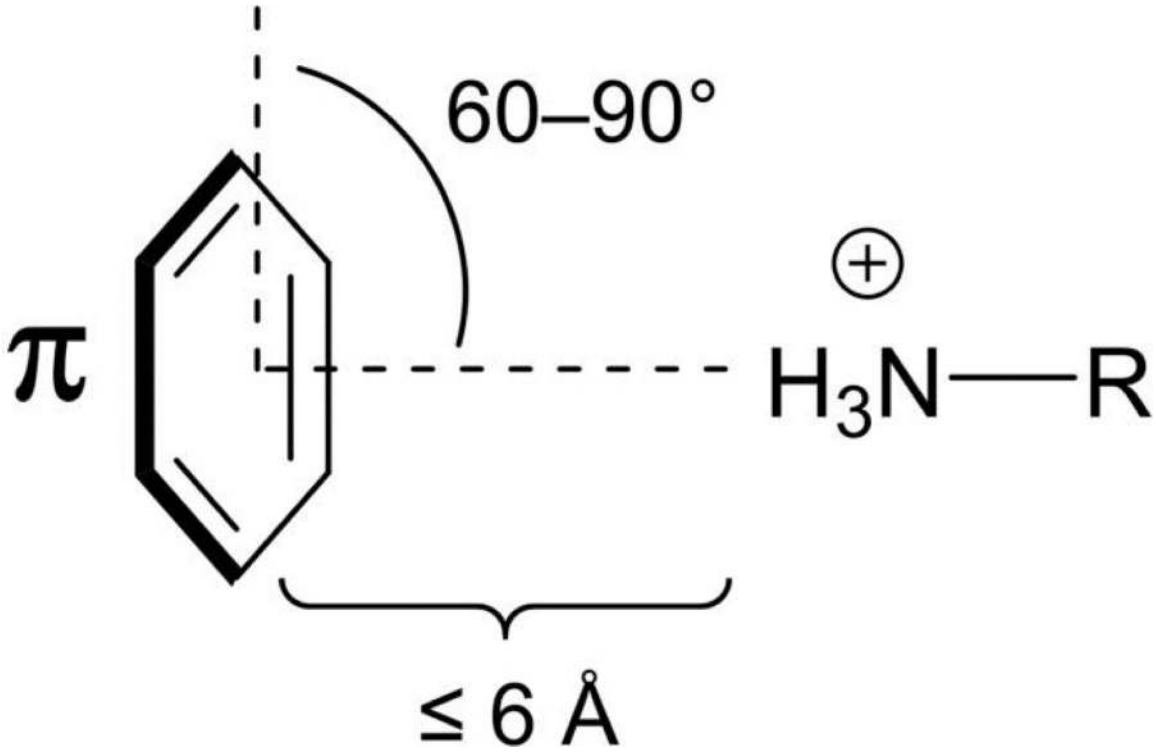

Figure 1.
Basic geometric criteria for the π-cation interaction as exemplified with benzene and an ammonium cation.

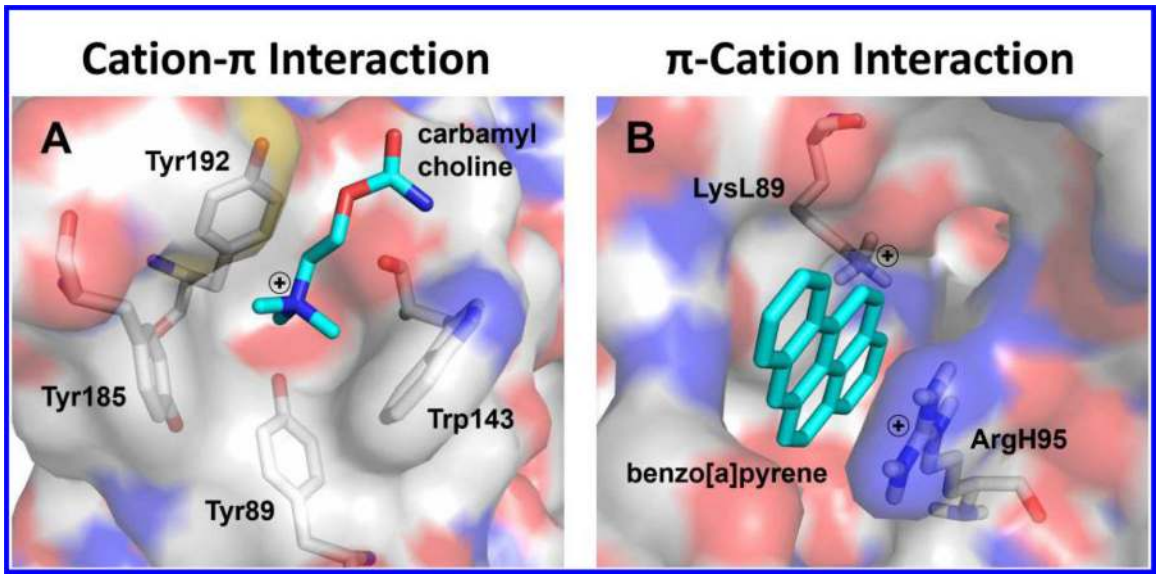

Figure 2.

Comparison of the cation-π and π-cation interactions in ligand-protein recognition. (A) Carbamylcholine binding to acetylcholine binding protein. Model from PDB code 1UV6 (ref. 7). (B) Benzo[a]pyrene binding to monoclonal antibody 4D5. Model from reported data (ref. 16).

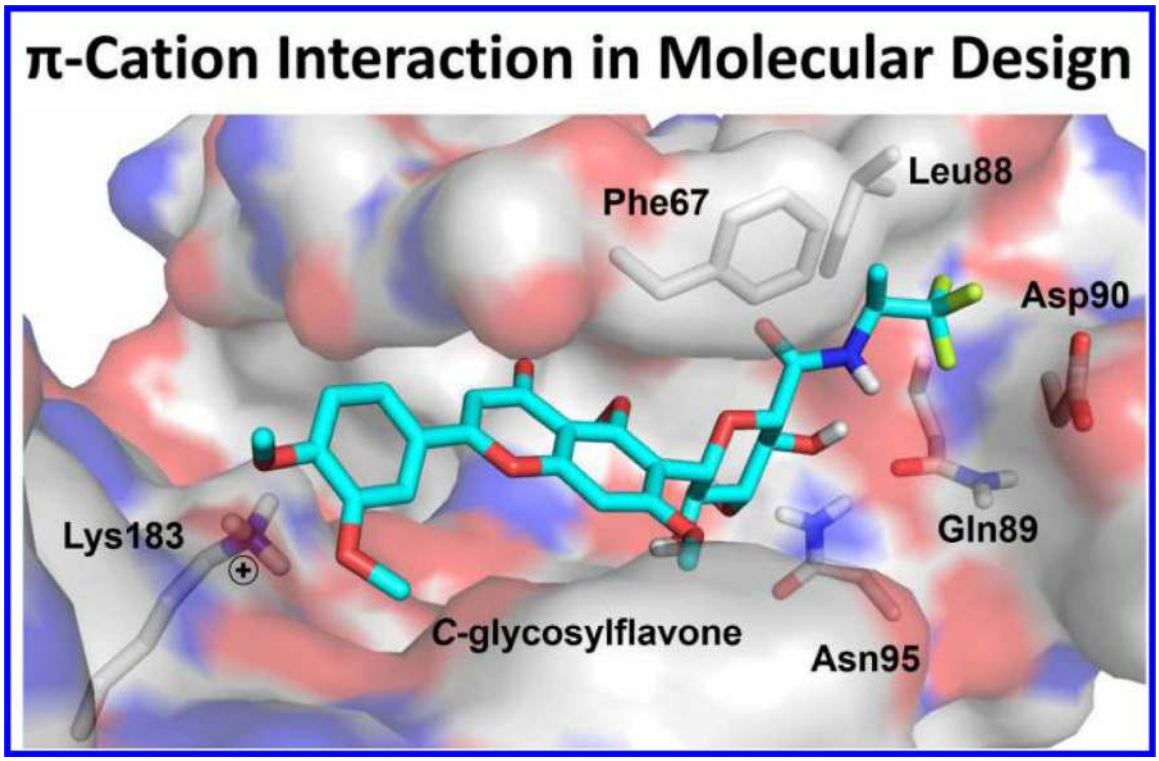

Figure 3.

Application of π-cation interactions in computer-aided drug design of GSK-3β inhibitors. The new inhibitor containing a *C*-glycosylflavone scaffold binding to GSK-3β, and the catechol ring forms a π-cation interaction with Lys183. Model from reported data (ref. 26).

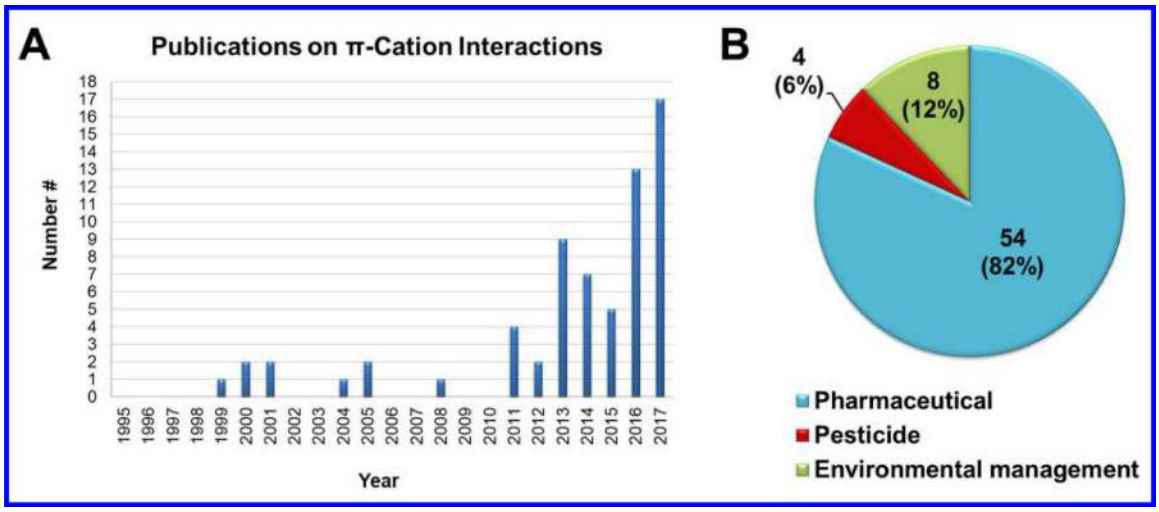

Figure 4.

Publications on π-cation interactions in ligand-protein recognition from 1995 to 2017. (A) A chronology of publication counts. (B) Distribution of research focuses on pharmaceuticals, pesticides, and environmental management.

Table 1.

Reviewed π-Cation Interactions in Ligand-Protein Recognition from 1995 to 2017

class	ligand	target protein	Functional relevance	ref.
inhibitor-enzyme	PF-04802367	GSK-3β	Alzheimer	17
	pyrimidin-4-ones	GSK-3β	Alzheimer	18–21
	imidazo-isoquinolines quinazolinones	GSK-3β	psychiatric disorder	22
	benzothiazinones	GSK-3β	diabetes	23
	aryl anilinomaleimides	GSK-3β	depression	24
	6-*C*-glycosylflavones	GSK-3β	Alzheimer	25, 26
	aminoindane triazines	ROCK1	cancer	27
	CAY10576	ROCK2	cancer	28
	imidazolinones	p38 kinase and ERK2	cancer	29
	aryl thieno[2,3-*c*]pyridines	CDK8	cancer	30
	thymoquinone	PBD-Plkl	cancer	31
	polyaromatic ligands	Bcl-xL	cancer	32
	hexahydrobenzonaphthyridinones	PARP-1	cancer	33
	lithospermic acid	Ku86	cancer	34
	salvianolic acid B	XRCC4	cancer	35
	scopolin	UROD	cancer	36
	5-isoxazolylbenzimidazoles	CREBBP	cancer	37
	IRC-083864	CDC25	cancer	38
	S-1360	HIV-1 integrase	HIV/AIDS	39
	tetrahydropyrimidine-2(1*H*)-ones	glycoprotein 41	HIV/AIDS	40
	oseltamivir analogues	neuraminidase	influenza virus	41, 42
	naphthoquinones	neuraminidase	influenza virus	43
	hesperetin	CHIKV proteins nsP1 and nsP4	chikungunya virus	44
	thiadiazoles	CHIKV envelope glycoproteins E1 and E2	chikungunya virus	45
	baicalein	DENV proteins NS3/NS2B, NS5 and E	dengue virus	46
	ceftaroline	PBP2A	Antimicrobial resistance	47
	S02030 analogues	ADC-7	Antimicrobial resistance	48
	2,8-diazaspiro[4.5]decan-1-ones	PHD2	anemia	49
	(*S*)-tryptophan-betaxanthin rosmarinic acid	Sirtl	aging	50
	aryl 5,6-dihydropyrimidine-2(1*H*)-thiones	GABA-AT	epileptic disorder	51
	quinoline-4-carboxamides	CYP2C9	drug-drug interaction, drug metabolism	52
	puerarin	tyrosinase	skin disorders	53
	aryl-copper complexes	20S proteasome	cancer	54
	PMS1062	PLA2	inflammation	55
	aryl lactosamines	galectin-3	fibrosis	56
	NVS-2	MIF	inflammation	57
	5-aminosalicylic derivatives	MPO	inflammation	58

class	ligand	target protein	Functional relevance	ref.
ligand-receptor	pyrazole-4-carboxamides	SQR	respiratory chain in mitochondria	59–62
	volatile benzene analogues	NMDA receptor	anesthetics	63
	granisetrons	5-HT_3R	emetics	64
	N-aryl-sulfonamide thiophene-carboxamide	K_{2P}2.1	electrogenesis, ischemia and anesthesia	65
	benzoazepines	V1aR	platelet aggregation,	66
	benzodiazepines		glycogenolysis,	
	1-benzenesulfonyl-2,3-dihydro-1*H*-indoles		vascular contraction	
	benzimidazoles benzothiophenes	CB1/2 receptor	neuropathic pain	67
	salicyl-hydrazones	TrkA	cancer	68
	biquinoline-pyridines	EGFR	cancer	69
	phenyl pyrrolinones	uPAR	cancer	70
	2-methyl-1*H*-indoles	IL-2R	immune response	71
ligand-transporter	flavonoid derivative 3d	HSA	drug delivery	72
	glipizide and gliclazide	HSA	diabetes	73
	imidazolium/pyridinium analogues	HSA	antibiotics	74
hapten-antibody	PAHs	mAb 4D5	pollutant detection, cancer	15, 16
	PAHs	mAb B[a]P-13	pollutant detection, cancer	75
	PAHs	mAbs anti-PAH, 4D5, and 8E11	pollutant detection, cancer	76
	PAHs	RHD	Pollutant bioremediation	77
	PCBs	mAb S2B1	pollutant detection, cancer	78–80