CHAPTER TWENTY-EIGHT

Drug Design Strategies for GPCR Allosteric Modulators

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Contents

1. Introduction 442
   1.1 The relevance of allosteric receptor modulation in today's therapeutic drug research 442
   1.2 The medicinal chemist's jargon of allosterism: NAM, PAM, SAM, allosteric agonists, ago-PAMs, bitopic ligands, probe dependency 443
   1.3 What is so unique about designing allosteric modulators? 443
   1.4 How do allosteric ligands exert their function? 444
2. Structure–Activity Relationships of Allosteric Ligands 444
   2.1 High-throughput screening of allosteric modulators: "Flat SAR" 444
   2.2 Functional switches 445
   2.3 Can functional switches be "designed"? 447
3. Functional Selectivity 448
   3.1 Probe dependency 448
   3.2 Receptor hetero- or homo-oligomerization 448
   3.3 Biased signaling 449
4. What to Optimize: IC_{50}? EC_{50}? E_{MAX}? Fold-Shift? Log($\alpha\beta$)? 449
   4.1 "Pure PAMs" 450
   4.2 Are compounds with ago-PAM activity and pure PAMs truly different? 450
5. Do *In Vitro* Profiles Translate to *In Vivo* Pharmacology? 452
6. Assessing Allosteric Site Occupancy Through Radioligands and Pet Agents 453
7. Medicinal Chemistry Strategies for Allosteric Ligands 454
8. Conclusions 455
References 455

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ABBREVIATIONS

Ago-PAM allosteric ligand acting as agonist in the absence of orthosteric ligand and also potentiating the effect of an agonist
GPCR G-protein-coupled receptor
NAM negative allosteric modulator
PAM positive allosteric modulator
Pure PAM positive allosteric modulator not showing functional activity in the absence of an orthosteric ligand
SAM silent allosteric modulator

1. INTRODUCTION

1.1. The relevance of allosteric receptor modulation in today's therapeutic drug research

A large fraction of marketed prescription drugs are ligands acting at cell membrane G-protein-coupled receptors (GPCRs), making this class of proteins one of the two most fruitful therapeutic target families, together with enzymes.[1,2] Recently, terms such as "nondruggable GPCRs" have been coined to describe a unique group of GPCRs having strong biological hypothesis validation, but for which medicinal chemistry efforts based on orthosteric ligands (those binding at the same site than the endogenous ligand) have failed to produce marketed drugs (or even clinical development candidates).[3] These receptors remain attractive as biological targets for new drugs, but a novel medicinal chemistry strategy must be developed to modulate their biological effects.

Recently, a new "wave" of drug discovery research has emerged to fill this gap, purposely aiming to modulate target receptors by the use of allosteric ligands, which interact with the receptor at a binding site topographically distinct from the endogenous ligand. By binding at this new receptor region, challenging chemical space may be avoided. Moreover, enhanced subtype selectivity profiles may be obtained compared with that of an orthosteric agent binding to a highly conserved site, potentially leading to improved safety and pharmacology profiles. Furthermore, the lack of desensitization arising from receptor overstimulation under constant exposure to an agonist, and preservation of the temporal and local patterns of physiological activity of the endogenous ligand are additional appealing attributes of allosteric modulators.[3–6]

As research in allosteric modulator drug design intensifies, some empirical observations are emerging. The objective of this review is to briefly discuss

these concepts and present a number of medicinal chemistry strategies to address current challenges in a productive manner from the drug discovery standpoint.

1.2. The medicinal chemist's jargon of allosterism: NAM, PAM, SAM, allosteric agonists, ago-PAMs, bitopic ligands, probe dependency

The binding interactions between a given allosteric ligand and a GPCR can generate a number of different conformational states, both on their own and when an orthosteric ligand is bound. The consequence of this added complexity results in pharmacological texture that is ligand-, receptor-, and cell dependent.[4] The terminology used to describe such a plethora of possibilities has recently been discussed in a number of excellent reviews.[5–7] The reader's familiarity with these terms is assumed.

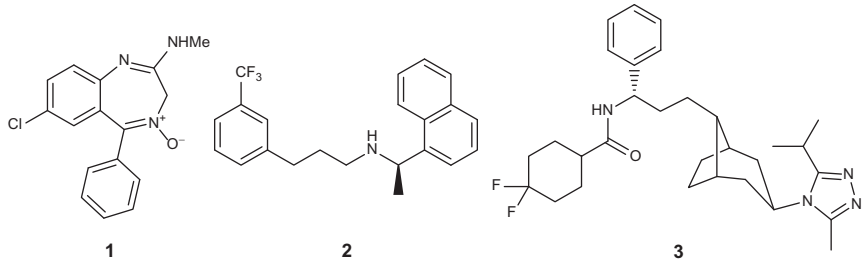
1.3. What is so unique about designing allosteric modulators?

Benzodiazepines such as Librium, **1**, acting as $GABA_A$ receptor modulators, have inadvertently become the earliest clinical success story of allosteric modulation. Several drug candidates acting through allosteric mechanisms are currently undergoing clinical trials. The phenomenon appears quite broad in scope, as allosteric modulators have been reported for family A, B, and C GPCRs, as well as ion channels, kinases, and phospholipases.[5]

In retrospect, a number of "noncompetitive receptor antagonist" projects (e.g., CRF-1, NK_1, CGRP, GnRh receptors) had actually been toiling on negative allosteric modulators (NAMs) instead.[8] Thus, this is not necessarily "uncharted territory" for the medicinal chemist working to design drugs. However, it should be noted that thorough differentiation between antagonists and NAMs is not trivial or even currently possible (e.g., with orphan receptors of unknown endogenous agonist).[9]

Recently, Cinacalcet, **2**, a calcium-sensing receptor (CaSR) positive allosteric modulator (PAM), and Maraviroc, **3**, a CCR5 NAM, have reached the market. Besides the obvious merit of helping patients, these two drugs highlight the potential of allosteric ligands to accomplish unique biochemical tasks. Cinacalcet potentiates the effects of an inorganic agonist (Ca^{2+}) on a class C GPCR (CaSR) through a stimulus-biased mechanism (see Section 3.3).[10] Maraviroc precludes the functional outcome derived from interactions between small proteins called chemokines and the surface subunit of the HIV-1 envelope glycoprotein (gp120) signaling through CCR5, one of the main chemokine receptors involved in the HIV entry process. Thus, **3**

competes favorably with other mechanisms of action such as chemically modified chemokines and monoclonal antibodies.[11]



1 2 3

1.4. How do allosteric ligands exert their function?

For decades, medicinal chemists have learned to design drugs that bind at orthosteric sites using classical concepts such as "lock and key," where the rigidity of the binding site is a fundamental premise. Such rigidity supports the use of linear drug design strategies, where different structural regions can be optimized independently, and then the final drug candidate emerges from a combination of optimized fragments.

Affinity is a key optimization parameter and remains so in allosteric modulator drug design. However, two allosteric drugs may bind at the same receptor with the same affinity, yet provide different responses not only from the functional perspective (e.g., positive or negative modulation) but also by differing in the specific signal transduction pathway being engaged. This functional selectivity has been rationalized by considering protein dynamics concepts: the flexible nature of the protein receptor backbone and the changes in free energy landscape arising upon binding.[12] The existence of multiple distinct allosteric binding sites on the same target would also be consistent with experimental observations, and some evidence indicates this may be possible.[13] Thus, establishing structure–functional outcome relationships often leads to challenges in optimization strategies, adding unpredictability and complexity to drug discovery efforts.

2. STRUCTURE–ACTIVITY RELATIONSHIPS OF ALLOSTERIC LIGANDS

2.1. High-throughput screening of allosteric modulators: "Flat SAR"

From a tactical viewpoint, the process to discover an optimized drug candidate from an initial screening hit is divided in stages. After each stage, the qualities of the chemical entities are becoming closer to those desired

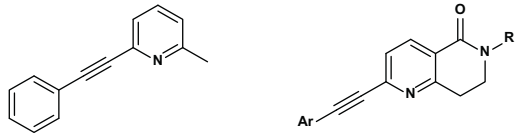
for clinical success. As a consequence of progress in parallel synthesis and high-throughput screening technologies, screening campaigns based on functional readouts may produce a large number of confirmed hits, depending on library size and biological activity cutoffs. For example, a recent mGlu3 receptor "triple add"-based screening on a collection containing 829,000 compounds delivered 23 agonist hits, 121 PAM hits, and 866 antagonist hits after concentration–response curves and selectivity counter-screens.[14]

Before starting a lead identification or optimization program, a prioritization exercise should be undertaken, as not every hit will correspond to a series with chemically tractable SAR.[15] The specific hit prioritization strategy followed depends on the library composition (singletons and close analogs), and it includes considerations of favorable ligand metrics.[16] However, early efforts developing SAR from HTS allosteric modulator hits revealed that the phenomenon known as "*flat SAR*" appears considerably more widespread than with orthosteric ligands. This is the characteristic shown by some (but not all) hits, whereby very small changes of structure lead to inactive compounds, or point toward very shallow and narrow SAR patterns. Flat SAR is seen often with PAMs.[17] Thus, chemical tractability of allosteric modulators cannot be taken for granted. Unfortunately, physicochemical attributes and good ligand metrics do not foretell of allosteric modulator SAR tractability. Thus, the goal for hit prioritization of allosteric modulators is to select those chemotypes with *both* SAR tractability and encouraging ligand efficiency/physicochemical property attributes, therefore adding value to drug discovery programs through the discovery of such truly optimizable allosteric ligand chemical series.

2.2. Functional switches

Alternations of agonist/antagonist activity with small structural changes in a given chemotype are not unknown for orthosteric ligands.[18,19] However, it appears as though allosteric modulators show this phenomenon with a relatively high frequency. In addition, patterns of structural factors governing these switches can be subtle.[20]

The mGlu5 receptor has gained notoriety (and made drug discovery efforts more challenging) for the apparently unpredictable way in which these switches occur, in particular, with analogs derived from MPEP (**4**), an early tool compound. However, when close analogs are designed and their biological activity analyzed systematically, some trends can be picked up. For example, two independent reports on a number of *N*-substituted 2-(arylethynyl)-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one analogs (**5**, **6**;



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5 (Ar=Ph)
6 (Ar=3-F-Ph)

Compound	R	$mGlu_5$ EC_{50} or IC_{50} (nM)	% Glu Max	Functionality
6a	H	290	72	PAM
6b	CH_3	170	34	NAM
6c	*t*-Bu	54	40	PAM
6d	*n*-Bu	56	46	PAM
6e	$CH_2(CH_2)_3$	660	34	NAM
6f	$CH_2(CH_2)_4$	130	53	PAM

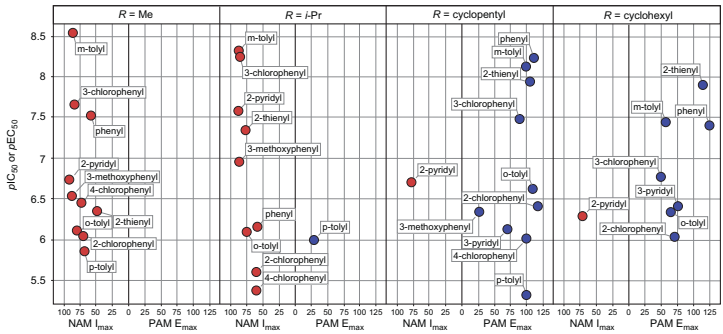


Figure 28.1 Switches in functional potency and efficacy for a series of *N*-substituted 2-(arylethynyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one analogs (**5**), Ar as specified in the table.

Fig. 28.1) showed that *N*-methyl or *N*-isopropyl substituents delivered predominantly NAMs, while increasing the *N*-substituent to cyclopentyl or cyclohexyl primarily yielded PAMs.[21,22]

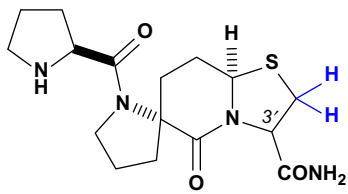
It is important to note that not all chemical series binding to an allosteric site of a given receptor will present switches to the same degree. From a strategic viewpoint, the process of lead optimization is greatly facilitated when a chemotype is chosen where functional switches are nonexistent or present themselves only sporadically.

The untoward possibility exists that metabolites derived from allosteric modulator drugs may have different functional activity than the "parent." While specific examples of metabolic functional switches have not been published, it is clear from the literature that many of the changes that lead to functional switches could occur through hepatic metabolism. Again, this is not unique to allosteric site ligands, but the higher frequency with which

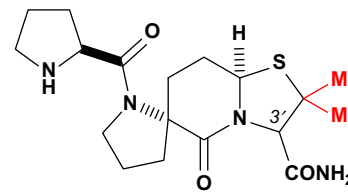
these functional switches are seen in *in vitro* tests with these ligands may lead to an increased risk of misinterpreting observations from *in vivo* pharmacological studies, or when establishing pharmacokinetic/pharmacodynamic relationships if such metabolites remain in circulation. Therefore, conducting a comprehensive metabolite identification study may be necessary to support conclusions from *in vivo* tests.

2.3. Can functional switches be "designed"?

The challenge represented by switches of functional activity between positive and negative allosterism within a chemotype can be transformed into an opportunity to design compounds with specific properties. For example, the synthesis of dimethyl derivatives of [5.6.5] spiro bicyclic lactam Pro-Leu-Gly-NH_2 peptidomimetics **7** and **8** was carried out to test the hypothesis that by placing geminal methyl groups on the β-methylene carbon of the thiazolidine ring steric bulk would be introduced into the topological space that the β-methylene carbon is believed to occupy when binding to the dopamine D_2 receptor. As a result of this modification, a PAM was converted into a NAM.[23]

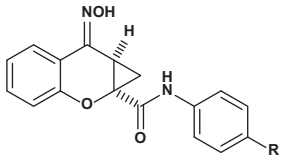


7 (3′=*S* (▮▮▮▮))
8 (3′=*R* (▬))
D2R PAMs



9 (3′=*S* (▮▮▮▮))
10 (3′=*R* (▬))
D2R NAMs

Importantly, the integration of theoretical and experimental methods in protein dynamics and crystallography, NMR, and FRET/BRET techniques is beginning to shed light on possible allosteric signal transmission mechanisms, aiming to facilitate the design of much improved allosteric drugs.[24] A strategy was explored using a FRET-based binding assay to identify compound **11** as an mGlu2 receptor silent allosteric modulator (SAM). Although **11** was relatively weak ($K_i = 6.6$ μM), higher-affinity close analogs with mGlu2 NAM functionality were quickly obtained.[25] While this exercise provided "proof of concept" that SAMs may be stepping stones in programs aiming for identification of allosteric ligands using novel technologies, the *predictive* use of such strategy is far from being realized.



Compound	*R*	FRET K_i (μM)	NAM IC_{50} (μM)
11	F	6.6	Not active up to 100 μM
12	Cl	1.0	0.8
13	Me	0.6	1.5
14	OMe	0.8	1.0

3. FUNCTIONAL SELECTIVITY

Allosteric modulators, even those with very closely related chemical structures, can vary in their capacity to activate or inhibit functional responses in cells upon binding to a GPCR. This may originate from a number of different mechanisms.

3.1. Probe dependency

Theoretical support and experimental evidence exist, demonstrating that the specific nature of the effect of an allosteric modulator at a given receptor may vary with different orthosteric ligands.[26] Because of probe dependency, it is important to use a physiologically relevant orthosteric ligand (typically an agonist) during screening. This may be an issue when dealing with endogenous ligands which are unstable (e.g., acetylcholine); are intrinsic components of cellular systems, thus making their exact concentration variable (e.g., GABA or glutamate); have weak affinities for the orthosteric site, requiring prohibitively high concentrations for *in vitro* testing due to cell toxicity (e.g., glutamate at the mGlu7 receptor); or when more than one endogenous agonist exist (e.g., GLP-1(7-36)NH_2 and oxyntomodulin, endogenous GLP-1 receptor agonists[27]; L-serine-*O*-phosphate as endogenous agonist at mGlu4 receptor[28]).

In some cases, a stable (e.g., the cholinergic agonist pilocarpine) or a potent nonendogenous agonist (e.g., synthetic group 3 mGlu receptor agonist L-AP4) may be used, provided some measures are taken to mitigate the risk introduced. If more than one endogenous agonist exist, occasional testing against all known modulators may be advisable. If so, early characterization in appropriate *in vitro* and *in vivo* screens is recommended.

3.2. Receptor hetero- or homo-oligomerization

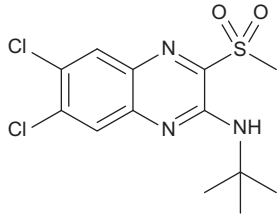
Adding complexity to this picture, functional effects derived from GPCR activation may be mediated by receptor hetero- or homo-oligomerization. For example, dopamine, serotonin, and glutamate play a role in the pathophysiology of schizophrenia. In the brain, a functional cross talk between the

serotonin receptor 5-HT_{2A} and the mGlu2 receptor has been demonstrated[29]; however, its biological significance has been challenged.[30]

3.3. Biased signaling

Upon ligand binding, GPCRs generate second messengers (e.g., cAMP, calcium, phosphoinositides) by acting through different signaling pathways besides heterotrimeric G-proteins, such as β-arrestins and GPCR kinases.[31] If the endogenous orthosteric ligand acts by stabilizing a subset of receptor conformations considered "unbiased," allosteric ligands might stabilize a different receptor conformation subset, leading to signaling through different pathways. Thus, GPCR potentiation by ligands does not always lead to uniform activation of all potential signaling pathways mediated by a given receptor. When comparing structurally different ligands, some of these may be biased toward producing subsets of receptor behaviors.[32]

This introduces a challenge, as well as an opportunity, to design compounds aiming specifically at a biological pathway inducing therapeutically meaningful agonist bias.[33] The first evidence that an allosteric modulator used in clinical practice (Cinacalcet) exhibits stimulus bias was recently reported.[10] Previously, GLP-1 receptor allosteric ligands **15** and **16** were found to differentially modulate endogenous and exogenous peptide responses in a pathway-selective manner.[27] The detection of such stimulus bias at a GPCR requires investigation across multiple signaling pathways and the development of methods to quantify the effects of allosteric ligands on orthosteric ligand affinity and cooperativity at each pathway. Evaluating compounds in the appropriate tissue for a given therapeutic indication will mitigate this risk.



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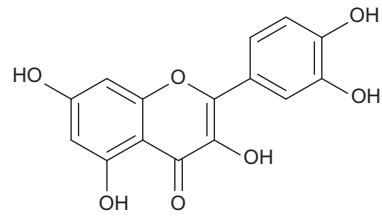

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4. WHAT TO OPTIMIZE: IC_{50}? EC_{50}? E_{MAX}? FOLD-SHIFT? LOG($\alpha\beta$)?

While allosteric modulation has been reported for a variety of receptor classes, the compound optimization strategy for allosteric ligands of different biological targets requires careful consideration of compound-dependent

attributes, as well as the specific biological modulation aimed for. In other words, two allosteric modulator programs at two different targets within the same family (i.e., mGlu2 or mGlu3 receptors) may optimize compounds toward a different set of allosteric ligand properties.

4.1. "Pure PAMs"

Quantification of pharmacological effects of allosteric ligands is more complex than for orthosteric ligands.[34] Generally, concentration–response curves are compared using *in vitro* tests, measuring the orthosteric agonist functional response in the presence of increasing concentrations of allosteric modulator. Excellent discussions of these experiments and the mathematical models used have recently been published.[5,6,35] In simple systems, using EC_{50}, E_{MAX}, and orthosteric agonist fold-shift values (for PAMs) or IC_{50} values (for NAMs) may provide guidance to select improved compounds. Dealing with more complex systems requires a combination of parameters related to the agonist and the allosteric ligand affinities (K_A and K_B, respectively), their capacity to exhibit agonism when acting alone (τ_A and τ_B, respectively), and two cooperativity factors quantifying the effect of the allosteric ligand on the affinity of the orthosteric ligand (α) or the effect of the modulator on the efficacy of the orthosteric ligand (β, Fig. 28.2).

4.2. Are compounds with ago-PAM activity and pure PAMs truly different?

When developing SAR for PAMs, an alternation is sometimes seen between positive allosteric modulation not showing functional activity in the absence of an orthosteric ligand (pure PAM), and allosteric ligand acting as agonist in the absence of orthosteric ligand and also potentiating the effect of an agonist (ago-PAM) activity upon minor structural changes within the same chemotype. Generally, the agonist EC_{50} values are above those for modulation. This may hinder *in vitro* determinations based on the "triple add" protocol, as the agonist activity causes desensitization and attenuates the functional response.

Mechanistically, true PAMs require a certain endogenous agonist tone to exert their effect, whereas ago-PAMs might act independently of the agonist tone. The translation of these *in vitro* effects to functional electrophysiology and behavioral readouts was recently explored by comparing optimized

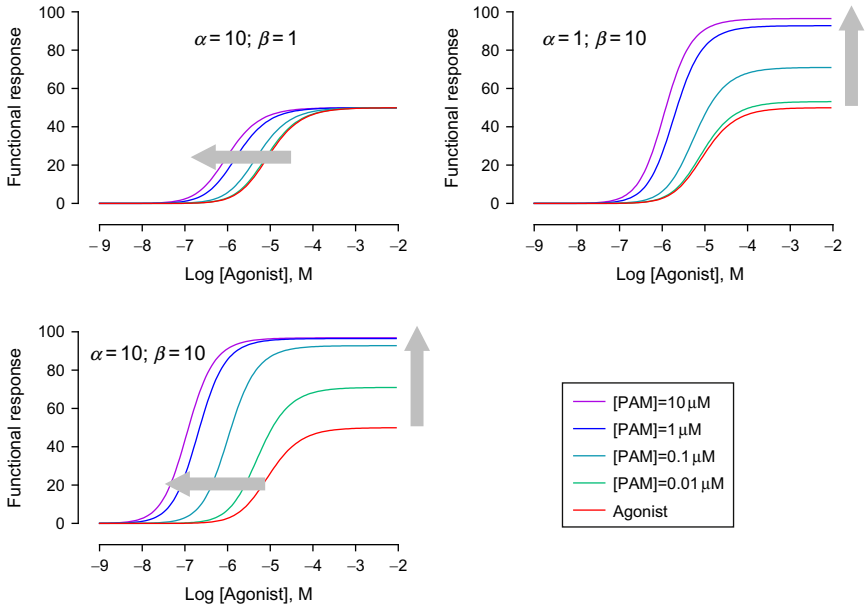
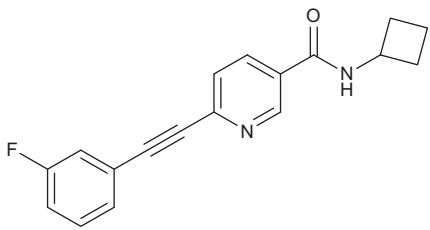


Figure 28.2 Computer simulation of curves showing the impact of allosteric modulation on an agonist functional response for different combinations of α and β. Calculations based on Leach equation [6], using the following parameters: $pK_A = 5$; $pK_B = 7$; $E_m = 100$; $\tau_A = 1$; $\tau_B = 0$; $n_H = 1.5$.

mGlu5 receptor ago-PAMs such as VU0360172 (**17**) with maximal intrinsic agonist activity in cell lines, along with close structural analogs acting as pure PAMs such as VU0361747 (**18**), devoid of intrinsic agonist activity.[36]



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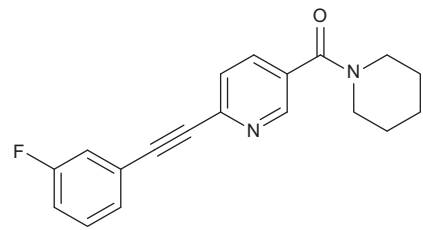

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Testing these compounds with cell lines engineered to have different levels of mGlu5 receptor expression, ago-PAM activity was only seen with high expression levels. All compounds examined in this study behaved as pure PAMs in native systems studied, regardless of whether they exhibited

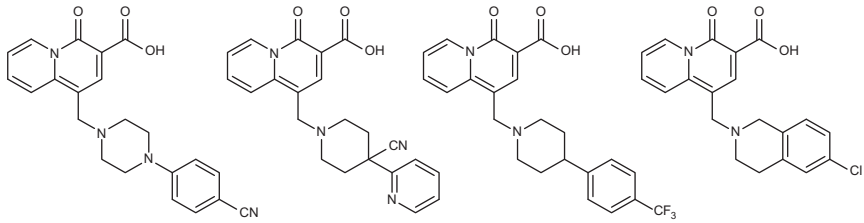
agonist activity in overexpressing cell lines. Pure PAMs and ago-PAMs showed identical efficacy in reversing amphetamine-induced hyperlocomotor activity, a preclinical model of potential antipsychotic effects.

These studies suggest that the presence of ago-PAM activity observed in overexpressing cell lines may not represent functionally relevant agonist activity in native systems. However, this does not rule out the possibility that functionally relevant ago-PAM activity can be observed. The studies with **17** and **18** were followed up with efforts to optimize compounds with authentic ago-PAM activity using a cell line expressing low levels of mGlu5 receptors. This effort yielded compounds that showed robust agonist activity in astrocytes and hippocampal neurons. Thus, it is possible to develop true ago-PAMs that behave very differently from pure PAMs or compounds that only show ago-PAM activity in overexpressing cell lines.[37] Another example of how the level of receptor expression in cell lines used during *in vitro* screens affects the functional pharmacology observed for different physiological and pharmacological GLP-1 receptor ligands was recently reported.[38]

Again, the key message is that there is no one-size-fits-all strategy. From target validation through lead optimization, judgment should be used based on the specific nature of the target and the biological modulation desired for a given pharmacological action.

5. DO *IN VITRO* PROFILES TRANSLATE TO *IN VIVO* PHARMACOLOGY?

While secondary screens are important elements of drug discovery research in an allosteric modulator program, they are not always capable of explaining disconnects that arise between *in vitro* and *in vivo* pharmacology. As an example, piperazine **19**[39] and 4-cyanopiperidine **20**[40] were recently reported as highly M_1-selective PAMs. Both of these PAMs exhibited good pharmacokinetic properties, sufficient brain penetration, and were efficacious in a mouse contextual fear-conditioning model of episodic memory, a task that requires the hippocampus, where the M_1 receptor is densely expressed. During the course of the SAR work on PAMs **19** and **20**, closely related piperidines **21** and **22** were characterized and evaluated in the aforementioned mouse contextual fear-conditioning model. However, **21**or **22** did not exhibit any activity in this assay, despite high plasma and CSF exposures and excellent FLIPR potency at the mouse receptor.[41]



19 20 21 22

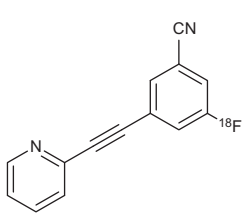
The exact reason for the *in vitro–in vivo* disconnect is not obvious given the very subtle molecular modification between a piperidine or piperazine/4-cyanopiperidine. In terms of their overall profiles, they were similar or more potent than **19** and **20** in a Gαs-coupled Ca^{2+} FLIPR assay and also exhibited similar pharmacological behavior in their ability to sensitize the response to varying doses of acetylcholine in the presence of a fixed concentration of PAM. Last, **21** and **22** were also evaluated for activity in the β-arrestin pathway, which recruits different signaling proteins than the Gαs-coupled Ca^{2+} release measured by the FLIPR assay, in the presence and absence of an EC_{15} concentration of ACh. Both PAMs behaved comparably in both FLIPR and β-arrestin assays relative to **19** and **20**, suggesting that possible different effects of these compounds on these specific signaling pathways are not responsible for the lack of *in vivo* activity. Thus, in addition to keeping a keen eye toward primary and secondary screens, one should be aware of potential *in vitro–in vivo* divide that may occur during optimization.

6. ASSESSING ALLOSTERIC SITE OCCUPANCY THROUGH RADIOLIGANDS AND PET AGENTS

As allosteric modulators represent a novel strategy of producing drug action, it is imperative to count on tools to directly measure receptor engagement, thus enhancing survival of new molecular entities through the discovery and development lifecycle.[42] Different allosteric modulators can act not only at multiple distinct, overlapping sites but also at non-overlapping sites. For compounds acting in a fully competitive manner at a defined site, PET occupancy has a predictable relationship with efficacy. Thus, a critical issue in developing a successful allosteric PET ligand is to confirm that it acts in a fully competitive manner at a defined site. Indeed, PET-based occupancy using [^{18}F]-FPEB (**23**) correlates with efficacy.[37]

In spite of challenges encountered with the design of allosteric modulators, a number of allosteric PET ligands have reached clinical testing and

proof-of-concept studies and are becoming key translational tools to determine receptor occupancy. Indeed, allosteric PET agents such as [^{18}F]-FPEB (**23**), [^{11}C]-ABP688 (**24**), and [^{18}F]-SP203B (**25**) have already been successfully used in the clinic to assess receptor occupancy at the mGlu5 receptor.[43]



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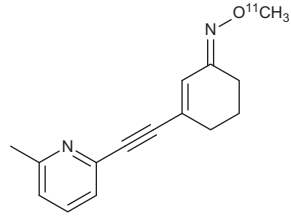

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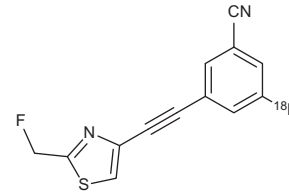

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7. MEDICINAL CHEMISTRY STRATEGIES FOR ALLOSTERIC LIGANDS

a. Attention during hit selection is vital. Do not take SAR for granted, and do explore chemical tractability, ideally using libraries. Physicochemical properties of initial hits are important, but are not the sole predictor of chemical tractability, so one should not prioritize hits based only on ligand metrics.

b. Consider stimulus bias and functional switches in your hit selection. Thoroughly profile hits in binding and functional GPCR screens. Preferably, work with chemotypes not showing the PAM⇆NAM switch. It is generally possible to "lock" the functional switch to a given chemotype.

c. Do invest in secondary screens early on. For example, if the primary screen is a calcium mobilization assay, a GTPγ^{32}S-binding assay would be helpful to confirm the functional activity of the different series under investigation. In addition, *in vitro* screens in native tissue (e.g., brain slice electrophysiology) will go a long way to support the biological activity of the compounds under study.

d. After every few rounds of SAR iteration, confirm that the pharmacology remains unchanged. Compounds with very similar profiles *in vitro*, and for DMPK *in vivo*, may behave significantly differently during studies using *in vivo* models.

e. For *in vivo* imaging work and *ex vivo* receptor occupancy studies, it is preferred to work with a radioligand in the same chemotype. Candidate radioligand compounds should be thoroughly characterized to support

the competitive nature of their interactions with the drug candidate compounds.

f. SAR at these targets tends to be nonlinear. The "rank order" of substituents in a given series may not translate identically to a different (yet very closely related) chemotype leading to cases of "nonadditive" SAR. Whenever possible, select "islands" of substituents leading to good compounds, and develop SAR using libraries, even with very similar cores.

g. When interpreting results from *in vivo* or metabolism-enabled *in vitro* tests, consider the potential presence of metabolites, which may have opposite pharmacology and confound biological readouts.

8. CONCLUSIONS

GPCR allosteric ligand design is at a stage where scholarship is still developing, and descriptive reports far exceed detailed mechanistic and structural understanding of this phenomenon.[44] Today, designing allosteric ligands presents a number of challenges beyond those typically faced with their orthosteric counterparts. In addition to the usual physicochemical, pharmacokinetic and safety/toxicology optimization, and translation into the clinical setting, knowledge of how chemical structure impacts attributes such as differential modulation of ligand affinity and efficacy, probe dependency, and functional selectivity is currently developing.

At the same time, allosteric ligands hold the promise of improved molecular selectivity, tissue selectivity, and pathways specificity, all of which may contribute to realizing the vision of personalized medicine. Naturally, this requires profound knowledge of very complex biological systems. Thus, medicinal chemists have before us a unique opportunity to add value to drug discovery programs by embracing collaborations in disciplines laying at the interface between chemistry, *in vitro* pharmacology, protein dynamics, and molecular biology.

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