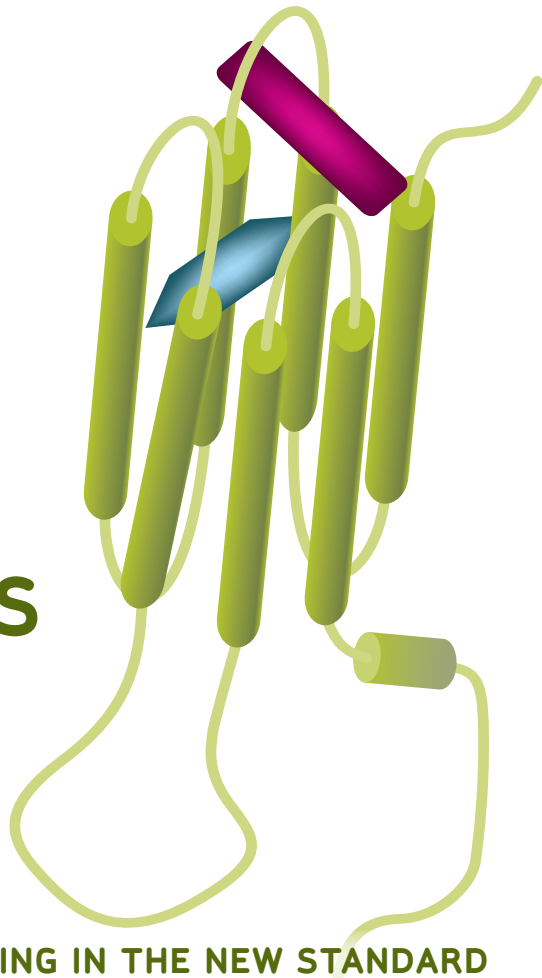


GPCR*Profiler*®
ALLOSTERIC SERVICES

Allosteric*Profiler*™ and Allosteric*Screener*™ services

ALLOSTERIC COMPOUNDS— THE FUTURE OF GPCR DRUG DISCOVERY.

Historically, GPCR/7TM drug development has been focused on compounds that interact with the receptors' orthosteric site, the site at which the native ligand binds. Even though the GPCR family has been a prolific drug target demonstrating the past success of this approach, there are clear limitations that have hampered past and recent drug development campaigns. For example, the orthosteric binding site can be highly conserved within a ligand family making it extremely difficult to generate receptor-specific compounds. Moreover, intellectual property has severely restricted the chemical space in which to work for orthosteric ligands thus hindering drug development for many valuable receptors. More and more researchers recognize that many of these constraints can be surmounted by exploiting completely new GPCR interaction sites that are topographically distinct from a receptor's orthosteric site, otherwise know as allosteric sites **(Figure 1)**.

USHERING IN THE NEW STANDARD FOR ALLOSTERIC PROFILING

Millipore began innovating GPCR selectivity profiling by becoming the first outsource provider to perform cell-based functional assays. Since the introduction of GPCR*Profiler*® services, we have continued to enhance our services by adding convenient safety & disease panels as well as FlexLab℠ custom services for more detailed pharmacological analysis. We are ushering the new era for allosteric drug discovery with our introduction of **Allosteric*Profiler*** services—the first fully validated selectivity-profiling service capable of detecting both orthosteric and allosteric compounds for over 155 GPCRs. Millipore is diligent to ensure that potential off-target interactions are not missed, by providing an elite service in which we can detect agonist, positive allosteric and antagonist or negative allosteric activity. With the addition of our **Allosteric*Screener*** service to our FlexLab capabilities, Millipore can also be your partner to identify new positive allosteric modulators for your favorite GPCR.

Distinct interactions sites for allosteric compounds

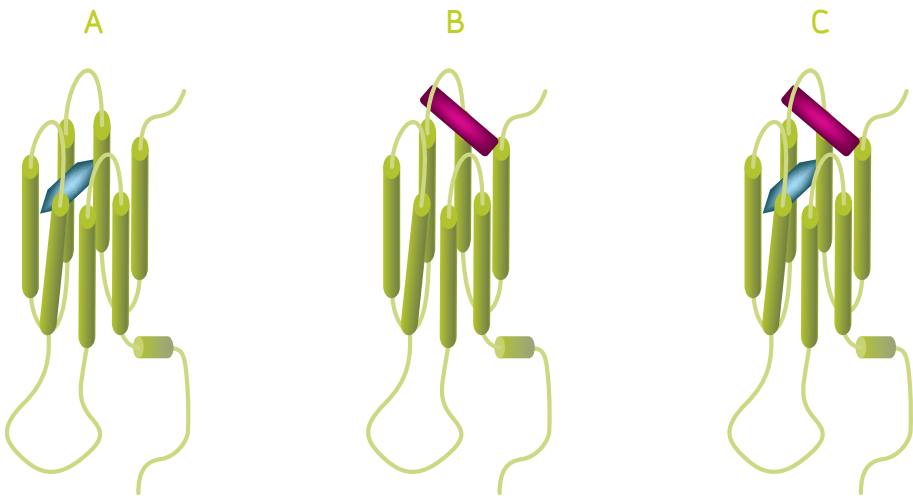


Figure 1.

Represented are the theoretical binding sites for an orthosteric compound (**A**) and an allosteric compound (**B**). Orthosteric and allosteric compounds can simultaneously occupy distinct sites on a GPCR to modify the receptor's activity (**C**).

WHY THE GREAT INTEREST IN ALLOSTERIC COMPOUNDS?

Although a sparse number of allosteric compounds exist for a limited number of class A, B and C GPCRs more allosteric compounds are routinely being identified and pursued for clinical development. Cinacalcet (Sensipar®, Amgen) is an example of a positive allosteric modulator that has successfully been introduced into the market. Why the interest? Many characteristics of allosteric compounds make them attractive therapeutics.

- **Specificity.** Because allosteric sites are less conserved than orthosteric sites, many allosteric compounds have been found to be more selective within a ligand family compared to orthosteric compounds. However, the extent of allosteric compound selectivity across a board spectrum of GPCRs remains to be thoroughly tested (see **Figure 5A**).
- **Range of activities.** Like their orthosteric counterparts, an allosteric compound may behave as an agonist or inverse agonist. But unlike orthosteric compounds, allosteric compounds may behave as non-competitive modulators – either enhancing (i.e., **positive allosteric modulator, PAM**) or reducing the activity of a native ligand (i.e., **negative allosteric modulator, NAM**). In some cases, a single allosteric compound may have mixed activities at a single target (see **Figure 5**).
- **Temporal and spatial regulation.** As allosteric modulators typically lack innate signaling activity at GPCRs, augmentation or depression of GPCR signaling by a modulator will only occur when the native ligand is released and locally available to interact with the GPCR. Thus, with respect to temporal and spatial GPCR activation, allosteric modulators offer greater physiological control compared to orthosteric compounds.
- **Reduce risk of overdose.** The non-competitive nature of allosteric modulators dictates that there is finite level of cooperativity between the allosteric and orthosteric sites. This ultimately limits the influence that an allosteric modulator will have on the orthosteric site, regardless of how high the concentration of the allosteric modulator is elevated. Therefore, it has been suggested that this saturablility reduces the chance of overdose upon exposure to an inadvertently high dose of an allosteric modulator.

WHAT TO CONSIDER WHEN SCREENING ALLOSTERIC MODULATORS?

Allosteric compounds are a new breed of GPCR compounds, which require modifications to the typical screening methods.

- **Functionality vs. affinity.** The first consideration is that many of the common properties for describing orthosteric GPCR ligands (affinity, potency and efficacy) are independent properties. In turn, allosteric modulators can differentially influence these individual properties. Beyond the challenge of employing traditional equilibrium competition binding assays to actually detect allosteric modulators (see **Figure 2**) is the challenge of how to interpret the data. For example, an allosteric modulator that appears to decrease affinity of a radioligand may actually enhance the potency or efficacy of the native ligand in a functional assay. This is why Allosteric*Profiler* services was designed around functional assays – because the functional consequence of an allosteric modulator is what is important.
- **Ligand-dependency.** Another drawback to binding assays is that they typically use high-affinity orthosteric antagonists/inverse agonists as the radiolabelled probes. The cooperativity seen between the orthosteric (i.e. traditional radioligand) and allosteric sites is highly dependent on the probes used in the assay. Therefore, it is impossible to discern the effect of the allosteric modulator on the native ligand using binding assays with radiolabeled antagonists. That is why Allosteric*Profiler* services predominately uses native ligands as reference ligands.
- **Functional range.** Like traditional orthosteric compounds, it is likely that allosteric molecules may have different activities when interacting with off-target receptors (e.g., PAM activity on-target, but agonist activity off-target, see **Figure 5A, C**). The purpose of selectivity-profiling is to alert the researcher of all possible off-target hits that may be detrimental to drug development in order for a chemist to modify the molecule to reduce these off-target interactions. Therefore, it is vital to use a selectivity profiling system that does not miss possible off-target hits. That is why Allosteric*Profiler* services was designed to capture 3 different activities: agonist, PAM and NAM/antagonist activity (see **Figures 3 & 4**).

Difficulty in Detecting Agonists and Allosteric Modulators by Binding Assays

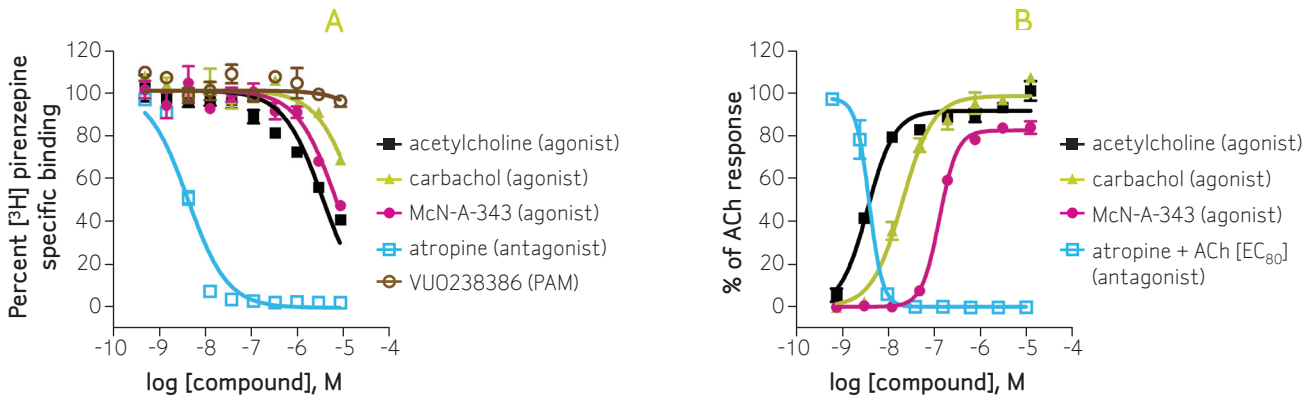


Figure 2.

Stable cells expressing M_1 receptor (**Cat. No. HTS044C**) or membranes derived from these cells (**Cat. No. HTS044M**) were used in Ca^{2+} flux or radioligand equilibrium competition binding assays, respectively. Both radioligand binding assays (**A**) and functional assays (**B**) were capable of identifying the orthosteric antagonist, atropine (open, blue squares). **A**) However, typical M_1 orthosteric agonists were poorly detected by traditional radioligand binding, most likely due to the mixture of low and high affinity sites, of which the former predominates in an antagonist labeled binding assay. Additionally, since allosteric modulators do not directly compete with the orthosteric site nor cooperate with all orthosteric ligands in the same manner, ligands like the positive allosteric modulator, VU0238386, are not detected by equilibrium binding assays. **B**) However, functional assays readily detect and discriminate between the potency of the M_1 agonists as well as identify the modulator activity of VU0238386 (see **Figure 5**). Competition curves were fit to a single binding site and functional assays were fit using a variable slope.

WHAT ALLOWS ALLOSTERIC*Profiler* SERVICES TO EFFECTIVELY PICK UP SO MANY ACTIVITIES?

The design of Allosteric*Profiler* services is based on a two addition protocol. Like our standard service, the first addition is to monitor agonist activity that a test compound might possess (see **Figure 3A**). The second addition is a dose response of a reference agonist on top of either vehicle or test compound treated wells to reliably evaluate how the test compound influences the reference agonist's potency and efficacy (see **Figure 3B**). Thus, this modified second addition protocol allows one to identify possible PAMs (either leftward shift in the potency and/or increase efficacy of the reference agonist) or antagonist/NAM activities (either rightward shift in the potency and/or decrease efficacy of the reference agonist) (see **Figure 4**).

Data that is returned from AllostericProfiler services includes:

- Percent activation from 1st addition (agonist detection, see **Figure 5A**).
- Dose response curves from 2nd addition, which can aid in identifying more subtle activities of your compound. (see **Figure 5B**).
- Dose ratios from 2nd addition (PAM and antagonist/NAM detection, see **Figure 5C**).
- And as always, we include result highlights and recommendations in every report, which are delivered to you about 1-3 weeks after project commencement, depending on project scope.

Allosteric*Profiler* Service Assay Design

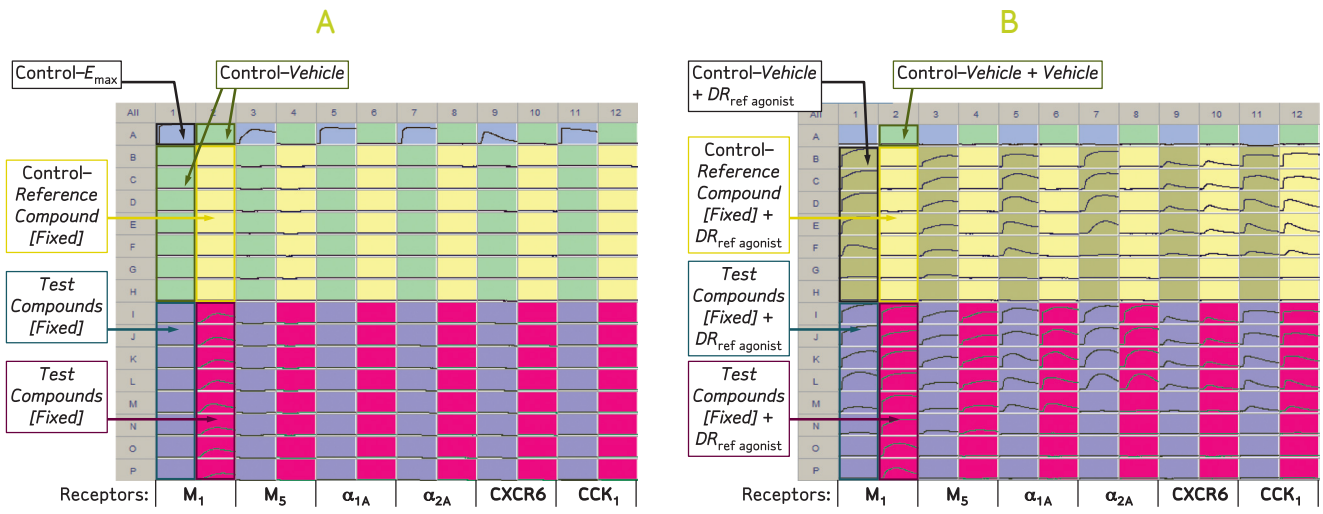


Figure 3.

Shown in panels A and B, is an example of an Allosteric*Profiler* service selectivity screen performed in a 384-well format with the identical plate shown in panels A and B (half of plate is shown for simplicity). **A**) Shown in rows A-H are the controls for the 1st addition experiment to identify agonist activity: vehicle (green), a single concentration of reference antagonist (yellow) or an E_{max} concentration of reference agonist (blue). Likewise, shown in rows I-P are wells treated with two test compounds (VU0152099, blue; and VU0238386, magenta, provided by Vanderbilt Program in Drug Discovery) at a single concentration. Note that test compound VU0238386 had some inherent agonist activity at M_1 receptor (column 2, rows I-P). **B**) Shown in rows A-H of Panel B are the controls for the 2nd addition experiment, in which the reference agonist for each receptor is added to the wells as a single point, serially diluted concentration curve to identify PAM and antagonist/NAM activity: vehicle alone (green), vehicle + reference agonist (olive) and reference antagonist (if available) + reference agonist (yellow). Likewise, shown in rows I-P are wells treated with test compounds followed by treatment with reference agonist. Demonstrating the robust PAM activity of VU0238386, cells expressing M_1 receptors had an enhance response when challenged with a low concentration of reference agonist following pre-treatment with VU0238386 compared to vehicle (Well 20 vs. well 1H). Shown are stable cell lines expressing the indicated receptors: M_1 (**Cat. No. HTS044C**, columns 1&2), M_5 (**Cat. No. HTS075C**, columns 3&4), α_{1A} (**Cat. No. HTS087C**, columns 5&6), α_{2A} (**Cat. No. HTS096C**, columns 7&8), CXCR6 (**Cat. No. HTS054C**, columns 9&10) and CCK_1 (**Cat. No. HTS184C**, columns 11&12). The reference agonist used for cell lines expressing M_1 and M_5 receptors was acetylcholine, epinephrine for α_{1A} and α_{2A} receptor lines, CXCL16 for CXCR6 receptor line and sulfated CCK8 for CCK_1 receptors expressing cells.

Screening Premise for Allosteric*Profiler* Service

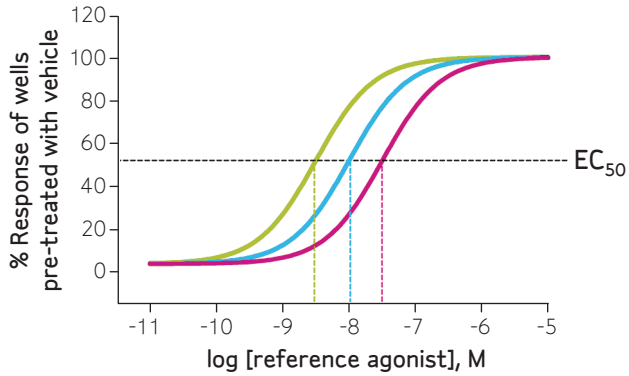


Figure 4.

Shown is a graph of theoretical curves demonstrating three possible outcomes of an experiment in which wells containing a fixed concentration of test compounds are challenged with a reference agonist. For reference, the blue line would be vehicle control wells treated with reference agonist, and any test compound that had a dose response curve that overlapped with the vehicle control wells would be determined NOT to have activity at the receptor. Whereas, wells pre-treated with a test compound resulting in the green line (leftward-shifted from the blue curve) or the magenta line (which is rightward-shifted from the blue curve) would be indicative of either a PAM or an antagonist/NAM, respectively. Note, although not depicted on this graph, it is possible that test compounds may also either enhance (PAM) or diminish (NAM) the reference agonist's top response.

Data Generated From Allosteric*Profiler* Services

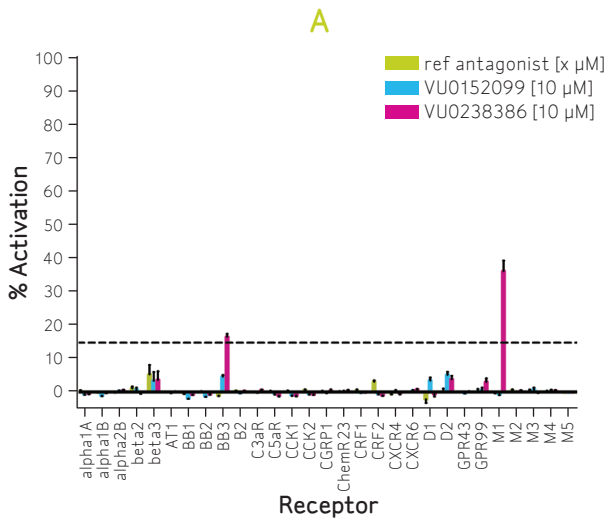
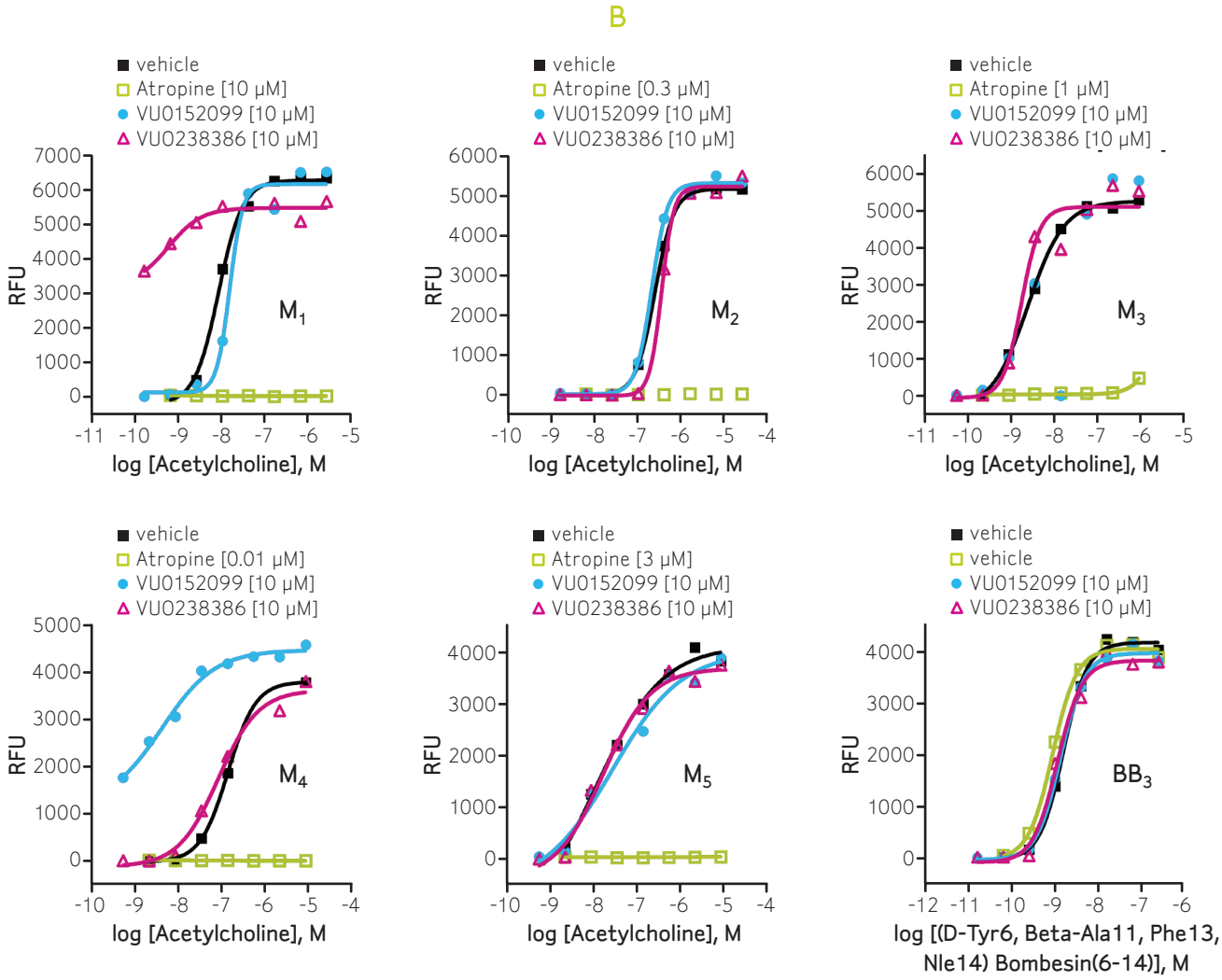


Figure 5.

GPCRProfiler's Allosteric*Profiler* service is a data rich service allowing identification of agonist, PAM and antagonist/NAM activities for compounds. An Allosteric*Profiler* screen was performed using two small molecules VU0238386 and VU0152099 (formally identified as M_1 and M_4 PAMs, respectively) to identify their functional selectivity among 30 different receptors. **A**) Data generated from the 1st addition protocol (detailed in **Figure 3A**) was used to identify agonist activity. Percent response is calculated as the response of each molecule compared to the top response of wells treated with an E_{max} concentration of the receptor's specific reference agonist. The dotted line defines a threshold of 15% response. VU0238386 was found to have a degree of agonist activity at M_1 and BB_3 receptors (**Cat. No. HTS160C**) in this screen and was later confirmed by dose response studies. (see next page)

Data Generated From Allosteric*Profiler* Services (continued)



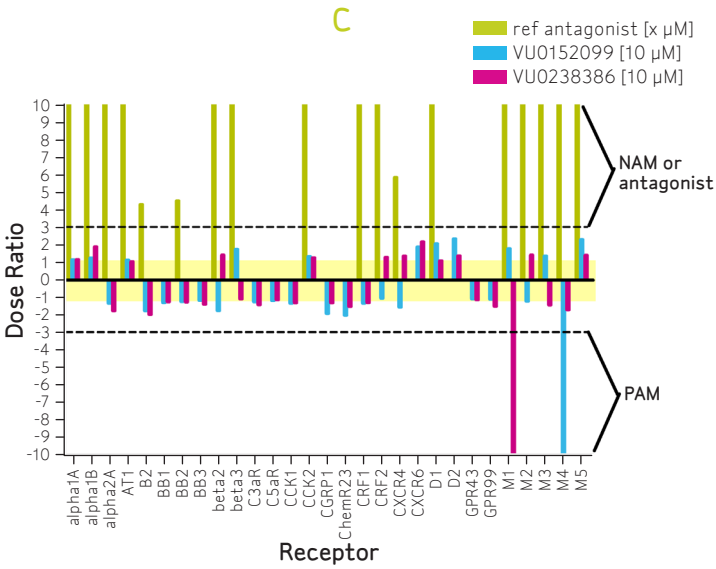


Figure 5. (continued)

B) Sample dose response curves for reference agonists generated following incubation with control and test compounds from the 2nd addition protocol, (detailed in **Figure 3B**) to identify PAM or antagonist/NAM activities. VU0152099 displayed M_4 receptor selective PAM activity (leftward shift in potency and upward shift in efficacy) and VU0238386 had M_1 receptor specific PAM activity (leftward-shift in potency) while lacking any additional activity at BB_3 receptors. **C**) Graphical display of dose ratios generated from 2nd addition assays (shown in **Figure 5A**) for test and control compounds. Dose ratio is defined as $Test_{EC50}/Vehicle_{EC50}$ (EC_{50} of reference agonist in the presence of test compound) / (EC_{50} of reference agonist in the presence of vehicle control) and for ease of viewing dose ratio values of <1 were plotted as (-1/dose ratio) and viewing area was limited to either 10 or -10. Dose ratio of 1 or -1 in this graph would indicate that compounds behaved identical to vehicle control wells (no discernable activity), whereas compounds with dose ratio >3 would be identified as NAM/antagonist hits and those with dose ratio of <-3 as PAM hits. If incomplete dose response curves were found for reference antagonist treated wells, dose ratio was defined as >10.

INTERESTED IN UNCOVERING NEW ALLOSTERIC MODULATORS FOR A PARTICULAR GPCR?

Millipore's Allosteric*Screener* services, the latest of our FlexLab custom services, is designed to facilitate identification of new PAMs for a target of interest. We can work with you to design a screen that is appropriate for your target to increase the likelihood of uncovering PAMs in your compound libraries.

Allosteric*Screener* services are setup similarly to our standard GPCR*Profiler* service with a modification that the 2nd addition is an $\leq EC_{30}$ concentration of reference agonist allowing detection of compounds that potentiate the reference agonist's response (see **Figure 6 & 7**). Like traditional services, we can detect agonist activity as well; thus pure agonists, pure PAMs or compounds with mixed behavior can be identified up front using Allosteric*Screener* services.

Allosteric*Screener* Service is Designed to Identify Hits with PAM Activity

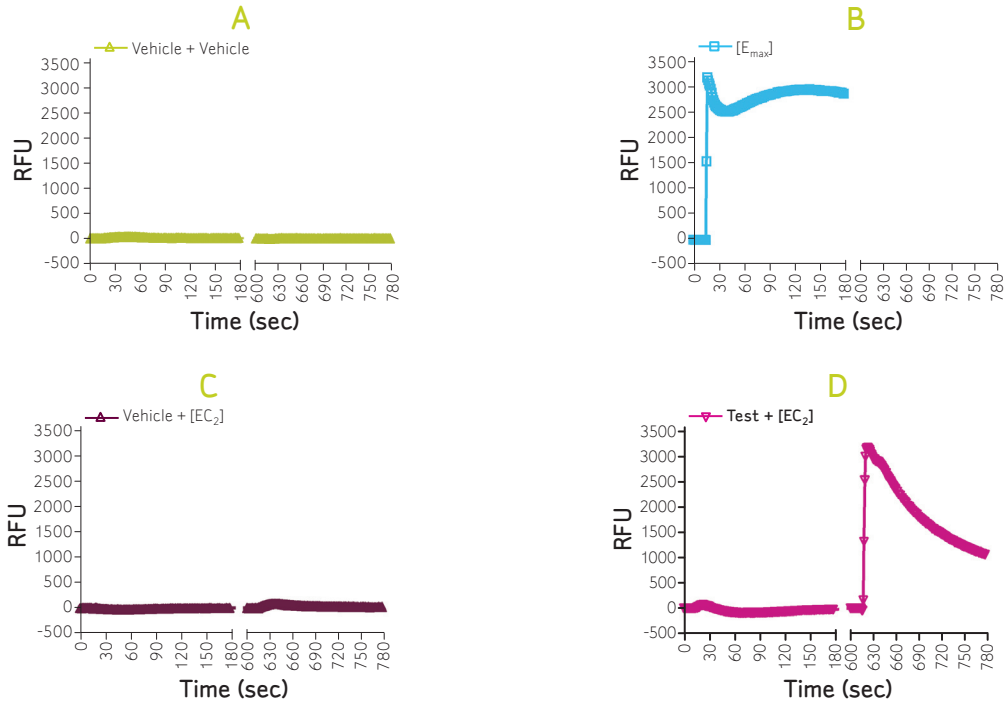


Figure 6.

Allosteric*Screener* experiments are designed to detect both agonists and PAMs at a single receptor in higher throughput screening. After a baseline read, compounds are added to cells expressing a GPCR at 10 sec to detect agonist activity. After an additional 10 minutes of incubation the cells are then challenged with a pre-determined low concentration of a reference agonist to detect signal augmentation, indicative of a PAM. Examples of kinetic traces obtained from M_4 receptor cell line (**Cat. No. HTS117C**) treated with **A**) vehicle control (1st and 2nd addition) – **no response**; **B**) E_{max} of reference agonist, 10 µM acetylcholine (1st addition) – **agonist response**; **C**) vehicle (1st addition) and reference agonist, acetylcholine, at an EC_2 concentration (2nd addition) – **minimal positive response**; and **D**) M_4 PAM, VU152129, (1st addition) and acetylcholine at an EC_2 concentration (2nd addition) – **enhanced response** (i.e., increase of the 2nd addition response seen in panel C).

Allosteric*Screener* Assay Design

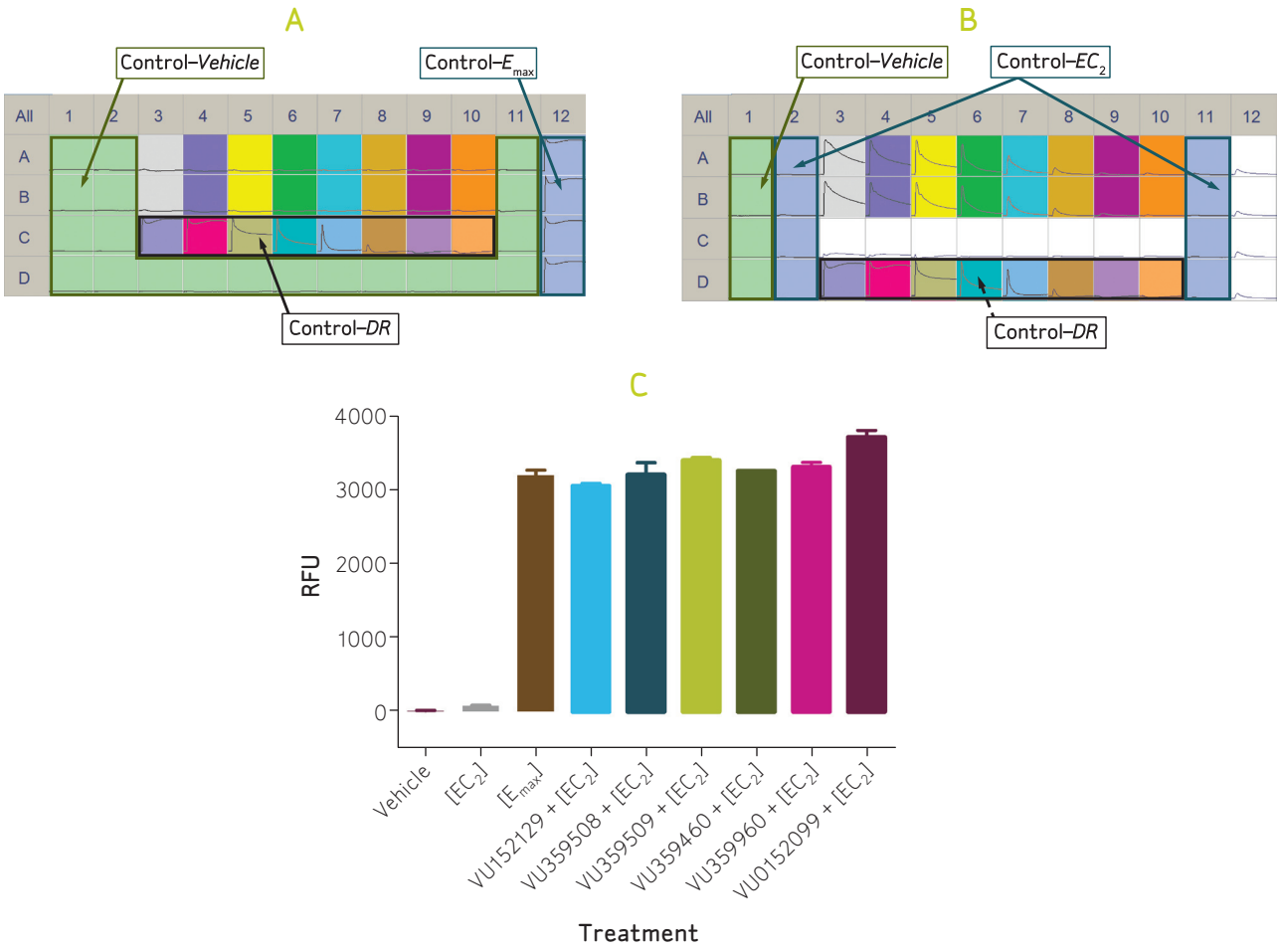


Figure 7.

Shown in panels A and B, is an example of an Allosteric*Screener* experiment performed against M_4 receptor in a 96-well format with the identical plate shown in panels A and B (half of plate is shown for simplicity and similar controls are also included in 384-well format). **A**) Several controls incorporated into the 1st addition experiment (identifying agonist activity) are wells treated with vehicle (green); E_{max} reference agonist, acetylcholine, (blue); and a reference agonist dose response (row C, columns 3-10) to calculate the appropriate concentration for the 2nd addition experiment. In the remaining wells, the test compound, VU152129, was spotted in duplicate wells at multiple concentrations. **B**) The same wells form panel A, were then treated with either vehicle (green) as a negative control, a dose response of reference agonist (row D, columns 3-10) to empirically verify the concentration of agonist added to test wells or an EC_2 concentration of reference agonist to determine if any well treated with test compound had an augmented signal compared to control wells (blue). **C**) Following this experimental design, a variety of test compounds were identified as M_4 potentiators when tested at 10 µM without having innate agonist activity (data not shown).

GPCR*Profiler* SERVICES ORDERING INFORMATION

Affordable Full Panel & Safety Panels

▲ = *NEW*

Class	Ligand Type	GPCR Family	GPCR Target (Human unless noted)
A	non-peptide	Acetylcholine (muscarinic)	M1
A	non-peptide	Acetylcholine (muscarinic)	M2
A	non-peptide	Acetylcholine (muscarinic)	M3
A	non-peptide	Acetylcholine (muscarinic)	M4
A	non-peptide	Acetylcholine (muscarinic)	M5
A	non-peptide	Adenosine	A1
A	non-peptide	Adenosine	A2B
A	non-peptide	Adenosine	A3
A	non-peptide	Adrenergic	α1A
A	non-peptide	Adrenergic	α1B
A	non-peptide	Adrenergic	α1D
A	non-peptide	Adrenergic	α2A
A	non-peptide	Adrenergic	β1
A	non-peptide	Adrenergic	β2
A	non-peptide	Adrenergic	β3
A	peptide	Anaphylotoxin	C3aR
A	peptide	Anaphylotoxin	C5aR
A	peptide	Angiotensin	AT1
A	peptide	Apelin	APJ
A	peptide	Bombesin	BB1
A	peptide	Bombesin	BB2
A	peptide	Bombesin	BB3
A	peptide	Bradykinin	B2
B	peptide	Calcitonin	CGRP1
C	non-peptide	Calcium sensor	CaS
A	non-peptide	Cannabinoid	CB1
A	non-peptide	Cannabinoid	CB2
A	peptide	Chemoattractant	ChemR23 / CMLKR1
A	peptide	Chemokine	CCR1
A	peptide	Chemokine	CCR10
A	peptide	Chemokine	CCR2B
A	peptide	Chemokine	CCR3
A	peptide	Chemokine	CCR4
A	peptide	Chemokine	CCR5, rhesus macaque

Class	Ligand Type	GPCR Family	GPCR Target (Human unless noted)
A	peptide	Chemokine	CCR6
A	peptide	Chemokine	CCR7
A	peptide	Chemokine	CCR8
A	peptide	Chemokine	CCR9
A	peptide	Chemokine	CX3CR1
A	peptide	Chemokine	CXCR1 / IL-8a
A	peptide	Chemokine	CXCR2 / IL-8b
A	peptide	Chemokine	CXCR3
A	peptide	Chemokine	CXCR4
▲ A	peptide	Chemokine	CXCR5
A	peptide	Chemokine	CXCR6
A	peptide	Chemokine	XCR1 / GPR5
A	peptide	Cholecystokinin	CCK1 / CCKa
A	peptide	Cholecystokinin	CCK2 / CCKb
B	peptide	CRF Receptor	CRF1
B	peptide	CRF Receptor	CRF2
A	non-peptide	Dopamine	D1
A	non-peptide	Dopamine	D2L
▲ A	non-peptide	Dopamine	D4
A	non-peptide	Dopamine	D5
A	peptide	Endothelin	ETA
A	peptide	Endothelin	ETB
A	non-peptide	Free Fatty Acid	FFA1 / GPR40
A	non-peptide	Free Fatty Acid	FFA2 / GPR41
A	non-peptide	Free Fatty Acid	FFA3 / GPR43
C	non-peptide	GABAB	GABAB1b
A	peptide	Galanin	GAL1
A	peptide	Galanin	GAL2
A	peptide	Ghrelin	Ghrelin / GHSR-1a / Growth Hormone Secretagogue Receptor
B	peptide	Glucagon	GIP
B	peptide	Glucagon	GLP-1
B	peptide	Glucagon	glucagon / GCG
B	peptide	Glucagon	secretin receptor / SEC

▲ = *NEW*

Class	Ligand Type	GPCR Family	GPCR Target (Human unless noted)
▲ C	non-peptide	Glutamate (metabotropic)	mGlu1
C	non-peptide	Glutamate (metabotropic)	mGlu2
A	peptide	Glycoprotein hormone	TSH / TSHR
A	peptide	GnRH	GnRH / LHRH
A	non-peptide	Histamine	H1
A	non-peptide	Histamine	H2
A	non-peptide	Histamine	H3
A	non-peptide	α-Ketoglutarate	OXGR1 / GPR99 / GPR80
A	peptide	KiSS1-derived peptide	KiSS1 / GPR54
A	non-peptide	Leukotriene	BLT1
A	non-peptide	Leukotriene	CysLT1
A	non-peptide	Leukotriene	CysLT2
A	non-peptide	Lysophospholipid	LPA1 / EDG2
A	non-peptide	Lysophospholipid	LPA3 / EDG7
A	non-peptide	Lysophospholipid	LPA5 / GPR92
A	non-peptide	Lysophospholipid	S1P1 / EDG1
A	non-peptide	Lysophospholipid	S1P2 / EDG5
A	non-peptide	Lysophospholipid	S1P3 / EDG3
A	non-peptide	Lysophospholipid	S1P4 / EDG6
A	non-peptide	Lysophospholipid	S1P5 / EDG8
A	peptide	Mas-related gene	MRGPRD / MrgD
A	peptide	Mas-related gene	MRGX1 / MRGPRX1
A	peptide	Mas-related gene	MRGX2 / MRGPRX2
A	peptide	Melanin-concentrating hormone	MCHR1 / GPR24
A	peptide	Melanin-concentrating hormone	MCHR2
A	peptide	Melanocortin	MC2
A	peptide	Melanocortin	MC4
A	peptide	Melanocortin	MC5
A	peptide	Motilin	Motilin Receptor / MTLR / GPR36
A	peptide	Neuromedin U	NMU1
A	peptide	Neuromedin U	NMU2
A	peptide	Neuropeptide B / W	NPBW1 / GPR7

Class	Ligand Type	GPCR Family	GPCR Target (Human unless noted)
A	peptide	Neuropeptide Y	Y2
A	peptide	Neuropeptide Y	Y4
A	peptide	Neurotensin	NTR1 / NTS1
A	peptide	N-formylpeptide	FPR1
A	peptide	N-formylpeptide	FPRL1 / AXL / HM63
A	non-peptide	Nicotinic Acid	GPR109A
A	peptide	Opioid	δ / OP1 / DOP / DOR
A	peptide	Opioid	κ / OP2 / KPO / KOR
A	peptide	Opioid	μ / OP3 / MOP / MOR
A	peptide	Opioid	NOP / ORL1 / OP4
A	peptide	Orexin	OX1
A	peptide	Orexin	OX2
A	peptide	Oxytocin	OT
A	peptide	Peptide P518	GPR103 / QRFP
A	non-peptide	P2Y / Purinergic (metabotropic)	P2Y1
A	non-peptide	P2Y / Purinergic (metabotropic)	P2Y2
A	non-peptide	P2Y / Purinergic (metabotropic)	P2Y4
A	non-peptide	P2Y / Purinergic (metabotropic)	P2Y11
▲ A	non-peptide	P2Y / Purinergic (metabotropic)	P2Y12
A	non-peptide	Platelet Activating Factor	PAF
A	peptide	Prokineticin	PK1 / PKR1
A	peptide	Prokineticin	PK2 / PKR2
A	peptide	Prolactin-releasing peptide	PRP / PrRP / GPR10
A	non-peptide	Prostanoid	DP
A	non-peptide	Prostanoid	EP1
A	non-peptide	Prostanoid	EP2
A	non-peptide	Prostanoid	EP3
A	non-peptide	Prostanoid	EP4
A	non-peptide	Prostanoid	FP
A	non-peptide	Prostanoid	IP1 / PF12

▲ = *NEW*

Class	Ligand Type	GPCR Family	GPCR Target (Human unless noted)
A	non-peptide	Prostanoid	TP / TXA2 / PGH2
A	peptide	Protease-activated	Trypsin activated PARs
A	peptide	Protease-activated	Thrombin activated PARs
B	peptide	PTH receptor	PTH1
B	peptide	PTH receptor	PTH2
A	non-peptide	Serotonin	5-HT1A
A	non-peptide	Serotonin	5-HT2A
A	non-peptide	Serotonin	5-HT2B
A	non-peptide	Serotonin	5-HT2C
▲ A	non-peptide	Serotonin	5-HT6
A	peptide	Somatostatin	sst2
A	peptide	Somatostatin	sst3
A	peptide	Somatostatin	sst4
A	peptide	Somatostatin	sst5
A	non-peptide	SPC / LPC / proton-sensor	GPR68 / OGR1
A	peptide	Tackykinin /neurokinin	NK1
A	peptide	Tackykinin /neurokinin	NK2
A	peptide	Tackykinin /neurokinin	NK3
A	peptide	TRH	TRH
A	peptide	Urotensin II	UT / UT1 / GPR14
A	peptide	Vasopressin	V1A
A	peptide	Vasopressin	V1B
A	peptide	Vasopressin	V2
B	peptide	VIP / PACAP	PAC1 long isoform / PACAP
B	peptide	VIP / PACAP	VPAC1 / VIP1
B	peptide	VIP / PACAP	VPAC2 / VIP2

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