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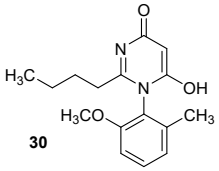

30

APJ/HEK293
cAMP EC_{50} (nM) 3 (100%)

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Discovery and SAR of Aryl Hydroxy Pyrimidinones as Potent Small Molecule Agonists of the GPCR APJ

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ABSTRACT

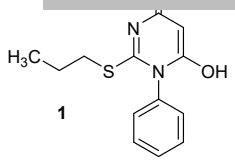
This article describes the discovery of aryl hydroxy pyrimidinones and the medicinal chemistry efforts to optimize this chemotype for potent APJ agonism. APJ is a G-protein coupled receptor whose natural agonist peptide, apelin, displays hemodynamic improvement in the cardiac function of heart failure patients. A high throughput screen was undertaken to identify small molecule hits that could be optimized to mimic the apelin in vitro response. A potent and low molecular weight aryl hydroxy pyrimidinone analog **30** was identified through optimization of an HTS hit and medicinal chemistry efforts to improve its properties.

1. Introduction

Heart failure (HF) occurs when the heart muscle can no longer provide the body with an adequate blood supply and represents a serious disease of unmet medical need for patients. Greater than 5 million people are currently living with HF in the United States, and this population is expected to grow as the mean population age increases.[1] One million people will be hospitalized this year due to HF, resulting in both societal and economic burdens for both families and government health care systems. New medicines that seek to relieve symptoms, reduce hospitalization rates, improve the quality of life and extend life represent significant ongoing efforts in pharmaceutical research.[2,3]

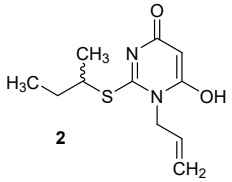
The APJ receptor[4] was deorphanized in 1998 with the identification of a peptide (apelin) as the endogenous agonist.[5] The linear apelin peptide exists as a 77 amino acid preproprotein. This peptide is proteolytically truncated to shorter active variants, the major contributor of which is a 13-mer peptide known as pyroglutamated apelin-13 (pyr[1])apelin-13. In recent clinical studies, (pyr[1])apelin-13 demonstrated improvements in cardiac performance.[6-8] Newby and co-workers have shown that agonism of the apelin/APJ system provides beneficial hemodynamic effects, including cardiac output and ejection fraction increases without significant change in blood pressure or heart rate.[9-11] Significant progress has been made in recent years by several groups working to design peptido-mimetic[12-17] and small molecule[18-26] agonists of APJ. The medicinal chemistry goals for our work on this target were to discover, validate, and optimize a small molecule agonist of the APJ receptor that could mimic the effects of the endogenous ligand (pyr[1])apelin-13.

To meet the first goal, a high-throughput screen (HTS) was developed based on the ability of (pyr[1])apelin-13 to signal though the G-protein (Gi) to inhibit forskolin stimulated cAMP production in a HEK293 cell line (APJ agonism).[5,27] The HTS was run on the BMS screening deck at a 10 μM single point concentration. Compounds that displayed >20% inhibition of forskolin stimulated cAMP (Ymax) and <20% efficacy against a parental HEK293 cell line lacking the APJ receptor were selected. As part of the screening triage process, confirmed hits were counter-screened against the AT1 receptor. Any cross-activity with the AT1 receptor was important to characterize given that the AT1 receptor is the closest homologue to the APJ receptor.[4] This triage process lead to the discovery of two weakly active small molecule aryl hydroxy pyrimidinone (AHP) agonists, **1** and **2** (Figure 1), that were intriguing due to their low molecular weights and full agonist responses.



1

APJ/HEK293
cAMP EC_{50} (nM) 5000 (100%)
MW = 262 g/mol



2

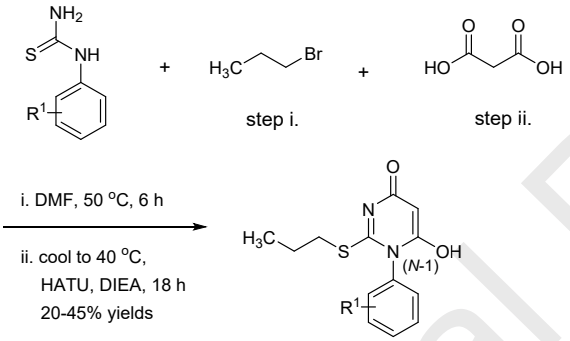
APJ/HEK293
cAMP EC_{50} (nM) 4400 (100%)
MW = 240 g/mol

pyrGluRPRLSHKGPMPF
(pyr[1])apelin-13

APJ/HEK293
cAMP EC_{50} (nM) 0.07 (100%)

Figure 1. Structures and potencies of aryl hydroxy pyrimidinone HTS Hits, **1** and **2** vs. (pyr[1])apelin-13.

Though weakly active, these hits represented excellent small molecule starting points to initiate a SAR campaign. Optimization efforts on the AHP chemotype began by utilizing library synthesis to explore SAR at the *N*-1 position of the AHP core. A 2-step/1-pot synthetic route was developed that utilized commercially available thiourea starting materials (Scheme 1).



Scheme 1. Synthesis of sulfur sidechain AHP analogs.

To produce AHP analogs using this synthetic route, substituted phenyl thioureas were alkylated with 1-bromo propane. Condensation of the subsequent S-alkylated intermediate (not shown) with malonic acid[28] in a HATU facilitated coupling/cyclization reaction sequence produced a variety of substituted phenyl AHP analogs. As part of this work, variations at the *N*-1 position with acyclic groups were also explored, but it was found that substituted phenyl analogs provided significantly better activity (Table 1).

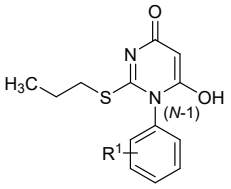
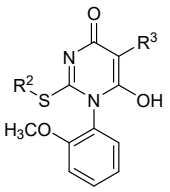


Table 1. *N*-1 substituted phenyl SAR of the AHP core.

cmpd	R^1	hAPJ EC_{50} (nM)[a]
1	H	5000 ± 4800
3	2-OCH_3	64 ± 90
4	3-OCH_3	940 ± 650
5	4-OCH_3	6800 ± 2200
6	2-CH_3	100 ± 50
7	3-CH_3	2900 ± 1200
8	4-CH_3	2600 ± 110
9	2-Cl	250 ± 140
10	2-F	160 ± 55
11	2-Br	155 ± 10
12	2-CF_3	90 ± 60
13	2-CH_2CH_3	140 ± 34
14	2-OCH_2CH_3	100 ± 90

[a]Data represent the mean SEM, n = 2 or more determinations

The data from this work showed that ortho substitution on the phenyl ring provided analogs with nearly 50-fold potency increases relative to phenyl analog **1**. The 2-methoxy phenyl analog **3**, displayed full APJ agonism with an EC50 of 60 nM in the HEK293 cell line. The 3-methoxy phenyl analog **4** and 4-methoxy phenyl analog **5** displayed a 16-fold and 113-fold potency decrease, respectively, compared to analog **3**. A similar trend was noted for the methyl substituted analogs were meta analog **7** and para analog **8** were less potent than ortho methyl analog **6**. Electron withdrawing and donating groups (**10-14**) were tolerated at the ortho position with only minor changes in potency relative to analog **3**. Importantly, all analogs displayed activations (Ymax) consistent with full agonism observed with (pyr[1])apelin-13.

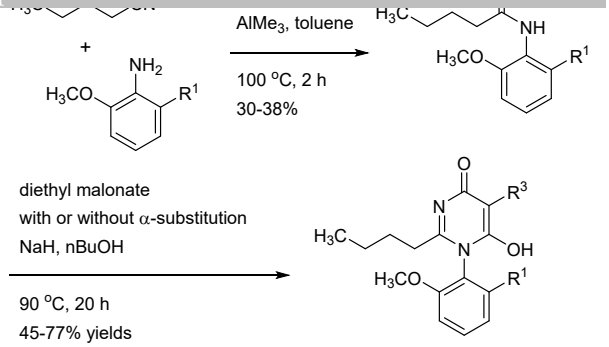


cmpd	R^2	R^3	hAPJ EC_{50} (nM)[a]
3	propyl	H	64 ± 90
15	isopropyl	H	23 ± 4
16	isobutyl	H	78 ± 35
17	butyl	H	200 ± 90
18	propyl	methyl	1400 ± 840
19	propyl	ethyl	860 ± 230
20	propyl	butyl	1700 ± 70
21	propyl	benzyl	340 ± 74
22	propyl	allyl	570 ± 160
23	propyl	isopropyl	450 ± 230
S-24	propyl	H	40 ± 34
R-25	propyl	H	160 ± 65

[a]Data represent the mean ± SEM, n = 2 or more determinations.

different sidechains (R^2) and α-substitution (R^3) on the malonic acid component were introduced while maintaining a 2-methoxy phenyl ring at the *N*-1 position of the AHP ring (Table 2) employing the same chemistry as shown in Scheme 1.

Table 2. Sidechain and malonic acid substitution SAR of the AHP core.



Modification of the thioether sidechain (R^2) showed that various alkyl groups were equally preferred (compounds **3**, **15**, **16**). Substitution off the malonic acid derived carbon (R^3) resulted in analogs (**18-23**) with a decrease in potency relative to compounds substituted with an H at R^3 .

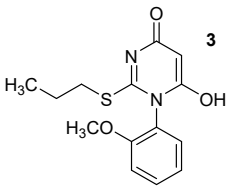
The presence of ortho substituents on adjoining planar rings can lead to atropisomers.[29] Chiral super critical fluid chromatography (SFC) was employed to establish if atropisomers were observed and to identify conditions to separate stable atropisomers from the presumed racemic mixture. Conditions were identified that lead to baseline separation of the two atropisomers of 2-methoxyphenyl analog **3**, ***S*-24** and ***R*-25** (Table 2). The single atropisomers ***S*-24** and ***R*-25** were found to be stable to isomerization for 24 hours at 60 °C in DMSO. The absolute configurations of ***S*-24** and ***R*-25** were confirmed by single crystal X-ray diffraction analysis of each individual atropisomer.[30,31] The dihedral angle of the 6,6-ring system was nearly perpendicular at 82° in the crystalline form. The S-isomer (***S*-24**) was found to be more active than the R-isomer (***R*-25**) by a factor of four.

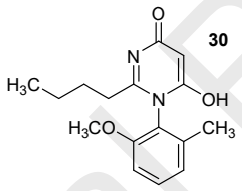
While the in vitro biotransformation work on compound **3** did not show oxidation or displacement of the sulfur, replacing the sulfur with a carbon linkage would generate analogs that would have less potential for in vivo metabolic activation. Aliphatic sidechain AHP analogs were synthesized from commercially available 2-methoxy aniline derivatives and valeronitrile via a similar addition/cyclization sequence[32] utilized for the sulfur sidechain analogs (Scheme 2).

Scheme 2. Synthesis of aliphatic sidechain AHP analogs.

These analogs where then assayed to compare their potencies relative to sulfur sidechain AHP analog 3 (Table 3).

Table 3. AHP analogs containing an aliphatic sidechain.





	3	30
Metabolic stability HRM (% remaining)	91, 96, 94	95, 82, 95
CYP inhibition (IC_{50})	>20 uM	>20 uM
PAMPA (pH 5.5, 7.4; nm/sec)	230, 12	131, 10
PXR(EC_{50})	>50 uM	>14 uM
hERG flux (IC_{50})	>80 uM	>80 uM
mouse PK (10 mg/kg; PO) Cmax	4400 nM	1680 nM
mouse PK (10 mg/kg; PO) Tmax	4 h	4 h
mouse PK (10 mg/kg; PO) AUCtotal	29000 nM*h	10200 nM*h

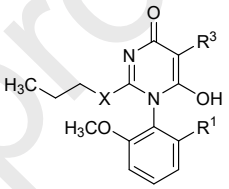
The direct sulfur vs. carbon analog comparison demonstrated that the carbon analog **26** had modestly improved potency compared to the sulfur analog **3**. Compound **26** was also found to exist as a mixture of atropisomers, like the sulfur sidechain analog **3**. Chiral SFC separation allowed for the isolation of single atropisomers **27** and **28**.[30] Exchanging the sulfur of the AHP side chain with a smaller carbon atom did not alter the atropisomer stability profile of the series. The fast eluting isomer **27** was nearly equipotent with the slow eluting isomer **28**.

The increased potency seen with ortho phenyl substitution strongly suggested that the bioactive conformation is one where the phenyl ring is orthogonal to the AHP core. Further stabilization of this apparent bioactive conformation could be achieved by adding a C6 substituent.

This hypothesis was supported when 2,6-disubstitution on the N-1 phenyl ring provided a further improvement in agonist activity (Table 3). The racemic 2-methoxy-6-methyl phenyl analog **29** displayed excellent potency hAPJ/cAMP EC_{50} = 5 nM, while the separated atropisomers **30** and **31** were of nearly equal potency of

…nds through SAR that exist as a mixture of atropisomers, it is common to try to remove the C2 axis of chirality so that analogs no longer require late stage chiral purification.[29] Installation of a 2,6-dimethoxyphenyl ring at the *N*-1 position of the AHP core was achieved with compound **32**. Importantly the achiral analog **32** maintained good potency relative to racemic **29**. The combination of a substituted malonic acid component (4-methoxy-benzyl) with the *N*-1 2,6-dimethoxyphenyl ring resulted in a potent hybrid analog **33**, that suggested further modification at this position would be tolerated for potency.

During investigations of AHP compounds like **3** and **26**, instability was observed in PBS solutions that were used for preparing in vivo dosing samples.[30] For example, after 8 hours, 1 week and 2 weeks at room temperature as a PBS buffer solution, compound **28** was found to have decreasing purities of 92%, 57% and 48%, respectively. It was observed that for unstable analogs, a ring-opened degradant was identified as a major component[30], albeit with less potency relative to the parent molecules. The medicinal chemistry focus shifted quickly toward identifying AHP analogs that were stable in PBS solution. Interestingly, analogs that contain 2,6-disubstitution on the lower phenyl ring were found



cmpd	X	R^1	R^3	hAPJ EC_{50} (nM)[a]
3[b]	S	H	H	64 ± 90
26[b]	CH_2	H	H	22 ± 36
27[c]	CH_2	H	H	24 ± 16
28[d]	CH_2	H	H	31 ± 40
29[b]	CH_2	methyl	H	5 ± 4
30[c]	CH_2	methyl	H	3 ± 1
31[d]	CH_2	methyl	H	2 ± 1
32[e]	CH_2	methoxy	H	11 ± 10
33[e]	CH_2	methoxy	4-OCH_3-Bn	13 ± 3

[a]Data represent the mean ± SEM, n = 2 or more determinations. [b]racemic mixture of atropisomers. [c]fast eluting single atropisomer. [d]slow eluting single atropisomer. [e]C2-symmetric achiral molecule.

to be stable in PBS solution after exposure up to 2 weeks with no measurable degradation.

Compounds **3** and **30** were selected for study in selectivity assays and mouse PK (Figure 2).[30] Metabolic stability for **3** and **30** were excellent and the compounds showed good off target liability profiles versus CYP, PXR, and hERG. Importantly, mouse PK (10 mg/kg; PO) was acceptable for both analogs and established compounds **3** and **30** as potential in vivo tool molecules.

Figure 2. Profiling and PK data of AHP compounds **3** and **30**.

In conclusion, through an HTS campaign, aryl hydroxy pyrimidinones were discovered as a new class of small molecules that provide full agonist activation of the APJ receptor, consistent with that of the native pep-tide ligand (pyr[1])apelin-13. Medicinal

chem[illegible]lier, potency led to 2,6-disubstitution on the *N*-1 phenyl ring combined with replacement of the thioether with an aliphatic sidechain. Through this work, potent and orally bioavailable analogs were identified. Efforts to further modify the AHP chemotype to provide analogs with potencies on par with (pyr[1])apelin-13, will be described in due course.

Acknowledgments

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