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Discovery of TD-0212, an Orally Active Dual Pharmacology AT_1 Antagonist and Neprilysin Inhibitor (ARNI)

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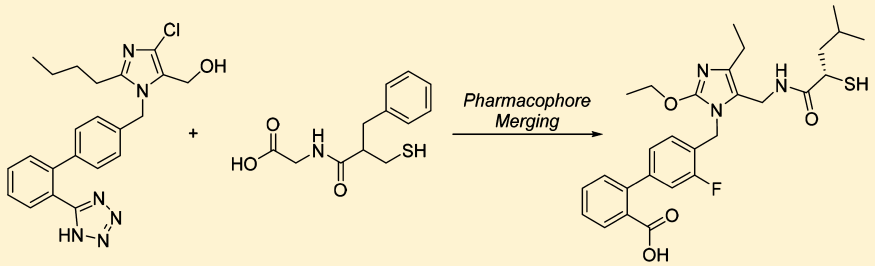
Supporting Information



ABSTRACT: Dual inhibition of angiotensin-converting enzyme (ACE) and neprilysin (NEP) by drugs such as omapatrilat produces superior antihypertensive efficacy relative to ACE inhibitors but is associated with a higher risk of life-threatening angioedema due to bradykinin elevations. We hypothesized that dual AT_1 (angiotensin II type 1 receptor) blockade and NEP inhibition with a single molecule would produce similar antihypertensive efficacy to omapatrilat without the risk of angioedema since ACE (the rate limiting enzyme in bradykinin metabolism) would remain uninhibited. Merging the structures of losartan (an AT_1 antagonist) and thiorphan (a NEP inhibitor) led to the discovery of a novel series of orally active, dual AT_1 antagonist/NEP inhibitors (ARNIs) exemplified by compound **35** (TD-0212). In models of renin-dependent and -independent hypertension, **35** produced blood pressure reductions similar to omapatrilat and combinations of AT_1 receptor antagonists and NEP inhibitors. Upper airway angioedema risk was assessed in a rat tracheal plasma extravasation (TPE) model. Unlike omapatrilat, **35** did not increase TPE at antihypertensive doses. Compound **35** therefore provides the enhanced activity of dual AT_1/NEP inhibition with a potentially lower risk of angioedema relative to dual ACE/NEP inhibition.

KEYWORDS: *Angiotensin, AT_1 antagonist, neprilysin inhibitor, dual pharmacology, heterodimer*

Angiotensin II is a potent vasoconstrictive peptide in the renin angiotensin system (RAS) that activates the G-protein coupled AT_1 receptor.[1] Other primary actions of angiotensin II include stimulation of aldosterone secretion by the kidneys, renal reabsorption of sodium,[2] and cardiac stimulation.[3] An AT_1 receptor antagonist (ARB) blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking binding of angiotensin II to the AT_1 receptor.[4] Numerous ARBs (Figure 1) have been described in the literature, and several have been approved by the FDA for the treatment of conditions such as hypertension and heart failure.[5]

Natriuretic peptides [atrial natriuretic peptide (ANP), brain-derived natriuretic peptide (BNP), and C-type natriuretic peptide (CNP)] effect peripheral vasodilation, increased renal sodium excretion, reduction of RAS activity, and promotion of antihypertrophic and antifibrotic effects, which are mediated through activation of guanylate cyclase signaling pathways. NEP is a zinc metalloprotease enzyme,[6] inhibition of which potentiates the activity of the cardiac natriuretic peptide system

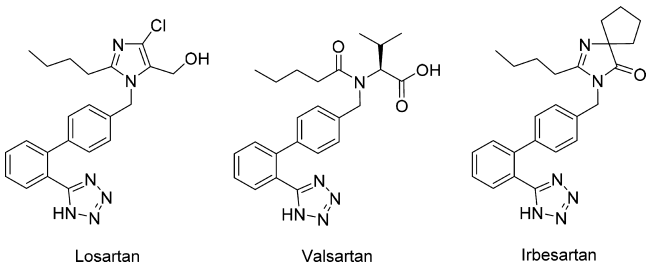


Figure 1. Selected FDA-approved ARBs.

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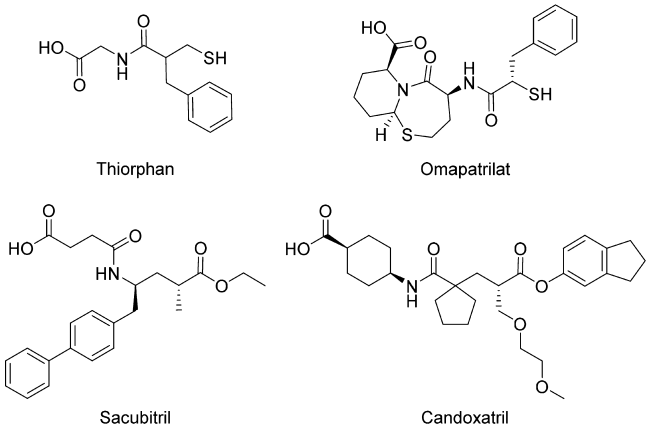
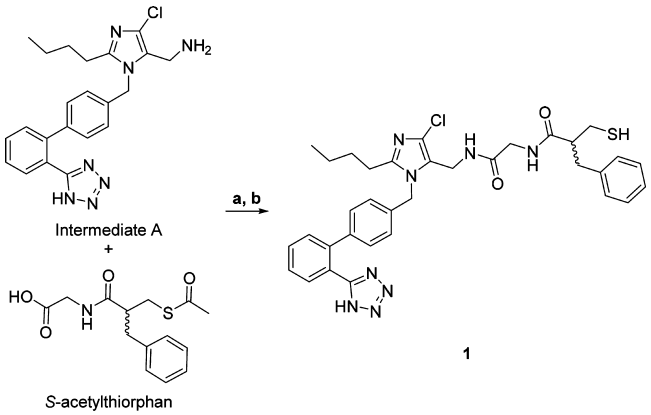


Figure 2. Selected NEP and ACE/NEP inhibitors.

Scheme 1. Synthesis of Losartan−Thiorphan Heterodimer 1[a]



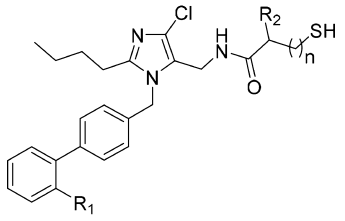
[a]Reagents and conditions: (a) EDC, HOBt, DIPEA, DMF, rt; (b) NaOH, MeOH, rt.

(CNPS) by inhibiting breakdown of the natriuretic peptides, mainly ANP.[7,8] To date, only one NEP inhibitor (sacubitril, Figure 2) has been approved by the FDA for clinical use (in a fixed-dose combination with the ARB valsartan).

Since the RAS and the CNPS are interconnected and both are critical in cardiovascular homeostasis, simultaneous inhibition of both systems has the potential to provide superior reductions in blood pressure, increased responder rates, improved cardiac performance, reduction of target-organ damage, and improvements in long-term outcomes in hypertensives and chronic heart failure (CHF) patients.

Dual inhibition of the RAS and CNPS with a single molecule has been attempted by different companies in a number of R&D programs. Omapatrilat is an agent that inhibits both ACE (RAS) and NEP (CNPS). Clinical hypertension trials established its efficacy in patients with mild to moderate hypertension, and the 25,000 patient OCTAVE study demonstrated broadly superior antihypertensive efficacy of omapatrilat relative to the ACE inhibitor enalapril.[9] Heart failure trials showed comparable efficacy between omapatrilat and lisinopril (another ACE inhibitor) in improving exercise tolerance in patients with NYHA class II/III heart failure, with a strong suggestion that omapatrilat improved clinical outcomes in heart failure to a greater extent than lisinopril (IMPRESS trial).[10] However, the 3-fold higher incidence of angioedema observed for omapatrilat relative to lisinopril and the incidence of life threatening angioedema in the OCTAVE study led to an unfavorable risk−benefit profile and the program was discontinued in 2002. While ACE is the predominant rate limiting enzyme in the metabolism of bradykinin, NEP, APP, DPP-IV, and other zinc metallopeptidases also play a role in bradykinin breakdown. The prevailing hypothesis is that dual inhibition of ACE and NEP by omapatrilat results in significantly greater elevation of bradykinin levels relative to ACE inhibition alone, which in a subset of patients can lead to excessive vascular leakage, fluid extravasation, and angioedema.[11]

Table 1. Exploration of S_1' and Biphenyl Substitution



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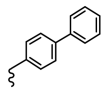
compound	R_1	R_2	n	AT_1 pK_i	NEP pIC_{50}
losartan	-	-	-	8.3	<5
thiorphan	-	-	-	<5	8.7
omapatrilat	-	-	-	<5	9.7
1	-	-	1	8	5.9
2	CN_4H	*rac*-CH_2Ph	1	7.8	5.7
3	CN_4H	*rac*-*i*-Bu	1	8	5.5
4	CO_2H	*rac*-CH_2Ph	1	7.1	5.1
5	CO_2H	*rac*-*i*-Bu	1	7.4	7.2
6	CO_2H	(*R*)-*i*-Bu	1	7	7.4
7	CO_2H	(*S*)-*i*-Bu	1	7.8	7.2
8	CO_2H		1	7.5	6.5
9	CO_2H	*rac*-*n*-Bu	1	6.9	6.2
10	CO_2H	*rac*-*i*-Pr	1	6.9	5.6
11	CO_2H	*rac*-*i*-Pentyl	1	6.9	6.5
12	CO_2H	rac-sec-Bu	1	6.2	5.9
13	CO_2H		1	6.6	6.2
14	CO_2H		1	7.3	6
15	CO_2H	*rac*-$CH(Et)_2$	1	7.3	7.4
16	CO_2H		1	6.4	6.2
17	CO_2H		1	6.4	5.7
18	CO_2H		1	6.8	6.4
19	CO_2H	*rac*-$CH(CH_3)Ph$	1	7.1	5.9
20	CO_2H	(*R*)-*i*-Bu	0	6.9	8.6
21	CO_2H	(*S*)-*i*-Bu	0	7.2	9

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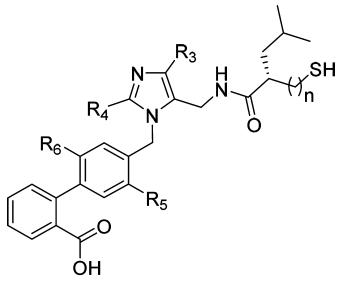
Table 2. Exploration of Imidazole Headgroup and Biphenyl Substitution



7, 21-35

compound	R_3	R_4	R_5	R_6	n	AT_1 pK_i	NEP pIC_{50}	% inhibition of ang-II pressor response (3 mg/kg, iv)	urinary cGMP fold increase over vehicle (3 mg/kg, iv)
losartan						8.3	<5	67	
omapatrilat						<5	9.7		5.3
7	Cl	*n*-Bu	H	H	1	7.8	7.2	11	2.2
21	Cl	*n*-Bu	H	H	0	7.2	9		
22	Me	*n*-Bu	H	H	1	7.3	7.1		
23	Me	*n*-Bu	H	H	0	6.7	9.2		
24	Et	*n*-Bu	H	H	1	8.3	6.9	68	2.6
25	Et	*n*-Bu	H	H	0	7.4	8.5	18	3.2
26	Cyclopropyl	*n*-Bu	H	H	1	8.2	6.9	55	1.8
27	Cyclopropyl	*n*-Bu	H	H	0	7.5	9.0	5	4
28	*i*-Bu	*n*-Bu	H	H	1	8.1	6.9		
29	*i*-Bu	*n*-Bu	H	H	0	7.5	7.7	32	1.9
30	Et	PrO	H	H	1	8.6	7.3	65	1.9
31	Et	PrO	H	H	0	7.7	9	23	3.8
32	Et	EtO	H	H	1	8.9	7.5	67	2.9
33	Et	EtO	H	H	0	8.2	9	57	3.6
34	Et	EtO	F	H	1	9.1	7.8	85	1.8
35	Et	EtO	F	H	0	8.9	9.2	76	3.5
36	Et	EtO	H	F	1	8.9	7.1		
37	Et	EtO	H	F	0	8.3	8.5	57	3.3
38	Et	EtO	F	F	0	8.3	7.8		

Our expectation was that inhibition of the RAS with an AT_1 antagonist/NEP inhibitor (ARNI) rather than an ACE/NEP inhibitor would result in an efficacy profile similar to that of omapatrilat without the risk for bradykinin elevation since ACE would remain uninhibited. A similar strategy led to the approval in 2015 of Entresto (LCZ696, a fixed dose 1:1 coformulation of the ARB valsartan with the NEP inhibitor prodrug sacubitril) for the treatment of CHF.[12] An alternative to coformulation is to design a molecule with potent activity at two different targets.[13] Potential benefits of this approach include matched pharmacodynamic (PD) effects on the targets of interest, thereby maximizing the potential synergy between the two mechanisms, and reduced potential for drug−drug interactions compared to drug cocktails. We therefore set out to design an ARNI by chemically merging the structure of an ARB with that of a NEP inhibitor.

The 5-position of the imidazole ring in the ARB losartan has been shown to accommodate a wide range of substituents, including some that provide a second pharmacological activity.[14−18] Using a similar strategy, we linked a losartan analog (Intermediate A) to the terminal carboxylic acid of thiorphan, a thiol-based inhibitor of NEP. While thiol-based drugs are associated with complex PK/PD relationships and development risks,[19] thiorphan was preferred over other NEP inhibitors due to its low molecular weight and high potency (Scheme 1). Heterodimer **1** maintained potent binding affinity at the AT_1 receptor relative to losartan (Table 1) but was significantly less potent than thiorphan in the NEP inhibition assay.

This data suggested that the AT_1 active site was more tolerant than that of NEP with respect to addition of a second pharmacophore. Removing the glycine spacer (compound **2**) led to a minor loss of potency at both targets. However, the lower molecular weight and reduced conformational flexibility of **2** was considered more conducive to achieving oral activity, and so **2** became the focal point of our early optimization efforts.

Assuming the thiorphan fragment of **2** binds to NEP in a similar fashion to thiorphan itself, the benzyl substituent (R_2) of **2** would occupy the S_1' subsite of the enzyme. Replacement of the benzyl group with another S_1' substituent commonly utilized in NEP inhibitors (*rac*-isobutyl, **3**) had little impact on potency at either target (Table 1). Surprisingly, the first significant improvement in NEP potency was achieved by modification of the ARB region of the molecule. Replacing the tetrazole moiety (R_1) on the biphenyl fragment with a carboxylic acid (**5** vs **3**) afforded a 1.7 log unit gain in NEP pIC_{50} when the S_1' group was *rac*-isobutyl. Synthesis of the individual enantiomers of **5** revealed that the AT_1 receptor had a clear preference for *S*-enantiomer **7**. An extensive survey of other alkyl and aromatic groups in the S_1' pocket (compounds **8**−**19**) demonstrated that the *S*-isobutyl group maintained the best balance of potency at the two targets. Replacing the *β*-thiol zinc-chelator (**7**) with an

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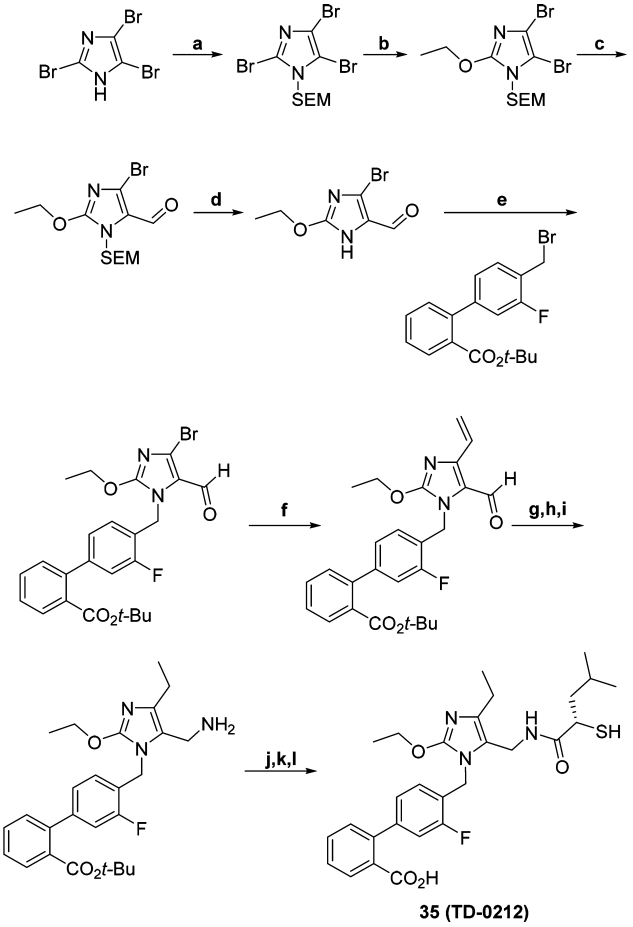
Scheme 2. Synthesis of 35 (TD-0212)[a]



[a]Reagents and conditions: (a) SEMCl, DIPEA, DCM, rt; (b) KO*t*-Bu, EtOH, reflux; (c) DMF, *n*-BuLi, THF, −78 °C; (d) TFA, 0 °C; (e) K_2CO_3, DMF; (f) $Pd(PPh_3)_4$, $(C_2H_3)Sn(n\text{-}Bu)_3$, DMF, 90 °C; (g) $NH_2OH.HCl$, pyridine, H_2O; (h) H_2, $Pd(OH)_2$, EtOH; (i) $NaBH_3CN$, $TiCl_3$, NH_4OAc, MeOH, 0 °C; (j) (*S*)-2-(acetylthio)-4-methylpentanoic acid, HATU, DIPEA, DMF, rt; (k) TFA, DCM, rt; (l) NaOH, MeOH, H_2O, rt.

α-thiol (**21**) increased NEP potency to a level similar to that of thiorphan, but simultaneously reduced AT_1 potency. Since the α-thiols (low AT_1, high NEP activity) provided a distinct profile to the β-thiols (high AT_1, low NEP activity), both series were progressed to SAR studies focused on the imidazole headgroup substituents.

Replacement of the imidazole 4-Cl substituent [R_3, (Table 2)] with a methyl group (**23**, **24**) reduced the AT_1 activity in both the α- and β-thiol series. The bulky *i*-Bu (**28**) group was not tolerated by NEP in the α-thiol series. Intermediate-size alkyls such as ethyl (**24**) and cyclopropyl (**26**) were relatively well-tolerated by both active sites. At the 2-position of the imidazole (R_4), insertion of an oxygen atom into the alkyl chain (**30** vs **24**) was slightly beneficial in terms of both AT_1 and NEP potency. An additional gain in AT_1 potency was realized by shortening the alkoxy chain from four atoms to three atoms (**32** vs **30**). The AT_1 potency of this ARNI series was now greater than that of the parent ARB, losartan. Using compounds **32** and **33** as starting points, a limited substitution scan on the biphenyl fragment was performed. Adding a fluorine atom *ortho*- to the headgroup maintained NEP activity and significantly boosted AT_1 potency in the α-thiol series (**35** vs **33**). Alternative fluorine substitution

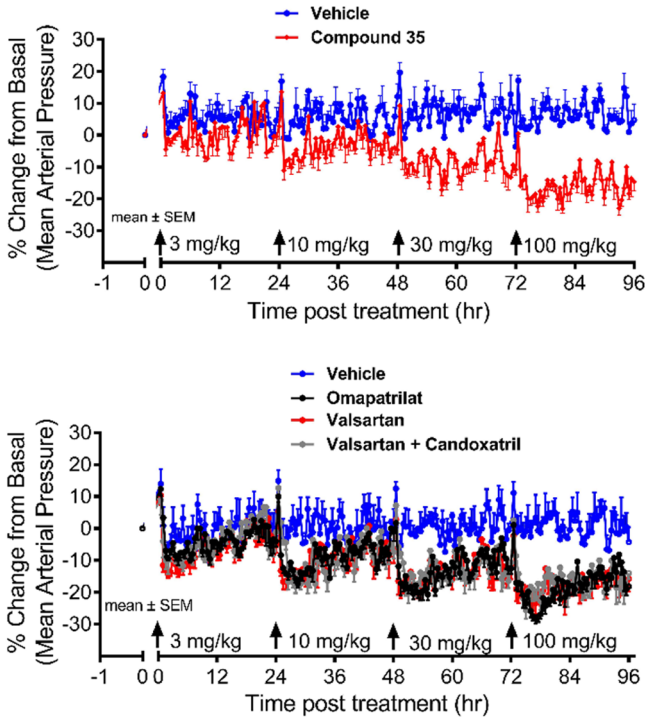


Figure 3. Comparison of 24 h average MAP reductions following oral administration of **35**, omapatrilat, valsartan, or a valsartan/candoxatril combination in conscious SHR.

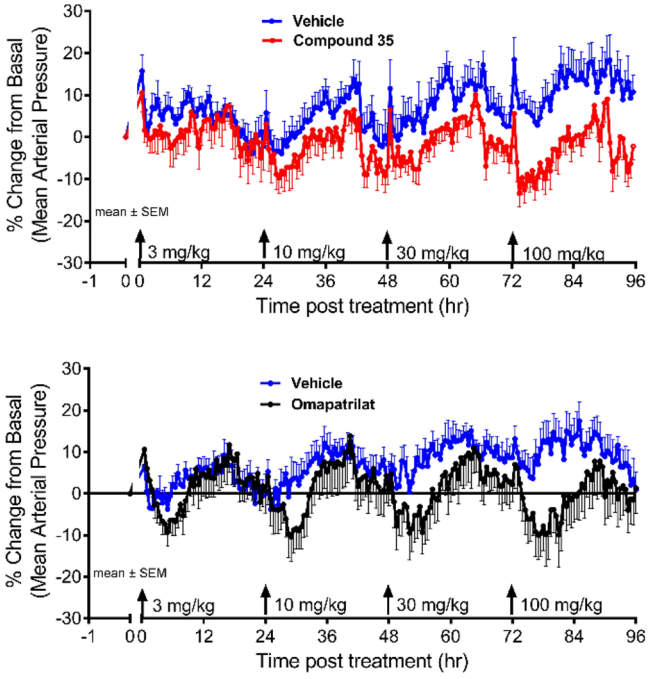


Figure 4. Comparison of antihypertensive efficacy and duration following oral administration of **35** or omapatrilat in conscious DOCA-salt hypertensive rats.

patterns were neutral at AT_1 but deleterious to NEP relative to the parent molecule. Biphenyl substitutions did not have a significant effect in the β-thiol analogs.

To determine the *in vivo* activity of these novel dual pharmacology molecules, a rat pharmacodynamic (PD) assay was developed to simultaneously measure AT_1 antagonism via inhibition of the angiotensin-II-evoked pressor response and

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Table 3. Selectivity Profile of Compound 35, Valsartan, and Omapatrilat against Related Targets

	potency		
target	35	valsartan	omapatrilat
AT_2[a]	5.6	<5.0	ND
ACE[b]	<5.0	ND	10
APP[b]	<5.0	ND	6.7
ECE-1[b]	7.1	ND	ND

[a] pK_i. [b] pIC_{50}.

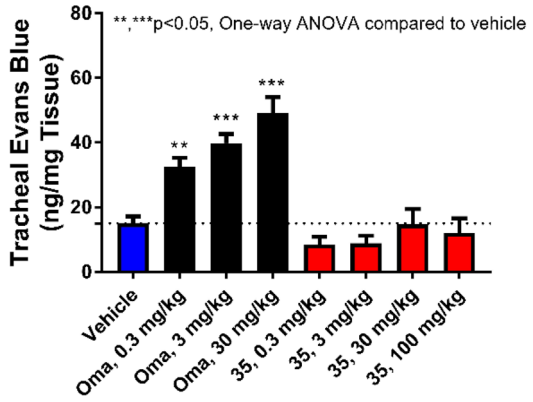

Figure 5. Comparison of tracheal plasma extravasation following administration of vehicle, omapatrilat, or **35** in normotensive rats.

NEP inhibition via potentiation of ANP-induced elevation of urinary cyclic guanosine monophosphate (cGMP) output relative to vehicle.[20] Compounds were dosed IV in the PD assay to determine the intrinsic activity of the parent molecule without oral absorption playing a role. In general, *in vivo* activity correlated with *in vitro* activity (Table 2). Compounds with pK_i values >8.0 at AT_1 inhibited the angiotensin-II blood pressure response to a similar extent as losartan. With respect to NEP inhibition, pIC_{50} values of >8.0 generally produced more than 3-fold increases in urinary cGMP relative to vehicle. None of the compounds were as active as omapatrilat in this assay, in keeping with their reduced *in vitro* potency relative to omapatrilat.

On the basis of its activity in the PD assay and rat pharmacokinetics (see Supporting Information), compound **35** (Scheme 2) was advanced to a dose−response study in the spontaneously hypertensive rat (SHR) model, which is known to be sensitive to ARBs.[21] In this model, telemetry is used to monitor blood pressure for a period of 24 h after oral dosing of the compound. Efficacy was determined by the peak percent fall in mean arterial pressure (MAP) from baseline, while duration of action was reflected by the vehicle-adjusted % change in AUC over 24 h. Administration of sequential escalating doses of 3, 10, 30, and 100 mg/kg of **35** at 24 h intervals between the successive doses produced dose-dependent reductions in MAP (Figure 3). At doses of 10 mg/kg and above, the duration of effect was sustained for 24 h. In comparison to vehicle treatment the effect was statistically significant at 10 mg/kg and higher doses ($p < 0.05$, two way ANOVA with Bonferroni post hoc analysis).

Omapatrilat and valsartan produced a dose-dependent reduction in MAP similar in magnitude to **35**. The addition of the NEP inhibitor prodrug candoxatril (at a dose of 100 mg/kg) to valsartan did not result in further blood pressure lowering in the SHR model relative to valsartan alone, which is consistent with its non-RAS action. The estimated ED_{10} (dose required to produce an average 10% reduction in the 24 h average MAP) for **35** (ED_{10} = 13 mg/kg) was comparable to that of omapatrilat, valsartan, and the valsartan/candoxatril combination (ED_{10} = 15, 17, and 15 mg/kg respectively).

In vivo NEP inhibition after oral dosing was determined using the deoxycorticosterone acetate (DOCA) salt rat model of hypertension. The DOCA model is insensitive to ARBs and therefore considered a model for low-renin hypertension. Compound **35** produced a dose-dependent reduction of blood pressure in the DOCA model (Figure 4). The potency and duration of effect of **35** (ED_{10} = 44 mg/kg) were comparable to omapatrilat (ED_{10} = 66 mg/kg).

Additional *in vitro* studies confirmed that **35** is a potent, competitive antagonist of the AT_1 receptor, with a selectivity for AT_1 over AT_2 of approximately 2000-fold (Table 3). In contrast to losartan, which is classified as a surmountable AT_1 antagonist,[22] **35** was found to be partially insurmountable in an inositol phosphate accumulation assay (<5% vs 87% accumulation, respectively). Compound **35** is also a potent, selective, and competitive inhibitor of NEP, exhibiting 120-fold selectivity for inhibition of human recombinant NEP over human recombinant ECE-1, and no measurable activity at human ACE or APP at a concentration of 10 μM.

In order to assess the risk of angioedema with **35** relative to that with omapatrilat, a rat tracheal plasma extravasation (TPE) model was developed based on a method described by Sulpizio et al.[23] In this model, TPE was used as a surrogate to assess the propensity of compounds to promote upper airway angioedema by measuring the extent of Evans Blue dye leakage into peritracheal tissue at different antihypertensive doses. Omapatrilat produced a robust increase in TPE at low oral subactive doses of 0.3 and 3 mg/kg. In contrast, **35** had no effect at doses of up to 100 mg/kg (Figure 5).

The combined results from *in vivo* pharmacology studies indicate that **35** is as effective as omapatrilat in terms of antihypertensive activity. Unlike omapatrilat, **35** does not increase tracheal plasma extravasation in rats, which is indicative of a low risk for causing angioedema. Taken together, **35** can be described as an ARB-equivalent of omapatrilat with a lower risk of angioedema. Additional studies with **35** will be reported in future publications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00462.

In vitro and in vivo assay procedures; representative synthetic procedures and compound characterization data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AT_1, angiotensin II type 1 receptor; ACE, angiotensin-converting enzyme; NEP, neprilysin; TPE, tracheal plasma extravasation; RAS, renin angiotensin-system; ARB, AT_1 receptor antagonist; ANP, atrial natriuretic peptide; BNP, brain-derived natriuretic peptide; CNP, C-type natriuretic peptide; CNPS, cardiac natriuretic peptide system; APP, aminopeptidase P; DPP-IV, Dipeptidyl Peptidase IV; CHF, chronic heart failure; SHR, spontaneously hypertensive rat; MAP, mean arterial pressure; DOCA, deoxycorticosterone acetate; cGMP, guanosine monophosphate; ED_{10}, dose required to produce an average 10% reduction in the 24h average MAP; ECE, endothelin converting enzyme 1

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