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Discovery of nor-seco himbacine analogs as thrombin receptor antagonists

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ABSTRACT

Discovery of a novel nor-seco himbacine analog as potent thrombin receptor (PAR-1) antagonist is described. Despite low plasma level, these new analogs showed excellent ex vivo efficacy in the monkey platelet aggregation assay. A potent hydroxy metabolite generated in vivo was identified as the agent responsible for the ex vivo efficacy. Following this discovery, the metabolite series was optimized to obtain analogs that showed very good ex vivo efficacy along with excellent pharmacokinetic profile in c. monkey.

Antiplatelet agents play an essential role in the treatment of atherothrombosis.[1,2] Upon rupture of an atherosclerotic plaque, the platelet activation mechanism and coagulation mechanism synergize leading to the formation of a thrombus at the site of injury which often occludes the coronary artery. The obstruction of blood flow and the resulting myocardial underperfusion can lead to a spectrum of clinical conditions known as *acute coronary syndrome* (ACS) that include Q-wave myocardial infarction, non-Q-wave myocardial infarction and unstable angina.[3] Aggregated platelets contribute significantly to the formation of arterial thrombi and as such and antiplatelet agents such as aspirin and clopidogrel comprise the current standard of care for ACS. However, there remains an unmet clinical need for antiplatelet drugs with greater potency and improved safety margin with regard to hemorrhagic side effects, which are complicating factors for the current antiplatelet treatments.[4]

As part of our efforts to address this need, we have reported the discovery of vorapaxar[5] (SCH 530348) which is a potent antagonist of the platelet surface thrombin receptor, also known as protease activated receptor-1 (PAR-1).[6–12] In preclinical non-human primate models of ex vivo platelet aggregation and arterial thrombosis, SCH 530348 showed potent antiplatelet effects without change in template bleeding times.[13] In a Phase-II clinical study in patients who underwent non-emergent PCI, SCH 530348 met the primary end point of absence of significant TIMI major plus minor bleeding when compared with placebo.[14] For the secondary outcome endpoint, SCH 530348 was associated with a non-statistically significant numerical reduction in periprocedural myocardial infarction. Two additional Phase-II studies conducted in Japanese patients (one in patients with acute coronary syndromes and the other in patients with ischemic stroke) have confirmed the lack of significant TIMI bleedings associated with the drug.[13] Additionally, the study performed in Japanese patients with acute coronary syndromes demonstrated a significant reduction in periprocedural myocardial infarctions. Complete results of two large scale clinical studies on vorapaxar are anticipated in the near future.[15,16]

The tricyclic ring skeleton of vorapaxar is derived from the natural product himbacine, although it has an absolute chirality opposite to that of the natural product. In an extensive SAR study of the tricyclic himbacine-based PAR-1 antagonists, we have made several modifications to the right-hand side ring (C-ring) by introducing substituents, and by replacing the C-ring with aryl and heterocyclic rings.[17–20] As reported previously, the tetrahydrothiopyranyl analog **2** (Fig. 1), which has the C_7 carbon of the tricyclic skeleton replaced with a sulfur atom, has PAR-1 affinity comparable to the prototypical PAR-antagonist **1**.[19] Despite the fact that the utility of compound **2** was limited due to its potential in vivo metabolism to the corresponding less active sulfone, it lent itself

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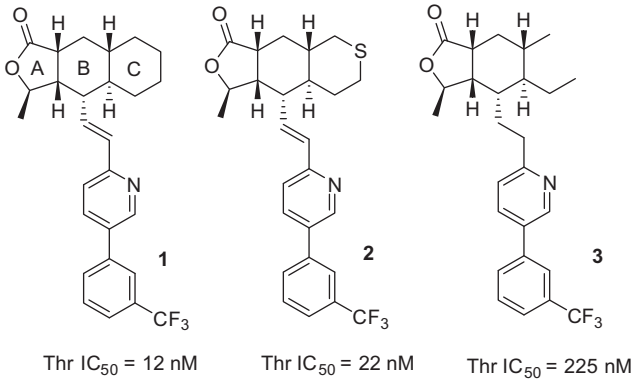
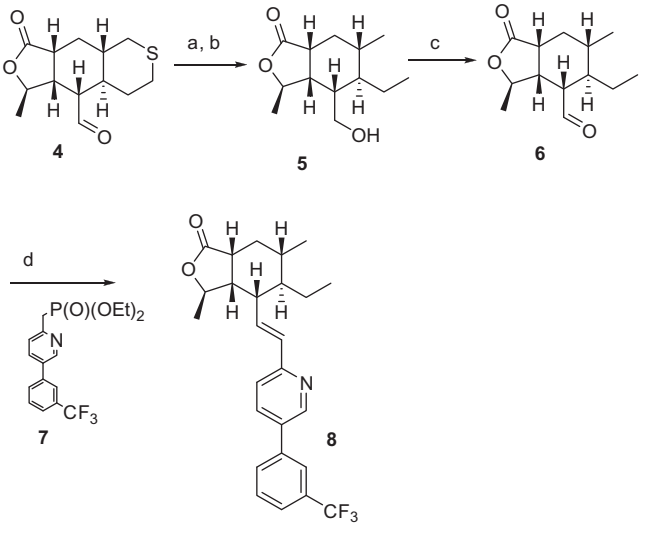


Figure 1.

to the discovery of a new C-ring-opened chemical series which we now wish to report. Raney nickel desulfuration of **2** resulted in the anticipated sulfur extrusion with concomitant reduction of the double bond to give **3**. This new bicyclic analog showed an encouraging, albeit modest PAR-1 binding (IC_{50} = 225 nM). Since we knew from the previous SAR studies in the original tricyclic series that the trans-ethylene-linked pyridine was essential for optimal PAR-1 affinity, we synthesized the trans-ethenyl analog **8** as shown in Scheme 1.

The synthesis started with the previously reported aldehyde[19] which was reduced to the corresponding alcohol and subsequently reduced under Raney nickel conditions to provide the desulfurated, nor-seco himbacine intermediate **5**. The alcohol was oxidized to the corresponding aldehyde which was subjected to Horner–Wadsworth–Emmons reaction with phosphonate **7** to give the target compound **8**. In line with our expectation, this novel nor-seco himbacine analog **8** showed PAR-1 affinity comparable to the parent tricyclic analog **1** in the radioligand binding assay. We further set out to explore the SAR of the nor-seco himbacine series of PAR-1 antagonists in detail.

A modified synthetic approach that facilitated the SAR study in this series is shown in Scheme 2. Commercially available (*E*)-2-methyl-2-pentenal was subjected to Horner–Wadsworth–Emmons



Scheme 1. Reagent and condition: (a) $NaBH_4$, MeOH; (b) Ra-Ni, MeOH-THF, heated at reflux; (c) TPAP, NMO, 4 Å molecular sieves; (d) **7**, BuLi, THF then **6**.

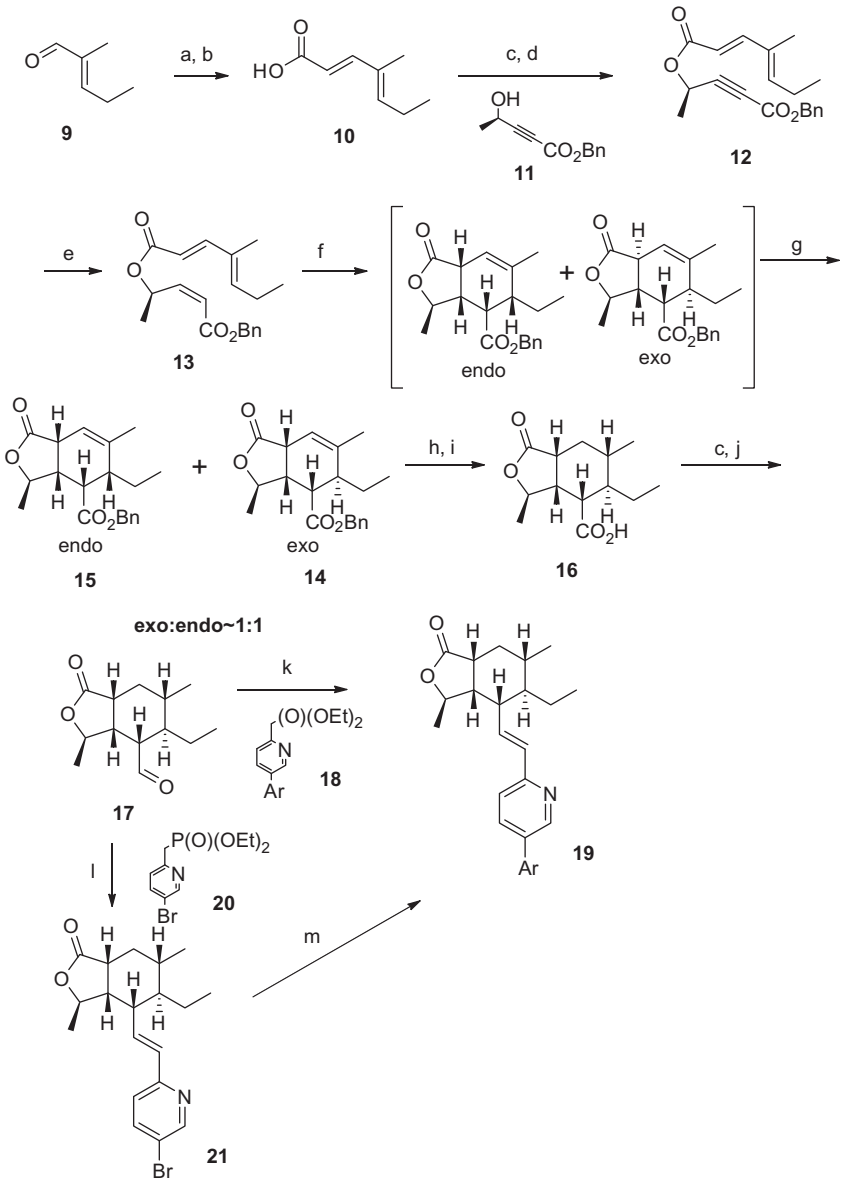
reaction, followed by saponification to provide the dienoic acid **10**. The acid was converted to its acid chloride and coupled with the previously reported alcohol **11** to provide the ester **12**.[17] Hydrogenation of the alkyne with Lindlar catalyst gave the *cis*-olefin **13**. Intramolecular Diels–Alder cyclization of **13** at 185 °C, followed by in situ treatment with DBU to effect C_7 epimerization, gave a mixture of exo and endo products (~1:1) in 66% yield. The two isomers were separated by silica gel column chromatography and the *exo* isomer was used for the subsequent transformations. Debenzylation of **14** over Pd-C/H_2 followed by double bond reduction over PtO_2/H_2 gave the carboxylic acid **16** which was converted to the aldehyde **17** via its acid chloride. Coupling of several substituted pyridyl phosphonates **18** with the aldehyde **17** gave the substituted nor-seco analogs represented by structure **19**. Alternatively, aldehyde **17** was coupled with phosphonate **20** to give the bromo-substituted pyridyl analog **21** which could be further elaborated to the desired target **19** by Suzuki coupling as shown.

The in vitro binding assays were carried out as described before on PAR-1 receptors isolated from human platelets and [^{3}H]haTRAP as the radioligand.[21] Table 1 presents the in vitro PAR-1 binding affinity for the nor-seco analogs. Similar to the tricyclic himbacine series, both the *ortho* and *meta* substituted phenyl derivatives showed excellent binding affinity (compound **19a**–**h**). Specific requirements for disubstitution of the phenyl ring was also noted. The 2,3 dichloro substituted analog (**19i**) was very potent (IC_{50} = 13 nM), whereas the corresponding 2,5-dichloro analog **19j** (IC_{50} = 513 nM), showed considerably weaker affinity. Selected analogs were evaluated in a rat pharmacokinetic assay at an oral dose of 10 mg/kg and the plasma levels were analyzed up to 6 h. As shown in Table 1, the rat plasma levels of the parent were uniformly low for these compounds.

A number of PAR-1 antagonists from this series were also tested in a cynomolgus monkey ex vivo platelet aggregation inhibition assay. In this assay, the drug was dosed orally in HPβCD and blood samples were drawn at various time points. A 1 μM solution of haTRAP was added to the whole blood to initiate platelet aggregation, which was quantified using an aggregometer. This assay provided a direct measurement of the antiaggregatory response of the drug under conditions of PAR-1 activation by an exogenously added agonist.[22] Compound **19b** showed about 45% inhibition of platelet aggregation at 3 mg/kg oral dose at the 24-h time point whereas at the same dose analog **19c** completely inhibited haTRAP-induced platelet aggregation at 24 h. Upon further dosing down **19c** showed robust platelet aggregation inhibition even at 1 mg/kg with 69% inhibition of aggregation at 24 h. Compound **19i** also showed excellent inhibition of haTRAP induced platelet aggregation (95% at 24 h) at a 3 mg/kg dose.

Analysis of the monkey plasma levels from efficacy studies indicated relatively low plasma concentrations for the parent drugs and high plasma levels of a (M+16) metabolite. For example **19c** showed an $AUC_{(0-24\ h)}$ = 451 ng h/mL (Cmax = 62 ng/mL). However, M+16 metabolite concentration was three times higher ($AUC_{(0-24\ h)}$ = 1400 ng h/mL, Cmax = 98 ng/mL). In a similar fashion, **19i** also showed considerable amount of circulating hydroxy metabolite (parent $AUC_{(0-24\ h)}$ = 573 ng h/mL; (M+16) metabolite $AUC_{(0-24\ h)}$ = 813 ng h/mL). Since these compounds showed high efficacy despite the low plasma level of the parent, we suspected that the circulating hydroxy metabolite might likely be contributing to the observed efficacy. This prompted our effort to identify and characterize the hydroxy metabolite generated in vivo.

Analysis of the rat plasma samples from PK studies using LC-ESI/MS/MS on the Micromass Q–T of mass spectrometer indicated the presence of a major M+16 metabolite arising from the metabolism of the six-membered carbocyclic ring. In an effort to further confirm this characterization, **19c** was incubated with rat liver microsomes and the major hydroxy metabolite isolated. Proton



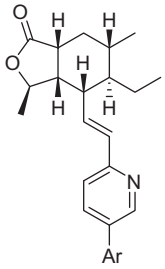
Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) KOH, THF-MeOH-H_2O; (c) $(COCl)_2$, cat. DMF; (d) **11**, Et_3N, DMAP; (e) H_2, Lindlar catalyst, quinoline; (f) toluene, 185 °C, in a sealed tube; (g) DBU, rt; (h) **14**, H_2, Pd-C; (i) H_2, PtO_2; (j) Bu_3SnH, cat. $Pd(Ph_3P)_4$; (k) **18**, LHMDS then $Ti(O^iPr)_4$ and **17**; (l) **20**, LHMDS then $Ti(O^iPr)_4$ and **17**; (m) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene–ethanol–water, 100 °C in a sealed tube.

NMR study indicated that this metabolite corresponded to the C_{7a} hydroxylated derivative **22** (Fig. 2). In order to further corroborate the identity of this oxidative metabolite, we synthesized an authentic sample by treating **19c** with LHMDS followed by oxidation with (*1S*)-(+)-(10-camphorsulfonyl)oxaziridine to give **22**. This synthetic sample of **22** was identical to the sample isolated from liver microsomal incubation of **19c**.

In the rat pharmacokinetic studies, hydroxyl derivative **22** showed a fivefold improvement in parent AUC under similar dosing conditions. In the *c. monkey* ex vivo efficacy assay, the 7a-hydroxy metabolite **22** showed 100% inhibition of platelet aggregation at 24 h at a 3 mg/kg oral dose and at a lower dose of 1 mg/kg, complete inhibition was maintained up to 6 h. Analysis of the *c. monkey* plasma samples showed excellent plasma concentration of parent **22**. The monkey AUC of **22** at an oral dose of 1 mg/kg was 4280 ng h/mL which was more than nine times the AUC of **19c** following a 3 mg/kg oral dose.

Thus the original nor-seco derivatives seemed to be liable to fast in vivo oxidation to the C_7 hydroxy derivatives. The relatively low plasma levels of the parents that we observed for the original series in the rat PK studies could be explained by this facile metabolic conversion. Since the hydroxylated metabolite **22** showed improved pharmacokinetic profile while retaining the potency of its parent **19c**, we decided to further evaluate the C_{7a}-OH analogs of other nor-seco derivatives. The synthesis of these compounds is described in Scheme 3. The intermediate **21** was readily oxidized at it C_{7a} position via the lactone enolate to give **23** which was converted to the target analogs **24a**–**l**. Representative examples of PAR-1 binding and ex vivo studies of 7a-hydroxy nor-seco derivates are presented in Table 2. The phenyl analog **24a** showed excellent binding affinity. As before, substitutions at both the *ortho* and *meta* positions of the phenyl group were tolerated very well, the corresponding *para* substituted analogs were either inactive (**24e**) or substantially less potent (**24h**). We also evaluated several heteroaryl analogs that replaced the phenyl substituent on the pyridine moiety. Substitution with 3-thiophene (**24j**) and 3-furan (**24k**) moieties resulted in analogs with excellent potencies compared with the corresponding pyridyl analog **24i**. Non-aromatic

Table 1
Binding, PK and ex-vivo data for compounds **19a–k**



Compound #	Ar	PAR-1 IC_{50} (nM)	Rat AUC[a]	*C. monkey* ex vivo platelet aggregation inhibition[b]
19a	Phenyl	8.8	672	
19b	(2-Fluoro)-phenyl	22	852	45% (3 mpk/24 h)
19c	(3-Fluoro)-phenyl	15	230	100% (3 mpk/24 h)
19d	(2-Chloro)-phenyl	25		
19e	(3-Chloro)-phenyl	28		
19f	(2-Methyl)-phenyl	20		
19g	(3-Methyl)-phenyl	45		
19h	(3-Cyano)-phenyl	21		
19i	(2,3-Dichloro)-phenyl	13	1146	95% (3 mpk/24 h)
19j	(2,5-Dichloro)-phenyl	513		

[a] AUC from 0 to 6 h in ng h/mL and at 10 mg/kg oral dose (0.4% methylcellulose).
[b] Reduction in haTRAP induced platelet aggregation in *c. monkey* following oral dose (20% PEG-HPBCD).

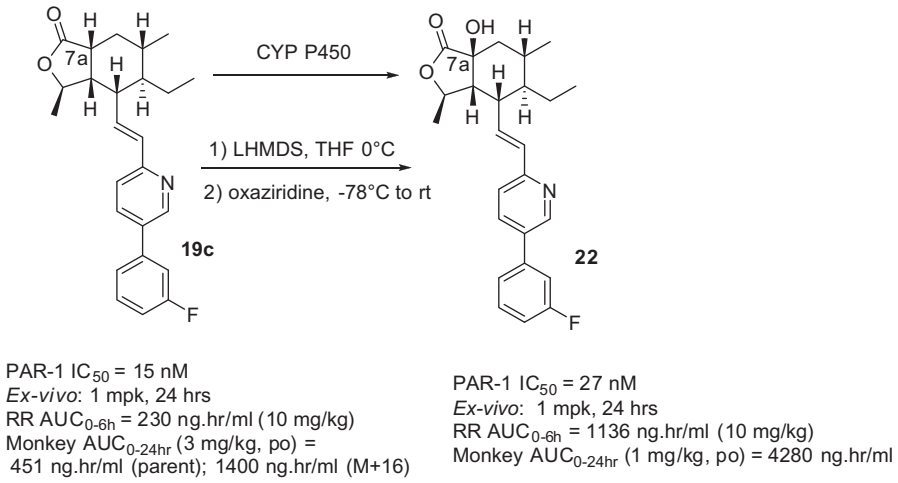
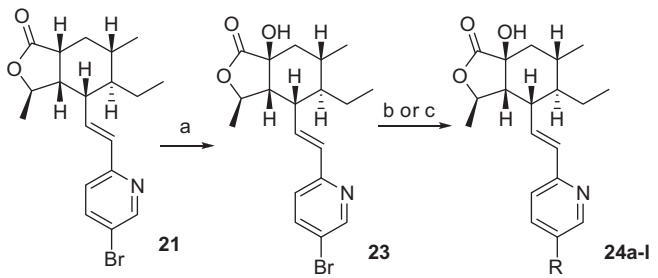


Figure 2.

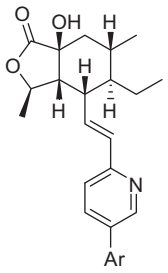


Scheme 3. Reagent and condition: (a) LHMDS then (*1S*)-(+)-(10-camphorsulfonyl)oxaziridine; (b) $ArB(OH)_2$, cat. $Pd(Ph_3P)_4$, K_2CO_3, toluene–ethanol–water, 100 °C in a sealed tube; for compounds **24a–k**; (c) pyrrolidine, cat. $Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, K_3PO_4, toluene, 100 °C; for compound **24l**.

heterocycles were also tolerated in the place of phenyl group (e.g., **24l**).

Several of the hydroxylated nor-seco analogs were evaluated in the rat pharmacokinetic assay. In general, the rat pharmacokinetic profile was greatly improved from the C_{7a}-H parent series (Tables 1 and 2). In the ex vivo platelet aggregation inhibition assay in cynomolgus monkey, several of these compounds showed impressive oral antiplatelet effect that lasted, in many cases, for 24 h. For example **24a** completely inhibited the platelet aggregation at 3 mg/kg dose (Fig. 3) for 24 h. At a lower dose of 1 mg/kg, it inhibited ~65% of the platelet aggregation at the 24 h time point, and even at 0.3 mg/kg dose it showed partial inhibition at earlier time points. The (3-cyano)-phenyl analog **24d** showed only moderate rat plasma level, however the monkey efficacy was comparable to **24a**. Despite good rat plasma level, the (3-methoxy)phenyl

Table 2
Binding, PK and ex-vivo data for compounds **24a–l**



Compound #	Ar	PAR-1 IC_{50} (nM)	Rat AUC[a]	Ex vivo[b]	Monkey AUC[c]
24a	Phenyl	6.4	3297	65% (1 mpk/24 h)	3825 (1 mg/kg)
24b	(2-Methyl)-phenyl	33	3159	55% (3 mpk/6 h)	2720 (3 mg/kg)
24c	(3-Methyl)-phenyl	35	203	100% (3 mpk/6 h)	2770 (3 mg/kg)
24d	(3-Cyano)-phenyl	20	1084	60% (1 mpk/24 h)	6284 (1 mg/kg)
24e	(4-Cyano)-phenyl	Inactive	–	–	–
24f	(2-Methoxy)-phenyl	8.1	168	–	–
24g	(3-Methoxy)-phenyl	18	2441	Inactive (1 mpk)	1210 (1 mg/kg)
24h	(4-Methoxy)-phenyl	451	–	–	–
24i	3-Pyridyl	49	1895	45% (3 mpk/24 h)	–
24j	3-Thiophene	4.6	397	90% (3 mpk/24 h)	4740 (3 mg/kg)
24k	3-Furan	8.6	148	35% (3 mpk/24 h)	4110 (3 mg/kg)
24l	1-Pyrrolidine	64	486	100% (3 mpk/6 h)	–

[a] AUC from 0 to 6 h in ng h/mL and at 10 mg/kg oral dose (0.4% methylcellulose).
[b] Reduction in haTRAP induced platelet aggregation in *c. monkey* following oral dose (20% PEG-HPBCD) of the hydrochloride salt.
[c] AUC from 0 to 24 h in ng h/mL (data obtained from the ex-vivo plasma sample).

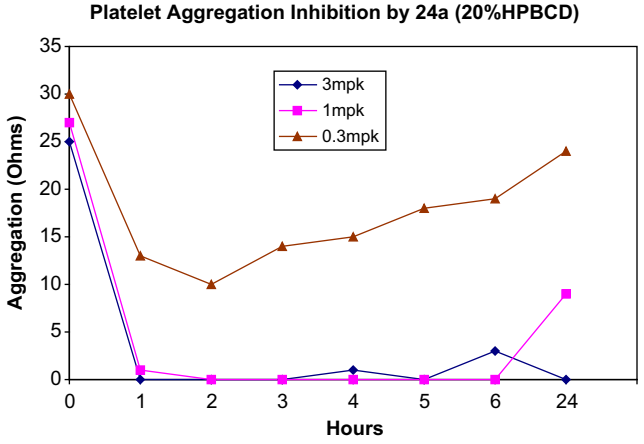


Figure 3. Ex vivo platelet aggregation inhibition in cynomolgus monkey following a single oral dose (3 mg/kg, 1 mg/kg and 0.3 mg/kg in 20% PEG-HPBCD) **24a**.

analog **24g** did not show any efficacy at a 1 mg/kg dose. The 3-pyridyl analog **24i** showed good rat plasma level and efficacy up to 24 h at a 3 mg/kg dose. Though the 3-thiophene and 3-furan analogs showed very poor rat plasma levels, analog **24j** inhibited 90% of platelet aggregation (3 mpk/24 h) and analog **24k** inhibited about 35% of platelet aggregation (3 mpk/24 h). The 1-pyrrolidine analog **24l** showed low rat plasma level, however it maintained good efficacy up to 6 h at a 3 mg/kg dose.

Due to the excellent ex vivo efficacy and rat plasma level exhibited by compound **24a**, it was subjected to a full monkey pharmacokinetic assay. Cynomolgus monkeys were dosed at 1 mg/kg oral dose in 0.4%MC and 1 mg/kg iv dose in 20% HPBCD. Compound **24a** showed an oral bioavailability of 78% with $AUC_{(0-24\ h)}$ = 3980 ng h/mL. The oral Cmax was 397 ng/mL with a Tmax of 1.0 h. Also, the half-life was 10.7 h. The compound showed a low volume of distribution (Vd(ss) = 1.5 (L/kg)) and showed a clearance of 3.3 mL/min/kg. Since, many of earlier analogs showed extremely slow clearance,[18,19] we decided to evaluate the clearance of [^{3}H]**24a** in *c. monkey*. Following a 1 mg/kg iv dose of ^{3}**H–24a** in the *c. monkey*, total excreted radioactivity in urine and bile was quantified. It was found that the entire radioactivity was accounted for by 6 days indicating a very ideal clearance profile for this analog.

In summary, we have discovered a novel series of thrombin receptor antagonists by truncation of the tricyclic ring system of the prototypical compounds and by introduction of a C_{7a}-hydroxyl group, guided by the major active in vivo metabolite. Further optimization of the aryl substitution resulted in the discovery of several potent analogs with single-digit nanomolar PAR-1 affinity and excellent oral efficacy in an ex vivo cynomolgus monkey platelet aggregation inhibition model. The benchmark nor-seco analog **24a** showed complete ablation of agonist-induced ex vivo platelet aggregation following 1 mg/kg oral dose and a robust pharmacokinetic profile in rat and monkey models.

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