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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 14 (2004) 4867–4872

Identification of 4-piperazin-1-yl-quinazoline template based aryl and benzyl thioureas as potent, selective, and orally bioavailable inhibitors of platelet-derived growth factor (PDGF) receptor

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Received 30 September 2003; revised 19 July 2004; accepted 20 July 2004
Available online 7 August 2004

Dedicated to Frank A. Heath, in memoriam

Abstract—4-[4-(*N*-Substituted-thio-carbamoyl)-1-piperazinyl]-6-methoxy-7-alkoxyamino-quinazoline derivatives such as **14** (CT53986) have been identified to be potent and selective inhibitors of the phosphorylation of PDGFR. SAR-investigations are described in the arylamine segment, C-7 appendage, and the thiourea moiety. Bioisosteres of thiourea (cyanoguanidine), and of quinazoline (quinoline-3-carbonitrile) were synthesized and are compared for their in vitro inhibitory activity. PK profiles of the optimized compounds in rat, dog, and cynomolgus monkey are described.

1. Introduction

Kinase inhibition represents a novel mechanism-based approach to selectively block certain signaling pathways, which are known to mediate disease processes caused by over-expression of cell division and differentiation. Highly successful clinical trials employing Gleevec (imatinib), a bcr/abl kinase inhibitor, for the treatment of chronic myelogenous leukemia (CML) has validated kinase inhibition as a therapeutic strategy for disease management.[1]

In the last few years, several tyrosine kinase inhibitors have been designed, which display high selectivity and potency for their target kinases. Most of the inhibitors have been directed against epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER-2; erbB-2), fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR) tyrosine kinases. A number of these inhibitors have entered clinical trials.[2] Platelet-derived growth factor (PDGF) receptor tyrosine kinases are potent inducers of growth and mobility in several cell types such as fibroblasts, endothelial cells, brain glial cells, and smooth muscle cells. PDGFRs are classified within the RTK type III subfamily along with αPDGFR, βPDGFR, Flt-3, c-Kit, and CSF-1R. Abnormal PDGFR-induced cell proliferation leads to proliferative disorders such as atherosclerosis, pulmonary fibrosis, restenosis following PTCA, cirrhosis, and cancer. Within restenosis lesions, PDGF plays a major role in the vascular response to injury. PDGF-TK is known to be autophosphorylated in the course of receptor activation such that an inhibitor of PDGFR phosphorylation is expected to possess therapeutic potential in the treatment of various proliferative disorders.[3]

Keywords: PDGF receptor tyrosine kinase.
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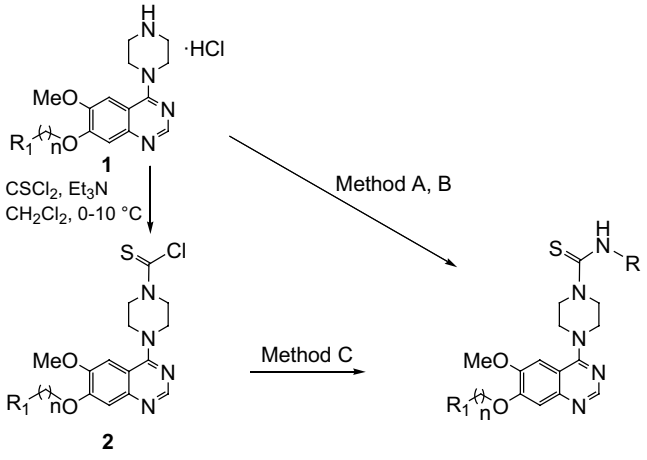
doi:10.1016/j.bmcl.2004.07.041

Recently, we reported that 4-[4-(*N*-substituted-thio-carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives exhibit potency and selectivity for βPDGFR inhibition.[4] Unfortunately, these compounds do not possess acceptable water solubility or favorable PK-profiles in vivo. In SD rats, the plasma concentrations varied significantly from subject to subject, implying that there might be polymorphic metabolism of these analogues. In our continuing investigation of the 4-piperazinyl-quinazolines as antagonists of the PDGFR-TK family,[5] we now describe the optimization of these thioureas with the goal of improving aqueous solubility, potency, and selectivity. SAR is focused on the thiourea moiety, and the aryl or benzyl amines. Insertion of a methylene unit linker between the thiourea and its aryl group to make benzyl thioureas accomplished both modification of the distance and the orientation of an aryl/hetroaryl ring relative to the thiourea moiety. We also describe our approach to improving the aqueous solubility and achieving desirable pharmacokinetic properties (high oral bioavailability and long plasma half life) of analogues without loss of inhibitory activity through the incorporation of amino-alkoxy chains at the C-7 position of the quinazoline ring.

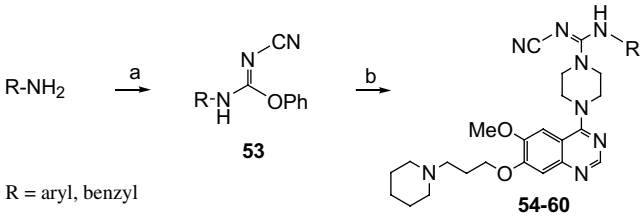
The synthesis of thiourea analogues described here was achieved by one of the three routes outlined in Scheme 1. Commercially available isothiocyanates were coupled with piperazines **1**[5] in CH_2Cl_2 in the presence of Et_3N (method A). Alternatively, amines[6] were first reacted with thiocarbonyl diimidazole (TCDI) in CH_3CN and the resulting mixture of isothiocyanate/amino thiocarbonyl imidazole was treated with **1** in the presence of Et_3N (method B).[7] In a few cases, **1** was first treated with thiophosgene in the presence of Et_3N, followed by reaction of the chloro-thio-carbamate **2** with the appropriate amine (method C).[8]



R_1 = piperidine, morpholine, pyrrolidine

3-13 (n = 3, R = benzylic); **14-31** (n = 2, R = benzylic)
32-36 (n = 3, R = aryl); **37-52** (n = 2, R = aryl)

Scheme 1. Reagents and conditions: method A: RNCS, CH_2Cl_2, Et_3N; method B: (a) R-NH_2, TCDI, CH_3CN; (b) **1**, Et_3N, CH_2Cl_2; method C: R-NH_2, Et_3N, CH_2Cl_2.



R = aryl, benzyl

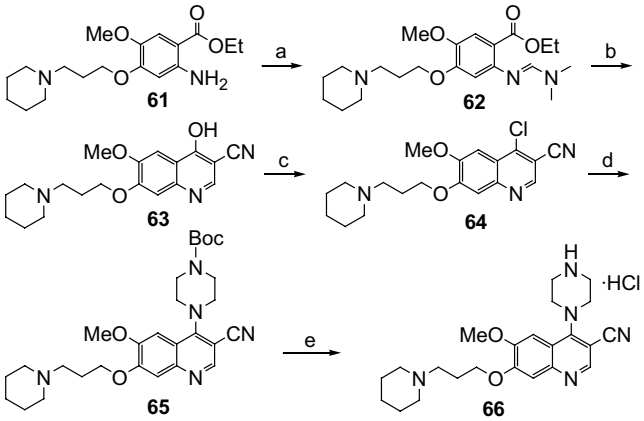
Scheme 2. Reagents and conditions: (a) $(PhO)_2C{=}N{-}CN$, *i*-PrOH, Δ; (b) **1**, CH_3CN/*i*-PrOH, Δ.

Cyanoguanidines, which are bioisosteres of thiourea were synthesized as shown in Scheme 2 (**54–60**). The appropriate amines were first treated with diphenyl cyano-carbonimidate in 2-propanol at reflux. The resulting intermediate *N*-cyano-carboximidic acid phenyl esters (**53**) were isolated by filtration and reacted with **1** in CH_3CN/*i*-PrOH at reflux to yield the corresponding cyanoguanidines.

The synthesis of quinoline-3-carbonitrile analogues is described in Scheme 3.[9] Amine **61**[5] was converted to amidine **62** by reaction with DMF–DMA in DMF at reflux. Cyclization to the hydroxy-quinoline (**63**) was accomplished by treating **62** with the lithium anion of CH_3CN in THF at −78 °C, followed by an AcOH quench. The chloroquinoline (**64**) was prepared by refluxing **63** in an excess of $SOCl_2$. Chloroquinoline **64** was then treated with Boc–piperazine in DMF in the presence of Et_3N to afford **65**. HCl (4 N)/dioxane deprotection yielded the 4-piperazine quinazoline-3-carbonitrile scaffold (**66**), which was then converted to thioureas **67–72** (Table 6) by the methods shown in Scheme 1.

2. Results and discussion

We have recently reported our findings that within the 4-[4-(*N*-substituted-carbamoyl)-1-piperazinyl]-quinazoline series of βPDGFR kinase inhibitors, thiourea analogues exhibit more specificity for βPDGFR over other RTKs,



Scheme 3. Reagents and conditions: (a) DMF–DMA, DMF, Δ; (b) *n*-BuLi, CH_3CN, THF, −78 °C, AcOH, 25 °C; (c) $SOCl_2$, Δ; (d) Boc–piperazine, CH_2Cl_2, Et_3N; (e) 4 N HCl, dioxane.

Flt-3, and CSF-1R than the corresponding urea analogues.[4] We hypothesize that both urea and thiourea moieties are occupying the ATP binding pocket, since the inhibition mechanism of these compounds is via reversible competition with ATP. The enhanced acidity and steric bulk of the thiourea function could induce the observed selectivity for βPDGFR. We have now investigated the structure–activity relationship in a series of various substituted heterocyclic, aryl, and benzyl thiourea analogues with the goal of improving aqueous solubility and modulating the physiochemical properties.

In efforts to improve the aqueous solubility, we have investigated the effect of incorporating various basic side chains at C-7 of the quinazoline ring system. We and others have recently reported that the addition of a 3-aminoalkoxy group at either C-6 or C-7 of various 4-quinazolines often results in improved cellular activity.[5,10] These tertiary amine containing analogues also appeared to possess improved aqueous solubility versus their 6,7-dimethoxyquinazoline analogues. In general, C-7 propyloxy linkers yielded more potent compounds than the ethoxy linkers (e.g., **32** vs **43** shows a sixfold activity increase). A similar improvement in kinase inhibitory activity has been reported in a series of anilinoquinazoline VEGF RTK inhibitors where C-7-propyloxy linkers were found to be more potent than ethoxy or butyloxy linkers.[11]

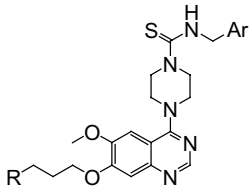
Curiously, when piperidine was utilized as the basic group on the C-7 linker, more potent compounds were obtained than with morpholine or pyrrolidine substituent, when tested in the presence of human plasma. Both the aryl and benzyl thiourea series displayed this effect (**14** vs **15**, **25** vs **26** and **27**, and **37** vs **38** and **39**). When plasma was absent, this trend was not observed.

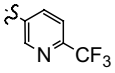
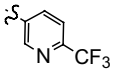
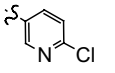
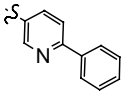
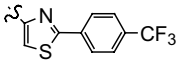
Insertion of one methylene unit between the thiourea moiety and aryl ring (benzyl thiourea series) generally has been found to enhance inhibitory activity. Thus, the distance and orientation of the aryl ring with respect to the thiourea moiety also seems to be important. Benzyl thioureas yielded potent compounds in both the C-7-ethoxy and C-7-propyloxy linker series.

Among the various benzyl thioureas investigated, 2-aminomethyl 5-Me-pyrazine containing analogues were found to be the most potent and selective compounds, in the presence of human plasma, for both the C-7 propyloxy (**3**, Table 1) and ethoxy series (**14**, Table 2). SAR around these two leads is as follows. From thiourea **3**, removal of N-1 of the pyrazine ring retained the activity (**4**). Further removal of 5-Me group of the pyrazine ring (**8**) reduced the activity (sixfold), and its substitution with –Ph (**9**) reduced the activity (2.5-fold). Interestingly, substitution of 5-Me with $–CF_3$ (**6**), and –Cl (**7**) retained the activity of parent compound **4**.

In the homologous C-7 ethoxy series (Table 2), removal of the N-4 and 5-Me from the pyrazine ring of **14** together reduced the activity (34-fold; **23** vs **14**). Similar to the C-7 propyloxy series, pyridyl (N-4) analogues

Table 1. In vitro activity of benzyl thioureas with C-7 propyloxy linkers



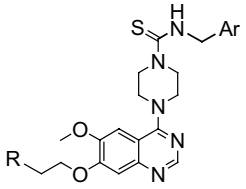
Compound #	R	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
			w/plasma[a]	No plasma
3			0.054	0.141
4			0.092	0.141
5			0.060	0.030
6			0.057	0.005
7			0.062	0.024
8			0.322	0.055
9			0.133	0.025
10			2.458	13.40
11			0.097	0.081
12			0.453	0.635
13			4.476	3.09

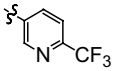
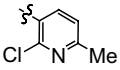
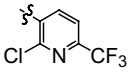
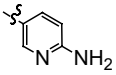
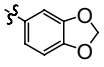
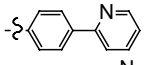
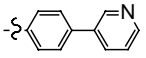
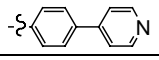
[a] 45% Human plasma was used.

α-substituted with $–CF_3$ (**16**), and –Cl (**17**) showed potent activity comparable to the parent compound **14**. In contrast, the amino-pyridine (**20**) displayed reduced activity (30-fold; **20** vs **16** and **17**).

These results indicate that benzyl thioureas with relatively small substituents on the benzyl ring are suitable for potent activity. Heterocyclic rings with electron-withdrawing groups were preferred (**20** vs **16** and **17**). The most preferred position for substitution is the 4-position (**17** vs **24**, and **16** vs **19**). The 3,4-disubstitution retained the activity in comparison with 4-substitution, whereas 3,5-disubstitution reduced the activity (**26**, **25** vs **19**, **18**). Excellent selectivity for PDGFR over Flt-3 was also demonstrated by the 5-methyl pyrazine analogue **14** (Table 7), and it was eventually chosen as our lead candidate for further exploration.

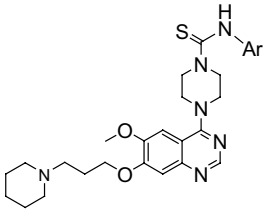
Table 2. In vitro activity of benzyl thioureas with C-7 ethoxy linkers



Compound #	R	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
			w/plasma	No plasma
14			0.061	0.057
15			0.239	1.360
16			0.095	1.033
17			0.084	1.013
18			0.353	1.152
19			1.4	1.13
20			2.93	5.817
21	Piperidine	4-Pyridinyl	3.59	12.1
22	Piperidine	3-Pyridinyl	0.718	2.11
23	Piperidine	2-Pyridinyl	n.d.	4.094
24			0.771	1.795
25			0.129	0.024
26	Morpholine	3,4-MDO-phenyl	0.265	0.102
27	Pyrrolidine	3,4-MDO-phenyl	0.166	0.005
28			0.310	0.165
29			1.49	2.13
30			5.19	14.8
31			5.04	9.53

For the aryl thioureas (Tables 3 and 4), SARs have been found to be slightly different from those for the benzyl thioureas. For example, in the benzyl thiourea series: 3-pyridylmethyl >4-pyridylmethyl >2-pyridylmethyl (**8** vs **10**, **22** vs **21** vs **23**), whereas for the aryl thioureas: 4-pyridyl > 3-pyridyl (**43** vs **44**). A similar trend is seen in biaryls where the directly attached ring is a pyridyl ring (**34** vs **35**). Biaryls in which the second ring is 2-pyridyl yielded potent compounds in the aryl thiourea series (**33** and **49**), but not in the benzyl thiourea series (**29**, **30**,

Table 3. In vitro activity of aryl thioureas with C-7 propyloxy linkers



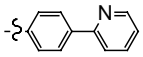
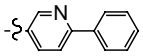
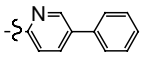
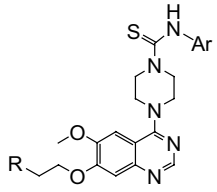
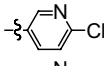
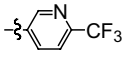
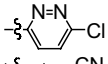
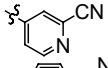
Compound #	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
		w/plasma	No plasma
32	4-Pyridinyl	0.069	0.221
33		0.108	0.226
34		0.271	0.365
35		0.55	1.98
36	4-O-*i*-Pr-phenyl	0.558	0.071

Table 4. In vitro activity of aryl thioureas with C-7 ethoxy linkers



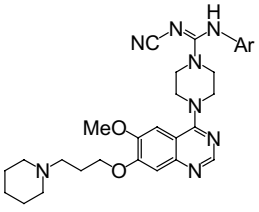
Compound #	R	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
			w/plasma	No plasma
37	Piperidine	4-CN-phenyl	0.475	0.453
38	Morpholine	4-CN-phenyl	1.18	0.922
39	Pyrrolidine	4-CN-phenyl	21.58	0.467
40	Piperidine	4-Br-phenyl	0.391	1.013
41	Morpholine	4-Br-phenyl	0.545	0.180
42	Pyrrolidine	4-Br-phenyl	0.474	0.357
43	Piperidine	4-Pyridinyl	0.406	0.244
44	Piperidine	3-Pyridinyl	4.98	3.76
45			0.511	0.892
46			1.06	4.10
47			1.33	0.426
48			1.79	1.54
49			0.156	0.185
50			0.434	0.804
51			5.04	2.0
52			0.74	0.107

and **31**). The pyridyl-N-oxide analogue (**50**) exhibits reduced activity (twofold). These results indicate that the pyridyl ring in the aryl thioureas **33** and **49** is ideally placed for optimum binding.

The high potency of several thiourea analogues prompted us to evaluate cyanoguanidines (**54–60**). Cyanoguanidine is a well known bioisostere of thiourea. The two possess many similar physicochemical properties and their pharmacological equivalence has been demonstrated in H2-receptor antagonists. Unfortunately, these analogues exhibited greatly diminished activity (Table 5) in spite of our previous observations that such cyanoguanidine/thiourea bioisosteric substitutions in the 6,7-dimethoxy series had resulted in retention of modest potency.[4b]

We also synthesized cyanoquinoline analogues (**67–72**). Recently Wissner et al.[9] have discovered that the carbocyano group of the cyanoquinoline can be bioisosteric with the azomethine group of quinazolines in some cases. This can be true when the azomethine–nitrogen is hydrogen bonded to the protein through a bridging water molecule. The nitrile displaces the bridging water molecule in such compounds. Such substitutions in other kinase inhibitors (EGFR and HER-2) have yielded compounds comparable in potency to the parent quinazoline in both enzyme and cellular assays. As shown in Table 6, substitution of the quinazoline ring with its bioisostere cyanoquinoline resulted in either retention or slight enhancement of the inhibitory activity for all the aryl and benzyl thiourea analogues investigated (**67** vs **32**, **69** vs **34**, **71** vs **9**, and **72** vs **5**). However, cyanoquinolines in this series lacked the desired PK properties and high selectivity for βPDGFR.

Table 5. In vitro activity of cyanoguanidine analogues



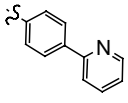
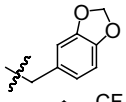
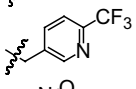
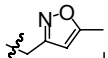
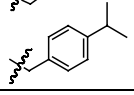
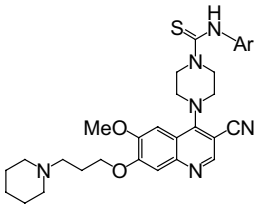
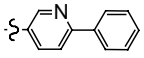
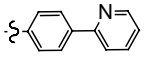
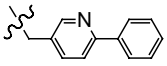
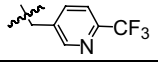
Compound #	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
		w/plasma	No plasma
54	4-Pyridinyl	17.1	31.70
55		0.371	0.420
56	4-*t*-Bu-phenyl	1.554	0.805
57		0.597	0.329
58		2.18	3.42
59		2.375	10.45
60		0.977	0.928

Table 6. In vitro activity of quinoline 3-carbonitrile analogues



Compound #	Ar	βPDGFR IC_{50} (μM) in MG63 cells	
		w/plasma	No plasma
67	4-Pyridinyl	0.135	0.248
68	4-CN-phenyl	0.126	0.005
69		0.280	0.150
70		0.134	0.229
71		0.102	0.012
72		0.014	0.003

Some of the more potent compounds prepared were evaluated for inhibitory activity on the related PDGFR kinase family members including c-Kit, Flt-3, and CSF-1R. The compounds were evaluated for their inhibition of βPDGFR phosphorylation in accordance with our previously reported whole cell assays,[12] and the resulting IC_{50} values are listed in Table 7. These compounds inhibited βPDGFR autophosphorylation with IC_{50} values of <500 nM, and were >75–300-fold less potent against Flt-3, and CSF-1R (data not shown). This general kinase specificity profile demonstrates that these thiourea analogues are highly specific βPDGFR inhibitors with similar specificity profiles to ST1571 (Gleevec), which inhibits βPDGFR and c-Kit but not Flt-3 or CSF-1R.[13]

A comparison of the specificities of **16**, **17**, and **19** with that for **3** and **4** suggests that specific substitutions in the aryl ring have important enzyme interactions that may be influenced by the electronics of this ring. Likewise, a comparison of the specificity of **11** and **28** suggests that the C-7 linker also affects kinase specificity.

As shown in Table 7, the IC_{50} value of **14** on PDGFR phosphorylation measured in CHO cells is 255 nM, as compared to that of 61 nM in MG63 cells (Table 2). The difference may, in part, be due to a 5–10-fold higher level of PDGFR found in CHO cells versus in MG63 cells (unpublished data).

Compounds with high potency (IC_{50} < 200 nM) and at least 60 min $T_{1/2}$ in human liver microsomes were screened for their in vivo profile in rat. The three most promising compounds from this set were subsequently

Table 7. Kinase specificity of potent analogues

Compound #	βPDGFR inhibition IC_{50}, μM[a]	c-Kit inhibition IC_{50}, μM[a]	Flt-3 inhibition IC_{50}, μM[a]
43	0.982	2.97	>30
45	0.360	0.501	19.75
49	0.0746	0.109	3.19
14	0.255	0.898	>30
16	0.155	0.246	>30
17	0.0502	0.075	>30
25	0.040	0.064	2.91
19	0.105	0.798	6.77
28	0.294	1.80	>30
32	0.581	1.85	24.20
34	0.105	0.195	5.55
3	1.35	1.528	>30
4	0.141	0.247	>30
11	0.0859	0.0548	>30
72	0.011	0.021	0.044

[a] CHO cell lines expressing wild-type βPDGFR or βPDGFR/c-Kit, βPDGFR/Flt-3, and βPDGFR/CSF-1R chimeric receptors were grown to confluency in 96 well microtiter plates under standard tissue culture conditions. Phosphorylation assays were performed as described for βPDGFR phosphorylation assay in MG63 cells.

studied in dog and monkey: **25** (CT53605), **14** (CT53986), and **49** (CT54254) (Table 8). In dog, all three analogues had $T_{1/2} > 7$ h and oral bioavailability >25%. They were further studied in monkey, where they displayed long half-lives and good oral exposure.

In summary, we have discovered that the 4-[4-(*N*-substituted-thiocarbamoyl)-1-piperazinyl]-6-methoxy-7-aminoalkoxy-quinazolines (e.g., **14**, **25**, **49**) possess significant selectivity toward βPDGFR. In this series of compounds, both benzyl and aryl thioureas exhibited the desired potency/selectivity profile. When optimally substituted at C-7 position of the quinazoline ring with basic side chains, these compounds also exhibited improved water solubility, and a favorable pharmacokinetic profile, including high oral bioavailability and long plasma half life in rat, dog, and cynomolgus monkey.

Table 8. Pharmacokinetic data of selected analogues

	Analogue		
	14	**49**	**25**
Rat			
Dose iv/po (mg/kg)	30	10	30
F (%)	13.7	8.82	39.1
$T_{1/2}$ (h)	14.1	17.4	26.7
C_{max} (μg/mL)	239	34.1	146
AUC_{PO} (μg h mL^{-1})	32.2	26.9	69.0
Dog			
Dose iv/po (mg/kg)	8.69	5	8.09
F (%)	38.8	30.2	101.6
$T_{1/2}$ (h)	10.8	7.58	15.7
C_{max} (μg/mL)	297	38.9	456
AUC_{PO} (μg h mL^{-1})	1507	333	3117
Monkey			
Dose iv/po (mg/kg)	10	10	10
F (%)	n.d.	68%	n.d.
$T_{1/2}$ (h)	20.9	8.46	9.25
C_{max} (μg/mL)	235	143	92.5
AUC_{PO} (μg h mL^{-1})	832	1510	477

n.d.=not determined.

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