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Optimization of highly selective 2,4-diaminopyrimidine-5-carboxamide inhibitors of Sky kinase

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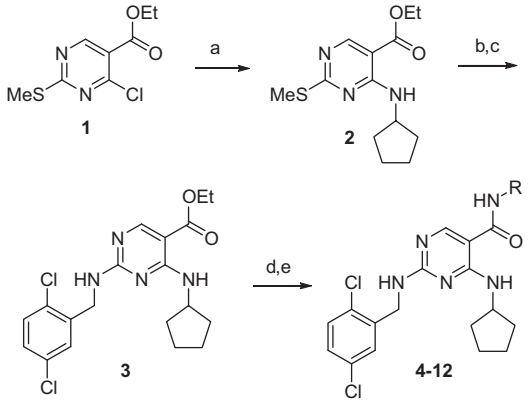
ABSTRACT

Optimization of the ADME properties of a series of 2,4-diaminopyrimidine-5-carboxamide inhibitors of Sky kinase resulted in the identification of highly selective compounds with properties suitable for use as in vitro and in vivo tools to probe the effects of Sky inhibition.

In the preceding paper, we reported the discovery and initial SAR of a series of 2,4-diaminopyrimidine-5-carboxamide inhibitors of Sky kinase.[1] Sky is a tyrosine kinase receptor for the Gas6 (growth arrest specific gene 6) ligand, which plays a critical role as a platelet response amplifier, enhancing platelet aggregration and granule secretion to known endogenous agonists.[2,3] Previous studies from our laboratories have demonstrated that Sky specific antibodies inhibit human platelet degranulation and aggregation to the same extent as Gas6 inhibition, and result in comparable efficacy to clopidogrel treatment in a mouse model of thrombosis with no significant increase in bleeding time.[4] Therefore, Sky inhibitors are of interest as an arterial anti-thrombosis treatment with a reduced risk of bleeding side affects.

Our initial structure–activity relationship (SAR) studies in the 2,4-diaminopyrimidine-5-carboxamide series demonstrated that high kinase selectivity could be achieved by filling the Ala571 subpocket with a benzylamino substituent at the 2-position of the pyrimidine core. However, early compounds suffered from high clearance and poor oral bioavailability due to rapid first pass metabolism. We undertook further SAR studies to improve the metabolic stability of the 2,4-diaminopyrimidine-5-carboxamide template.

Amide sidechain analogs were prepared as described in Scheme 1. Condensation of **1** with cyclopentyl amine afforded the 4-(cyclopenthylamino)-pyrimidine **2**. Oxidation of the thiomethyl and displacement of the resulting sulfone with 2,5-dichlorobenzylamine provided the 2,4-diaminopyrimidine **3**. Hydrolysis of the ester and amide bond formation yielded the desired analogs **4–14**. Analogs with a 3,5-dichloroanilino substituent at the pyrimidine 2-position were prepared as described in Scheme 2. Condensation of **25** with neat 2,5-dichloroaniline provided the 2-aminopyrimidinone **26**,[5] which was



Scheme 1. (a) cyclopentylamine, Et_3N, CH_3CN, 80 °C; (b) *m*-CPBA, CH_2Cl_2, 0 °C; (c) 2,5-dichlorobenzylamine, Et_3N, 1,4-dioxane, reflux; (d) NaOH, MeOH, reflux; (e) RNH_2, HATU, Et_3N, DMF.

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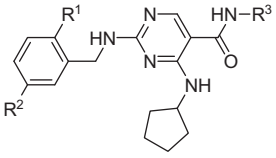
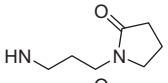
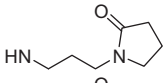
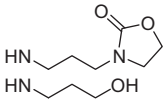
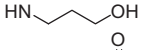
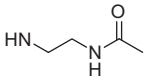
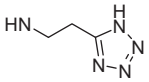
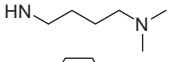
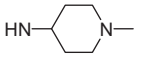
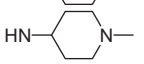
converted to the chloride by refluxing in thionyl chloride. The chloride was then displaced with a primary amine to give the 2,4-diaminopyrimidine ester **27**. Hydrolysis of the ester and subsequent amide bond formation with the *N*-methyl-4-aminopiperidine yielded analogs **15**–**19**.

As previously reported, both the 2-methoxybenzyl analog **4** and the 2,5-dichlorobenzyl analog **5** exhibited rapid HLM and RLM metabolism (Table 1).[1] The electron-rich benzyl ring of analog **4** appeared to be a likely site of metabolism upon visual inspection. However, replacing the methoxy ether with electron-withdrawing halogen atoms had no affect on the metabolic stability, indicating that the primary site of metabolism was elsewhere in the molecule. Metabolite identification by LC-MS-MS methods after incubation in human microsomes indicated the primary metabolite was actually the product of oxidative hydroxylation at the α-carbonyl carbon in the butyrolactam ring. Our attempts to directly block that site of metabolism by replacement of the methylene with an oxygen atom resulted in **6** with significant improvement in Sky inhibition potency, however, no improvement in HLM or RLM stability was observed. We hypothesized that although the primary site of metabolism was blocked, alternative sites of metabolism on the highly lipophilic compound ($c\log P = 6.06$) now became dominant. Since the butyrolactam ring is exposed to the solvent face,[1] the affect of other polar solubilizing groups in the amide sidechain on the microsomal stability was examined. To keep the $c\log P$ low, we opted to conduct the amide sidechain SAR with the 2-methoxybenzyl group at the 2-position of the pyrimidine ring. Replacing the butyrolactam ring with a hydroxyl group (**7**) resulted in improved Sky inhibition activity, but had no affect on HLM stability and reduced aqueous solubility and cellular permeability. Likewise, a pendant acetamide (**8**) gave no improvement in HLM stability. A dramatic improvement in HLM stability was observed in the introduction of an acidic tetrazole (**9**, HLM $t_{1/2} = 60$ min), along with a modest increase in the RLM half-life and improved aqueous solubility and permeability. However, the presence of the acidic tetrazole in the amide sidechain led to a threefold decrease in Sky inhibition activity and, counter-intuitively, significantly increased dofetilide binding activity. We found that improved HLM stability could also be obtained by the introduction of basic amines in the amide sidechain. A *N*,*N*-dimethyl-4-aminobutyl chain exhibited similar Sky inhibition activity (**10**, $IC_{50} = 0.50$ μM), a 2.9-fold increase in HLM stability (HLM $t_{1/2} = 40$ min), and excellent aqueous solubility. A (1-methylpiperidin-4-yl)amino sidechain also exhibited similar Sky inhibition activity (**11**, $IC_{50} = 0.52$ μM), good aqueous solubility, a twofold increase in HLM stability ($t_{1/2} = 40$ min), and improved metabolic stability in rat liver microsomes (RLM $t_{1/2} = 56$ min). As observed previously, replacement of the 2-methoxybenzyl group with the 2,5-dichlorobenzyl group resulted in decreased HLM stability (**12**, HLM $t_{1/2} = 14$ min) and decreased solubility and permeability, presumably due to the increased lipophilicity of the 2,5-dichlorobenzyl group ($c\log P = 5.77$). However, analog **12** exhibited excellent RLM stability. The increased RLM stability of **11** and **12** translated into 41% and 32% oral bioavailability in the rat, respectively

Table 1
Amide sidechain SAR and ADME properties



ID	R^1	R^2	R^3-NH	Sky IC_{50} (μM)	P-Selection aggregation IC_{50} (μM)	Platelet aggregation IC_{50} (μM)	cLogP	PSA	HLM t1/2 (min)	RLM t1/2 (min)	Solubility (μM)	Permeability[c] (10^{-6} cm/s)	Dofetilide binding (%I @ 10 μM)
4	OMe	H		0.40	17	46	4.34	108	14	16	81.6	1.5	7
5	Cl	Cl		0.36	3.1	28	5.85	99.3	6	4	3.9	0.1	23
6	Cl	Cl		0.070	7.4	29	6.06	108	2	<5	1.3	0	33
7	OMe	H		0.16	10	46	6.96	108	11	NT	7.8	0.9	35
8	OMe	H		0.38	6.6	NT	3.61	117	5	NT	7.8	1.9	35
9	OMe	H		1.3	NT	NT	3.46	143	60	22	12	21	79
10	OMe	H		0.50	7.1	24	4.58	91	40	NT	200	NT	28
11	OMe	H		0.52	1.5	8.8	4.09	91	34	56	80	1.2	27
12	Cl	Cl		0.27	1.2	7.2	5.77	82	14	60	7.8	0.02	47

[a] IC_{50} data is an average of duplicate runs using an ELISA kinase assay with 60 μM ATP.
[b] Aqueous solubility measured at pH 6.5.
[c] PAMPA artificial membrane assay.

Table 2
In vivo rat PK profile of selected compounds.[a]

Analog	$t_{1/2}$ (hr)	Cl (mL/min/kg)	Vdss (L/kg)	AUC (ng·hr/mL)	Cmax (ng/mL)	*F* (%)
11	3.5	73	18	302	74	41
12	8	40	25	680	35	32
13	0.2	40	0.4	0	25	0
19	13	55	2.7	0	0	0

[a] Values are means of duplicate experiments. Sprague-Dawley rats were dosed as a suspension in 5% PEG-200/95% (0.5% w:w) methyl-cellulose. IV dose = 1 mg/kg, PO dose = 5 mg/kg.

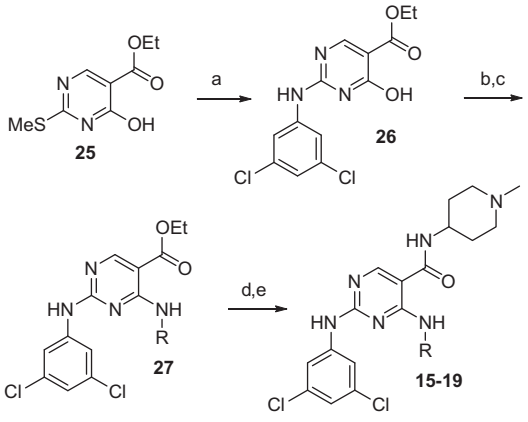
(Table 3). While the in vivo clearance for analogs **11** and **12** remained at or above the hepatic blood flow for the rat, we believe that the increased volume of distribution reflects an increase in protein binding that reduces the plasma free fraction. In any event, the resulting improved oral bioavailability of analogs **11** and **12** represents a significant improvement over earlier analogs.[1]

In addition to the improved oral bioavailability in the rat, analogs **11** and **12**, which contain the *N*-methyl-4-aminopiperidine amide sidechain, also exhibit superior functional activity in both the functional P-selectin and platelet aggregation assays versus the corresponding analogs **4** and **5** with the *N*-(3-aminopropyl)-butyrolactam amide sidechain. The P-selectin assay measures the expression of P-selectin on the surface of platelets as a biomarker for platelet activation.[6]

While the improved RLM stability directly translated into improved oral bioavailability in the rat, we focused upon improving the HLM stability to ensure future druggability. Our attempts to improve the HLM stability by blocking metabolism of the amide sidechain appeared to be stymied by the overall lipophilicity of the compounds. We turned to decreasing the lipophilicity by introducing polar substituents into the 4-amino group which binds in the ribose region of the ATP binding site (Table 3), a strategy also recently demonstrated for other members of the HGFR kinase family.[7] We found that introduction of a basic amine into the 4-amino cyclic ring led to improved Sky inhibition activity (**13** and **14**, Sky IC_{50} = 0.19 and 0.04 μM, respectively), as well as improved HLM stability ($t_{1/2}$ = 38 and 23 min, respectively). Although the additional basic amine resulted in good aqueous solubility, cellular permeability was drastically reduced. Indeed, analog **13** exhibited no oral bioavailability in the rat (Table 2), presumably due to the poor absorption across the gut wall. Therefore, we sought to further improve the metabolic stability and increase cellular permeability of the series. We recognized that the benzylic methylene in the 2-amino group represented a potential site of metabolism. We found that the 2-aminobenzyl group could be replaced by a 2-anilino group, specifically a 3,5-dichloroanilino group, which exhibited single-digit nanomolar Sky inhibition activity and excellent HLM and RLM stability (**15**, Sky IC_{50} = 0.002 μM, HLM $t_{1/2}$ = 120 min, RLM $t_{1/2}$ = 60 min). However, the *trans*-2,4-diaminocyclohexane ring again resulted in poor permeability. Accordingly, we sought to replace the basic amine in the ribose binding region with neutral polar groups. Replacing the *trans*-2,4-diaminocyclohexane ring with a 4-aminotetrahydropyran gave similar Sky inhibition potency (**16**, Sky IC_{50} = 0.002 μM) and moderate HLM stability, but poor permeability. A cyclic amide sidechain also exhibited potent Sky inhibition and good HLM stability, but poor cellular permeability (**17**, Sky IC_{50} = 0.002 μM, PAMPA permeability = 0.2×10^{-6} cm/sec) In contrast, alcohol-containing sidechains resulted in potent Sky inhibition and good HLM stability with a relative increase in permeability (**18** and **19**, PAMPA permeability = 2.0 and 1.4×10^{-6} cm/sec, respectively). Analog **19** also exhibited good aqueous solubility and was chosen for PK dosing. Unfortunately, analog **19** exhibited increased in vivo clearance and no detectable plasma levels after oral dosing in the rat (Table 2). Although we were successful in improving the Sky inhibition activity, metabolic stability in HLM and RLM, and aqueous solubility via incorporation of polar functionality in the 3-amino sidechain that binds in the ribose binding region, these polar functionalities result in poor cellular permeability that severely limits the oral bioavailability.

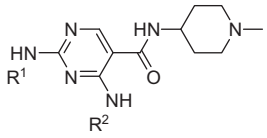
The >100-fold improvement in Sky inhibition that was achieved by the incorporation of polar functionalities into the 4-amino sidechain did not translate into significantly improved activity in the platelet activation functional assays (Table 3). Analog **15** exhibited submicromolar activity in the P-selectin inhibition assay (IC_{50} = 0.40 μM) and single digit micromolar activity in the platelet aggregation assay (IC_{50} = 1.4 μM). While analogs **16** and **19** showed P-selectin inhibition activity comparable to analogs **11** and **12**, analogs **17** and **18** exhibited the most potent activity in the P-selectin assay in this series (P-selectin IC_{50} = 0.43 and 0.58 μM, respectively). Analog **15** may show superior functional activity because of better cellular permeability than is predicted by the PAMPA artificial membrane permeability assay.

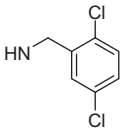
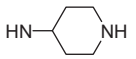
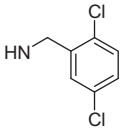
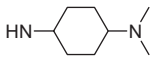
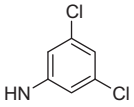
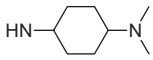
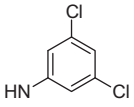
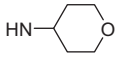
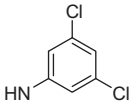
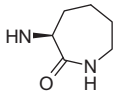
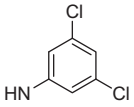
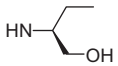
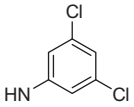
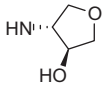
We hypothesized that reducing the polar surface area and the number of basic amines and potential hydrogen bond donors by replacing the amide sidechain with a small heterocyclic ring or neutral atom would lead to improved cellular permeability and subsequently improved functional activity and oral bioavailability, (Table 4). On the basis of SAR data from another series identified in our HTS (data not shown), we chose to replace the amide sidechain with a 3-methylisoxazole while maintaining the basic amine in the ribose binding region. Analogs **20** and **21** exhibited potent Sky inhibition (Sky IC_{50} = 0.092 and 0.0007 μM, respectively) and good functional activity in the P-selectin assay (IC_{50} = 1.6 and 1.0 μM, respectively). Although the PAMPA permeability data predicts that the more potent **21** would possess poor cellular permeability, the decreased polar surface area of **21** did result in improved functional activity. However, both analogs **20** and **21** exhibited reduced HLM and RLM stability, as well as significant dofetilide binding and CYP2D6 inhibition. To remove the dofetilide binding and CYP2D6 inhibition and improve the cellular permeability, we replaced the basic amine in the ribose binding region with the 3-amino-4-hydroxy-tetrahydrofuran moiety of **19**. We found that a 3-pyridyl ring was a good replacement for the amide sidechain, as analog **22** showed good Sky inhibition potency (Sky IC_{50} = 0.044 μM) with improved HLM and RLM stability, aqueous solubility, and PAMPA permeability. However, **22** was still a potent inhibitor of CYP2D6 and showed no improvement in dofetilide binding inhibition.



Scheme 2. (a) 3,5-dichloroaniline, neat, 150 °C; (b) $SOCl_2$, reflux; (c) R-NH_2, Et_3N, CH_3CN, reflux; (d) NaOH, MeOH, reflux; (e) *N*-Methyl-4-aminopiperidine, HATU, Et_3N, DMF.

Table 3
2-Benzylamino and 2-Anilino SAR and ADME properties



ID	R^1-NH	R^2-NH	Sky IC_{50} (μM)	P-Selection aggregation IC_{50} (μM)	Platelet aggregation IC_{50} (μM)	cLogP	PSA	HLM $t_{1/2}$ (min)	RLM $t_{1/2}$ (min)	Solubility (μM)	Permeability[c] (10^{-6} cm/s)	Dofetilide binding Ki (μM)
13			0.19	>80	8.5	3.91	94	38	60	200	<0.1	>50
14			0.041	1.1	NT	5.02	85	23	57	89	2.0	1.6
15			0.002	0.40	1.4	5.57	85	120	60	200	0.3	6.7
16			0.009	1.2	NT	4.48	91	35	NT	40	<0.1	NT
17			0.006	0.43	NT	4.81	111	41	NT	2.3	0.2	4.0
18			0.003	0.58	NT	4.75	102	37	NT	3.5	2.0	3.4
19			0.010	2.2	9.6	4.07	112	74	60	40	1.4	0.98

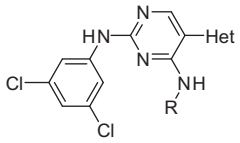
[a] IC_{50} data is an average of duplicate runs using an ELISA kinase assay with 60 M ATP.[b] Aqueous solubility measured at pH 6.5.[c] PAMPA artificial membrane assay.

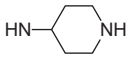
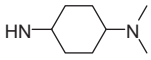
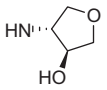
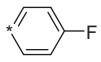
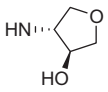
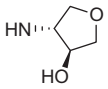
Conversion of the 3-pyridyl ring to a 4-fluorophenyl ring resulted in decreased CYP2D6 and dofetilide binding inhibition, but also resulted in a significant decrease in the Sky inhibition activity (**23**, Sky IC_{50} = 0.15 μM). We found that the most successful replacement of the amide sidechain was a simple bromine atom, which resulted in potent Sky inhibition (**24**, Sky IC_{50} = 0.015 μM), moderate functional P-selectin inhibition, good HLM and RLM stability, and no significant inhibition of CYP2D6 and dofetilide binding. However, the low aqueous solubility and PAMPA permeability was still not predictive of good oral bioavailability.

The broad kinase selectivity that we had previously observed for this series[1] was improved as the level of Sky inhibition activity increased throughout our SAR investigations (Table 5). Analogs **11** and **12**, with the *N*-(4-aminopiperidine) amide sidechain and 2-aminobenzyl group, exhibited improved selectivity against 32 kinases with significant activity in HGFR, Axl, and Mer, which are other members of the HGFR subfamily of kinases. The 2,5-dichlorobenzyl group in **12** resulted in additional activity in Abl, CKI-δ, and Lck. Conversion of the 2,5-dichlorobenzyl group to the 3,5-dichloroanilino group and addition of a basic amine in the ribose binding region resulted in greatly improved kinase selectivity, as analog **15** exhibited >100-fold selectivity against 47/48 kinases screened, with activity only against the fellow HGFR kinase family member, Mer. Replacement of the basic amine in the ribose binding region with the non-basic 3-amino-4-hydroxy-tetrahydrofuran ring in analog **19** resulted in >100-fold selectivity against all 48 kinases screened. In addition, replacement of the entire amide sidechain with a 3-methylisoxazole exhibited excellent selectivity in 46/48 kinases with some activity in MAP4K4 and Mer (analog **21**).

In summary, we found that improved rat liver microsome (RLM) stability in a series of 2,4-diaminopyrimidine-5-carboxamide inhibitors of Sky kinase could be achieved by modification of the amide sidechain. This effort resulted in analogs **11** and **12**, which exhibited good RLM stability and good oral bioavailability in the rat. To aid in future druggability, we were able to improve HLM stability by replacing the 2-benzylamino substituent with a 2-anilino group. Sky inhibition could also be improved by the addition of polar basic and non-basic functionalities in the 4-amino group that binds in the ribose binding region, although this resulted in reduced cellular permeability. The amide sidechain could be replaced with small heterocyclic rings or a non-basic bromine atom while maintaining potent Sky inhibition and functional P-selectin

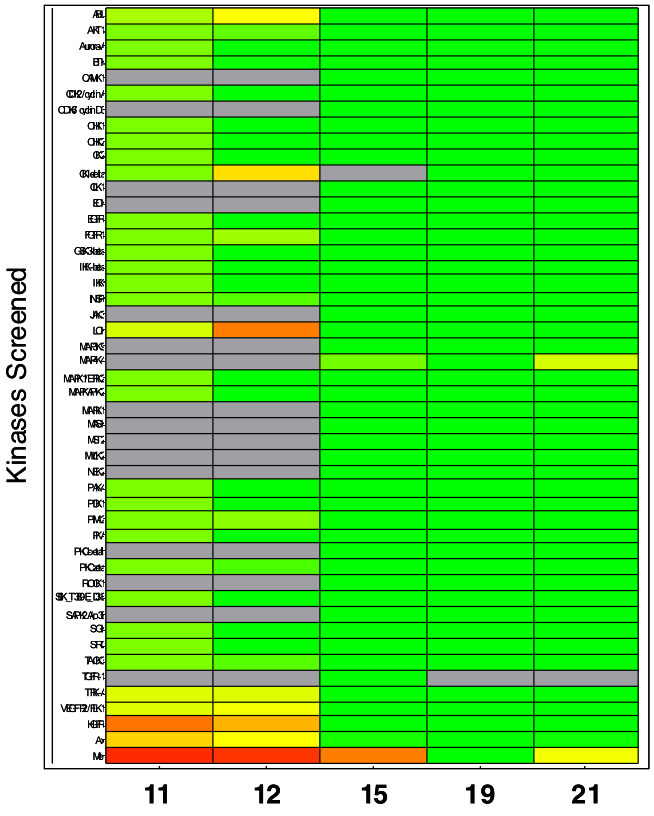
Table 4
Amide replacement SAR and ADME properties



ID	Het	R^2-NH	Sky IC_{50} (μM)	P-Selection IC_{50} (μM)	cLogP	PSA	HLM $t_{1/2}$ (min)	RLM $t_{1/2}$ (min)	Aqueous solubility (μM)[b]	Permeability[c] (10^{-6} cm/s)	Dofetilide binding Ki (μM)	CYP2D6 %I @ 3 μM
20			0.092	1.6	4.92	87.9	21	3	5.2	0.2	1.3	81
21			0.0007	1.0	6.04	79.1	28	6	2.3	0.03	0.35	69
22			0.044	3.0	4.52	92.2	120	31	200	1.0	1.5	88
23			0.15	>80	6.03	79.3	48	60	200	<0.01	2.7	24
24	Br		0.015	3.9	4.88	79.3	30	31	5.2	0.3	>100	1

[a] IC_{50} data is an average of duplicate runs using an ELISA kinase assay with 60 μM ATP. [b] Aqueous solubility measured at pH 6.5. [c] PAMPA artificial membrane assay.

Table 5
Heatmap of kinase selectivity for selected compounds.[a]



[a] Fold selectivity (kinase IC_{50}/Sky IC_{50}) colored by green = >100 fold, yellow = 10-100 fold, red = <10 fold. IC_{50} data for individual kinases can be found in the Supplementary Information available on-line.

activity. Analog **24** exhibited the best profile of Sky inhibition, functional activity, metabolic stability, and inhibition of CYP2D6 and dofetilide binding, although the aqueous solubility and cellular permeability are not predictive of good oral bioavailability. We believe that these results will aid in the future design of Sky inhibitors with improved drug-like properties, and that analogs **11** and **12** represent suitable tool compounds for use in in vitro and in vivo studies to probe the effects of Sky inhibition.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.12.028.

References and notes

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