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A novel series of piperazinyl-pyridine ureas as antagonists of the purinergic $P2Y_{12}$ receptor

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ABSTRACT

A novel series of $P2Y_{12}$ antagonists for development of drugs within the antiplatelet area is presented. The synthesis of the piperazinyl-pyridine urea derivatives and their structure–activity relationships (SAR) are described. Several compounds showed $P2Y_{12}$ antagonistic activities in the sub-micromolar range.

The 7-TM, G-protein-coupled receptor $P2Y_{12}$, also known as platelet ADP receptor, plays an important role in the amplification phase of platelet aggregation. Upon platelet activation, ADP released from the dense-granules interacts with the $P2Y_{12}$ receptor resulting in down regulation of adenylyl-cyclase, stabilizing the formed aggregates.[1] Inhibiting the $P2Y_{12}$ receptor has been proven to reduce the occurrence of secondary myocardial infarction in patients with acute coronary syndrome.[2] The first class of compounds used in clinical trials was thienopyrimidine pro-drugs, which active metabolite binds irreversibly to the receptor.[3] Recently, data from a large phase III trial comparing ticagrelor, the first reversible direct acting $P2Y_{12}$ antagonist,[4] with clopidogrel was published.[5] Ticagrelor was discovered via a medicinal chemistry program starting from adenosine triphosphate (ATP), the natural antagonist of the $P2Y_{12}$ receptor.[6] Recently reported series of $P2Y_{12}$ antagonists include piperazinyl-glutamate-pyrimidines,[7] thienopyrimidines,[8] anthroquinones,[9] adenosine analogs,[10] and dinucleoside polyphosphates and nucleotides.[11] The current letter describes the discovery of a novel class of $P2Y_{12}$ antagonists.

The novel class of antagonists was identified by a high-throughput-screening (HTS) of the AstraZeneca compound collection against the human $P2Y_{12}$ receptor and is featured by a piperazinyl-pyridine scaffold, as exemplified by the 'hit' compound **1**[12] (Fig. 1, binding: IC_{50} = 0.33 μM, GTPγS: IC_{50} = 0.68 μM[13]).

The 'hit' structure was an attractive starting point for a hit-to-lead campaign, since SAR investigations around both the pyridine ring (A) and the phenyl (C) could be made by parallel synthesis on chemically tractable building blocks, while retaining the piperazinyl ring (B) throughout the study. SAR exploration around the A-ring was facilitated by the commercial availability of 2- and 6-chloropyridines. Exploration of the C-ring could be made by reaction of the piperazinyl-pyridine scaffold (A–B) with isocyanates.

Compounds **5** and **6** (Scheme 1) were synthesized from commercially available 6-chloropyridines **2** and **3**, respectively, by a 2-step procedure from the ethyl ester with optional purification of the crude intermediate. Hydrolysis of compound **5** gave carboxylic acid **9**, transesterification gave methyl ester **10**, and N-methylation gave **17**. Compound **6** was subjected to Pd-catalyzed

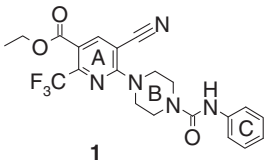

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Figure 1. Hit compound from HTS, composed of a pyridine (A), a piperazinyl (B), and a phenyl (C).

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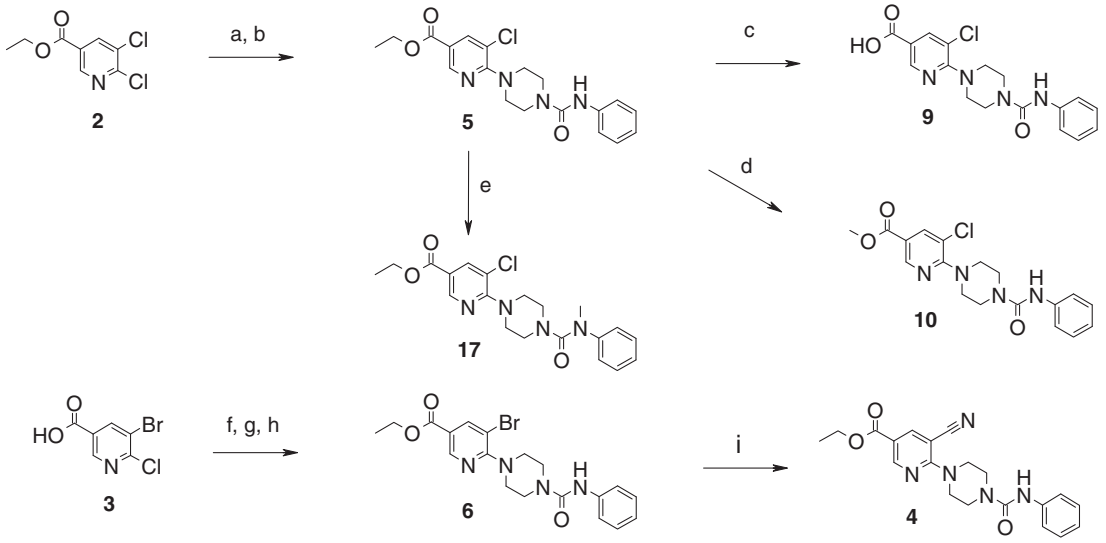
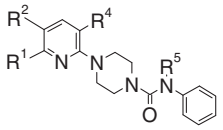


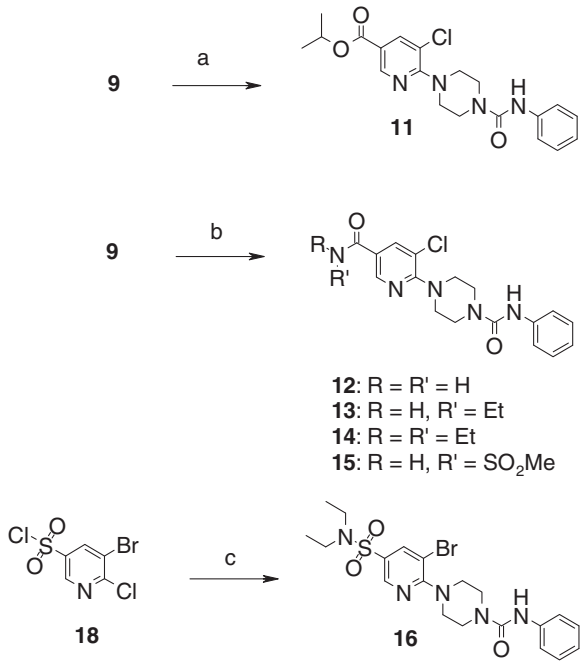
Scheme 1. Reagents and conditions: (a) piperazine, 1.2 equiv, TEA, 1.2 equiv, EtOH, microwave oven, single node heating, 120 °C, 10 min (61%); (b) PhNCO, 1.2 equiv, MeCN, rt, 20 h (94%), (c) LiOH, 1 M (aq), 10 equiv, THF, rt, 16 h (91%); (d) H_2SO_4, MeOH, reflux, 24 h (8%); (e) NaH, 5.0 equiv, MeI, 3.0 equiv, DMF, 0 °C, 5 min (38%); (f) H_2SO_4, EtOH, reflux, 5 h (78%); (g) piperazine, 1.2 equiv, TEA, 1.2 equiv, EtOH, microwave oven, single node heating, 120 °C, 10 min (66%); (h) PhNCO, 1.2 equiv, MeCN, rt, 16 h (95%); (i) KCN, 5.0 equiv, $Pd(OAc)_2$, 0.2 equiv, 1,5-bis(diphenylphosphino)pentane (DPPPE), 0.4 equiv, TMEDA, 4.0 equiv, toluene, 120 °C, 16 h (26%).

Table 1
Effects on potency by variation of substituents on pyridine (R^1, R^2, R^4) and by N-methylation (R^5)



Compd	R^1	R^2	R^4	R^5	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)
1	CF_3	COOEt	CN	H	0.32	0.68
4	H	COOEt	CN	H	0.92	2.6
5	H	COOEt	Cl	H	0.88	1.7
6	H	COOEt	Br	H	1.8	2.2
7	H	COOEt	H	H	4.1	3.8
8	CF_3	H	CN	H	>33	>33
9	H	COOH	Cl	H	>33	>33
10	H	COOMe	Cl	H	9.8	8.6
11	H	COO-*i*-Pr	Cl	H	2.4	8.5
12	H	$C(O)NH_2$	Cl	H	>33	ND
13	H	C(O)NH(Et)	Cl	H	>33	ND
14	H	$C(O)N(Et)_2$	Cl	H	>33	ND
15	H	$C(O)NHSO_2Me$	Cl	H	>33	ND
16	H	SO_2NEt_2	Br	H	>33	>33
17	H	COOEt	Cl	Me	9.6	9.7

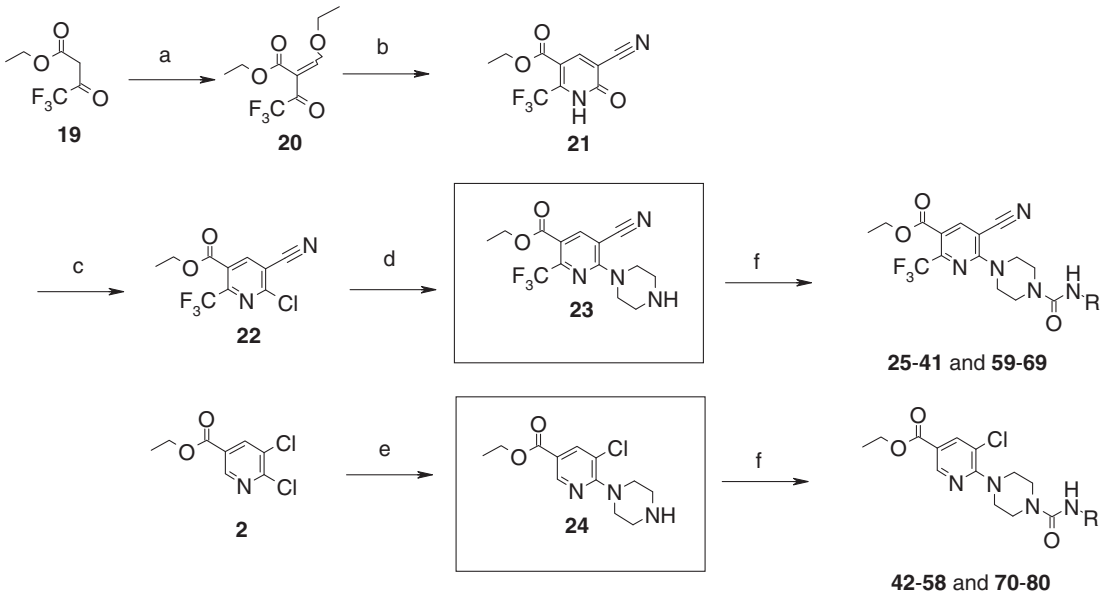
ND = not determined.



Scheme 2. Reagents and conditions: (a) *i*-PrOH, 1.1 equiv, DCC, 1.1 equiv, DMAP, 0.1 equiv, DCM, rt, 16 h (33%); (b) **12**: NH_3, excess, DCC, 2.0 equiv, DMAP, 0.2 equiv, DCM, rt, 35 min (22%); **13**: NH_2Et, 1.1 equiv, DCC, 1.1 equiv, DMAP, 0.1 equiv, DCM, rt, 7 h (8%); **14**: $SOCl_2$, 17 equiv, DCM, rt, 4.5 h; concentrate, then add $NHEt_2$, excess, DCM, rt, 1 h (62%, 2 steps); **15**: H_2NSO_2Me, 2.0 equiv, DCC, 2.0 equiv, DMAP, 2.0 equiv, DCM, rt, 4 h (36%); (c) $NHEt_2$, 3.3 equiv, TEA, 1.5 equiv, THF, 0 °C, 2.5 h; concentrate, then add piperazine, 1.2 equiv, TEA, 1.5 equiv, microwave oven, single node heating, 120 °C, 10 min; concentrate, then add PhNCO, 1.6 equiv, TEA, excess, rt, 30 min (13%, 3 steps).

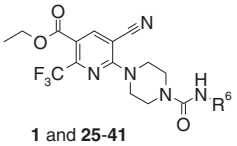
cyanation[14] to give **4**. Compounds **7** and **8** (Table 1) were synthesized from commercial starting materials in a manner similar to compound **5** in yields of 20% and 9% over two steps, respectively. Carboxylic acid **9** (Scheme 2) was activated by DCC or thionyl chloride and reacted with the appropriate alcohol, amine or sulfonamide to give isopropyl ester **11**, amides **12**–**14**, and acylsulfonamide **15**. Sulfonamide **16** was synthesized in three steps from commercial sulfonyl chloride **18**. Piperazinyl-pyridine scaffolds **23** and **24** to be used for parallel synthesis were made as outlined in Scheme 3. Commercial β-ketoester **19** was converted by a two-steps Hantzsch-type reaction[15] via the 3-oxybutanone **20**[16] into pyridone intermediate **21**. Subsequent 2-chlorination and reaction with piperazine presented compound **23**. Scale-up of **24** was made from **2** by reaction with piperazine. Reactions of compounds **23** and **24** with a range of isocyanates gave ureas in a typical yield of 60% after purification by HPLC.

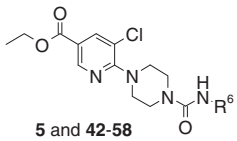
Compounds were screened in vitro, for receptor affinity using a radio-ligand binding assay and for potency in inhibiting receptor signaling using a GTPγS assay and cell membranes expressing re-



Scheme 3. Synthesis and reactions of compounds **23** and **24**, prepared for variation of the R group. Reagents and conditions: (a) $HC(OEt)_3$, 1.5 equiv, Ac_2O, 3.0 equiv, 120 °C, 2 h, then 140 °C, 5 h (64% of *E*/*Z* mixture); (b) $H_2NC(O)CH_2CN$, 1.0 equiv, NaOEt, 1.0 equiv, EtOH, rt, 16 h (83%); (c) $(COCl)_2$, 5.0 equiv, DMF, 0.1 equiv, DCM, reflux, 14 h (91%); (d) piperazine, 3.2 equiv, TEA, 2.1 equiv, EtOH, microwave oven, single node heating, 170 °C, 20 min (67%); (e) piperazine, 1.2 equiv, TEA, 1.2 equiv, EtOH, microwave oven, single node heating, 120 °C, 10 min (61%); (f) R-NCO, 1.2 equiv, THF, rt, 14 h (typical yield: 60%).

Table 2
Effects on potency by variation of pyridine substituents and of aryl group (R^6)


1 and **25-41**


5 and **42-58**

R^6	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)
Phenyl	**1**	0.33	0.68	**5**	0.88	1.7
2-Cl-phenyl	**25**	1.8	1.3	**42**	2.7	3.7
2-Me-phenyl	**26**	2.3	1.2	**43**	1.4	2.6
2-*i*-Pr-phenyl	**27**	1.9	1.0	**44**	1.4	2.0
2-OMe-phenyl	**28**	1.7	1.5	**45**	3.2	1.6
3-Cl-phenyl	**29**	0.49	0.21	**46**	0.17	0.28
3-Me-phenyl	**30**	0.21	0.18	**47**	0.24	0.42
3-CN-phenyl	**31**	1.8	0.95	**48**	NA	NA
3-OMe-phenyl	**32**	0.77	0.32	**49**	1.7	0.96
4-Cl-phenyl	**33**	0.31	0.30	**50**	0.60	0.85
4-Me-phenyl	**34**	1.1	1.06	**51**	0.60	1.1
4-*i*-Pr-phenyl	**35**	2.7	6.4	**52**	6.6	3.0
4-CN-phenyl	**36**	6.8	5.5	**53**	NA	NA
3,4-Di-F-phenyl	**37**	2.3	1.1	**54**	5.4	4.6
3,4-Di-Cl-phenyl	**38**	0.19	0.23	**55**	1.2	1.1
1-Naphthyl	**39**	NA	NA	**56**	0.11	0.10
2-Naphthyl	**40**	0.19	0.083	**57**	0.38	0.38
2-Phenylethyl	**41**	3.1	0.96	**58**	5.7	1.8

NA = compound not available.

combinant human $P2Y_{12}$ receptors.[17] The designed compounds, used to obtain an initial SAR around the pyridine ring (A), are listed in Table 1. Electron withdrawing groups like cyano (**4**) or chloro (**5**) in the pyridine 5-position (R^4) increased the potency, compared to hydrogen (**7**). The 3-ethoxycarbonyl substituent was important for potency (**1** vs **8**). The analogous carboxylic acid **9** was found to be inactive while the ester homologs **10** and **11** showed reduced potency, compared to ethyl ester **5**. Amide analogs such as carboxamides (**12**–**14**), acyl sulfonamide (**15**), and sulfonamide (**16**) were all inactive.

The importance of the urea *N*–*H* was investigated by making the *N*-methyl analog (**17**) of compound **5**. Compound **17** showed a 5- to 11-fold lower potency compared to **5**, see Table 1. Thus the urea *N*–*H* was found to be important for potency and was retained in the subsequent urea library. The low solubility[18] (<0.1 μM) of **1** could be improved by shifting from 2-CF_3/5-CN to 2-H/5-Cl pyridines. For example, compounds **4**, **5**, and **6** (Table 1) had solubilities of 90, 40, and 1.7 μM, respectively.

Given the SAR of the pyridine ring (A), two piperazinyl-pyridine scaffolds (A–B) were selected for variations of the C-ring.

Compound **1** was found to be the most potent of the tested compounds with A-ring variations (Table 1), however with low solubility (<0.1 μM) as a drawback.

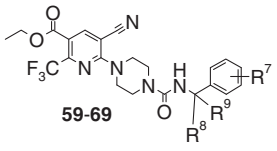
Compound **5** presented a combination of reasonable solubility and potency. Thus, the A–B scaffolds of compounds **1** and **5** were used as starting materials (compounds **23** and **24**) and reacted with isocyanates in a parallel format to form a library of ureas aimed to explore the SAR of the C-ring.

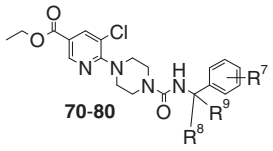
The BigPicker program[19] was used to select 80 isocyanates, that would provide a urea-library of high diversity with regard to structural and physicochemical properties. Additional criteria were in-house availability of the isocyanates as well as chemical feasibility. Parallel synthesis gave a set of 141 compounds, of which 67 originated from compound **23** and 74 from compound **24**. There were 63 matched-pairs, out of the 141 compounds, providing an excellent opportunity for a detailed analysis. Potency in *both* binding and GTPγS assays were determined for a total of 125 compounds. The library compounds showed first-order proportionality between the IC_{50} values from the two assays.[20] Selected non-benzylic ureas are included in Table 2 while all synthesized benzylic ureas are listed in Table 3.

The library compounds showed a potency range from 0.1 to >33 μM in both the affinity assay (binding) and functional activity (GTPγS) assay. This means that C-ring substituents have a major effect on potency.[19] The potency difference between compounds **1** and **5** was also reflected in the two subseries of compounds, that is, 2-H/5-Cl pyridines (**5**, **42**–**58** and **70**–**80**) are generally less potent than 2-CF_3/5-CN pyridines (**1**, **25**–**41** and **59**–**69**). 1-Naphthyl (**56**) and 2-naphthyl (**40** and **57**) compounds were more potent than the unsubstituted phenyl compounds (**1** and **5**) that were equipotent with the unsubstituted benzyls (**59** and **70**) and branched benzyls (**68** and **79**). Elongation to 2-phenethyl (**41** and **58**) gave equipotency to the phenyl compounds **1** and **5** in the functional assay, but lowered the binding affinity 7- to 10-fold.

For both scaffolds in the phenyl series, monosubstitution in the 2-position of the phenylureas with either lipophilic (Cl, Me, *i*-Pr), bulky (*i*-Pr), or electron withdrawing (Cl) or donating (OMe) groups gave compounds with lower or similar potency to compounds with the unsubstituted phenyl (**1** and **5**). Monosubstitution with lipophilic groups (Cl or Me) in the 3-position gave 3–6 times higher GTPγS potency than their unsubstituted phenyl analogs. In the 4-position of the phenylureas, introduction of lipophilic groups (Cl or Me) had minor effects on potency, while branching (*i*-Pr) or an electron withdrawing group (CN) gave reduced potency. 3,4-Bis-substitution with electron withdrawing, but less lipophilic groups (F) gave reduced potency, while substitution with electron-withdrawing, but more lipophilic groups (Cl), gave increased or similar potency, which showed that lipophilicity is a required

Table 3
Effects on potency of benzyl ureas by variation of pyridine substituents and of benzyl group (R^7, R^8, R^9)

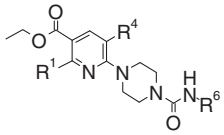




R^7	R^8	R^9	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)
H	H	H	**59**	0.58	0.27	**70**	2.4	1.7
2-Cl	H	H	**60**	0.50	0.33	**71**	NA	NA
2-Me	H	H	**61**	0.51	0.35	**72**	1.1	0.70
3-F	H	H	**62**	0.82	0.24	**73**	2.7	3.0
3-Me	H	H	**63**	0.75	0.45	**74**	1.7	1.1
4-F	H	H	**64**	0.47	0.11	**75**	1.6	2.0
4-Me	H	H	**65**	0.32	0.18	**76**	0.97	0.46
4-OMe	H	H	**66**	0.43	0.64	**77**	4.6	5.0
3,4-Di-Cl	H	H	**67**	0.48	0.27	**78**	0.78	0.45
H	(*S*)-Me	H	**68**	0.33	0.19	**79**	0.95	1.4
3-C(CH_3)=CH_2	Me	Me	**69**	0.59	0.49	**80**	0.61	0.58

NA = compound not available.

Table 4
Effects on potency of 2-CF_3, 5-CN and 2-H, 5-Cl pyridines by variation of the R^6 substituent



R^1	R^4	R^6	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)	R^1	R^4	R^6	Compd	Binding IC_{50} (μM)	GTPγS IC_{50} (μM)
CF_3	CN		**81**	1.0	0.76	H	Cl		**84**	1.9	2.3
CF_3	CN		**82**	>33	ND	H	Cl		**85**	5.6	2.1
CF_3	CN		**83**	>33	ND	H	Cl		**86**	10	29

ND = not determined.

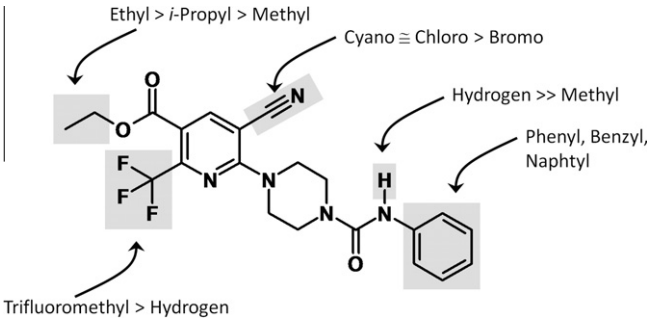


Figure 2. SAR for piperazinyl-pyridine ureas against $P2Y_{12}$.

feature in this region. This observation is underlined by the potency of the 1- and 2-naphthyls (**40**, **56** and **57**) mentioned above. The substitutions made on the aryl group in the benzyl series (Table 3) had little or no effect on potency. Examples of variation of the C-ring beyond phenyls, benzyls, and naphthyls are shown in Table 4. Phenyl-substituted cyclopropyl **81** retained the potency levels of 2-phenylethyl **41**. The potency of compounds with heteroaromatic C-rings spanned from no potency (e.g., isoxazole **82**) to moderate potency (e.g., thiophenes **84** and **85**). Non-aromatic substituents in this position in general gave compounds with no or low potency, exemplified by *i*-propyl compound **83** and tetrahydropyranyl compound **86**.

These data suggest that 1-naphthyl, 2-naphthyl, or lipophilic 3-substituted phenyl groups are preferred as C-ring, and this could be further investigated. The SAR is summarized in Figure 2 below.

In vitro clearance in rat liver microsomes was determined for a selection of potent compounds with different types of C-rings: **1**, **33**, **40**, and **64**. All showed high clearance (i.e., low metabolic stability) with CL_{int} values of 713, 519, 432 and 720 μM/min/mg, respectively. In vitro clearance in human liver microsomes for compounds **40** and **64** were 280 and 565 μM/min/mg, respectively. Metabolite studies showed the corresponding carboxylic acid as the only metabolite of compound **1** in both rat liver microsomes and human liver microsomes.[21]

In summary, we have identified a new series of piperazinyl-pyridine ureas, with several compounds showing sub-micromolar potencies towards $P2Y_{12}$. Our SAR investigations showed that the 3-ethoxycarbonyl substituent on the pyridine ring, the urea *N*–*H* of the linker, and the aromatic ring (C-ring) contribute significantly to potency. Furthermore, we have shown that solubility could be increased by shifting from 2-CF_3/5-CN to 2-H/5-Cl pyridines. Our efforts to further improve the properties, including solubility and metabolic stability, of compounds containing the piperazinyl-pyridine scaffold will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.088.

References and notes

1. (a) Cattaneo, M. *Eur. Heart J. Suppl.* **2008**, *10*, 133; (b) Storey, R. F. *Curr. Pharm. Des.* **2006**, *12*, 1255.
2. Yusuf, S.; Zhao, F.; Mehta, S. R.; Chrolavicius, S.; Tognoni, G.; Fox, K. K. *N. Eng. J. Med.* **2001**, *345*, 494.
3. (a) Savi, P.; Pereillo, J. M.; Uzabiaga, M. F.; Combalbert, J.; Picard, C.; Maffrand, J. P.; Pascal, M.; Herbert, J. M. *Thromb. Haemost.* **2000**, *84*, 891; (b) Sugidachi, A.; Ogawa, T.; Kurihara, A.; Hagihara, K.; Jakubowski, J. A.; Hashimoto, M.; Niitsu, Y.; Asai, F. *J. Thromb. Haemost.* **2007**, *5*, 1545.
4. van Giezen, J. J. J.; Nilsson, L.; Berntsson, P.; Wissing, B.; Giordanetto, F.; Tomlinson, W.; Greasley, P. J. *J. Thromb. Haemost.* **2009**, *7*, 1556.
5. Wallentin, L.; Becker, R. C.; Budaj, A.; Cannon, C. P.; Emanuelsson, H.; Held, C.; Horrow, J.; Husted, S.; James, S.; Katus, H.; Mahaffey, K. W.; Scirica, B. M.; Skene, A.; Steg, P. G.; Storey, R. F.; Harrington, R. A. *N. Eng. J. Med.* **2009**, *361*, 1045.
6. (a) Springthorpe, B.; Bailey, A.; Barton, P.; Birkinshaw, T. N.; Bonnert, R. V.; Brown, R. C.; Chapman, D.; Dixon, J.; Guile, S. D.; Humphries, R. G.; Hunt, S. F.; Ince, F.; Ingall, A. H.; Kirk, I. P.; Leeson, P. D.; Leff, P.; Lewis, R. J.; Martin, B. P.; McGinnity, D. F.; Mortimore, M. P.; Paine, S. W.; Pairaudeau, G.; Patel, A.; Rigby, A. J.; Riley, R. J.; Teobald, B. J.; Tomlinson, W.; Webborn, P. J. H.; Willis, P. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6013; (b) van Giezen, J. J. J.; Humphries, R. G. *Semin. Thromb. Hemost.* **2005**, *31*, 195.
7. (a) Parlow, J. J.; Burney, M. W.; Case, B. L.; Girard, T. J.; Hall, K. A.; Harris, P. K.; Hiebsch, R. R.; Huff, R. M.; Lachance, R. M.; Mischke, D. A.; Rapp, S. R.; Woerndle, R. S.; Ennis, M. D. *J. Med. Chem.* **2010**, *53*, 2010; (b) Parlow, J. J.; Burney, M. W.; Case, B. L.; Girard, T. J.; Hall, K. A.; Harris, P. K.; Hiebsch, R. R.; Huff, R. M.; Lachance, R. M.; Mischke, D. A.; Rapp, S. R.; Woerndle, R. S.; Ennis, M. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1388; (c) Parlow, J. J.; Burney, M. W.; Case, B. L.; Girard, T. J.; Hall, K. A.; Hiebsch, R. R.; Huff, R. M.; Lachance, R. M.; Mischke, D. A.; Rapp, S. R.; Woerndle, R. S.; Ennis, M. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4657; (d) Parlow, J. J.; Burney, M. W.; Case, B. L.; Girard, T. J.; Hall, K. A.; Hiebsch, R. R.; Huff, R. M.; Lachance, R. M.; Mischke, D. A.; Rapp, S. R.; Woerndle, R. S.; Ennis, M. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6148.
8. Kortum, S. W.; Lachance, R. M.; Schweitzer, B. A.; Yalamanchili, G.; Rahman, H.; Ennis, M. D.; Huff, R. M.; TenBrink, R. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5919.
9. Baqi, Y.; Atzler, K.; Köse, M.; Glänzel, M.; Müller, C. E. *J. Med. Chem.* **2009**, *52*, 3784.
10. Douglass, J. G.; deCamp, J. B.; Fulcher, E. H.; Jones, W.; Mahanty, S.; Morgan, A.; Smirnov, D.; Boyer, J. L.; Watson, P. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2167.
11. Douglass, J. G.; Patel, R. I.; Yerxa, B. R.; Shaver, S. R.; Watson, P. S.; Bednarski, K.; Plourde, R.; Redick, C. C.; Brubaker, K.; Jones, A. C.; Boyer, J. L. *J. Med. Chem.* **2008**, *51*, 1007.
12. Purchased from Maybridge Chemical Company, Cornwall UK.
13. Potencies were determined in a $P2Y_{12}$ receptor filtration binding assay and a $P2Y_{12}$ receptor GTPγS signalling assay. See Supplementary data for details on the screening assays.
14. Sundmeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707.
15. Mosti, L.; Menozzi, G.; Schenone, P.; Dorigo, P.; Gaion, R. M.; Belluco, P. *Farmaco* **1992**, *47*, 427.
16. (a) Jones, R. G. *J. Am. Chem. Soc.* **1951**, *73*, 3684; (b) Palanki, M. S. S.; Erdman, P. E.; Gayo-Fung, L. M.; Shevlin, G. I.; Sullivan, R. W.; Goldman, M. E.; Ransone, L. J.; Bennett, B. L.; Manning, A. M.; Suto, M. J. *J. Med. Chem.* **2000**, *43*, 3995.
17. Screening values are given as single values or as a mean of two measurements with maximum four times difference between highest and lowest screening value. In the SAR discussion, a difference in potency between compounds $\geqslant$3 times is considered significant. See Supplementary data for details on the screening assays.
18. See Supplementary data for screening procedure for solubility.
19. Blomberg, N.; Cosgrove, D. A.; Kenny, P. W.; Kolmodin, K. *J. Comput. Aided Mol. Des.* **2009**, *23*, 513.
20. See Supplementary data for graph.
21. Compound (initial concentration 10 μM) after 60 min at 1 mg compound/mL protein.