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Approach to Dual-Acting Platelet Activating Factor (PAF) Receptor Antagonist/Thromboxane Synthase Inhibitor (TxSI) Based on the Link of PAF Antagonists and TxSIs

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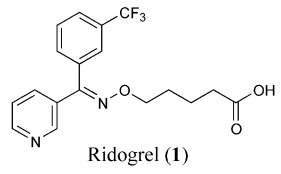
Abstract—A series of compounds (**22**–**36**) which possess dual-acting PAF antagonist/TxSI have been generated by the approach of linking the known PAF antagonists and TxSIs, such as Ridogrel (**1**).

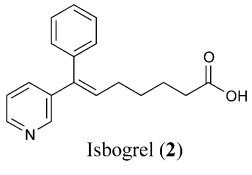
Introduction

Platelet activating factor (PAF) is a mediator of inflammation and plays important roles in the pathology of ischemia/thrombosis,[1] septic shock,[2] asthma.[3] Thromboxane A_2 (TxA_2) is a potent vasoconstrictor and platelet aggregating agent, may make an important contribution to the pathogenesis of various circulatory and certain renal disorders.[4–7] Therefore, it has been proposed that novel agents combined PAF antagonist and TxA_2 synthase inhibitor (TxSI) would be more beneficial than either agent alone in the treatment of these disorders. To avoid the complications associated with administration of two separate drugs we have engaged in a program to synthesize agents that possess both the above biological activities in the same molecule.

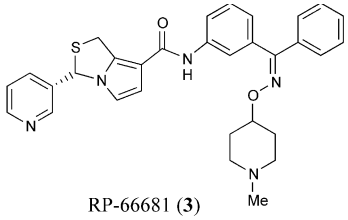
When our program started, dual-acting PAF antagonist/TxSI compounds had not been reported in detail. In general, the design of dual-acting agents has been based on structural modification of one of the two potential component structures, so that known SAR



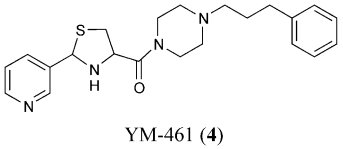
Ridogrel (**1**)



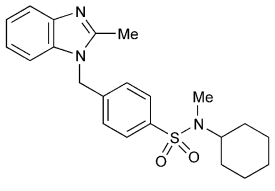
Isbogrel (**2**)



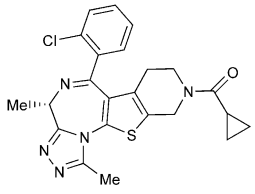
RP-66681 (**3**)



YM-461 (**4**)



BB-182 (**5**)



E-6123 (**6**)

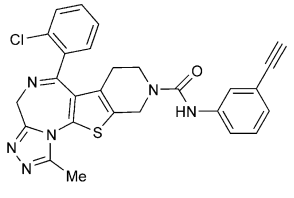


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Figure 1.

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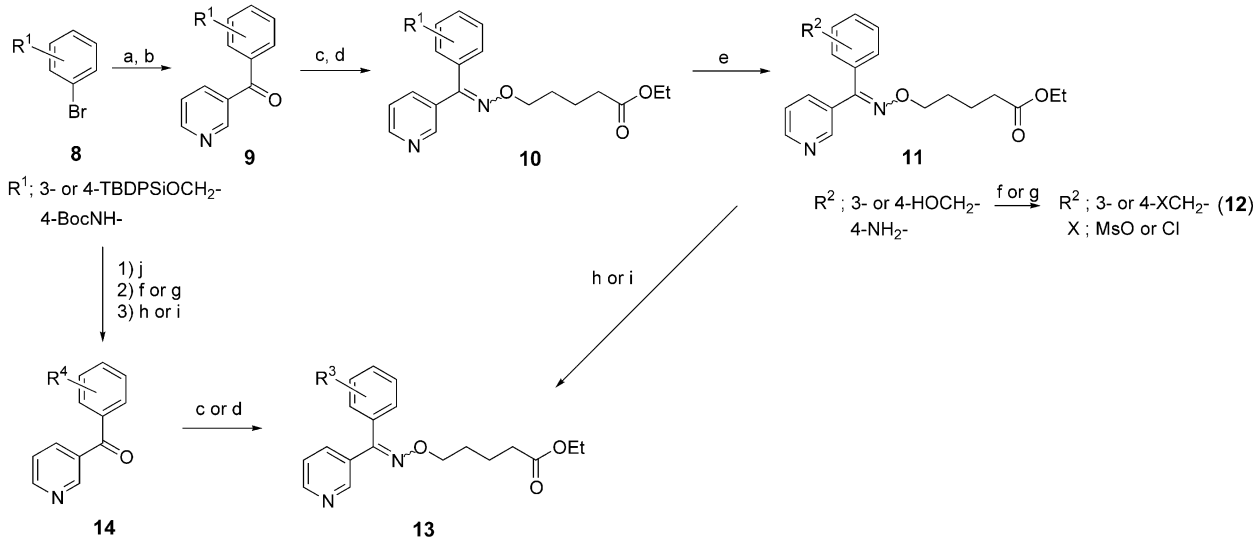
features of the other component may be incorporated. In contrast with them, we have examined the feasibility of a novel approach to the design of these dual-acting agents, that is to say, the covalent linking of known PAF antagonist and TxSI compounds.

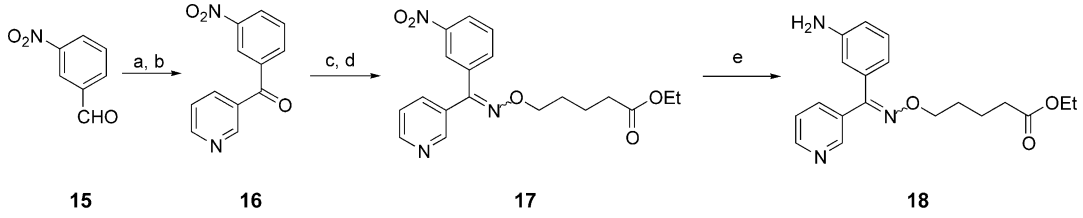
We decided to utilize the potent TxSI, Ridogrel (**1**)[8] as a template. Since potent PAF antagonists, such as RP-66681 (**3**),[9] YM-461 (**4**),[10] BB-182 (**5**),[11] E-6123 (**6**) and its analogue (**7**)[12] possess phenyl groups and cyclohexyl groups, and, on the other hand, the TxSI modified the phenyl groups of Ridogrel (**1**) and Isbogrel (**2**),[13] had been reported (Fig. 1). In this paper, we describe the synthesis and pharmacology of dual-acting PAF antagonist and TxSI compounds by linking PAF antagonist compounds to Ridogrel (**1**) via covalently phenyl-containing fragment.

Chemistry

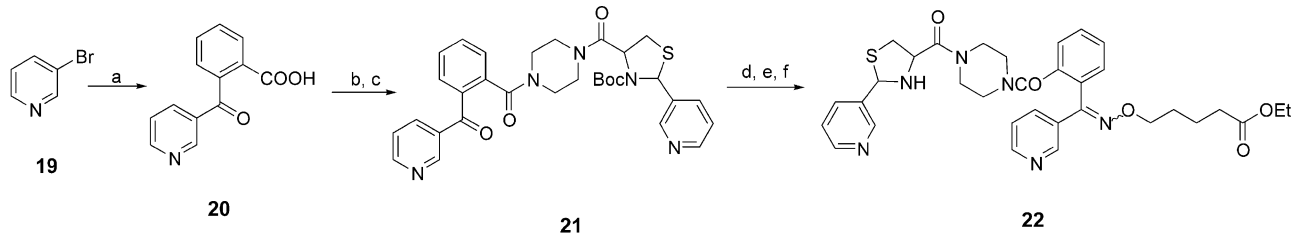
The synthesis of these hybrid compounds is illustrated in Schemes 1–3. The substituted bromobenzene (**8**) which was reacted with nicotinaldehyde in the presence of ^{n}BuLi gave the carbinols, followed by oxidation with MnO_2, led to the ketones (**9**). Reaction with $NH_2OH{\cdot}HCl$ followed by alkylation with ethyl 5-bromovalerate afforded the esters (**10**). Deprotection with TBAF or TFA yielded the alcohols or amine (**11**), respectively. The target compounds (**13**) were provided



Scheme 1. Reagents and conditions: (a) nicotinaldehyde, ^{n}BuLi, THF, −78 °C; (b) MnO_2, CH_2Cl_2, 50 °C, 62–69% (two steps); (c) $NH_2OH{\cdot}HCl$, EtOH–Py, reflux; (d) $Br(CH_2)_4COOEt$, NaH, DMF, 60–95% (two steps); (e) TBAF, THF, quant or TFA, 0 °C, quant; (f) MsCl, TEA, CH_2Cl_2, quant; (g) $SOCl_2$, CH_2Cl_2, 80%-quant; (h) amines, NaH, DMF, 0 °C or K_2CO_3, $_{18}C_6$, THF, 80 °C, 6-92%; (i) (1) carboxylic acids, $(COCl)_2$, NaH, cat. DMF, THF; (2) Py–CH_2Cl_2, 92%-quant; (j) (1) nicotinonitrile, ^{n}BuLi, THF, −78 °C; (2) concd HCl, 55–79%.

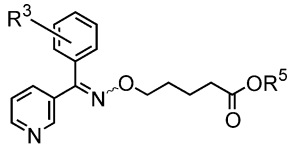


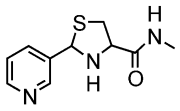
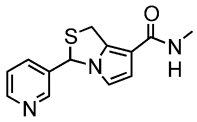
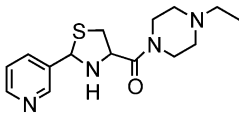
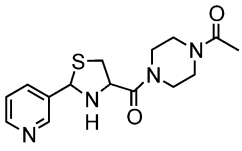
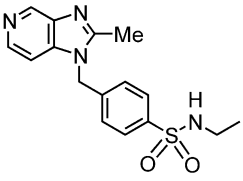
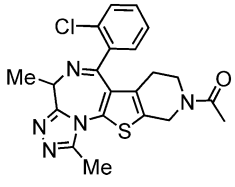
Scheme 2. Reagents and conditions: (a) 3-bromopyridine, ^{n}BuLi, THF, −78 °C, 61%; (b) MnO_2, CH_2Cl_2, reflux, 96%; (c) $NH_2OH{\cdot}HCl$, EtOH–Py, reflux, quant; (d) $Br(CH_2)_4COOEt$, NaH, DMF, 81%; (e) H_2, 10% Pd/C, AcOH, MeOH, 93%.



Scheme 3. Reagents and conditions: (a) phthalic anhydride, ^{n}BuLi, Et_2O, −78 °C, 49%; (b) (1) *N*-BOC-piperazine, DCC, HOBT, THF; (2) TFA, 0 °C, 62%; (c) *N*-Boc-2-(3-pyridyl)thiazolidine-4-carboxylic acid, DCC, HOBT, DMF, 57%; (d) $NH_2OH{\cdot}HCl$, EtOH–Py, reflux; (e) $Br(CH_2)_4COOEt$, NaH, DMF; (f) TFA, 0 °C, 30% (three steps).

Table 1. In vitro PAF antagonist and TxA_2 synthase inhibitory activities of compounds **22**–**37**



Compd	R^3	R^5	Position	*E*/*Z*	PAF antagonist activity[a] IC_{50} (μM)	TxA_2 synthase inhibition[b] IC_{50} (μM)
23		Et	3	2:3	>1.0	0.021
24		Et	4	3:4	>1.0	0.021
25		Et	3	2:3	0.45	0.0012
26		Et	4	2:3	0.55	0.0036
27		Et	3	2:3	0.20	0.088
28		Et	4	1:1	0.28	0.072
29		H	3	2:3	>1.0	0.012
22		Et	2	2:3	0.56	>1.0
30		Et	3	2:3	0.48	0.052
31		Et	4	2:3	0.61	0.044
32		Et	3	10:0	0.068	0.0047
33		Et	3	0:10	0.068	0.0058
34		H	3	10:0	>1.0	0.0018
35		Et	3	2:3	0.06	0.065
36		Et	4	2:3	0.10	0.072
37	H	Et		2:3	NT[c]	0.0010
(±)-E6123 (**6**)					0.036	NT
UK74505[14]					0.029	NT
Ozagrel					NT	0.024
Isbogrel (**2**)					NT	0.00089

[a]Inhibition of the PAF-induced platelet aggregation in rabbit platelet rich plasma (PRP). This was performed according to the method of Terashita et al. with slight modification.[15]

[b]Inhibition of TxB_2 production by incubating prostaglandin H_2(PGH_2) with human platelet microsomes. This was performed according to the method of Terashita et al. with slight modification.[16]

[c]NT, not tested.

by condensation of the amine (**11**) and the carboxylic acids, or reaction of the leaving groups-containing compounds (**12**) and the amines. In the case of compounds **32** and **33**, these were synthesized in considerably lower yield in order to be obtained much more compounds coupling one amine molecule with two ester molecules. On the other hand, the ketones (**14**) having the hydroxyl or amino group were given by treatment with nicotinonitrile in replacement of nicotinaldehyde in one-pot. Similar methodology enabled the synthesis of the target compounds (**13**) via the ketones (**14**) in shorter steps (Scheme 1).

The 3-amino compound (**18**) was prepared as shown in Scheme 2 by reduction of the nitro (**17**) with H_2/10% Pd/C.

The 2-substituted target compound (**22**) was provided as shown in Scheme 3 by reaction of 3-bromopyridine and phthalic anhydride in the first step, and alkylation with ethyl 5-bromovalerate in the final step. All the compounds shown in Table 1 were provided by similar methodology.[17]

Results and Discussion

Table 1 summarizes the in vitro activity for a selection of compounds derived from Ridogrel (**1**). All compounds except for **32**–**34** were tested as mixtures of *E*/*Z* isomers. The ratios were obtained from the peak height of proton in the 3-pyridyl moieties for the isomers. When compounds with a substituent on the phenyl group were compared with **37**, the phenyl analogues were observed to be weaker TxSIs. Especially, introducing substituent at the 2-position (**22**) was considerably less active, nevertheless PAF antagonist activity was maintained. Compounds **27**, **28**, **30**, and **31** showed weaker TxSI activity, while the incorporation of a piperazinyl moiety improved PAF antagonist activity. In addition, the methylene groups for linking the piperazinyl moiety to the phenyl group were preferable to the carbonyl groups (**27**, **28** vs **22**, **30**). Replacement of the ester moiety with a carboxyl group indicated more potent TxSI activity (**29**, **34**). On the contrary, these compounds were almost completely PAF antagonistic inactive.

Furthermore, representative examples of the dual-acting compounds were tested in or ex vivo after oral administration. PAF antagonist activity was assessed in the mouse, using a PAF-induced death assay.[14] As the results, the ED_{50} values for compounds **35** and **36** showed 2.3 and 0.5 mg/kg, respectively. On the other hand, TxSI activity was assessed by ex vivo inhibition of serum TxB_2 production in the rat.[16] As the results, the ED_{50} values for compounds **23**–**28** were in the range 0.24–5.0 mg/kg.

In conclusion, we have shown that it is feasible to covalently phenyl moiety the PAF antagonists to Ridogrel, so as to give a novel agent which express potent dual PAF antagonist/TxSI activity in vitro. Our further work will be reported elsewhere.[18]

References and Notes

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