On the Bioisosteric Potential of Diazines: Diazine Analogues of the Combined Thromboxane A_2 Receptor Antagonist and Synthetase Inhibitor Ridogrel†

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In this SAR study the bioisosteric potential of diazines in the field of combined antithrombotic thromboxane A_2 synthetase inhibitors and receptor antagonists was investigated. In this context, two series of (*E*)- and (*Z*)-*ω*-[[(aryldiazinylmethylene)amino]oxy]alkanoic acids were synthesized of which pentanoic acid derivatives with a 2-pyrazinyl, 4-pyridazinyl, or 5-pyrimidinyl group were found to exhibit this dual activity, while 4-pyrimidinyl as well as 3-pyridazinyl analogues showed only receptor antagonistic activity and 2-pyrimidinyl congeners were inactive. In the series of diazine analogues of Ridogrel (**1**), replacement of the 3-pyridyl group by a 2-pyrazinyl, 4-pyridazinyl, or 5-pyrimidinyl moiety led to compounds that inhibit thromboxane A_2 synthetase in gel-filtered human platelets comparable to **1** (IC_{50} of 0.006, 0.016, and 0.039 μM, respectively, versus 0.007 μM). Radioligand-binding studies with [^{3}H]SQ 29,548 in washed human platelets revealed that these diazine analogues block the thromboxane A_2 receptor with an IC_{50} of 11, 6.0, and 1.5 μM, respectively. This compares well with the $IC_{50} = 1.7$ μM of **1**. Finally, testing of inhibition of collagen-induced platelet aggregation in human platelet-rich plasma with 2-pyrazinyl, 4-pyridazinyl, or 5-pyrimidinyl congeners of Ridogrel indicated that these heteroaromatic moieties may serve as bioisosteric substitutes of a 3-pyridyl group in dual-acting antiplatelet agents.

One of the metabolic pathways of arachidonic acid is initiated in human blood platelets by the enzyme cyclooxygenase leading to the formation of an unstable cyclic endoperoxide, prostaglandin H_2 (PGH_2). Once produced inside platelets, PGH_2 is converted by the enzyme thromboxane synthetase (TxS) to thromboxane A_2 (TXA_2),[1] a potent vasoconstrictor and platelet-aggregating agent. TXA_2 migrates to the cell surface and binds to the TXA_2/prostaglandin endoperoxide receptor (α-receptor[2]) thereby initiating a cascade of events that leads to platelet aggregation.

Many studies provide evidence that TXA_2 is involved in the pathogenesis of thrombotic/vasoocclusive disorders.[3] First attempts to interfere with the formation and pathological action of TXA_2 led to the development of compounds inhibiting the key enzyme of TXA_2 formation, namely TxS. However, most thromboxane synthetase inhibitors (TxSI) proved to be poor antiplatelet agents due to the fact that inhibition of TxS leads to an accumulation of PGH_2, which may also bind to the TXA_2/prostaglandin endoperoxide receptor mimicking the prothrombotic effects of TXA_2.[3] This lack of efficacy of TxSIs could be overcome by using them in combination with a TXA_2 receptor antagonist (TxRA).[4]

One of the first antiplatelet agents identified and developed as a combined TxSI and TxRA is Ridogrel (**1**, Figure 1).[5] It is a highly potent, selective, and long-acting TxSI ($IC_{50} = 6 \times 10^{-9}$M),[6] but only a weakly active TxRA ($IC_{50} = 1.7 \times 10^{-6}$ M).[7] During the last decade, much effort has been devoted to structural modifications within the class of combined TxSI/TxRA with the objective to obtain antiplatelet agents exhibiting both activities equipotently in a nanomolar or subnanomolar range. A large number of these compounds are derived from Ridogrel, thus containing a 3-pyridyl system and a carboxyalkyl chain as characteristic moieties (for a review see ref 8). For both TxSI and TxRA activity, a distance of 8.5−10 Å between the carbon atom of the carboxylic group and the sp^2-hybridized nitrogen atom of the pyridine ring is essential.[9]

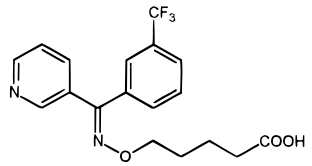

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Figure 1.

Besides the large number of dual active 3-pyridyl derivatives, only a few examples of combined TxSI/TxRA containing other *N*-heteroaromatic rings are described in the literature, e.g., as 1-imidazolyl-derived compounds.[10]

In continuation of our ongoing investigations of the bioisosteric potential of diazines, we now became interested in two series of diaza analogues of Ridogrel, both derived from diazinyl phenyl ketones (**2**−**7**) or diazinyl 3-(trifluoromethyl)phenyl ketones (**8**−**13**) (see Figure 2).

† Dedicated with best personal wishes to Prof. Dr. Ernst Mutschler on the occasion of his 65th birthday.
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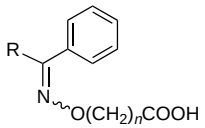
Table 1. Physical and Biological Data of Compounds ***E*-21a−f−23a−f** and ***Z*-21a−f−23a−f**[a]



compd	R	config	*n*	synth method	yield, %	recryst solvent	mp, °C	formula	IC_{50} (μM) TXA_2 receptor antagonism	IC_{50} (μM) TXA_2 synthetase inhibition	EC_{50} (μM) inhibition of collagen-induced platelet aggregation
***E*-21a**	3-pyrid[b]	*E*	3	A	70	DIPE[c]	108	$C_{15}H_{15}N_3O_3$			4% (273)
***Z*-21a**	3-pyrid	*Z*	3	A	75	DIPE/EA[d]	114	$C_{15}H_{15}N_3O_3$			2% (273)
***E*-21b**	4-pyrid	*E*	3	A	65	DIPE/EA	133	$C_{15}H_{15}N_3O_3$			245
***Z*-21b**	4-pyrid	*Z*	3	A	76	DIPE/EA	89	$C_{15}H_{15}N_3O_3$			21% (273)
***E*-21c**	2-pyrim[e]	*E*	3	A,B	81	H_2O	145	$C_{15}H_{15}N_3O_3$			0% (273)
***Z*-21c**	2-pyrim	*Z*	3	B	82	DIPE/EA	126	$C_{15}H_{15}N_3O_3$			0% (273)
***E*-21d**	4-pyrim	*E*	3	A	76	DIPE/EA	135	$C_{15}H_{15}N_3O_3$			34% (273)
***Z*-21d**	4-pyrim	*Z*	3	A	79	DIPE/PE[f]	107	$C_{15}H_{15}N_3O_3$			38% (273)
***E*-21e**	5-pyrim	*E*	3	A	75	DIPE/PE	79	$C_{15}H_{15}N_3O_3$			46% (273)
***Z*-21e**	5-pyrim	*Z*	3	A	75	DIPE	130	$C_{15}H_{15}N_3O_3$			17% (273)
***E*-21f**	2-pyraz[g]	*E*	3	A	76	DIPE	130	$C_{15}H_{15}N_3O_3$			47% (273)
***Z*-21f**	2-pyraz	*Z*	3	A	73	DIPE	87	$C_{15}H_{15}N_3O_3$			19% (273)
***E*-22a**	3-pyrid	*E*	4	A	77	DIPE/EA	149	$C_{16}H_{17}N_3O_3$	104	>100.000	47% (278)
***Z*-22a**	3-pyrid	*Z*	4	A	79	DIPE/EA	103	$C_{16}H_{17}N_3O_3$	71	>100.000	217
***E*-22b**	4-pyrid	*E*	4	A	69	DIPE/EA	94	$C_{16}H_{17}N_3O_3$	33	0.260	227
***Z*-22b**	4-pyrid	*Z*	4	A	94	DIPE/EA	72	$C_{16}H_{17}N_3O_3$	13	8.800	163
***E*-22c**	2-pyrim	*E*	4	A,B	80	H_2O/EtOH	165	$C_{16}H_{17}N_3O_3$	3%	>100.000	0% (273)
***Z*-22c**	2-pyrim	*Z*	4	B	75	DIPE	80	$C_{16}H_{17}N_3O_3$	15%	>10.000	0% (273)
***E*-22d**	4-pyrim	*E*	4	A	92	DIPE/EA	84	$C_{16}H_{17}N_3O_3$	30	>100.000	274
***Z*-22d**	4-pyrim	*Z*	4	A	43	EA[h]	oil[i]	$C_{16}H_{17}N_3O_3$	25	>100.000	255
***E*-22e**	5-pyrim	*E*	4	A	80	DIPE/PE	94	$C_{16}H_{17}N_3O_3$	20	0.075 ± 0.008	40% (278)
***Z*-22e**	5-pyrim	*Z*	4	A	72	DIPE	86	$C_{16}H_{17}N_3O_3$	7.2	0.573 ± 0.21	191
***E*-22f**	2-pyraz	*E*	4	A	77	DIPE	73	$C_{16}H_{17}N_3O_3$	47	0.079 ± 0.006	91
***Z*-22f**	2-pyraz	*Z*	4	A	94	DIPE	71	$C_{16}H_{17}N_3O_3$	24	0.620	94
***E*-23a**	3-pyrid	*E*	5	A	87	DIPE/EA	103	$C_{17}H_{19}N_3O_3$			203
***Z*-23a**	3-pyrid	*Z*	5	A	80	DIPE/EA	102	$C_{17}H_{19}N_3O_3$			204
***E*-23b**	4-pyrid	*E*	5	A	90	DIPE/EA	103	$C_{17}H_{19}N_3O_3$	7.1	3.800 ± 2.9	59
***Z*-23b**	4-pyrid	*Z*	5	A	90	DIPE/EA	73	$C_{17}H_{19}N_3O_3$	7.7	>10.000	81
***E*-23c**	2-pyrim	*E*	5	A,B	81	H_2O/EtOH	147	$C_{17}H_{19}N_3O_3$			0% (273)
***Z*-23c**	2-pyrim	*Z*	5	B	79	DIPE	90	$C_{17}H_{19}N_3O_3$			0% (273)
***E*-23d**	4-pyrim	*E*	5	A	73	DIPE/EA	104	$C_{17}H_{19}N_3O_3$	5.0	>10.000	112
***Z*-23d**	4-pyrim	*Z*	5	A	77	DIPE/EA	62	$C_{17}H_{19}N_3O_3$	25	>10.000	236
***E*-23e**	5-pyrim	*E*	5	A	18	EA[h]	oil[i]	$C_{17}H_{19}N_3O_3$			
***Z*-23e**	5-pyrim	*Z*	5	A	73	DIPE/PE	94	$C_{17}H_{19}N_3O_3$	8.8	>10.000	127
***E*-23f**	2-pyraz	*E*	5	A	51	DIPE	84	$C_{17}H_{19}N_3O_3$			131
***Z*-23f**	2-pyraz	*Z*	5	A	53	DIPE	71	$C_{17}H_{19}N_3O_3$			216

[a] For details, see the Experimental Section. [b] pyrid = pyridazinyl. [c] DIPE = diisopropyl ether. [d] EA = ethyl acetate. [e] pyrim = pyrimidinyl. [f] PE = petroleum ether. [g] pyraz = pyrazinyl. [h] Column chromatography. [i] No satisfactory elemental analysis obtained.

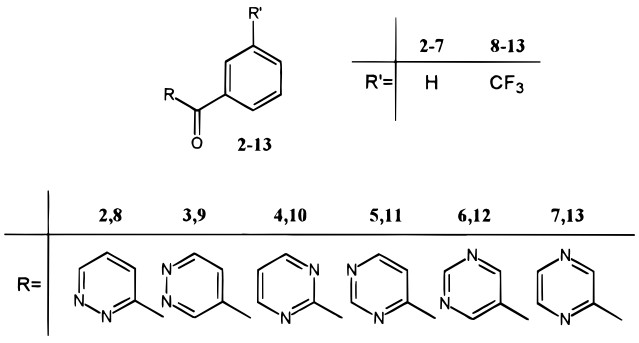


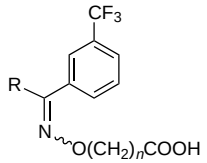
Figure 2.

Considering the different positions of the nitrogen atoms in the diazine systems employed, we envisaged elongation and shortening, respectively, of the ω-carboxyalkyl side chain by one methylene group compared to the lead compound Ridogrel in order to obtain compounds covering the optimal distance range 8.5−10 Å between an sp^2-hybridized nitrogen atom of the diazine systems and the carbon atom of the carboxylic group. Here we report on the synthesis of these novel compounds (**21**−**25**), on their TxS inhibitory and TxR antagonistic activities, and on their effect on human platelet aggregation.

Synthesis

The compounds listed in Tables 1 and 2 were prepared as depicted in Scheme 1; for the synthesis of the starting aryl diazinyl ketones **2**−**13**, see ref 11. In general, preparation of the target (*E*)- and (*Z*)-ω-[[(aryldiazinylmethylene)amino]oxy]alkanoic acids **21**−**25** was carried out starting from mixtures of (*E*)- and (*Z*)-aryl diazinyl ketoximes **14** and **15** which were prepared by reaction of ketones **2**−**13** with hydroxylamine according to ref 11. Alkylation of the oximes **14** and **15** with appropriate ethyl ω-bromoalkanoates (Scheme 1) yielded mixtures of (*E*)- and (*Z*)-ketoxime ethers **16a,b**, **17a,b**, **18a,b, 16d**−**f**, **17d**−**f**, **18d**−**f, 19b**, **20b**, **19d**−**f**, and **20d**−**f** (method A). Chromatographic separation then led to pure (*E*)- and (*Z*)-isomers which finally gave the target free carboxylic acids **21a,b**, **22a,b**, **23a,b, 21d**−**f**, **22d**−**f**, **23d**−**f, 24b**, **25b, 24d**−**f**, and **25d**−**f** in isomerically pure form upon alkaline hydrolysis.

Table 2. Physical and Biological Data of Compounds ***E*-24a–f–25a–f** and ***Z*–24a–f–25a–f**[a]



compd	R	config	*n*	synth method	yield, %	recryst solvent	mp, °C	formula	IC50 (μM) TXA2 receptor antagonism	IC50 (μM) TXA2 synthetase inhibition	EC50 (μM) inhibition of collagen-induced platelet aggregation
***E/Z*-24a**	3-pyrid[b]	*E/Z*[c]	4	B	85	DIPE[d]/PE[e]	47	$C_{17}H_{16}F_3N_3O_3$	10	>100.000	78
***E*-24b**	4-pyrid	*E*	4	A	73	DIPE	99	$C_{17}H_{16}F_3N_3O_3$	6.0	0.016 ± 0.02	52
***Z*-24b**	4-pyrid	*Z*	4	A	80	DIPE	98	$C_{17}H_{16}F_3N_3O_3$	1.8	6.633 ± 0.09	30
***E*-24c**	2-pyrim[f]	*E*	4	B	88	DIPE/EA[g]	110	$C_{17}H_{16}F_3N_3O_3$	99	>10.000	272
***Z*-24c**	2-pyrim	*Z*	4	B	81	DIPE/PE	79	$C_{17}H_{16}F_3N_3O_3$	52	>10.000	214
***E*-24d**	4-pyrim	*E*	4	A	73	DIPE/PE	89	$C_{17}H_{16}F_3N_3O_3$	1.4	>10.000	19
***Z*-24d**	4-pyrim	*Z*	4	A	82	DIPE/PE	49	$C_{17}H_{16}F_3N_3O_3$	2.5	>100.000	71
***E*-24e**	5-pyrim	*E*	4	A	75	DIPE/PE	78	$C_{17}H_{16}F_3N_3O_3$	1.5	0.039 ± 0.03	32
***Z*-24e**	5-pyrim	*Z*	4	A	72	DIPE/PE	87	$C_{17}H_{16}F_3N_3O_3$	0.36	6.100 ± 1.4	12
***E*-24f**	2-pyraz[h]	*E*	4	A	77	DIPE/PE	68	$C_{17}H_{16}F_3N_3O_3$	11	0.006 ± 0.002	190
***Z*-24f**	2-pyraz	*Z*	4	A	79	DIPE/PE	67	$C_{17}H_{16}F_3N_3O_3$	1.5	2.900	65
***E/Z*-25a**	3-pyrid	*E/Z*[i]	5	B	61	DIPE/PE	40	$C_{18}H_{18}F_3N_3O_3$			241
***E*-25b**	4-pyrid	*E*	5	A	84	DIPE/EA	131	$C_{18}H_{18}F_3N_3O_3$	29	0.693 ± 0.18	186
***Z*-25b**	4-pyrid	*Z*	5	A	80	DIPE	105	$C_{18}H_{18}F_3N_3O_3$	21	>10.000	26% (291)
***E*-25c**	2-pyrim	*E*	5	B	84	DIPE/EA	108	$C_{18}H_{18}F_3N_3O_3$			291
***Z*-25c**	2-pyrim	*Z*	5	B	59	EA[j]	oil[k]	$C_{18}H_{18}F_3N_3O_3$			
***E*-25d**	4-pyrim	*E*	5	A	82	DIPE/EA	126	$C_{18}H_{18}F_3N_3O_3$	1.1	>10.000	25
***Z*-25d**	4-pyrim	*Z*	5	A	52	EA[j]	oil[k]	$C_{18}H_{18}F_3N_3O_3$			184
***E*-25e**	5-pyrim	*E*	5	A	79	DIPE/EA	106	$C_{18}H_{18}F_3N_3O_3$			200
***Z*-25e**	5-pyrim	*Z*	5	A	85	DIPE/PE	87	$C_{18}H_{18}F_3N_3O_3$			291
***E*-25f**	2-pyraz	*E*	5	A	72	DIPE/PE	57	$C_{18}H_{18}F_3N_3O_3$			251
***Z*-25f**	2-pyraz	*Z*	5	A	74	DIPE/PE	61	$C_{18}H_{18}F_3N_3O_3$			47% (291)
1	3-pyridyl	*E*	4	*l*				$C_{19}H_{19}F_3N_2O_3$	1.7[m]	0.007 ± 0.002	41

[a] For details, see the Experimental Section. [b] pyrid = pyridazinyl. [c] *E/Z* ratio = 2:1. [d] DIPE = diisopropyl ether. [e] PE = petroleum ether. [f] pyrim = pyrimidinyl. [g] EA = ethyl acetate. [h] pyraz = pyrazinyl. [i] *E/Z* ratio = 3:1. [j] Column chromatography. [k] No satisfactory elemental analysis obtained. [l] From Janssen. [m] See ref 7.

Since pure (*E*)-ketoxime ***E*-14c**[11] could be obtained easily by fractional crystallization, pure (*E*)-ketoxime ethers ***E*-16c**, ***E*-17c**, and ***E*-18c** became available by alkylation of ***E*-14c** with the appropriate ethyl ω-bromoalkanoates. Alkaline hydrolysis finally gave isomerically pure acids ***E*-21c**, ***E*-22c**, and ***E*-23c**.

For a more convenient synthesis of compounds **16c–20c**, **19a**, and **20a** ethyl ω-(aminooxy)alkanoates **29–31** were reacted with ketones **4**, **8,** and **10**. This approach (method B) gave higher yields than the reaction sequence according to method A. The required educts **29–31** were prepared via a slight modification of a two-step procedure previously described for the preparation of ethyl (aminooxy)acetate[12] consisting of alkylation of *N*-hydroxyphthalimide with ethyl ω-bromoalkanoates and subsequent hydrazinolysis (Scheme 2).

Since **19a** and **20a** could not be separated by column chromatography or crystallization, these esters were hydrolyzed to give (*E*) and (*Z*) mixtures of the free carboxylic acids **24a** and **25a**, the isomer ratio of which was established by ^{1}H-NMR spectroscopy.

The configuration of the target compounds **21–25** was assigned mainly by ^{1}H-NMR spectroscopy considering the chemical shifts observed for the heteroaromatic protons adjacent to the CN double bond.[15] By comparison of these chemical shift patterns with those of the corresponding (*E*)- and (*Z*)-ketoximes **14** and **15** (the configurational assignment of which had been carried out previously[11] by homonuclear NOE difference spectroscopy as well as ^{13}C-NMR spectroscopy), unequivocal assignment of the stereochemistry was possible for all new compounds. A detailed presentation of these spectroscopic investigations has been published recently.[13,14]

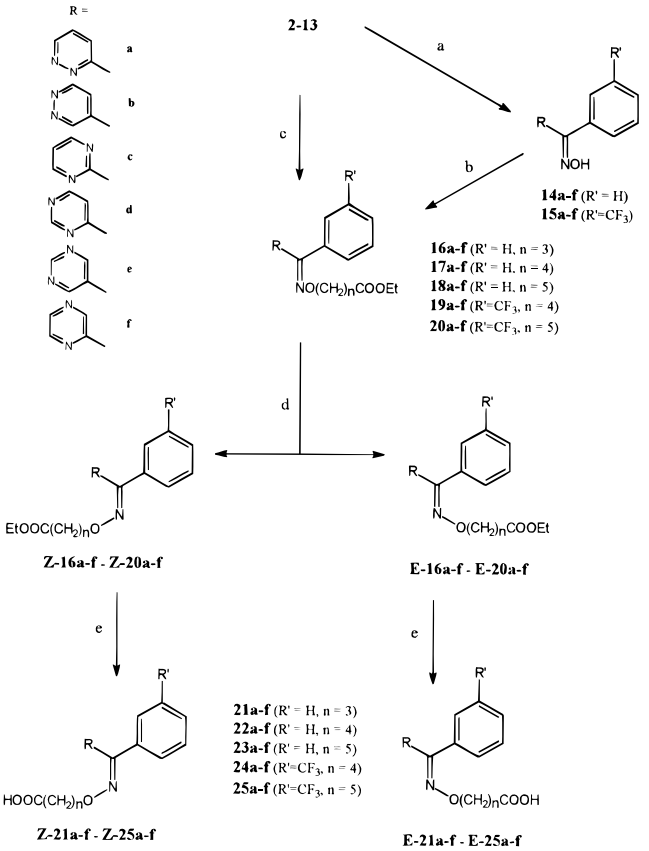
Results and Discussion

The compounds listed in Tables 1 and 2 were initially tested for *in vitro* inhibition of collagen-induced platelet aggregation in human platelet-rich plasma (PRP). The most potent compounds out of this first test series, all (*E*)- and (*Z*)-aza-Ridogrel derivatives **24** and congeners thereof lacking of the trifluoromethyl group (**22**), were further tested in the following two assays: (a) displacement of the high-affinity radiolabeled ligand [^{3}H]SQ 29,548 from the PGH_2/TXA_2 receptor on human gel-filtered platelets and (b) inhibition of TXB_2 formation by human gel-filtered platelets incubated with [^{14}C]-arachidonic acid.

The test results are listed as IC_{50}/EC_{50} values in Tables 1 and 2. Formally, the six possible position isomers of the three diazine rings can be divided into two groups: the first group of ring systems represents "aza 3-pyridyl" moieties with an additional nitrogen atom in position 2 (3-pyridazinyl system), 4 (4-pyridazinyl system), 5 (5-pyrimidinyl system), or 6 (2-pyrazinyl system). The second group consists of two ring systems, i.e., the 2-pyrimidinyl and the 4-pyrimidinyl system, which lack of a nitrogen atom in position 3 related to the oxime ether side chain.

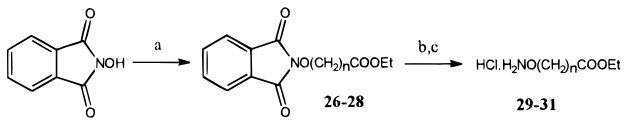
Starting with the oxime ethers **21–23** derived from the parent diazinyl phenyl ketones **2–7**, we first examined the influence of the presence of different diazine

Scheme 1[a]



[a] Reagents and conditions: (a) see ref 11; (b) NaH, DMF, $Br(CH_2)_{3,4,5}COOEt$; (c) Na_2CO_3, CH_3OH/H_2O, $HCl{\cdot}H_2NO(CH_2)_{3,4,5}COOEt$; (d) MPLC (eluent: CH_2Cl_2/CH_3COOEt); (e) 1 N NaOH, EtOH.

Scheme 2[a]



[a] Reagents and conditions: (a) CH_3COONa, DMSO, $Br(CH_2)_{3,4,5}COOEt$, 50 °C; (b) $N_2H_4{\cdot}H_2O$, EtOH, 70 °C; (c) ethereal HCl, 40 °C.

systems on platelet antiaggregatory activity. All aza 3-pyridyl pentanoic acid derivatives ***E*-22a,b,e,f** inhibit collagen-induced platelet aggregation with EC_{50} values in the range ~90−300 μM. In the second group, only the 4-pyrimidinyl derivative ***E*-22d** exhibits platelet antiaggregatory activity comparable to that of the analogues of the first group. Butanoic acids **21** turned out to be less potent while some hexanoic acids **23** showed higher antiplatelet activity (see Table 1). The most potent representative within this series (EC_{50} = 59 μM) is compound ***E*-23b**. It is of interest to note that similar trends with regard to the length of the side chain and the nature of the diazine system are observed also with (*Z*) configurated compounds ***Z*-21**, ***Z*-22**, and ***Z*-23**.

In order to gain insight into the bioisosteric potential of the six isomeric diazine systems with regard to thromboxane synthetase inhibition and receptor antagonism, the appropriate assays with selected compounds, as mentioned above, were performed. The 2- or the 4-pyrimidinyl-derived compounds **22c** and **22d** did not show any TxSI activity. Within the group of aza-3-pyridyl analogues, the second nitrogen atom in position 2 (compounds **22a**) also leads to TxSI inactive compounds. In contrast, formal incorporation of the additional nitrogen atom into position 4 (4-pyridazinyl derivative ***E*-22b**) results in a compound with slight TxSI activity (IC_{50} of 260 nM). An additional nitrogen atom in position 5 or 6 (5-pyrimidinyl or 2-pyrazinyl derivatives) results in higher TxSI activity: the pentanoic acid derivatives ***E*-22e** and ***E*-22f** inhibit TxS with IC_{50} values of 75 and 79 nM, respectively. The (*Z*)-isomers turned out to be much less potent. Thus, the 3-pyridyl moiety in Ridogrel-type compounds can be replaced only by 4-pyridazinyl, 5-pyrimidinyl, or 2-pyrazinyl moieties without complete loss of TxSI activity. In this series elongation of the side chain does not lead to compounds with enhanced TxSI activity.

Tests of compounds **22a**−**f**, **23b**, **23d**, and ***Z*-23e** with regard to their thromboxane receptor antagonism gave the following results: a 2-pyrimidinyl system is also deleterious for TxRA activity, whereas the 4-pyrimidinyl-derived acids **22d** and **23d** exhibit receptor antagonistic activity in the range 5.0−30 μM. Employment of a "4-, 5-, or 6-aza-3-pyridyl" system is associated with TxRA activity in a similar range (IC_{50} 7.1−104 μM), while 3-pyridazinyl derived acids **22a** exhibit only low TxRA activity (IC_{50} 71 and 104 μM, respectively). It should be noted that the configuration at the CN double bond does not influence TxRA activity as significantly as observed in the assay for TxSI activity. Nor did we find in this series marked differences in activity between pentanoic and hexanoic acid derivatives.

In a further step of our study, we prepared and tested compounds **24** and **25** as diazine analogues of Ridogrel. Since we had found within the series of compounds **21**−**23** that butanoic acids were more or less inactive as inhibitors of human platelet aggregation, we now limited the variation of the length of the side chain to pentanoic and hexanoic acid derivatives.

Here, we observed structure−activity relationships similar to those we had found within the series of compounds **21**−**23**: the 4-pyridazinyl analogue of Ridogrel, ***E*-24b** exhibits comparable antiaggregatory activity (EC_{50} = 52 μM) since replacement of the 3-pyridyl moiety in **1** by the 4-pyridazinyl system does not significantly affect both TxSI and TxRA activity. The corresponding (*Z*)-isomer (***Z*-24b**) is also active as an antiplatelet compound, but its activity results mainly from its micromolar TxRA activity (IC_{50} = 1.8 μM), since TxSI activity is strongly reduced due to (*Z*) configuration. Elongation of the carboxyalkyl side chain by one methylene group (***E*-25b** and ***Z*-25b**) reduces both TxSI and TxRA activity. The 3-pyridazinyl analogues ***E*/*Z*-24a** which were tested as a 2:1 mixture of (*E*)- and (*Z*)-isomers, exhibited no TxSI and low TxRA activity. Replacement of the 3-pyridyl moiety in **1** by a 2-pyrimidinyl system is also deleterious for both activities and results in a low antiplatelet activity. In contrast, incorporation of a 4-pyrimidinyl system (***E*-24d** and ***Z*-24d**) leads to a receptor antagonistic activity similar to that of **1**, which is not affected by elongation of the side chain, but again no TxSI activity at all could be detected. Like the 4-pyridazinyl analogues, also 5-pyrimidinyl and 2-pyrazinyl congeners (***E*-24e** and ***E*-24f**) exhibit TxSI activity in the nanomolar range. Again, TxSI activity is significantly reduced upon change from (*E*) to (*Z*) configuration at the CN double bond, while

TxRA activity is 10-fold higher in (*Z*)-isomers. In fact, the most potent TxRA in this series is the 5-pyrimidinyl derived pentanoic acid ***Z*-24e** ($IC_{50} = 0.36\ \mu M$), but its TxSI activity is in the mixeomolar range due to the (*Z*) configuration. On the other hand, the most potent TxSI of the Ridogrel analogues ($IC_{50} = 6.0$ nM), the 2-pyrazinyl derivative ***E*-24f**, exhibits a 10-fold lower TxRA activity compared to that of **1**.

Conclusion

On the basis the structure−activity relationships observed in this study, it turned out that only the 2-pyrazinyl, 4-pyridazinyl, and 5-pyrimidinyl systems are appropriate bioisosteric moieties for the 3-pyridyl system in the dual active platelet antiaggregatory compound Ridogrel. While 2-pyrimidinyl analogues showed neither TxSI nor significant TxRA activity and 3-pyridazinyl as well as 4-pyrimidinyl congeners were only active as TxRA, the 2-pyrazinyl, 4-pyridazinyl, and 5-pyrimidinyl analogues exhibit a dual activity comparable to that of Ridogrel. Thus, it might be of interest to utilize the bioisosteric potential of the latter heteroaryl groups for further developments of antiplatelet compounds with combined TxSI/TxRA activity.

Experimental Section

(a) Chemistry. Melting points were determined on a Reichert-Kofler hot-stage microsope and are uncorrected. Infrared spectra were run from KBr pellets or neat oils between NaCl disks on a Mattson Galaxy Series FTIR 3000 spectrophotometer or on a JASCO IRA-1 spectrophotometer. Mass spectra (MS, electron-impact ionization, 70 eV) were taken on a Varian MAT 311A or on a Varian MAT 44/S instrument. NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C), on a Bruker AC 80 (80 MHz for ^{1}H, 20 MHz for ^{13}C), or on a Bruker AM 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C). The center of the solvent signal was used as an internal standard, which was related to tetramethylsilane with δ 2.49 (DMSO-d_6), 2.04 (acetone-d_6), or 7.24 ($CDCl_3$) for ^{1}H, and δ 39.5 (DMSO-d_6), 29.8 (acetone-d_6), or 77.0 ($CDCl_3$) for ^{13}C, respectively. Microanalyses were obtained for C, H, N and are within ±0.3% of the theoretical value unless noted otherwise. TLC was performed on silica gel plates (Macherey-Nagel Polygram SIL G/UV 254 or Merck, silica gel 60, F-254) and visualized using an UV lamp or iodine vapour. Column chromatography was performed using Merck silica gel 60 (230−400 mesh), and medium-pressure liquid chromatography (MPLC) was carried out using Merck LiChroprep Si 60 (230−400 mesh), detection at 280 nm. Petroleum ether refers to the fraction of bp 40−60 °C. The yields given and separations of (*E*)- and (*Z*)-isomers are not optimized. Detailed synthetic procedures as well as spectroscopic data for the full set of compounds are given in ref 15.

General Procedure for the Preparation of Ketoxime Ethers 16a−f−20a−f. Method A. To an ice-cooled suspension of 144 mg (3.6 mmol) of NaH (60% suspension in paraffine oil, washed with dry *n*-hexane) in 6 mL of dry DMF was added a solution of 3 mmol of aryl diazinyl ketoxime (**14a−f**, **15b**, or **15d−f**)[11] in 6 mL of dry DMF. After the mixture was stirred for 10 min at 0 °C, 3.3 mmol of the appropriate ethyl ω-bromoalkanoate in 6 mL of dry DMF was added slowly. After complete addition, stirring was continued for 1 h at room temperature. Then the reaction mixture was poured onto ice, diluted with 10 mL of saturated aqueous $NaHCO_3$ solution, and extracted exhaustively with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and rotary evaporated to give an oily residue. The residue was purified by column chromatography (eluent: CH_2Cl_2 + EtOAc = 1 + 1), and then chromatographic separation of (*E*)- and (*Z*)-isomers was performed by MPLC using mixtures of CH_2Cl_2/EtOAc (ratio thus adjusted to result in R_f values of about 0.25 for the faster eluted component, i.e., the (*Z*)-isomer).

(*Z*)-Ethyl4-[[[Phenyl(3-pyridazinyl)methylene]amino]-oxy]butanoate (*Z*-16a) and the (*E*)-Isomer *E*-16a. Compounds ***Z*-16a** and ***E*-16a** were prepared from **14a**[11] and ethyl 4-bromobutanoate. Chromatographic separation by MPLC afforded 430 mg (46%) of ***Z*-16a** (faster eluted component) and 310 mg (33%) of ***E*-16a** (slower eluted component).

Compound ***Z*-16a** was obtained as a yellowish oil: ^{1}H NMR (acetone-d_6) δ (ppm) 9.26 (dd, $J_{4,6} = 1.9$ Hz, $J_{5,6} = 4.8$ Hz, 1H, pyridazine H-6), 7.84 (dd, $J_{4,6} = 1.9$ Hz, $J_{4,5} = 8.4$ Hz, 1H, pyridazine H-4), 7.80 (dd, $J_{5,6} = 4.8$ Hz, $J_{4,5} = 8.4$ Hz, 1H, pyridazine H-5), 7.25−7.60 (m, 5H, Ph), 4.21 (t, 2H, OCH_2), 4.05 (q, 2H, OCH_2CH$_3$), 2.34 (t, 2H, CH_2CO), 1.97 (quint, 2H, CH$_2$CH_2CH$_2$), 1.17 (t, 3H, OCH$_2$CH_3); IR (oil) 1715 (C=O) cm^{-1}; MS *m*/*z* 313 (M$^+$, 1), 182 (100), 181 (55), 115 (21), 87 (26), 77 (23). Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

Compound ***E*-16a** was obtained as a yellowish oil: ^{1}H NMR (acetone-d_6) δ (ppm) 9.17 (dd, $J_{4,6} = 1.8$ Hz, $J_{5,6} = 4.9$ Hz, 1H, pyridazine H-6), 8.16 (dd, $J_{4,6} = 1.8$ Hz, $J_{4,5} = 8.6$ Hz, 1H, pyridazine H-4), 7.70 (dd, $J_{5,6} = 4.9$ Hz, $J_{4,5} = 8.6$ Hz, 1H, pyridazine H-5), 7.40 (s, 5H, Ph), 4.28 (t, 2H, OCH_2), 4.06 (q, 2H, OCH_2CH$_3$), 2.39 (t, 2H, CH_2CO), 2.05 (quint, 2H, CH$_2$CH_2-CH$_2$), 1.18 (t, 3H, OCH$_2$CH_3); IR (oil) 1720 (C=O) cm^{-1}; MS *m*/*z* 313 (M$^+$, 2), 182 (100), 181 (55), 115 (20), 87 (23), 77 (20). Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

The synthesis of compounds **16b**, **16d−f**, **17a−f**, **18a−f**, **19b**, **19d−f**, **20b**, and **20d−f** from educts **14a−f**, **15b**, or **15d−f**,[11] and ethyl 4-bromobutanoate, ethyl 5-bromopentanoate, or ethyl 6-bromohexanoate was carried out similarly as described for the preparation of **16a** from **14** and ethyl 4-bromobutanoate.[15]

General Procedure for the Preparation of Ketoxime Ethers 16c−18c, **19a**, **19c**, **20a**, and **20c. Method B.** A mixture of 3 mmol of aryl diazinyl ketone **4**, **8**, or **10**,[11] 3.6 mmol of the appropriate ethyl ω-(aminooxy)alkanoate hydrochloride (**29−31**), and 3.6 mmol of Na_2CO_3 in 12 mL of MeOH and 24 mL of water was stirred at 70 °C until the solids were dissolved completely. After 10 min of additional heating, the reaction mixture was acidified to pH 4 with acetic acid and stirred for 3 h at 70 °C. After being cooled to room temperature, the reaction mixture was diluted with 20 mL of saturated $NaHCO_3$ solution and exhaustively extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and rotary-evaporated to give an oily residue. The residue was purified by column chromatography (eluent: CH_2Cl_2 + EtOAc = 1 + 1), and then chromatographic separation of (*E*)- and (*Z*)-isomers was performed by MPLC using mixtures of CH_2Cl_2/EtOAc (ratio thus adjusted to result in R_f values of about 0.25 for the faster eluted component, i.e., the (*Z*)-isomer).

(*Z*)-Ethyl 4-[[[Phenyl(2-pyrimidinyl)methylene]amino]-oxy]butanoate (*Z*-16c) and the (*E*)-Isomer *E*-16c. Compounds ***Z*-16c** and ***E*-16c** were prepared from **4**[11] and **29**. Chromatographic separation by MPLC afforded 376 mg (40%) of ***Z*-16c** (faster eluted component) and 526 mg (57%) of ***E*-16c** (slower eluted component).

Compound ***Z*-16c** was obtained as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 8.88 (d, $J_{4/6,5} = 4.8$ Hz, 2H, pyrimidine H-4/6), 7.25−7.50 ("s", 5H, Ph), 7.32 (t, $J_{4/6,5} = 4.8$ Hz, 1H, pyrimidine H-5), 4.19 (t, 2H, OCH_2), 4.08 (q, 2H, OCH_2CH$_3$), 2.31 (t, 2H, CH_2CO), 1.96 (quint, 2H, CH$_2$CH_2CH$_2$), 1.21 (t, 3H, OCH$_2$CH_3); IR (oil) 1730 (C=O) cm^{-1}; MS *m*/*z* 313 (M$^+$, 1), 183 (31), 182 (49), 115 (45), 87 (66), 85 (19), 80 (100), 77 (32). Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

Compound ***E*-16c** was obtained as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 8.78 (d, $J_{4/6,5} = 4.8$ Hz, 2H, pyrimidine H-4/6), 7.40 ("s", 5H, Ph), 7.24 (t, $J_{4/6,5} = 4.8$ Hz, 1H, pyrimidine H-5), 4.35 (t, 2H, OCH_2), 4.08 (q, 2H, OCH_2CH$_3$), 2.35 (t, 2H, CH_2CO), 2.03 (quint, 2H, CH$_2$CH_2CH$_2$), 1.21 (t, 3H, OCH$_2$CH_3); IR (oil) 1730 (C=O) cm^{-1}; MS *m*/*z* 313 (M$^+$, 1), 183 (35), 182 (55), 115 (85), 87 (98), 85 (31), 80 (100), 77 (33). Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

The preparation of compounds **17c**, **18c**, **19a**, **19c**, **20a**, and **20c** from **4**, **8**, or **10**[11] and ethyl 5-(aminooxy)pentanoate hydrochloride (**30**) or ethyl 6-(aminooxy)hexanoate hydrochlo-

ride (**31**) was carried out similarly as described for the preparation of **16c** from **4** and **29**.[15]

General Procedure for the Preparation of Ethyl ω-(Aminooxy)alkanoate Hydrochlorides 29−31. *N*-Hydroxyphthalimide (8.2 g, 50 mmol) was dissolved in 50 mL of DMSO at 60 °C, 4.1 g (50 mmol) of NaOAc was added portionwise, and the resulting red solution was stirred for another 10 min. Then a solution of 50 mmol of the appropriate ethyl ω-bromoalkanoate in 10 mL of DMSO was added dropwise. After 30 min of additional heating, the reaction mixture was cooled to room temperature, diluted with 100 mL of water and 30 mL of 2 N NaOH, and then exhaustively extracted with diethyl ether. The combined organic layers were washed with water and saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and rotary-evaporated to give an oily residue. The residue was purified by distillation in a kugelrohr apparatus to yield ethyl *N*-ω-(phthalimidooxy)-alkanoates **26−28**. A solution of 25 mmol of **26−28** in 50 mL of EtOH was heated to 75 °C and treated with 1.3 mL (25 mmol) of $N_2H_4 \cdot H_2O$. After complete addition, the reaction mixture was cooled to 40 °C, and then 6 mL of saturated ethereal HCl was added. The precipitated 1,4-dihydroxyphthalimide was filtered off and washed several times with CH_2Cl_2. The filtrate was rotary-evaporated to dryness and recrystallized from EtOAc to give ethyl ω-(aminooxy)alkanoate hydrochlorides **29−31** in 76−88% yield.

General Procedure for the Preparation of Acids 21a−f−25a−f. To a solution of 1 mmol of compounds **16a−f−20a−f** in 6 mL of EtOH was added 0.6 mL (1.1 mmol) of 2 N NaOH. The reaction mixture was stirred for 24 h at room temperature, acidified to pH 3−4 with 2 N HCl, diluted with 20 mL of water, and exhaustively extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated to dryness. For yields, recrystallization solvents, and melting points, see Tables 1 and 2.

(*E*)-4-[[[Phenyl(3-pyridazinyl)methylene]amino]oxy]-butanoic Acid (*E*-21a). Compound ***E*-21a** was prepared from ***E*-16a** and obtained as colorless crystals upon recrystallization: ^{1}H NMR ($CDCl_3$) δ (ppm) 9.17 (dd, $J_{4,6} = 1.9$ Hz, $J_{5,6} = 4.8$ Hz, 1H, pyridazine H-6), 8.80 (s, 1H, O*H*), 8.11 (dd, $J_{4,6} = 1.9$ Hz, $J_{4,5} = 8.6$ Hz, 1H, pyridazine H-4), 7.54 (dd, $J_{5,6} = 4.8$ Hz, $J_{4,5} = 8.6$ Hz, 1H, pyridazine H-5), 7.40 ("s", 5H, Ph), 4.30 (t, 2H, OCH_2), 2.43 (t, 2H, CH_2CO), 2.05 (quint, 2H, CH_2CH_2-CH_2); IR (KBr) 1715 (C=O) cm^{-1}; MS *m*/*z* 285 (M^+, <1), 267 (30), 168 (20), 131 (18), 119 (24), 76 (20), 69 (100). Anal. ($C_{15}H_{15}N_3O_3$) C, H, N.

(*Z*)-4-[[[Phenyl(3-pyridazinyl)methylene]amino]oxy]-butanoic Acid (*Z*-21a). Compound ***Z*-21a** was prepared from ***Z*-16a** and obtained as colorless crystals upon recrystallization: ^{1}H NMR ($CDCl_3$) δ (ppm) 10.40 (s, 1H, O*H*), 9.21 (dd, $J_{4,6} = 1.9$ Hz, $J_{5,6} = 4.8$ Hz, 1H, pyridazine H-6), 7.63 (dd, $J_{4,6} = 1.9$ Hz, $J_{4,5} = 8.7$ Hz, 1H, pyridazine H-4), 7.57 (dd, $J_{5,6} = 4.8$ Hz, $J_{4,5} = 8.7$ Hz, 1H, pyridazine H-5), 7.25−7.50 (m, 5H, Ph), 4.22 (t, 2H, OCH_2), 2.34 (t, 2H, CH_2CO), 1.99 (quint, 2H, $CH_2CH_2CH_2$); IR (KBr) 1723 (C=O) cm^{-1}; MS *m*/*z* 285 (M^+, <1), 267 (71), 266 (36), 237 (26), 182 (21), 168 (44), 108 (44), 91 (78), 87 (20), 43 (100). Anal. ($C_{15}H_{15}N_3O_3$) C, H, N.

The preparation of compounds **21b−f**, **22a−f−25a−f** from **16b−f**, **17a−f−20a−f** was carried out similarly to the procedure given for the synthesis of **21a**.[15]

(b) Biochemistry. Materials and Methods. SQ 29,548-5,6-^3H(*N*) (code NET-936) and sucrose-^{14}C(*U*) (code NEC-100) were purchased from New England Nuclear (Dreieich, FRG), Sepharose 2B from Pharmacia, and Collagen and SKF dilution buffer from Hormon-Chemie (Munich, FRG). All other chemicals were of the highest purity commercially available.

Collagen-Induced Platelet Aggregation *in Vitro*. Blood was obtained from healthy volunteers who had refrained from taking any medication for at least 14 days prior to venipuncture. The blood was mixed with trisodium citrate solution (3.8% w/v) at ratio of 9:1. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were obtained from the blood by centrifugation (Rotixa KS, Hettich) at 1000 rpm for 10 min at 10 °C and 4000 rpm for 10 min at 10 °C, respectively. PRP was then adjusted to a concentration of 2.5×10^5 cells/mL (PRP 250). Platelet aggregation tests were performed in a two-channel aggregometer (Labor aggregometer, FRG) and recorded on two recorders (LKB Clinicon 2066A, Goerz, AU) at a paper speed of 0.5 mm/s.

PRP 250 (400 μL) and 50 μL of a solution of the test compound or vehicle solution (8 g/L NaCl, 200 mg/L KCl, 1g/L $NaHCO_3$, 50 mg/L $NaH_2PO_4 \cdot H_2O$, 306 mg/L $CaCl_2 \cdot 2H_2O$, 203 mg/L $MgCl_2 \cdot 6H_2O$) were incubated 10 min at room temperature followed by 5 min at 37 °C before addition of collagen (20 μL; 0.53 μg/mL final concentration). After the addition of collagen, the optical density of the stirred PRP 250 (500 units/min) was recorded for 4 min. All experiments were performed at least as duplicates. Values were expressed as percent inhibition of aggregation, which represented the percentage of light transmission standardized to PRP 250 and PPP samples, yielding 0% and 100% light transmission, respectively. The EC_{50}, i.e., the concentration of the test compound required for half the maximal inhibition of collagen-induced platelet aggregation, was calculated from the concentration versus inhibition of aggregation curve.

Thromboxane Synthetase Inhibition. Inhibition of TXB_2 formation by human gel-filtered platelets incubated with [^{14}C]arachidonic acid was measured as described before.[7] This test procedure allowed the quantification of free AA, 12-hydroxyeicosatetraenoic acid (12-HETE); 12-hydroxyheptadecatrienoic acid (HHT); prostaglandins D_2, E_2, and $F_{2\alpha}$; and thromboxane B_2 (TXB_2). Thromboxane synthetase inhibition is characterized by a decrease in TXB_2 and a corresponding increase in the "classical" prostaglandins. Cyclooxygenase inhibition is seen by a decrease of andoperoxide-derived products and an increase in 12-HETE.

Thromboxane Receptor Antagonism. The binding of the test compounds was determined by measuring the displacement of the high-affinity ligand [^{3}H]SQ 29,548 according to ref 7. Nonspecific binding was determined by adding U 46,619 (30 μM final concentration), replacing the test compound. IC_{50} values listed in Tables 1 and 2 represent the concentration of test compound causing 50% displacement of [^{3}H]SQ 29,548.

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References

(1) (a) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2294−8. (b) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. Synthesis and structure of the platelet aggregation factor thromboxane A_2. *Nature* **1985**, *315*, 511−3.

(2) Mais, D. E.; Saussy, D. L.; Chaikhouni, A.; Kochel, P. J.; Knapp, D. R.; Hamanaka, N.; Halushka, P. V. Pharmacologic Characterisation of Human and Canine Thromboxane A_2/Prostaglandin H_2 Receptors in Platelets and Blood Vessels: Evidence for Different Receptors. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 418−24

(3) Fiddler, G.; Lumley, P. Preliminary Clinical Studies with Thromboxane Synthase Inhibitors and Thromboxane Receptor Blockers—A Review. *Circulation* **1990**, *81*, 69−78.

(4) (a) Bertelè, V.; De Gaetano, G. Potentiation by Dazoxiben, a Thromboxane Synthetase Inhibitor, of Platelet Aggregation Inhibitory Activity of a Thromboxane Receptor Antagonist or Prostacyclin. *Eur. J. Pharmacol.* **1982**, *85*, 331−3. (b) Gresele, P.; Arnout, J.; Deckmyn, H.; Huybrechts, E.; Pieters, G.; Vermylen, J. Role of Proaggregatory and Antiaggregatory Prostaglandins in Hemostasis: Studies with a Combined Thromboxane Synthase Inhibition and Thromboxane Receptor Antagonism. *J. Clin. Invest.* **1987**, *80*, 1435−45.

(5) Freyne, E. J. E.; Raeymaekers, A. H. M.; Sipido, V.; Venet, M. G. Preparation of [[(3-pyridylmethylene)amino]oxy]alkanoates as blood platelet aggregation inhibitors. *Eur. Pat. Appl.* EP 221,601, 13 May 1987; *Chem. Abstr.* **1987**, *107*, 115497.

(6) De Clerck, F.; Beetens, J.; de Chaffoy de Courcelles, D.; Freyne, E.; Janssen, P. A. J. R68070: Thromboxane A_2 Synthetase Inhibition and Thromboxane A_2 / prostaglandine Endoperoxide Receptor Blockade Combined in One Molecule − I. Biochemical Profile In Vitro. *Thromb. Haemostasis* **1989**, *61*, 35−42.

(7) Soyka, R.; Heckel, A.; Nickl, J.; Eisert, W.; Müller, T. H.; Weisenberger, H. 6,6-Disubstituted Hex-5-enoic Acid Derivatives as Combined Thromboxane A_2 Receptor Antagonists and Synthetase Inhibitors. *J. Med. Chem.* **1994**, 37, 26−39.
(8) Baghwat, S. S. Novel antithrombotic agents with combined thromboxane receptor antagonist (TxRA)/thromboxane synthase inhibitor (TxSI) activities. *Drugs Future* **1994**, *19*, 765−77.
(9) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z. I.; Nishikawa, K. Thromboxane Synthetase Inhibitors (TxSI). Design, Synthesis, and Evaluation of a Novel Series of ω-Pyridylalkenoic Acids. *J. Med. Chem.* **1985**, *28*, 287−94.
(10) Cozzi, P.; Giordani, A.; Menichincheri, M.; Pillan, A.; Pinciroli, V.; Rossi, A.; Tonani, R.; Volpi, D.; Tamburin, M.; Ferrario, R.; Fusar, D.; Salvati, P. Agents Combining Thromboxane Receptor Antagonism with Thromboxane Synthase Inhibition: [[[2-(1*H*-Imidazol-1-yl)ethylidene]amino]oxy]alkanoic Acids. *J. Med. Chem.* **1994**, *37*, 3588−604.
(11) Heinisch, G.; Holzer, W.; Langer, T.; Lukavsky, P. Aryl Diazinyl Ketoximes: Synthesis and Configurational Assignment. *Heterocycles* **1996**, *43*, 151−72.
(12) Rougny, A.; Daudon, M. Utilisation dimides N-hydroxyles pour la synthèse dialkoxylamines primaires. (N-hydroxy imides for the synthesis of primary alkoxy amines.) *Bull. Soc. Chim. Fr.* **1976**, 5, 833−38.
(13) Heinisch, G.; Holzer, W.; Langer, T.; Lukavsky, P. On the Stereochemistry of Novel Antithrombotic Aryl Diazinyl Ketoxime Ethers. *Sci. Pharm.*, in press.
(14) Heinisch, G.; Langer, T.; Lukavsky, P. Complete Assignment of the ^{13}C NMR Spectra of Aryl Diazinyl Ketones and Aryl Diazinyl Ketoxime Ethers. *J. Magn. Reson.*, in press.
(15) (a) Lukavsky, P. Diploma Thesis, University of Vienna, 1992. (b) Lukavsky, P. Ph.D. Thesis, University of Innsbruck, 1995.

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