6,6-Disubstituted Hex-5-enoic Acid Derivatives as Combined Thromboxane A_2 Receptor Antagonists and Synthetase Inhibitors

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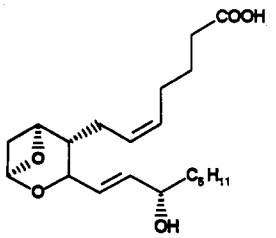
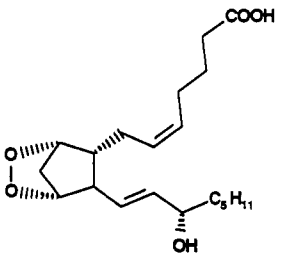
A series of ω-disubstituted alkenoic acid derivatives were designed and synthesized as antithrombotic inhibitors of thromboxane A_2 synthetase and thromboxane A_2 receptor antagonists. Hexenoic acid derivatives with a 3-pyridyl group and a 4-(2-benzenesulfonamidoethyl)phenyl substituent were found to be optimal with regard to the dual mode of action. The most potent compound, (*E*)-6-(4-(2-(((4-chlorophenyl)sulfonyl)amino)ethyl)phenyl)-6-(3-pyridyl)hex-5-enoic acid (**36**), inhibits thromboxane A_2 synthetase in gel-filtered human platelets with an IC_{50} value of 4.5 ± 0.5 nM ($n = 4$), whereas an inhibitory effect on cyclooxygenase is seen only at a much higher concentration (IC_{50}: 240 μM). Radioligand-binding studies with [^{3}H]SQ 29,548 in washed human platelets revealed that **36** blocks the prostaglandin H_2/thromboxane A_2 receptor with an IC_{50} of 19 ± 5 nM ($n = 5$) and is therefore 85-fold more potent than another combined thromboxane A_2 synthetase inhibitor/receptor antagonist, Ridogrel (**4**). Compound **36** inhibits the collagen-induced platelet aggregation in human platelet-rich plasma and whole blood with an EC_{50} of 1 μM (Ridogrel: 16 μM) and 100 nM, respectively, and was selected for further development.

The endothelial cell lining of blood vessels separates platelets in the circulating blood from thrombogenic structures in the vascular wall. In the case of the rupture of an atherosclerotic plaque or other lesions of the vascular wall, numerous external stimuli such as collagen, thrombin, adenosine diphosphate (ADP), and serotonin bind to specific receptors on the platelet membrane and trigger platelet aggregation. This activation includes the instantaneous release of arachidonic acid (AA) from the platelet membrane, which is rapidly converted to thromboxane A_2 (TXA_2)[1] (**1**) by two enzymes: cyclooxygenase catalyzes the transformation of AA to prostaglandin H_2 (PGH_2) (**2**), which is further converted to TXA_2 by the action of thromboxane A_2 synthetase. Both PGH_2 and TXA_2 easily diffuse out of platelets and bind to specific PGH_2/TXA_2 receptors,[2] thereby activating additional platelets in the local environment of a vessel wall injury. This positive feedback mechanism results in an almost explosive burst of PGH_2/TXA_2, which are both potent platelet-aggregating and vasoconstricting agents. Due to the rapid degradation of PGH_2 and TXA_2, no systemic activation occurs.

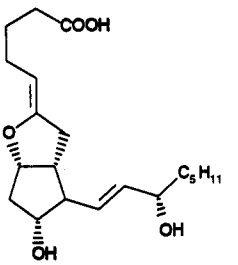


1 Thromboxane A_2 (TXA_2)



2 Prostaglandin H_2 (PGH_2)

Endothelial cells stimulated by thrombin, bradykinin, or other mediators also release AA from their membranes which, in contrast to platelets, is converted to prostaglandin I_2 (prostacyclin, PGI_2) (**3**) via PGH_2. PGI_2, by increasing intracellular cAMP, is the most potent endogenous inhibitor of platelet aggregation independent of the stimulus and a strong vasodilatory agent. It has been demonstrated[3-6] that PGH_2 released from activated platelets is the major precursor of PGI_2 produced by adjacent endothelial and smooth muscle cells. This shift of PGH_2 from activated platelets to adjacent cells of the vascular wall represents a highly effective local antithrombotic feedback mechanism.



3 Prostacyclin (PGI_2)

Many studies provide evidence that TXA_2 plays a crucial role in the pathogenesis of various circulatory and certain renal disorders.[7-9] Acetylsalicylic acid (ASA) was the first antiplatelet drug to become available. By inhibiting cyclooxygenase, ASA suppresses the formation not only of prothrombotic PGH_2 and TXA_2 but also of the antithrombotic agent PGI_2, even at very low doses.[10]

In order to overcome the lack of selectivity of cyclooxygenase inhibitors, thromboxane synthetase inhibitors (TxSI) and thromboxane receptor antagonists (TxRA) have been developed by numerous research groups.[11] Several clinical studies with TxSIs have demonstrated a reduction of TXA_2 metabolites and a significant elevation of PGI_2 metabolites due to the shift of PGH_2. First clinical results, however, have been disappointing. This lack of efficacy was explained by the fact that the accumulated PGH_2 mimicked the prothrombotic effects of TXA_2.[8]

Selective antagonists of the PGH_2/TXA_2 receptor offer another strategy for antithrombotic therapy. These drugs

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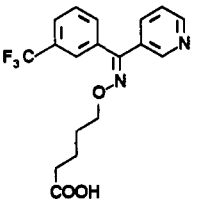
impede the actions of both PGH_2 and TXA_2 on platelet and vessel wall receptors without an increase of the local synthesis of antithrombotic prostaglandins.

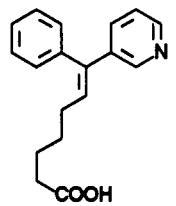
In theory, the combination of a TxSI and a TxRA should overcome the limitations of the single approaches. Recent studies in animals[4] and human volunteers[12] demonstrated that the combination was more effective than either compound alone with respect to the increased biosynthesis of PGI_2. Several compounds have been reported which combine both modes of action (TxSI + TxRA) in one molecule.[13] One of these, Ridogrel (R-68070) (4) is currently under clinical investigation.[14] A drawback of Ridogrel is its weak receptor antagonism (IC_{50}: 18 μM in the presence of plasma proteins) compared to its potent TxSI activity (IC_{50}L: 4 nM). We have therefore initiated a research program to synthesize compounds which exert both strong TXA_2 receptor blockade as well as synthetase inhibition.



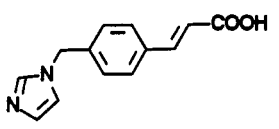
4 Ridogrel

Compound Design

TXA_2 synthetase from human platelets is a cytochrome P450 enzyme which contains 1 heme/polypeptide chain.[15] Essential structural features of TxSIs, like Ridogrel (4), Isbogrel (5), or Ozagrel (6), are a basic nitrogen atom of a 3-substituted pyridine or a *N*-substituted imidazole ring and a carboxylic group separated by a distance of 0.85–1 nm.[16] It was postulated that the pyridine or imidazole moiety forms a complex via the nitrogen atom with the heme group of the catalytic site of TXA_2 synthetase.[17] Following Isbogrel, we started with (*E*)-6-pyridylhex-5-enoic acid derivatives as the TXA_2-synthetase-inhibiting part of our compounds. If we assume a staggered conformation for the carboxyalkyl chain of compound **36**, the distance between the carbon atom of the carboxylic acid and the nitrogen atom of the pyridine ring is between 0.75 and 0.96 nm, dependent on the orientation of the pyridine ring.

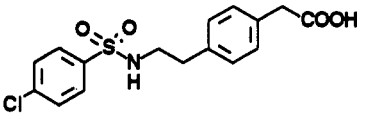


5 Isbogrel



6 Ozagrel

Numerous non-prostanoid TxRAs have a carboxylic acid and a benzenesulfonamide group separated by a spacer as common structural elements.[11] Daltroban (7) is a typical example of this class of TXA_2 antagonists. The correct orientation of a 3-substituted pyridine ring, a benzenesulfonamide group, and a carboxylic acid in one molecule should result in compounds with combined TXA_2 synthetase inhibition and receptor antagonism.



7 Daltroban

Chemistry

The compounds described in Tables 1–3 were prepared as depicted in the corresponding schemes. The ketones **8–10** were synthesized by a Friedel–Crafts acylation of the corresponding acetylated amines and nicotinic acid chloride in a melt of DMF and aluminum trichloride. Usual Friedel–Crafts conditions gave only poor yields. The ketones **8** and **9** were isolated as a mixture of the para, meta, and ortho isomers. After removal of the protecting group, the amines were reacted with sulfonic acid chlorides to yield the isomeric pure sulfonamides **11a,b** and **12–14** after recrystallization or column chromatography. They were then olefinated under Wittig conditions to give the acids **32–34**, **36**, **37**, **59–61**, **65**, **66**, and **74**. In all cases except for the compounds **65**, **66**, and **74**, the *E*- and *Z*-isomers could be separated by either column chromatography or recrystallization. The ratio of the diastereomers depended on the reaction temperature. Low temperatures favored the formation of the desired *E*-isomer. For compound **36**, we have found at −20 °C an *E*/*Z*-ration of 85:15 for the crude product which improved to 5000:1 after two recrystallization steps. The configuration at the C–C double bond was confirmed by NMR spectroscopy. The butenoic acid derivative **59** was obtained only in 12% yield due to the fact that the corresponding Wittig reagent gave predominantly acrylic acid on base treatment even at −40 °C. By catalytic hydrogenation of the double bond with palladium on charcoal, compounds **62–64** were obtained in about 50% yield. In this reaction, the consumption of hydrogen must be watched carefully to avoid reduction of the *p*-chlorophenyl moiety.

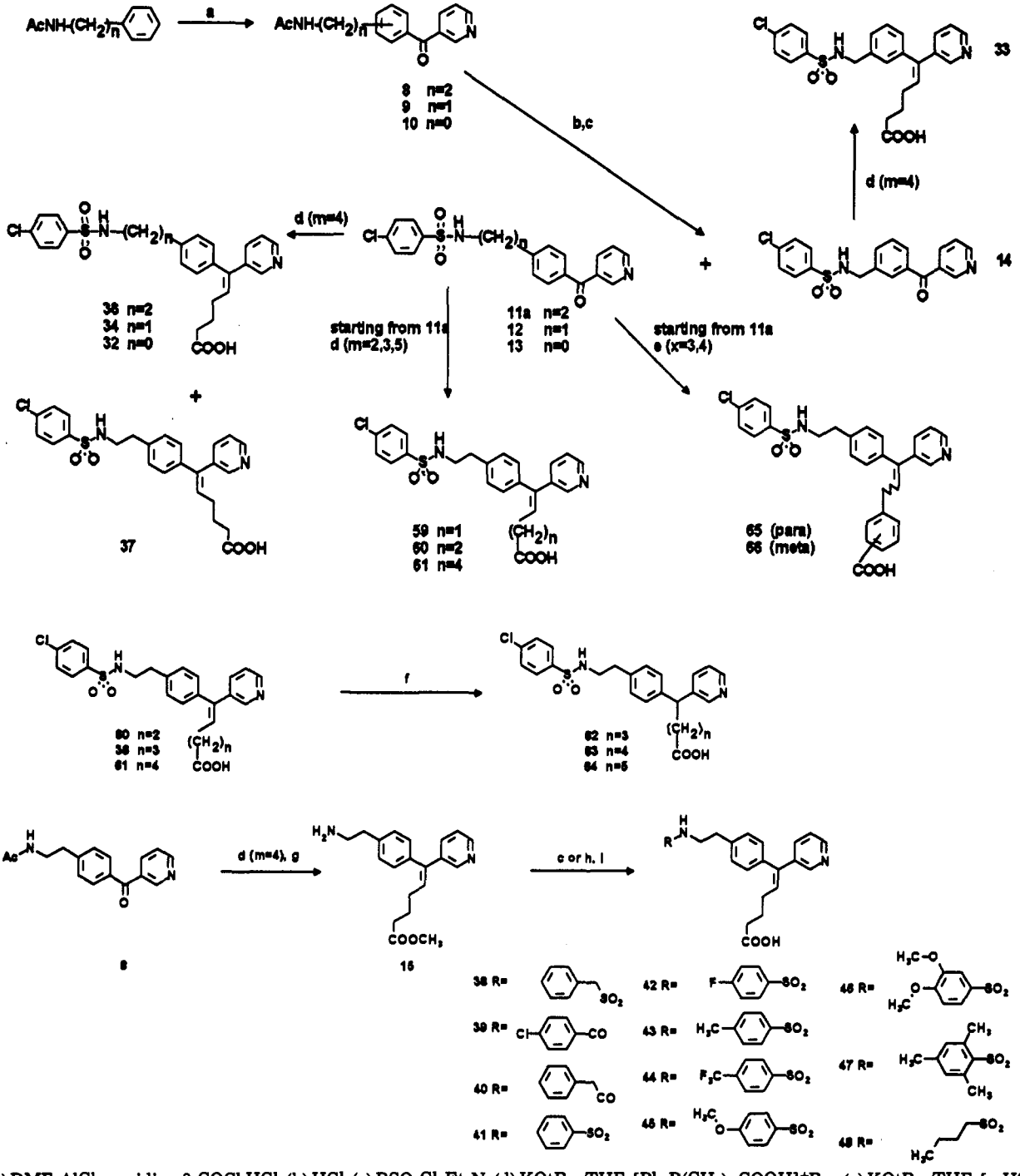
For a more convenient synthesis of the derivatives **38–48**, we prepared the intermediate **15** as a mixture of *E*/*Z*-isomers by olefination of **8** followed by deprotection of the amine and esterification by treatment with methanolic hydrochloric acid at room temperature. After sulfonylation/acylation of **15** and saponification of the esters, the isomeric pure (*E*) acids could be isolated by column chromatography.

The ylide for the preparation of the tetrazole derivative **74** (Scheme 2) was synthesized by refluxing (4-cyanobutyl)-triphenylphosphonium bromide with sodium azide in DMF. The corresponding ketone for the synthesis of **31** could easily be obtained from 3-benzoylpyridine by nitration, reduction,[18] and acetylation. Wittig reaction followed by deprotection and esterification with methanolic hydrochloric acid led to **16**, which was further reacted with *p*-chlorobenzenesulfonic acid chloride to give **31**.

For the regioselective preparation of **35**, we needed the ketone **17** which was obtained by lithiation with butyllithium of the Boc-protected 3-(2-aminoethyl)bromobenzene and reaction with nicotinic aldehyde followed by oxidation with activated MnO_2, according to Scheme 2. Deprotection with hydrochloric acid and sulfonylation gave **18** which was then transformed to **35** by a Wittig olefination reaction.

The oxime ether derivative **68** was prepared by alkylation of the corresponding oxime **19** with ethyl 2-bromopropionate. The yield of this transformation was only

Scheme 1[a]



[a] (a) DMF, $AlCl_3$, pyridine-3-COCl·HCl; (b) HCl; (c) RSO_2Cl, Et_3N; (d) KOtBu, THF, $[Ph_3P(CH_2)_mCOOH]^+Br^-$; (e) KOtBu, THF, [x-HOOC-$C_6H_4PPh_3]^+Br^-$; (f) H_2, Pd/C; (g) HCl, MeOH; (h) RCOCl, Et_3N; (i) NaOH.

6% due to preferred alkylation of the sulfonamide. The reaction of **11a** with hydroxylamine gave predominantly the undesired *Z*-isomer, but the *E*-isomer **19** could be separated by column chromatography in 10% yield. The stereochemistry was confirmed by X-ray analysis.

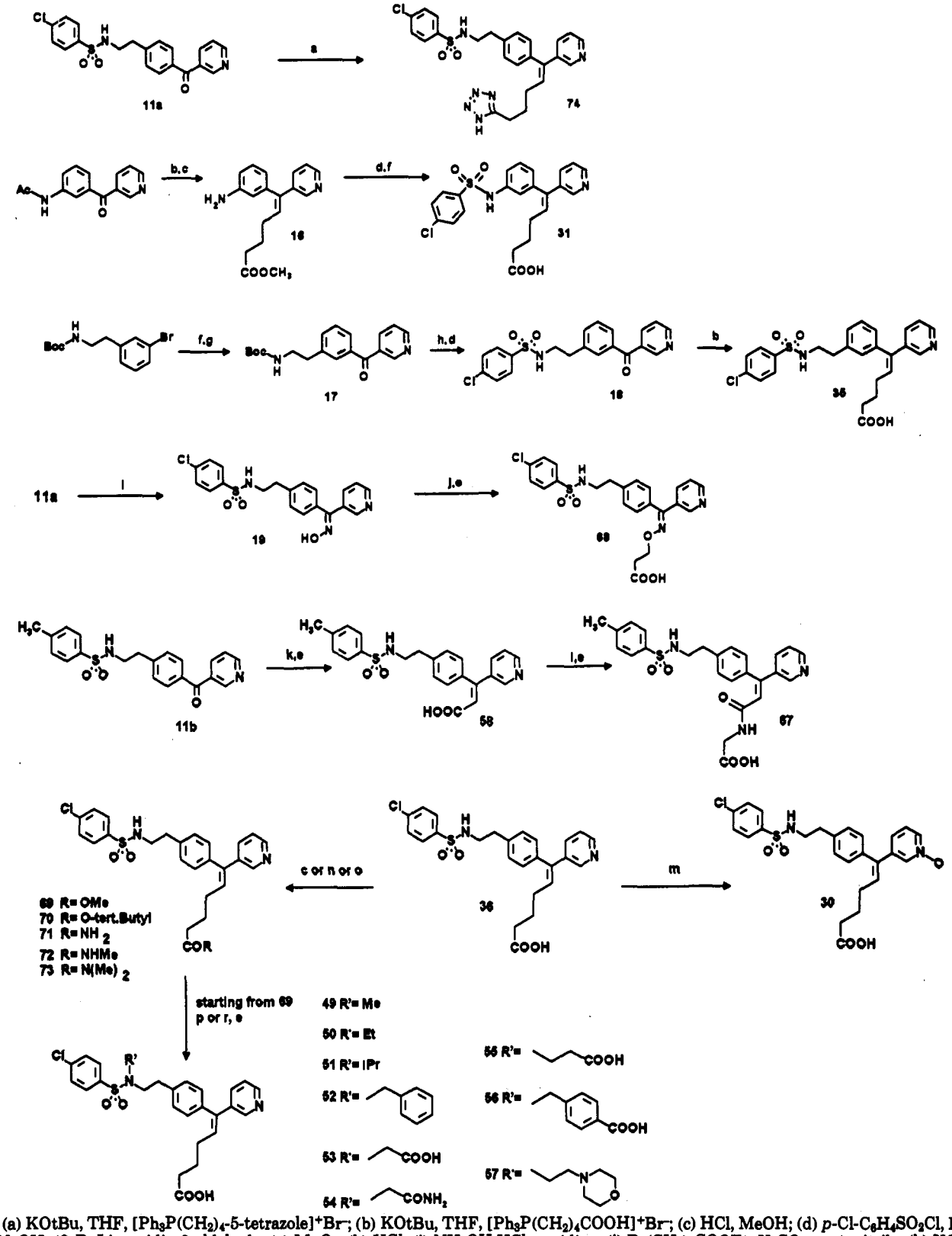
The acid **58** was obtained by a Wittig–Horner-type reaction starting from **11b**. **58** was further transformed to **67** by reaction with ethyl glycinate in the presence of *N,N'*-carbonyldiimidazole and subsequent saponification of the resulting ethyl ester.

Oxidation of **36** with 1 equiv of MCPBA at room temperature yielded exclusively the *N*-oxide **30** without epoxidation of the C–C double bond. The ester **69** was obtained by reaction of **36** with methanolic hydrochloric acid, whereas **70** was prepared by reaction of potassium *tert*-butoxide with the corresponding acid chloride which was formed in situ from **36** and oxalyl chloride. Reaction of **36** with ammonia, methylamine, or dimethylamine in the presence of *N,N'*-carbonyldiimidazole gave the amides **71–73**.

The *N*-substituted derivatives **49–57** were prepared by alkylation of **36** with the appropriate bromides or iodides in the presence of potassium *tert*-butoxide or by Michael addition to ethyl acrylate in the case of **55**.

The ketone **22** was obtained as depicted in Scheme 3 by acylation with nicotinic acid chloride in the absence of aluminum trichloride due to the well-known tendency of pyrroles to polymerize in the presence of Lewis acids.

Scheme 2[a]

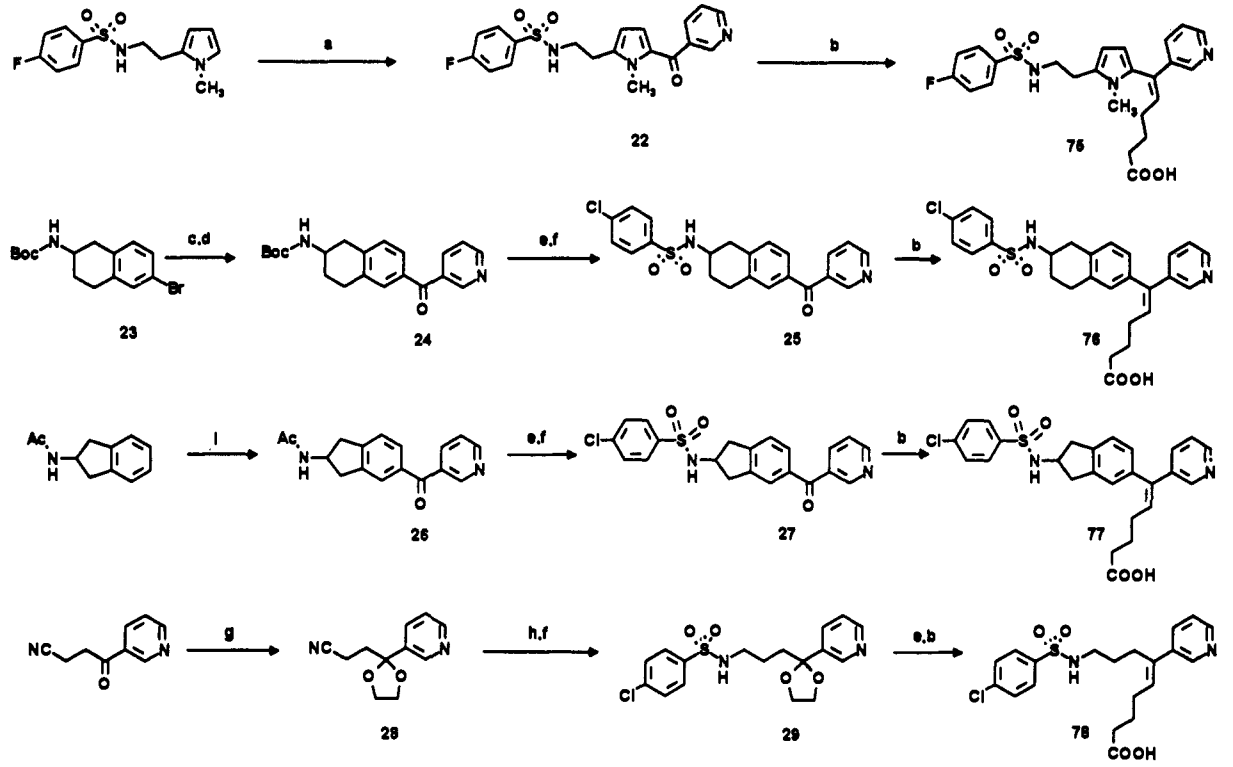


[a] (a) KOtBu, THF, $[Ph_3P(CH_2)_4$-5-tetrazole$]^+Br^-$; (b) KOtBu, THF, $[Ph_3P(CH_2)_4COOH]^+Br^-$; (c) HCl, MeOH; (d) p-Cl-$C_6H_4SO_2Cl$, Et_3N; (e) NaOH; (f) BuLi, pyridin-3-aldehyde; (g) MnO_2; (h) HCl; (i) NH_2OH·HCl, pyridine; (j) $Br(CH_2)_2COOEt$, K_2CO_3, acetonitrile; (k) KOtBu, THF, $(EtO)_2POCH_2COOEt$; (l) CDI, THF, H_2NCH_2COOEt; (m) MCPBA, $CHCl_3$; (n) ClCOCOCl, CH_2Cl_2, KOtBu; (o) CDI, THF, NH_3/NH_2CH_3/$NH(CH_3)_2$; (p) KOtBu, RX (X = Br, I); (r) Triton B, DMF, methyl acrylate.

The tetrahydronaphthalene derivative **23** was prepared by reduction of the corresponding oximino precursor with $TiCl_3/NaBH_4$ followed by protection of the resulting amine as *tert*-butyl carbamate. Attempts to reduce with $LiAlH_4$ resulted only in a complex mixture of products. Metalation of **23** with 2 equiv of butyllithium and reaction with pyridin-3-aldehyde followed by oxidation of the resulting alcohol with activated manganese dioxide gave the ketone **24** in a yield of 41%. Deprotection of the amino group, sulfonylation, and Wittig reaction yielded compound **76**.

Friedel–Crafts acylation of 2-(acetylamino)indan with nicotinic acid chloride, according to the preparation of **8**, gave the ketone **26** which was further converted to **27** by cleavage of the acetyl group and reaction with *p*-chlo-

Scheme 3[a]



[a] (a) Pyridine-3-COCl; DMF; (b) KOtBu, THF, $[Ph_3P(CH_2)_4COOH]^+Br^-$; (c) BuLi, pyridin-3-aldehyde; (d) MnO_2; (e) HCl; (f) p-Cl-$C_6H_4SO_2Cl$, Et_3N; (g) $HO(CH_2)_2OH$, TsOH; (h) H_2, Ra-Ni; (i) pyridine-3-COCl, $AlCl_3$, DMF.

robenzenesulfonic acid chloride. After Wittig olefination of **27** and separation of the geometrical isomers by column chromatography, **77** could be isolated in 51% yield.

Starting from 2-cyanoethyl 3-pyridyl ketone,[19] the intermediate **29** was obtained via **28** as depicted in Scheme 3. After removal of the protecting group with hydrochloric acid, the resulting ketone was olefinated to gave **78** in 40% yield.

In Vitro Pharmacology

The compounds described above were initially tested in the following three 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, (b) inhibition of TXB_2 formation by human gel-filtered platelets incubated with [^{14}C]arachidonic acid, and (c) inhibition of collagen-induced platelet aggregation in human platelet-rich plasma (PRP).

The test results are listed as IC_{50}/EC_{50} values in Tables 1–3. TXA_2 synthetase inhibition in intact platelets demonstrates that the test compounds could penetrate the cell membrane. Starting from 6-phenyl-6-(3-pyridyl)-hex-5-enoic acid as the TXA_2-synthetase-inhibiting moiety, we first examined in which way the benzenesulfonamide part must be added for potent TXA_2 antagonistic activity. Independent of the position of the 4-chlorobenzenesulfonamide group, all compounds **31–36** are potent TxSIs, indicating that the TxSI activity is not influenced by the substitution pattern in the phenyl ring. As expected, the oxidation of **36** to the *N*-oxide **30** is associated with a reduction in TxSI activity by a factor of 10 000. The most potent receptor antagonistic activity was found in compounds **35** and **36** which differ only in the regiochemistry on the phenyl ring.

The large discrepancy between the affinities of **31** and **32** for the PGH_2/TXA_2 receptor and the EC_{50} for the inhibition of platelet aggregation is presumably a consequence of high protein binding in the aggregation assay where plasma proteins are present. For the compound **32**, the IC_{50} value of 0.27 μM increases to more than 100 μM if plasma proteins are added to the receptor binding assay.

The importance of the *E*-configuration of the double bond is demonstrated by isomers **36** and **37**. Receptor antagonistic as well as synthetase inhibitory activities are significantly reduced by the change from the *E*- to the *Z*-configuration.

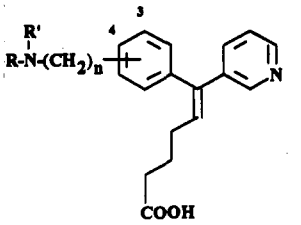
After identification of compound **36** as a potent TxRA and TxSI, we investigated the importance of the sulfonamide element. Replacement of the sulfonamide by a carboxamide (**36** → **39**; **38** → **40**) is associated by a decrease in both TxRA and TxSI activities. This effect could be explained by the different conformation of a sulfonamide compared to that of a carboxamide.

Substitution of the chlorine atom in the para position by a fluorine atom (**42**) or a methyl (**43**), trifluoromethyl (**44**), or methoxy (**45**) group has only a minor influence on both activities. The introduction of additional lipophilic substituents (**46** and **47**) results in a clearly reduced inhibition of collagen-induced platelet aggregation, presumably due to increased protein binding.

Replacement of the hydrogen atom of the sulfonamide group by simple alkyl groups (**49–51**) does not affect the TxRA and TxSI activities very significantly. Further substituents of various sizes and functionalities at the nitrogen atom (**52–57**) are relatively well tolerated, indicating a steric tolerance within this part of compound **36**.

To get deeper insight into the structure–activity relationships of **36**, we have varied the length of the carboxyalkyl chain. As expected, the propenoic acid **58** and the butenoic acid derivative **59** are weak TxSIs since the maximal distances between the carboxylic acid group and

Table 1. Physical Constants and in Vitro Activity of Compounds 30–57[a]



no.	R	R'	n	postn	config	formula	mp (°C)	IC50 (μM) TXA2 receptor antagonism	IC50 (μM) TXA2 synthetase inhibition	inhibn of collagen-induced plat aggreg EC50 (μM)
30	4-Cl-$C_6H_4SO_2$ (*N*-oxide)	H	2	4	*E*	$C_{25}H_{25}ClN_2O_5S$	122–124	1.1	45	>100
31	4-Cl-$C_6H_4SO_2$	H	0	3	*E*	$C_{23}H_{21}ClN_2O_4S$	187–188	0.06	0.007	40
32	4-Cl-$C_6H_4SO_2$	H	0	4	*E*	$C_{25}H_{21}ClN_2O_4S$	109–111	0.27	0.005	>100
33	4-Cl-$C_6H_4SO_2$	H	1	3	*E*	$C_{24}H_{23}ClN_2O_4S$	148	0.021	0.005	3.8
34	4-Cl-$C_6H_4SO_2$	H	1	4	*E*	$C_{24}H_{23}ClN_2O_4S$	172	0.055	0.007	5.0
35	4-Cl-$C_6H_4SO_2$	H	2	3	*E*	$C_{25}H_{25}ClN_2O_4S$	127–128	0.012	0.004	1.7
36	4-Cl-$C_6H_4SO_2$	H	2	4	*E*	$C_{25}H_{25}ClN_2O_4S$	164	0.019	0.004	1.0
37	4-Cl-$C_6H_4SO_2$	H	2	4	*Z*	$C_{25}H_{25}ClN_2O_4S$	94–95	0.38	0.49	43
38	$PhCH_2SO_2$	H	2	4	*E*	$C_{25}H_{28}N_2O_4S$	oil	0.26	0.005	5.3
39	4-Cl-C_6H_4CO	H	2	4	*E*	$C_{25}H_{25}ClN_2O_3$	144–145	0.21	0.043	55
40	$PhCH_2CO$	H	2	4	*E*	$C_{27}H_{28}N_2O_3$	88–90	1.2	0.021	9.5
41	$PhSO_2$	H	2	4	*E*	$C_{25}H_{28}N_2O_4S$	99–101	0.081	0.005	3.4
42	4-F-$C_6H_4SO_2$	H	2	4	*E*	$C_{25}H_{25}FN_2O_4S$	foam	0.066	0.004	3.1
43	4-Me-$C_6H_4SO_2$	H	2	4	*E*	$C_{26}H_{28}N_2O_4S$	foam	0.033	0.005	0.7
44	4-CF_3-$C_6H_4SO_2$	H	2	4	*E*	$C_{25}H_{25}F_3N_2O_4S$	140–142	0.028	0.006	2.8
45	4-MeO-$C_6H_4SO_2$	H	2	4	*E*	$C_{26}H_{28}N_2O_5S$	104–106	0.052	0.005	10
46	3,4-$(MeO)_2$-$C_6H_3SO_2$	H	2	4	*E*	$C_{27}H_{30}N_2O_6S$	foam	0.34	0.005	16
47	2,4,6-Me_3-$C_6H_2SO_2$	H	2	4	*E*	$C_{28}H_{32}N_2O_4S$	79–82	0.042	0.019	30
48	*n*-$C_4H_9SO_2$	H	2	4	*E*	$C_{23}H_{30}N_2O_4S$	84–86	1.1	0.005	3.4
49	4-Cl-$C_6H_4SO_2$	Me	2	4	*E*	$C_{26}H_{27}ClN_2O_4S$	157–158	0.025	0.015	24
50	4-Cl-$C_6H_4SO_2$	Et	2	4	*E*	$C_{27}H_{29}ClN_2O_4S$	83–84	0.033	0.004	13
51	4-Cl-$C_6H_4SO_2$	iPr	2	4	*E*	$C_{28}H_{31}ClN_2O_4S$	108–109	0.051	0.025	>100
52	4-Cl-$C_6H_4SO_2$	benzyl	2	4	*E*	$C_{32}H_{31}ClN_2O_4S$	82–84	0.062	0.043	11
53	4-Cl-$C_6H_4SO_2$	$HOOCCH_2$	2	4	*E*	$C_{27}H_{27}ClN_2O_6S$	158–160	0.061	0.31	44
54	4-Cl-$C_6H_4SO_2$	H_2NCOCH_2	2	4	*E*	$C_{27}H_{28}ClN_3O_5S$	177–178	0.049	0.005	9.2
55	4-Cl-$C_6H_4SO_2$	$HOOCCH_2CH_2$	2	4	*E*	$C_{28}H_{29}ClN_2O_6S$	183–184	0.12	0.1	>100
56	4-Cl-$C_6H_4SO_2$	4-$HOOCC_6H_4CH_2$	2	4	*E*	$C_{33}H_{31}ClN_2O_6S$	147	0.028	0.046	>100
57	4-Cl-$C_6H_4SO_2$	$O(CH_2CH_2)_2NCH_2CH_2$	2	4	*E*	$C_{31}H_{36}ClN_3O_5S$	113–114	0.058	0.004	21
4	Ridogrel					$C_{16}H_{17}F_3N_2O_3$		1.7[b]	0.004[c]	16
20	CGS-22652					$C_{22}H_{29}ClN_2O_4S$		0.006	0.006[d]	5.8

[a] For details, see the Experimental Section. [b] 5.2 μM (ref 14f). [c] 0.008 μM (ref 14b). [d] 0.004 μM (ref 13q).

the pyridine nitrogen atom are only 0.62 and 0.73 nm, respectively. It is remarkable that with the exception of **58**, the butenoic, pentenoic, hexenoic, and heptenoic acid derivatives **59**, **60**, **36**, and **61** are all potent TxRAs though the length of the alkyl chain differs by three methylene groups.

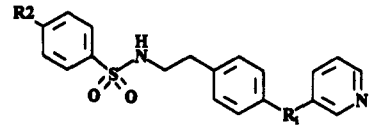
Reduction of the double bond (**62**–**64**) is associated by a decrease of TxRA activity, whereas the TxSI activity is reduced only in the case of **62** and **64**. Replacement of the flexible alkyl chain by a more rigid benzene ring (**65** and **66**) weakens the TxRA activity in comparison to that in **36**. The introduction of an amide function into the carboxyalkyl chain (**67**) is deleterious for both TxRA and TxSI activities. Assuming that the carboxyalkyl chain of compound **36** mimicks the α-chain of TXA_2 (**1**), we could understand that polar groups in this part of the molecule are not well tolerated. Replacement of the C–C double bond by an oxime ether function (**68**) similar to Ridogrel is compatible with potent receptor antagonism but results in a 15-fold reduced synthetase inhibitory activity.

The methyl ester of compound **36** (**69**) is an unexpected potent TxRA and TxSI, presumably due to partial hydrolysis to the corresponding acid **36** under the assay conditions. This assumption is confirmed by the decreased receptor affinity and synthetase inhibitory activity of the more stable *tert*-butyl ester **70**. The carboxylic acid could be exchanged for a tetrazole group (**74**) without a loss of TxRA potency but with a 5-fold decrease in TxSI activity.

Replacement of the benzene ring by a *N*-methylpyrrole (**75**) does not impair TxSI activity but receptor binding. TXA_2 receptor affinity could be slightly improved in comparison to that of **36** by fixation of the *p*-chlorobenzenesulfonamide group in a more rigid tetralin (**76**) or indane (**77**) ring system, whereas a more flexible system represented by compound **78** results in a decrease of TXA_2 receptor affinity.

After we had filed a patent[13v] claiming compound **36** and the analogues, Bhagwat et al.[13e,m–q] published combined thromboxane A_2 antagonists/synthetase inhibitors which are structurally similar to our compounds. They have connected the three essential structural elements (benzenesulfonamide, pyridine ring, and carboxylic acid) by a branched alkyl chain. One of the most potent compounds from this series, **20** (CGS-22652), blocks the TXA_2 receptor on gel-filtered platelets and the TXA_2 synthetase with an IC_{50} of 6 nM in our assays. In the presence of plasma proteins, however, the antagonistic activity (IC_{50}) is reduced from 6 to 1200 nM, presumably due to a high plasma-protein binding[13q] which explains the surprisingly moderate inhibition of the collagen-induced platelet aggregation (IC_{50}: 5.8 μM). A further

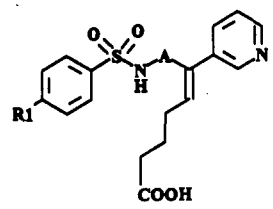
Table 2. Physical Constants and in Vitro Activity of Compounds 58–74[a]

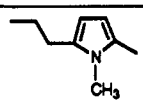
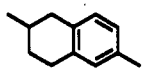
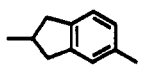


no.	R1	R2	config	formula	mp (°C)	IC_{50} (μM) TXA_2 receptor antagonism	IC_{50} (μM) TXA_2 synthetase inhibition	inhibn of collagen-induced plat aggreg EC_{50} (μM)
58	HOOCCH=C	Me	*E*	$C_{23}H_{22}N_2O_4S$	169–171	1.2	2.7	>100
59	$HOOCCH_2CH$=C	Cl	*E*	$C_{23}H_{21}ClN_2O_4S$	203	0.012	1.0	37
60	$HOOC(CH_2)_2CH$=C	Cl	*E*	$C_{24}H_{23}ClN_2O_4S$	154–155	0.042	0.021	36
61	$HOOC(CH_2)_4CH$=C	Cl	*E*	$C_{26}H_{27}ClN_2O_4S$	foam	0.019	0.024	1.5
62	$HOOC(CH_2)_3CH$	Cl	*R/S*	$C_{24}H_{25}ClN_2O_4S$	70	0.074	0.098	12
63	$HOOC(CH_2)_4CH$	Cl	*R/S*	$C_{25}H_{27}ClN_2O_4S$	foam	0.084	0.002	1.2
64	$HOOC(CH_2)_5CH$	Cl	*R/S*	$C_{26}H_{29}ClN_2O_4S$	foam	0.21	0.031	1.2
65	4-HOOC-C_6H_4CH=C	Cl	*E/Z*	$C_{28}H_{23}ClN_2O_4S$		0.13	0.027	52
66	3-HOOC-C_6H_4CH=C	Cl	*E/Z*	$C_{28}H_{23}ClN_2O_4S$		0.1	0.004	30
67	$HOOCCH_2NHCOCH$=C	Me	*E*	$C_{25}H_{25}N_3O_5S$	104–106	3.0	15	>100
68	$HOOC(CH_2)_2ON$=C	Cl	*E*	$C_{23}H_{22}ClN_3O_5S$	109–110	0.026	0.06	4.3
69	$MeOOC(CH_2)_3CH$=C	Cl	*E*	$C_{26}H_{27}ClN_2O_4S$	88–89	0.036	0.033	11
70	t-$BuOOC(CH_2)_3CH$=C	Cl	*E*	$C_{29}H_{33}ClN_2O_4S$	103–104	0.2	0.15	60
71	$H_2NCO(CH_2)_3CH$=C	Cl	*E*	$C_{25}H_{26}ClN_3O_3S$	104–105	0.094	0.039	28
72	$MeHNCO(CH_2)_3CH$=C	Cl	*E*	$C_{26}H_{28}ClN_3O_3S$	102–103	0.17	0.25	24
73	$Me_2NCO(CH_2)_3CH$=C	Cl	*E*	$C_{27}H_{30}ClN_3O_3S$	131–132	0.3	0.044	40
74	5-tetrazolyl$(CH_2)_3CH$=C	Cl	*E/Z*	$C_{25}H_{25}ClN_6O_2S$	foam	0.012	0.021	9.5

[a] For details, see the Experimental Section.

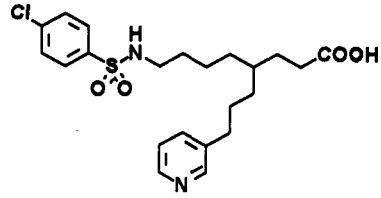
Table 3. Physical Constants and in Vitro Activity of Compounds 75–78[a]



no.	A	R1	config	formula	mp (°C)	IC_{50} (μM) TXA_2 receptor antagonism	IC_{50} (μM) TXA_2 synthetase inhibition	inhibn of collagen-induced plat aggreg EC_{50} (μM)
75		F	*E*	$C_{24}H_{26}FN_3O_4S$	190	0.23	0.004	1.1
76		Cl	*E*	$C_{27}H_{27}ClN_2O_4S$	172–174	0.013	0.008	5.0
77		Cl	*E*	$C_{26}H_{25}ClN_2O_4S$	75 dec	0.009	0.001	0.56
78	$CH_2CH_2CH_2$	Cl	*E*	$C_{20}H_{23}ClN_2O_4S$	112–113	0.33	0.024	47

[a] For details, see the Experimental Section.

shortcoming of this compound is the fact that it represents a racemate.



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36 as a potent TXA_2 receptor antagonist and TXA_2 synthetase inhibitor was also tested in vitro for collagen-induced platelet aggregation inhibition in human whole blood and showed an IC_{50} of 90–130 nM. This effect cannot be explained by phosphodiesterase inhibition because the IC_{50} is in the micromolar range (34 μM). Similarly, a decrease of the elevated 6-keto-PGF_{1a} levels in whole blood after collagen stimulation was seen starting only at the high concentration of 30 μM **36** which was interpreted as the beginning of cyclooxygenase inhibition (see Table 4). This result is important since a functioning cyclooxygenase is vital for the endoperoxide shift to occur; an inhibition of this enzyme at therapeutic concentrations would result in the loss of the benefit of the combined mechanisms.

After oral administration (10 mg/kg) of **36** in rats, we have found plasma levels, measured by HPLC, of 1025 ±

Table 4. 6-Keto-PGF_{1a} Levels in Collagen-Stimulated Human Whole Blood in the Presence of Increasing Amounts of Compound 36[a]

36 (nM)	c[b]	coll[c]	0.1	0.3	1.0	3.0	10	30	100	300
6k[d] (pg/mL)	59	330	416	641	812	995	1099	1430	1342	1669
36 (μM)	1	3	10	30	100	300				
6k (pg/mL)	1371	1204	1284	1221	1008	644				

[a] For details, see the Experimental Section. [b] Control. [c] Collagen only. [d] 6-Keto-PGF_{1a}.

102 ng/mL (n = 3) at 1 h which declined to 150 ± 86 ng/mL (n = 3) after 8 h. By comparison with the plasma levels after iv administration of 10 mg/kg (data not shown), we calculated an absolute bioavailability of 35%.

Conclusion

We succeeded in the synthesis of combined TXA_2 receptor antagonists and synthetase inhibitors by integration of essential structural elements of pure TxRAs and TxSIs in one molecule. One of the most active compounds, **36**, binds to the PGH_2/TXA_2 receptor and inhibits the TXA_2 synthetase in the lower nanomolar range. Compound **36** is highly selective with respect to platelet cyclooxygenase and phosphodiesterase inhibition. Due to its potent antiaggregatory activity in human platelet-rich plasma as well as in whole blood, **36** was selected for further development.

Experimental Section

(a) Chemistry. Melting points were determined in a Büchi capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on Bruker AC200 and Bruker AMX400 instruments. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on a Finnigan MAT 8230 or a AEI MS-902 mass spectrometer in either EI or fast-atom-bombardment mode. Microanalyses were performed on a CHN-Rapid (Heraeus). Silica gel (Baker, 30–60 μm) was used for column chromatography. TLC was performed on silica gel plates (Macherey-Nagel Polygram Sil G/UV 254 or Merck, silica gel 60, F-254).

4-(2-(Acetylamino)ethyl)phenyl 3-Pyridyl Ketone (8). $AlCl_3$ (180 g, 1.35 mol) is mixed with 35 mL of DMF, and the temperature rises to 70 °C. Then, 67 g (0.38 mol) of nicotinic acid chloride hydrochloride are added followed by 49 g (0.3 mol) of (2-(acetylamino)ethyl)benzene at 90 °C. After 2 h, the mixture is cooled and 60 mL of ethylene chloride are added. The mixture is poured onto ice water and 180 mL of concentrated HCl and washed three times with $CHCl_3$. The aqueous phase is made alkaline with NaOH and then extracted three times with ethylene chloride. The organic phase is dried and rotary-evaporated to yield 70 g as an oil which consists of 8 (78%), the meta isomer (14%), and the ortho isomer (8%) (HPLC). An analytical sample was twice recrystallized from toluene: mp 80–83 °C; ^{1}H NMR ($CDCl_3$) 1.97 (s, 6H), 2.92 (t, 2H), 3.55 (q, 2H), 5.5 (s, 1H), 7.35 (d, 2H), 7.45 (dd, 1H), 7.8 (d, 2H), 8.1 (dt, 1H), 8.82 (dd, 1H), 9.0 (d, 1H); IR (CH_2Cl_2) 3460 (NH), 1665 (C=O) cm^{-1}. Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

4-((Acetylamino)methyl)phenyl 3-Pyridyl Ketone (9). The analogous preparation to 8 yields an oil which consists of 9 (60%) and the meta isomer (40%). An analytical sample of 9 was obtained by recrystallization from EtOAc/diisopropyl ether: mp 92 °C; ^{1}H NMR ($CDCl_3$) 2.1 (s, 3H), 4.55 (d, 2H), 6.0 (s, 1H), 7.4–7.5 (m, 3H), 7.8 (d, 2H), 8.1 (dt, 1H), 8.8 (d, 1H), 9.0 (s, 1H); IR (CH_2Cl_2) 3460 (NH), 1665 (C=O) cm^{-1}. Anal. ($C_{15}H_{14}N_2O_2$) C, H, N.

4-(Acetylamino)phenyl 3-Pyridyl Ketone (10). Its preparation is analogous to 8, yield 44%: mp 190 °C (methanol); ^{1}H NMR (DMSO-d_6) 2.1 (s, 3H), 7.6 (dd, 1H), 7.8 (s, 4H), 8.1 (dt, 1H), 8.8–8.9 (m, 2H), 10.35 (s, 1H); IR (CH_2Cl_2) 3450 (NH), 1665 + 1650 (C=O) cm^{-1}. Anal. ($C_{14}H_{12}N_2O_2$) C, H, N.

4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl 3-Pyridyl Ketone (11a). A 155-g portion (0.58 mol) of the mixture containing 8 and its isomers (see above) are dissolved in 800 mL of 6 N HCl and are refluxed for 16 h. The reaction mixture is concentrated by evaporation, and the residue is dissolved in a mixture of 200 mL of water, 500 mL of dioxane, and 50 g of $NaHCO_3$; 126 g (0.6 mol) of 4-chlorobenzenesulfonic acid chloride in 150 mL of dioxane and 10 N NaOH are slowly added in such a way that the pH value is between 8–10. The reaction mixture is poured onto ice, and the precipitate is suction-filtered and recrystallized from toluene, followed by a second recrystallization from ethanol to yield 92.5 g (40%) of 11a: mp 157 °C; ^{1}H NMR (DMSO-d_6) 2.9 (t, 2H), 3.3 (q, 2H), 4.65 (s, 1H), 7.25 (d, 2H), 7.4–7.5 (m, 3H), 7.7–7.8 (m, 4H), 8.1 (dt, 1H), 8.8 (dd, 1H), 8.95 (d, 1H); IR (CH_2Cl_2) 3370 (NH), 1665 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{20}H_{17}ClN_2O_3S$) C, H, N, Cl, S.

4-((((4-Chlorophenyl)sulfonyl)amino)methyl)phenyl 3-Pyridyl Ketone (12) and 3-((((4-Chlorophenyl)sulfonyl)amino)methyl)phenyl 3-Pyridyl Ketone (14). To a mixture of 27.6 g (0.11 mol) of 9 and the meta isomer (see above) and 27.6 g (0.13 mol) of 4-chlorobenzenesulfonic acid chloride in 250 mL of DMF is added 5 mL of triethylamine. After 48 h, the solvent is evaporated down and the residue is separated by column chromatography using petroleum ether/EtOAc 1:1 as eluant to give 6.2 g (14%) of 14 and 4.1 g (8%) of 12. 12: mp 116 °C (EtOAc/diisopropyl ether); ^{1}H NMR (DMSO-d_6) 4.15 (s, 2H), 7.45 (d, 2H), 7.55–7.85 (m, 6H), 8.1 (dt, 1H), 8.4 (s, 1H), 8.85 (m, 2H); IR (KBr) 1655 (C=O), 1335 + 1155 (SO_2) cm^{-1}. Anal. ($C_{19}H_{15}ClN_2O_3S$) C, H, N, Cl, S. 14: mp 149 °C (EtOAc); ^{1}H NMR (DMSO-d_6) 4.15 (s, 2H), 7.45–7.65 (m, 7H), 7.75 (d, 2H), 8.1 (dt, 1H), 8.4 (s, 1H), 8.85 (m, 2H); IR (KBr) 1655 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{19}H_{15}ClN_2O_3S$) C, H, N, Cl, S.

4-(((4-Chlorophenyl)sulfonyl)amino)phenyl 3-Pyridyl Ketone (13). A 24-g portion (0.1 mol) of 10 is refluxed for 1 h in 200 mL of 6 N HCl. The solvent is evaporated down, and the residue is dissolved in 280 mL of CH_2Cl_2. To this solution is added 21.1 g (0.1 mol) of 4-chlorobenzenesulfonic acid chloride followed by 60 mL of Et_3N. After 2 h, the mixture is washed with water and the organic phase is dried and rotary-evaporated. The residue is purified by silica chromatography using CH_2Cl_2/acetone 19:1 as eluant and by recrystallization from ethanol to yield 12.2 g (33%) of 13: mp 196 °C; ^{1}H NMR (DMSO-d_6) 7.3 (d, 2H), 7.55 (dd, 1H), 7.6–7.8 (m, 4H), 7.85 (d, 2H), 8.05 (dt, 1H), 8.8 (m, 2H), 11.0 (s, 1H); IR (KBr) 1650 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{16}H_{13}ClN_2O_3S$) C, H, N, Cl, S.

(*E*/*Z*)-Methyl 6-(4-(2-Aminoethyl)phenyl)-6-(3-pyridyl)-hex-5-enoate (15). At −40 °C, 52.8 g (0.2 mol) of 8 is added to a suspension of 115.3 g (0.26 mol) of (4-carboxybutyl)triphenylphosphonium bromide and 80.8 g (0.72 mol) of potassium *tert*-butoxide in 700 mL of THF and the mixture is stirred for 2 h. The reaction mixture is decomposed by the addition of ice water and evaporated down. The residue is taken up in water and washed with EtOAc. The aqueous phase is acidified to pH 5–6 (citric acid) and extracted with EtOAc. The organic phase is dried and evaporated down, and the residue is dissolved in 200 mL of 6 N HCl. The solution is refluxed for 18 h and concentrated by evaporation, and the residue is dissolved in 300 mL of saturated methanolic hydrochloric acid. After 1 h, the reaction mixture is evaporated down, mixed with 500 mL of water, and neutralized by the addition of sodium carbonate. The aqueous phase is extracted with CH_2Cl_2, and the organic phase is dried and concentrated by evaporation to yield 34 g (52%) of 15 as a mixture of isomers, E/Z = 6:1; oil: ^{1}H NMR of the main component ($CDCl_3$) 1.8 (quint, 2H), 2.15–2.35 (m, 4H), 2.75 (t, 2H), 3.0 (t, 2H), 3.6 (s, 3H), 6.05 (t, 1H), 7.05–7.25 (m, 5H), 7.45 (dt, 1H), 8.45 (dd, 1H), 8.5 (d, 1H); IR (CH_2Cl_2) 1735 (C=O) cm^{-1}. Anal. ($C_{20}H_{24}N_2O_2$) C, H, N.

(*E*)-Methyl 6-(3-Aminophenyl)-6-(3-pyridyl)hex-5-enoate (16). 16 is prepared according to the synthesis of 15 starting

from 3-(acetylamino)phenyl 3-pyridyl ketone and (4-carboxybutyl)triphenylphosphonium bromide, yield 60%; oil: ^{1}H NMR ($CDCl_3$) 1.8 (quint, 2H), 2.2 (q, 2H), 2.3 (t, 2H), 3.6 (s, 3H), 3.7 (s, 2H), 6.05 (t, 1H), 6.45 (d, 1H), 6.55 (d, 1H), 6.65 (dd, 1H), 7.1–7.2 (m, 2H), 7.45 (dt, 1H), 8.45 (dd, 1H), 8.55 (d, 1H); IR (CH_2Cl_2) 3470 + 3390 (NH_2), 1735 (C=O) cm^{-1}. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl 3-Pyridyl Ketone (17). A 80-mL volume (0.2 mol) of butyllithium (2.5 M in hexane) is slowly added to 25 g (80 mmol) of 3-(2-((*tert*-butoxycarbonyl)amino)ethyl)bromobenzene in 400 mL of THF at −70 °C. The mixture is stirred for 30 min, and then, 8.6 g (80 mmol) of pyridin-3-aldehyde is slowly added. After being stirred for 2 h, the reaction mixture is poured on ice water and the aqueous phase is extracted with EtOAc. The organic phase is dried and evaporated down, and the residue is dissolved in a mixture of chloroform and 200 g of manganese dioxide. The suspension is stirred for 2 h and then filtered with suction. The filtrate is evaporated down, and the residue is chromatographed on silica gel with CH_2Cl_2/acetone 9:1 to yield 10.2 g (39%) of 17 as an oil: ^{1}H NMR ($CDCl_3$) 1.4 (s, 9H), 2.9 (t, 2H), 3.4 (q, 2H), 7.4–7.5 (m, 3H), 7.65 (m, 2H), 8.1 (dt, 1H), 8.8 (dd, 1H), 9.0 (d, 1H); IR (CH_2Cl_2) 3450 (NH), 1710 + 1665 (C=O) cm^{-1}. Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

3-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl 3-Pyridyl Ketone (18). A 10-g portion (30 mmol) of 17 in 80 mL of 2 N HCl is heated to 40 °C for 1 h. The reaction mixture is evaporated down, and the residue is suspended in 150 mL of CH_2Cl_2. To this suspension is added 6.6 g (31 mmol) of 4-chlorobenzenesulfonic acid chloride followed by 20 mL of triethylamine. The reaction mixture is stirred for 1 h, washed with water, and evaporated down. The residue is crystallized from EtOAc/diisopropyl ether to give 6.95 g (56%) of 18: mp 127–128 °C; ^{1}H NMR ($CDCl_3$) 2.9 (t, 2H), 3.3 (q, 2H), 4.75 (t, 1H), 7.35–7.5 (m, 5H), 7.6 (s, 1H), 7.65 (dd, 1H), 7.75 (d, 2H), 8.1 (dt, 1H), 8.8 (dd, 1H), 8.95 (d, 1H); IR (CH_2Cl_2) 3370 (NH), 1665 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{20}H_{17}ClN_2O_3S$) C, H, N, Cl, S.

(*E*)-4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl) 3-Pyridyl Ketoxime (19). A mixture of 58 g (0.14 mol) of 11a, 12.6 g (0.18 mol) of hydroxylamine hydrochloride, 250 mL of ethanol, and 75 mL of pyridine is refluxed for 1 h. The reaction mixture is cooled, and the precipitate which consists predominately of the *Z*-isomer is filtered with suction. The mother liquid is concentrated to give an additional amount of the *Z*-isomer. The mother liquid is evaporated down, and the residue is twice chromatographed on silica gel using CH_2Cl_2/EtOAc 2:1 as eluant. The slower running fraction is collected to yield 5.7 g (10%) of 19: mp 171–174 °C; ^{1}H NMR (DMSO-d_6) 2.3 (t, 2H), 3.05 (t, 2H), 7.3 (s, 4H), 7.5 (dd, 1H), 7.65 (d, 2H), 7.8 (d, 2H), 7.84 (t, 1H), 7.88 (s, 1H), 8.63 (d, 1H), 8.7 (dd, 1H); IR (KBr) 3300 (NH), 1330 + 1155 (SO_2) cm^{-1}. Anal. ($C_{20}H_{16}ClN_3O_3S$) C, H, N, Cl, S.

5-(2-(((4-Fluorophenyl)sulfonyl)amino)ethyl)-*N*-methylpyrrol-2-yl 3-Pyridyl Ketone (22). A solution of 14.1 g (50 mmol) of 2-(2-(((4-fluorophenyl)sulfonyl)amino)ethyl)-*N*-methylpyrrole in 100 mL of toluene and 50 mL of DMF is combined with 9.8 g (55 mmol) of nicotinic acid chloride hydrochloride, added in batches. The mixture is refluxed for 2 h, poured onto ice, neutralized, and extracted with ethylene chloride. The crude product is chromatographed on silica gel with ethylene chloride/ethanol 20:1 and subsequently recrystallized from EtOAc to yield 4.6 g (24%) of 22: mp 140 °C; ^{1}H NMR ($CDCl_3$) 2.9 (t, 2H), 3.3 (t, 2H), 3.9 (s, 3H), 4.85 (t, 1H), 6.0 (d, 1H), 6.65 (d, 1H), 7.1–7.3 (d + d, 2H), 7.4 (dd, 1H), 7.8–7.95 (d + d, 2H), 8.05 (dt, 1H), 8.75 (dd, 1H), 8.95 (d, 1H); IR (CH_2Cl_2) 3360 (NH), 1625 (C=O), 1340 + 1150 (SO_2) cm^{-1}. Anal. ($C_{19}H_{18}FN_3O_3S$) C, H, N, S.

2-((*tert*-Butoxycarbonyl)amino)-6-bromo-1,2,3,4-tetrahydronaphthaline (23). A 55.8-g portion (0.152 mol) of titanium tetrachloride is dropped cautiously into 700 mL of ethylene glycol dimethyl ether at 0 °C. Subsequently, 22.3 g (0.6 mol) of $NaBH_4$ and then a solution of 33.5 g (0.14 mol) of 6-bromo-2-oximino-1,2,3,4-tetrahydronaphthalene are added. After being stirred for 4 h, the mixture is poured on ice, made alkaline with concentrated ammonia, and filtered over Celite. The filtrate is extracted with CH_2Cl_2 and evaporated down. The residue is dissolved in ether, and the hydrochloride is precipitated by addition of isopropyl-alcoholic HCl; 170 mL of 1 N NaOH and subsequently 17.5 g (80 mmol) of di-*tert*-butyl dicarbonate are added to a solution of the crude hydrochloride in 300 mL of dioxane/water 2:1 at 0 °C. After being stirred for 12 h, the mixture is evaporated, mixed with water, and extracted with EtOAc. The organic phase is evaporated down, and the residue is crystallized from petroleum ether to yield 20.1 g (44%) of 23: mp 111 °C; ^{1}H NMR ($CDCl_3$) 1.45 (s, 9H), 1.6–1.8 (m, 1H), 2.0–2.1 (m, 1H), 2.55 (dd, 1H), 2.85 (t, 2H), 3.1 (dd, 1H), 3.95 (m, 1H), 6.9 (d, 1H), 7.2 (m, 2H); IR (CH_2Cl_2) 3440 (NH), 1710 (C=O) cm^{-1}. Anal. ($C_{15}H_{20}BrNO_2$) C, H, N, Br.

2-((*tert*-Butoxycarbonyl)amino)-1,2,3,4-tetrahydronaphth-6-yl 3-Pyridyl Ketone (24). 24 is prepared according to the synthesis of 17 starting from 23, yield 41%: mp 115 °C (EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) 1.45 (s, 9H), 1.7–1.9 (m, 1H), 2.05–2.2 (m, 1H), 2.7 (dd, 1H), 2.95 (t, 2H), 3.2 (dd, 1H), 4.0 (m, 1H), 7.2 (d, 1H), 7.45 (dd, 1H), 7.55 (m, 2H), 8.1 (d, 1H), 8.8 (d, 1H), 9.0 (s, 1H); IR (CH_2Cl_2) 3440 (NH), 1710 + 1660 (C=O) cm^{-1}. Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

2-(((4-Chlorophenyl)-sulfonyl)amino)-1,2,3,4-tetrahydronaphth-6-yl 3-Pyridyl Ketone (25). 25 is prepared according to the synthesis of 18 starting from 24, yield 75%: mp 170–172 °C (EtOAc/petroleum ether); ^{1}H NMR (DMSO-d_6) 1.6–1.9 (m, 2H), 2.65–3.0 (m, 4H), 3.5 (m, 1H), 7.2 (d, 1H), 7.5 (m, 2H), 7.6 (dd, 1H), 7.65 (d, 2H), 7.9 (d, 2H), 8.0 (d, 1H), 8.1 (dt, 1H), 8.75–8.85 (m, 2H); IR (KBr) 1650 (C=O), 1330 + 1155 (SO_2) cm^{-1}. Anal. ($C_{22}H_{19}ClN_2O_3S$) C, H, N, Cl, S.

2-(Acetylamino)indan-5-yl 3-Pyridyl Ketone (26). Its preparation is analogous to the synthesis of 8 starting from 2-(acetylamino)indan, yield 48%: mp 165–167 °C (isopropyl alcohol); ^{1}H NMR (DMSO-d_6/CD_3OD) 2.0 (s, 3H), 3.0 (dt, 2H), 3.4 (2dd, 2H), 4.7 (m, 1H), 7.6 (d, 1H), 7.7–7.85 (m, 3H), 8.25 (dd, 1H), 8.95 (dd, 1H), 9.02 (d, 1H); IR (KBr) 3260 (NH), 1675 + 1640 (C=O) cm^{-1}. Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

2-(((4-Chlorophenyl)sulfonyl)amino)indan-5-yl 3-Pyridyl Ketone (27). 27 is prepared according to the synthesis of 11a starting from 26, yield 65%: mp 215–217 °C (methanol); ^{1}H NMR (DMSO-d_6/CD_3OD) 2.8 (dt, 2H), 3.1 (2dd, 2H), 4.0 (m, 1H), 7.35 (d, 1H), 7.5–7.65 (m, 3H), 7.7 (d, 2H), 7.9 (d, 2H), 8.1 (dt, 1H), 8.25 (d, 1H), 8.85 (m, 2H); IR (KBr 1645 (C=O), 1320 + 1150 (SO_2) cm^{-1}. Anal. ($C_{21}H_{17}ClN_2O_3S$(C, H, N, Cl, S.

2-(2-Cyanoethyl)-2-(3-pyridyl)-1,3-dioxolane (28). A mixture of 16 g (0.1 mol) of 2-cyanoethyl 3-pyridyl ketone, 100 mL of ethyl glycol, and 20.9 g (0.11 mol) of *p*-toluenesulfonic acid in 150 mL of toluene is refluxed for 40 h using a Dean–Stark trap. The reaction mixture is evaporated down, and the residue is taken up in chloroform and washed with a solution of K_2CO_3 and water. Purification was effected by silica gel chromatography using ethylene chloride/ethanol 50:1 to yield 9.75 g (47%) of 28 as an oil: ^{1}H NMR ($CDCl_3$) 2.25 (t, 2H), 2.5 (t, 2H), 3.8 (m, 2H), 4.1 (m, 2H), 7.3 (dd, 1H), 7.75 (dt, 2H), 8.6 (dd, 1H), 8.7 (d, 1H); IR (CH_2Cl_2) 2240 (CN) cm^{-1}. Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

2-(3-(((4-Chlorophenyl)sulfonyl)amino)propyl)-2-(3-pyridyl)-1,3-dioxolane (29). A 2-g portion (10 mmol) of 28 is dissolved in 20 mL of methanolic ammonia and hydrogenated with 0.2 g of Raney Ni at 5 bar for 26 h. The catalyst is filtered off, and the solution is evaporated down. The residue is dissolved in 20 mL of chloroform. To this solution are added 2.2 g (11 mmol) of 4-chlorobenzenesulfonic acid chloride and subsequently 1.5 mL of triethylamine. The reaction mixture is stirred for 1 h, washed with water, and evaporated down. The residue is purified by chromatography on silica gel with ethylene chloride/ethanol 40:1 followed by crystallization from EtOAc/diisopropyl ether to yield 2.5 g (68%) of 29: mp 135–136 °C; ^{1}H NMR ($CDCl_3$) 1.6 (quint, 2H), 1.9 (t, 2H), 3.0 (q, 2H), 3.75 (m, 2H), 4.0 (m, 2H), 4.85 (t, 1H), 7.25 (dd, 1H), 7.45 (d, 2H), 7.7 (dt, 1H), 7.8 (d, 2H), 8.5 (dd, 1H), 8.62 (d, 1H); IR (CH_2Cl_2) 3370 (NH), 1130 + 1160 (SO_2) cm^{-1}. Anal. ($C_{17}H_{19}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl-6-(3-pyridyl)hex-5-enoic Acid *N*-Oxide (30). To a solution of 0.61 g (1.3 mmol) of 36 in 50 mL chloroform is added 0.49 g (1.4 mmol) of MCPBA (50–55%) at 25 °C. The mixture is stirred for 30 min, and the solvent is evaporated down. The residue is dissolved in 10 mL of EtOAc, and the product is precipitated by the addition of 60 mL of ether. The precipitate

is suction-filtered and crystallized from EtOAc/ethanol to yield 0.34 g (54%) of **30**: mp 122–124 °C; ^{1}H NMR (DMSO-d_6/CD_3-OD) 1.65 (quint, 2H), 2.0–2.25 (m, 4H), 2.7 (t, 2H), 3.0 (q, 2H), 6.3 (t, 1H), 7.1 (d, 1H), 7.2–7.3 (m, 2H), 7.35 (dd, 1H), 7.65 (d, 2H), 7.75–7.95 (m, 3H), 8.1 (dd, 1H); IR (KBr) 1710 (C=O), 1335 + 1155 (SO_2) cm^{-1}. Anal. ($C_{25}H_{25}ClN_2O_5S$) C, H, N, Cl, S.

(*E*)-6-(3-(((4-Chlorophenyl)sulfonyl)amino)phenyl)-6-(3-pyridyl)hex-5-enoic Acid (31). A mixture of 3 g (10 mmol) of **16**, 2.3 g (10 mmol) of 4-chlorobenzenesulfonic acid chloride, and 5 mL of Et_3N in 100 mL of CH_2Cl_2 is stirred for 1 h. The reaction mixture is washed with water and evaporated down. The crude product is heated in a mixture of 40 mL of ethanol and 8 mL of 4 N NaOH to 50 °C for 30 min. The reaction mixture is diluted with water and neutralized by the addition of citric acid (10%). The aqueous phase is extracted with EtOAc, and the organic phase is dried and evaporated down. Purification was effected by chromatography on silica gel with EtOAc and recrystallization from isopropanol/diisopropyl ether to yield 1.8 g (39%) of **31**: mp 187–188 °C; ^{1}H NMR (DMSO-d_6) 1.6 (quint, 2H), 1.95 (q, 2H), 2.15 (t, 2H), 6.2 (t, 2H), 6.8–6.9 (m, 2H), 7.1 (dd, 1H), 7.25–7.4 (m, 3H), 7.55–7.7 (m, 4H), 8.3 (d, 1H), 8.45 (dd, 1H); IR (KBr) 3240 (NH), 1710 (br, C=O), 1335 + 1165 (SO_2) cm^{-1}. Anal. ($C_{23}H_{21}ClN_2O_4S$), C, H, N, Cl, S.

(*E*)-6-(3-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-6-(3-pyridyl)hex-5-enoic Acid (35). **35** is olefinated according to the preparation of **36** starting from **18** and (4-carboxybutyl)triphenylphosphonium bromide, yield 68%: mp 127–128 °C (EtOAc/diisopropyl ether); ^{1}H NMR (DMSO-d_6) 1.65 (quint, 2H), 2.0–2.25 (m, 4H), 2.7 (t, 2H), 3.0 (q, 2H), 6.1 (t, 1H), 6.95 (s + d, 2H), 7.15 (d, 1H), 7.3 (m, 2H), 7.5 (dt, 1H), 7.62 (d, 2H), 7.3 (m, 3H), 8.4 (m, 2H), 11.95 (s, 1H); IR (KBr) 3250 (NH), 1700 (C=O), 1330 + 1155 (SO_2) cm^{-1}. Anal. ($C_{25}H_{25}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-6-(3-pyridyl)hex-5-enoic acid (36) and the *Z*-Isomer 37. A 222-g portion (0.5 mol) of (4-carboxybutyl)triphenylphosphonium bromide is suspended in 2000 mL of THF and cooled to −20 °C. To this suspension is added 156 g (1.4 mol) of potassium *tert*-butoxide followed by **11a** (155 g, 0.39 mol). The mixture is stirred for 1.5 h while the temperature is allowed to rise to 10 °C. The reaction mixture is poured onto 5000 mL of ice water. The aqueous phase is washed with EtOAc and then adjusted to pH 5 by addition of citric acid. The precipitate is suction-filtered and recrystallized from ethanol/water to yield 140 g (75%) of **36**: mp 164 °C; ^{1}H NMR (DMSO-d_6) 1.7 (quint, 2H), 2.0–2.35 (m, 4H), 2.75 (t, 2H), 3.05 (q, 2H), 6.15 (t, 1H), 7.05 (d, 2H), 7.2 (d, 2H), 7.3 (dd, 1H), 7.5 (dt, 1H), 7.65 (d, 2H), 7.7–7.95 (d + t, 3H), 8.38 (d, 1H), 8.43 (dd, 1H), 12.0 (s, 1H); IR (KBr) 3290 (NH), 1705 (C=O), 1330 + 1155 (SO_2) cm^{-1}. Anal. ($C_{25}H_{25}ClN_2O_4S$) C, H, N, Cl, S.

The mother liquid is evaporated down, and the residue is chromatographed over a silica gel column with ethylene chloride/EtOAc 6:4 + 3% acetic acid. The faster running fraction is collected and evaporated down, and the residue is crystallized from EtOAc/ether to yield 7.8 g (3%) of **37**: mp 94–95 °C; ^{1}H NMR (DMSO-d_6) 1.65 (quint, 2H), 2.05 (q, 2H), 2.3 (t, 2H), 2.65 (t, 2H), 3.0 (q, 2H), 6.2 (t, 1H), 7.05 (s, 4H), 7.45 (dd, 1H), 7.52 (dt, 1H), 7.62 (d, 2H), 7.78 (d + t, 3H), 8.32 (dd, 1H), 8.55 (d, 1H), 12.0 (s, 1H); IR (CH_2Cl_2) 3360 (NH), 1710 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{25}H_{25}ClN_2O_4S$) C, H, N, Cl, S.

According to the synthesis of **36** starting from **12**, **13**, and **14**, compounds **34**, **32**, and **33** were synthesized.

(*E*)-6-(4-(2-(((4-(Trifluoromethyl)phenyl)sulfonyl)amino)-ethyl)phenyl)-6-(3-pyridyl)hex-5-enoic Acid (44). A mixture of 3.25 g (10 mmol) of **15**, 2.5 g (10 mmol) of 4-(trifluoromethyl)-benzenesulphonic acid chloride, and 2 mL of Et_3N in 30 mL of CH_2Cl_2 is stirred for 30 min. Then the reaction mixture is washed with water, dried, and evaporated down. The residue is purified over a silica gel column with EtOAc as eluant. The crude product is heated in a mixture of 30 mL of ethanol and 2 mL of 10 N NaOH for 30 min to 50–60 °C. The solvent is evaporated down, and the residue is taken up in 50 mL of water and washed with EtOAc. The aqueous phase is adjusted to pH 5 by addition of citric acid and extracted with EtOAc. The organic layer is dried and evaporated down, and the residue is chromatographed over a silica gel column using EtOAc. The crude product is recrystallized from EtOAc/petroleum ether to yield 2.45 g (47%) of **44**: mp 140–142 °C; ^{1}H NMR ($CDCl_3$) 1.65 (quint, 2H), 2.1–2.35 (m, 4H), 2.8 (t, 2H), 3.3 (q, 2H), 6.2 (t, 1H), 7.05–7.25 (m, 5H), 7.55 (dt, 1H), 7.75 (d, 2H), 7.9 (d, 2H), 8.45 (d, 1H), 8.55 (s, 1H); IR (CH_2Cl_2) 1715 (C=O), 1325 + 1165 (SO_2) cm^{-1}. Anal. ($C_{26}H_{25}F_3N_2O_4S$) C, H, N, S.

According to the preparation of **44**, compounds **38–43** and **45–48** were synthesized.

(*E*)-6-(4-(2-(*N*-Ethyl-((4-chlorophenyl)sulfonyl)amino)-ethyl)phenyl)-6-(3-pyridyl)hex-5-enoic acid (50). To a solution of 2 g (4 mmol) of **69** in 10 mL of DMF is added 0.5 g (4 mmol) of potassium *tert*-butoxide at 0 °C followed by 0.62 g (4 mmol) of ethyl iodide. The mixture is stirred for 1 h at 20 °C and the reaction quenched by the addition of water. The aqueous phase is extracted with EtOAc, and the organic phase is washed with water and concentrated by evaporation. The residue is dissolved in 20 mL of ethanol and 5 mL of 2 N NaOH and is stirred for 12 h at ambient temperature. The reaction mixture is rotary-evaporated, and the residue is taken up in water and washed with EtOAc. The aqueous phase is acidified by the addition of citric acid and extracted with EtOAc. The organic layer is evaporated down, and the residue is purified by silica gel chromatography using CH_2Cl_2/EtOAc/acetic acid 6:4:0.3 as eluant followed by crystallization from EtOAc/diisopropyl ether to yield 0.8 g (39%) of **50**: mp 83–84 °C; ^{1}H NMR ($CDCl_3$) 1.1 (t, 3H), 1.8 (quint, 2H), 2.2 (q, 2H), 2.3 (t, 2H), 2.9 (t, 2H), 3.25 (q, 2H), 3.4 (t, 2H), 6.1 (t, 1H), 7.05 (d, 2H), 7.2 (d + dd, 3H), 7.45 (m, 3H), 7.75 (d, 2H), 8.45 (dd, 1H), 8.52 (d, 1H); IR (CH_2Cl_2) 1710 (C=O), 1340 +1160 (SO_2) cm^{-1}. Anal. ($C_{27}H_{29}ClN_2O_4S$) C, H, N, Cl, S.

According to the preparation of **50** starting from **69** and methyl iodide, isopropyl bromide, benzyl bromide, tert-butyl bromoacetate, iodoacetamide, ethyl 4-(bromomethyl)benzoate, *N*-(2-chloroethyl)morpholine, respectively, compounds **49**, **51–54**, **56**, and **57** were synthesized.

(*E*)-6-(4-(2-*N*-(2-Carboxyethyl)-((4-chlorophenyl)sulfonyl)-amino)ethyl)phenyl)-6-(3-pyridyl)hex-5-enoic Acid (55). To a mixture of 5 g (10 mmol) of **69** and 1 mL of benzyltrimethylammonium hydroxide (40% w/w in methanol; Triton B) in 60 mL of dioxane is added 1.5 mL (13.8 mmol) of ethyl acrylate, and the mixture is stirred for 24 h. Then, 1.5 mL (13.8 mmol) of ethyl acrylate is added, and the mixture is stirred for an additional 24 h. The reaction mixture is evaporated down, the residue is taken up in water, and the aqueous phase is extracted with EtOAc. The organic layer is concentrated by evaporation, and the residue is saponified according to the synthesis of **50**, yield 52%: mp 183–184 °C; ^{1}H NMR (DMSO-d_6) 1.65 (q, 2H), 2.05–2.25 (m, 4H), 2.45 (t, 2H + DMSO), 2.85 (t, 2H), 3.25–3.45 (m, 4H), 6.18 (t, 1H), 7.05 (d, 2H), 7.3 (m, 3H), 7.5 (dt, 1H), 7.7 (d, 2H), 7.85 (d, 2H), 8.45 (m, 2H), 12.2 (s, 1H); IR (KBr) 1730 (C=O), 1340 + 1155 (SO_2) cm^{-1}. Anal. ($C_{26}H_{29}ClN_2O_6S$) C, H, N, Cl, S.

(*E*)-3-(4-(2-(((4-Methylphenyl)sulfonyl)amino)ethyl)-phenyl)-3-(3-pyridyl)prop-2-enoic Acid (58). To a solution of 9.6 g (84 mmol) of potassium *tert*-butoxide and 9.85 g (43 mmol) of triethyl phosphonoacetate in 100 mL of THF and 25 mL of DMF is added 15.5 g (40 mmol) of 4-(2-(((4-methylphenyl)-sulfonyl)amino)ethyl)phenyl 3-pyridyl ketone (**11b**) (prepared according to the synthesis of **11a**), and the mixture is refluxed for 5 h. The reaction is quenched by addition of ice water, and the aqueous phase is extracted with CH_2Cl_2. The organic phase is dried and rotary-evaporated, and the residue is purified by silica gel chromatography using ethylene chloride/EtOAc 9:1 as eluant. The faster running fraction is collected and evaporated down, and the residue is dissolved in 70 mL of ethanol and 2.5 mL of 15 N NaOH. The mixture is refluxed for 30 min and concentrated by evaporation. The residue is dissolved in water, and the pH value is adjusted to 3–4 by addition of HCl. The precipitate is suction-filtered and further purified by column chromatography on silica gel with ethylene chloride/ethanol/acetic acid 95:5:0.3. The slower running fraction is collected, and the residue is crystallized from ethylene chloride to yield 1.9 g (27%) of **58**: mp 168–171 °C; ^{1}H NMR (DMSO-d_6) 2.4 (s, 3H), 2.7 (t, 2H), 3.0 (q, 2H), 6.4 (s, 1H), 7.1 (d, 2H), 7.2 (d, 2H), 7.4 (d + dd, 3H), 7.6 (dt, 1H), 7.7 (m, 3H), 8.4 (d, 1H), 8.55 (d, 1H), 12.25 (s, 1H); IR (KBr) 3260 (NH), 1675 (C=O) cm^{-1}. Anal. ($C_{22}H_{23}N_2O_4S$) C, H, N, Cl, S.

(*E*)-4-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-4-(3-pyridyl)but-3-enoic Acid (59). **59** is prepared by reaction of **11a** and (2-carboxyethyl)triphenylphosphonium bromide at −40 °C according to the synthesis of **36**, yield 12%: mp 203 °C; ^{1}H NMR (DMSO-d^6) 2.75 (t, 2H), 3.05 (m, 4H), 6.3 (t, 1H), 7.05 (d, 2H), 7.25 (d, 2H), 7.35 (dd, 1H), 7.55 (dt, 1H), 7.65 (d, 2H), 7.8 (d + t, 3H), 8.38 (d, 1H), 8.45 (dd, 1H), 12.3 (s, 1H); IR (KBr) 1725 (C=O), 1340 + 1160 (SO_2) cm^{-1}. Anal. ($C_{23}H_{23}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-5-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-5-(3-pyridyl)pent-4-enoic Acid (60). **60** is prepared according to the synthesis of **36** starting from **11a** and (3-carboxypropyl)triphenylphosphonium bromide, yield 70%: mp 154–155 °C (EtOAc/diisopropyl ether); ^{1}H NMR (DMSO-d_6) 2.2–2.4 (m, 4H), 2.75 (t, 2H), 3.05 (q, 2H), 6.15 (t, 1H), 7.05 (d, 2H), 7.22 (d, 2H), 7.3 (dd, 1H), 7.5 (dt, 1H), 7.7 (d, 2H), 7.85 (d + t, 3H), 8.38 (d, 1H), 8.45 (dd, 1H), 12.15 (s, 1H); IR (KBr) 1720 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{24}H_{23}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-7-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-7-(3-pyridyl)hept-6-enoic Acid (61). **61** is prepared according to the synthesis of **36** starting from **11a** and (5-carboxypentyl)triphenylphosphonium bromide, yield 83%; foam: ^{1}H NMR ($CDCl_3$) 1.4–1.7 (m, 4H), 2.15 (q, 2H), 2.25 (t, 2H), 2.8 (t, 2H), 3.25 (t, 2H), 5.3 (s, 1H), 6.15 (t, 1H), 7.1 (m, 4H), 7.2 (dd, 1H), 7.4–7.5 (m, 3H), 7.75 (d, 2H), 8.45 (dd, 1H), 8.5 (d, 1H); IR (KBr) 1710 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{26}H_{27}ClN_2O_4S$) C, H, N, Cl, S.

6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl)-6-(3-pyridyl)hexanoic Acid (63). A 3.0-g portion (6.2 mmol) of **36** is dissolved in 50 mL of 0.3 N NaOH and hydrogenated with 1 g of palladium/charcoal (10%) at 40 °C and 5 bar for 2 h. The catalyst is removed by suction filtering, and the filtrate is adjusted to pH 4–5. The precipitate is suction-filtered and chromatographed over a silica gel column using ethylene chloride/EtOAc/acetic acid 9:1:0.3 to yield 1.6 g (53%) of **63** as an oil: ^{1}H NMR ($CDCl_3$) 1.3 (m, 2H), 1.65 (m, 2H), 2.05 (q, 2H), 2.3 (t, 2H), 2.75 (t, 2H), 3.2 (q, 2H), 3.9 (t, 1H), 7.0 (d, 2H), 7.15 (d, 1H), 7.22 (dd, 1H), 7.4 (d, 2H), 7.55 (dt, 1H), 7.7 (d, 2H), 8.4 (dd, 1H), 8.5 (d, 1H); IR (CH_2Cl_2) 1715 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{25}H_{27}ClN_2O_4S$) C, H, N, Cl, S.

According to the synthesis of **63** starting from **60** and **61**, compounds **62** and **64** were prepared.

4-(2-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-2-(3-pyridyl)ethenyl)benzoic Acid (65). **65** is prepared according to the synthesis of **36** starting from **11a** and ((4-carboxyphenyl)methyl)triphenylphosphonium bromide, mixture of isomers, E/Z = 3:1: mass spectrum m/z (rel intensity) 518 (M^+, 20), 520 (M^+, 7), 315 (100), 175 (3), 111 (3); IR (KBr) 1690 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{28}H_{23}ClN_2O_4S$) C, H, N, Cl, S.

3-(2-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)-phenyl)-2-(3-pyridyl)ethenyl)benzoic Acid (66). **66** is prepared according to the synthesis of **36** starting from **11a** and ((3-carboxyphenyl)methyl)triphenyl)methyl)triphenylphosphonium bromide, mixture of isomers, E/Z = 3:1: mass spectrum m/z (rel intensity) 518 (M^+, 25), 520 (M^+, 8), 315 (100), 175 (20), 111 (20); IR (KBr) 1700 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{28}H_{23}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-*N*-(3-(4-(2-(((4-Methylphenyl)sulfonyl)amino)ethyl)-phenyl)-3-(3-pyridyl)prop-2-enoyl)glycine (67). To 1.5 g (3.55 mmol) of **58** in 30 mL of THF is added 0.9 g (5.5 mmol) of *N,N'*-carbonyldiimidazole followed by 0.8 g (5.5 mmol) of glycine ethyl ester hydrochloride. The suspension is refluxed for 30 min and concentrated by evaporation. The residue is dissolved in EtOAc, washed with water, and evaporated down. The residue is purified by silica gel chromatography using EtOAc as eluant. The crude product is heated in 15 mL of ethanol and 0.5 mL of 15 N NaOH for 30 min to 75 °C. The reaction mixture is evaporated down, and the residue is taken up in water and washed with CH_2Cl_2. The aqueous phase is adjusted to pH 5 by addition of HCl, and the precipitate is filtered with suction to yield 0.74 g (43%) of **67**: mp 104–106 °C; ^{1}H NMR (DMSO-d_6) 2.35 (s, 3H), 2.7 (t, 2H), 3.0 (q, 2H), 3.75 (d, 2H), 6.5 (s, 1H), 7.1 (m, 4H), 7.4 (d + dd, 3H), 7.6 (dt, 1H), 7.7 (d + t, 3H), 8.35 (t, 1H), 8.45 (d, 1H), 8.55 (dd, 1H), 12.5 (s, 1H); IR (KBr) 1725 + 1650 (br, C=O) cm^{-1}. Anal. ($C_{25}H_{25}N_3O_5S$) C, H, N, Cl, S.

(*E*)-*O*-2-Carboxyethyl 4-(2-(((4-Chlorophenyl)sulfonyl)-amino)ethyl)phenyl 3-Pyridyl Ketoxime (68). A 5.6-g portion (13.5 mmol) of **19**, 3.6 g (20 mmol) of ethyl 2-bromopropionate, 6.9 g (50 mmol) of K_2CO_3, and 0.5 g of tetrabutylammonium chloride in 200 mL of acetonitrile are refluxed for 6 h. The reaction mixture is evaporated down, and the residue is purified by chromatography on silica gel with CH_2Cl_2/ethanol 40:1. The second fraction is collected to yield 0.6 g of the crude ethyl ester. The ester is saponified in 3 mL of 1 N NaOH for 3 h at room temperature. The reaction mixture is diluted with water and washed with EtOAc. The aqueous layer is acidified by addition of citric acid, and the precipitate is filtered off and recrystallized from ethanol/diethyl ether to give 0.37 g (6%) of **68**: mp 109–110 °C; ^{1}H NMR (DMSO-d_6) 2.6 (t, 2H), 2.75 (t, 2H), 3.05 (q, 2H), 4.35 (t, 2H), 7.25 (s, 4H), 7.4 (dd, 1H), 7.6–7.8 (2d + m, 5H), 7.85 (t, 1H), 8.55 (d, 1H), 8.6 (dd, 1H); IR (KBr) 1720 (C=O), 1335 + 1155 (SO_2) cm^{-1}. Anal. ($C_{23}H_{22}ClN_3O_5S$) C, H, N.

(*E*)-Methyl 6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)-ethyl)phenyl)-6-(3-pyridyl)hex-5-enoate (69). A 12.1-g portion (25 mmol) of **36** is refluxed in 130 mL of 1.5 N methanolic HCl for 2 h. The solvent is evaporated down, and the residue is taken up in water and neutralized by the addition of sodium carbonate. The aqueous phase is extracted with EtOAc, and the organic layer is washed with water and evaporated down. The residue is crystallized from EtOAc/diisopropyl ether to yield 10.1 g (81%) of **69**: mp 88–89 °C; ^{1}H NMR ($CDCl_3$) 1.7 (quint, 2H), 2.2 (q, 2H), 2.3 (t, 2H), 2.8 (t, 2H), 3.12 (s, 3H), 3.3 (q, 2H), 4.7 (t, 1H), 6.1 (t, 1H), 7.1 (m, 4H), 7.15 (dd, 1H), 7.45 (dt + d, 3H), 7.8 (d, 2H), 8.45 (m, 2H); IR (CH_2Cl_2) 1735 (C=O), 1335 + 1160 (SO_2) cm^{-1}. Anal. ($C_{26}H_{27}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-*tert*-Butyl 6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl)-6-(3-pyridyl)hex-5henoate (70). To a solution of 14.5 g (30 mmol) of **36** in CH_2Cl_2 is slowly added 5.1 g (40 mmol) of oxalyl chloride at 0 °C. The mixture is stirred for 30 min at 20 °C and then evaporated down. The residue is dissolved in 100 mL of THF, and 9 g (80 mmol) of potassium *tert*-butoxide is slowly added. The mixture is stirred for 20 min and concentrated by evaporation. Purification was effected by chromatography on silica gel with CH_2Cl_2/acetone 30:1 and recrystallization from ether/diisopropyl ether to yield 2.9 g (18%) of **70**: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) 1.4 (s, 9H), 1.75 (q, 2H), 2.1–2.25 (m, 4H), 2.8 (t, 2H), 3.3 (q, 2H), 4.65 (t, 1H), 6.1 (t, 1H), 7.1 (m, 4H), 7.18 (dd, 1H), 7.4–7.5 (dt + d, 3H), 7.8 (d, 2H), 8.45 (m, 2H); IR (CH_2Cl_2) 3370 (NH), 1725 (C=O), 1340 + 1160 (SO_2) cm^{-1}. Anal. ($C_{28}H_{33}ClN_2O_4S$) C, H, N, Cl, S.

6-(4-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl)-6-(3-pyridyl)hex-5-enoic Acid Amide (71). To 2.43 g (5 mmol) of **36** in 20 mL of THF is added 1.64 g (10 mmol) of *N,N'*-carbonyldiimidazole followed by 1 g (60 mmol) of dry ammonia. The mixture is heated to 50 °C for 30 min and concentrated by evaporation. The residue is taken up in water, and the aqueous phase is extracted with EtOAc. The organic layer is evaporated down, and the residue is purified by silica chromatography using CH_2Cl_2/ethanol 30:1 as eluant followed by recrystallization from EtOAc/diisopropyl ether to yield 1.85 g (76%) of **71**: mp 104–105 °C; ^{1}H NMR ($CDCl_3$) 1.6 (quint, 2H), 2.1 (m, 4H), 2.8 (t, 2H), 3.3 (q, 2H), 5.4 (s, 1H), 6.25 (t + s, 2H), 6.6 (t, 1H), 7.0–7.2 (m, 5H), 7.5 (dt + d, 3H), 7.75 (d, 2H), 8.45 (dd, 1H), 8.6 (d, 1H); IR (CH_2Cl_2) 3500 (NH_2), 3360 (NH), 1675 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{25}H_{26}ClN_3O_3S$) C, H, N, Cl, S.

According to the synthesis of **71** starting from **36**, compounds **72** and **73** were synthesized.

5-(5-(2-(((4-Chlorophenyl)sulfonyl)amino)ethyl)phenyl)-5-(3-pyridyl)pent-4-enyl)tetrazole (74). **74** is prepared according to the synthesis of **36** starting from **11a** and (4-(5-tetrazolyl)butyl)triphenylphosphonium bromide, yield 52%; oil as a mixture of isomers, E/Z = 3:1: ^{1}H NMR of the main component ($CDCl_3$/CD_3OD) 1.95 (quint, 2H), 2.2 (t, 2H), 2.75–3.0 (m, 4H), 3.2 (q, 2H), 6.12 (t, 1H), 7.0 (d, 2H), 7.12 (d, 2H), 7.25 (dd, 1H), 7.5 (d, 2H), 7.75 (dt, 1H), 7.8 (d, 2H), 8.4 (m, 2H); IR (CH_2Cl_2) 1330 + 1160 (SO_2) cm^{-1}; mass spectrum m/z (rel intensity) 508 (M^+, 40), 510 (M^+, 15), 425 (100), 427 (35), 262 (40). Anal. ($C_{25}H_{25}ClN_6O_2S$) C, H, N, Cl, S.

(*E*)-6-(5-(2-(((4-Fluorophenyl)sulfonyl)amino)ethyl)-*N*-methylpyrrol-2-yl)-6-(3-pyridyl)hex-5-enoic Acid (75). **75** is olefinated according to the synthesis of **36** starting from **22** and (4-carboxybutyl)triphenylphosphonium bromide, yield 55%: mp 190 °C (isopropyl alcohol/water); ^{1}H NMR (DMSO-d_6) 1.75 (quint, 2H), 2.05–2.3 (m, 4H), 2.7 (t, 2H), 3.0 (s + q, 5H), 5.85 (s, 2H), 6.4 (t, 1H), 7.3 (dd, 1H), 7.35–7.5 (m, 3H), 7.8–7.95 (m, 3H), 8.35 (d, 1H), 8.42 (dd, 1H), 12.0 (s, 1H); IR (KBr) 3270 (NH), 1715 (C=O), 1320 + 1150 (SO_2) cm^{-1}. Anal. ($C_{24}H_{26}FN_3O_4S$) C, H, N, S.

(*E*)-6-(2-(((4-Chlorophenyl)sulfonyl)amino)-1,2,3,4-tetrahydronaphth-6-yl)-6-(3-pyridyl)hex-5-enoic Acid (76). **76** is olefinated according to the synthesis of **36** starting from **25** and (4-carboxybutyl)triphenylphosphonium bromide, yield 62%: mp 172–173 °C (EtOAc/isopropyl alcohol); ^{1}H NMR (DMSO-d_6) 1.55–1.9 (m, 4H), 2.0–2.25 (m, 4H), 2.6–2.9 (m, 4H), 3.4 (m, 1H), 6.1 (t, 1H), 6.8 (d + s, 2H), 7.0 (d, 1H), 7.3 (dd, 1H), 7.5 (dt, 1H), 7.7 (d, 2H), 7.8–8.0 (d + d, 3H), 8.4 (m, 2H), 11.95 (s, 1H); IR (KBr) 3270 (NH), 1675 (C=O), 1330 + 1160 (SO_2) cm^{-1}. Anal. ($C_{27}H_{27}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-6-(2-(((4-Chlorophenyl)sulfonyl)amino)indan-5-yl)-6-(3-pyridyl)hex-5-enoic Acid (77). **77** is olefinated according to the synthesis of **36** starting from **27** and (4-carboxybutyl)-triphenylphosphonium bromide. Separation of the *E*/*Z*-isomers is performed by column chromatography on silica gel with ethylene chloride/EtOAc 7:3 + 3% acetic acid, yield 51%: mp 75–78 °C (ethanol); ^{1}H NMR (DMSO-d_6) 1.65 (quint, 2H), 2.2 (q, 2H), 2.3 (t, 2H), 2.65–2.8 (m, 2H), 3.0 (dd, 2H), 3.95 (q, 1H), 6.1 (t, 1H), 6.85 (s + d, 2H), 7.15 (d, 1H), 7.3 (dd, 1H), 7.5 (dt, 1H), 7.7 (d, 2H), 7.85 (d, 2H), 8.2 (d, 1H), 8.4 (m, 2H); IR (CH_2Cl_2) 1710 (C=O), 132 5 + 1160 (SO_2) cm^{-1}. Anal. ($C_{28}H_{25}ClN_2O_4S$) C, H, N, Cl, S.

(*E*)-9-(((4-Chlorophenyl)sulfonyl)amino)-6-(3-pyridyl)-non-5-enoic Acid (78). A 2.0-g portion (5.2 mmol) of **29** is heated in 20 mL of 4 N HCl to 50 °C for 5 h. The solution is neutralized, and the precipitate is suction-filtered. The crude product is olefinated according to the synthesis of **36**. Purification is effected by chromatography on silica gel with ethylene chloride/ethanol 40:1 followed by crystallization from EtOAc to yield 0.9 g (40%) of **78**: mp 112–113 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) 1.5 (quint, 2H), 1.75 (quint, 2H), 2.2–2.4 (m, 4H), 2.55 (t, 2H), 2.85 (t, 2H), 5.7 (t, 1H), 7.3 (dd, 1H), 7.5 (d, 1H), 7.65 (dt, 1H), 7.75 (d, 2H), 8.35–8.56 (s + d, 2H); IR (CH_2Cl_2) 1710 (C=O), 1330 + 1155 (SO_2) cm^{-1}. Anal. ($C_{20}H_{23}ClN_2O_4S$) C, H, N, Cl, S.

(b) Biochemistry. Materials and Methods. SQ 29,548-5,6-^3H(N) (code NET-936), the 6-keto-PGF$_{1\alpha}$ RIA kit (code NEK-008), cAMP-2,8-^3H (code NET-275), and sucrose-^{14}C(U) (code NEC-100) were purchased from New England Nuclear (Dreieich, FRG), U 46,619 from Sigma, and Sepharose 2B from Pharmacia. Collagen and SKF dilution buffer were obtained from Hormon-Chemie (Munich, FRG). All other chemicals were of the highest purity commercially available. All experiments were performed at least as duplicates.

Thromboxane Receptor Antagonism. Blood was obtained from volunteers who had not taken any medication for at least 1 week by puncture of an antecubital vein and anticoagulated with trisodium citrate (13 mM final concentration). Platelet-rich plasma (PRP) was prepared by centrifugation at 170*g* for 10 min.

Sepharose 2B columns (175- × 23-mm diameter) were prepared in elution buffer (90 mM NaCl, 14 mM trisodium citrate, 5 mM glucose, and 50 mM TRIS, pH 7.4, 309 milliosmolar) and conditioned by the passage of human citrated plasma. PRP was applied to the columns, and gel-filtered platelets (GFP) eluted with the buffer.

The binding of the test compounds was determined by measuring the displacement of the high-affinity ligand [^{3}H]SQ 29,548. A 100-μL portion of the test compound solution was added to 750 μL of GFP or PRP, respectively, followed by 50 μL (7.4 kBq) of [^{14}C]sucrose and 100 μL of [^{3}H]SQ 29,548 to yield 0.5 nM as the final ligand concentration. Nonspecific binding was determined by adding U 46,619 (30 μM final concentration), replacing the test compound.

After incubation for 60 min at room temperature, the samples were centrifuged at 10 000*g* for 20 s, the supernatant was removed, and 100 μL was counted for ^{3}H and ^{14}C. The platelet pellet was dissolved in 500 μL of 0.2 N NaOH. A 450-μL value of this solution was mixed with 25 μL of 5 N HCl and counted for ^{3}H and ^{14}C. After correction for spill over and extracellular space in the pellet, the concentration of the test compound causing 50% displacement was calculated.

Thromboxane Synthetase Inhibition. Blood was obtained from volunteers who had not taken any medication for at least 1 week by puncture of an antecubital vein, anticoagulated with trisodium citrate (13 mM final concentration), and centrifuged at 360*g* for 30 min. The thrombocyte layer on top of the erythrocytes was collected and recentrifuged at 320*g* for 25 min to sediment contaminating erythrocytes.

The enriched PRP was applied to a 20- × 1.5-cm Sepharose 2B column and eluted with ACD (85 mM trisodium citrate, 65 mM citric acid, and 111 mM dextrose) containing 100 μg/mL apyrase, 2 U/mL heparin, and 140 nM PGE$_1$. The resulting GFP suspension contained <0.1% of plasma proteins.

Portions of 0.5 mL of GFP were incubated with 6 μg of [^{14}C]-AA (specific activity: 2 GBq/mmol) for 20 min at 37 °C, and the reaction was terminated by the addition of 33 μL of 0.5 M citric acid. The mixture was extracted three times with ethyl acetate, and the combined extracts were dried under nitrogen.

Residues were taken up in 50 μL of ethyl acetate and applied to TLC plates (Merck, silica gel 60, 0.25 mm). After chromatography (chloroform/methanol/water/acetic acid 90:8:1:0.8, by volume), the dried plates were covered with X-ray film (Agfa-Gevaert Osray T4) for 3 days and the autoradiographs used for localization of the AA metabolites. The spots were scraped from the plates, mixed with Instagel (Packard), and counted for ^{14}C activity. This 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 endoperoxide-derived products and an increase in 12-HETE.

Phosphodiesterase (PDE) Inhibition. The enzyme used was a crude preparation of the soluble PDE from human platelets; 10 mL of PRP was centrifuged at 40 000*g* for 10 min and the platelet resuspended in 2 mL of distilled H_2O. After freezing and thawing, the suspension was centrifuged at 10 000*g* for 2 min and the supernatants were pooled and stored at −80 °C. The necessary dilution to produce a time-linear cAMP hydrolysis under standard assay conditions was determined in a separate experiment and was usually around 1:10.

To determine the PDE inhibition, 100 μL of PDE mix (300 mM TRIS, 9 mM $MgCl_2$, 90 mM AMP, 3 mM cAMP, and 15 μL of [^{3}H]cAMP/20 mL mix), 100 μL of the test compound, and 100 μL of PDE are incubated for 15 min at 37 °C. To stop the hydrolysis, 250 μl of $ZnSO_4$ (0.266 M) and 250 μL of $Ba(OH)_2$ (0.226 M) are added and, after reacting, the sample is centrifuged at 10 000*g* for 2 min. Supernatant (500 μL) is mixed with 4 mL of Instagel and counted. Uninhibited control values are obtained by adding water instead of the test compound, and background values receive $ZnSO_4$ before the enzyme. The method is based on the fact that nascent $Zn(OH)_2$ and $BaSO_4$ will adsorb AMP but not cAMP. Thus, the activity remaining in the supernatant represents unhydrolyzed [^{3}H]cAMP which permits the calculation of the amount hydrolyzed.

Human Whole-Blood Platelet Aggregation. Blood (36 mL) was drawn from an antecubital vein and carefully mixed with 4 mL of trisodium citrate (13 mM final concentration); 2 mL-aliquots were pipetted into polypropylene tubes (60- × 14-mm diameter) and incubated at 37 °C for 10 min while being stirred with a Teflon-coated bar (8- × 3-mm diameter) at 140 rpm. Collagen in SKF buffer was added to give the desired final concentrations; the control received solvent only. Samples (10 μL) from the incubates were pipetted immediately before collagen and 1, 2, 3, 5, 10, 20, and 30 min thereafter into 10 μL of counting solution (saline containing 1.8% formaldehyde). The remaining single platelets were determined using an Ultra-Flo 100 (Becton Dickinson) single-platelet counter. Platelet numbers were expressed as the percent of the control sample count at time zero and plotted against time. As a measure of platelet aggregation, the area between the time curves of the control and the aggregated

samples was determined. Percent inhibition of aggregation was calculated using the areas of the control samples.

Prostacyclin Formation. Prostacyclin formation was determined by measuring the stable metabolite 6-keto-$PGF_{1\alpha}$ in collagen-stimulated blood samples. The remainders of the aggregation samples were centrifuged for 1 min at 10 000*g*, and the supernatant plasma was removed and stored at −80 °C until assayed. The assay was performed as described in the NEN brochure with the exception of using only half of the indicated reagent volumes, which has been shown to yield accurate and reliable results.

(c) Pharmacology. Collagen-Induced Aggregation in Platelet-Rich Plasma. Blood was taken from healthy volunteers who had refrained from taking any medication for at least 14 days prior to the venipuncture. The blood was collected into one-tenth of its volume of a trisodium citrate solution (130 mmol/L). Platelet-rich plasma was prepared by centrifugation at 150*g* for 20 min.

The aggregation tests were performed in six channel aggregometers (built by Feinmechanik and Elektronik Werkstatt, Dr. K. Thomae GmbH, Biberach, FRG).

The photometric output was recorded on six channel recorders (R-10, Rikadenki) at a paper speed of 50 mm/min. Platelet-poor plasma prepared from the blood of each volunteer (centrifugation at 10 000*g* for 5 min) was used to preadjust the photometric measurement to the minimal optical density.

Platelet-rich plasma (300 μL) and 3 μL of a solution of the test compound or vehicle solution were pipetted into a cuvette and stirred with a 3-mm long bar (diameter of 1 mm) with 1250 rotations/min for a 10-min preincubation at 37 °C in the aggregometer; 3 μL of a diluted collagen solution (prepared from the 1 mg/mL commercial batch; Hormon Chemie, Munich, FRG) was added to the stirred platelet-rich plasma to achieve a final concentration of 0.5, 1.0, or 1.5 μg/mL collagen. After the addition of the collagen, the optical density of the stirred platelet-rich plasma was recorded for 10 min. All experiments were performed in duplicate.

The lowest concentration of collagen sufficient to induce a reproducible aggregatory response in PRP supplemented with the vehicle was used for all following experiments with PRP of that donor to evaluate the inhibition of platelet aggregation.

The maximal change in the optical density of the PRP due to platelet aggregation was determined from each photometric tracing. The difference in the collagen-induced optical density change between vehicle- and compound-treated PRP was divided by the difference in the optical density between vehicle-treated PRP (before aggregation) and platelet-poor plasma to calculate the relative inhibition of aggregation in percentages. 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 relative inhibition of aggregation curve.

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