Synthesis and Structure–Activity Relationships of Novel Benzimidazole and Imidazo[4,5-*b*]pyridine Acid Derivatives as Thromboxane A_2 Receptor Antagonists

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A series of 1-benzylbenzimidazole and 3-benzylimidazo[4,5-*b*]pyridine substituted in the 2-position by an alkanoic or mercaptoalkanoic acid chain was synthesized for evaluation as potential thromboxane A_2/prostaglandin H_2 (TXA_2/PGH_2) receptor antagonists. The affinity of each compound for washed human platelet TXA_2/PGH_2 receptors was determined by radioligand binding studies using [^{125}I]PTA-OH. Structure–activity relationships led to the conclusions that 2-alkanoic acid derivatives were slightly more potent than 2-mercaptoalkanoic acids and that compounds possessing a 3,3-dimethylbutanoic acid in the 2-position were definitely the most potent with K_i values of 4–39 nM (**11a**, **11g–x**, **37a**, **37f–o**, **23a–c**). The replacement of this 3,3-dimethylbutanoic acid side chain by a shorter one led to a marked decrease of affinity (**11b** and **11c**; K_i = 5600 and 1700 nM, respectively). Compounds of benzimidazole and imidazo[4,5-*b*]pyridine series displayed similar potencies (**11q** and **23c** have K_i values of 6 and 7 nM, respectively). The interesting pharmacological profile of compound **23a** (UP 116-77: 4-[3-[(4-chlorophenyl)methyl]-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoic acid) and its excellent tolerance led us to select this derivative for further development.

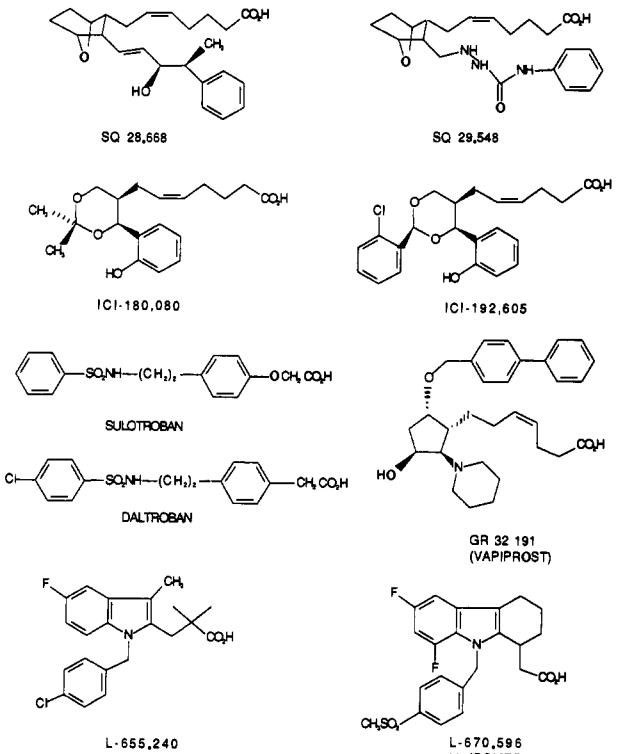
Introduction

Thromboxane A_2 (TXA_2) is one of the predominant metabolites of arachidonic acid in various cells or tissues including platelets, lung, and kidney.[1-3] Its potent constrictor effect on vascular smooth muscles[2,4] as its pro-aggregating action on platelets[2,5] has been implicated in a variety of cardiovascular, renal, and respiratory diseases.[3] Inhibition of biological effects of TXA_2 can be expected by inhibiting thromboxane synthesis or blocking TXA_2/PGH_2 receptors.

Despite the considerable effort made in the area of TXA_2 synthetase inhibitors,[6] clinical trials with these agents were very disappointing,[7] probably because TXA_2 synthetase inhibitors lead to an accumulation of prostaglandin H_2 (PGH_2) that shares a common receptor with TXA_2[8,9] and can exhibit the same pharmacological profile. For this reason, we were interested in developing new TXA_2/PGH_2 receptor antagonists. Many structures have been synthesized in this area[6] (Chart I) and can be structurally divided into several families: analogues of TXA_2 or PGH_2 such as SQ-26,668,[10] SQ-29,548,[11] ICI-180,080,[12] ICI-192,-605,[13] and GR 32191[14] (vapiprost) on the one hand, sulfonyl derivatives, analogues of sulotroban,[15] and daltroban,[16] on the the other hand, and indole derivatives such as L-655,240[17] and L-670,596[18] described by Merck Frosst.

We focused our effort on a new family, namely benzimidazole and imidazo[4,5-*b*]pyridine acid derivatives structurally related to indole derivatives of Merck Frosst. The present work aims to describe and discuss structure–activity relationships of these series of new non-prostanoid, non-sulotroban related TXA_2 receptor antagonists.

Chart I. TXA_2 Receptor Antagonists



Chemistry

The synthesis of mercaptoalkanoic acids **8** is outlined in Scheme I. Reaction of halonitrobenzenes **1** with substituted benzylamines **2** was conveniently achieved by either heating in THF at reflux with K_2CO_3 or by direct heating at 135 °C of the two reagents without solvent.[19,20] The nitro compounds **3** were prepared in some cases in several steps from nitroanilines **1'**. In a first stage, these nitroanilines were treated with tosyl chloride in pyridine. The resulting sulfonamides **2'** were then alkylated with an appropriately substituted benzyl chloride in 4 N sodium hydroxyde at reflux. The alkylated sulfonamides **3'** were then hydrolyzed in propionic acid in the presence of concentrated sulfuric acid to give the corresponding nitro

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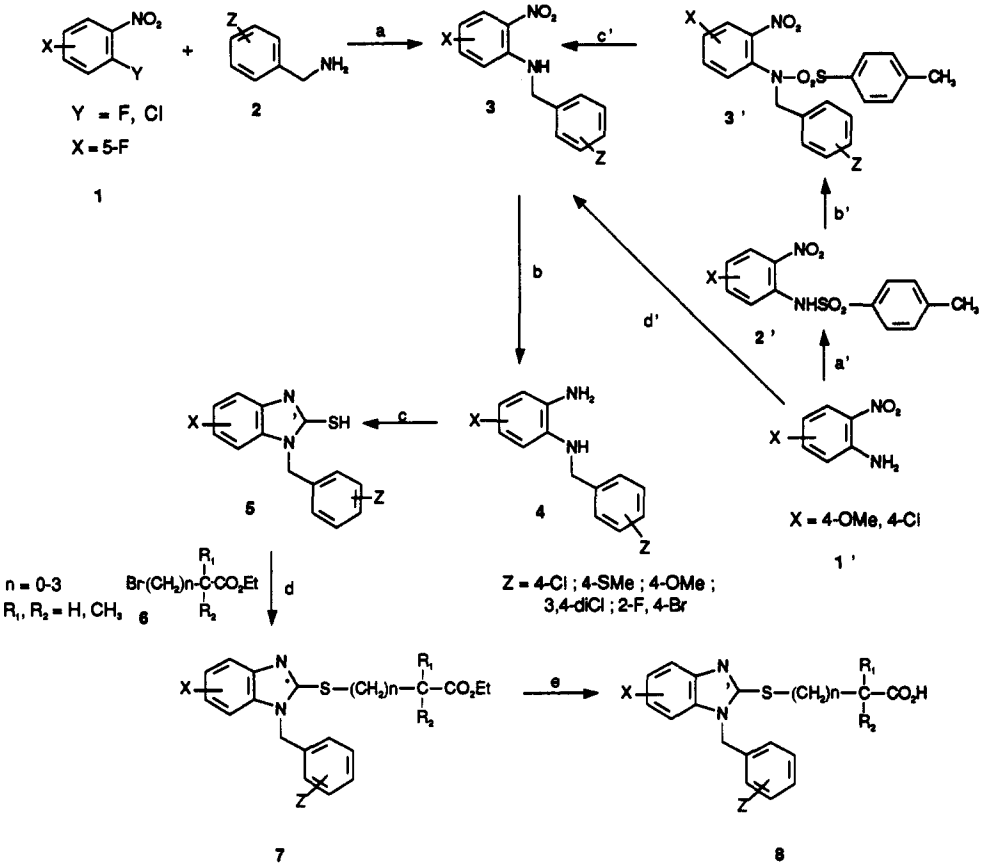
Scheme I[a]



[a] (a) K_2CO_3, THF, Δ; or direct heating without solvent at 135 °C; (b) H_2, Raney Ni, THF; (c) CS_2, EtOH, Δ, 12 h; (d) K_2CO_3, acetone, Δ, 5 h; (e) concentrated HCl, AcOH, H_2O, Δ, 4 h; (a') TsCl, pyridine; (b') 4 N NaOH, substituted benzyl halide, Δ; (c') propionic acid, H_2SO_4, 95 °C, 1 h 30 min; (d') substituted benzyl chloride, AcONa, I_2, 120 °C, 12 h.

derivatives **3**.[19,20] An alternative preparation of compounds **3** consisted in the direct treatment of nitroanilines **1'** with an appropriate benzyl chloride in the presence of iodine and sodium acetate without solvent at 120 °C.[21]

Reduction of nitro compounds **3** was performed by catalytic hydrogenation with palladium on carbon and led to diamino compounds **4**. Condensation of **4** with carbon disulfide in EtOH at reflux afforded 2-mercaptobenzimidazoles **5**.[19] Target carboxylic acids **8** were prepared by a two-step procedure from compounds **5**, by alkylation with an appropriate ethyl bromoalkanoate **6** in presence of K_2CO_3 in acetone or 2-butanone at reflux followed by hydrolysis in AcOH/HCl at reflux.

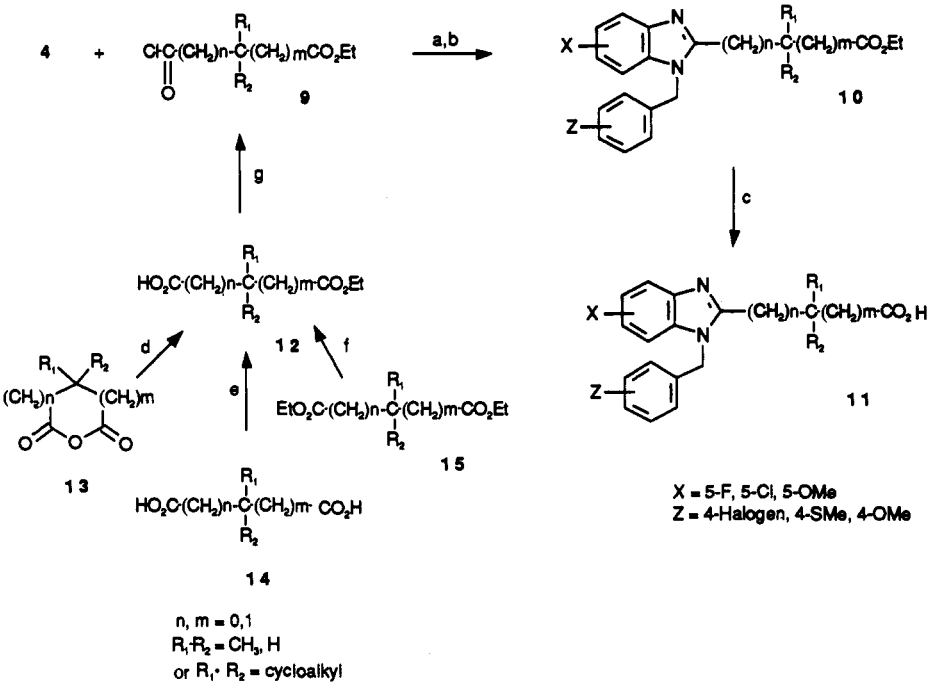
The synthesis of alkanoic acids **11** proceeded from diamino compounds **4** as depicted in Scheme II. Cyclization reaction was achieved by treatment of **4** with the appropriate acid chloride **9** in $CHCl_3$ followed by heating the intermediary amide in EtOH/HCl to afford esters **10**; hydrolysis of esters **10** provided the target acids **11**.[19] Preparation of acid chlorides **9** was achieved by various methods as depicted in Scheme II. When the length of the chain was sufficient, the best method consisted of treatment of a cyclic anhydride **13** with EtOH, affording an ester acid compound **12** which upon treatment with $SOCl_2$ in toluene led to desired acid chloride **9**. When this method was inadequate, monoesterifiation of diacids **14** or monosaponification of appropriate diesters **15**[22,23] provided ester acids **12** which were similarly converted into acid chlorides **9** as described above.

Imidazo[4,5-*b*]pyridine analogues **21** of mercaptoalkanoic acids **8** were prepared in the same way as described in Scheme III, proceeding from 2-chloro-3-nitropyridines **16**.[24-26] Condensation of compounds **16** with substituted benzylamines **2** was performed in xylene at reflux in the presence of 1 equiv of 2-methyl-5-ethylpyridine and afforded 2-(benzylamino)-3-nitropyridines **17** which led to target acids **21** by the same procedure as described above for acids **8**.

Imidazo[4,5-*b*]pyridine analogues **23** of alkanoic acids **11** were synthesized as depicted in Scheme IV. Since cyclization of diamino compounds **18** using acid chlorides **9** and subsequent treatment with EtOH/HCl failed, this cyclization was performed by using aldehyde **26** in a two-step procedure. In the first step, diamino compounds **18** were refluxed in EtOH/AcOH in the presence of aldehyde **26** affording intermediary Schiff bases which were treated in a second step by iodine in 1,2-dimethoxyethane[27] at reflux to afford esters **22**.

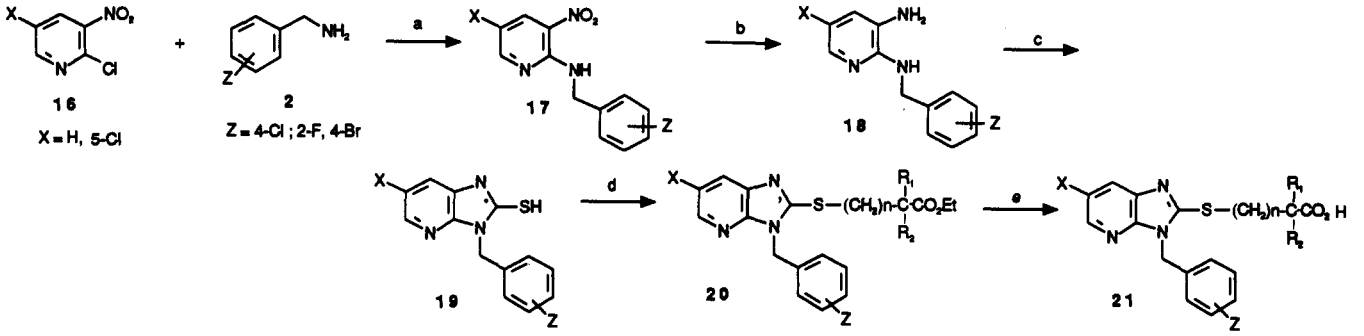
Aldehyde **26** was prepared by a Rosenmund type hydrogenation of acid chloride **25** with palladium on carbon in the presence of 2,6-lutidine.[19] Acid chloride **25** was obtained in two steps proceeding from 3,3-dimethylglutaric anhydride: treatment with EtOH at reflux followed by chlorination with $SOCl_2$ in toluene. The same procedure was used for the synthesis of compound **33** (Scheme V) which is a 4,4-dimethylpentanoic acid derivative. Aldehyde **31** was prepared in five steps from aldehyde **26**.[19] Treatment of **26** with ethylene glycol in toluene/PTSA afforded the dioxolane ester **27** which gave alcohol **28** after reduction of ester with $LiBH_4$. Conversion of the alcohol into its mesylate **29** followed by reaction of KCN in acetonitrile in the presence of 18-crown-6 ether led to the dioxolane nitrile **30**. Deprotection with HCl/Acetone afforded aldehyde **31**. Reaction between aldehyde **31** and

Scheme II[a]



[a] (a) $CHCl_3$, TEA, 2 h; (b) concentrated HCl, EtOH, Δ, 10 h; (c) HCl, AcOH, H_2O, Δ, 4 h; (d) EtOH, Δ, 12 h; (e) EtOH, H_2SO_4, Δ; (f) NaOH (1 equiv), EtOH; (g) $SOCl_2$, toluene, 80 °C, 2 h.

Scheme III[a]



[a] (a) 2-Methyl-5-ethylpyridine, xylene, Δ, 30 h; (b) H_2, Raney Ni, THF; (c) CS_2, EtOH, Δ, 12 h; (d) 6, K_2CO_3, acetone, Δ, 5 h; (e) concentrated HCl, AcOH, H_2O, Δ, 4 h.

diamino compound **4a** was performed as described above for compounds **18** and **26** and gave nitrile **32** which was hydrolyzed in NaOH/EtOH at reflux to provide acid **33**.

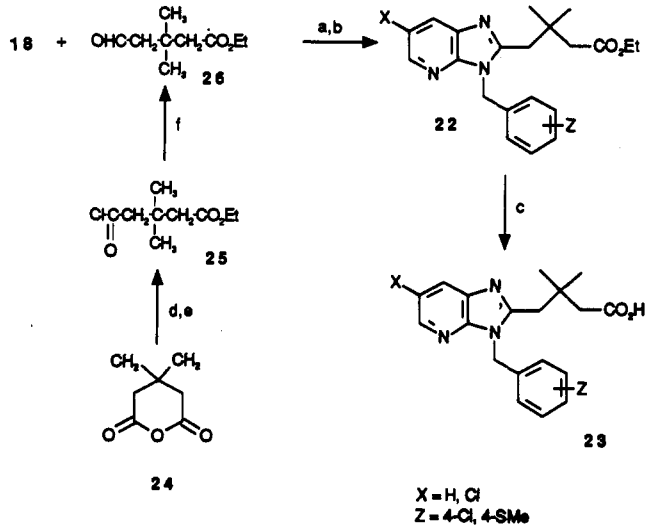
Some alkanoic acids **11** were synthesized by another method shown in Scheme VI. Cyclization of diamino compounds of formula **34** with appropriate acid chloride **9**, under the same conditions used for diamino compounds of formula **4** (Scheme II), led to esters **35**. These esters **35** were alkylated by a substituted benzyl halide in DMF with 1 equiv of NaH to afford alkylated benzimidazole alkanoic esters **36** which upon hydrolysis yielded acids **37**. Amide derivative **44** of the carboxylic acid **37a** was synthesized from **37a** by treatment with oxalyl chloride at 0 °C and reaction of the intermediary acid chloride with NH_4OH. The corresponding nitrile **45** was prepared by dehydration of amide **44** with $POCl_3$ in $CHCl_3$ at reflux.

Results and Discussion

In vitro SAR study. As indicated in Table VI, a large range of variations on the carboxylic acid side chain was performed (R in Table VI structures), and this part of the molecule has proven to be highly important to the activity. In the mercaptoalkanoic acid series (formula **8**), there is no significant variation in the activity when the length or the substituents on the acid side chain are modified; all compounds have almost the same affinity and are equipotent to sulotroban. In the alkanoic acid series, comparison between **11b** and **11c** indicates that the introduction of two methyl groups on the carbon in β-position of the imidazole ring improves the potency. The comparison of compounds **11a**, **11c**, and **33** indicates that the length of the R chain is very important (**11a** > **33** > **11c**). A three-carbon chain between the imidazole ring and the terminal carboxylic acid seems to be ideal with the β-carbon substituted by two methyls (**11a**). Replacement of these two methyls on the latter by various cycloalkyl groups leads to a decrease of affinity (**11d**, **11e**, and **11f**).

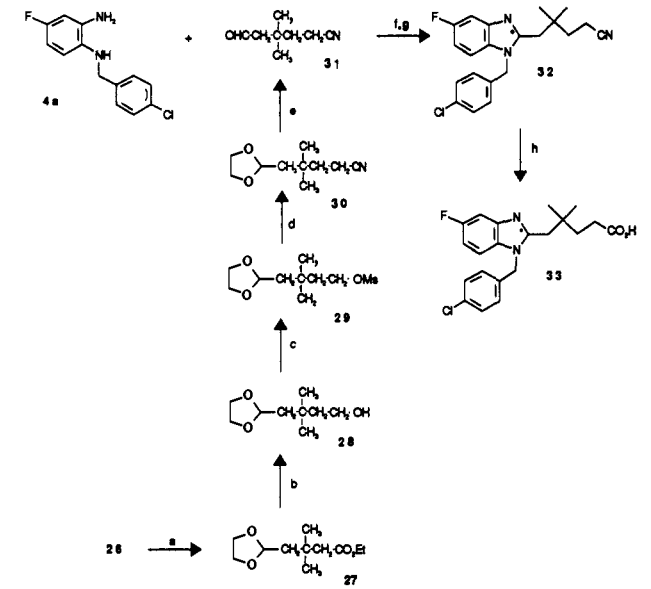
Results of Table VII confirm the primordial importance of the two methyl groups borne by the β-carbon (R_1 and R_2 in Table VII structures). The suppression of one of these methyls yields a much less potent compound (**37e** vs **37a**), and the replacement of at least one methyl by an ethyl group leads to a significant decrease of potency (**37b** and **37c** vs **37a**). The introduction of a very bulky group, like a phenyl, on the β-carbon (**37d**) strongly decreases the activity.

Scheme IV[a]



[a] (a) AcOH, EtOH, 4 h; (b) I_2, 1,2-dimethoxyethane, 50 °C, 16 h; (c) concentrated HCl, AcOH, H_2O, Δ, 4 h; (d) EtOH, Δ, 12 h; (e) $SOCl_2$, toluene, 80 °C, 2 h; (f) H_2, 5% Pd/C, 2,6-lutidine, THF.

Scheme V[a]



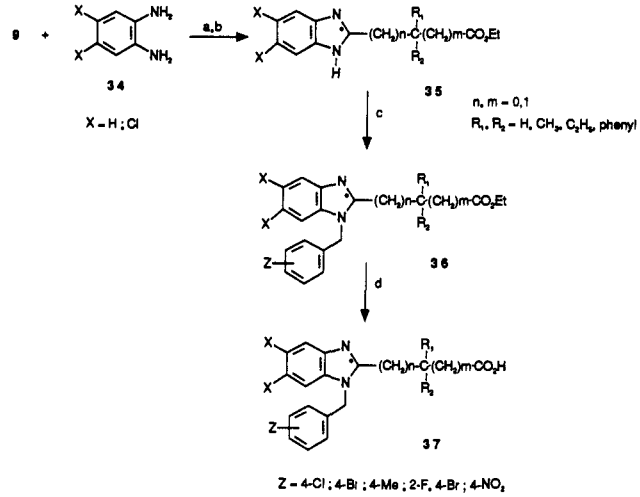
[a] (a) Ethylene glycol, PTSA, toluene, Δ; (b) $LiAlH_4$, Et_2O, 10 °C; (c) MsCl, TEA, $CHCl_3$, 5 °C; (d) KCN, 18-crown-6 ether, CH_3CN, Δ, 8 h; (e) concentrated HCl, acetone, 5 h; (f) AcOH, EtOH, 4 h; (g) I_2, 1,2-dimethoxyethane, 50 °C, 16 h; (h) NaOH pellets, EtOH, H_2O, Δ, 15 h.

Results concerning compounds **44** and **45** (see Table X) clearly show that an acidic function at the extremity of the side chain is necessary to obtain high affinities since the replacement of the terminal carboxylic acid of **37a** with a carboxamide (**44**) or a carbonitrile (**45**) leads to a significant loss of activity.

As suggested by these results, the optimal side chain is a 3,3-dimethylbutanoic acid, (R_1 = R_2 = CH_3; **11a** and **37a**) and does not support over bulky substituents on the β-carbon (**37a** > **37c** > **37d**).

As indicated in Table VIII, the nature of the X_1 substituent at the 5-position of the benzimidazole ring seems to be important. A substitution with a halogen such as chlorine is favorable but more especially with a fluorine (**11a** and **11j–o**). A bulky substituent like bromine (**11i**) or methoxy (**11g**) is rather unfavorable. The introduction of a chlorine in the 6-position (X_2 in the Table

Scheme VI[a]



[a] (a) $CHCl_3$/THF, TEA; (b) concentrated HCl, EtOH, Δ, 12 h; (c) substituted benzyl halide, NaH, DMF, 90 °C, 5 h; (d) concentrated HCl, AcOH, H_2O, Δ, 4 h.

VIII structures) of the benzimidazole ring leads to a loss of activity (**37f**) which could indicate that this position is sensitive to steric and/or electronic effects. Various modifications on the nature of X_3 and X_4 substituents do not modify significantly binding affinities. The best substituents for X_3 are OCH_3 (**11n**, **11u**), SCH_3 (**11k**, **11q**), Cl (**11a**, **11n**), and Br (**11m**, **11t**), while SO_2CH_3 (**11w**, **11x**) and OH (**37n**) seem to be unfavorable. This might be due to a steric effect for **11w** and **11x** and to the presence of an acidic proton for **37n**. The introduction of a fluorine in the 2-position of the benzyl moiety does not change the biological activity (**11l** and **37o**). Interestingly, compound **37g**, which has no substituent either on the benzimidazole or on the benzyl, is poorly active. This suggests that it is important that at least one of the substituents (X_1, X_3, X_4) must be different from hydrogen.

Table IX shows that almost the same rules can be stated in the imidazo[4,5-*b*]pyridine series: Alkanoic acid derivatives are more potent than mercaptoalkanoic acid derivatives (**21** vs **23**), and a chlorine in the 6-position (X_1 of Table IX structures) is beneficial (**23a** vs **23b**). Comparison between compounds **23a** and **11h** on the one hand and between **23c** and **11q**, on the other hand, demonstrates that the replacement of the benzimidazole nucleus by an imidazo[4,5-*b*]pyridine nucleus leads to compounds with the same affinity for TXA_2/PGH_2 receptor.

Our derivatives being structurally related to L-655,240 and L-670,596, it is interesting to compare our SAR study with Merck Frosst results. The present work clearly shows that the indole nucleus of L-655,240 can be replaced by an imidazole or imidazo[4,5-*b*]pyridine, provided that the alkanoic acid side chain is a 3,3-dimethylbutanoic chain. Indeed, compound **11c** which possesses the same acid side chain as L-655,240 displays a very low affinity as compared to **11a** (see Table VI). Others derivatives with a three-carbon side chain (**11b** and **11v**) are even less potent, indicating that the optimal length of this chain, for the derivatives described herein, is different from that proposed by Merck Frosst. This may be due to the absence, in our series, of the methyl substituent present at the 3-position of L-655,240. This methyl has been shown to play an important role in the activity of L-655,240[17] and likely contributes to rigidify its structure. Concerning the substitutions on the benzimidazole and imidazo[4,5-*b*]-pyridine on the one hand and on the benzyl group on the

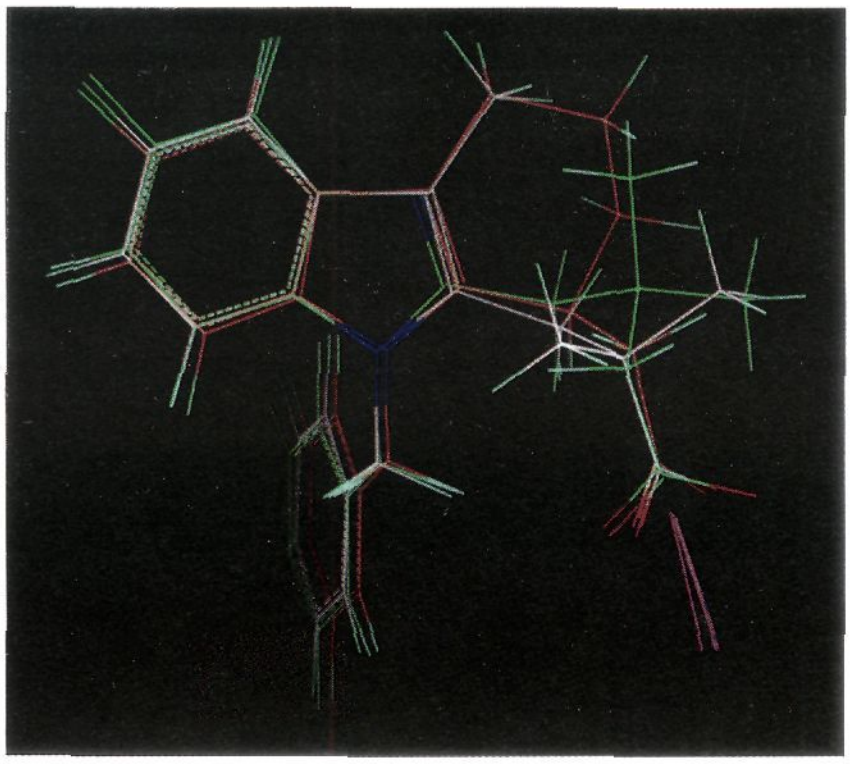
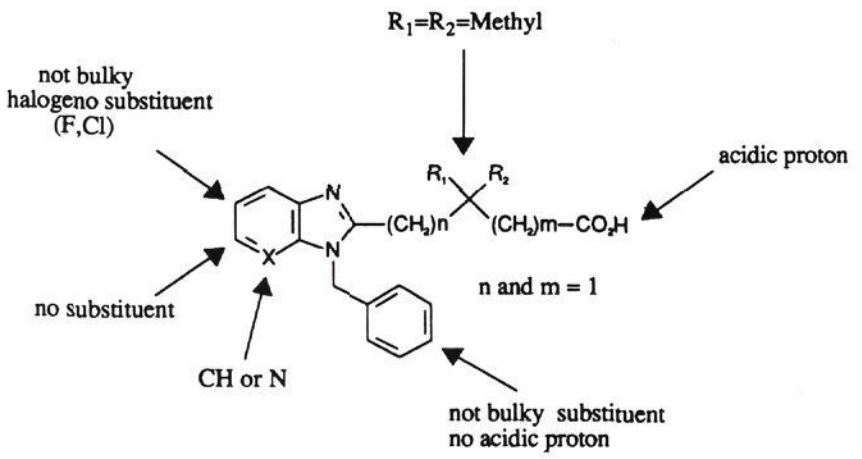


Figure 1. Superimposition of L-655,240 (carbons in white), compound **46** (carbons in orange), and compound **11a** (carbons in green).

Chart II. In Vitro SAR Study



other hand, we have found almost the same rules as that found for L-655,240.[31]

In conclusion, the key structural variations investigated in in vitro SAR studies are summarized in Chart II.

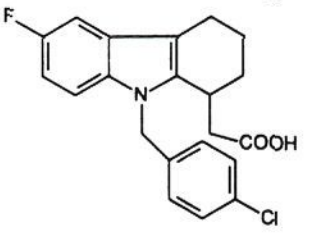
Biology of UP 116-77 (23a). UP 116-77 (**23a**) was selected as the lead compound and tested in vivo on the inhibition of 11,9-epoxymethano-PGH_2 (1 μM) induced platelet aggregation (U-IPA) on guinea pig platelet-rich plasma (PRP) 1 h after per os administration. As shown in Table XI, **23a** exhibits a potent oral activity at 1 and 0.3 mg/kg with a K_i value of 21.4 ± 5.6 nM. It is currently under pharmacological development.

Molecular Modeling and Optimization of the Propionic Acid Side Chain. As indicated in in vitro SAR study section, the use of the 2,2-dimethylpropanoic side chain of L-655,240 in our series led to compounds with low affinities. So compounds **11b**, **11c**, and **11v**, which possess two carbon atoms between the carboxylate and the imidazole, were synthesized, but their potencies were quite low (Tables VI and X).

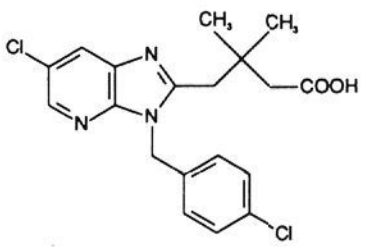
For the molecular modeling study we used L-655,240 and compound **46** (analogue of L-670,596, described by Merck Frosst and synthesized in our laboratory according to ref 33, K_i = 15.3 nM, see Table X and Chart III) because of their particularly rigid structures.

Since the replacement of the propionic acid side chain of compound **11b** by a 3,3-dimethylbutanoic acid side chain (**11a**) improved the activity considerably, leading to a compound more potent than **46**, consequently, the substitution of the 3-methylindole by a benzimidazole did not hinder interactions with the receptor as we could expect from the first results with **11b**, **11c**, and **11v**. We wanted to understand why this substitution decreased the potency in the case of compounds possessing a propanoic acid side chain (**11b**, **11c**, **11v**) and how the introduction of a 3,3-dimethylbutanoic acid side chain (**11a**) could improve it in this series.

Chart III. Structures of **46** and **23a**, Non-Prostanoid- and Non-Sulotroban-Related Antagonists



46 (MERCK FROSST)[33]



23a (UP 116-77)[19]

Using molecular modeling we sought a means of superimposing benzimidazole and indole rings of compounds L-655,240, **46**, and **11a** on the one hand, and the carboxylic acid of these compounds on the other hand. After reduction of the symmetries two solutions were found. In the first one, the bond carbon sp^3–carbon sp^3 of L-655,240 and **46** was not greatly removed from a stable staggered conformation, whereas in the second one (Figure 1), this bond was quite near from an unstable eclipsed conformation. However, the last conformation was stabilized by the 3-methyl on the indole of L-655,240 and by the cyclic system of **46**. In the case of compounds **11b**, **11c**, and **11v**, the first solution was acceptable, while, because of the absence of the 3-methyl on the benzimidazole, the second one was quite unstable and unacceptable. For these reasons, we could suggest that the conformation at the TXA_2 receptor of compounds L-655,240, **46**, and **11a** was the one found in the second solution (Figure 1). We have arbitrarily used the *S* isomer of compound **46** for the calculations; it had no influence on the result since others used compounds (L-655,240 and **11a**) have no chiral center.

To validate this model, it would be interesting to propose new structures. Some could have the capacity to maintain the carbon sp^3–carbon sp^3 bond between the benzimidazole and the carboxylic acid in a roughly eclipsed conformation, while others could not. One method was to include this bond in a ring, the size of which would drive the value of the dihedral angle.

Three compounds were proposed. The first one, **42**, was able to adopt a roughly eclipsed conformation by means of a cyclopentyl ring. The second one, **41**, was chosen because of its completely eclipsed conformation forced by a cyclobutyl ring. The last one, **43**, was stabilized by a cyclohexene ring in a completely staggered conformation. The two first rings were synthesized in their trans isomer form, while the last one was in the cis conformation.

The conformation being chosen after trials to superimpose all the configurations of each compound on the model.

As expected, compound **42** is much more potent than compounds **11b**, **11c**, and **11v**, but also than **41** and **43** (see Table X). Although we have not completely recovered the potency of compound **46**, by using molecular modeling, we have obtained a compound (**42**) 40-fold more potent than **11b**. However, because of a complex synthetic process and the existence in this series of more potent compounds, this work could be considered as a textbook case and was not continued.

Conclusion

The study of this series of benzimidazole and imidazo[4,5-*b*]pyridine acid derivatives has resulted in the discovery of new potent non-prostanoid TXA_2 antagonists, since in vitro, the best compound (**11n**, Table VIII), with a K_i of 4 nM, is about 160-fold more potent than sulotroban (Table VI).

The various modifications performed in this series led to the conclusion that the 3,3-dimethylbutanoic acid side chain in the 2-position of the imidazole nucleus is of primordial importance for the activity. The compounds possessing this side chain exhibited high affinity (K_i values in the range 4–39 nM) for washed human platelet TXA_2/PGH_2 receptors. Among these compounds, the derivative **23a** (UP 116-77) is of a great interest since it is a potent orally active TXA_2 receptor antagonist (see Table XI). Furthermore, its tolerance in animal is excellent as the maximal tolerated doses per os in rat and dog were determinated at 800 and 1000 mg/kg, respectively, for a period of 14 days of treatment. Therefore, **23a** was selected for further investigation in number of pharmacological models in which TXA_2 is believed to be implicated.

Experimental Section

^{1}H NMR spectra were measured at 200 MHz on a Bruker 200 spectrometer and recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to internal reference Me_4Si. Melting points were recorded on an Electrothermal digital capillary melting point apparatus and are uncorrected. Chromatography was performed on silica gel (mesh 70–230) using indicated solvent mixtures. Elemental analyses were obtained by using a CARLO ERBA MOD-106 elemental analyzer. Starting materials were commercially available or their preparation could be found in ref 19.

Method A. 2-[[(4-Chlorophenyl)methyl]amino]-5-fluoronitrobenzene (3a). To a solution of 30 g (188 mmol) of 2,5-difluoronitrobenzene and 26.7 g (188 mmol) of 4-chlorobenzylamine in 300 mL of THF were added 40 g (289 mmol) of potassium carbonate, and the mixture was refluxed for 8 h. After cooling, the reaction mixture was added to 1.7 L of water and 50 mL of concentrated hydrochloric acid. The crystals obtained were filtered off and washed with water and then with isopropyl ether to give 41.9 g (83%) of **3a**: mp 160 °C; ^{1}H NMR (DMSO-d_6) 4.63 (d, J = 5.5 Hz, 2 H, NCH_2Ph), 6.9 (dd, J = 2.8 and 8.5 Hz, 1 H, H_a), 7.4–7.5 (m, 5 H, H_b + 4 H arom), 7.86 (dd, J = 2.8 and 8.5 Hz, 1 H, H_d), 8.7 (t, J = 5.5 Hz, 1 H, $NHCH_2$).

Method B. 2-[[(4-Chlorophenyl)methyl]amino]-5-chloronitrobenzene (3m). A mixture of 25 g (130 mmol) of 2,5-dichloronitrobenzene and 36.9 g (260 mmol) of 4-chlorobenzylamine was heated for 2 h at 135 °C, the temperature was always kept below 140 °C. After cooling, the mixture was taken up with water and extracted with ethyl acetate. After drying over magnesium sulfate and evaporation under vacuum, the residue was taken up with ether and the crystals obtained were filtered off and washed with ether to give 22.3 g (58%) of 3m: mp 120 °C; ^{1}H NMR (DMSO-d_6) 4.61 (d, J = 5.5 Hz, 2 H, NCH_2Ph), 6.9 (d, J = 8 Hz, 1 H, H_a), 7.38 (br s, 4 H arom), 7.49 (dd, J = 2.5 and 8 Hz, 1 H, H_b), 8.05 (d, J = 2.5 Hz, 1 H, H_d), 8.79 (t, J = 5.5 Hz, 1 H, $NHCH_2$).

Method C. (a) 2-[[(4-Methylphenyl)sulfonyl]amino]-5-methoxynitrobenzene (2'a). A solution of 50 g (297 mmol) of 4-methoxy-2-nitroaniline in 300 mL of pyridine was stirred at 0 °C, 56.7 g (297 mmol) of tosyl chloride was added portionwise at 0 °C, and the mixture was then stirred for 2 h at room temperature, left to stand overnight, and poured into an ice/water mixture. The crystals obtained were filtered off and washed with water and then with isopropyl ether to give 72.8 g (76%) of **2'a**: mp 99 °C; ^{1}H NMR (DMSO-d_6) 2.39 (s, 3 H, CH_3Ph), 3.8 (s, 3 H, OCH_3), 7–7.15 (m, 2 H, H_a + H_b), 7.3–7.65 (m, 5 H, H_d + 4 H $PhCH_3$), 10 (br s, 1 H, NH).

(b) *N*-(4-Chlorobenzyl)-*N*-[(4-methylphenyl)sulfonyl]-2-nitro-4-methoxyaniline (3'a). To 56.5 mL of 4 N sodium hydroxide solution were added 72.8 g (226 mmol) of **2'a** and 29.2 g (181 mmol) of 4-chlorobenzyl chloride. The mixture was refluxed for 4 h, a further 43.7 g (271 mmol) of 4-chlorobenzyl chloride was then added, and the resulting mixture was refluxed for another 45 min. After cooling, 12.2 mL of 35% sodium hydroxide solution was added to the reaction mixture, which was refluxed for 3 h and then cooled before water and ether were added. The insoluble material was filtered off and washed with water and ether to give 90 g (89%) of **3'a**, mp 124 °C. Evaporation of the ether layer yielded an additional 10 g of **3'a**: mp 124 °C; ^{1}H NMR ($CDCl_3$) 2.43 (s, 3 H, CH_3Ph), 3.8 (s, 3 H, OCH_3), 4.65 (d, J = 14.7 Hz, 1 H, CH_2Ph), 4.91 (d, J = 14.7 Hz, 1 H, CH_2Ph), 6.77 (d, J = 9.3 Hz, 1 H, H_a), 6.9 (dd, J = 2.6 and 9.3 Hz, 1 H, H_b), 7.12–7.3 (m, 7 H, H_d + 4 H PhCl + 2 H $PhCH_3$), 7.5 (d, J = 8 Hz, 2 H, $PhCH_3$).

(c) 2-[[(4-Chlorophenyl)methyl]amino]-5-methoxynitrobenzene (3l). To 940 mL of propionic acid and 102 mL of concentrated sulfuric acid was added 100 g (223 mmol) of **3'a**. The mixture was heated at 95 °C for 1 h 30 min, and the solution was concentrated to half its volume by evaporation under vacuum and then poured onto ice and neutralized with ammonium hydroxide. The crystals obtained were filtered off and washed with water and isopropyl ether to give 60 g (92%) of **3l**: mp 135 °C; ^{1}H NMR (DMSO-d_6) 3.8 (s, 3 H, OCH_3), 4.61 (d, J = 5.5 Hz, 2 H, NCH_2Ph), 7–7.15 (m, 2 H, H_a + H_b), 7.3–7.5 (m, 5 H, H_d + 4 H PhCl), 8.8 (t, J = 5.5 Hz, 1 H, $NHCH_2$).

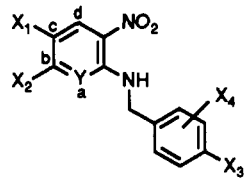
Method D. 2-[[[4-(Methylthio)phenyl]methyl]amino]-5-fluoronitrobenzene (3b). Anhydrous sodium acetate (14.4 g, 175 mmol), 24.8 g (159 mmol) of 2-amino-5-fluoronitrobenzene, and 27.6 g (159 mmol) of 4-(methylthio)benzyl chloride were mixed together with 0.3 g (1.2 mmol) of iodine. The mixture was heated with stirring at 120 °C for 12 h and then cooled, taken up with a dilute hydrochloric acid solution, and extracted with ethyl acetate. The organic layer was washed with dilute HCl and then with water, dried over magnesium sulfate, and evaporated under vacuum. The oil obtained crystallized in isopropyl ether to give 23.8 g (53%) of **3b**: mp 117 °C; ^{1}H NMR (DMSO-d_6) 2.45 (s, 3 H, SCH_3), 4.59 (d, J = 5.5 Hz, 2 H, NCH_2Ph), 6.92 (dd, J = 2.8 and 8.5 Hz, 1 H, H_a), 7.15–7.53 (m, 5 H, H_b + 4 H $PhSCH_3$), 7.87 (dd, J = 2.8 and 8.5 Hz, 1 H, H_d), 8.65 (t, J = 5.5 Hz, 1 H, $NHCH_2$).

Method E. 2-[[(4-Chlorophenyl)methyl]amino]-3-nitro-5-chloropyridine (17a). A solution of 20.9 g (147 mmol) of 4-chlorobenzylamine and 15.7 g (81 mmol) of 2,5-dichloro-3-nitropyridine[19] in 250 mL of xylene and 20 mL of 2-methyl-5-ethylpyridine was refluxed for 30 h. After cooling, water was added to the reaction mixture and the resulting mixture was then extracted with ethyl acetate. The organic phase was washed with a dilute solution of hydrochloric acid and dried over magnesium sulfate. The solvent was evaporated off under vacuum, and the residue was crystallized from isopropyl ether to give 21.1 g (61%) of **17a**: mp 120 °C; ^{1}H NMR ($CDCl_3$) 4.78 (d, J = 5.7 Hz, 2 H, NCH_2Ph), 7.3 (br s, 4 H, PhCl), 8.37 (d, J = 2.3 Hz, 1 H, H_b), 8.44 (d, J = 2.3 Hz, 1 H, H_d), 8.6 (br t, J = 5.7 Hz, 1 H, $NHCH_2$).

All compounds of formula 3 or 17 were synthesized according to one of the five methods described above, and corresponding data are summarized in Table I.

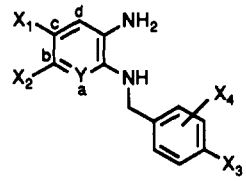
Hydrogenation of Compounds 3 and 17: Typical Procedure. 2-[[(4-Chlorophenyl)methyl]amino]-5-fluoroaniline (4a). A solution of 41.7 g (155 mmol) of **3a** in 1 L of THF was hydrogenated at ordinary temperature and pressure in the presence of 5 g of Raney nickel. When theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and

Table I. Preparation and Physical Properties of Compounds 3 and 17



no.	X_1	X_2	X_3	X_4	Y	method	yield, %	mp, °C
3a	F	H	Cl	H	CH	A	83	160–161
3b	F	H	SCH_3	H	CH	D	53	117–118
3c	F	H	Cl	3-Cl	CH	B	62	110–111
3d	F	H	Br	2-F	CH	A	76	130–131
3e	F	H	Br	H	CH	A	78	163–164
3f	Cl	H	SCH_3	H	CH	D	57	74–75
3g	Br	H	Cl	H	CH	B	68	118–119
3h	F	H	OCH_3	H	CH	A	80	106–108
3i	Cl	H	Br	2-F	CH	B	69	130–131
3j	Cl	H	Br	H	CH	B	71	136–137
3k	Cl	H	OCH_3	H	CH	B	63	114–116
3l	OCH_3	H	Cl	H	CH	C	71	135–136
3m	Cl	H	Cl	H	CH	B	58	120–122
3n	Cl	H	Cl	3-Cl	CH	B	65	129
17a	Cl	H	Cl	H	N	E	61	120
17b	H	H	Cl	H	N	E	69	100
17c	Cl	H	Br	2-F	N	E	63	75–77
17d	Cl	H	SCH_3	H	N	E	70	88

Table II. Preparation and Physical Properties of Compounds 4 and 18



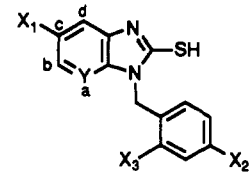
no.	X_1	X_2	X_3	X_4	Y	yield, %	mp, °C
4a	F	H	Cl	H	CH	87	99
4b	F	H	SCH_3	H	CH	90	112–113
4c	F	H	Cl	3-Cl	CH	92	104–105
4d	F	H	Br	2-F	CH	88	oil
4e	F	H	Br	H	CH	93	97–98
4f	Cl	H	SCH_3	H	CH	85	131–132
4g	Br	H	Cl	H	CH	90	149–150
4h	F	H	OCH_3	H	CH	95	123–124
4i	Cl	H	Br	2-F	CH	91	89–91
4j	Cl	H	Br	H	CH	85	152–153
4k	Cl	H	OCH_3	H	CH	84	108
4l	OCH_3	H	Cl	H	CH	89	90–92
4m	Cl	H	Cl	H	CH	86	138–139
4n	Cl	H	Cl	3-Cl	CH	85	80
18a	Cl	H	Cl	H	N	91	oil
18b	H	H	Cl	H	N	88	132
18c	Cl	H	Br	2-F	N	90	97
18d	Cl	H	SCH_3	H	N	80	116

the solvent was evaporated under vacuum to give 34.1 g (84%) of **4a**: mp 99 °C; ^{1}H NMR (DMSO-d_6) 4.27 (br s, 2 H, NCH_2Ph), 5.00 (br s, 3 H, NH + NH_2), 6.1–6.3 (m, 2 H, H_a + H_b), 6.41 (dd, J = 2.2 and 10.5 Hz, 1 H, H_d), 7.4 (br s, 4 H, PhCl).

All compounds of formulas **4** and **18** were prepared by this hydrogenation procedure, and corresponding data are shown in Table II.

1-[(4-Chlorophenyl)methyl]-2-mercapto-5-fluorobenzimidazole (5a). Carbon disulfide (25 mL) was added to 35.2 g (140 mmol) of **4a** dissolved in 500 mL of ethanol. The mixture was refluxed for 12 h and allowed to return to room temperature. After the mixture stood for a few hours, the crystals were filtered off and washed with ethanol and then with 2-propanol and ether to give 33 g (80%) of **5a**: mp 215 °C; ^{1}H NMR (DMSO-d_6) 5.5 (s, 2 H, NCH_2Ph), 6.92–7.1 (m, 2 H, H_a + H_b), 7.21–7.32 (m, 1 H, H_d), 7.4 (br s, 4 H, PhCl).

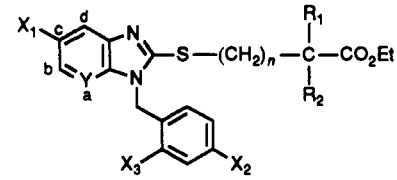
Table III. Preparation of Compounds 5 and 19



no.	X_1	X_2	X_3	Y	yield, %[a]	mp, °C
5a	F	Cl	H	CH	80	215
19a	Cl	Cl	H	N	83	260
19b	H	Cl	H	N	85	216
19c	Cl	Br	F	N	78	240

[a] Yield is calculated from diamines 4 or 18.

Table IV. Preparation of Compounds 7 and 20



no.	X_1	X_2	X_3	n	R_1	R_2	Y	yield, %[a]
7a	F	Cl	H	2	H	H	CH	84
7b	F	Cl	H	3	H	H	CH	80
7c	F	Cl	H	0	CH_3	H	CH	78
7d	F	Cl	H	0	CH_3	CH_3	CH	80
20a	Cl	Cl	H	2	H	H	N	80
20b	H	Cl	H	2	H	H	N	85
20c	Cl	Br	F	2	H	H	N	78[b]
20d	Cl	Cl	H	0	CH_3	CH_3	N	80

[a] Crude yield of product used directly as an oil in the next stage. [b] mp 94 °C.

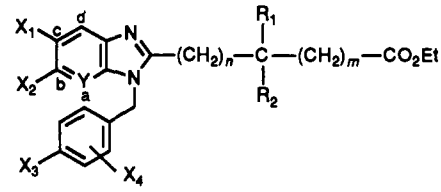
Compounds of formula **5** or **19** were synthesized according to the same procedure, and corresponding data are shown in Table III.

Ethyl 4-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]mercaptobutanoate (7a). A mixture of 9 g (30 mmol) of **5a** and 4.4 mL (30 mmol) of ethyl 4-bromobutyrate was refluxed for 5 h in 100 mL of acetone in the presence of 6.2 g (45 mmol) of K_2CO_3. The solvent was evaporated off under vacuum, the residue was taken up in water and extracted with ethyl acetate, and the extract was washed with a dilute solution of NaOH. The organic phase was dried over magnesium sulfate and evaporated under vacuum to give 11.9 g (84%) of **7a**: oil; ^{1}H NMR (DMSO-d_6) 1.15 (t, J = 7.5 Hz, 3 H, CH_3 ester), 1.95 (m, 2 H, CH_2), 2.34 (t, J = 7.2 Hz, 2 H, CH_2CO_2H), 3.37 (t, J = 7.1 Hz, 2 H, SCH_2), 4.1 (q, J = 7.5 Hz, 2 H, CH_2 ester), 5.42 (s, 2 H, CH_2PhCl), 7.05 (m, 1 H, H_a), 7.2 (d, J = 8.4 Hz, 2 H, PhCl), 7.42 (d, J = 8.4 Hz, 2 H, PhCl), 7.45–7.54 (m, 2 H, H_b + H_d).

Compounds of formulas **7** and **20** were synthesized according to the same procedure starting from appropriate ethyl bromoalkanoates; corresponding data are shown in Table IV.

Method F. Ethyl 4-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoate (10a). A solution of 10 g (40 mmol) of **4a** in 100 mL of $CHCl_3$, stabilized with amylene, and 6 mL (40 mmol) of triethylamine was stirred at room temperature. A solution of 8.25 g (40 mmol) of the acid chloride ethyl ester of 3,3-dimethylglutaric acid[19] in 20 mL of $CHCl_3$, stabilized with amylene, was added dropwise at room temperature. The mixture was then stirred for 2 h at room temperature, the crystals formed were filtered off, and the solvent was evaporated under vacuum. The residue obtained was dissolved in 200 mL of EtOH and 30 mL of concentrated HCl, and the mixture was refluxed for 10 h. The solvents were evaporated off to dryness, and the residue was taken up with water and then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated under vacuum to give 14 g (86%) of **10a**: oil; ^{1}H NMR (DMSO-d_6) 1.09 (s, 6 H, $C(CH_3)_2$), 1.13 (t, J = 7.4 Hz, 3 H, CH_3 ester), 2.54 (s, 2 H, CH_2CO_2Et), 2.97 (s, 2 H, CH_2), 4.07 (q, J = 7.4 Hz, 2 H, CH_2 ester), 5.57 (s, 2 H, CH_2PhCl), 6.98–7.12 (m, 3 H, H_a + 2 H PhCl), 7.37–7.48 (m, 4 H, H_b + H_d + 2 H PhCl).

Table V. Preparation and Physical Properties of Compounds of Formula 10, 22, and 36



no.	X_1	X_2	X_3	X_4	Y	*n*	*m*	R_1	R_2	method	yield, %[a]
10a	F	H	Cl	H	CH	1	1	CH_3	CH_3	F	86
10b	F	H	Cl	H	CH	1	0	H	H	F	83
10c	F	H	Cl	H	CH	1	0	CH_3	CH_3	F	87
10d	F	H	Cl	H	CH	1	1	CH_2CH_2		F	91
10e	F	H	Cl	H	CH	1	1	$CH_2(CH_2)_2CH_2$		F	75
10f	F	H	Cl	H	CH	1	1	$CH_2(CH_2)_3CH_2$		F	70
10g	OCH_3	H	Cl	H	CH	1	1	CH_3	CH_3	F	75
10h	Cl	H	Cl	H	CH	1	1	CH_3	CH_3	F	88
10i	Br	H	Cl	H	CH	1	1	CH_3	CH_3	F	88
10j	F	H	Cl	3-Cl	CH	1	1	CH_3	CH_3	F	80
10k	F	H	SCH_3	H	CH	1	1	CH_3	CH_3	F	92
10l	F	H	Br	2-F	CH	1	1	CH_3	CH_3	F	95
10m	F	H	Br	H	CH	1	1	CH_3	CH_3	F	89
10n	F	H	OCH_3	H	CH	1	1	CH_3	CH_3	F	91
10o	F	H	Cl	2-F	CH	1	1	CH_3	CH_3	F	85
10p	Cl	H	Cl	3-Cl	CH	1	1	CH_3	CH_3	F	87
10q	Cl	H	SCH_3	H	CH	1	1	CH_3	CH_3	F	93
10r	Cl	H	Cl	2-F	CH	1	1	CH_3	CH_3	F	92
10s	Cl	H	Br	2-F	CH	1	1	CH_3	CH_3	F	91
10t	Cl	H	Br	H	CH	1	1	CH_3	CH_3	F	85
10u	Cl	H	OCH_3	H	CH	1	1	CH_3	CH_3	F	88
22a	Cl	H	Cl	H	N	1	1	CH_3	CH_3	H	39
22b	H	H	Cl	H	N	1	1	CH_3	CH_3	H	43
22c	Cl	H	SCH_3	H	N	1	1	CH_3	CH_3	H	47
36a	H	H	Cl	H	CH	1	1	CH_3	CH_3	G	53
36b	H	H	Cl	H	CH	1	1	CH_3	C_2H_5	G	54
36c	H	H	Cl	H	CH	1	1	C_2H_5	C_2H_5	G	56
36d	H	H	Cl	H	CH	1	1	C_6H_5	H	G	51
36e	H	H	Cl	H	CH	1	1	CH_3	H	G	53
36f	Cl	Cl	Cl	H	CH	1	1	CH_3	CH_3	G	61
36g	H	H	H	H	CH	1	1	CH_3	CH_3	G	57
36h	H	H	CH_3	H	CH	1	1	CH_3	CH_3	G	52
36i	H	H	F	H	CH	1	1	CH_3	CH_3	G	56
36j	H	H	OCH_3	H	CH	1	1	CH_3	CH_3	G	51
36k	H	H	Br	H	CH	1	1	CH_3	CH_3	G	57
36l	H	H	H	3-CF_3	CH	1	1	CH_3	CH_3	G	48
36m	H	H	NO_2	H	CH	1	1	CH_3	CH_3	G	53
36n	H	H	Br	2-F	CH	1	1	CH_3	CH_3	G	60
36o	H	H	Cl	H	CH	0	1	CH_3	CH_3	G	20

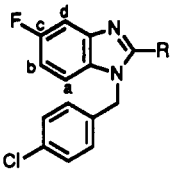
[a] Crude yield of product used directly in the next stage.

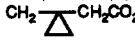
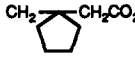
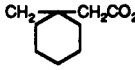
Method G. Ethyl 4-[1-[(4-Chlorophenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutanoate (36a). (a) Ethyl 4-(Benzimidazol-2-yl)-3,3-dimethylbutanoate (35a). A solution of 139.2 g (674 mmol) of the acid chloride ethyl ester of 3,3-dimethylglutaric acid[19] in 125 mL of $CHCl_3$, stabilized with amylene, was added dropwise, at a temperature of between 5 and 10 °C, to a solution of 72.8 g (674 mmol) of *o*-phenylenediamine and 95 mL (674 mmol) of triethylamine in 1 L of anhydrous THF. The mixture was stirred at 0 °C for 2 h and then at 50 °C for 1 h. The crystals formed were filtered off, and the solvents were evaporated to dryness under vacuum. The residue was dissolved in 4.4 L of EtOH and 440 mL of concentrated HCl, and the mixture was refluxed for 12 h. The solvents were evaporated off, and the residue was taken up with water and then neutralized with a 1 N solution of NaOH and extracted with Et_2O. The organic layer was dried over magnesium sulfate and evaporated under vacuum to give 99 g (56%) of **35a**: mp 123 °C; ^{1}H NMR (DMSO-d_6) 1.07 (s, 6 H, $C(CH_3)_2$), 1.2 (t, J = 7.5 Hz, 3 H, CH_3 ester), 2.4 (s, 2 H, CH_2CO_2Et), 2.85 (s, 2 H, CH_2), 4.05 (q, J = 7.5 Hz, 2 H, CH_2 ester), 7.15 (m, 2 H, arom), 7.55 (m, 2 H, arom).

(b) Ethyl 4-[1-[(4-Chlorophenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutanote (36a). To a suspension of 1.4 g (35 mmol) of 60% NaH in 50 mL of anhydrous DMF was added 9 g (35 mmol) of **35a**. The mixture was stirred for 1 h at 50 °C, 5.6 g (35 mmol) of 4-chlorobenzyl chloride was then added, and the solution obtained was heated for 5 h at 90 °C. The solvent was concentrated under vacuum and the residue was taken up with water and then extracted with Et_2O. The organic phase was washed with water, dried over magnesium sulfate, and evaporated off to dryness to give 12.9 g (95%) of **36a**: oil; ^{1}H NMR (DMSO-d_6) 1.1 (s, 6 H, $C(CH_3)_2$), 1.15 (t, J = 7.3 Hz, 3 H, CH_3 ester), 2.55 (s, 2 H, CH_2CO_2Et), 2.96 (s, 2 H, CH_2), 4.04 (q, J = 7.3 Hz, 2 H, CH_2 ester), 5.58 (s, 2 H, CH_2PhCl), 7.04–7.25 (m, 4 H, H_a + H_d + 2 H PhCl), 7.32–7.5 (m, 3 H, H_b + 2 H PhCl), 7.61 (m, 1 H, H_c).

Method H. Ethyl 4-[3-[(4-Chlorophenyl)methyl]-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoate (22a). To a solution of 16.5 g (61.5 mmol) of **18a** dissolved in 25 mL of EtOH and 25 mL of acetic acid was added 12.1 g (70 mmol) of ethyl 4-formyl-3,3-dimethylbutanoate **26**,[19] and the mixture was stirred for 4 h at room temperature. The solvents were evaporated off, the residue was dissolved in 200 mL of 1,2-dimethoxyethane, 20 g (79 mmol) of iodine was added, and the solution was heated 16 h at 50 °C. The solvent was evaporated under vacuum and the residue taken up with water and extracted with Et_2O. The organic layer was washed with water, dried over magnesium sulfate, and evaporated to dryness to provide the crude product. Column chromatography on silica gel (elution cyclohexane/ethyl acetate, 7:3) provided 10 g (39%) of **22a** as a colorless liquid: ^{1}H NMR ($CDCl_3$) 1.15 (s, 6 H, $C(CH_3)_2$), 1.24 (t, J = 7.1 Hz, 3 H, CH_3 ester), 2.46 (s, 2 H, CH_2CO_2Et), 2.96 (s, 2 H, CH_2), 4.11 (q, J = 7.1 Hz, 2 H, CH_2 ester), 5.5 (s, 2 H, CH_2PhCl), 7.08 (d, J = 8 Hz, 2 H, PhCl), 7.26 (d, J = 8 Hz, 2 H, PhCl), 7.99 (d, J = 2 Hz, 1 H, H_d), 8.3 (d, J = 2 Hz, 1 H, H_b).

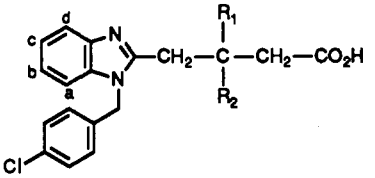
Table VI. Product Characterization and in Vitro Activity: Modifications of the 2-Poisition Acid Side Chain



no.	R	yield, %[a]	formula[b]	mp, °C	competition with [125I]PTA-OH in human platelets: % inhibition[f] 10^{-7} M	% inhibition[f] 10^{-5} M	K_i, μM
8a	$S(CH_2)_3CO_2H$	71	$C_{18}H_{16}ClFN_2O_2S$	176–178	8 ± 3	93 ± 3	nd
8b	$S(CH_2)_4CO_2H$	75	$C_{19}H_{18}ClFN_2O_2S·0.25H_2O$	184–186	28 ± 5	100 ± 1	nd
8c	$SCH(CH_3)CO_2H$	78	$C_{17}H_{14}ClFN_2O_2S·0.25H_2O$	139–140	9 ± 3	83 ± 2	nd
8d	$SC(CH_3)_2CO_2H$	81	$C_{18}H_{16}ClFN_2O_2S$	197–199	3 ± 2	83 ± 5	0.67
11a	$CH_2C(CH_3)_2CH_2CO_2H$	65	$C_{20}H_{20}ClFN_2O_2$	164–165	94 ± 1	100 ± 1	0.0078
11b	$CH_2CH_2CO_2H$	68	$C_{17}H_{14}ClFN_2O_2$	238–240[e]	0 ± 1	64 ± 3	5.6
11c	$CH_2C(CH_3)_2CO_2H$	65	$C_{19}H_{18}ClFN_2O_2$	248–250	0 ± 1	50 ± 3	1.7
11d		45	$C_{20}H_{18}ClFN_2O_2$	181–183	80 ± 1	98 ± 2	0.052
11e		59	$C_{22}H_{22}ClFN_2O_2$	164–165	71 ± 2	100 ± 2	0.042
11f		50	$C_{23}H_{24}ClFN_2O_2$	182–184	0 ± 3	98 ± 4	0.87
33	$CH_2C(CH_3)_2CH_2CH_2CO_2H$	74[c]	$C_{21}H_{22}ClFN_2O_2$[d]	184–186	56 ± 9	87 ± 2	0.023
sulotroban					13 ± 3*	95 ± 2*	0.650

[a] Yield of hydrolysis (method I) calculated from corresponding crude esters. [b] All elemental analyses for C, H, and N were within ±0.4% of the calculated values unless otherwise noted. [c] Yield calculated from nitrile 32. [d] C: calcd, 64.86; found, 64.4. [e] Hydrochloride. [f] Values are mean ± SEM of three or six (*) determinations.

Table VII. Product Characterization and in Vitro Activity: Modifications of the Substituents at the Butanoic Acid β-Carbon



no.	R_1	R_2	yield, %[a]	formula[b]	mp, °C	competition with [125I]PTA-OH in human platelets: % inhibition[c] 10^{-7} M	% inhibition[c] 10^{-5} M	K_i, μM
37a	CH_3	CH_3	64	$C_{20}H_{21}ClN_2O_2$	170–171	85 ± 5	100 ± 2	0.031
37b	CH_3	C_2H_5	50	$C_{21}H_{23}ClN_2O_2$	120–123	57 ± 1	100 ± 1	nd
37c	C_2H_5	C_2H_5	70	$C_{22}H_{25}ClN_2O_2$	139–140	35 ± 6	97 ± 2	0.16
37d	C_6H_5	H	60	$C_{24}H_{21}ClN_2O_2$	173–174	0 ± 1	17 ± 8	nd
37e	CH_3	H	47	$C_{19}H_{19}ClN_2O_2$	201–202	10 ± 4	100 ± 1	nd

[a] Yield of hydrolysis (method I) calculated from corresponding crude esters. [b] All elemental analyses were within ±0.4% of theoretical values for C, H, and N. [c] Values are mean ± SEM of three determinations.

All compounds of formula **10**, **22**, or **36** were synthesized either by method F, G, or H, and experimental data are summarized in Table V.

The preparation of appropriate acid chlorides of formula **9** could be found in ref 19.

Ethyl *trans*-2-[1-[(4-Chlorophenyl)methyl]-5-benzimidazol-2-yl]cyclobutane-1-carboxylate (38). **38** was prepared according to method F, proceeding from the acid chloride ethyl ester of *trans*-cyclobutane-1,2-dicarboxylic acid:[19,28,29] oil; ^{1}H NMR ($CDCl_3$) 1.2 (t, J = 7.5 Hz, 3 H, CH_3 ester), 2.1–2.45 (m, 3 H, CH_2CH_2), 2.5–2.7 (m, 1 H, CH_2CH_2), 3.65 (q, J = 9 Hz, 1 H, $CHCO_2Et$), 3.88–4.1 (m, 3 H, CH + CH_2 ester), 5.25 (d, J = 16.8 Hz, 1 H, CH_2Ph), 5.4 (d, J = 16.8 Hz, 1 H, CH_2Ph), 6.85 (m, 4 H, H_a + H_b + 2 H PhCl), 7.25 (d, J = 9 Hz, 2 H, PhCl), 7.45 (dd, J = 2.7 and 8.5 Hz, 1 H, H_d).

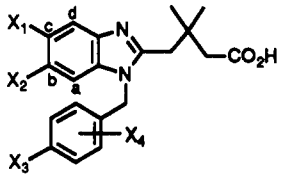
Ethyl *trans*-2-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]cyclopentane-1-carboxylate (39). **39** was prepared according to method F, proceeding from the acid chloride ethyl ester of *trans*-cyclopentane-1,2-dicarboxylic acid:[19,30] oil; ^{1}H NMR (DMSO-d_6) 1.2 (t, J = 7.5 Hz, 3 H, CH_3 ester), 1.5–1.9 (m, 4 H, cyclopentane), 1.92–2.25 (m, 2 H, cyclopentane), 3.45 (q, J = 10 Hz, 1 H, $CHCO_2Et$), 3.67 (q, J = 10 Hz, 1 H, CH), 4.00 (q, J = 7.5 Hz, 2 H, CH_2 ester), 5.56 (t, 2 H, CH_2PhCl), 6.96–7.1 (m, 3 H, H_a + 2 H PhCl), 7.35–7.5 (m, 4 H, H_b + H_d + 2 H PhCl).

Ethyl *cis*-5-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]cyclohexene-4-carboxylate (40). **40** was prepared according to method F, proceeding from the acid chloride ethyl ester of *cis*-cyclohexene-4,5-dicarboxylic acid:[19] mp 136 °C; ^{1}H NMR ($CDCl_3$) 1.00 (t, J = 8 Hz, 3 H, CH_3 ester), 2.4–2.65 (m, 3 H, allylic methylenes), 2.75–3.00 (m, 2 H, $CHCO_2Et$ + 1 H allylic), 3.58 (br q, 1 H, CH), 4.15 (q, J = 8 Hz, 2 H, CH_2 ester), 5.39 (s, 2 H, CH_2PhCl), 5.65–5.82 (m, 2 H, ehtylenic), 6.82–7.05 (m, 4 H, H_a + H_b + 2 H PhCl), 7.28 (d, J = 8.5 Hz, 2 H, PhCl), 7.54 (dd, J = 2.8 and 2.5 Hz, 1 H, H_d).

5-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]-4,4-dimethylvaleronitrile (32). **32** was prepared according to method H, proceeding from diamine **4a** and 5-formyl-4,4-dimethylvaleronitrile:[19] oil; ^{1}H NMR (DMSO-d_6) 0.98 (s, 6 H, $C(CH_3)_2$), 1.8 (t, J = 7.5 Hz, 2 H, CH_2CH_2CN), 2.56 (t, J = 7.5 Hz, 2 H, CH_2CN), 2.79 (s, 2 H, CH_2), 5.58 (s, 2 H, CH_2PhCl), 6.95–7.13 (m, 3 H, H_a + 2 H PhCl), 7.35–7.51 (m, 4 H, H_b + H_d + 2 H PhCl).

5-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]-4,4-dimethylpentanoic Acid (33). To a solution of 3 g (8

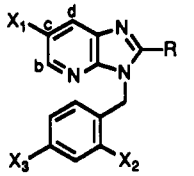
Table VIII. Product Characterization and in Vitro Activity: Variations on Substituents on Benzimidazole Ring and Benzyl Group



								competition with [125I]PTA-OH in human platelets		
								% inhibition[g]		
no.	X_1	X_2	X_3	X_4	yield, %[a]	formula[b]	mp, °C	10^{-7} M	10^{-5} M	K_i, μM
11g	OCH_3	H	Cl	H	58	$C_{21}H_{23}ClN_2O_3$	174–176	44 ± 5	100 ± 3	nd
11h	Cl	H	Cl	H	85	$C_{20}H_{20}Cl_2N_2O_2$	205–207	74 ± 5	99 ± 1	0.023
11i	Br	H	Cl	H	55	$C_{20}H_{20}BrClN_2O_2 \cdot 0.25H_2O$	219–221	38 ± 2*	67 ± 4*	nd
11j	F	H	Cl	3-Cl	59	$C_{20}H_{19}Cl_2FN_2O_2$	177–180	89 ± 6	92 ± 2	0.006
11k	F	H	SCH_3	H	50	$C_{21}H_{23}FN_2O_2S$	154–155	100 ± 5	100 ± 3	0.005
11l	F	H	Br	2-F	45	$C_{20}H_{19}BrF_2N_2O_2$	145–147	98 ± 5	100 ± 3	0.015
11m	F	H	Br	H	48	$C_{20}H_{20}BrFN_2O_2$	172–174	92 ± 1	95 ± 3	0.012
11n	F	H	OCH_3	H	59	$C_{21}H_{23}FN_2O_3$	137–138	79 ± 8	100 ± 8	0.004
11o	F	H	Cl	2-F	55	$C_{20}H_{19}ClF_2N_2O_2$[c]	186–188	58 ± 3	77 ± 8	nd
11p	Cl	H	Cl	3-Cl	50	$C_{20}H_{19}Cl_3N_2O_2$	183–184	71 ± 1	92 ± 4	0.012
11q	Cl	H	SCH_3	H	56	$C_{21}H_{23}ClN_2O_2S$	138–139	87 ± 4	89 ± 6	0.006
11r	Cl	H	Cl	2-F	78	$C_{20}H_{19}Cl_2FN_2O_2$	186–188	77 ± 5	87 ± 4	nd
11s	Cl	H	Br	2-F	56	$C_{20}H_{19}BrClFN_2O_2$	176–177	74 ± 3	95 ± 1	nd
11t	Cl	H	Br	H	60	$C_{20}H_{20}BrClN_2O_2$	160–161	98 ± 2	100 ± 4	0.013
11u	Cl	H	OCH_3	H	48	$C_{21}H_{23}ClN_2O_3$	144–145	95 ± 2	100 ± 4	0.020
11w	F	H	SO_2CH_3	H	74[d]	$C_{21}H_{23}FN_2O_4S$	221–222	100 ± 2	100 ± 4	0.037
11x	Cl	H	SO_2CH_3	H	70[d]	$C_{21}H_{23}ClN_2O_4S$	161–162	69 ± 3	82 ± 4	nd
37f	Cl	Cl	Cl	H	61	$C_{20}H_{19}Cl_3N_2O_2$	197–199	14 ± 8	100 ± 3	nd
37g	H	H	H	H	61	$C_{20}H_{22}N_2O_2 \cdot 0.5H_2O$	160–161	13 ± 3	95 ± 1	nd
37h	H	H	CH_3	H	70	$C_{21}H_{24}N_2O_2$	147–148	52 ± 2	100 ± 2	nd
37i	H	H	F	H	75	$C_{20}H_{21}FN_2O_2$	180–181	66 ± 6	100 ± 4	nd
37j	H	H	OCH_3	H	77	$C_{21}H_{24}N_2O_3$	149–150	89 ± 3	100 ± 2	0.031
37k	H	H	Br	H	83	$C_{20}H_{21}BrN_2O_2$[e]	171–172	86 ± 5	96 ± 4	0.016
37l	H	H	H	3-CF_3	70	$C_{21}H_{21}F_3N_2O_2$	164–165	49 ± 4	100 ± 1	nd
37m	H	H	NO_2	H	40	$C_{20}H_{21}N_3O_4$	192–194	83 ± 2	100 ± 1	0.060
37n	H	H	OH	H	15[f]	$C_{20}H_{22}N_2O_3 \cdot 0.25H_2O$	215–216	50 ± 1	96 ± 5	nd
37o	H	H	Br	2-F	67	$C_{20}H_{20}BrFN_2O_2 \cdot 0.5H_2O$	147–148	88 ± 1	99 ± 2	0.011

[a] Yield of hydrolysis (method I) calculated from corresponding crude esters. [b] All elemental analyses for C, H, and N were within ±0.4% of the calculated values unless otherwise noted. [c] C: calcd, 61.15; found, 61.8. [d] Yield of oxydation calculated from methylthio compound.[e] C: calcd, 59.86; found, 59.3. [f] Yield of demethylation calculated from **37j**. [g] Values are mean ± SEM of three or six (*) determinations.

Table IX. Product Characterization and in Vitro Activity: Imidazo[4,5-*b*]pyridine Series



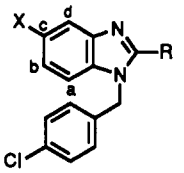
								competition of [125I]PTA-OH in human platelets		
								% inhibition[d]		
no.	X_1	X_2	X_3	R	yield, %[a]	formula[b]	mp, °C	10^{-7} M	10^{-5} M	K_i, μM
21a	Cl	H	Cl	$S(CH_2)_3CO_2H$	89	$C_{17}H_{15}Cl_2N_3O_2S \cdot 0.5H_2O$	160–161	6 ± 2	39 ± 3	nd
21b	H	H	Cl	$S(CH_2)_3CO_2H$	83	$C_{17}H_{14}ClN_3O_2S$[c]	121–122	27 ± 5	64 ± 1	nd
21c	Cl	F	Br	$S(CH_2)_3CO_2H$	85	$C_{17}H_{14}BrClFN_3O_2S$	156–158	24 ± 7	60 ± 1	nd
21d	Cl	H	Cl	$SC(CH_3)_2CO_2H$	85	$C_{17}H_{15}Cl_2N_3O_2S$	188–189	30 ± 1	100 ± 2	nd
23a	Cl	H	Cl	$CH_2C(CH_3)_2CH_2CO_2H$	75	$C_{19}H_{19}Cl_2N_3O_2$	137	97 ± 1	100 ± 2	0.021 ± 0.006[e]
23b	H	H	Cl	$CH_2C(CH_3)_2CH_2CO_2H$	70	$C_{19}H_{20}ClN_3O_2$	138–140	41 ± 8	62 ± 1	0.039
23c	Cl	H	SCH_3	$CH_2C(CH_3)_2CH_2CO_2H$	72	$C_{20}H_{22}ClN_3O_2S$	125–126	82 ± 5	87 ± 5	0.007

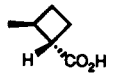
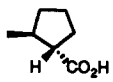
[a] Yield of hydrolysis (method J) calculated from corresponding crude esters. [b] All elemental analyses for C, H, and N were within ±0.4% of theoretical values unless otherwise noted. [c] C: calcd, 56.42; found, 56.0. [d] Values are mean ± SEM of three determinations. [e] K_i value is mean ± SEM of five independent experiments.

mmol) of **32** in 30 mL of water and 30 mL of ethanol was added 3 g of NaOH in pellets, and the mixture was heated at reflux for 15 h. After cooling, 100 mL of water was added, and the resulting solution was washed with Et_2O. The aqueous layer was acidified with sulfur dioxide, and the crystals obtained were filtered off, washed with water and Et_2O, and then dried to give 2.3 g (74%) of **33**: mp 184–186 °C; ^1H NMR (DMSO-d_6) 0.97 (s, 6 H, $C(CH_3)_2$), 1.68 (t, J = 8 Hz, 2 H, $CH_2CH_2CO_2H$), 2.27 (t, J = 8 Hz, 2 H, CH_2CO_2H), 2.77 (s, 2 H, CH_2), 5.55 (s, 2 H, CH_2PhCl), 6.93–7.11 (m, 3 H, H_a + 2 H PhCl), 7.31–7.46 (m, 4 H, H_b + H_d + 2 H PhCl), 12.1 (br s, 1 H, CO_2H).

Typical Procedure for the Preparation of Target Acids: Method I. 4-[1-[(4-Chlorophenyl)methyl]-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic Acid (11a). A solution of 9 g (22 mmol) of ester **10a** in a mixture of 90 mL of concentrated hydrochloric acid, 270 mL of water, and 250 mL of acetic acid was refluxed for 4 h, and the solvents were removed under vacuum. The residue was taken up with a 1 N solution of NaOH, and the

Table X. Product Characterization and in Vitro Activity: Molecular Modeling Studies



						competition with [125I]PTA-OH in human platelets		
						% inhibition[e]		
no.	R	X	yield, %[a]	formula[b]	mp, °C	10^{-7} M	10^{-5} M	K_i, μM
11v	$C(CH_3)_2CH_2CO_2H$	H	62	$C_{19}H_{19}ClN_2O_2 \cdot 0.75H_2O$	98–100	0 ± 1	28 ± 4	nd
41		F	50	$C_{19}H_{16}ClFN_2O_2$	173–175	2 ± 1	97 ± 3	0.81
42		F	51	$C_{20}H_{18}ClFN_2O_2$	210–211	37 ± 4	100 ± 5	0.14
43		F	67	$C_{21}H_{18}ClFN_2O_2$	185–186	15 ± 3	96 ± 1	0.51
44	$CH_2C(CH_3)_2CH_2CONH_2$	H	70[c]	$C_{20}H_{22}ClN_3O$	167–168	7 ± 7	90 ± 1	nd
45	$CH_2C(CH_3)_2CH_2CN$	H	78[d]	$C_{20}H_{20}ClN_3$	120–122	0 ± 1	0 ± 1	nd
46[f]						100 ± 1	100 ± 1	0.0153

[a] Yield of hydrolysis (method I) calculated from crude esters. [b] All elemental analyses for C, H, and N were within ±0.4% of theoretical values. [c] Yield calculated from acid **37a**. [d] Yield calculated from amide **44**. [e] Values are mean ± SEM of three determinations. [f] Compound **46** (Chart III) was synthesized according to Merck Frosst[33] and tested in our laboratory.

resulting mixture was washed with Et_2O. The aqueous layer was acidified by having sulfur dioxide bubbled through it until the pH was 5–6, and the crystals formed were filtered off and washed with water and isopropyl ether to give 5.3 g (65%) of acid **11a**: mp 165–165 °C; ^{1}H NMR (DMSO-d_6) 1.07 (s, 6 H, $C(CH_3)_2$), 2.45 (s, 2 H, CH_2CO_2H), 2.96 (s, 2 H, CH_2), 5.57 (s, 2 H, CH_2PhCl), 7.00–7.15 (m, 3 H, H_a + 2 H PhCl), 7.35–7.5 (m, 4 H, H_b + H_d + 2 H PhCl), 11.5 (br s, 1 H, CO_2H).

Method J. 4-[3-[(4-Chlorophenyl)methyl]-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoic Acid (23a). A solution of 16.4 g (39 mmol) of **22a** in 60 mL of concentrated HCl, 240 mL of water, and 240 mL of acetic acid was refluxed for 8 h, and the solvents were evaporated under vacuum. The residue was taken up with ether, and the organic layer was washed with a 1 N NaOH solution. The aqueous layer was washed with AcOEt, acidified with a diluted solution of HCl to pH = 1, and then extracted with CH_2Cl_2 and chromatographed on silica gel (CH_2Cl_2/acetone/MeOH, 90:10:2) to give an oil which crystallized in isopropyl ether to give 11.5 g (75%) of **23a**: mp 137 °C; ^{1}H NMR (DMSO-d_6) 1.05 (s, 6 H, $C(CH_3)_2$), 2.46 (s, 2 H, CH_2CO_2H), 2.98 (s, 2 H, CH_2), 5.56 (s, 2 H, CH_2PhCl), 7.17 (d, J = 8.4 Hz, 2 H, PhCl), 7.38 (d, J = 8.4 Hz, 2 H, PhCl), 8.24 (d, J = 2.1 Hz, 1 H, H_d), 8.35 (d, J = 2.1 Hz, 1 H, H_b), 10.8 (br s, 1 H, CO_2H).

All acid derivatives of formula **8**, **11**, **21**, **23**, and **37** were prepared by one of these two procedures, and experimental data are summarized in Tables VI–X.

Compounds **41**, **42**, and **43** were also prepared by this procedure proceeding from esters **38**, **39**, and **40** (Table X).

4-[1-[(4-Hydroxyphenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutanoic Acid (37n). A solution of 2.7 g (7.6 mmol) of 4-[1-[(4-methoxyphenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutanoic acid **37j** in 40 mL of AcOH and 48 mL of 48% HBr was refluxed for 3 h, and the solvents were evaporated off under vacuum. The residue was taken up with a 1 N solution of NaOH so as to adjust the pH to 9–10, and the resulting aqueous phase was washed with Et_2O and then acidified with sulfur dioxide to pH 5.5. The crystals obtained were filtered off, washed with water and then with Et_2O, and chromatographed on silica gel in a 9:1 $CHCl_3$/MeOH eluent to give 0.4 g (15%) of **37n**: mp 215–216 °C; ^{1}H NMR (DMSO-d_6) 1.07 (s, 6 H, $C(CH_3)_2$), 2.44 (s, 2 H, CH_2CO_2H), 2.99 (s, 2 H, CH_2), 5.41 (s, 2 H, CH_2PhOH), 6.96 (d, J = 8.4 Hz, 2 H, PhOH), 7.14–7.19 (m, 2 H, H_a + H_d), 7.45–7.49 (m, 1 H, H_b), 7.59–7.63 (m, 1 H, H_c), 9.4 (br s, 2 H, OH + CO_2H).

4-[1-[[4-(Methylsulfonyl)phenyl]methyl]-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic Acid (11w). A solution of 3 g (7.7 mmol) of 4-[1-[[4-(methylthio)phenyl]methyl]-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid **11k** in 100 mL of methanol was cooled to 0 °C, and 3.8 g (32 mmol) of 70% 3-chloroperbenzoic acid was added. The mixture was then stirred at room temperature for 10 h, and the crystals obtained were filtered off and washed with methanol and then dried to give 2.4 g (74%) of **11w**: mp 221–223 °C; ^{1}H NMR (DMSO-d_6) 1.1 (s, 6 H, $C(CH_3)_2$), 2.47 (s, 2 H, CH_2CO_2H), 2.99 (s, 2 H, CH_2), 3.2 (s, 3 H, SO_2CH_3), 5.71 (s, 2 H, $CH_2PhSO_2CH_3$), 6.98–7.11 (m, 1 H, H_a), 7.26 (d, J = 7.5 Hz, 2 H, $PhSO_2CH_3$), 7.4–7.52 (m, 2 H, H_b + H_d), 7.9 (d, J = 7.5 Hz, 2 H, $PhSO_2CH_3$), 10.3 (br s, 1 H, CO_2H).

4-[1-[[4-(Methylsulfonyl)phenyl]methyl]-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid (11x) was prepared according to the same procedure as for **11w**, proceeding from the corresponding acid **11q**: mp 228–230 °C; ^{1}H NMR (DMSO-d_6) 1.1 (s, 6 H, $C(CH_3)_2$), 2.45 (s, 2 H, CH_2CO_2H), 2.98 (s, 2 H, CH_2), 3.18 (s, 3 H, SO_2CH_3), 5.7 (s, 2 H, $CH_2PhSO_2CH_3$), 7.18–7.3 (m, 3 H, H_a + 2 H $PhSO_2CH_3$), 7.4–7.5 (d, J = 8.5 Hz, 1 H, H_b), 7.7 (d, J = 2.5 Hz, 1 H, H_d), 7.88 (d, J = 8.5 Hz, 2 H, $PhSO_2CH_3$), 10.8 (br s, 1 H, CO_2H).

4-[1-[(4-Chlorophenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutanamide (44). To a solution of 11.4 g (32 mmol) of acid **37a** in 100 mL of $CHCl_3$ stabilized with amylene was added dropwise 5 mL (57 mmol) of oxalyl chloride while the temperature was maintained at 0 °C. At the end of the addition the reaction mixture was stirred for 1 h at room temperature. The solvents were evaporated under vacuum, and the residue was slowly added to 100 mL of 28% NH_4OH with vigorous stirring for 5 h. The mixture was taken up with $CHCl_3$, and the organic layer was dried over magnesium sulfate and evaporated under vacuum to give an oil which crystallized in isopropyl ether and was recrystallized in CH_3CN to give 8 g of **44** (70%): mp 167–168 °C; ^{1}H NMR (DMSO-d_6) 1.05 (s, 6 H, $C(CH_3)_2$), 2.22 (s, 2 H, CH_2CONH_2), 2.98 (s, 2 H, CH_2), 5.57 (s, 2 H, CH_2PhCl), 6.68 (br s, 1 H, $CONH_2$), 7.08–7.17 (m, 4 H, H_a + H_d + 2 H PhCl), 7.36–7.4 (m, 3 H, H_b + 2 H PhCl), 7.55–7.72 (m, 2 H, H_c + 1 H $CONH_2$).

4-[1-[(4-Chlorophenyl)methyl]benzimidazol-2-yl]-3,3-dimethylbutyronitrile (45). A mixture of 27 g (7.6 mmol) of amide **44**, 2.3 mL of $POCl_3$, and 50 mL of $CHCl_3$ was refluxed for 5 h, and the solvents were evaporated under vacuum. The residue was taken up with water and extracted with AcOEt; the organic layer was dried and evaporated under vacuum to give an oily residue which crystallized in ether to give 2.0 g (78%) of **45**: mp 120–122 °C; ^{1}H NMR (DMSO-d_6) 1.09 (s, 6 H, $C(CH_3)_2$), 2.89 (s, 2 H, CH_2CN), 2.91 (s, 2 H, CH_2), 5.56 (s, 2 H, CH_2PhCl), 7.09

Table XI. Biology of UP 116-77 (23a)

in vitro activity K_i (nM)[a]	in vivo activity % inhibition U-IPA[b]	
	0.3 mg/kg po	1 mg/kg po
21.4 ± 5.6 (n = 5)	44 ± 9 (n = 27)	81 ± 6 (n = 24)

[a] K_i was determined by the inhibition of [125I]PTA-OH binding to human washed platelets and represents the average ± SEM of five independent experiments. [b] Inhibition of 11,9-epoxymethano-PGH_2 (1 μM) induced platelet aggregation (U-IPA) of guinea pig platelet-rich plasma (PRP) 1 h after per os administration.

(d, J = 8.4 Hz, 2 H, PhCl), 7.15–7.18 (m, 2 H, H_a + H_d), 7.38 (d, J = 8.4 Hz, 2 H PhCl), 7.4–7.46 (m, 1 H, H_b), 7.62–7.67 (m, 1 H, H_c).

Binding Assays. Preparation of Washed Human Platelets. Washed platelets were obtained according to a previously described method.[32] Blood was drawn via venipuncture from human volunteers into disodium EDTA (5 mM) and indomethacin (20 μM) (final concentrations). The blood was centrifuged at 200g for 15 min at room temperature to prepare platelet-rich plasma (PRP). The latter was centrifuged at 2000g for 20 min at room temperature. The platelet pellet was resuspended in buffer (50 mM Tris, HCl/100 mM NaCl/5 mM dextrose/20 μM indomethacin, pH 7.4) to a concentration of 5 × 10^8 platelets/mL.

Radioligand Binding Assays. Receptor binding studies were carried out as previously described[32] with slight modifications. Incubations (200 μL) were performed at 37 °C for 30 min in polystyrene tubes containing incubation buffer (50 mM Tris, HCl/100 mM NaCl/5 mM dextrose/20 μM indomethacin, pH 7.4), 5 × 10^7 platelets, 0.1 nM [125I]PTA-OH (≈60000 cpm) and various concentrations of the tested compounds (10^{-7} and 10^{-5} M for screening tests and 10^{-9} to 10^{-6} M for K_i determination). The reaction was terminated by the addition of 3 mL of cold washing buffer (50 mM Tris, HCl/100 mM NaCl, pH 7.4), followed by rapid filtration through Whatman GF/B glass fiber filters which were washed two more times with 3 mL of buffer. The radioactivity was determined by solid scintillation spectroscopy using a Kontron Gamma Counter at a counting efficiency of 76%. Nonspecific binding was defined as that remaining in presence of (*R,S*)-6-fluoro-9-(*p*-chlorobenzyl)-1,2,3,4-tetrahydrocarbazole-1-acetic acid **46** (Chart III), a specific non-prostanoid thromboxane A_2 receptor antagonist previously described by Merck Frosst.[33] Each assay was performed in triplicate.

Data Analysis. Competition data were analyzed using the nonlinear regression program LIGAND[34] adapted for an IBM-PC[35] and obtained from Elsevier-Biosoft (Cambridge, England). The concentration of unlabeled tested drug causing 50% displacement of [125I]PTA-OH from its binding site (IC_{50} value) was calculated by log-logit linear regression independent binding sites. A two-site model was accepted over a one-site fit only if it was preferred ($p < 0.05$) using the partial F-test of the program. Inhibition constant (K_i) value was calculated according to the Cheng–Prusoff equation: $K_i = IC50/(1 + L/K_d)$ in which L and K_d correspond to the concentration and dissociation constant of [125I]PTA-OH, respectively. Each K_i value was determined from one experiment, each assay being performed in triplicate. For compound **23a**, the K_i value was determined from five independent experiments.

Molecular Modeling. Experiments were performed with the Sybyl software package,[36] and homemade softwares running on a Vaxstation 2000 with a PS 390 and on a Silicon Graphics 4D/340 VGX. For the conformational search of the compounds a Monte Carlo/procedure with the algorithm of Metropolis was used.[37] The lower energy conformations were gathered in families. The same procedure was used for the superimposition of two molecules.

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