1-Imidazolyl(alkyl)-Substituted Di- and Tetrahydroquinolines and Analogues: Syntheses and Evaluation of Dual Inhibitors of Thromboxane A_2 Synthase and Aromatase

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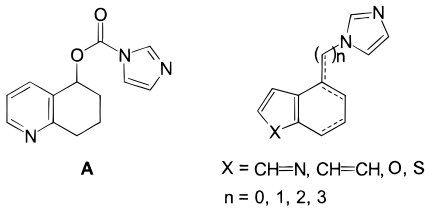
A series of 1-imidazolyl(alkyl)-substituted quinoline, isoquinoline, naphthalene, benzo[*b*]furan, and benzo[*b*]thiophene derivatives was synthesized as dual inhibitors of thromboxane A_2 synthase (P450 TxA_2) and aromatase (P450 arom). Dual inhibition of these enzymes could be a novel strategy for the treatment of mammary tumors and the prophylaxis of metastases. The most potent dual inhibitors, 5-(2-imidazol-1-ylethyl)-7,8-dihydroquinoline **(31) (**P450 TxA_2: $IC_{50} = 0.29\ \mu M$; P450 arom: $IC_{50} = 0.50\ \mu M$) and its 5,6-saturated analogue **30** (P450 TxA_2: $IC_{50} = 0.68\ \mu M$; P450 arom: $IC_{50} = 0.38\ \mu M$), showed a stronger inhibition of both target enzymes than the reference compounds (dazoxiben: $IC_{50} = 1.1\ \mu M$; aminoglutethimide: $IC_{50} = 18.5\ \mu M$). For the determination of the in vivo activity, the influence of selected compounds on serum TxB_2 concentration was examined in rats. Compound **30** (8.5 mg/kg body weight) led to a reduction of the TxB_2 serum level of 78%, 71%, and 51% after 3, 5, and 8 h, respectively (dazoxiben: 60%, 34%, and 36%). Selectivity was studied toward some enzymes of the steroidogenic and eicosanoid pathways. P450 17 was inhibited by selected compounds only at high concentrations. Compound **30** inhibited P450 scc by 13% (25 μM). Compound **31** did not affect cyclooxygenase and lipoxygenase.

Introduction

Aromatase (P450 arom) is a microsomal enzyme complex consisting of a cytochrome P450 hemoprotein and a NADPH cytochrome reductase.[1] It catalyzes the conversion of androgens into estrogens, a process involving three enzymatic hydroxylations. Recently, highly active inhibitors of P450 arom have been developed, some of which turned out to be effective therapeutics for estrogen-dependent breast cancer.[2−5] Thromboxane A_2 synthase (P450 TxA_2) is an enzyme involved in the arachidonic acid metabolism converting prostaglandin H_2 into thromboxane A_2.[6] In contrast to P450 arom it is not a mixed function oxidase but an isomerase. There is some homology between P450 arom and P450 TxA_2 (36%, identical amino acids 23%).[7] The region of greatest homology is the heme binding region which is closely located to the active site.

P450 TxA_2 might be a promising target for the prophylaxis of tumor metastases. Several tumor tissues contain elevated concentrations of TxA_2,[8] and in various cancer cell lines proliferation can be induced by the addition of TxA_2 analogues.[9,10] Prostacyclin, the functional antagonist of TxA_2, and its stable analogues display antimetastatic activity in spontaneously metastasizing tumors.[11] Moreover, experimental metastases can be prevented by the application of P450 TxA_2 inhibitors.[12] Inhibition of both enzymes, P450 arom and P450 TxA_2, could be a novel strategy for the treatment of mammary tumors and the prophylaxis of metastases.

Chart 1. Compound **A** and the Title Compounds



The heme iron plays a pivotal role in the catalytic mechanism of both enzymes.[13,14] Very important for the inhibition of both enzymes is a heterocyclic nitrogen capable of complexing the heme iron.[15,16]

In the class of pyridyl- and azolylmethyl-substituted tetrahydronaphthalenes, we have performed several structure−activity studies[17,18] resulting in some highly active aromatase inhibitors.[18] Systematic screening of these compounds for inhibition of P450 TxA_2 led to a large number of mediocre P450 TxA_2 inhibitors, which we have used for the development of a pharmacophore model.[19] Using this model, a strategy was derived to increase P450 TxA_2 inhibition by introduction of a nitrogen into the benzene nucleus of the tetrahydronaphthalene moiety. This heteroatom should be capable of interacting with the binding site of the C15 hydroxy group of prostaglandin H_2. Following this strategy, compound **A** (Chart 1) was discovered to be a potent inhibitor of P450 TxA_2 recently ($IC_{50} = 1.6\ \mu M$; dazoxiben: $IC_{50} = 1.1\ \mu M$).[20] However, it is not suitable as a candidate for drug development because it is subject to acidic hydrolysis.[20]

The present study describes structural modifications aimed at the development of hydrolytically stable dual

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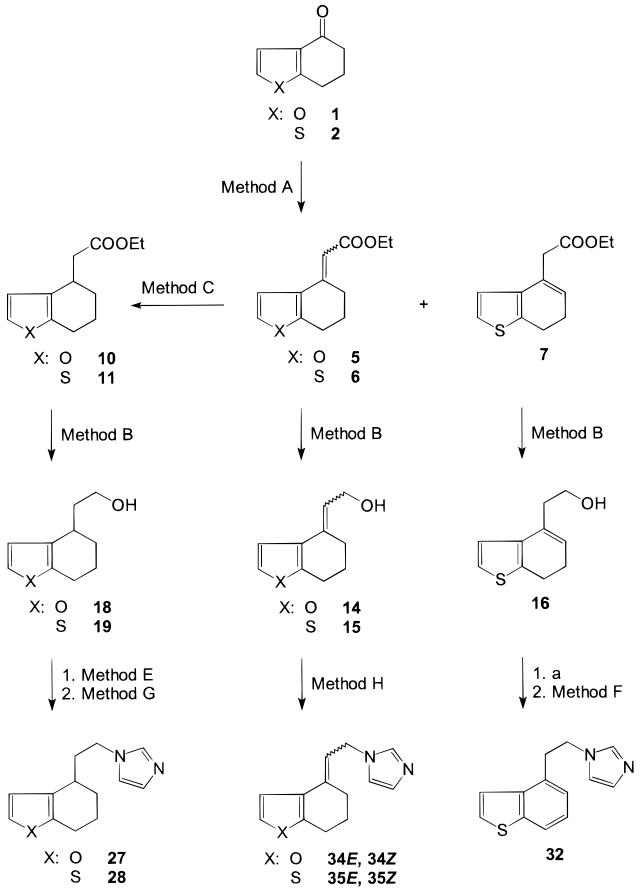
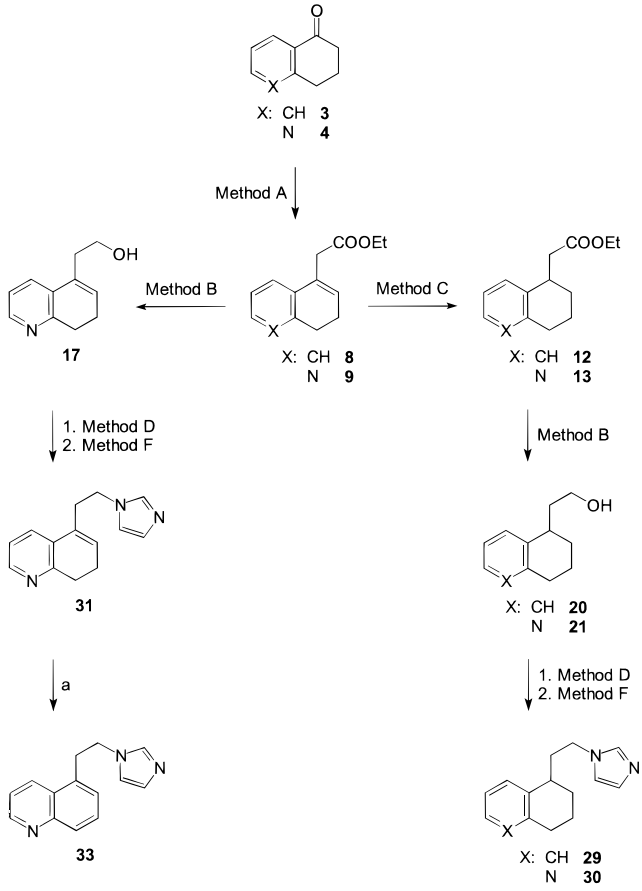
Scheme 1[a]



[a] Reagents and conditions: (method A) $(EtO)_2POCH_2COOEt$, NaOEt; (method B) $LiAlH_4$; (method C) Pd/C, H_2; (method E) PPh_3, CBr_4; (method F) imidazole, NaI, Na_2CO_3, acetone; (method G) imidazole sodium salt; (method H) 1,1′-carbonyldiimidazole; (a) PPh_3, CBr_4.

Scheme 2[a]



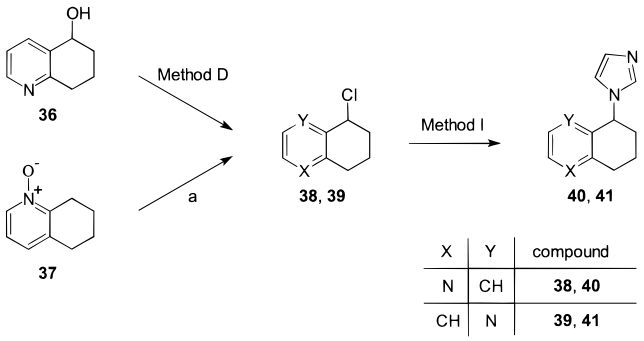
[a] Reagents and conditions: (method A) $(EtO)_2POCH_2COOEt$, NaOEt; (method B) $LiAlH_4$; (method C) Pd/C, H_2; (method D) $SOCl_2$; (method F) imidazole, NaI, Na_2CO_3, acetone; (a) Pd/C, mesitylene, 170 °C.

inhibitors of P450 TxA_2 and P450 arom. In the following the syntheses of imidazolyl(alkyl)-substituted quinoline, isoquinoline, naphthalene, benzo[*b*]furan, and benzo[*b*]-thiophene derivatives are described as well as the evaluation of the compounds for inhibition of the target enzymes in vitro. For the determination of the in vivo activity, the influence of selected compounds on serum TxB_2 concentration was examined in rats. Selectivity was studied toward certain enzymes of the steroidogenic and eicosanoid pathways (P450 17, P450 scc, cyclooxygenase, and lipoxygenase).

Chemistry

In Schemes 1 and 2 the synthesis of compounds with an ethyl spacer is shown. The ketones **1**,[21] **2**,[22] and **4**[23] were prepared as described. Compounds **1**−**4** were reacted in a Wittig−Horner reaction to give the esters **5**−**9** (method A). In contrast to the literature[24] not only the thiophene ester **6** was formed but also the corresponding endo isomer **7**. The furan derivative led to exo product (**5**) only, while the six-membered compounds **3** and **4** resulted in endo products only (compounds **8** and **9**). The *E*,*Z* mixtures **5** and **6** were reduced with $LiAlH_4$ to the corresponding *E*,*Z* alcohols **14** and **15**,[25] which were reacted with CDI (1,1′-carbonyldiimidazole) to give the 1-imidazolylethylidene-substituted compounds **34*E***/**34*Z*** and **35*E***/**35*Z***. The separation of the isomers was accomplished by column chromatography. Structural assignment was performed by ^1H NMR.[24] In the case of the *E* isomers the signals of the vinyl protons appear as double doublets at 6.19 ppm (**35*E***), whereas in the case of the *Z* isomers the signals appear as triplets at 5.90 ppm (**35*Z***). The unsaturated esters **5**, **6**, **8,** and **9** were catalytically hydrogenated to give the racemic esters **10**, **11,**[24] **12**, and **13** (method C). The latter were reduced with $LiAlH_4$ to give the alcohols **18**, **19**,[25] **20**, and **21** (method B). The benzo[*b*]furan **18** and the benzo-[*b*]thiophene **19** were reacted with CBr_4 and PPh_3 to give the bromides **23** and **24** (method E). Subsequent treatment with imidazole sodium salt yielded the racemic compounds **27** and **28** (method G). The naphthalene **20** and the quinoline **21** were transformed to the chlorides **25** and **26** by treatment with thionyl chloride (method D) and then reacted with NaI, imidazole, and Na_2CO_3 to yield compounds **29** and **30** as racemates (method F). Reduction of the esters **7** and **9** with $LiAlH_4$ gave the corresponding alcohols **16** and **17** (method B). The quinoline **17** was transformed to the chloride **22** by treatment with thionyl chloride (method D) and then reacted with NaI, imidazole, and Na_2CO_3 to give the 7,8-dihydroquinoline **31** (method F). Subsequent dehydrogenation with Pd/C in mesitylene yielded the corresponding quinoline **33**. Treatment of the alcohol **16** with CBr_4 and PPh_3 led to a mixture of products, which was

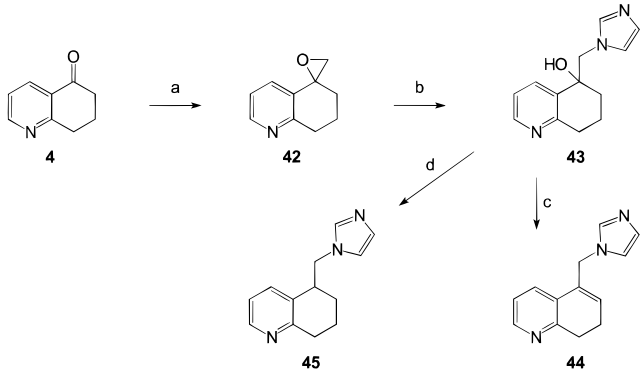
Scheme 3[a]



X	Y	compound
N	CH	**38**, **40**
CH	N	**39**, **41**

[a] Reagents and conditions: (method D) $SOCl_2$; (method I) imidazole, K_2CO_3, DMF; (a) $POCl_3$, Et_3N.

Scheme 4[a]



[a] Reagents and conditions: (a) $(CH_3)_3SI$, NaH, DMSO/THF; (b) imidazole, NaH, DMF; (c) CH_3COOH, H_2SO_4; (d) CH_3COOH, H_2SO_4, Pd/C, H_2, 9 bar.

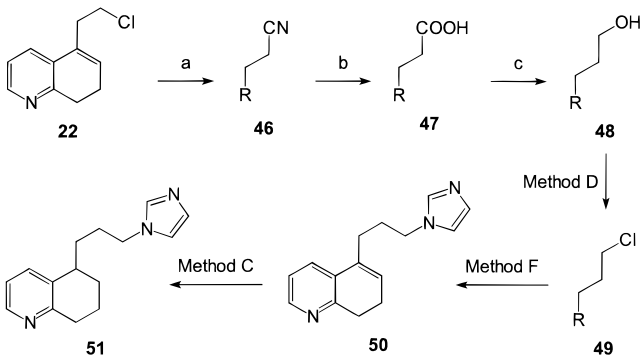
subsequently reacted with NaI, imidazole, and Na_2CO_3 in acetone. From the reaction mixture the benzo[*b*]-thiophene **32** was obtained in reasonable yields.

Scheme 3 shows the synthesis of the 1-imidazolyl-substituted compounds **40** and **41**. The alcohol **36** was prepared as described.[23] The *N*-oxide **37** was obtained from 5,6,7,8-tetrahydroquinoline[26] by reaction with H_2O_2 in acetic acid. The alcohol **36** was transformed to the corresponding chloride **38** by treatment with thionyl chloride (method D). Compound **37** was converted with $POCl_3$ and triethylamine to the chloride **39**. The halo compounds **38** and **39** were reacted with imidazole and K_2CO_3 in DMF to give the 1-imidazolyl-substituted compounds **40** and **41** (method I).

In Scheme 4 the synthesis of compounds with a methyl spacer is outlined. The ketone **4** was reacted, as described for similar compounds,[27] with trimethylsulfonium iodide and NaH in DMSO/THF to give the oxirane **42**. Treatment with imidazole sodium salt in DMF yielded the tertiary alcohol **43**, which was dehydrated by acetic acid and concentrated H_2SO_4. From the resulting mixture either the 7,8-dihydroquinoline **44** was isolated or the racemic tetrahydroquinoline **45** was obtained after catalytic hydrogenation.

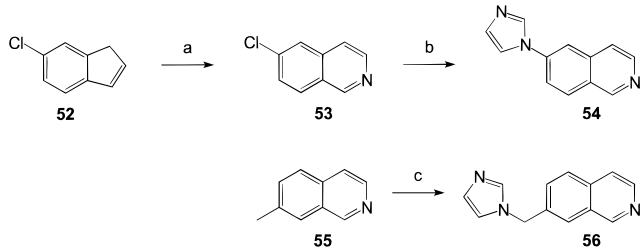
The propyl spacer-containing compounds were prepared according to Scheme 5. The chloride **22** (method D) was reacted with NaCN in DMSO to give the nitrile **46**, which was hydrolyzed under acidic conditions to yield the corresponding carboxylic acid **47**. Reduction with $LiAlH_4$ gave the alcohol **48**, which was transformed to the chloride **49** by treatment with thionyl chloride

Scheme 5[a]



[a] Reagents and conditions: (a) NaCN, DMSO; (b) H_2SO_4, 110 °C; (c) $LiAlH_4$; (method D) $SOCl_2$; (method F) imidazole, NaI, Na_2CO_3, acetone; (method C) Pd/C, H_2.

Scheme 6[a]



[a] Reagents and conditions: (a) 1. O_3, 2. Na_2CO_3, $(CH_3)_2S$, 3. NH_3(aq); (b) Cu, imidazole sodium salt; (c) 1. NCS, *hν*, 2. imidazole, NaI, Na_2CO_3, acetone.

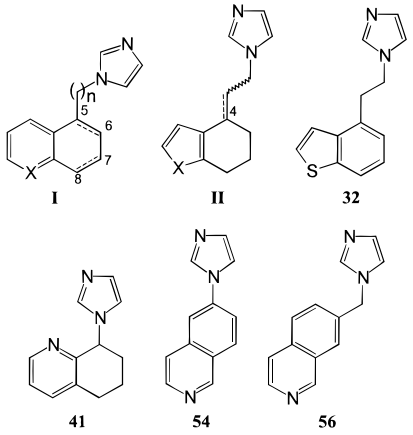
(method D). Compound **49** was reacted with NaI, imidazole, and Na_2CO_3 in acetone to yield the dihydroquinoline **50** (method F). Catalytic hydrogenation gave the tetrahydroquinoline **51** (method C).

Scheme 6 shows the synthesis of compounds with an isoquinoline basic structure. The chloroindene **52**[28] and the methylisoquinoline **55**[29] were prepared as described. The chloroisoquinoline **53** was obtained by ozonolysis of **52**, subsequent reduction with dimethyl sulfide, and cyclization with NH_3. Compound **53** was reacted with imidazole sodium salt and copper in DMF to give compound **54**. Compound **55** was halogenated by *N*-chlorosuccinimide and subsequently reacted with NaI, imidazole, and Na_2CO_3 to yield **56**.

Biological Properties

Inhibition of TxA_2 Synthase in Vitro. Using the procedure recently described by us,[30] the compounds were tested against P450 TxA_2 (Table 1). IC_{50} values were determined for compounds exhibiting inhibition values higher than 80%. Elongation of the spacer in compound **40**, which is a weak inhibitor, leads to a strong increase in inhibition. The maximum effect is reached at a spacer length of $n = 2$ (compound **30**). Introduction of a Δ5-double bond results in an increase in activity (compounds **44**, **31**, and **50**). As seen with the saturated compounds maximum activity is shown by the ethylene compound **31**, the most active compound of this study. Aromatization of **31** to the quinoline **33** diminishes activity by a factor of 4. Replacement of the pyridine moiety in the saturated ethylene compound **30** by benzene (**29**), furan (**27**), or thiophene (**28**) also decreases activity. The introduction of an exocyclic double bond in compounds **34** and **35** reduces activity

Table 1. Inhibition of the Target Enzymes P450 TxA_2 and P450 Arom in Vitro



					P450 TxA_2[a]		P450 arom[b]
no.	structure	X	*n*	double bonds	%[c,d]	IC_{50}, μM[d]	IC_{50}, μM[d]
40	I	N	0		72		6.40
45	I	N	1			2.00	0.16
44	I	N	1	Δ5		1.50	0.17
30	I	N	2			0.63	0.38
31	I	N	2	Δ5		0.29	0.50
33	I	N	2	Δ5, Δ7		1.20	0.35
29	I	CH	2			3.4	0.70
51	I	N	3			2.30	0.35
50	I	N	3	Δ5		0.68	0.22
27	II	O				1.01	0.92
28	II	S				1.23	0.44
34*E*	II	O		Δ4		3.55	2.40
34*Z*	II	O		Δ4		4.10	6.00
35*E*	II	S		Δ4		1.70	0.68
35*Z*	II	S		Δ4		1.26	3.90
32						5.30	3.56
41					49		111
54					70		3.06
56						5.4	1.38

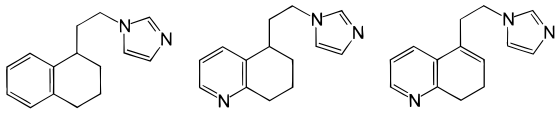
[a] Human whole blood; collagen challenge (53.6 μL/mL); TxA_2 synthase-catalyzed formation of malondialdehyde determined by thiobarbituric acid assay[30] (IC_{50} value of dazoxiben under identical experimental conditions: 1.1 μM). [b] Human placental microsomes; testosterone concentration: 2.5 μM (experimental procedure, ref 31; IC_{50} value of aminoglutethimide under identical experimental conditions: 18.5 μM). [c] Concentration of inhibitor: 50 μM. [d] Mean values of at least two experiments; the standard deviations were within ±5%.

only in the case of the furan compound. The configuration of the double bond affects activity only marginally. Restriction of the conformational flexibility of the ethylene compound **33** leads to a decrease in activity as shown with the isoquinolines **54** and **56**.

Inhibition of Aromatase in Vitro. The inhibitory activities of the compounds toward aromatase were determined using human placental microsomes and [1β,2β-^{3}H]testosterone according to the previously described procedure[31] (Table 1). The saturated methylene compound **45** and its 5,6-dehydro analogue **44** were found to be the best inhibitors in this study. They showed a competitive type of inhibition exhibiting K_i values of approximately 10 nM (data not given). Compound **40** lacking the spacer shows a strong decrease in inhibition, whereas elongation of the spacer results in a moderate reduction of inhibitory potency in the case of the saturated compounds **30** and **51**. The introduction of one (Δ5) or two (Δ5 and Δ7) double bonds does not strongly affect inhibition. In the case of the propylene compound **51**, it leads to a moderate enhancement of potency. Compound **50** is almost as active as **45**. Replacement of the pyridine moiety in the ethylene compound **30** by furan (**27**) and benzene (**29**) decreases inhibition slightly; replacement by thiophene (**28**) does not change activity. Aromatization of **28** to the benzo[*b*]thiophene **32** diminishes activity strongly. The introduction of an exocyclic double bond in compounds **27** and **28** reduces activity (compounds **34** and **35**). The *E* isomers show higher activity than the corresponding *Z* isomers. Restriction of the conformational flexibility of **33** resulting in the isoquinolines **54** and **56** leads to a decrease in activity.

In Vivo Activity: TxB_2 Formation. For the assessment of the in vivo inhibition, P450 TxA_2 was chosen rather than P450 arom[31] because the former assay is easier to perform. After stability at pH 7.4 and 2.0 had been demonstrated (no degradation observed after 24 h), homologous compounds **29**−**31** were applied to rats and the serum TxB_2 levels were determined after 2, 3, 5, and 8 h by radioimmunoassay[32] (Table 2). The test compounds and dazoxiben show a strong reduction of the TxB_2 concentration after 2 h. In the case of compound **31**, which is the most active inhibitor in vitro, no inhibition was observed after 5 h indicating that the Δ5 double bond diminishes in vivo activity. In contrast

Table 2. Effect of Selected Compounds on the TxB_2 Serum Level in Rats[a]



		reduction of the TxB_2 serum level, % inhib (mean ± SD)[b]			
no.	dose, mg/kg bw[c]	2 h	3 h	5 h	8 h
29	8.4	83[d] ± 5.0	59[d] ± 6.0	62[d] ± 12.5	16 ± 12.1
	4.2		50[d] ± 6.1		−8 ± 7.6
30	8.5	77[d] ± 4.8	78[d] ± 2.9	71[d] ± 8.0	51[d] ± 8.5
	4.2		56[d] ± 4.9		6 ± 11.8
31	8.4	67[d] ± 9.1		13 ± 16.4	
	4.2	64[d] ± 4.1		−8 ± 10.6	
dazoxiben	10.0	56[d] ± 8.1	60[d] ± 3.8	34[d] ± 8.0	36[d] ± 7.4

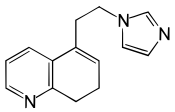
[a] Each group consisted of 6−8 male Sprague−Dawley rats; the animals received a single dose of the inhibitor, po, dissolved in 0.01 N HCl. [b] Blood withdrawal at the indicated time after application. [c] Dose of inhibitor: equimolar to dazoxiben HCl; bw = body weight. [d] Significantly different from control group (Student's *t*-test), $p \leq 0.05$.

Table 3. Inhibition of P450 17[a] by Selected Compounds

no.	% inhibition[b]	no.	% inhibition[b]
29	>80[d]	**44**	69
30	49[c]	**45**	11
31	21	**50**	79
33	22	**51**	59
40	14		

[a] Rat testicular microsomes; progesterone concentration: 25 μM; inhibitor concentration: 125 μM; reference ketoconazole: 62% inhibition (experimental procedure, ref 33). [b] The given values are mean values of at least two experiments; the standard deviations were within ±5%. [c] IC_{50} = 125 μM. [d] IC_{50} = 20 μM.

Table 4. Selective Inhibition of P450 TxA_2 by Compound **31**: Effect on Formation of PGE_2, 12-HETE, and 12-HHT[a]



31

compound	PGE_2[a,b] IC_{50}, μM[d]	12-HETE[a,c] % inhibition[d]	12-HHT[a,c] IC_{50}, μM[d]
31	ni	ni	0.173
indomethacin	0.017	ni	0.011

[a] Bovine platelet suspension; stimulated by calcium ionophore A 23187 (final concentration: 20 μM; experimental procedure, ref 34); reverse-phase HPLC analysis. [b] UV detection at 192 nm. [c] UV detection at 232 nm. [d] Mean values of 2 experiments, control group: 4 experiments; ni = no inhibition.

to **31**, compound **30** exhibits a strong, long-lasting effect; after 8 h the serum level is still decreased by 51% (Table 2).

Inhibition of P450 17 and P450 scc. The inhibitory activities of selected compounds toward P450 17 were determined for the assessment of possible effects on glucocorticoid biosynthesis. Rat testicular microsomes were used as the enzyme source and nonlabeled progesterone as the substrate.[33] Only compounds **29**, **30**, **44**, **50**, and **51** show inhibitory activity at the high concentration used (125 μM; Table 3).

The best in vivo inhibitor of this study, compound **30**, was tested toward P450 scc,[31] the key enzyme of steroidogenesis. It shows only marginal activity, inhibiting the enzyme by 13% at a concentration of 25 μM.

Selective Inhibition of P450 TxA_2. The best in vitro inhibitor of P450 TxA_2, compound **31**, was tested for selectivity to the target enzyme[34] (Table 4). Compound **31** affects neither cyclooxygenase nor another preceding enzyme of the arachidonic acid cascade nor lipoxygenase.

Discussion

The present paper shows that it is possible to inhibit both target enzymes P450 arom and P450 TxA_2 strongly without affecting other P450 enzymes markedly. As expected it is not the same compound showing maximum inhibitory activity toward both P450 arom and P450 TxA_2. The most potent aromatase inhibitors are the imidazolylmethyl compounds **44** and **45**, whereas the most active P450 TxA_2 inhibitor is the imidazolylethyl compound **31**. Compounds showing strong dual inhibition are **30**, **31**, and **50**. In vivo, the saturated racemic compound **30** is superior to the Δ5 compounds as shown with **30** and **31**.

In conclusion, the application of a dual inhibitor of both target enzymes might be an appropriate strategy to enhance remission rates in hormone-dependent breast cancer. Because of its superiority in the in vivo studies, compound **30** seems to be a suitable candidate for further development.

Experimental Section

Melting points were determined on a Kofler melting point apparatus (Thermopan, Reichert) and are uncorrected. Elemental analyses were performed by the University of Saarland, FR 11.1 Inorganic Chemistry, and are within ±0.4% of the calculated values. ^{1}H NMR spectra were measured on a Bruker AW 80 (80 MHz) or Bruker AM 400 (400 MHz). ^{13}C NMR spectra were measured on a Bruker AM 400 (100 MHz) or Bruker Avance PRX 500 (120 MHz). Column chromatography was performed on Macherey-Nagel Kieselgel 60, flash chromatography on sds Silice 60 A.C.C., and TLC analyses on Macherey-Nagel ALUGRAM SIL G/UV_{254}. IR spectra were performed on a Perkin-Elmer infrared spectrometer 398. GCMS spectra were measured on a Hewlett-Packard G 1800 A (GCD; column HP 5). The following HPLC equipment was used: pump, Jasco 880-PU; detector, Jasco 870-UV; column, Macherey-Nagel ET 250/4 Nucleosil 120-5 C_{18}; flow, 1 mL/min; eluent, water/methanol 40:60 (v:v) 0.5 mM triethylamine; JCL6000 chromatography data system (Jones Chromatography Ltd.).

Method A. Synthesis of Ethyl (7,8-Dihydroquinolin-5-yl)acetate, 9. Sodium (1.6 g, 68.0 mmol) was added to dry ethanol (70 mL) under a nitrogen atmosphere. To the resulting solution was added triethyl phosphonoacetate (15.5 g, 68.0 mmol) in one portion. After stirring for 10 min **4** (10.0 g, 68.0 mmol) was added within 5 min and the mixture was stirred for 2.5 h at 80 °C. The reaction mixture was cooled to room temperature, diluted with water (140 mL) and extracted with ethyl acetate. The organic phases were washed with water and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was distilled to yield **9** (67%) as a colorless oil: $bp_{0.01}$ 90−110 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.20 (t, ^3J = 7.2 Hz, 3H, -*CH*$_3$); 2.41−2.57 (m, 2H, *H7*); 2.90−3.11 (m, 2H, *H8*); 3.40 (d, ^4J = 1.0 Hz, 2H, -*CH*$_2$-COOR); 4.13 (q, ^3J = 7.2 Hz, 2H, -*CH*$_2$-CH$_3$); 6.04 (t, ^3J = 4.0 Hz, 1H, *H6*); 7.07 (dd, ^3J = 8.0 and 4.8 Hz, 1H, *H3*); 7.43 (dd, ^3J = 8.0, ^4J = 4.8 Hz, 1H, *H4*); 8.29 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H, *H2*).

Ethyl (6,7-Dihydro-5*H*-benzo[*b*]furan-4-ylidene)acetate, 5. Prepared from **1**, purified by column chromatography with hexane/ethyl acetate 12:1, yield 81% as a yellow oil (*E*/*Z* mixture). For analytical reasons some *E* isomer was separated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, ^3J = 7.1 Hz, 3H, -*CH*$_3$); 1.96 (qt, ^3J = 6.2 Hz, 2H, *H6*); 2.73 (t, ^3J = 6.2 Hz, 2H, *H7*); 3.08 (td, ^3J = 6.2 Hz, ^4J = 1.8 Hz, 2H, *H5*); 4.18 (q, ^3J = 7.1 Hz, 2H, -*CH*$_2$-CH$_3$); 5.86 (t, ^4J = 1.8 Hz, 1H, -*CH*-COOR); 6.49 (d, ^3J = 2.2 Hz, 1H, *H3*); 7.27 (t, ^3J = 2.2 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3140, 3120, 2980, 2940, 2900, 2840, 1700, 1630, 1620, 1515, 1335, 1190, 1180, 1032, 870, 760.

Ethyl (6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-ylidene)-acetate, 6.[24] Prepared from **2**, purified by column chromatography with *n*-hexane/ethyl acetate 15:1, yield 72% as a yellow oil (*E*/*Z* mixture). For analytical reasons some *E* isomer was separated: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, ^3J = 7.1 Hz, 3H, -*CH*$_3$); 1.95 (qt, ^3J = 6.2 Hz, 2H, *H6*); 2.88 (t, ^3J = 6.2 Hz, 2H, *H7*); 3.14 (td, ^3J = 6.2 Hz, ^4J = 1.8 Hz, 2H, *H5*); 4.17 (q, ^3J = 7.1 Hz, 2H, -*CH*$_2$-CH$_3$); 6.11 (t, ^4J = 1.8 Hz, 1H, -*CH*-COOR); 7.06 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.20 (t, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3100, 2970, 2930, 2860, 1705, 1610, 1395, 1305, 1280, 1170, 1145, 1048, 868,710.

Ethyl (6,7-Dihydrobenzo[*b*]thiophen-4-yl)acetate, 7. Prepared from **2**, purified by column chromatography with *n*-hexane/ethyl acetate 15:1, yield 8% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, ^3J = 7.1 Hz, 3H, -*CH*$_3$); 2.40−2.46 (m, 2H, H6); 2.85 (t, ^3J = 8.8 Hz, 2H, *H7*); 3.34 (d, ^4J = 0.9

Hz, 2H, -CH_2-COOR); (q, ^3J = 7.1 Hz, 2H, -CH_2-CH_3); 5.68 (tt, ^3J = 4.4 Hz, ^4J = 0.9 Hz, 1H, *H5*); 6.95 (d,^3J = 5.3 Hz, 1H, *H3*); 7.20 (t, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3100, 2880, 2930, 2820, 1735, 1610, 1435, 1330, 1250, 1155, 1030, 870, 650.

Ethyl (7,8-Dihydronaphthalen-5-yl)acetate, 8. Prepared from **3**, yield 74% as a colorless oil: $bp_{0.01}$ 115−120 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.19 (t, ^3J = 7.2 Hz, 3H, -CH_3); 2.21−2.41 (m, 2H, *H7*); 2.68−2.88 (m, 2H, *H8*); 3.40 (s, 2H, -CH_2-COOR); 4.12 (q, ^3J = 7.2 Hz, 2H, -CH_2-CH_3); 5.97 (t, ^3J = 4.8 Hz, 1H, *H6*); 7.08−7.19 (m, 4H, *Ar-H*).

Method B. Synthesis of 2-(5,6,7,8-Tetrahydroquinolin-5-yl)ethanol, 21. $LiAlH_4$ (0.8 g, 21.0 mmol) was suspended in dry ether under a nitrogen atmosphere. A solution of **13** (5.0 g, 23.0 mmol) in dry ether was added dropwise to keep the reaction mixture slightly boiling. After stirring for 1 h at room temperature, the suspension was carefully hydrolyzed with water till no more hydrogen was produced. The solid was filtered off and washed thoroughly with ether. The filtrate was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield **21** (89%) as a colorless oil. The crude product was submitted to the next step without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.60−2.08 (m, 6H, *H6*, *H7*, -CH_2-CH_2-OH); 2.37 (br s, 1H, -*OH*); 2.85−3.09 (m, 3H, *H5*, *H8*); 3.78 (t, ^3J = 6.4 Hz, 2H, -CH_2-OH); 7.03 (dd, ^3J = 8.0 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.48 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, *H4*); 8.32 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3250, 2920, 2880, 1580.

2-(6,7-Dihydrobenzo[*b*]thiophen-4-yl)ethanol, 16. Prepared from **7**, yield 95% as a yellow oil, pure compound, checked by TLC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (td, ^3J = 4.4 Hz, ^3J = 8.8 Hz, 2H, *H6*); 2.48 (td, ^3J = 7.1 Hz, ^4J = 4.4 Hz, 2H, -CH_2-CH_2-OH); 2.74 (t, ^3J = 8.8 Hz, 2H, *H7*); 3.52 (td, ^3J = 7.1 Hz, ^3J = 5.3 Hz, 2H, -CH_2-OH); 4.52 (t, ^3J = 5.3 Hz, 1H, -*OH*); 5.55 (tt, ^3J = 4.4 Hz, ^4J = 1.3 Hz, 1H, *H5*); 7.01 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.24 (d, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3320, 2930, 2880, 2830, 1735.

2-(6,7-Dihydro-5*H*-benzo[*b*]furan-4-ylidene)ethanol, 14. Prepared from **5**, yield 76% as a yellow oil, pure compound, checked by TLC (*E*/*Z* mixture). For analytical reasons some *E* isomer was separated: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (qt, ^3J = 6.2 Hz, 2H, *H6*); 2.33 (t, ^3J = 5.5 Hz, 2H, *H5*); 2.63 (t, ^3J = 6.2 Hz, 2H, *H7*); 4.08 (t, ^3J = 6.0 Hz, 2H, -CH_2-OH); 4.56 (t, ^3J = 5.3 Hz, 1H, -*OH*); 5.64 (t, ^3J = 6.6 Hz, 1H, -*CH*-CH_2-OH); 6.61 (d, ^3J = 1.8 Hz, 1H, *H3*); 7.45 (d, ^3J = 1.8 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3320, 2930, 2860, 2840, 1658, 1522, 1440, 1430, 1335, 1230, 1135, 1000, 900, 750.

2-(6,7-Dihydro-5*H*-benzo[*b*]thiophen-4-ylidene)ethanol, 15. Prepared from **6**, yield 79% as a yellow oil, pure compound, checked by TLC (*E*/*Z* mixture). For analytical reasons some *E* isomer was separated: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (t, ^3J = 6.2 Hz, 2H, *H6*); 2.37 (t, 2H, *H5*); 2.77 (t, ^3J = 6.2 Hz, 2H, *H7*); 4.11 (t, ^3J = 5.7 Hz, 2H, -CH_2-OH); 4.61 (t, ^3J = 5.3 Hz, 1H, -*OH*); 5.90 (t, ^3J = 6.6 Hz, 1H, -*CH*-CH_2-OH); 7.22 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.24 (d, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3320, 2930, 2860, 2840, 1640.

2-(7,8-Dihydroquinolin-5-yl)ethanol, 17. Prepared from **9**, yield 80% as a yellow oil, pure compound, checked by TLC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (br s, 1H, -*OH*); 2.25−3.03 (m, 6H, *H7*, *H8*, -CH_2-CH_2-OH); 3.78 (t, ^3J = 6.4 Hz, 2H, -CH_2-OH); 5.98 (t, ^3J = 4.0 Hz, 1H, *H6*); 7.08 (dd, ^3J = 8.0 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.48 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, *H4*); 8.32 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3250, 3040, 2920, 2870, 1640, 1570.

2-(4,5,6,7-Tetrahydrobenzo[*b*]furan-4-yl)ethanol, 18. Prepared from **10**, yield 91% as a yellow oil, pure compound, checked by TLC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.49 (m, 1H, *H5*; 1H, -*OH*); 1.61−1.78 (m, 1H, *H5*; 1H, -CH_2-CH_2-OH); 1.88−1.92 (m, 1H, -CH_2-CH_2-OH; 2H, *H6*); 2.57 (t, ^3J = 5.7 Hz, 2H, *H7*); 2.71−2.78 (m, 1H, *H4*); 3.78 (t, ^3J = 6.6 Hz, 2H, -CH_2-OH); 6.26 (d, ^3J = 1.8 Hz, 1H, *H3*); 7.24 (d, ^3J = 1.8 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3340, 2940, 2860, 1500.

2-(4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-yl)ethanol, 19. Prepared from **11**, yield 95% as a yellow oil, pure compound, checked by TLC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 1H, -*OH*); 1.50−1.58 (m, 1H, *H5*); 1.68−1.81 (m, 1H, -CH_2-CH_2-OH; 1H, *H5*); 1.89−1.98 (m, 2H, *H6*); 2.01−2.10 (m, 1H, -CH_2-CH_2-OH); 2.76 (t, ^3J = 5.7 Hz, 2H, *H7*); 2.85−2.93 (m, 1H, *H4*); 3.78 (t, ^3J = 6.6 Hz, 2H, -CH_2-OH); 6.86 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.05 (d, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3320, 2940, 2860.

2-(1,2,3,4-Tetrahydronaphthalen-1-yl)ethanol, 20. Prepared from **12**, yield 84% as a colorless oil, pure compound, checked by TLC: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.38 (br s, 1H, -*OH*); 1.62−2.05 (m, 6H, *H2*, *H3*, -CH_2-CH_2-OH); 2.63−3.04 (m, 3H, *H1*, *H4*); 3.76 (t, ^3J = 6.4 Hz, 2H, -CH_2-OH); 7.03−7.15 (m, 4H, *Ar-H*); IR (film) (cm^{-1}) 3340, 3060, 2940, 2880.

Method C. Synthesis of Ethyl (5,6,7,8-Tetrahydroquinolin-5-yl)acetate, 13. Compound **9** (0.78 g, 3.6 mmol) was dissolved in ethanol (40 mL) and 10% Pd/C (0.1 g) was added. The reaction mixture was evacuated three times and then hydrogenated under atmospheric pressure on a shaker till no more hydrogen was consumed (≈4 h). The catalyst was filtered off and washed with ethanol. The solvent was removed under reduced pressure and the residue was purified by bulb distillation to yield **13** (94%) as a colorless oil: $bp_{0.01}$ 95−100 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.24 (t, ^3J = 7.2 Hz, 3H, -CH_3); 1.71−1.98 (m, 4H, *H6*, *H7*); 2.50−2.62 (m, 2H, -CH_2-COOR); 2.86−3.46 (m, 3H, *H5*, *H8*); 4.16 (q, ^3J = 7.2 Hz, 2H, -CH_2-CH_3); 7.03 (dd, ^3J = 7.2 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.45 (dd, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, *H4*); 8.36 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H, *H2*).

Ethyl (4,5,6,7-Tetrahydrobenzo[*b*]furan-4-yl)acetate, 10. Prepared from **5**, purified by flash chromatography with CH_2Cl_2/methanol 50:1, yield 50% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, ^3J = 7.1 Hz, 3H, -CH_3); 1.38−1.45 (m, 1H, *H5*); 1.74−1.80 (m, 1H, *H5*); 1.91−1.95 (m, 2H, *H6*); 2.35 (dd, ^3J = 8.4 Hz, ^2J = 15.0 Hz, 1H, -CH_2-COOR); 2.55−2.60 (m, 2H, *H7*; 1H, -CH_2-COOR); 3.10 (m, 1H, *H4*); 4.17 (q, ^3J = 7.1 Hz, 2H, -CH_2-CH_3); 6.20 (d, ^3J = 1.8 Hz, 1H, *H3*); 7.22 (d, ^3J = 1.8 Hz, 1H, *H2*); IR (film) (cm^{-1}) 2980, 2940, 2870, 1735, 1450, 1375, 1285, 1250, 1175, 1040, 900, 730.

Ethyl (4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-yl)acetate, 11.[24] Prepared from **6** in THF with 2.5-fold excess of Pd/C, purified by flash chromatography with hexane/ethyl acetate 20:1, yield 66% as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, ^3J = 7.1 Hz, 3H, -CH_3); 1.52−1.60 (m, 1H, *H5*); 1.74−1.83 (m, 1H, *H5*); 1.87−2.00 (m, 2H, *H6*); 2.40 (dd, ^3J = 9.1 Hz, ^2J = 15.0 Hz, 1H, -CH_2-COOR); 2.70 (dd, ^3J = 5.3 Hz, ^2J = 15.0 Hz, 1H, -CH_2-COOR); 2.76 (t, ^3J = 6.2 Hz, 2H, *H7*); 3.22−3.28 (m, 1H, *H4*); 4.17 (q, ^3J = 7.1 Hz, 2H, -CH_2-CH_3); 6.81 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.04 (d, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 2980, 2930, 2860, 1738, 1495, 1370, 1280, 1175, 1150, 1032, 875, 732.

Ethyl (1,2,3,4-Tetrahydronaphthalen-1-yl)acetate, 12. Prepared from **8**, purified by distillation, yield 90% as a yellow oil: $bp_{0.01}$ 95−100 °C (oil bath); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, ^3J = 7.2 Hz, 3H, -CH_3); 1.69−1.88 (m, 4H, *H2*, *H3*); 2.49−2.84 (m, 4H, *H4*, -CH_2-COOR); 3.25−3.43 (m, 1H, *H1*); 4.17 (q, ^3J = 7.2 Hz, 2H, -CH_2-CH_3); 7.03−7.15 (m, 4H, *Ar-H*).

5-[3-(Imidazol-1-yl)propyl]-5,6,7,8-tetrahydroquinoline, 51. Prepared from **50**, purified by bulb distillation, yield 59% as a yellow oil: $bp_{0.01}$190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−1.93 (m, 8H, *H6*, *H7*, -CH_2-CH_2-CH_2-Im); 2.79−2.96 (m, 3H, *H5*, *H8*); 3.97 (t, ^3J = 7.0 Hz, 2H, -CH_2-Im); 6.91 (s, 1H, *H′4*); 7.05 (dd, ^3J = 7.8 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.08 (s, 1H, *H′5*); 7.34 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, *H4*); 7.48 (s, 1H, *H′2*); 8.36 (dd, ^3J = 4.8 Hz, ^4J = 1.5 Hz,1H, *H2*); IR (KBr) (cm^{-1}) 3100, 2930, 1570, 1510, 1445, 1230, 1080, 805, 750; GCMS (70−250 °C, 15 °C/min) >99% pure, t_R = 17.34 min, (*m*/*z*) 241.15 (M^+).

Method D. Synthesis of 5-(2-Chloroethyl)-5,6,7,8-tetrahydroquinoline Hydrochloride, 26. Freshly distilled $SOCl_2$ (0.43 g, 3.6 mmol) was added dropwise to a solution of **21** (0.35 g, 2.0 mmol) in dry $CHCl_3$ (6 mL) at −8 to 0 °C under a nitrogen atmosphere. The mixture was slowly warmed and then refluxed for 2 h. After cooling to room temperature, solvent and excess thionyl chloride were removed under reduced pressure to yield **26** (95%) as a beige solid. The crude

product was submitted to the next step without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.80−2.21 (m, 6H, *H6*, *H7*, -CH_2-CH_2Cl); 3.27−3.55 (m, 3H, *H5*, *H8*); 3.65 (t, ^3J = 6.4 Hz, 2H, -CH_2Cl); 7.67 (dd, ^3J = 8.0 Hz, ^3J = 5.6 Hz, 1H, *H3*); 8.19 (d, ^3J = 8.0 Hz, 1H, *H4*); 8.53 (d, ^3J = 5.6 Hz, 1H, *H2*).

5-(2-Chloroethyl)-7,8-dihydroquinoline Hydrochloride, 22. Prepared from **17**, yield 84% as a beige solid, pure compound, checked by TLC: ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.45−2.70 (m, 2H, *H7*); 2.93 (t, $^3J \approx$ 6.8 Hz, 2H, -CH_2-CH_2Cl); 3.45−3.77 (m, 4H, *H8*, -CH_2Cl); 6.31 (t, ^3J = 4.8 Hz, 1H, *H6*); 7.71 (dd, ^3J = 7.2 Hz, ^3J = 5.6 Hz, 1H, *H3*); 8.07 (d,^3J = 7.2 Hz, 1H, *H4*); 8.44 (d, ^3J = 5.6 Hz, 1H, *H2*).

1-(2-Chloroethyl)-1,2,3,4-tetrahydronaphthalene, 25. Prepared from **20**, yield quantitative as a yellow oil, pure compound, checked by TLC: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.66−2.22 (m, 6H, *H2*, *H3*, -CH_2-CH_2Cl); 2.69−3.08 (m, 3H, *H1*, *H4*); 4.46−4.71 (m, 2H, -CH_2Cl); 7.05−7.16 (m, 4H, *Ar-H*).

5-Chloro-5,6,7,8-tetrahydroquinoline Hydrochloride, 38. Prepared from **36**, yield quantitative as a beige solid, pure compound, checked by TLC: ^{1}H NMR (80 MHz, DMSO-d_6) δ 1.90−2.33 (m, 4H, *H6*, *H7*); 3.08−3.30 (m, 2H, *H8*); 5.71 (t, ^3J = 4.0 Hz, 1H, *H5*); 7.86 (dd, ^3J = 8.0 Hz, ^3J = 4.8 Hz, 1H, *H3*); 8.50 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, *H4*); 8.74 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, *H2*).

5-(3-Chloropropyl)-7,8-dihydroquinoline Hydrochloride, 49. Prepared from **48**, yield quantitative as a beige solid, pure compound, checked by TLC: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97−2.69 (m, 6H, *H7*, -CH_2-CH_2-CH_2Cl); 3.52−3.71 (m, 4H, *H8*, -CH_2*Cl*); 6.25 (t, ^3J = 4.5 Hz, 1H, *H6*); 7.64−7.70 (m, 1H, *H3*); 8.07 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, *H4*); 8.40 (dd, ^3J = 5.9 Hz, ^4J = 1.2 Hz, 1H, *H2*).

Method E. Synthesis of 4-(2-Bromoethyl)-4,5,6,7-tetrahydrobenzo[*b*]furan, 23. CBr_4 (11.7 g, 35.4 mmol) and triphenylphosphine (9.3 g, 35.4 mmol) were added to a solution of **18** (4.9 g, 29.5 mmol) in dry THF (120 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, warmed to room temperature and stirred overnight. The suspension was filtered, the filtrate evaporated, and the residue purified by flash chromatography with petroleum ether (40−80 °C) to yield **23** (78%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35−1.44 (m, 1H, *H5*); 1.72−1.82 (m, 1H, *H5*); 1.86−1.97 (m, 2H, *H6*, 1H, -CH_2-CH_2Br); 2.14−2,23 (m, 1H, -CH_2-CH_2Br); 2.57 (t, ^3J = 6.2 Hz, 2H, *H7*); 2.77−2.84 (m, 1H, *H4*); 3.47−3.54 (m, 2H, -CH_2Br); 6.26 (d, ^3J = 2.2 Hz, 1H, *H3*); 7.24 (d, ^3J = 2.2 Hz, 1H, *H2*); IR (film) (cm^{-1}) 2940, 2860, 1505, 1445, 1260, 1225, 1040, 895, 735.

4-(2-Bromoethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene, 24. Prepared from **19**, purified by flash chromatography with petroleum ether (40−80 °C), yield 87% as a beige oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48−1.55 (m, 1H, *H5*); 1.74−1.84 (m, 1H, *H5*); 1.88−2.04 (m, 2H, *H6*, 1H, -CH_2-CH_2Br); 2.26−2,34 (m, 1H, -CH_2-CH_2Br); 2.76 (t, ^3J = 6.2 Hz, 2H, *H7*); 2.94−2.99 (m, 1H, *H4*); 3.45−3.52 (m, 2H, -CH_2Br); 6.86 (d, ^3J = 5.3 Hz, 1H, *H3*); 7.06 (d, ^3J = 5.3 Hz, 1H, *H2*); IR (film) (cm^{-1}) 2940, 2860, 1450, 1435, 1260, 1255, 880, 730, 710, 660.

Method F. Synthesis of 5-[2-(Imidazol-1-yl)ethyl]-5,6,7,8-tetrahydroquinoline, 30. A mixture of **21** (1.3 g, 5.6 mmol), dry NaI (0.84 g, 5.6 mmol), imidazole (1.9 g, 27,9 mmol) and Na_2CO_3 (3.0 g, 27.9 mmol) in dry acetone (10 mL) was refluxed for 72 h. The solvent was evaporated and the residue dissolved in $CHCl_3$ (30 mL) and filtered. The filtrate was extracted with water and dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography with $CHCl_3$/methanol 9:1 followed by crystallization from ether at 4 °C yielded **30** (71%) as colorless crystals: mp 40−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−2.17 (m, 6H, *H6*, *H7*, -CH_2-CH_2-Im); 2.78−2.97 (m, 3H, *H5*, *H8*); 4.01−4.06 (m, 2H, -CH_2-Im); 6.96 (s, 1H, *H′4*); 7.07 (dd, ^3J = 7.7 Hz, ^3J = 4.7 Hz, 1H, *H3*); 7.10 (s, 1H, *H′5*); 7.34 (dd, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, *H4*); 7.52 (s, 1H, *H′2*); 8.38 (dd, ^3J = 4.7 Hz, ^4J = 1.4 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 2930, 1570, 1505, 1440, 1230, 1075, 905, 810; GCMS (70−250 °C, 15 °C/min) >99% pure, t_R = 16.33 min, (*m*/*z*) 227.20 (M$^+$).

1-[2-(Imidazol-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalene, 29. Prepared from **25**, the residue was dissolved in $CHCl_3$ and extracted with HCl (5%). The aqueous phases were made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was distilled to yield **29** (30%) as a colorless oil: $bp_{0.01}$ 140−150 °C (oil bath); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−2.21 (m, 6H, *H2*, *H3*, -CH_2-CH_2-Im); 2.75−2.82 (m, 3H, *H1*, *H4*); 4.01−4.05 (m, 2H, -CH_2-Im); 6.95 (s, 1H, *H′4*); 7.04−7.15 (m, 5H, *Ar-H*, *H′5*); 7.50 (s, 1H, *H′2*); IR (KBr) (cm^{-1}) 2930, 1510, 1450, 1230, 1110, 1075, 905, 760, 740, 660; GCMS (70−250 °C, 15 °C/min) >99% pure, t_R = 15.77 min, (*m*/*z*) 226.20 (M$^+$).

5-[2-(Imidazol-1-yl)ethyl]-7,8-dihydroquinoline, 31. Prepared from **22**, purified by flash chromatography with $CHCl_3$/methanol 9:1, yield 64% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34−2,39 (m, 2H, *H7*); 2.85−2.96 (m, 4H, -CH_2-CH_2-Im, *H8*); 4.10 (t, ^3J = 7.1 Hz, 2H, -CH_2-CH_2-Im); 5.80 (t, ^3J = 4.8 Hz, 1H, *H6*); 6.86 (s, 1H, *H′4*); 6.95 (s, 1H, *H′5*); 7.15 (dd, ^3J = 7.5 Hz, ^3J = 4.9 Hz, 1H, *H3*); 7.39 (m, 2H, *H4*, *H′2*); 8.36 (dd, ^3J = 4.9 Hz, ^4J = 1.3 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 2945, 1685, 1585, 1440, 1290, 1180, 1120, 895; GCMS (70−250 °C, 15 °C/min) >95% pure, t_R = 16.23 min, (*m*/*z*) 225.20 (M$^+$).

5-[3-(Imidazol-1-yl)propyl]-7,8-dihydroquinoline, 50. Prepared from **49**, purified by flash chromatography with $CHCl_3$/methanol 9:1, yield 70% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97−2.04 (m, 2H, -CH_2-CH_2-CH_2-Im); 2.39−2.44 (m, 4H, *H7*, -CH_2-CH_2-CH_2-Im); 2.96 (t, ^3J = 8.1 Hz, 2H, *H8*); 4.00 (t, ^3J = 6.9 Hz, 2H, -CH_2-CH_2-CH_2-Im); 5.90 (t, ^3J = 4.0 Hz, 1H, *H6*); 6.92 (s, 1H, *H′4*); 7.09−7.12 (m, 2H, *H3*, *H′5*); 7.32 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, *H4*); 7.49 (s, 1H, *H′2*); 8.32 (dd, ^3J = 4.9 Hz, ^4J = 1.4 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3100, 2940, 1565, 1510, 1440, 1230, 1075, 905, 815, 750; GCMS (70−250 °C, 15 °C/min) >99% pure, t_R = 17.48 min, (*m*/*z*) 239.15 (M$^+$).

Method G. Synthesis of 1-[2-(4,5,6,7-Tetrahydrobenzo-[*b*]furan-4-yl)ethyl]-1*H*-imidazole, 27. Imidazole sodium salt (1.81 g,18.1 mmol) was added to a solution of **23** (3.0 g, 13.9 mmol) in dry DMF (70 mL) and the resulting mixture was stirred for 2 h at room temperature. The mixture was poured into water (300 mL) and extracted with ethyl acetate, and the organic phases were washed with a saturated solution of NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with CH_2Cl_2/methanol 20:1 to yield **27** (89%) as a beige oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.45 (m, 1H, *H5*); 1.68−1.79 (m, 1H, *H5*); 1.82−2.00 (m, 2H, *H6*, 1H, -CH_2-CH_2-Im); 2.10−2.19 (m, 1H, -CH_2-CH_2-Im); 2.58 (t, ^3J = 5.7 Hz, 2H, *H7*); 2.59−2.66 (m, 1H, *H4*); 4.03 (t, ^3J = 7.7 Hz, 2H, -CH_2-Im); 6.20 (d, ^3J = 1.8 Hz, 1H, *H3*); 6.94 (br s, 1H, *H′5*); 7.07 (br s, 1H, *H′4*); 7.26 (d, ^3J = 1.8 Hz, 1H, *H2*); 7.52 (br s, 1H, *H′2*); ^{13}C NMR (120 MHz, $CDCl_3$) δ 21.10, 22.94, 28.73, 30.48, 36.76, 44.89, 108.85, 118.62, 119.34, 129.42, 136.89, 140.56, 150.83; IR (film) (cm^{-1}) 3380, 3100, 2940, 2870, 1630, 1508, 1445, 1230, 1110, 1080, 908, 735, 665; GCMS (100−300 °C, 15 °C/min) >99% pure, t_R = 9.98 min, (*m*/*z*) 216.10 (M$^+$).

1-[2-(4,5,6,7-Tetrahydrobenzo[*b*]thiophen-4-yl)ethyl]-1*H*-imidazole, 28. Prepared from **24**, purified by flash chromatography with $CHCl_2$/methanol 18:1, yield 87% as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.57 (m, 1H, *H5*); 1.73−1.82 (m, 1H, *H5*); 1.91−2.03 (m, 2H, *H6*, 1H, -CH_2-CH_2-Im); 2.21−2.23 (m, 1H, -CH_2-CH_2-Im); 2.76−2.79 (m, 2H, *H7*, 1H, *H4*); 4.03 (t, ^3J = 7.7 Hz, 2H, -CH_2-Im); 6.78 (d, ^3J = 4.9 Hz, 1H, *H3*); 6.94 (br s, 1H, *H′5*); 7.08 (d, ^3J = 4.9 Hz, 1H, *H2*); 7.09 (br s, 1H, *H′4*); 7.66 (br s, 1H, *H′2*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.53, 24.94, 27.97, 33.11, 36.91, 44.99, 118.68, 122.15, 125.93, 128.56, 136.47, 136.73, 137.22; IR (film) (cm^{-1}) 3120, 2940, 2500, 1950, 1715, 1675, 1515, 1440, 1390, 1365, 1260, 1110, 1080, 880, 735, 665; GCMS (100−300 °C, 15 °C/min) >96% pure, t_R = 9.13 min, (*m*/*z*) 232.15 (M$^+$).

Method H. Synthesis of 1-[2-(4,5,6,7-Tetrahydrobenzo-[*b*]furan-4-ylidene)ethyl]-1*H*-imidazole, 34. 1,1′-Carbonyldiimidazole (0.99 g, 6.1 mmol) and **14** (1.0 g, 6.1 mmol) were

reacted at room temperature for 12 h under a nitrogen atmosphere. The reaction mixture was diluted with water (25 mL), acidified with 0.5 M HCl and extracted with CH_2Cl_2. The aqueous phase was alkalized with 2 M NaOH and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The mixture of isomers was separated by flash chromatography with CH_2Cl_2/dry ethanol 25:1 to yield **34*E*** (39%) and **34*Z*** (11%) as yellow oils. **34*E***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59−1.70 (m, 1H, *H6*); 1.87−1.96 (m, 1H, *H6*); 2.05−2.12 (m, 1H, *H7*); 2.25−2.31 (m, 1H, *H7*); 2.59−2.74 (m, 2H, *H5*); 5.03 (d, ^3J = 17.7 Hz, 1H, -CH_2-Im); 5.31 (d, ^3J = 10.4 Hz, 1H, -CH_2-Im); 6.12 (dd, ^3J = 10.4 Hz, ^3J = 17.7 Hz, 1H, -*CH*-CH_2-Im); 6.27 (d, ^3J = 1.8 Hz, 1H, *H3*); 6.91 (s, 1H, *H′5*); 7.07 (s, 1H, *H′4*); 7.35 (d, ^3J = 1.8 Hz, 1H, *H2*); 7.44 (s, 1H, *H′2*); IR (film) (cm^{-1}) 3400, 3100, 2940, 2860, 1640, 1625, 1510, 1495, 1415, 1225, 1070, 900, 740, 665; GCMS (*m*/*z*) 214.05 (M$^+$); HPLC (216 nm) >99% pure, t_R = 7.53 min.

34*Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93−1.99 (m, 2H, *H6*); 2.38−2.42 (m, 1.4H, *H7*); 2.48−2.51 (m, 0.6H, *H7*); 2.71−2.77 (m, 2H, *H5*); 4.70 (d, ^3J = 7.4 Hz, 0.6H, -CH_2-Im); 4.82 (d, ^3J = 7.1 Hz, 1.4H, -CH_2-Im); 5.33 (t, ^3J = 7.1 Hz, 0.7H, -*CH*-CH_2-Im); 5.64 (t, ^3J = 7.4 Hz, 0.3H, -*CH*-CH_2-Im); 6.42−6.43 (m, 1H, *H3*); 6.94 (s, 0.3H, *H′5*); 6.97 (s, 0.7H, *H′5*); 7.09 (s, 1H, *H′4*); 7.26 (d, ^3J = 1.8 Hz, 0.3H, *H2*); 7.33 (d, ^3J = 2.2 Hz, 0.7H, *H2*); 7.57 (s, 0.3H, *H′2*); 7.58 (s, 0.7H, *H′2*); IR (film) (cm^{-1}) 3380, 3110, 2940, 2860, 1660, 1510, 1440, 1230, 1110, 1070, 740, 660; GCMS (*m*/*z*) 214.05 (M$^+$); HPLC (244 nm) >96% pure, t_R = 8.83 min (20%), t_R = 9.73 min (76%).

1-[2-(4,5,6,7-Tetrahydrobenzo[*b*]thiopen-4-ylidene)ethyl]-1*H*-imidazole, 35. Prepared from **15**, yield **35*E*** (36%) and **35*Z*** (24%) as yellow oils. **35*E***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59−1.69 (m, 1H, *H6*); 1.88−1.97 (m, 1H, *H6*); 2.12−2.19 (m, 1H, *H7*); 2.29−2.35 (m, 1H, *H7*); 2.79−2.94 (m, 2H, *H5*); 5.00 (d, ^3J = 17.1 Hz, 1H, -CH_2-Im); 5.36 (d, ^3J = 10.4 Hz, 1H, -CH_2-Im); 6.19 (dd, ^3J = 10.4 Hz, ^3J = 17.1 Hz, 1H, -*CH*-CH_2-Im); 6.79 (d, ^3J = 4.9 Hz, 1H, *H3*); 6.85 (s, 1H, *H′5*); 7.06 (s, 1H, *H′4*); 7.14 (d, ^3J = 4.9 Hz, 1H, *H2*); 7.33 (s, 1H, *H′2*); IR (KBr) (cm^{-1}) 3440, 3095, 2940, 2920, 2840, 1645, 1505, 1440, 1280, 1235, 1070, 910, 850, 740, 670; GCMS (*m*/*z*) 230.15 (M$^+$); HPLC (256 nm) >99% pure, t_R = 13.26 min.

35*Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95−2.01 (m, 2H, *H6*); 2.55 (t, ^3J = 5.8 Hz, 2H, *H7*); 2.88 (t, ^3J = 6.1 Hz, 2H, *H5*); 4.73 (d, ^3J = 7.2 Hz, 2H, -CH_2-Im); 5.90 (t, ^3J = 7.2 Hz, 1H, -*CH*-CH_2-Im); 6.95 (s, 1H, *H′5*); 7.06 (d, ^3J = 5.1 Hz, 1H, *H3*); 7.09 (s, 1H, *H′4*); 7.12 (d, ^3J = 5.1 Hz, 1H, *H2*); 7.58 (s, 1H, *H′2*); IR (film) (cm^{-1}) 3400, 3100, 2940, 2860, 1640, 1480, 1450, 1225, 1110, 1080, 1070, 905, 880, 730, 665; GCMS (*m*/*z*) 230.15 (M$^+$); HPLC (236 nm) >99% pure, t_R = 10.80 min.

Method I. Synthesis of 5-(Imidazol-1-yl)-5,6,7,8-tetrahydroquinoline, 40. Compound **38** (0.4 g, 2.0 mmol), imidazole (0.4 g, 6.0 mmol) and triturated K_2CO_3 (0.5 g) were suspended in DMF (4 mL) and then stirred for 14 h at room temperature and for an additional 8 h at 50 °C. After cooling to room temperature, ether (50 mL) was added and the resulting mixture was stored at −18 °C overnight. The precipitate was filtered off, the solvents were removed under reduced pressure, and the residue was purified by flash chromatography with $CHCl_3$/methanol 9:1 and crystallized from hexane/ethyl acetate to yield **40** (50%) as colorless crystals: mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97−2.34 (m, 4H, *H6*, *H7*); 3.01−3.11 (m, 2H, *H8*); 5.37 (dd, ^3J = 8.4 Hz, ^3J = 5.4 Hz, 1H, *H5*); 6.82 (s, 1H, *H′4*); 7.08−7.16 (m, 3H, *H3*, *H4*, *H′5*); 7.52 (s, 1H, *H′2*); 8.50 (dd, ^3J = 4.6 Hz, ^4J = 1.5 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3090, 2945, 1570, 1490, 1445, 1250, 1225, 1085, 905, 810, 760, 660. Anal. ($C_{12}H_{13}N_3$) C, H, N.

8-(Imidazol-1-yl)-5,6,7,8-tetrahydroquinoline, 41. Prepared from **39**, crystallized from hexane/ethyl acetate, yield 19% as colorless crystals: mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86−1.91 (m, 2H, *H6*); 2.25−2.32 (m, 2H, *H7*); 2.85−2.94 (m, 2H, *H5*); 5.41 (t, ^3J = 7.8 Hz, 1H, *H8*); 6.80 (s, 1H, *H′4*); 7.04 (s, 1H, *H′5*); 7.19 (dd, ^3J = 7.8 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.38 (s, 1H, *H′2*); 7.51 (dd, ^3J = 7.8 Hz, ^4J = 0.7 Hz, 1H, *H4*); 8.46 (dd, ^3J = 4.8 Hz, ^4J = 0.7 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3080, 2940, 1725, 1305, 1200, 780. Anal. ($C_{12}H_{13}N_3$) C, H, N.

Synthesis of 1-[2-(Benzo[*b*]thiophen-4-yl)ethyl]-1*H*-imidazole, 32. CBr_4 (4.55 g, 13.7 mmol) was added to a solution of **16** (1.65 g, 9.2 mmol) in dry CH_2Cl_2. A solution of triphenylphosphine (2.64 g, 10.1 mmol) in dry CH_2Cl_2 was added dropwise under cooling keeping the temperature of the reaction mixture below 30 °C. The solution was stirred for 3 h at room temperature. The solvent was removed under reduced pressure and the precipitate was extracted with petroleum ether (40−80 °C). The solvent was removed and the crude product submitted to method F and purified by flash chromatography with CH_2Cl_2/methanol 30:1 to yield **32** (30%) as a beige oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (t, ^3J = 7.1 Hz, 2H, -CH_2-CH_2-Im); 4.82 (t, ^3J = 7.1 Hz, 2H, -CH_2-CH_2-Im); 6.81 (br s, 1H, *H′5*); 6.99 (dd, ^3J = 7.1 Hz, ^5J = 0.9 Hz, 1H, *H5*); 7.02 (br s, 1H, *H′4*); 7.25 (dd, ^3J = 7.1 Hz, ^3J = 8.0 Hz, 1H, *H6*); 7.30 (dd, ^3J = 5.3 Hz, ^5J = 0.9 Hz, 1H, *H3*); 7.36 (br s, 1H, *H′2*); 7.40 (d, ^3J = 5.3 Hz, 1H, *H2*); 7.79 (d, ^3J = 8.0 Hz, 1H, *H7*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.95, 47.61, 118.74, 120.76, 121.45, 124,49, 126.89, 129.31, 132.12, 136.92, 138.35, 140.29; IR (film) (cm^{-1}) 3330, 3110, 2936, 2870, 1660, 1590, 1510, 1450, 1410, 1230, 1110, 1080, 765, 745, 665; GCMS (100−300 °C, 15 °C/min) >97% pure, t_R = 9.27 min, (*m*/*z*) 228.05 (M$^+$).

Synthesis of 5-[2-(Imidazol-1-yl)ethyl]quinoline, 33. 10% Pd/C (0.1 g) was added to a solution of **31** in mesitylene (80 mL) and refluxed for 18 h. The mixture was allowed to cool to room temperature and extracted with 5% HCl. The acidic phase was washed with $CHCl_3$, alkalized (pH 9−10) with solid Na_2CO_3 and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with $CHCl_3$/methanol 17:1 and crystallized from hexane/ethyl acetate 5:1 to yield **33** (34%) as yellow crystals: mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (t, ^3J = 7.1 Hz, 2H, -CH_2−CH_2−Im); 4.31 (t, ^3J = 7.1 Hz, 2H, -CH_2-CH_2-Im); 6.79 (s, 1H, *H′4*); 7.03 (s, 1H, *H′5*); 7.24 (d, ^3J = 7.1 Hz, 1H, *H6*), 7.36 (s, 1H, *H′2*); 7.45 (dd, ^3J = 8.7 Hz, ^3J = 4.2 Hz, 1H, *H3*); 7.62 (dd, ^3J = 8.4 Hz, ^3J = 7.1 Hz, 1H, *H7*); 8.05 (d, ^3J = 8.5 Hz, 1H, *H8*); 8.21 (d, ^3J = 8.7 Hz, 1H, *H4*); 8.96 (dd, ^3J = 4.2 Hz, ^4J = 1.6 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3090, 1630, 1600, 1570, 1510, 1500, 1450, 1435, 1290, 1280, 1235, 1080, 1070, 910, 840, 795, 665, 630; GCMS (*m*/*z*) 223.30 (M$^+$); HPLC (230 nm) >99% pure, t_R = 13.23 min.

Synthesis of 5,6,7,8-Tetrahydroquinoline 1-Oxide, 37. H_2O_2 (25 mL, 30% solution) was added to a solution of 5,6,7,8-tetrahydroquinoline (30.0 g, 225.2 mmol) in acetic acid (200 mL) and stirred for 1 h at 70−80 °C. This procedure was repeated three times. The reaction mixture was heated at 80 °C overnight and evaporated under reduced pressure. The residue was dried over P_4O_{10} to yield **37** (quantitative) as a light yellow oil. The crude product was submitted to the next step without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.63−2.02 (m, 4H, *H6*, *H7*); 2.69−3.00 (m, 4H, *H5*, *H8*); 7.01−7.05 (m, 2H, *H3*, *H4*); 8.12−8.21 (m, 1H, *H2*).

Synthesis of 8-Chloro-5,6,7,8-tetrahydroquinoline, 39. A solution of $POCl_3$ (4.4 g, 27.6 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of **37** (1.2 g, 8.1 mmol) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere. After 1 mL was added, the simultaneous addition of a solution of $N(C_2H_5)_3$ (2.8 g, 26.6 mmol) in CH_2Cl_2 (15 mL) was started with equal dropping velocity to keep the solvent slightly boiling. After the addition was completed, the mixture was stirred for a further 15 min and poured onto ice (40 g). The organic phase was separated and extracted with 5% HCl. The aqueous phases were combined, washed with CH_2Cl_2, alkalized with solid Na_2CO_3 and extracted with ethyl acetate. The organic phase was washed with water and dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield **39** (66%) as beige oil. The crude product was submitted to the next step without further purification: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.75−2.47 (m, 4H,*H6*, *H7*); 2.71−2.91 (m, 2H, *H5*); 5.23−5.33 (m, 1H,

H8); 7.11 (dd, ^3J = 8.0 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.42 (d, ^3J = 8.0 Hz, 1H, *H4*); 8.46 (d, ^3J = 4.8 Hz, 1H, *H2*).

Synthesis of Spiro-5,6,7,8-tetrahydroquinoline-5,2′-oxirane, 42. 60% NaH (0.54 g, 22.5 mmol) was washed with dry ether under a nitrogen atmosphere to remove the mineral oil and dried in a nitrogen stream. After suspension in dry DMSO (25 mL), the mixture was heated to 60 °C till the formation of H_2 was finished (≈2 h). The solution was diluted with THF (25 mL) and cooled to −3 °C. A solution of $(CH_3)_3SI$ (4.6 g, 22.5 mmol) in DMF (10 mL) was quickly added dropwise and the resulting mixture was stirred for a few minutes at 0 °C. **4** (3.0 g, 20.4 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h and for a further 14 h at room temperature. The solution was poured into ice-cold brine (100 mL) and extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was distilled to yield **42** (67%) as a colorless oil: $bp_{0.01}$ 80−85 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.71−2.23 (m, 4H, *H6*, *H7*); 2.88−3.10 (m, 4H, *H8*, *H′3*); 7.06 (dd, ^3J = 8.0 Hz, ^3J = 4.8 Hz, 1H, *H3*); 7.35 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, *H4*); 8.41 (dd, ^3J = 4.8, J^4 = 1.6; 1H, *H2*); IR (film) (cm^{-1}) 3040, 2940, 1590, 1570, 1440, 1420, 1340, 1035, 920, 800.

Synthesis of 5-[(Imidazol-1-yl)methyl]-5,6,7,8-tetrahydroquinolin-5-ol Dihydrochloride, 43. 60% NaH (0.46 g, 19.1 mmol) was added in portions to a solution of imidazole (1.3 g, 19.1 mmol) in dry DMSO (20 mL). After the formation of H_2 had stopped, **42** (2.5 g, 15.5 mmol) was added dropwise within 1 min, and the reaction mixture was stirred for 17 h at room temperature. The solution was poured into ice-cold brine (60 mL) and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the free base as a yellow oil. The residue was dissolved in acetone (10 mL) and precipitated with concentrated HCl. The solvent was removed under reduced pressure, and the residue was crystallized from water/methanol 1:1 by addition of acetone. The mixture was stored overnight at 4 °C and filtered with suction to yield **43** (67%) as colorless crystals: mp 130 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.77−2.09 (m, 4H, *H6*, *H7*); 3.10−3.27 (m, 2H, *H8*); 4.52 (d, ^2J = 14.0 Hz, 1H, -CH_2-Im); 4.65 (d, ^2J = 14 Hz, 1H, -CH_2-Im); 6.68 (br, s, 1H, -*OH*); 7.70−7.71 (m, 2H, *H′4*, *H′5*); 7.80 (dd, ^3J = 7.8 Hz, ^3J = 4.8 Hz, 1H, *H3*); 8.21 (d, ^3J = 7.8 Hz, 1H, *H4*); 8.72−8.74 (m, 1H, *H2*); 9.16 (s, 1H, *H′2*); 13.72 (br s, 2H, *H1*, *H′3*).

Synthesis of 5-[(Imidazol-1-yl)methyl]-7,8-dihydroquinoline, 44. Compound **43** (1.5 g, 4.96 mmol) was heated in a mixture of acetic acid (12.5 mL) and concentrated H_2SO_4 (1.75 mL) for 10 h at 120 °C. After cooling to room temperature the reaction mixture was poured into ice-cold water (50 mL), alkalized with Na_2CO_3, and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was recrystallized two times from *n*-hexane/ethyl acetate to yield **44** (32%) as colorless needles: mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48−2.53 (m, 2H, *H7*); 3.02 (t, ^3J = 8.3 Hz, 2H, *H8*); 4.91 (s, 2H, -CH_2-Im); 5.96 (t, ^3J = 4.5 Hz, 1H, *H6*); 6.94 (s, 1H, *H′4*); 7.05−7.09 (m, 2H, *H3*, *H′5*); 7.27 (dd, ^3J = 8.3 Hz, ^4J = 0.8 Hz, 1H, *H4*); 7.55 (s, 1H, *H′2*); 8.34 (dd, ^3J = 8.3 Hz, ^4J = 0.8 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3110, 2950, 1435, 1290, 1230, 1070, 905, 830, 745, 660. Anal. ($C_{13}H_{13}N_3$) C, H, N.

Synthesis of 5-[(Imidazol-1-yl)methyl]-5,6,7,8-tetrahydroquinoline, 45. Compound **43** (1.5 g, 4.96 mmol) was heated in a mixture of acetic acid (12.5 mL) and concentrated H_2SO_4 (1.75 mL) for 10 h at 120 °C. After cooling to room temperature, 10% Pd/C (0.1 g) was added. The mixture was evacuated three times and hydrogenated (9 bar) for 24 h at 30 °C. The catalyst was filtered off. The filtrate was poured into ice-cold water and alkalized with Na_2CO_3. The mixture was extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was recrystallized two times from *n*-hexane/ethyl acetate to yield **45** (29%) as colorless needles: mp 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67−1.93 (m, 4H, *H6*, *H7*); 2.87−3.25 (m, 3H, *H5*, *H8*); 4.05−4.16 (m, 2H, -CH_2-Im); 6.89 (s, 1H, *H′4*); 7.04 (dd, ^3J = 7.8 Hz, ^3J = 4.6 Hz, 1H, *H3*); 7.08−7.10 (m, 2H, *H4*, *H′5*); 7.38 (s, 1H, *H′2*); 8.43 (dd, ^3J = 4.6 Hz, ^4J = 1.6 Hz, 1H, *H2*); IR (KBr) (cm^{-1}) 3110, 2940, 1580, 1450, 1230, 1080, 920, 860, 810, 750. Anal. ($C_{13}H_{15}N_3$·0.27H_2O) C, H, N.

Synthesis of 3-(7,8-Dihydroquinolin-5-yl)propionitrile, 46. Powdered **22** (4.3 g, 18.8 mmol) was added to a solution of NaCN (2.3 g, 46.7 mmol) in dry DMSO (20 mL) at 90 °C. The mixture was stirred for 30 min at 100 °C, cooled, poured into ice-cold brine (150 mL), and extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield **46** (89%) as a yellow oil. The crude product was submitted to the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42−2.49 (m, 2H, *H7*); 2.57 (t, ^3J = 7.3 Hz, 2H, -CH_2-CH_2-CN); 2.79 (t, ^3J = 7.3 Hz, 2H, -CH_2-CH_2-CN); 2.95−3.01 (m, 2H, *H8*); 6.05 (t, ^3J = 4.4 Hz, 1H, *H6*); 7.15 (dd, ^3J = 7.8 Hz, ^3J = 5.0 Hz, 1H, *H3*); 7.38 (d, ^3J = 7.8 Hz, 1H, *H4*); 8.35 (d, ^3J = 5.0 Hz, 1H, *H2*); IR (film) (cm^{-1}) 3050, 2940, 2245, 1640, 1565.

Synthesis of 3-(7,8-Dihydroquinolin-5-yl)propionic Acid, 47. Compound **46** (3.0 g, 16.3 mmol) was hydrolyzed in a mixture of concentrated H_2SO_4 (10 mL) and water (10 mL) for 3 h at 110 °C. After cooling the solution was poured into ice-cold water (60 mL), alkalized with NaOH (pH 11), washed with ethyl acetate, and acidified with 5 M HCl (pH 4). The solution was stored for 17 h at 4 °C, and the precipitate was filtered off and dried at 60 °C to yield **47** (60%) as a colorless powder: mp 270−271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.31−2.83 (m, 8H, *H7*, *H8*, -CH_2-CH_2-COOH); 5.93 (t, ^3J = 4.4 Hz, 1H, *H6*); 7.22 (dd, ^3J = 7.8 Hz, ^3J = 5.0 Hz, 1H, *H3*); 7.59 (dd, ^3J = 7.8 Hz, ^4J = 1.1 Hz, 1H, *H4*); 8.27 (dd, ^3J = 5.0 Hz, ^4J = 1.1 Hz, 1H, *H2*); 12.14 (br s, 1H, -*COOH*).

Synthesis of 3-(7,8-Dihydroquinolin-5-yl)propan-1-ol, 48. $LiAlH_4$ (0.8 g, 21.0 mmol) was suspended in dry ether (30 mL) under a nitrogen atmosphere. With vigorous stirring **47** (1.9 g, 9.3 mmol) was added in portions and the mixture was stirred for 1 h at room temperature. Further treatment according to method B yielded **48** (51%) as a colorless solid: mp 82−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 1H, -*OH*); 1.75−2.53 (m, 6H, *H7*, -CH_2-CH_2-CH_2OH); 2.96 (t, ^3J = 8.1 Hz, 2H, *H8*); 3.72 (t, ^3J = 5.9 Hz, 2H, -CH_2OH); 5.94 (t, ^3J = 4.4 Hz, 1H, *H6*); 7.12 (dd, ^3J = 7.7 Hz, ^3J = 4.9 Hz, 1H, *H3*); 7.49 (d, ^3J = 7.7 Hz, 1H, *H4*); 8.30 (dd, ^3J = 4.9 Hz, ^4J = 1.5 Hz, 1H, *H2*); IR (film) (cm^{-1}) 2920, 2860, 2830, 1640, 1580, 1440, 1360, 1340, 1060, 1015, 920, 830, 815, 755.

Synthesis of 6-Chloroisoquinoline, 53. A vigorously stirred solution of **52** (5.0 g, 33.2 mmol) in methanol/CH_2Cl_2 5:2 (100 mL) was fumigated with ozone at −78 °C. To determine the end of the reaction, the exhausting gas was passed through a 10% aqueous solution of KI (2−3 h). Unreacted ozone was removed by flushing the reaction vessel with nitrogen. $NaHCO_3$ (3.5 g, 42.0 mmol) and dimethyl sulfide (6.6 mL) were added, the cooling bath was removed, and the mixture was stirred for 6 h. Subsequently 25% aqueous ammonia (40 mL) was added and the mixture stirred for further 15 h. The reaction mixture was extracted with CH_2Cl_2 and the combined organic phases were extracted with 5% HCl. The aqueous phase was washed with CH_2Cl_2 and alkalized with Na_2CO_3 (pH 10). The precipitate was filtered with suction and dried to yield **53** (64%) as beige needles: mp 39−40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.57 (m, 2H, *H4*, *H7*); 7.81 (s, 1H, *H5*); 7.91 (d, ^3J = 8.7 Hz, 1H, *H8*); 8.55 (d, ^3J = 5.6 Hz, 1H, *H3*); 9.23 (s, 1H, *H1*).

Synthesis of 6-(Imidazol-1-yl)isoquinoline, 54. 60% NaH (0.62 g, 25.8 mmol) was washed with dry ether to remove the mineral, dried in a nitrogen stream, and suspended in dry DMF (3 mL). Imidazole (1.75 g, 25.8 mmol) was added in portions under cooling. After the formation of H_2 was finished, **53** (1.4 g, 8.6 mmol) and copper powder (60 mg) were added and the mixture was heated at 150 °C for 3 h. The solution was cooled to room temperature, diluted with water (10 mL) and extracted with $CHCl_3$. The organic phase was dried over

$MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography with $CHCl_3$/methanol 9:1 to yield **54** (5%) as yellow crystals: mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H, *H′4*); 7.45 (s, 1H, *H′5*); 7.67−7.71 (m, 2H, *H4*, *H7*); 7.81 (d, ^4J = 1.8 Hz, 1H, *H5*); 8.04 (s, 1H, *H′2*); 8.13 (d, ^3J = 8.7 Hz, 1H, *H8*); 8.62 (d, ^3J = 5.8 Hz, 1H, *H3*); 9.31 (s, 1H, *H1*); IR (KBr) (cm^{-1}) 3100, 1630, 1500, 1305, 1110, 940, 875, 770, 650. Anal. ($C_{12}H_9N_3$) C, H, N.

Synthesis of 7-[(Imidazol-1-yl)methyl]isoquinoline, 56. *N*-Chlorosuccinimide (1.5 g, 11.2 mmol) was added to a solution of **55** (1.5 g, 10.5 mmol) in dry $CHCl_3$ (200 mL) under nitrogen. The mixture was exposed to UV light and refluxed for 3 h. The reaction mixture was cooled to 10 °C and filtered, and the solvent was removed under reduced pressure. The crude intermediate was submitted to method F and purified by flash chromatography with $CHCl_3$/methanol 9:1 followed by bulb distillation to yield **56** (23%) as light yellow crystals: $bp_{0.01}$ 170 °C; mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (br s, 0.26H, crystal water); 5.33 (s, 2H, -CH_2-Im); 6.96 (s, 1H, *H′4*); 7.15 (s, 1H, *H′5*); 7.48 (dd, ^3J = 8.5 Hz, ^4J = 1.7 Hz, 1H, *H6*); 7.64−7.66 (m, 2H, *H4*, *H8*); 7.72 (s, 1H, *H′2*); 7.84 (d, ^3J = 8.5 Hz, 1H, *H5*); 8.57 (d, ^3J = 5.7 Hz, 1H, *H3*); 9.23 (s, 1H, *H1*); IR (KBr) (cm^{-1}) 3100, 1670, 1630, 1590, 1500, 1360, 1285, 1275, 1225, 1080, 1030, 855, 740, 720, 670, 470. Anal. ($C_{13}H_{11}N_3$·0.13H_2O) C, H, N.

Biological Methods. 1. Enzyme Preparation. The enzymes were prepared according to the literature: P450 arom,[31] P450 17,[33] and P450 scc.[31]

2. Enzyme Assays. The enzyme assays were performed as described: P450 17[33] and P450 scc.[31]

3. Inhibition of P450 TxA_2. The assay was performed according to our described procedure.[30] Citrated human whole blood (0.5 mL) was preincubated with a solution of inhibitor in ethanol/K-Na-phosphate buffer, pH 7.4 (10 μL) (0.01 M KH_2PO_4, 0.05 M Na_2HPO_4 (1:1/v:v); control: vehicle; blank: dazoxiben HCl, 100 μM) for 10 min at 37 °C. Collagen suspension (50 μL; final collagen concentration: 53.6 μg/mL) was added and incubation was continued for another 10 min at 37 °C. The reaction was terminated by the addition of 0.4 mL of trichloroacetic acid (20% in 0.6 M HCl). The mixture was subjected to centrifugation at 4400*g* (10 min) and the supernatant (0.5 mL) pipetted into a solution of thiobarbituric acid (TBA) (0.53% TBA in the phosphate buffer described above) (0.5 mL). After heating for 30 min at 70 °C and cooling for another 30 min at room temperature, the samples were measured spectrofluorimetrically (λ excitation: 533 nm; λ emission: 550 nm).

4. Inhibition of P450 Arom. This assay was performed according to described methods[31,35,36] monitoring enzyme activity by measuring the ^3H_2O formed from [1β,2β-^{3}H]testosterone during aromatization. Each incubation tube contained 0.225 μCi of [1β,2β-^{3}H]testosterone, 5 μM unlabeled testosterone, 2 mM NADPH, 20 mM glucose-6-phosphate, 1 EU glucose-6-phosphate dehydrogenase, and inhibitor (0−250 μM) in phosphate buffer (0.05 M, pH 7.4). The test compounds had been dissolved in EtOH and diluted with buffer. The final EtOH concentration of control and inhibitor incubation was 2%. Each tube was preincubated for 5 min at 30 °C in a shaking water bath. Microsomal protein (0.5 mg) was added to start the reaction. The total volume of each incubation was 0.5 mL. The reaction was terminated by withdrawing 100-μL aliquots at 0, 7, 14, and 21 min and pipetting them into 200 μL of a cold 1 mM $HgCl_2$ solution. After addition of 200 μL of an aqueous dextran-coated charcoal (DCC) suspension (2%), the vials were shaken for 20 min and centrifuged at 1500*g* for 5 min to separate the charcoal-adsorbed steroids. Aliquots of the supernatant were assayed for ^3H_2O by counting in a scintillation mixture in a Beckman liquid scintillation spectrometer (LS 8000).

5. Selective Inhibition of P450 TxA_2. Inhibition toward cyclooxygenase and lipoxygenase was examined by determination of the PGE_2, 12-HHT, and 12-HETE concentrations according to described procedures.[34]

6. In Vivo Test: Effect on TxB_2 Plasma Concentration. The test was performed similar to a described procedure.[32] Male Sprague−Dawley rats (about 250 g) were classified in groups of 6−8 animals and starved for 16 h. The test compounds were administered by gavage (vehicle: 0.01 M HCl, 1.5 mL/300 g body weight). Control rats were given the vehicle. Two, 3, 5, and 8 h after administration, blood (1.5 mL) was withdrawn from the heart under ether anesthesia and immediately cooled on ice. The blood was allowed to clot for exactly 60 min at 37 °C in an agitated water bath. The serum was separated by centrifugation at 2500*g* (15 min, 4 °C) and stored at −26 °C until tested. Serum TxB_2 levels were determined by radioimmunoassay using the protocol described in the kit (DRG Instruments, Marburg, FRG). The serum samples were diluted (1:100) using the buffer of the kit. Apart from the incubation, all steps were performed at 4 °C.

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