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Design, synthesis, and biological activity of non-basic compounds as factor Xa inhibitors: SAR study of S1 and aryl binding sites

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Abstract—Compound **7** was identified as the active metabolite of **6** by HPLC and mass spectral analysis. Modification of lead compound **7** by transformation of its *N*-oxide 6–6 biaryl ring system and fused aromatics produced a series of non-basic fXa inhibitors with excellent potency in anti-fXa and anticoagulant assays. The optimized compounds **73b** and **75b** showed sub to one digit micromolar anticoagulant activity (PTCT2). Particularly, anti-fXa activity was detected in plasma of rats orally administered with 1 mg/kg of compound **75b**.

1. Introduction

Thromboembolic events occur suddenly and are sometimes fatal. Even if a patient can survive a thromboembolic event, their convalescence tends to take a long time.

Therefore, prophylaxis of thromboembolism is an important consideration. Warfarin has been commonly prescribed for the prevention of thromboembolic disorders because it is the only anticoagulant that can be administered orally. Warfarin, a vitamin K antagonist, has some difficulties, however, such as food and drug interactions, the necessity of regular monitoring and so on.[1] Several groups have been searching for orally active anticoagulants without any drawbacks. Recently, AstraZeneca received its first regulatory approval for Exanta™ (ximelagatran), a direct thrombin inhibitors, in France for the prevention of venous thromboembolic events following major orthopedic (hip or knee replacement) surgery.[2] Although thrombin is one of the adequate targets for anticoagulation, there are a few reports in which direct factor Xa (fXa) inhibitors decrease the likelihood of bleeding tendency compared with direct thrombin inhibitors.[3]

We had previously reported the discovery of a selective and orally active fXa inhibitor, **DX-9065a**;[4] however, its oral bioavailability was not sufficient.

In this letter, we report on the course of study for new S1 site and aryl binding site fitting moieties, which have weakly- or non-basic structures, because the oral availability of **DX-9065a** is considered to be ruined by its three highly polarized parts, an amidine, an acetimidoyl, and a carboxylic group.

2. Design

The amidinonaphthalene and the acetimidoylpyrrolidine moieties of **DX-9065a** are important for anti-fXa activity, but no interaction was observed between the carboxylic acid moiety and the enzyme. Decarboxylated **DX-9065a** with its acetimidoylpyrrolidine transformed to pyrrolidine, compound **1**, still retained anti-fXa activity, but did not show an improved intestinal absorption ratio.

An exchange of the amidinonaphthalene moiety of **1** for a pyridylphenyl group gave compound **2**. Although compound **2** exhibited weak anti-fXa activity with an

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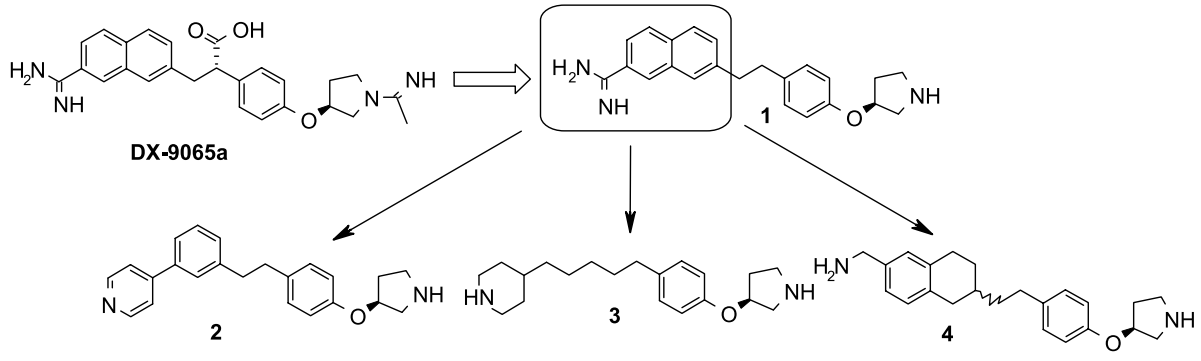


Figure 1. **DX-9065a** and its derivatives.

IC_{50} value of 250 μM, it showed a 71% intestinal absorption ratio. In contrast, replacement of the amidinonaphthalene moiety with a piperidinylalkyl moiety (compound **3**, secondary amine) or an aminomethylnaphthalene (compound **4**, primary amine) did not improve the intestinal absorption ratio and almost diminished the anti-fXa activity (Fig. 1 and Table 1).

A reported potent fXa inhibitor **5**[5] has a pyridylpiperidinyl moiety, which possesses bulkiness similar to that of the pyridylpheny moiety. Our previous X-ray crystallographic study revealed that the 6-chloronaphthalene structure is an appropriate moiety to bind the S1 site of fXa. It was presumed that the pyridylphenyl structure of **2** plays a role as an aryl binding site interacting moiety. Those facts encouraged us to hybridize **2** and **5** to afford a weakly basic compound **6**[6] whose anti-fXa IC_{50} value was 0.12 μM.

Although the in vitro fXa IC_{50} value of **6** was four times weaker than that of **5**, compound **6** showed higher human anti-fXa activity in rat plasma compared with **5**, after a 30 mg/kg oral administration in rats. The anti-fXa activity of **6** reached maximum inhibition of fXa amidolytic activity, 63%, at 4 h and 10% inhibition could still be detected at 24 h after oral administration (Fig. 2). On the other hand, a high performance liquid chromatography (HPLC) study revealed that the maximum plasma concentration (C_{max}) 2.29 μg/mL of **6** was observed at 2 h, and **6** could not be detected at 24 h after oral administration. Furthermore, one new major peak in the serum sample (4 h after oral administration) was detected. Those observations strongly suggested the existence of an active metabolite. In mass spectral analysis, the molecular weight of the presumed metabolite was 507, which was equal to *M* (molecular weight of parent compound **6**) + 16. Since the increase in molecular weight by 16 was considered to be the result of oxidative metabolism, three different types of oxidized compounds of **7**,[6] **8**, and **9**, were synthesized (Fig. 3).

Table 1. Intestinal absorption ratio of DX-9065a and its derivatives

Compound	fXa (IC_{50}: μM)	fIIa (IC_{50}: μM)	Absorption ratio (%)
DX-9065a	0.085	2000	15.1 ± 0.7
1	0.54	140	16.3 ± 2.6
2	250	>1200	71.1 ± 1.1
3	350	>1200	28.1 ± 6.7
4	640	>1200	19.9 ± 2.7

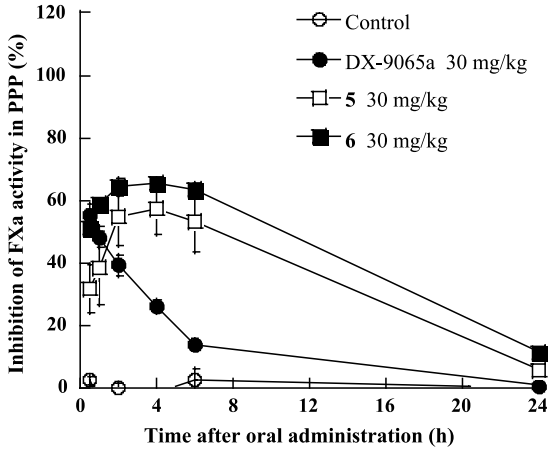


Figure 2. Ex vivo anti-fXa activity on the oral administration of **DX-9065a**, **5**, and **6**.

Among them, compound **7** was identified as the active metabolite of **6** by HPLC and mass spectral analysis. Compound **7** also showed high anti-fXa activity of IC_{50} value 17 nM. This fact proved the possibility of a good fitness of the 6–6 biaryl ring system, such as a pyridylphenyl moiety and its oxidative derivative, to the aryl binding site of fXa.

Previously, we reported that a 7-amidinonaphthalene moiety could replace the 5–6 fused aromatics, such as 6-amidinoindole or 5-amidinobenzo[*b*]thiophene.[7]

A series of optimizations of compound **6** was carried out on the basis of the above and our previous finding, namely that a pyridylphenyl moiety was converted to several 6–6 heteroaromatics and its oxide, and 6-chloronaphthalene was transformed to 5–6 fused chloro-aromatics (Fig. 4).

3. Chemistry

Preparation of **1**–**4** is shown in Scheme 1. The Wittig reaction of phosphonium salt **10**[4] with aldehyde **11**,[4] followed by catalytic hydrogenation gave the nitrile deriv-

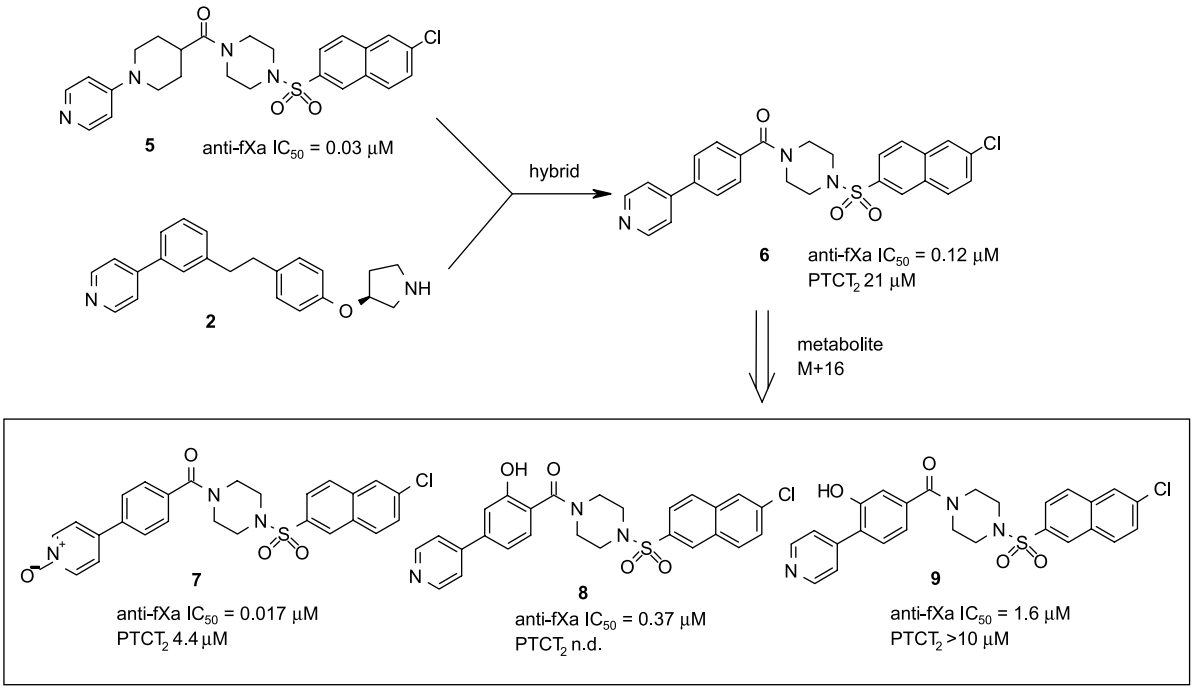


Figure 3. Hybrid compound **6** and presumed structures of its metabolites.

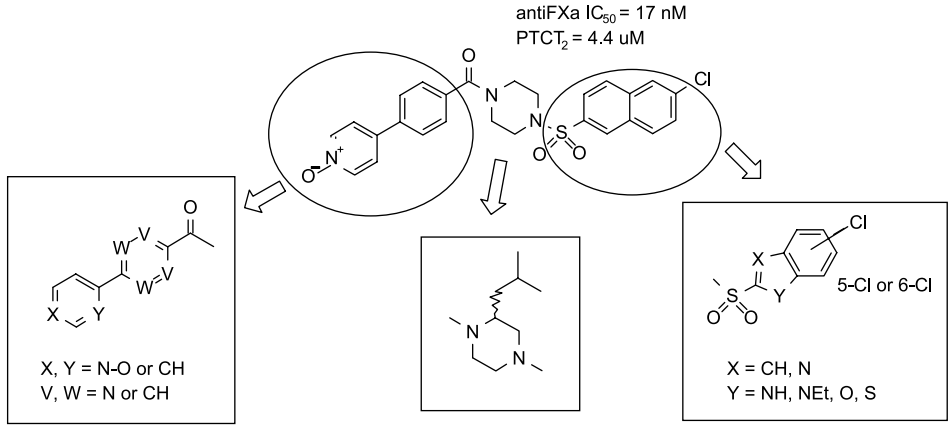
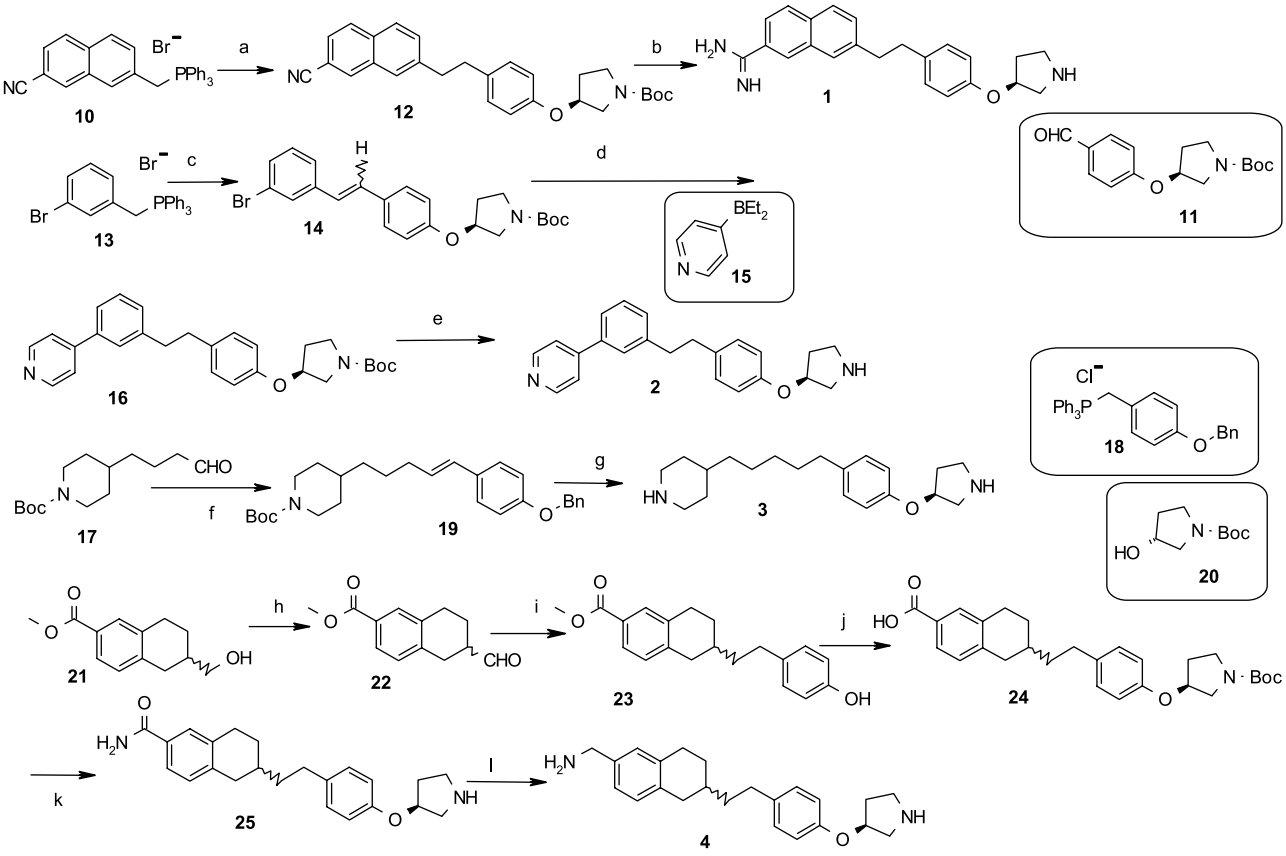


Figure 4. Replacement of the chloronaphthalene part, biaryl part, and linker part of compound **7**.

ative **12**. The Pinner reaction of **12** gave the amidino derivative **1**. The Wittig reaction of phosphonium salt **13**[8] with aldehyde **11** afforded olefin **14**. The Suzuki–Miyaura coupling of olefin **14** and borane **15**,[9] followed by hydrogenation and deprotection, gave the 4-pyridyphenyl derivative **2**. The Wittig reaction of aldehyde **17**[10] and phosphonium salt **18**[11] gave olefin **19**. Hydrogenation and debenzylation of olefin **19**, followed by the Mitsunobu reaction and deprotection, gave the piperidine derivative **3**. Aldehyde **22** was prepared from the reported alcohol **21**[12] by the Swern oxidation. The Wittig reaction of phosphonium salt **18** and aldehyde **22**, followed successively by hydrogenation and debenzylation, afforded phenol **23**. The Mitsunobu reaction of phenol **23** with alcohol **20**,[4] followed by hydrolysis gave carboxylic acid **24**. After amidation of carboxylic acid **24**, followed by deprotection of the Boc group gave amide **25**. Reduction of amide **25** with $LiAlH_4$ gave the aminomethyltetraline derivative **4**.

General procedures A, B, or C (Scheme 2) were employed for the preparation of 4-(4-pyridyl)benzoylpiperazine derivatives **6**, **8**, and **36**–**41**. In procedure A, bicyclic sulfonyl groups were first introduced onto the commercially available Boc-piperazine **26**; whereas biaryl carbonyl groups were first introduced onto the piperazine **26** in procedure B. In procedure C, the prepared arylsulfonypiperazines were further derived to piperazine derivatives.

Carboxylic acids **28** and **29** were prepared as illustrated in Scheme 3. After the Suzuki–Miyahara coupling of



Scheme 1. Reagents and conditions: (a) (i) **11**, DBU, THF, (ii) 10% Pd–C, H_2, MeOH, 85% (two steps); (b) (i) satd HCl–EtOH, (ii) satd NH_3–EtOH, 15% (two steps); (c) **11**, DBU, THF, 83%; (d) (i) 4-(diethylboryl)pyridine (**15**), $Pd(PPh_3)_4$, KOH, TBAB, THF, 39%, (ii) H_2, 10% Pd–C, 82%, (e) TFA, CH_2Cl_2, 85%; (f) **18**, NaH, THF, EtOH, 76%; (g) (i) H_2, 10% Pd–C, 65%, (ii) **20**, DEAD, PPh_3, THF, 53%, (iii) TFA, CH_2Cl_2, 70%; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 37%; (i) (i) **18**, NaH, THF, EtOH, and then NaH, MeOH, 56%, (ii) H_2, 10% Pd–C, 80%; (j) (i) **20**, DEAD, PPh_3, THF, 42%, (ii) NaOH aq, EtOH, THF, 73%; (k) (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, (ii) NH_3 aq, 90% (two steps), (iii) 10% TFA–CH_2Cl_2, 73%; (l) LAH, THF, 62%.

bromobenzene **42**[13] or **43**[14] with borane **15** gave the corresponding carboxylic acid **28** or ester **44**. Ester **44** was hydrolyzed to give carboxylic acid **29**.

Syntheses of arylsulfonyl chlorides **30**–**33** are shown in Scheme 4.

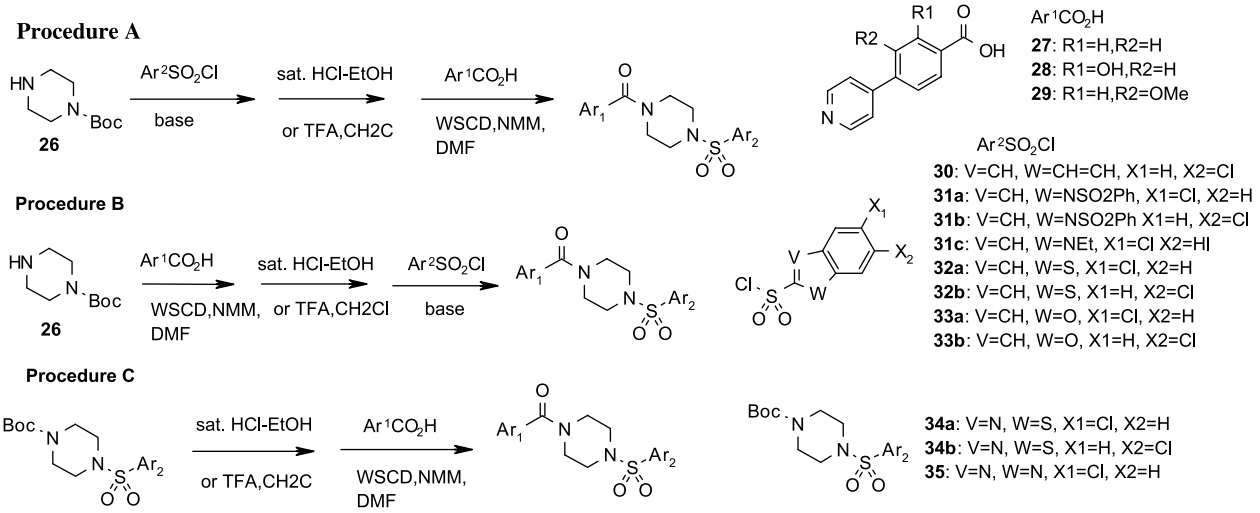
(6-Chloronaphthalen-2-yl)sulfonyl chloride **30** was synthesized via successive β-sulfonylation and chlorination of commercially available 2-chloronaphthalene **45**. *N*-Sulfonylation or *N*-ethylation of commercially available chloroindoles **46a**,**b** afforded indole derivatives **47a**–**c**. Introduction of an SO_2 function onto the 2-position of indole derivatives **47a**–**c**, followed by oxidative chlorination gave indolylsulfonyl chlorides **31a**–**c**. In a similar manner as described above, a chlorosulfonyl moiety was introduced onto the 2-position of chlorobenzo[*b*]thiophenes **48a**,**b**[15,16] and chlorobenzofurans **49a**,**b**[17] to give sulfonyl chlorides **32a**,**b**, **33a**,**b**.

tert-Butyl 4-arylsulfonyl-1-piperazinecarboxylate derivatives **34a**,**b** and **35** were prepared as illustrated in Scheme 5. Coupling reaction of **50a**,**b**[18] and *tert*-butyl 1-piperazinecarboxylate **26**, followed by oxidation with *m*-CPBA, afforded sulfonylpiperazine derivatives **34a**,**b**. 1-Benzimidazolylsulfonylpiperazine derivative **35** was synthesized from **52**[19] via intermediate **53**.

Preparation of phenol **9** and indoles **54a**,**b** is shown in Scheme 6. Demethylation of compound **36** with boron tribromide gave the hydroxy derivative **9**. Removal of the phenylsulfonyl group of **37a**,**b** under alkaline conditions gave **54a**[6] and **54b**, respectively.

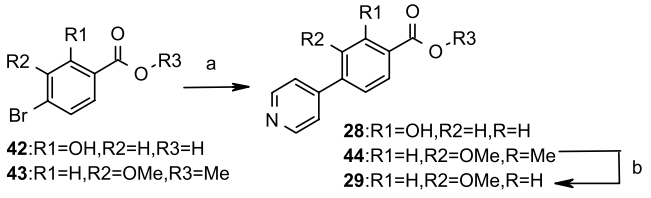
Preparation of *N*-oxide derivatives **7** and **55**–**59** was attained by *m*-CPBA oxidation of the corresponding pyridine precursors (**6**, **37**–**41**, and **54** in Scheme 7).

Preparation of **68a**,**b**, **69a**,**b**, **73a**,**b**, **74a**,**b**, **75a**,**b**, and **80** is shown in Scheme 8. A condensation reaction of the amidino derivative **61**, prepared from commercially available **60**, and dialdehyde **62**[20] gave phenylpyrimidine **63**. Hydrolysis of compound **63** afforded the carboxylic derivative **64**. Preparation of **66** or **67** was obtained by sulfonylation of **26** with sulfonyl chloride **31a** or **32a**, followed by deprotection. Condensation of the piperazine **66** and carboxylic acid **64** or **65**[21] gave pyridine **68a**[6] or **68b**. Oxidation with *m*-CPBA of **68a**,**b** gave *N*-oxide **69a**,**b**. Condensation of piperazine **66** and 5-bromo-2-pyrimidinecarboxylic acid[22] afforded bromopyr-



Compound No.	Ar¹	Ar²	Procedure	Ar^1CO_2H	Ar^2SO_2Cl
6	R1=H,R2=H	V=CH, W=CH=CH, X1=H, X2=Cl	A	**27**	**30**
8	R1=OH,R2=H	V=CH, W=CH=CH, X1=H, X2=Cl	B	**28**	**30**
36	R1=H,R2=OMe	V=CH, W=CH=CH, X1=H, X2=Cl	B	**29**	**30**
37a	R1=H,R2=H	V=CH, W=NSO2Ph, X1=Cl, X2=H	B	**27**	**31a**
37b	R1=H,R2=H	V=CH, W=NSO2Ph X1=H, X2=Cl	A	**27**	**31b**
37c	R1=H,R2=H	V=CH, W=NEt, X1=Cl X2=H	B	**27**	**31c**
38a	R1=H,R2=H	V=CH, W=S, X1=Cl, X2=H	B	**27**	**32a**
38b	R1=H,R2=H	V=CH, W=S, X1=H, X2=Cl	B	**27**	**32b**
39a	R1=H,R2=H	V=CH, W=O, X1=Cl, X2=H	A	**27**	**33a**
39b	R1=H,R2=H	V=CH, W=O, X1=H, X2=Cl	A	**27**	**33b**
40a	R1=H,R2=H	V=N, W=S, X1=Cl, X2=H	C	**27**	-
40b	R1=H,R2=H	V=N, W=S, X1=H, X2=Cl	C	**27**	-
41	R1=H,R2=H	V=N, W=N, X1=Cl, X2=H	C	**27**	-

Scheme 2.



Scheme 3. Preparation of carboxylic acids **28** and **29**. Reagents and conditions: (a) diethyl(4-pyridyl)borane, $Pd(PPh_3)_4$, TBAB, KOH, THF/H_2O, 21% (**28**); (b) 1 N HCl, reflux, 38% (from **43**).

imidine **70**. Suzuki–Miyaura coupling of **70** and 4-pyridylboronic acid gave the pyridylpyrimidinyl derivative **72a**. *N*-Oxide **73a** was obtained from **72a** by *m*-CPBA oxidation.

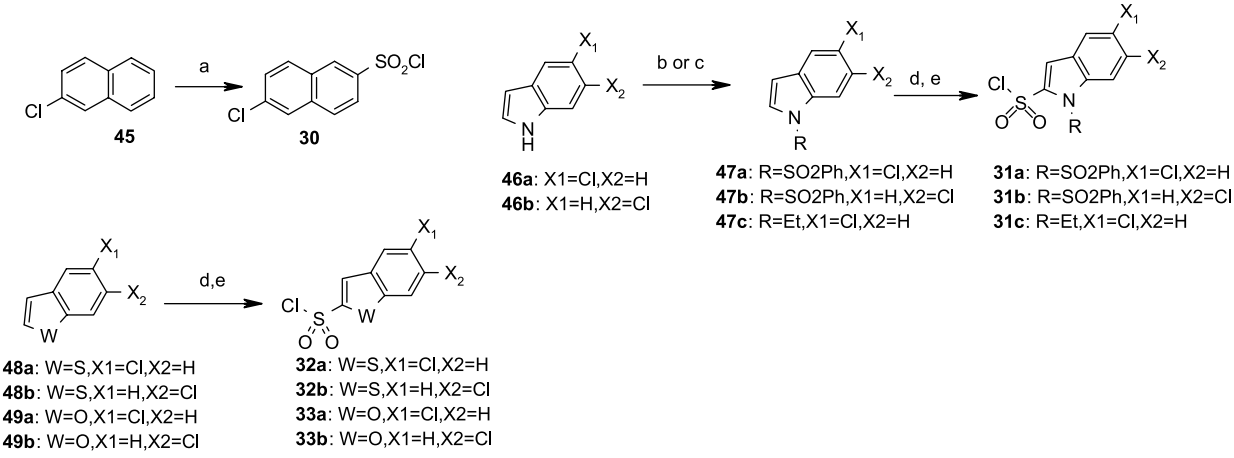
Compounds **72b**, **74a**,**b**, **73b**, and **75a**,**b** were prepared using the same procedure described for the preparation of **72a** and **73a**.

Successive reduction, Wittig reaction, catalytic debenzylation of **76**,[23] followed by sulfonylation, afforded **79**. After removal of the phenylsulfonyl group of **79**, the dephenylsulfonylated compound obtained was condensed with 5-bromo-2-pyrimidinecaroxylic acid, followed by the Suzuki–Miyaura coupling to give **80**.

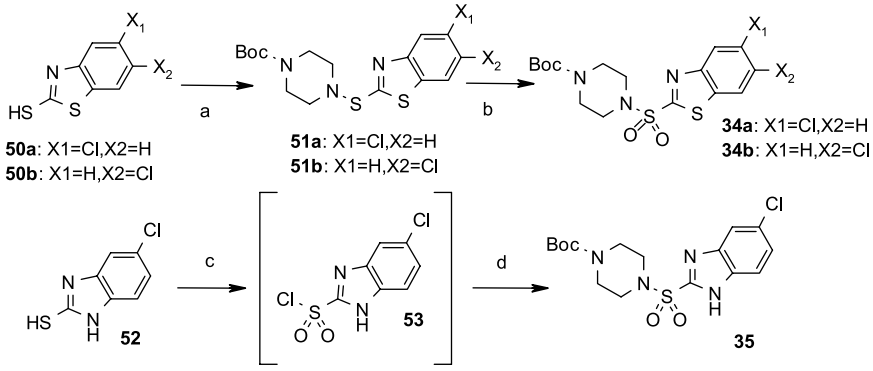
4. Result and discussion

Anti-fXa activities, anti-fIIa activities, and the plasma recalcification times (PRCT) of the synthesized compounds are shown in Tables 2 and 3.

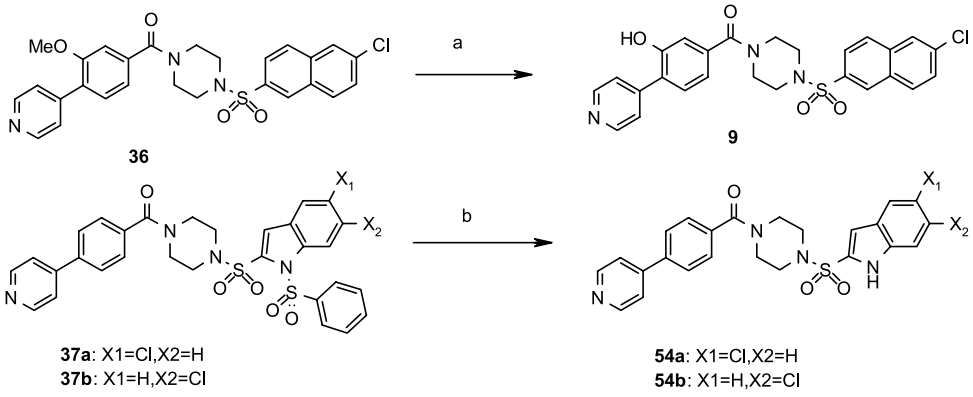
Anti-fXa activities of 5-chloroindole derivative **55a**[6] or 6-chlorobenzo[*b*]thiophene derivative **56b** were equal to or higher than that of 6-naphthalene derivative **7**. This result confirms the ability of non-basic 5–6 bicyclic aromatics to serve as moieties for the S1 binding site of fXa as well as amidino 5–6 bicyclic aromatics. In contrast, lower anti-fXa activities were observed for 5- and 6-chlorobenzothiazole derivatives (**58a** and **58b**), 6-chlorobenzofuran **57b**, and 5-chlorobenzimidazole **59** compared with those activities for **55a** and **56b**. Unexpectedly, compound **55c**, which is an *N*-ethylated derivative of **55a**, did not exhibit any anti-fXa activity, and this result did not correlate with the previously reported highly potent *N*-alkylated amidino-indole derivatives.[7] Since previous X-ray crystallographic analysis suggested that the 6-chloronaphthalene bicyclic ring was more deeply accommodated in the S1 site of fXa than was the 7-amidinonaphthalene moiety of **DX-9065a**, alkylation on the nitrogen atom of the indole ring would make a fatal steric hindrance against the binding between inhibitor and enzyme (data not shown).



Scheme 4. Preparation of sulfonyl chlorides **30**, **31**, **32**, **33**. Reagents and conditions: (a) (i) concd H_2SO_4, (ii) $SOCl_2$/DMF, 17%; (b) *n*-BuLi, $PhSO_2Cl$, THF, 93% (**47a**), 55% (**47b**); (c) NaOH, EtBr, *n*-$Bu_4N^+Cl^-$, PhH–H_2O, 93% (**47c**); (d) *t*-BuLi, THF or Et_2O, SO_2 (g); (e) NCS, CH_2Cl_2, 64% (**31a**), 79% (**31b**), 40% (**31c**); 68% (**32a**), 85% (**32b**), 62% (**33a**), 64% (**33b**).



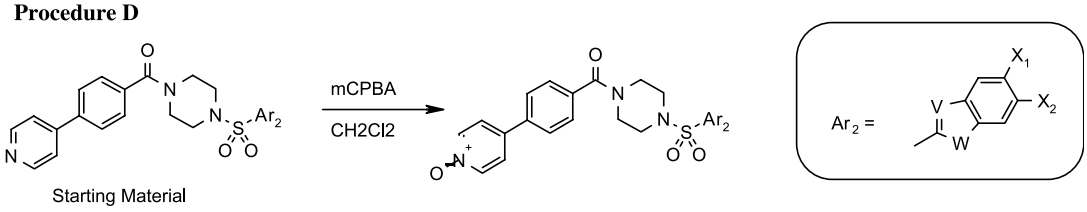
Scheme 5. Preparation of *tert*-butyl 4-arylsulfonyl-1-piperazinecarboxylates **34**, **35**. Reagents and conditions: (a) *tert*-butyl 1-piperazinecarboxylate, I_2, KI, NaOH, H_2O, 48% (**51a**), 33% (**51b**); (b) *m*-CPBA, DME, 25% (**34a**), 29% (**34b**); (c) Cl_2, AcOH; (d) *tert*-butyl 1-piperazinecarboxylate, acetone, H_2O, 79%.



Scheme 6. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 30%; (b) KOH, MeOH, 78% (**54a**), 53% (**54b**).

As was seen in the case of 4-pyridylphenyl derivatives, enhanced in vitro anti-fXa and anticoagulant activities were confirmed about the *N*-oxide of 2-pyridylphenyl derivatives. The *N*-oxide 2-pyridylphenyl moiety **69a** converted from the *N*-oxide 4-pyridylphenyl moiety **55a** retained the latter's anti-fXa activity, and showed slightly improved anticoagulant activity (PTCT2 1.05 μM) compared with that of **55a** (PTCT2 2.55 μM). Replacement of the phenyl ring of the 4-pyridylpheny of **55a** with a 2,5-disubstituted pyrimidine ring, whose symmetrical structure seemed to be favorable to mimic the phenyl ring, was investigated in order

Procedure D



product No.	Starting Material	Ar_2	yeild
7	**6**	V=CH, W=CH=CH, X1=H, X2=Cl	63%
55a	**54a**	V=CH, W=NH, X1=Cl, X2=H	70%
55b	**54b**	V=CH, W=NH X1=H, X2=Cl	86%
55c	**37c**	V=CH, W=NEt, X1=Cl, X2=H	57%
56a	**38a**	V=CH, W=S, X1=Cl, X2=H	66%
56b	**38b**	V=CH, W=S, X1=H, X2=Cl	52%
57a	**39a**	V=CH, W=O, X1=Cl, X2=H	76%
57b	**39b**	V=CH, W=O, X1=H, X2=Cl	99%
58a	**40a**	V=N, W=S, X1=Cl, X2=H	60%
58b	**40b**	V=N, W=S, X1=H, X2=Cl	99%
59	**41**	V=N, W=NH, X1=Cl, X2=H	71%

Scheme 7.

to optimize the inhibitor. *N*-Oxide 5-(4-pyridyl)pyrimidin-2-yl derivative **73a** showed 2-fold increased anticoagulant activity compared with **55a**; however, *N*-oxide 2-(4-pyridyl)pyrimidin-5-yl derivative **69b** was less active than **55a**. As a result of SAR consideration, *N*-oxide 5-(2-pyridyl)pyrimidin-2-yl derivatives possessing 5-chloroindole or 6-cholorobenzo[*b*]thiophen as an S1 binding site were designed and synthesized. Both compounds **73b** and **75b** showed strong anti-fXa and anticoagulant activities; particularly, 5-chloroindole derivative **73b** exhibited the best PTCT2 of 0.52 μM.

Although X-ray crystallographic analysis would have been useful to elucidate the binding mode, neither the co-crystal of **73b** and fXa nor the **73b** soaked fXa crystal was obtained because of its insufficient solubility. An X-ray crystallographic analysis was successfully carried out for a complex of compound **80** and fXa. But we could not decide the location of isobutyl moiety, because of the low electron density level of it. The analysis showed that a pyridyl–pyrimidinyl moiety and a 5-chloroindole moiety interacted with the aryl binding site and the S1 site, respectively (Figs. 5 and 6). The nitrogen of the indole formed a hydrogen bond with the amide carbonyl oxygen of Gly-218 on the main chain (Fig. 7). The hydrogen bond would be one of the reasons for the higher activity of indole derivatives compared with the corresponding naphthalene or benzo[*b*]thiophene derivatives. Almost all *N*-oxide pyridine compounds described herein exhibited higher in vitro activities than their precursor pyridines. Guertin's group has reported the X-ray study of fXa inhibitor **FXV673**.[24a] The result exhibited that pyridine *N*-oxide was located in cation hole of fXa, which was made by some basic amino acids.[24b] It is conceivable that the interaction between *N*-oxide pyridine and the cation hole made a much tighter interaction than that with pyridine.

Ex vivo anti-fXa activity was investigated in plasma after oral administration. Anti-fXa activities in plasma after oral administration of **73a**,**b**, **75a**,**b** in the rat are shown in Figure 8. Compound **73b**, which is the highest anticoagulant activity (PTCT2) in vitro, showed low anti-fXa activity in rat plasma after 1 mg/kg oral administration. In contrast with **73b**, compound **75b** showed excellent anti-fXa activity. Based on these data, it is expected that **75b** is the most desirable as an orally active fXa inhibitor in a series of the *N*-oxide pyridine derivatives.

5. Conclusion

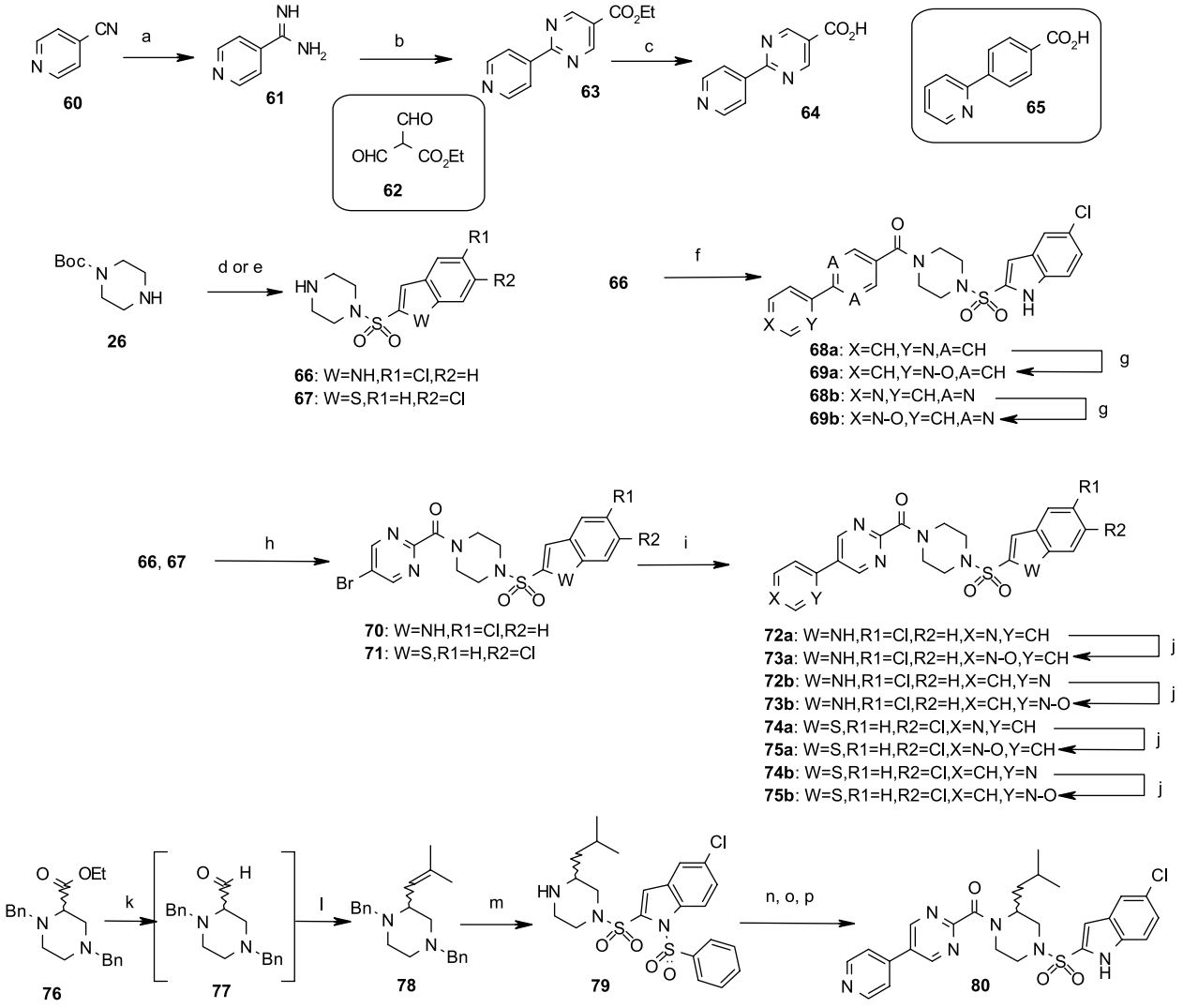
The exchange of the amidinonaphthalene of **DX-9065a** for a less basic moiety led to compound **6**, which has 6-chloronaphthalene and 4-pyridylphenyl to interact with the S1 and aryl binding sites, respectively. Although compound **6** showed potent anti-fXa activity in a rat ex vivo study, a pharmcokinetic study of **6** revealed that *N*-oxide **7** was an active metabolite from **6** in the rat. The optimization study for the *N*-oxide 6–6 biaryl ring system and fused aromatics of **7** resulted in compounds **73b** and **75b**, which showed sub to one digit micromolar anticoagulant activity (PTCT2). Particularly, anti-fXa activity was detected in plasma after a 1 mg/kg oral administration of compound **75b** to the rat.

Discovery of a non-basic fXa inhibitor such as **75b** might offer useful information to improve the pharmacokinetic profile.

6. Experimental

6.1. General

Melting points were determined on a Büchi 520 apparatus in glass capillary tubes and are uncorrected. Column chromatography was performed with Merck silica gel 60 (particle size 0.060–0.200 or 0.040–0.063 mm), Sephadex



Scheme 8. Reagents and conditions: (a) NaOMe, MeOH, reflux then NH_4Cl, reflux, 42%; (b) **62**, NaOEt, EtOH, 15%; (c) 1 N NaOH, reflux then H^+, 93%; (d) (i) **31a**, Et_3N, CH_2Cl_2, (ii) 0.2 N NaOH–MeOH, (iii) HCl–EtOH; (e) (i) **32b**, Et_3N, CH_2Cl_2, (ii) HCl–EtOH, 54% (**66**), 87% (**67**); (f) **64** or **65**, WSCD, HOBt, NMM, DMF, 71% (**68a**), 30% (**68b**); (g) *m*-CPBA, CH_2Cl_2, 52% (**69a**), 22% (**69b**); (h) 5-bromo-2-pyrimidinecarboxylic acid, WSCD, HOBt, NMM, CH_2Cl_2, 90% (**70**), 89% (**71**); (i) 4-pyridylboronic acid or 2-pyridylboronic acid, $Pd(PPh_3)_4$, CsF, DME/MeOH, reflux, 40% (**72a**), 51% (**72b**), 49% (**74a**), 82% (**74b**); (j) *m*-CPBA, CH_2Cl_2, 50% (**73a**), 20% (**73b**), 56% (**75a**), 21% (**75b**); (k) DIBAH, CH_2Cl_2, −78 °C; (l) isopropyltriphenylphosphonium iodide, *n*-BuLi, THF, −78 °C, rt, 32%; (m) (i) H_2, $Pd(OH)_2$, HCl, EtOH, 85%, (ii) **31a**, Et_3N, CH_2Cl_2, 78%; (n) 1 N NaOHaq, 1,4-dioxane/H_2O, 80 °C; (o) 5-bromo-2-pyrimidinecarboxylic acid, WSCD, HOBt, NMM, CH_2Cl_2; (p) 4-pyridylboronic acid, $Pd(PPh_3)_4$, CsF, DME/MeOH, reflux, 50%.

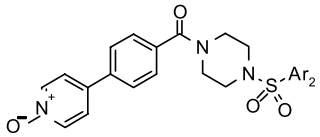
LH-20 (Amersham Biosciences Corp.), or Daiaion HP-20 (highly porous polymer type synthetic adsorbent; Mitsubishi Chemical Industries). Preparative HPLC was performed by using a reverse-phase ODS column (Sensyu Pak ODS-H-5301 20 × 300 mm), a mobile phase of acetonitrile/water (5/95–10/90), and a flow rate of 10 mL/min. Thin-layer chromatography (TLC) was performed on Merck pre-coated TLC aluminum sheets with silica gel 60 F_{254}, and detected by UV quenching at 254 nm or by spraying with phosphomolybdic acid or ninhydrin. All analytical samples were found to be homogeneous by TLC.

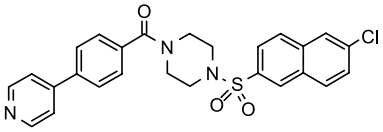
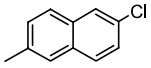
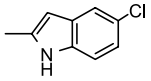
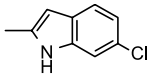
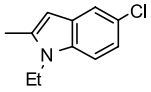
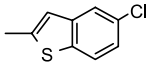
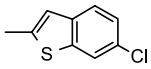
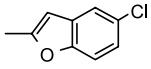
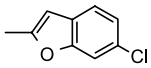
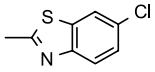
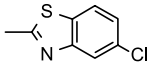
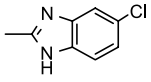
^1H NMR spectra were recorded on a JEOL FX90Q or a JEOL JNM-EX400 spectrometer and chemical shifts are given in ppm (δ) from tetramethylsilane as the internal standard. Mass spectra were performed with a JEOL JMS-AX505W (EI, CI) or a JEOL JMS-HX110 (FD, FAB) spectrometer. IR spectra were recorded on a HITACHI 270-30 spectrometer.

6.2. Preparation of the crystals

Purified human Gla-less fXa was purchased from Hematologic Technologies Inc. Without further purification, purchased protein sample was dialyzed against 5 mM Maleate Imidazole, pH 5.0/4 mM $CaCl_2$/10 mM benzamidine, and concentrated to 7.5 mg/mL using microcon-10 (Millipore Co., MA). Concentrated Gla-less fXa was mixed with an equal volume of reservoir solution (15% PEG6000/1 mM $CaCl_2$/0.3 M AcONa/0.1 M Maleate imidazole, pH 5.0) and vapor-equilibrated

Table 2. Transformation of chloronaphthalene part



Compound	Ar^2 =	fXa (IC_{50}: nM)	fIIa (IC_{50}: μM)	[a]PTCT2 in human plasma (μM)	PTCT2 in rat plasma (μM)
6		123	1.5	>5	>5
7		17	0.14	5.3	7.8
55a		4.7	0.15	2.55	2.3
55b		100	0.93	9.2	>10
55c		>10,000	NT	NT	NT
56a		8.6	0.32	3.4	3.9
56b		68	1.5	9.9	>10
57a		700	37.5	NT	NT
57b		40	1.4	6.0	10.2
58a		1900	NT	NT	NT
58b		210	12.5	>10	>10
59		280	>10	24.4	30

[a] Clotting time doubling concentration for prothrombin time.

against the same solution at 20 °C. After several days, 2 mM of compound **80** was added to the drop and then benzamidine/Gla-less fXa crystal[25] was seeded to the drop using streak seeding method.[26] Obtained microcrystal was then grown to enough size for X-ray experiment using macro-seeding method.[26]

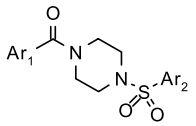
6.3. X-ray data collection and processing

Co-crystal was sealed in grass capillary together with mother liquor. All X-ray data set was collected at room temperature on an R-Axis IIc imaging plate detector (RIGAKU, Japan) using an RU200 rotating anode generator (RIGAKU, Japan). Data processing was carried out using *d*trek*.[27]

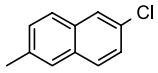
6.4. Structure solution and crystallographic refinement

Previously reported Gla-less fXa structure (PDB code 1HCG[28]) was used as initial structure. Phase refinement and model rebuilding was carried out using *refmac5*[29] and *Turbo Frodo*.[30] Low resolution data

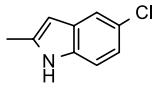
Table 3. Transformation of biaryl part



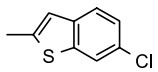
Ar2=Nap=

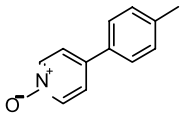
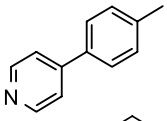
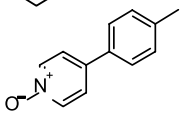
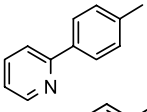
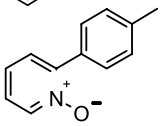
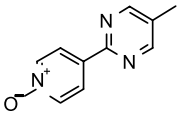
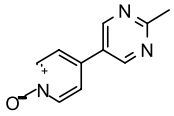
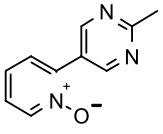
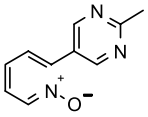
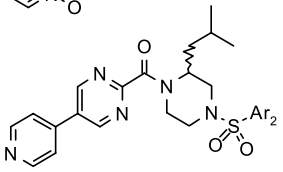


Ar2=Ind=



Ar2=BT=



Compound	Ar^1 =	Ar^2 =	fXa (IC_{50}: nM)	fIIa (IC_{50}: μM)	PTCT2 in human plasma (μM)	PTCT2 in rat plasma (μM)
7		Nap	17	0.14	5.3	7.8
54a		Ind	7	0.66	>10	>10
55a		Ind	4.7	0.15	2.55	2.3
68a		Ind	16	2.0	>5	>5
69a		Ind	6.9	1.55	1.05	2.5
69b		Ind	14	0.58	4.1	4.8
73a		Ind	4.6	10.2	1.7	3.8
73b		Ind	4.7	28	0.52	2.8
75a		BT	12	7.7	1.8	4.7
75b		BT	6.3	25	1.3	8.9
80		Ind	18	19	>10	>10

(<25 $Å^2$) were included and Babinet bulk solvent scaling[31] was applied. Stereochemistry checks indicate that the refined protein model is good agreement with expectations within each resolution range. The statistics of the crystallographic refinement are shown in Table 4. Atomic coordinates have been deposited with the Protein Data Bank (PDB code: 1WU1).

6.5. Anti-fXa activity in vitro

Anti-fXa activity in vitro was measured by using a chromogenic substrate S-2222 (Chromogenix, Inc.) and human fXa (Cosmo Bio-ERL). Aqueous DMSO (5% v/v; 10 μL) or inhibitors in aqueous DMSO (10 μL) and 0.05 U/mL human fXa (10 μL) were mixed with 0.1 M

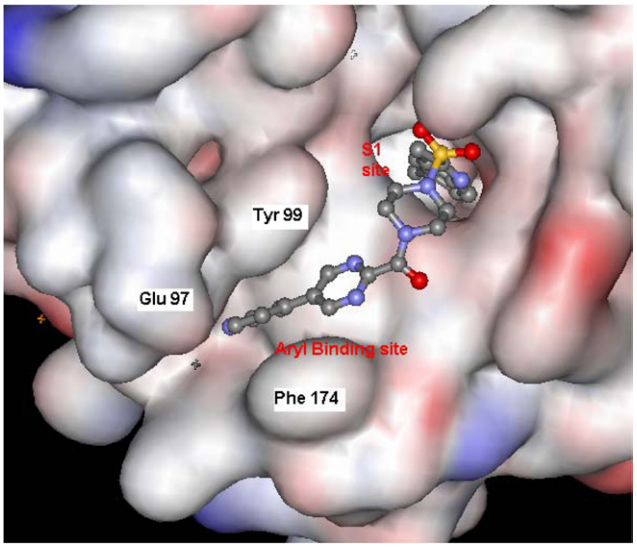


Figure 5. The binding mode of compound **80** as viewed from the top. The surface view is the active site of Gla-less fXa. The stick drawning (gray; carbon, blue; nitrogen, red; oxygen, yellow; sulfur) indicates **80** with protons omitted.

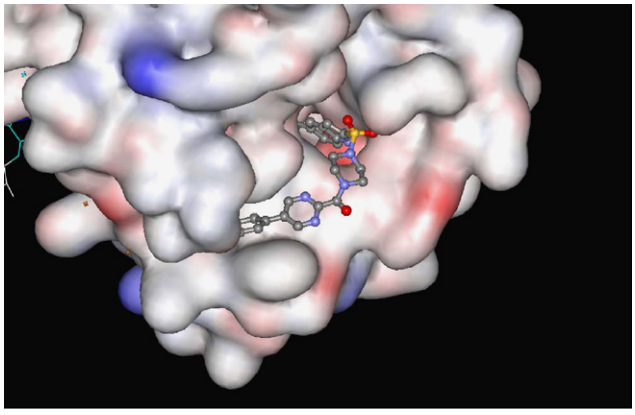


Figure 6. The binding mode of compound **80** (2).

Tris–0.2 M NaCl–0.2% BSA buffer (pH 7.4; 40 μL). The reaction was started by the addition of 0.75 M S-2222 (40 μL). After the mixture was stirred for 10 s at room temperature, the increases of optical density (OD/min) were measured at 405 nm. Anti-fXa activity (inhibition %) was calculated as follows: anti-fXa activity = 1 – [(OD/min) of sample/(OD/min) of control]. The IC_{50} value was obtained by plotting the inhibitor concentration against the anti-fXa activity.

6.6. Anti-fIIa activity in vitro

Anti-thrombin activity in vitro was measured by using chromogenic substrate S-2266 (Chromogenix, Inc.) and human thrombin (Sigma Chemical, Inc.). Aqueous DMSO (5% v/v; 10 μL) or inhibitors in aqueous DMSO (10 μL) and 4 U/mL human thrombin (10 μL) were mixed with 0.1 M Tris–0.2 M NaCl–0.2% BSA buffer (pH 7.4; 40 μL). The reaction was started by the addition of 0.50 M S-2266 (40 μL). After the mixture was stirred for 10 s at room temperature, the increases of optical density (OD/min) were measured at 405 nm.

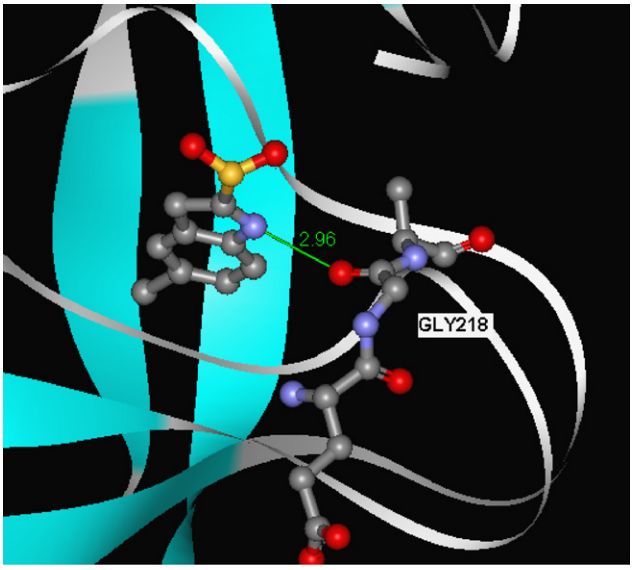


Figure 7. The binding interactions between the 5-chloroindole moiety of compound **80** and Gly 218 of fXa as viewed from the top. The hydrogen bond is depicted as a green line.

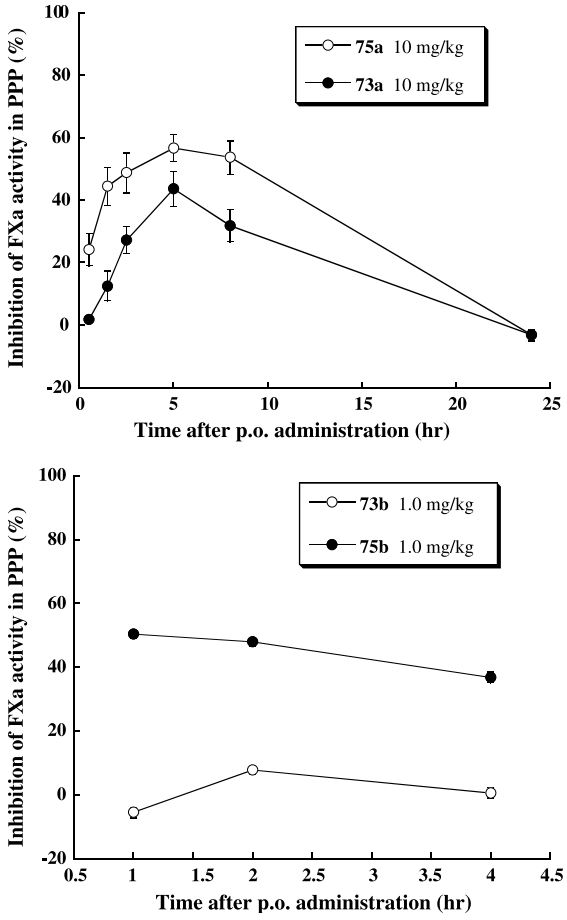


Figure 8. Ex vivo anti-fXa activity following the oral administration of **73a**,**b** and **75a**,**b**. PPP means platelet poor plasma.

Table 4. Crystal and diffraction data of human fXa with compound **80**

Crystal parameters	
Space group	$P2_12_12_1$
a (Å)	56.6
b (Å)	72.5
c (Å)	79.0
Resolution (Å)	2.3
R_{sym}[a] (%)	6.4 (33.8)
Completeness[a] (%)	90.6 (84.3)
No. of reflections, redundancy	13,656
Refinement	
No. of protein atoms (occupancy ≠ 0)	2156
Average *B* value for protein and ligand atoms (Å^2)	46.7, 57.5
Range of data	25.0–2.3
R value	19.1
Weighted rsmd from ideality	
Bond length (Å)	0.022
Bond angle (Å)	2.12

[a] Figures in parentheses represent statistics in the last shell of data (highest resolution).

Anti-thrombin activity (inhibition %) was calculated as follows: anti-thrombin activity = 1 − [(OD/min) of sample/(OD/min) of control]. The IC_{50} value was obtained from the inhibition %. on the statistical probability paper.

6.7. Anti-coagulant activity in vitro

Anti-coagulant activity in vitro was evaluated with the plasma clotting time doubling concentration for prothrombin time (PTCT2). Plasma (20 μL) was mixed with inhibitors in saline (20 μL) in the process tube. Coagulation was started by the addition of SIMPLASTIN (Organon Teknica, Inc.) (40 μL).

6.8. Anti-fXa activity and anti-coagulant activity ex vivo

Male wister rats were fasted overnight. Synthetic compounds were dissolved in 0.5% (w/v) methylcellose solution and administered orally to rats via a stomach tube. For control rats, 0.5% (w/v) methylcellose solution was administered orally. Rats were anesthetized with halothane at several time points when blood samples were collected into tubes containing trisodiumcitrate. After blood samples were centrifuged, the platelet poor plasma (PPP) samples were used for measuring their anti-fXa activities or anti-coagulant activities. Anti-fXa activity: Plasma (5 μL) was mixed with 0.1 M Tris–0.2 M NaCl–0.2% BSA buffer (pH 7.4; 40 μL), H_2O (5 μL) and 0.1 U/mL human fXa (10 μL). The reaction was started by the addition of 0.75 M S-2222 (40 μL). After the mixture was stirred for 10 s at room temperature, the increases of optical density (OD/min) were measured at 405 nm. Anti-fXa activity (inhibition %) was calculated as follows; anti-fXa activity = 1 − [(OD/min) of sample/(OD/min) of control]. Anti-coagulant activity: Plasma (20 μL) was mixed with inhibitors in saline (20 μL) in the process tube. Coagulation was started by the addition of SIMPLASTIN (40 μL). Anti-coagulant activity was evaluated by comparing the prolongation rate of prothrombin time versus that of the control.

6.9. *tert*-Butyl (3*S*)-3-{4-[-2-(7-cyano-2-naphthyl)ethyl]-phenoxy}-1-pyrrolidinecarboxylate (12)

To a solution of [(7-cyano-2-naphthyl)methyl]triphenylphosphonium bromide (**10**) (6.36 g, 12.5 mmol) and *tert*-butyl (3*S*)-3-(4-formylphenoxy)-1-pyrrolidinecarboxylate (**11**) (3.00 g, 11.4 mmol) in dry THF (100 mL)–EtOH (100 mL) was added DBU (1.90 g, 12.5 mmol) at room temperature. The mixture was stirred for 19.5 h at room temperature. After removal of the solvent, the residue was purified by silica gel column chromatography with hexane/ethyl acetate (3/1) as an eluent, providing *tert*-butyl (3*S*)-3-{4-[-2-(7-cyano-2-naphthyl)-ethenyl]phenoxy}-1-pyrrolidinecarboxylate as a mixture of *E* and *Z* forms. The mixture of *E* and *Z* and 10% Pd–C (50% wet) (1.47 g) in THF (50 mL)–EtOH (100 mL) was shaken at room temperature under a current of hydrogen (1 atm). After filtration of the catalyst, followed by evaporation of the filtrate, the residue was purified by silica gel column chromatography with hexane/ethyl acetate (3/1) as an eluent, yielding colorless viscous oil (3.53 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.20 (2H, m), 2.90–3.10 (4H, m), 3.40–3.60 (4H, m), 6.77 (2H, d, *J* = 8.8 Hz), 7.08 (2H, d, *J* = 8.8 Hz), 7.40–8.00 (5H, m), 8.13 (1H, s). No further purification was attempted on this compound, which was used directly in the next step.

6.10. 7-{4-[(3*S*)-Pyrrolidinyloxy]phenethyl}-2-naphthalenecarboxamidine dihydrochloride (1)

A solution of **12** (3.53 g, 8.2 mmol) in dry EtOH (100 mL)–CH_2Cl_2 (30 mL) was saturated with HCl gas with ice cooling and left to stand for 21.5 h at room temperature. After distilling off the solvents and HCl, a solution of the resulting residue in EtOH (130 mL) was saturated with NH_3 gas with ice cooling and left to stand for 18 h at room temperature. After evaporation of the solvent, the resulting residue was purified using HP-20 column chromatography (acetonitrile/H2O, 5/95–12/88). After the addition of a small amount of concentrated HCl to selected fractions, the solvents were removed to give the crude compound (2.54 g). After a part (1.00 g) of the crude compound was dissolved in H_2O, a solution was adjusted to pH 5.0 by mixing it with an ion-exchange resin. After filtration of the resin, evaporation of the filtrate gave **1** (0.22 g, 15%) as a pale yellow amorphous solid.

$[\alpha]_D$ +7.9 (*c* 1.510, 24 °C, H_2O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05–2.20 (2H, m), 2.90–3.00 (2H, m), 3.05–3.10 (2H, m), 3.20–3.50 (4H, m), 5.08 (1H, br), 6.88 (2H, d, *J* = 8.8 Hz), 7.19 (2H, d, *J* = 8.8 Hz), 7.63 (1H, dd, *J* = 8.3, 1.6 Hz), 7.78 (1H, dd, *J* = 8.8, 1.6 Hz), 7.85 (1H, s), 7.99 (1H, d, *J* = 8.3 Hz), 8.09 (1H, d, *J* = 8.8 Hz), 8.42 (1H, s), 9.20–9.60 (6H, m). Anal. Calcd for $C_{23}H_{25}N_3O{\cdot}2HCl{\cdot}1.5H_2O$: C, 60.13; H, 6.58; Cl, 15.43; N, 9.15. Found: C, 60.55; H, 6.59; Cl, 15.38; N, 9.24. MS (FAB): *m*/*z* 360 $(M+H)^+$. HRMS (FAB) Calcd for $C_{23}H_{26}N_3O$: 360.2076. Found: 360.2071. IR (ATR): cm^{-1} 3027, 2935, 2738, 1673, 1608, 1506, 1452, 1390, 1371, 1230, 1203, 1178, 1062, 964, 906, 842.

6.11. (*E*,*Z*)-3-Bromo-4′-[[(3*S*)-1-*tert*-butoxycarbonyl-3-pyrrolidinyl]oxy]stilbene (14)

To a solution of 4-[[(3*S*)-1-*tert*-butoxycarbonyl-3-pyrrolidinyl]oxy]benzaldehyde (**11**) (3.47 g, 11.2 mmol) and 3-bromobenzyltriphenylphosphonium bromide (**13**) (6.32 g, 12.3 mmol) in THF (50 mL) and EtOH (50 mL) was added 1,8-diazabicyclo[5.4.0]-7-undecene (1.85 mL, 12.3 mmol) in an ice bath. The reaction mixture was stirred for 18 h at room temperature, concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (chloroform) gave **14** (4.38 g, 83%, *E*/*Z* = 65/35) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (9H, s), 2.00–2.22 (2H, br), 3.43–3.68 (4H, m), 4.85 and 4.90 (total 1H, each broad s), 6.43 (0.65H, d, J = 12.8 Hz), 6.55 (0.65H, d, J = 12.8 Hz), 6.72 (1.3H, d, J = 7.9 Hz), 6.86 (0.70H, d, J = 8.7 Hz), 6.88 (0.35H, d, J = 15.9 Hz), 7.04 (0.35H, d, J = 15.9 Hz), 7.13–7.63 (6H, m). Anal. Calcd for $C_{23}H_{26}BrNO_3 \cdot 0.2CHCl_3$: C, 59.51; H, 5.63; N, 2.99. Found: C, 59.14; H, 5.60; N, 2.80. MS (FAB): *m*/*z* 344 [(M+H−Boc)$^+$, ^{79}Br], 346 [(M+H−Boc)$^+$, ^{81}Br]. IR (KBr) cm^{-1}: 2974, 2890, 1695, 1608, 1587, 1509, 1479, 1413, 1368, 1245, 1167, 1119, 1068, 993, 975, 897, 873, 834. No further purification was attempted on this compound, which was used directly in the next step.

6.12. 4-[3-[2-[4-[[(3*S*)-1-*tert*-Butoxycarbonyl-3-pyrrolidinyl]oxy]phenyl]ethyl]phenyl]pyridine (16)

To a solution of **14** (468 mg, 1.0 mmol) and diethyl(4-pyridyl)borane (**15**) (147 mg, 1.0 mmol) in THF (5 mL) was added tetrabutylammonium bromide (161 mg, 0.50 mmol), potassium hydroxide (336 mg, 6.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol). The mixture was refluxed for 28 h, and then AcOEt and H_2O were added. The separated organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (AcOEt/hexane = 2/1) gave a pyridine derivative (171 mg, *E*–*Z* mixture) as a pale yellow oil.

To a solution of pyridine derivative (171 mg, 0.39 mol, *E*–*Z* mixture) in EtOH (20 mL) was added 10% palladium–carbon (50% wet) (68 mg). The mixture was stirred for 16 h at room temperature under hydrogen atmosphere. After filtration of the catalyst, the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt) gave **16** (140 mg, 32%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (9H, s), 2.00–2.25 (2H, br), 2.91 (2H, d, J = 6.8 Hz), 2.96 (2H, d, J = 6.8 Hz), 3.40–3.70 (4H, m), 4.85 (1H, broad s), 6.79 (2H, d, J = 8.3 Hz), 7.05–7.15 (2H, m), 7.20–7.50 (4H, m), 7.47 (2H, d, J = 6.3 Hz), 8.64 (2H, d, J = 6.3 Hz). No further purification was attempted on this compound, which was used directly in the next step.

6.13. 4-[3-[2-[4-[[(3*S*)-3-Pyrrolidinyl]oxy]phenyl]ethyl]-phenyl]pyridine bis(trifluoroacetate) (2)

To a solution of **16** (138 mg, 0.31 mmol) in CH_2Cl_2 (3.0 mL) was added anisole (0.1 mL) and trifluoroacetic acid (3.0 mL) at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. Precipitation of the residue from MeOH–Et_2O gave **2** (151 mg, 85%) as a colorless needle crystal.

Mp 118–120 °C. $[\alpha]_D$ +7.9 (*c* 0.50, 24 °C, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.03–2.22 (2H, m), 2.85–2.99 (4H, m), 3.20–3.50 (4H, m), 5.08 (1H, br), 6.88 (2H, d, J = 8.3 Hz), 7.20 (2H, d, J = 8.3 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.47 (1H, dd, J = 7.8, 7.8 Hz), 7.71 (1H, d, J = 7.8 Hz), 7.75 (1H, s), 7.97 (2H, d, J = 6.3 Hz), 8.77 (2H, d, J = 6.3 Hz), 9.00 (2H, broad s), 9.10 (1H, broad s). Anal. Calcd for $C_{23}H_{24}N_2O \cdot 2CF_3COOH$: C, 56.65; H, 4.58; F, 1991; N, 4.89. Found: C, 56.47; H, 4.65; F, 19.81; N, 4.77. MS (FAB): *m*/*z* 345 (M+H)$^+$. IR (KBr) cm^{-1} 1670, 1634, 1510, 1418, 1236, 1204, 1126, 986, 970, 834, 800.

6.14. 4-[5-(4-Benzyloxyphenyl)-4-pentenyl]-1-(*tert*-butoxycarbonyl)piperidine (19)

To a solution of sodium hydride (60% in oil, 119 mg) in THF (5.0 mL) was added **18** (1.78 g, 3.58 mmol) and EtOH (1.0 mL) at 0 °C. The reaction mixture was stirred for 10 min and then a solution of **17** (1.77 g, 7.79 mmol) in THF (1.0 mL) was added. After stirring for 10 min, H_2O and AcOEt were added to the reaction mixture. Separated organic layer was dried over $MgSO_4$, concentrated in vacuo. Purification of the residue by silica gel column chromatography ($CHCL_3$) gave **19** (398 mg, 76%, *E*–*Z* mixture) as a colorless amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05–1.20 (2H, m), 1.22–1.55 (14H, m), 1.65–1.75 (2H, m), 2.15–2.25 (1H, m), 2.27–2.35 (1H, m), 2.55–2.75 (2H, m), 4.00–4.18 (2H, m), 5.02–5.08 (2H, m), 5.50–5.60 and 6.00–6.10 (total 1H, each m), 6.28–6.37 (1H, m), 7.20–7.29 (2H, m), 7.30–7.47 (5H, m). No further purification was attempted on this compound, which was used directly in the next step.

6.15. 4-[5-[4-[[(3*S*)-3-Pyrrolidinyl]oxy]phenyl]pentyl]-piperidine bis(trifluoroacetate) (3)

To a solution of **19** (460 mg, 1.1 mol, *E*–*Z* mixture) in THF (50 mL) was added 10% palladium–carbon (50% wet) (46 mg). The mixture was stirred for 72 h at room temperature under hydrogen atmosphere. After filtration of the catalyst, the filtrate was concentrated in vacuo. To a solution of the residue in MeOH (50 mL) was added 10% palladium–carbon (50% wet) (46 mg) and the mixture was stirred, again, for 24 h at room temperature under hydrogen atmosphere. After filtration of the catalyst, followed by concentration of the filtrate in vacuo, purification of the residue by silica gel column chromatography (hexane/AcOEt = 9/1) gave 1-(*tert*-butoxycarbonyl)-4-[5-(4-hydroxyphenyl)-4-pentenyl]piperidine (240 mg, 65%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.15 (2H, m), 1.18–1.40 (7H, m), 1.45 (9H, s), 1.52–1.67 (4H, m), 2.52 (2H, t, J = 7.8 Hz), 2.61–2.73 (2H, m), 4.05 (2H, br), 5.19 (1H, br), 6.75 (2H, d, J = 8.3 Hz), 7.02 (2H, d, J = 8.3 Hz). No further purification was attempted on this compound, which was used directly in the next step.

To a solution of 1-(*tert*-butoxycarbonyl)-4-[5-(4-hydroxyphenyl)-4-pentenyl]piperidine (240 mg, 0.69 mmol) and **20** (194 mg, 0.69 mmol) in THF (5.0 mL) was added PPh_3 (181 mg, 0.69 mmol) and diethyl azodicarboxylate (0.107 mL, 0.69 mmol) at 0 °C. After stirring for 5 days at room temperature, the reaction mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (toluene/AcOEt = 19/1) gave 1-(*tert*-butoxycarbonyl)-4-[5-[4-[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]pentyl]piperidine (190 mg) as a pale yellow oil. To a solution of 1-(*tert*-butoxycarbonyl)-4-[5-[4-[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]pentyl]piperidine (190 mg) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (50 mL) and the mixture was stirred for 1 h at room temperature. After concentration of the reaction mixture, purification of the residue by short silica gel column chromatography (20%MeOH–CH_2Cl_2) gave a crude residue. Trifluoroacetic acid was added to the residue, which was then concentrated in vacuo. Purification of the residue by SEPHADEX LH-20 column chromatography (MeOH) gave **3** (140 mg, 36%) as a colorless oil.

$[\alpha]_D$ +12.3 (*c* 0.46, 25 °C, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ 1.25–1.45 (8H, m), 1.50–1.65 (3H, m), 1.85–1.95 (2H, m), 2.20–2.40 (2H, m), 2.50–2.60 (2H, m), 2.90–3.00 (2H, m), 3.25–3.40 (2H, m), 3.40–3.60 (4H, m), 5.10–5.20 (1H, m), 6.87 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{20}H_{32}N_2O{\cdot}2CF_3COOH{\cdot}H_2O$: C, 51.24; H, 6.45; N, 4.98. Found: C, 51.48; H, 6.36; N, 4.91. MS (FAB): *m*/*z* 317 $(M+H)^+$. IR (KBr) cm^{-1} 2932, 2860, 2520, 1678, 1614, 1510, 1440, 1394, 1298, 1200, 1136, 1068, 970, 834.

6.16. Methyl [(6*R*,*S*)-6-formyl-5,6,7,8-tetrahydro-2-naphthyl]carboxylate (22)

To a solution of oxalyl chloride (2.70 mL, 28 mmol) in CH_2Cl_2 (75 mL) at −78 °C under Argon atmosphere was added a solution of dimethylsulfoxide (5.20 g, 67 mmol) in CH_2Cl_2 (2.0 mL). After the reaction mixture was stirred for 1.5 h at −78 °C, the reaction mixture was added a solution of aldehyde **21** (3.11 g, 14 mmol) in CH_2Cl_2 (3.0 mL)–DMSO (5.0 mL) was added and stirred again for 2 h. To the reaction mixture, Et_3N (18.9 mL, 0.14 mol) was added and stirred for 0.5 h at −78 °C. After warming the reaction mixture up to room temperature, the reaction mixture was added to CH_2Cl_2 and H_2O. Separated organic layer was washed with 10% aqueous citric acid solution and H_2O, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt = 2/1) gave **22** (1.15 g, 37%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75–1.90 (1H, m), 2.20–2.30 (1H, m), 2.60–2.70 (1H, m), 2.85–2.95 (2H, m), 3.03 (2H, d, J = 7.3 Hz), 3.90 (3H, s), 7.15–7.25 (1H, m), 7.75–7.80 (2H, m), 9.80 (1H, s). MS (FAB): *m*/*z* 219 $(M+H)^+$. No further purification was attempted on this compound, which was used directly in the next step.

6.17. Methyl [(6*R*,*S*)-6-[2-(4-hydroxyphenyl)ethyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxylate (23)

Starting with **22** (0.84 g, 3.8 mmol) and **18** (2.20 g, 5.0 mmol) and following the procedure for the preparation of **19** gave the crude product of methyl [(6*R*,*S*)-6-[2-[4-(benzyloxy)phenyl]-ethenyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxylate (0.39 g, *E*–*Z* mixture) as a colorless amorphous powder. Starting with the crude ester and following the procedure for the preparation of 1-(*tert*-butoxycarbonyl)-4-[5-(4-hydroxyphenyl)-4-pentenyl]piperidine gave **23** (0.24 g, 44%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40–1.50 (1H, m), 1.60–1.70 (2H, m), 1.70–1.80 (1H, m), 1.95–2.05 (1H, m), 2.45–2.55 (1H, m), 2.70–3.00 (2H, m), 2.66 (2H, t, J = 7.8 Hz), 3.89 (3H, s), 4.61 (1H, s), 6.76 (2H, d, J = 8.3 Hz), 7.07 (2H, d, J = 8.3 Hz), 7.12 (1H, d, J = 7.8 Hz), 7.70–7.80 (2H, m). MS (FAB): *m*/*z* 311 $(M+H)^+$. IR (KBr) cm^{-1} 3428, 3032, 2916, 2848, 1692, 1612, 1594, 1574, 1516, 1434, 1358, 1336, 1296, 1268, 1250, 1220, 1198, 1144, 1126, 1104, 972, 824. No further purification was attempted on this compound, which was used directly in the next step.

6.18. [(6*R*,*S*)-6-[2-[4[[(3*S*)-1-(*tert*-Butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]ethyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxylic acid (24)

Starting with **23** (203 mg, 0.65 mmol) and **20** (273 mg, 1.5 mmol) and following the procedure for the preparation of 1-(*tert*-butoxycarbonyl)-4-[5-[4-[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]pentyl]piperidine gave the crude product of methyl [(6*R*,*S*)-6-[2-[4[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]ethyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxylate (130 mg) as a pale yellow oil. To a solution of the crude product in EtOH (8.0 mL) was added a solution of sodium hydroxide (370 mg, 9.3 mmol) in H_2O (1.3 mL). The reaction mixture was stirred for 40 h at room temperature and then AcOEt and HClaq were added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (5% MeOH–CH_2Cl_2) gave **24** (100 mg, 33%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40–1.50 (1H, m), 1.46 (9H, s), 1.60–1.70 (2H, m), 1.70–1.80 (1H, m), 2.00–2.10 (2H, m), 2.10–2.20 (1H, m), 2.45–2.55 (1H, m), 2.75–3.00 (2H, m), 2.60–2.70 (2H, m), 3.45–3.65 (4H, m), 4.85 (1H, broad s), 6.79 (2H, d, J = 8.3 Hz), 7.10–7.20 (3H, m), 7.75–7.85 (2H, m). MS (FAB): *m*/*z* 466 $(M+H)^+$. HRMS (FAB) Calcd for $C_{28}H_{36}NO_5$: 466.2593. Found: 466.2587. IR (KBr) cm^{-1} 2980, 2924, 1688, 1612, 1576, 1510, 1480, 1408, 1366, 1338, 1294, 1234, 1168, 1114, 1062, 978, 928, 896, 874, 824.

6.19. [(6*R*,*S*)-6-[2-[4[[(3*S*)-3-Pyrrolidinyl]oxy]phenyl]ethyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxamide (25)

To a solution of **24** (417 mg, 0.89 mmol) in CH_2Cl_2 (2.0 mL) was added oxalyl chloride (0.11 mL, 1.3 mmol) and dimethylformamide (two drops) at 0 °C. After stirring for 45 min, the reaction mixture was added to aqueous NH_3 (28%) (20 mL) and vigorously stirred for 12.5 h. The separated aqueous layer was extracted by CH_2Cl_2 several times. The organic layers were combined, washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (2% MeOH–CH_2Cl_2) gave [(6*R*,*S*)-6-[2-[4[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]ethyl]-5,6,7,8-tetrahydro-2-naphthyl]-carboxamide(377 mg, 91%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40–1.50 (1H, m), 1.46 (9H, s), 1.60–1.70 (2H, m), 1.70–1.80 (1H, m), 2.00–2.10 (2H, m), 2.10–2.20 (1H, m), 2.45–2.55 (1H, m), 2.75–3.00 (2H, m), 2.60–2.70 (2H, m), 3.45–3.65 (4H, m), 4.85 (1H, broad s), 6.79 (2H, d, J = 8.3 Hz), 7.10–7.20 (3H, m), 7.51 (1H, d, J = 7.8 Hz), 7.56 (1H, s). MS (FAB): *m*/*z* 465 $(M+H)^+$. HRMS (FAB) Calcd for $C_{28}H_{37}N_2O_4$: 465.2753. Found: 465.2751. IR (KBr) cm^{-1} 3357, 3160, 2927, 1662, 1625, 1508, 1415, 1394, 1361, 1236, 1164, 1124, 1097, 898, 811.

To a solution of [(6*R*,*S*)-6-[2-[4[[(3*S*)-1-(*tert*-butoxycarbonyl)-3-pyrrolidinyl]oxy]phenyl]-ethyl]-5,6,7,8-tetrahydro-2-naphthyl]carboxamide (324 mg, 0.74 mmol) in CH_2Cl_2 (20.0 mL) was added trifluoroacetic acid (2.0 mL) at 0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was concentrated in vacuo. Purification of the residue by silica gel column chromatography (20% MeOH–CH_2Cl_2) followed by precipitation of the eluent from Et_2O gave **25** (282 mg, 73%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40–1.50 (1H, m), 1.55–1.70 (3H, m), 1.90–2.00 (1H, m), 2.10–2.25 (2H, m), 2.40–2.50 (1H, m), 2.60–2.70 (2H, m), 2.70–3.00 (2H, m), 3.20–3.50 (4H, m), 5.08 (1H, broad s), 6.88 (2H, d, J = 8.8 Hz), 7.11 (1H, d, J = 7.8 Hz), 7.17 (2H, d, J = 8.8 Hz), 7.19 (1H, broad s), 7.58 (1H, d, J = 7.8 Hz), 7.59 (1H, s), 7.83 (1H, broad s), 9.15 (2H, broad s). MS (FAB): *m*/*z* 365 $(M+H)^+$. HRMS (FAB) Calcd for $C_{23}H_{39}N_2O_2$: 365.2229. Found: 365.2238. IR (KBr) cm^{-1} 3672, 3420, 3164, 2932, 2856, 2780, 2468, 1686, 1614, 1570, 1508, 1422, 1384, 1298, 1230, 1198, 1134, 1060, 1028, 970, 832.

6.20. [(6*R*,*S*)-6-[2-[4-[[(3*S*)-3-Pyrrolidinyl]oxy]phenyl]-ethyl]-5,6,7,8-tetrahydro-2-naphthyl]methylamine dihydrochloride (4)

To a suspension of lithium aluminum hydride (150 mg, 4.0 mmol) in THF (10 mL) was added a solution of **25** (94.5 mg, 0.18 mmol) in THF (2.0 mL) at 50 °C. The reaction mixture was refluxed for 2 h, combined with lithium aluminum hydride solution (1.0 M in THF) (2.0 mL), and refluxed for 1.5 h more before being quenched via the dropwise addition of aqueous sodium hydroxide solution (10%) and H_2O. The resulting solution was filtered through a pad of celite to remove the white precipitate. The filtrate was added to concd HCl and concentrated in vacuo. Purification of the residue by HP-20 column chromatography (8% CH_3CN–H_2O) and SEPHADEX LH-20 column chromatography (MeOH) gave a crude residue. Precipitation of the residue from MeOH–Et_2O gave **4** (47.1 mg, 62%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, CD_3OD): δ 1.40–1.50, 1.60–1.80 (total 4H, each m), 1.95–2.05, 2.20–2.30 (total 3H, each m), 2.40–2.50, 2.70–3.00 (total 4H, each m), 2.60–2.70 (2H, m), 3.40–3.50 (4H, m), 4.02 (2H, s), 5.14 (1H, br), 6.85–6.95 (2H, m), 7.10–7.20 (5H, m). Anal. Calcd for $C_{23}H_{30}N_2O{\cdot}2HCl$: C, 65.24; H, 7.62; Cl, 16.75; N, 6.62. Found: C, 64.91; H, 7.45; Cl, 16.63; N, 6.41. MS (FAB): *m*/*z* 351 $(M+H)^+$. HRMS (FAB) Calcd for $C_{23}H_{31}N_2O$: 351.2436. Found: 351.2433. IR (KBr) cm^{-1} 3448, 2916, 1594, 1508, 1454, 1434, 1384, 1238, 1202, 1058, 816.

6.21. General procedure A: preparation of 1-[(6-chloro-2-naphthyl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (6)

To a mixture of *tert*-butyl 1-piperazinecarboxylate (**26**) (569 mg, 3.1 mmol), **27** (654 mg, 2.8 mmol), 1-hydroxybenzotriazole (374 mg, 2.8 mmol), and *N*-methylmorphorine (0.336 mL, 3.1 mmol) in dimethylformamide (40 mL) was added 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (796 mg, 4.2 mmol). The reaction mixture was stirred for 7 h at room temperature and then concentrated in vacuo. Purification of the residue by silica gel column chromatography (2% MeOH–CH_2Cl_2) and then precipitation of the eluent from hexane gave 1-(*tert* butoxycarbonyl)-4-[4-(4-pyridyl)-benzoyl]piperazine (905 mg, 89%) as a colorless amorphous solid.

To a solution of 1-(*tert*-butoxycarbonyl)-4-[4-(4-pyridyl)benzoyl]piperazine (367 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (10 mL) at 0 °C. The reaction mixture was stirred for 1 h and concentrated in vacuo. Precipitation of the residue from THF gave [4-(4-pyridyl)benzoyl]piperazine (1.28 g) as a colorless amorphous solid. To a solution of [4-(4-pyridyl)benzoyl]piperazine (1.19 g) and diisopropylethylamine (1.68 mL, 9.6 mmol) in CH_2Cl_2 (100 mL) was added **30** (691 mg, 2.6 mmol) at room temperature. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% MeOH–CH_2Cl_2) and then added to 1 N HCl–EtOH solution. The solution was concentrated in vacuo, and precipitation from THF gave **6** (1.05 g, 81%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95–3.25 (4H, m), 3.43 (2H, br s), 3.60 (2H, br s), 7.56 (2H, d, J = 8.3 Hz), 7.74 (1H, dd, J = 8.8, 2.0 Hz), 7.83 (1H, dd, J = 8.8, 2.0 Hz), 8.01 (2H, d, J = 8.3 Hz), 8.19 (1H, d, J = 8.8 Hz), 8.25–8.40 (4H, m), 8.51 (1H, s), 8.94

(2H, d, $J = 6.8$ Hz). Anal. Calcd for $C_{26}H_{22}ClN_3O_3S \cdot HCl \cdot 0.5H_2O$: C, 58.10; H, 4.50; Cl, 13.19; N, 7.82; S, 5.97. Found: C, 58.12; H, 4.67; Cl, 13.12; N, 7.66; S, 6.10. MS (FAB) *m/z* 492 $(M+H)^+$. IR (ATR) cm^{-1} 3019, 2487, 2086, 1994, 1631, 1604, 1430, 1344, 1280, 1259, 1160, 1110, 1079, 954, 939, 823.

Compounds **37b**, and **39a**,**b** were prepared according to procedure A.

6.22. 1-[(6-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine (37b)

Colorless amorphous powder (yield, 39%). But this compound was purified only by silica gel column chromatography without being transformed into the HCl salt.

^1H NMR (400 MHz, $CDCl_3$): δ 2.80–4.30 (8H, m), 7.34 (1H, dd, $J = 8.5$, 1.7 Hz), 7.43–7.62 (9H, m), 7.69 (2H, d, $J = 7.8$ Hz), 8.04 (2H, d, $J = 7.3$ Hz), 8.33 (1H, s), 8.70 (2H, broad s). Anal. Calcd for $C_{30}H_{25}ClN_4O_5S_2$: C, 58.01; H, 4.06; Cl, 5.71; N, 9.02; S, 10.32. Found: C, 58.34; H, 4.23; Cl, 5.78; N, 8.85; S, 9.96. MS (FAB) *m/z* 621 $[(M+H)^+, Cl^{35}]$, 623 $[(M+H)^+, Cl^{37}]$. IR (KBr) cm^{-1} 3064, 2918, 2854, 1637, 1595, 1448, 1389, 1350, 1282, 1263, 1186, 1157, 1113, 1007, 926, 818.

6.23. 1-[(5-Chlorobenzo[*b*]furan-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (39a)

Colorless powder (yield, 65%).

Mp 192–220 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.20–3.55 (6H, br), 3.60–3.90 (2H, br), 7.61 (1H, dd, $J = 8.8$, 2.0 Hz), 7.61 (2H, d, $J = 8.8$ Hz), 7.68 (1H, s), 7.84 (1H, d, $J = 8.8$ Hz), 7.94 (1H, d, $J = 2.0$ Hz), 8.05 (2H, d, $J = 8.8$ Hz), 8.34 (2H, d, $J = 5.9$ Hz), 8.95 (2H, d, $J = 5.9$ Hz). Anal. Calcd for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.6H_2O$: C, 54.47; H, 4.23; Cl, 13.40; N, 7.94; S, 6.06. Found: C, 54.48; H, 4.14; Cl, 13.41; N, 7.83; S, 6.17. MS (FAB) *m/z* 482 $[(M+H)^+, Cl^{35}]$, 484 $[(M+H)^+, Cl^{37}]$. IR (KBr) cm^{-1} 3401, 2474, 1647, 1630, 1603, 1441, 1425, 1356, 1281, 1163, 945.

6.24. 1-[(6-Chlorobenzo[*b*]furan-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (39b)

Colorless powder (yield, 57%).

Mp 192–210 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.20–3.45 (4H, br), 3.35–3.55 (2H, br), 3.65–3.85 (2h, br), 7.48 (1H, d, $J = 8.8$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 7.73 (1H, s), 7.80–8.10 (2H, m), 7.86 (1H, d, $J = 8.8$ Hz), 7.98 (1H, s), 8.04 (2H, d, $J = 7.8$ Hz), 8.20–8.32 (0.5H, m), 8.60–9.49 (1H, br), 8.90–8.93 (0.5H, m). Anal. Calcd for $C_{24}H_{20}ClN_3O_4S \cdot HCl \cdot 0.3H_2O$: C, 55.03; H, 4.16; Cl, 13.54; N, 8.02; S, 6.12. Found: C, 55.06; H, 4.12; Cl, 13.62; N, 7.89; S, 6.11. MS (FAB) *m/z* 482 $[(M+H)^+, Cl^{35}]$, 484 $[(M+H)^+, Cl^{37}]$. IR (KBr) cm^{-1} 2467, 1643, 1606, 1431, 1363, 1282, 1167, 931, 816.

6.25. General procedure B: preparation of 1-(6-chloro-2-naphthylsulfonyl)-4-[2-hydroxy-4-(4-pyridyl)benzoyl]piperazine hydrochloride (8)

To a solution of *tert*-butyl 1-piperazinecarboxylate (**26**) (856 mg, 4.6 mmol) in CH_2Cl_2 (150 mL) were added Et_3N (765 μL, 5.5 mmol) and **30** (1.20 g, 4.6 mmol) at room temperature. The reaction mixture was stirred for 15 min and washed with H_2O. The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. To the residue was added EtOH solution saturated with HCl (30 mL). The reaction mixture was stirred for 3 min and concentrated in vacuo. Recrystallization of the residue from AcOEt gave 1-[(6-chloro-2-naphthyl)sulfonyl]piperazine (1.62 g, quant.) as a colorless solid.

Mp 248–251 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.19 (8H, d, $J = 7.3$ Hz), 7.75 (1H, dd, $J = 8.8$, 2.0 Hz), 7.86 (1H, dd, $J = 8.8$, 2.0 Hz), 8.22 (1H, d, $J = 8.8$ Hz), 8.26–8.32 (2H, m), 8.56 (1H, s), 8.63 (2H, br s). MS (FAB) *m/z* 311 $[(M+H)^+, Cl^{35}]$, 313 $[(M+H)^+, Cl^{37}]$.

To a mixture of 1-[(6-chloro-2-naphthyl)sulfonyl]piperazine (231 mg, 0.66 mmol), **28** (91 mg, 0.42 mmol), *N*,*N*-dimethylaminopyridine (61 mg, 0.50 mmol), and diisopropylethylamine (0.44 mL, 2.5 mmol) in *N*,*N*-dimethylformamide (6.0 mL)–CH_2Cl_2 (6.0 mL) was added 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (97 mg, 0.50 mmol). The reaction mixture was stirred for 42 h at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.5% MeOH–CH_2Cl_2) and then added to 1 N HCl–EtOH solution. The solution was concentrated in vacuo, precipitation from THF gave **8** (27 mg, 13%) as a colorless amorphous solid.

^1H NMR (400 MHz, DMSO-d_6): δ 2.90–3.40 (8H, m), 7.25–7.40 (3H, m), 7.70–7.80 (1H, m), 7.80–7.90 (1H, m), 8.15–8.25 (3H, m), 8.25–8.35 (2H, m), 8.50–8.60 (1H, m), 8.91 (2H, d, $J = 6.4$ Hz), 10.41 (1H, broad s). Anal. Calcd for $C_{26}H_{22}ClN_3O_4S \cdot 1.1HCl \cdot 1.7H_2O$: C, 53.96; H, 4.62; Cl, 12.86; N, 7.26; S, 5.54. Found: C, 53.62; H, 4.58; Cl, 13.10; N, 7.34; S, 5.94. MS (FAB) *m/z* 535 $[(M+H)^+, Cl^{35}]$, 537 $[(M+H)^+, Cl^{37}]$. HRMS (FAB) Calcd for $C_{26}H_{23}ClN_3O_4S$: 508.1098. Found: 508.1087. IR (KBr) cm^{-1} 3396, 3048, 2872, 1620, 1414, 1342, 1162, 1134, 938, 810.

Compounds **36**, **37a**, **37c**, and **38a**,**b** were prepared according to procedure B.

6.26. 1-(6-Chloro-2-naphthylsulfonyl)-4-[3-methoxy-4-(4-pyridyl)benzoyl]piperazine hydrochloride (36)

Colorless amorphous powder (yield, 57%).

^1H NMR (400 MHz, DMSO-d_6): δ 3.00–4.00 (8H, m), 3.81 (3H, s), 7.08 (1H, d, $J = 8.8$ Hz), 7.17 (1H, s), 7.55 (1H, d, $J = 8.8$ Hz), 7.74 (1H, dd, $J = 8.8$, 2.0 Hz), 7.83 (1H, d, $J = 8.3$ Hz), 8.04 (2H, d, $J = 6.3$ Hz), 8.19 (1H, d, $J = 8.8$ Hz), 8.25–8.30 (2H, m), 8.52 (1H, s), 8.85 (2H, d, $J = 6.3$ Hz). Anal. Calcd for $C_{27}H_{24}ClN_3O_4S \cdot 0.8HCl \cdot 1.7H_2O$: C, 55.74; H, 4.89; Cl, 10.97; N, 7.22;

S, 5.51. Found: C, 55.59; H, 4.90; Cl, 10.90; N, 7.23; S, 5.52. MS (FAB) *m/z* 522 [$(M+H)^+$, Cl^{35}], 524 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{27}H_{25}ClN_3O_4S$: 522.1254. Found: 522.1274. IR (KBr) cm^{-1} 3412, 1630, 1460, 1432, 1402, 1344, 1334, 1314, 1290, 1240, 1158, 1138, 1108, 1076, 944, 814.

6.27. 1-[(5-Chloroindol-1-phenylsulfonyl-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine (37a)

Colorless powder (yield, 52%). But this compound was purified only by silica gel column chromatography without being transformed into the HCl salt.

Mp 134–136 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.45–3.53 (4H, br), 3.53–3.98 (4H, br), 7.40–7.50 (4H, m), 7.52–7.60 (6H, m), 7.70 (2H, d, $J = 8.3$ Hz), 8.01 (2H, d, $J = 8.3$ Hz), 8.24 (1H, d, $J = 9.3$ Hz), 8.73 (2H, br). Anal. Calcd for $C_{30}H_{25}ClN_4O_5S_2 \cdot 0.1CH_2Cl_2$: C, 57.42; H, 4.03; Cl, 6.76; N, 8.90; S, 10.19. Found: C, 57.10; H, 4.35; Cl, 6.58; N, 8.80; S, 10.04.

MS (FAB) *m/z* 621 [$(M+H)^+$, Cl^{35}], 623 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{30}H_{26}ClN_4O_5S_2$: 621.1033. Found: 621.1019. IR (KBr) cm^{-1} 3064, 2950–2840, 1650–1570, 1433, 1387, 1348, 1186, 1155, 817, 728.

6.28. 1-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (37c)

Colorless powder (yield, 64%).

Mp 142–147 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, $J = 6.8$ Hz), 3.15–3.37 (4H, br), 3.38–3.57 (2H, br), 3.65–3.87 (2H, br), 4.47 (2H, q, $J = 6.8$ Hz), 7.17 (1H, s), 7.41 (1H, dd, $J = 2.0$, 8.8 Hz), 7.63 (2H, d, $J = 8.3$ Hz), 7.73 (1H, d, $J = 8.8$ Hz), 7.81 (1H, d, $J = 2.0$ Hz), 8.05 (2H, d, $J = 8.3$ Hz), 8.31 (2H, d, $J = 6.4$ Hz), 8.94 (2H, d, $J = 6.4$ Hz). Anal. Calcd for $C_{26}H_{25}ClN_4O_3S \cdot 1.1HCl \cdot 1.2H_2O$: C, 54.71; H, 5.03; Cl, 13.04; N, 9.82; S, 5.62. Found: C, 54.51; H, 5.11; Cl, 13.06; N, 9.68; S, 5.71. MS (FAB) *m/z* 509 [$(M+H)^+$, Cl^{35}], 511 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{26}H_{26}ClN_4O_3S$: 509.1414. Found: 509.1427. IR (KBr) cm^{-1} 3396, 2544, 1631, 1435, 1338, 1149, 935, 818, 714, 576.

6.29. 1-[(5-Chlorobenzo[*b*]thien-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (38a)

Pale yellow powder (yield, 62%).

Mp 223–224 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.02–4.00 (8H, m), 7.51 (2H, d, $J = 8.8$ Hz), 7.62 (1H, dd, $J = 8.8$, 2.0 Hz), 7.71 (2H, d, $J = 5.4$ Hz), 7.82 (2H, d, $J = 8.3$ Hz), 8.04 (1H, s), 8.17 (1H, d, $J = 2.0$ Hz), 8.19 (1H, d, $J = 8.8$ Hz), 8.65 (2H, d, $J = 5.4$ Hz). Anal. Calcd for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl$: C, 53.93; H, 3.96; Cl, 13.27; N, 7.86; S, 12.00. Found: C, 53.79; H, 4.07; Cl, 13.37; N, 7.70; S, 12.07. MS (FAB) *m/z* 498 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 2466, 1644, 1494, 1428, 1353, 1280, 1160, 997, 941, 725.

6.30. 1-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (38b)

Colorless powder (yield, 87%).

Mp 232–233 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.03–3.88 (8H, m), 7.56–7.61 (3H, m), 8.02 (2H. d, $J = 8.8$ Hz), 8.09 (2H. d, $J = 8.8$ Hz), 8.29 (2H. d, $J = 6.3$ Hz), 8.34 (1H, d, $J = 2.0$ Hz), 8.94 (2H, d, $J = 6.3$ Hz). Anal. Calcd for $C_{24}H_{20}ClN_3O_3S_2 \cdot HCl \cdot H_2O$: C, 52.17; H, 4.20; Cl, 12.83; N, 7.61; S, 11.61. Found: C, 52.18; H, 4.14; Cl, 12.84; N, 7.56; S, 11.70. MS (FAB) *m/z* 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 1627, 1459, 1430, 1346, 1326, 1284, 1259, 1151, 997, 937, 727, 580.

6.31. General procedure C: preparation of 1-[(5-chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (40a)

To a solution of **34a** (293 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) was added saturated HCl–EtOH solution (10 mL). The reaction mixture was stirred for 0.5 h at room temperature, concentrated in vacuo, and precipitated of the residue from AcOEt to give [(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine (165 mg, 66%) as a colorless amorphous solid.

To a mixture of [(5-chlorobenzothiazol-2-yl)sulfonyl]-piperazine (160 mg, 0.45 mmol), **28** (107 mg, 0.45 mmol), 1-hydroxybenztriazole (61 mg, 0.45 mmol), and *N*-methylmorpholine (0.15 mL, 1.4 mmol) in CH_2Cl_2 (5.0 mL) was added 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (130 mg, 0.68 mmol). The reaction mixture was stirred for 24 h at room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography (2–5% MeOH–CH_2Cl_2) and then added to 1 N HCl–EtOH solution. The solution was concentrated in vacuo, and precipitation from AcOEt gave **40a** (152 mg, 62%) as a colorless powder.

Mp 152–154 °C (decomp.). ^1H NMR (400 MHz, DMSO-d_6): δ 3.28–3.90 (8H, m), 7.61 (2H, d, $J = 8.3$ Hz), 7.77 (1H, dd, $J = 8.8$, 2.0 Hz), 8.04 (2H, d, $J = 8.3$ Hz), 8.28 (2H, d, $J = 6.4$ Hz), 8.38 (1H, d, $J = 8.8$ Hz), 8.43 (1H, d, $J = 2.0$ Hz), 8.93 (2H, d, $J = 6.4$ Hz). Anal. Calcd for $C_{23}H_{19}ClN_4O_3S_2 \cdot HCl \cdot 0.6H_2O$: C, 50.57; H, 3.91; Cl, 12.98; N, 10.26; S, 11.74. Found: C, 50.72; H, 3.90; Cl, 13.22; N, 9.99; S, 11.35. MS (FAB) *m/z* 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}]. IR (ATR) cm^{-1} 2464, 2059, 1974, 1639, 1598, 1423, 1348, 1322, 1278, 1257, 1168, 1133, 1112, 1051, 1004, 948, 902, 856, 819.

Compounds **40b** and **41** were prepared according to procedure C.

6.32. 1-[(6-Chlorobenzothiazol-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (40b)

Colorless powder (yield, 67%).

Mp 211–213 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.28–3.90 (8H, m), 7.55 (2H, d, $J = 8.3$ Hz), 7.77 (1H,

dd, $J = 8.8$, 2.0 Hz), 7.85–7.93 (4H, m), 8.29 (1H, d, $J = 8.8$ Hz), 8.50 (1H, d, $J = 2.0$ Hz), 8.73 (2H, d, $J = 6.4$ Hz). Anal. Calcd for $C_{23}H_{19}ClN_4O_3S_2 \cdot 0.25HCl \cdot 0.5H_2O$: C, 53.42; H, 3.95; Cl, 8.57; N, 10.83; S, 12.40. Found: C, 53.22; H, 3.91; Cl, 8.41; N, 10.70; S, 12.59. MS (FAB) *m/z* 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{23}H_{20}ClN_4O_3S_2$: 499.0665. Found: 499.0675. IR (ATR) cm^{-1} 1629, 1430, 1363, 1276, 1263, 1176, 1106, 1006, 944, 813.

6.33. 1-[[5(6)-Chlorobenzimidazol-2-yl]sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine hydrochloride (41)

Colorless powder (yield, 50%).

Mp 170–180 °C (decomp.). ^1H NMR (400 MHz, DMSO-d_6): δ 3.30–4.00 (8H, br), 7.43 (1H, d, $J = 8.8$, 2.0 Hz), 7.62 (2H, d, $J = 7.8$ Hz), 7.75 (1H, d, $J = 8.8$ Hz), 7.80 (1H, s), 8.07 (2H, d, $J = 8.8$ Hz), 8.38 (2H, d, $J = 5.9$ Hz), 8.97 (2H, d, $J = 5.9$ Hz). Anal. Calcd for $C_{23}H_{20}ClN_5O_3S \cdot HCl \cdot 1.8H_2O \cdot 0.5EtOH$: C, 50.23; H, 4.85; N, 12.20. Found: C, 49.96; H, 4.55; N, 12.04. MS (FAB) *m/z* 482 [$(M+H)^+$, Cl^{35}], 484 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{23}H_{21}ClN_5O_3S$: 482.1054. Found: 482.1024. IR (KBr) cm^{-1} 1631, 1431, 1365, 1282, 1155.

6.34. 2-Hydroxy-4-(4-pyridyl)benzoic acid (28)

To a solution of 4-bromo-2-hydroxybenzoic acid (**31**) (297.6 mg, 1.4 mmol), diethyl(4-pyridyl)borane (265 mg, 1.8 mmol), tetrabutylammonium bromide (224.8 mg, 0.70 mmol), and tetrakis(triphenylphosphine)palladium(0) (161 mg, 0.14 mmol) in tetrahydrofuran (20 mL) was added potassium hydroxide (301 mg, 5.4 mmol)/H_2O (0.5 mL) at room temperature. The mixture was refluxed for 2.5 h, and then AcOEt and H_2O and potassium hydroxide was added. The separated aqueous layer was washed with AcOEt and acidified with 1 N HCl. The precipitate was collected and washed with tetrahydrofuran to give **29b** (70 mg, 21%) as a pale yellow amorphous powder.

^1H NMR (400 MHz, DMSO-d_6): δ 7.3–7.4 (2H, m), 7.78 (2H, d, $J = 4.4$ Hz), 7.92 (1H, d, $J = 6.3$ Hz), 8.69 (2H, d, $J = 5.9$ Hz). MS (EI) *m/z* 215 M^+. HRMS (EI) Calcd for $C_{12}H_9NO_3$: 215.0582. Found: 215.0585. IR (KBr) cm^{-1} 3428, 1678, 1630, 1518, 1492, 1424, 1368, 1316, 1284, 1214, 1142, 1066, 936, 860, 850, 816.

6.35. Methyl 3-methoxy-4-(pyridin-4-yl)benzoate (44)

Starting with **43** (0.64 g, 2.6 mmol) and **31** (0.60 g, 4.1 mmol) and following the procedure for the preparation of **28** gave **44** (yield, 92%) as a pale yellow amorphous mass. No further purification was attempted on this compound, which was used directly in the next step.

6.36. 3-Methoxy-4-(pyridin-4-yl)benzoic acid hydrochloride (29)

A solution of **44** (584 mg) in 1 N HCl aqueous solution (20 mL) was refluxed for 5.5 h and then was added to H_2O and CH_2Cl_2. The separated aqueous layer was washed with CH_2Cl_2 and filtered to remove the precipitate, followed by concentration of the filtrate in vacuo. Precipitation of the residue from THF–H_2O gave **29** (253 mg, 38% from **43**) as a colorless amorphous solid.

^1H NMR (400 MHz, $CDCl_3$): δ 3.93 (3H, s), 7.65–7.75 (3H, m), 8.20 (2H, d, $J = 5.4$ Hz), 8.94 (2H, d, $J = 6.3$ Hz). Anal. Calcd for $C_{13}H_{11}NO_3 \cdot HCl \cdot 0.1H_2O$: C,58.37; H, 4.60; Cl, 13.25; N, 5.24. Found: C, 58.36; H, 4.48; Cl, 13.35; N, 5.22. MS (FAB) *m/z* 230 $(M+H)^+$. HRMS (FAB) Calcd for $C_{13}H_{12}NO_3$: 230.0817. Found: 230.0830. IR (ATR) cm^{-1} 2645, 1704, 1627, 1602, 1498, 1452, 1407, 1365, 1247, 1197, 1110, 1014, 877, 842, 811.

6.37. 6-Chloro-2-naphthylsulfonyl chloride (30)[24]

The suspension of 2-chloronaphthalene (**45**) (50.6 g, 0.31 mol) in concd H_2SO_4 (16.6 mL, 0.31 mol) was stirred for 6 h at 160 °C. After it had cooled to room temperature, the reactant solution was diluted with DMF (200 mL). To the solution was added $SOCl_2$ (34.1 mL, 0.47 mol) at 0 °C. The reaction mixture was stirred for 90 min at 0 °C. The precipitate was collected and dissolved in AcOEt. The solution was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. Recrystallization of the residue from hexane gave **30** (14.2 g, 17%) as a colorless solid.

Mp 102–104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, dd, $J = 8.8$, 2.0 Hz), 7.93–8.07 (4H, m), 8.58 (1H, d, $J = 1.0$ Hz). MS (EI) *m/z* 260 (M^+, Cl^{35}), 262 (M^+, Cl^{37}).

6.38. 5-Chloro-1-phenylsulfonylindole (47a)

To a solution of 5-chloroindole (**46a**) (2.86 g, 19 mmol) in THF (40 mL) at −78 °C under Argon atmosphere was added *n*-butyl lithium solution (1.61 M in hexane) (12.3 mL, 20 mmol). After the reaction mixture was stirred for 1 h at −78 °C, a solution of phenylsulfonyl chloride (3.5 g, 20 mmol) in THF (10 mL) was added. After it was warmed up from −78 °C to room temperature for 4 h, the reaction mixture was stirred for 1 h and added to H_2O and AcOEt. The separated aqueous layer was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt/hexane = 20/1) gave **47a** (5.38 g, 93%) as a colorless amorphous powder.

^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (1H, d, $J = 3.4$ Hz), 7.26 (1H, dd, $J = 8.3$, 2.0 Hz), 7.45 (2H, t, $J = 7.3$ Hz), 7.50 (1H, d, $J = 2.0$ Hz), 7.56 (1H, t, $J = 7.3$ Hz), 7.59 (1H, d, $J = 7.3$ Hz), 7.86 (2H, d, $J = 7.3$ Hz), 7.92 (1H, d, $J = 8.3$ Hz). Anal. Calcd for $C_{14}H_{10}ClNO_2S$: C,57.63; H, 3.45; Cl, 12.15; N, 4.80; S, 10.99. Found: C, 57.82; H, 3.58; Cl, 11.91; N, 4.79; S, 10.92. MS (EI) *m/z* 291 M^+. HRMS (EI) Calcd for $C_{14}H_{10}ClNO_2S$: 291.0121. Found: 291.0101. IR (KBr) cm^{-1} 3120, 1440, 1373, 1193, 1170, 1116, 1089, 1068, 991, 875, 811.

6.39. 6-Chloro-1-phenylsulfonylindole (47b)

Starting with **46b** (0.78 g, 5.1 mmol) and following the procedure for the preparation of **47a** gave **47b** (yield, 55%) as a colorless amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (1H, d, J = 3.9 Hz), 7.21 (1H, dd, J = 8.3, 1.2 Hz), 7.40–7.60 (5H, m), 7.88 (2H, d, J = 7.3 Hz), 8.03 (1H, s). Anal. Calcd for $C_{14}H_{10}ClNO_2S$: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80; S, 10.99. Found: C, 57.48; H, 3.75; Cl, 12.34; N, 4.87; S, 10.87. MS (FAB) m/z 291 (M^+, Cl^{35}), 293 (M^+, Cl^{37}). IR (KBr) cm^{-1} 3105, 3059, 1603, 1523, 1481, 1460, 1446, 1421, 1369, 1265, 1205, 1184, 1174, 1132, 1092, 1065, 995, 899, 866, 808.

6.40. 5-Chloro-1-ethylindole (47c)

To a solution of 5-chloroindole (**46a**) (1.52 g, 10 mmol) in benzene (10 mL) was added 50% NaOH aqueous solution (10 mL), tetrabutylammonium bromide (161 mg, 0.50 mmol), and bromoethane (1.64 g, 15 mmol). After being stirred for 40 h at room temperature, the reaction mixture was added to saturated aqueous NH_4Cl solution and CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography (AcOEt/hexane = 20/1) gave **47c** (1.68 g, 93%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (3H, t, J = 7.3 Hz), 4.16 (2H, q, J = 7.3 Hz), 6.43 (1H, d, J = 2.4 Hz), 7.14 (1H, d, J = 2.4 Hz), 7.15 (1H, d, J = 8.3 Hz), 7.26 (1H, J = 8.3 Hz), 7.59 (1H, s). MS (EI) m/z 179 (M^+, Cl^{35}), 181 (M^+, Cl^{37}). No further purification was attempted on this compound, which was used directly in the next step.

6.41. (5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl chloride (31a)

To a solution of **47a** (5.38 g, 18 mmol) in Et_2O (100 mL) was added *tert*-butyl lithium (1.78 M in pentane) (10.4 mL, 19 mmol) at −78 °C under argon atmosphere. After the reaction mixture was warmed up to −40 °C, SO_2 gas was introduced to the mixture at −78 °C. After the reaction mixture was warmed up to room temperature, it was stirred at room temperature for an hour and concentrated in vacuo. To the residue was added hexane and Et_2O, and collecting the precipitate gave a colorless powder. To a solution of the powder in CH_2Cl_2 (150 mL) was added *N*-chlorosuccinimido (2.47 g, 19 mmol). After stirring the reaction mixture at room temperature for 8 h, CH_2Cl_2 and H_2O were added. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt, 20/1) gave a crude residue. Recrystallization of the residue from EtOH gave **31a** (4.41 g, 64%) as a brown amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.54 (2H, m), 7.58 (1H, dd, J = 2.0, 9.3 Hz), 7.63 (1H, t, J = 7.3 Hz), 7.64 (1H, s), 7.67 (1H, d, J = 2.0 Hz), 8.06 (2H, d, J = 7.3 Hz), 8.26 (1H, d, J = 9.3 Hz). Anal. Calcd for $C_{14}H_9Cl_2NO_4S_2$: C, 43.09; H, 2.32; Cl, 18.27; N, 3.59; S, 16.43. Found: C, 42.98; H, 2.51; Cl, 18.36; N, 3.59; S, 16.47. MS (EI) m/z 291 (M^+, Cl^{35}), 293 (M^+, Cl^{37}). IR (KBr) cm^{-1} 3120, 1504, 1375, 1172, 1120, 1012, 837, 725, 621, 594, 548.

6.42. (6-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl chloride (31b)

Starting with **47b** (0.78 g, 2.6 mmol) and following the procedure for the preparation of **31a** gave **31b** (yield, 79%) as a colorless amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, dd, J = 8.3, 1.6 Hz), 7.48–7.67 (4H, m), 7.68 (1H, s), 8.08 (2H, d, J = 7.3 Hz), 8.35 (1H, s). Anal. Calcd for $C_{14}H_9Cl_2NO_4S_2$: C, 43.09; H, 2.32; Cl, 18.17; N, 3.59; S, 16.43. Found: C, 43.32; H, 2.67; Cl, 18.25; N, 3.64; S, 16.22. MS (FAB) m/z 389 (M^+, Cl^{35} + Cl^{35}), 391 (M^+, Cl^{35} + Cl^{37}), 393 (M^+, Cl^{37} + Cl^{37}). IR (KBr) cm^{-1} 3122, 1604, 1568, 1498, 1448, 1390, 1379, 1268, 1232, 1188, 1173, 1126, 1111, 1090, 1072, 1014, 924.

6.43. (5-Chloro-1-ethylindol-2-yl)sulfonyl chloride (31c)

Starting with **47c** (0.89 g, 4.9 mmol) and following the procedure for the preparation of **31a** gave **31c** (yield, 40%) as a brown amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (3H, t, J = 7.3 Hz), 4.59 (2H, q, J = 7.3 Hz), 7.36 (1H, s), 7.39 (1H, d, J = 8.8 Hz), 7.45 (1H, dd, J = 2.0, 8.8 Hz), 7.73 (1H, d, J = 2.0 Hz). MS (EI) m/z 277 (M^+, Cl^{35}), 279 (M^+, Cl^{37}). No further purification was attempted on this compound, which was used directly in the next step.

6.44. (5-Chlorobenzo[*b*]thien-2-yl)sulfonyl chloride (32a)

Starting with **48a** (1.68 g, 10 mmol) and following the procedure for the preparation of **31a** gave **32a** (yield, 68%) as a yellow amorphous mass.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (1H, dd, J = 8.8, 2.0 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.96 (1H, d, J = 2.0 Hz), 8.08 (1H, s). MS (EI) m/z 266 (M^+, Cl^{35}), 268 (M^+, Cl^{37}). HRMS (EI) Calcd for $C_8H_4Cl_2O_2S_2$: 265.9030. Found: 265.9045. IR (KBr) cm^{-1} 3104, 1492, 1376, 1184, 1168, 1078, 997, 887, 630.

6.45. (6-Chlorobenzo[*b*]thien-2-yl)sulfonyl chloride (32b)

Starting with **48b** (2.34 g, 14 mmol) and following the procedure for the preparation of **31a** gave **32b** (yield, 85%) as a pale yellow powder.

Mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, dd, J = 8.3, 1.5 Hz), 7.90 (1H, d, J = 8.3 Hz), 7.92 (1H, s), 8.11 (1H, s). MS (EI) m/z 266 (M^+, Cl^{35}), 268 (M^+, Cl^{37}). HRMS (EI) Calcd for $C_8H_4Cl_2O_2S_2$:

265.9030. Found: 265.9022. IR (KBr) cm^{-1} 3102, 3068, 1587, 1481, 1375, 1357, 1324, 1184, 1157, 1132, 1106, 1049, 1002, 867, 809, 700, 665, 592, 545, 487, 428.

6.46. (5-Chlorobenzo[*b*]furan-2-yl)sulfonyl chloride (33a)

Starting with **49a** (1.68 g, 11 mmol) and following the procedure for the preparation of **31a** gave **33a** (yield, 62%) as a pale yellow needle crystal.

Mp 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (1H, dd, J = 8.8, 2.0 Hz), 7.59 (1H, s), 7.61 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 2.0 Hz). Anal. Calcd for $C_8H_4Cl_2O_3S$: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77. Found: C, 38.33; H, 1.71; Cl, 28.16; S, 12.57. MS (EI) m/z 250 [M^+, Cl^{35}], 252 [M^+, Cl^{37}]. IR (KBr) cm^{-1} 1531, 1392, 1275, 1240, 1163, 1080, 933, 908, 876.

6.47. (6-Chlorobenzo[*b*]furan-2-yl)sulfonyl chloride (33b)

Starting with **49b** (362 mg, 2.4 mmol) and following the procedure for the preparation of **31a** gave **33b** (yield, 64%) as a pale green needle crystal.

Mp 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, dd, J = 8.8, 2.0 Hz), 7.62 (1H, s), 7.69 (1H, br s), 7.70 (1H, d, J = 8.8 Hz). Anal. Calcd for $C_8H_4Cl_2O_3S$: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77. Found: C, 38.31; H, 1.60; Cl, 28.34; S, 12.60. MS (EI) m/z 250 [M^+, Cl^{35}], 252 [M^+, Cl^{37}]. IR (KBr) cm^{-1} 1698, 1529, 1392, 1167, 935, 854, 814.

6.48. 1-*tert*-Butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfenyl]piperazine (51a)

To a solution of *tert*-butyl 1-piperazinecarboxylate (**26**) (5.6 g, 30 mmol), 5-chloro-2-mercaptobenzothiazole (**50a**) (1.2 g, 6.0 mmol), and sodium hydroxide (0.48 g, 12 mmol) in H_2O (25 mL) was added dropwise a solution of iodine (1.5 g, 12 mmol) and potassium iodide (1.7 g, 10 mmol) in H_2O (25 mL) over a period of one hour. The precipitate was collected and washed with H_2O to give **51a** (1.1 g, 48%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (9H, s), 3.24 (4H, br s), 3.58 (4H, br s), 7.26 (1H, m), 7.70 (1H, d, J = 8.3 Hz), 7.81 (1H, s). MS (FAB) m/z 386 [$(M+H)^+$, Cl^{35}], 388 [$(M+H)^+$, Cl^{37}].

No further purification was attempted on this compound, which was used directly in the next step.

6.49. 1-*tert*-Butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine (34a)

To a suspension of **51a** (1.1 g, 2.9 mmol) and potassium carbonate (1.3 g, 9.4 mmol) in EtOH (30 mL) and H_2O (10 mL) was added dropwise a solution of *m*-CPBA (2.1 g, 8.6 mmol) in EtOH (25 mL) in an ice bath. After the reaction mixture was stirred at room temperature for 24hr, saturated aqueous sodium thiosulfate and ethyl acetate were added. The separated organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel column chromatography (2% MeOH–CH_2Cl_2) gave **34a** (0.29 g, 25%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (9H, s), 3.35–3.43 (4H, m), 3.51–3.58 (4H, m), 7.55 (1H, dd, J = 8.8 and 1.5 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.18 (1H, d, J = 1.5 Hz). MS (FAB) m/z 418 [$(M+H)^+$, Cl^{35}], 420 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{16}H_{21}ClN_3O_4S_2$: 418.0662. Found: 418.0657. IR (ATR) cm^{-1} 2971, 2929, 2850, 1697, 1455, 1428, 1365, 1280, 1247, 1168, 1124, 1095, 904.

6.50. 1-*tert*-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulfenyl]piperazine (51b)

Starting with **50b** (1.2 g, 6.0 mmol) and following the procedure for the preparation of **51a** gave **51b** (yield, 33%) as a pale yellow amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (9H, s), 3.24 (4H, br s), 3.58 (4H, br s), 7.37 (1H, dd, J = 8.8, 2.0 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 2.0 Hz). MS (FAB) m/z 386 [$(M+H)^+$, Cl^{35}], 388 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 2971, 2923, 2857, 2358, 1693,1461, 1434, 1394, 1365, 1280, 1261, 1157, 1103, 1079, 1002. No further purification was attempted on this compound, which was used directly in the next step.

6.51. 1-*tert*-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulfonyl]piperazine (34b)

Starting with **51b** (0.77 g, 2.0 mmol) and following the procedure for the preparation of **34a** gave **34b** (yield, 29%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (9H, s), 3.35–3.43 (4H, m), 3.50–3.58 (4H, m), 7.59 (1H, dd, J = 8.8, 2.0 Hz), 7.97 (1H, d, J = 2.0 Hz), 8.10 (1H, d, J = 8.8 Hz). MS (FAB) m/z 418 [$(M+H)^+$, Cl^{35}], 420 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{16}H_{21}ClN_3O_4S_2$: 418.0662. Found: 418.0632. IR (KBr) cm^{-1} 3093, 2973, 2929, 2867, 1697, 1590, 1544, 1473, 1365, 1355, 1328, 1307, 1280, 1261, 1247, 1159, 1101, 1056, 1024, 995, 952, 883, 865, 815.

6.52. 1-(*tert*-Butoxycarbonyl)-4-[[5(6)-chlorobenzimidazol-2-yl]sulfonyl]piperazine (35)

To a suspension of **52** (1.84 g, 9.9 mmol) in 20% AcOH–H_2O solution (60 mL) was introduced Cl_2 gas for 70 min under 7 °C. The yellow precipitate was collected and washed with cool water. To a solution of the precipitate in H_2O (18 mL) and acetone (20 mL) was added *tert*-butyl 1-piperazinecarboxylate (**26**) (3.91 g, 21 mmol). The reaction mixture was stirred for 20 h at room temperature and concentrated in vacuo. The precipitate was collected to give **35** (3.16 g, 79%) as a pale yellow powder.

Mp 210–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (9H, s), 3.33–3.41 (4H, m), 3.53–3.59 (4H, m), 7.30–7.60 (2H, m), 7.72–7.88 (1H, m). Anal. Calcd for

$C_{16}H_{21}ClN_4O_4S{\cdot}0.3H_2O$: C, 47.30; H, 5.36; Cl, 8.73; N, 13.797; S, 7.89. Found: C, 47.30; H, 5.24; Cl, 9.98; N, 13.58; S, 7.89. MS (FAB) *m/z* 401 [$(M+H)^+$, Cl^{35}], 403 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3212, 2983, 1666, 1435, 1367, 1356, 1279, 1176, 1165, 1147, 1138, 974, 949.

6.53. 1-(6-Chloro-2-naphthylsulfonyl)-4-[3-hydroxy-4-(4-pyridyl)benzoyl]piperazine hydrochloride (9)

To a solution of BBr_3 (0.115 mL, 1.2 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of **36** (105 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) at −78 °C under argon atmosphere. The reaction mixture was stirred for 23 h at temperatures from −78 °C to room temperature, and then CH_2Cl_2, H_2O, and saturated aqueous $NaHCO_3$ were added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (3% MeOH–CH_2Cl_2), and then to a solution of the residue in THF was added 1 N HCl–EtOH. The precipitate was dissolved in MeOH–H_2O and concentrated in vacuo to give **9** (36.4 mg, 30%) as a colorless amorphous powder.

^1H NMR (400 MHz, DMSO-d_6): δ 3.00–3.80 (8H, m), 6.85–6.95 (1H, m), 7.01 (1H, d, J = 1.4 Hz), 7.49 (1H, d, J = 8.8 Hz), 7.72 (1H, dd, J = 8.8, 2.0 Hz), 7.81 (1H, dd, J = 8.5, 1.7 Hz), 7.94 (2H, d, J = 6.4 Hz), 8.19 (1H, d, J = 8.8 Hz), 8.25–8.30 (2H, m), 8.51 (1H, s), 8.75 (2H, d, J = 5.9 Hz), 10.67 (1H, s). MS (FAB) *m/z* 508 [$(M+H)^+$, Cl^{35}], 510 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{26}H_{23}ClN_3O_4S$: 508.1098. Found 508.1121. IR (KBr) cm^{-1} 3855, 1630, 1604, 1437, 1346, 1335, 1162, 1136, 1108, 1080, 953, 930, 812.

6.54. 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[4-(4-pyridyl) benzoyl]piperazine hydrochloride (54a)

A solution of **37a** (100 mg, 0.16 mmol) in 0.2 N KOH–MeOH solution was stirred for 1 h at 0 °C, and for 5 h at room temperature. The reaction mixture was neutralized with saturated HCl–EtOH solution and then concentrated in vacuo. To the residue was added a few drops of Et_3N, CH_2Cl_2 and H_2O. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% MeOH–CH_2Cl_2), and then the residue was added to 1 N HCl–EtOH and H_2O. The solution was concentrated in vacuo to give **54a** (68 mg, 78%) as a pale yellow powder.

Mp 185–188 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 2.94–3.25 (4H, br), 3.30–3.41 (4H, br), 7.03 (1H, s), 7.33 (1H, d, J = 8.8 Hz), 7.52 (1H, d, J = 8.8 Hz), 7.59 (2H, d, J = 7.3 Hz), 7.80 (1H, s), 8.03 (2H, d, J = 7.3 Hz), 8.33 (2H, d, J = 5.9 Hz), 8.95 (2H, d, J = 5.9 Hz), 12.5 (1H, s). Anal. Calcd for $C_{24}H_{21}ClN_4O_3S{\cdot}HCl{\cdot}1.5H_2O$: C, 52.95; H, 4.63; Cl, 13.02; N, 10.29; S, 5.89. Found: C, 53.34; H, 4.74; Cl, 12.87; N, 9.92; S, 5.77. MS (FAB) *m/z* 481 [$(M+H)^+$, Cl^{35}], 483 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3390-2855, 1635-1605, 1435, 1351, 1282, 1155, 811, 723, 577.

6.55. 1-[(6-Chloroindol-2-yl)sulfonyl]-4-[4-(4-pyridyl)benzoyl]piperazine (54b)

Starting with **37b** (0.38 g, 0.61 mmol) and following the procedure for the preparation of **54a** gave **54b** (yield, 53%) as a colorless amorphous powder. But this compound was purified only by silica gel column chromatography without being transformed into the HCl salt.

^1H NMR (400 MHz, $CDCl_3$): δ 2.70–4.20 (8H, m), 7.02 (1H, broad s), 7.23 (1H, dd, J = 8.3, 1.8 Hz), 7.42–7.50 (5H, m), 7.62–7.68 (3H, m), 8.62 (2H, d, J = 5.9 Hz), 8.78 (1H, broad s). Anal. Calcd for $C_{24}H_{21}ClN_4O_3S{\cdot}0.5H_2O$: C, 58.83; H, 4.53; Cl, 7.24; N, 11.43; S, 6.54. Found: C, 59.30; H, 4.68; Cl, 7.50; N, 10.97; S, 6.48. MS (FAB) *m/z* 481 [$(M+H)^+$, Cl^{35}], 483 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3114, 3030, 2918, 2854, 1628, 1601, 1460, 1435, 1360, 1282, 1263, 1161, 1111, 1057, 1009, 953, 818.

6.56. 4-[4-({4-[(6-Chloro-2-naphthyl)sulfonyl]piperazin-yl}carbonyl)phenyl]pyridine *N*-oxide (7)

To a solution of **6** (300 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (382 mg) at −20 °C. After the reaction mixture was stirred for 21 h, saturated aqueous $Na_2S_2O_4$ was added. After the reaction mixture was stirred again for 30 min, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography (2–5% MeOH–CH_2Cl_2) and precipitation of the eluent from Et_2O gave **7** (200 mg, 63%) as a colorless powder.

Mp 239–244 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.90–3.40 (4H, m), 3.40–4.20 (4H, m), 7.43 (2H, d, J = 8.3 Hz), 7.47 (2H, d, J = 7.3 Hz), 7.55–7.65 (3H, m), 7.76 (1H, dd, J = 8.8, 1.5 Hz), 7.90–8.0 (3H, m), 8.26 (2H, d, J = 7.3 Hz), 8.31 (1H, s). Anal. Calcd for $C_{26}H_{22}ClN_3O_4S{\cdot}0.8H_2O$: C, 59.78; H, 4.55; Cl, 6.79; N, 8.04; S, 6.14. Found: C, 59.82; H, 4.45; Cl, 6.85; N, 7.94; S, 6.29. MS (FAB) *m/z* 508 [$(M+H)^+$, Cl^{35}], 509 [$(M+H)^+$, Cl^{37}]. IR (ATR) cm^{-1} 1623, 1454, 1428, 1342, 1326, 1280, 1253, 1201, 1155, 1133, 1110, 1079, 1008, 954, 943, 885, 836, 804.

6.57. 4-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (55a)

Starting with **54a** (153 mg, 0.32 mmol) and following the procedure for the preparation of **7** gave **55a** (yield, 70%) as a colorless powder.

Mp >250 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.00–3.20 (4H, br), 3.34–3.58 (2H, br), 3.60–3.84 (2H, br), 7.03 (1H, s), 7.34 (1H, d, J = 8.8Hz), 7.47 (2H, d, J = 7.3 Hz), 7.51 (1H, d, J = 8.8 Hz), 7.79 (2H, d,

J = 5.9 Hz), 7.80 (1H, s), 7.81 (2H, d, J = 7.3 Hz), 8.28 (2H, d, J = 5.9 Hz), 12.43 (1H, br). Anal. Calcd for $C_{24}H_{21}ClN_4O_4S{\cdot}0.2H_2O$: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41. Found: C, 57.60; H, 4.38; Cl, 7.26; N, 11.09; S, 6.16. MS (FAB) m/z 497 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3120–2850, 1655–1632, 1462, 1360, 1250, 1161, 953, 725, 579.

6.58. 4-[4-[[4-[(6-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (55b)

Starting with **54b** (100 mg, 0.22 mmol) and following the procedure for the preparation of **7** gave **55b** (yield, 57%) as a colorless amorphous powder.

^1H NMR (400 MHz, $CDCl_3$): δ 2.90–4.10 (8H, m), 7.02 (1H, d, J = 1.5 Hz), 7.22 (1H, dd, J = 8.8, 1.5 Hz), 7.46 (2H, d, J = 8.3 Hz), 7.47 (1H, s), 7.50 (2H, d, J = 7.3 Hz), 7.60 (2H, d, J = 8.3 Hz), 8.29 (2H, d, J = 7.3 Hz), 8.63 (1H, d, J = 8.8 Hz), 9.32 (1H, broad s). Anal. Calcd for $C_{24}H_{21}ClN_4O_4S{\cdot}1.7H_2O$: C, 54.64; H, 4.66; Cl, 6.72; N, 10.62; S, 6.08. Found: C, 54.63; H, 4.65; Cl, 6.91; N, 10.42; S, 6.07. MS (FAB) m/z 497 [$(M+H)^+$, Cl^{35}], 499 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3423, 3107, 2862, 1597, 1469, 1352, 1290, 1238, 1159, 955, 837.

6.59. 4-[4-[[4-[(5-Chloro-1-ethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (55c)

Starting with **37c** (502 mg, 0.99 mmol) and following the procedure for the preparation of **7** gave **55c** (yield, 86%) as a colorless powder.

Mp 128–135 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 6.8 Hz), 3.18–3.38 (4H, br), 3.40–3.61 (2H, br), 3.62–3.84 (2H, br), 4.46 (2H, q, J = 6.8 Hz), 7.16 (1H, s), 7.41 (1H, dd, J = 8.8, 2.0 Hz), 7.52 (2H, d, J = 7.3 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.78–7.88 (5H, m), 8.28 (2H, d, J = 7.3 Hz). Anal. Calcd for $C_{26}H_{25}ClN_4O_4S{\cdot}0.4H_2O$: C, 58.67; H, 4.89; Cl, 6.66; N, 10.53; S, 6.02. Found: C, 58.73; H, 4.91; Cl, 6.88; N, 10.26; S, 5.96. MS (FAB) m/z 525 [$(M+H)^+$, Cl^{35}], 527 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3396, 2930-2850, 1637, 1473, 1338, 1259, 1149, 937, 831.

6.60. 4-[4-[[4-[(5-Chlorobenzo[*b*]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (56a)

Starting with **38a** (0.30 g, 0.60 mmol) and following the procedure for the preparation of **7** gave **56a** (yield, 66%) as a colorless amorphous form.

^1H NMR (400 MHz, DMSO-d_6): δ 3.02–3.90 (8H, m), 7.59 (2H, d, J = 8.3 Hz), 7.64 (1H, d, J = 2.0 Hz), 8.01–8.05 (3H, m), 8.18 (1H, d, J = 2.0 Hz), 8.20 (1H, d, J = 8.8 Hz), 8.31 (2H, d, J = 6.3 Hz), 8.94 (2H, d, J = 6.3 Hz). Anal. Calcd for $C_{24}H_{20}ClN_3O_3S_2{\cdot}0.8H_2O$: C, 54.55; H, 4.12; Cl, 6.71; N, 7.95; S, 12.14. Found: C, 54.66; H, 4.09; Cl, 6.95; N, 7.77; S, 11.87. MS (FAB) m/z 514 [$(M+H)^+$, Cl^{35}], 516 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 1627, 1457, 1428, 1355, 1284, 1259, 1174, 1160, 995, 939, 831, 723, 553.

6.61. 4-[4-[[4-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (56b)

Starting with **38b** (0.41 g, 0.82 mmol) and following the procedure for the preparation of **7** gave **56b** (yield, 52%) as a colorless amorphous form.

^1H NMR (400 MHz, DMSO-d_6): δ 3.16–3.88 (8H, m), 7.48 (2H, d, J = 8.3 Hz), 7.58 (1H, dd, J = 8.8, 2.0 Hz), 7.77 (1H, d, J = 7.3 Hz), 7.79 (1H, s), 7.81 (2H, d, J = 8.8 Hz), 8.08 (2H, d, J = 8.8 Hz), 8.27 (1H, d, J = 7.3 Hz), 8.33 (1H, s). Anal. Calcd for $C_{24}H_{20}ClN_3O_4S_2{\cdot}0.5H_2O$: C, 53.82; H, 4.22; Cl, 6.62; N, 7.84; S, 11.97. Found: C, 53.66; H, 4.22; Cl, 6.81; N, 7.61; S, 11.72. MS (FAB) m/z 514 [$(M+H)^+$, Cl^{35}], 516 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 2917, 2537, 1616, 1589, 1490, 1473, 1452, 1427, 1348, 1322, 1278, 1265, 1157, 1132, 1103, 997, 939, 727, 580.

6.62. 4-[4-[4-[(5-Chlorobenzo[*b*]furan-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine *N*-oxide (57a)

Starting with **39a** (193 mg, 0.40 mmol) and following the procedure for the preparation of **7** gave **57a** (yield, 76%) as a colorless powder.

Mp 192–194 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.20–3.50 (4H, br), 3.50–4.05 (4H, br), 7.34 (1H, s), 7.45–7.53 (6H, m), 7.62 (2H, d, J = 7.8 Hz), 7.69 (1H, s), 8.27 (2H, d, J = 7.8 Hz). Anal. Calcd for $C_{24}H_{20}ClN_3O_5S{\cdot}0.25H_2O$: C, 57.37; H, 4.11; Cl, 7.06; N, 8.36; S, 6.38. Found: C, 57.31; H, 4.30; Cl, 7.17; N, 8.22; S, 6.40. MS (FAB) m/z 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 1624, 1442, 1363, 1358, 1281, 1259, 1246, 1159, 1120, 1078, 955, 804.

6.63. 4-[4-[4-[(6-Chlorobenzo[*b*]furan-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine *N*-oxide (57b)

Starting with **39b** (110 mg, 0.23 mmol) and following the procedure for the preparation of **7** gave **57b** (yield, 99%) as a colorless powder.

Mp 249–252 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.20–3.50 (4H, br), 3.50–4.10 (4H, br), 7.35–7.41 (2H, br), 7.46–7.55 (4H, br), 7.58–7.67 (4H, m), 8.27 (2H, d, J = 5.9 Hz). MS (FAB) m/z 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{24}H_{21}ClN_3O_5S$: 498.0890. Found 498.0901. IR (KBr) cm^{-1} 1633, 1462, 1431, 1284, 1259, 1165, 1111, 1055, 1009, 943, 931, 833.

6.64. 4-[4-[[4-[(5-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (58a)

Starting with **40a** (82.0 mg, 0.16 mmol) and following the procedure for the preparation of **7** gave **58a** (yield, 60%) as a colorless powder.

Mp 260–262 °C (decomp.). ^1H NMR (400 MHz, $CDCl_3$): δ 3.40–4.00 (8H, m), 7.50 (2H, d, J = 7.3 Hz), 7.51 (2H, d, J = 8.3 Hz), 7.58 (1H, dd, J = 8.8, 2.0 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.93 (1H, d, J = 8.8 Hz), 8.19

(1H, d, $J = 2.0$ Hz), 8.27 (2H, d, $J = 7.3$ Hz). Anal. Calcd for $C_{23}H_{19}ClN_4O_4S_2 \cdot 0.1H_2O$: C, 53.45; H, 3.74; Cl, 6.86; N, 10.84; S, 12.41. Found: C, 53.19; H, 3.72; Cl, 7.09; N, 10.70; S, 12.19. MS (FAB) *m/z* 515 [$(M+H)^+$, Cl^{35}], 517 [$(M+H)^+$, Cl^{37}].

IR (ATR) cm^{-1} 1633, 1465, 1432, 1365, 1351, 1284, 1245, 1170, 1106, 1056, 1004, 937, 815.

6.65. 4-[4-[[4-[(6-Chlorobenzothiazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (58b)

Starting with **40b** (90.0 mg, 0.18 mmol) and following the procedure for the preparation of **7** gave **58b** (yield, 99%) as a colorless powder.

Mp 261–263 °C (decomp.). ^1H NMR (400 MHz, DMSO-d_6): δ 3.30–3.85 (8H, m), 7.50 (2H, d, $J = 8.3$ Hz), 7.77 (1H, dd, $J = 8.8$, 2.0 Hz), 7.80 (2H, d, $J = 7.3$ Hz), 7.83 (2H, d, $J = 8.3$ Hz), 8.28 (2H, d, $J = 7.3$ Hz), 8.29 (1H, d, $J = 8.8$ Hz), 8.50 (1H, d, $J = 2.0$ Hz). Anal. Calcd for $C_{23}H_{19}ClN_4O_4S_2$: C, 53.64; H, 3.72; Cl, 6.88; N, 10.88; S, 12.45. Found: C, 53.64; H, 3.99; Cl, 6.63; N, 10.90; S, 12.30. MS (FAB) *m/z* 515 [$(M+H)^+$, Cl^{35}], 517 [$(M+H)^+$, Cl^{37}]. IR (ATR) cm^{-1} 1635, 1463, 1427, 1363, 1351, 1286, 1241, 1170, 1110, 1054, 1002, 939, 904, 827, 806.

6.66. 4-[4-[[5(6)-Chlorobenzimidazol-2-yl]sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine *N*-oxide (59)

Starting with **41** (191 mg, 0.40 mmol) and following the procedure for the preparation of **7** gave **59** (yield, 71%) as a colorless powder.

Mp >265 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 3.30–3.85 (8H, br), 7.41 (1H, dd, $J = 8.8$, 2.0 Hz), 7.49 (2H, d, $J = 7.8$ Hz), 7.68–7.83 (2H, br), 7.80 (2H, d, $J = 6.8$ Hz), 7.83 (2H, d, $J = 7.8$ Hz), 8.27 (2H, d, $J = 6.8$ Hz). Anal. Calcd for $C_{23}H_{20}ClN_5O_4S \cdot 0.4H_2O$: C, 54.69; H, 4.15; Cl, 7.02; N, 13.86; S, 6.35. Found: C, 54.46; H, 4.04; Cl, 7.40; N, 13.88; S, 6.10. MS (FAB) *m/z* 498 [$(M+H)^+$, Cl^{35}], 500 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 1645, 1433, 1371, 1248, 1180, 966, 933.

6.67. 4-Amidinopyridine hydrochloride (61)

To a solution of 4-cyanopyridine (**60**) (10 g, 96 mmol) in MeOH (50 mL) was added NaOMe (5.4 g, 0.10 mol) under an argon atmosphere. After the reaction mixture was refluxed for 1.5 h, NH_4Cl (11 g, 0.20 mmol) was added. After the reaction mixture was again refluxed for 1 h and concentrated in vacuo. Crystallization of the residue from H_2O gave **61** (6.3 g, 42%) as colorless needle crystals.

Mp 104–106 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.82 (2H, d, $J = 5.9$ Hz), 8.87 (2H, d, $J = 5.9$ Hz), 9.68 (4H, broad s). MS (FAB) *m/z* 122 $(M+H)^+$. HRMS (FAB) Calcd for $C_6H_8N_3$: 122.0718. Found: 122.0714. IR (ATR) cm^{-1} 3374, 3081, 2944, 1695, 1641, 1548, 1519, 1471, 1409, 1066, 1004, 842.

6.68. Ethyl 2-(4-pyridyl)-5-pyrimidinecarboxylate (63)

To a solution of NaOEt (590 mg, 8.3 mmol) in EtOH (50 mL) was added 4-amidinopyridine hydrochloride (1.31 g, 8.3 mmol), and then a solution of (ethoxycarbonyl)malonedialdehyde (1.20 g, 8.3 mmol) in EtOH (50 mL) was added dropwise to the mixture. The reaction mixture was refluxed for 6 h, and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Crystallization of the residue from EtOH gave **63** (279 mg, 15%) as a colorless amorphous solid.

^1H NMR (400 MHz, DMSO-d_6): δ 1.46 (3H, t, $J = 7.3$ Hz), 4.48 (2H, q, $J = 7.3$ Hz), 8.35 (2H, d, $J = 5.9$ Hz), 8.82 (2H, d, $J = 5.9$ Hz), 9.38 (2H, s). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.80; H, 4.78; N, 18.25. MS (FAB) *m/z* 230 $(M+H)^+$. IR (KBr) cm^{-1} 3037, 2985, 1949, 1720, 1585, 1571, 1538, 1432, 1405, 1386, 1363, 1322, 1288, 1255, 1213, 1137, 1110, 1072, 1035, 1012.

6.69. 2-(4-Pyridyl)-5-pyrimidinecarboxylic acid (64)

Starting with **63** (0.40 g, 1.7 mmol) and following the procedure for the preparation of **29** gave **64** (yield, 93%) as a colorless amorphous powder.

^1H NMR (400 MHz, DMSO-d_6): δ 8.32 (2H, d, $J = 5.9$ Hz), 8.82 (2H, d, $J = 5.9$ Hz), 9.38 (2H, s). Anal. Calcd for $C_{10}H_7N_3O_2 \cdot 0.1H_2O$: C, 59.17; H, 3.58; N, 20.70. Found: C, 59.09; H, 3.49; N, 20.69. MS (EI) *m/z* 201 M^+. IR (KBr) cm^{-1} 3108, 3060, 1704, 1614, 1577, 1536, 1427, 1407, 1382, 1367, 1319, 1257, 1224, 1211, 1145, 1037, 1031, 892, 860, 825.

6.70. 1-[(5-Chloroindol-2-yl)sulfonyl]piperazine hydrochloride (66)

To a solution of (5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl chloride (**31a**) (4.41 g, 11 mmol) in CH_2Cl_2 was added 1-(*tert*-butoxycarbonyl)piperazine (**26**) (2.21 g, 12 mmol) and Et_3N (1.65 mL, 12 mmol) in an ice bath. The mixture was stirred for 3 h at room temperature and washed with water. The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (hexane/ethyl acetate = 20/1) gave 1-(*tert*-butoxycarbonyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (3.63 g, 6.7 mmol) as a colorless amorphous mass.

^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 3.35–3.42 (4H, br), 3.50–3.55 (4H, br), 7.40–7.48 (4H, m), 7.53–7.58 (2H, m), 8.00–8.25 (2H, m), 8.23 (1H, d, $J = 8.8$ Hz). No further purification was attempted on this compound, which was used directly in the next step.

To a solution of 1-(*tert*-butoxycarbonyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (3.63 g, 6.7 mmol) in MeOH was added 0.2 N NaOH–MeOH solution in an ice bath. The reaction mixture was stir-

red for 12.5 h at room temperature and neutralized with saturated aqueous NH_4Cl, and then CH_2Cl_2 and H_2O were added. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. To a solution of the residue was added saturated HCl–EtOH solution (30 mL). The reaction mixture was stirred for 0.5 h at room temperature and concentrated in vacuo to give **66** (1.25 g, 54%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.25–3.43 (8H, br), 7.46 (1H, d, J = 8.8 Hz), 7.64 (1H, d, J = 8.8), 7.93 (1H, s), 9.33 (1H, br), 12.7 (1H, br). Anal. Calcd for $C_{12}H_{14}ClN_3O_2S{\cdot}HCl{\cdot}0.5H_2O$: C, 41.75; H, 4.67; Cl, 20.54; N, 12.17; S, 9.29. Found: C, 41.78; H, 4.98; Cl, 20.40; N, 11.88; S, 9.34. MS (EI$^+$) m/z 298 (M^+, Cl^{35}), 300 (M^+, Cl^{37}). IR (KBr) cm^{-1} 3396, 3162, 2790, 2445, 1456, 1360, 1309, 1153, 955, 798, 723, 588.

6.71. 1-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]piperazine hydrochloride (67)

To a solution of **32b** (1.00 g, 3.7 mmol) in CH_2Cl_2 (100 mL) was added *tert*-butyl 1-piperazinecarboxylate (**26**) (697 mg, 3.7 mmol) and Et_3N (0.52 mL, 3.7 mmol) in an ice bath. The mixture was stirred for 3 h at room temperature and concentrated in vacuo. The residue was added to AcOEt and 1 N HCl. The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. To a solution of the residue was added saturated HCl–EtOH solution (10 mL). The reaction mixture was stirred for 0.5 h at room temperature, and concentrated in vacuo. Precipitation of the residue from AcOEt gave **67** (1.1 g, 87%) as a colorless powder.

Mp 244–247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.20–3.38 (8H, m), 7.59 (1H, dd, J = 8.8, 2.0 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.16(1H, s), 8.36 (1H, d, J = 8.8 Hz), 9.29 (2H, br s). Anal. Calcd for $C_{12}H_{13}ClN_2O_2S_2{\cdot}HCl$: C, 40.80; H, 3.99; Cl, 20.07; N, 7.93; S, 18.15. Found: C, 40.64; H, 4.04; Cl, 20.06; N, 7.90; S, 17.91. MS (FAB) m/z 317 [(M+H)$^+$, Cl^{35}], 319[(M+H)$^+$, Cl^{37}]. IR (KBr) cm^{-1} 2944, 2734, 2607, 2474, 1589, 1492, 1357, 1182, 1155, 1064, 952, 863, 730, 580.

6.72. 1-(5-Chloroindol-2-yl)sulfonyl-4-[4-(pyrid-2-yl)benzoyl]piperazine hydrochloride (68a)

To a mixture of **66** (716 mg, 2.1 mmol), **65** (423 mg, 2.1 mmol), 1-hydroxybenztriazole (288 mg, 2.1 mmol), and *N*-methylmorpholine (862 mg, 8.5 mmol) in DMF (100 mL) was added 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408 mg, 2.1 mmol). The reaction mixture was stirred for 22 h at room temperature and concentrated in vacuo. To the residue were added CH_2Cl_2 and H_2O. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% MeOH–CH_2Cl_2) and then the residue was added to 1 N HCl–EtOH solution. Concentration of the solution in vacuo gave **68a** (730 mg, 71%) as a colorless powder.

Mp 178–193 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.92–3.26 (4H, br), 3.35–3.78 (4H, br), 7.03 (1H, d, J = 2.0 Hz), 7.34 (1H, dd, J = 8.8, 2.4 Hz), 7.47–7.56 (4H, m), 7.80 (1H, d, J = 2.0 Hz), 8.02–8.16 (4H, m), 8.73 (1H, d, J = 4.9 Hz), 12.40 (1H, s). Anal. Calcd for $C_{24}H_{21}ClN_4O_3S{\cdot}0.9HCl{\cdot}1.6H_2O$: C, 53.13; H, 4.66; Cl, 12.41; N, 10.33; S, 5.91. Found: C, 53.29; H, 4.89; Cl, 12.40; N, 10.15; S, 5.92. MS (FAB) m/z 481 [(M+H)$^+$, Cl^{35}], 483 [(M+H)$^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{24}H_{22}ClN_4O_3S$: 481.1101. Found: 481.1119. IR (ATR) cm^{-1} 3097, 1608, 1432, 1351, 1280, 1265, 1153, 1108, 950, 935, 809.

6.73. 2-[4-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine *N*-oxide (69a)

Starting with **68a** (200 mg, 0.42 mmol) and following the procedure for the preparation of **7** gave **69a** (yield, 52%) as a colorless powder.

Mp 160–172 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.04–3.18 (4H, br), 3.37–3.83 (4H, br), 7.03 (1H, s), 7.33 (1H, d, J = 8.8 Hz), 7.38–7.44 (2H, m), 7.45 (2H, d, J = 7.3 Hz), 7.50 (1H, d, J = 8.8 Hz), 7.61–7.67 (1H, m), 7.80 (1H, s), 7.85 (2H, d, J = 7.3 Hz), 8.33 (1H, m), 12.40 (1H, br). Anal. Calcd for $C_{24}H_{21}ClN_4O_4S{\cdot}0.2H_2O$: C, 57.59; H, 4.31; Cl, 7.08; N, 11.19; S, 6.41. Found: C, 57.72; H, 4.58; Cl, 7.13; N, 10.86; S, 6.29. MS (FAB) m/z 497 [(M+H)$^+$, Cl^{35}], 499 [(M+H)$^+$, Cl^{37}]. IR (KBr) cm^{-1} 3090–2850, 1637, 1431, 1238, 1159, 953, 723.

6.74. 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine hydrochloride (68b)

Starting with **66** (336 mg, 1.0 mmol) and **64** (201 mg, 1.0 mmol) and following the procedure for the preparation of **68a** gave **68b** (yield, 30%) as a pale yellow powder.

Mp 179–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.08 (2H, br), 3.18 (2H, br), 3.52 (2H, br), 3.77 (2H, br), 7.04 (1H, d, J = 1.5 Hz), 7.34 (1H, dd, J = 2.0 and 8.8 Hz), 7.50 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 2.0 Hz), 8.48–8.53 (2H, m), 8.91–8.95 (2H, m), 9.07 (2H, s), 12.46 (1H, br s). Anal. Calcd for $C_{22}H_{19}ClN_6O_3S{\cdot}HCl{\cdot}1.3H_2O{\cdot}0.2EtOH$: C, 48.74; H, 4.35; Cl, 12.84; N, 15.22; S, 5.81. Found: C, 48.87; H, 4.38; Cl, 12.82; N, 15.02; S, 5.86. MS (FAB) m/z 483 [(M+H)$^+$, Cl^{35}], 485 [(M+H)$^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{22}H_{20}ClN_6O_3S$: 483.1006. Found: 483.1005. IR (ATR) cm^{-1} 3075, 1631, 1419, 1349, 1282, 1153, 1112, 950, 933, 879, 809.

6.75. 4-[5-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine *N*-oxide (69b)

Starting with **68b** (100 mg, 1.1 mmol) and following the procedure for the preparation of **69a** gave **69b** (yield, 22%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.09 (2H, br), 3.16 (2H, br), 3.53 (2H, br), 3.75 (2H, br), 7.03 (1H, s), 7.32 (1H, dd, J = 8.8, 2.0 Hz), 7.50 (1H, d, J = 8.8 Hz), 7.79 (1H, d, J = 2.0 Hz), 8.27 (2H, d, J = 7.3 Hz), 8.34 (2H, d, J = 7.3 Hz), 8.95 (2H, s), 12.42 (1H, br s). Anal. Calcd for $C_{22}H_{19}ClN_6O_4S{\cdot}H_2O$: C, 51.11; H, 4.09; Cl, 6.86; N, 16.26; S, 6.20. Found: C, 51.29; H, 4.34; Cl, 6.80; N, 15.90; S, 6.08. MS (FAB) m/z 499 [$(M+H)^+$, Cl^{35}], 501 [$(M+H)^+$, Cl^{37}]. IR (ATR) cm^{-1} 3112, 1619, 1577, 1415, 1355, 1245, 1155, 1112, 1097, 952, 879, 802.

6.76. 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (70)

To a mixture of **66** (436 mg, 1.3 mmol), 5-bromo-2-pyrimidinecarboxylic acid (263 mg, 1.3 mmol), 1-hydroxybenztriazole (176 mg, 1.3 mmol), and *N*-methylmorpholine (0.286 mL, 2.6 mmol) in CH_2Cl_2 (10 mL) was added 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (374 mg, 2.0 mmol). The reaction mixture was stirred for 1 h at room temperature and concentrated in vacuo. The residue was added to AcOEt and H_2O. The separated organic layer was dried over $MgSO_4$ and concentrated in vacuo. Precipitation of the residue from petroleum ether gave **70** (565 mg, 90%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.14–3.17 (2H, m), 3.25–3.29 (2H, m), 3.52–3.55 (2H, m), 3.92–3.95 (2H, m), 7.97 (1H, s), 7.32–7.40 (2H, m), 7.69 (1H, s), 8.79 (1H, br s), 8.84 (2H, s). Anal. Calcd for $C_{17}H_{15}BrClN_5O_3S$: C, 42.12; H, 3.12; N, 14.45; S, 6.61. Found: C, 42.40; H, 3.27; N, 13.98; S, 6.29. MS (FAB) m/z 484 [$(M+H)^+$, Cl^{35} and Br^{79}], 486 [$(M+H)^+$, Cl^{35} and Br^{81}, Cl^{37} and Br^{79}], 488 [$(M+H)^+$, Cl^{37} and Br^{81}]. HRMS (FAB) Calcd for $C_{17}H_{16}Br^{81}Cl^{37}N_5O_3S$: 487.9801. Found: 487.9784. IR (ATR) cm^{-1} 3226, 3156, 3029, 1735, 1635, 1533, 1509, 1481, 1438, 1407, 1359, 1351, 1315, 1276, 1195, 1157, 1116, 1108, 1054, 1010, 954, 937, 802.

6.77. 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(6-chlorobenzothiophen-2-yl) sulfonyl]piperazine (71)

Starting with 5-bromo-2-pyrimidinecarboxylic acid (470 mg, 2.3 mmol) and **67** (818 mg, 2.3 mmol) and following the procedure for the preparation of **70** gave **71** (yield, 89%) as a colorless amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19–3.23 (2H, m), 3.29–3.33 (2H, m), 3.53–3.56 (2H, m), 3.93–3.97 (2H, m), 7.46 (1H, dd, J = 8.8 and 1.5 Hz), 7.77 (1H, s), 7.83 (1H, d, J = 8.8 Hz), 7.88 (1H, d, J = 1.5 Hz), 8.84 (2H, s). Anal. Calcd for $C_{17}H_{14}BrClN_4O_3S_2$: C, 40.69; H, 2.81; N, 11.17; S, 12.78. Found: C, 40.90; H, 2.87; N, 10.92; S, 12.87. MS (FAB) m/z 501 [$(M+H)^+$, Cl^{35} and Br^{79}], 503 [$(M+H)^+$, Cl^{35} and Br^{81}, Cl^{37} and Br^{79}], 505 [$(M+H)^+$, Cl^{37} and Br^{81}]. IR (ATR) cm^{-1} 2854, 1641, 1542, 1492, 1450, 1415, 1357, 1278, 1195, 1155, 1133, 1118, 1103, 1058, 1012, 995, 939, 867, 811.

6.78. 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride (72a)

To a solution of **70** (485 mg, 1.0 mmol) and (4-pyridyl)boronic acid (197 mg, 1.6 mmol) in 1,2-dimethoxyethane (10 mL)-methanol (10 mL) was added cesium fluoride (1.00 g, 6.6 mmol) and tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.10 mmol) at room temperature. The mixture was refluxed for 1 h and then concentrated in vacuo. The residue was added to CH_2Cl_2 and H_2O. The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% MeOH–CH_2Cl_2) and then to a solution of the residue in CH_2Cl_2 was added 1 N HCl–EtOH. The precipitate was collected to give **72a** (216 mg, 40%) as a colorless powder.

Mp 203–204 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.96 (2H, br s), 3.16 (2H, br s), 3.38 (2H, br s), 3.81 (2H, br s), 7.05 (1H, d, J = 2.0 Hz), 7.35 (1H, dd, J = 8.8, 2.0 Hz), 7.51 (1H, d, J = 8.8 Hz), 7.81 (1H, d, J = 1.5 Hz), 8.13 (2H, d, J = 5.9 Hz), 8.87 (2H, d, J = 5.9 Hz), 9.37 (2H, s), 12.48 (1H, s). Anal. Calcd for $C_{22}H_{19}ClN_6O_3S{\cdot}0.9HCl{\cdot}1.4H_2O$: C, 48.84; H, 4.23; Cl, 12.45; N, 15.53; S, 5.93. Found: C, 49.11; H, 4.27; Cl, 12.26; N, 15.34; S, 5.91. MS (FAB) m/z 483 [$(M+H)^+$, Cl^{35}], 485 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{22}H_{20}ClN_6O_3S$: 483.1006. Found: 483.0997. IR (ATR) cm^{-1} 3000, 2925, 2867, 2696, 1643, 1606, 1417, 1344, 1186, 1149, 1112, 1004, 956, 912, 858.

6.79. 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine (72b)

Starting with **70** (500 mg, 1.0 mmol) and (2-pyridyl)boronic acid (229 mg, 1.1 mmol) and following the procedure for the preparation of **72a** gave **72b** (yield, 51%) as a colorless powder. But this compound was purified only by silica gel column chromatography without being transformed into the HCl salt.

Mp 248–251 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90–2.98 (2H, m), 3.10–3.15 (2H, m), 3.30–3.41 (2H, m), 3.75–3.85 (2H, m), 7.05 (1H, d, J = 2.0 Hz), 7.35 (1H, dd, J = 8.8, 2.0 Hz), 7.47–7.53 (2H, m), 7.80 (1H, d, J = 2.0 Hz), 8.00 (1H, dt, J = 8.3 and 2.0 Hz), 8.17 (1H, d, J = 8.3 Hz), 8.76 (1H, d, J = 4.4 Hz), 9.47 (2H, s), 12.47 (1H, s). Anal. Calcd for $C_{22}H_{19}ClN_6O_3S{\cdot}0.9H_2O$: C, 52.94; H, 4.20; N, 16.84; S, 6.42. Found: C, 53.29; H, 3.98; N, 16.52; S, 6.41. MS (FAB) m/z 483 [$(M+H)^+$, Cl^{35}], 485 [$(M+H)^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{22}H_{20}ClN_6O_3S$: 483.1006. Found: 483.0994. IR (ATR) cm^{-1} 3272, 2933, 2867, 1635, 1500, 1411, 1342, 1193, 1145, 1118, 1097, 954, 802.

6.80. 1-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride (74a)

Starting with **71** (500 mg, 1.0 mmol) and (4-pyridyl)-boronic acid (197 mg, 1.6 mmol) and following the procedure for the preparation of **72a** gave **74a** (yield, 49%) as a yellow powder.

Mp 243–245 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03–3.06 (2H, m), 3.20–3.23 (2H, m), 3.41–3.44 (2H, m), 3.83–3.86 (2H, m), 7.61 (1H, dd, J = 8.8, 2.0 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.13 (1H, s), 8.30–8.40 (3H, m), 8.90–9.02 (2H, br), 9.40–9.46 (2H, m). Anal. Calcd for $C_{22}H_{18}ClN_5O_3S{\cdot}HCl{\cdot}0.7H_2O$: C, 48.13; H, 3.74; Cl, 12.91; N, 12.75; S, 11.68. Found: C, 47.95; H, 3.78; Cl, 13.13; N, 12.65; S, 11.53. MS (FAB) m/z 500 [(M+H)$^+$, Cl^{35}], 502 [(M+H)$^+$, Cl^{37}]. IR (ATR) cm^{-1} 3448, 1637, 1589, 1481, 1419, 1348, 1330, 1191, 1143, 1122, 1054, 998, 946, 852, 829, 802.

6.81. 1-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine hydrochloride (74b)

Starting with **71** (400 mg, 0.80 mmol) and (2-pyridyl)boronic acid (109 mg, 0.88 mmol) and following the procedure for the preparation of **72a** gave **74b** (yield, 82%) as a yellow powder.

Mp 228–231 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.01–3.10 (2H, m), 3.17–3.26 (2H, m), 3.39–3.47 (2H, m), 3.79–3.87 (2H, m), 7.52 (1H, dd, J = 7.3 and 4.9 Hz), 7.61 (1H, d, J = 8.8 Hz), 8.01 (1H, dt, J = 1.5 and 7.3 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.12 (1H, s), 8.18 (1H, d, J = 7.3 Hz), 8.35 (1H, s), 8.76 (1H, d, J = 4.9 Hz), 9.48 (2H, s). Anal. Calcd for $C_{22}H_{18}ClN_5O_3S_2{\cdot}HCl{\cdot}0.5H_2O$: C, 48.44; H, 3.70; Cl, 13.00; N, 12.84; S, 11.76. Found: C, 48.53; H, 3.56; Cl, 13.04; N, 12.72; S, 11.85. MS (FAB) m/z 500 [(M+H)$^+$, Cl^{35}], 502 [(M+H)$^+$, Cl^{37}]. IR (ATR) cm^{-1} 3054, 1652, 1621, 1494, 1427, 1353, 1276, 1147, 1120, 1099, 1052, 998, 946, 890, 852, 800.

6.82. 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine *N*-oxide (73a)

Starting with **72a** (536 mg, 1.1 mmol) and following the procedure for the preparation of **7** gave **73a** (yield, 50%) as a pale yellow amorphous powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95 (2H, br), 3.15 (2H, br), 3.37 (2H, br), 3.79 (2H, br), 7.05 (1H, s), 7.34 (1H, dd, J = 8.8 and 1.5 Hz), 7.51 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 1.5 Hz), 7.95 (2H, d, J = 7.3 Hz), 8.37 (2H, d, J = 7.3 Hz), 9.28 (2H, s), 12.47 (1H, s). Anal. Calcd for $C_{22}H_{19}ClN_6O_4S{\cdot}0.5H_2O{\cdot}0.2EtOH$: C, 52.02; H, 4.13; Cl, 6.86; N, 16.25; S, 6.20. Found: C, 52.03; H, 3.99; Cl, 7.18; N, 15.99; S, 6.16. MS (FAB) m/z 499 [(M+H)$^+$, Cl^{35}], 501 [(M+H)$^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{22}H_{20}ClN_6O_4S$: 499.0955. Found: 499.0970. IR (ATR) cm^{-1} 3108, 2921, 2859, 1643, 1498, 1417, 1351, 1307, 1243, 1193, 1182, 1155, 1114, 1054, 950, 890, 846, 809.

6.83. 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine *N*-oxide (73b)

Starting with **72b** (154 mg, 0.32 mmol) and following the procedure for the preparation of **7** gave **73b** (yield, 20%) as a pale yellow powder.

Mp 155–160 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10–3.20 (2H, m), 3.20–3.30 (2H, m), 3.50–3.60 (2H, m), 3.85–3.95 (2H, m), 6.97 (1H, s), 7.30–7.52 (5H, m), 7.68 (1H, s), 8.39 (1H, d, J = 5.9 Hz), 9.28 (2H, s), 9.50 (1H, s). MS (FAB) m/z 499 [(M+H)$^+$, Cl^{35}], 501 [(M+H)$^+$, Cl^{37}]. HRMS (FAB) Calcd for $C_{22}H_{20}ClN_6O_4S$: 499.0955. Found: 499.0943. IR (ATR) cm^{-1} 3118, 2923, 2859, 1643, 1500, 1432, 1415, 1353, 1309, 1276, 1230, 1195, 1155, 1112, 1054, 1014, 950, 890, 844, 809.

6.84. 4-[2-[[4-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine *N*-oxide (75a)

Starting with **74a** (140 mg, 0.28 mmol) and following the procedure for the preparation of **7** gave **75a** (yield, 56%) as a colorless powder.

Mp 233–236 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.24 (2H, br), 3.34 (2H, br), 3.60 (2H, br), 3.98 (2H, br), 7.47 (1H, dd, J = 8.8, 2.0 Hz), 7.52 (2H, d, J = 7.3 Hz), 7.79 (1H, s), 7.83 (1H, d, J = 8.8 Hz), 7.88 (1H, br s), 8.33 (2H, d, J = 7.3 Hz), 9.00 (2H, s). Anal. Calcd for $C_{22}H_{18}ClN_5O_4S{\cdot}0.4H_2O$: C, 50.50; H, 3.62; Cl, 6.78; N, 13.39; S, 12.26. Found: C, 50.24; H, 3.62; Cl, 7.14; N, 13.19; S, 12.04. MS (FAB) m/z 516 [(M+H)$^+$, Cl^{35}], 518 [(M+H)$^+$, Cl^{37}]. IR (ATR) cm^{-1} 3018, 1637, 1496, 1484, 1442, 1417, 1351, 1247, 1193, 1155, 1112, 1056, 1043, 1029, 991, 937, 862, 848.

6.85. 2-[2-[[4-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine *N*-oxide (75b)

Starting with **74b** (164 mg, 0.33 mmol) and following the procedure for the preparation of **7** gave **75b** (yield, 21%) as a pale yellow powder.

Mp 271–273 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.24 (2H, t, J = 4.9 Hz), 3.33 (2H, t, J = 4.9 Hz), 3.63 (2H, t, J = 4.9 Hz), 3.99 (2H, t, J = 4.9 Hz), 7.36–7.53 (4H, m), 7.78 (1H, s), 7.84 (1H, d, J = 8.3 Hz), 7.88 (1H, br s), 8.36–8.39 (1H, m), 9.29 (2H, s). Anal. Calcd for $C_{22}H_{18}ClN_5O_4S_2$: C, 51.21; H, 3.52; Cl, 6.87; N, 13.57; S, 12.43. Found: C, 50.91; H, 3.44; Cl, 6.95; N, 13.36; S, 12.27. MS (FAB) m/z 516 [(M+H)$^+$, Cl^{35}], 518 [(M+H)$^+$, Cl^{37}]. IR (ATR) cm^{-1} 3054, 3029, 1639, 1490, 1432, 1417, 1346, 1322, 1238, 1187, 1147, 1116, 995, 956, 941, 854, 823, 800.

6.86. 1,4-Dibenzyl-2-(2-methyl-2-propenyl)piperazine (78)

To a solution of 1,4-dibenzyl-2-ethoxycarbonylpiperazine (**76**) (19.6 g, 58 mmol) in CH_2Cl_2 (400 mL) was added diisobutylaluminum hydride (0.95 M in hexane) (122 mL) at −78 °C. The reaction mixture was stirred for 2.5 h, added to saturated aqueous NH_4Cl (150 mL) at −78 °C, and then warmed up to room temperature. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. No fur-

ther purification was attempted on this residue, which was used directly in the next step. To a solution of isopropyltriphenylphosphonium iodide (25.0 g, 58 mmol) inTHF (300 mL) was added *n*-butyllithium (1.53 M in hexane) (37.8 mL) at −78 °C. The reaction mixture was stirred for 0.5 h at −78 °C, added to a solution of the residue in THF (50 mL) at −78 °C, and stirred over night at a temperature from −78 °C to room temperature. The reaction mixture was added to saturated aqueous NH_4Cl and AcOEt. The separated aqueous layer was extracted with AcOEt. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/AcOEt = 20/1) gave **78** (6.0 g, 32%) as pale yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (3H, s), 0.91 (3H, s), 2.00 (1H, t, J = 10.7 Hz), 2.04–2.21 (2H, m), 2.64–2.72 (3H, m), 3.00–3.18 (2H, m), 3.40–3.55 (2H, m), 4.06 (1H, d, J = 13.7 Hz), 5.13 (1H, d, J = 8.8 Hz), 7.16–7.45 (10H, m). MS (FAB) m/z 321 $(M+H)^+$. HRMS (FAB) Calcd for $C_{22}H_{29}N_2$: 321.2331. Found: 321.2326. IR (ATR) cm^{-1} 3500, 3100–2700, 1737, 1603, 1495, 1452, 1375, 1300, 1155, 1122, 1024, 735.

6.87. 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine (79)

To a solution of **78** (5.20 g, 16 mmol) in EtOH (300 mL) was added palladium hydroxide (683 mg, 4.9 mmol) and concd HCl aq (3.0 mL). The reaction mixture was stirred for 2 h at room temperature under hydrogen atmosphere. After filtration of the catalyst, followed by evaporation of the filtrate, precipitation of the residue from CH_2Cl_2–hexane gave 2-(2-methylpropyl)piperazine dihydrochloride (2.95 g, 85%) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86–1.30 (1H, m), 1.73 (3H, s), 1.76 (3H, s), 3.10–3.47 (7H, m), 4.36–4.45 (1H, m), 5.18 (1H, d, J = 9.3 Hz). MS (EI) m/z 143 M^+. IR (KBr) cm^{-1} 3500, 3200-2350, 1759, 1680, 1570, 1446, 1321, 1078, 984, 930, 609, 525.

To a solution of 2-(2-methylpropyl)piperazine dihydrochloride (1.50 g, 7.0 mmol) in CH_2Cl_2 (150 mL) was added **31a** (2.72 g, 7.0 mmol) and Et_3N (2.91 mL, 20.91 mmol), The reaction mixture was stirred for 13 h at room temperature and then added to H_2O. The separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH_2Cl_2/MeOH = 20/1) gave **79** (2.69 g, 78%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (1H, t, J = 5.9 Hz), 1.50–1.52 (1H, m), 1.66–1.69 (7H, m), 2.70–2.79 (1H, m), 2.90–3.12 (3H, m), 3.55–3.83 (3H, m), 5.02 (1H, d, J = 8.3 Hz), 7.35–7.48 (4H, m), 7.51–7.58 (2H, m), 8.02 (2H, d, J = 8.3 Hz), 8.22 (1H, d, J = 8.8 Hz). MS (FAB) m/z 496 [$(M+H)^+$, Cl^{35}], 498 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3600–3300, 3150–2750, 1516, 1448, 1389, 1352, 1186, 833, 613, 567. No further purification was attempted on this compound, which was used directly in the next step.

6.88. 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-methylpropyl)-1-[(5-(4-pyridyl)pyrimidin-2-yl)carbonyl]piperazine hydrochloride (80)

Starting with **79** (2.57 g, 5.2 mmol) and following the procedure for the preparation of **54a** gave 1-[(5-chloroindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine (929 mg, 2.6 mmol, 50%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78–1.30 (2H, m), 1.69 (3H, s), 1.70 (3H, s), 1.63–1.80 (1H, m), 2.39–2.55 (1H, m), 2.90–3.07 (2H, m), 3.48–3.70 (3H, m), 4.90 (1H, d, J = 8.3 Hz), 6.92–6.99 (1H, m), 7.31 (1H, dd, J = 8.8, 2.0 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.65–7.69 (1H, m), 8.72 (1H, br). MS (FAB) m/z 356 [$(M+H)^+$, Cl^{35}], 358 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3450–3200, 3100–2750, 1506, 1439, 1350, 1309, 1159, 962, 802, 752, 580.

Starting with 1-[(5-chloroindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine (909 mg, 2.6 mmol) and (5-bromopyrimidin-2-yl)carboxylic acid (623 mg, 3.1 mmol), and following the procedure for the preparation of **70** gave 1-[(5-bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-methylpropyl)piperazine (465 mg, 0.86 mmol, 34%) as a brown amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70–1.28 (2H, m), 1.52–1.54 (1H, m), 1.60–1.75 (1H, m), 1.79 (3H, s), 1.82 (3H, s), 2.53–2.90 (2H, m), 3.34–3.48 (0.5H, m), 3.53–3.62 (0.5H, m), 3.68–3.79 (1H, m), 3.83–3.97 (0.5H, m), 4.54–4.66 (0.5H, m), 5.64 (1H, br), 6.95 (1H, br), 7.34 (1H, dd, J = 8.8, 2.0 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.69 (1H, s), 8.73 (1H, s), 8.82 (2H, br). Anal. Calcd for $C_{21}H_{23}BrClN_5O_3S$: C, 46.63; H, 4.29; N, 12.95; S, 5.93. Found: C, 46.88; H, 4.06; N, 12.77; S, 6.03. MS (FAB) m/z 538 [M^+, (Cl^{35}, Br^{79})], 540 [M^+, (Cl^{37}, Br^{79}), (Cl^{35}, Br^{81})], 542 [M^+, (Cl^{37}, Br^{81})]. IR (KBr) cm^{-1} 3450–2800, 1637, 1446, 1406, 1358, 1161, 953, 814, 702, 627, 579.

Starting with1-[(5-bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-methylpropyl)piperazine (444 mg, 0.822 mmol) and 4-pyridylboronic acid (181 mg, 1.5 mmol), and following the procedure for the preparation of **72** gave **80** (393 mg, 81%) as a yellow powder.

Mp 174–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84–1.62 (2H, m), 1.75 (3H, s), 1.77 (3H, s), 2.26–2.41 (1H, m), 2.55–2.70 (1H, m), 3.18–3.50 (2H, m), 3.55–3.68 (1H, m), 3.70–4.45 (2H, m), 5.36–5.58 (1H, m), 7.04 (1H, s), 7.34 (1H, d, J = 8.8 Hz), 7.51 (1H, d, J = 8.8 Hz), 7.80 (1H, s), 8.16 (2H, br), 8.90 (2H, br), 9.37 (2H, s), 12.48 (1H, br). Anal. Calcd for $C_{26}H_{27}ClN_6O_3S{\cdot}HCl{\cdot}H_2O$: C, 52.61; H, 5.09; N, 14.16; S, 5.40. Found: C, 52.82; H, 4.97; N, 14.05; S, 5.75. MS (FAB) m/z 539 [$(M+H)^+$, Cl^{35}], 541 [$(M+H)^+$, Cl^{37}]. IR (KBr) cm^{-1} 3500–2750, 1635, 1583, 1500, 1417, 1356, 1157, 953, 810, 710, 633, 576.

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