Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 12 (2004) 2251–2273

$C_{17,20}$-Lyase inhibitors I. Structure-based de novo design and SAR study of $C_{17,20}$-lyase inhibitors

Nobuyuki Matsunaga,[a,*] Tomohiro Kaku,[a] Fumio Itoh,[a] Toshimasa Tanaka,[a] Takahito Hara,[b] Hiroshi Miki,[c] Masahiko Iwasaki,[d] Tetsuya Aono,[a] Masuo Yamaoka,[b] Masami Kusaka[b] and Akihiro Tasaka[a]

[a]*Medicinal Chemistry Research Laboratories, Pharmaceutical Research Division: Takeda Chemical Industries, Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*
[b]*Pharmacology Research Laboratories I, Pharmaceutical Research Division: Takeda Chemical Industries, Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*
[c]*Pharmaceutical Discovery Center, Pharmaceutical Research Division: Takeda Chemical Industries, Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*
[d]*Drug Analysis and Pharmacokinetics Research Laboratories, Pharmaceutical Research Division: Takeda Chemical Industries, Ltd, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan*

Received 6 January 2004; revised 6 February 2004; accepted 8 February 2004

Abstract—Novel nonsteroidal $C_{17,20}$-lyase inhibitors were synthesized using de novo design based on its substrate, 17α-hydroxypregnenolone, and several compounds exhibited potent $C_{17,20}$-lyase inhibition. However, in vivo activities were found to be short-lasting, and in order to improve the duration of action, a series of benzothiophene derivatives were evaluated. As a result, compounds **9h**, (*S*)-**9i**, and **9k** with nanomolar enzyme inhibition ($IC_{50} = 4$–9 nM) and **9e** ($IC_{50} = 27$ nM) were identified to have powerful in vivo efficacy with extended duration of action. The key structural determinants for the in vivo efficacy were demonstrated to be the 5-fluoro group on the benzothiophene ring and the 4-imidazolyl moiety. Superimposition of **9k** and 17α-hydroxypregnenolone demonstrated their structural similarity and enabled rationalization of the pharmacological results. In addition, selected compounds were also identified to be potent inhibitors of human enzyme with IC_{50} values of 20–30 nM.

1. Introduction

Prostate cancer is now the most prevalent cancer in males in the U.S. and Europe. The prostate cancer in about 80% of these patients grows androgen dependently and responds to first-line endocrine therapy. At present, the standard treatment includes orchidectomy and its medical equivalent, the administration of gonadotropin-releasing hormone (GnRH) analogues, which abolish the production of testosterone in the testes. However, these treatments do not inhibit adrenal androgen production and therefore are frequently combined with an androgen receptor antagonist to block the action of residual adrenal androgens.[1,2] This combination strategy is recognized as combined androgen blockade (CAB), although to date none of the androgen antagonists achieve effective therapeutic results due to suboptimal pharmacokinetic properties or substantial efficacy-limiting adverse effects. Furthermore, androgen antagonists lead to the selection for androgen receptor mutations in prostate cancers, which recognize the antagonists as agonists.[3–6]

An alternative target would be $C_{17,20}$-lyase, which is one of the key enzymes responsible for the biosynthesis of androgens, and the mechanism of this reaction has been studied in some detail.[7–9] This enzyme catalyzes the conversion of 17α-hydroxypregnenolone and 17α-hydroxyprogesterone into the weak androgens, dehydroepiandrosterone and androstenedione, respectively, in testes and adrenal glands. These weak androgens are subsequently converted into more potent androgens such as testosterone and dihydrotestosterone in prostate cancer cells. The inhibition of $C_{17,20}$-lyase could prevent initial androgen production and consequently prevent

Keywords: $C_{17,20}$-Lyase; Androgen; Testosterone; Benzo[*b*]thiophene.
* Corresponding author. Tel.: +81-06-6300-6706; fax: +81-06-6300-6306; e-mail: matsunaga_nobuyuki@takeda.co.jp

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.02.007

subsequent production of the more potent androgens. Therefore, the use of $C_{17,20}$-lyase inhibitors may offer a promising therapeutic approach either as a single agent or in combination with castration, for the treatment of androgen-dependent prostate cancer.[10,11]

Several categories of steroidal and nonsteroidal $C_{17,20}$-lyase inhibitors have been reported,[12–42] and of these compounds, only ketoconazole had been used clinically in the treatment of patients suffering advanced prostate cancer (Fig. 1).[12–14] However, ketoconazole was withdrawn from clinical use because of the significant adverse effects due to inhibition of other P450 enzymes at clinical doses.[15] In recent years, other nonsteroidal $C_{17,20}$-lyase inhibitors have entered clinical trials, including CB-7630 (British Technology Group),[16,17] GI-111924 (GlaxoSmithKline)[18] and YM-116 (Yamanouchi).[19]

At the beginning of this study, no lead compound was available therefore the initial target molecules (**1**–**6**) were designed as mimetics of the substrate, 17α-hydroxypregnenolone (Fig. 2). In the known $C_{17,20}$-lyase inhibitors, the critical structures for enzyme inhibition were thought to be the lone pair of the nitrogen atom in the imidazole or pyridine ring, which should be able to interact with the heme iron in $C_{17,20}$-lyase. Thus the imidazole ring was combined with a steroid mimetic ring system such as *trans*-stilbenes (**1**, **2**: A–D ring of the steroid), *cis*-stilbene (**3**: A–C ring), biphenyl (**4**: A–C ring), and naphthalene (**5**: B–C ring, **6**: A–B ring). Because **6** was found to be a lead compound exhibiting marked in vivo efficacy, as well as potent in vitro activity, derivatives containing variations of the fused ring system in the place of the naphthalene ring were synthesized. Among these, the benzothiophene derivative was identified as a new lead and a series of benzothiophene derivatives (**8** and **9**) were synthesized.

This paper describes the de novo design, synthesis, and pharmacological activities of these $C_{17,20}$-lyase inhibitors. The pharmacological activities include inhibitory activity of rat $C_{17,20}$-lyase and inhibitory effects on testosterone biosynthesis in male rats. Furthermore, selected compounds were evaluated for inhibitory activity of recombinant human $C_{17,20}$-lyase.

2. Chemistry

Synthesis of the *trans*-stilbene derivatives **1** and **2** is shown in Scheme 1. Diethyl benzylphosphonate (**10**) and 3-bromobenzaldehyde (**11**) were subjected to Horner–Emmons olefination to give the *trans*-stilbene **12**, which was reacted with imidazole in the presence of NaH and CuO to give **1**. Reaction of 3-bromobenzyl bromide (**13**) and imidazole gave the benzylimidazole **14**, which was followed by Heck reaction with styrene affording **2**.

Synthesis of the *cis*-stilbene derivative **3** is shown in Scheme 2. Sonogashira reaction of methyl 3-bromobenzoate (**15**) with phenylacetylene gave **16**, which was

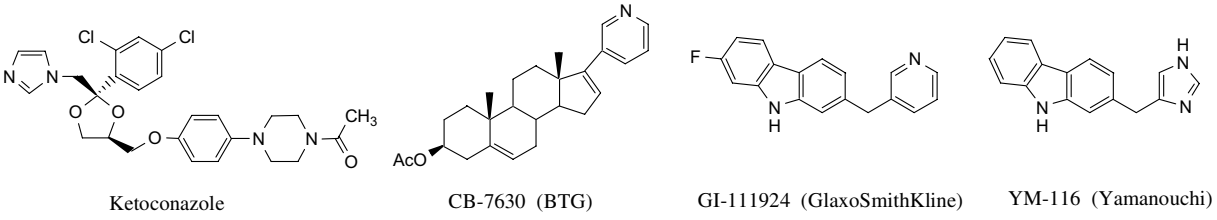


Figure 1. Structures of some known $C_{17,20}$-lyase inhibitors.

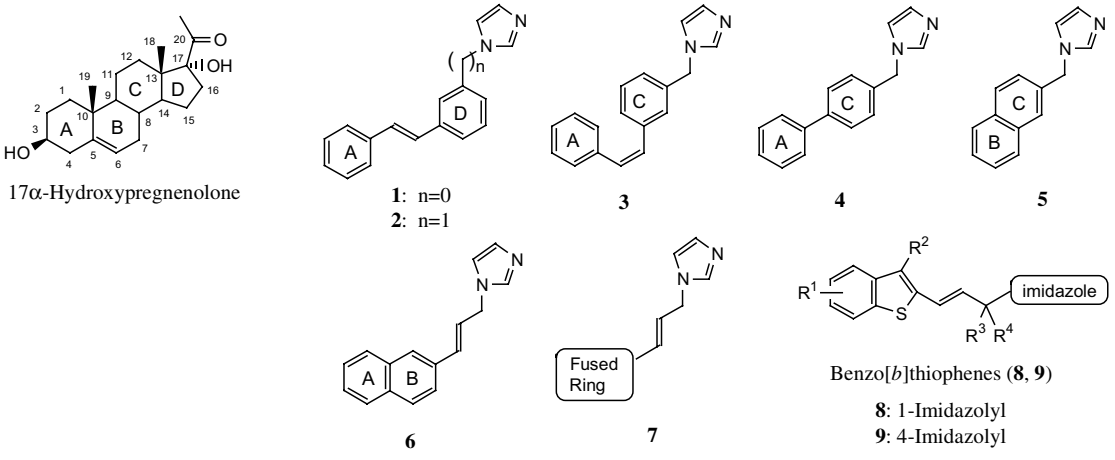
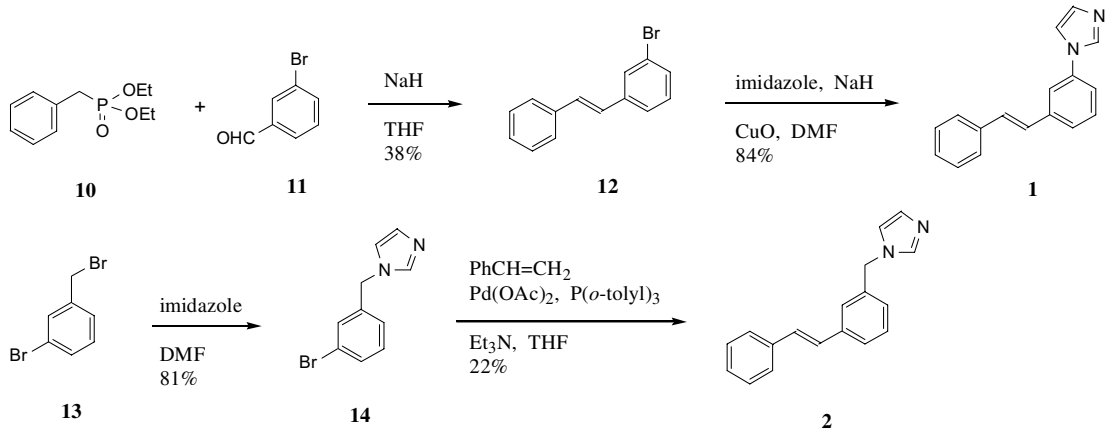
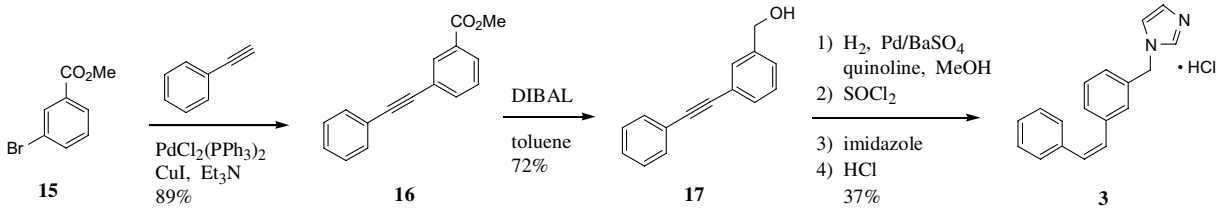


Figure 2. Design of target compounds for $C_{17,20}$-lyase inhibitors.



10 11 12 1 13 14 2

Scheme 1.



15 16 17 3

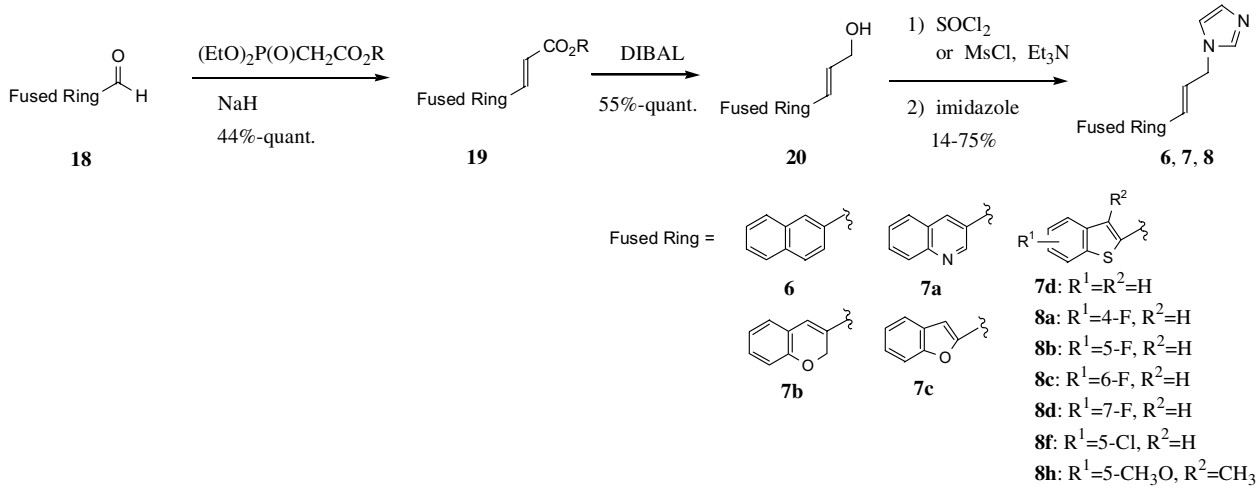
Scheme 2.

converted into the alcohol **17** with diisobutylaluminium hydride (DIBAL). Compound **17** was converted into **3** as follows: catalytic hydrogenation of the acetylene, chlorination of the hydroxyl group, nucleophilic substitution with imidazole, and then treatment with HCl.

The biphenyl derivative **4** and the naphthalene derivative **5** were prepared by chlorination of 4-biphenylmethanol or 2-naphthylmethanol, respectively, followed by treatment with imidazole (schemes not shown).

Scheme 3 shows the synthesis of the fused ring derivatives. Horner–Emmons olefination of aldehydes **18** with ethyl (or methyl) diethylphosphonoacetate afforded the corresponding (*E*)-olefins **19**. Reduction of the esters with DIBAL provided the alcohols **20**. Chlorination or methanesulfonylation of the hydroxyl group followed by displacement by imidazole gave **6**, **7a**–**d**, **8a**–**d**, **8f** and **8h**.

Preparation of benzothiophene intermediates were shown in Scheme 4. Benzothiophene skeletons were constructed by a known procedure[43] as follows. Starting thiophenols **21** were alkylated with α-chloroketones or bromoacetaldehyde diethylacetal in the presence of potassium carbonate, and the resulting products were

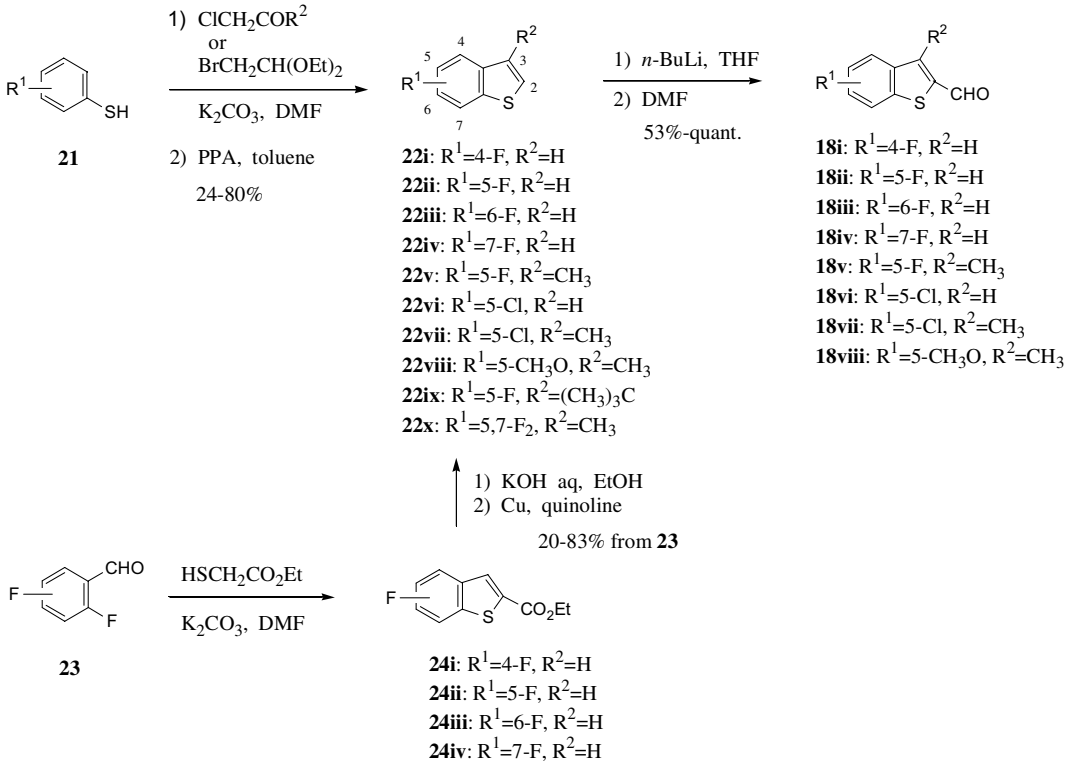


18 19 20 6, 7, 8

6 7a 7b 7c

7d: R^1=R^2=H
8a: R^1=4-F, R^2=H
8b: R^1=5-F, R^2=H
8c: R^1=6-F, R^2=H
8d: R^1=7-F, R^2=H
8f: R^1=5-Cl, R^2=H
8h: R^1=5-CH_3O, R^2=CH_3

Scheme 3.

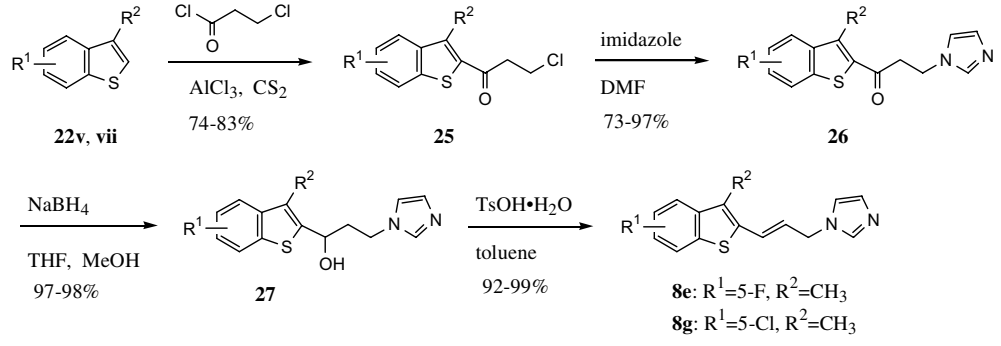


Scheme 4.

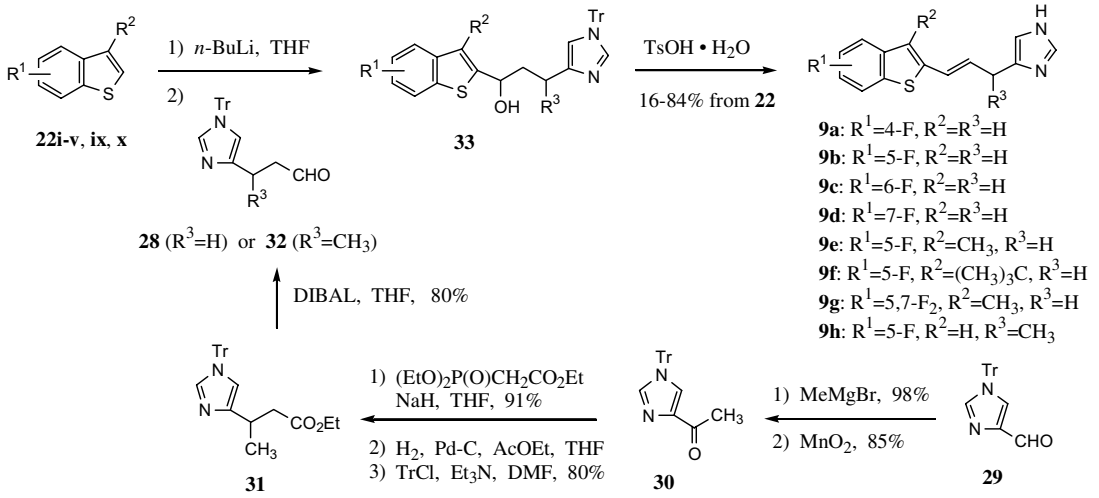
cyclized by heating with polyphosphoric acid (PPA) in toluene to give benzothiophenes **22v**–**x**. However, these procedures resulted in poor yields for the reaction of fluorothiophenols (**21**, $R^1 = F$) with bromoacetaldehyde diethylacetal, and thus preparation of fluorobenzothiophenes **22i**–**iv** ($R^1 = F$, $R^2 = H$) was achieved by the alternative procedures.[44,45] The reaction of difluorobenzaldehydes **23** and ethyl thioglycolate in the presence of potassium carbonate provided the benzothiophene esters **24i**–**iv**. Alkaline hydrolysis of the esters followed by decarboxylation of the resulting carboxyl group in the presence of Cu in quinoline provided **22i**–**iv**. Compounds **22i**–**viii** were converted to the corresponding aldehydes **18i**–**viii** by lithiation with *n*-BuLi followed by addition to DMF.

The benzothiophene derivatives bearing a 1-imidazolyl moiety were prepared as shown in Scheme 5. Friedel–Crafts acylation of benzothiophenes **22v**,**vii** with 3-chloropropionyl chloride afforded the 2-acylated compounds **25**, which were substituted with imidazole to provide the 1-imidazolyl compounds **26**. Reduction of the ketones with $NaBH_4$ gave alcohols **27**, and these compounds were dehydrated by heating with *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) in toluene to furnish **8e** and **8g**.

The benzothiophene derivatives bearing a 4-imidazolyl moiety were synthesized by two general strategies based on the same intermediates **22**. In the first approach (Scheme 6), benzothiophenes **22i**–**v**,**ix**,**x** were lithiated by *n*-BuLi and reacted with aldehydes **28** or **32** to afford compound **33**. Dehydration and detritylation of **33** were accomplished by heating with $TsOH{\cdot}H_2O$ to give **9a**–**h**. Compound **28**[46] was prepared from urocainic acid according to known procedures, and **32** was prepared

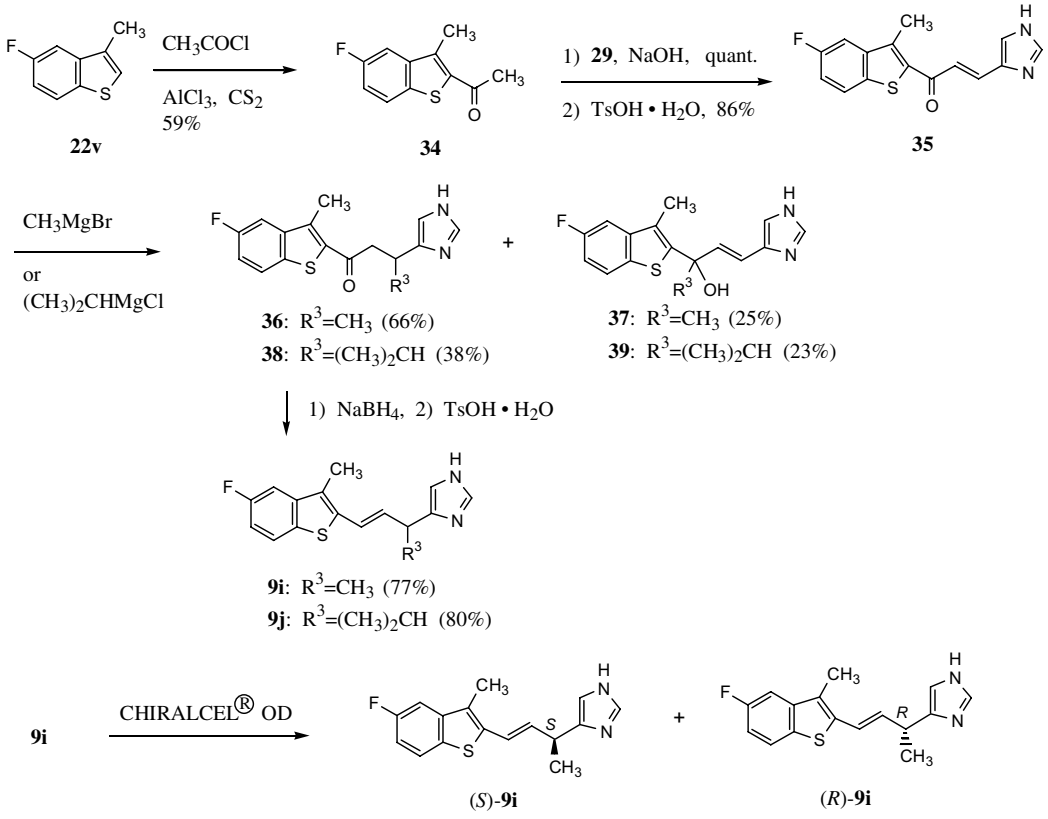


Scheme 5.



Scheme 6.

from 1-trityl-1*H*-imidazole-4-carboxaldehyde (**29**).[47] Grignard reaction of **29** with methylmagnesium bromide followed by oxidation with MnO_2 gave the acetylimidazole **30**. Subsequent Horner–Emmons olefination, catalytic hydrogenation, and re-protection of the partially detritylated imidazole afforded the branched compound **31**. Reduction of **31** with DIBAL then provided **32**. The second approach is shown in Scheme 7. Friedel–Crafts acylation of **22v** with acetyl chloride afforded the 2-acetylbenzothiophene **34**. Claisen–Schmidt reaction of **34** and **29** followed by removal of the trityl group using $TsOH{\cdot}H_2O$ yielded the α,β-unsaturated ketone **35**, which upon treatment with methylmagnesium bromide gave a mixture of isomers. These were separated by column chromatography on silica gel to provide the desired Michael adduct **36** and the 1,2-adduct **37**. A similar procedure employing isopropylmagnesium chloride provided **38** and **39**. Compounds **36** and **38** were converted to **9i** and **9j**, respectively, by $NaBH_4$ reduction followed by dehydration. Optical resolution of the racemic compound **9i** into enantiomers (*S*)-**9i** and (*R*)-**9i** was accomplished by HPLC using Chiralcel® OD.



Scheme 7.

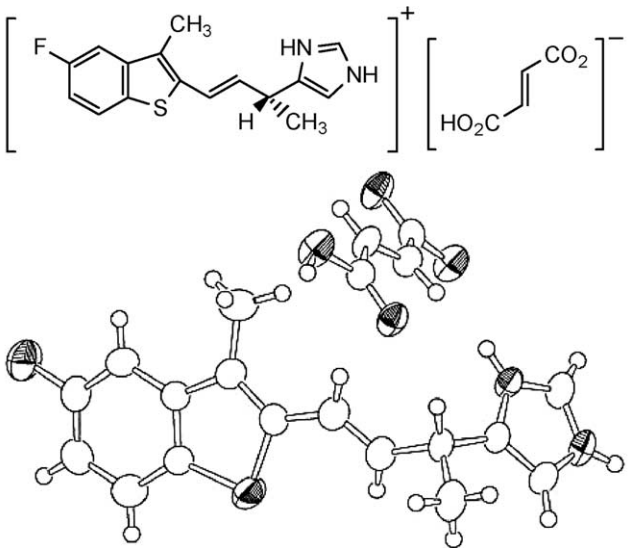


Figure 3. Crystal structure of (*R*)-**9i** as the fumarate.

The stereochemistry of (*S*)-**9i** and (*R*)-**9i** was determined by single-crystal X-ray analysis of (*R*)-**9i** as the fumarate (Fig. 3).

Scheme 8 shows the synthesis of the benzothiophene derivative possessing a *gem*-dimethyl group adjacent to the imidazole. Compound **24ii** was converted to the phosphonate **40** by the following procedures: reduction using $LiAlH_4$, chlorination of the resulting hydroxyl group with thionyl chloride, and phosphonylation with triethyl phosphite. Horner–Emmons olefination of **40** with **44** followed by detritylation with pyridinium chloride in methanol then furnished **9k**. Preparation of the imidazole intermediate **44** started with the reaction of the α-bromoketone **41**[48] and formamide to construct the imidazole **42**. Protection of the imidazole was accomplished by the treatment with chlorotriphenylmethane (TrCl) in the presence of triethylamine to afford the tritylated imidazole **43**, which was reduced by DIBAL to yield **44**.

3. Results and discussion

3.1. Enzyme inhibitory activity (in vitro study)

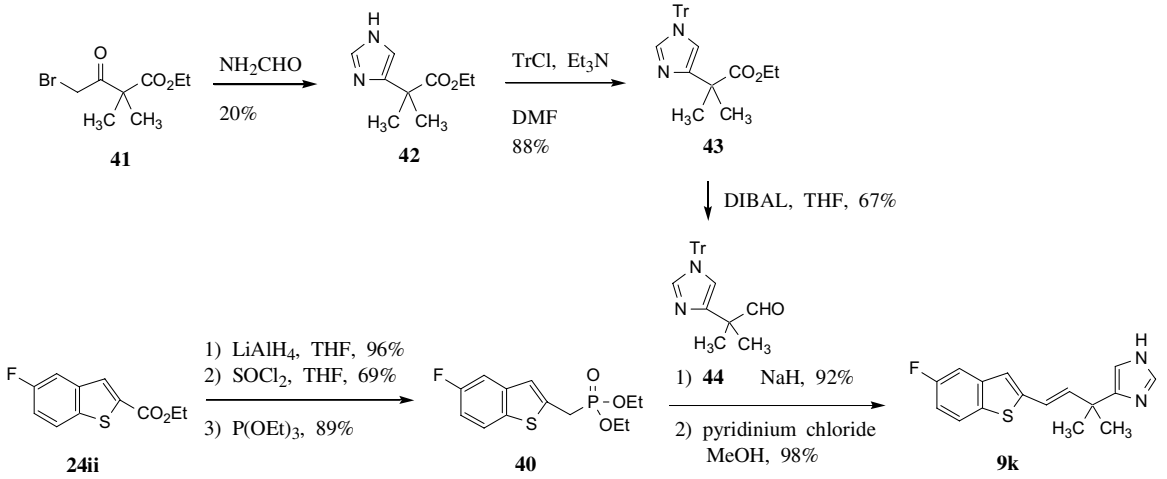
Test compounds were evaluated in vitro for the inhibition of rat microsomal $C_{17,20}$-lyase, which was prepared from rat testes. Inhibitory activity was measured using the radiometric assay described by Brodie and co-workers[27] with some modifications.

3.2. Inhibitory effects on testosterone biosynthesis in rats (in vivo study)

Test compounds were orally administrated to male rats ($n = 5$) at a dose of 25 mg/kg. After 2 and 5 h, the serum testosterone concentrations were measured by a specific radioimmunoassay and expressed as percent values of the control.

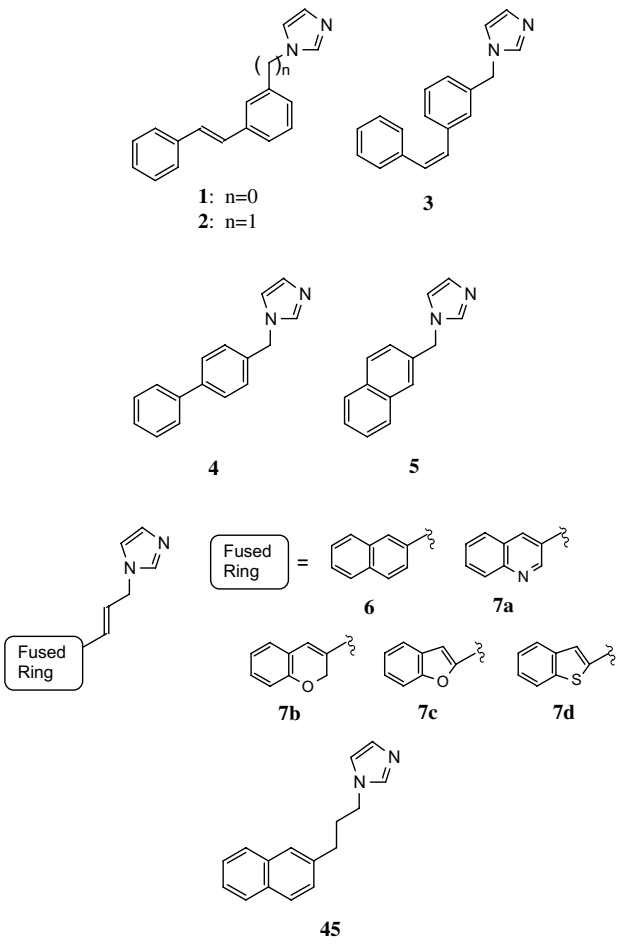
3.3. Screening of steroid mimetic ring systems

Table 1 shows pharmacological activities of the initial target compounds possessing a steroid mimetic ring system. In the in vitro assay, the A–C ring mimetics (**3** and **4**), B-C ring mimetic (**5**) and the A–B ring mimetic (**6**) were found to be potent inhibitors with IC_{50} values of 10–53 nM. The A–D ring mimetics (**1** and **2**) were moderate inhibitors. The most potent inhibitor was biphenyl derivative **4**[49] with an IC_{50} value of 10 nM. In the in vivo evaluation, **4** reduced the serum testosterone concentration to 8% of the control at 2 h after treatment, but showed poor efficacy at 5 h (63% of the control). The most active compound at 5 h was the naphthalene derivative **6**, which reduced the testosterone concentration to 8% and 26% of the control at 2 and 5 h, respectively. Since compound **6** exhibited superior in vitro and in vivo activities to those of ketoconazole, it was identified as the lead compound. It is noteworthy that the propenyl group is an important structure for the duration of in vivo action because compound **45** with an IC_{50} value of 42 nM showed potent testosterone reduc-



Scheme 8.

Table 1. Pharmacological activities of initial target compounds



Compd no.	$C_{17,20}$-Lyase inhibition IC_{50} (nM)	T concn (in vivo)[c] % of control	
	Rat	2 h	5 h
1	270	nt	nt
2	91	nt	nt
3[a]	24	8	135
4	10	8	63
5	53	13	55
6	26	8	26
7a	95	nt	nt
7b	29	14	28
7c[b]	39	15	86
7d	16	5	17
45[b]	42	14	226
Ketoconazole	240	28	115

nt: Not tested.
[a] HCl salt.
[b] Fumarate.
[c] Test compounds and ketoconazole were administrated orally at a dose of 25 mg/kg to male rats. After 2 and 5 h, the serum testosterone (T) concentration was measured by radioimmunoassay and shown as the % values of that of control.

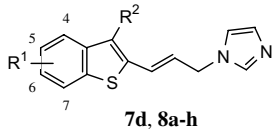
tion at 2 h after treatment (14% of the control) but led to an increase of the testosterone concentration above the control at 5 h (226% of the control). Similarly, compound **3** increased the testosterone concentration at 5 h (135% of the control) in spite of comparable testosterone reduction to **6** at 2 h after treatment. These increases were probably due to cancellation of the negative feedback control caused by transient suppression of the testosterone levels as previously reported.[17,32,33]

Variations of the fused ring system in the place of the naphthalene ring were evaluated, and 2*H*-chromene, benzofuran and benzothiophene derivatives (**7b**, **7c**, and **7d**) exhibited potent inhibitory activity with IC_{50} values of 16–39 nM, while quinoline derivative **7a** showed moderate inhibition. In vivo evaluation revealed that **7d** had more potent efficacy than **6**, in reducing the serum testosterone concentration to 5% and 17% of the control at 2 and 5 h after treatment, respectively. These data suggested that benzothiophene derivative **7d** had an attractive scaffold and additional targets were designed focusing on benzothiophene analogues.

3.4. Pharmacological activities of benzothiophene derivatives

3.4.1. Effects of R^1 and R^2. The in vivo efficacy of **7d** was sufficient at 2 h after treatment, but extended duration of action even at 5 h was required. Several benzothiophene compounds were reported to be metabolized in vivo by a pathway involving the hydroxylation of the benzothiophene nuclei, followed by conversion to O-glucuronides.[50] This knowledge led us to synthesize derivatives carrying a metabolically resistant substituent such as a fluoro or a chloro group on the benzothiophene ring (Table 2). The data revealed that substituents on the benzothiophene ring (R^1 and R^2) showed no significant difference in the inhibitory activity. For example, a fluoro, chloro, or methoxy group at the 5-position showed the same range of activity as the unsubstituted derivative (comparison of **8e**–**h** and **7d**; $IC_{50} = 16$–33 nM). Introduction of a methyl group at the R^2 position had no influence on activity (comparison of **8b** and **8e**, **8f** and **8g**). The substitution position of a fluoro group on the benzothiophene had only a minor effect on activity (**8a**–**d**; $IC_{50} = 10$–26 nM). We also explored the effects of

Table 2. Pharmacological activities of 1-imidazolyl derivatives



7d, **8a-h**

Compd no.	R^1	R^2	$C_{17,20}$-Lyase inhibition IC_{50} (nM)	T concn (in vivo)[a] % of control	
			Rat	2 h	5 h
7d	H	H	16	5	17
8a	4-F	H	20	28	52
8b	5-F	H	25	14	10
8c	6-F	H	26	17	22
8d	7-F	H	10	17	23
8e	5-F	CH_3	25	2	8
8f	5-Cl	H	29	8	29
8g	5-Cl	CH_3	26	7	30
8h	5-CH_3O	CH_3	33	13	70

[a] 25 mg/kg (po).

the substituent on the benzothiophene ring in 4-imidazolyl series (Table 3). As was observed for the 1-imidazolyl derivatives, the position of the fluoro group at R^1 and the methyl group at R^2 did not have a marked influence on enzyme inhibition (**9a**–**e**,**g**; $IC_{50} = 19$–32 nM), although a bulky *tert*-butyl group at R^2 such as **9f** led to a reduced activity.

In the in vivo assay, all the tested compounds showed a reduction in the serum testosterone concentration at 2 h after treatment, although to different extents, and the differences in the duration became clear at 5 h after treatment. The substituent at R^1 in 1-imidazolyl inhibitors had a major influence on the in vivo efficacy (Table 2). The 5-fluoro derivatives (**8b** and **8e**) reduced the serum testosterone concentration more effectively than 4-, 6-, and 7-fluoro compounds (**8a**, **8c**, and **8d**), 5-chloro compound (**8f** and **8g**), and 5-methoxy compound (**8h**) at 5 h after treatment. In the case of 4-imidazolyl compounds as well as 1-imidazolyl analogues, the 5-fluoro group was critical for the extended duration of in vivo efficacy, and compounds **9b** and **9e** reduced the testosterone concentration to 4% and 2% of the control, respectively, even at 5 h after treatment (Table 3). These results clearly demonstrate that the 5-fluoro group on the benzothiophene ring is the key structural determinant for the duration of the in vivo action. In addition, the orientation of the imidazole ring appears to be important for in vivo potency, with 4-imidazolyl compounds displaying more potent testosterone reduction than 1-imidazolyl analogues (comparison of **8b** and **9b**, **8e** and **9e**).

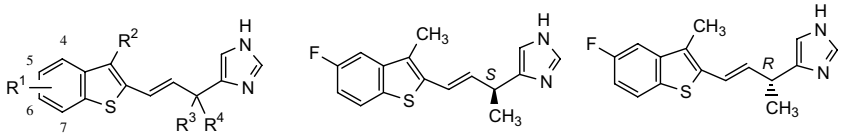
3.4.2. Effects of R^3 and R^4. The effects of substituents at the R^3 and R^4 were investigated (Table 3). The methyl group at R^3 led to nanomolar inhibitors as illustrated by **9h** and **9i** with IC_{50} values of 4 and 9 nM, respectively. The bulky isopropyl group such as **9j** resulted in a modest decrease in the activity relative to their unsubstituted compound. The enantiomers of **9i** were separated to establish, which enantiomer of **9i** (and by analogy **9h**) was responsible for the excellent activity. The enzyme inhibitory activity of (*S*)-**9i** and (*R*)-**9i**, with IC_{50} values of 9 and 8 nM, respectively, indicated that both the β-methyl group in (*S*)-**9i** and the α-methyl group in (*R*)-**9i** were able to confer potent inhibitory activity. The *gem*-dimethyl group (**9k**) also exhibited increased inhibitory activity with an IC_{50} value of 6 nM.

These nanomolar inhibitors **9h**, **9i**, and **9k** also had strong in vivo efficacy, and their effects at 5 h after treatment were comparable with that of **9e**. The most potent in vivo efficacy at 5 h in this study was achieved by (*S*)-**9i**, which was more effective than the other enantiomer (*R*)-**9i**, in reducing in the testosterone concentration to 1% of the control.

3.5. Structural comparison of 9k with 17α-hydroxypregnenolone

The superimposition of **9k** (bold line) with 17α-hydroxypregnenolone (thin line) and the steroidal inhibitor CB-7630 (dotted line) is shown in Figure 4, which shows that the benzothiophene ring and the propenyl linker in **9k** overlap the steroid nucleus of the substrate. Furthermore, the superimposition might explain the increase in the enzyme inhibition by the methyl groups in the propenyl linker. It is clear that the α-methyl group in **9k** and the C-16 methylene group in

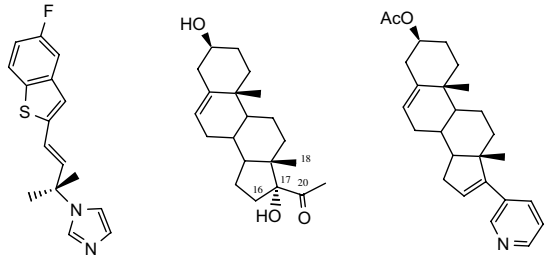
Table 3. Pharmacological activities of 4-imidazolyl derivatives



9 (*S*)-**9i** (*R*)-**9i**

Compd no.	R^1	R^2	R^3	R^4	$C_{17,20}$-Lyase inhibition IC_{50} (nM)	T concn (in vivo)[a] % of control	
					Rat	2 h	5 h
9a	4-F	H	H	H	19	7	25
9b	5-F	H	H	H	23	12	4
9c	6-F	H	H	H	27	14	23
9d	7-F	H	H	H	25	5	16
9e	5-F	CH_3	H	H	27	3	2
9f	5-F	$(CH_3)_3C$	H	H	300	nt	nt
9g	5,7-F_2	CH_3	H	H	32	26	46
9h	5-F	H	CH_3	H	4	7	2
9i	5-F	CH_3	CH_3	H	9	5	2
9j	5-F	CH_3	$(CH_3)_2CH$	H	140	nt	nt
9k	5-F	H	CH_3	CH_3	6	12	3
(*S*)-**9i**	(*S*)-Enantiomer of **9i**				9	8	1
(*R*)-**9i**	(*R*)-Enantiomer of **9i**				8	13	10

nt: Not tested.
[a] 25 mg/kg (po).



9k 17α-Hydroxypregnenolone CB-7630

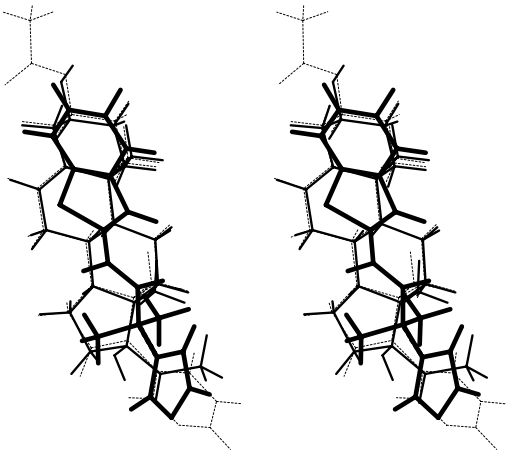


Figure 4. Superimposition of **9k** (bold line) with 17α-hydroxypregnenolone (thin line) and CB-7630 (dotted line).

17α-hydroxypregnenolone share the same regions of space. Also, the β-methyl group in **9k** and the C-18 methyl group in 17α-hydroxypregnenolone occupy similar regions of space. Thus the methyl groups may contribute to more precise mimicry of the steroid nucleus, and consequently enhance the hydrophobic interactions of the molecule and $C_{17,20}$-lyase leading to a increased enzyme inhibitory activity. From the results of **9h**, (*S*)-**9i**, (*R*)-**9i**, and **9k**, the insertion of either the β-methyl group or the α-methyl group in the propenyl group would be needed for nanomolar enzyme inhibition.

3.6. Human enzyme inhibitory activity (in vitro study)

Selected compounds were evaluated for inhibitory activity of human recombinant $C_{17,20}$-lyase. The potent inhibitors for rat enzyme also had potent human enzyme inhibitory activity with IC_{50} values of 20–30 nM (Table 4).

4. Conclusions

We have discovered novel and potent $C_{17,20}$-lyase inhibitors through structure-based de novo design. To improve the duration of the in vivo action, a series of benzothiophene derivatives were examined, which resulted in the identification of **9h**, (*S*)-**9i**, and **9k** with nanomolar enzyme inhibition ($IC_{50} = 4$–9 nM) and **9e** ($IC_{50} = 27$ nM) and potent in vivo efficacy with extended duration. The key structural features required for potent in vivo efficacy were demonstrated to be the 5-fluoro group on the benzothiophene ring and the 4-imidazolyl moiety. Selected compounds were found to be potent inhibitors of human enzyme with IC_{50} values of 20–30 nM and these results suggest that some benzothiophene inhibitors described in this paper may be promising agents for the treatment of prostate cancer.

Table 4. IC_{50} values of selected compounds toward human $C_{17,20}$-lyase

Compd no.	$C_{17,20}$-Lyase inhibition IC_{50} (nM)
	Human
6	26
7d	30
9b	25
9e	22
9h	21
9i	20
(*S*)-**9i**	21
(*R*)-**9i**	29
9k	29

5. Experimental

5.1. Chemistry

Melting points were determined on a Yanaco MP-500V micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Shimadzu FTIR-8200PC spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in ppm with tetramethylsilane as the internal standard, and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck). Solutions in organic solvents were dried over anhydrous magnesium sulfate unless otherwise noted.

5.2. 1-Bromo-3-[(*E*)-2-phenylethenyl]benzene (12)

To a suspension of NaH (60% dispersion in oil, 0.63 g, 15.8 mmol) in THF (80 mL) was added diethyl benzylphosphonate (**10**, 3.04 g, 14.6 mmol) with ice cooling, and the mixture was stirred for 1 h. 3-Bromobenzaldehyde (**11**, 2.50 g, 13.5 mmol) was added, and the mixture was stirred for an additional 24 h at room temperature and then quenched with saturated aqueous NH_4Cl. After the separation of the layers, the organic layer was dried and concentrated. The residue was chromatographed on silica gel using hexane–AcOEt (1:1) as an eluent, followed by recrystallization from CH_2Cl_2–AcOEt to give **12** (1.33 g, 38%) as colorless prisms. Mp 87–89 °C. IR (KBr): 3024, 1585, 1425, 1073, 967 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.00 (1H, d, $J = 16.3$ Hz), 7.11 (1H, d, $J = 16.3$ Hz), 7.17–7.54 (8H, m), 7.67 (1H, t,

$J = 1.8$ Hz). Anal. Calcd for $C_{14}H_{11}Br$: C, 64.89; H, 4.28. Found: C, 64.99; H, 4.31.

5.3. 1-{3-[(*E*)-2-Phenylethenyl]phenyl}-1*H*-imidazole (1)

To a suspension of NaH (60% dispersion in oil, 0.329 g, 8.22 mmol) in DMF (3 mL) was added imidazole (610 mg, 8.96 mmol), and the mixture was stirred for 10 min. Then **12** (712 mg, 2.75 mmol) and CuO (77 mg, 0.968 mmol) were added, and the mixture was heated at 150 °C for 7 h, cooled, and partitioned between CH_2Cl_2 and water. The organic layer was separated, dried, and concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–AcOEt (1:1) as an eluent, followed by recrystallization from hexane–CH_2Cl_2 to give **1** (569 mg, 84%) as a colorless powder. Mp 78–79 °C. IR (KBr): 1605, 1503, 1306, 1059 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.12 (1H, d, $J = 16.2$ Hz), 7.17–7.59 (12H, m), 7.91 (1H, s). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.85; H, 5.67; N, 11.25.

5.4. 1-(3-Bromobenzyl)-1*H*-imidazole (14)

A mixture of 3-bromobenzyl bromide (**13**, 25.0 g, 0.100 mol) and imidazole (14.97 g, 0.220 mol) in DMF (100 mL) was stirred at 100 °C for 2 h. After removal of the solvent, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was dried and concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (10:1) as an eluent to give **14** (19.10 g, 81%) as a colorless oil. IR (Neat): 3110, 1505, 1231, 1074 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.09 (2H, s), 6.90 (1H, s), 7.01–7.32 (4H, m), 7.45 (1H, d, $J = 8.0$ Hz), 7.54 (1H, m).

5.5. 1-{3-[(*E*)-2-Phenylethenyl]benzyl}-1*H*-imidazole (2)

A mixture of **14** (1.05 g, 4.43 mmol), styrene (1.2 mL, 10.5 mmol), palladium(II) acetate (93 mg, 0.414 mmol), tris(2-methylphenyl)phosphine (1.45 g, 4.75 mmol), and Et_3N (2.0 mL, 14.3 mmol) in THF (25 mL) was refluxed for 18 h under an argon atmosphere. The insoluble material was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (20:1) as an eluent to give **2** as crystals (254 mg, 22%). Mp 141–142 °C (CH_2Cl_2–cyclohexane). IR (KBr): 1601, 1510, 1231, 1076, 963 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.15 (2H, s), 6.94 (1H, t, $J = 1.4$ Hz), 7.08 (4H, m), 7.25–7.43 (5H, m), 7.45–7.62 (4H, m). Anal. Calcd for $C_{18}H_{16}N_2 \cdot 0.1H_2O$: C, 72.90; H, 5.17; N, 9.45. Found: C, 72.79; H, 5.12; N, 9.31.

5.6. Methyl 3-(2-phenylethynyl)benzoate (16)

To a mixture of methyl 3-bromobenzoate (**15**, 11.07 g, 51.5 mmol), CuI (112 mg, 1.24 mmol), $PdCl_2(PPh_3)_2$ (1.0 g, 1.42 mmol) in Et_3N (300 mL) was added phenyl acetylene (6.0 mL, 54.6 mmol), and the mixture was stirred at 50 °C for 24 h under an argon atmosphere. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel using hexane–AcOEt (3:1) as an eluent, followed by recrystallization from hexane–CH_2Cl_2 to give **16** (10.77 g, 89%). Mp 77–79 °C. IR (KBr): 1726, 1440, 1255, 1145 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.94 (3H, s), 7.31–7.60 (6H, m), 7.71 (1H, m), 8.00 (1H, m), 8.22 (1H, m). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.31; H, 5.19.

5.7. [3-(2-Phenylethynyl)phenyl]methanol (17)

To a solution of **16** (10.45 g, 44.2 mmol) in CH_2Cl_2 (200 mL) was added dropwise diisobutylaluminum hydride (1.5 M solution in toluene, 65 mL, 97.5 mmol) at −70 °C. The mixture was stirred for 2 h, cautiously quenched with 1 N HCl, and allowed to warm up to room temperature. After the separation of the layers, the aqueous layer was further extracted with AcOEt and the organic layers were combined, dried and concentrated. The residue was chromatographed on silica gel using hexane–AcOEt (5:1) as an eluent, followed by recrystallization from hexane gave **17** (6.60 g, 72%). Mp 41–43 °C. IR (KBr): 3263, 1604, 1494, 1041 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.71 (2H, s), 7.30–7.60 (9H, m). Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.30; H, 5.78.

5.8. 1-{3-[(*Z*)-2-Phenylethenyl]benzyl}-1*H*-imidazole hydrochloride (3)

A mixture of **17** (1.76 g, 8.47 mmol), 5% $Pd/BaSO_4$ (43 mg) and quinoline (45 mg, 0.348 mmol) in MeOH (20 mL) was stirred at room temperature for 50 min under a hydrogen atmosphere. The catalyst was filtered off and the solvent was evaporated to give a colorless oil (1.78 g, quant.). The oil was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled with an ice bath. Thionyl chloride (1.8 mL, 24.7 mmol) was added and the mixture was refluxed for 2 h and concentrated. The residue was diluted with AcOEt, and the solution was washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was heated at 100 °C for 2 h with imidazole (1.40 g, 20.5 mmol) in DMF (20 mL). After removal of the solvent, the residue was diluted with AcOEt, and the solution was washed with water, dried, and concentrated. The residue was chromatographed on silica gel using AcOEt as an eluent, and the product was treated with 4 N HCl–AcOEt. The precipitate was collected by filtration and washed with AcOEt to give **3** (1.55 g, 37%) as colorless crystals. Mp 112–114 °C (AcOEt). IR (KBr): 3064, 1567, 1446, 1278, 1075 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 5.37 (2H, s), 6.63 (1H, d, $J = 12.2$ Hz), 6.70 (1H, d, $J = 12.2$ Hz), 7.08–7.40 (9H, m), 7.68 (2H, m), 9.22 (1H, s). Anal. Calcd for $C_{18}H_{17}N_2Cl \cdot 0.1H_2O$: C, 72.40; H, 5.81; N, 9.38. Found: C, 72.30; H, 5.72; N, 9.46.

5.9. 1-([1,1′-Biphenyl]-4-ylmethyl)-1*H*-imidazole (4)

To a solution of 4-biphenylmethanol (0.91 g, 4.9 mmol) in THF (10 mL) was added thionyl chloride (1.5 mL,

20 mmol) with ice cooling. The mixture was stirred at room temperature for 5 h and concentrated, and the residue was heated at 100 °C for 2 h with imidazole (2.72 g, 40 mmol) in DMF (10 mL). The mixture was diluted with AcOEt, and the solution was washed with water, dried, and concentrated. The residue was crystallized from AcOEt–hexane to give **4** as colorless crystals (0.65 g, 56%). Mp 143.5–145 °C. IR (KBr): 3108, 1508, 1487, 1233, 745 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.17 (2H, s), 6.95 (1H, t, $J = 1.2$ Hz), 7.12 (1H, s), 7.23 (2H, d, $J = 8.2$ Hz), 7.34–7.50 (3H, m), 7.53–7.61 (5H, m). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.94; H, 6.00; N, 11.88.

5.10. 1-(2-Naphthylmethyl)-1*H*-imidazole (5)

Prepared from 2-naphthylmethanol in 62% yield by the method described for **4**. Mp 82–85 °C (hexane–AcOEt). IR (KBr): 3057, 1502, 1225, 1074, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.28 (2H, s), 6.94 (1H, t, $J = 1.3$ Hz), 7.12 (1H, t, $J = 1.3$ Hz), 7.26 (1H, dd, $J = 8.4$, 1.8 Hz), 7.45–7.63 (4H, m), 7.74–7.88 (3H, m). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.78; H, 5.55; N, 13.52.

5.11. Synthesis of 1-[(*E*)-3-aryl-2-propen-1-yl]-1*H*-imidazoles (6, 7, 8): General procedure for the synthesis of 19

To a suspension of sodium hydride (60% dispersion in oil, 1.56 g, 39.0 mmol) in THF (100 mL) was added methyl diethylphosphonoacetate or ethyl diethylphosphonoacetate (39.0 mmol) with ice cooling, and the mixture was stirred for 1 h. A solution of the aldehyde **18** (commercially available or prepared in Scheme 4, 38.4 mmol) in THF (30 mL) was added, and the mixture was stirred for 1 h, diluted with water, and extracted with AcOEt. The extract was dried and concentrated, and the residue was chromatographed on silica gel using hexane–AcOEt as an eluent to give **19**.

5.11.1. Methyl (*E*)-3-(2-naphthyl)-2-propenoate. 84% yield. Mp 80–83 °C (hexane–cyclohexane). IR (KBr): 1735, 1436, 1315, 1172, 985 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.84 (3H, s), 6.56 (1H, d, $J = 16.0$ Hz), 7.51 (2H, m), 7.67 (1H, dd, $J = 8.8$, 1.6 Hz), 7.86 (5H, m). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.11; H, 5.69.

5.11.2. Ethyl (*E*)-3-(3-quinolinyl)-2-propenoate. 44% yield from quinoline-3-carboxaldehyde. Mp 87–88 °C (CH_2Cl_2–cyclohexane). IR (KBr): 1706, 1635, 1185, 751 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.38 (3H, t, $J = 7.1$ Hz), 4.32 (2H, q, $J = 7.1$ Hz), 6.68 (1H, d, $J = 16.2$ Hz), 7.60 (1H, t, $J = 7.5$ Hz), 7.77 (3H, m), 8.12 (1H, d, $J = 8.4$ Hz), 8.25 (1H, d, $J = 2.2$ Hz), 9.10 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.89; H, 5.72; N, 6.16.

5.11.3. Ethyl (*E*)-3-(2*H*-chromen-3-yl)-2-propenoate. 73% yield from 2*H*-chromene-3-carboxaldehyde. Mp 68–70 °C (hexane). IR (KBr): 2972, 1704, 1274, 1191 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (3H, t, $J = 7.2$ Hz), 4.24 (2H, q, $J = 7.2$ Hz), 4.96 (2H, s), 5.76 (1H, d, $J = 16.2$ Hz), 6.72 (1H, s), 6.85 (1H, d, $J = 8.4$ Hz), 6.89 (1H, m), 7.06 (1H, dd, $J = 7.7$, 1.8 Hz), 7.17 (1H, dt, $J = 7.7$, 1.8 Hz), 7.37 (1H, d, $J = 16.2$ Hz). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.80; H, 6.19.

5.11.4. Ethyl (*E*)-3-(benzo[*b*]furan-2-yl)-2-propenoate. 63% yield from benzo[*b*]furan-2-carboxaldehyde. Mp 73–76 °C (hexane–AcOEt). IR (KBr): 2982, 1713, 1638, 1451, 1264, 1173 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.1$ Hz), 4.28 (2H, q, $J = 7.1$ Hz), 6.58 (1H, d, $J = 15.7$ Hz), 6.93 (1H, s), 7.24 (1H, dt, $J = 1.4$, 6.8 Hz), 7.36 (1H, dt, $J = 1.4$, 7.6 Hz), 7.46 (1H, m), 7.55 (1H, d, $J = 15.7$ Hz), 7.59 (1H, m). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.93; H, 5.53.

5.11.5. Ethyl 3-(benzo[*b*]thiophen-2-yl)-2-propenoate. 98% yield from benzo[*b*]thiophene-2-carboxaldehyde. Mp 48–50 °C (EtOH). IR (KBr): 1701, 1630, 1269, 1167, 1038, 955, 824, 747, 727 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.2$ Hz), 4.28 (2H, q, $J = 7.2$ Hz), 6.30 (1H, d, $J = 15.6$ Hz), 7.32–7.41 (2H, m), 7.46 (1H, s), 7.73–7.82 (2H, m), 7.87 (1H, d, $J = 15.6$ Hz).

5.11.6. Ethyl 3-(4-fluorobenzo[*b*]thiophen-2-yl)-2-propenoate. 80% yield from **18i**. Mp 81.5–83 °C (EtOH). IR (KBr): 1701, 1628, 1568, 1466, 1456, 1264, 1159, 984, 849, 772 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.2$ Hz), 4.28 (2H, q, $J = 7.2$ Hz), 6.31 (1H, d, $J = 15.8$ Hz), 7.02 (1H, dd, $J = 10.0$, 8.0 Hz), 7.34 (1H, dt, $J = 5.2$, 8.0 Hz), 7.56 (1H, d, $J = 8.0$ Hz), 7.56 (1H, s), 7.86 (1H, d, $J = 15.8$ Hz). Anal. Calcd for $C_{13}H_{11}FO_2S$: C, 62.38; H, 4.43. Found: C, 62.45; H, 4.42.

5.11.7. Ethyl 3-(5-fluorobenzo[*b*]thiophen-2-yl)-2-propenoate. 94% yield from **18ii**. Mp 90–91 °C (EtOH). IR (KBr): 1701, 1636, 1443, 1314, 1177, 957, 806, 517 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.0$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 6.31 (1H, d, $J = 15.8$ Hz), 7.14 (1H, dt, $J = 2.6$, 8.8 Hz), 7.41 (1H, s), 7.43 (1H, dd, $J = 8.8$, 2.6 Hz), 7.72 (1H, dd, $J = 8.8$, 4.8 Hz), 7.85 (1H, d, $J = 15.8$ Hz). Anal. Calcd for $C_{13}H_{11}FO_2S$: C, 62.38; H, 4.43. Found: C, 62.52; H, 4.20.

5.11.8. Ethyl 3-(6-fluorobenzo[*b*]thiophen-2-yl)-2-propenoate. Quantitative yield from **18iii**. Mp 87–88 °C (EtOH). IR (KBr): 1711, 1634, 1267, 1169, 1146, 835 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.0$ Hz), 4.27 (2H, q, $J = 7.0$ Hz), 6.26 (1H, d, $J = 15.8$ Hz), 7.11 (1H, dt, $J = 2.4$, 8.8 Hz), 7.41 (1H, s), 7.48 (1H, dd, $J = 8.8$, 2.4 Hz), 7.71 (1H, dd, $J = 8.8$, 5.2 Hz), 7.84 (1H, d, $J = 15.8$ Hz). Anal. Calcd for $C_{13}H_{11}FO_2S$: C, 62.38; H, 4.43. Found: C, 62.36; H, 4.42.

5.11.9. Ethyl 3-(7-fluorobenzo[*b*]thiophen-2-yl)-2-propenoate. Quantitative yield from **18iv**. Mp 55.5–56.5 °C (EtOH). IR (KBr): 1717, 1628, 1470, 1298, 1269, 1169,

831 cm^{-1} ; ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.2$ Hz), 4.28 (2H, q, $J = 7.2$ Hz), 6.34 (1H, d, $J = 15.8$ Hz), 7.08 (1H, dd, $J = 9.6$, 8.0 Hz), 7.32 (1H, dt, $J = 5.0$, 8.0 Hz), 7.48 (1H, d, $J = 3.4$ Hz), 7.56 (1H, d, $J = 8.0$ Hz), 7.86 (1H, d, $J = 15.8$ Hz). Anal. Calcd for $C_{13}H_{11}FO_2S$: C, 62.38; H, 4.43. Found: C, 62.33; H, 4.15.

5.11.10. Ethyl 3-(5-chlorobenzo[*b*]thiophen-2-yl)-2-propenoate. Quantitative yield from **18vi**. Mp 100 °C (EtOH). IR (KBr): 1711, 1630, 1319, 1173, 1152, 957, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.0$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 6.31 (1H, d, $J = 15.6$ Hz), 7.33 (1H, dd, $J = 8.6$, 2.0 Hz), 7.39 (1H, s), 7.70 (1H, d, $J = 8.6$ Hz), 7.74 (1H, d, $J = 2.0$ Hz), 7.84 (1H, d, $J = 15.6$ Hz). Anal. Calcd for $C_{13}H_{11}ClO_2S$: C, 58.54; H, 4.16. Found: C, 58.52; H, 4.10.

5.11.11. Ethyl 3-(5-methoxy-3-methylbenzo[*b*]thiophen-2-yl)-2-propenoate. 98% yield from **18viii**. Mp 108 °C (EtOH). IR (KBr): 1709, 1628, 1460, 1308, 1171, 833 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.35 (3H, t, $J = 7.0$ Hz), 2.49 (3H, s), 3.89 (3H, s), 4.28 (2H, q, $J = 7.0$ Hz), 6.26 (1H, d, $J = 15.6$ Hz), 7.04 (1H, dd, $J = 8.8$, 2.4 Hz), 7.12 (1H, d, $J = 2.4$ Hz), 7.63 (1H, d, $J = 8.8$ Hz), 8.03 (1H, d, $J = 15.6$ Hz). Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.15; H, 5.95.

5.12. General procedure for the synthesis of 20

To a solution of **19** (11.2 mmol) in THF (50 mL) was added diisobutylaluminum hydride (DIBAL, 1.5 M solution in toluene, 18.0 mL, 27.0 mmol) at −78 °C. The reaction mixture was stirred for 2 h, cautiously quenched by the addition of water, diluted with 1 N HCl, and allowed to warm to room temperature. The mixture was extracted with AcOEt, and the extract was washed with aqueous $NaHCO_3$, dried and concentrated to give **20**.

5.12.1. (*E*)-3-(2-Naphthyl)-2-propen-1-ol. 86% yield. Mp 112–114 °C (CH_2Cl_2–cyclohexane). IR (KBr): 3267, 1089, 965 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.38 (2H, br), 6.48 (1H, dt, $J = 5.6$, 16.0 Hz), 6.78 (1H, d, $J = 16.0$ Hz), 7.45 (2H, m), 7.60 (1H, dd, $J = 8.8$, 1.8 Hz), 7.79 (4H, m). Anal. Calcd for $C_{13}H_{12}O$: C, 83.93; H, 6.45. Found: C, 83.99; H, 6.45.

5.12.2. (*E*)-3-(3-Quinolinyl)-2-propen-1-ol. 55% yield. Mp 102–103 °C (AcOEt–CH_2Cl_2). IR (KBr): 3232, 1498, 1340, 1100, 782 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.03 (1H, br), 4.40 (2H, d, $J = 4.6$ Hz), 6.75 (1H, dt, $J = 5.0$, 16.1 Hz), 6.76 (1H, d, $J = 16.1$ Hz), 7.52 (1H, t, $J = 7.3$ Hz), 7.66 (1H, m), 7.76 (1H, d, $J = 8.0$ Hz), 8.00 (1H, d, $J = 1.8$ Hz), 8.07 (1H, d, $J = 8.4$ Hz), 8.96 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.58; H, 5.91; N, 7.48.

5.12.3. (*E*)-3-(2*H*-Chromen-3-yl)-2-propen-1-ol. 91% yield. Mp 96–98 °C (AcOEt–hexane). IR (KBr): 3240, 2908, 1486, 1039 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.28 (2H, t, $J = 5.3$ Hz), 4.96 (2H, s), 5.74 (1H, dt, $J = 5.7$, 16.2 Hz), 6.36 (2H, m), 6.85 (2H, m), 7.01 (1H, dd, $J = 1.8$, 7.4 Hz), 7.11 (1H, dt, $J = 1.8$, 7.5 Hz). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.67; H, 6.47.

5.12.4. (*E*)-3-(Benzo[*b*]furan-2-yl)-2-propen-1-ol. 87% yield. Mp 55–59 °C (AcOEt–hexane). IR (KBr): 3335, 1678, 1557, 1453, 1254, 955 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.38 (2H, d, $J = 2.2$ Hz), 6.59 (3H, m), 7.14–7.32 (2H, m), 7.40–7.55 (2H, m). Anal. Calcd for $C_{11}H_{10}O$: C, 75.84; H, 5.79. Found: C, 76.01; H, 5.83.

5.12.5. (*E*)-3-(Benzo[*b*]thiophen-2-yl)-2-propen-1-ol. 96% yield. Mp 116–120 °C (diisopropylether). IR (KBr): 3281, 1088, 1005, 953, 741, 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.35 (2H, dd, $J = 5.6$, 1.6 Hz), 6.29 (1H, d, $J = 15.4$, 5.6 Hz), 6.86 (1H, d, $J = 15.4$ Hz), 7.15 (1H, s), 7.24–7.35 (2H, m), 7.65–7.78 (2H, m). Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found: C, 69.10; H, 5.18.

5.12.6. (*E*)-3-(4-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-ol. Quantitative yield. Mp 89 °C (AcOEt). IR (KBr): 3235, 1462, 1221, 1013, 963, 766 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.36 (2H, d, $J = 5.4$ Hz), 6.30 (1H, dt, $J = 15.8$, 5.4 Hz), 6.86 (1H, d, $J = 15.8$ Hz), 6.98 (1H, dd, $J = 10.2$, 8.0 Hz), 7.23 (1H, dt, $J = 5.0$, 8.0 Hz), 7.25 (1H, s), 7.52 (1H, d, $J = 8.0$ Hz). Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found: C, 63.72; H, 4.53.

5.12.7. (*E*)-3-(5-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-ol. 98% yield. IR (KBr): 3285, 1443, 1177, 955, 868 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.35 (1H, d, $J = 5.4$ Hz), 6.30 (1H, dt, $J = 15.8$, 5.4 Hz), 6.85 (1H, d, $J = 15.8$ Hz), 7.05 (1H, dt, $J = 2.6$, 8.8 Hz), 7.10 (1H, s), 7.34 (1H, dd, $J = 9.2$, 2.6 Hz), 7.67 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found: C, 63.43; H, 4.26.

5.12.8. (*E*)-3-(6-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-ol. Quantitative yield. Mp 135–137 °C (diisopropylether). IR (KBr): 3299, 1566, 1468, 1254, 1086, 951, 856, 588 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.35 (2H, d, $J = 5.6$ Hz), 6.24 (1H, dt, $J = 15.8$, 5.6 Hz), 6.84 (1H, d, $J = 15.8$ Hz), 7.06 (1H, dt, $J = 2.2$, 8.8 Hz), 7.10 (1H, s), 7.44 (1H, dd, $J = 8.8$, 2.2 Hz), 7.61 (1H, dd, $J = 8.8$, 5.2 Hz). Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found: C, 63.36; H, 4.23.

5.12.9. (*E*)-3-(7-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-ol. Quantitative yield. Mp 81.5–83 °C (AcOEt). IR (KBr) 3299, 1466, 1086, 953, 781, 710 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.37 (2H, d, $J = 5.4$ Hz), 6.33 (1H, dt, $J = 15.8$, 5.4 Hz), 6.87 (1H, d, $J = 15.8$ Hz), 6.99 (1H, dd, $J = 9.8$, 8.0 Hz), 7.17 (1H, d, $J = 3.6$ Hz), 7.27 (1H, dt, $J = 5.2$, 8.0 Hz), 7.47 (1H, d, $J = 8.0$ Hz). Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found: C, 63.57; H, 4.42.

5.12.10. (*E*)-3-(5-Chlorobenzo[*b*]thiophen-2-yl)-2-propen-1-ol. 83% yield, mp 148–150 °C (AcOEt). IR (KBr): 3293, 1078, 1009, 806 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.33–4.38 (2H, br m), 6.30 (1H, dt, $J = 15.6$, 5.4 Hz), 6.85 (1H, d, $J = 15.6$ Hz), 7.08 (1H, s), 7.25 (1H, dd, $J = 8.6$, 2.2 Hz), 7.65 (1H, d, $J = 8.6$ Hz), 7.65 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{11}H_9ClOS$: C, 58.80; H, 4.04. Found: C, 58.69; H, 4.13.

5.12.11. (*E*)-3-(5-Methoxy-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-ol. Quantitative yield. Mp 80 °C (diisoprorylether). IR (KBr): 3376, 1597, 1458, 1229, 949, 837 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.26 (1H, s), 2.37 (3H, s), 3.88 (3H, s), 4.36 (1H, dd, $J = 5.6$, 1.4 Hz), 6.25 (1H, dt, $J = 15.6$, 5.6 Hz), 6.92–7.02 (2H, m), 7.07 (1H, d, $J = 2.4$ Hz), 7.60 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.52; H, 6.09.

5.13. General procedure for the synthesis of 6, 7, and 8

5.13.1. For 6, 7d, 8a–d, 8f and 8h. To a solution of **20** (9.6 mmol) in CH_2Cl_2 (50 mL) was added thionyl chloride (2.1 mL, 28.8 mmol). The mixture was refluxed for 2 h and concentrated, and the residue was heated at 100 °C for 2 h with imidazole (1.10 g, 16.2 mmol) in DMF (20 mL). The mixture was diluted with water and extracted with AcOEt, and the extract was washed with water, dried, and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (9:1) as an eluent to give **6**, **7d**, **8a–d**, **8f** and **8h**.

5.13.2. For 7a, 7b and 7c. To a mixture of **20** (6.5 mmol) and triethylamine (1.81 mL, 13.0 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (0.77 mL, 10.0 mmol). The mixture was stirred at room temperature for 6 h, washed with water, dried and concentrated, and the residue was heated at 100 °C with imidazole (0.89 g, 13.0 mmol) in DMF (10 mL) for 4 h. The mixture was diluted with AcOEt, and the solution was washed with water, dried and concentrated. The residue was chromatographed on silica gel using CH_2Cl_2–MeOH (9:1) as an eluent to give **7a**, **7b**, and **7c**.

5.13.3. 1-[(*E*)-3-(2-Naphthyl)-2-propen-1-yl]-1*H*-imidazole (6). 50% yield. Mp 112–113 °C (CH_2Cl_2–hexane). IR (KBr): 1506, 1226, 977, 825 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.76 (2H, d, $J = 6.2$ Hz), 6.40 (1H, dt, $J = 15.7$, 6.2 Hz), 6.68 (1H, d, $J = 15.7$ Hz), 7.00 (1H, s), 7.49 (4H, m), 7.78 (4H, m). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.77; H, 5.82; N, 11.73.

5.13.4. 1-[(*E*)-3-(3-Quinolinyl)-2-propen-1-yl]-1*H*-imidazole (7a). 15% yield. Mp 146–148 °C (AcOEt). IR (KBr): 3105, 1506, 1494, 1425, 1226, 807 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.80 (2H, d, $J = 4.8$ Hz), 6.50 (1H, m), 6.63 (1H, d, $J = 16.2$ Hz), 7.01 (1H, s), 7.15 (1H, s), 7.55 (2H, m), 7.74 (2H, m), 8.05 (2H, m), 8.97 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.40; H, 5.54; N, 17.78.

5.13.5. 1-[(*E*)-3-(2*H*-Chromen-3-yl)-2-propen-1-yl]-1*H*-imidazole (7b). 20% yield. Mp 115–117 °C (CH_2Cl_2–AcOEt–hexane). IR (KBr): 3107, 1506, 1486, 1045 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.28 (2H, t, $J = 5.3$ Hz), 4.96 (2H, s), 5.74 (1H, dt, $J = 5.7$, 16.2 Hz), 6.36 (2H, m), 6.85 (2H, m), 7.01 (1H, dd, $J = 7.4$, 1.8 Hz), 7.11 (1H, dt, $J = 1.8$, 7.5 Hz). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.49; H, 5.79; N, 11.69.

5.13.6. 1-[(*E*)-3-(Benzo[*b*]furan-2-yl)-2-propen-1-yl]-1*H*-imidazole (7c). 14% yield as the fumarate. Mp 121–124 °C (MeOH). IR (KBr): 3086, 1698, 1451, 1254, 1184, 754 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.86 (2H, d, $J = 4.4$ Hz), 6.51 (2H, m), 6.63 (2H, s), 6.90 (1H, s), 6.99 (1H, m), 7.16–7.36 (3H, m), 7.46–7.64 (2H, m), 7.77 (1H, s). Anal. Calcd for $C_{18}H_{16}N_2O_5 \cdot 0.1H_2O$: C, 63.19; H, 4.77; N, 8.19. Found: C, 63.13; H, 4.67; N, 8.31.

5.13.7. 1-[(*E*)-3-(Benzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (7d). 60% yield. Mp 130–132 °C (AcOEt). IR (KBr): 1503, 1433, 1223, 1074, 953, 758, 665 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.74 (2H, d, $J = 6.0$ Hz), 6.20 (1H, dt, $J = 15.4$, 6.0 Hz), 6.68 (1H, d, $J = 15.4$ Hz), 6.98 (1H, s), 7.13 (1H, s), 7.16 (1H, s), 7.29–7.36 (2H, m), 7.56 (1H, s), 7.67–7.78 (2H, m). Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 69.88; H, 4.83; N, 11.80.

5.13.8. 1-[(*E*)-3-(4-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8a). 75% yield. Mp 116–117 °C (AcOEt). IR (KBr): 1566, 1503, 1468, 1426, 1242, 1209, 1074, 949, 916, 802, 764, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.75 (2H, d, $J = 5.8$ Hz), 6.22 (1H, dt, $J = 15.8$, 5.8 Hz), 6.69 (1H, d, $J = 15.8$ Hz), 6.95–7.04 (2H, m), 7.13 (1H, s), 7.22–7.32 (2H, m), 7.53 (1H, d, $J = 8.0$ Hz), 7.57 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 65.06; H, 4.25; N, 10.85.

5.13.9. 1-[(*E*)-3-(5-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8b). 75% yield. Mp 123 °C (AcOEt). IR (KBr): 3102, 1508, 1441, 1175, 963, 872, 804, 748 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.74 (2H, dd, $J = 5.8$, 1.4 Hz), 6.22 (1H, dt, $J = 15.8$, 5.8 Hz), 6.65 (1H, dd, $J = 15.8$, 1.4 Hz), 6.98 (1H, s), 7.07 (1H, dt, $J = 2.4$, 8.8 Hz), 7.11 (1H, s), 7.35 (1H, dd, $J = 9.4$, 2.4 Hz), 7.55 (1H, s), 7.67 (1H, dd, $J = 8.8$, 5.2 Hz), 7.13 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 64.98; H, 4.47; N, 10.81.

5.13.10. 1-[(*E*)-3-(6-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8c). 64% yield. Mp 108–109 °C (AcOEt). IR (KBr): 1505, 1466, 1250, 1221, 1073, 955, 855, 820, 752, 665 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.74 (2H, d, $J = 6.0$ Hz), 6.16 (1H, dt, $J = 15.8$, 6.0 Hz), 6.64 (1H,

d, $J = 15.8$ Hz), 6.98 (1H, s), 7.02–7.13 (3H, m), 7.44 (1H, dd, $J = 8.8$, 2.2 Hz), 7.56 (1H, s), 7.63 (1H, dd, $J = 8.8$, 5.2 Hz). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 65.22; H, 4.33; N, 10.86.

5.13.11. 1-[(*E*)-3-(7-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8d). 68% yield. Mp 125 °C (AcOEt). IR (KBr): 1526, 1464, 1426, 1416, 1231, 1078, 947, 843, 812, 789, 756, 714, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.76 (2H, d, $J = 5.8$ Hz), 6.27 (1H, dt, $J = 15.6$, 5.8 Hz), 6.65 (1H, d, $J = 15.6$ Hz), 6.98–7.07 (2H, m), 7.14 (1H, s), 7.18 (1H, d, $J = 3.6$ Hz), 7.29 (1H, dt, $J = 5.0$, 8.0 Hz), 7.49 (1H, d, $J = 8.0$ Hz), 7.60 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 65.09; H, 4.33; N, 10.93.

5.13.12. 1-[(*E*)-3-(5-Chlorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8f). 74% yield. Mp 150 °C (AcOEt). IR (KBr): 3090, 1431, 1074, 949, 866, 843, 812, 756 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.74 (2H, d, $J = 5.8$ Hz), 6.23 (1H, dt, $J = 15.8$, 5.8 Hz), 6.65 (1H, d, $J = 15.8$ Hz), 6.98 (1H, s), 7.09 (1H, s), 7.13 (1H, s), 7.27 (1H, dd, $J = 8.8$, 2.0 Hz), 7.56 (1H, s), 7.66 (1H, d, $J = 8.8$ Hz), 7.67 (1H, d, $J = 2.0$ Hz). Anal. Calcd for $C_{14}H_{11}ClN_2S$: C, 61.20; H, 4.04; N, 10.20. Found: C, 61.33; H, 4.02; N, 10.10.

5.13.13. 1-[(*E*)-3-(5-Methoxy-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8h). 31% yield. Mp 133–135 °C (AcOEt). IR (KBr): 1595, 1458, 1427, 1227, 1202, 833, 665 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.88 (3H, s), 4.75 (2H, dd, $J = 6.0$, 1.4 Hz), 6.16 (1H, dt, $J = 15.6$, 6.0 Hz), 6.81 (1H, dt, $J = 15.6$, 1.4 Hz), 6.98 (1H, dd, $J = 8.8$, 2.6 Hz), 6.99 (1H, s), 7.07 (1H, d, $J = 2.6$ Hz), 7.12 (1H, s), 7.57 (1H, s), 7.60 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.68; N, 9.87.

5.13.14. 1-[3-(2-Naphthyl)propan-1-yl]-1*H*-imidazole fumarate (45). A mixture of **6** (0.73 g, 3.1 mmol) and 10% Pd–C (0.30 g) in ethanol (15 mL) was stirred at room temperature for 16 h under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated to give an oil, which was treated with fumaric acid (0.30 g) in AcOEt–MeOH to give **45** as colorless crystals (0.75 g, 68%). Mp 130–132 °C (AcOEt). IR (KBr): 3139, 1694, 1287, 1269 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.14 (2H, m), 2.71 (2H, t, $J = 7.5$ Hz), 4.03 (2H, t, $J = 7.1$ Hz), 6.63 (2H, s), 6.95 (1H, s), 7.25 (1H, s), 7.34–7.54 (3H, m), 7.66–7.77 (2H, m), 7.80–7.92 (2H, m), 8.31 (1H, s). Anal. Calcd for $C_{20}H_{20}N_2$-$O_4 \cdot 0.1H_2O$: C, 67.82; H, 5.75; N, 7.91. Found: C, 67.71; H, 5.58; N, 7.95.

5.14. General procedures for the synthesis of benzo[*b*]thiophenes (22): From thiophenols

5.14.1. 5-Fluoro-3-methylbenzo[*b*]thiophene (22v). To a mixture of 4-fluorothiophenol (33.50 g, 261.4 mmol) and chloroacetone (21.1 mL, 265.0 mmol) in DMF (250 mL) was added potassium carbonate (71.87 g, 520 mmol) with ice cooling. The mixture was stirred for 2 h, diluted with AcOEt, and washed with water. The organic solution was dried and concentrated, and the residue was heated with polyphosphoric acid (145 g) in toluene (400 mL) at 100 °C for 12 h. The mixture was concentrated, carefully neutralized with aqueous potassium carbonate with ice cooling, and extracted with AcOEt. The extract was dried and concentrated, and the residue was purified by distillation (73–74 °C/0.4 mmHg) to give **22v** (28.71 g, 66%) as a colorless oil. IR (neat): 1603, 1445, 1250, 1204 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.41 (3H, s), 7.10 (1H, dt, $J = 2.2$, 8.8 Hz), 7.15 (1H, s), 7.37 (1H, dd, $J = 9.6$, 2.2 Hz), 7.76 (1H, dd, $J = 8.8$, 4.8 Hz).

Compounds described below were prepared similarly from the corresponding thiophenol with chloroacetone, bromoacetaldehyde diethylacetal, or 1-chloro-3,3-dimethyl-2-butanone.

5.14.2. 5-Chlorobenzo[*b*]thiophene (22vi). Yield 29%. A colorless crystals. ^1H NMR ($CDCl_3$) δ: 7.26–7.33 (2H, m), 7.50 (1H, d, $J = 5.6$ Hz), 7.77–7.81 (2H, m).

5.14.3. 5-Chloro-3-methylbenzo[*b*]thiophene (22vii). Yield 80%. A colorless oil. IR (neat): 1076, 831 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.41 (3H, s), 7.13 (1H, s), 7.31 (1H, dd, $J = 8.4$, 2.0 Hz), 7.69 (1H, d, $J = 2.0$ Hz), 7.75 (1H, d, $J = 8.4$ Hz).

5.14.4. 5-Methoxy-3-methylbenzo[*b*]thiophene (22viii). Yield 24%. A colorless oil. IR (neat): 1599, 1456, 1262, 1227 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.41 (3H, d, $J = 1.2$ Hz), 3.90 (3H, s), 7.01 (1H, dd, $J = 8.8$, 2.4 Hz), 7.09 (1H, d, $J = 1.2$ Hz), 7.15 (1H, d, $J = 2.4$ Hz), 7.71 (1H, d, $J = 8.8$ Hz).

5.14.5. 5-Fluoro-3-*tert*-butylbenzo[*b*]thiophene (22ix). Yield 25%. A colorless oil. IR (neat): 2965, 1443, 1227, 1127 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (9H, s), 6.98 (1H, s), 7.00 (1H, dt, $J = 2.6$, 8.8 Hz), 7.32 (1H, dd, $J = 9.4$, 2.6 Hz), 7.67 (1H, dd, $J = 8.8$, 5.2 Hz).

5.14.6. 5,7-Difluoro-3-methylbenzo[*b*]thiophene (22x). Yield 33%. Crystals. IR (KBr): 1624, 1576, 1418, 1111, 984, 839 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.40 (3H, s), 6.88 (1H, dt, $J = 2.2$, 9.2 Hz), 7.18 (1H, s), 7.21 (1H, dd, $J = 9.2$, 2.2 Hz).

5.15. From 2-fluorobenzaldehydes: Synthesis of 24

5.15.1. Ethyl 5-fluorobenzo[*b*]thiophene-2-carboxylate (24ii). To a mixture of 2,5-difluorobenzaldehyde (23.81 g, 167.5 mmol) and potassium carbonate (30.16 g, 218.2 mmol) in DMF (250 mL) was added ethyl thioglycolate (18.4 mL, 167.5 mmol) dropwise with ice

cooling. The mixture was stirred at room temperature for 14 h and at 60 °C for 6 h, poured into water, and extracted with AcOEt. The extract was washed with water, dried, and concentrated, and the residue was suspended in EtOH and collected by filtration to give **24ii** as crystals (20.10 g, 53%). Mp 90–91 °C (EtOH). IR (KBr): 1715, 1530, 1260, 1206, 889, 808, 750 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (3H, t, $J = 7.2$ Hz), 4.42 (2H, q, $J = 7.2$ Hz), 7.23 (1H, dt, $J = 2.6$, 9.0 Hz), 7.54 (1H, dd, $J = 9.0$, 2.6 Hz), 7.81 (1H, dd, $J = 9.0$, 4.8 Hz), 8.01 (1H, s). Anal. Calcd for $C_{11}H_9FO_2S$: C, 58.91; H, 4.05. Found: C, 58.93; H, 3.86.

5.16. Synthesis of 22

5.16.1. 5-Fluorobenzo[*b*]thiophene (22ii). A mixture of **24ii** (18.90 g, 84.3 mmol), potassium hydroxide (25.81 g, 460 mmol), water (200 mL), and EtOH (200 mL) was heated at reflux for 1.5 h. The mixture was concentrated, acidified with 2 N HCl, and extracted with AcOEt–THF, and the extract was dried and concentrated to give 5-fluorobenzo[*b*]thiophene-2-carboxylic acid as colorless crystals (16.43 g, 99%).A mixture of this carboxylic acid (16.10 g, 82.1 mmol), powdered copper (1.70 g), and quinoline (75 mL) was heated at 185 °C for 2 h. The reaction mixture was cooled and diluted with AcOEt and 2 N HCl. After the insoluble material was filtered off, the organic layer was separated, dried, and concentrated. The residue was chromatographed on silica gel using hexane as an eluent to give **22ii** (11.47 g, 92 %) as a colorless oil. IR (neat): 1424, 1248, 1127 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.11 (1H, dt, $J = 2.6$, 8.8 Hz), 7.29 (1H, d, $J = 5.4$ Hz), 7.49 (1H, dd, $J = 9.6$, 2.6 Hz), 7.53 (1H, d, $J = 5.4$ Hz), 7.80 (1H, dd, $J = 8.8$, 4.8 Hz).

5.16.2. 4-Fluorobenzo[*b*]thiophene (22i). 66% yield from the 2,6-difluorobenzaldehyde. A colorless oil. IR (neat): 1564, 1456, 1420, 1337, 1242, 918, 745, 689 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.03 (1H, ddd, $J = 10.2$, 8.0, 0.8 Hz), 7.24–7.35 (1H, dt, $J = 5.0$, 8.0 Hz), 7.45 (2H, s), 7.65 (1H, d, $J = 8.0$ Hz).

5.16.3. 6-Fluorobenzo[*b*]thiophene (22iii). 20% yield from 2,4-difluorobenzaldehyde. A colorless oil. IR (neat): 1470, 912 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.12 (1H, dt, $J = 2.6$, 8.8 Hz), 7.30 (1H, d, $J = 5.4$ Hz), 7.39 (1H, d, $J = 5.4$ Hz), 7.56 (1H, dd, $J = 8.4$, 2.6 Hz), 7.75 (1H, dd, $J = 8.8$, 5.2 Hz).

5.16.4. 7-Fluorobenzo[*b*]thiophene (22iv). 83% yield from 2,3-difluorobenzaldehyde. A colorless oil. IR (neat): 1559, 1507, 1458, 1399, 1247, 1011, 787, 689 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.04 (1H, dd, $J = 9.6$, 8.0 Hz), 7.28–7.39 (2H, m), 7.48 (1H, d, $J = 5.4$ Hz), 7.62 (1H, d, $J = 8.0$ Hz).

5.17. General procedure for the synthesis of 18

5.17.1. 5-Fluorobenzo[*b*]thiophene-2-carboxaldehyde (18ii). To a solution of **22ii** (5.80 g, 38.1 mmol) in THF (120 mL) was added *n*-BuLi (1.59 M solution in hexane, 28.0 mL, 44.5 mmol) at −78 °C, and the mixture was stirred for 1 h. DMF (6.20 mL, 80.1 mmol) was added, and the mixture was stirred for an additional 1 h, quenched by the addition of aqueous NH_4Cl, and allowed to warm to room temperature. After the separation of the layers, the aqueous layer was further extracted with AcOEt. The organic layers were combined, dried, and concentrated to give **18ii** as colorless crystals (6.77 g, 99%). Mp 122 °C (EtOH). IR (KBr): 1671, 1522, 1169, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.29 (1H, dt, $J = 2.4$, 8.8 Hz), 7.61 (1H, dd, $J = 8.8$, 2.4 Hz), 7.86 (1H, dd, $J = 8.8$, 4.6 Hz), 7.99 (1H, s), 10.11 (1H, s). Anal. Calcd for C_9H_5FOS: C, 59.99; H, 2.80. Found: C, 60.14; H, 2.82.

5.17.2. 4-Fluorobenzo[*b*]thiophen-2-carboxaldehyde (18i). Quantitative yield. Mp 73 °C (EtOH). IR (KBr): 1671, 1559, 1470, 1223, 1179, 1132, 779 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.10 (1H, dd, $J = 9.8$, 8.0 Hz), 7.48 (1H, dt, $J = 5.0$, 8.0 Hz), 7.68 (1H, d, $J = 8.0$ Hz), 8.15 (1H, s), 10.12 (1H, s). Anal. Calcd for C_9H_5FOS: C, 59.99; H, 2.80. Found: C, 59.85; H, 2.87.

5.17.3. 6-Fluorobenzo[*b*]thiophen-2-carboxaldehyde (18iii). Yield 53%. Mp 106 °C (diisopropylether). IR (KBr): 1667, 1601, 1518, 1258, 1190, 1130, 858, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.21 (1H, dt, $J = 2.4$, 8.8 Hz), 7.59 (1H, dd, $J = 8.8$, 2.4 Hz), 7.92 (1H, dd, $J = 8.8$, 5.0 Hz), 8.01 (1H, s), 10.08 (1H, s). Anal. Calcd for C_9H_5FOS: C, 59.99; H, 2.80. Found: C, 60.07; H, 2.78.

5.17.4. 7-Fluorobenzo[*b*]thiophen-2-carboxaldehyde (18iv). Quantitative yield. Mp 79–81.5 °C (EtOH). IR (KBr): 1661, 1468, 1248, 1140, 775, 708, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.22 (1H, dd, $J = 9.6$, 8.0 Hz), 7.42 (1H, dt, $J = 4.8$, 8.0 Hz), 7.76 (1H, d, $J = 8.0$ Hz), 8.06 (1H, d, $J = 3.4$ Hz), 10.13 (1H, s). Anal. Calcd for C_9H_5FOS: C, 59.99; H, 2.80. Found: C, 59.83; H, 2.86.

5.17.5. 5-Fluoro-3-methylbenzo[*b*]thiophene-2-carboxaldehyde (18v). Yield 90%. Mp 150–152 °C (EtOH). IR (KBr): 1653, 1534, 1445, 1169, 853, 662 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.76 (3H, s), 7.28 (1H, dt, $J = 2.6$, 8.8 Hz), 7.54 (1H, dd, $J = 9.6$, 2.6 Hz), 7.82 (1H, dd, $J = 8.8$, 4.8 Hz), 10.33 (1H, s). Anal. Calcd for $C_{10}H_7FOS$: C, 61.84; H, 3.63. Found: C, 61.94; H, 3.54.

5.17.6. 5-Chlorobenzo[*b*]thiophene-2-carboxaldehyde (18vi). Yield 83%, mp 135 °C (EtOH). IR (KBr): 1678, 1516, 1140 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.48 (1H, dd, $J = 8.8$, 2.0 Hz), 7.84 (1H, d, $J = 8.8$ Hz), 7.94 (1H, d, $J = 2.0$ Hz), 7.97 (1H, s), 10.12 (1H, s). Anal. Calcd for C_9H_5ClOS: C, 54.97; H, 2.56. Found: C, 54.89; H, 2.52.

5.17.7. 5-Chloro-3-methylbenzo[*b*]thiophene-2-carboxaldehyde (18vii). Yield 65%. Mp 176–179 °C (AcOEt).

IR (KBr): 1655, 1202, 1078, 870, 806 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.77 (3H, s), 7.47 (1H, dd, $J = 8.6$, 2.0 Hz), 7.80 (1H, d, $J = 8.6$ Hz), 7.87 (1H, d, $J = 2.0$ Hz), 10.33 (1H, s). Anal. Calcd for $C_{10}H_7ClOS$: C, 57.01; H, 3.35. Found: C, 57.14; H, 3.28.

5.17.8. 5-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxaldehyde (18iii). Yield 60%. Mp 146 °C (EtOH). IR (KBr): 1653, 1460, 1198, 829, 667 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.76 (3H, s), 3.91 (3H, s), 7.17 (1H, dd, $J = 8.8$, 2.6 Hz), 7.25 (1H, d, $J = 2.6$ Hz), 7.73 (1H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89. Found: C, 63.95; H, 4.96.

5.18. Preparation of 25

5.18.1. 3-Chloro-1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)propan-1-one. To a mixture of **22v** (9.97 g, 60.0 mmol) and 3-chloropropionyl chloride (7.45 mL, 78.0 mmol) in carbon disulfide (100 mL) was added $AlCl_3$ (16.00 g, 120.0 mmol) with ice cooling. The mixture was stirred at room temperature for 2 h, poured onto crushed ice, diluted with 1 N HCl, and extracted with AcOEt. The extract was washed with water and aqueous $NaHCO_3$, dried, and concentrated, and the residue was suspended in EtOH and collected by filtration to give the title compound as colorless crystals (12.75 g, 83%). Mp 110–112 °C (EtOH). IR (KBr): 1649, 1518, 1368, 1289, 1179, 1152, 876, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.74 (3H, s), 3.42 (2H, t, $J = 6.6$ Hz), 3.93 (2H, t, $J = 6.6$ Hz), 7.28 (1H, dt, $J = 2.2$, 8.8 Hz), 7.53 (1H, dd, $J = 9.4$, 2.2 Hz), 7.79 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{12}H_{10}ClFOS$: C, 56.14; H, 3.93. Found: C, 56.11; H, 3.92.

5.18.2. 3-Chloro-1-(5-chloro-3-methylbenzo[*b*]thiophen-2-yl)propan-1-one. 74% yield from **22vii**. Mp 93 °C (EtOH). IR (KBr): 1667, 1510, 1346, 1179, 1080, 804 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.75 (3H, s), 3.42 (2H, t, $J = 6.6$ Hz), 3.93 (2H, t, $J = 6.6$ Hz), 7.47 (1H, dd, $J = 8.4$, 2.2 Hz), 7.78 (1H, d, $J = 8.4$ Hz), 7.87 (1H, d, $J = 2.2$ Hz). Anal. Calcd for $C_{12}H_{10}Cl_2OS$: C, 52.76; H, 3.69. Found: C, 52.86; H, 3.61.

5.19. Preparation of 26

5.19.1. 1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-one. To a solution of 3-chloro-1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)propan-1-one (10.97 g, 42.7 mmol) in DMF (100 mL) was added imidazole (11.64 g, 171.0 mmol), and the mixture was stirred at room temperature for 1 h, poured into water, and extracted with AcOEt. The extract was washed with water, dried, and concentrated, and the residue was chromatographed on silica gel using AcOEt–EtOH (10:1) as an eluent to give the title compound as colorless crystals (12.00 g, 97%). Mp 122–125 °C (AcOEt). IR (KBr): 1667, 1508, 1433, 1175, 1084, 853, 739, 662 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.72 (3H, s), 3.39 (2H, t, $J = 6.4$ Hz), 4.44 (2H, t, $J = 6.4$ Hz), 7.00 (1H, s), 7.05 (1H, s), 7.28 (1H, dt, $J = 2.2$, 8.8 Hz), 7.52 (1H, dd, $J = 9.4$, 2.2 Hz), 7.58 (1H, s), 7.78 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{15}H_{13}FN_2OS$: C, 62.48; H, 4.54; N, 9.72. Found: C, 62.47; H, 4.63; N, 9.74.

5.19.2. 1-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-one. 73% yield. Mp 106 °C (AcOEt). IR (KBr): 1671, 1508, 1356, 1285, 1225, 1194, 1094, 1078, 804 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.73 (3H, s), 3.39 (2H, t, $J = 6.4$ Hz), 4.44 (2H, t, $J = 6.4$ Hz), 6.99 (1H, s), 7.05 (1H, s), 7.47 (1H, dd, $J = 8.8$, 1.8 Hz), 7.58 (1H, s), 7.76 (1H, d, $J = 8.8$ Hz), 7.85 (1H, d, $J = 1.8$ Hz). Anal. Calcd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 9.19. Found: C, 59.13; H, 4.24; N, 9.24.

5.20. Preparation of 27

5.20.1. 1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-ol. To a solution of 1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-one (9.00 g, 31.2 mmol) in THF–MeOH (1:1, 120 mL) was added $NaBH_4$ (1.18 g, 31.2 mmol) with ice cooling. The mixture was stirred for 0.5 h, concentrated, diluted with water, and extracted with AcOEt. The extract was dried and concentrated to give the title compound as colorless crystals (8.92 g, 98%). mp 100–102 °C (AcOEt). IR (KBr): 3144, 1445, 1179, 1078, 922, 745, 656 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.00–2.42 (2H, m), 2.17 (3H, s), 4.03–4.37 (2H, m), 4.87 (1H, dd, $J = 9.4$, 2.4 Hz), 6.95 (1H, s), 7.02 (1H, s), 7.08 (1H, dt, $J = 2.6$, 8.8 Hz), 7.28 (1H, dd, $J = 9.6$, 2.6 Hz), 7.51 (1H, s), 7.72 (1H, dd, $J = 8.8$, 5.2 Hz). Anal. Calcd for $C_{15}H_{15}FN_2OS$: C, 62.05; H, 5.21; N, 9.65. Found: C, 62.03; H, 5.18; N, 9.75.

5.20.2. 1-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-ol. 97% yield. Mp 160 °C (AcOEt). IR (KBr): 3146, 1514, 1449, 1080, 802, 745 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.04–2.40 (2H, m), 4.00–4.14 (1H, m), 4.25–4.40 (1H, m), 4.78 (1H, dd, $J = 9.6$, 4.8 Hz), 6.93 (1H, s), 6.95 (1H, s), 7.27 (1H, dd, $J = 8.4$, 2.0 Hz), 7.49 (1H, s), 7.58 (1H, d, $J = 2.0$ Hz), 7.70 (1H, d, $J = 8.4$ Hz). Anal. Calcd for $C_{15}H_{15}ClN_2OS$: C, 58.72; H, 4.93; N, 9.13. Found: C, 58.64; H, 4.76; N, 9.14.

5.21. 1-[(*E*)-3-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8e)

A mixture of 1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-1-yl)propan-1-ol (5.00 g, 17.2 mmol) and *p*-toluenesulfonic acid monohydrate (9.83 g, 51.7 mmol) in toluene (150 mL) was heated at reflux for 3 h. The mixture was concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt, and the extract was washed with brine, dried, and concentrated to give **8e** as pale brown crystals (4.65 g, 99%). Mp 132–134 °C (AcOEt). IR (KBr): 1443, 1225, 1169, 959, 860, 828,

797 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 4.76 (2H, d, $J = 6.2$ Hz), 6.19 (1H, dt, $J = 15.4$, 6.2 Hz), 6.80 (1H, d, $J = 15.4$ Hz), 6.99 (1H, s), 7.08 (1H, dt, $J = 2.4$, 8.8 Hz), 7.13 (1H, s), 7.29 (1H, dd, $J = 9.6$, 2.4 Hz), 7.56 (1H, s), 7.65 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{15}H_{13}FN_2S$: C, 66.15; H, 4.81; N, 10.29. Found: C, 66.10; H, 4.75; N, 10.21.

5.22. 1-[(*E*)-3-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (8g)

92% yield. Mp 145 °C (AcOEt). IR (KBr): 3106, 1507, 1437, 1231, 1074, 951, 839, 804 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.34 (3H, s), 4.77 (2H, dd, $J = 6.0$, 1.4 Hz), 6.19 (1H, dt, $J = 15.6$, 6.0 Hz), 6.80 (1H, dt, $J = 15.6$, 1.4 Hz), 7.00 (1H, s), 7.13 (1H, s), 7.29 (1H, dd, $J = 8.4$, 2.2 Hz), 7.57 (1H, s), 7.61 (1H, d, $J = 2.2$ Hz), 7.65 (1H, d, $J = 8.4$ Hz). Anal. Calcd for $C_{15}H_{13}ClN_2S$: C, 62.38; H, 4.54; N, 9.70. Found: C, 62.43; H, 4.48; N, 9.66.

5.23. 4-Acetyl-1-triphenylmethyl-1*H*-imidazole (30)

To a solution of **29**[47] (30.52 g, 90.2 mmol) in THF (500 mL) was added methylmagnesium bromide (3.0 M solution in ether, 32.0 mmol, 96.0 mmol) with ice cooling, and the mixture was stirred for 1 h. The reaction was quenched with aqueous NH_4Cl, layers were separated, and the aqueous phase was further extracted with AcOEt. The organic layers were combined, dried, and concentrated, and the residue was suspended in ether and collected by filtration to give 1-(1-triphenylmethyl-1*H*-imidazol-4-yl)ethanol as colorless crystals (31.40 g, 98%). IR (KBr): 1493, 1445, 1133, 1088, 750, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, d, $J = 6.6$ Hz), 4.85 (1H, q, $J = 6.6$ Hz), 6.72 (1H, s), 7.09–7.40 (16H, m). Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.30; H, 6.14; N, 7.91.This compound (31.00 g, 87.5 mmol) was dissolved in CH_2Cl_2 (300 mL) and manganese(IV) oxide (8.0 g) was added, and the mixture was stirred at room temperature for 12 h. The insoluble material was filtered through Celite pad and the filtered cake was washed with CH_2Cl_2, and the filtrate was concentrated. The residue was suspended in EtOH and collected by filtration to give **30** as colorless crystals (26.35 g, 85%). mp 166–167 °C (EtOH). IR (KBr): 1669, 1534, 1179, 754, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s), 7.09–7.16 (6H, m), 7.30–7.37 (9H, m), 7.44 (1H, d, $J = 1.4$ Hz), 7.58 (1H, d, $J = 1.4$ Hz). Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.65; H, 5.57; N, 8.04.

5.24. Ethyl 3-(1-triphenylmethyl-1*H*-imidazol-4-yl)butylate (31)

To a suspension of sodium hydride (60% dispersion in oil, 3.60 g, 90.0 mmol) in THF (100 mL) was added ethyl diethylphosphonoacetate (20.18 g, 90.0 mmol) with ice cooling, and the mixture was stirred for 1 h. A solution of **30** (20.00 g, 56.8 mmol) in THF (100 mL) was added, and the mixture was stirred at room temperature for 2 h and refluxed for 18 h, diluted with water, and extracted with AcOEt. The extract was dried and concentrated to give ethyl 3-(1-triphenylmethyl-1*H*-imidazol-4-yl)-2-methyl-2-propenoate (21.83 g, 91%). This compound was dissolved in THF–AcOEt (1:1, 400 mL) and 10% Pd–C (20.00 g) was added, and the mixture was stirred at room temperature for 4 h under a hydrogen atmosphere. The catalyst was filtered through Celite pad and the filtrate was concentrated. The residue was dissolved in DMF (250 mL) and the solution was cooled with ice bath. Triethylamine (7.2 mL, 52.0 mmol) and chlorotriphenylmethane (14.50 g, 52.0 mmol) were added, and the mixture was stirred at room temperature for 96 h, washed with water, and extracted with AcOEt. The extract was dried and concentrated, and the residue was chromatographed on silica gel eluting with hexane–AcOEt (4:1) to AcOEt to give **31** as colorless crystals (17.56 g, 80%). Mp 100–102 °C (AcOEt–hexane). IR (KBr): 1726, 762, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, t, $J = 7.0$ Hz), 1.27 (3H, d, $J = 7.0$ Hz), 2.44 (1H, dd, $J = 15.0$, 8.0 Hz), 2.73 (1H, dd, $J = 15.0$, 6.6 Hz), 3.20–3.28 (1H, m), 4.07 (2H, q, $J = 7.0$ Hz), 6.54 (1H, s), 7.08–7.35 (16H, m). Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.24; H, 6.67; N, 6.66.

5.25. 3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)butanal (32)

To a solution of **31** (17.59 g, 41.4 mmol) in THF (260 mL) was added DIBAL (0.96 M solution in hexane, 43.0 mL, 41.3 mmol) at −78 °C, and the reaction mixture was stirred for 1 h. DIBAL (0.96 M solution in hexane, 40.0 mL, 38.4 mmol) was additionally added, and the mixture was stirred for an additional 45 min, quenched by the addition of EtOH (20 mL) followed by water (20 mL), and allowed to warm to room temperature. The insoluble material was filtered through Celite pad and the filtered cake was washed with AcOEt. The filtrate was concentrated and the residue was chromatographed on silica gel using hexane–AcOEt (1:1) as an eluent to give **32** as colorless crystals (12.45 g, 80%). mp 105.5–106 °C (AcOEt–hexane). IR (KBr): 1721, 1491, 1441, 754, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, d, $J = 7.0$ Hz), 2.58 (1H, ddd, $J = 16.2$, 7.0, 2.2 Hz), 2.82 (1H, ddd, $J = 16.2$, 7.0, 2.2 Hz), 3.34 (1H, sextet, $J = 7.0$ Hz), 6.55 (1H, s), 7.08–7.17 (6H, m), 7.29–7.37 (10H, m), 9.76 (1H, t, $J = 2.2$ Hz). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.82; H, 6.22; N, 7.39.

5.26. Synthesis of 4-[(*E*)-3-(benzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazoles (9a–h): General procedure for the synthesis of 33

5.26.1. 1-(5-Fluorobenzo[*b*]thiophen-2-yl)-3-(1-triphenylmethyl-1*H*-imidazol-4-yl)-propan-1-ol. To a solution of **22ii** (2.50 g, 16.4 mmol) in THF (50 mL) was added *n*-BuLi (1.59 M solution in hexane, 10.3 mL, 16.4 mmol) at −78 °C, and the mixture was stirred for 1 h. A solution of **28** (6.01 g, 16.4 mmol) in THF (10 mL) was added, and the mixture was stirred for 1 h, allowed to warm up

to −50 °C over 1 h, quenched by the addition of aqueous NH_4Cl. After the separation of layers, the aqueous layer was further extracted with AcOEt. The organic layer was combined, dried, and concentrated, and the residue was crystallized from acetone to give the title compound as colorless crystals (4.62 g, 55%). mp 206–208 °C (AcOEt–hexane). IR (KBr): 3063, 1447, 1138, 1128, 1088, 1001, 862, 756, 747, 704, 658 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.16–2.33 (2H, m), 2.65–2.90 (2H, m), 5.17 (1H, dd, $J = 6.6$, 4.6 Hz), 6.56 (1H, d, $J = 1.2$ Hz), 7.01 (1H, dt, $J = 2.6$, 8.8 Hz), 7.11–7.18 (7H, m), 7.31–7.39 (11H, m), 7.70 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{33}H_{27}FN_2OS$: C, 76.42; H, 5.25; N, 5.40. Found: C, 76.16; H, 5.21; N, 5.40.

5.27. General procedure for the synthesis of 9a–h

5.27.1. 4-[(*E*)-3-(5-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9b). A mixture of 1-(5-fluorobenzo[*b*]thiophen-2-yl)-3-(1-triphenylmethyl-1*H*-imidazol-4-yl)-propan-1-ol (11.27 g, 21.7 mmol), *p*-toluene- sulfonic acid monohydrate (12.44 g, 65.4 mmol), water (0.77 mL, 43 mmol), and 1,2-dimethoxyethane (500 mL) was heated at reflux for 2 h. The mixture was concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt–THF. The extract was concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (40:1 to 8:1) as an eluent to give **9b** as colorless crystals (0.49 g, 9%) and 1-(5-fluorobenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-4-yl)propan-1-ol as a colorless amorphous solid (4.50 g). The propan-1-ol was heated at reflux for 1 h with *p*-toluenesulfonic acid monohydrate (4.00 g, 21.0 mmol) in toluene (450 mL). The mixture was concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt–THF. The extract was concentrated and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (20:1) as an eluent, followed by crystallization with ether to give **9b** as colorless crystals (2.73 g, 65%). mp 196–197 °C (AcOEt). IR (KBr): 1441, 1175, 955, 868, 835, 806 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.58 (2H, d, $J = 6.8$ Hz), 6.31 (1H, dt, $J = 15.8$, 6.8 Hz), 6.68 (1H, d, $J = 15.8$ Hz), 6.87 (1H, s), 7.02 (1H, dt, $J = 2.6$, 8.8 Hz), 7.02 (1H, s), 7.31 (1H, dd, $J = 9.2$, 2.6 Hz), 7.63 (1H, s), 7.64 (1H, dd, $J = 8.8$, 5.2 Hz). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.10; H, 4.29; N, 10.84. Found: C, 65.06; H, 4.35; N, 10.82.

Compounds **9a** and **9c**–**h** were prepared from the corresponding **22** with **28** (for **9a** and **9c**–**g**) or **32** (for **9h**) by similar procedures.

5.27.2. 4-[(*E*)-3-(4-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9a). 84% yield from **22i**. Mp 131–132 °C (AcOEt). IR (KBr): 1568, 1462, 1248, 1211, 955, 774 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.55 (2H, d, $J = 6.8$ Hz), 6.29 (1H, dt, $J = 15.4$, 6.8 Hz), 6.69 (1H, d, $J = 15.4$ Hz), 6.83 (1H, s), 6.96 (1H, dd, $J = 10.4$, 8.0 Hz), 7.18 (1H, s), 7.22 (1H, dt, $J = 4.8$, 8.0 Hz), 7.50 (1H, d, $J = 8.0$ Hz), 7.61 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 65.18; H, 4.31; N, 10.86.

5.27.3. 4-[(*E*)-3-(6-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9c). 19% yield from **22iii**. Mp 171 °C (AcOEt). IR (KBr): 3069, 2830, 1566, 1468, 1250, 949, 856, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.56 (2H, d, $J = 6.6$ Hz), 6.24 (1H, dt, $J = 15.6$, 6.6 Hz), 6.65 (1H, d, $J = 15.6$ Hz), 6.86 (1H, s), 7.01 (1H, s), 7.03 (1H, dt, $J = 2.2$, 8.8 Hz), 7.40 (1H, dd, $J = 8.8$, 2.2 Hz), 7.57 (1H, dd, $J = 8.8$, 5.2 Hz), 7.61 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 64.99; H, 4.26; N, 10.86.

5.27.4. 4-[(*E*)-3-(7-Fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9d). 62% yield from **22iv**. Mp 119 °C (AcOEt). IR (KBr): 1464, 1238, 945, 818, 777, 710 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 3.55 (2H, d, $J = 6.6$ Hz), 6.33 (1H, dt, $J = 15.6$, 6.6 Hz), 6.68 (1H, d, $J = 15.6$ Hz), 6.83 (1H, s), 6.97 (1H, dd, $J = 9.8$, 8.0 Hz), 7.10 (1H, d, $J = 3.8$ Hz), 7.25 (1H, dt, $J = 4.8$, 8.0 Hz), 7.45 (1H, d, $J = 8.0$ Hz), 7.61 (1H, s). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84. Found: C, 65.01; H, 4.50; N, 10.83.

5.27.5. 4-[(*E*)-3-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9e). 70% yield from **22v**. Mp 170–171 °C (AcOEt). IR (KBr): 1599, 1445, 955, 810, 625 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.60 (2H, d, $J = 7.0$ Hz), 6.27 (1H, dt, $J = 15.4$, 7.0 Hz), 6.81 (1H, d, $J = 15.4$ Hz), 6.87 (1H, s), 7.03 (1H, dt, $J = 2.4$, 8.8 Hz), 7.25 (1H, dd, $J = 10.0$, 2.4 Hz), 7.62 (1H, dd, $J = 8.8$, 4.6 Hz), 7.63 (1H, s). Anal. Calcd for $C_{15}H_{13}FN_2S$: C, 66.15; H, 4.81; N, 10.29. Found: C, 65.96; H, 4.88; N, 10.14.

5.27.6. 4-[(*E*)-3-(3-*tert*-Butyl-5-fluorobenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9f). 16% yield from **22ix**. An amorphous solid. IR (KBr): 2963, 1570, 1449, 1229, 1182, 970, 820, 797 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.44 (9H, s), 3.66 (2H, d, $J = 6.6$ Hz), 6.58 (1H, dt, $J = 15.8$, 6.6 Hz), 6.77 (1H, d, $J = 15.8$ Hz), 6.89 (1H, s), 6.99 (1H, dd, $J = 11.0$, 8.8 Hz), 7.23 (1H, d, $J = 11.0$ Hz), 7.53 (1H, dd, $J = 8.8$, 4.4 Hz), 7.62 (1H, s).

5.27.7. 4-[(*E*)-3-(5,7-Difluoro-3-methylbenzo[*b*]thiophen-2-yl)-2-propen-1-yl]-1*H*-imidazole (9g). 37% yield from **22x**. Mp 152–153 °C (AcOEt). IR (KBr): 3086, 2822, 2640, 1422, 972, 839, 818, 623 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.37 (3H, s), 3.63 (2H, d, $J = 6.0$ Hz), 6.58–6.79 (2H, m), 6.89 (1H, s), 7.12–7.21 (2H, m), 7.64 (1H, s). Anal. Calcd for $C_{15}H_{12}F_2N_2S$: C, 62.05; H, 4.17; N, 9.65. Found: C, 62.00; H, 4.18; N, 9.52.

5.27.8. 4-[(*E*)-4-(5-Fluorobenzo[*b*]thiophen-2-yl)-3-buten-2-yl]-1*H*-imidazole (9h). 41% yield from **22ii**. Mp 153–154 °C (AcOEt). IR (KBr): 1447, 1177, 955, 868, 804, 627 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.47 (3H, d, $J = 7.0$ Hz), 3.69 (1H, quint, $J = 7.0$ Hz), 6.28 (1H, dd, $J = 15.6$, 7.0 Hz), 6.63 (1H, d, $J = 15.6$ Hz), 6.81 (1H, s), 7.02 (1H, dt, $J = 2.6$, 8.8 Hz), 7.03 (1H, s), 7.31 (1H, dd,

$J = 9.6$, 2.6 Hz), 7.61 (1H, s), 7.64 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{15}H_{13}FN_2S$: C, 66.15; H, 4.81; N, 10.29. Found: C, 66.16; H, 4.68; N, 10.27.

5.28. 2-Acetyl-5-fluoro-3-methylbenzo[*b*]thiophene (34)

To a mixture of **22v** (9.97 g, 60.0 mmol) and acetyl chloride (5.55 mL, 78.0 mmol) in carbon disulfide (100 mL) was added $AlCl_3$ (16.0 g, 120.0 mmol) with ice cooling. The mixture was stirred at room temperature for 2 h, poured onto crushed ice, diluted with 1 N HCl, and extracted with AcOEt. The extract was washed with water and aqueous $NaHCO_3$, dried, and concentrated, and the residue was suspended in EtOH and collected by filtration to give **34** as crystals (7.43 g, 59%). mp 80 °C (EtOH). IR (KBr): 1649, 1522, 1441, 1377, 1360, 1294, 1238, 1184, 845, 826 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.64 (3H, s), 2.72 (3H, s), 7.26 (1H, dt, $J = 2.2$, 8.8 Hz), 7.52 (1H, dd, $J = 9.4$, 2.2 Hz), 7.78 (1H, dd, $J = 8.8$, 4.6 Hz). Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found: C, 63.40; H, 4.13.

5.29. (*E*)-1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-4-yl)-2-propen-1-one (35)

To a mixture of **34** (7.13 g, 34.2 mmol) and **29** (12.18 g, 36.0 mmol) in THF–MeOH (1:1, 240 mL) was added 6 N NaOH (15 mL) with ice cooling, and the mixture was stirred at room temperature for 4 h and diluted with water. The precipitate was collected by filtration and washed with EtOH to give (*E*)-1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1-triphenylmethyl-1*H*-imidazol-4-yl)-2-propen-1-one as colorless crystals (18.35 g, quantitative yield). This compound (5.10 g, 9.7 mmol) was suspended in 1,2-dimethoxyethane (150 mL) and *p*-toluenesulfonic acid monohydrate (5.71 g, 30.0 mmol) was added, and the mixture was refluxed for 2 h and cooled. The precipitate was collected by filtration and dissolved in AcOEt–THF, and the solution was washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was suspended in ether and collected by filtration to give **35** as crystals (2.37 g, 86%). mp 223–226 °C decomp. (MeOH). IR (KBr): 1661, 1607, 1518, 1292, 1181, 860, 804, 652 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.73 (3H, s), 7.40 (1H, d, $J = 15.0$ Hz), 7.46 (1H, dt, $J = 2.4$, 8.8 Hz), 7.71 (1H, d, $J = 15.0$ Hz), 7.71 (1H, s), 7.85 (1H, dd, $J = 10.2$, 2.4 Hz), 7.87 (1H, s), 8.12 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for $C_{15}H_{11}FN_2OS$: C, 62.92; H, 3.87; N, 9.78. Found: C, 62.91; H, 3.70; N, 9.71.

5.30. 1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-4-yl)-1-butanone (36) and (*E*)-2-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-4-(1*H*-imidazol-4-yl)-3-buten-2-ol (37)

To a suspension of **35** (10.74 g, 37.5 mmol) in THF (900 mL) was added methylmagnesium bromide (3.0 M solution in ether, 41.5 mL, 124.5 mmol) with ice cooling, and the mixture was stirred for 0.5 h and quenched with 20% NH_4Cl. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layers were combined, dried, and concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (40:1 to 10:1) to give **36** as an amorphous solid (7.51 g, 66%) and **37** as crystals (2.79 g, 25%).

36: IR (KBr): 1671, 1514, 1296, 1167, 805, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (3H, d, $J = 7.0$ Hz), 2.71 (3H, s), 3.17 (1H, dd, $J = 17.0$, 5.8 Hz), 3.34 (1H, dd, $J = 17.0$, 7.4 Hz), 3.50–3.67 (1H, m), 6.85 (1H, s), 7.25 (1H, dt, $J = 2.6$, 8.8 Hz), 7.50 (1H, dd, $J = 9.4$, 2.6 Hz), 7.57 (1H, s), 7.76 (1H, dd, $J = 8.8$, 4.8 Hz).

37: mp 169–172 °C (AcOEt). IR (KBr): 3125, 1605, 1443, 1167, 1132, 1088, 970, 922, 853, 801, 656 cm^{-1}. ^1H NMR ($CDCl_3$+CD_3OD) δ: 1.82 (3H, s), 2.32 (3H, s), 6.48 (1H, d, $J = 16.0$ Hz), 6.51 (1H, d, $J = 16.0$ Hz), 6.90 (1H, s), 7.03 (1H, dt, $J = 2.4$, 8.8 Hz), 7.25 (1H, dd, $J = 9.8$, 2.4 Hz), 7.50 (1H, s), 7.66 (1H, dd, $J = 8.8$, 5.0 Hz). Anal. Calcd for $C_{16}H_{15}FN_2OS$: C, 63.56; H, 5.00; N, 9.26. Found: C, 63.28; H, 5.13; N, 9.00.

5.31. 1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-4-yl)-4-methyl-1-pentanone (38) and (*E*)-3-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-1-(1*H*-imidazol-4-yl)-4-methyl-1-penten-3-ol (39)

To a suspension of **35** (500 mg, 1.75 mmol) in THF (40 mL) was added isopropylmagnesium chloride (2.0 M solution in THF, 2.8 mL, 5.6 mmol) with ice cooling, and the mixture was stirred for 1 h and quenched with 20% NH_4Cl. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layers were combined, dried, and concentrated, and the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (40:1 to 10:1) to give **38** as an amorphous solid (222 mg, 38%) and **39** as an amorphous solid (135 mg, 23%).

38: IR (KBr): 2961, 1672, 1514, 1165, 806, 662 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (3H, d, $J = 7.0$ Hz), 0.99 (3H, d, $J = 7.0$ Hz), 2.07–2.22 (1H, m), 2.67 (3H, s), 3.18–3.26 (2H, m), 3.43 (1H, dd, $J = 17.4$, 9.6 Hz), 6.82 (1H, s), 7.24 (1H, dt, $J = 2.6$, 8.8 Hz), 7.48 (1H, dd, $J = 9.8$, 2.6 Hz), 7.54 (1H, s), 7.76 (1H, dd, $J = 8.8$, 4.8 Hz).

39: IR (KBr): 2969, 1605, 1443, 1132, 1111, 972, 922, 801, 660 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.92 (3H, d, $J = 6.6$ Hz), 1.03 (3H, d, $J = 6.6$ Hz), 2.37 (3H, s), 2.48 (1H, sept, $J = 6.6$ Hz), 6.60 (1H, d, $J = 15.8$ Hz), 6.76 (1H, d, $J = 15.8$ Hz), 6.93 (1H, s), 7.01 (1H, dt, $J = 2.6$, 8.8 Hz), 7.24 (1H, dd, $J = 9.8$, 2.6 Hz), 7.55 (1H, s), 7.65 (1H, dd, $J = 8.8$, 4.8 Hz).

5.32. 4-[(*E*)-4-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-buten-2-yl]-1*H*-imidazole (9i)

To a solution of **36** (7.51 g, 24.8 mmol) in THF–MeOH (5:1, 150 mL) was added $NaBH_4$ (0.95 g, 25.0 mmol) with ice cooling. The mixture was stirred for 1 h, poured into 20% NH_4Cl, and extracted with AcOEt. The extract

was dried and concentrated to give 1-(5-fluoro-3-methylbenzo[*b*]thiophen-2-yl)-3-(1*H*-imidazol-4-yl)-1-butan-1-ol as colorless crystals. This alcohol was heated at reflux for 1 h with *p*-toluenesulfonic acid monohydrate (14.27 g, 75.0 mmol) in 1,2-dimethoxyethane (150 mL). The mixture was concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt–THF. The extract was dried and concentrated, and the residue was chromatographed on silica gel using AcOEt–EtOH (10:1) as an eluent, followed by recrystallization to give **9i** as colorless prisms (5.49 g, 77%). mp 158–159 °C. IR (KBr): 1601, 1443, 1169, 941, 847, 826, 800, 658, 631 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.50 (3H, d, $J = 7.0$ Hz), 2.32 (3H, s), 3.73 (1H, quint, $J = 7.0$ Hz), 6.25 (1H, dd, $J = 15.6$, 7.0 Hz), 6.77 (1H, d, $J = 15.6$ Hz), 6.86 (1H, s), 7.03 (1H, dt, $J = 2.6$, 8.8 Hz), 7.25 (1H, dd, $J = 9.8$, 2.6 Hz), 7.62 (1H, dd, $J = 8.8$, 4.8 Hz), 7.63 (1H, s). Anal. Calcd for $C_{16}H_{15}FN_2S$: C, 67.11; H, 5.28; N, 9.78. Found: C, 67.01; H, 5.15; N, 10.03.

5.33. 4-[(*E*)-1-(5-Fluoro-3-methylbenzo[*b*]thiophen-2-yl)-4-methyl-1-penten-3-yl]-1*H*-imidazole (9j)

Prepared from **38** by the method described for **9i** in 80% yield. An amorphous solid. IR (KBr): 2961, 1601, 1445, 1169, 953, 920, 851, 799, 656, 631 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.95 (3H, d, $J = 7.2$ Hz), 0.99 (3H, d, $J = 7.2$ Hz), 2.14–2.30 (1H, m), 2.32 (3H, s), 3.33 (1H, dd, $J = 9.0$, 7.2 Hz), 6.28 (1H, dd, $J = 15.6$, 9.0 Hz), 6.76 (1H, d, $J = 15.6$ Hz), 6.86 (1H, s), 7.03 (1H, dt, $J = 2.6$, 8.8 Hz), 7.24 (1H, dd, $J = 9.6$, 2.6 Hz), 7.63 (1H, dd, $J = 8.8$, 4.8 Hz), 7.63 (1H, s).

5.34. Optical resolution of 9i

Separation of **9i** into its enantiomers (*S*)-**9i** and (*R*)-**9i** was carried out by HPLC using Chiralcel® OD (4.6 mm i.d. × 250 mm) with detection at 254 nm. Elution with a mixture of 2-propanol–hexane (8:92) at a flow rate of 0.7 mL/min at room temperature gave (*S*)-**9i** and (*R*)-**9i**. (*S*)-**9i**: retention time = 23.0 min. $[\alpha]_D^{20}$ −5.1 (*c* 0.498, MeOH). (*R*)-**9i**: retention time = 29.1 min. $[\alpha]_D^{20}$ +5.0 (*c* 0.503, MeOH).

5.35. Ethyl 2-methyl-2-(1*H*-imidazol-4-yl)propanoate (42)

A mixture of **41**[48] (54.5 g, 230 mmol) and formamide (220 g, 4.88 mol) was heated at 120 °C for 2 h and at 160 °C for 18 h. The mixture was cooled to room temperature, diluted with aqueous $NaHCO_3$, and extracted with AcOEt. The extract was concentrated and then excess formamide was removed by distillation under reduced pressure. The residue was crystallized from ether to give **42** as colorless crystals (8.40 g, 20%). mp 91.5–93.0 °C (AcOEt–hexane). IR (KBr): 2988, 1719, 1264, 1161, 1140, 982, 853, 631 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.24 (3H, t, $J = 7.2$ Hz), 1.58 (6H, s), 4.16 (2H, q, $J = 7.2$ Hz), 6.90 (1H, s), 7.60 (1H, s). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.11; H, 7.62; N, 15.30.

5.36. Ethyl 2-methyl-2-(1-triphenylmethyl-1*H*-imidazol-4-yl)propanoate (43)

To a mixture of **42** (4.00 g, 22.0 mmol) and triethylamine (3.66 mL, 26.3 mmol) in DMF (50 mL) was added chlorotriphenylmethane (6.22 g, 22.3 mmol) with ice cooling. The mixture was stirred at room temperature for 2 h, diluted with water, and extracted with AcOEt. The extract was washed with water, dried, and concentrated, and the residue was suspended in diisopropylether and collected by filtration to give **43** as colorless crystals (8.20 g, 88%). mp 118–119 °C (AcOEt–hexane). IR (KBr): 1726, 1493, 1447, 1252, 1142, 758, 745, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.16 (3H, t, $J = 7.0$ Hz), 1.52 (6H, s), 4.10 (2H, q, $J = 7.0$ Hz), 6.65 (1H, d, $J = 1.0$ Hz), 7.10–7.15 (6H, m), 7.31–7.34 (10H, m). Anal. Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.30; H, 6.46; N, 6.81.

5.37. 2-Methyl-2-(1-triphenylmethyl-1*H*-imidazol-4-yl)propanal (44)

Prepared from **43** by the method described for **32** in 67% yield. Mp 114–115.5 °C (AcOEt–hexane). IR (KBr): 1721, 1493, 1447, 1184, 748, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.39 (6H, s), 6.66 (1H, d, $J = 1.2$ Hz), 7.09–7.16 (6H, m), 7.30–7.35 (9H, m), 7.41 (1H, d, $J = 1.2$ Hz), 9.60 (1H, s). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.04; H, 6.06; N, 7.53.

5.38. Diethyl (5-fluorobenzo[*b*]thiophen-2-yl)methylphosphonate (40)

To a suspension of $LiAlH_4$ (1.69 g, 44.6 mmol) in THF (100 mL) was added a solution of **24ii** (10.00 g, 44.6 mmol) in THF (80 mL) with ice cooling. The mixture was stirred at room temperature for 1 h, quenched by the addition of water, and diluted with 1 N HCl. After separation of the layers, the aqueous layer was further extracted with AcOEt. The organic layers were combined, washed with aqueous $NaHCO_3$, dried, and concentrated to give (5-fluorobenzo[*b*]thiophen-2-yl)methanol as colorless crystals (7.80 g, 96%). mp 94 °C (diisopropylether–hexane). IR (KBr): 3277, 1605, 1449, 1013, 874, 814 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.93 (2H, s), 7.07 (1H, dt, $J = 2.6$, 8.8 Hz), 7.18 (1H, s), 7.39 (1H, dd, $J = 9.6$, 2.6 Hz), 7.74 (1H, dd, $J = 8.8$, 4.8 Hz). Anal. Calcd for C_9H_7FOS: C, 59.32; H, 3.87. Found: C, 59.18; H, 3.90. This alcohol (2.98 g, 16.4 mmol) was dissolved in THF (15 mL) and the solution was cooled with an ice bath. Thionyl chloride (3.50 mL, 48.0 mmol) was added, and the mixture was stirred at room temperature for 2 h and at reflux for 1 h, concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt. The extract was dried and concentrated, and the residue was chromatographed on silica gel using hexane as an eluent to give 2-chloromethyl-5-fluorobenzo[*b*]thiophene as colorless crystals (2.26 g, 69%). This compound (2.00 g, 9.97 mmol) was heated at 160 °C for 3 h with triethylphosphite (3.46 g, 20.8 mmol), and then excess triethylphosphite was removed under reduced pressure.

The residue was chromatographed on silica gel using hexane–AcOEt (1:1) as an eluent to give **40** (2.69 g, 89%) as a colorless oil. IR (neat): 1445, 1051, 1026 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.30 (6H, t, $J = 7.2$ Hz), 3.43 (2H, d, $J = 21.4$ Hz), 4.09 (2H, q, $J = 7.2$ Hz), 4.13 (2H, q, $J = 7.2$ Hz), 7.05 (1H, ddt, $J = 2.4$, 1.0, 8.8 Hz), 7.17 (1H, dd, $J = 2.4$, 1.0 Hz), 7.36 (1H, dd, $J = 9.6$, 2.4 Hz), 7.68 (1H, dd, $J = 8.8$, 4.8 Hz).

5.39. 4-(*E*)-4-(5-Fluorobenzo[*b*]thiophen-2-yl)-2-methyl-3-buten-2-yl]-1*H*-imidazole (9k)

To a suspension of sodium hydride (60% dispersion in oil, 370 mg, 9.2 mmol) in THF (8 mL) was added a solution of **40** (2.54 g, 8.4 mmol) in THF (10 mL) with ice cooling, and the mixture was stirred for 1 h. A solution of **44** (3.20 g, 8.4 mmol) in THF (20 mL) was added, and the mixture was stirred at room temperature for 18 h, diluted with water, and extracted with AcOEt. The extract was dried and concentrated, and the residue was suspended in diisopropylether and collected by filtration to give 4-[(*E*)-4-(5-fluorobenzo[*b*]thiophen-2-yl)-2-methyl-3-buten-2-yl]-1-triphenylmethyl-1*H*-imidazole (4.08 g, 92%). This compound (3.94 g, 7.45 mmol) was heated with pyridinium chloride (1.04 g, 9.0 mmol) in MeOH (60 mL) at 60 °C for 4.5 h. The mixture was concentrated, diluted with aqueous $NaHCO_3$, and extracted with AcOEt–THF. The extract was dried and concentrated, and the residue was chromatographed on silica gel using AcOEt–EtOH (20:1) as an eluent to give **9k** as colorless crystals (2.22 g, 98%). mp 160–163 °C (AcOEt–hexane). IR (KBr): 1599, 1443, 1175, 1127, 957, 870, 801, 629 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.52 (6H, s), 6.37 (1H, d, $J = 16.0$ Hz), 6.55 (1H, d, $J = 16.0$ Hz), 6.85 (1H, s), 7.01 (1H, dt, $J = 2.4$, 8.8 Hz), 7.02 (1H, s), 7.30 (1H, dd, $J = 9.4$, 2.4 Hz), 7.63 (1H, dd, $J = 8.8$, 4.8 Hz), 7.64 (1H, s). Anal. Calcd for $C_{16}H_{15}FN_2S$: C, 67.11; H, 5.28; N, 9.78. Found: C, 67.31; H, 5.28; N, 9.82.

5.40. Single-crystal X-ray analysis of (*R*)-9i

An analytical sample of (*R*)-**9i** as the fumarate for X-ray analysis was obtained by recrystallization from MeOH. X-ray measurement was performed on a Rigaku AFC5R diffractometer with Cu-Kα radiation. Crystal data for (*R*)-**9i** fumarate: $[C_{16}H_{16}FN_2S]^+[C_4H_3O_4]^-$, $M = 402.4$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 15.567(1)$ Å, $b = 15.700(1)$ Å, $c = 7.977(1)$ Å, $V = 1949.7(4)$ $Å^3$, $D_{calcd} = 1.371$ g/cm^3, $Z = 4$; Final R values were $R_1 = 0.047$ for 2080 reflections with $F_o > 4\sigma(F_o)$, $wR_2 = 0.123$ for all the 3375 reflections. The absolute configuration was determined by the Flack parameter[52] of 0.03(4). Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 228638).

5.41. Molecular modeling studies

The conformations of **9k**, 17α-hydroxypregnenolone, and CB-7630 were generated using the Discover cvff force field (ver. 98.0, Molecular Simulations Inc., San Diego, CA). The superimposition between **9k** and 17α-hydroxypregnenolone was created as follows. It was hypothesized that one of the imidazole nitrogen of **9k** and the pyridine nitrogen of CB-7630 exist at similar positions because both atoms probably make the coordinate bonds with the heme iron in the enzyme. According to this hypothesis, **9k** and CB-7630 were superimposed using the overlap function of Insight II (ver. 2000, Molecular Simulations Inc., San Diego, CA) under the condition that the two nitrogen atoms existed close in space. After some trials, an overlap was chosen on the basis of the intersection volume between two molecules. Conformational stability of **9k** was also considered by comparing with the most stable conformation, which was generated in the previous search. The adopted conformation of **9k** differed only by 9 kcal/mol from the most stable conformation. Then, the steroidal scaffold with the most stable conformation of 17α-hydroxypregnenolone was overlaid on that of CB-7630 using the overlap selected above.

5.42. Assay of inhibitory activity on rat $C_{17,20}$-lyase

Inhibitory activity against rat $C_{17,20}$-lyase was determined by the method described previously with some modifications.[27] Testes excised from 13-week old, male SD rats were homogenized, and testicular microsomes were prepared by a series of centrifugations. The reaction mixture contains 75 mM phosphate buffer (pH 7.4), 7 μg of the microsome protein, 10 nM [1,2-^{3}H]-17α-hydroxyprogesterone (NEN), 5 mM NADPH (Oriental Yeast), and test compounds in a total volume of 20 μL. The test compounds were serially diluted with dimethylformamide, and then fivefold diluted with distilled water. Test compound solution, 5 μL, was added to the reaction mixture. The reaction was terminated by addition of 40 μL of ethyl acetate after 15 min incubation at 37 °C, then vortexed for 30 s and briefly centrifuged. The organic phase, 30 μL, was applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and the products (androstenedione and testosterone) were separated in the toluene–acetone (7:2) solvent system. Detection of the spots and measurement of the radioactivity as PSL were performed with a BAS2000 Bio-image analyzer (FUJIX). The concentration of the test compounds necessary to reduce the concentration of the products by 50% (the concentration in the control group in which no test compound is added is set to 100%) was calculated.

5.43. Assay of inhibitory activity on human $C_{17,20}$-lyase

Human $C_{17,20}$-lyase was expressed in *E. Coli* with N-terminal sequence modification (MALLLAVF) as described previously. [51] The vector pCWori$^+$ was obtained as a generous gift from Dr. F. W. Dahlquist (University of Oregon). The membrane fraction prepared from *E. Coli* expressing human $C_{17,20}$-lyase was used for the following assay.

The reaction mixture contains 75 mM phosphate buffer (pH 7.4), 1 mM magnesium chloride, 0.5 pmol of recombinant $C_{17,20}$-lyase, 0.5 pmol of recombinant cytochrome b5 (Pan Vera), 20.8 ng of recombinant NADPH-cytochrome P450 reductase (Pan Vera), 10 nM [1,2-^{3}H]-17α-hydroxypregnenolone (Amersham), 5 mM NADPH (Oriental Yeast), and test compounds in a total volume of 20 μL. The reaction was terminated by addition of 40 μL of ethyl acetate after 15 min incubation at 37 °C, then vortexed for 30 s and briefly centrifuged. The organic phase, 30 μL, was applied to silica gel thin layer chromatography plates (Whatman, LHPK). The substrate and the product (DHEA) were separated in the cyclohexane–ethyl acetate (3:2) solvent system. The following procedures were the same as the assay of rat enzyme inhibitory activity described above, and IC_{50} value was determined.

5.44. Assay of inhibitory effects on testosterone biosynthesis in rats

Test compounds were suspended in 0.5% methylcellulose and orally administered to 9 or 10-week old, male SD (Sprague-Dawley) rats at a dose of 25 mg/kg. The rats in the control group received 0.5% methylcellulose. Blood samples were obtained 2 and 5 h after the administration. The serum testosterone concentrations were determined by a specific radioimmunoassay kit (Dia Sorin s.r.l, Italy). The percentage of the testosterone concentration of the group of rats, which received test compounds to that of the control group was calculated (T/C, %), and regarded as the inhibitory activity.

Acknowledgements

We thank Drs. A. Miyake and T. Naka for helpful discussions throughout this work, and Mr. A. Fujishima and Ms. K. Higashikawa for measuring a single-crystal X-ray Analysis, and Dr. F. W. Dahlquist (University of Oregon) for providing pCWori$^+$.

References and notes

1. Crawford, E. D.; Eisenberger, M. A.; McLeod, D. G.; Spaulding, J. T.; Benson, R.; Dorr, F. A.; Blumenstein, B. A.; Davis, M. A.; Goodman, P. J. *New Engl. J. Med.* **1989**, *321*, 419.
2. Labrie, F.; Belanger, A.; Simard, J.; Labrie, C.; Dupont, A. *Cancer Suppl.* **1993**, *71*, 1059.
3. Hara, T.; Miyazaki, J.; Araki, H.; Yamaoka, M.; Kanzaki, N.; Kusaka, M.; Miyamoto, M. *Cancer Res.* **2003**, *63*, 149.
4. Taplin, M.-E.; Bubley, G. J.; Ko, Y.-J.; Small, E. J.; Upton, M.; Rajeshkumar, B.; Balk, S. P. *Cancer Res.* **1999**, *59*, 2511.
5. Culig, Z.; Hobisch, A.; Cronauer, M. V.; Cato, A. C.; Hittmair, A.; Radmayr, C.; Eberle, J.; Bartsch, G.; Klocker, H. *Mol. Endocrinol.* **1993**, *7*, 1541.
6. Tan, J.; Sharief, Y.; Hamil, K. G.; Gregory, C. W.; Zang, D.-Y.; Sar, M.; Gumerlock, P. H.; deVere White, R. W.; Pretlow, T. G.; Harris, S. E.; Wilson, E. M.; Mohler, J. L.; French, F. S. *Mol. Endocrinol.* **1997**, *11*, 450.
7. Akhtar, M.; Corina, D. L.; Miller, S. L.; Shyadehi, A. Z.; Wright, J. N. *J. Chem. Soc., Perkin Trans. 1* **1994**, 263.
8. Swinney, D. C.; Mak, A. Y. *Biochemistry* **1994**, *33*, 2185.
9. Akhtar, M.; Corina, D.; Miller, S.; Shyadehi, A. Z.; Wright, J. N. *Biochemistry* **1994**, *33*, 4410.
10. Wauwe, J. P. V.; Janssen, P. A. J. *J. Med. Chem.* **1989**, *32*, 2231.
11. Jarman, M.; Smith, H. J.; Nicholls, P. J.; Simons, C. *Nat. Prod. Rep.* **1998**, 495.
12. Rajfer, J.; Sikka, S. C.; Rivera, F.; Handelsman, D. J. *J. Clin. Endocrinol. Metab.* **1986**, *63*, 1193.
13. Trachtenberg, J. *J. Urol.* **1984**, *132*, 61.
14. Williams, G.; Kerle, D. J.; Doble, A.; Dunlop, H.; Smith, C.; Allen, J.; Yeo, T.; Blooms, S. R. *Br. J. Urol.* **1986**, *58*, 45.
15. Coster, R. D.; Wouters, W.; Bruynseels, J. *J. Steroid Biochem. Mol. Biol.* **1996**, *56*, 133.
16. Potter, G. A.; Barrie, S. E.; Jarman, M.; Rowlands, M. G. *J. Med. Chem.* **1995**, *38*, 2463.
17. Barrie, S. E.; Potter, G. A.; Goddard, P. M.; Haynes, B. P.; Dowsett, M.; Jarman, M. *J. Steroid Biochem. Mol. Biol.* **1994**, *50*, 267.
18. Cherry, P. C.; Cocker, J. D.; Searle, A. D. WO 94/27989; *Chem. Abstr.* **1995**, *123*, 83368.
19. Ideyama, Y.; Kudoh, M.; Tanimoto, K.; Susaki, Y.; Nanya, T.; Nakahara, T.; Ishikawa, H.; Yoden, T.; Okada, M.; Fujikura, T.; Akaza, H.; Shikama, H. *Prostate* **1998**, *37*, 10.
20. L-39 (University of Maryland): Long, B. J.; Grigoryev, D. N.; Nnane, I. P.; Liu, Y.; Ling, Y.-z.; Brodie, A. M. *Cancer Res.* **2000**, *60*, 6630.
21. BW 19 (University of the Saarland): Hartmann, R. W.; Wächter, G.; Hector, M.; Wachall, B. 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, CA, Apr. 6–10, 2002, #1020.
22. Nnane, I. P.; Long, B. J.; Ling, Y.-z.; Grigoryev, D. N.; Brodie, A. M. *Br. J. Cancer* **2000**, *83*, 74.
23. Njar, V. C. O.; Brodie, A. M. H. *Curr. Pharm. Des.* **1999**, *5*, 163.
24. Njar, V. C. O.; Kato, K.; Nnane, I. P.; Grigoryev, D. N.; Long, B. J.; Brodie, A. M. H. *J. Med. Chem.* **1998**, *41*, 902.
25. Ling, Y.-z.; Li, J.-s.; Liu, Y.; Kato, K.; Klus, G. T.; Brodie, A. *J. Med. Chem.* **1997**, *40*, 3297.
26. Li, J.-s.; Li, Y.; Son, C.; Brodie, A. M. H. *J. Med. Chem.* **1996**, *39*, 4335.
27. Li, J.-s.; Li, Y.; Son, C.; Brodie, A. M. H. *Prostate* **1995**, *26*, 140.
28. Njar, V. C. O.; Klus, G. T.; Johnson, H. H.; Brodie, A. M. H. *Steroids* **1997**, *62*, 468.
29. Recanatini, M.; Bisi, A.; Cavalli, A.; Belluti, F.; Gobbi, S.; Rampa, A.; Valenti, P.; Palzer, M.; Palusczak, A.; Hartmann, R. W. *J. Med. Chem.* **2001**, *44*, 672.
30. Hartmann, R. W.; Hector, M.; Wachall, B. G.; Palusczak, A.; Palzer, M.; Huch, V.; Veith, M. *J. Med. Chem.* **2000**, *43*, 4437.
31. Hartmann, R. W.; Hector, M.; Haidar, S.; Ehmer, P. B.; Reichert, W.; Jose, J. *J. Med. Chem.* **2000**, *43*, 4266.
32. Zhuang, Y.; Wachall, B. G.; Hartmann, R. W. *Bioorg. Med. Chem.* **2000**, *8*, 1245.
33. Wachall, B. G.; Hector, M.; Zhuang, Y.; Hartmann, R. W. *Bioorg. Med. Chem.* **1999**, *7*, 1913.
34. Njar, V. C. O.; Hector, M.; Hartmann, R. W. *Bioorg. Med. Chem.* **1996**, *4*, 1447.
35. Wächter, G. A.; Hartmann, R. W.; Sergejew, T.; Grün, G. L.; Ledergerber, D. *J. Med. Chem.* **1996**, *39*, 834.
36. McCague, R.; Rowlands, M. G.; Barrie, S. E.; Houghton, J. *J. Med. Chem.* **1990**, *33*, 3050.

37. Barrie, S. E.; Jarman, M. *Endocrine-Relat. Cancer* **1996**, *3*, 25.
38. Burkhart, J. P.; Gates, C. A.; Laughlin, M. E.; Resvick, R. J.; Peet, N. P. *Bioorg. Med. Chem.* **1996**, *4*, 1411.
39. Guarna, A.; Occhiato, E. G.; Machetti, F.; Giacomelli, V. *J. Org. Chem.* **1999**, *64*, 4985.
40. Arth, G. E.; Patchett, A. A.; Jefopoulus, T.; Bugianesi, R. L.; Peterson, L. H. *J. Med. Chem.* **1971**, *14*, 675.
41. Ayub, M.; Levell, M. J. *J. Steroid Biochem.* **1987**, *28*, 521.
42. Angelastro, M. R.; Laughlin, M. E.; Schatzman, G. L.; Bey, P.; Blohm, T. R. *Biochem. Biophys. Res. Commun.* **1989**, *162*, 1571.
43. Plé, P. A.; Marnett, L. J. *J. Heterocycl. Chem.* **1988**, *25*, 1271.
44. Chapman, N. B.; Clarke, K.; Saraf, S. D. *J. Chem. Soc. (C)* **1967**, 731.
45. Beck, J. B. *J. Org. Chem.* **1972**, *37*, 3224.
46. Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E.; Bhatnager, A. *J. Med. Chem.* **1991**, *34*, 725.
47. Burger, A.; Bernabe, M. *J. Med. Chem.* **1971**, *14*, 883.
48. Julia, P. M.; Igolen, J.; Igolen, H. *Bull. Soc. Chim. Fr.* **1962**, 1060.
49. Compound **4** was unknown when we were developing this study, but was reported by Hartmann recently.[33]
50. Machinist, J. M.; Mayer, M. D.; Shet, M. S.; Ferrero, J. L.; Rodrigues, A. D. *Drug Metab. Dispos.* **1995**, *23*, 1163.
51. Imai, T.; Globerman, H.; Gertner, J. M.; Kagawa, N.; Waterman, M. R. *J. Biol. Chem.* **1993**, *268*, 19681.
52. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.