学位の種類	博士（薬科学）
報告番号	乙第１８８３号
学位記番号	論　第１９８号
氏名	西田　晴行
授与年月日	平成 29 年 9 月 28 日
学位論文の題名	酸関連疾患治療の課題克服を目指したカリウムイオン競合型アシッドブロッカー(P-CABs)の探索合成研究
論文審査担当者	主査：　樋口 恒彦 副査：　中川 秀彦，中村 精一，山村 壽男

名古屋市立大学学位論文

酸関連疾患治療の課題克服を目指したカリウムイオン競合型アシッドブロッカー（P-CABs）の探索合成研究

2017 年度（2017 年 9 月）

西田 晴行

1. 本論文は、2017 年 9 月に名古屋市立大学大学院薬学研究科において審査されたものである。

   主査　樋口　恒彦　教授
   副査　中川　秀彦　教授
   副査　中村　精一　教授
   副査　山村　寿男　准教授

2. 本論文は、学術情報雑誌に収載された次の報文を基礎とするものである。

   1) Haruyuki Nishida, Atsushi Hasuoka, Yasuyoshi Arikawa, Osamu Kurasawa, Keizo Hirase, Nobuhiro Inatomi, Yasunobu Hori, Fumihiko Sato, Naoki Tarui, Akio Imanishi, Mitsuyo Kondo, Terufumi Takagi, and Masahiro Kajino.
      Discovery, synthesis, and biological evaluation of novel pyrrole derivatives as highly selective potassium-competitive acid blockers.
      Bioorg. Med. Chem., **20**, 3925-3938 (2012).
   2) Haruyuki Nishida, Yasuyoshi Arikawa, Keizo Hirase, Toshihiro Imaeda, Nobuhiro Inatomi, Yasunobu Hori, Jun Matsukawa, Yasushi Fujioka, Teruki Hamada, Motoo Iida, Mitsuyoshi Nishitani, Akio Imanishi, Hideo Fukui, Fumio Itoh, and Masahiro Kajino.
      Identification of a novel fluoropyrrole derivative as a potassium-competitive acid blocker with long duration of action
      Bioorg. Med. Chem., **25**, 3298-3314 (2017).
   3) Haruyuki Nishida, Ikuo Fujimori, Yasuyoshi Arikawa, Keizo Hirase, Koji Ono, Kazuo Nakai, Nobuhiro Inatomi, Yasunobu Hori, Jun Matsukawa, Yasushi Fujioka, Akio Imanishi, Hideo Fukui, and Fumio Itoh.
      Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion
      Bioorg. Med. Chem., **25**, 3447-3460 (2017).

3. 本論文の基礎となる研究は、武田薬品工業株式会社において梶野正博博士、伊藤文雄博士および稲富信博博士の指導の下に行われた。

略語表

Ac	acetyl	アセチル
ADME-Tox	absorption, distribution, metabolism, excretion and toxicity	吸収、分布、代謝、排泄および毒性
Ar	aryl	アリール
AUC	area under the curve	曲線下面積
Bn	benzyl	ベンジル
Boc	*tert*-butoxycarbonyl	*tert*-ブトキシカルボニル
Cmax	maximum plasma or stomach concentration	最大血漿中または胃内濃度
CYP2C19	hepatic cytochrome P450 2C19	肝シトクローム P450 2C19
CYP3A4	hepatic cytochrome P450 3A4	肝シトクローム P450 3A4
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	ジアザビシクロウンデセン
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone	2,3-ジクロロ-5,6-ジシアノ-*p*-ベンゾキノン
DIBAL-H	Diisobutylaluminium hydride	水素化ジイソブチルアルミニウム
DMAP	*N*,*N*-dimethyl-4-aminopyridine	*N*,*N*-ジメチル-4-アミノピリジン
DMB	2,4-dimethoxybenzyl	2,4-ジメトキシベンジル
DME	1,2-dimethoxyethane	1,2-ジメトキシエタン
DMF	*N*,*N*-dimethylformamide	*N*,*N*-ジメチルホルムアミド
DMPK	drug metabolism and pharmacokinetics	薬物代謝および薬物動態
DMSO	dimethyl sulfoxide	ジメチルスルホキシド
DSC	differential scanning calorimetry	示差走査熱量測定
EM	extensive metabolizer	酵素活性通常者
ESI	electrospray ionization	エレクトロスプレーイオン化
GERD	gastro-esophageal reflux disease	胃食道逆流症
hERG	human ether-a-go-go-related gene	ヒト遅延整流性カリウムチャネル遺伝子
H.Pylori	Helicobacter pylori	ヘリコバクター・ピロリ
H_2RAs	H_2 receptor antagonists	ヒスタミン H_2 受容体拮抗薬
HPLC	high-performance liquid chromatography	高速液体クロマトグラフィー
HRMS	high-resolution mass spectrometry	高分解能質量分析
HTS	high-throughput screening	ハイスループットスクリーニング
IC_{50}	half-maximal inhibitory concentration	50%阻害濃度
ip	intraperitoneal	腹腔内の
iv	intravenous	静脈内の

LC/MS/MS	liquid chromatography with tandem mass spectrometry	液体クロマトグラフィー・タンデム質量分析
LDA	lithium diisopropylamide	リチウムジイソプロピルアミド
LLE	ligand-lipophilicity efficiency	脂溶性効率
log D	distribution coefficient	分配係数
LPZ	lansoprazole	ランソプラゾール
Me	methyl	メチル
mp	melting point	融点
MS	molecular sieves	モレキュラーシーブス
NBS	*N*-bromosuccinimide	*N*-ブロモスクシンイミド
NCS	*N*-chlorosuccinimide	*N*-クロロスクシンイミド
NMO	*N*-methylmorpholine *N*-oxide	*N*-メチルモルホリン *N*-オキシド
NSAIDs	nonsteroidal anti-inflammatory drugs	非ステロイド性抗炎症薬
PAMPA	parallel artificial membrane permeability assay	人工膜透過性試験
P-CAB	potassium-competitive acid blocker	カリウムイオン競合型アシッドブロッカー
Ph	phenyl	フェニル
PLsis	phospholipidosis	ホスホリピドーシス
PM	poor metabolizer	酵素活性欠損者
po	per os	経口投与
PPI	proton pump inhibitor	プロトンポンプ阻害薬
Py	pyridyl	ピリジル
RLU	relative light unit	相対発光量
rt	room temperature	室温
SAR	structure-activity relationship	構造活性相関
TG-DTA	thermogravimetry-differential thermal analysis	熱重量・示差熱同時測定
THF	tetrahydrofuran	テトラヒドロフラン
TLC	thin-layer chromatography	薄層クロマトグラフィー
TPAP	tetrapropylammonium perruthenate	過ルテニウム酸テトラプロピルアンモニウム
Ts	tosyl	トシル
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene	キサントホス

理論の部

実験の部

引用文献および脚注

第 1 章　緒言

第 1 節　胃酸と酸関連疾患

胃酸は胃底部および胃体部の粘膜に存在する胃底腺の壁細胞から分泌され、ペプシノーゲン、粘液と共に胃液の主成分を構成する。その働きとしては、タンパク質分解酵素であるペプシンの活性化、カルシウム、鉄などの吸収への寄与、経口で侵入する病原微生物の殺菌などが挙げられる。一方で、胃酸は強力な組織傷害性を示し、胃潰瘍・十二指腸潰瘍や逆流性食道炎などを引き起こす病的因子としての一面を有する。胃酸が関連し、胃酸の分泌を抑制することにより臨床的効果が得られる疾患群は酸関連疾患と呼ばれ、その原因や治療法が明確ではなかった時代より、長年の間、人類を苦しめてきた歴史がある。例えば、胃炎／胃潰瘍は人類最古の疾患の一つとされ、その主な原因となっているピロリ菌（*Helicobacter Pylori: H.pylori*）に人類が最初に感染したのは、人類がまだアフリカ以外には存在していなかった約 5 万 8000 年前とする研究成果が発表されている [1]。また、歴史上の記録を見ると古代ギリシャのヒポクラテスは著書の中で胃潰瘍に言及しており、マケドニアのアレキサンダー大王に攻め込まれたギリシャ兵達が胃潰瘍に苦しんだという記録が残っている。

胃潰瘍・十二指腸潰瘍は消化性潰瘍とも言われ、胃酸やペプシンによる自己消化作用により粘膜欠損を認める疾患で、痛み、場合によっては出血を伴い、重篤な消化管出血に至ることもある。近年、その主な発症原因が *H.pylori* の感染であることが判明し、再発防止のために除菌治療が積極的に行われるようになった。また、最近では、非ステロイド性抗炎症薬（NSAIDs）や低用量アスピリンの使用も主な発症原因の一つとなっている。逆流性食道炎は胃食道逆流症（GERD）の一部で、食道内への胃酸の逆流により食道の粘膜に炎症を起こす疾患と定義される。胸やけや呑酸などの症状を伴い、QOL の大きな低下を引き起こす。「No acid, no ulcer（酸なきところに潰瘍なし）」という言葉に象徴されるように、胃酸と酸関連疾患の関係については様々な臨床研究が進められ、近年、攻撃因子を抑制する観点からは、胃酸の分泌を抑制することが最も有効な治療手段と認識されるようになった。すなわち、胃潰瘍・十二指腸潰瘍では pH3 以上 [2]、逆流性食道炎では pH4 以上 [3, 4]、*H.pylori* 除菌では pH5 以上 [5] に、胃内 pH を一定時間以上、上昇させる程度に胃酸の分泌を抑制する必要があることが分かっている。そのような事実背景から、酸関連疾患治療薬については、より強く、長く胃酸分泌を抑制して胃内の pH を制御できる薬剤を求めて研究開発が行われてきた。

第 2 節　酸関連疾患治療薬の歴史と変遷

① 制酸薬の時代

古代ギリシャ時代には、今で言うストレス性潰瘍を避けるためには旅行に出るとか、海を見るなどの気分転換が推奨され、薬剤としては、貝殻を粉末にして服用していたという記録が残っている。また古代エジプト時代のパピルスにも同じような記録が確認されていることから、かなり古い時代から貝殻、すなわち炭酸カルシウムで胃酸を中和し、胃の痛みを抑えていたと推定される。しかしながら、胃酸を中和する古典的な制酸薬には症状を軽減させる効果は認められるものの、作用時間がきわめて短時間であり、潰瘍治癒効果はかなり限定的という大きな課題があった。実際、後述するヒスタミン H_2 受容体拮抗薬が上市されるまでは、社会復帰するために、非常に多くの消化性潰瘍患者には外科的手術を受ける必要があり、その治療効果は十分とは言えなかった。

② ヒスタミン H_2 受容体拮抗薬（histamine H_2 receptor antagonist: H_2RA）の登場

1960 年代後半に酸を胃内に送り込む胃プロトンポンプの存在が明確になり [6]、胃酸分泌機構の解明が加速された。胃酸の分泌を刺激する生理活性物質としては、現在までにヒスタミン、アセチルコリン、ガストリンが知られており、壁細胞基底の側面細胞膜に存在するヒスタミン H_2 受容体、ムスカリン M_3 受容体、ガストリン CCK_2 受容体にそれぞれ作用することが分かっている（Figure 1）。

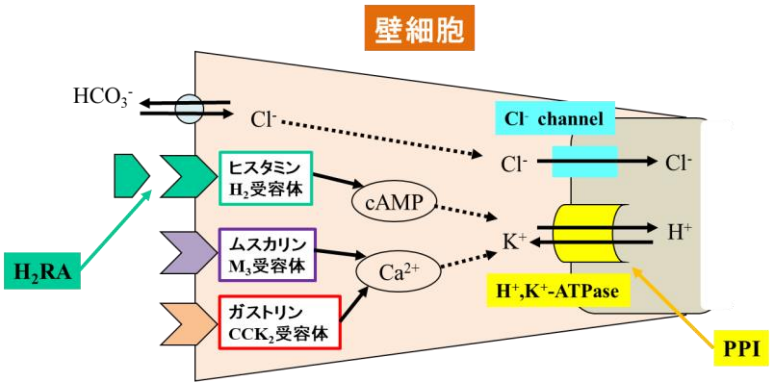


Figure 1. Schematic diagram of gastric acid secretion in the gastric wall cells.

このような壁細胞への刺激をブロックするタイプの薬剤としては、最初にムスカリン受容体を遮断する抗コリン薬などが使用されたが、その臨床効果は満足できるものではなかった。しかし、胃に存在するヒスタミン受容体は小腸のヒスタミン受容体と異なることが分かったことで薬剤の開発が加速し、1970 年代後半に経口投与で強力な酸分泌抑制作用を示す H_2RA が上市された（1976 年：Cimetidine の上市）。H_2RA の登場は、消化性潰瘍の治

療効果を劇的に向上させ、手術以外に治療の選択肢のなかった症状の患者が、薬で治療できるようになるなど、多くの消化性潰瘍患者に福音をもたらした。しなしながら、H_2RA には反復投与による作用の減弱が認められる、夜間の効果に比べて日中の効果が弱いという特徴があり、難治性潰瘍や GERD に対しては十分な治療効果を発揮できないという課題があった。

③ プロトンポンプ阻害薬（proton pump inhibitor: PPI）の上市

胃プロトンポンプの正体は、その後、膜タンパク質である H^+,K^+-ATPase と判明した [7]。H^+,K^+-ATPase は P 型 ATPase ファミリーに分類され、細胞膜の内外に水素イオンとカリウムイオンを能動輸送させることにより、胃酸の元になる水素イオンを胃腔内に送り込む働きを有している。胃酸分泌の最終段階にあるこの酵素を効果的／効率的に抑制することが最も優れた酸関連疾患の治療戦略であることは明白であり、その後、鋭意研究が進められ、1990 年代になって H^+,K^+-ATPase を直接阻害する PPI が上市された（Figure 1）。ランソプラゾール（Lansoprazole: LPZ）に代表される市販の PPI はいずれもベンズイミダゾール誘導体であり、酸性条件下で活性化されて阻害効果を発揮する（Figure 2）。酸の存在下でピリジン窒素が分子内の炭素を求核的に攻撃して形成されるスピロ化合物は、開環してスルフェン酸となった後に脱水してスルフェンアミド（LPZ の場合は AG-2000）に変換される。それが活性本体として H^+,K^+-ATPase の Cys813 残基と非可逆的に S-S 共有結合を形成し、酵素活性を阻害しているものと推定されている。

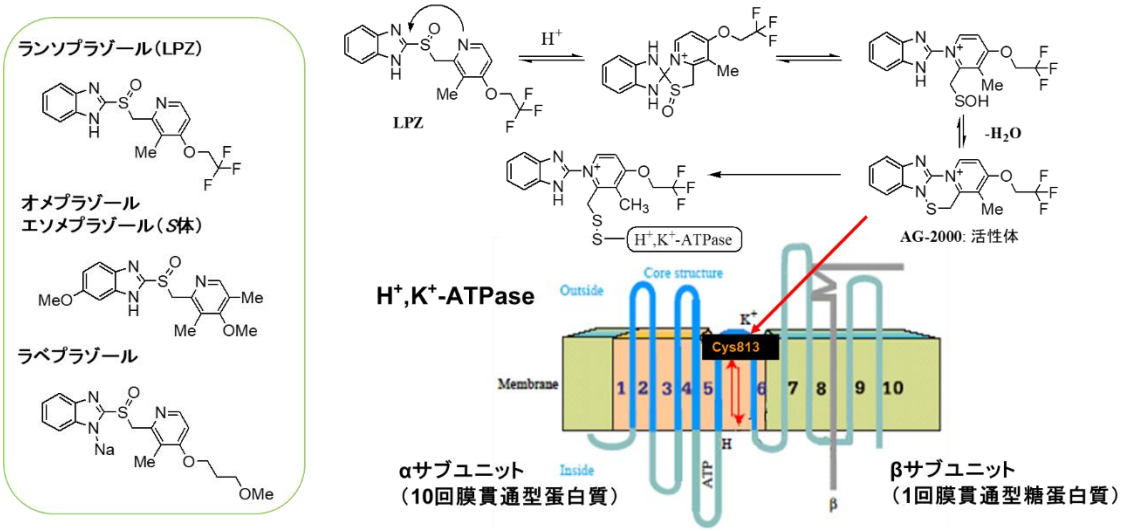


Figure 2. Chemical structures of PPIs and estimated mechanism of action of LPZ.

PPI は H_2RA よりも強力かつ持続的に胃酸分泌を抑制するため、消化性潰瘍だけでなく GERD に対しても高い治療成績を示し、酸関連疾患治療の第一選択薬の地位を築くと共に多

くの酸関連疾患患者の QOL 改善に大きく貢献する薬剤となった。

第 3 節　酸関連疾患治療薬の現状と課題

PPI は胃酸分泌の最終段階である H^+,K^+-ATPase を阻害して酸分泌を抑制するため、「最強の酸分泌抑制薬」と認知され、もうこれ以上の薬剤は出てこないと考えられてきた。しかしながら、臨床データの蓄積とともに PPI で症状をコントロールできない GERD 患者や PPI を用いた除菌療法における *H.pylori* の除菌率低下が報告されるなど[8]、2000 年頃から PPI による薬物治療の限界や課題が次第に明らかとなってきた。そこで、壁細胞における H^+,K^+-ATPase の挙動や PPI（LPZ）の特性、阻害の作用メカニズムなども考慮してその原因が分析され、主に以下 4 つに纏められた。これらのうち最低一つの原因によって、十分な治療効果が得られないケースが出てくるものと考えられた[9–14]。

① 効果の発現時間がばらつく

PPI（LPZ）は酸性条件下で活性本体に変換された後に H^+,K^+-ATPase に作用する（Figure 2）。すなわち、酸に不安定な特性が阻害効果発現の駆動力となっている。したがって、経口投与で効果を発揮させるために腸溶性製剤に設計されており、消化管内の移動は胃の蠕動運動の状態や胃排出能に大きく影響される。そのため食事などの影響により小腸で吸収されるまでの時間にばらつきが生じ[15]、結果として薬効の発現時間が一定しない。

② 効果の個人差が大きい

市販されている PPI は、程度の差はあるものの、いずれも遺伝子多型のある CYP2C19 によって主として代謝される特性を有しているため、CYP2C19 の欠損した poor metabolizer (PM) と正常な extensive metabolizer (EM) の患者では代謝速度が異なり血中濃度や AUC に差が出てくる。それに伴い酸分泌抑制効果、すなわち胃内 pH に差が認められ、結果として疾患の治癒率に個人差が生じることになる[16]。例えば、日本人の GERD 患者に LPZ 30mg を 8 週間連日投与したときの治癒率は homoEM（代謝が速い）、heteroEM（中程度）、PM（遅い）の患者でそれぞれ 45.8%、67.9%、84.6%であり、GERD 患者に対する LPZ の治療効果と CYP2C19 活性は有意に相関することがわかっている[17]。

③ 夜間の酸逆流を十分に抑制できない

壁細胞の H^+,K^+-ATPase の形態は、酸分泌休止状態（休止期）と酸分泌活動状態（活動期）で顕著に異なる。休止期にはその多くが管状小胞として細胞質に存在し、プロトンポンプとして機能していない（Figure 3A）[18]。食事などの酸分泌刺激により活動期になると、管状小胞が分泌細管の膜上に移動して分泌細管（acid space）側に露出し、初めてプロトンポンプとして働く。PPI（LPZ）は、腸から吸収されて壁細胞の acid space に到達後、酸性環境下

で活性体へと変換され、H^+,K^+-ATPase と S-S 結合（共有結合）を形成して阻害効果を発揮する（Figure 3B）。血中濃度が高い状態では分泌細管膜上のポンプを効果的に阻害して酸分泌を抑制するが、血中濃度が下がった状態で酸分泌刺激を受けた場合、分泌細管膜上に移行した活性のあるポンプ（アクティブポンプ）を十分に阻害できない（Figure 3C）。PPI（LPZ）の血中半減期は 1.5 時間程度と短いことから、24 時間にわたって作用を持続することが難しい。このため服用から時間の経過した夜間などの酸分泌が十分に抑制できないと考えられる。

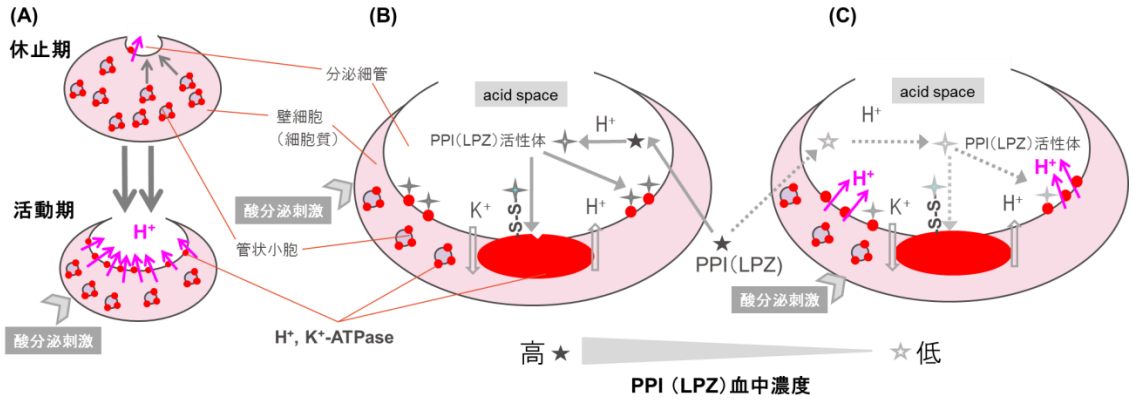


Figure 3. Shape changes of parietal cells and inhibitory action of PPI (LPZ) on H^+,K^+-ATPase.[19]

④ 最大薬効の発現までに 5 日間程度を要する

H^+,K^+-ATPase は、活動期においても全てが acid space 側に露出してプロトンポンプとして機能している訳ではなく、細胞質内の管状小胞にも休止状態で存在する（Figure 3A、Figure 4A-1）。酸分泌刺激がなくなると分泌細管膜上の H^+,K^+-ATPase は管状小胞に戻るが（Figure 4B-1）、PPI（LPZ）の血中濃度が低くなった状態で新たに次の酸分泌刺激を受けた場合、阻害されていない H^+,K^+-ATPase も膜上に移行するため、酸分泌抑制効果は明らかに弱まる（Figure 4C-1）。しかしながら、投薬を繰り返すことにより、阻害された H^+,K^+-ATPase の数が徐々に増えてくる（Figure 4C-2）。阻害ポンプ数が一定になるまで、すなわち最大の阻害効果が発揮されるまでに大体 5 日間くらい必要となる（Figure 4C-5）。なお、H^+,K^+-ATPase の半減期は約 50 時間で 1 日に約 25%のポンプが新たに生合成される[20,21]。そのため、PPI（LPZ）の酵素阻害で完全に胃酸分泌を止めることは難しい。

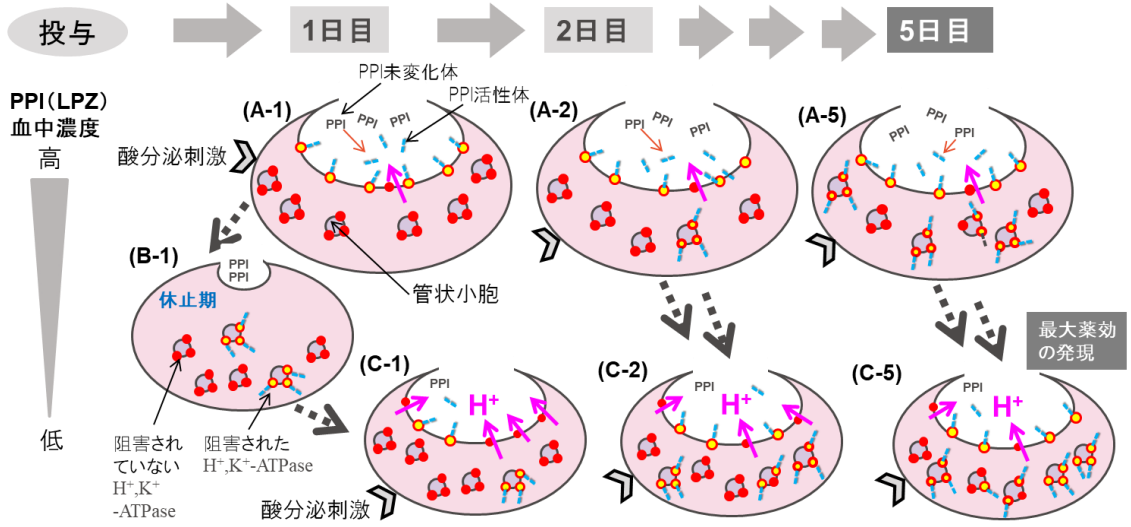
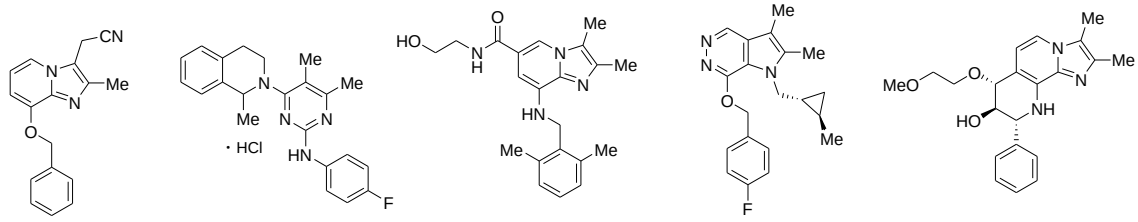


Figure 4. H^+,K^+-ATPase inhibitory properties of PPI (LPZ) and its maximal efficacy.[19]

第 4 節　研究方針および論文の概要

このような背景の下、既存の酸関連疾患治療薬の課題を解決し、より高い治療効果が得られる薬剤の創製を目指して探索を開始した。その過程で、異なる作用メカニズムで H^+,K^+-ATPase を阻害するカリウムイオン競合型アシッドブロッカー（Potassium-Competitive Acid Blocker: P-CAB）に着眼した（Figure 5）。



SCH 28080
(Schering-Plough)

Revaprazan (YH-1855)
(Yuhan)

AZD0865
(AstraZeneca)

CS-526
(Ube, Sankyo, Novartis)

Soraprazan (BY-359)
(Nycomed)

Figure 5. Structures of several reported potassium-competitive acid blockers.

PPI（LPZ）が H^+,K^+-ATPase と共有結合を形成して構造的に酵素活性を阻害するのに対して（非可逆的阻害）、P-CAB は K^+イオンと競合して H^+,K^+-ATPase とイオン結合を形成することにより機能的に酵素活性を阻害する（可逆的阻害）。1980 年代から多くの製薬会社により研究され、開発が試みられてきたが、作用持続が不十分あるいは肝毒性が認められるなどの理由から欧米や日本における開発の成功事例はなかった[22-29]。しかしながら、既に酸に

安定な複数のケモタイプの化合物が報告されており、適切なケモタイプを選択して壁細胞の分泌細管内に長く留まることができる P-CAB を上手く設計できれば PPI（LPZ）の課題は一気にすべて解決できると考えた（Figure 6）。

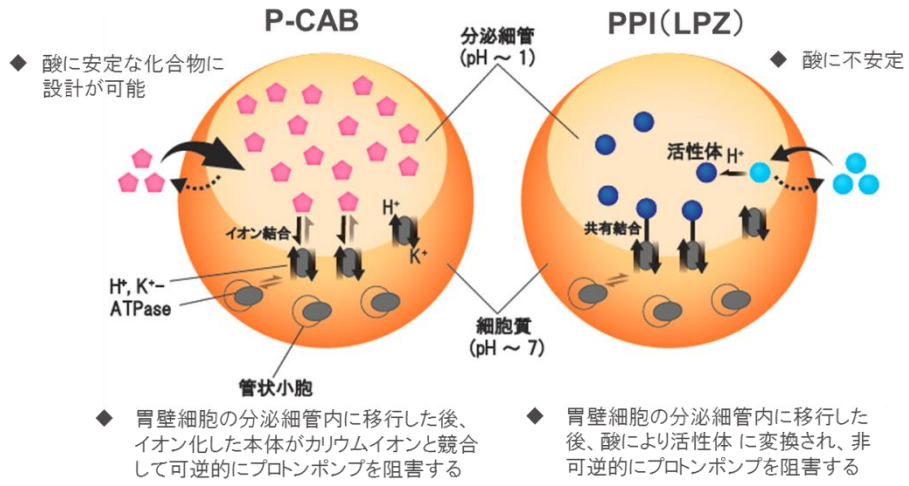


Figure 6. Mechanism of action of P-CAB and PPI (LPZ) in gastric parietal cells.

本論文では、筆者が武田薬品工業株式会社において取り組んだ探索合成研究について論じる。第 2 章では本研究方針に基づいた新規リード化合物の創出について論じる。第 3 章ではピロール誘導体の log D 低減による ADME-Tox 特性の改善と持続性向上を志向したリード化合物の最適化の戦略について論じる。さらに、第 4 章では適度な効果の持続性を目指した構造変換の戦略について論じる。

第 2 章 新規リード化合物の創出

第 1 節 背景および分子設計の戦略

酸関連疾患治療の課題を克服する優れた酸分泌抑制薬を見出す取り組みの一環として 2003 年から H^+,K^+-ATPase 阻害活性を指標とした自社化合物ライブラリーのハイスループットスクリーニング（HTS）が開始された。約 56 万化合物を評価した結果、H^+,K^+-ATPase に対する阻害作用は弱く（IC_{50} = 540 nM）、オフターゲットの一つで心臓への作用が懸念される Na^+,K^+-ATPase 阻害活性との選択性も 5 倍以下と十分ではないが、酸に安定で比較的強い塩基性を持ったピロール誘導体 **1** がヒット化合物として見出された（Figure **7**）[30]。化合物 **1** はその化学構造から可逆的に H^+,K^+-ATPase を阻害する P-CAB タイプの化合物と考えられたが、分子量が 400 以下（398.48）と小さく構造変換の余地が大きいことに加えて、既知の P-CAB に共通する構造的特徴、すなわち基本となる骨格にベンジルオキシ基あるいはベンジルアミノ基が導入された化学構造を有していなかった。したがって、H^+,K^+-ATPase との相互作用様式や物性の違いから、既知 P-CAB で懸念される有効性や安全性面の課題の克服が期待された。そこで、有望なリード化合物の創出を目指し、ヒット化合物 **1** のポテンシャルを見極めるべく、構造変換を行った（Figure 7）。

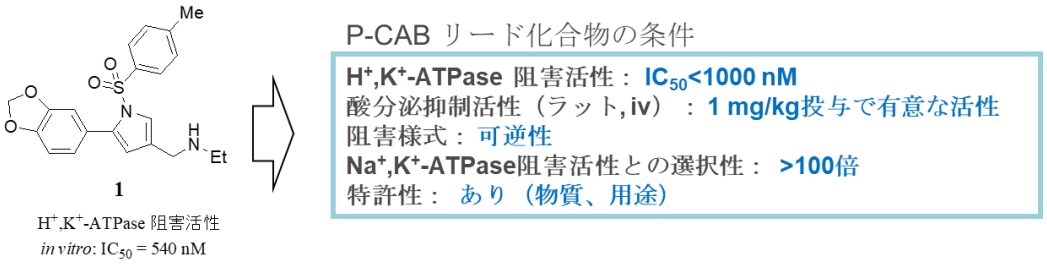


Figure 7. Chemical structure of hit compound **1** and requisites of P-CAB lead compounds.

合成した化合物の 1 次評価にはブタ胃由来の H^+,K^+-ATPase を用い、in vitro 阻害活性を測定して IC_{50} 値を求め、同時に Na^+,K^+-ATPase 阻害活性との選択性を確認した。2 次評価はラットを用いた in vivo 評価とし、1 mg/kg の薬物を静脈内投与（iv）した際のヒスタミン刺激による胃酸分泌の抑制率（%）を求めた。PPI である LPZ はこの系で約 90%の酸分泌抑制作用を示すことがわかっており、最終的には in vivo で 90%以上の抑制活性が最低限必要と考えられた。構造変換に当たっては、ピロール誘導体に焦点を当て、強い活性の発現に必要な部分構造を見極めながら活性の向上を目指した。

第 2 節 合成

第 1 節で論じた分子設計に基づき、以下の化合物を合成することにした（Figure 8）。

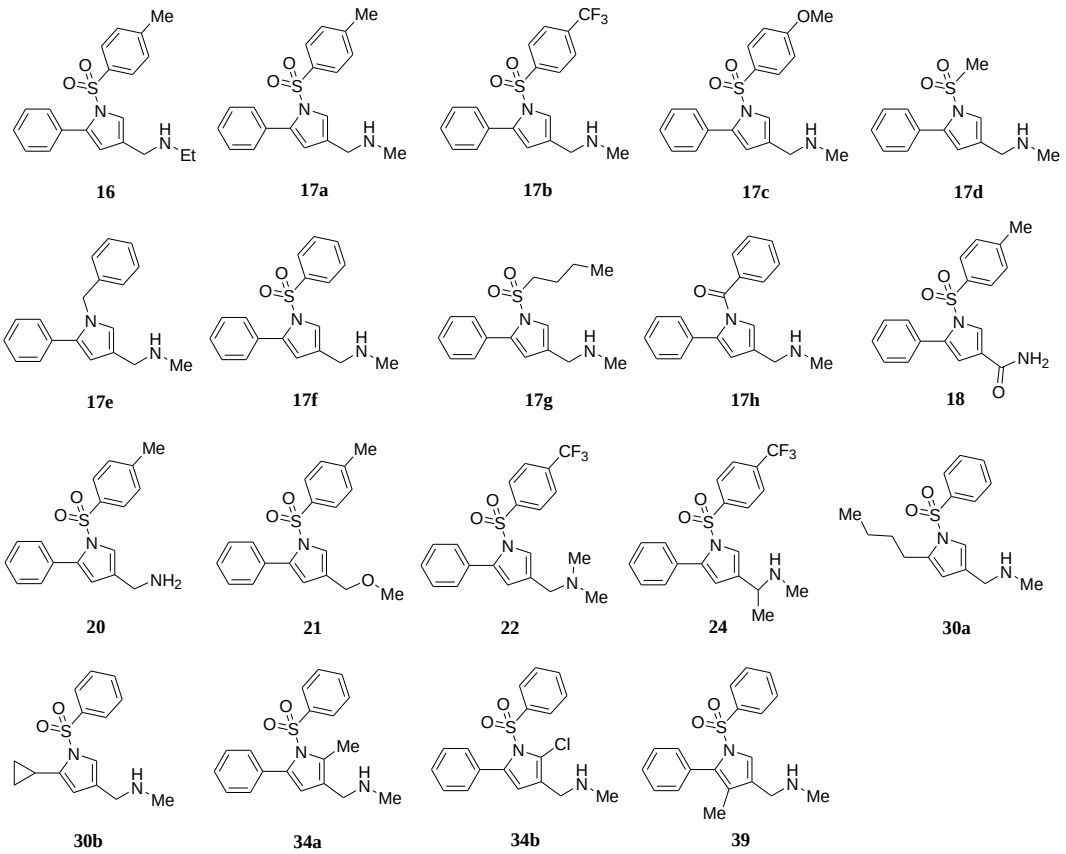
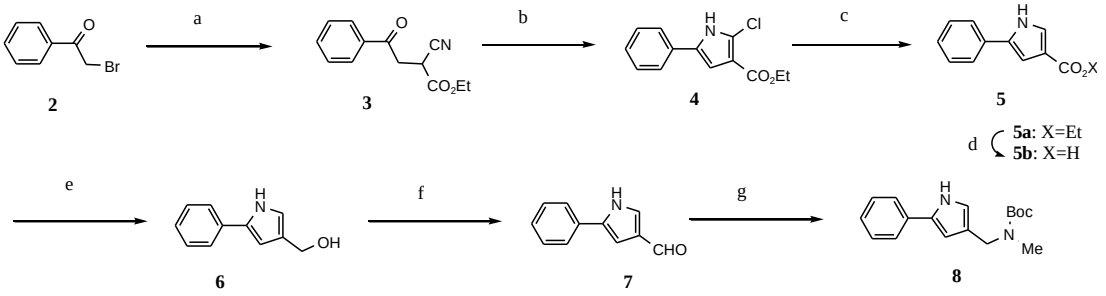


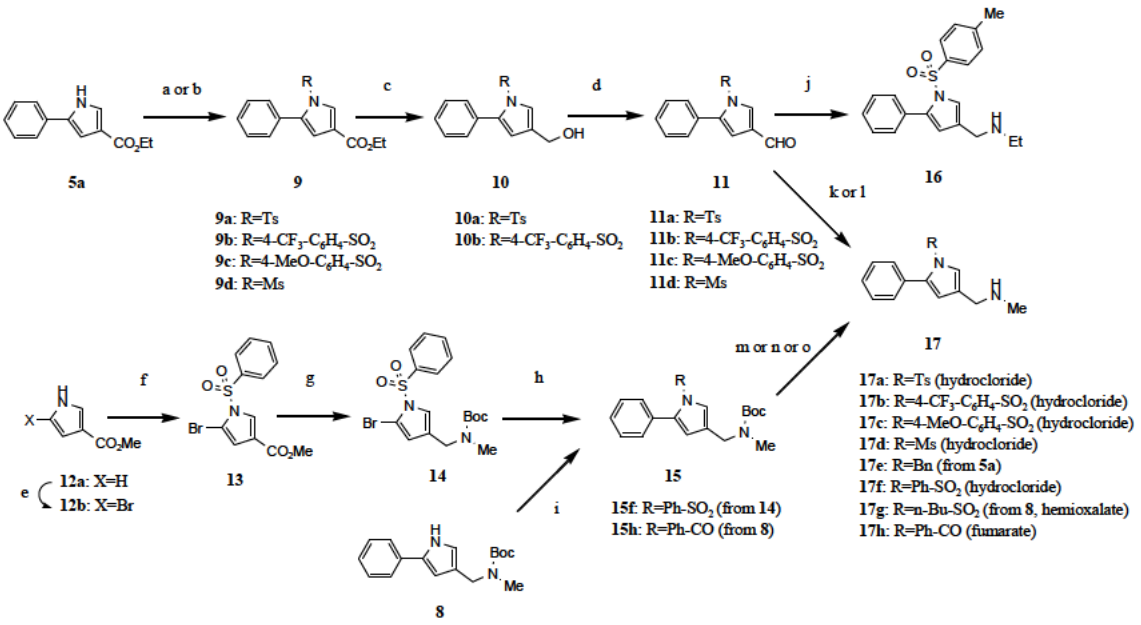
Figure 8. Structures of synthesized compounds in Chapter 2

鍵中間体 **4**、**5a**、**5b** および **8** の合成は Scheme 1 に示す方法を用いて行った。市販の α-ブロモアセトフェノン（**2**）とシアノ酢酸エチルの縮合反応により **3** を得た後、酸性条件下で環化して **4** とし、その加水素化分解により脱 Cl 体 **5a** を得た。カルボン酸 **5b** については **5a** をアルカリ加水分解することにより得た。また、**5a** は、水素化ジイソブチルアルミニウム（DIBAL-H）で OH 体 **6** に変換の後、過ルテニウム酸テトラプロピルアンモニウム（TPAP）と *N*-メチルモルホリン *N*-オキシド（NMO）を用いた条件下で酸化してホルミル体 **7** に導いた。**7** を還元的アミノ化反応の後、$(Boc)_2O$ で処理することにより Boc 保護体 **8** とした。



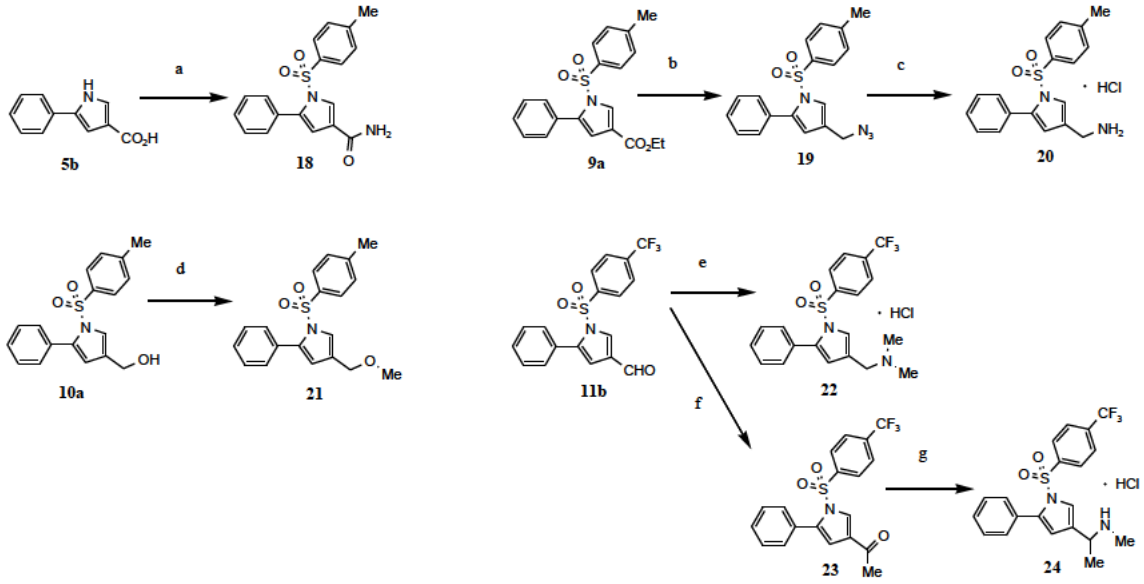
Scheme 1. Reagents and conditions: a) ethyl cyanoacetate, K_2CO_3, acetone, rt; b) HCl (g), THF, rt; c) H_2, 10 % Pd-C, EtOH, rt; d) 8N NaOH, MeOH, THF, 55 °C; e) 1.5 mol/L DIBAL-H in toluene, THF, –78 °C; f) NMO, TPAP, MS4A, MeCN, rt; g) 1) 40% $MeNH_2$ in MeOH, rt; 2) $NaBH_4$, rt; 3) $(Boc)_2O$, MeCN, rt.

化合物 **16** および **17a**–**h** の合成は鍵中間体 **5a**、**8** または市販試薬 **12a** を原料として Scheme 2 に示す方法で行った。塩基性条件下で **5a** をスルホニル化またはベンジル化した後、DIBAL-H で処理して対応するアルコール体 **10** とし、さらに、TPAP と NMO を用いた条件下で酸化してホルミル体 **11** に変換した。得られた **11** を還元的アミノ化反応によりエチルアミノ基を有する **16** およびメチルアミノ基を有する **17a**–**e** にそれぞれ導いた。市販の **12a** をピリジンの存在下、*N*-ブロモスクシンイミド（NBS）で Br 化して **12b** に変換の後、塩基性条件下で塩化ベンゼンスルホニルと縮合して **13** を得た。**13** を Scheme 1 と同様の方法で Boc 体 **14** に変換の後、フェニルボロン酸を用いた鈴木・宮浦カップリング反応により **15f** に導き、それを強酸と処理することにより目的とする **17f** を得た。また、塩基性条件下で鍵中間体 **8** をスルホニル化あるいはベンゾイル化し、強酸条件下で Boc 基を除去することにより、それぞれ目的とする **17g** および **17h** へと導いた。**16** および **17e** についてはフリー体、**17a**–**d** および **17f** は塩酸塩、**17g** は 0.5 シュウ酸塩、**17h** はフマル酸塩としてそれぞれ単離した。



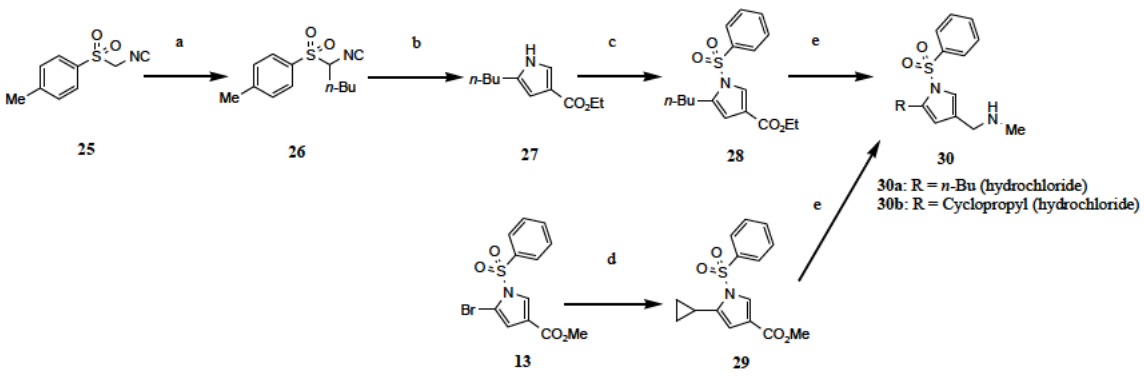
Scheme 2. Reagents and conditions: a) NaH, RCl, DMF, rt; b) NaH, BnBr, DMF, rt; c) 1.5 mol/L DIBAL-H in toluene, THF, –78 °C; d) NMO, TPAP, MS4A, MeCN, rt; e) NBS, Py, THF, –20 °C; f) NaH, Ph-SO_2Cl, DMF, rt; g) 1) 1.5 mol/L DIBAL-H in toluene, THF, –78 °C; 2) NMO, TPAP, MS4A, MeCN, rt; 3) $MeNH_2$-HCl, $NaBH_3CN$, MeOH, rt; 4) $(Boc)_2O$, EtOAc, rt; h) Ph-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C; i) NaH, 15-crown-5, RCl, DMF, rt; j) $EtNH_2$-HCl, MS4A, $NaBH_3CN$, MeOH, rt; k) 1) $MeNH_2$-HCl, MS4A, $NaBH_3CN$, MeOH, rt; 2) 4N HCl/EtOAc, EtOAc; l) 1) 40% $MeNH_2$ in MeOH, MeOH, $NaBH_4$, rt; 2) 4N HCl/EtOAc, EtOAc; m) 4N HCl/EtOAc, EtOAc, rt; n) 1) 4N HCl/EtOAc, EtOAc, 60 °C; 2) $(COOH)_2$, EtOAc, Et_2O; o) 1) 4N HCl/EtOAc, MeOH, rt; 2) fumaric acid, MeOH, EtOAc.

化合物 **18**、**20**、**21**、**22** および **24** については、中間体 **5b**、**9a**、**10a** あるいは **11b** を用いて Scheme 3 に示す方法で合成した。すなわち、**5b** をトシル（Ts）化の後、室温でアンモニア溶液と反応させることによりアミド体 **18** へと導いた。**9a** を DIBAL-H で還元して対応するアルコール体（**10a**）とした後、PPh_3、2,3-ジクロロ-5,6-ジシアノ-*p*-ベンゾキノン（DDQ）および *n*-Bu_4NN_3 を用いてアジド体 **19** に変換し [31]、続いて接触水素化反応を行うことによりアミン体 **20** を得た。また、**10a** を塩基性条件下でメチル化してメチルエーテル体 **21** へ導き、**11b** をジメチルアミンの存在下、還元的アミノ化反応によりジメチルアミノ体 **22** に変換した。さらに、**11b** を Grignard 試薬との反応とその後の酸化反応によりアセチル体 **23** とし、還元的アミノ化反応を行って **24** へと導いた。**20**、**22** および **24** はいずれも塩酸塩として単離した。



Scheme 3. Reagents and conditions: a) 1) NaH, TsCl, DMF, rt; 2) 25%NH_3, rt; b) 1) DIBAL-H, THF, rt; 2) DDQ, PPh_3, *n*-Bu_4NN_3, CH_2Cl_2, rt; c) 1) 10%Pd-C, H_2, AcOH, MeOH, rt; 2) 4N HCl/EtOAc, EtOAc; d) NaH, MeI, DMF, rt; e) 1) 2M Me_2NH/THF, MeOH, rt; 2) $NaBH_4$, rt; 3) 4N HCl /EtOAc, EtOAc; f) 1) MeMgBr, THF, ether, 10 °C; 2) MnO_2, CH_2Cl_2, rt; g) 1) 40% $MeNH_2$ in MeOH, MS4A, EtOH, 70 °C; 2) $NaBH_4$, rt; 3) 4N HCl/EtOAc, EtOAc.

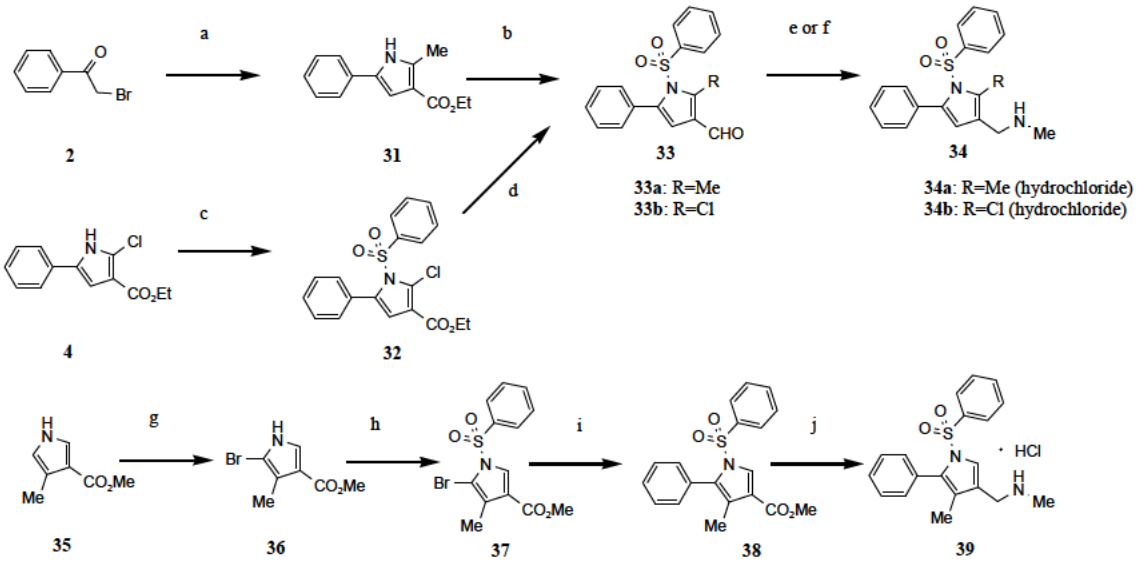
ピロール 5 位の Ph 基を *n*-ブチル基あるいはシクロプロピル基へ変更した化合物 **30a–b** については Scheme 4 に示す方法で合成した。すなわち、市販の **25** を 1-ヨードブタンと反応させて **26** とし、アクリル酸エチルとの反応 [32] を経てピロール **27** に変換した後、塩基性条件下でスルホニル化して **28** とした。また、**13** とシクロプロピルボロン酸の鈴木・宮浦カップリング反応により **29** とした。得られたエステル中間体 **28** および **29** を Scheme 2 と同様の方法を用いて **30a** および **30b** へと導いた。



Scheme 4. Reagents and conditions: a) 1-iodobutane, TBAI, 30% NaOH, CH_2Cl_2, rt; b) CH_2=$CHCO_2Et$, *t*-BuOK, THF, rt; c) NaH, Ph-SO_2Cl, THF, rt; d) cyclopropylboronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, H_2O, toluene, 100 °C; e) 1) 1.5 mol/L DIBAL-H in toluene, THF, -78 °C;

2) TPAP, NMO, MS4A, MeCN, rt; 3) 2M $MeNH_2$ in THF, rt; 4) $NaBH_4$, MeOH, rt; 5) 4N HCl/EtOAc, EtOAc.

ピロール 2 位あるいは 4 位へ置換基を導入した化合物については Scheme 5 に示す方法により合成した。市販の α-ブロモアセトフェノン（**2**）をアセト酢酸エチルと縮合し、酢酸アンモニウムを用いて酢酸中で環化させることにより 2 位に Me 基が導入された **31** へと導いた。その後、Scheme 2 と同様の方法を用い、スルホニル化反応、還元反応および酸化反応を経てホルミル体 **33a** とした。2 位に Cl 原子が導入された鍵中間体 **4** に対しては通常の塩基性条件下ではスルホニル化反応が進行しなかったが、15-crown-5 を添加することにより高収率でスルホニル体 **32** に導くことができた。その後、同様に、還元反応および酸化反応を経てホルミル体 **33b** とした。また、市販の **35** を NBS で Br 化の後、スルホニル化反応により **37**、続いて鈴木・宮浦カップリング反応により 4 位に Me 基が導入されたエステル中間体 **38** に導いた。得られた **33a**、**33b** および **38** に対し、Scheme 2 の中間体 **11** または **9** から **17** を得る方法を適用して、目的とする **34a**、**34b** および **39** に変換した。



Scheme 5. Reagents and conditions: a) 1) NaH, $MeCOCH_2CO_2Et$, DMF, rt; 2) $AcONH_4$, AcOH, 80 °C; b) 1) NaH, Ph-SO_2Cl, DMF, rt; 2) 1.5 mol/L DIBAL-H in toluene, THF, –78 °C; 3) NMO, TPAP, MS4A, MeCN, rt; c) NaH, THF, 15-crown-5, Ph-SO_2Cl, rt; d) 1) 1.5 mol/L DIBAL-H in toluene, THF, –78 °C; 2) MNO, TPAP, MS4A, MeCN, rt; e) 1) $MeNH_2$-HCl, MS4A, $NaBH_3CN$, MeOH, rt; 2) 4N HCl/EtOAc, EtOAc; f) 1) 40% $MeNH_2$ in MeOH, MeOH, $NaBH_4$, rt; 2) 4N HCl/EtOAc, EtOAc; g) NBS, Py, THF, 5 °C; h) NaH, Ph-SO_2Cl, DMF, rt; i) Ph-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C; j) 1) 1.5 mol/L DIBAL-H in toluene, THF, -78 °C; 2) NMO, TPAP, MS4A, MeCN, rt; 3) $MeNH_2$-HCl, $NaBH_3CN$, MeOH, rt; 4) 4N HCl/EtOAc, EtOAc.

第 3 節 化合物の評価および考察

第 1 項 ヒット化合物からの合成展開と初期リード化合物 **17a** の選定

ヒット化合物 **1** からの合成展開を効率的に進めるに当たり、活性発現に必要な部分構造を見極めるための幾つかの化合物の活性の比較を試みた。まず、ピロール環に直結する 3,4-メチレンジオキシフェニル基を Ph 基に変更しても、活性はおおよそ保持された（化合物 **16**、IC_{50} = 650 nM）。次に、**16** の 3 位置換基の窒素原子上の Et 基を Me 基に変更したところ活性は 10 倍以上向上した（化合物 **17a**、IC_{50} = 46 nM）。更に、**17a** では Na^+,K^+-ATPase 阻害との選択性が 100 倍以上に向上し、2 次評価の in vivo ラット動物モデル（1 mg/kg、iv 投与）において、弱いながらも有意な 66%の酸分泌抑制活性が認められた。そこで、**17a** の特性を詳細に調べたところ、pH 1.2 の第 1 液（日本薬局方）中で安定に存在すること（酸に安定）、その H^+,K^+-ATPase 阻害様式は、可逆的かつ K^+イオン競合型の P-CAB であることが判明した（Figure 9 および 10）。

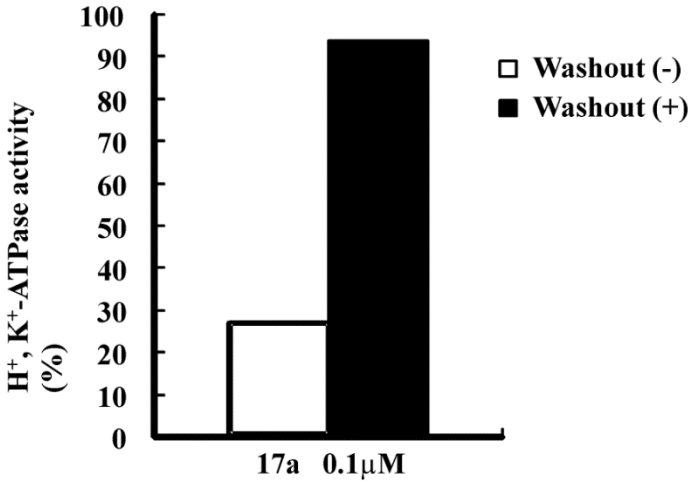


Figure 9. Effect of washout on the inhibition of H^+,K^+-ATPase by compound **17a**. The activity of the H^+,K^+-ATPase was measured with and without washout of compound **17a**. Data with or without washout were expressed as percentage of the H^+,K^+-ATPase activity in control (n = 2).

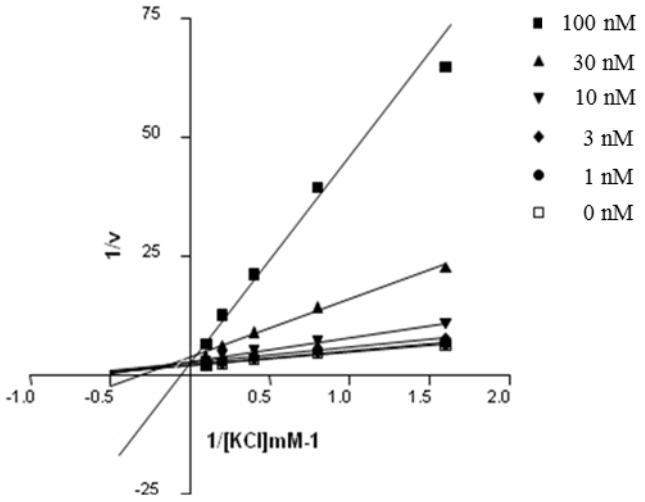


Figure 10. Lineweaver-Burk plots of K^+ concentration versus H^+,K^+-ATPase activity in the presence of a various concentration of **17a**.

次に、H^+,K^+-ATPase との相互作用を推定するために、Ca^{2+}-ATPase (PDB ID, 1IWO[33])の 3 次元結晶構造から H^+,K^+-ATPase のホモロジーモデルを構築し[34]、化合物 **17a** のドッキング解析を試みたところ[35]、**17a** の強い活性を支持する相互作用が示唆されたが、その結合の様式は既知の P-CAB を代表する SCH 28080 とはかなり異なると推定された（Figure 11）。すなわち、化合物 **17a** については、ピロール 1 位に位置するトシル基が Tyr928 側鎖との π–π 相互作用により Tyr928 付近の空間（脂溶性ポケット : LP-2 サイト）に密接に結合して Tyr925 および Tyr928 の側鎖と 2 つの水素結合を形成している、また、ピロール 5 位のフェニル基は、Phe124 側鎖と CH–π 相互作用によって結合し、さらに、ピロール 3 位の N-メチルアミノメチル基は、Val331 の主鎖と水素結合を形成して予測されるカチオン流路を効率的に占有していると考えられた。一方、SCH 28080 はベンジルオキシ基が Phe124 付近の空間（脂溶性ポケット : LP-1 サイト）に位置して Phe124 と相互作用していると考えられたが、Tyr928 周辺の π–π 相互作用や Tyr925、Tyr928、および Val331 との水素結合は認められない結果となった。したがって、**17a** のピロール 1 位に位置するフェニルスルホニル基部分、3 位の N-メチルアミノメチル基部分、および 5 位のフェニル基部分は、H^+,K^+-ATPase 阻害作用の発現に重要と推定された。

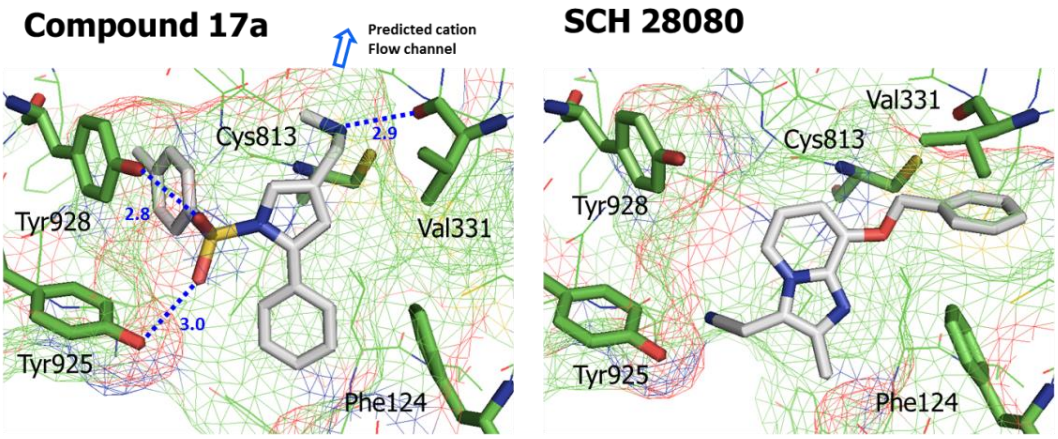


Figure 11. Binding models of compound **17a** and SCH 28080 with H^+,K^+-ATPase. Several residues near compound **17a** are shown in stick representations. Three hydrogen bonds between compound **17a** and H^+,K^+-ATPase are shown in blue dash lines. The distances (Å) between heavy atoms participating in these hydrogen bonds are also described in blue letters. The predicted cation flow channel is indicated by the blue arrow.

以上のことから、本系統化合物は P-CAB の作用メカニズムを有する新規酸関連疾患治療薬の創製に繋がる可能性があると判断し、**17a** をリード化合物に選定して（lead 1）、構造活性相関（SAR）の精査を進めた（Figure 12）。

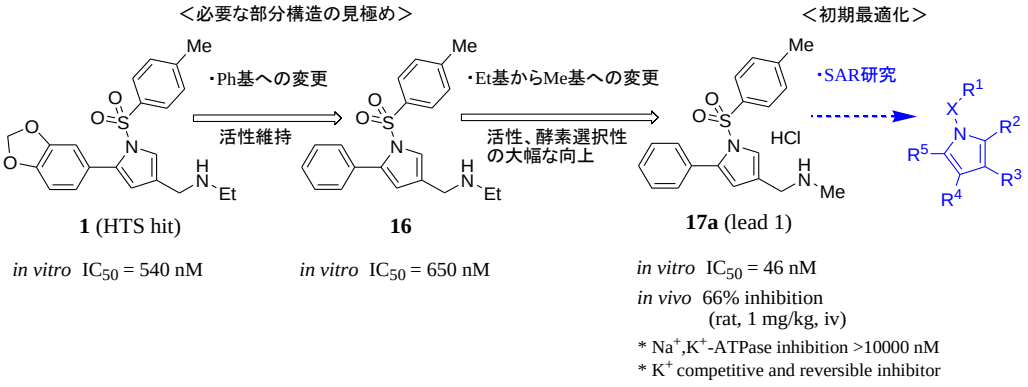


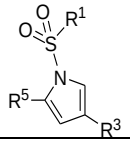
Figure 12. Early synthetic strategy from **1** and generation of lead compound **17a**.

第 2 項 ピロール誘導体の構造活性相関

ピロール誘導体の P-CAB としてのポテンシャルを明らかにすることを目的として、lead 1 誘導体の SAR を詳しく調べた。その結果、3 位（R^3）については、塩基性を有する必要が

あること、特に *N*-メチルアミノメチル基が強力な阻害活性を示し、その他の置換基では明らかに活性が低下することがわかった（Table 1）。

Table 1 Effects of benzodioxol moiety at 5-position (R^5), substituent at 1-position (R^1) and basic moiety at 3-position (R^3) on inhibitory activities.



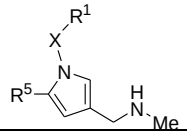
Compound	R^1	R^3	R^5	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)
1	4-Me-C_6H_4			540	39 (10 mg/kg, iv)[a]
16	4-Me-C_6H_4		Ph	650	53 (10 mg/kg, iv)[a]
17a	4-Me-C_6H_4		Ph	46	66
18	4-Me-C_6H_4		Ph	>10000	NT[b]
21	4-Me-C_6H_4		Ph	>10000	–3 (10 mg/kg, iv)[a]
20	4-Me-C_6H_4		Ph	860	NT[b]
17b	4-CF_3-C_6H_4		Ph	110	73
22	4-CF_3-C_6H_4		Ph	710	59 (10 mg/kg, iv)[a]
24	4-CF_3-C_6H_4		Ph	2300	–4

[a] Acid secretion in rats (10 mg/kg, iv, % inhibition)

[b] Not tested

また、1 位置換基（X および R^1）としては、**17f** と比較した **17d**、**17g**、**17e** および **17h** のアッセイ結果から芳香環が直結したスルホニル基が好ましく、その他では活性が低下すること、5 位（R^5）についても **30a** および **30b** のアッセイ結果から 1 位と同様に直結の芳香環が好ましいことがわかった（Table 2）。2 位（R^2）、4 位（R^4）への置換基の導入による明らかな優位性は確認されず、2 位（R^2）では in vivo 活性が減弱する傾向が認められた（Table 3）。得られたアッセイ結果は、H^+,K^+-ATPase ホモロジーモデルとのドッキング解析を否定するものではなく、おおよそ、その妥当性を支持した。

Table 2 Effects of sulfonyl moiety at 1-position (X and R^1) and aromatic moiety at 5-position (R^5) on inhibitory activities.

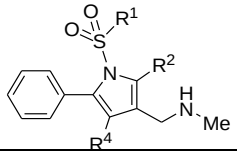


Compound	R^1	X	R^5	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)
17a	4-Me-C_6H_4	SO_2	Ph	46	66
17c	4-MeO-C_6H_4	SO_2	Ph	30	95
17f	Ph	SO_2	Ph	9.4	96
17d	Me	SO_2	Ph	>10000	27 (10 mg/kg, iv)[a]
17g	*n*-Bu	SO_2	Ph	830	NT[b]
17e	Ph	CH_2	Ph	510	84 (10 mg/kg, iv)[a]
17h	Ph	CO	Ph	>10000	NT[b]
30a	Ph	SO_2	*n*-Bu	250	–8
30b	Ph	SO_2	Cyclopropyl	1500	NT[b]

[a] Acid secretion in rats (10 mg/kg, iv, % inhibition)

[b] Not tested

Table 3 Effect of substituents (R^2 and R^4) on pyrrole ring on inhibitory activities.



Compound	R^1	R^2	R^4	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)
17a	4-Me-C_6H_4	H	H	46	66
17f	Ph	H	H	9.4	96
34a	Ph	Me	H	25	77
34b	Ph	Cl	H	40	49
39	Ph	H	Me	29	95

第 3 項 新規リード化合物 **17c** の薬理作用と課題

本ピロール誘導体の SAR 評価を進める過程で、in vivo 評価（ラット、1 mg/kg、iv 投与）において、LPZ（約 90%抑制）よりも強い酸分泌抑制活性を示す複数の化合物を見出すに至った（Table 2 および Table 3 にその一部を示した）。その中で、95%の強力な酸分泌抑制活性を示し、物理化学的安定性およびヒト代謝安定性に優れた化合物 **17c** を薬効の精査化合物に選定した。**17c** を 1 mg/kg でイヌに経口投与（po）したところ、LPZ より強力かつ持続的に胃酸分泌を抑制し、投与 24 時間後においても有意な酸分泌抑制作用が認められた（Figure 13）。

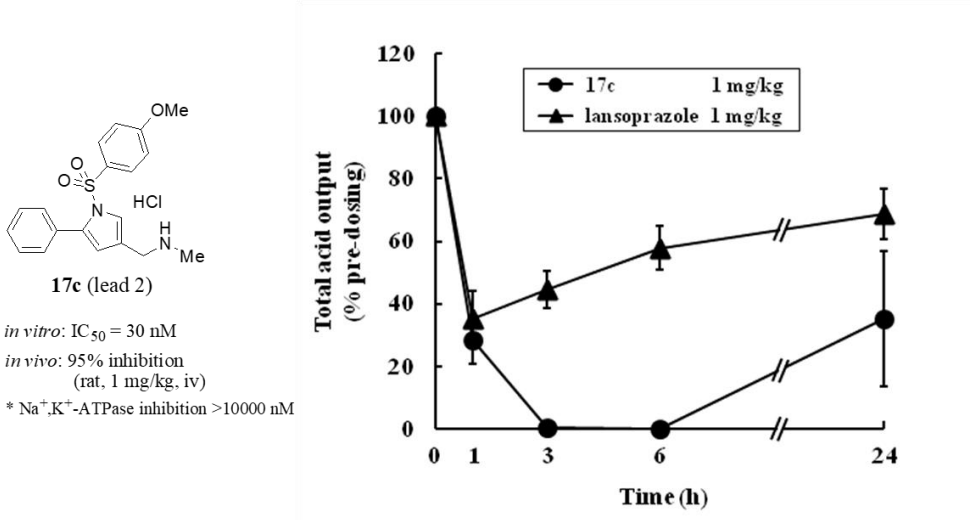


Figure 13. Effects of **17c** and lansoprazole given orally on histamine-stimulated gastric acid secretion in Heidenhain-pouch dogs.

以上の結果より、**17c** を新規リード化合物（lead 2）として、さらに評価を進めた。その結果、強い酸分泌抑制作用を有する一方で、細胞傷害性、hERG 阻害、PLsis のポテンシャルなど薬物動態／毒性面（ADME-Tox）に大きな課題があることが明らかとなった。

このように ADME-Tox 特性の大幅な改善は必要であるが、その課題を解決することができれば、本ピロール誘導体は PPI（LPZ）の課題を克服し、高い安全性を有する新規酸関連疾患治療薬（P-CAB）に繋がる可能性を持つことが明確に示されたと言える。

第 4 節 小括

HTS から得られたヒット化合物を基に、新規ピロール誘導体を合成し、H^+,K^+-ATPase 阻害活性に対する SAR を調べた。その結果、活性の向上を図りつつ、P-CAB として活性発現

に重要と考えられる部分構造を明らかにした。合成した化合物の中で **17a** は、P-CAB の作用メカニズムで強力かつ高選択的に H^+,K^+-ATPase を阻害し、リード化合物としてのポテンシャルを示した（lead 1）。また、**17c** はラットおよびイヌ動物モデルにおいて、LPZ よりも強力かつ持続的な酸分泌抑制作用を示し、新規リード化合物（lead 2）に選定された。**17c** には ADME-Tox 面で克服すべき大きな課題が認められたが、今後の最適化研究により、PPI（LPZ）の課題を克服し、ヒトにおいて持続性を発揮する安全性に優れた新規 P-CAB に繋がる可能性が示された。

第 3 章 効果の持続性向上を志向したリード化合物の最適化

第 1 節 背景および分子設計の戦略

PPI（LPZ）の課題を完全に克服する新規 P-CAB を創製するために、化合物 **17c** をリードとして、ADME-Tox 特性に優れ、開発リスクの低い化合物の探索を目指した。まず、誘導化の方向性を探るために、構造と毒性パラメータの相関を調べたが、方向性の決定は困難であった。そこで、活性の弱い誘導体に範囲を広げて、系統的・網羅的に ADME-Tox 評価を実施したところ、具体的な化学構造ではないが、化合物の脂溶性の指標とされる実測 log D[36] と細胞傷害性との間に明確な相関を見出すことができた（Figure 14）。また hERG 阻害活性についても log D の低下に相関してわずかながらに低減される傾向を見出した[37, 38]。本 log D はクロマトグラフ法で得られた実測値であり、HPLC 分析で pH 7.4 における標準化合物に対する相対保持時間から算出される。創薬段階で実施可能な手法として簡易かつ迅速な測定が可能となっている。

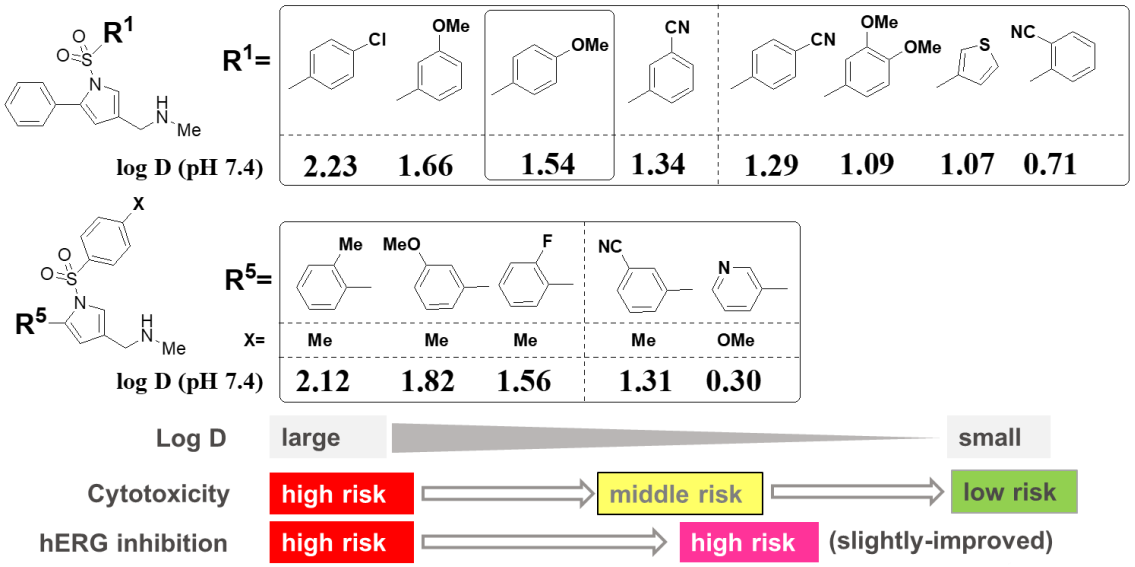


Figure 14. Correlation between measured log D value and *in vitro* toxic data on a series of pyrrole derivatives (based on data on file, Takeda Pharmaceutical Company Limited)

この知見により本系統化合物の log D を大きく下げることができれば ADME-Tox 特性の改善は可能という仮説を立てることができた。本仮説は、H^+,K^+-ATPase ホモロジーモデルとのドッキング解析と LLE 値（ligand-lipophilicity efficiency、LLE = pIC_{50}–log D）[39] を指標とした 1 位置換基（R^1）の最適化に活用され、最終的に、強い活性と優れた ADME-Tox 特性を有する **TAK-438**（ボノプラザン：vonoprazan fumarate）の同定に至った（Figure 15）[40–42]。

加えて、log D の低減が酸分泌抑制作用の持続性向上に繋がる可能性を考え、その低減効果を最大化することを目指した構造修飾を進める大きな原動力となった。すなわち、5 位に極性の高い置換基（ヘテロ芳香環）を導入して log D を低下させることを出発点とする最適化により、より優れた ADME-Tox 特性（より高い安全性）と更なる持続性の向上を同時に達成できると考えた。

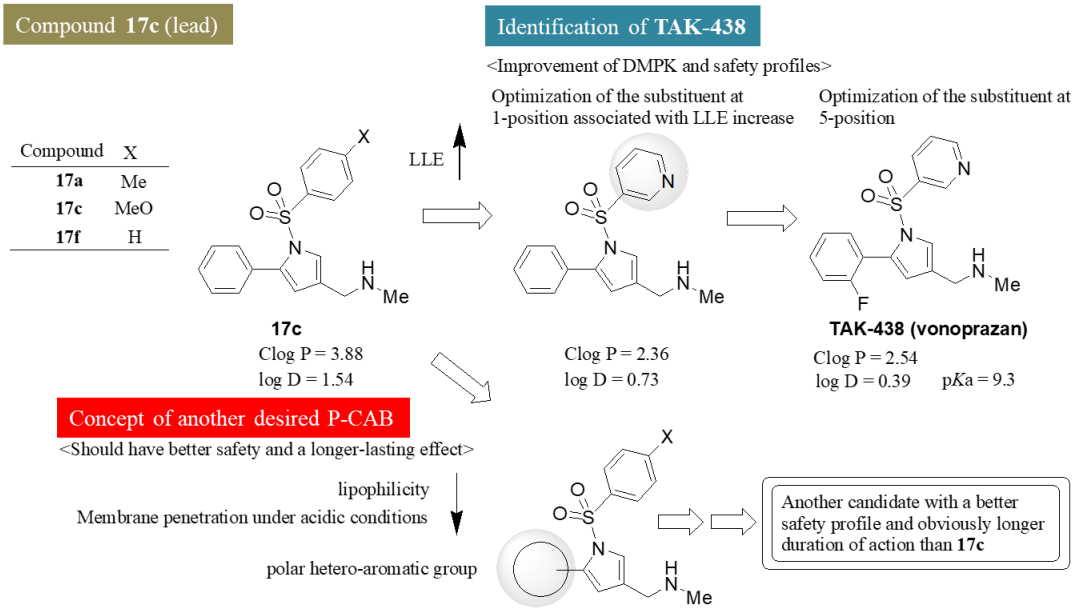


Figure 15. Another approach to identification of a novel pyrrole derivative as a P-CAB with better safety and a longer-lasting effect

第 2 節 合成

第 1 節で論じた分子設計に基づき、以下の化合物を合成することにした（Figure 16）。

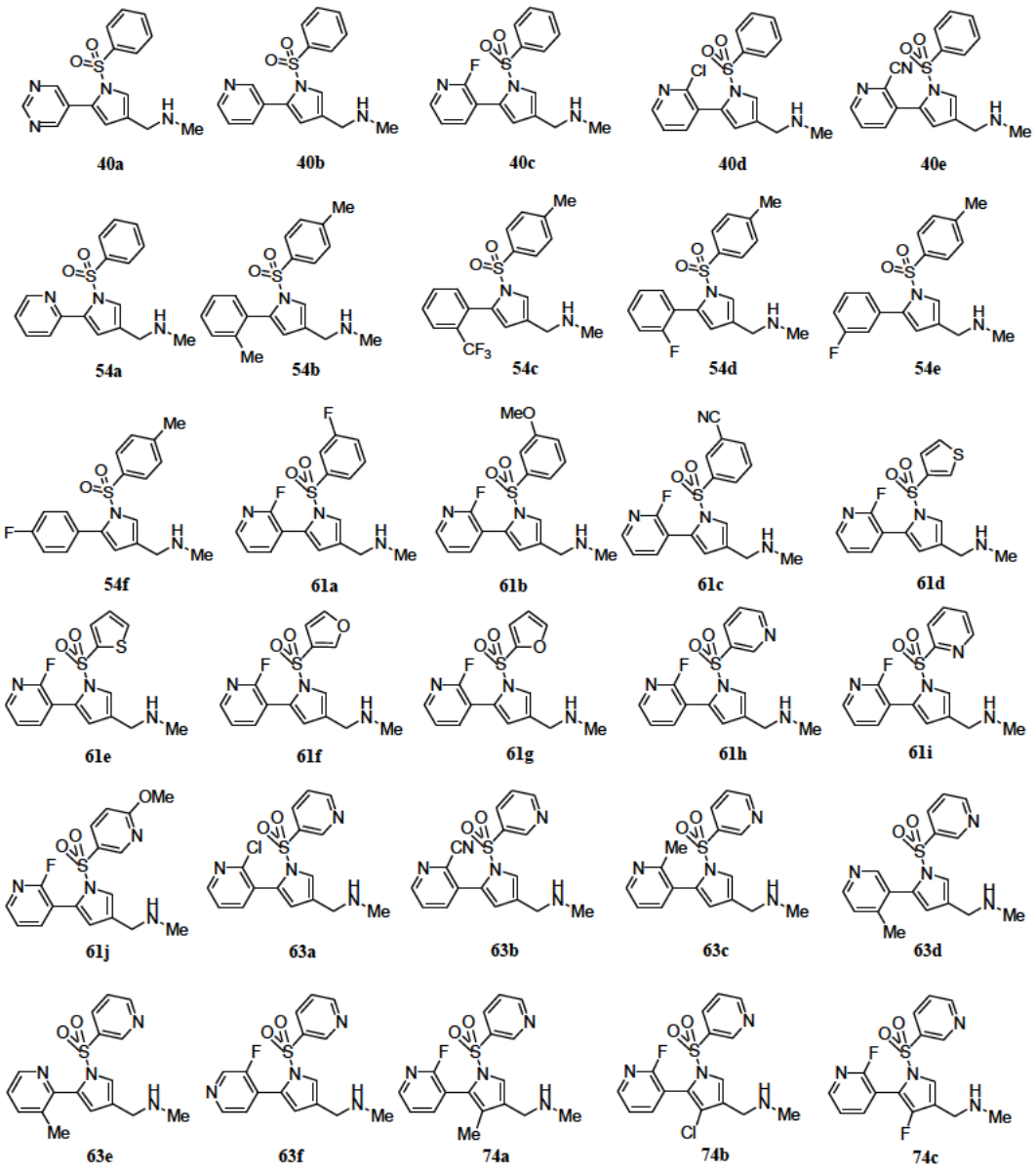
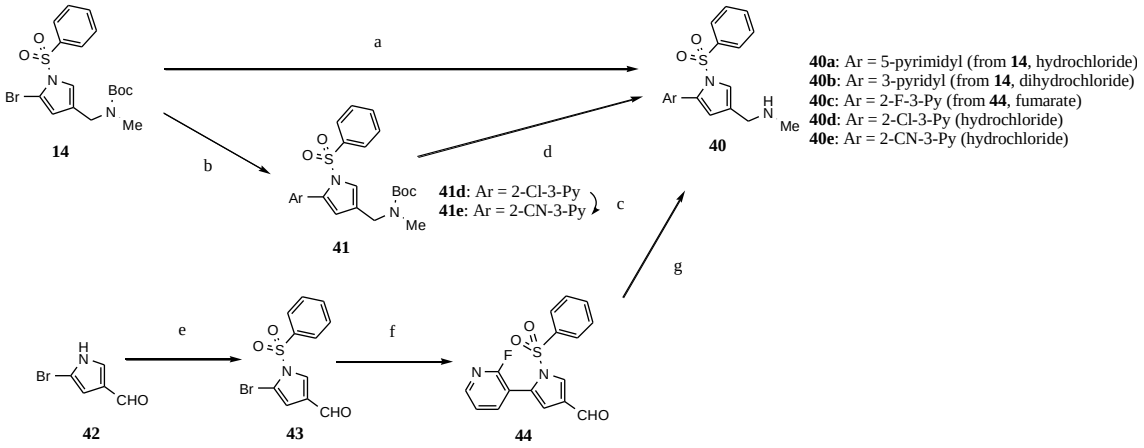


Figure 16. Structures of synthesized compounds in Chapter 3

5 位にヘテロ芳香環を有する化合物 **40a–e** の合成は、ブロモ中間体 **14** あるいは **42** から Scheme 6 に示す方法で行った。すなわち、化合物 **14** を対応するボロン酸と鈴木-宮浦カップリング反応で縮合させた後に強酸で処理することにより **40a** および **40b** へと導いた。また、塩基性条件下におけるスルホニル化反応により **42** を **43** とし、2-F-3-Py ボロン酸と鈴木

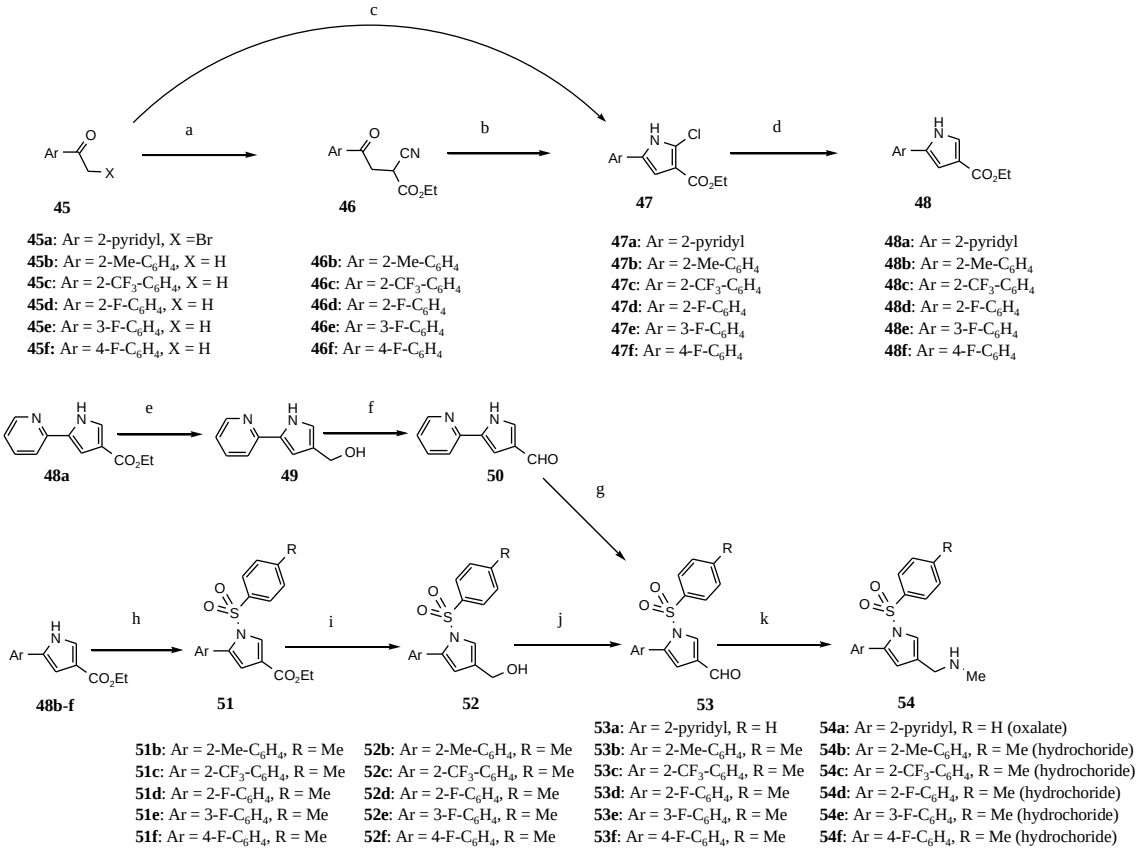
-宮浦カップリング反応を行って **44** に変換した後、還元的アミノ化反応により *N*-メチルアミノメチルパーツを含む **40c** を得た。さらに、化合物 **14** から鈴木-宮浦カップリング反応で調製した 2-Cl-3-Py 誘導体 **41d** に対しては、Pd 触媒を用いたシアノ化反応を行って 2-CN-3-Py 誘導体 **41e** を合成した。**41d** および **41e** を塩酸で処理して Boc 基を脱保護することにより、それぞれ目的とする化合物 **40d** および **40e** とした。**40a**、**40d** および **40e** は塩酸塩、**40b** は二塩酸塩、**40c** はフマル酸塩として単離した。



Scheme 6. Reagents and conditions: (a) (1) Ar-B(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, H$_2$O, 90 °C; (2) 4 mol/L HCl/EtOAc, MeOH, 70 °C; (b) Ar-B(O-*i*Pr)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, DME, H$_2$O, 105 °C; (c) Zn(CN)$_2$, Pd(PPh$_3$)$_4$, DMF, 120 °C; (d) 4 mol/L HCl/EtOAc, EtOH, room temperature (rt), or 4 mol/L HCl/EtOAc, MeOH, EtOAc, rt; (e) NaH, Ph-SO$_2$Cl, THF, rt; (f) 2-F-3-Py-B(OH)$_3$, Pd(PPh$_3$)$_4$, NaHCO$_3$, DME, H$_2$O, 80 °C; (g) (1) 40% MeNH$_2$ in MeOH, MeOH, rt; (2) NaBH$_4$, rt; (3) fumaric acid, EtOH.

ピロール 5 位に 2-ピリジル基を導入した **54a**、置換フェニル基を導入した **54b–f** の合成は Scheme 7 に示す方法を用いて行った。まず、市販の α-ブロモケトン **45a** をシアノ酢酸エチルと縮合させ（**45a** については対応する **46** の単離を実施しなかった）、酸性条件下における環化反応によりクロロピロール **47a** とした後、加水素分解反応によりエチルエステル中間体 **48a** へと導いた。**48a** は DIBAL-H で還元してアルコール **49** とし、続いて TPAP、NMO 系で酸化してアルデヒド **50** に変換した後、スルホニルクロリドと反応させて **53a** とした。次に、アセトフェノン誘導体 **45b–f** の臭素化反応で得られた α-ブロモケトン誘導体をそれぞれシアノ酢酸エチルと縮合させて中間体 **46b–f** に変換し、酸性条件下における環化反応によりクロロピロール **47b–f** とした後、加水素分解反応によりエチルエステル中間体 **48b–f** へと導いた。**48b–f** は先にスルホニル化反応を行って **51** とし、続いて還元反応、酸化反応を行うことにより、**52** を経由してアルデヒド **53b–f** とした。得られたアルデヒド **53** を Scheme 6 に示した方法と同様に処理することにより目的とする **54** を得た。**54a** はシュウ酸塩、**54b–**

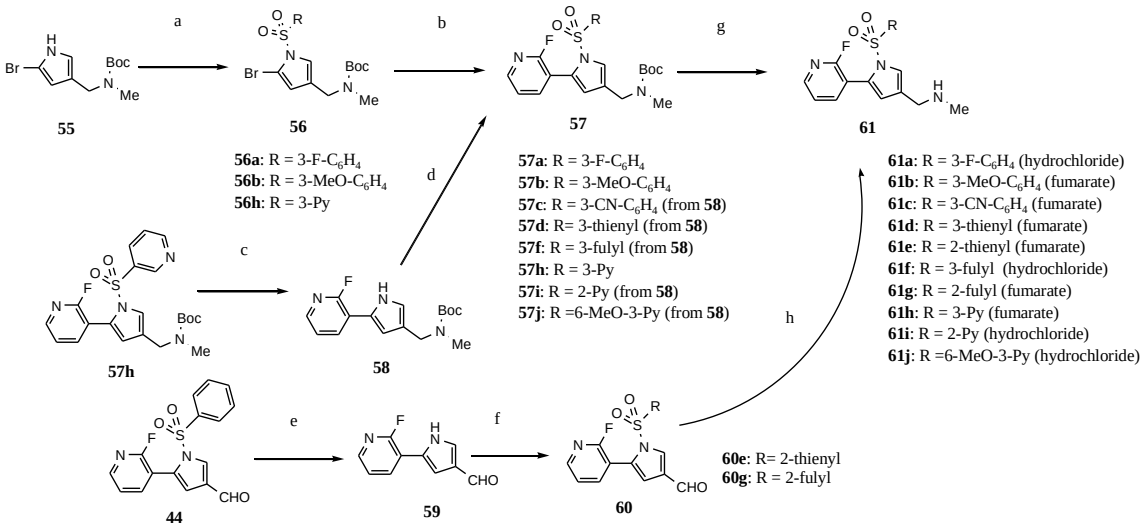
f は塩酸塩として単離した。



Scheme 7. Reagents and conditions: (a) (1) Br_2, Et_2O, rt, or Br_2, Et_2O, $CHCl_3$, rt, or $CuBr_2$, AcOEt, refluxed temperature; (2) ethyl cyanoacetate, K_2CO_3, 40–45 °C, then rt, acetone; (b) HCl(g), THF, rt, or 4 mol/L HCl/EtOAc, rt; (c) (1) ethyl cyanoacetate, K_2CO_3, acetone, 45 °C; (2) 4 mol/L HCl/EtOAc, 60 °C; (3) 4 mol/L HCl/EtOAc, EtOAc; (d) H_2, 10% Pd–C, EtOH, 50 °C or rt; (e) 1.5 mol/L DIBAL-H in toluene, THF, −50 °C; (f) TPAP, NMO, MS4Å, MeCN, rt; (g) NaH, THF, 15-crown-5, Ph-SO_2Cl, rt; (h) NaH, DMF, TsCl, rt; (i) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C; (j) TPAP, MNO, MS4Å, MeCN, rt; (k) 40% $MeNH_2$ in MeOH, MeOH, $NaBH_4$, rt, or methylamine hydrochloride, $NaBH_3CN$, THF, rt.

ピロール 1 位に各種アリールスルホニル基を導入した化合物については、Scheme 8 に示すように、**55** から出発し、Boc 保護中間体 **57** を経由することにより合成するか、**44** から出発し、アルデヒド **60** を経由することにより合成した。中間体 **55**、**58** および **59** のスルホニル化反応に関しては、塩基性条件下における 15-クラウン-5 の添加が、必須あるいは効果的であった。実際、高極性基を有するスルホニル化剤の場合、15-クラウン-5 の添加なしに反応は進行しないことがほとんどであった（スルホニル化剤の低い反応性、あるいは低い安定性に起因すると推定された）。 15-クラウン-5 は、分子内にナトリウムイオンを保持して

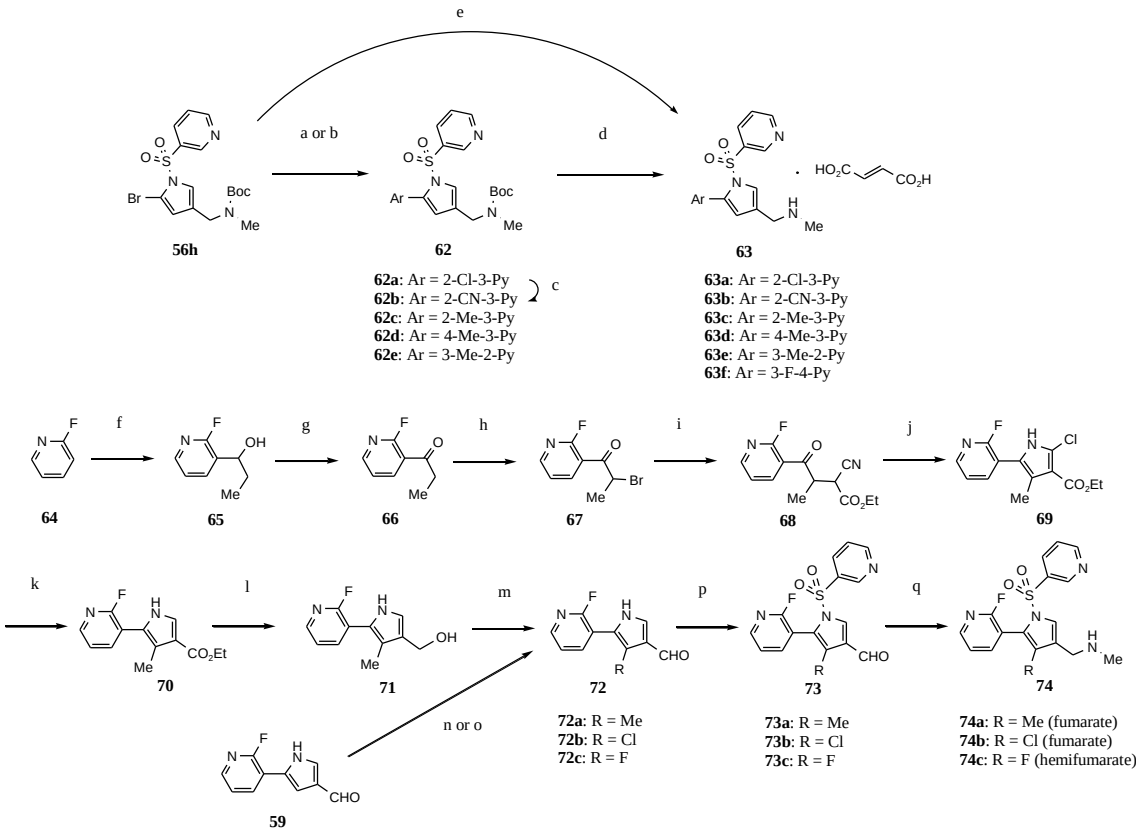
カチオンの影響を弱めることにより、ピロールアニオンの反応性を大きく向上させると推測された。**56** から **57** を経由して目的物 **61** へと導く反応、**44** から **59** への脱保護反応、**60** から目的物 **61** へと導く反応については、いずれも前述した方法を用いて行った。また、中間体 **58** は **57h** をアルカリ加水分解することにより調製した。**61a**、**61f**、**61i** および **61j** は塩酸塩として、**61b–e**、**61g** および **61h** はフマル酸塩として単離した。



Scheme 8. Reagents and conditions: (a) NaH, 15-crown-5, R-SO_2Cl, THF, rt; (b) 2-F-3-Py-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 105 °C; (c) 8 mol/L NaOH, THF, MeOH, rt; (d) NaH, 15-crown-5, R-SO_2Cl, THF, 0 °C, then rt; (e) 8 mol/L NaOH, THF, MeOH, rt; (f) NaH, THF, 15-crown-5, R-SO_2Cl, rt; (g) 4 mol/L HCl/EtOAc, EtOH, rt or (1) 4 mol/L HCl/EtOAc, MeOH, EtOAc, rt; (2) $NaHCO_3$, H_2O; (3) fumaric acid, MeOH or EtOH, EtOAc; (h) (1) 40% $MeNH_2$ in MeOH, MeOH, rt; (2) $NaBH_4$, rt; (3) fumaric acid, MeOH, EtOAc.

ピロール 5 位のピリジル基を種々変更した誘導体、ピロール 4 位へメチル基あるいはハロゲン原子を導入した誘導体については、それぞれ中間体 **56h**、市販の 2-フルオロピリジン（**64**）および中間体 **59** を出発原料として Scheme 9 に示す方法を用いて合成した。すなわち、**56h** を鈴木-宮浦カップリング反応または右田-小杉-Stille カップリング反応で **62** へと導き、これを前述と同様の方法を用いて脱保護することにより目的とする **63** を得た。また、市販の **64** を LDA で処理した後、プロピオンアルデヒドと反応させることによって第二級アルコール **65** とし、ピリジン-三酸化硫黄錯体を用いた酸化反応によりケトン **66** に変換した。これを臭素化して α-ブロモ誘導体 **67** とした後、*N*,*N*-ジイソプロピルエチルアミンの存在下でシアノ酢酸エチルと反応させて **68** とし、酸性条件下で環化して **69**、続いて脱ハロゲン化することによりエステル中間体 **70** を得た。その後は前述と同様の方法を用いて **70** から **71**、**72a** および **73a** を経由して目的とする **74a** を得た。さらに、鍵中間体 **59** を NCS で塩素化することにより **72b**、1-フルオロ-2,6-ジクロロピリジニウムトリフラートを用いて F 化するこ

とにより **72c** へ変換し、それぞれ前述と同様の方法を用いてスルホニル化および還元アミノ化を行って目的とする **74b** および 7**4c** へと導いた。**63a–f**、**74a** および **74b** はフマル酸塩、**74c** は 0.5 フマル酸塩として単離した。



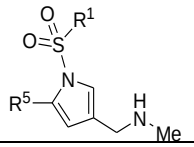
Scheme 9. Reagents and conditions: (a) Ar-B(OH)$_2$, Na_2CO_3, $Pd(PPh_3)_4$, DME, H_2O, 105 °C; (b) 3-Me-2-($SnBu_3$)Py, $Pd(PPh_3)_4$, toluene, 120 °C; (c) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 120 °C; (d) (1) 4 mol/L HCl/EtOAc, MeOH, EtOAc, rt or 70 °C; (2) $NaHCO_3$, H_2O; (3) fumaric acid, MeOH or EtOH, EtOAc; (e) (1) 3-F-4-Py-B(OH)$_2$, $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O, 80 °C; (2) 4 mol/L HCl/EtOAc, MeOH, 70 °C; (3) $NaHCO_3$, H_2O; (4) fumaric acid, MeOH, EtOAc; (f) LDA, THF, −78 °C, then propionaldehyde, THF, −78 °C; (g) SO_3-Py, Et_3N, DMSO, rt; (h) Br_2, 25% HBr, AcOH, rt; (i) ethyl cyanoacetate, *i*Pr_2NEt, THF, rt; (j) 4 mol/L HCl/EtOAc, EtOAc, rt; (k) H_2, 10% Pd–C, Et_3N, EtOH, 60 °C; (l) 1.5 mol/L DIBAL-H in toluene, THF, −78 °C, then 0 °C; (m) TPAP, NMO, MS4Å, MeCN, rt; (n) NCS, DMF, 80 °C (R = Cl); (o) 1-fluoro-2,6-dichloropyridinium triflate, THF, MeCN, rt (R = F); (p) NaH, THF, 15-crown-5, 3-Py-SO_2Cl, rt; (q) (1) 40% $MeNH_2$ in MeOH, MeOH, THF, rt; (2) $NaBH_4$, rt; (3) fumaric acid, EtOH, EtOAc; or (1) methylamine hydrochloride, $NaBH(OAc)_3$, MeOH, rt; (2) fumaric acid, MeOH, EtOAc, or fumaric acid, EtOH, EtOAc.

第 3 節 化合物の評価および考察

第 1 項 ピロール 5 位置換基の効果

まず、R^5 を 5-ピリミジル基とした **40a**、3-Py 基とした **40b**、2-Py 基とした **54a** を評価したところ、Ph 体 **17f** と比較して in vitro 活性は大きく減弱したが、Clog P からの予測以上に log D が低下し、細胞傷害性（ATP content）や hERG 阻害活性が顕著に改善された（Table 4）。特に 3-Py 体 **40b** は最も大きい LLE を示し（6.81）、代謝安定性や溶解度なども良好であった。したがって、**40b** はラット iv 投与の in vivo 評価で有意な抑制作用を示さなかったが（1 mg/kg で 4%抑制）、更なる誘導化を検討する余地はあると判断した。

Table 4 Effects of the substituent at position 5 (R^5) on activities and properties of pyrrole compounds



Compound	R^5	R^1	Clog P	log D	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	LLE	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content at 100 μM (%control)	hERG % inhibition at 10 μM FCS (-)
17a	Ph	4-Me-C_6H_4	4 21	1 83	46	5 51	66	(38 6)[a]	NT[b]
17c	Ph	4-MeO-C_6H_4	3 88	1 54	30	5 98	95	(22 1)[a]	89 1
17f	Ph	Ph	3 71	1 44	9 4	6 59	96	(53 8)[a]	87 5
40a	5-Pyrimidyl	Ph	1 42	–0 4	410	6 79	NT[b]	97 5	24 2
40b	3-Py	Ph	2 36	0 08	130	6 81	4	95	43 3
54a	2-Py	Ph	2 57	0 28	120	6 64	NT[b]	91 2	48 0
54b	2-Me-C_6H_4	4-Me-C_6H_4	4 41	2 12	62	5 09	92	(0 3)[a]	NT[b]
54c	2-CF_3-C_6H_4	4-Me-C_6H_4	5 15	1 94	88	5 12	86	(0 5)[a]	NT[b]
54d	2-F-C_6H_4	4-Me-C_6H_4	4 39	1 56	34	5 91	91	(8)[a]	NT[b]
54e	3-F-C_6H_4	4-Me-C_6H_4	4 39	1 98	19	5 74	77	(0 6)[a]	NT[b]
54f	4-F-C_6H_4	4-Me-C_6H_4	4 39	2 05	90	5 00	86	(0 4)[a]	NT[b]
40c	2-F-3-Py	Ph	2 56	–0 09	26	7 68	99	59 9	57 0
40d	2-Cl-3-Py	Ph	2 88	–0 1	43	7 47	99	76 3	40 9
40e	2-CN-3-Py	Ph	2 17	–0 32	120	7 24	99	82 1	32 9

[a] ATP content at 30 μM (% control)

[b] Not tested

5 位における 3-Py 基の塩基性は H^+,K^+-ATPase との相互作用（Figure 11）や胃移行性において有利には働かないと考えられたことから、次に、3-Py 基の塩基性を低減しつつ、活性の向上が期待できる置換基を持つ化合物の活性評価を行った。その結果、オルト位に F 原子を導入した 2-F-C_6H_4 誘導体 **54d** には **17a**（リード 1）と比較すると細胞傷害性や CYP3A4 阻害が強まる傾向は認められるが、in vivo 活性が明らかに向上し、log D が低下する化合物特性があることがわかった。**54d** は 3-F-C_6H_4 誘導体 **54e** や 4-F-C_6H_4 誘導体 **54f** よりも log D

が低く、ADME-Tox 特性面で総合的に有利と考えられること、2-Me-C_6H_4 誘導体 **54b** や 2-CF_3-C_6H_4 誘導体 **54c** と比較して log D が低く、実際に細胞傷害性や CYP3A4 阻害が弱いこと等に着目して、3-Py 基の 2 位に電子求引性基を有するハイブリッド型誘導体 **40c–e** をデザインした。いずれの化合物も、**40b**（log D = 0.08）と比較してさらに低い log D を示しながら、ラット in vivo の活性を大幅に向上させ、リード化合物 **17c** よりも強力な 99%の酸分泌抑制活性を示した。2-CN-3-Py 誘導体 **40e** は併せて非常に優れた ADME-Tox プロファイルを示したが、in vitro 活性がやや弱く（IC_{50} = 120 nM）、一方で、2-F-3-Py 誘導体 **40c** と 2-Cl-3-Py 誘導体 **40d** は ADME-Tox 特性面が不十分であった。以上の結果を勘案し、1 位の置換基については、LLE 値の最も高い 2-F-3-Py 誘導体 **40c** を基に検討を進めることとした。

第 2 項 ピロール 5 位に 2-フルオロフェニル基を導入したときの log D 低減効果

2-フルオロフェニル基の F 原子の log D 低減効果について、明確な説明は困難であった。しかし、良く似たコンホメーションを取ることが多いとされる単結晶中のコンホメーションに着目して **17a**、**54d**、**54e** および **54f** の単結晶 X 線結晶構造解析を行ったところ、F 原子の存在や置換位置に関係なくほぼ同様のコンホメーションを取っており、明確な差が認められないこと、2-F-C_6H_4 誘導体 **54d** では F 原子と分子内のスルホニル酸素やトシル基との距離（最短距離）が **54e** および **54f** と比較して明らかに近いという知見が得られ、水溶液中においても 2-F-C_6H_4 誘導体は F 原子とスルホニル酸素やトシル基との距離が近く、分子内で何らかの相互作用が生じている可能性が示唆された（Figure 17）。そこで、D_2O 中と DMSO-d_6 中の NMR を測定し（^1H, ^{13}C, ^{19}F）、いくつかの考察を試みた。

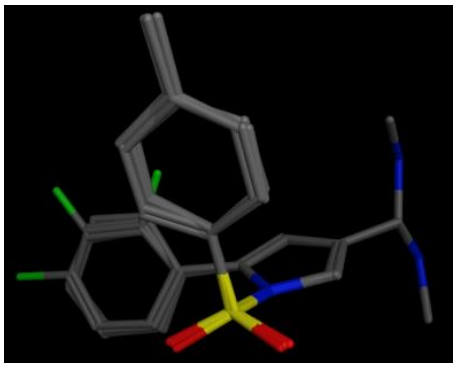
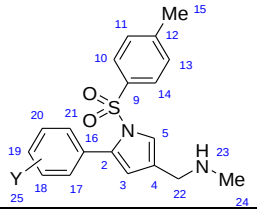


Figure 17. Superposition of single-crystal structures obtained by X-ray structural analysis for **17a**, 2-F-C_6H_4 (*ortho*) compound **54d**, 3-F-C_6H_4 (*meta*) compound **54e**, and 4-F-C_6H_4 (*para*) compound **54f**. Steric conformations among these pyrrole compounds were almost comparable in single-crystal structures including non-fluorinated compound **17a**, but the shortest distance between oxygen atoms and the fluorine atom in each single-crystal structure was 4.34 Å in *ortho* compound **54d**, 5.53 Å in

meta compound **54e**, and 5.80 Å in *para* compound **54f**. In addition, the shortest distance between a fluorine and the center of benzene ring of the tosyl group was 4.02 Å in *ortho* compound **54d**, 6.06 Å in *meta* compound **54e**, and 7.26 Å in *para* compound **54f**. pK_a values of **54d**, **54e**, **54f**, and **17a** were 9.48, 9.31, 9.40, and 9.49, respectively, and there were no significant differences among these four compounds.

まず、各誘導体のトシル基とメチルアミノメチル基の D_2O 中における ^{13}C-NMR の化学シフト間にほとんど差が認められないことから、水溶液中においても単結晶中と同じように、F 原子の存在や置換位置に関係なくほぼ同様のコンホメーションを取っていると考えられた（Table 5）。また、トシル基に注目して詳細にデータを確認したところ、^{13}C-NMR の化学シフトが各誘導体で同等であるのに対し、^{1}H-NMR の化学シフトに関しては **54d** でわずかに低磁場シフトが観察された。この低磁場シフトは F 原子の磁気異方性効果によるものと推定され、水溶液中においても単結晶中と同様に **54d** の F 原子と分子内のトシル基との距離が近いことに起因して認められると考えられた。さらに、DMSO-d_6 溶液における ^{19}F-NMR を測定して、D_2O 溶液における ^{19}F-NMR の化学シフトと比較したところ、**54d** とその他誘導体でその挙動に明確な違いが認められ、**54d** では D_2O 中の低磁場シフトが観察されなかった。これは **54d** の F 原子が他の誘導体の F 原子とは異なって、D_2O 中でスルホニル酸素と分子内相互作用していることによるものと解釈できるかもしれない。酸素に非常に近い位置にある F 原子は、近接する酸素を分極して水分子との水素結合を強める可能性などが報告されており [43]、F 原子とスルホニル酸素の距離の近さが log D の低減に寄与している可能性もあると考えられた。

Table 5 NMR analysis of pyrrole compounds regarding the effect of fluorine substitution at position 5



Compound	**54d**		**54e**		**54f**		**17a**	
Y	2-F		3-F		4-F		H	
	^{1}H-NMR (600MHz, D_2O) δ (ppm)	^{13}C-NMR (151MHz, D_2O) δ (ppm)	^{1}H-NMR (600MHz, D_2O) δ (ppm):	^{13}C-NMR (151MHz, D_2O) δ (ppm)	^{1}H-NMR (600MHz, D_2O) δ (ppm)	^{13}C-NMR (151MHz, D_2O) δ (ppm)	^{1}H-NMR (600MHz, D_2O) δ (ppm)	^{13}C-NMR (151MHz, D_2O) δ (ppm)
2		132 22		138 42		138 74		139 92
3	6 446	119 89	6 397	119 08	6 353	118 72	6 362	118 69
4		119 99		119 87		119 73		119 96
5	7 775	127 68	7 736	127 99	7 722	127 56	7 722	127 68
9		135 90		136 00		136 10		136 14
10, 14	7 321	129 65	7 305	129 65	7 280	129 62	7 284	129 58
11, 13	7 318	132 80	7 290	132 68	7 280	132 66	7 284	132 65
12		149 80		149 74		149 65		149 58
15	2 388	23 49	2 371	23 47	2 371	23 47	2 371	23 46
16		120 71		134 81		128 99		133 00
17		163 33	6 943	120 22	7 170	135 52	7 201	133 43
18	7 152	117 87		164 40	7 090	117 34	7 380	130 53
19	7 522	134 62	7 208	118 53		165 74	7 475	131 79
20	7 185	126 58	7 361	132 24	7 090	117 34	7 380	130 53
21	7 075	135 88	7 011	129 45	7 170	135 52	7 201	133 43
22	4 131	47 00	4 118	46 98	4 115	47 04	4 119	47 02
23								
24	2 686	34 35	2 672	34 31	2 677	34 32	2 675	34 31
	^{19}F-NMR (376MHz, D_2O) δ (ppm)	^{19}F-NMR Difference[a] (ppm)	^{19}F-NMR (376MHz, D_2O) δ (ppm)	^{19}F-NMR Difference[a] (ppm)	^{19}F-NMR (376MHz, D_2O) δ (ppm)	^{19}F-NMR Difference[a] (ppm)	^{19}F-NMR (376MHz, D_2O) δ (ppm)	^{19}F-NMR Difference[a] (ppm)
25	–113 970	0 289	–115 577	1 309	–114 016	1 887		

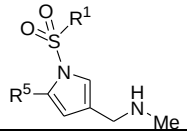
[a] Difference in the chemical shift between D_2O and DMSO-d_6 solutions

第 3 項 ピロール 1 位置換基の効果

2-F-3-Py 誘導体 **40c** を基準としてピロール 1 位置換基（R^1）の影響を調べた（Table 6）。その結果、**40c** の 1 位 Ph 基に置換基を導入した **61a–c** については log D = –0.36 に低減した **61c** を含め、ADME-Tox 面で明確な改善は認められなかった。また 1 位の Ph 基をチエニル基に変更した **61d**、**61e** ではいずれも log D の大きな低下が認められ、かつ強い活性を維持して LLE は 8 以上となったが、hERG 阻害活性の改善は認められなかった。さらにフリル基に変換した **61f**、**61g** はチエニル基以上に log D が低下し、高い LLE を示したが、in vivo 活性の明らかな低下が認められた。一方で、3-Py 誘導体 **61h** および 2-Py 誘導体 **61i** では共に

in vitro 活性は著しく低下したが、3-Py 誘導体 **61h** は log D = –0.85 にもかかわらず in vivo で強力な酸分泌抑制作用を示し（96%の抑制活性）、hERG 阻害活性を大幅に改善しながら、高い LLE（7.53）を反映した優れた ADME-Tox パラメータを示した。また、H^+,K^+-ATPase ホモロジーモデルとのドッキング解析では 3-Py 基の導入により Tyr928 側鎖との π–π 相互作用は弱まるものの、脂溶性ポケット：LP-2 サイトの奥に極性スペースが存在し、ピリジン窒素と水 1 分子を介して水素結合を形成して結合が強まる（離れにくくなる）可能性も示唆された。以上の結果より、1 位に 3-Py スルホニル基を有する **61h** を基に更なる最適化を進めることとした。

Table 6 Effects of substituents at the first position (R^1) on activities and properties of pyrrole compounds



Compound	R^5	R^1	Clog P	log D	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	LLE	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content at 100 μM (%control)	hERG % inhibition at 10 μM FCS (-)
17a	Ph	4-Me-C_6H_4	4 21	1 83	55	5 43	66	(38 6)[a]	NT[b]
17c	Ph	4-MeO-C_6H_4	3 88	1 54	30	5 98	95	(22 1)[a]	89 1
17f	Ph	Ph	3 71	1 44	9 4	6 59	96	(53 8)[a]	87 5
40c	2-F-3-Py	Ph	2 56	–0 09	26	7 68	99	59 9	57 0
61a	2-F-3-Py	3-F-C_6H_4	2 71	0 23	33	7 25	99	65 9	56 2
61b	2-F-3-Py	3-MeO-C_6H_4	2 72	0 10	28	7 45	92	30 6	72 8
61c	2-F-3-Py	3-CN-C_6H_4	2 00	–0 36	89	7 41	99	46 7	46 7
61d	2-F-3-Py	3-thienyl	2 28	–0 83	32	8 32	98	64 0	60 0
61e	2-F-3-Py	2-thienyl	2 28	–0 69	32	8 18	96	74 9	63 0
61f	2-F-3-Py	3-furyl	1 74	–1 31	92	8 35	82	77 4	59 3
61g	2-F-3-Py	2-furyl	1 74	–1 15	59	8 38	74	68 7	49 1
61h	2-F-3-Py	3-Py	1 21	–0 85	210	7 53	96	85 7	4 4
61i	2-F-3-Py	2-Py	1 21	0 05	120	6 97	81	78 6	NT[b]

[a] ATP content at 30 μM (% control)

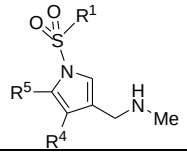
[b] Not tested

第 4 項 化合物 **61h** 周辺誘導体および代表化合物のラット胃灌流液 pH 試験

SAR に加えて化学構造と ADME-Tox パラメータとの相関を理解するために、化合物 **61h** の周辺誘導体をデザイン、合成して詳細に特性を調べた（Table 7）。その結果、1 位（R^1）の 3-Py 基 6 位に MeO 基を導入した化合物 **61j** では in vitro 活性が約 5 倍向上したが（IC_{50} = 40 nM）、細胞傷害性面で所望の水準を下回った。当初は 30 μM で ATP 含量 50%以上が P-CAB としての目標であったが、本最適化ではより高い安全性を目指し、100 μM で ATP 含量 80%以上という極めて高い水準を目標に設定した。5 位置換基（R^5）を 2-Cl-3-Py 基へ変更した **63a** は優れた ADME-Tox プロファイルを維持しながら in vitro 活性を向上させたが（IC_{50} =

120 nM)、in vivo 活性がわずかに減弱した。2-CN-3-Py 基へ変更した **63b** については log D = –1.29 まで低下し、活性が大きく減弱した（IC_{50} = 530 nM)。また、オルト位にメチル基が置換された 2 種の 3-Py 誘導体 **63c** および **63d** については、in vitro 活性は維持されたものの（**63c**: IC_{50} = 250 nM、**63d**: IC_{50} = 230 nM)、in vivo 活性がそれぞれ大幅に減弱し、5 位 Py 基の塩基性が不利に働くことが明らかになった。3-Me-2-Py 基に変更した **63e** や 3-F-4-Py 基とした **63f** など、他のオルト置換 Py 基を持つ化合物については、予想通り、強い活性は認められなかった。ピロール 4 位置換基（R^4）に関しては、電子求引性基の導入効果を含めて水素原子以外の可能性を改めて探ったところ、Me 基を導入した **74a** および Cl 原子を導入した **74b** に活性の維持と細胞傷害性が強くなる傾向が確認された。一方で、F 原子を導入した **74c** については in vitro および in vivo 活性が共に向上し、それに加えて極めて弱い細胞傷害性を示すなど、優れた ADME-Tox プロファイルが認められた。なお、ピロール 2 位への置換基導入については第 2 章 Table 3 の結果を勘案して実施しなかった。

Table 7 Effects of substituents (R^5, R^1, and R^4) on activities and properties of pyrrole compounds



Compound	R^5	R^1	R^4	Clog P	log D	In vitro H^+,K^+-ATPase inhibition (IC_{50}, nM)	LLE	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content at 100 μM (%control)	hERG % inhibition at 10 μM FCS (-)
17c	Ph	4-MeO-C_6H_4	H	3 88	1 54	30	5 98	95	(22 1)[a]	89 1
61h	2-F-3-Py	3-Py	H	1 21	–0 85	210	7 53	96	85 7	4 4
61j	2-F-3-Py	6-MeO-3-Py	H	1 97	0 24	40	7 16	97	47 6	33 1
63a	2-Cl-3-Py	3-Py	H	1 53	–0 5	120	7 42	92	82 9	10 6
63b	2-CN-3-Py	3-Py	H	0 81	–1 29	530	7 57	48	85 3	1 9
63c	2-Me-3-Py	3-Py	H	1 18	0 06	250	6 54	–41	107 2	NT[b]
63d	4-Me-3-Py	3-Py	H	1 18	–0 51	230	7 15	–54	86 0	8 3
63e	3-Me-2-Py	3-Py	H	1 39	0 53	1300	5 36	5	88 7	NT[b]
63f	3-F-4-Py	3-Py	H	1 21	–0 34	290	6 88	48	78 8	18 8
74a	2-F-3-Py	3-Py	Me	1 36	–0 4	220	7 07	93	47 1	30 3
74b	2-F-3-Py	3-Py	Cl	1 77	0 48	99	6 52	95	64 5	41 3
74c	2-F-3-Py	3-Py	F	1 45	0 04	49	7 27	98	100 2	39 8

[a] ATP content at 30 μM (% control)

[b] Not tested

合成した化合物の中で化合物 **40e**、**61h** および **74c** は、低い log D と強力な酸分泌抑制作用を有し、優れた ADME-Tox プロファイルを示したため、麻酔ラットにおけるヒスタミン刺激時の胃灌流液 pH に対する pH 上昇効果を調べた（Figure 18)。

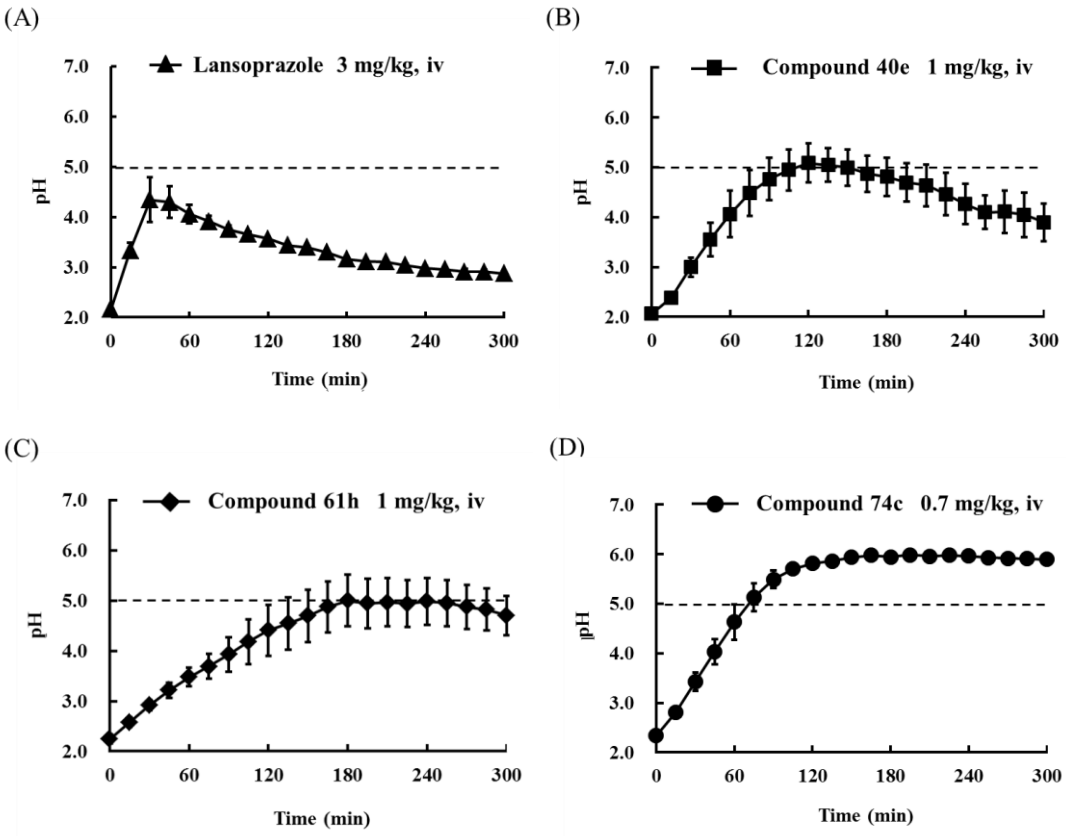


Figure 18. Effects of intravenous administration of lansoprazole (A) and compounds **40e** (B), **61h** (C), and **74c** (D) on pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats. Each data point represents mean ± SE from three or four rats.

その結果、LPZ では 3 mg/kg 投与においても pH5 に到達することなく、pH 4 を少し超える程度まで pH を上げた後に徐々に効果が減弱したのに対し（Figure 18A）、化合物 **40e**、**61h** および **74c** は、いずれも 1 mg/kg 以下の低用量で pH を 5 またはそれ以上に上昇させた。化合物 **40e** は、1 mg/kg 投与後 2 時間以内に灌流液の pH を 5 以上としたが、その後、pH は徐々に低下した（Figure 18B）。化合物 **61h** は、1 mg/kg 投与で灌流液の pH を約 5 としたが、ピーク値の pH5 に到達するまでに 150～180 分を要した（Figure 18C）。一方で、**74c** は 0.7 mg/kg 投与で速やかに pH6 まで上昇させ、しかもその作用は 5 時間持続した（Figure 18D）。以上の結果より、**74c** を精査化合物に選択した。

第 5 項 精査化合物 **74c** の経口投与における酸分泌抑制作用とその有用性

化合物 **74c** のラットおよびイヌへの経口投与における胃酸分泌抑制作用を調べたところ、LPZ よりもはるかに強力かつ持続的な作用を示した。**74c** は、麻酔したラットのヒスタミン刺激による酸分泌を用量に応じて抑制し、4 mg/kg 投与では完全に抑制した（Figure 19）。この結果は **74c** が PPI とは異なり、酸による活性化を必要としないことに起因すると考えられた。

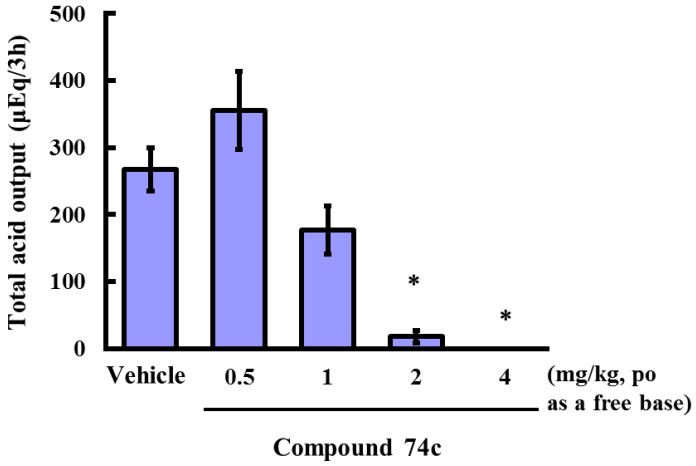


Figure 19. Effects of oral administration of compound **74c** on histamine-stimulated acid secretion in anesthetized rats. Each column represents the mean ± SE from six rats. Statistical significance of the difference was determined by the one-tailed Shirley-Williams test; *p < 0.025 compared to vehicle.

また、化合物 **74c** は 0.8 mg/kg の低用量でハインデンハイン・ポーチ犬におけるヒスタミン刺激による胃酸分泌を投与 1 時間後からほぼ完全に抑制し、投与後 6 時間まで 100%の抑制作用を示すなど、その作用持続は、3 mg/kg 投与の LPZ よりもはるかに長かった（Figure 20）。さらに、その効果は、1 mg/kg 投与のリード化合物 **17c** のものと比較して明らかに長く、投与後 48 時間においても顕著な抑制作用が観察された。

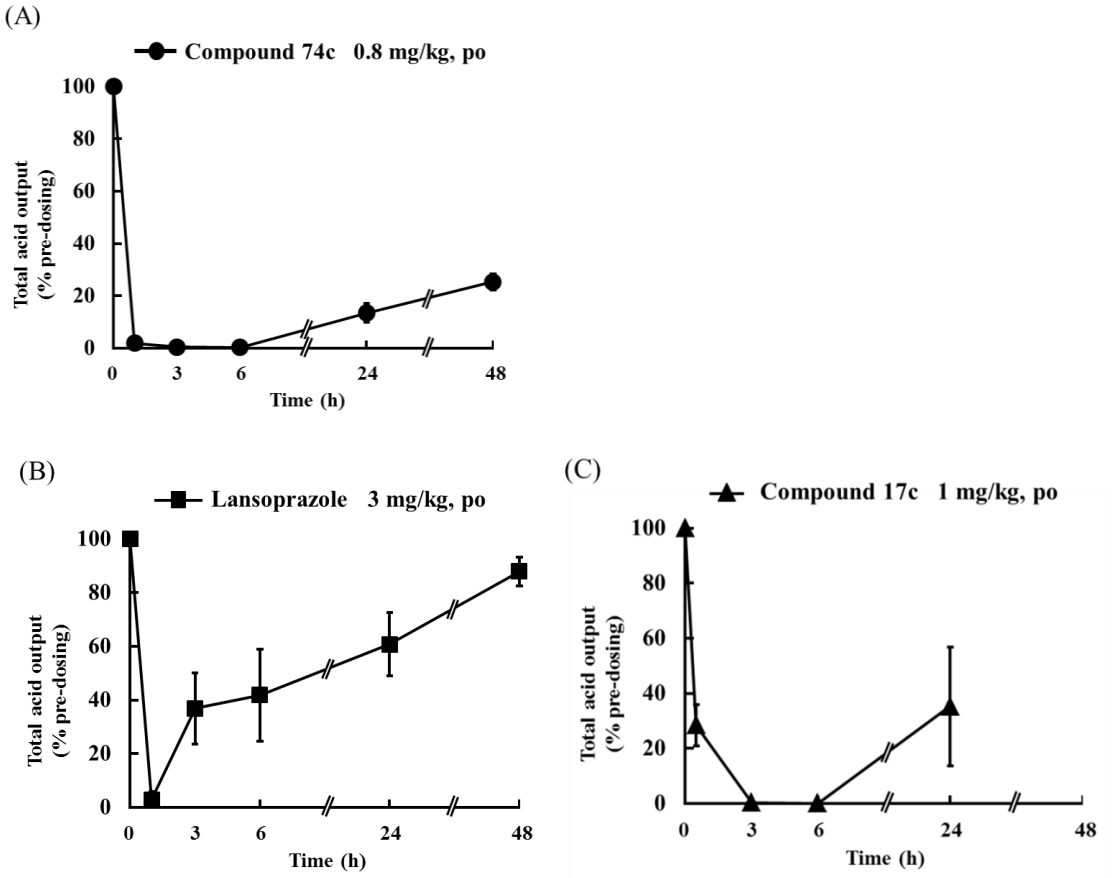
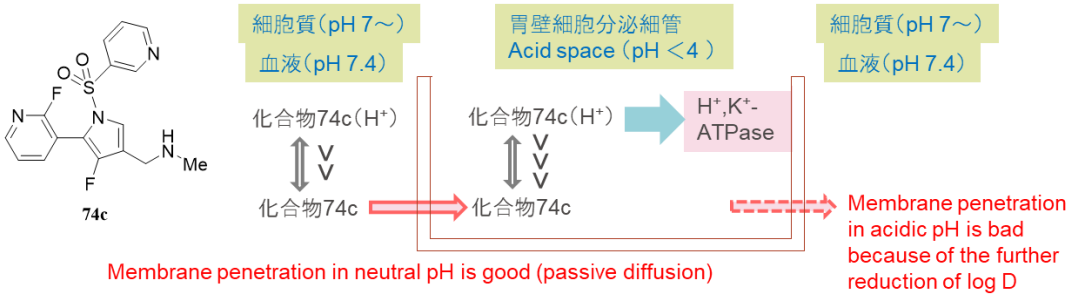


Figure 20. Effects of oral administration of compound **74c** (A), lansoprazole (B), or lead compound **17c** (C) on histamine-stimulated acid secretion in Heidenhain pouch dogs. Each data point represents mean ± SE from three or four dogs.

74c では log D（pH7.4）が 0.04 に低減され、ピロール 4 位 F 原子の電子求引効果により側鎖アミノ基共役酸の p*K*a はやや低めの 8.54 （**17c** は 9.48、**TAK-438** は 9.3）に設計されている。生体内では大部分がイオン型として存在するが、pH が中性付近の環境下では非常に良好な膜透過性を示す。一方で、pH が低下した酸性環境下では膜透過に関与する非イオン型の存在比率が下がることによりさらに脂溶性（log D）が低下し、膜透過性が低下すると考えられる。実際、**74c** では人工膜を用いた試験（PAMPA）において、pH 5 の弱酸性域で顕著な膜透過性の低下が確認された（Figure 21）。したがって、**74c** は酸性環境下の分泌細管内に速やかに移行し（効果の立ち上がりが早い）、そこで長時間留まる（長く作用が持続する）と推定された。



Compound	Clog P	log D at pH 7.4	pK_a	H^+,K^+-ATPase inhibition (IC_{50}, nM)	Acid secretion in rats (1 mg/kg, iv, % inhibition)	PAMPA[a] pH 7.4 Pe(nm/sec)	PAMPA[a] pH 5.0 Pe (nm/sec)
17c (lead 2)	3.88	1.54	9.48	30	95	246	198
74c	1.45	0.04	8.54	49	98	256 →	47

[a] Parallel artificial membrane permeability assay

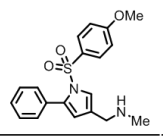
Figure 21. Profiles of compound **74c** and its drug transfer behavior to the stomach.

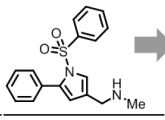
また、**74c** は優れた耐酸性を示し、代謝消失に対する CYP2C19 および CYP2D6 の寄与は限定的で小さかった。さらに、**74c** はヒトにおいて **TAK-438** よりも長い持続性を発揮すると予想された。以上の結果より、**74c** は PPI（LPZ）の課題を解決しながら、非常に長い持続性と高い安全性を両立する優れた P-CAB として期待できること、必要が生じた場合に **TAK-438** の代替化合物として有用と結論付けた。

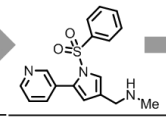
第 4 節 小括

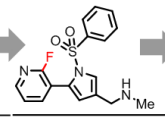
化合物 **17c** をリードとして、強い酸分泌抑制作用と長い作用持続性を有し、ADME-Tox 特性に優れた P-CAB の創製を目指した。まず、ピロール誘導体の構造と毒性パラメータの相関を徹底的に解析し、log D の低減により ADME-Tox 特性の改善は可能という仮説を構築した。次に log D の低減が酸分泌抑制作用の持続性向上に繋がる可能性に着眼して、ピロール 5 位置換基の変更を出発点とする新規誘導体合成を展開した。その結果、5 位置換基を 3-Py 基として log D を低減した **40b**、2-F-3-Py 基として活性を向上させた **40c**、**40c** の 1 位置換基を 3-Py 基として ADME-Tox プロファイルを改善した **61h** を経て、優れたプロファイルを有する **74c** を同定することに成功した（Figure 22）。**74c** は、ラットおよびイヌの経口投与において強力かつ持続的な酸分泌抑制作用を示し、新規 P-CAB として有望と考えられた。

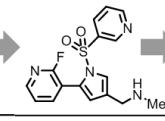
lead



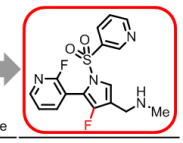








candidate



Compound	17c	17f	40b	40c	61h	74c
Clog P	3.88	3.71	2.36	2.56	1.21	1.45
log D (pH7.0)	1.54	1.44	0.08	–0.09	–0.85	0.04
H^+,K^+-ATPase inhibition (IC_{50}, nM)	30	9.4	130	26	210	49
LLE	5.98	6.59	6.81	7.68	7.53	7.27
Acid secretion in rats (1a mg/kg, iv, % inhibition)	95	96	4	99	96	98
ATP content at 100 μM (%control)	(22.1)[a]	(53.8)[a]	95	59.9	85.7	100.2
hERG % inhibition at 10 μM, FCS (-)	89.1	87.5	43.3	57.0	4.4	39.8

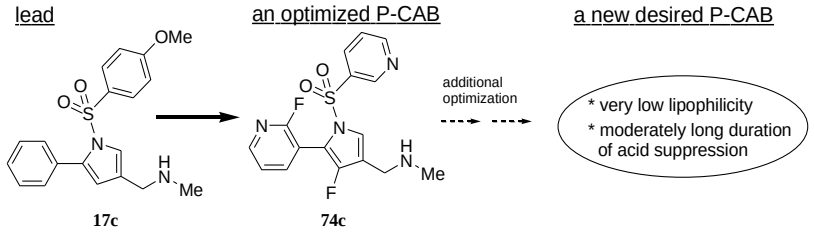
[a] ATP content at 30 μM (% control)
[b] Not tested

Figure 22. Identification of candidate compound **74c** by optimization from lead compound **17c**.

第 4 章 適度な効果の持続性を目指した更なる最適化

第 1 節 背景および分子設計の戦略

第 3 章で選定した化合物 **74c** は、0.8 mg/kg のイヌ po 投与で投与 1 時間後からほぼ 100%の胃酸分泌を抑制し、48 時間後においても約 80%の抑制作用を示した。細胞傷害性が極めて低く、PPI（LPZ）の課題を克服し、ヒトにおいて高い安全性と強力かつ持続的な酸分泌抑制効果が期待できる有望化合物として精査が進められた。実際、長い作用持続を有する優れた P-CAB として大きな可能性を有するが、一方で、ヒトにおける持続性を動物データから正確に外挿することは困難であり、ヒトにおいて持続が少し長すぎる可能性がわずかながら懸念された。胃酸分泌抑制作用の持続性に影響を及ぼす主な要因としては、in vitro および in vivo における H^+,K^+-ATPase 阻害の強さ、標的部位である胃への薬剤の移行・分布、および胃からの消失などが考えられるが、その寄与の割合は個々の化合物の特性次第であり、予測は簡単ではない。リード化合物 **17c** および **74c** をラットに iv 投与後、10 分、1 時間、4 時間および 24 時間後の血漿および胃を採取して薬物濃度を測定し、活性の立ち上がりや持続性との相関を調べたところ、**74c** の高い胃移行性と 24 時間後の胃内滞留性が確認された（Figure 23）。そこで、化合物の作用を総合的に理解してより優れた P-CAB のオプションを増やすことを目的として、ADME-Tox 特性に優れた **74c** を基に、実際の胃移行挙動を確認しながら、本系統化合物の持続性を精密にコントロールする持続性の最適化を試みた。最適化に当たっては他のケモタイプ[44]や中心骨格の変換[45]も検討対象であったが、有効性面および毒性面で特性が明らかとなりつつあったピロール誘導体は引き続き重要との認識であった。



Cpd	Clog P	log D	pKa	In vitro H^+,K^+-ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma (P) and stomach (S) after intravenous administration at a dose of 0 2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								P	S	P	S	P	S	P	S	P	S
17c	3 88	1 54	9 48	30	95	(22 1)[b]	89 1	17 2	361 4	7 3	387 7	2 9	244	0	0	56	3730
74c	1 45	0 04	8 54	49	98	100 2	39 8	51 5	602 2	15	752 1	0	628 6	0	130 5	54	10277

[a] All values are the average of the data of three rats

[b] ATP content at 30 μM (% control)

Figure 23. Concept of new aimed compound and characteristics of P-CAB **74c**.

第 2 節 合成

第 1 節で論じた分子設計に基づき、以下の化合物を合成することにした（Figure 24）。

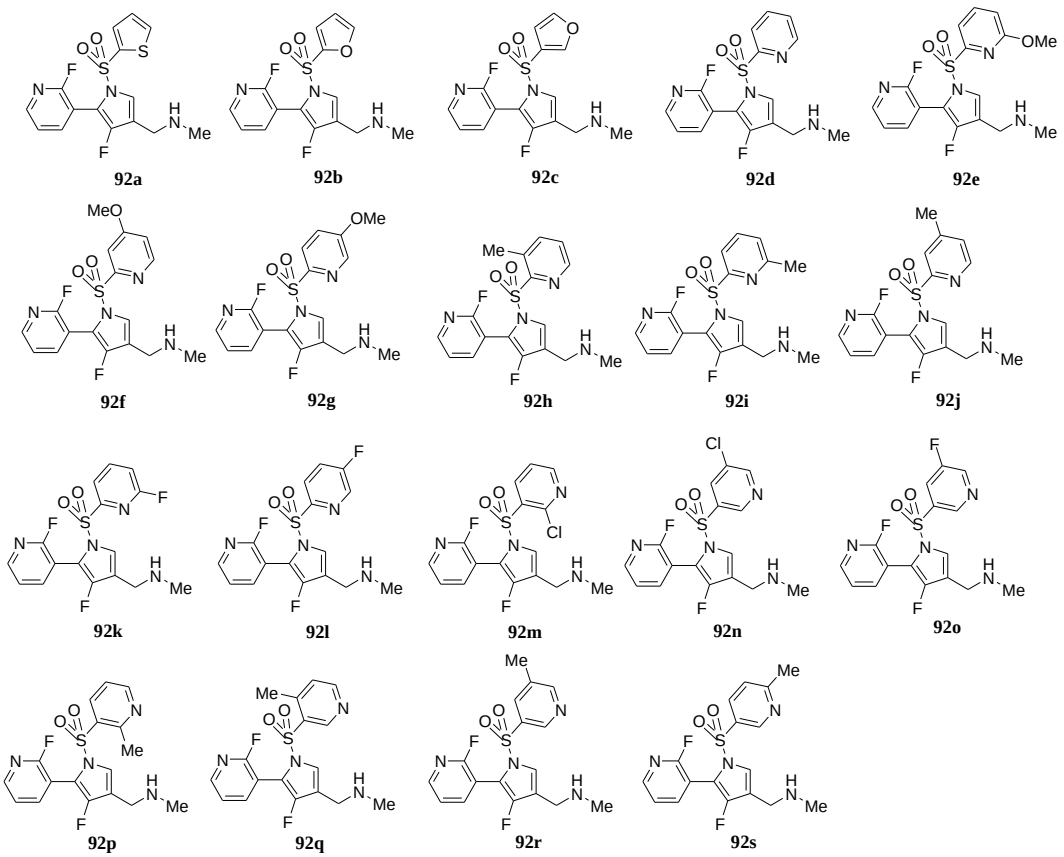
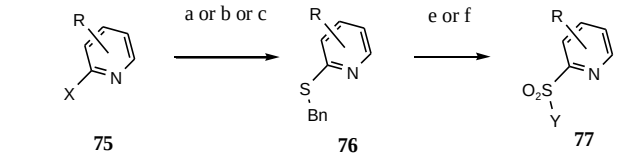


Figure 24. Structures of synthesized compounds in Chapter 4

市販されていない 2-Py スルホニル化試薬の合成は、Scheme 10 に示す方法で行った。まず、市販の 2-ハロピリジン **75** とベンジルチオールの芳香族求核置換反応あるいはパラジウムカップリング反応[46]により、対応する 2-（ベンジルチオ）ピリジン **76** を得た。 6-MeO 誘導体 **76h** については、ナトリウムメトキシドによる置換反応により化合物 **76b** から導いた。続いて、NCS を用いた **76** の酸化反応[47]により目的とするハロゲン化スルホニル **77** を得た。**76a** および **76d** の反応生成物（スルホニルクロリド）は不安定であったため、KF で処理してそれぞれ安定なスルホニルフルオリド **77a** および **77d** として単離した。



75 **76** **77**

75a: R = 5-F, X = Br
75b: R = 6-F, X = F
75c: R = 3-Me, X = Br
75d: R = 4-Me, X = Br
75e: R = 6-Me, X = Cl
75f: R = 4-MeO, X = Cl
75g: R = 5-MeO, X = Br

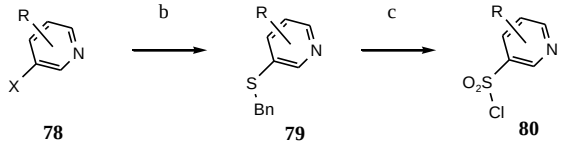
76a: R = 5-F
76b: R = 6-F
76c: R = 3-Me
76d: R = 4-Me
76e: R = 6-Me
76f: R = 4-MeO
76g: R = 5-MeO
76h: R = 6-MeO

d

77a: R = 5-F, Y = F
77b: R = 6-F, Y = Cl
77c: R = 3-Me, Y = Cl
77d: R = 4-Me, Y = F
77e: R = 6-Me, Y = Cl
77f: R = 4-MeO, Y = Cl
77g: R = 5-MeO, Y = Cl
77h: R = 6-MeO, Y = Cl

Scheme 10. Reagents and conditions: (a) BnSH, NaH, THF, rt or 60 °C; (b) BnSH, K_2CO_3, DMSO, 150 °C; (c) BnSH, $Pd_2(dba)_3$, Xantphos, *i*Pr_2NEt, toluene, 80 °C; (d) NaOMe, MeOH, 60 °C; (e) NCS, AcOH, H_2O, then KF, rt; (f) NCS, AcOH, H_2O, rt.

市販されていない 3-Py スルホニル化試薬 **80** については、Scheme 11 に示す方法で合成した。市販あるいは別途調製した **78** をベンジルチオールとパラジウムカップリング反応を用いて縮合し、**79** とした。トリフラート誘導体 **78a** については、塩基性条件下で **78f** より導いた。続いて、得られた縮合体 **79** を前述と同じ方法で酸化して目的とする **80** を得た。



78 **79** **80**

78a: R = 5-Cl, X = OTf
78b: R = 5-F, X = Br
78c: R = 2-Me, X = Br
78d: R = 4-Me, X = Br
78e: R = 5-Me, X = Br
78f: R = 5-Cl, X = OH

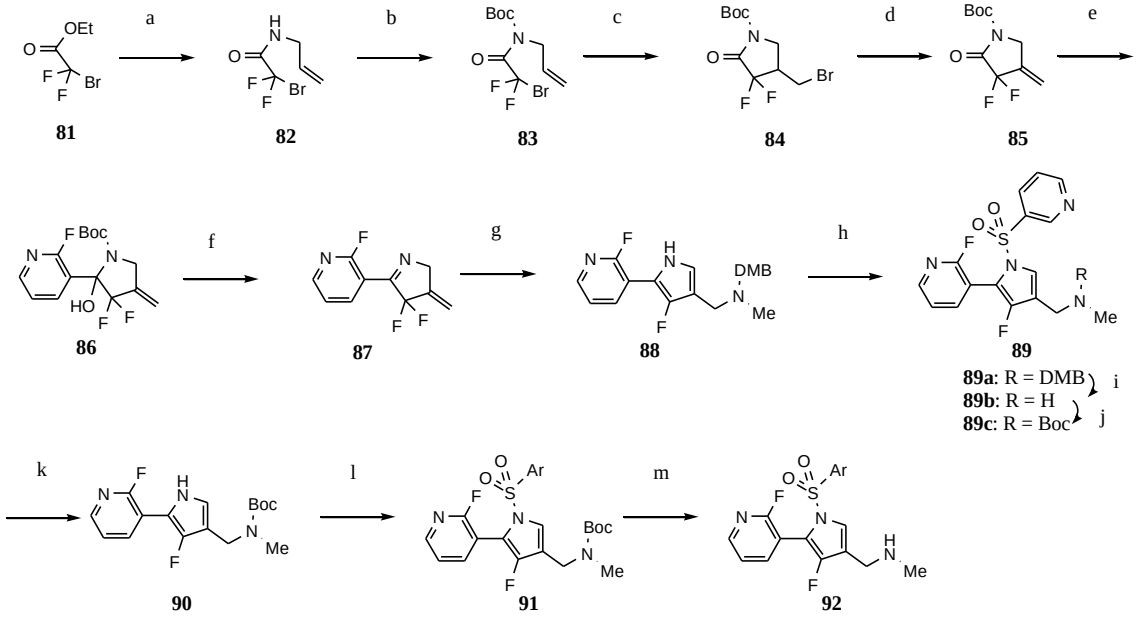
a

79a: R = 5-Cl
79b: R = 5-F
79c: R = 2-Me
79d: R = 4-Me
79e: R = 5-Me

80a: R = 5-Cl
80b: R = 5-F
80c: R = 2-Me
80d: R = 4-Me
80e: R = 5-Me

Scheme 11. Reagents and conditions: (a) *N*-Phenyl-bis(trifluoromethanesulfonimide), Et_3N, THF, rt; (b) BnSH, $Pd_2(dba)_3$, Xantphos, *i*Pr_2NEt, toluene, 80 °C; (c) NCS, AcOH, H_2O, rt.

新規 4-フルオロピロール誘導体 **92** の合成は Scheme 12 に示す方法で行った。当初、ピロール 4 位への F 原子の導入にはピロール中間体への直接的な F 化反応を用いていた（Scheme 9）。しかしながら、低収率に加えて位置選択性が低く、精密なカラム精製が必要であること、また高価な F 化試薬を用いていることなど様々な課題があり、実用的な合成法の開発が必要であった。そこで、フルオロピロールの合成法について種々検討した結果、γ-ラクタム **85** のカルボニル基に対する求核剤（ピリジルリチウム）の付加反応および **87** に対する求核剤（強塩基処理した DMBNHMe）の F 脱離を伴った S_N2'反応（アリル転位）を鍵反応とする新規フルオロピロール合成法の開発に成功した（Scheme 12）。



91a: Ar = 2-thienyl
91b: Ar = 2-fulyl
91c: Ar = 3-furyl
91d: Ar = 2-Py
91e: Ar = 6-MeO-2-Py
91f: Ar = 4-MeO-2-Py
91g: Ar = 5-MeO-2-Py
91h: Ar = 3-Me-2-Py
91i: Ar = 6-Me-2-Py
91j: Ar = 4-Me-2-Py
91k: Ar = 6-F-2-Py
91l: Ar = 5-F-2-Py
91m: Ar = 2-Cl-3-Py
91n: Ar = 5-Cl-3-Py
91o: Ar = 5-F-3-Py
91p: Ar = 2-Me-3-Py
91q: Ar = 4-Me-3-Py
91r: Ar = 5-Me-3-Py
91s: Ar = 6-Me-3-Py

92a: Ar = 2-thienyl (hydrochloride)
92b: Ar = 2-fulyl (hydrochloride)
92c: Ar = 3-fulyl (hydrochloride)
92d: Ar = 2-Py (hydrochloride)
92e: Ar = 6-MeO-2-Py (hydrochloride)
92f: Ar = 4-MeO-2-Py (hydrochloride)
92g: Ar = 5-MeO-2-Py (hydrochloride)
92h: Ar = 3-Me-2-Py (fumarate)
92i: Ar = 6-Me-2-Py (hydrochloride)
92j: Ar = 4-Me-2-Py (succinate)
92k: Ar = 6-F-2-Py (hydrochloride)
92l: Ar = 5-F-2-Py (hydrochloride)
92m: Ar = 2-Cl-3-Py (hydrochloride)
92n: Ar = 5-Cl-3-Py (hydrochloride)
92o: Ar = 5-F-3-Py (hydrochloride)
92p: Ar = 2-Me-3-Py (fumarate)
92q: Ar = 4-Me-3-Py (fumarate)
92r: Ar = 5-Me-3-Py (fumarate)
92s: Ar = 6-Me-3-Py (hemifumarate)

Scheme 12. Reagents and conditions: (a) allylamine, rt; (b) Boc_2O, DMAP, MeCN, rt; (c) CuBr, 2,2′-bipyridyl, 1,2-dichloroethane, 80 °C; (d) DBU, THF, 0 °C, then rt; (e) LDA, 2-fluoropyridine, THF, −78 °C; (f) HCl, AcOH, rt; (g) NaH, DMBNHMe, THF, 0 °C; (h) NaH, 15-crown-5, pyridine-3-sulfonyl chloride, THF, 0 °C; (i) (1) $ClCO_2CH(Cl)CH_3$, THF, 0 °C; (2) Et_3N, THF, 65 °C; (3) EtOH, reflux; (4) 1 mol/L NaOH, $NaHCO_3$, H_2O, EtOAc, rt; (j) Boc_2O, THF, rt; (k) 1 mol/L NaOH, *i*PrOH, THF, rt; (l) NaH, 15-crown-5, Ar-sulfonyl chloride or Ar-sulfonyl fluoride, THF, rt; (m) 4 mol/L HCl/EtOAc, *i*PrOH or EtOH, EtOAc, rt, or (1) 4 mol/L HCl/EtOAc, *i*PrOH or EtOH, EtOAc, rt; (2) $NaHCO_3$, EtOAc; (3) fumaric acid or succinic acid, EtOH or MeOH, EtOAc.

文献[48]記載の方法を参考に、**81** を無溶媒条件下でアリルアミンと反応させてアミド **82** に変換し、DMAP の存在下で Boc_2O と反応させて Boc 保護体 **83** とした後、環化反応[49]により **84** を得た。**84** を塩基処理して **85** とした後、リチオ化したフルオロピリジンの求核付加

反応により **86** に導き、酸性条件下で脱水を伴う脱保護反応を行うことにより **87** とした。**87** を新規 S_N2'反応によって **88** に変換し、15-crown-5 を用いたスルホニル化反応により **89a** とした後、DMB 基の脱保護[50]および Boc 基による保護を行って **89c** とし、塩基性条件下で脱スルホニル化することにより鍵中間体 **90** に導いた。得られた **90** にスルホニルハライド **77** あるいは **80** を反応させて **91** とし、強酸で脱保護して目的とする **92** を得た。**92a–g**、**92i** および **92k–o** は塩酸塩、**92h** および **92p–r** はフマル酸塩、**92s** は 0.5 フマル酸塩、**92j** はコハク酸塩として単離した。本合成法によって 100g 単位での合成が可能となり、合成上の課題が解決された。

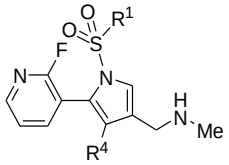
第 3 節 化合物の評価および考察

第 1 項 ピロール 4 位 F 原子の効果および 1 位ヘテロ環の結合位置の影響

本系統化合物の薬物動態に対するピロール 4 位 F 原子の効果および 1 位ヘテロ環の結合位置の影響を明確にするために、強い in vivo 活性が認められた **61h**、**61d** および **61e** について、ラット iv 投与 10 分、1 時間、4 時間および 24 時間後の血漿および胃の薬物濃度を測定して薬物動態を評価した（Table 8）。その結果、**74c** の 4 位に F 原子を持たない **61h** のデータから、**74c** の胃移行性（AUC）は **61h** と比較して有意に高く、胃への移行速度（最大濃度に達する時間）も明らかに早いことがわかった。これは Figure 18 に示したヒスタミン刺激による胃灌流液の pH 挙動差を明確に説明する結果となったが、主に化合物の物理化学的物性（log D や p*K*a 等）によって決定される膜透過性に起因していると推定され、Figure 21 に示した考察を支持している。すなわち、F 原子の導入による **74c** の化学構造および適度な log D（0.04）と p*K*a（8.54）のバランスが早い効果の立ち上がりと長い持続性に繋がる速やかな胃への移行と長い胃内滞留を可能にしていると考えられた（主に p*K*a の低下により中性域の膜透過が促進され、log D の低下により分泌細管内に長時間滞留する）。また、1 位にチエニル基を有する化合物 **61d**（3-チエニル体）および **61e**（2-チエニル体）の結果より、ヘテロ環の結合位置により AUC に大きな差が認められ、胃への移行速度や消失速度などの挙動が大きく異なることが分かった。これらの結果は、**61i**（2-Py 体）のように in vivo 活性が低かった化合物でも F 基導入により薬物動態が改善されて in vivo 活性が向上する可能性に加えて、胃への移行速度や胃からの消失速度が異なる安全性に優れた化合物を見出せる可能性を示唆している。そこで、速やかな胃移行と適度な胃内滞留を期待して **92a–d** を評価したところ、いずれも所望する方向性に沿った胃濃度プロファイル、すなわち速やかな胃への移行と **74c** より明らかに早い胃からの消失挙動が確認された。残念ながら **92a** は hERG 阻害面、**92b** は活性面で不十分であったが、3-フリル誘導体 **92c** および 2-Py 誘導体 **92d** は優れた in vivo 活性と ADME-Tox 特性を示した。特に **92d** は優れた胃移行性に加えて良好な ADME-Tox パラメータを示し、投与 24 時間後においても適度に薬物の残留が認められるな

ど、所望の化合物特性に近かった。以上の結果から **92d** を基に 1 位への置換基の導入効果について検討を進めることとした。

Table 8 Effects of a fluorine atom at position 4 (R^4) and of a binding site for heteroaromatics at the first position (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



Compound	**74c**	**61h**	**61d**	**61e**	**61i**	**92a**	**92b**	**92c**	**92d**
R^4	F	H	H	H	H	F	F	F	F
R^1	3-Py	3-Py	3-thienyl	2-thienyl	2-Py	2-thienyl	2-furyl	3-furyl	2-Py

Cpd	Clog P	log D	In vitro H ,K -ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng h/mL or ng h/g) in rat plasma (P) and stomach (S) after intravenous administration at a dose of 0 2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								P	S	P	S	P	S	P	S	P	S
74c	1 45	0 04	49	98	100 2	39 8	14 4	51 5	602 2	15	752 1	0	628 6	0	130 5	54	10277
61h	1 21	–0 85	210	96	85 7	4 4	4 2	37 1	420	8 4	532 2	0	540 9	0	19 6	35	7646
61d	2 28	–0 83	32	98	64	60	1 4	23 5	406 7	8 9	613 7	0	639 6	0	41 7	29	9152
61e	2 28	–0 69	32	96	74 9	63	NT[b]	20 8	522 3	8 8	592 4	0	210 3	0	0	27	3815
61i	1 21	0 05	120	81	78 6	NT[b]	–9 7	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
92a	2 52	0 54	72	98	77 5	56 1	20 5	36 6	411 5	12 2	954 8	0	826 7	0	17 4	42	11717
92b	1 98	0 2	79	75	90 8	28 7	5 6	26 5	592 5	6 5	706 3	0	253 6	0	0	26	4566
92c	1 98	0 45	60	95	100 5	44 5	12 8	37 4	635 4	11 5	687 7	0	193 8	0	0	41	3865
92d	1 45	0 44	97	95	94 8	9	7 7	36	616 7	7 9	809 2	0	337 1	0	2 1	33	5757

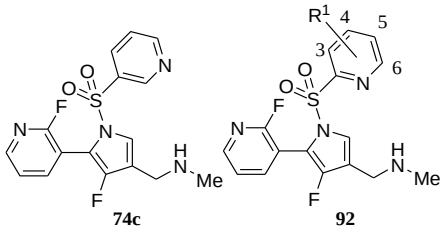
[a] All values are the average of the data of three rats

[b] Not tested

第 2 項 ピロール 1 位ピリジル基への置換基導入の効果

優れたプロファイルを示した **92d** を基に、ピロール 1 位（R^1）2-Py 基への置換基の導入効果を調べた。その結果、**92e**、**92f**、**92g**、**92i** および **92j** に強い in vivo 活性が認められたが、AUC などの胃移行特性には置換基の種類と位置により大きな差が認められた（Table 9）。その中で、4-Me-2-Py 誘導体 **92j** は強い in vitro 活性（IC_{50} = 73 nM）を有し、良好な ADME-Tox 特性を維持しながら log D が 0.48 となり、高い AUC（10378 ng·h/g）に加えて、速やかな胃への移行特性と 24 時間後の適度な残留性を示した。24 時間持続する作用が P-CAB の目指す創薬コンセプトとなっており、完全な消失よりも 24 時間後においても適度に残留する方が好ましいと考えられた。

Table 9 Effects of a substituent on the 2-pyridyl group at the first position (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



74c **92**

Compound	R^1	Compound	R^1
92d	H	**92i**	6-Me
92e	6-MeO	**92j**	4-Me
92f	4-MeO	**92k**	6-F
92g	5-MeO	**92l**	5-F
92h	3-Me		

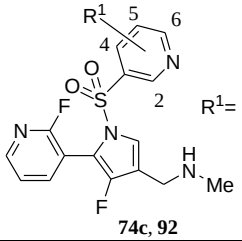
Cpd	Clog P	log D	In vitro H ,K -ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng h/mL or ng h/g) in rat plasma (P) and stomach (S) after intravenous administration at a dose of 0 2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								P	S	P	S	P	S	P	S	P	S
74c	1 45	0 04	49	98	100 2	39 8	14 4	51 5	602 2	15	752 1	0	628 6	0	130 5	54	10277
92d	1 45	0 44	97	95	94 8	9	7 7	36	616 7	7 9	809 2	0	337 1	0	2 1	33	5757
92e	2 21	1 03	150	98	69 8	82 3	55 8	43 5	772 8	14 9	1255	0	970 8	0	47 9	50	14434
92f	1 81	0 51	140	95	84 5	38 7	19	37 2	617 2	10 1	773 4	0	268 3	0	8 8	38	4964
92g	1 81	0 64	280	95	80	17 6	7 7	54 2	623 5	13 1	806 2	0	426 5	0	0	52	6761
92h	1 95	0 32	510	54	79 1	NT[b]	29	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
92i	1 95	0 71	210	91	83 8	13 9	22 9	41 7	1083 9	10 3	999 2	0	527	0	3 3	41	8550
92j	1 95	0 48	73	92	85 5	45 1	4 3	39 4	946 9	8 1	926 6	0	681 7	0	28 9	35	10378
92k	1 62	0 7	240	NT	74	NT[b]	46	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
92l	1 62	0 42	100	87	86 5	NT[b]	21 7	25	369 3	5	525 7	0	346 7	0	0	22	5179

[a] All values are the average of the data of three rats

[b] Not tested

また、3-Py 体 **74c** についてもピロール 1 位（R^1）3-Py 基への置換基導入の影響を調べた（Table 10）。その結果、いずれも in vitro 活性が大きく低下し、ADME-Tox 特性の悪化を示す化合物が多かったが、**92o**、**92p**、**92q** および **92s** に強い in vivo 活性が認められた。その中で 5-F-3-Py 誘導体 **92o** は 99%抑制の強い in vivo 活性を示し、良好な ADME-Tox プロファイルを維持しながら log D が 0.83 となり、高い AUC（6599 ng·h/g）と 24 時間後の適度な残留性を示した。

Table 10 Effects of a substituent on the 3-pyridyl group at position 1 (R^1) of the pyrrole ring on activities and various properties of pyrrole compounds



74c, **92**

Compound	R^1	Compound	R^1
74c	H	**92p**	2-Me
92m	2-Cl	**92q**	4-Me
92n	5-Cl	**92r**	5-Me
92o	5-F	**92s**	6-Me

Cpd	Clog P	log D	In vitro H ,K -ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	ATP content % control at 100 μM	hERG % inhibition at 10 μM	CYP3A4 % inhibition at 10 μM	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng h/mL or ng h/g) in rat plasma (P) and stomach (S) after intravenous administration at a dose of 0 2 mg/kg (as free base)									
								C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
								P	S	P	S	P	S	P	S	P	S
74c	1 45	0 04	49	98	100 2	39 8	14 4	51 5	602 2	15	752 1	0	628 6	0	130 5	54	10277
92m	2 19	0 75	390	NT[b]	86 9	NT[b]	53 1	28	539	10 1	722 1	0	427 4	0	0	33	6568
92n	2 19	1 44	160	NT[b]	66 9	NT[b]	45 9	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
92o	1 62	0 83	200	99	88 9	22 7	27	43	330 4	8 3	605 5	0	425 2	0	38 3	38	6599
92p	1 95	0 48	210	92	97 4	14 8	30 1	25 3	507	8	577	0 3	299 7	0	0	32	4806
92q	1 95	0 43	120	98	90 9	28 2	40	50 1	359 6	8 4	618 5	0	250 7	0	0	41	4248
92r	1 95	0 61	140	87	86 9	NT[b]	49 7	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]	NT[b]
92s	1 95	0 62	180	97	76 7	24 8	–1 2	40 1	671 5	10 8	1124	0	1182 8	0	219 1	41	18284

[a] All values are the average of the data of three rats

[b] Not tested

第 3 項 代表化合物のラット胃灌流液 pH 試験

合成した化合物の中で **92c**、**92d**、**92e**、**92f**、**92g**、**92i**、**92j**、**92o** および **92s** については、麻酔ラットにおけるヒスタミン刺激時の胃灌流液 pH の上昇効果を調べた（Figure 25）。

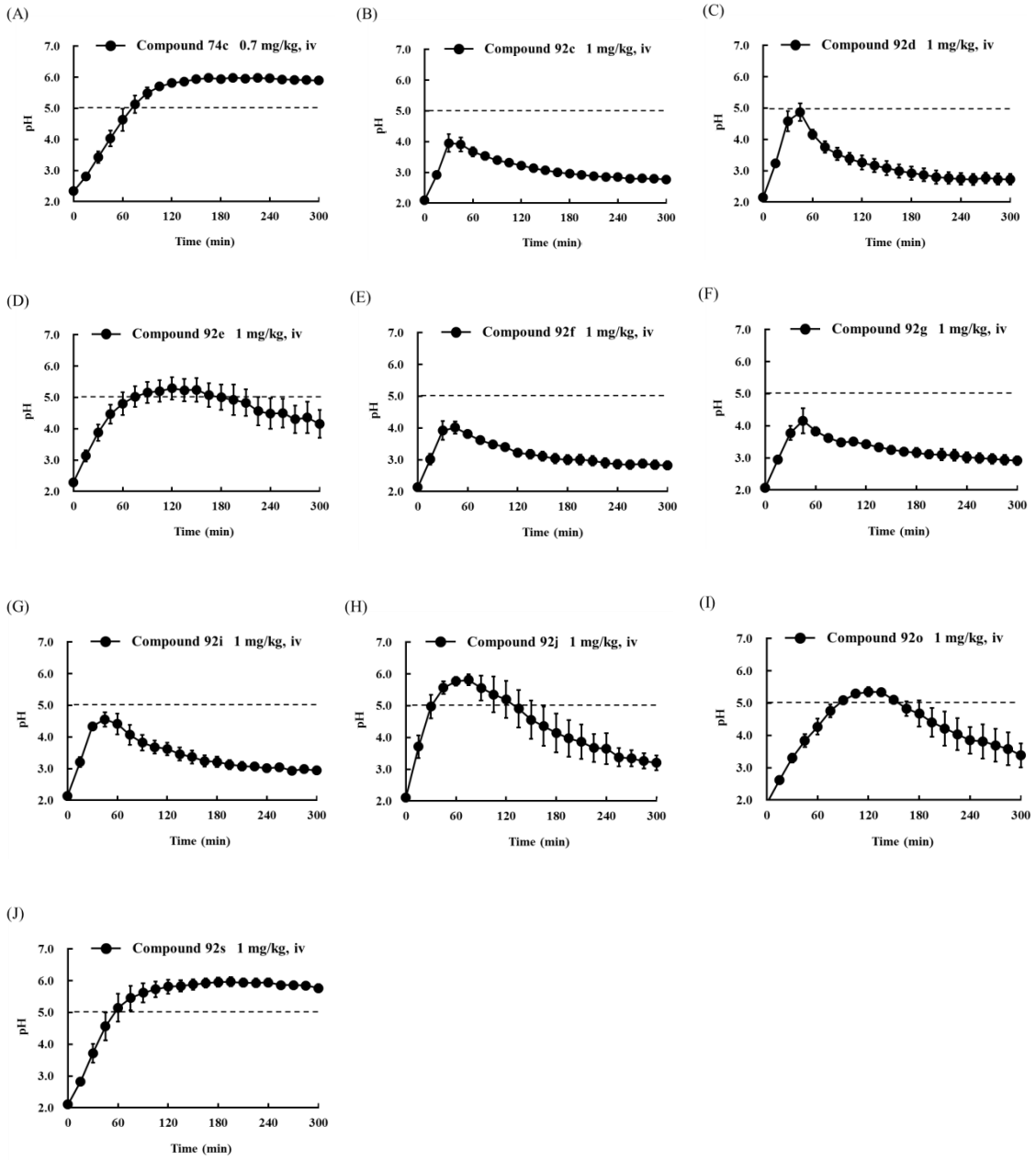


Figure 25. Effects of intravenous administration of compounds **74c** (A), **92c** (B), **92d** (C), **92e** (D), **92f** (E), **92g** (F), **92i** (G), **92j** (H), **92o** (I), and **92s** (J) on the pH of gastric perfusate under conditions of histamine stimulation in anesthetized rats. Each data point represents mean ± SE from three to six rats.

その結果、6-Me-3-Py 誘導体 **92s**（Figure 25J）以外は明らかに **74c** と異なる pH プロファイルを示し、その中で、**92d**、**92e**、**92j**、**92o** は 1 mg/kg で胃灌流液の pH を 5 あるいはそれ以上にする強い pH 上昇作用を示した。置換基を導入していない 2-Py 体 **92d** は灌流液の pH を約 5 まで速やかに上昇させたが、その後、pH は急速に低下した（Figure 25C）。胃の AUC レベルや24時間後の残留性も考慮するとやはり P-CAB としての持続性はやや不足していると判断された。6-MeO-2-Py 体 **92e** は強い pH 上昇作用と **74c** より短い持続性を示した（Figure 25D）。残念ながら CYP3A4 阻害作用は強かったが、適度な持続性が認められた。4-Me-2-Py 体 **92j** は良好な ADME-Tox 特性を維持しながら、灌流液の pH を約 6 まで急速に上昇させた（Figure 25H）。その後、pH は緩やかに低下し、薬物の胃内濃度の挙動を反映する適度な持続性が観察された。**74c** に F 原子を導入した 5-F-3-Py 体 **92o** は **92j** と同様に良好な ADME-Tox プロファイルと適度な持続性を示したが、その胃移行性を反映して活性の立ち上がりがやや遅く、最大効果発現までに約 2 時間を要した（Figure 25I）。以上の結果から **92j** を精査化合物に選定した。

第 4 項 精査化合物 **92j** の経口投与における酸分泌抑制作用とその有用性

化合物 **92j** のラットおよびイヌ経口投与における酸分泌抑制作用を調べた。その結果、**92j** は麻酔したラットのヒスタミン刺激による酸分泌を LPZ よりもはるかに強く用量に応じて抑制した（Figure 26）。

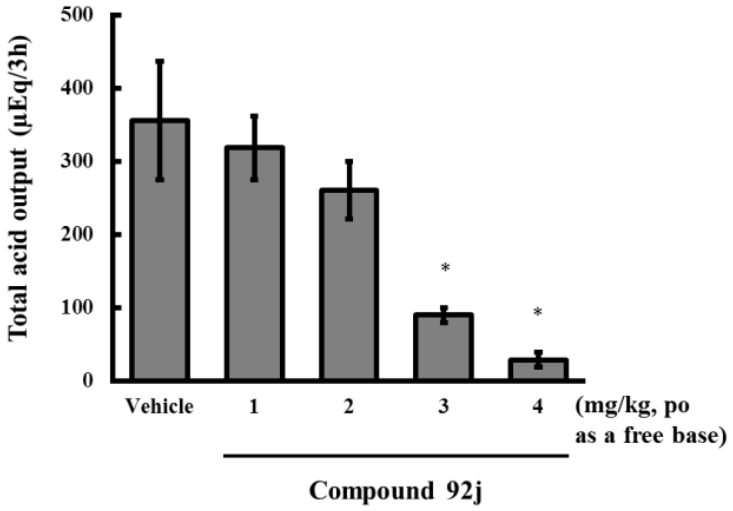


Figure 26. Effects of oral administration of compound **92j** on histamine-stimulated gastric acid secretion in anesthetized rats. Each column represents mean ± SE from seven or eight rats. Statistical significance of the difference was determined by the one-tailed Shirley-Williams test; $*p < 0.025$ compared to vehicle.

また、化合物 **92j** は 1 mg/kg 投与でハイデンハイン・ポーチ犬におけるヒスタミン刺激による胃酸分泌を投薬 1 時間後から完全に抑制し、6 時間後まで 100%の抑制作用を持続するなど、その作用持続時間は 3 mg/kg 投与の LPZ よりもはるかに長かった（Figure 27）。さらに、その効果の持続性は、0.8 mg/kg 投与の **74c** と比較すると明らかに短かったが、1 mg/kg 投与の **92d** よりは明らかに長かった。また、投与 24 時間後においても明らかな酸分泌抑制作用が観察された。

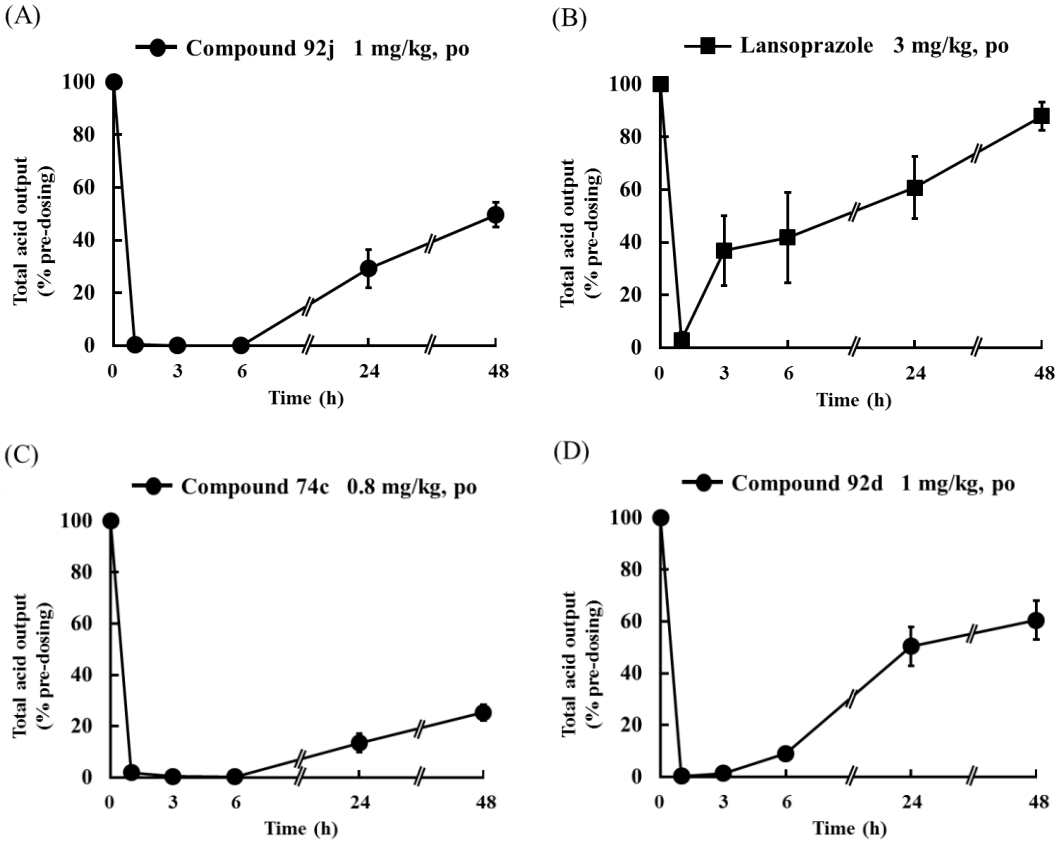
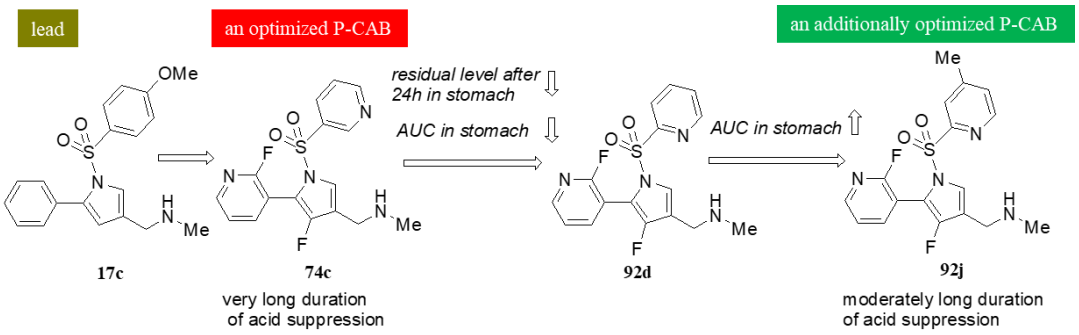


Figure 27. Effects of oral administration of compound **92j** (A), lansoprazole (B), compound **74c** (C), and compound **92d** (D) on histamine-stimulated gastric acid secretion in Heidenhain pouch dogs. Each data point represents mean ± SE from three or four dogs.

92j は、log D = 0.48（**17c** は 1.54、**TAK-438** は 0.39、**74c** は 0.04）で Clog P = 1.94（**17c** は 3.88、**TAK-438** は 2.54、**74c** は 1.45）の低い脂溶性、側鎖アミノ基共役酸の p*K*a = 8.73 のやや低めの塩基性（**17c** は 9.48、**TAK-438** は 9.3、**74c** は 8.54）を持つように設計されているため、この物理化学的特性に基づいて、胃の分泌細管内に迅速に移行し、適度な時間そこに留まることができる。そのため、**92j** は単回投与後に速やかに効果（pH 上昇作用）を発現し、適度な作用持続を有すると推定された（Figure 28）。



Cpd	Clog P	log D (pH 7 4)	p*Ka*	In vitro H^+,K^+ -ATPase inhibitory activities (IC_{50}, nM)	In vivo Acid secretion in rats (1 mg/kg, iv, % inhibition)	Rat cassette dosing[a] Concentrations (ng/mL or ng/g) and AUC (ng·h/mL or ng·h/g) in rat plasma (P) and stomach (S) after intravenous administration at a dose of 0 2 mg/kg (as free base)									
						C_{10min}		C_{1h}		C_{4h}		C_{24h}		AUC	
						P	S	P	S	P	S	P	S	P	S
17c	3 88	1 54	9 48	30	95	17 2	361 4	7 3	387 7	2 9	244	0	0	56	3730
74c	1 45	0 04	8 54	49	98	51 5	602 2	15	752 1	0	628 6	0	130 5	54	10277
92d	1 45	0 44	NT[b]	97	95	36	616 7	7 9	809 2	0	337 1	0	2 1	33	5757
92j	1 95	0 48	8 73	73	92	39 4	946 9	8 1	926 6	0	681 7	0	28 9	35	10378

[a] All values are the average of the data of three rats

[b] Not tested

Figure 28. Identification of a novel potent P-CAB called **92j**, which has moderately long duration of acid suppression

また、**92j** は良好な耐酸性を示し、代謝消失に対する CYP2C19 および CYP2D6 の寄与は小さかったことに加え、**74c** と同様に優れた DMPK および安全性プロファイルを示した。さらに、**92j** はヒトにおいて適度な持続性を発揮することが予想された。以上の結果より、**92j** は PPI（LPZ）の課題を解決しながら、適度に長い持続性と高い安全性を両立する優れた P-CAB として期待できること、必要が生じた場合に **TAK-438** の代替化合物として有用と結論付けた。

第 4 節 小括

第 3 章で論じた化合物 **74c** の作用持続に関する懸念を出発点として、強力かつ適度にコントロールされた持続性を有し、ADME-Tox 特性に優れた P-CAB の創製を目指した。まず、ピロール誘導体の特性を理解するために、胃内濃度の推移を評価する系を立ち上げ、次に ADME-Tox 特性に優れた **74c** を基に化学構造と胃移行性、さらには持続性との相関を解析しながら新規誘導体合成を展開した。その結果、4 位に F 原子、1 位に 2-Py 基を有する化合物に好ましい胃濃度推移の可能性を見出し、最終的に 4 位に F 原子、1 位に 4-Me-2-Py 基、5 位に 2-F-3-Py 基を有する **92j** を最も好ましい化合物として選定した。得られた **92j** は優れた ADME-Tox 特性を示し、ラットおよびイヌにおいて強力かつ適度に持続する酸分泌抑制

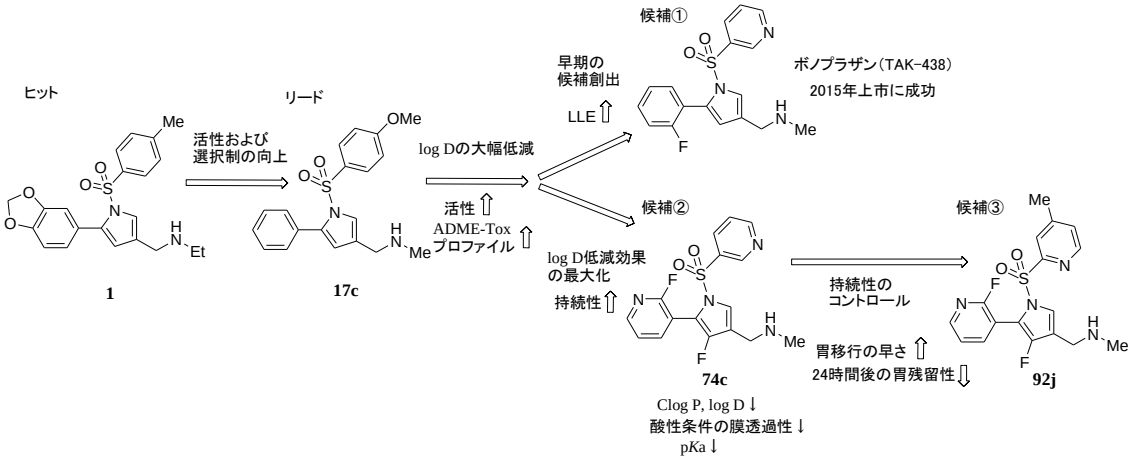
作用を示した。その効果の持続性は、LPZ よりもはるかに長く、**74c** と比較して明らかに短い特徴を有し、新規 P-CAB として有望と考えられた。

第 5 章 結語

PPI（LPZ）による酸関連疾患治療の課題を克服する究極の酸分泌抑制薬の創製を目指し、カリウムイオン競合型アシッドブロッカーの可能性への着眼およびヒット化合物 **1** からの合成展開により新規 P-CAB リード化合物 **17c** を見出した。得られた **17c** について、log D の低減効果を最大化する最適化を検討し、ピロール 5 位および 1 位への極性基の導入と 4 位への F 原子導入により極めて強力かつ持続的な酸分泌抑制作用を有する **74c** を見出した。また、新たなオプションとして、持続性をコントロールして最適化することに挑戦し、**74c** の 1 位置換基を 4-Me-2-Py スルホニル基に変更することにより所望の持続性プロファイルを有する **92j** を見出した。

結果的に、リード **17c** より化合物特性の異なる 3 つの開発候補化合物の創製に成功したが、その中で、先行していたボノプラザンが 2015 年 2 月に上市に至った。その過程で、ヒトにおいて、PPI（LPZ）の課題を解決する優れた有効性に加えて高い安全性を有することが確認され、本ピロール誘導体の医薬品としての有用性が明らかとなった[51–55]。ボノプラザンは臨床薬理試験において、投薬初日から速やかな胃内の pH 上昇作用と 24 時間持続する酸分泌抑制効果を示し、逆流性食道炎、胃潰瘍、十二指腸潰瘍などの酸関連疾患や *H.pylori* 除菌を対象とした国内臨床第 3 相試験においても、良好な有効性、安全性および忍容性が確認された。例えば、逆流性食道炎の治癒試験では、通常 PPI による 8 週間の治療で得られる効果が 4 週間で得られ、重症の患者に対しても高い治療効果を示した。また、*H.pylori* 除菌では 92.6%の一次除菌率と 98%の二次除菌率を示し、今後の除菌治療の戦略が見直される可能性をも示唆した。

以上、実際の創薬研究における研究方針に関する知見、ヒトへの適用に関する知見など、今後への指針を与える有用な成果が得られた。



謝辞

本論文の執筆に際し、名古屋市立大学大学院薬学研究科教授 中川秀彦先生には終始懇篤なご指導、ご高配を賜りました。ここに厚く御礼申し上げます。また、主査／副査として有益なご助言・ご指導を頂きました名古屋市立大学大学院薬学研究科教授 樋口恒彦先生、名古屋市立大学大学院薬学研究科教授 中村精一先生、名古屋市立大学大学院薬学研究科准教授 山村寿男先生、多大なるご支援を賜りました名古屋市立大学創薬基盤科学研究所特任教授 宮田直樹先生に心から感謝申し上げます。

本研究の機会を与えていただきました、武田薬品工業株式会社 元取締役研究開発統括職 大川滋紀博士、元化学研究所長 三宅昭夫博士、元化学研究所長 石原雄二博士、元化学研究所長 加藤金芳博士、元化学研究所長 内川治博士、化学研究所長 一川隆史博士に深謝いたします。

本研究は終始､武田薬品工業株式会社 元CMC研究センター製薬研究所長 梶野正博博士、元化学研究所リサーチマネージャー 伊藤文雄博士、元エクストラバリュー創薬ユニット主席研究員 稲富信博博士のご指導のもとに行われました。ここに心から感謝申し上げます。

化合物の分子設計、合成において多大なご協力と有益なご助言を頂きました武田薬品工業株式会社 中枢創薬ユニット主任研究員 有川泰由博士、人材・組織開発室主席部員 平瀬慶造氏、JPBUJMA 部 ME セントラル課長代理 藤森郁男氏、癌創薬ユニット主任研究員 小野宏司博士、本部長室主席部員 蓮岡淳博士、癌創薬ユニット主任研究員 倉澤修氏、アライアンスグループ付課長代理 今枝稔博博士、プロジェクトマネジメントグループ主席部員 中井一夫博士、化学研究所主席研究員 遠藤聡史博士、化学研究所主任研究員 高木輝文氏に深謝いたします。また、本研究の薬理試験をご担当いただきました武田薬品工業株式会社 実験推進グループ課長代理 堀靖亘博士、エクストラバリュー創薬ユニット主任研究員 松川純博士、CMSO 日本オフィス長 佐藤文彦博士、元創薬研究所 久徳順政氏、松下耕蔵氏、本研究の化合物スクリーニング試験をご担当頂きました生物分子研究所長 樽井直樹博士、生物分子研究所主任研究員 今西章夫氏、近藤光代女史、河本眞紀子女史、本研究の構造解析、物性評価をご担当いただきました化学研究所主任研究員 長野洋一氏、化学研究所 飯田基雄氏、西谷充祥氏、熊谷安美女史、横溝美幸女史、開発分析研究所リサーチマネージャー 池田幸弘博士、元開発分析研究所主任研究員 堤俊一郎博士、開発分析研究所主席研究員 辛島正俊博士、本研究の薬物動態および安全性関連の試験をご担当いただきました薬物動態研究所主任研究員 藤岡泰博士、濱田輝基氏、薬剤安全性研究所主席研究員 福井英夫博士、本論文の作成を進めるにあたり、有益なアドバイスを頂きました化学研究所リサーチマネージャー 田中稔祐博士、循環代謝創薬ユニット主席研究員 松永伸之博士、循環代謝創薬ユニット主任研究員 石地雄二博士に深謝いたします。

最後に、本研究の遂行、本論文の執筆に際して終始支えてくれました 妻 西田愛由美、あたたかく応援してくれました 母 西田幸子、義母 木村フミ子、実弟 西田元之に感謝いたします。

Experimental section

General

The pK_a values were measured by pH-metric assays using a Sirius T3 system (Sirius Analytical Ltd., UK). The assay measures the concentration of H^+ ions in solution between pH 2 and 12 using a pH electrode (Ag/AgCl). Melting points were determined on a Yanagimoto micro melting point apparatus or Büche B-545 or by differential scanning calorimetry (DSC) or TG-DTA analyses. DSC analyses were performed using a DSC1 system (Mettler Toledo, Switzerland). The thermograms were obtained at a temperature of 25–300 °C and a heating rate of 5 °C/min under nitrogen gas at a flow rate of 40 mL/min. The powders (~1 mg) were weighed in an aluminum pan, crimped, and then placed in the thermal analysis chamber. TG-DTA analyses were conducted by from Sumika Chemical Analysis Service, Ltd. Nuclear magnetic resonance (^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR) spectra were recorded on a Varian Gemini-200, a Varian Mercury-300, a Jeol JNM-AL400, a Bruker AV-300M, a Bruker AV-400 or a Bruker AV- 600 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane or sodium 3-(trimethylsilyl)-1-propane-1,1,2,2,3,3-d_6-sulfonate as an internal standard for ^{1}H and ^{13}C-NMR, with sodium trifluoroacetate as the internal standard for ^{19}F-NMR (−76.53 ppm). Coupling constants are reported in hertz (Hz). Spectral splitting patterns were designated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; and m, multiplet. High-resolution mass spectrometry (HRMS) experiments were carried out by Takeda Analytical Laboratories, Ltd., or Sumika Chemical Analysis Service, Ltd. All mass spectrometry (MS) experiments were conducted using electrospray ionization (ESI) in positive or negative ion mode. Elemental analyses were performed by Takeda Analytical Laboratories, Ltd., or Sumika Chemical Analysis Service, Ltd. Thin-layer chromatography (TLC) analyses were carried out on Merck Kieselgel 60 F_{254} plates or Fuji Silysia Chemical, Ltd., Chromatorex NH-TLC plates. Silica gel column chromatography was run by means of Merck 0.063–0.200 mm silica gel 60, Fuji Silysia Chemical Ltd. 100–200 mesh Chromatorex NH silica DM1020 or Purif-Pack (SI 60 μM or NH 60 μM, Fuji Silysia Chemical Ltd.). Commercial reagents and solvents were used without additional purification.

Experiments concerning Chapter 2

2.1. Ethyl 2-cyano-4-oxo-4-phenylbutanoate (3)

Potassium carbonate (13.8 g, 99.8 mmol) was added to ethyl cyanoacetate (37 mL, 348 mmol), and the mixture was stirred at 40 °C for 45 min. A solution of **2** (10.0 g, 50.2 mmol) in acetone (100 mL) was added dropwise over 30 min. After the dropwise addition was completed, the mixture was stirred at room temperature for 18 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Excess ethyl cyanoacetate contained in the obtained oil was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc=8/1-1/1) to give **3** (10.4 g, 90%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ: 1.35 (3H, t, *J* = 7.2 Hz), 3.55 (1H, dd, *J* = 16.0, 5.6 Hz), 3.80 (1H, dd, *J* = 16.0, 7.0 Hz), 4.16 (1H, dd, *J* = 7.0, 5.6 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 7.40-7.70 (3H, m), 7.90-8.00 (2H, m).

2.2. Ethyl 2-chloro-5-phenyl-1*H*-pyrrole-3-carboxylate (4)

HCl gas (28 g) was bubbled through a solution of **3** (5.0 g, 21.6 mmol) in THF (60 mL) under ice-cooling, and the mixture was stirred at room temperature for 3 h. Then, N_2 gas was introduced to substitute HCl gas and then the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc =6/1) to give **4** (4.24 g, 79%) as a solid: ^{1}H NMR ($CDCl_3$) δ: 1.37 (3H, t, *J* = 6.8 Hz), 4.33 (2H, q, *J* = 6.8 Hz), 6.87 (1H, d, *J* = 3.2 Hz), 7.20-7.60 (5H, m), 8.79 (1H, br).

2.3. Ethyl 5-phenyl-1*H*-pyrrole-3-carboxylate (5a).

To a solution of **4** (8.5 g, 34.0 mmol) in EtOH (50 mL) was added 10% palladium carbon (50% wet, 0.5 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 - 1/1) to give **5a** (4.50 g, 62%) as colorless crystals: mp 148-150 °C; ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, *J* = 7.2 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 6.91 (1H, m), 7.20-7.70 (6H, m), 8.77 (1H, br).

2.4. 5-Phenyl-1*H*-pyrrole-3-carboxylic acid (5b)

To a solution of **5a** (700 mg, 3.25 mmol) in MeOH (30 mL) and THF (30 mL) was added dropwise 1N NaOH (30 mL), and the mixture was stirred at 60 °C for 2 h. To this mixture was added dropwise 8N NaOH (30 mL) at 55 °C, and then the mixture was stirred overnight at 55 °C. The mixture was concentrated under reduced pressure to half volume at 60°C, and then acidified with 6N HCl. The resulting insoluble product was collected by filtration and rinsed with H_2O to give **5b** (462mg, 76%) as a white solid: ^{1}H NMR (DMSO-d_6) δ: 6.83 (m, 1H), 7.10-7.27 (m, 1H,), 7.31-7.49 (m, 3H), 7.54-7.84 (m, 2H), 11.84 (br, 2H).

2.5. (5-Phenyl-1*H*-pyrrol-3-yl)methanol (6)

To a solution of **5a** (2.16 g, 10.0 mmol) in THF (100 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (24 mL, 36 mmol) at -78 °C over 10 min. The mixture was further stirred at -78°C for 1 h, water (2 mL) was added dropwise over 2 min, and the mixture was further stirred at room temperature for 1 h. To the reaction mixture were added Celite and anhydrous magnesium sulfate, the mixture was filtered and the filtrate was concentrated under reduced pressure to give **6** (1.51 g, 87%) as a solid. ^{1}H NMR (DMSO-d_6) δ: 4.34 (d, J = 5.4 Hz, 2H), 4.60 (t, J = 5.4 Hz, 1H), 6.45-6.46 (m, 1H), 6.74 (br, 1H), 7.11-7.15 (m, 1H), 7.31-7.35 (m, 2H), 7.57-7.59 (m, 2H), 11.05 (s, 1H).

2.6. 5-Phenyl-1*H*-pyrrole-3-carbaldehyde (7)

To a solution of **6** (1.51 g, 8.72 mmol) in acetonitrile (45 mL) were added tetra-*n*-propylammonium perruthenate (0.46 g, 1.31 mmol), *N*-methylmorpholine *N*-oxide (2.36 g, 20.2 mmol) and molecular sieves 4A powder (4.5 g), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1 - 1/1) to give **7** (0.92 g, 62%) as pale yellow crystals: mp 137-139 °C; ^{1}H NMR ($CDCl_3$)δ: 6.95 (1H, m), 7.29-7.32 (1H, m), 7.40-7.44 (2H, m), 7.50-7.52 (3H, m), 9.02 (1H, br), 9.84 (1H, s).

2.7. *tert*-Butyl methyl[(5-phenyl-1*H*-pyrrol-3-yl)methyl]carbamate (8)

To a solution of **7** (0.92 g, 5.37 mmol) in MeOH (92 mL) was added 40% methylamine solution (1.26 g, 12.3 mmol) at room temperature and the mixture was stirred for 30 min. To the reaction mixture was added sodium borohydride (305 mg, 8.06 mmol) at room temperature and the mixture was stirred for 10 min. Water (200 mL) was added and the mixture was further stirred for 1 h. Brine (50 mL) was added and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in acetonitrile (48 mL), and di-*tert*-butyl bicarbonate (1.41 g, 6.46 mmol) was added dropwise at room temperature. The mixture was stirred for 1.5 h and partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 - 4/1) to give **8** (0.99 g, 64%) as colorless crystals: mp 100-102 °C; ^{1}H-NMR ($CDCl_3$)δ: 1.50 (9H, s), 2.84 (3H, s), 4.30 (2H, s), 6.45 (1H, s), 6.75 (1H, s), 7.18-7.22 (1H, m), 7.34-7.38 (2H, m), 7.44-7.46 (2H, m), 8.37 (1H, br).

2.8. Ethyl 1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxylate (9a)

Sodium hydride (60% in oil, 408 mg, 10.2 mmol) was suspended in DMF (5 mL). To the suspension was added a solution of **5a** (2.0 g, 9.3 mmol) in DMF (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. A solution of 4-methylbenzenesulfonyl chloride (1.94 g, 10.2 mmol) in DMF (5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature

for 1 h. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1 - 1/1) to give **9a** (2.90 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, *J* = 7.2 Hz), 2.36 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 6.52 (1H, d, *J* = 1.8 Hz), 7.05-7.40 (9H, m), 8.07 (1H, d, *J* = 1.8Hz).

Compounds **9b-d** were prepared from **5a** in a manner similar to that described for compound **9a**.

2.9. Ethyl 5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrole-3-carboxylate (9b)

A colorless oil (77%): ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.1 Hz), 3.80 (2H, q, *J* = 7.1 Hz), 6.56 (1H, d, *J* = 2.0 Hz), 7.16 (2H, d, *J* = 7.3 Hz), 7.29-7.41 (3H, m), 7.44 (2H, d, *J* = 8.8 Hz), 7.57 (2H, d, *J* = 8.6 Hz), 8.09 (2H, d, *J* = 2.0 Hz).

2.10. Ethyl 1-[(4-methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxylate (9c)

A colorless oil (97%): ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, *J*=7.4 Hz), 3.82 (3H, s), 4.30 (2H, q, *J*=7.4 Hz), 6.51 (1H, d, *J*=1.8 Hz), 6.74 (2H, d, *J*=9.0 Hz), 7.15-7.40 (7H, m), 8.07 (1H, d, *J*=1.8 Hz).

2.11. Ethyl 1-(methylsulfonyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (9d)

Colorless crystals (57%): mp 125-126 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 6.8 Hz), 2.91 (3H, s), 4.31 (2H, q, *J* = 6.8 Hz), 6.69 (1H, d, *J* = 2.2 Hz), 7.20-7.55 (5H, m), 7.92 (1H, d, *J* = 2.2 Hz).

2.12. {1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanol (10a)

To a solution of **9a** (2.85 g, 7.7 mmol) in THF (30 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (12.8 mL, 19.3 mmol) at -78 °C over 30 min. The mixture was further stirred at -78°C for 1 h, 1 N HCl (20 mL) was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-EtOAc = 6/1 - 1/1) to give **10a** (2.29 g, 91%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 4.55 (2H, d, *J* = 4.8 Hz), 6.19 (1H, d, *J* = 2.2 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.15-7.45 (8H, m).

2.13. (5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl)methanol (10b)

Compound **10b** was prepared from **9b** using a similar procedure as for the preparation of compound **10a**. A pale red solid (88%): ^{1}H NMR ($CDCl_3$) δ: 4.58 (2H, s), 6.23 (1H, d, *J* = 1.7 Hz), 7.19-7.22 (2H, m), 7.29-7.33 (2H, m), 7.37-7.43 (2H, m), 7.45 (2H, d, *J* = 8.3 Hz), 7.57 (2H, d, *J* = 8.3 Hz).

2.14. 1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11a)

To a solution of **10a** (1.50 g, 4.6 mmol) in acetonitrile (10 mL) were added tetra-*n*-propylammonium perruthenate (150 mg, 0.43 mmol), *N*-methylmorpholine *N*-oxide (932 mg, 6.9 mmol) and molecular sieves 4A powder (1.5 g), and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1 -1/1) to give **11a** (1.23 g, 82%) as a pale-brown oil: ^{1}H NMR ($CDCl_3$) δ: 2.37 (3H, s), 6.55 (1H, d, *J* = 2.2Hz), 7.05-7.50 (9H, m), 8.10 (1H, d, *J* = 2.2Hz).

2.15. 5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrole-3-carbaldehyde (11b)

Compound **11b** was prepared from **10b** in a manner similar to that described for compound **11a**. A white solid (68%): ^{1}H NMR ($CDCl_3$) δ 6.60 (1H, d, *J* = 1.7 Hz), 7.13-7.16 (2H, m), 7.29-7.33 (2H, m), 7.41-7.45 (3H, m), 7.58 (2H, d, *J* = 8.6 Hz), 8.12 (1H, d, *J* = 2.0 Hz), 9.90 (1H, s).

2.16. 1-[(4-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11c)

Compound **11c** was prepared from **9c** in a manner similar to that described for compound **10a** and **11a**. A pale red oil (65%): ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 6.55 (1H, d, *J*=1.8 Hz), 6.74 (2H, d, *J*=8.8 Hz), 7.15-7.45 (7H, m), 8.10 (1H, d, *J*=1.8 Hz), 9.87 (1H, s)

2.17. 1-(Methylsulfonyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (11d)

Compound **11d** was prepared from **9d** in a manner similar to that described for compound **10a** and **11a**. A white solid (51%): ^{1}H NMR ($CDCl_3$) δ 2.95 (3H, s), 6.73 (1H, d, *J* = 1.8 Hz), 7.40-7.60 (5H, m), 7.96 (1H, d, *J* = 1.8 Hz), 9.89 (1H, s).

2.18. Methyl 5-bromo-1*H*-pyrrole-3-carboxylate (12b)

A solution of methyl 1*H*-pyrrole-3-carboxylate (4.48 g, 35.8 mmol) in THF (70 mL) was cooled to -78°C, *N*-bromosuccinimide (6.30 g, 35.4 mmol) was added, pyridine (five drops) was added, and the mixture was left standing in a freezer (-20°C) for 3 days. The reaction mixture was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-EtOAc = 9/1 - 1/1) to give **12b** (3.59 g, 49%) as a pale-yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.58 (1H, m), 7.36 (1H, m), 8.60 (1H, br s).

2.19. Methyl 5-bromo-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (13)

Sodium hydride (60% in oil, 1.11 g, 27.8 mmol) was washed with hexane, and suspended to DMF (50 mL). To the suspension was slowly added a solution of **12b** (5.06 g, 24.8 mmol) in DMF (10 mL) at 0°C. After stirring at room temperature for 30 min, a solution of benzenesulfonyl chloride (3.3 mL, 25.8 mmol) in DMF (5 mL) was added at 0°C, and the mixture was stirred at room temperature for 30 min, poured into ice water and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 - 1/1) to give **13** (8.46 g, 99%) as crystals: mp 70-72 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s), 6.68 (1H, d, *J*=2.1 Hz), 7.55-7.60 (2H, m), 7.67-7.72 (1H, m), 7.96-7.99 (2H, m), 8.08 (1H, d, *J*=2.1 Hz).

2.20. *tert*-Butyl {[5-bromo-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (14)

Compound **14** was prepared from **13** in a manner similar to that described for compounds **6, 7** and **8**. A white solid (51%): ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.79 (3H, br s), 4.17 (2H, br s), 6.24 (1H, br s), 7.35 (1H, br s), 7.51-7.57 (2H, m), 7.62-7.68 (1H, m), 7.90-7.94 (2H, s).

2.21. *tert*-Butyl methyl{[5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl} carbamate (15f)

A mixture of **14** (1.04 g, 2.42 mmol), phenylboronic acid (448.2 mg, 3.68 mmol), Na_2CO_3 (770.8 mg, 7.27 mmol) and tetrakis (triphenylphosphine) palladium (421.1 mg, 0.36 mmol) in DME (25 mL) and H_2O (25 mL) was stirred at 105°C for 12 h under Ar_2 atmosphere. After cooling, a solution of $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, water, brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give **15f** (0.97 g, 94%) as crystals: mp 84-86°C; ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.80 (3H, br s), 4.22 (2H, brs), 6.09 (1H, br s), 7.19-7.23 (2H, m), 7.26-7.38 (8H, m), 7.47-7.53 (1H, m).

2.22. *tert*-Butyl [(1-benzoyl-5-phenyl-1*H*-pyrrol-3-yl)methyl]methylcarbamate (15h)

To a suspension of NaH (60% in oil, 97 mg) in THF (10 mL) was added a solution of **8** (483 mg, 1.69 mmol), 15-crown-5 (447 mg) and BzCl (261 mg) at 0°C. The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 9/1 - 4/1) to give **15h** (210 mg, 32%) as a pale red oil: ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.85 (3H, s), 4.26 (2H, s), 6.37 (1H, s), 6.96 (1H, s), 7.18-7.28 (5H, m), 7.37-7.42 (2H, m), 7.51-7.56 (1H, m), 7.74-7.77 (2H, m).

2.23. *N*-({1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methyl) ethanamine (16)

11a (300 mg, 0.92 mmol) was dissolved in methanol (30 mL), and molecular sieves 4A powder (600 mg), ethylamine hydrochloride (376 mg, 4.61 mmol) and sodium cyano borohydride (69 mg, 1.10 mmol) were added to the mixture. The reaction mixture was stirred at room temperature for 1 h. The mixture was filtered with Celite and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 6/1 - 1/1) to give **16** (50 mg, 15%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.13 (3H, t, J = 7.0 Hz), 2.35 (3H, s), 2.68 (2H, q, J = 7.0 Hz), 3.64 (2H, s), 6.15 (1H, d, J = 1.8 Hz), 7.08 (2H, d, J = 8.2 Hz), 7.20-7.40 (9H, m); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_2S$ $(M+H)^+$ m/z 355.1475, found m/z 355.1440.

2.24. *N*-Methyl-1-{1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanamine hydrochloride (17a)

Free base of compound **17a** was prepared from **11a** and methyl ammonium chloride using a similar procedure as for the preparation of compound **16**. A brown oil (7%): ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 2.44 (3H, s), 3.59 (2H, s), 6.13 (1H, d, J = 1.8 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.20-7.40 (9H, m).

Obtained free base of **17a** (213 mg, 242 mg) was dissolved in EtOAc (5 mL each). A 4N HCl/EtOAc solution (0.3 mL each) was added, and the each mixture was stirred at room temperature for 15 min. After combined, the resulting mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **17a** (428 mg, 85%) as a pale red solid: ^{1}H NMR (DMSO-d_6) δ 2.35

(3H, s), 2.50 (3H, s), 3.97 (2H, s), 6.43 (1H, d, *J* = 1.8 Hz), 7.13-7.43 (9H, m), 7.70 (1H, s), 8.98 (2H, br s); Anal. Calcd for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.44; H, 5.72; N, 7.26.

2.25. *N*-Methyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl) methanamine hydrochloride (17b)

11b (65 mg) was dissolved in MeOH (5 mL). 40% methylamine methanol solution (50 mg) was added at room temperature and the mixture was stirred for 15 min. To the reaction mixture was added sodium borohydride (24 mg) at room temperature and the mixture was stirred for 10 min. 1N HCl (5 mL) was added, and the mixture was stirred for 5 min. The mixture was basified with a saturated aqueous sodium hydrogen carbonate and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 4:1 to EtOAc) and the obtained oil was dissolved in ethyl acetate (5 mL). 4N HCl/EtOAc (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **17b** (50mg, 68%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.50-2.51 (3H, m), 3.99 (2H, s), 6.48 (1H, s), 7.13-7.15 (2H, m), 7.35-7.38 (2H, m), 7.42-7.46 (1H, m), 7.61 (2H, d, *J* = 8.3 Hz), 7.78-7.78 (1H, m), 7.92 (2H, d, *J* = 8.5 Hz), 9.03 (2H, br); HRMS (ESI) calcd for $C_{19}H_{17}F_3N_2O_2S$ $(M+H)^+$ m/z 395.1036, found m/z 395.1012.

2.26. 1-{1-[(4-Methoxyphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (17c)

Compound **17c** was prepared from **11c** using a similar procedure as for the preparation of compound **17a**. Pale red crystals (54%): mp 185-188 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 3.80 (3H, s), 3.98 (2H, s), 6.45 (1H, d, *J* = 2.2 Hz), 6.74 (2H, d, *J* = 7.0 Hz), 7.10-7.40 (7H, m), 7.64 (1H, d, *J* = 2.2 Hz), 9.82 (2H, br); Anal. Calcd for $C_{19}H_{21}ClN_2O_3S$: C, 58.08; H, 5.39; N, 7.13. Found: C, 58.13; H, 5.49; N, 6.78.

2.27. *N*-Methyl-1-[1-(methylsulfonyl)-5-phenyl-1*H*-pyrrol-3-yl]methanamine hydrochloride (17d)

Compound 1**7d** was prepared from **11d** using a similar procedure as for the preparation of compound **17a**. Colorless crystals (55%): mp 183-185 °C; ^{1}H NMR (DMSO-d_6) δ 2.54 (3H, s), 3.22 (3H, s), 4.00 (2H, s), 6.53 (1H, m), 7.45 (5H, m), 7.51 (1H, m), 9.09 (2H, br); Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$: C, 51.91; H, 5.70; N, 9.31. Found: C, 51.91; H, 5.62; N, 9.13.

2.28. 1-(1-Benzyl-5-phenyl-1*H*-pyrrol-3-yl)-*N*-methylmethanamine (17e)

Compound 1**7e** was prepared from **5a** using a similar procedure as for the preparation of compounds **9a** (benzyl bromide was used instead of TsCl), **10a**, **11a** and **16** (methyl ammonium chloride was used instead of ethyl ammonium chloride). A colorless oil (34 %): ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 3.65 (2H, s), 5.09 (2H, s), 6.23 (1H, d, *J* = 2.1 Hz), 6.66 (1H, d, *J* = 2.1 Hz), 7.02 (2H, d, *J* = 6.3 Hz), 7.20-7.40 (8H, m); HRMS (ESI) calcd for $C_{19}H_{20}N_2$ $(M+H)^+$ m/z 277.1699, found m/z 277.1670.

2.29. *N*-Methyl-1-[5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methanamine hydrochloride (17f)

To a solution of **15f** (637 mg, 1.49 mmol) in MeOH (10 mL) was added 4N HCl/EtOAc (4 mL), the mixture was stirred at room temperature for 3 h. The mixture was treated with active carbon, filtrated and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH to give **17f** (394mg, 73%) as crystals: mp 229-231 °C; ^{1}H NMR ($CDCl_3$) δ 2.55 (3H, s), 3.98 (1H, s), 6.47 (1H, d, *J* = 1.8 Hz), 7.12-7.15 (2H, m), 7.23-7.37 (7H, m), 7.47-7.53 (1H, m), 7.65 (1H, d, *J* = 1.8 Hz), 9.83 (2H, br s); Anal. Calcd for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.40; H, 5.29; N, 7.61.

2.30. 1-[1-(Butylsulfonyl)-5-phenyl-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hemi oxalate (17g)

To a solution of **8** (70 mg, 0.244 mmol) in DMF (7 mL) was added sodium hydride (60% in oil, 98 mg) at room temperature and the mixture was stirred at room temperature for 30 min. Butane-1-sulfonyl chloride (230 mg) was added, and the resulting mixture was stirred overnight, poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1 - 4:1) and the resulting oil was dissolved in MeOH (5 mL) and 4N HCl/EtOAc (1 mL) was added. The mixture was stirred at 60°C for 20 min, concentrated under reduced pressure, basified with a solution of $NaHCO_3$, and extracted with EtOAc. Oxalic acid (10 mg) was added to the extract, and the mixture was concentrated under reduced pressure. The residue was crystallized from Et_2O/EtOAc to give **17g** (17.9 mg, 21%) as a pale violet solid: ^{1}H NMR (DMSO-d_6) δ 0.75 (3H, t, *J* = 7.2 Hz), 1.14-1.38 (4H, m), 2.56 (3H, s), 3.21 (2H, t, *J* = 7.2 Hz), 4.01 (2H, s), 6.48 (1H, s), 7.44 (5H, br), 7.48 (1H, s); HRMS (ESI) calcd for $C_{16}H_{22}N_2O_2S$ $(M+H)^+$ m/z 307.1475, found m/z 307.1446.

2.31. {4-[(Methylamino)methyl]-2-phenyl-1*H*-pyrrol-1-yl}(phenyl)methanone fumarate (17h)

To a solution of **15h** in EtOAc (2 mL) and MeOH (1 mL) was added dropwise 4N HCl/EtOAc (2 mL) at room temperature. After stirring for 4 h at room temperature, the mixture was concentrated under reduced pressure. The residue was basified with a Na_2CO_3 solution, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 3/1 - 1/3) and the obtained oil was dissolved in EtOAc (5 mL). To this solution was added a solution of fumaric acid (37 mg) in MeOH (2 mL), and the mixture was concentrated under reduced pressure. The residue was crystallized with EtOH to give **17h** (66 mg, 30%) as a pale red solid: ^{1}H NMR (DMSO-d_6) δ 2.47 (3H, s), 3.86 (2H, s), 6.43 (2H, s), 6.60-6.61 (1H, m), 7.20-7.32 (6H, m), 7.51-7.56 (2H, m), 7.65-7.67 (1H, m), 7.77-7.78 (2H, m); Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$ 0.5EtOH: C, 67.12; H, 5.87; N, 6.52. Found: C, 67.04; H, 5.55; N, 6.67.

2.32. 1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole-3-carboxamide (18)

To a solution of **5b** (200 mg, 1.07 mmol) in DMF (5 mL) was added NaH (60% in oil, 107 mg) at 0°C. The mixture was stirred at room temperature, and tosyl chloride (448 mg, 2.35 mmol) was added. After stirring at room temperature for 1 h, 25% NH_3 solution (1 mL) was added, and the mixture was stirred at room temperature for 1h. After dilution with H_2O, the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1 - 1:1) and crystallized from hexane/iPr_2O to give **18** (32 mg, 9 %) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 5.64 (2H, br), 6.40 (1H, d, *J* = 2.2 Hz), 7.05-7.45 (9H, m), 7.98 (1H, d, *J* = 2.2 Hz); Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.38; H, 4.74; N, 8.15.

2.33. 4-(Azidomethyl)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-1*H*-pyrrole (19)

To a solution of **9a** (500 mg, 1.35 mmol) in THF (10 mL) was added dropwise 1.5 M DIBAL-H in toluene (2.70 mL, 4.06 mmol) at -78°C, and the mixture was stirred at room temperature for 30 min. 1N HCl (6 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 15 min and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. A solution of the residue in CH_2Cl_2 (2 mL) was added to a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (612 mg, 2.7 mmol), triphenylphosphine (532 mg, 2.03 mmol) and tetra-*n*-butylammoniumazide (768 mg, 2.7 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 - 1/1) to give **19** (233 mg, 49%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 4.48 (2H, s), 6.19 (1H, d, *J* = 2.2 Hz), 7.09 (2H, d, *J* = 8.6 Hz), 7.15-7.40 (8H, m), 7.46 (1H, d, *J* = 2.2 Hz).

2.34. 1-{1-[(4-Methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrol-3-yl}methanamine hydrochloride (20)

To a solution of **19** (230 mg, 0.563 mmol) in MeOH (10 mL) was added 10% palladium carbon (50% water-containing product, 150 mg), and the mixture was stirred under H_2 atmosphere at room temperature for 18 h. To the reaction mixture was added acetic acid (1 mL), and the mixture was stirred under a H_2 atmosphere at room temperature for 18 h. The reaction mixture was filtrated, and a solution of $NaHCO_3$ was added to the filtrate, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane/EtOAc = 9/1 to EtOAc), and the obtained oil was dissolved in EtOAc (5 mL), 4N HCl/EtOAc (0.5 mL) was added, and the mixture was concentrated under reduced pressure. The residue was crystallized from EtOAc to give **20** (10 mg, 4%) as colorless crystals: mp 198-201°C; ^{1}H NMR (DMSO-d_6) δ 2.35 (3H, s), 3.89 (2H, s), 6.39 (1H, d, *J* = 1.8 Hz), 7.10-7.20 (2H, m), 7.22-7.50 (7H, m), 7.66 (1H, d, *J* = 1.8 Hz), 8.20 (3H, br); Anal. Calcd for $C_{18}H_{19}ClN_2O_2S$ 0.25H_2O: C, 58.85; H, 5.35; N, 7.63. Found: C, 58.61; H, 5.45;

N, 7.36.

2.35. 4-(Methoxymethyl)-1-[(4-methylphenyl)sulfonyl]-2-phenyl-1*H*-pyrrole (21)

To a solution of **10a** (200 mg, 0.61 mmol) in DMF (1 mL) was added NaH (60% in oil, 37mg, 0.92 mmol) and MeI (57 □L, 0.92 mmol) at 0°C. After being stirred at room temperature for 1 h, 1N HCl (5 mL) was added to the mixture. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 - 1:1) to give **21** (105 mg, 50%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.35 (3H, s), 3.36 (3H, s), 4.30 (2H, s), 6.16 (1H, d, *J* = 1.8 Hz), 7.06-7.40 (10H, m); HRMS (ESI) calcd for $C_{19}H_{19}NO_3S$ $(M+H)^+$ m/z 342.1158, found m/z 342.1141.

2.36. *N*, *N*-Dimethyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl) methanamine hydrochloride (22)

Using **11b** (80 mg), 2M dimethylamine in THF solution (1 mL) and sodium borohydride (24 mg), a similar procedure as the preparation of compound **17b** was performed to give **22** (59 mg, 63%) as colorless crystals: mp 185-188°C; ^{1}H NMR (DMSO-d_6) δ 2.67 (6H, s), 4.12 (2H, s), 6.56-6.56 (1H, m), 7.15-7.17 (2H, m), 7.34-7.38 (2H, m), 7.42-7.46 (1H, m), 7.63 (2H, d, *J*=8.3 Hz), 7.85 (1H, d, *J*=1.7 Hz), 7.92 (2H, d, *J*=8.3 Hz), 10.68 (1H, br); Anal. Calcd for $C_{20}H_{20}ClF_3N_2O_2S$ $0.5H_2O$: C, 52.92; H, 4.66; N, 6.17. Found: C, 53.24; H, 4.63; N, 5.82.

2.37. 1-(5-Phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl)ethanone (23)

To a solution of 1M MeMgBr in THF (16 mL, 16 mmol) and Et_2O (16 mL) was added dropwise a solution of **11b** (600 mg, 1.58 mmol) in THF (4 mL) and Et_2O (4 mL) at 10°C. The mixture was stirred at 10°C for 1 h, and then poured into ice water. The resulting mixture was poured into a saturated solution of NH_4Cl, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give pale brown oil (0.63 g). To a solution of the obtained oil in CH_2Cl_2 (30 mL) was added MnO_2 (2.77 g, 31.9 mmol) at room temperature. The mixture was stirred at room temperature for 4 h, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1 - 4:1) to give **23** (461 mg, 74%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.49 (3H, s), 6.57 (1H, d, *J* = 1.9 Hz), 7.12-7.16 (2H, m), 7.28-7.33 (2H, m), 7.39-7.41 (1H, m), 7.43 (2H, d, *J* = 8.4 Hz), 7.57 (2H, d, *J* = 8.4 Hz), 8.06 (1H, d, *J* = 1.9 Hz).

2.38. *N*-Methyl-1-(5-phenyl-1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1*H*-pyrrol-3-yl) ethanamine hydrochloride (24)

A mixture of **23** (200 mg, 0.51 mmol), 40% $MeNH_2$ in MeOH (400 mg, 5.2 mmol) and MS4A in EtOH (10 mL) was stirred at 70°C for 1.5 h, and then cooled to room temperature. $NaBH_4$ (58 mg, 1.53 mmol) was added at room temperature, and the mixture was stirred for 1.5 h, quenched with 1N HCl (50 mL). The resulting mixture was stirred for 30 min, basified with a saturated solution of $NaHCO_3$, and then extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$,

and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/MeOH = EtOAc to 4:1) and the obtained oil was dissolved in ethyl acetate (5 mL). 4N HCl/EtOAc (1 mL) was added and the mixture was concentrated under reduced pressure. The residue was crystallized from iPr_2O/EtOAc to give **24** (52 mg, 23%) as colorless crystals: mp 205-208 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (3H, d, *J* = 6.7 Hz), 2.37 (3H, s), 4.28 (1H, q, *J* = 6.7 Hz), 6.55 (1H, s), 7.14-7.45 (5H, m), 7.63 (2H, d, *J* = 8.4 Hz), 7.78 (1H, s), 7.92 (2H, d, *J* = 8.4 Hz); Anal. Calcd for $C_{20}H_{20}ClF_3N_2O_2S$ $0.5H_2O$: C, 52.92; H, 4.66; N, 6.17. Found: C, 53.19; H, 4.53; N, 6.05.

2.39. 1-[(1-Isocyanopentyl)sulfonyl]-4-methylbenzene (26)

A mixture of *p*-toluenesulfonylmethyl isocyanide **25** (9.75 g, 50 mmol), tetrabutylammonium iodide (3.69 g, 10 mmol), 1-butyl iodide (11.3 mL, 100 mmol), CH_2Cl_2 (100 mL) and 30% NaOH solution (100 mL) was stirred at room temperature for 12 hr. The mixture was diluted with water (200 mL), and then extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained gum-like residue was extracted three times with diethyl ether (100 mL). The extract was concentrated under reduced pressure to give **26** (10.8 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.91-0.97 (3H, m), 1.32-1.66 (4H, m), 1.80-1.90 (1H, m), 2.10-2.25 (1H, m), 2.49 (3H, s), 4.42-4.47 (1H, m), 7.41-7.51 (2H, m), 7.86-7.88 (2H, m).

2.40. Ethyl 5-butyl-1*H*-pyrrole-3-carboxylate (27)

A solution of **26** (10.8 g, 43.0 mmol) and ethyl acrylate (4.78 mL, 43.0 mmol) in THF (120 mL) was added dropwise to a suspension of potassium *tert*-butoxide (5.79 g, 51.6 mmol) in THF (80 mL) while stirring at room temperature over 1 h. The mixture was further stirred at room temperature for 30 min, and then diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19/1 - 4/1) to give **27** (6.56g, 78%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.89-0.95 (3H, m), 1.24-1.45 (5H, m), 1.55-1.65 (2H, m), 2.55-2.60 (2H, m), 4.23-4.30 (2H, m), 6.33 (1H, s), 7.30 (1H, s), 8.11 (1H, br).

2.41. Ethyl 5-butyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (28)

To a solution of **27** (978 mg, 5.0 mmol) in THF (50 mL) was added sodium hydride (60% in oil, 240 mg, 6.0 mmol) under Ar atmosphere. After stirring at room temperature for 30 min, benzenesulfonyl chloride (0.77 mL, 6.0 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19/1 - 4/1), and the obtained solid was washed with hexane to give **28** (780 mg, 47%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.84-0.89 (3H, m), 1.26-1.37 (5H, m), 1.47-1.55 (2H, m), 2.59-2.64 (2H, m), 4.25-4.32 (2H, m), 6.37 (1H, m), 7.52-7.66 (3H, m), 7.79-7.82 (2H, m), 7.92 (1H, s).

2.42. Methyl 5-cyclopropyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (29)

A mixture of **13** (2.11g, 6.13 mmol), cyclopropylboronic acid (683 mg, 7.95 mmol), palladium(II) acetate (69 mg, 0.31 mmol), tricyclohexylphosphine (174 mg, 0.62 mmol) and tripotassium phosphate (4.55 g, 21.5 mmol) in toluene (27 mL) and water (1.3 mL) was stirred at 100°C for 4 h under Ar atmosphere. After cooled to room temperature, the reaction mixture was diluted with H_2O (50 mL), and the mixture was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1 - 4/1) to give **29** (406mg, 22%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.30-0.36 (2H, m), 0.71-0.77 (2H, m), 2.00-2.08 (1H, m), 3.79 (3H, s), 6.19 (1H, s), 7.51-7.56 (2H, m), 7.63-7.66 (1H, m), 7.85-7.88 (2H, m), 7.94 (1H, s).

Compounds **30a** and **30b** were prepared form **28** and **29** respectively using a similar procedure as for the preparation of compound **17b** from **9b**.

2.43. 1-[5-Butyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (30a)

Colorless crystals (53%): mp 139-140 °C; ^{1}H NMR (DMSO-d_6) δ 0.79-0.85 (3H, m), 1.24-1.48 (4H, m), 2.48 (3H, s), 2.58-2.63 (2H, m), 3.91 (2H, s), 6.25 (1H, s), 7.54 (1H, s), 7.66-7.88 (5H, m), 8.91 (2H, br); Anal. Calcd for $C_{16}H_{23}ClN_2O_2S$: C, 56.04; H, 6.75; N, 8.17. Found: C, 55.97; H, 6.97; N, 8.15.

2.44. 1-[5-Cyclopropyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (30b)

Colorless crystals (40%): mp 198-199 °C; ^{1}H-NMR (DMSO-d_6) δ 0.22-0.27 (2H, m),0.75-0.81 (2H, m), 1.97-2.05 (1H, m), 2.47 (3H, s), 3.87 (2H, s), 6.09 (1H, s), 7.55 (1H, s), 7.66-7.91 (5H, m), 8.92 (2H, br); Anal. Calcd for $C_{15}H_{19}ClN_2O_2S$ 0.5H_2O: C, 53.64; H, 6.00; N, 8.34. Found: C, 53.88; H, 5.71; N, 8.10.

2.45. Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (31)

A solution of ethyl acetoacetate (13.02 g, 100 mmol) in DMF (40 mL) was added dropwise to a stirred suspension of NaH (60% in oil, 2.88 g) at 0 °C. The mixture was stirred at 0°C for 20 min, and then a solution of phenacyl bromide **2** (20.0 g, 100 mmol) in DMF (20 mL) was added dropwise slowly. The reaction mixture was stirred at room temperature for 1.5 h, poured into ice water, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give ethyl 2-acetyl-4-oxo-4-phenylbutanoate (32.4 g, crude) as an oil. A mixture of thus obtained oil (32.4 g) and $AcONH_4$ (11.6 g) in AcOH (150 mL) was stirred at 80°C for 20 h. The reaction mixture was concentrated under reduced pressure, and the residue was taken up EtOAc, washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1 - 7/2) to give **31** (15.6 g, 68%) as a solid: ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.0 Hz), 2.59 (3H, s), 4.30 (2H, q, *J* = 7.0 Hz), 6.84 (1H, d, *J*=2.8 Hz), 7.18-7.27 (1H, m), 7.36 (2H, t, *J* = 7.7 Hz), 7.43-7.51 (2H, m), 8.52 (1H, br).

2.46. Ethyl 2-chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (32)

To a solution of **4** (1.0 g, 4.0 mmol) in THF (40 mL) was added sodium hydride (60% in oil, 488 mg) at room temperature and the mixture was stirred for 30 min. 15-Crown-5 (2.65 g) was added dropwise and the mixture was stirred at room temperature for 30 min. To this mixture was added benzenesulfonyl chloride (1.84 g), and the mixture was further stirred at room temperature for 24 h, poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc=17:3) to give **32** (1.27 g, 81%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, t, *J* = 7.2 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 6.55 (1H, s), 7.38-7.50 (7H, m), 7.60-7.71 (3H, m).

2.47. 2-Methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (33a)

Compound **33a** was prepared from **31** in a manner similar to that described for compound **9a**, **10a** and **11a**. A colorless oil (6%): ^{1}H NMR ($CDCl_3$) δ 2.88 (3H, s), 6.47 (1H, s), 7.18-7.61 (10H, m), 10.00 (1H, s).

2.48. 2-Chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (33b)

Compound **33b** was prepared from **32** in a manner similar to that described for compound **10a** and **11a**. A colorless oil (41%): ^{1}H NMR ($CDCl_3$) δ 6.52 (1H, s), 7.32-7.52 (7H, m), 7.62-7.69 (3H, m), 9.93 (1H, s).

2.49. *N*-Methyl-1-[2-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl] methanamine hydrochloride (34a)

Compound **34a** was prepared from **33a** in a manner similar to that described for compound **17a**. Colorless crystals (35%): mp 183-184 °C; ^{1}H NMR (DMSO-d_6) δ 2.44 (3H, s), 2.50 (3H, s), 3.91 (2H, s), 6.40 (1H, s), 7.22-7.28 (2H, m), 7.34-7.49 (5H, m), 7.57 (2H, t, *J* = 7.8 Hz), 7.72 (1H, t, *J* = 6.8 Hz), 8.84 (2H, br s); Anal. Calcd for $C_{19}H_{20}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.38; H, 5.59; N, 7.23.

2.50. 1-[2-Chloro-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (34b)

Compound **34b** was prepared from **33b** in a manner similar to that described for compound **17b**. Colorless crystals (61%): mp 180-182 °C; ^{1}H NMR (DMSO-d_6) δ 2.43 (3H, s), 3.89 (2H, s), 6.61 (1H, s), 7.36-7.46 (5H, m), 7.62-7.69 (4H, m), 7.75-7.82 (1H, m), 8.97 (2H, br); Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_2S$: C, 54.41; H, 4.57; N, 7.05. Found: C, 54.30; H, 4.57; N, 7.01.

2.51. Methyl 5-bromo-4-methyl-1*H*-pyrrole-3-carboxylate (36)

To a solution of methyl 4-methyl-1*H*-pyrrole-3-carboxylate **35** (5.0 g, 35.9 mmol) in THF (60 mL) was added NBS (6.39 g, 35.9 mmol) at -78 °C. After being stirred 15 min at -78 °C, pyridine (5 drops) was added, and the mixture was stood at 5 °C for 18 h in a refrigerator. The mixture was concentrated under reduced pressure, diluted with H_2O, and extracted with EtOAc. The extract was

washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 - 2/1) to give **36** (4.05 g, 52%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 3.80 (3H, s), 7.35-7.40 (1H, m), 8.45 (1H, br).

2.52. Methyl 5-bromo-4-methyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (37)

Compound **37** was prepared from **36** in a manner similar to that described for compound **13**. A brown solid (69%): ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 3.79 (3H, s), 7.45-7.70 (3H, m), 7.85-7.95 (2H, m), 8.06 (1H, s).

2.53. Methyl 4-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate (38)

Compound **38** was prepared from **37** in a manner similar to that described for compound **15a**. A pale-yellow oil (87%): ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s), 3.85 (3H, s), 6.98 (2H, d, J = 8.4 Hz), 7.20-7.60 (8H, m), 8.08 (1H, s).

2.54. *N*-Methyl-1-[4-methyl-5-phenyl-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methanamine hydrochloride (39)

Compound **39** was prepared from **38** in a manner similar to that described for compound **10a**, **11a** and **17a**. Colorless crystals (20%): mp 186-187°C; ^{1}H NMR (DMSO-d_6) δ 1.78 (3H, s), 2.58 (3H, s), 3.99 (2H, s), 6.95-7.10 (2H, m), 7.20 (1H, m), 7.30-7.65 (6H, m), 7.70-7.90 (2H, m), 8.91 (2H, br); Anal. Calcd for $C_{19}H_{21}ClN_2O_2S$ 0.5H_2O: C, 59.13; H, 5.95; N, 7.26. Found: C, 59.50; H, 5.52; N, 7.32.

2.55. Measurement of H^+, K^+-ATPase activity

According to the method of Wallmark et al.,[56] a gastric mucosal microsomal fraction was prepared from the stomach of porcine. First, the stomach was removed, washed with tap water, immersed in 3 mol/L NaCl solution, and the surface of the mucosa was wiped with a paper towel. The gastric mucosa was detached, chopped, and homogenized in a homogenizing buffer consisting of 0.25 mol/L saccharose, 1 mmol/L EDTA and 10 mmol/L Tris HCl pH 6.5 using polytron (Kinematica). The obtained homogenate was centrifuged at 20,000 × g for 30 min and the supernatant was centrifuged at 100,000 × g for 90 min. The precipitate was suspended in a homogenizing buffer and layered over 7.5% (w/w) Ficoll in a homogenizing buffer, and centrifuged at 100,000 × g for 5 h. The microsomal fraction appearing at the interface between the both layers was collected and centrifuged at 100,000 × g for 90 min. The pellet was collected and suspended in a homogenizing buffer to give a concentration of 0.5 mg of protein per mL. The resulting suspension was stored at -80 °C until use and used as the gastric microsomes. The obtained microsomal fraction was used as H^+, K^+-ATPase standard product. Protein was determined with a protein assay kit (Bio-Rad, Hercules, CA, USA) using bovine serum albumin as a standard.

The activity of H^+, K^+-ATPase from the porcine stomach was measured as follows: the enzyme mixture contained, in volume of 40 μL, 50 mmol/L HEPES-Tris pH 6.5 containing 5 mmol/L $MgCl_2$,

10 μmol/L of valinomycin in 0.1% DMSO solution and 0.1 μg of the gastric microsomes as an enzyme source in the presence or absence of 10 mmol/L KCl. The 5μL of various concentration of the test compound in 10% DMSO solution, was added to the enzyme mixture and incubated at 37 °C for 30 min. The enzyme reaction was started by adding 5 μL of a 2 mmol/L ATP solution. The reaction was stopped with 15 μL malachine green reagents (0.12% malachite green: 7.5% hexaammonium heptamolybdate: 11% Tween 20=100:25:2). After allowing to stand at room temperature for 15 min, the resulting reaction product of inorganic phosphorus with malachite green was colorimetrically determined at a wavelength of 620 nm. The ATPase activity was determined by the inorganic phosphate released from ATP hydrolysis according to the method of Fiske and Subbarow.[57] The activity of H^+, K^+-ATPase was calculated from the difference between ATPase activities with or without K^+. The inhibitory effects of the test compounds were expressed as percentage inhibition with respect to the K^+-stimulated H^+, K^+-ATPase activity in the control. The values of IC_{50} were calculated using sigmoidal dose response equation in GraphPad Prism (GraphPad Software Inc., San. Diego, CA, USA).

2.56. Inhibition test of histamine-stimulated acid secretion in anesthetized rats

Seven-week-old male Jcl:Sprague-Dawley (SD) rats were used. The animals were fasted for 24 h but had free access to water before the experiment. The pylorus was ligated after anesthetization with urethane (1.2 g/kg, ip) and the abdomen was closed. Drugs and the vehicle were given intravenously just after the pylorus ligation. Three min later, histamine 2HCl (30 mg/kg/10 mL) was injected subcutaneously. Three h after histamine administration, the rats were sacrificed by CO_2 asphyxiation and the stomachs were removed. The gastric contents were collected and centrifuged at 3000 rpm for 10 min. The volume of each sample was measured and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L NaOH (COM-555SC; Hiranuma Sangyo Co., Ltd., Japan), and the total acid output during the 3 h period (μEq/3 h) was calculated.

2.57. Washout reversibility test on the inhibition of H^+, K^+-ATPase

Gastric microsomes were incubated with 0.1 μM compound (final concentration of DMSO was 1%) at 37°C for 30 min in assay buffer consisting of 50 mmol/L HEPES-Tris buffer pH 6.5, 5 mmol/L $MgCl_2$, 10 mmol/L KCl, and then aliquots of the reaction mixture were taken to determine H^+, K^+ ATPase activity. From the remaining reaction mixture, the compound was washed out by ultrafiltration through 30 kDa cut-off membranes. Residues were resuspended in the same volume of the assay buffer without the compound. The reaction was initiated by the addition of 2 mmol/L ATP and the reaction mixture was incubated at 37°C for 20 min. The reaction was stopped with malachite green reagents (0.12% malachite green: 7.5% hexaammonium heptamolybdate: 11% tween 20 = 100:25:2). The ATPase activity was determined by the inorganic phosphate released from ATP hydrolysis according to the method of Fiske and Subbarow.[57] The K^+-stimulated H^+, K^+-ATPase activity obtained with 1% DMSO solution was calculated as 100 % control. Data were expressed as

percentage of the ATPase activity in vehicle with or without washout.

2.58. Measurement of Na^+, K^+-ATPase inhibitory activity

The activity of Na^+, K^+-ATPase from porcine cerebral cortex (Sigma) was measured as described for H^+, K^+-ATPase except the components of the enzyme mixture that contained in volume of 40 μL, 4 μg of Na^+, K^+-ATPase, 50 mmol/L Tris-HEPES (pH 7.5), 2 mmol/L $MgCl_2$ with or without 100 mmol/L NaCl and 10 mmol/L KCl.

2.59. Inhibition test of histamine-stimulated acid secretion in Heidenhain pouch dogs

Drugs and the vehicle were given orally (0.2 mL/kg) to the dogs in a blind manner. Histamine 2HCl (30 μg/kg) was injected subcutaneously 1 day before and 1, 3, 6 and 24 h after drugs and the vehicle administration. The gastric juice from the pouch was collected continuously for three consecutive 30 min periods after each dosing with histamine 2HCl. The volume of gastric juice was measured and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L NaOH solution (COM-555SC; Hiranuma Sangyo Co., Ltd, Japan). The total acid output during the 90 min period (μEq/90 min) from each time was calculated and expressed as a percentage of the pre-dosing value measured 1 day before the administration.

Experiments concerning Chapter 3

3.1. *N*-Methyl-1-[1-(phenylsulfonyl)-5-(pyrimidin-5-yl)-1*H*-pyrrol-3-yl]methanamine hydrochloride (40a)

A mixture of *tert*-butyl {[5-bromo-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate **14** (170 mg, 0.40 mmol), pyrimidin-5-ylboronic acid (123 mg, 0.99 mmol), Na_2CO_3 (147 mg, 1.39 mmol) and tetrakis(triphenylphosphine)palladium (46 mg, 0.040 mmol) in DME (10 mL) and H_2O (5 mL) was stirred at 90 °C for 3 h under Ar atmosphere. After cooling to room temperature, the mixture was poured into H_2O, and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–1/3), and the resulting oil was dissolved in MeOH (20 mL), and then 4 mol/L HCl/EtOAc (2 mL) was added. The mixture was stirred at 70 °C for 30 min, and concentrated under reduced pressure. The residue was suspended in EtOAc and collected by filtration to obtain **40a** (42.0 mg, 29%) as a white solid: mp 179 °C; ^{1}H-NMR (DMSO-d_6) δ 2.50 (3H, m), 4.00 (2H, t, *J* = 5.8 Hz), 6.71 (1H, d, *J* = 1.8 Hz), 7.44–7.47 (2H, m), 7.55–7.60 (2H, m), 7.73–7.78 (1H, m), 7.89 (1H, d, *J* = 1.8 Hz), 8.62 (2H, s), 9.18 (2H, br), 9.23 (1H, s); HRMS (ESI) calcd for $C_{16}H_{16}N_4O_2S$ $(M+H)^+$ *m/z* 329.1067, found *m/z* 329.1026.

3.2. *N*-Methyl-1-[1-(phenylsulfonyl)-5-(pyridin-3-yl)-1*H*-pyrrol-3-yl]methanamine dihydrochloride (40b)

Compound **40b** was prepared from **14** in a manner similar to that described for compound **40a**. A white solid (49%): mp 187 °C; ^{1}H-NMR (DMSO-d_6) δ 2.47 (3H, t, *J* = 5.5 Hz), 3.98 (2H, t, *J* = 5.5 Hz), 6.72 (1H, d, *J* = 1.8 Hz), 7.45–7.58 (4H, m), 7.70–7.76 (2H, m), 7.88 (1H, d, *J* = 1.3 Hz), 7.95–7.98 (1H, m), 8.53 (1H, d, *J* = 1.8 Hz), 8.76 (1H, dd, J=1.3, 5.3 Hz), 9.34 (2H, br), 1H not detected; HRMS (ESI) calcd for $C_{17}H_{17}N_3O_2S$ $(M+H)^+$ *m/z* 328.1114, found *m/z* 328.1085.

3.3. 5-Bromo-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (43)

To a solution of 5-bromo-1*H*-pyrrole-3-carbaldehyde **42** (3.50 g, 20.1 mmol) in THF (70 mL) was carefully added sodium hydride (60% in oil, 1.21 g, 30.3 mmol) under Ar atmosphere, and the mixture was stirred at room temperature for 10 min. After benzenesulfonyl chloride (4.27 g, 24.2 mmol) was added, the mixture was further stirred for 1 h, poured into H_2O, and then extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–7/3), and crystallized from diisopropyl ether to produce **43** (5.40 g, 85%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 6.73 (1H, d, *J* = 2.0 Hz), 7.58–7.63 (2H, m), 7.70–7.75 (1H, m), 7.98–8.01 (2H, m), 8.10 (1H, d, *J* = 2.0 Hz), 9.77 (1H, s).

3.4. 5-(2-Fluoropyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (44)

A degassed mixture of 5-Bromo-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde **43** (3.15 g, 10.0

mmol), (2-fluoropyridin-3-yl)boronic acid (2.83 g, 20.1 mmol), $NaHCO_3$ (2.53 g, 30.1 mmol) and tetrakis(triphenylphosphine)palladium (870 mg, 0.75 mmol) in DME (80 mL) and H_2O (20 mL) was stirred at 80 °C for 5 h under N_2 atmosphere. After cooling to room temperature, a solution of $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–2/3) to produce compound **44** (2.25 g, 68%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 6.71 (1H, d, *J* = 1.7 Hz), 7.24–7.28 (1H, m), 7.42–7.48 (4H, m), 7.62–7.68 (1H, m), 7.70–7.76 (1H, m), 8.14 (1H, d, *J* = 1.9 Hz), 8.28–8.31 (1H, m), 9.90 (1H, s).

3.5. 1-[5-(2-Fluoropyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (40c)

To a stirred mixture of 5-(2-Fluoropyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrole-3-carbaldehyde **44** (160 mg, 0.48 mmol) and 40% methanol solution of methylamine (188 mg, 2.42 mmol) in MeOH (16 mL) was added sodium borohydride (55 mg, 1.45 mmol) at room temperature under N_2 atmosphere, and the mixture was stirred at room temperature for 30 min, quenched with a solution of $NaHCO_3$, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (EtOAc/MeOH = 99/1), and then crystalized from a solution of fumaric acid (57 mg, 0.4911 mmol) in EtOH (5 mL). The obtained crystals were collected by filtration and rinsed with EtOH to produce **40c** (92 mg, 41%) as colorless crystals: mp 191–192 °C; ^{1}H-NMR (DMSO-d_6) δ 2.39 (3H, s), 3.79 (2H, s), 6.48 (2H, s), 6.51 (1H, d, *J* = 1.5 Hz), 7.38–7.42 (1H, m), 7.46–7.49 (2H, m), 7.54–7.60 (2H, m), 7.67–7.77 (3H, m), 8.30–8.33 (1H, m), 3H not detected; Anal. Calcd for $C_{21}H_{20}FN_3O_6S$: C, 54.66; H, 4.37; N, 9.11. Found: C, 54.57; H, 4.31; N, 9.02.

3.6. *tert*-Butyl {[5-(2-chloropyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (41d)

To a solution of diisopropylamine (8.3 g, 82.0 mmol) in THF (70 mL) was added dropwise a 1.6 mol/L hexane solution of *n*-BuLi (50 mL, 80 mmol) at −78 °C, and the mixture was stirred at the same temperature for 15 min. To this mixture was slowly added a solution of 2-chloropyridine (6.6 g, 58.1 mmol) in THF (10 mL), and then the resulting mixture was stirred at the same temperature for 2 h. To the obtained reaction mixture was added dropwise a solution of triisopropoxyborane (15.1 g, 80.3 mmol) in THF (10 mL) at the same temperature, and the mixture was stirred for 30 min, added MeOH (10mL), and then concentrated under reduced pressure. A suspension of the obtained residue, compound **14** (7.94 g, 18.5 mmol), tetrakis(triphenylphosphine)palladium (3.21 g, 2.78 mmol) and Na_2CO_3 (19.7 g, 186 mmol) in DME (80 mL) and H_2O (40 mL) was stirred at 105 °C for 4 h under Ar atmosphere. After cooling to room temperature, the reaction mixture was diluted with H_2O, and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, H_2O and brine, dried

over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–2/1) to obtain compound **41d** (1.88 g, 22%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.83 (3H, s), 4.26 (2H, brs), 6.26 (1H, d, *J* = 1.8 Hz), 7.26–7.31 (1H, m), 7.37 (1H, d, *J* = 1.8 Hz), 7.40–7.42 (4H, m), 7.55–7.60 (1H, m), 7.68–7.71 (1H, m), 8.40–8.43 (1H, m).

3.7. tert-Butyl {[5-(2-cyanopyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (41e)

A degassed mixture of **41d** (378 mg, 0.81825 mmol), zinc cyanide (196 mg, 1.64 mmol) and tetrakis(triphenylphosphine)palladium (189 mg, 0.16 mmol) in DMF (10 mL) was stirred for 2 h at 120 °C under Ar atmosphere. After cooling to room temperature, the mixture was partitioned between EtOAc and H_2O, and filtered through celite pad, washed through EtOAc. The organic layer of the filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–2/1) to obtain compound **41e** (250 mg, 67%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.82 (3H, brs), 4.27 (2H, brs), 6.44 (1H, brs), 7.33–7.45 (5H, m), 7.52–7.63 (2H, m), 7.94–7.96 (1H, m), 8.67–8.69 (1H, m).

3.8. 1-[5-(2-Chloropyridin-3-yl)-1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (40d)

To a solution of compound **41d** (259 mg, 0.56 mmol) in EtOH (2 mL) was added 4 mol/L HCl/EtOAc (2 mL), and the mixture was stirred at room temperature for 2 h, concentrated under reduced pressure, and then recrystallized from EtOH to produce compound **40d** (124 mg, 56%) as colorless crystals: mp 215–216 °C; ^{1}H-NMR (DMSO-d_6) δ 2.51 (3H, s), 4.00 (2H, s), 6.57–6.61 (1H, m), 7.46–7.52 (3H, m), 7.57–7.62 (3H, m), 7.74–7.83 (2H, m), 8.49–8.51 (1H, m), 9.04–9.23 (2H, m); Anal. Calcd for $C_{17}H_{17}Cl_2N_3O_2S$: C, 51.26; H, 4.30; N, 10.55. Found: C, 51.28; H, 4.23; N, 10.56.

3.9. 3-{4-[(Methylamino)methyl]-1-(phenylsulfonyl)-1*H*-pyrrol-2-yl}pyridine-2-carbonitrile hydrochloride (40e)

To a solution of compound **41e** (250 mg, 0.55 mmol) in EtOAc (5mL) and MeOH (3 mL) was added 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 4h, concentrated under reduced pressure, and then recrystallized from EtOH to produce compound **40e** (127 mg, 59%) as colorless crystals: mp 240–250 °C (decomposition); ^{1}H-NMR (DMSO-d_6) δ 2.49 (3H, s), 4.03 (2H, s), 6.80 (1H, d, *J* = 1.8 Hz), 7.45–7.48 (2H, m), 7.56–7.61 (2H, m), 7.75–7.94 (4H, m), 8.81–8.83 (1H, m), 9.21 (2H, brs); Anal. Calcd for $C_{18}H_{17}ClN_4O_2S$: C, 55.59; H, 4.41; N, 14.41. Found: C, 55.46; H, 4.31; N, 14.32.

3.10. Ethyl 2-cyano-4-(2-methylphenyl)-4-oxobutanoate (46b)

To a stirred solution of 2-methylacetophenone **45b** (13.42 g, 100 mmol) in Et_2O (100 mL) was added

dropwise bromine (16.0 g, 100 mmol), and the mixture was stirred at room temperature for 30 min, poured into ice H_2O, extracted with Et_2O. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to obtain a crude oil of 2-bromo-1-(2-methylphenyl)ethanone. K_2CO_3 powder (27.6 g, 200 mmol) was added to ethyl cyanoacetate (79.2 g 700 mmol), and the mixture was stirred at 43–45 °C for 45 min. To this stirred suspension was added a solution of crude 2-bromo-1-(2-methylphenyl)ethanone in acetone (150 mL) over a period of 30 min, and then the mixture was stirred at room temperature for 16 h, filtered and concentrated under reduced pressure. The residue was taken up with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10/1–8/1) to yield compound **46b** (46.4 g, about 100%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.9 Hz), 2.53 (3H, s), 3.50 (1H, dd, *J* = 5.2, 18.7 Hz), 3.71 (1H, dd, *J* = 7.1, 17.9 Hz), 4.11–4.20 (1H, m), 4.31 (2H, q, *J* = 7.9 Hz), 7.25–7.34 (2H, m), 7.41–7.49 (1H, m), 7.72 (1H, d, *J* = 7.7 Hz).

3.11. Ethyl 2-cyano-4-oxo-4-[2-(trifluoromethyl)phenyl]butanoate (46c)

Compound **46c** was prepared from compound **45c** using a similar procedure as for the preparation of compound **46b**. An oil (66%): ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 3.34–3.46 (1H, m), 3.59−3.70 (1H, m), 4.08−4.22 (1H, m), 4.32 (2H, q, *J* = 7.2 Hz), 7.57−7.80 (4H, m).

3.12. Ethyl 2-cyano-4-(2-fluorophenyl)-4-oxobutanoate (46d)

A mixture of compound **45d** (28.6 g, 207 mmol) and $CuBr_2$ (92.6 g, 415 mmol) in EtOAc (400 mL) was refluxed for 4h, and filtered after cooling. The filtrate was concentrated in vacuo to obtain a crude oil of 2-bromo-1-(2-fluorophenyl)ethanone. K_2CO_3 powder (88.0 g, 635 mmol) was added to ethyl cyanoacetate (168 g 1.48 mol), and the mixture was stirred at 40–45 °C for 45 min. To this stirred suspension was added a solution of crude 2-bromo-1-(2-fluorophenyl)ethanone in acetone (360 mL) over a period of 1 h at 40–45 °C, and then the mixture was stirred at 40–45 °C for 1 h, cooled to room temperature, filtered and concentrated under reduced pressure. The residue was taken up with EtOAc (300 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 50/1–4/1) to yield compound **46d** (64.0 g, about 100%) as a pale brown oil: ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 3.55–3.80 (2H, m), 4.11 (1H, t, *J* = 6.0 Hz), 4.24–4.34 (2H, m), 7.15–7.29 (2H, m), 7.55–7.62 (1H, m), 7.94 (1H, dt, *J* = 1.8 Hz, 7.5 Hz).

3.13. Ethyl 2-cyano-4-(3-fluorophenyl)-4-oxobutanoate (46e)

Compound **46e** was prepared from compound **45e** using a similar procedure as for the preparation of compound **46d**. A brown oil (about 100%): ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 3.52 (1H, dd, *J* = 5.4 Hz, 18.0 Hz), 3.76 (1H, dd, *J* = 6.9 Hz, 18.0 Hz), 4.08−4.17 (1H, m), 4.30 (2H, q, *J* = 7.2 Hz), 7.30−7.35 (1H, m), 7.45–7.52 (1H, m), 7.63–7.66 (1H, m), 7.73–7.76 (1H, m).

3.14. Ethyl 2-cyano-4-(4-fluorophenyl)-4-oxobutanoate (46f)

Compounds **46f** was prepared from compounds **45f** using a similar procedure as for the preparation of compound **46b**. A solid (86%): ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 3.44-3.58 (1H, m), 3.67−3.81 (1H, m), 4.11–4.20 (1H, m), 4.31 (2H, q, *J* = 7.2 Hz), 7.13−7.27 (2H, m), 7.97−8.05 (2H, m).

3.15. Ethyl 2-chloro-5-(pyridin-2-yl)-1*H*-pyrrole-3-carboxylate hydrochloride (47a)

2-Bromo-1-(pyridin-2-yl)ethanone hydrobromide **45a** (20.0 g, 71.1 mmol) and K_2CO_3 (14.8 g, 107 mmol) were suspended in acetone (100 mL), and the suspension was stirred at room temperature for 1.5 hr. To a solution of ethyl cyanoacetate (60.4 g, 534 mmol) in acetone (100 mL) was added K_2CO_3 powder (29.6 g, 214 mmol), and the mixture was stirred at 45 °C for 1 hr. To this mixture was added dropwise the suspension obtained earlier by small portions at 45 °C, and the resulting mixture was stirred at 45 °C for 3 h, filtered after cooled to room temperature, and then concentrated under reduced pressure. The residue was taken up with EtOAc, washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. To the obtained oil was added 4 mol/L HCl/EtOAc (250 mL) and the mixture was stirred at 60 °C for 3 h, and concentrated under reduced pressure. A solution of $NaHCO_3$ was added to the residue and the mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1), then added dropwise 4 mol/L HCl/EtOAc (20 mL) after dissolved in EtOAc (20 mL), concentrated under reduced pressure, and crystalized from EtOAc to yield compound **47a** (3.08 g, 15%) as a white solid: ^{1}H-NMR (DMSO-d_6) δ 1.30 (3H, t, *J* = 7.0 Hz), 4.25 (2H, q, *J* = 7.0 Hz), 7.48–7.54 (2H, m), 8.13–8.19 (2H, m), 8.61–8.63 (1H, m), 13.47 (1H, br), 1H not detected.

3.16. Ethyl 2-chloro-5-(2-methylphenyl)-1*H*-pyrrole-3-carboxylate (47b)

HCl gas was bubbled through a stirred and ice-cooled solution of **46b** (46.4 g, 189 mmol) in THF (200 mL) until the solution was saturated. The mixture was stirred at room temperature for 1 h, treated with N_2 gas to substitute HCl gas and then concentrated in vacuo. The residue was taken up with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1) and crystalized from diisopropylether/*n*-hexane to produce compound **47b** (2.72 g, 10%) as a pale yellow solid: mp 133 °C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 2.44 (3H, s), 4.33 (2H, q, *J* = 7.2 Hz), 6.67 (1H, d, J = 3.2 Hz), 7.21–7.31 (4H, m), 8.43 (1H, brs); Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.76; H, 5.36; N, 5.27.

3.17. Ethyl 2-chloro-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxylate (47c)

A mixture of **46c** (10.17 g, 34.0 mmol) and 4 mol/L HCl/EtOAc (100 mL) was stirred at room temperature for 24 h, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1) to yield compound **47c** (6.37 g, 59%) as a solid: ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 6.77 (1H, d, J = 3.3 Hz), 7.41–7.76 (4H,

m), 8.58 (1H, br).

3.18. Ethyl 2-chloro-5-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (47d)

Compound **47d** was prepared from compound **46d** using a similar procedure as for the preparation of compound **47c**. A pale brown solid (53%): mp 133 °C; ^{1}H-NMR ($CDCl_3$) δ 1.38 (3H, t, *J* = 7.2 Hz), 4.33 (2H, q, *J* = 7.2 Hz), 6.99 (1H, d, *J* = 3.3 Hz), 7.08−7.25 (3H, m), 7.55–7.60 (1H, m), 9.08 (1H, brs); Anal. Calcd for $C_{13}H_{11}$ ClFNO$_2$: C, 58.33; H, 4.14; N, 5.23. Found: C, 58.54; H, 4.19; N, 5.24.

3.19. Ethyl 2-chloro-5-(3-fluorophenyl)-1*H*-pyrrole-3-carboxylate (47e)

Compound **47e** was prepared from compound **46e** using a similar procedure as for the preparation of compound **47c**. A pale brown solid (32%): mp 160 °C; ^{1}H-NMR ($CDCl_3$) δ 1.38 (3H, t, *J* = 7.2 Hz), 4.33 (2H, q, *J* = 7.2 Hz), 6.88 (1H, d, *J* = 3.0 Hz), 6.89−7.38 (4H, m), 8.65 (1H, brs); Anal. Calcd for $C_{13}H_{11}$ ClFNO$_2$: C, 58.33; H, 4.14; N, 5.23. Found: C, 58.58; H, 4.25; N, 5.26.

3.20. Ethyl 2-chloro-5-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (47f)

Compound **47f** was prepared from compound **46f** using a similar procedure as for the preparation of compound **47b**. A solid (47%): mp 170 °C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 4.33 (2H, q, *J* = 7.2 Hz), 6.79 (1H, d, *J* = 3.2 Hz), 7.00–7.12 (2H, m), 7.39–7.48 (2H, m), 8.84 (1H, brs); Anal. Calcd for $C_{13}H_{11}$ ClFNO$_2$: C, 58.33; H, 4.14; N, 5.23. Found: C, 58.37; H, 4.17; N, 5.17.

3.21. Ethyl 5-(pyridin-2-yl)-1*H*-pyrrole-3-carboxylate (48a)

To a solution of compound **47a** (2.73 g, 9.5 mmol) in EtOH (200 mL) was added 10% palladium carbon (50% wet, 2.73 g) under N_2 atmosphere, and then the mixture was stirred at 50 °C for 2 h under hydrogen atmosphere. The reaction mixture was filtrated, concentrated under reduced pressure, and then extracted with EtOAc after added a solution of $NaHCO_3$. The extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain **48a** as a white solid (1.73 g, 84%): ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 7.13–7.15 (1H, m), 7.19–7.23 (1H, m), 7.43–7.44 (1H, m), 7.75–7.83 (2H, m), 8.51–8.54 (1H, m), 12.11 (1H, brs).

3.22. Ethyl 5-(2-methylphenyl)-1*H*-pyrrole-3-carboxylate (48b)

A solution of compound **47b** (2.07 g, 7.85 mmol) in EtOH (40 mL) was hydrogenated in the presence of 10% palladium carbon (50% wet, 0.3 g) under atmospheric pressure for 16 h. Catalyst was removed by filtration, rinsed with EtOAc, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/2) to produce compound **48b** (1.73 g, 96%) as a white solid: mp 130 °C; ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.44 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 6.72 (1H, s), 7.21–7.39 (4H, m), 7.49 (1H, d, J = 1.9 Hz), 8.56 (1H, br) ; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.99; H, 6.57; N, 6.02.

3.23. Ethyl 5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxylate (48c)

Compound **48c** was prepared from compound **47c** using a similar procedure as for the preparation of compound **48b**. A white solid (51%): mp 180°C; ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 6.81 (1H, s), 7.42–7.61 (5H, m), 8.69 (1H, br); Anal. Calcd for $C_{14}H_{12}F_3NO_2$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.08; H, 4.27; N, 4.90.

3.24. Ethyl 5-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate (48d)

Compound **48d** was prepared from compound **47d** using a similar procedure as for the preparation of compound **48b**. A pale brown solid (18%): mp 98 °C; ^{1}H-NMR ($CDCl_3$) δ 1.67 (3H, t, *J* = 7.2 Hz), 4.31 (2H, q, *J* = 7.2 Hz), 7.03–7.05 (1H, m), 7.08–7.25 (3H, m), 7.49–7.50 (1H, m), 7.58–7.66 (1H, m), 9.22 (1H, brs); Anal. Calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 66.58; H, 5.09; N, 5.93.

3.25. Ethyl 5-(3-fluorophenyl)-1*H*-pyrrole-3-carboxylate (48e)

Compound **48e** was prepared from compound **47e** using a similar procedure as for the preparation of compound **48b**. A white solid (83%): mp 139–140 °C; ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, t, *J* = 7.2 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 6.92–7.00 (2H, m), 7.15–7.50 (4H, m), 8.71 (1H, brs); Anal. Calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 66.85; H, 5.19; N, 5.90.

3.26. Ethyl 5-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (48f)

Compound **48f** was prepared from compound **47f** using a similar procedure as for the preparation of compound **48b**. A white solid (91%): mp 168 °C; ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.1 Hz), 4.31 (2H, q, *J* = 7.1 Hz), 6.83–6.86 (1H, m), 7.09 (2H, t, *J* = 8.7 Hz), 7.41–7.49 (3H, m), 8.70 (1H, brs); Anal. Calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 66.76; H, 5.17; N, 5.96.

3.27. [5-(Pyridin-2-yl)-1*H*-pyrrol-3-yl]methanol (49)

To a solution of compound **48a** (1.62 g, 7.49 mmol) in THF (30 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (15 mL, 22.5 mmol) at –50 °C, and the mixture was further stirred at 0 °C for 1 h. H_2O (3 mL) was added to the reaction mixture and the mixture was stirred at room temperature for 1 h, then filtered by using Celite and anhydrous MgSO4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–1/3) to obtain compound **49** (1.15 g, 88%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 4.61 (2H, s), 6.73–6.74 (1H, m), 6.88–6.89 (1H, m), 7.02–7.07 (1H, m), 7.50–7.54 (1H, m), 7.61–7.66 (1H, m), 8.43–8.45 (1H, m), 9.71 (1H, brs).

3.28. 5-(Pyridin-2-yl)-1*H*-pyrrole-3-carbaldehyde (50)

To a solution of **49** (0.96 g, 5.5 mmol) in MeCN (50 mL) were added tetra-*n*-propylammonium perruthenate (194 mg, 0.55 mmol), *N*-methylmorpholine *N*-oxide (2.98 g, 22.0 mmol) and molecular sieves 4 Å powder (5 g), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (100 mL), filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–1/1) to obtain **50** (270 mg, 29%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ

7.14–7.18 (2H, m), 7.52 (1H, br), 7.61–7.64 (1H, m), 7.69–7.74 (1H, m), 8.49–8.51 (1H, m), 9.85 (1H, s), 10.28 (1H, br).

3.29. Ethyl 5-(2-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxylate (51b)

To a solution of **48b** (1.52 g, 6.6 mmol) in DMF (10 mL) was added sodium hydride (60% in oil, 310 mg, 7.8 mmol) at 0 °C, the mixture was stirred at the same temperature for 10 min. 4-Methylbenzenesulfonyl chloride (1.45 g, 7.6 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 1.5 h, poured into iced H_2O and extracted with Et_2O. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to yield **51b** (2.35 g, 92%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 1.83 (3H, s), 2.40 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 6.46 (1H, s), 6.88 (1H, d, *J* = 6.6 Hz), 7.05–7.35 (7H, m), 8.10 (1H, s).

3.30. Ethyl 1-[(4-methylphenyl)sulfonyl]-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carboxylate (51c)

Compound **51c** was prepared from compound **48c** using a similar procedure as for the preparation of compound **51b**. A white solid (86%): ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.39 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 6.59 (1H, d, *J* = 1.7 Hz), 7.16 (2H, d, *J* = 8.5 Hz), 7.26 (2H, d, *J* = 8.5 Hz), 7.32–7.37 (1H, m), 7.51–7.64 (3H, m), 8.09 (1H, d, *J* = 1.9 Hz).

3.31. Ethyl 5-(2-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxylate (51d)

Compound **51d** was prepared from compound **48d** using a similar procedure as for the preparation of compound **51b**. A pale brown solid (95%): mp 64 °C; ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 2.39 (3H, s), 4.30 (2H, q, *J* = 7.2 Hz), 6.59 (1H, d, *J* = 1.8 Hz), 7.00 (1H, t, *J* = 8.7 Hz), 7.07–7.43 (7H, m), 8.07 (1H, d, *J* = 1.8 Hz).

3.32. Ethyl 5-(3-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxylate (51e)

Compound **51e** was prepared from compound **48e** using a similar procedure as for the preparation of compound **51b**. A colorless oil (94%): ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 2.38 (3H, s), 4.30 (2H, q, *J* = 7.2 Hz), 6.53 (1H, d, *J* = 1.8 Hz), 6.81–6.85 (1H, m), 6.99–7.14 (4H, m), 7.23–7.30 (3H, m), 8.06 (1H, d, *J* = 1.8 Hz).

3.33. Ethyl 5-(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carboxylate (51f)

Compound **51f** was prepared from compound **48f** using a similar procedure as for the preparation of compound **51b**. A white solid (93%): mp 108 °C; ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, *J* = 7.1 Hz), 2.38 (3H, s), 4.31 (2H, q, *J* = 7.1 Hz), 6.51 (1H, d, *J* = 1.8 Hz), 6.99 (2H, t, *J* = 8.7 Hz), 7.08–7.27 (6H, m), 8.06 (1H, d, *J* = 1.8 Hz); Anal. Calcd for $C_{20}H_{18}FNO_4S$: C, 62.00; H, 4.68; N, 3.62. Found: C, 62.05; H, 4.62; N, 3.59.

3.34. {5-(2-Methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}methanol (52b)

To a solution of **51b** (2.70 g, 7.0 mmol) in THF (30 mL) was added dropwise a 1.5 mol/L solution of diisobutylaluminum hydride in toluene (11.7 mL, 17.6 mmol) at −78 °C. The mixture was further

stirred at −78 °C for 1 h, quenched with 1 mol/L HCl (18 mL), then filtered on Celite pad and rinsed with EtOAc. The combined filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1–2/1) to yield **52b** (2.13 g, 89%) as a viscous oil: ^{1}H-NMR ($CDCl_3$) δ 1.91 (3H, s), 2.38 (3H, s), 4.58 (2H, s), 6.11 (1H, s), 6.90 (1H, t, *J* = 6.2 Hz), 7.05–7.17 (4H, m), 7.23–7.32 (4H, m), 7.43 (1H, s).

3.35. {1-[(4-Methylphenyl)sulfonyl]-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methanol (52c)

Compound **52c** was prepared from compound **51c** using a similar procedure as for the preparation of compound **52b**. A viscous oil (about 100%): ^{1}H-NMR ($CDCl_3$) δ 2.38 (3H, s), 4.58 (2H, s), 6.24 (1H, s), 7.15 (2H, d, *J* = 8.1 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 7.32–7.37 (1H, m), 7.43–7.46 (1H, m), 7.50–7.56 (2H, m), 7.59–7.66 (1H, m), 1H not detected.

3.36. {5-(2-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}methanol (52d)

Compound **52d** was prepared from compound **51d** using a similar procedure as for the preparation of compound **52b**. A pale brown solid (94%): mp 112 °C; ^{1}H-NMR ($CDCl_3$) δ 2.38 (3H, s), 4.56 (2H, d, *J* = 5.7 Hz), 6.25 (1H, d, *J* = 2.1 Hz), 6.98–7.18 (6H, m), 7.28–7.42 (4H, m).

3.37. {5-(3-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}methanol (52e)

Compound **52e** was prepared from compound **51e** using a similar procedure as for the preparation of compound **52b**. A colorless oil (82%): ^{1}H-NMR ($CDCl_3$) δ 2.37 (3H, s), 4.55 (2H, d, *J* = 5.1 Hz), 6.21 (1H, d, *J* = 1.8 Hz), 6.86–6.90 (1H, m), 7.03–7.13 (5H, m), 7.23–7.30 (3H, m), 7.40–7.41 (1H, m).

3.38. {5-(4-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}methanol (52f)

Compound **52f** was prepared from compound **51f** using a similar procedure as for the preparation of compound **52b**. A solid (99%): mp 100–101 °C; ^{1}H-NMR ($CDCl_3$) δ 2.37 (3H, s), 4.56 (2H, s), 6.18 (1H, d, *J* = 2.1 Hz), 6.99 (2H, t, *J* = 8.7 Hz), 7.08–7.27 (6H, m), 7.41 (1H, d, *J* = 0.9 Hz), 1H not detected; Anal. Calcd for $C_{18}H_{16}FNO_3S$: C, 62.59; H, 4.67; N, 4.06. Found: C, 62.59; H, 4.62; N, 3.97.

3.39. 1-(Phenylsulfonyl)-5-(pyridin-2-yl)-1*H*-pyrrole-3-carbaldehyde (53a)

To a solution of **50** (80 mg, 0.46 mmol) in THF (16 mL) was added sodium hydride (60% in oil, 56 mg, 1.40 mmol) at room temperature under N_2 atmosphere, the mixture was stirred at room temperature for 30 min. 15-Crown-5 (307 mg, 1.39 mmol) was added dropwise and the mixture was stirred at room temperature for 15 min. To this mixture was added benzenesulfonyl chloride (165 mg, 0.934 mmol), and the resulting mixture was stirred at room temperature for 1 h, poured into a solution of NaCl, and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1–1/1), and crystalized from iPr_2O to produce **53a** (85

mg, 59%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 6.86 (1H, d, *J* = 1.8 Hz), 7.25–7.29 (1H, m), 7.50–7.55 (3H, m), 7.61–7.67 (1H, m), 7.70–7.76 (1H, m), 7.83–7.87 (2H, m), 8.17 (1H, d, *J* = 1.8 Hz), 8.43–8.46 (1H, m), 9.90 (1H, s).

3.40. 5-(2-Methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carbaldehyde (53b)

To a solution of **52b** (2.12 g, 6.21 mmol) in MeCN (12 mL) were added tetra-*n*-propylammonium perruthenate (0.16 g, 0.46 mmol), *N*-methylmorpholine *N*-oxide (1.00 g, 8.54 mmol) and molecular sieves 4 Å powder (1.85 g), and the mixture was stirred at room temperature for 1 h, diluted with EtOAc and filtered through Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–3/1) to obtain **53b** (1.58 g, 75%) as a solid: mp 103–104 °C; ^{1}H-NMR ($CDCl_3$) δ 1.80 (3H, s), 2.41 (3H, s), 6.50 (1H, s), 6.90 (1H, d, *J* = 6.2 Hz), 7.07–7.35 (7H, m), 8.12 (1H, s), 9.89 (1H, s); Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.41; H, 5.12; N, 3.97.

3.41. 1-[(4-Methylphenyl)sulfonyl]-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (53c)

Compound **53c** was prepared from compound **52c** using a similar procedure as for the preparation of compound **53b**. A white solid (72%): ^{1}H-NMR ($CDCl_3$) δ 2.40 (3H, s), 6.63 (1H, d, *J* = 1.7 Hz), 7.16 (2H, d, *J* = 8.3 Hz), 7.25 (2H, d, *J* = 8.3 Hz), 7.36–7.42 (1H, m), 7.53–7.64 (3H, m), 8.12 (1H, d, *J* = 1.9 Hz), 9.88 (1H, s).

3.42. 5-(2-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carbaldehyde (53d)

Compound **53d** was prepared from compound **52d** using a similar procedure as for the preparation of compound **53b**. A white solid (73%): mp 147–148 °C; ^{1}H-NMR ($CDCl_3$) δ 2.40 (3H, s), 6.62 (1H, d, *J* = 1.8 Hz), 7.00 (1H, t, *J* = 9.0 Hz), 7.11–7.45 (7H, m), 8.10 (1H, d, *J* = 2.1 Hz), 9.86 (1H, s); Anal. Calcd for $C_{18}H_{14}FNO_3S$: C, 62.96; H, 4.11; N, 4.08. Found: C, 62.91; H, 4.09; N, 3.99.

3.43. 5-(3-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carbaldehyde (53e)

Compound **53e** was prepared from compound **52e** using a similar procedure as for the preparation of compound **53b**. A brown oil (82%): ^{1}H-NMR ($CDCl_3$) δ 2.39 (3H, s), 6.57 (1H, d, *J* = 1.8 Hz), 6.79–6.85 (1H, m), 6.98–7.34 (7H, m), 8.11 (1H, d, *J* = 1.8 Hz), 9.88 (1H, s).

3.44. 5-(4-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-3-carbaldehyde (53f)

Compound **53f** was prepared from compound **52f** using a similar procedure as for the preparation of compound **53b**. A solid (78%): mp 121–122 °C; ^{1}H-NMR ($CDCl_3$) δ 2.39 (3H, s), 6.54 (1H, d, *J* = 2.1 Hz), 7.00 (2H, t, *J* = 8.4 Hz), 7.09–7.27 (6H, m), 8.10 (1H, d, *J* = 1.8 Hz), 9.87 (1H, s); Anal. Calcd for $C_{18}H_{14}FNO_3S$: C, 62.96; H, 4.11; N, 4.08. Found: C, 62.75; H, 4.18; N, 4.00.

3.45. *N*-Methyl-1-[1-(phenylsulfonyl)-5-(pyridin-2-yl)-1*H*-pyrrol-3-yl]methanamine oxalate (54a)

To a solution of **53a** (78 mg, 0.25 mmol) in MeOH (10 mL) was added 40% methylamine methanol solution (100 mg, 1.28 mmol) at room temperature. After stirred for 10 min, sodium borohydride (29

mg, 0.77 mmol) was added at room temperature, and the reaction mixture was stirred for 1 h and then quenched with 1 mol/L HCl (20 mL). After stirred for 10 min, the mixture was basified with a solution of $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (EtOAc/MeOH = 1/0–7/3) and dissolved in EtOAc (10 mL). Oxalic acid (50 mg) was added, and the mixture was stirred for 15 min. The resulting crystals were collected by filtration to obtain **54a** (47 mg, 45%) as colorless crystals: mp 146–148 °C; ^{1}H-NMR (DMSO-d_6) δ 2.55 (3H, s), 4.02 (2H, s), 6.70 (1H, d, J = 1.8 Hz), 7.33–7.38 (1H, m), 7.51–7.54 (1H, m), 7.63–7.68 (2H, m), 7.74–7.91 (5H, m), 8.44–8.46 (1H, m), 3H not detected; HRMS (ESI) calcd for $C_{17}H_{17}N_3O_2S$ $(M+H)^+$ m/z 328.1114, found m/z 328.1085.

3.46. *N*-Methyl-1-{5-(2-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl} methanamine hydrochloride (54b)

To a solution of **53b** (0.46 g, 1.36 mmol) was added methylamine hydrochloride (1.11 g, 13.6 mmol) and sodium cyano borohydride (0.26 g, 4.14 mmol), and the mixture was stirred at room temperature for 20 h and then concentrated under reduced pressure. A solution of $NaHCO_3$ was added, and then the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/MeOH = 1/0–5/1) and dissolved in EtOAc (5 mL). 4 mol/L HCl/EtOAc (2 mL) was added, and the mixture was concentrated in vacuo. The residue was crystalized from *n*-hexane/EtOAc to produce **54b** (0.37 g, 70%) as colorless crystals: mp 192–193 °C; ^{1}H-NMR (DMSO-d_6) δ 1.79 (3H, s), 2.38 (3H, s), 3.32 (3H, s), 4.00 (2H, s), 6.34 (1H, d, J = 1.8 Hz), 6.84 (1H, d, J = 6.2 Hz), 7.11–7.21 (2H, m), 7.25–7.36 (6H, m), 7.72 (1H, s), 9.02 (1H, br); Anal. Calcd for $C_{20}H_{23}ClN_2O_2S$: C, 61.45; H, 5.93; N, 7.17. Found: C, 61.23; H, 5.96; N, 7.22.

3.47. *N*-Methyl-1-{1-[(4-methylphenyl)sulfonyl]-5-[2-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl} methanamine hydrochloride (54c)

Compound **54c** was prepared from compound **53c** using a similar procedure as for the preparation of compound **54b**. White crystals (35%): mp 195–196 °C; ^{1}H-NMR (DMSO-d_6) δ 2.39 (3H, s), 2.50 (3H, s), 3.32 (2H, s), 6.43 (1H, s), 7.12 (1H, d, J = 6.8 Hz), 7.37 (4H, s), 7.63–7.79 (4H, m), 8.92 (2H, br); Anal. Calcd for $C_{20}H_{20}ClF_3N_2O_2S$: C, 53.99; H, 4.53; N, 6.30. Found: C, 53.91; H, 4.55; N, 6.24.

3.48. 1-{5-(2-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (54d)

Compound **54d** was prepared from compound **53d** using a similar procedure as for the preparation of compound **54b**. White crystals (76%): mp 172 °C; ^{1}H-NMR (DMSO-d_6) δ 2.37 (3H, s), 3.32 (3H, s), 3.97 (2H, s), 6.48 (1H, d, J = 1.8 Hz), 7.02–7.08 (1H, m), 7.18–7.34 (6H, m), 7.47–7.55 (1H, m), 7.74 (1H, d, J = 1.8 Hz), 9.01 (2H, brs); Anal. Calcd for $C_{19}H_{20}ClFN_2O_2S$: C, 57.79; H, 5.10; N, 7.09.

Found: C, 57.57; H, 5.21; N, 6.79.

3.49. 1-{5-(3-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (54e)

Compound **54e** was prepared from compound **53e** using a similar procedure as for the preparation of compound **54b**. White crystals (69%): mp 164–165 °C; ^{1}H-NMR (DMSO-d_6) δ 2.36 (3H, s), 3.32 (3H, s), 3.98 (2H, s), 6.48 (1H, d, J = 1.8 Hz), 6.94–7.00 (2H, m), 7.25–7.45 (6H, m), 7.73 (1H, d, J = 1.8 Hz), 8.94 (2H, brs); Anal. Calcd for $C_{19}H_{20}ClFN_2O_2S$: C, 57.79; H, 5.10; N, 7.09. Found: C, 57.82; H, 5.20; N, 6.87.

3.50. 1-{5-(4-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (54f)

Compound **54f** was prepared from compound **53f** using a similar procedure as for the preparation of compound **54b**. White crystals (71%): mp 224 °C; ^{1}H-NMR (DMSO-d_6) δ 2.36 (3H, s), 2.51 (3H, s), 3.97 (2H, s), 6.43 (1H, d, J = 1.8 Hz), 7.16–7.36 (8H, m), 7.71 (1H, s), 9.05 (1H, brs), 1H not detected; Anal. Calcd for $C_{19}H_{20}ClFN_2O_2S$: C, 57.79; H, 5.10; N, 7.09. Found: C, 57.57; H, 5.09; N, 6.97.

3.51. tert-Butyl ({5-bromo-1-[(3-fluorophenyl)sulfonyl]-1*H*-pyrrol-3-yl}methyl) methylcarbamate (56a)

Sodium hydride (60% in oil, 440 mg, 11.0 mmol) was washed twice with *n*-hexane, and suspended in THF (20 mL). To this suspension was added dropwise a solution of *tert*-butyl [(5-bromo-1*H*-pyrrol-3-yl)methyl]methylcarbamate **55** in THF (10 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min. 15-Crown-5 (2,45 g, 11.1 mmol) was added, and then a solution of 3-fluorobenzenesulfonyl chloride (1.96 g, 10.1 mmol) in THF (5 mL) were added dropwise at the same temperature, and the resulting mixture was stirred at room temperature for 1 h, then diluted with H_2O and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5/1) to produce **56a** (3.62 g, 91%) as a brown oil: ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.80 (3H, brs), 4.18 (2H, brs), 6.27 (1H, brs), 7.33–7.38 (2H, m), 7.48–7.64 (2H, m), 7.71–7.74 (1H, m).

3.52. *tert*-Butyl ({5-bromo-1-[(3-methoxyphenyl)sulfonyl]-1*H*-pyrrol-3-yl}methyl) methylcarbamate (56b)

Compound **56b** was prepared from compound **55** using a similar procedure as for the preparation of compound **56a**. A brown oil (96%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.79 (3H, brs), 3.85 (3H, s), 4.17 (2H, brs), 6.24 (1H, brs), 7.13–7.17 (1H, m), 7.33 (1H, brs), 7.40–7.50 (3H, m).

3.53. *tert*-Butyl {[5-bromo-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (56h)

Compound **56h** was prepared from compound **55** using a similar procedure as for the preparation of

compound **56a**. Colorless crystals (68%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.80 (3H, brs), 4.18 (2H, brs), 6.28 (1H, brs), 7.35 (1H, brs), 7.48–7.52 (1H, m), 8.18–8.22 (1H, m), 8.85–8.88 (1H, m), 9.12–9.13 (1H, m).

3.54. *tert*-Butyl ({1-[(3-fluorophenyl)sulfonyl]-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl}methyl) methylcarbamate (57a)

A suspension of compound **56a** (455 mg, 1.02 mmol), (2-fluoropyridin-3-yl)boronic acid (173 mg, 1.23 mmol), tetrakis(triphenylphosphine)palladium (178 mg, 0.154 mmol) and Na_2CO_3 (258 mg, 2.43 mmol) in DME (10 mL) and water (5 mL) was stirred at 105 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with H_2O, and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/1) to obtain **57a** (214 mg, 45%) as a pale yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.83 (3H, s), 4.24 (2H, brs), 6.28 (1H, s), 7.10–7.14 (1H, m), 7.19–7.33 (4H, m), 7.37–7.44 (1H, m), 7.71–7.77 (1H, m), 8.25–8.27 (1H, m).

3.55. *tert*-Butyl ({5-(2-fluoropyridin-3-yl)-1-[(3-methoxyphenyl)sulfonyl]-1*H*-pyrrol-3-yl} methyl)methylcarbamate (57b)

Compound **57b** was prepared from compound **56b** using a similar procedure as for the preparation of compound **57a**. A pale-yellow oil (64%): ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.81 (3H, s), 3.74 (3H, s), 4.23 (2H, br), 6.26 (1H, brs), 6.85–6.87 (1H, m), 6.99–7.09 (2H, m), 7.20–7.40 (3H, m), 7.70–7.79 (1H, m), 8.22–8.23 (1H, m).

3.56. *tert*-Butyl {[5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (57h)

Compound **57h** was prepared from compound **56h** using a similar procedure as for the preparation of compound **57a**. A pale-yellow oil (69%): ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.82 (3H, s), 4.23 (2H, brs), 6.29 (1H, brs), 7.23–7.27 (1H, m), 7.34–7.39 (2H, m), 7.66–7.73 (2H, m), 8.25–8.27 (1H, m), 8.66 (1H, d, J = 2.4 Hz), 8.78–8.80 (1H, m).

3.57. *tert*-Butyl {[5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (58)

To a solution of compound **57h** (4.78 g, 10.7 mmol) in THF (20 mL) and MeOH (10 mL) was added 8 mol/L NaOH (4 mL) under ice cooling, and the mixture stirred at room temperature for 4h. After evaporated to about half volume of the solvent under reduced pressure, H_2O was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 19/1–0/1) to obtain **58** (2.84 g, 87%) as a pale-yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.50 (9H, s), 2.84 (3H, brs), 4.30 (2H, brs), 6.63 (1H, brs), 6.84 (1H, brs), 7.17–7.22 (1H, m), 7.93–8.01 (2H, m), 8.95 (1H, brs).

**3.58. *tert*-Butyl ({1-[(3-cyanophenyl)sulfonyl]-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl}methyl)

methylcarbamate (57c)

Compound **57c** was prepared from **58** using a similar procedure as for the preparation of compound **56a** from **55**. **A** colorless oil (95%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.84 (3H, s), 4.25 (2H, brs), 6.30 (1H, brs), 7.25–7.33 (2H, m), 7.54–7.63 (2H, m), 7.66–7.77 (2H, m), 7.83–7.86 (1H, m), 8.27–8.29 (1H, m).

3.59. *tert*-Butyl {[5-(2-fluoropyridin-3-yl)-1-(thiophen-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (57d)

Compound **57d** was prepared from **58** using a similar procedure as for the preparation of compound **56a** from **55**. A pale-yellow oil (94%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.83 (3H, s), 4.24 (2H, brs), 6.28 (1H, brs), 6.97–6.99 (1H, m), 7.20–7.26 (1H, m), 7.32–7.35 (2H, m), 7.58–7.60 (1H, m), 7.72–7.77 (1H, m), 8,22–8.24 (1H, m).

3.60. *tert*-Butyl {[5-(2-fluoropyridin-3-yl)-1-(furan-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (57f)

Compound **57f** was prepared from **58** using a similar procedure as for the preparation of compound **56a** from **55**. A pale yellow oil (73%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.84 (3H, s), 4.25 (2H, brs), 6.31 (1H, s), 6.35 (1H, d, J = 1.1 Hz), 7.21–7.26 (1H, m), 7.28(1H, d, J = 1.9 Hz), 7.41 (1H, t, J = 1.7 Hz), 7.59 (1H, dd, J = 1.5 Hz, 0.8 Hz), 7.78 (1H, t, J = 9.1 Hz), 8.25 (1H, d, J = 4.9 Hz).

3.61. *tert*-Butyl {[5-(2-fluoropyridin-3-yl)-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (20i)

Compound **57i** was prepared from **58** using a similar procedure as for the preparation of compound **56a** from **55**. A colorless oil (65%): ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.82 (3H, s), 4.24 (2H, brs), 6.28 (1H, s), 7.18–7.30 (1H, m), 7.39–7.43 (1H, m), 7.46–7.54 (1H, m), 7.63 (1H, d, J = 7.9 Hz), 7.76–7.88 (2H, m), 8.19–8.26 (1H, m), 8.60–8.65 (1H, m).

3.62. *tert*-Butyl ({5-(2-fluoropyridin-3-yl)-1-[(6-methoxypyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl} methyl)methylcarbamate (57j)

Compound **57j** was prepared from **58** using a similar procedure as for the preparation of compound **56a** from **55**. A colorless oil (80%): ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.82 (3H, brs), 3.97 (3H, s), 4.23 (2H, brs), 6.27 (1H, s), 6.68–6.71 (1H, m), 7.23–7.33 (2H, m), 7.49–7.52 (1H, m), 7.74–7.79 (1H, m), 8.20–8.22 (1H, m), 8.24–8.26 (1H, m).

3.63. 5-(2-Fluoropyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (59)

Compound **59** was prepared from **44** using a similar procedure as for the preparation of compound **58** from **57h**. A pale brown solid (79%): ^{1}H-NMR (DMSO-d_6) δ 6.99 (1H, d, J = 1.5 Hz), 7.43–7.48 (1H, m), 7.88 (1H, s), 8.12–8.15 (1H, m), 8.27–8.34 (1H, m), 9.77 (1H, s), 12.28 (1H, brs).

3.64. 5-(2-Fluoropyridin-3-yl)-1-(thiophen-2-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (60e)

Compound **60e** was prepared from **59** using a similar procedure as for the preparation of compound **53a** from **50**. A white solid (48%): ^{1}H-NMR ($CDCl_3$) δ 6.74 (1H, d, J = 1.9 Hz), 7.04 (1H, dd, J =

4.9 Hz, 3.8 Hz), 7.27–7.31 (2H, m), 7.72 (1H, dd, *J* = 4.9 Hz, 1.5 Hz), 7.77–7.83 (1H, m), 8.09 (1H, d, *J* = 1.5 Hz), 8.30–8.33 (1H, m), 9.89 (1H, s).

3.65. 5-(2-Fluoropyridin-3-yl)-1-(furan-2-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (60g)

Compound **60g** was prepared from **59** using a similar procedure as for the preparation of compound **53a** from **50**. A white solid (83%): ^{1}H-NMR ($CDCl_3$) δ 6.51 (1H, dd, *J* = 3.7 Hz, 1.8 Hz), 6.76 (1H, d, *J* = 1.9 Hz), 6.84 (1H, dd, *J* = 3.7 Hz, 0.7 Hz), 7.26–7.30 (1H, m), 7.60 (1H, dd, *J* = 1.7 Hz, 1.0 Hz), 7.76–7.82 (1H, m), 8.10 (1H, d, *J* = 1.7 Hz), 8.30–8.33 (1H, m), 9.90 (1H, s).

3.66. 1-{1-[(3-Fluorophenyl)sulfonyl]-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (61a)

Compound **61a** was prepared from **57a** using a similar procedure as for the preparation of compound **40d** from **41d**. Colorless crystals (54%): mp 211–212 °C; ^{1}H-NMR (DMSO-d_6) δ 2.51 (3H, s), 3.99 (2H, s), 6.67 (1H, d, *J* = 1.8 Hz), 7.33–7.36 (2H, m), 7.41–7.46 (1H, m), 7.65–7.76 (3H, m), 7.87 (1H, d, *J* = 1.8 Hz), 8.34–8.36 (1H, m), 9.18 (2H, brs); Anal. Calcd for $C_{17}H_{16}ClF_2N_3O_2S$: C, 51.07; H, 4.03; N, 10.51. Found: C, 51.01; H, 4.04; N, 10.46.

3.67. 1-{5-(2-Fluoropyridin-3-yl)-1-[(3-methoxyphenyl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine fumarate (61b)

To a solution of compound **57b** (303 mg, 0.637 mmol) in EtOAc (1 mL) and MeOH (1 mL) was added dropwise 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by a solution of $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 1/1–1/9), and then dissolved in EtOAc (2 mL). A solution of fumaric acid (46 mg) in MeOH (2 mL) was added to the solution, and then the mixture was concentrated under reduced pressure. The residue was recrystallized from EtOH/H_2O (9/1) to produce **61b** (138 mg, 44%) as colorless crystals: mp 177 °C; ^{1}H-NMR (DMSO-d_6) δ 2.40 (3H, s), 3.75 (3H, s), 3.82 (2H, s), 6.47 (2H, s), 6.53 (1H, d, *J* = 1.5 Hz), 6.86–6.88 (1H, m), 7.05–7.08 (1H, m), 7.27–7.31 (1H, m), 7.38–7.51 (2H, m), 7.69–7.75 (2H, m), 8.31–8.32 (1H, m), 3H not detected; Anal. Calcd for $C_{22}H_{22}FN_3O_7S$: C, 53.76; H, 4.51; N, 8.55. Found: C, 53.61; H, 4.53; N, 8.58.

3.68. 3-({2-(2-Fluoropyridin-3-yl)-4-[(methylamino)methyl]-1*H*-pyrrol-1-yl}sulfonyl) benzonitrile fumarate (61c)

Compound **61c** was prepared from **57c** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (44%): mp 149 °C; ^{1}H-NMR (DMSO-d_6) δ 2.40 (3H, s), 3.82 (2H, s), 6.47 (2H, s), 6.57 (1H, d, *J* = 1.8 Hz), 7.39–7.44 (1H, m), 7.71–7.81 (4H, m), 7.95–7.96 (1H, m), 8.21–8.24 (1H, m), 8.32–8.34 (1H, m), 3H not detected; Anal. Calcd for $C_{22}H_{19}FN_4O_6S$: C, 54.32; H, 3.94; N, 11.52. Found: C, 54.25; H, 4.01; N, 11.52.

3.69. 1-[5-(2-Fluoropyridin-3-yl)-1-(thiophen-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-

methylmethanamine fumarate (61d)

Compound **61d** was prepared from **57d** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (63%): mp 173–175 °C; ^{1}H-NMR (DMSO-d_6) δ 2.41 (3H, s), 3.81 (2H, s), 6.48 (2H, s), 6.53 (1H, d, *J* = 1.8 Hz), 7.08–7.10 (1H, m), 7.38–7.42 (1H, m), 7.64–7.79 (3H, m), 8.08–8.10 (1H, m), 8.30–8.32 (1H, m), 3H not detected; Anal. Calcd for $C_{19}H_{18}FN_3O_6S_2$: C, 48.81; H, 3.88; N, 8.99. Found: C, 48.87; H, 3.90; N, 8.95.

3.70. 1-[5-(2-Fluoropyridin-3-yl)-1-(thiophen-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (61e)

Compound **61e** was prepared from **60e** using a similar procedure as for the preparation of compound **40c** from **44**. Colorless crystals (75%): mp 204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.40 (3H, s), 3.80 (2H, s), 6.48 (2H, s), 6.55 (1H, d, *J* = 1.5 Hz), 7.18 (1H, dd, *J* = 4.9 Hz, 4.2 Hz), 7.40–7.45 (1H, m), 7.47 (1H, dd, *J* = 4.0 Hz, 1.3 Hz), 7.62 (1H, d, *J* = 1.5 Hz), 7.75–7.82 (1H, m), 8.11 (1H, dd, *J* = 5.1 Hz, 1.3 Hz), 8.31–8.33 (1H, m), 3H not detected; Anal. Calcd for $C_{19}H_{18}FN_3O_6S_2$: C, 48.81; H, 3.88; N, 8.99. Found: C, 48.88; H, 4.09; N, 9.06.

3.71. 1-[5-(2-Fluoropyridin-3-yl)-1-(furan-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (61f)

To a solution of compound **57f** (253 mg, 0.581 mmol) in EtOAc (3 mL) and *i*PrOH (2 mL) was added dropwise 4 mol/L HCl/EtOAc (6 mL), and the mixture was stirred at room temperature for 2.5 h, and then concentrated in vacuo. The residue was recrystallized from EtOAc/EtOH (1/1) to obtain **61f** (134 mg, 62%) as colorless crystals: mp 205 °C; ^{1}H-NMR (DMSO-d_6) δ 2.53 (3H, s), 4.00 (2H, s), 6.63–6.67 (2H, m), 7.43 (1H, ddd, *J*=7.1 Hz, 5.0 Hz, 1.9 Hz), 7.75 (1H, d, *J* = 1.9 Hz), 7.80 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 1.9 Hz), 7.94 (1H, t, *J* = 1.9 Hz), 8.27–8.30 (1H, m), 8.31–8.37 (1H, m), 9.03 (2H, brs); Anal. Calcd for $C_{15}H_{15}ClFN_3O_3S$: C, 48.45; H, 4.07; N, 11.30. Found: C, 48.48; H, 4.04; N, 11.34.

3.72. 1-[5-(2-Fluoropyridin-3-yl)-1-(furan-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (61g)

Compound **61g** was prepared from **60g** using a similar procedure as for the preparation of compound **40c** from **44**. Colorless crystals (66%): mp 197 °C; ^{1}H-NMR (DMSO-d_6) δ 2.41 (3H, s), 3.81 (2H, s), 6.48 (2H, s), 6.58 (1H, d, *J* = 1.9 Hz), 6.72 (1H, dd, *J* = 3.7 Hz, 1.8 Hz), 7.10 (1H, dd, *J* = 3.7 Hz, 0.8 Hz), 7.40–7.44 (1H, m), 7.57 (1H, d, *J* = 1.8 Hz), 7.78–7.84 (1H, m), 8.07 (1H, dd, *J* = 1.8 Hz, 0.8 Hz), 8.30–8.33 (1H, m), 3H not detected; Anal. Calcd for $C_{19}H_{18}FN_3O_7S$: C, 50.55; H, 4.02; N, 9.31. Found: C, 50.65; H, 4.15; N, 9.48.

3.73. 1-[5-(2-Fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (61h)

Compound **61h** was prepared from **57h** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (29%): mp 183–184 °C; ^{1}H-NMR (DMSO-d_6) δ 2.39

(3H, s), 3.78 (2H, s), 6.48 (2H, s), 6.56 (1H, d, J = 1.8 Hz), 7.40–7.44 (1H, m), 7.61–7.65 (1H, m), 7.72–7.79 (2H, m), 7.89–7.93 (1H, m), 8.32–8.34 (1H, m), 8.62 (1H, d, J = 1.8 Hz), 8.88–8.90 (1H, m), 3H not detected; Anal. Calcd for $C_{20}H_{19}FN_4O_6S$: C, 51.94; H, 4.14; N, 12.12. Found: C, 51.92; H, 4.23; N, 12.04.

3.74. 1-[5-(2-Fluoropyridin-3-yl)-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (61i)

Compound **61i** was prepared from **57i** using a similar procedure as for the preparation of compound **40d** from **41d**. Colorless crystals (15%): mp 198 °C; ^{1}H-NMR (DMSO-d_6) δ 2.53 (3H, s), 3.34 (2H, s), 6.64 (1H, d, J = 1.3 Hz), 7.38 (1H, ddd, J = 7.2 Hz, 5.0 Hz, 1.9 Hz), 7.61–7.88 (4H, m), 8.10 (1H, dt, J = 7.8 Hz, 1.7 Hz), 8.24–8.38 (1H, m), 8.71 (1H, dt, J = 3.9 Hz, 0.8 Hz), 8.93 (2H, brs); HRMS (ESI) calcd for $C_{16}H_{15}FN_4O_2S$ $(M+H)^+$ m/z 347.0973, found m/z 347.0936.

3.75. 1-{5-(2-fluoropyridin-3-yl)-1-[(6-methoxypyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (61j)

Compound **61j** was prepared from **57j** using a similar procedure as for the preparation of compound **40d** from **41d**. Colorless crystals (29%): mp 223–225 °C; ^{1}H-NMR (DMSO-d_6) δ 2.52 (3H, s), 3.94 (3H, s), 3.99 (2H, s), 6.65 (1H, d, J = 1.8 Hz), 6.99–7.02 (1H, m), 7.42–7.47 (1H, m), 7.73–7.80 (2H, m), 7.84 (1H, d, J = 1.8 Hz), 8.27–8.28 (1H, m), 8.34–8.36 (1H, m), 9.10 (2H, brs). Anal. Calcd for $C_{17}H_{18}ClFN_4O_3S$: C, 49.45; H, 4.39; N, 13.57. Found: C, 49.16; H, 4.42; N, 13.44.

3.76. *tert*-Butyl {[5-(2-chloropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (62a)

Compound **62a** was prepared from **56h** using a similar procedure as for the preparation of compound **57a** from **56a**. A pale-yellow oil (42%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.84 (3H, brs), 4.26 (2H, brs), 6.29 (1H, brs), 7.29–7.38 (3H, m), 7.63–7.72 (2H, m), 8.43–8.45 (1H, m), 8.66 (1H, d, J = 2.4 Hz), 8.78–8.80 (1H, m).

3.77. *tert*-Butyl {[5-(2-cyanopyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl} methylcarbamate (62b)

Compound **62b** was prepared from **62a** using a similar procedure as for the preparation of compound **41e** from **41d**. A pale-yellow oil (57%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.83 (3H, brs), 4.27 (2H, brs), 6.48 (1H, brs), 7.38–7.43 (2H, m), 7.55–7.67 (2H, m), 7.93 (1H, d, J = 7.5 Hz), 8.60–8.61 (1H, m), 8.71–8.73 (1H, m), 8.81–8.83 (1H, m).

3.78. *tert*-Butyl methyl{[5-(2-methylpyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}carbamate (62c)

Compound **62c** was prepared from **56h** by use of (2-methylpyridin-3-yl)boronic acid following a similar procedure as for the preparation of compound **57a** from **56a**. A brownish oil (22%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.09 (3H, s), 2.85 (3H, s), 4.27 (2H, brs), 6.14 (1H, brs), 7.10–7.14 (1H, m), 7.26–7.38 (3H, m), 7.56–7.60 (1H, m), 8.54–8.56 (1H, m), 8.60–8.61 (1H, m), 8.78–8.80 (1H, m).

3.79. *tert*-Butyl methyl{[5-(4-methylpyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}carbamate (62d)

Compound **62d** was prepared from **56h** by use of (4-methylpyridin-3-yl)boronic acid following a similar procedure as for the preparation of compound **57a** from **56a**. A colorless oil (52%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.11 (3H, s), 2.85 (3H, s), 4.27 (2H, s), 6.15 (1H, s), 7.18 (1H, d, *J* = 4.9 Hz), 7.34–7.39 (2H, m), 7.58–7.62 (1H, m), 7.94 (1H, s), 8.49 (1H, d, *J* = 5.3 Hz), 8.64 (1H, d, *J* = 2.3 Hz), 8.80 (1H, dd, *J* = 4.9 Hz, 1.5 Hz).

3.80. *tert*-Butyl methyl{[5-(3-methylpyridin-2-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}carbamate (62e)

A degassed mixture of the compound **56h** (563 mg, 1.31 mmol), 3-methyl-2-(tributylstannanyl)pyridine (1.0 g, 2.62 mmol), and tetrakis(triphenylphosphine)palladium (454 mg, 0.39 mmol) in toluene was stirred at 120 °C for 30 h under Ar atmosphere. After cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1) to obtain compound **62e** (129 mg, 22%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 1.45 (9H, s), 2.26 (3H, s), 2.80 (3H, brs), 4.25 (2H, brs), 6.26 (1H, brs), 7.23–7.27 (2H, m), 7.39–7.44 (1H, m), 7.60 (1H, d, *J* = 6.9 Hz), 7.99–8.03 (1H, m), 8.36 (1H, d, *J* = 4.5 Hz), 8.78–8.80 (1H, m), 8.86–8.87 (1H, m).

3.81. 1-[5-(2-Chloropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (63a)

To a solution of compound **62a** (280 mg, 0.605 mmol) in MeOH (10 mL) was added dropwise 4 mol/L HCl/EtOAc (2 mL), and the mixture was stirred at 70 °C for 30 min, and then concentrated in vacuo. A solution of $NaHCO_3$ was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL), and a solution of fumaric acid (116 mg, 1.0 mmol) in MeOH (3 mL) was added dropwise to the solution. The resulting crystals were collected by filtration and rinsed with EtOAc to obtain **63a** (197 mg, 68%) as colorless crystals: mp 170–174 °C; ^{1}H-NMR (DMSO-d_6) δ 2.40 (3H, s), 3.81 (2H, s), 6.49 (2H, s), 6.52 (1H, d, *J* = 1.9 Hz), 7.47–7.52 (1H, m), 7.61–7.73 (3H, m), 7.90–7.94 (1H, m), 8.50 (1H, dd, *J* = 4.9 Hz, 1.9 Hz), 8.63–8.64 (1H, m), 8.90 (1H, dd, *J* = 4.5 Hz, 1.5 Hz), 3H not detected. Anal. Calcd for $C_{20}H_{19}ClN_4O_6S$: C, 50.16; H, 4.00; N, 11.70. Found: C, 49.98; H, 4.06; N, 11.63.

3.82. 3-{4-[(Methylamino)methyl]-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-2-yl}pyridine-2-carbonitrile fumarate (63b)

Compound **63b** was prepared from **62b** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (39%): mp 204–205 °C; ^{1}H-NMR (DMSO-d_6) δ 2.39 (3H, s), 3.83 (2H, s), 6.48 (2H, s), 6.74 (1H, d, *J* = 1.8 Hz), 7.60–7.65 (1H, m), 7.78–7.83 (2H, m), 7.88–7.95 (2H, m), 8.58–8.59 (1H, m), 8.80–8.82 (1H, m), 8.89–8.91 (1H, m), 3H not detected.

Anal. Calcd for $C_{21}H_{19}N_5O_6S$: C, 53.73; H, 4.08; N, 14.92. Found: C, 53.54; H, 4.03; N, 14.92.

3.83. *N*-Methyl-1-[5-(2-methylpyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methanamine fumarate (63c)

Compound **63c** was prepared from **62c** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (32%): mp 203–204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.00 (3H, s), 2.43 (3H, s), 3.83 (2H, s), 6.42 (1H, s), 6.47 (2H, s), 7.20–7.24 (1H, m), 7.28–7.31 (1H, m), 7.59–7.63 (1H, m), 7.70 (1H, s), 7.80–7.84 (1H, m), 8.49–8.51 (2H, m), 8.88–8.90 (1H, m), 3H not detected. Anal. Calcd for $C_{21}H_{22}N_4O_6S$: C, 55.01; H, 4.84; N, 12.22. Found: C, 54.94; H, 4.90; N, 12.25.

3.84. *N*-Methyl-1-[5-(4-methylpyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methanamine fumarate (63d)

Compound **63d** was prepared from **62d** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (48%): mp 184 °C; ^{1}H-NMR (DMSO-d_6) δ 1.89 (3H, s), 2.43 (3H, s), 3.84 (2H, s), 6.45 (1H, d, J = 1.9 Hz), 6.48 (2H, s), 7.29 (1H, d, J = 4.9 Hz), 7.60–7.65 (1H, m), 7.73 (1H, d, J = 1.9 Hz), 7.81–7.85 (1H, m), 7.98 (1H, s), 8.47 (1H, d, J = 4.9 Hz), 8.51 (1H, d, J = 1.9 Hz), 8.90 (1H, dd, J = 4.9 Hz, 1.5 Hz), 3H not detected. Anal. Calcd for $C_{21}H_{22}N_4O_6S$: C, 55.01; H, 4.84; N, 12.22. Found: C, 54.73; H, 4.79; N, 12.16.

3.85. *N*-Methyl-1-[5-(3-methylpyridin-2-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methanamine fumarate (63e)

Compound **63e** was prepared from **62e** using a similar procedure as for the preparation of compound **61b** from **57b**. Colorless crystals (53%): mp 185–186 °C; ^{1}H-NMR (DMSO-d_6) δ 2.18 (3H, s), 2.44 (3H, s), 3.86 (2H, s), 6.46 (2H, s), 6.52 (1H, d, J = 1.8 Hz), 7.32–7.36 (1H, m), 7.66–7.74 (3H, m), 8.17–8.21 (1H, m), 8.28–8.30 (1H, m), 8.87–8.90 (2H, m), 3H not detected; Anal. Calcd for $C_{21}H_{22}N_4O_6S$: C, 55.01; H, 4.84; N, 12.22. Found: C, 54.95; H, 4.82; N, 12.24.

3.86. 1-[5-(3-Fluoropyridin-4-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (63f)

A degassed mixture of compound **56h** (215 mg, 0.50 mmol), (3-fluoropyridin-4-yl)boronic acid (120 mg, 0.76 mmol), tetrakis(triphenylphosphine)palladium (87 mg, 0.075 mmol) and $NaHCO_3$ (126 mg, 1.50 mmol) in DME (8 mL) and water (2 mL) was stirred at 80 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with a solution of $NaHCO_3$, and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 1/1), and then the obtained a pale-yellow oil (60 mg) was dissolved in MeOH (5 mL). 4 mol/L HCl/EtOAc (1.5 mL) was added to the solution, and the mixture was stirred at 70 °C for 30 min, and then concentrated in vacuo. A solution of $NaHCO_3$ was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in EtOAc (5 mL), and a solution of

fumaric acid (19 mg, 0.164 mmol) in MeOH (1 mL) was added to the solution. The resulting crystals were collected by filtration and rinsed with EtOAc to obtain **63f** (45 mg, 19%) as colorless crystals: mp 201 °C; ^{1}H-NMR (DMSO-d_6) δ 2.37 (3H, s), 3.78 (2H, s), 6.49 (2H, s), 6.64 (1H, d, J = 1.5 Hz), 7.30–7.33 (1H, m), 7.62–7.66 (1H, m), 7.77 (1H, d, J = 1.5 Hz), 7.94–7.98 (1H, m), 8.49–8.51 (1H, m), 8.64 (1H, d, J = 1.5 Hz), 8.69 (1H, d, J = 2.3 Hz), 8.90 (1H, dd, J = 4.9 Hz, 1.5 Hz), 3H not detected. Anal. Calcd for $C_{20}H_{19}FN_4O_6S$: C, 51.94; H, 4.14; N, 12.12. Found: C, 51.73; H, 4.13; N, 12.15.

3.87. 1-(2-Fluoropyridin-3-yl)propan-1-ol (65)

To a solution of diisopropylamine (15.8 g, 156 mmol) in THF (100mL) was added dropwise a 1.6 mol/L hexane solution of *n*-BuLi (95 mL, 152 mmol) at −78°C, and the mixture was stirred for 15 min. A solution of 2-fluoropyridine **64** (11.6 g, 119 mmol) in THF (10 mL) was added dropwise to the mixture at the same temperature. After stirring for 30 min, a solution of propionaldehyde (9.02 g, 155 mmol) in THF (10 mL) was added to the mixture, which was stirred for further 1 h. The reaction was quenched by H_2O, and the mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to obtain compound **65** (12.4 g, 67%) as a brown oil: ^{1}H-NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.74–1.87 (2H, m), 2.02 (1H, brs), 4.88–4.94 (1H, m), 7.19–7.24 (1H, m), 7.89–7.96 (1H, m), 8.11–8.13 (1H, m).

3.88. 1-(2-Fluoropyridin-3-yl)propan-1-one (66)

To a mixture of compound **65** (12.3 g, 79 mmol) and Et_3N (65 mL) in DMSO (130 mL) was added pyridine sulfur trioxide complex (25.6 g, 161 mmol), and the mixture was stirred at room temperature for 14 h. The reaction was quenched by H_2O, and the resulting mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1) to produce **66** (10.6 g, 87%) as a brown oil: ^{1}H-NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.2 Hz), 3.01–3.09 (2H, m), 7.30–7.35 (1H, m), 8.31–8.39 (2H, m).

3.89. 2-Bromo-1-(2-fluoropyridin-3-yl)propan-1-one (67)

To a mixture of compound **66** (12.9 g, 84 mmol) and 25% HBr in AcOH (70 mL) was added dropwise bromine (4.4 mL, 86 mmol) at a room temperature. After stirring for 3 h, the mixture was concentrated under reduced pressure to obtain compound **67** (29.6 g, about 100%) as a crude red brownish oil. ^{1}H-NMR ($CDCl_3$) δ 1.91 (3H, d, J = 6.6 Hz), 5.30–5.37 (1H, m), 7.35–7.40 (1H, m), 8.35–8.44 (2H, m).

3.90. Ethyl 2-cyano-4-(2-fluoropyridin-3-yl)-3-methyl-4-oxobutanoate (68)

To a solution of ethyl cyanoacetate (11.5 g, 102 mmol) and *N*-ethyldiisopropylamine (45 mL, 258 mmol) in THF (50 mL) was added dropwise a solution of compound **67** (29.6 g, crude) in THF (50mL) at room temperature, and then the mixture was stirred for 14 h. The insoluble solid was

removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The separated organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2:1) to obtain compound **68** (18.8 g, 85% from **66** (2 steps)) as a brown oil: ^{1}H-NMR ($CDCl_3$) δ 1.24–1.39 (3H, m), 1.44–1.48 (3H, m), 3.75–4.34 (4H, m), 7.36–7.41 (1H, m), 8.32–8.40 (1H, m), 8.44–8.46 (1H, m).

3.91. Ethyl 2-chloro-5-(2-fluoropyridin-3-yl)-4-methyl-1*H*-pyrrole-3-carboxylate (69)

To a solution of compound **68** (19.4 g, 73.4 mmol) in EtOAc (20 mL) was added 4 mol/L HCl/EtOAc (90 mL) at room temperature. After stirring for 18 h, the mixture was concentrated under reduced pressure. The residue was partitioned between H_2O and EtOAc. The separated organic layer was washed successively with H_2O, a solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from *n*-hexane/ EtOAc to produce compound **69** (14.3 g, 69%) as a yellow solid: ^{1}H-NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.2 Hz), 2.37 (3H, s), 4.34 (2H, q, J = 7.2 Hz), 7.26–7.31 (1H, m), 7.82–7.89 (1H, m), 8.15–8.18 (1H, m), 8.87 (1H, brs).

3.92. Ethyl 5-(2-fluoropyridin-3-yl)-4-methyl-1*H*-pyrrole-3-carboxylate (70)

A mixture of compound **69** (10.0 g, 35.4 mmol), Et_3N (5.5 mL, 39.5 mmol), and 10% Pd-C (50% wet, 1.43 g) in EtOH (250 mL) was stirred at 60°C for 3 h under hydrogen atmosphere. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between H_2O and EtOAc. The separated organic layer was successively washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from *n*-hexane/EtOAc to obtain compound **70** (7.93 g, 90%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 2.44 (3H, s), 4.30 (2H, q, J = 7.2 Hz), 7.26–7.30 (1H, m), 7.52–7.54 (1H, m), 7.87–7.93 (1H, m), 8.12–8.15 (1H, m), 8.92 (1H, brs).

3.93. [5-(2-Fluoropyridin-3-yl)-4-methyl-1*H*-pyrrol-3-yl]methanol (71)

To a solution of compound **70** (5.0 g, 20.1 mmol) in THF (50 mL) was added dropwise a 1.5mol/L solution of DIBAL-H in toluene (45 mL) at −78°C, and the mixture was stirred at 0°C for 1 h. The reaction was quenched by H_2O, and then the mixture was filtered. The filtrate was extracted with EtOAc. The extract was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was suspended in iPr_2O and collected by filtration to produce compound **71** (1.72 g, 41%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ 1.32 (1H, brt, J = 4.5 Hz), 2.29 (3H, s), 4.62 (2H, d, J = 4.5 Hz), 6.91–6.92 (1H, m), 7.23–7.28 (1H, m), 7.88–7.95 (1H, m), 8.06–8.09 (1H, m), 8.57 (1H, brs).

3.94. 5-(2-Fluoropyridin-3-yl)-4-methyl-1*H*-pyrrole-3-carbaldehyde (72a)

To a solution of compound **71** (1.72 g, 8.24 mmol) in MeCN (35 mL) were added

tetra-*n*-propyl-ammonium perruthenate (103 mg, 0.293 mmol), *N*-methylmorpholine *N*-oxide (1.44 g, 12.3 mmol), and molecular sieves 4 Å powder (0.89 g). After stirring at room temperature for 48 h, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/2) to obtain compound **72a** (527 mg, 31%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 2.50 (3H, s), 7.26–7.33 (1H, m), 7.49–7.50 (1H, m), 7.90–7.97 (1H, m), 8.16–8.18 (1H, m), 9.00 (1H, brs), 9.93 (1H, s).

3.95. 4-Chloro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (72b)

To a solution of compound **59** (660 mg, 3.47 mmol) in DMF (20mL) was added *N*-chlorosuccinimide (641 mg, 4.80 mmol), and the mixture was heated to 80°C. After stirring for 40min, the mixture was cooled to room temperature, and then partitioned between EtOAc and H_2O. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3:2–1:1) to obtain compound **72b** (320 mg, 44%) as a white powder: ^{1}H-NMR (DMSO-d_6) δ 7.49–7.54 (1H, m), 7.86 (1H, d, *J* = 2.3 Hz), 8.12–8.19 (1H, m), 8.30–8.32 (1H, m), 9.80 (1H, s), 12.48 (1H, brs).

3.96. 4-Fluoro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (72c)

To a solution of compound **59** (660 mg, 3.47 mmol) in MeCN (30 mL) and THF (30 mL) was added 2,6-dichloro-1-fluoropyridinium triflate (1.32 g, 4.18 mmol) at room temperature. After stirring at the same temperature for 2 h, the mixture was partitioned between EtOAc and a solution of $NaHCO_3$. The separated organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 3/2–3/7) to obtain compound **72c** (110mg, 15%) as a pale yellow solid: ^{1}H-NMR ($CDCl_3$) δ 7.30–7.36 (2H, m), 8.11–8.12 (1H, m), 8.25–8.32 (1H, m), 9.21 (1H, brs), 9.90 (1H, s).

3.97. 5-(2-Fluoropyridin-3-yl)-4-methyl-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (73a)

Compound **73a** was prepared from **72a** using a similar procedure as for the preparation of compound **53a** from **50**. A white solid (61%): ^{1}H-NMR ($CDCl_3$) δ 2.04 (3H, m), 7.31–7.35 (1H, m), 7.38–7.43 (1H, m), 7.64–7.77 (2H, m), 8.09 (1H, s), 8.33–8.36 (1H, m), 8.61–8.63 (1H, m), 8.84–8.86 (1H, m), 9.98 (1H, s).

3.98. 4-Chloro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (73b)

Compound **73b** was prepared from **72b** using a similar procedure as for the preparation of compound **53a** from **50**. A white solid (81%): ^{1}H-NMR ($CDCl_3$) δ 7.35–7.39 (1H, m), 7.42–7.46 (1H, m), 7.69–7.73 (1H, m), 7.76–7.82 (1H, m), 8.14 (1H, s), 8.39–8.41 (1H, m), 8.64 (1H, dd, *J* = 2.5 Hz, 0.6 Hz), 8.89 (1H, dd, *J* = 4.8 Hz, 1.6 Hz), 9.97 (1H, s).

3.99. 4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrole-3-carbaldehyde (73c)

Compound **73c** was prepared from **72c** using a similar procedure as for the preparation of compound **53a** from **50**. A colorless oil (49%): ^{1}H-NMR ($CDCl_3$) δ 7.33–7.38 (1H, m), 7.41–7.46 (1H, m), 7.68–7.72 (1H, m), 7.79–7.86 (1H, m), 8.00 (1H, d, *J* = 4.5 Hz), 8.37–8.39 (1H, m), 8.65 (1H, d, *J* = 2.3 Hz), 8.88 (1H, dd, *J* = 4.7 Hz, 1.7 Hz), 9.92 (1H, s).

3.100. 1-[5-(2-Fluoropyridin-3-yl)-4-methyl-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (74a)

Compound **74a** was prepared from **73a** using a similar procedure as for the preparation of compound **40c** from **44**. Colorless crystals (32%): mp 173–175 °C; ^{1}H-NMR (DMSO-d_6) δ 1.76 (3H, s), 2.42 (3H, s), 3.75 (2H, s), 6.50 (2H, s), 7.42–7.46 (1H, m), 7.59–7.75 (3H, m), 7.84–7.88 (1H, m), 8.33–8.35 (1H, m), 8.56–8.57 (1H, m), 8.86–8.88 (1H, m), 3H not detected; Anal. Calcd for $C_{21}H_{21}FN_4O_6S$: C, 52.94; H, 4.44; N, 11.76. Found: C, 52.66; H, 4.42; N, 11.76.

3.101. 1-[4-chloro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (74b)

To a solution of methylamine hydrochloride (591 mg, 8.75 mmol) in MeOH (mL) was added compound **73b** (320 mg, 0.875 mmol) at room temperature, and the mixture was stirred for 30 min. $NaBH(OAc)_3$ (557 mg, 2.63 mmol) was added to the mixture, which was stirred at room temperature for 3 h and then evaporated under reduced pressure. The residue was partitioned between EtOAc and a solution of $NaHCO_3$. The separated organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (EtOAc/MeOH = 99/1–19/1), and then dissolved in EtOAc (8 mL). A solution of fumaric acid (102 mg, 0.879 mmol) in MeOH (2 mL) was added to the solution, and then the mixture was concentrated under reduced pressure. The residue was recrystallized from EtOAc/MeOH to produce **74b** (52mg, 12%) as colorless crystals: mp 156 °C; ^{1}H-NMR (DMSO-d_6) δ 2.39 (3H, s), 3.70 (2H, s), 6.65 (2H, s), 7.48–7.53 (1H, m), 7.63–7.68 (1H, m), 7.81 (1H, s), 7.84–7.96 (2H, m), 8.40–8.42 (1H, m), 8.65 (1H, d, *J* = 1.9 Hz), 8.93 (1H, dd, *J* = 4.9 Hz, 1.5 Hz), 3H not detected. Anal. Calcd for $C_{20}H_{18}ClFN_4O_6S$: C, 48.34; H, 3.65; N, 11.28. Found: C, 48.20; H, 3.74; N, 11.29.

3.102. Bis{1-[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine}fumarate (74c)

To a solution of methylamine hydrochloride (911 mg, 13.5 mmol) in MeOH (20 mL) was added a solution of compound **73c** (277 mg, 0.792 mmol) in MeOH (4 mL) at room temperature. After stirring for 5 min, $NaBH(OAc)_3$ (953 mg, 4.50 mmol) was added in one portion at room temperature and the mixture was stirred for 2 h. The reaction was quenched by H_2O, and the mixture was concentrated under reduced pressure. The resulting residue was extracted with EtOAc, and the

extract was successively washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (EtOAc), and then dissolved in EtOAc (2 mL). The resulting solution was added to a solution of fumaric acid (38.2 mg, 0.329 mmol) in EtOH (2 mL) at room temperature and the mixture was concentrated under reduced pressure. The resulted solid was recrystallized from EtOH/H_2O. The crystals were collected by filtration and dried in vacuo to obtain compound **74c** (165mg, 49%) as colorless crystals: mp 185–187 °C; ^{1}H-NMR (DMSO-d_6) δ 2.32 (3H, s), 3.64 (2H, s), 6.50 (1H, s), 7.47–7.51 (1H, m), 7.61–7.66 (2H, m), 7.88–7.94 (2H, m), 8.36–8.38 (1H, m), 8.62 (1H, d, J = 2.4 Hz), 8.90 (1H, d, J = 4.8 Hz), 2H not detected. Anal. Calcd for $C_{18}H_{16}F_2N_4O_4S$: C, 51.18; H, 3.82; N, 13.26. Found: C, 51.13; H, 3.77; N, 13.27.

In case of the crystallization by adding slightly excess of fumaric acid in MeOH to EtOAc solution of free base, 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine fumarate (monofumarate) was yielded as colorless crystals: mp 146–148 °C; ^{1}H-NMR (DMSO-d_6) δ 2.35 (3H, s), 3.69 (2H, s), 6.55 (2H, s), 7.47–7.52 (1H, m), 7.62–7.69 (2H, m), 7.88–7.94 (2H, m), 8.37–8.39 (1H, m), 8.63 (1H, d, J = 2.3 Hz), 8.92 (1H, dd, J = 4.9 Hz, 1.5 Hz), 3H not detected; Anal. Calcd for $C_{20}H_{18}F_2N_4O_6S$: C, 50.00; H, 3.78; N, 11.66. Found: C, 49.82; H, 3.71; N, 11.67.

3.103. Measurement of H^+, K^+-ATPase activity

This procedure was performed using the method described above (**2.55**).

3.104. An assay of inhibition of acid secretion in anesthetized rats by intravenous administration

This assay was performed by the method described above (**2.56**).

3.105. An assay of inhibition of acid secretion in anesthetized rats by oral administration

A test compound at doses of 0.5, 1, 2, or 4 mg/kg (as the free base) or vehicle was administered orally 1 h before pylorus ligation and histamine 2HCl (30 mg/kg, subcutaneous) administration. Gastric contents were collected 3 h after histamine administration, and total acid output was calculated.

3.106. Measurement of pH of a gastric perfusate during histamine stimulation in anesthetized rats

Rats were anesthetized with urethane (1.2 g/kg, intraperitoneal injection). The abdomen was opened, and the stomach was exposed. Cannulas were introduced into the stomach from the duodenum and also from the forestomach, and the esophagus was ligated. The stomach was perfused with saline at a rate of 0.5 mL/min, and the pH of the perfusate was continuously measured with a glass electrode (6961-15C and 2461A-15T; Horiba, Kyoto, Japan). Histamine 2 HCl (8 mg/kg/h) was infused intravenously via the cervical vein. When pH stabilized, a test compound or vehicle was administered intravenously. The pH level of the perfusate was measured for 5 h after administration

of the drug or vehicle.

3.107. An assay of inhibition of acid secretion in Heidenhain pouch dogs

This assay was performed using an approach similar to a above method (**2.59**). Compounds or vehicle were given orally (0.2 mL/kg) to the dogs in a blinded manner. Histamine 2 HCl (30 μg/kg) was injected subcutaneously 1 day before and 1, 3, 6, 24 and 48 h after administration of a drug or vehicle. Gastric juice from the pouch was collected continuously for three consecutive 30-min periods after each dosing with histamine 2 HCl. The volume of gastric juice was measured and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L NaOH solution (COM-555SC; Hiranuma Sangyo Co., Ltd., Japan). The total acid output during the 90 min period (μEq/90 min) at each time point was calculated and expressed as a percentage of the pre-dosing value measured 1 day before the administration.

3.108. A cytotoxicity assay

HepG2 cells were seeded at 2×10^4 cells/well in a 96-well white plate, and cultured in DMEM supplemented with 0.5% fetal bovine serum and a test compound for 1 day. The cell viability was determined by cellular ATP content. The latter was measured by means of ATPLite™-M (PerkinElmer). ATP content was calculated to the following. ATP content (% of control) = (RLU of test compound ÷ RLU of 1% DMSO) × 100.

3.109. Whole-cell patch-clamp for an hERG inhibition assay

hERG/HEK cells stably expressing hERG potassium channel were established by Takeda Pharmaceutical Company[58]. The cells were cultured at 37°C and 5% CO_2 in the minimum Eagle's medium (MEM) supplemented with 10% of fetal bovine serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate, and 0.2 mg/mL Geneticin (Invitrogen Corp., Carlsbad, CA). Whole-cell voltage clamp recordings of hERG currents were performed on hERG/HEK cells. Borosilicate glass pipettes (Harvard Apparatus, Kent, U.K.) were pulled and firepolished to attain final resistances of 2.0–3.5 MΩ. The pipette solution consisted of 130 mM KCl, 7 mM NaCl, 1 mM $MgCl_2$, 5 mM ATP-2Na, 5 mM EGTA, and 5 mM HEPES; pH 7.2. Series resistances values were less than 6 MΩ and were compensated by 60–85%. Cells were perfused with Tyrode's solution consisting of 137 mM NaCl, 4 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 11 mM glucose and 10 mM HEPES pH 7.4. Whole-cell currents were recorded using an Axopatch 200B amplifier and Clampex software (Molecular Devices Corp., Sunnyvale, CA). Membrane currents were low-pass-filtered at 1 kHz and sampled at 2.5 kHz with a Digidata 1320 data acquisition system (Molecular Devices Corp.). The membrane potential was held at –75 mV, and depolarization pulses set to 10 mV for 0.5 sec were applied. Tail currents were measured at –40 mV. The protocol was repeated every 5 sec or 10 sec, allowing for complete recovery of the current between test pulses. The experiments were conducted at rt. A amplitudes of currents were measured after a steady-state level of drug blockade was reached at each concentration. The percentage of hERG

inhibition was calculated from the peak amplitudes of the tail current before and after the drug applications.

3.110. PAMPA

Donor wells were filled with 200 µL of PRISMA HT buffer (pH 7.4, pION inc.) containing 10 µmol/L test compounds. The filter on the bottom of each acceptor well was coated with 4 µL of a GIT-0 Lipid Solution (pION Inc.) and filled with 200 µL of Acceptor Sink Buffer (pION Inc.). The acceptor filter plate was placed on the donor plate and incubated for 3 h at room temperature. After that, the amount of the test compound in both the donor and acceptor wells was measured by LC/MS/MS.

3.111. X-ray structure analysis

All analyses were conducted on a Rigaku R-AXIS RAPID-191R diffractometer using graphite monochromated Cu-K α radiation. The structure was solved by direct methods in SIR2008 and was refined using full-matrix least-squares on F^2 with SHELXL-2013/4.[59] All non-H atoms were refined with anisotropic displacement parameters.

Crystal data for compound **17a**: $C_{19}H_{21}N_2O_2S^+ \cdot Cl^-$, MW = 376.90; crystal size, 0.16 × 0.10 × 0.05 mm; colorless, block; monoclinic, space group $P2_1/n$, a = 7.61861(17) Å, b = 30.9046(8) Å, c = 8.12703(19) Å, $\alpha = \gamma = 90°$, β = 103.043(7)°, V = 1864.14(9) Å^3, Z = 4, Dx = 1.343 g/cm^3, T = 100 K, μ = 2.980 mm^{-1}, λ = 1.54187 Å, R_1 = 0.055, wR_2 = 0.130.

Crystal data for compound **54d**: $C_{19}H_{20}FN_2O_2\ S^+ \cdot Cl^-$, MW = 394.89; crystal size, 0.15 × 0.15 × 0.06 mm; colorless, platelet; monoclinic, space group $P2_1/n$, a = 7.6032(7) Å, b = 30.876(3) Å, c = 8.2198(8) Å, $\alpha = \gamma = 90°$, β = 102.381(7)°, V = 1884.8(3) Å^3, Z = 4, Dx = 1.392 g/cm^3, T = 100 K, μ = 3.053 mm^{-1}, λ = 1.54187 Å, R_1 = 0.076, wR_2 = 0.149.

Crystal data for compound **54e**: $C_{19}H_{20}FN_2O_2\ S^+ \cdot Cl^-$, MW = 394.89; crystal size, 0.33 × 0.13 × 0.11 mm; colorless, block; monoclinic, space group $P2_1/n$, a = 7.6633(5) Å, b = 31.0682(19) Å, c = 8.1413(6) Å, $\alpha = \gamma = 90°$, β = 102.340(7)°, V = 1893.5(2) Å^3, Z = 4, Dx = 1.385 g/cm^3, T = 100 K, μ = 3.039 mm^{-1}, λ = 1.54187 Å, R_1 = 0.052, wR_2 = 0.136.

Crystal data for compound **54f**: $C_{19}H_{20}FN_2O_2\ S^+ \cdot Cl^-$, MW = 394.89; crystal size, 0.27 × 0.20 × 0.05 mm; colorless, chip; triclinic, space group P-1, a = 7.5691(9) Å, b = 9.5845(10) Å, c = 14.1450(14) Å, α = 104.394(7)°, β = 97.005(7)°, γ = 101.481(7)°, V = 958.04(18) Å^3, Z = 2, Dx = 1.369 g/cm^3, T = 100 K, μ = 3.003 mm^{-1}, λ = 1.54187 Å, R_1 = 0.059, wR_2 = 0.132.

CCDC 1526437 for compound **17a**, CCDC 1526434 for compound **54d**, CCDC 1526435 for compound **54e**, and CCDC 1526436 for compound **54f** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Experiments concerning Chapter 4

4.1. 2-(Benzylsulfanyl)-5-fluoropyridine (76a)

To a suspension of sodium hydride (60% in oil, 295 mg, 7.39 mmol) in THF (20 mL) was added benzyl mercaptan (917 mg, 7.39 mmol) at 0 °C. To this suspension was added dropwise a solution of 2-bromo-5-fluoropyridine **75a** (1.0 g, 5.68 mmol) in THF (8 mL) at the same temperature. The reaction mixture was gradually warmed to room temperature and stirred for 28 h. The reaction was quenched by H_2O and the resulting mixture was concentrated, and then extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/0–19/1) to afford compound **76a** (179 mg, 14%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 4.40 (2H, s), 7.09–7.17 (1H, m), 7.19–7.33 (4H, m), 7.35–7.41 (2H, m), 8.34 (1H, d, *J* = 2.8 Hz).

4.2. 2-(Benzylsulfanyl)-6-fluoropyridine (76b)

Compound **76b** was prepared from 2,6-difluoropyridine **75b** following a similar procedure for compound **76a** from **75a**. A colorless oil (96%): ^{1}H-NMR ($CDCl_3$) δ 4.39 (2H, s), 6.56–6.60 (1H, m), 7.00–7.03 (1H, m), 7.20–7.32 (4H, m), 7.38–7.42 (1H, m), 7.50–7.58 (1H, m).

4.3. 2-(Benzylsulfanyl)-3-methylpyridine (76c)

To a suspension of sodium hydride (60% in oil, 465 mg, 11.6 mmol) in THF (45 mL) was added benzyl mercaptan (1.44 g, 11.6 mmol) at room temperature for 15 min. To this suspension was added 2-bromo-3-methylpyridine **75c** (2.0 g, 11.6 mmol), and the reaction mixture was gradually warmed to 60 °C and stirred for 1.5 h. The reaction was quenched by H_2O and the resulting mixture was concentrated under reduced pressure, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/0–97/3) to afford compound **76c** (1.79 g, 72%) as a gray oil: ^{1}H-NMR ($CDCl_3$) δ 2.23 (3H, s), 4.49 (2H, s), 6.93 (1H, dd, *J* = 7.6 Hz, 4.9 Hz), 7.19–7.35 (5H, m), 7.39–7.48 (1H, m), 8.32 (1H, dd, *J* = 4.9 Hz, 1.1 Hz).

4.4. 2-(Benzylsulfanyl)-4-methylpyridine (76d)

Compound **76d** was prepared from 2-bromo-4-methylpyridine **75d** following a similar procedure for compound **76c** from **75c**. A brown oil (56%): ^{1}H-NMR ($CDCl_3$) δ 2.26 (3H, s), 4.43 (2H, s), 6.82 (1H, d, *J* = 5.1 Hz), 6.99 (1H, s), 7.17–7.32 (3H, m), 7.35–7.44 (2H, m), 8.31 (1H, d, *J* = 5.1 Hz).

4.5. 2-(Benzylsulfanyl)-6-methylpyridine (76e)

A mixture of 2-chloro-6-methylpyridine **75e** (1.30 g, 10.2 mmol), potassium carbonate (2.12 g, 15.3 mmol) and benzyl mercaptan (1.90 g, 15.3 mmol) in DMSO (10 mL) was stirred at 150 °C for 3 h. After cooled to room temperature, H_2O was added and extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 15/1) to

afford compound **76e** (1.90 g, 87%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 2.52 (3H, s), 4.41 (2H, s), 6.81–6.83 (1H, m), 6.93–6.95 (1H, m), 7.20–7.42 (6H, m).

4.6. 2-(Benzylsulfanyl)-4-methoxypyridine (76f)

A mixture of 2-chloro-4-methoxypyridine **75f** (786 mg, 5.47 mmol), tris(dibenzylideneacetone) dipalladium(0) (202 mg, 0.22 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (256 mg, 0.44 mmol), *N*-ethyldiisopropylamine (1.56 g, 12.0 mmol) and benzyl mercaptan (683 mg, 5.50 mmol) in toluene (10 mL) was stirred at 80 °C for 26 h under Ar atmosphere. The reaction mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/0–19/1) to afford compound **76f** (454 mg, 38%) as an orange oil: ^{1}H-NMR ($CDCl_3$) δ 3.79 (3H, s), 4.43 (2H, s), 6.57 (1H, dd, *J* = 5.9 Hz, 2.5 Hz), 6.68 (1H, d, *J* = 2.3 Hz), 7.19–7.34 (3H, m), 7.36–7.44 (2H, m), 8.27 (1H, d, *J* = 5.7 Hz).

4.7. 2-(Benzylsulfanyl)-5-methoxypyridine (76g)

Compound **76g** was prepared from 2-bromo-5-methoxypyridine **75g** following a similar procedure for compound **76f** from **75f**. A yellow oil (quant.): ^{1}H-NMR ($CDCl_3$) δ 3.83 (3H, s), 4.37 (2H, s), 6.99–7.10 (2H, m), 7.19–7.31 (3H, m), 7.33–7.40 (2H, m), 8.21 (1H, dd, *J* = 2.6 Hz, 0.9 Hz).

4.8. 2-(Benzylsulfanyl)-6-methoxypyridine (76h)

A mixture of 2-(benzylsulfanyl)-6-fluoropyridine **76b** (199 mg, 0.91 mmol) and 28% sodium methoxide methanol solution (2 mL) was stirred at 60 °C for 2 h. The reaction mixture was concentrated in vacuo. H_2O was added to the residue, which was extracted with EtOAc. The extract was washed with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel and concentrated under reduced pressure to obtain compound **76h** (182 mg, 86%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 3.93 (3H, s), 4.43 (2H, s), 6.41–6.43 (1H, m), 6.74–6.77 (1H, m), 7.19–7.40 (6H, m).

4.9. 5-Fluoropyridine-2-sulfonyl fluoride (77a)

To a solution of compound **76a** (244 mg, 1.11 mmol) in AcOH (3 mL) and H_2O (1.5 mL) was added *N*-chlorosuccinimide (594 mg, 4.45 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and then stirred for 2 h. To this reaction mixture was added potassium fluoride (65 mg, 1.11 mmol), the resulting mixture was stirred for 1 h, and then concentrated in vacuo. H_2O was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1–3/1) to afford compound **77a** (69.0 mg, 35%) as a white solid: ^{1}H-NMR ($CDCl_3$) δ 7.75 (1H, ddd, *J* = 8.7 Hz, 7.4 Hz, 2.7 Hz), 8.20 (1H, dd, *J* = 8.8 Hz, 4.1 Hz), 8.66 (1H, d, *J* = 2.8 Hz).

4.10. 6-Fluoropyridine-2-sulfonyl chloride (77b)

To a solution of compound **76b** (310 mg, 1.42 mmol) in AcOH (3 mL) and H_2O (1.5 mL) was added

N-chlorosuccinimide (776 mg, 5.81 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and then stirred for 5 h, and then concentrated in vacuo.

Toluene was added to the residue, and the resulting mixture was filtrated. The filtrate was concentrated under reduced pressure to obtain compound **77b** (240 mg, 87%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 7.99–8.03 (1H, m), 8.12–8.19 (1H, m), 1H not detected.

4.11. 3-Methylpyridine-2-sulfonyl chloride (77c)

To a suspension of compound **76c** (1.79 g, 8.32 mmol) in AcOH (16 mL) and H_2O (8 mL) was added *N*-chlorosuccinimide (3.33 g, 25.0 mmol) at room temperature. After stirring for 2 h, the mixture was concentrated under reduced pressure, then neutralized by a solution of $NaHCO_3$, and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1-3/2) to afford compound **77c** (153 mg, 10%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 2.78 (3H, s), 7.57 (1H, dd, *J* = 7.9 Hz, 4.5 Hz), 7.82 (1H, ddd, *J* = 7.7 Hz, 1.5 Hz, 0.8 Hz), 8.61 (1H, dd, *J* = 4.5 Hz, 1.1 Hz).

4.12. 4-Methylpyridine-2-sulfonyl fluoride (77d)

Compound **77d** was prepared from **76d** following a similar procedure for compound **77a** from **76a**. A pale-yellow oil (30%): ^{1}H-NMR ($CDCl_3$) δ 2.54 (3H, s), 7.50 (1H, dt, *J* = 4.9 Hz, 0.7 Hz), 7.95 (1H, d, *J* = 0.8 Hz), 8.69 (1H, d, *J* = 4.9 Hz)

4.13. 6-Methylpyridine-2-sulfonyl chloride (77e)

Compound **77e** was prepared from **76e** following a similar procedure for compound **77c** from **76c**. A colorless oil (29%): ^{1}H-NMR ($CDCl_3$) δ 2.72 (3H, s), 7.49–7.52 (1H, m), 7.86–7.90 (2H, m).

4.14. 4-Methoxypyridine-2-sulfonyl chloride (77f)

Compound **77f** was prepared from **76f** following a similar procedure for compound **77c** from **76c**. A pale yellow oil (crude mixture): ^{1}H-NMR ($CDCl_3$) δ 3.99 (3H, s), 7.11 (1H, dd, *J* = 5.6 Hz, 2.4 Hz), 7.60 (1H, d, *J* = 2.4 Hz), 8.61 (1H, d, *J* = 5.5 Hz).

4.15. 5-Methoxypyridine-2-sulfonyl chloride (77g)

Compound **77g** was prepared from **76g** following a similar procedure for compound **77c** from **76c**. A white solid (79%): ^{1}H-NMR ($CDCl_3$) δ 4.00 (3H, s), 7.38 (1H, dd, *J* = 8.9 Hz, 2.8 Hz), 8.08 (1H, d, *J* = 8.7 Hz), 8.43 (1H, d, *J* = 2.8 Hz).

4.16. 6-Methoxypyridine-2-sulfonyl chloride (77h)

Compound **77h** was prepared from **76h** following a similar procedure for compound **77c** from **76c**. A colorless oil (52%): ^{1}H-NMR ($CDCl_3$) δ 4.06 (3H, s), 7.08 (1H, dd, *J* = 8.1 Hz, 0.6 Hz), 7.65 (1H, dd, *J* = 6.9 Hz, 0.6 Hz), 7.68–7.86 (1H, m).

4.17. 5-Chloropyridin-3-yl trifluoromethanesulfonate (78a)

To a solution of 5-chloropyridin-3-ol (**78f**) (1.30 g, 10.0 mmol) in THF (50 mL) was added Et_3N (1.21 g, 12.0 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide

(3.93 g, 11.0 mmol) at room temperature. After stirring for 20 min, the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and 1 mol/L HCl. The separated aqueous layer was extracted with EtOAc again. The combined extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 99/1–19/1) to afford compound **78a** (1.73 g, 66%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 7.69 (1H, t, *J* = 2.3 Hz), 8.52 (1H, d, *J* = 2.3 Hz), 8.64 (1H, d, *J* = 1.9 Hz).

4.18. 3-(Benzylsulfanyl)-5-chloropyridine (79a)

A mixture of compound **78a** (1.73 g, 6.60 mmol), tris(dibenzylideneacetone)dipalladium(0) (121 mg, 0.132 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (153 mg, 0.26 mmol), *N*-ethyldiisopropylamine (1.88 g, 14.5 mmol) and benzyl mercaptan (861 mg, 6.93 mmol) in toluene (15 mL) was stirred at 80 °C for 3 h. The reaction mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/0–19/1) to afford compound **79a** (1.63 g, quant.) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 4.12 (2H, s), 7.21–7.36 (5H, m), 7.53 (1H, t, *J* = 2.1 Hz), 8.36 (2H, d, *J* = 1.9 Hz).

4.19. 3-(Benzylsulfanyl)-5-fluoropyridine (79b)

Compound **79b** was prepared from **78b** following a similar procedure for compound **79a** from **78a**. An orange oil (quant.): ^{1}H-NMR ($CDCl_3$) δ 4.14 (2H, s), 7.23–7.36 (6H, m), 8.26 (1H, d, *J* = 2.6 Hz), 8.32 (1H, t, *J* = 1.6 Hz).

4.20. 3-(Benzylsulfanyl)-2-methylpyridine (79c)

Compound **79c** was prepared from **78c** following a similar procedure for compound **79a** from **78a**. A yellow solid (59%): ^{1}H-NMR ($CDCl_3$) δ 2.56 (3H, s), 4.08 (2H, s), 7.03 (1H, dd, *J* = 7.6 Hz, 5.0 Hz), 7.21–7.34 (5H, m), 7.48 (1H, dd, *J* = 7.8 Hz, 1.6 Hz), 8.30 (1H, dd, *J* = 4.8 Hz, 1.6 Hz).

4.21. 3-(Benzylsulfanyl)-4-methylpyridine (79d)

Compound **79d** was prepared from **78d** following a similar procedure for compound **79a** from **78a**. A yellow oil (59%): ^{1}H-NMR ($CDCl_3$) δ 2.27 (3H, s), 4.07 (2H, s), 7.06 (1H, d, *J* = 4.9 Hz), 7.14–7.35 (5H, m), 8.30 (1H, d, *J* = 5.3 Hz), 8.45 (1H, s).

4.22. 3-(Benzylsulfanyl)-5-methylpyridine (79e)

Compound **79e** was prepared from **78e** following a similar procedure for compound **79a** from **78a**. A yellow oil (95%): ^{1}H-NMR ($CDCl_3$) δ 2.26 (3H, d, *J* = 0.8 Hz), 4.09 (2H, s), 7.20–7.33 (5H, m), 7.37 (1H, dt, *J* = 2.1 Hz, 0.8 Hz), 8.25 (1H, d, *J* = 1.3 Hz), 8.33 (1H, d, *J* = 2.1 Hz).

4.23. 5-Chloropyridine-3-sulfonyl chloride (80a)

To a solution of compound **79a** (1.63 g, 6.60 mmol) in AcOH (9 mL) and H_2O (3 mL) was added *N*-chlorosuccinimide (3.53 g, 26.4 mmol) at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc and H_2O. The

separated aqueous layer was extracted again with EtOAc. The combined extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 19/1–9/1) to afford compound **80a (**1.26 g, 90%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 8.29 (1H, t, *J* = 2.2 Hz), 8.91 (1H, d, *J* = 2.2 Hz), 9.12 (1H, d, *J* = 1.9 Hz).

4.24. 5-Fluoropyridine-3-sulfonyl chloride (80b)

Compound **80b** was prepared from **79b** following a similar procedure for compound **80a** from **79a**. A colorless oil (62%): ^{1}H-NMR ($CDCl_3$) δ 8.04 (1H, dt, *J* = 7.0 Hz, 2.2 Hz), 8.85 (1H, d, *J* = 2.7 Hz), 9.10 (1H, s).

4.25. 2-Methylpyridine-3-sulfonyl chloride (80c)

Compound **80c** was prepared from **79c** following a similar procedure for compound **80a** from **79a**. A colorless oil (27%): ^{1}H-NMR ($CDCl_3$) δ 3.03 (3H, s), 7.40 (1H, dd, *J* = 8.1 Hz, 4.7 Hz), 8.33 (1H, dd, *J* = 8.1 Hz, 1.7 Hz), 8.80 (1H, dd, *J* = 4.7 Hz, 1.7 Hz).

4.26. 4-Methylpyridine-3-sulfonyl chloride (80d)

Compound **80d** was prepared from **79d** following a similar procedure for compound **80a** from **79a**. A colorless oil (quant.): ^{1}H-NMR ($CDCl_3$) δ 2.82 (3H, s), 7.34–7.44 (1H, m), 8.77 (1H, d, *J* = 4.9 Hz), 9.19 (1H, s).

4.27. 5-Methylpyridine-3-sulfonyl chloride (80e)

Compound **80e** was prepared from **79e** following a similar procedure for compound **80a** from **79a**. A colorless oil (74%): ^{1}H-NMR ($CDCl_3$) δ 2.52 (3H, s), 7.96–8.22 (1H, m), 8.78 (1H, d, *J* = 1.5 Hz), 9.06 (1H, d, *J* = 2.3 Hz).

4.28. 2-Bromo-2,2-difluoro-*N*-(prop-2-en-1-yl)acetamide (82)

Ethyl bromodifluoroacetate **81** (100 g) was cooled to 0 °C, and allylamine (39 mL) was added dropwise. The resulting mixture was stirred at room temperature for 14 h, and then concentrated under reduced pressure. H_2O was added to the residue, and the mixture was extracted with EtOAc, and then the extract was washed successively with 1 mol/L HCl, H_2O, a solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to produce compound **82** (105 g, quant.) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 3.99 (2H, dd, *J* = 6.1 Hz, 5.7 Hz), 5.22–5.26 (1H, m), 5.26–5.33 (1H, m), 5.77–5.94 (1H, m), 6.31 (1H, brs).

4.29. *tert*-Butyl [bromo(difluoro)acetyl]prop-2-en-1-ylcarbamate (83)

To a solution of **82** (154 g, 0.72 mol) and DMAP (8.82 g, 1.42 mol) in MeCN (750 mL) was added dropwise Boc_2O (173 g, 0.79 mol) at 0 °C. The mixture was stirred at room temperature for 14 h, and concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The extract was washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain compound **83** (211 g, 93%) as a brown oil: ^{1}H-NMR ($CDCl_3$) δ 1.54 (9H, s), 4.29 (2H, ddd, *J* = 5.7 Hz, 1.5 Hz, 1.1 Hz), 5.23 (1H,

ddt, *J* = 10.2 Hz, 1.1 Hz, 1.5 Hz), 5.25 (1H, ddt, *J* = 17.0 Hz, 1.5 Hz, 1.1 Hz), 5.85 (1H, ddt, *J* = 17.0 Hz, 10.2 Hz, 5.7 Hz).

4.30. *tert*-Butyl (4*RS*)-4-(bromomethyl)-3,3-difluoro-2-oxopyrrolidine-1-carboxylate (84)

A suspension of **83** (50.0 g, 0.159 mol) and copper bromide (6.91 g, 0.048 mol) in 1,2-dichloroethane (500 mL) was heated to 80°C under N_2 atmosphere. 2,2′-Bipyridyl (7.51 g, 0.048 mol) was added, and the obtained mixture was stirred at 80 °C for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was suspended in THF (150 mL), and insoluble materials were filtered off, and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1), and the obtained solid was washed with iPr_2O to produce compound **84** (32.3 g, 65%) as a white solid: mp 117 °C; ^{1}H-NMR ($CDCl_3$) δ 1.57 (9H, s), 2.82–3.06 (1H, m), 3.40 (1H, dd, *J* = 10.7 Hz, 10.0 Hz), 3.48 (1H, ddd, *J* = 11.3 Hz, 8.1 Hz, 0.8 Hz), 3.67 (1H, dd, *J* = 10.7 Hz, 4.9 Hz), 4.09 (1H, dd, *J* = 11.3 Hz, 8.1 Hz); Anal. Calcd for $C_{10}H_{14}BrF_2NO_3$: C, 38.24; H, 4.49; N, 4.46. Found: C, 38.32; H, 4.48; N, 4.42.

4.31. *tert*-Butyl 3,3-difluoro-4-methylidene-2-oxopyrrolidine-1-carboxylate (85)

To a solution of compound **84** (50.1 g, 0.159 mol) in THF (400 mL) was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (25.0 mL, 0.167 mol) at 0 °C over 15 min, and then the mixture was stirred at room temperature for 1 h. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1), and the obtained solid was washed with iPr_2O to produce compound **85** as a white solid (28.1 g, 76%): mp 81 °C; ^{1}H-NMR ($CDCl_3$) δ 1.57 (9H, s), 4.32–4.39 (2H, m), 5.69–5.76 (1H, m), 5.92–6.06 (1H, m); Anal. Calcd for $C_{10}H_{13}F_2NO_3$: C, 51.50; H, 5.62; N, 6.01. Found: C, 51.53; H, 5.56; N, 5.97.

4.32. *tert*-Butyl (2*RS*)-3,3-Difluoro-2-(2-fluoropyridin-3-yl)-2-hydroxy-4-methylidenepyrrolidine-1-carboxylate (86)

To a solution of diisopropylamine (23.9 g, 0.236 mol) in anhydrous THF (175 mL) was added dropwise a 1.6 mol/L hexane solution (136 mL, 0.218 mol) of *n*-butyllithium at -78°C under N_2 atmosphere, and the mixture was stirred at the same temperature for 15 min. To this obtained solution was added dropwise a solution of 2-fluoropyridine (21.9 g, 0.226 mol) in anhydrous THF (25 mL) at the same temperature over 30 min, and then the mixture was stirred for 2 h. To the obtained suspension was added dropwise a solution of compound **85** (25.0 g, 0.1072 mol) in anhydrous THF (50 mL) at the same temperature, and the resulting mixture was stirred for 3 h. A solution of NH_4Cl was added, and the mixture was extracted with EtOAc. The extract was washed successively with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1), and the obtained crystals were washed with iPr_2O to produce compound **86**

(23.7 g, 67%) as colorless crystals: mp 130 °C; ^{1}H-NMR ($CDCl_3$) δ 1.16 (3.6H, brs), 1.44 (5.4H, brs), 3.55 (0.4H, brs), 4.19–4.40 (2H, m), 4.75 (0.6H, brs), 5.56 (1H, s), 5.78 (1H, s), 7.28 (1H, ddd, *J* = 7.5 Hz, 2.8 Hz, 1.9 Hz), 8.13 (1H, ddd, *J* = 9.8 Hz, 7.5 Hz, 1.9 Hz), 8.19–8.26 (1H, m); Anal. Calcd for $C_{15}H_{17}F_3N_2O_3$: C, 54.54; H, 5.19; N, 8.48. Found: C, 54.50; H, 5.20; N, 8.47.

4.33. 3-(4,4-Difluoro-3-methylidene-3,4-dihydro-2*H*-pyrrol-5-yl)-2-fluoropyridine (87)

To a solution of compound **86** (20.0 g, 60.6 mmol) in AcOH (70 mL) was added dropwise concentrated HCl (20 mL). The mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure. A solution of $NaHCO_3$ was added to the residue, and the mixture was extracted with EtOAc. The extract was washed successively with a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to obtain compound **87** (11.6 g, 90%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 4.79 (2H, ddd, *J* = 4.9 Hz, 2.6 Hz, 2.5 Hz), 5.58–5.65 (1H, m), 5.84–5.93 (1H, m), 7.33 (1H, ddd, *J* = 7.5 Hz, 4.9 Hz, 1.7 Hz), 8.32–8.45 (2H, m).

4.34. 1-(2,4-Dimethoxyphenyl)-*N*-{[4-fluoro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl]methyl} -*N*-methylmethanamine (88)

Sodium hydride (60% in oil, 2.23 g, 55.8 mmol) was washed twice with *n*-hexane and suspended in THF (180 mL). A solution of 1-(2,4-dimethoxyphenyl)-*N*-methylmethanamine (9.09 g, 50.2 mmol) in THF (10 mL) was added dropwise to this suspension at 0 °C, and then the mixture was stirred at 60 °C for 18 h. After cooled to 0 °C, a solution of compound **87** (9.64 g, 45.4 mmol) in THF (10 mL) was added dropwise, and then the mixture was stirred at the same temperature for 1 h. Ice-cooled solution of NaCl were added, and the mixture was extracted with EtOAc. The extract was washed successively with a solution of NH_4Cl, a solution of $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (EtOAc) to obtain compound **88** (16.8 g, 99%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ 2.24 (3H, s), 3.51 (2H, s), 3.54 (2H, s), 3.79 (3H, s), 3.80 (3H, s), 6.45 (1H, s), 6.42–6.50 (1H, m), 6.68 (1H, dd, *J* = 4.7 Hz, 3.6 Hz), 7.18–7.29 (2H, m), 7.98 (1H, ddd, *J* = 4.5 Hz, 1.9 Hz, 1.5 Hz), 8.25 (1H, ddd, *J* = 10.2 Hz, 8.0 Hz, 1.9 Hz), 8.67 (1H, s).

4.35. 1-(2,4-Dimethoxyphenyl)-*N*-{[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl) -1*H*-pyrrol-3-yl]methyl}-*N*-methylmethanamine (89a)

To a suspension of sodium hydride (60% in oil, 1.57 g, 39.3 mmol) in THF (100 mL) was added dropwise a solution of compound **88** (9.8 g, 26.2 mmol) in THF (30 mL) at 0 °C, and the mixture was stirred at the same temperature for 10 min. 15-Crown-5 (8.66 g, 39.3 mmol) was added dropwise, and the resulting mixture was stirred for 10 min. To this mixture was added pyridine-3-sulfonyl chloride (6.98 g, 39.3 mmol) slowly, and the obtained mixture was stirred for 15 min at the same temperature, then poured into ice-cooled H_2O, and extracted with EtOAc. The extract was washed successively with a solution of $NaHCO_3$ and brine, dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 6/1–3/1), and the obtained crystals were washed with iPr_2O to produce compound **89a** (9.25 g, 68%) as colorless crystals: mp 93–97 °C; ^{1}H-NMR ($CDCl_3$) δ 2.22 (3H, s), 3.45 (2H, s), 3.47 (2H, s), 3.81 (3H, s), 3.84 (3H, s), 6.44–6.50 (2H, m), 7.15–7.22 (1H, m), 7.27–7.37 (2H, m), 7.40 (1H, d, *J* = 5.3 Hz), 7.67 (1H, ddd, *J* = 8.1 Hz, 2.3 Hz, 1.7 Hz), 7.81 (1H, ddd, *J* = 9.2 Hz, 7.3 Hz, 1.9 Hz), 8.30 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.67 (1H, d, *J* = 1.9 Hz), 8.78 (1H, dd, *J* = 4.9 Hz, 1.5 Hz); Anal. Calcd for $C_{25}H_{24}F_2N_4O_4S$: C, 58.36; H, 4.70; N, 10.89. Found: C, 58.34; H, 4.70; N, 10.90.

4.36. 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine (89b)

To a solution of compound **89a** (5.68 g, 11.0 mmol) in THF (25 mL) was added a solution of 1-chloroethyl chlorocarbonate (1.58 g, 11.1 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 15 min. Et_3N (4.63 mL, 33.0 mmol) was added dropwise and the obtained mixture was stirred at 65 °C for 16 h. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure. H_2O was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. EtOH (25 mL) was added to the residue, and the mixture was refluxed for 1.5 h, and concentrated under reduced pressure. EtOAc was added to the residue, and the precipitated solid was filtrated. To the obtained solid were successively added EtOAc, 1 mol/L NaOH and a solution of $NaHCO_3$, and then the mixture was stirred at room temperature for 10 min. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 1/1–1/4) to obtain compound **89b** (3.10 g, 77%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 2.45 (3H, s), 3.64 (2H, s), 7.28–7.34 (2H, m), 7.38 (1H, ddd, *J* = 8.1 Hz, 4.9 Hz, 0.6 Hz), 7.67 (1H, ddd, *J* = 8.1 Hz, 2.3 Hz, 1.7 Hz), 7.81 (1H, ddd, *J* = 9.2 Hz, 7.3 Hz, 1.9 Hz), 8.31 (1H, ddd, *J* = 4.7 Hz, 1.9 Hz, 0.9 Hz), 8.67 (1H, d, *J* = 2.3 Hz), 8.81 (1H, dd, *J* = 4.9 Hz, 1.7 Hz), 1H not detected.

4.37. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate (89c)

To a solution of compound **89b** (500 mg, 1.37 mmol) in THF (5 mL) was added di-*tert*-butyl dicarbonate (329 mg, 1.51 mmol) at room temperature and the mixture was stirred for 5 min. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–2/1) to produce compound **89c** (383 mg, 60%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.86 (3H, s), 4.26 (2H, s), 7.25–7.39 (3H, m), 7.62–7.65 (1H, m), 7.77–7.82 (1H, m), 8.29–8.31 (1H, m), 8.63–8.64 (1H, m), 8.79–8.81 (1H, m).

4.38. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl]methyl}methylcarbamate

(90)

Compound **89c** (1.0 g, 2.153 mmol) was dissolved in THF (8 mL) and *i*PrOH (2 mL), and 1 mol/L NaOH (5 mL) was added under ice-cooling. After stirring at room temperature for 18 h, the solvent was evaporated under reduced pressure, H_2O was added to the residue and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4/1–2/1) to obtain compound **90** (752 mg, quant.) as a pale-yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 2.88 (3H, s), 4.31 (2H, s), 6.67 (1H, br), 7.21–7.26 (1H, m), 7.98–8.00 (1H, m), 8.19–8.26 (1H, m), 9.65 (1H, br)

4.39. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(thiophen-2-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}methylcarbamate (91a)

To a suspension of sodium hydride (60% in oil, 37 mg, 0.93 mmol) in THF (2 mL) were added dropwise a solution of compound **90** (200 mg, 0.62 mmol) in THF (1 mL), then 15-crown-5 (205 mg, 0.93 mmol) and 2-thiophenesulfonyl chloride (136 mg, 0.74 mmol) at room temperature. After stirred for 1 h, the reaction mixture was diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 6/1–3/2) to obtain compound **91a** (276 mg, 95%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.87 (3H, s), 4.27 (2H, brs), 7.19–7.33 (4H, m), 7.63 (1H, dd, *J* = 5.0 Hz, 1.0 Hz), 7.84 (1H, ddd, *J* = 9.2 Hz, 7.4 Hz, 1.9 Hz), 8.25–8.32 (1H, m).

4.40. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-2-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}methylcarbamate (91b)

Compound **91b** was prepared from **90** by use of furan-2-sulfonyl chloride following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (87%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.89 (3H, s), 4.28 (2H, brs), 6.45 (1H, dd, *J* = 3.6 Hz, 1.9 Hz), 6.76 (1H, d, *J* = 3.6 Hz), 7.21–7.33 (2H, m), 7.49–7.56 (1H, m), 7.83 (1H, ddd, *J* = 9.2 Hz, 7.4 Hz, 2.0 Hz), 8.26–8.33 (1H, m).

4.41. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-3-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}methylcarbamate (91c)

Compound **91c** was prepared from **90** by use of furan-3-sulfonyl chloride following a similar procedure as for the preparation of compound **91a** from **90**. A pale yellow oil (92%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.89 (3H, s), 4.28 (2H, brs), 6.30 (1H, brs), 7.15–7.25 (1H, m), 7.27–7.32 (1H, m), 7.38–7.44 (1H, m), 7.58 (1H, dd, *J* = 1.5 Hz, 0.9 Hz), 7.78–7.90 (1H, m), 8.27–8.32 (1H, m).

4.42. *tert*-Butyl {[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrol-3-yl] methyl}methylcarbamate (91d)

Compound **91d** was prepared from **90** by use of pyridine-2-sulfonyl chloride following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (95%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.87 (3H, s), 4.27 (2H, brs), 7.23–7.30 (1H, m), 7.33 (1H, d, *J* = 5.7 Hz), 7.51 (1H, ddd, *J* = 7.7 Hz, 4.7 Hz, 1.1 Hz), 7.60 (1H, d, *J* = 7.9 Hz), 7.78–7.92 (2H, m), 8.26 (1H, ddd, *J* = 4.9 Hz, 2.0 Hz, 1.0 Hz), 8.61 (1H, ddd, *J* = 4.7 Hz, 1.7 Hz, 0.9 Hz).

4.43. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methoxypyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91e)

Compound **91e** was prepared from **90** by use of 6-methoxypyridine-2-sulfonyl chloride **77h** following a similar procedure as for the preparation of compound **91a** from **90**. A brown oil (quant.): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.88 (3H, s), 3.83 (3H, s), 4.29 (2H, brs), 6.91 (1H, d, *J* = 8.1 Hz), 7.15 (1H, d, *J* = 7.2 Hz), 7.21–7.25 (1H, m), 7.34–7.36 (1H, m), 7.61 (1H, dd, *J* = 8.1, 7.2 Hz), 7.78–7.83 (1H, m), 8.21–8.23 (1H, m).

4.44. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methoxypyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91f)

Compound **91f** was prepared from **90** by use of 4-methoxypyridine-2-sulfonyl chloride **77f** following a similar procedure as for the preparation of compound **91a** from **90**. A pale yellow oil (39%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.87 (3H, s), 3.84 (3H, s), 4.27 (2H, brs), 6.94 (1H, dd, *J* = 5.6 Hz, 2.4 Hz), 7.07 (1H, d, *J* = 2.4 Hz), 7.28 (1H, dd, *J* = 5.3 Hz, 2.1 Hz), 7.31 (1H, d, *J* = 5.7 Hz), 7.87 (1H, ddd, *J* = 9.2 Hz, 7.5 Hz, 1.8 Hz), 8.26 (1H, d, *J* = 4.7 Hz), 8.39 (1H, d, *J* = 5.7 Hz).

4.45. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methoxypyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91g)

Compound **91g** was prepared from **90** by use of 5-methoxypyridine-2-sulfonyl chloride **77g** following a similar procedure as for the preparation of compound **91a** from **90**. A yellow oil (93%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.87 (3H, s), 3.91 (3H, s), 4.26 (2H, brs), 7.16 (1H, dd, *J* = 8.8 Hz, 2.9 Hz), 7.24–7.30 (1H, m), 7.32 (1H, d, *J* = 5.5 Hz), 7.52 (1H, d, *J* = 8.9 Hz), 7.87 (1H, ddd, *J* = 9.2 Hz, 7.4 Hz, 2.1 Hz), 8.23 (1H, d, *J* = 2.4 Hz), 8.26 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz).

4.46. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(3-methylpyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91h)

Compound **91h** was prepared from **90** by use of 3-methylpyridine-2-sulfonyl chloride **77c** following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (47%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.43 (3H, s), 2.90 (3H, s), 4.32 (2H, brs), 7.20 (1H, ddd, *J* = 7.4 Hz, 5.0 Hz, 1.7 Hz), 7.29 (1H, d, *J* = 5.7 Hz), 7.36 (1H, dd, *J* = 7.8 Hz, 4.6 Hz), 7.61 (1H, dd, *J* = 7.8 Hz, 0.8 Hz), 7.76–7.85 (1H, m), 8.19 (1H, ddd, *J* = 4.9 Hz, 2.0 Hz, 1.0 Hz), 8.29 (1H, dd, *J* = 4.5 Hz, 0.9 Hz).

4.47. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methylpyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91i)

Compound **91i** was prepared from **90** by use of 6-methylpyridine-2-sulfonyl chloride **77e** following a similar procedure as for the preparation of compound **91a** from **90**. A brown oil (91%): ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H, s), 2.53 (3H, s), 2.86 (3H, s), 4.26 (2H, brs), 7.23–7.32 (3H, m), 7.44 (1H, d, *J* = 7.5 Hz), 7.65–7.70 (1H, m), 7.86–7.92 (1H, m), 8.24–8.25 (1H, m).

4.48. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91j)

Compound **91j** was prepared from **90** by use of 4-methylpyridine-2-sulfonyl fluoride **77d** following a similar procedure as for the preparation of compound **91a** from **90**. A yellow oil (70%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.38 (3H, s), 2.86 (3H, s), 4.27 (2H, brs), 7.24–7.34 (3H, m), 7.36 (1H, s), 7.87 (1H, ddd, *J* = 9.2 Hz, 7.5 Hz, 1.9 Hz), 8.26 (1H, d, *J* = 3.8 Hz), 8.45 (1H, d, *J* = 4.9 Hz).

4.49. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-fluoropyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91k)

Compound **91k** was prepared from **90** by use of 6-fluoropyridine-2-sulfonyl chloride **77b** following a similar procedure as for the preparation of compound **91a** from **90**. A brown oil (33%): ^{1}H-NMR ($CDCl_3$) δ 1.47 (9H, s), 2.88 (3H, s), 4.28 (2H, brs), 7.14–7.18 (1H, m), 7.26–7.30 (2H, m), 7.52–7.55 (1H, m), 7.83–7.98 (2H, m), 8.25–8.27 (1H, m).

4.50. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-2-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91l)

Compound **91l** was prepared from **90** by use of 5-fluoropyridine-2-sulfonyl fluoride **77a** following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (29%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.88 (3H, s), 4.27 (2H, brs), 7.24–7.34 (2H, m), 7.52 (1H, ddd, *J* = 8.7 Hz, 7.5 Hz, 2.8 Hz), 7.68 (1H, dd, *J* = 8.7 Hz, 4.1 Hz), 7.85 (1H, ddd, *J* = 9.2 Hz, 7.4 Hz, 2.0 Hz), 8.27 (1H, ddd, *J* = 4.8 Hz, 1.8 Hz, 0.9 Hz), 8.45 (1H, d, *J* = 2.6 Hz).

4.51. *tert*-Butyl ({1-[(2-chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl) -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91m)

Compound **91m** was prepared from **90** by use of commercially available 2-chloropyridine-3-sulfonyl chloride following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (91%): ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 2.92 (3H, s), 4.32 (2H, brs), 7.18 (1H, dd, *J* = 7.9 Hz, 4.9 Hz), 7.22–7.30 (1H, m), 7.47 (1H, brs), 7.56 (1H, dd, *J* = 7.9 Hz, 1.9 Hz), 7.73–7.83 (1H, m), 8.21–8.27 (1H, m), 8.57 (1H, dd, *J* = 4.7 Hz, 1.9 Hz).

4.52. *tert*-Butyl ({1-[(5-chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl) -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91n)

Compound **91n** was prepared from **90** by use of 5-chloropyridine-3-sulfonyl chloride **80a** following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (78%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.88 (3H, s), 4.27 (2H, s), 7.26 (1H, s), 7.33 (1H, ddd, *J* = 7.3 Hz, 5.2 Hz, 1.5 Hz), 7.61 (1H, t, *J* = 2.1 Hz), 7.80 (1H, ddd, *J* = 9.2 Hz, 7.5 Hz, 1.9 Hz), 8.26–8.38 (1H, m), 8.50

(1H, d, *J* = 1.9 Hz), 8.76 (1H, d, *J* = 2.3 Hz).

4.53. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-3-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91o)

Compound **91o** was prepared from **90** by use of 5-fluoropyridine-3-sulfonyl chloride **80b** following a similar procedure as for the preparation of compound **91a** from **90**. A white solid (62%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.88 (3H, s), 4.27 (2H, s), 7.27–7.43 (3H, m), 7.65–7.93 (1H, m), 8.33 (1H, d, *J* = 4.9 Hz), 8.45 (1H, s), 8.68 (1H, d, *J* = 2.7 Hz).

4.54. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(2-methylpyridin-3-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91p)

Compound **91p** was prepared from **90** by use of 2-methylpyridine-3-sulfonyl chloride **80c** following a similar procedure as for the preparation of compound **90a** from **90**. A yellow oil (86%): ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 2.61 (3H, s), 2.92 (3H, s), 4.32 (2H, s), 7.03 (1H, dd, *J* = 8.1 Hz, 4.7 Hz), 7.21–7.26 (1H, m), 7.34 (1H, dd, *J* = 8.1 Hz, 1.7 Hz), 7.42 (1H, brs), 7.79 (1H, ddd, *J* = 9.2 Hz, 7.3 Hz, 2.1 Hz), 8.19–8.26 (1H, m), 8.63 (1H, dd, *J* = 4.9 Hz, 1.5 Hz).

4.55. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-3-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91q)

Compound **91q** was prepared from **90** by use of 4-methylpyridine-3-sulfonyl chloride **80d** following a similar procedure as for the preparation of compound **91a** from **90**. A pale yellow oil (53%): ^{1}H-NMR ($CDCl_3$) δ 1.49 (9H, s), 2.36 (3H, s), 2.92 (3H, s), 4.32 (2H, s), 7.19 (1H, d, *J* = 5.1 Hz), 7.23–7.31 (1H, m), 7.41 (1H, brs), 7.82 (1H, dt, *J* = 8.3 Hz, 1.9 Hz), 8.18–8.26 (2H, m), 8.58 (1H, d, *J* = 5.1 Hz).

4.56. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methylpyridin-3-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91r)

Compound **91r** was prepared from **90** by use of 5-methylpyridine-3-sulfonyl chloride **80e** following a similar procedure as for the preparation of compound **91a** from **90**. A yellow oil (77%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.35 (3H, d, *J* = 0.4 Hz), 2.86 (3H, s), 4.26 (2H, brs), 7.26 (1H, s), 7.32 (1H, ddd, *J* = 7.3 Hz, 5.2 Hz, 1.5 Hz), 7.38 (1H, brs), 7.76–7.90 (1H, m), 8.25–8.34 (1H, m), 8.46 (1H, d, *J* = 2.1 Hz), 8.63 (1H, d, *J* = 1.5 Hz).

4.57. *tert*-Butyl ({4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methylpyridin-3-yl)sulfonyl] -1*H*-pyrrol-3-yl}methyl)methylcarbamate (91s)

Compound **91s** was prepared from **90** by use of commercially available 6-methylpyridine-3-sulfonyl chloride following a similar procedure as for the preparation of compound **91a** from **90**. A colorless oil (83%): ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.62 (3H, s), 2.86 (3H, s), 4.26 (2H, s), 7.20 (1H, d, *J* = 8.0 Hz), 7.27–7.34 (2H, m), 7.51 (1H, dd, *J* = 8.0 Hz, 1.9 Hz), 7.76–7.86 (1H, m), 8.27–8.36 (1H, m), 8.50 (1H, d, *J* = 2.3 Hz).

4.58. 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(thiophen-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-

methylmethanamine hydrochloride (92a)

To a solution of compound **91a** (276 mg, 0.59 mmol) in EtOAc (2 mL) and *i*PrOH (1 mL) was added 4 mol/L HCl/EtOAc (5 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH to obtain compound **92a** as colorless crystals (168 mg, 70%): mp 196 °C; ^{1}H-NMR (DMSO-d_6) δ 2.56 (3H, s), 4.05 (2H, s), 7.22 (1H, dd, J = 5.1 Hz, 4.0 Hz), 7.48–7.56 (2H, m), 7.85 (1H, d, J = 5.5 Hz), 7.93 (1H, ddd, J = 9.5 Hz, 7.5 Hz, 2.0 Hz), 8.18 (1H, dd, J = 4.9 Hz, 1.3 Hz), 8.40 (1H, dq, J = 4.9 Hz, 0.9 Hz), 9.12 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_2S_2$: C, 44.39; H, 3.48; N, 10.35. Found: C, 44.31; H, 3.41; N, 10.35.

4.59. 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (92b)

Compound **92b** was prepared from **91b** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (77%): mp 229 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 4.07 (2H, s), 6.77 (1H, dd, J = 3.8 Hz, 1.7 Hz), 7.17 (1H, d, J = 3.8 Hz), 7.50 (1H, ddd, J = 7.1 Hz, 5.2 Hz, 1.4 Hz), 7.80 (1H, d, J = 5.5 Hz), 7.94 (1H, ddd, J = 9.3 Hz, 7.5 Hz, 1.6 Hz), 8.13 (1H, s), 8.40 (1H, d, J = 4.3 Hz), 9.04 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_3S$: C, 46.22; H, 3.62; N, 10.78. Found: C, 46.08; H, 3.50; N, 10.65.

4.60. 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(furan-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (92c)

Compound **92c** was prepared from **91c** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (76%): mp 234 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 6.72 (1H, dd, J = 1.9 Hz, 0.8 Hz), 7.49 (1H , ddd, J = 7.3 Hz, 5.0 Hz, 1.7 Hz), 7.85 (1H, d, J = 5.7 Hz), 7.91 (1H, ddd, J = 9.6 Hz, 7.5 Hz, 1.9 Hz), 7.96 (1H, t, J = 1.9 Hz), 8.33 (1H, dd, J = 1.5 Hz, 0.8 Hz), 8.36–8.41 (1H, m), 9.32 (2H, brs); Anal. Calcd for $C_{15}H_{14}ClF_2N_3O_3S$: C, 46.22; H, 3.62; N, 10.78. Found: C, 46.26; H, 3.58; N, 10.80.

4.61. 1-[4-Fluoro-5-(2-fluoropyridin-3-yl)-1-(pyridin-2-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine hydrochloride (92d)

To a solution of compound **91d** (221 mg, 0.477 mmol) in EtOAc (2 mL) and EtOH (2 mL) was added 4 mol/L HCl/EtOAc (4 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH/EtOAc (1/3) to obtain compound **92d** as colorless crystals (175 mg, 92%): mp 187–188 °C; ^{1}H-NMR (DMSO-d_6) δ 2.56 (3H, s), 4.06 (2H, s), 7.42–7.48 (1H, m), 7.72–7.92 (4H, m), 8.07–8.15 (1H, m), 8.33–8.38 (1H, m), 8.70–8.74 (1H, m), 9.18 (2H, brs); Anal. Calcd for $C_{16}H_{15}ClF_2N_4O_2S$: C, 47.94; H, 3.77; N, 13.98. Found: C, 48.01; H, 3.74; N, 14.04.

4.62. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methoxypyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (92e)

Compound **92e** was prepared from **91e** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (51%): mp 202–204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 3.79 (3H, s), 4.08 (2H, s), 7.21 (1H, d, J = 8.4 Hz), 7.32 (1H, d, J = 6.9 Hz), 7.42–7.46 (1H, m), 7.81–7.89 (2H, m), 7.94 (1H, dd, J = 8.4 Hz, 6.9 Hz), 8.33–8.35 (1H, m), 8.96 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.27; H, 3.90; N, 13.00.

4.63. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methoxypyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92f)

Compound **92f** was prepared from **91f** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (79%): mp 205–208 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 3.87 (3H, s), 4.06 (2H, s), 7.17 (1H, d, J = 2.3 Hz), 7.33 (1H, dd, J = 5.7 Hz, 2.7 Hz), 7.46 (1H, ddd, J = 6.9 Hz, 5.2 Hz, 1.5 Hz), 7.80 (1H, d, J = 5.7 Hz), 7.89 (1H, ddd, J = 9.3 Hz, 7.6 Hz, 1.7 Hz), 8.30–8.39 (1H, m), 8.51 (1H, d, J = 5.7 Hz), 9.01 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.47; H, 3.97; N, 12.97.

4.64. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methoxypyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92g)

Compound **92g** was prepared from **91g** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (88%): mp 229–233 °C; ^{1}H-NMR (DMSO-d_6) δ 2.54 (3H, s), 3.91 (3H, s), 4.03 (2H, s), 7.38–7.46 (1H, m), 7.51–7.58 (1H, m), 7.62–7.70 (1H, m), 7.75–7.87 (2H, m), 8.33 (1H, dt, J = 4.7 Hz, 0.8 Hz), 8.36 (1H, d, J = 3.0 Hz), 9.20 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_3S$: C, 47.39; H, 3.98; N, 13.00. Found: C, 47.35; H, 4.27; N, 12.77.

4.65. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(3-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine fumarate (92h)

To a solution of compound **91h** (107 mg, 0.223 mmol) in EtOAc (2 mL) and *i*PrOH (1 mL) was added 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure. A solution of $NaHCO_3$ was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by basic silica gel column chromatography (*n*-hexane/EtOAc = 4/1–1/1), and then the obtained oil (45 mg) was dissolved in EtOAc (2 mL). A solution of fumaric acid (13.6 mg, 0.117 mmol) in EtOH (2 mL) was added at room temperature, and the mixture was concentrated under reduced pressure. The residue was crystalized from EtOH/EtOAc (1/10) to produce compound **92h** as colorless crystals (51 mg, 46%): mp 150 °C; ^{1}H-NMR (DMSO-d_6) δ 2.35 (3H, s), 2.38 (3H, s), 3.73 (2H, s), 6.53 (2H, s), 7.32–7.39 (1H, m), 7.48 (1H, d, J = 5.7 Hz), 7.63 (1H, dd, J = 7.8 Hz, 4.4 Hz), 7.74–7.83 (1H, m), 7.93 (1H, d, J = 7.6 Hz), 8.27 (1H, d, J = 4.2 Hz), 8.41 (1H, d, J = 4.5 Hz), 3H not detected. Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.70; H, 4.16; N, 11.19.

4.66. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl}

-*N*-methylmethanamine hydrochloride (92i)

Compound **92i** was prepared from **91i** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (53%): mp 217–220 °C; ^{1}H-NMR (DMSO-d_6) δ 2.49 (3H, s), 2.54 (3H, s), 4.04 (2H, s), 7.43–7.48 (1H, m), 7.58–7.64 (2H, m), 7.79 (1H, d, J = 5.4 Hz), 7.88–7.99 (2H, m), 8.34–8.35 (1H, m), 9.21 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_2S$: C, 49.22; H, 4.13; N, 13.51. Found: C, 49.23; H, 4.11; N, 13.49.

4.67. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine succinate (92j)

To a solution of compound **91j** (333 mg, 0.696 mmol) in EtOAc (2 mL) and *i*PrOH (1 mL) was added 4 mol/L HCl/EtOAc (3 mL), and the mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure. The residue was crystalized from EtOAc, and the obtained crystals were recrystallized from EtOAc/EtOH (5/1) to produce 1-{4-fluoro-5-(2-fluoropyridin-3-yl) -1-[(4-methylpyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine hydrochloride (191 mg, 66 % from **91j**) as colorless crystals; mp 181–185 °C; ^{1}H-NMR (DMSO-d_6) δ 2.37 (3H, s), 2.56 (3H, s), 4.05 (2H, s), 7.45 (1H, ddd, J = 7.3 Hz, 5.0 Hz, 1.7 Hz), 7.54 (1H, s), 7.59–7.66 (1H, m), 7.77–7.90 (2H, m), 8.33–8.40 (1H, m), 8.55 (1H, d, J = 4.9 Hz), 9.11 (2H, brs); Anal. Calcd for $C_{17}H_{17}ClF_2N_4O_2S$: C, 49.22; H, 4.13; N, 13.51. Found: C, 49.30; H, 4.42; N, 13.61.

A solution of $NaHCO_3$ was added to the crystals (751 mg, 1.81 mmol), and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 1-{4-fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-2-yl) sulfonyl]-1*H*-pyrrol-3-yl}-*N*-methylmethanamine (647 mg, 62% from **91j)** as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 2.38 (3H, s), 2.45 (3H, s), 3.64 (2H, s), 7.23–7.30 (2H, m), 7.33 (1H, d, J = 5.7 Hz), 7.36 (1H, s), 7.88 (1H, ddd, J = 9.3 Hz, 7.4 Hz, 1.9 Hz), 8.22–8.29 (1H, m), 8.45 (1H, d, J = 4.5 Hz), 1H not detected.

The obtained oil (189 mg, 0.50 mmol) was dissolved in EtOAc (2 mL). A solution of succinic acid (59 mg, 0.50 mmol) in EtOH (2 mL) was added at room temperature, and the mixture was concentrated under reduced pressure. The resulting solid was recrystallized from EtOH/H_2O (10/1) to obtain compound **92j** as colorless crystals (232 mg, 58% from **91j**): mp 166–168 °C; ^{1}H-NMR (DMSO-d_6) δ 2.34 (3H, s), 2.36 (4H, s), 2.37 (3H, s), 3.66 (2H, s), 7.39–7.49 (2H, m), 7.52 (1H, s), 7.55–7.63 (1H, m), 7.86 (1H, ddd, J = 9.5 Hz, 7.4 Hz, 1.9 Hz), 8.34 (1H, ddd, J = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.54 (1H, d, J = 4.9 Hz), 3H not detected. Anal. Calcd for $C_{21}H_{22}F_2N_4O_6S$: C, 50.80; H, 4.47; N, 11.28. Found: C, 50.77; H, 4.52; N, 11.37.

4.68. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(6-fluoropyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92k)

Compound **92k** was prepared from **91k** following a similar procedure as for the preparation of compound **92d** from **91d**. Colorless crystals (53%): mp 215–218 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58

(3H, s), 4.08 (2H, s), 7.44–7.48 (1H, m), 7.65–7.78 (3H, m), 7.87–7.92 (1H, m), 8.28–8.37 (2H, m), 8.85 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.51; H, 3.38; N, 13.26.

4.69. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-2-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92l)

Compound **92l** was prepared from **91l** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (51%): mp 200–204 °C; ^{1}H-NMR (DMSO-d_6) δ 2.58 (3H, s), 4.07 (2H, s), 7.41–7.49 (1H, m), 7.80 (1H, d, J = 5.5 Hz), 7.82–7.91 (2H, m), 8.05 (1H, dt, J = 8.6 Hz, 2.8 Hz), 8.36 (1H, ddd, J = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.78 (1H, d, J = 2.8 Hz), 8.97 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.95; H, 3.46; N, 13.43.

4.70. 1-{1-[(2-Chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92m)

Compound **92m** was prepared from **91m** following a similar procedure as for the preparation of compound **92d** from **91d**. Colorless crystals (90%): mp 219 °C; ^{1}H-NMR (DMSO-d_6) δ 2.59 (3H, s), 4.09 (2H, s), 7.40–7.48 (1H, m), 7.52 (1H, dd, J = 8.0 Hz, 4.5 Hz), 7.72–7.79 (1H, m), 7.81–7.91 (1H, m), 7.93–8.02 (1H, m), 8.32–8.36 (1H, m), 8.75 (1H, dd, J = 4.7 Hz, 1.7 Hz), 9.21 (2H, brs). Anal. Calcd for $C_{16}H_{14}Cl_2F_2N_4O_2S$: C, 44.15; H, 3.24; N, 12.87. Found: C, 43.98; H, 3.41; N, 12.86.

4.71. 1-{1-[(5-Chloropyridin-3-yl)sulfonyl]-4-fluoro-5-(2-fluoropyridin-3-yl)-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92n)

Compound **92n** was prepared from **91n** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (95%): mp 211–216 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 7.52 (1H, ddd, J = 7.3 Hz, 5.1 Hz, 1.9 Hz), 7.93 (1H, ddd, J = 9.6 Hz, 7.5 Hz, 2.0 Hz), 8.01 (1H, d, J = 5.5 Hz), 8.11 (1H, t, J = 2.2 Hz), 8.43 (1H, ddd, J = 4.9 Hz, 1.8 Hz, 0.8 Hz), 8.57 (1H, d, J = 2.1 Hz), 9.05 (1H, d, J = 2.1 Hz), 9.33 (2H, brs); Anal. Calcd for $C_{16}H_{14}Cl_2F_2N_4O_2S$: C, 44.15; H, 3.24; N, 12.87. Found: C, 44.20; H, 3.56; N, 12.90.

4.72. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-fluoropyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine hydrochloride (92o)

Compound **92o** was prepared from **91o** following a similar procedure as for the preparation of compound **92a** from **91a**. Colorless crystals (65%): mp 228–233 °C; ^{1}H-NMR (DMSO-d_6) δ 2.57 (3H, s), 4.05 (2H, s), 7.51 (1H, ddd, J = 7.4 Hz, 5.1 Hz, 1.9 Hz), 7.92 (1H, ddd, J = 9.5 Hz, 7.6 Hz, 1.9 Hz), 8.01 (1H, d, J = 5.3 Hz), 8.05 (1H, dt, J = 7.7 Hz, 2.4 Hz), 8.36–8.46 (1H, m), 8.49 (1H, s), 9.03 (1H, d, J = 2.7 Hz), 9.36 (2H, brs); Anal. Calcd for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38. Found: C, 45.94; H, 3.35; N, 13.47.

4.73. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(2-methylpyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine fumarate (92p)

Compound **92p** was prepared from **91p** following a similar procedure as for the preparation of compound **92h** from **91h**. Colorless crystals (85%): mp 182–185 °C; ^{1}H-NMR (DMSO-d_6) δ 2.41 (3H, s), 2.49 (3H, s), 3.77 (2H, s), 6.53 (2H, s), 7.31 (1H, dd, *J* = 8.1 Hz, 4.7 Hz), 7.42 (1H, ddd, *J* = 7.2 Hz, 5.1 Hz, 1.7 Hz), 7.47 (1H, dd, *J* = 8.3 Hz, 1.5 Hz), 7.71 (1H, d, *J* = 5.7 Hz), 7.84 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 1.9 Hz), 8.28–8.34 (1H, m), 8.73 (1H, dd, *J* = 4.7 Hz, 1.7 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 51.06; H, 4.10; N, 11.37.

4.74. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(4-methylpyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine fumarate (92q)

Compound **92q** was prepared from **91q** following a similar procedure as for the preparation of compound **92h** from **91h**. Colorless crystals (78%): mp 205–208 °C; ^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, s), 2.40 (3H, s), 3.76 (2H, s), 6.53 (2H, s), 7.43 (1H, ddd, *J* = 7.3 Hz, 5.1 Hz, 1.8 Hz), 7.52 (1H, d, *J* = 5.1 Hz), 7.72 (1H, d, *J* = 5.7 Hz), 7.85 (1H, ddd, *J* = 9.5 Hz, 7.4 Hz, 1.9 Hz), 8.14 (1H, s), 8.32 (1H, ddd, *J* = 4.9 Hz, 1.9 Hz, 0.9 Hz), 8.70 (1H, d, *J* = 5.1 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.95; H, 4.11; N, 11.37.

4.75. 1-{4-Fluoro-5-(2-fluoropyridin-3-yl)-1-[(5-methylpyridin-3-yl)sulfonyl]-1*H*-pyrrol-3-yl} -*N*-methylmethanamine fumarate (92r)

Compound **92r** was prepared from **91r** following a similar procedure as for the preparation of compound **92h** from **91h**. Colorless crystals (76%): mp 178–182 °C; ^{1}H-NMR (DMSO-d_6) δ 2.33 (3H, s), 2.35 (3H, s), 3.70 (2H, s), 6.54 (2H, s), 7.50 (1H, ddd, *J* = 7.3 Hz, 5.1 Hz, 1.9 Hz), 7.63–7.71 (2H, m), 7.90 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 2.0 Hz), 8.36–8.41 (1H, m), 8.42 (1H, d, *J* = 2.3 Hz), 8.76 (1H, d, *J* = 1.3 Hz), 3H not detected; Anal. Calcd for $C_{21}H_{20}F_2N_4O_6S$: C, 51.01; H, 4.08; N, 11.33. Found: C, 50.88; H, 4.06; N, 11.31.

4.76. Bis{1-[4-fluoro-5-(2-fluoropyridin-3-yl)-1-(6-methypyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl] -*N*-methylmethanamine}fumarate (92s)

Compound **92s** was prepared from **91s** following a similar procedure as for the preparation of compound **92h** from **91h**. Colorless crystals (70%): mp 192–195 °C; ^{1}H-NMR (DMSO-d_6) δ 2.30 (3H, s), 2.56 (3H, s), 3.61 (2H, s), 6.51 (1H, s), 7.45–7.53 (2H, m), 7.60 (1H, d, *J* = 5.7 Hz), 7.79 (1H, dd, *J* = 8.3 Hz, 2.3 Hz), 7.91 (1H, ddd, *J* = 9.6 Hz, 7.5 Hz, 1.9 Hz), 8.35–8.40 (1H, m), 8.48 (1H, d, *J* = 2.3 Hz), 2H not detected; Anal. Calcd for $C_{19}H_{18}F_2N_4O_4S$: C, 52.29; H, 4.16; N, 12.84. Found: C, 52.32; H, 4.28; N, 12.86.

4.77. Measurement of H^+,K^+-ATPase activity

This procedure was performed using the method described above (**2.55**).

4.78. An assay of inhibition of acid secretion in anesthetized rats by intravenous administration

This assay was performed by the method described above (**2.56**).

4.79. An assay of inhibition of acid secretion in anesthetized rats by oral administration

This assay was conducted in a manner similar to a method reported above (**3.105**). A test compound

at doses of 1, 2, 3, or 4 mg/kg (as the free base) or vehicle was administered orally 1 h before pylorus ligation and histamine 2HCl (30 mg/kg, subcutaneous) administration. Gastric contents were collected 3 h after histamine administration, and the total acid output was calculated.

4.80. Measurement of pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats

This assay was performed by the method described above (**3.106**).

4.81. An assay of inhibition of acid secretion in Heidenhain pouch dogs

This assay was performed by the method described above (**3.107**).

4.82. A pharmacokinetic experiment in rats

Test compounds were administered intravenously via cassette dosing to fasted male Sprague-Dawley rats. After that, blood and the stomach were collected. The blood samples were centrifuged to obtain the plasma fraction. The plasma and a 20% stomach homogenate in saline were deproteinized with acetonitrile containing an internal standard. After centrifugation, the supernatant was diluted and centrifuged again. The compound concentrations in the supernatant were measured by LC/MS/MS.

4.83. A cytotoxicity assay

This assay was carried out by the method described above (**3.108**).

4.84. Whole-cell patch-clamp for a hERG inhibition assay

This assay was conducted using a procedure described above (**3.109**).

4.85. Measurement of CYP3A4-inhibitory activity

This activity of test compounds was evaluated by incubating 100 μmol/L testosterone with 10 nmol/L CYP3A4 derived from CYP3A4-expressing insect cells (BD Bioscience) in the presence of 10 μmol/L test compound. The reaction mixture was incubated for 15 min at 37 °C. The concentration of 6β-hydroxytestosterone was measured by means of an HPLC system equipped with an ultraviolet light detector.

References

1. Linz B., Balloux F., Moodley Y. *et al*. An African origin for the intimate association between humans and Helicobacter pylori. *Nature*, **445**, 915-918 (2007).
2. Howden C.W., Burget D.W., Hunt R.H. Appropriate acid suppression for optimal healing of duodenal ulcer and gastro-oesophageal reflux disease. *Scand J Gastroenterol*, **29** (Suppl 201), 79-82 (1994).
3. Bell N.J.V., Burget D., Howden C.W., Wilkinson J., Hunt R.H. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. *Digestion*, **51** (Suppl 1), 59-67 (1992).
4. Hunt R.H. Importance of pH control in the management of GERD. *Arch Intern Med,* **159** (7), 649-657 (1999).
5. Sachs G., Meyer-Rosberg K., Scott D.R., Melchers K. Acid, protons and Helicobacter pylori. *Yale J Biol Med*, **69**, 301-316 (1996).
6. Forte J.G., Forte G.M., Saltman P. K^+ - stimulated phosphatase of microsomes from gastric mucosa. *J Cell Physiol*, **69**, 293-304 (1967).
7. Ganser A.L., Forte J.G. K^+-stimulated ATPase in purified microsomes of bullfrog oxyntic cells. *Biochim Biophys Acta*, **307** (1), 169-180 (1973).
8. Graham D.Y., Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut*, **59**, 1143-1153 (2010).
9. 蘆田　潔. PPI 抵抗性 GERD に対する診療の現状 PPI 抵抗性 GERD に使用される薬剤の特徴と使用上の注意 開発中の薬剤,今後の展望. 医学と薬学, **71**, 591-596 (2014).
10. Fass R., Shapiro M., Dekel R., Sewell J. Systematic review: proton‐pump inhibitor failure in gastro‐oesophageal reflux disease–where next?. *Aliment Pharmacol Ther*, **22**, 79–94 (2005).
11. Dammann H.G., Burkhardt F. Pantoprazole versus omeprazole: influence on meal-stimulated gastric acid secretion. *Eur J Gastroenterol Hepatol*, **11** (11), 1277–1282 (1999).
12. Katz P.O., Hatlebakk J.G., Castell D.O. Gastric acidity and acid breakthrough with twice-daily omeprazole or lansoprazole. *Aliment Pharmacol Ther*, **14**, 709–714 (2000).
13. Ang T.L., Fock K.M. Nocturnal acid breakthrough: clinical significance and management. *J Gastroenterol Hepatol*, **21**, S125–S128 (2006).
14. Furuta T., Shirai N., Sugimoto M., Nakamura A., Hishida A., Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet*, **20** (3), 153–167 (2005).
15. Wada F., Murase K., Isomoto H. *et al*. Polymorphism of CYP2C19 and gastric emptying in patients with proton pump inhibitor-resistant gastric ulcers. *J Int Med Res*, **30**, 413-421 (2002).
16. Klotz U. Clinical impact of CYP2C19 polymorphism on the action of proton pump inhibitors: a review of a special problem. *Int J Clin Pharmacol Ther*, **44**, 297-302 (2006).

17. Furuta T., Shirai N., Watanabe F. *et al*. Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. *Clin Pharmacol Ther*, **72**, 453-460 (2002).
18. Forte J.G., Hanzel D.K., Okamoto C., Chow D., Urushidani T. Membrane and protein recycling associated with gastric HCl secretion. *J Intern Med Suppl*, **228** (s732), 17-26 (1990).
19. 西田 晴行. 新規カリウムイオン競合型アシッドブロッカーボノプラザンの創製. ファルマシア, **52** (6), 539-543 (2016)
20. Gedda K., Scott D., Besancon M., Lorentzon P., Sachs G. Turnover of the gastric H+, K^+-adenosine triphosphatase α subunit and its effect on inhibition of rat gastric acid secretion. *Gastroenterology*, **109** (4), 1134-1141 (1995).
21. Sachs G., Shin J.M., Briving C., Wallmark B., Hersey S. The pharmacology of the gastric acid pump: the H^+,K^+ ATPase. *Annu Rev Pharmacol Toxicol*, **35** (1), 277-305 (1995).
22. Parsons M.E., Keeling D.J. Novel approaches to the pharmacological blockade of gastric acid secretion. *Expert Opin Investig Drugs*, **14**, 411-421 (2005).
23. Kahrilas P.J., Dent J., Lauritsen K. *et al*. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. *Clin Gastroenterol Hepatol*, **5**, 1385-1391 (2007).
24. Berg A.L., Böttcher G., Andersson K. *et al*. Early stellate cell activation and veno-occlusive-disease (VOD)–like hepatotoxicity in dogs treated with AR-H047108, an imidazopyridine proton pump inhibitor. *Toxicol Pathol*, **36**, 727-737 (2008).
25. Dent J., Kahrilas P.J., Hatlebakk J. *et al*. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol*, **103**, 20-26 (2008).
26. Kaminski J.J., Bristol J.A., Puchalski C. *et al*. Antiulcer agents. 1. Gastric antisecretory and cytoprotective properties of substituted imidazo [1,2-a] pyridines. *J Med Chem,* **28**, 876–892 (1985).
27. Gedda K., Briving C., Svensson K., Maxvall I., Andersson K. Mechanism of action of AZD0865, a K^+-competitive inhibitor of gastric H^+, K^+-ATPase. *Biochem Pharmacol*, **73**, 198–205 (2007).
28. Ito K., Kinoshita K., Tomizawa A. *et al.* Pharmacological profile of novel acid pump antagonist 7-(4-fluorobenzyloxy)-2, 3-dimethyl-1-{[(1S, 2S)-2-methyl cyclopropyl] methyl}-1H-pyrrolo [2, 3-d] pyridazine (CS-526). *J Pharmacol Exp Ther*, **323**, 308–317 (2007).
29. Simon W.A., Herrmann M., Klein T. *et al.* Soraprazan: setting new standards in inhibition of gastric acid secretion. *J Pharmacol Exp Ther*, **321**, 866–874 (2007).
30. Kondo M., Kawamoto M., Hasuoka A. *et al*. High-throughput screening of potassium-competitive acid blockers. *J Biomol Screen*, **17** (2), 177–182 (2012).
31. Iranpoor N., Firouzabadi H., Akhlaghinia B., Nowrouzi N. A novel and highly selective

conversion of alcohols, thiols, and silyl ethers to azides using the triphenylphosphine/2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ)/n-Bu_4NN_3 system. *Tetrahedron Letters* **45**, 3291-3294 (2004).

32. Van Leusen A.M., Siderius H., Hoogenboom B.E., van Leusen D. A new and simple synthesis of the pyrrole ring system from Michael acceptors and tosylmethylisocyanides. *Tetrahedron lett*, **13** (52), 5337–5340 (1972).
33. Toyoshima C., Nomura H. Structural changes in the calcium pump accompanying the dissociation of calcium. *Nature*, **418**, 605–611 (2002).
34. Bower M.J., Cohen F.E., Dunbrack R.L.J. Prediction of protein side-chain rotamers from a backbone-dependent rotamer library: a new homology modeling tool. *J Mol Biol*, **267**, 1268–1282 (1997).
35. Jones G., Willett P., Glen R.C., Leach A.R., Taylor R. Development and validation of a genetic algorithm for flexible docking. *J Mol Biol*, **267**, 727–748 (1997).
36. Yamamoto K., Ikeda Y. Kinetic solubility and lipophilicity evaluation connecting formulation technology strategy perspective. *J Drug Deliv Sci Technol,* **33**, 13–18 (2016).
37. Nishida H. Discovery of Vonoprazan Fumarate (TAK-438) as a Novel, Potent and Long-Lasting Potassium-Competitive Acid Blocker. *Successful Drug Discovery*, **2**, 215-233 (2016).
38. 西田 晴行. 新規カリウムイオン競合型アシッドブロッカーボノプラザン（TAK-438）の創製. *Medchem News*, **25** (4), 198-206 (2015)
39. Leeson P.D., Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat Rev Drug Discov*, **6**, 881–890 (2007).
40. Arikawa Y., Nishida H., Kurasawa O. *et al*. Discovery of a novel pyrrole derivative 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine fumarate (TAK-438) as a potassium-competitive acid blocker (P-CAB). *J Med Chem*, **2012**, 55, 4446-4456.
41. Hori Y., Imanishi A., Matsukawa J. *et al*. 1-[5-(2-Fluorophenyl)-1-(pyridine-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate (TAK-438), a novel and potent potassium-competitive acid blocker for the treatment of acid-related diseases. *J Pharmacol Exp Ther*, **335**, 231-238 (2010).
42. Hori Y., Matsukawa J., Takeuchi T. *et al*. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. *J Pharmacol Exp Ther*, **337**, 797-804 (2011).
43. Böhm H.J., Banner D., Bendels S. *et al*. Fluorine in medicinal chemistry. *Chembiochem,* **5**, 637–643 (2004).
44. Imaeda T., Ono K., Nakai K. *et al*. Discovery, synthesis, and structure-activity relations of 3, 4-dihydro-1H-spiro (naphthalene-2,2′ -piperidin)-1-ones as potassium-competitive acid

blockers. *Bioorg Med Chem*, **25**, 3719-3735 (2017).

45. Arikawa Y., Hasuoka A., Nishida H. et al. Synthetic studies of five-membered heteroaromatic derivatives as potassium-competitive acid blockers (P-CABs). *Bioorg Med Chem Lett*, **25**, 2037-2040 (2015).
46. Itoh T., Mase T. (2004). A general palladium-catalyzed coupling of aryl bromides/triflates and thiols. *Org Lett*, **6** (24), 4587–4590 (2004).
47. Nishiguchi A., Maeda K., Miki S. Sulfonyl chloride formation from thiol derivatives by N-chlorosuccinimide mediated oxidation. *Synthesis*, **2006** (24), 4131-4134 (2006).
48. Nagashima H., Isono Y., Iwamatsu S. Copper-catalyzed cyclization of *N*-allylhalodifluoroacetamides: An efficient synthesis of α,α-difluorinated γ-lactams. *J Org Chem*, **66**, 315–319 (2001).
49. Rong X.X., Pan H.Q., Dolbier W.R. Jr., Smart B.E. Reactivity of fluorinated alkyl radicals in solution. Some absolute rates of hydrogen-atom abstraction and cyclization. *J Am Chem Soc*, **116** (10), 4521–4522 (1994).
50. Yang B.V., O'Rourke D., Li J. Mild and selective debenzylation of tertiary amines using α-chloroethyl chloroformate. *Synlett*, **1993** (3), 195-196 (1993).
51. Inatomi N, Matsukawa J, Sakurai Y, Otake K. Potassium-competitive acid blockers: Advanced therapeutic option for acid-related diseases. *Pharmacol Ther*, **168**, 12–22 (2016).
52. Sakurai Y., Nishimura A., Kennedy G. *et al*. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (vonoprazan) doses in healthy male Japanese/non-Japanese subjects. *Clin Transl Gastroenterol*, **6**, e94; doi:10.1038 /ctg.2015.18 (2015).
53. Jenkins H., Sakurai Y., Nishimura A. et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther*, **41**, 636–648 (2015).
54. Sakurai Y., Mori Y., Okamoto H. et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects-a randomised open-label cross-over study. *Aliment Pharmacol Ther*, **42**, 719–730 (2015).
55. Ashida K., Sakurai Y., Hori T. *et al*. Randomised clinical trial: vonoprazan, a novel potassium‐competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. *Aliment Pharmacol Ther*, **43**, 240–251 (2016).
56. Wallmark B., Sachs G., Mardh S., Fellenius E. Inhibition of gastric (H^++ K^+)-ATPase by the substituted benzimidazole, picoprazole. *Biochim Biophys Acta*, **728**, 31–38 (1983).
57. Fiske C.H., Subbarow Y. The colorimetric determination of phosphorus. *J Biol Chem*, **66**, 375–400 (1925).

58. Imai Y.N., Ryu S., Oiki S. Docking model of drug binding to the human ether-a-go-go potassium channel guided by tandem dimer mutant patch-clamp data: a synergic approach. *J Med Chem*, **52**, 1630–1638 (2009).
59. Sheldrick G.M. A short history of SHELX. *Acta Crystallogr A*, **64**, 112–122 (2008).