Identification, Synthesis, and Activity of Novel Blockers of the Voltage-Gated Potassium Channel Kv1.5

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The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. In the present study the discovery of ortho,ortho-disubstituted bisaryl compounds as blockers of the Kv1.5 channel is presented. Several compounds of this new class were synthesized and screened for their ability to block Kv1.5 channels expressed in *Xenopus* oocytes. The observed structure−activity relationship (SAR) is described by a pharmacophore model that consists of three hydrophobic centers in a triangular arrangement. The hydrophobic centers are matched by a phenyl or pyridyl ring of the bisaryl core and both ends of the side chains. The most potent compounds (e.g., **17c** and **17o**) inhibited the Kv1.5 channel with sub-micromolar half-blocking concentrations and displayed 3-fold selectivity over Kv1.3 and no significant effect on the HERG channel and sodium currents. In addition, compounds **17c** and **17m** have already shown antiarrhythmic effects in a pig model.

Introduction

Atrial fibrillation (AF) and atrial flutter are the most frequent cardiac arrhythmias. The incidence increases with age and is connected with increased morbidity and a doubling of mortality. AF affects about 3 million Americans and leads to more than 80 000 strokes each year in the US due to increased risk of thromboembolic events.[1]

It is well-known that atrial fibrillation or flutter are caused, or at least maintained, by reentrant wavelets. A well-established principle to extinguish or prevent such reentries is the increase of the myocardial refractoriness by prolongation of the action potential duration (APD). A major determinant of the action potential is the amount of repolarizing potassium currents, particularly the three delayed rectifier currents IK_r, IK_s, and IK_{ur} and the transient outward current I_{to}. Therefore, blockers of these currents can be expected to have antiarrhythmic effects.[2]

The presently available antiarrhythmics of classes I (sodium channel blockers) and III (potassium channel blockers) can terminate AF and reduce its recurrence, but may increase mortality due to a variety of adverse effects, including the risk of potentially lethal ventricular proarrhythmia (CAST-trial,[3] SWORD-trial[4]). Therefore, there is an unmet medical need for the development of safer and more efficient drugs for the treatment of atrial arrhythmias.[5,6]

Most of the available class III antiarrhythmics are blockers of IK_r (e.g., dofetilide, almokalant, ibutilide, D-sotalol). The new antiarrhythmic agent azimilide is a combined blocker of IK_r and IK_s.[7] However, since IK_r and IK_s are both present in the atrium and ventricle, undesired ventricular effects may be observed for these drugs which limit their use for the treatment of atrial arrhythmias.

In contrast to IK_r and IK_s, the ultrarapid delayed rectifier IK_{ur} has been found only in human atrial cells and not in the ventricles.[8−10] Therefore, it should be a promising target for the development of new atrial selective antiarrhythmics.

The molecular component that underlies IK_{ur} in the human atrium is the Kv1.5 channel.[8,9,11,12] Kv1.5 channels belong to the superfamily of voltage-gated potassium channels, comprising four pore-forming subunits, each subunit containing six transmembrane segments.[13]

During the past decade, several publications have pointed to the potential advantages which a selective Kv1.5 channel blocker could have for the treatment of AF.[8,10−12,14,15] In 1993 Nattel showed that 50 μM 4-aminopyridine, a putative Kv1.5 blocker, increased the action potential duration in isolated human atrial cells by 66%.[11] Due to the lack of selective Kv1.5 blockers, two groups have calculated the effect of Kv1.5 channel blockade in a mathematical model of the human atrial action potential.[16−18] Although these models imply different conclusions, both support the use of Kv1.5 blockers as new potential drugs for AF, particularly under the pathological conditions of chronic atrial fibrillation.

Since then, the search for potent and selective Kv1.5 blockers has begun. Several pharmaceutical companies have filed patents claiming compounds as blockers of the IK_{ur} some of which are depicted in Figure 1.[19] In 1998 Icagen and Eli Lilly published new indanes such as **1** as inhibitors of the Kv1.5 and Kv1.3 channel. Compound **1** was described to exhibit an IC_{50} of 0.1 μM on hKv1.5 expressed in CHO cells.[20] In a subsequent

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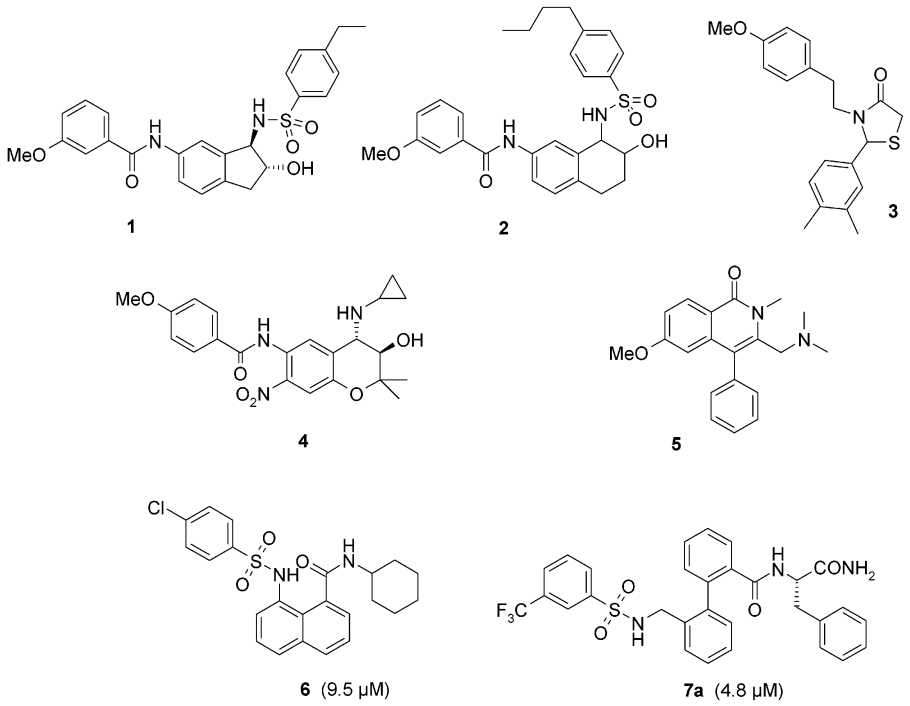


Figure 1. Known Kv1.5 blockers **1**−**5**, initial screening hit **6**, and lead compound **7a** (in brackets IC_{50} for human Kv1.5 as measured in *Xenopus* oocytes).

patent application by Icagen the indane ring was expanded to a tetrahydronaphthalene ring leading to the slightly more potent Kv1.5 blocker **2** (IC_{50} = 0.05 μM).[21] A completely different compound class are the thiazolidinones claimed by the same company with compound **3** being the most potent example showing an IC_{50} of 0.2 μM.[22] Nissan has also claimed many blockers of the Kv1.5 channel. An intensively characterized lead compound is the benzopyrane **4**, reported in the literature as NIP-142 (free amine) and NIP-141 (hydrochloride of NIP-142). It was shown that this compound inhibits hKv1.5 expressed in HEK293 cells with an IC_{50} value of 4.75 μM.[23] Merck reported several structural classes which inhibit Kv1.5 channels, the most recent class are isoquinolines as depicted by the preferred example **5**.[24]

In the present study, we report the discovery and subsequent structure−activity investigation of novel ortho,ortho-disubstituted bisaryl compounds as blockers of the Kv1.5 channel.[25]

Lead Identification

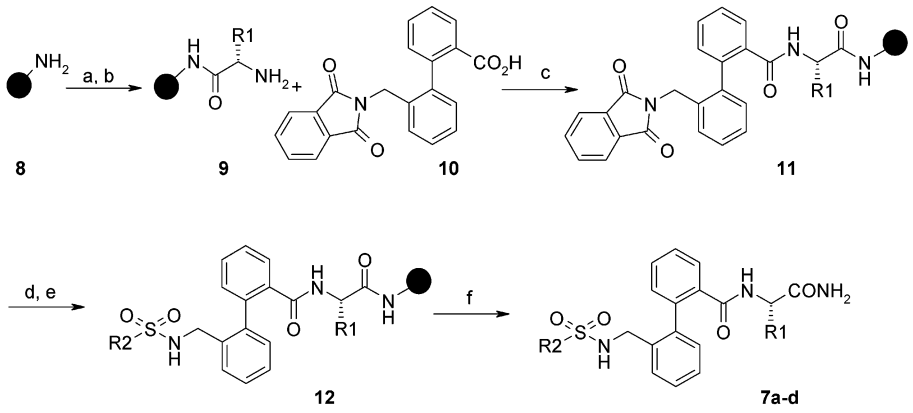
Starting from **1**, a micromolar inhibitor of the Kv1.5 channel, we searched for novel inhibitors within our company compound library using a 2-D similarity search.[26] Seventy-five compounds with a similarity coefficient of at least 0.8 were screened for inhibition of IK_{ur}. As a screening model we used *Xenopus* oocytes injected with cRNA of human Kv1.5.

Using this protocol we discovered the naphthalene derivative **6** that blocked Kv1.5 with moderate potency (IC_{50} = 9.5 μM). However, because of its chemical instability and insufficient physical properties, this compound was not regarded as a lead compound. At this time we were also working on 1,1′-disubstituted biphenyls with similar side chains to the initial screening hit **6** for a different project. Although the similarity between the two frameworks was not obvious we decided to investigate whether this framework could replace the 1,8-disubstituted naphthalene scaffold. Gratifyingly, using solid-phase synthesis (see Chemistry) we identified lead compound **7a** with an IC_{50} of 4.8 μM as the most potent compound from a newly synthesized biased library. Further lead optimization relied on parallel synthesis in solution to overcome restrictions imposed by the need for linkers in solid-phase synthesis.

Chemistry

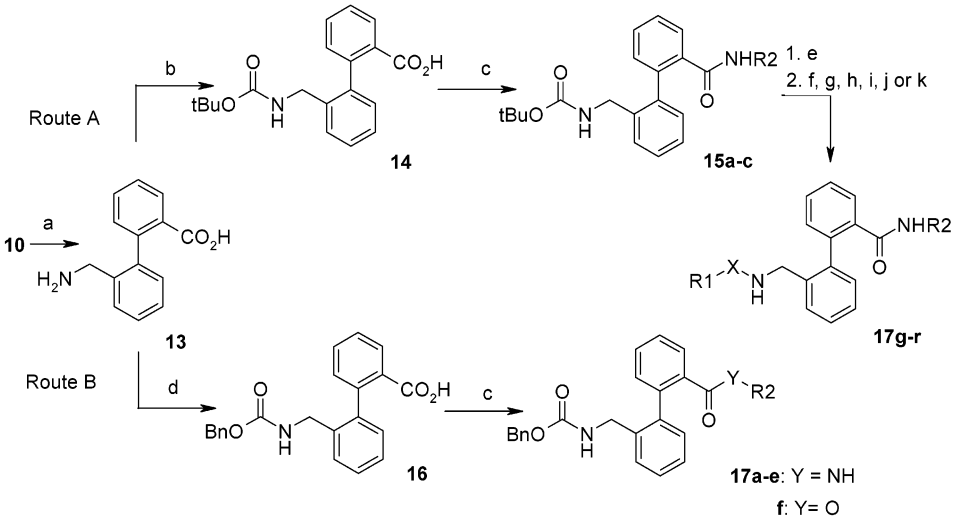
1. Solid-Phase Synthesis of 1,1′-Disubstituted Biphenyls. The 1,1′-disubstituted biphenyl scaffold obviously offers two sites of variation, one from the carboxylic acid functionality and one from the aminomethyl group. For a rapid evaluation of the chemical and biological space offered by this framework, we required a protocol that provided a diverse set of test compounds in a few steps (Scheme 1). The first site of diversity was introduced by attaching *N*-(fluorenylmethyloxy)carbonyl (*N*-Fmoc) protected amino acids to Rink amide polystyrene resin **8** using TOTU/HOBt/DIPEA as a coupling agent. The quantification of amino acid loading on the solid support was determined to be typically 0.9 mmol/g by quantitative Fmoc analysis. After piperidine mediated removal of the *N*-Fmoc protection group from the resin the *N*-phthalimide-protected aminomethylbiphenyl-carboxylic acid **10**[27] was loaded onto the derivatized Rink resin **9** to give resin **11** again using TOTU/HOBt/DIPEA as the coupling agent. The *N*-phthalimido protecting group was completely removed by treatment with 10% hydrazine in dimethylformamide (DMF). The second site of diversity was introduced by coupling a diverse set of sulfonyl chlorides in DMF in the presence of DIPEA to give the resin-bound sulfonamides **12**. Finally, standard trifluoroacetic acid (TFA) cleavage delivered the desired products **7**, which were generally purified by reversed phase HPLC.

Scheme 1[a]



[a] Reagents: (a) Fmoc amino acid, 1-hydroxybenzotriazol (HOBt), *O*-[(ethoxycarbonyl)cyanmethylenamino]-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate (TOTU), diisopropylethylamine (DIPEA); (b) piperidine, DMF; (c) HOBt, TOTU, DIPEA, DMF; (d) hydrazine, DMF; (e) R_2SO_2Cl, DIPEA, DMF; (f) TFA, CH_2Cl_2.

Scheme 2[a]



[a] Reagents: (a) hydrazine, MeOH, 40 °C; (b) di-*tert*-butyl dicarbonate, dioxane, aq NaOH; (c) diisopropyl carbodiimide (DIC), HOBt, THF or CH_2Cl_2; (d) benzyl *N*-succinimidocarbonate, dioxane, $NaHCO_3$; (e) TFA, CH_2Cl_2; (f) carboxylic acid, TOTU, *N*-methylmorpholine, DMF or acid chloride, triethylamine, CH_2Cl_2; (g) sulfonyl chloride, triethylamine, CH_2Cl_2; (h) chloroformate, triethylamine, or succinimidocarbonate, dioxane, $NaHCO_3$; (i) isocyanate, triethylamine, CH_2Cl_2; (j) sulfonyl carbamate, DIPEA, toluene, reflux; (k) aldehyde, $NaCNBH_3$, THF/MeOH.

2. Solution-Phase Synthesis of 1,1′-Disubstituted Biphenyls. To investigate the structure−activity relationship of the substituents on either aminomethyl or carboxylic functionality of the biphenyl scaffold in a systematic way we switched from solid-phase synthesis to parallel synthesis in solution (Scheme 2). As the removal of a *N*-phthalimido group is somewhat cumbersome in solution phase chemistry, we abandoned building block **10** and converted it into the Boc-protected intermediate **14**[28] which was isolated by crystallization after standard transformations. Formation of amides **15** was achieved using DIC/HOBt as the coupling reagents. After TFA-mediated removal of the Boc protecting group the amino functionality was subjected to various derivatization agents: amides **17i**,**m**,**q**,**r** were formed with acid chlorides or acids using TOTU as coupling reagent, sulfonamide **17h** was obtained by reaction with phenyl sulfonyl chloride, carbamates **17g**,**n**−**p** either with chloroformates or succinimidocarbonates, urea **17j** with phenyl isocyanate, sulfonylurea **17l** with ethyl *p*-methoxyphenyl sulfonyl carbamate, and finally amine **17k** by reductive amination with phenyl acetaldehyde.

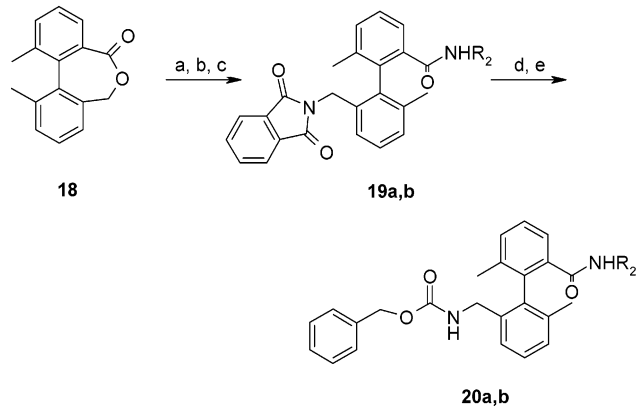
Whereas route A described above is ideal to probe the influence of substituent R1 and the linkage X on the activity as it is introduced in the last step, this is not true for R2. For a rapid evaluation of substituent R2, we relied on route B where we used the benzyl carbamate as a permanent R1 probe and permutated the side chain R2 in the final step.

The requisite benzyl carbamate **16** was prepared from precursor **13** by reaction with benzyl *N*-succinimidocarbonate, amides **17a**−**e** were prepared as described above and ester **17f** was formed using the same coupling agent.

As ortho,ortho-disubstituted biphenyl compounds can exist in two atropisomeric configurations, we further wished to investigate the role of axial chirality on activity. To this end, we synthesized analogues with two additional methyl groups in ortho position to obtain configurationally stable compounds that can be separated into the optical antipodes at ambient temperature.

The synthesis of axially chiral biphenyl compounds **20** can be accomplished employing the ortho-tetrasubstituted core **18** (Scheme 3). This intermediate is avail-

Scheme 3[a]



[a] Reagents: (a) potassium phthalimide, DMF, 150 °C; (b) $SOCl_2$; (c) amine, DIPEA, CH_2Cl_2; (d) hydrazine, ethanol; (e) benzyl *N*-succinimidocarbonate, DIPEA, CH_2Cl_2.

able in a multistep reaction sequence starting from 3-methyl-2-aminobenzoic acid.[29] The seven-membered lactone **18** was opened by heating with potassium phthalimide in DMF at 150 °C. As well as the compound with the intact *N*-phthalimide substituent, material with a partially hydrolyzed phthalimide group was also observed. The crude reaction mixture was treated with thionyl chloride which transformed the carboxylic acid into its acid chloride and reclosed any partially hydrolyzed phthalimide. Reaction with amines in dichloromethane yielded compounds **19**. After removal of the *N*-phthalimido protecting group by treatment with hydrazine in DMF the synthesis of the racemic compounds **20** was completed by acylation with benzyl *N*-succinimidocarbonate. The enantiomers were separated by preparative HPLC on a chiral column. The absolute stereochemistry of the antipodes was assigned by comparison with structurally closely related compounds relying on the sign of the optical rotation.[30]

3. Solution-Phase Synthesis of Ortho,Ortho-Disubstituted Phenylpyridines. For the synthesis of the ortho,ortho-disubstituted phenylpyridines a different synthetic strategy was employed using the Suzuki coupling reaction as the key step (Scheme 4, routes D and E). As illustrated in route D for the regioisomeric series **24** the central scaffold **23** was prepared in good yields by palladium-catalyzed cross coupling of the bromopyridine **21** with boronic acid **22** in the presence of sodium carbonate as a base.[31] Subsequent removal of the *N*-Boc group and reaction with succinimidocarbonates in the presence of triethylamine yielded compounds **24**. In a similar fashion the other regioisomers **34** and **35** (Figure 2) were prepared from the corresponding building blocks.

For the synthesis of the regioisomer with a pyridyl ring at the bottom position the inverse Suzuki coupling with bromide **25** and pyridyl boronic acid **26** according to route E proceeded in high yield (84% for **27**). Route E has the advantage of introducing diversity at the carboxylic acid site at a later stage. Deprotection of the ester **27** with lithium hydroxide yielded the free acid which was transformed into amide **28** using EDC/DMAP as the coupling reagent. *N*-Boc deprotection and acylation yielded phenylpyridine **29** as a representative of this regioisomeric series.

The requisite boronic acids **22** and **26** were either prepared from the corresponding bromide by halogen−metal exchange[32] or by direct lithiation of the pyridine **30** with *tert*-butyllithium and subsequent reaction with boronic acid trimethylester (Scheme 5). In accordance to previous observations[33] only the regioisomer **26** is formed by 4-selective lithiation in this reaction.

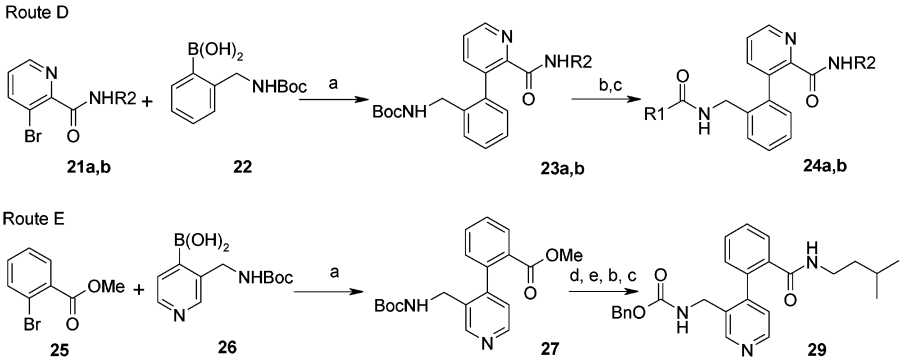
Figure 3 depicts all the building blocks employed in the Suzuki-couplings. Three of the four possible regioisomeric halogen pyridines (**21a**,**b**, **32**, and **33**) next to the pyridyl boronic acid **26** were employed. The amides were prepared using standard transformations from the commercially available acids.

Results and Discussion

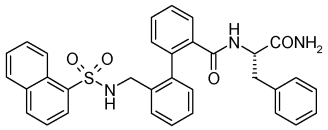
The most striking result from the initial solid-phase library is the higher potency of compounds bearing hydrophobic side chains. This is illustrated by examples **7a**−**d** with hydrophobic aromatic rings as substituents at both ends. Compound **7c** shows that aromatic rings are not mandatory: the benzyl group can be replaced by an isopropyl group without loss of blocking activity.

A study of the SAR of compounds **17** reveals a more detailed picture with regard to the side chain substituents and its linkages to the biphenyl scaffold. Variation of the upper right amide side chain R2 allowed a broad range of amines as shown in examples **17a**−**e**. Aliphatic, aromatic, heteroaromatic, basic, and amide functionalized side chains were all tolerated. In general, amides were more potent than the corresponding esters as illustrated with compound **17f** which shows a drastic loss in activity compared to **17a**. The linkage to the

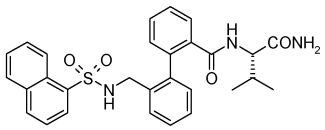
Scheme 4[a]



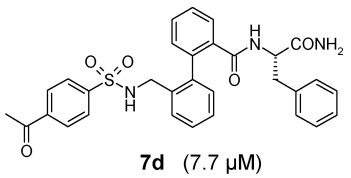
[a] Reagents: (a) $Pd(PPh_3)_4$, aq Na_2CO_3, 1,2-dimethoxyethane, reflux; (b) TFA, CH_2Cl_2; (c) *N*-succinimidocarbonate, triethylamine, CH_2Cl_2; (d) aq LiOH, MeOH, THF; (e) *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), DMAP, CH_2Cl_2.



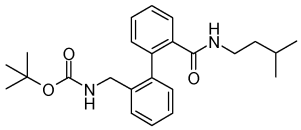
7b (9.1 μM)



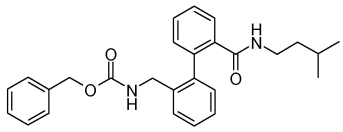
7c (11.2 μM)



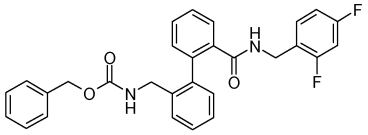
7d (7.7 μM)



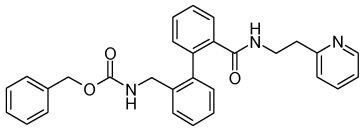
15a (3.5 μM)



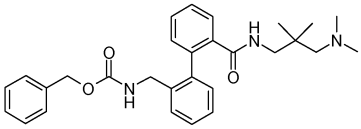
17a (0.8 μM)



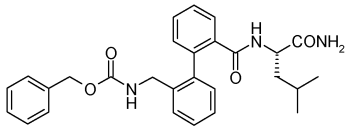
17b (1.2 μM)



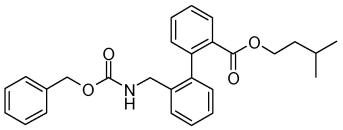
17c (0.7 μM)



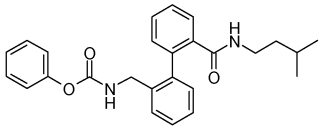
17d (2.2 μM)



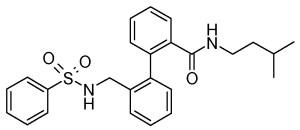
17e (0.3 μM)



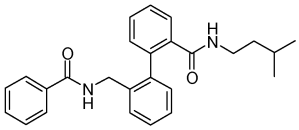
17f (8% inhibition at 10 μM)



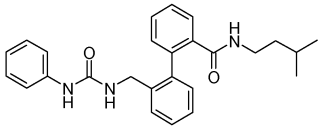
17g (3.3 μM)



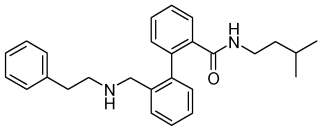
17h (2.6 μM)



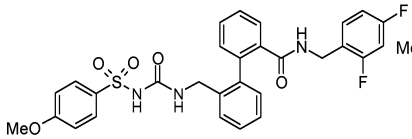
17i (4.1 μM)



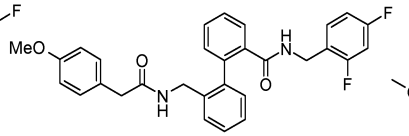
17j (4.5 μM)



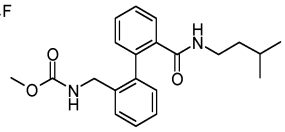
17k (4.0 μM)



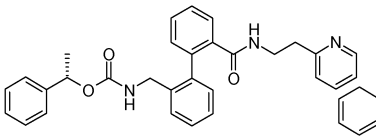
17l (7% inhibition at 10 μM)



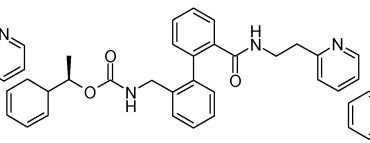
17m (1.2 μM)



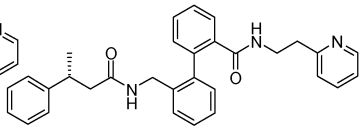
17n (7.1 μM)



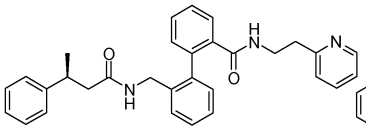
17o (0.16 μM)



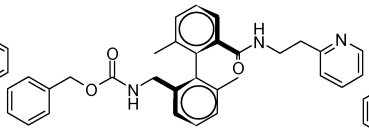
17p (2.4 μM)



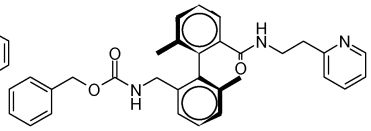
17q (0.3 μM)



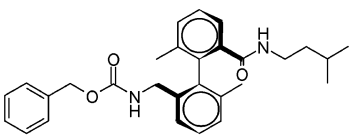
17r (1.0 μM)



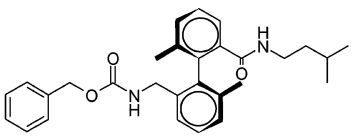
(R)-20a (1.7 μM)



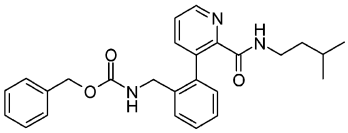
(S)-20a (0.7 μM)



(R)-20b (1 μM)



(S)-20b (1.3 μM)



24a (2.6 μM)

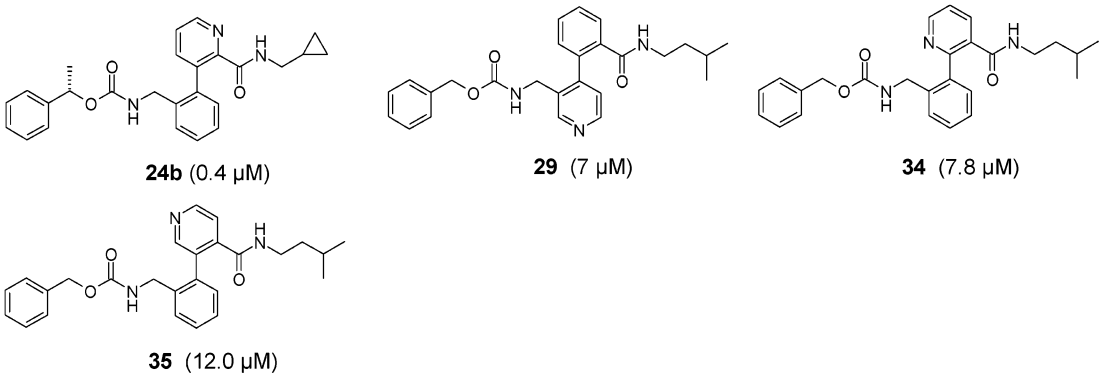
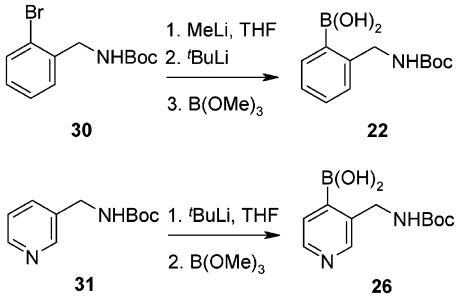


Figure 2. SAR for bisaryl compounds (in brackets IC_{50} for human Kv1.5, unless indicated otherwise, as measured in *Xenopus* oocytes).

Scheme 5



other side chain substituent R1 proved to be of minor importance. As seen by comparison of compounds **17g**−**k** there is no significant difference in activity between carbamate **17g**, sulfonamide **17h**, amide **17i**, urea **17j**, and amine **17k**. These data suggest that this portion of the compounds does not serve as hydrogen bond acceptor toward its binding site. However, the sulfonylurea **17l**, a molecule with an acidic linkage, shows greatly diminished potency compared to compound **17m** with the same side chains but an amide linkage.

Another remarkable result is the influence of size and stereochemistry of the linked lipophilic end group R1: larger groups such as the benzyl substituent in compound **17a** showed very good activity whereas a very small residue in this position as in the methyl carbamate **17n** displayed diminished activity. The best substituent in this position was the methyl-substituted benzyl group of compound **17o** having an IC_{50} value of 0.16 μM. Whereas the compounds with (*S*)-stereochemistry at the methyl bearing carbon such as **17o** or **17q** generally were very potent, the corresponding (*R*)-enantiomers such as **17p** or **17r** were 3- to 20-fold weaker in activity in most cases.

As disubstituted biphenyls can exist in two enantiomeric forms, we further investigated the importance of atropisomerism on activity. However, compounds **17** transform fast at room temperature on the NMR time scale from one enantiomeric form into the other. Conformationally stable atropisomers were obtained by additional methyl substituents in ortho position and could be separated by chiral HPLC. A comparison of the enantiomeric pairs (*R*)-**20a**/(*S*)-**20a** and (*R*)-**20b**/(*S*)-**20b** showed no significant difference in activity between the antipodes. Moreover, the enantiomeric pairs were comparable in blocking activity to the corresponding parent

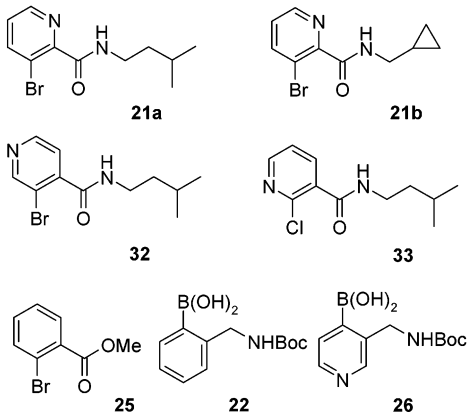


Figure 3. Halogenides and boronic acids used in routes D and E.

compounds **17c** and **17a** with a freely rotatable phenyl−phenyl bond. This finding suggests that the active conformation of the biphenyl inhibitors is one with the two phenyl rings strongly twisted.

Either phenyl ring of the biphenyl scaffold could be replaced by a pyridyl ring as the analogues **24a**, **29**, **34**, and **35** retained Kv1.5 activity, albeit slightly diminished compared to the corresponding biphenyl compound **17a**. Of the four different regioisomers investigated compound **24a** proved to be the most potent. Activity within this regioisomeric series could be further increased by optimizing the two side chains: A combination of the (*S*)-methylbenzylcarbamate and the cyclopropylmethylamide residues furnished compound **24b** with an IC_{50} of 0.4 μM which is close to the most active compounds found in the biphenyl series.

The SAR described above is supported by the results of pharmacophore identification for two chemical classes of Kv1.5 blockers, including the bisaryl compounds described herein.[34] The proposed pharmacophore consists of three hydrophobic centers in a triangular arrangement as depicted in Figure 4. The central hydrophobic center is matched by one of the phenyl rings of the biphenyl core. This is in accordance with the observation that the phenyl ring of the core can be replaced by a pyridyl unit as shown in compounds **24**, **29**, **34**, and **35**. The other two hydrophobic centers are matched by both ends of the side chains. For good activity hydrophobic residues are required which can be either aromatic or aliphatic as demonstrated by compounds **15a**, **17a**, and **17b**. The nature of the linkage between the core and the side chain is less critical as is

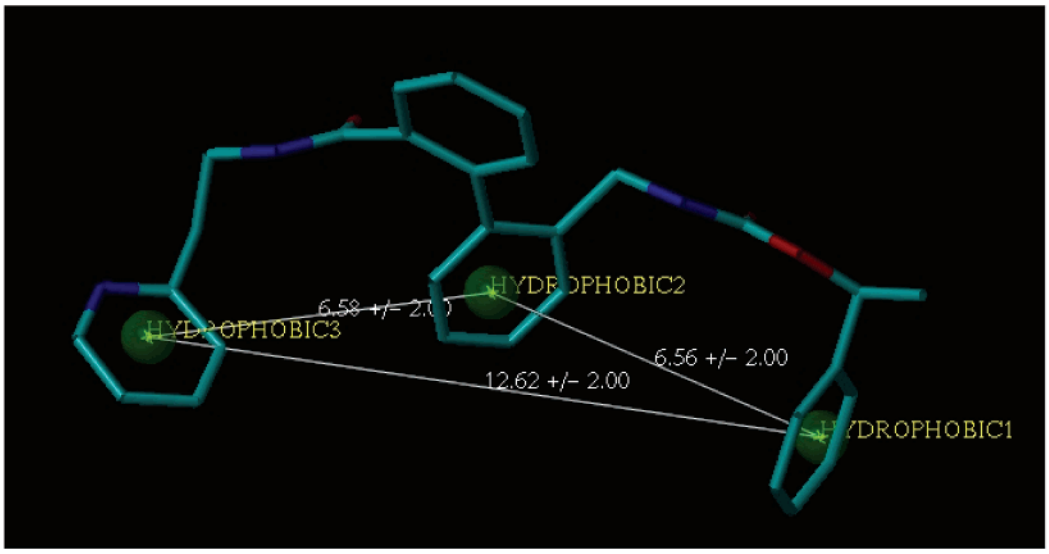


Figure 4. Pharmacophore model illustrated with compound **17o**.

Table 1. Inhibition of the HERG and Kv1.3 Channel in Comparison to Kv1.5

compound	HERG [inhibition at 10 μM, %]	Kv1.3 [IC_{50}, μM]	Kv1.5 [IC_{50}, μM]
17c	7	2.3	0.7
17o	11	0.5	0.16

observed in compounds **17g**−**k**. Presumingly, no hydrogen bonding between this portion of the molecule and the binding site takes place. However, the reason for the lack of activity of sulfonylurea **17l** remains unclear.

The comparable blocking activity of the axial chiral biphenyls **20** is also in good agreement with the optimized conformation of the pharmacophore model. The two phenyl rings in the model exhibit a dihedral angle of 40°.

To avoid the undesired ventricular effects observed for many potassium channel blockers selectivity toward the HERG channel is important. As could be shown with compounds **17c** and **17o** there was no significant effect on the IK_r current as assessed by voltage clamp techniques on *Xenopus* oocytes at 10 μM. Apart from compound **17d**, no effects on sodium channels were observed.

Selectivity toward the structurally closely related channel Kv1.3 is less pronounced; the bisaryl compounds generally reveal a 2- to 4-fold selectivity for Kv1.5 (Table 1).

Conclusion

The identification, synthesis, pharmacological testing, and resulting structure−activity relationship of various series of novel ortho,ortho-disubstituted bisaryls as blockers of the Kv1.5 channel have been described, and a pharmacophore model has been proposed. With compounds **17o** and others we succeeded in synthesizing compounds with Kv1.5 blocking activity in the submicromolar range. Moreover, the compounds showed no significant inhibition of HERG channels and no effect on sodium channels. The compounds described are currently under in vivo investigation as antiarrhythmic drugs in several animal models. The first more detailed in vivo data with compounds **17c** and **17m** (corresponds to S9947 and S20951 in the literature) were published very recently.[35]

Experimental Section

Chemistry. Solvents and other reagents were used as received without further purification. Rink amide polystyrene resin with a loading of 1.2 mmol/g was purchased from Novabiochem. Biphenyl building blocks **14** and **18** were synthesized according to refs 28 and 29, bromide **30** and pyridine **31** were prepared according to refs 36 and 37.

Column chromatography was carried out on Merck silica gel 60 (230−400 mesh). Reversed phase high-pressure chromatography was conducted on an Abimed Gilson instrument using a LiChrospher 100 RP-18e (5μm) column from Merck. Preparative racemic resolution was conducted on a Abimed Gilson instrument using a Chiralcel AD 250 × 20 mm column, and analytical resolution was performed on a Chiralcel AD 250 × 4.6 mm column. Thin-layer chromatography was carried out on TLC aluminum sheets with silica gel 60F254 from Merck. LC-MS analyses were performed on Agilent Series 1100 systems using a YMC J'sphere ODS H80 20 × 2.1 mm (4μm) column and a Merck Purosphere 55 × 2 mm (5μm) column. Varying ratios of acetonitrile and 0.1% trifluoroacetic acid in water were used as solvent systems. Melting points were obtained with a Büchi melting point apparatus B-540 and are not corrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 either on a Bruker DRX 400 or Varian Unity Plus 300. Chemical shifts are reported as δ values from an internal tetramethylsilane standard. Mass spectral data were either obtained on a VG Bio-Q triple Quadropole mass spectrometer using electro spray ionization or a VG ZAB 2-SEQ mass spectrometer using FAB ionization. Acurate mass measurements have been conducted with a Bruker Apex III FTICR mass spectrometer. Purity and characterization of compounds were established by a combination of LC-MS, high-resolution mass spectrometry (HRMS), and NMR analytical techniques.

General Methods for the Preparation of Biphenyl Compounds 7a−d by Solid-Phase Synthesis. 1. General Method for the Coupling of α-Fmoc-Amino Acids to Rink Amide Resin. A solution of 1.5 equiv each of HOBT, TOTU, DIPEA, and the α−Fmoc amino acid in DMF (5 mL/g of resin) was added to Rink amide polystyrene resin (loading 1.2 mmol/g), and the mixture was shaken at room temperature for 12 h. The resin was filtered off and washed three times with 10 mL each of DMF, once with 10 mL of toluene, once with 10 mL of methanol, and three times with 10 mL of dichloromethane. Determination of the loading according to the Fmoc method showed a loading of 0.9 mmol/g of carrier.

2. General Method for Removal of the Fmoc Protective Group (Compounds 9). For the removal of the Fmoc

protective group, the resin was preswollen in DMF at room temperature for 5 min. After addition of a solution of DMF/piperidine (4 mL/g of resin, 1:1), the mixture was shaken at room temperature for 20 min. The solution was filtered off with suction, and the process was repeated. The removal of an analytical sample showed complete reaction according to LC-MS investigation. After complete reaction, the resin was washed three times with dichloromethane and employed directly in the coupling.

3. General Method for the Coupling of the Resin-Bound Amino Acids with 2′-Phthalimidomethylbiphenyl-2-carboxylic Acid (Compounds 11). A solution of 12.2 mg (0.09 mmol) of HOBT, 29.5 mg (0.09 mmol) of TOTU, 16 μL (0.09 mmol) of DIPEA, and 32 mg (0.09 mmol) of 2′-phthalimidomethylbiphenyl-2-carboxylic acid[27] (**10**) in 5 mL of DMF was added to 100 mg of resin loaded with the amino acid, and the mixture was shaken at room temperature for 12 h. The resin was filtered off and washed three times with 10 mL each of DMF, once with 10 mL of toluene, once with 10 mL of methanol, and three times with 10 mL of dichloromethane.

4. General Method for the Removal of the Phthalimido Protective Group. Five mL of a 10% solution of hydrazine in DMF were added to 1 g of resin loaded with the Fmoc-protected amino compound, and the mixture was shaken at room temperature for 2 h. The resin was filtered off with suction. The resin was then washed three times each with 10 mL of DMF and dichloromethane. The removal of an analytical sample showed complete reaction according to LC-MS investigation.

5. General Method for Coupling with Sulfonyl Chlorides (Compounds 12). A solution of 16 μL (0.09 mmol) of DIPEA and 0.09 mmol of sulfonyl chloride in 3 mL of DMF was added to 100 mg of resin loaded with the functionalized 2′-aminomethylbiphenyl-2-carboxylic acid, and the mixture was shaken at room temperature for 12 h. The resin was filtered off and washed three times with 10 mL of DMF, once with 10 mL of toluene, once with 10 mL of methanol, and three times with 10 mL of dichloromethane.

6. General Method for Removal from the Resin (Compounds 7). For removal, the resin was suspended in dichloromethane/trifluoroacetic acid 3:1 (3 mL/0.1 g of resin) and shaken for 1 h. The resin was filtered and washed with 1 mL of dichloromethane. If necessary, the residue was purified by preparative HPLC.

2′-[(α,α,α,Trifluorotoluene-3-sulfonylamino)methyl]-biphenyl-2-carboxylic acid [(*S*)-1-carbamoyl-2-phenylethyl]amide (7a): mp 115°C. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 7.95−6.94 (18H, m), 6.70/6.30 (1H, 2 × d, J = 7.5 Hz), 5.43/5.39 (2H, 2 × br s), 4.60 (1H, m), 4.04/3.78 (1H, dd, J = 8.1, 12.1, and 2.0 Hz, 12.0 Hz), 3.93 (1H, m), 3.00 (2H, d, J = 7.3 Hz, rotamer 1), 2.94 (1H, dd, J = 6.4 Hz, 13.8 Hz, rotamer 2), 2.88 (1H, dd, J = 8.1 Hz, 13.8 Hz, rotamer 2). MS (ES) m/z: 582 (MH^+). HRMS calcd for $C_{30}H_{27}N_3O_4F_3S_1$ 582.1669; found, 582.1663; Dev: 1.0 ppm.

2′-[(Naphthalene-1-sulfonylamino)methyl]biphenyl-2-carboxylic acid [(*S*)-1-carbamoyl-2-phenylethyl]amide (7b): mp 140 °C. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 8.56/8.47 (1H, 2 × d, J = 8.6 Hz), 8.01−7.84 (3H, m), 7.59−6.78 (17H, m), 6.69/6.22 (1H, 2 × d, J = 7.7 and 7.2 Hz), 5.61 (1H, br s), 5.56/5.44 (1H, 2 × br s), 4.60 (1H, m), 4.00/3.73 (1H, dd, J = 7.8, 12.1, and 2.3 Hz, 12.0 Hz), 3.92/3.88 (1H, dd, J = 4.0, 12.1, and 6.0 Hz, 12.0 Hz), 2.96 (2H, m). MS (ES) m/z: 564 (MH^+). HRMS calcd for $C_{33}H_{30}N_3O_4S_1$ 564.1952; found, 564.1954; Dev: 0.4 ppm.

2′-[(Naphthalene-1-sulfonylamino)methyl]biphenyl-2-carboxylic acid [(*S*)-1-carbamoyl-3-methyl-butyl]-amide (7c): mp 205 °C. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 8.56/8.51 (1H, 2 × d, J = 8.2 Hz), 8.01−7.88 (3H, m), 7.58−6.92 (12H, m), 6.66/6.28 (1H, 2 × d, J = 8.2 and 8.9 Hz), 6.10/5.98 (1H, 2 × br s), 5.87/5.78 (1H, 2 × br s), 4.24 (1H, m), 4.01/3.76 (1H, dd, J = 7.8, 12.5, and 2.3 Hz, 12.5 Hz), 3.91 (1H, d, J = 5.0 Hz), 1.99 (1H, m), 0.93/0.86/0.85/0.84 (6H, 4 × d, J = 6.8 Hz). MS (ES) m/z: 516 (MH^+). HRMS calcd for for $C_{29}H_{30}N_3O_4S_1$ 516.1951; found, 516.1945; Dev: 1.2 ppm.

2′-[(4-Acetyl-benzenesulfonylamino)methyl]biphenyl-2-carboxylic acid [(*S*)-1-carbamoyl-2-phenylethyl)amide (7d): mp 180−183 °C. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 7.90/7.71 (2H, 2 × d, J = 8.7 and 8.6 Hz), 7.84/7.64 (2H, 2 × d, J = 8.6 and 8.7 Hz) 7.44−6.95 (14H, m), 6.75/6.29 (1H, 2 × d, J = 7.5 Hz), 5.50/5.43 (2H, 2 × br s), 4.60 (1H, m), 4.00 (1H, dd, J = 8.2 Hz, 12.0 Hz, rotamer 1), 4.00 (2H, d, J = 4.8 Hz, rotamer 2), 3.71 (1H, dd, J = 2.1 Hz, 12.0 Hz, rotamer 1) 2.95 (2H, m), 2.64/2.63 (3H, 2 × s). MS (ES) m/z: 556 (MH^+). HRMS calcd for for $C_{31}H_{30}N_3O_5S_1$ 556.1901; found, 556.1893; Dev: 1.4 ppm.

2′-Aminomethylbiphenyl-2-carboxylic Acid (13). A suspension of 10.0 g (28 mmol) of 2′-phthalimidomethylbiphenyl-2-carboxylic acid[27] (**10**) in 450 mL of methanol was treated with 20 mL of hydrazine monohydrate and heated at 40 °C for 1.5 h. The reaction mixture was concentrated, and the residue was taken up in 250 mL of dichloromethane. After the undissolved 2,3-dihydrophthalazine-1,4-dione was filtered, the mother liquor was concentrated and 4.8 g (76%) of 2′-aminomethylbiphenyl-2-carboxylic acid (**13**) was obtained as white crystals: ^{1}H NMR (DMSO-d_6): δ 8.31 (3H, br s), 7.47−7.26 (5H, m), 7.03 (1H, m), 6.97 (1H, m), 3.73 (1H, d, J = 12.5 Hz), 3.52 (1H, d, J = 12.5 Hz). MS (ES) m/z: 228 (MH^+).

[2′-(3-Methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid *tert*-Butyl Ester (15a). To a solution of 3.27 g (10 mmol) 2′-(*tert*-butoxycarbonylaminomethyl)-biphenyl-2-carboxylic acid[28] (**14**), 1.35 g (1.67 mL, 10.7 mmol) DIC and 1.45 g (10.7 mmol) HOBt in 50 mL THF was added at 0 °C 0.93 g (1.24 mL, 10.7 mmol) isopentylamine and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid and sodium bicarbonate solution. The organic phase was dried over magnesium sulfate, concentrated in vacuo, and purified by flash chromatography on silica gel to give 3.57 g (90%) of amide **15a** as a white solid: ^{1}H NMR ($CDCl_3$): δ 7.74 (1H, m), 7.47−7.12 (7H, m), 6.19 (1H, br s), 5.84 (1H, br s), 4.13 (1H, dd, J = 5.7 Hz, 15.5 Hz), 4.07 (1H, dd, J = 6.6 Hz, 15.5 Hz) 3.21−2.96 (2H, m), 1.37 (9H, s), 1.23 (1H, m), 0.93 (2H, m), 0.76 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.6 Hz). MS (ES) m/z: 397 (MH^+). HRMS calcd for $C_{24}H_{32}N_2O_3$, 396.2413; found, 396.2421; Dev: 2.0 ppm.

The following amides were prepared as described above.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid *tert*-butyl ester (15b): 3.82 g (87%): ^{1}H NMR (DMSO-d_6): δ 8.44 (1H, d, J = 4.8), 7.84 (1H, m) 7.66 (1H, dt, J = 1.8 Hz, 7.7 Hz), 7.51−7.16 (9H, m), 7.07 (1H, d, J = 7.7 Hz), 7.02 (1H, d, J = 7.3 Hz), 3.95 (1H, d, J = 5.8 Hz), 3.40−3.15 (2H, m) 2.48 (2H, m), 1.32 (9H, s). MS (ES) m/z: 432 (MH^+).

[2′-(2,4-Difluorobenzylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid *tert*-butyl ester (15c): 3.79 g (84%): mp 140°C. ^{1}H NMR (DMSO-d_6): δ 8.29 (1H, m) 7.57−6.99 (7H, m), 6.80 (1H, m), 6.51 (1H, m), 4.28 (1H, dd, J = 6.2 Hz, 15.7 Hz), 4.12 (1H, dd, J = 5.1 Hz, 15.7 Hz) 3.95 (2H, d, J = 5.9 Hz) 1.25 (9H, s). MS (ES) m/z: 453 (MH^+).

2′-(Benzyloxycarbonylaminomethyl)biphenyl-2-carboxylic Acid (16). Benzyl *N*-succinimidocarbonate (0.50 g, 2 mmol) dissolved in 2.5 mL of dioxane was added dropwise at 0 °C to a solution of 455 mg (2 mmol) of 2′-aminomethylbiphenyl-2-carboxylic acid (**13**) and 336 mg (4 mmol) of sodium hydrogencarbonate in 5 mL of dioxane and 5 mL of water. After the mixture was stirred at room temperature for 4 h, it was concentrated under vacuum, diluted with water, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under vacuum to yield 0.59 g (82%) of 2′-(benzyloxycarbonylaminomethyl)biphenyl-2-carboxylic acid (**16**): ^{1}H NMR ($CDCl_3$): δ 7.99 (1H, d, J = 7.7 Hz), 7.57−7.19 (11H, m), 7.07 (1H, d, J = 8.6 Hz), 5.00 (2H, s), 4.18 (2H, s). MS (ES) m/z: 362 (MH^+).

According to the method given for compound **15a** the following amides **17a**−**e** and ester **17f** were prepared on a 0.28 mmol scale in dichloromethane as solvent.

[2′-(3-Methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid benzyl ester (17a): 95 mg (79%): mp 112 °C. ^{1}H NMR ($CDCl_3$): δ 7.67 (1H, m), 7.50−7.12 (12H, m), 5.96 (1H, br s), 5.78 (1H, br s), 5.00 (2H, s), 4.18 (2H, d, J = 5.6 Hz) 3.12 (2H, m), 1.20 (1H, m), 1.01 (2H, q, J = 7.2 Hz), 0.76 (3H, d, J = 6.4 Hz), 0.74 (3H, d, J = 6.4 Hz). MS (ES) m/z: 431 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_2$, 431.2329; found, 431.2318; Dev: 2.6 ppm.

[2′-(2,4-Difluorobenzylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid benzyl ester (17b): 99 mg (73%): ^{1}H NMR ($CDCl_3$): δ 7.70 (1H, m), 7.46−7.08 (12H, m), 6.79−6.58 (4H, m), 5.65 (1H, br s), 4.90 (2H, m), 4.36 (1H, dd, J = 6.8 Hz, 15.4 Hz), 4.27−4.07 (3H, m). MS (ES) m/z: 487 (MH^+). HRMS calcd for $C_{29}H_{25}F_2N_2O_2$, 487.1828; found, 487.1820; Dev: 1.6 ppm.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid benzyl ester (17c): 85 mg (65%): mp 140 °C. ^{1}H NMR ($CDCl_3$): δ 8.45 (1H, d, J = 4.6 Hz), 7.63−7.01 (16H, m), 6.71 (1H, br s), 6.17 (1H, br s), 5.03 (2H, s), 4.28 (1H, dd, J = 6.3 Hz, 14.6 Hz), 4.16 (1H, dd, J = 4.9 Hz, 14.6 Hz), 3.56 (2H, m), 2.68 (2H, t, J = 6.4 Hz). MS (ES) m/z: 466 (MH^+). HRMS calcd for $C_{29}H_{28}N_3O_3$, 466.2125; found, 466.2117; Dev: 1.7 ppm.

[2′-(3-Dimethylamino-2,2-dimethylpropylcarbamoyl)-biphenyl-2-ylmethyl]carbamic acid benzyl ester (17d): 68 mg (51%). ^{1}H NMR ($CDCl_3$): δ 7.85 (1H br s), 7.55−7.07 (13H, m), 6.40 (1H, br s), 5.01 (2H, s), 4.30 (1H, dd, J = 7.0 Hz, 14.2 Hz), 4.11 (1H, dd, J = 5.4 Hz, 14.2 Hz), 3.10 (2H, d, J = 5.1), 2.21 (6H, s), 2.15 (1H, d, J = 14.0 Hz), 2.09 (1H, d, J = 14.0 Hz), 0.77 (3H, s), 0.71 (3H, s). MS (ES) m/z: 474 (MH^+). HRMS calcd for $C_{29}H_{36}N_3O_3$, 474.2757; found, 474.2766; Dev: 1.9 ppm.

[2′-(1-*S*-Carbamoyl-3-methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic acid benzyl ester (17e): 80 mg (60%): mp 140 °C. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 7.80/7.61 (1H, m), 7.49−7.14 (12H, m), 6.75/6.50 (1H, br d, J = 8.0 Hz), 5.90/5.83 (1H, br t, J = 6.0 Hz), 5.09 (1H, br s), 4.98 (2H, m), 4.70/4.50 (1H, br s), 4.32 (1H, m), 4.24−4.08 (2H, m), 1.42 (1H, m), 1.26 (2H, t, J = 7.2 Hz), 0.85 (3H, d, J = 6.6 Hz, Rotamer 1), 0.84 (3H, d, J = 6.6 Hz, Rotamer 1), 0.73 (6H, m, Rotamer 2). MS (ES) m/z: 474 (MH^+). HRMS calcd for $C_{28}H_{32}N_3O_4$, 474.2387; found, 474.2377; Dev: 2.2 ppm.

2′-(Benzyloxycarbonylaminomethyl)biphenyl-2-carboxylic acid 3-methyl-butyl ester (17f): 45 mg (37%): ^{1}H NMR ($CDCl_3$): δ 7.91 (1H, d, J = 7.7.Hz), 7.54−7.22 (11H, m), 7.05 (1H, dd. J = 1.5 Hz, 7.3 Hz), 5.16 (1H, br s), 5.02 (2H, s), 4.23 (1H, dd, J = 5.6 Hz, 14.5 Hz), 4.13 (1H, dd, J = 4.8 Hz, 14.5 Hz), 4.04 (2H, t, J = 6.8 Hz), 1.42 (1H, m), 1.27 (2H, q, J = 6.8 Hz), 0.81 (6H, d, J = 6.4 Hz). MS (ES) m/z: 432 (MH^+). HRMS calcd for $C_{27}H_{30}N_1O_4$, 432.2169; found, 432.2159; Dev: 2.3 ppm.

[2′-(3-Methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid Phenyl Ester (17g). *N*-Boc compound **15a** (136 mg, 0.34 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 6 mL of dichloromethane together with 76 mg (104 μL, 0.75 mmol) of triethylamine. Phenyl chloroformate (56 mg, 0.36 mmol) dissolved in 1 mL dichloromethane was slowly added at 5 °C, and the reaction mixture stirred at room-temperature overnight. The mixture was diluted with ethyl acetate, washed twice with water, dried over magnesium sulfate, concentrated, and purified by flash chromatography to yield 55 mg (39%) of compound **17g** as a resin: ^{1}H NMR ($CDCl_3$): δ 7.66−7.01 (13H, m), 6.40 (1H, br s), 5.87 (1H, br s), 4.32 (1H, dd, J = 6.8 Hz, 14.7 Hz), 4.20 (1H, dd, J = 4.4 Hz, 14.7 Hz), 3.14 (2H, m), 1.26 (1H, m), 1.05 (2H, q, J = 7.2 Hz), 0.77 (3H, d, J = 6.4 Hz), 0.75 (3H, d, J = 6.4 Hz). MS (ES) m/z: 417 (MH^+). HRMS calcd for $C_{26}H_{29}N_2O_3$, 417.2173; found, 417.2163; Dev: 2.3 ppm.

2′-(Benzenesulfonylaminomethyl)biphenyl-2-carboxylic Acid (3-Methylbutyl)amide (17h). *N*-Boc compound **15a** (136 mg, 0.34 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 5 mL of dichloromethane together with 76 mg (104 μL, 0.75 mmol) triethylamine. Benzenesulfonyl chloride (65 mg, 0.37 mmol) was slowly added at 0 °C and the mixture stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum and the residue stirred with 15 mL of water for 2 h, and the precipitate was filtered off with suction giving 100 mg (67%) of sulfonamide **17h**: mp 127°C. ^{1}H NMR ($CDCl_3$): δ 7.41−6.84 (13H, m), 6.75 (1H, dd, J = 2.2 Hz, 7.6 Hz), 5.54 (1H, br s), 3.81 (1H, dd, J = 8.1 Hz, 12.3 Hz), 3.63 (1H, dd, J = 2.7 Hz, 12.3 Hz), 3.25−2.91 (2H, m), 1.28 (1H, m), 1.09 (2H, m), 0.70 (3H, d, J = 6.3 Hz), 0.67 (3H, d, J = 6.3 Hz). MS (ES) m/z: 437 (MH^+). HRMS calcd for $C_{25}H_{29}N_2O_3S$, 437.1889; found, 437.1880; Dev: 2.1 ppm.

2′-(Benzoylaminomethyl)biphenyl-2-carboxylic Acid (3-Methylbutyl)amide (17i). *N*-Boc compound **15a** (136 mg, 0.34 mmol) was dissolved in 5 mL dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 5 mL of dichloromethane together with 76 mg (104 μL, 0.75 mmol) of triethylamine.) Benzoyl chloride (51 mg, 42 μL, 0.36 mmol) dissolved in dichloromethane was added slowly at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under vacuum, the residue was stirred with 25 mL of water, and the precipitate was filtered off with suction to obtain 75 mg (55%) amide **17i**: mp 147 °C. ^{1}H NMR ($CDCl_3$): δ 7.90 (1H, br s), 7.82 (1H, dd, J = 1.5 Hz, 8.1 Hz), 7.59−7.26 (10H, m), 7.15 (1H, dd, J = 1.5 Hz, 7.3 Hz), 6.01 (1H, br s), 4.67 (1H, dd, J = 7.0 Hz, 14.4 Hz), 4.23 (1H, dd, J = 3.9 Hz, 14.4 Hz), 3.19 (2H, m), 1.31 (1H, m), 1.12 (2H, q, J = 7.2 Hz), 0.78 (3H, d, J = 6.3 Hz), 0.76 (3H, d, J = 6.3 Hz). MS (ES) m/z: 401 (MH^+). HRMS calcd for $C_{26}H_{29}N_2O_2$, 401.2224; found, 401.2213; Dev: 2.7 ppm.

2′-[(3-Phenylureido)methyl]biphenyl-2-carboxylic Acid (3-Methylbutyl)amide (17j). *N*-Boc compound **15a** (136 mg, 0.34 mmol) dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 5 mL of dichloromethane together with 76 mg (104 μL, 0.75 mmol) of triethylamine. Phenyl isocyanate (43 mg, 39 μL, 0.36 mmol) dissolved in 0.5 mL of dichloromethane was added slowly at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under vacuum, the residue was stirred with 25 mL of water, and the precipitate was filtered off with suction to obtain 85 mg (60%) urea **17j**: mp 194 °C. ^{1}H NMR ($CDCl_3$): δ 7.62 (1H, m), 7.52−7.13 (11H, m), 7.00 (1H, m), 6.83 (1H, m), 6.23 (2H, m), 4.21 (2H, d, J = 5.4 Hz), 3.20 (2H, m), 1.30 (1H, m), 1.11 (2H, q, J = 7.2 Hz), 0.80 (3H, d, J = 6.6.Hz), 0.78 (3H, d, J = 6.6 Hz). MS (ES) m/z: 416 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_2$, 416.2333; found, 416.2326; Dev: 1.6 ppm.

2′-(Phenethylaminomethyl)biphenyl-2-carboxylic Acid (3-Methylbutyl)amide (17k). *N*-Boc compound **15a** (60 mg, 0.15 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 3 mL of THF/methanol (9/1). $NaCNBH_3$ (19 mg, 0.3 mmol) and phenylacetaldehyde (12 mg, 12 μL, 0.1 mmol) were added, and the mixture stirred at room temperature for 2 h. The solvents were removed, and the residue was dissolved in dichloromethane, washed with water, dried over sodium sulfate, and concentrated. Preparative RP-HPLC provided **17k** as trifluoroacetate (28 mg, 36%): ^{1}H NMR ($CDCl_3$): δ 9.98 (1H, br s), 9.62 (1H, br s) 7.57−6.99 (13H, m), 5.98 (1H, br t, J = 5.7 Hz), 4.13 (1H, m), 3.87 (1H, m), 3.36−3−14 (3H, m), 2.89 (1H, m), 1.52 (1H, m), 1.33 (2H, m), 0.89 (3H, d, J = 6.5 Hz), 0.85 (3H, d, J = 6.5 Hz). MS (ES) m/z: 401 (MH^+). HRMS calcd for $C_{27}H_{33}N_2O$, 401.2593; found, 401.2599; Dev: 1.5 ppm.

2′-[(4-Methoxybenzenesulfonylureido)methyl]biphenyl-2-carboxylic Acid 2,4-Difluorobenzylamide (17l). *N*-Boc compound **15c** (0.23 g, 0.5 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 10 mL of toluene. Ethyl *p*-methoxyphenylsulfonylcarbamate (128 mg, 0.5 mmol) and DIPEA (190 mg, 0.25 mL, 1.5 mmol) were added, and the mixture was stirred at room temperature for 3 h. The organic phase was washed with aqueous NH_4Cl solution, concentrated, and purified by preparative RP-HPLC to yield 120 mg (42%) of a white foam: ^{1}H NMR (DMSO-d_6): δ 10.62 (1H, s), 8.38 (1H, t, J = 5.8 Hz), 7.75 (2H, d, J = 8.8 Hz), 7.50−6.90 (12H, m), 6.79 (1H, dt, J = 2.4 Hz, 8.4 Hz), 6.58 (1H, m), 4.24−3.88 (4H, m), 3.81 (3H, s). MS (ES) *m*/*z*: 566 (MH^+). HRMS calcd for $C_{29}H_{26}F_2N_3O_5$, 566.1556; found, 566.1549; Dev: 1.2 ppm.

2′-[(4-Methoxybenzoylamino)methyl]biphenyl-2-carboxylic Acid 2,4-Difluorobenzylamide (17m). Compound **17m** was prepared from **15c** according to the method given for **17i** to yield 109 mg (64%) of amide **17m**: mp 138 °C. ^{1}H NMR (DMSO-d_6): δ 8.56 (1H, t, J = 5.0 Hz), 8.49 (1H, t, J = 5.7 Hz), 7.84−6.98 (11H, m), 6.76 (3H, m), 6.48 (1H, m), 4.21 (1H, dd, J = 6.1 Hz, 15.4 Hz) 4.12−3.99 (3H, m), 3.25 (1H, d, J = 13.7 Hz), 3.21 (1H, d, J = 13.7 Hz). MS (ES) *m*/*z*: 501 (MH^+). HRMS calcd for $C_{30}H_{27}F_2N_2O_3$, 501.1990; found, 501.1978; Dev: 2.4 ppm.

[2′-(3-Methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid Methyl Ester (17n). Compound **17n** was prepared from **15a** according to the method given for **17g**. Flash chromatography provided 29 mg (24%) of carbamate **17n** as a resin: ^{1}H NMR ($CDCl_3$): δ 7.72−7.17 (8H, m), 6.00 (1H, br s), 5.84 (1H, br s), 4.19 (2H, m), 3.60 (3H, s), 3.17 (2H, m), 1.24 (1H, m), 1.07 (2H, m), 0.81 (3H, d, J = 6.6 Hz), 0.79 (3H, d, J = 6.6 Hz). MS (ES) *m*/*z*: 355 (MH^+). HRMS calcd for $C_{21}H_{27}N_2O_3$, 355.2016; found, 355.2005; Dev: 3.1 ppm.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid 1-(*S*)-Phenylethyl Ester (17o). *N*-Boc compound **15b** (130 mg, 0.30 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 2 mL of dioxane and 2 mL of water together with 51 mg (0.60 mmol) of sodium hydrogencarbonate. (*S*)-α-Methylbenzyl *N*-succinimidocarbonate (85 mg, 0.33 mmol) dissolved in 2 mL of dioxane was slowly added and the mixture stirred at room temperature for 2 h, diluted with water, and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, concentrated, and purified by flash chromatography to yield 60 mg (42%) of **17o**. Two rotamers: ^{1}H NMR (DMSO-d_6): δ 8.44 (1H, m), 7.91 (1H, t, J = 5.5 Hz), 7.76 (1H, t, J = 5.5 Hz), 7.66 (1H, m), 7.48−7.00 (15H, m), 5.60 (1H, m), 4.00 (2H, d, J = 5.5 Hz), 3.28 (2H, m), 2.56 (2H, m), 1.41/1.40 (3H, 2 × d, J = 6.6 Hz). MS (ES) *m*/*z*: 480 (MH^+). HRMS calcd for $C_{30}H_{30}N_3O_3$, 480.2282; found, 480.2271; Dev: 2.2 ppm.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid 1-(*R*)-Phenylethyl Ester (17p). Compound **17p** was prepared according to the method given for **17o**: 60 mg (42%). ^{1}H NMR spectrum identical to **17o**. MS (ES) *m*/*z*: 480 (MH^+). HRMS calcd for $C_{30}H_{30}N_3O_3$, 480.2282; found, 480.2273; Dev: 1.8 ppm.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid 1-(*S*)-Phenylethyl Ester (17q). *N*-Boc compound **15b** (563 mg, 1.30 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue dissolved in 2 mL of DMF together with 222 mg (242 μL, 2.2 mmol) *N*-methylmorpholine. This mixture was added to a solution of 164 mg (153 μL, 1 mmol) of (*S*)-3-phenylbutyric acid and 492 mg (1.5 mmol) TOTU in 1 mL of DMF. The reaction mixture was stirred for 15 h at room temperature, diluted with water, extracted with ethyl acetate, concentrated and purified by RP-HPLC to yield 347 mg (59%) of amide **17q** as trifluoroacetate. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 8.65 (1H, d, J = 5.5 Hz), 8.38 (1H, m), 8.20−8.06 (2H, m), 7.59 (1H, br s), 7.47−6.95 (14H, m), 4.07−3.86 (2H, m), 3.84 (2H, m), 3.10 (1H, q, J = 7.1 Hz), 2.77 (2H, m), 2.33 (2H, m) 1.13/1.09 (3H, 2 × d, J = 7.1 Hz). MS (ES) *m*/*z*: 478 (MH^+). HRMS calcd for $C_{31}H_{32}N_3O_2$, 478.2495; found, 478.2483; Dev: 2.5 ppm.

[2′-(2-Pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid 1-(*R*)-Phenylethyl Ester (17r). Compound **17r** was prepared according to the method given for **17q**: 374 mg (63%). ^{1}H NMR spectrum identical to **17q**. MS (ES) *m*/*z*: 478 (MH^+). HRMS calcd for $C_{31}H_{32}N_3O_2$, 478.2495; found, 478.2487; Dev: 1.7 ppm.

2′-Phthalimido-6,6′-dimethylbiphenyl-2-carboxylic Acid (2-Pyridin-2-ylethyl)amide (19a). A solution of 0.70 g (2.9 mmol) 1,11-dimethyl-7*H*-dibenzo[*c*,*e*]oxepin-5-one[29] (**18**) and 0.54 g (2.9 mmol) potassium phthalimide in 10 mL of DMF was heated to 150 °C for 18 h. The solvent was then removed under vacuum, and the residue was heated to reflux in 10 mL of thionyl chloride and 20 mL of toluene for 5 h. The solvents were removed again, and the residue was coevaporated with toluene. The residue was dissolved in 10 mL of dichloromethane, 0.75 mL of DIPEA and 0.43 g (3.5 mmol) 2-(2-pyridyl)ethylamine were added, and the mixture was stirred at room temperature for 15 h. The mixture was diluted with dichloromethane, washed with aqueous citric acid, water, dried over sodium sulfate, and concentrated. Flash chromatography on silica gel provided 1.33 g (93%) of **19a** as a white solid: ^{1}H NMR ($CDCl_3$): δ 7.86−7.68 (5H, m), 7.88−7.20 (6H, m), 7.00 (1H, t J = 4.6 Hz), 6.21 (1H, br s), 4.65 (1H, d, J = 16.1 Hz), 4.35 (1H, d, J = 16.1 Hz), 3.28 (1H, m), 3.06 (1H, m).

2′-Phthalimido-6,6′-dimethylbiphenyl-2-carboxylic Acid (3-Methylbutyl)amide (19b). The compound was prepared as described for **19a**. Instead of 2-(2-pyridyl)ethylamine, 0.30 g (0.40 mL, 3.5 mmol) of isopentylamine was used. This gave 0.90 g (68%) of **19b** as a white solid: ^{1}H NMR ($CDCl_3$): δ 8.47 (1H, d, J = 4.6 Hz), 7.86−7.00 (15H, m), 6.20 (1H, br s), 4.67 (1H, d, J = 16.0 Hz), 4.37 (1H, d, J = 16.0 Hz), 3.50 (2H, m), 2.70 (2H, t, J = 6.5 Hz).

[6,2′-Dimethyl-6′-(2-pyridin-2-ylethylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid Benzyl Esters [(*R*)-20a and (*S*)-20a]. A solution of 1.33 g (2.7 mmol) of phthalimide **19a** and 0.20 g (0.20 mL, 4.1 mmol) of hydrazine monohydrate in 5 mL of ethanol was heated to reflux for 5 h. The mixture was concentrated and the residue dissolved in dichloromethane. The organic phase was washed with water, dried over sodium sulfate, and concentrated. The residue was dissolved in 10 mL of dry dichloromethane and mixed with 0.74 g (3.0 mmol) of benzyl-*N*-succinimidocarbonate and 1 mL of DIPEA. The reaction mixture was stirred at room temperature for 15 h, diluted with additional dichloromethane, washed with water, dried over sodium sulfate, and purified by flash chromatography to yield 0.93 g (70%) of *rac*-**20a** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 8.62 (1H, d, J = 5.1 Hz), 7.90 (1H, br s), 7.60−7.00 (14H, m), 6.32 (1H, br s), 5.04 (2H, s), 4.13 (1H, dd, J = 7.0 Hz, 14.3 Hz), 3.78−3.63 (2H, m), 3.53 (1H, m), 3.08 (2H, m), 1.87 (3H, 3), 1.79 (3H, s). HRMS calcd for $C_{31}H_{34}N_3O_3$, 496.2600; found, 496.2592; Dev: 1.6 ppm.

Separation by chiral HPLC of a 35 mg sample on a preparative Chiralcel AD column using *n*-heptane/2-propanol (10/1) as eluent provided both the dextrorotatory enantiomer (*R*)-**20a** and the levo rotatory enantiomer (*S*)-**20a** in >99% ee. ^{1}H NMR spectra were identical to that of the racemate.

[6,2′-Dimethyl-6′-(3-methylbutylcarbamoyl)biphenyl-2-ylmethyl]carbamic Acid Benzyl Esters [(*R*)-20b and (*S*)-20b]. The compound was prepared as described for compound *rac*-**20b**. Phthalimide **19b** (0.90 g, 2.0 mmol) provided 0.34 g (74%) of *rac*-**20b** as a colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.47−7.17 (11H, m), 6.09 (1H, br s), 5.83 (1H, br s), 5.03 (2H, s), 4.14 (1H, dd, J = 6.6 Hz, 14.7 Hz), 3.80 (1H, dd, J = 4.0 Hz, 14.7 Hz), 1.93 (3H, s), 1.92 (3H,s), 1.27 (1H, m), 1.07 (2H, q, J = 7.0 Hz), 0.79 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz). HRMS calcd for $C_{29}H_{35}N_2O_3$, 459.2648; found, 459.2640; Dev: 1.7 ppm.

Chiral HPLC separation of a 35 mg sample on a preparative Chiralcel AD column using *n*-heptane/2-propanol (10/1) as

eluent provided the dextrorotatory enantiomer (*R*)-**20b** in >99% ee and the levorotatory enantiomer (*S*)-**20b** in 96% ee. ^{1}H NMR spectra were identical to that of the racemate.

3-Bromopyridine-2-carboxylic Acid (3-Methylbutyl)-amide (21a). A solution of 505 mg (2.5 mmol) of 3-bromopyridine-2-carboxylic acid in 3 mL of thionyl chloride was heated to reflux for 3 h and then concentrated. The residue was coevaporated twice with toluene, dissolved in 12.5 mL of dichloromethane, and treated with 260 mg (0.35 mL, 3 mmol) of isopentylamine and 555 mg (0.77 mL, 5.5 mmol) triethylamine. The mixture was stirred for 18 h, diluted with further dichloromethane, washed with aqueous NH_4Cl solution, $NaHCO_3$ solution, dried over sodium sulfate, and concentrated to yield a colorless solid (0.51 g, 75%): ^{1}H NMR (DMSO-d_6): δ 8.51 (1H, dd, J = 1.3 Hz, 4.6 Hz), 8.52 (1H, br s), 8.15 (1H, dd, J = 1.3 Hz, 8.2 Hz), 7.42 (1H, dd, J = 4.6 Hz, 8.2 Hz), 3.27 (2H, m), 1.66 (1H, m), 1.41 (2H, q, J = 7.2 Hz), 0.90 (6H, d, J = 6.8 Hz). MS (ES) *m*/*z*: 271/273 (MH^+).

The following amides were prepared as described above.

3-Bromopyridine-2-carboxylic acid cyclopropylmethylamide (21b): solid (0.49 g, 77%): ^{1}H NMR ($CDCl_3$): δ 8.51 (1H, dd, J = 1.5 Hz, 4.6 Hz), 8.03 (1H, dd, J = 1.5 Hz, 8.1 Hz), 7.83 (1H, br s), 7.26 (1H, dd, J = 4.6 Hz, 8.1 Hz), 3.32 (2H, dd, J = 5.7 HZ, 7.1 Hz), 1.07 (1H, m), 0.56 (2H, m), 0.29 (2H, m). MS (ES) *m*/*z*: 255/257 (MH^+).

3-Bromopyridine-4-carboxylic acid (3-methylbutyl)-amide (32): yellow oil (0.56 g, 83%): ^{1}H NMR ($CDCl_3$): δ 8.78 (1H, s), 8.58 (1H, d, J = 4.9 Hz), 7.46 (1H, d, J = 4.9 Hz), 6.02 (1H, br s), 3.50 (2H, m), 1.71 (1H, m), 1.53 (2H, q, J = 7.2 Hz), 0.97 (6H, d, J = 6.6 HZ). MS (ES) *m*/*z*: 271/273 (MH^+).

2-Chloropyridine-3-carboxylic acid (3-methylbutyl)-amide (33): solid (0.51 g, 90%): ^{1}H NMR ($CDCl_3$): δ 8.45 (1H, dd, J = 2.0 Hz, 4.8 Hz), 8.11 (1H, dd, J = 2.0 Hz, 7.6 Hz), 7.35 (1H, dd, J = 4.8 HZ, 7.6 Hz), 6.44 (1H, br s), 3.51 (2H, dt, J = 5.8 Hz, 7.4 Hz), 1.71 (1H, m), 1.54 (2H, m), 0.97 (6H, d, J = 6.6 HZ). MS (ES) *m*/*z*: 227(MH^+).

2-(*tert*-Butoxycarbonylaminomethyl)phenylboronic Acid (22). *N*-Boc-2-bromobenzylamine[36] (**30**) (5.72 g, 20 mmol) was dissolved in THF under argon and cooled to − 78 °C. The solution was treated with 13.75 mL of MeLi (1.6 M in hexane, 22 mmol), and after 1 h, 28 mL (1.5 M in pentane, 42 mmol) of *tert*-BuLi was added. After another 1 h, trimethyl borate (9.0 mL, 80 mmol) was added at −78 °C. After warming to room temperature, the mixture was treated with dilute hydrochloric acid to pH 6 and extracted with dichloromethane, and the organic phase was washed with saturated NaCl solution and dried. A pale yellow solid foam (5.1 g, 100%) was obtained. MS (FAB, sample treated with glycerol): *m*/*z*: 308 (strong, $MH^+ + C_3H_4O$), 252 (weak, MH^+).

3-(*tert*-Butoxycarbonylaminomethyl)pyridyl-4-boronic Acid (26). In THF was dissolved 5.5 g (26.4 mmol) of *N*-Boc-3-aminomethylpyridine[37] (**31**), and the mixture was cooled to −78 °C and treated with 37 mL of *tert*-BuLi (1.5 M in pentane, 55.5 mmol). Then the deep-green mixture was slowly warmed to −20 °C. After addition of trimethyl borate (12 mL, 105.6 mmol), the mixture was warmed to room temperature and stirred overnight. After addition of dilute hydrochloric acid to pH 6, the solution was concentrated on a rotary evaporator and extracted with chloroform/2-propanol (3/1). The organic phase was dried and concentrated to yield 4.3 g (65%) of an orange solid which was employed without further purification. MS (FAB, sample treated with glycerol): *m*/*z*: 309 (strong, $MH^+ + C_3H_4O$), 253 (weak, MH^+).

General Method for the Suzuki Coupling. {2-[2-(3-Methylbutylcarbamoyl)pyridin-3-yl]benzyl}carbamic Acid *tert*-Butyl Ester (23a). To 10 mL of 1,2-dimethoxyethane, purged with argon, were added 58 mg (0.05 mmol) of $Pd(PPh_3)_4$ and 271 mg (1 mmol) bromide **21a**. After 10 min, 502 mg (2 mmol) of 2-(*tert*-butoxycarbonylaminomethyl)phenylboronic acid (**22**) and 1 mL of a 2 M sodium carbonate solution were added. The mixture was heated to reflux for 18 h under argon, diluted with dichloromethane after cooling, and washed with water. The organic phase was dried over sodium sulfate, concentrated, and purified by reversed phase chromatography to give 0.37 g (72%) of **23a** as trifluoroacetate: ^{1}H NMR ($CDCl_3$): δ 8.58 (1H, dd, J = 1.6 Hz, 4.8 Hz), 8.00 (1H, br s), 7.59 (1H, dd, J = 1.6 Hz, 7.7 Hz), 7.47−7.27 (4H, m), 7.02 (1H, d, J = 7.1 Hz), 5.88 (1H, br s), 4.19 (1H, dd, J = 6.2 Hz, 13.9 Hz), 3.90 (1H, dd, J = 3.4 Hz, 13.9 Hz), 3.33 (2H, m), 1.64 (1H, m), 1.47 (2H, m), 1.35 (9H, s), 0.92 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.6 Hz). MS (ES) *m*/*z*: 398 (MH^+).

{2-[2-(Cyclopropylmethylcarbamoyl)-pyridin-3-yl]benzyl}carbamic Acid *tert*-Butyl Ester (23b). Compound **23b** as trifluoroacetate (0.38 g, 77%) was prepared from **21a** according to the method given for **23a**: ^{1}H NMR ($CDCl_3$): δ 8.61 (1H, dd, J = 1.7 Hz, 4.6 Hz), 8.12 (1H, m) 7.62 (1H, dd, J = 1.7 Hz, 7.7 Hz), 7.48 (1H, dd, J = 4.6 Hz, 7.7 Hz), 7.41−7.28 (3H, m), 7.03 (1H, d, J = 7.1 Hz), 5.39 (1H, br s), 4.19 (1H, m), 3.91 (1H, m), 3.18 (2H, m), 1.41 (1H, s), 1.01 (1H, m), 0.51 (2H, m), 0.22 (2H, m). MS (ES) *m*/*z*: 382 (MH^+).

{2-[2-(3-Methylbutylcarbamoyl)pyridin-3-yl]benzyl}-carbamic Acid Benzyl Ester (24a). *N*-Boc compound **23a** (60 mg, 0.15 mmol) was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue coevaporated with toluene. The residue was dissolved in 3 mL of dry dichloromethane, and the solution was treated with 34 mg (0.34 mmol) of triethylamine and 41 mg (0.17 mmol) of benzyl *N*-succinimidocarbonate. After 18 h, the mixture was diluted with 20 mL of dichloromethane and washed with saturated $NaHCO_3$ solution, and the organic phase was dried over sodium sulfate and concentrated. After purification by reversed phase HPLC, 60 mg (73%) of a colorless substance was obtained as trifluoroacetate: ^{1}H NMR ($CDCl_3$): δ = 8.57 (1H, dd, J = 4.8, 1.5 Hz), 7.96 (1H, br s), 7.60 (1H, d, J = 7.7 Hz), 7.47−7.26 (9H, m), 7.02 (1H, m), 5.73 (1H, br s), 4.98 (2H, s), 4.27 (1H, dd, J = 14.0, 6.6), 3.98 (1H, dd, J = 14.0, 3.7 Hz), 3.27 (2H, m), 1.58 (1H, m), 1.40 (1H, m), 0.86 (6H, d, J = 6.6 Hz). MS (ES) *m*/*z*: 432 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_3$, 432.2282; found, 432.2271; Dev: 2.5 ppm.

{2-[2-(Cyclopropylmethylcarbamoyl)pyridin-3-yl]benzyl}carbamic Acid 1-(*S*)-Phenylethyl Ester (24b). Compound **24b** as trifluoroacetate (0.65 mg, 80%) was prepared from **23b** according to the method given for **24a**. Instead of benzyl *N*-succinimidocarbonate, 44 mg (0.17 mmol) 1-(*S*)-methylbenzyl *N*-succinimidocarbonate was employed. Two rotamers: ^{1}H NMR ($CDCl_3$): δ 8.52 (1H, m), 8.05/8.01 (1H, br s), 7.61 (1H, d, J = 7.7 Hz), 7.38−7.16 (9H, m), 6.96 (1H, d, J = 6.8 Hz), 5.64 (1H, br s), 5.58 (1H, m), 4.17 (1H, m), 3.89/3.81 (1H, 2 × dd, J = 3.2, 13.8, and 3.0 Hz, 13.8 Hz), 3.21−3.01 (2H, m), 1.89/1.84 (3H, 2 × d, J = 6.6 Hz), 0.94/0.86 (1H, 2 × m) 0.41/0.38 (2H, 2 × d, J = 7.7 and 8.0 Hz), 0.15/0.10 (2H, 2 × m). MS (ES) *m*/*z*: 430 (MH^+). HRMS calcd for $C_{26}H_{28}N_3O_3$, 430.2125; found, 430.2129; Dev: 1.0 ppm.

The following phenylpyridines were prepared as described above.

{2-[3-(3-Methylbutylcarbamoyl)pyridin-2-yl]benzyl}-carbamic acid benzyl ester (34): ^{1}H NMR ($CDCl_3$): δ 8.71 (1H, dd, J = 1.7 Hz, 4.9 Hz), 8.15 (1H, d, J = 1.7 Hz, 7.8 Hz), 7.49−7.24 (10H, m), 6.68 (1H, br s), 5.93 (1H, s), 4.96 (2H, s), 4.28 (2H, d, J = 4.6 Hz), 3.12 (2H, m), 1.11 (1H, m), 0.98 (2H, q, J = 7.2 Hz), 0.73 (6H, d, J = 6.4 Hz). MS (ES) *m*/*z*: 432 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_3$, 432.2282; found, 432.2289; Dev: 1.7 ppm.

{2-[4-(3-Methylbutylcarbamoyl)pyridin-3-yl]benzyl}-carbamic acid benzyl ester (35): ^{1}H NMR ($CDCl_3$): δ 8.67 (1H, d, J = 5.1 Hz), 8.58 (1H, br s), 7.7 (1H, d, J = 5.1 Hz), 7.68−7.18 (9H, m), 7.01 (1H, br s), 5.95 (1H, br s), 4.98 (1H, d, J = 12.3 Hz), 4.92 (1H, d, J = 12.3 Hz) 4.19 (2H, d, J = 5.7 Hz), 3.22 (1H, m), 3.02 (1H, m) 1.05 (1H, m), 0.99 (2H, m), 0.72 (3H, d, J = 6.4 Hz), 0.71 (3H, d, J = 6.4 Hz). MS (ES) *m*/*z*: 432 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_3$, 432.2282; found, 432.2289; Dev: 1.8 ppm.

2-[3-(Benzyloxycarbonylaminomethyl)pyridin-4-yl]benzoic Acid Methyl Ester (27). To a solution of 20 mL of 1,2-dimethoxyethane, purged with argon, 230 mg (0.2 mmol) of $Pd(PPh_3)_4$ and 0.86 g (4 mmol) of methyl 2-bromobenzoate (**25**) were added. After 10 min, 1.51 g (6 mmol) of 3-(*tert*-butoxy-

carbonylaminomethyl)pyridine-4-boronic acid and 4 mL of a 2 M sodium carbonate solution were added. The mixture was heated to reflux under argon for 13 h, diluted with dichloromethane after cooling, and washed with water. The organic phase was dried, concentrated, and purified by chromatography on silica gel to give 1.15 g (84%) of a viscous pale yellow oil: ^{1}H NMR ($CDCl_3$): δ 8.65 (1H, s), 8.54 (1H, d, J = 4.8 Hz), 8.05 (1H, d, J = 7.7 Hz), 7.70−7.43 (2H, m), 7.20 (1H, d, J = 7.7 Hz), 7.02 (1H, d, J = 4.8 Hz), 4.81 (1H, br s, NH), 4.20 (1H, dd, J = 14.7, 5.5 Hz), 4.05 (1H, dd, J = 14.7, 5.5 Hz), 3.69 (3H, s, Me), 1.38 (9H, s). MS (ES) m/z: 343 (MH^+).

{4-[2-(3-Methylbutylcarbamoyl)phenyl]pyridin-3-ylmethyl}carbamic Acid *tert*-Butyl Ester (28). A solution of 684 mg (2 mmol) ester **27** in 10 mL of a methanol−THF mixture (3/1) was treated with 4 mL (4 mmol) of a 1 M lithium hydroxide solution and stirred at room-temperature overnight. The solution was then diluted with water and adjusted to pH 3 using aqueous $KHSO_4$ solution. The solution was extracted three times with dichloromethane. The organic phases were combined, dried over sodium sulfate, and concentrated to yield 590 mg (90%) of the title compound: ^{1}H NMR (DMSO-d_6): δ 8.47 (1H, s), 8.44 (1H, d, J = 4.9 Hz), 7.96 (1H, dd, J = 1.2 Hz, 7.6 Hz), 7.65 (1H, dt, J = 1.5 Hz, 7.6 Hz), 7.56 (1H, dt, J = 1.2 Hz, 7.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.16 (1H, br t, J = 5.3 Hz), 7.07 (1H, d, J = 4.9), 3.90 (2H, m), 1.35 (9H, s). MS (ES) m/z: 329 (MH^+).

{4-[2-(3-Methylbutylcarbamoyl)phenyl]pyridin-3-ylmethyl}carbamic Acid Benzyl Ester (29). To a solution of 49 mg (0.15 mmol) acid **28** in 5 mL of dichloromethane were added 33 mg (0.17 mmol) of EDC, 4 mg (0.03 mmol) of DMAP, and 15 mg (20 μL, 0.17 mmol) of isopentylamine. The reaction mixture was stirred at room-temperature overnight, diluted with dichloromethane, washed with water, and concentrated. The residue was dissolved in 5 mL of dichloromethane/trifluoroacetic acid (3/1) and stirred at room temperature for 3 h. The mixture was then concentrated under vacuum and the residue coevaporated with toluene. The residue was dissolved in 3 mL of dry dichloromethane, and the solution was treated with 34 mg (0.34 mmol) of triethylamine and 41 mg (0.17 mmol) of benzyl *N*-succinimidocarbonate. After 18 h the mixture was diluted with 20 mL of dichloromethane and washed with saturated $NaHCO_3$ solution, and the organic phase was dried over sodium sulfate and concentrated. After purification by reversed phase HPLC, 61 mg (75%) of a colorless substance was obtained as trifluoroacetate: ^{1}H NMR ($CDCl_3$): δ 7.63 (1H, m), 7.51 (2H, m), 7.39−7.27 (8H, m), 7.14 (1H, m), 6.28 (1H, br s), 6.07 (1H, br s), 5.00 (2H, m), 4.37 (2H, br s), 3.18 (2H, m), 1.32 (1H, m), 1.20 (2H, m), 0.83 (6H, m). MS (ES) m/z: 432 (MH^+). HRMS calcd for $C_{26}H_{30}N_3O_3$, 432.2282; found, 432.2272; Dev: 2.1 ppm.

Electrophysiology. Kv1.5 channels from humans were expressed in *Xenopus laevis* oocytes. *Xenopus laevis* oocytes were obtained from tricaine (3-aminobenzoic acid ethyl ester, 1 g/L) anesthetized animals using standard procedures.[38] Ovaries were cut into small pieces and collagenase treated (2 mg/1 mL, Worthington, type II) in OR2 solution (NaCl 82.5 mM, KCl 2 mM, $MgCl_2$ 1 mM, HEPES 5 mM, pH 7.4) for 120 min or until no follicle was detectable on the surface of the oocytes. Oocytes were subsequently stored in recording solution ND 96 (NaCl 96 mM, KCl 2 mM, $CaCl_2$ 1.8 mM, $MgCl_2$ 1 mM, HEPES 5 mM, pH 7.4) with additional Na-pyruvate (275 mg/L), theophylline (90 mg/L), and gentamicin (50 mg/L) at 18 °C. Oocytes were individually injected with 0.2−0.5 ng of cRNA (52 nL/oocyte) encoding the human potassium channel Kv1.5. From 18 h after the injection on, two-microelectrode voltage-clamp recordings were carried out at room temperature (21−22 °C) with a Turbo Tec 10CD (NPI) amplifier and an ITC-16 interface combined with Pulse software (Heka). Data analysis was performed using Pulse/Pulsefit, IgorPro (Wavemetrics) and Origin (Microcal Software) software

The microelectrodes were filled with 3 M KCl solution and had resistances between 0.5 and 1 MΩ. During the electrophysiological experiments, the oocytes were continuously superfused with ND96. The test compounds were dissolved in DMSO at a concentration of 10 mM. This solution was added to ND96 shortly before the experiment. The pH of the perfusion solutions was adjusted daily. The effects of the compounds were calculated as the percentage inhibition of the Kv1.5 control current which was obtained when no compound was added to the solution. Current inhibition was determined for three to four different concentrations, with each compound tested at least two times. Dose−response curves were fitted with a general variable slope dose−response equation ($y = 100/(1 + 10\wedge((\log(IC_{50}) - x)k))$; k = Hill slope) in order to determine the inhibitory concentration IC_{50} for the respective compounds.

In an analogue manner IC_{50} values were obtained for Kv1.3 and HERG channel blocking activity in *Xenopus laevis* oocytes.

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