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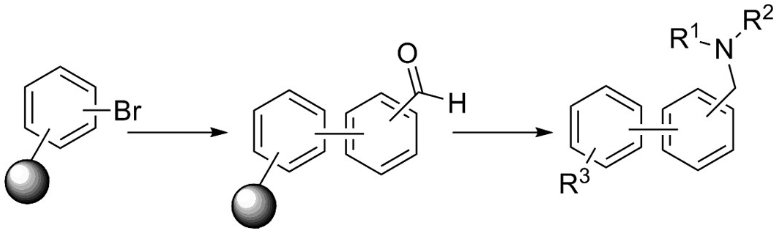

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Library of Biphenyl Privileged Substructures using a Safety-Catch Linker Approach

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A biphenyl privileged structure library containing three attachment points were synthesized using a catechol-based safety-catch linker strategy. The method requires the attachment of a bromo-acid to the linker, followed by a Pd-catalyzed Suzuki cross-coupling reaction. Further derivatization, activation of the linker with strong acid and aminolysis afforded the respective products in high purity and good overall yield. To show the versatility of the synthesis, a 199-member library was generated. The library samples both conformational and chemical diversity about a well-known privileged substructure.

Introduction

A considerable amount of time and effort is currently being spent to increase the efficiencies of drug discovery. Lead compound selection (not withstanding commercial and market interests) is based primarily on a number of parameters, including ADME profile, molecular weight, and a series of pharmacokinetic indicators.[1,2] There is increasing pressure on early stage discovery as currently marketed pharmaceuticals are directed toward approximately 500 known biological targets,[3] while genomic research will identify thousands more.[4] Thus, the pressure to accelerate the drug discovery process will increase substantially over the next few years. Privileged structures represent an ideal source of lead compounds, already possessing characteristics favorable for drug-like compounds.

The term privileged structure has gained prominence in the literature since it was first introduced some fifteen years ago.[5] However, by definition, privileged structures are not structures in their own right because they usually comprise only a substructure of any molecule.[6] For the medicinal chemists, the true utility of privileged substructures is the ability to synthesize one library based on one core scaffold and screen it against a variety of different receptors, yielding several active compounds against different biological targets.

Several groups have used these substructures in this manner. For example, combinatorial libraries based on privileged substructures have been synthesized by Nicolaou and colleagues, who used a benzopyran scaffold,[7] Schultz and co-workers, who made use of the purine scaffold,[8] and Hirschmann and Smith, who worked with glycosides.[9] Patchett and co-workers used privileged substructures as “hydrophobic anchors” (harnessing their capabilities to bind to proteinaceous surfaces) to which they appended peptide functionality to gain specificity.[10] Further, Hirschmann et al. believes that the attachment of genetically encoded and uncoded amino acid side chains to privileged substructures are a promising means to produce diverse libraries of compounds.[11]

The biphenyl framework is without doubt a privileged substructure and as such is found in 4.3% of all known drugs.[12] In addition, two of the top ten selling drugs contain the biphenyl scaffold, and these are Losartan, **1**, and Valsartan, **2**, with combined sales over \$2 billion dollars annually (Figure 1).[13] Activity includes D2 agonists,[14] matrix metalloproteinases,[15] factor Xa,[16] Ras farnesyl transferase,[17] $\alpha_2\beta_3$ inhibitor,[18] and a ETA receptor antagonist.[19] Biphenyls are also known to have potential as antitumor,[20] antihypertensive,[13,14] and act as anti-atherosclerotic agents.[21] Synthetic access to large libraries of biphenyl compounds would be valuable to a medicinal chemist’s armory.[16]

In recent years, we have been interested in establishing solid-phase chemistries that allow the synthesis of various libraries using several purpose built linkers.[22,23] The safety-catch linker **9** and **10** in Figure 2 was found to be versatile in producing cyclic peptides and peptoidal compounds.[24]

There are many examples in the literature describing safety-catch linkers. The first safety-catch linker for cyclic peptide synthesis was developed by Marshall and Flannigan.[25] The strategy involved oxidation of the sulfide to yield the activated sulfone. Likewise, Rothe et al. developed a similar linker, which also required oxidative activation (H_2O_2).[26] Routledge et al. used a different strategy in the

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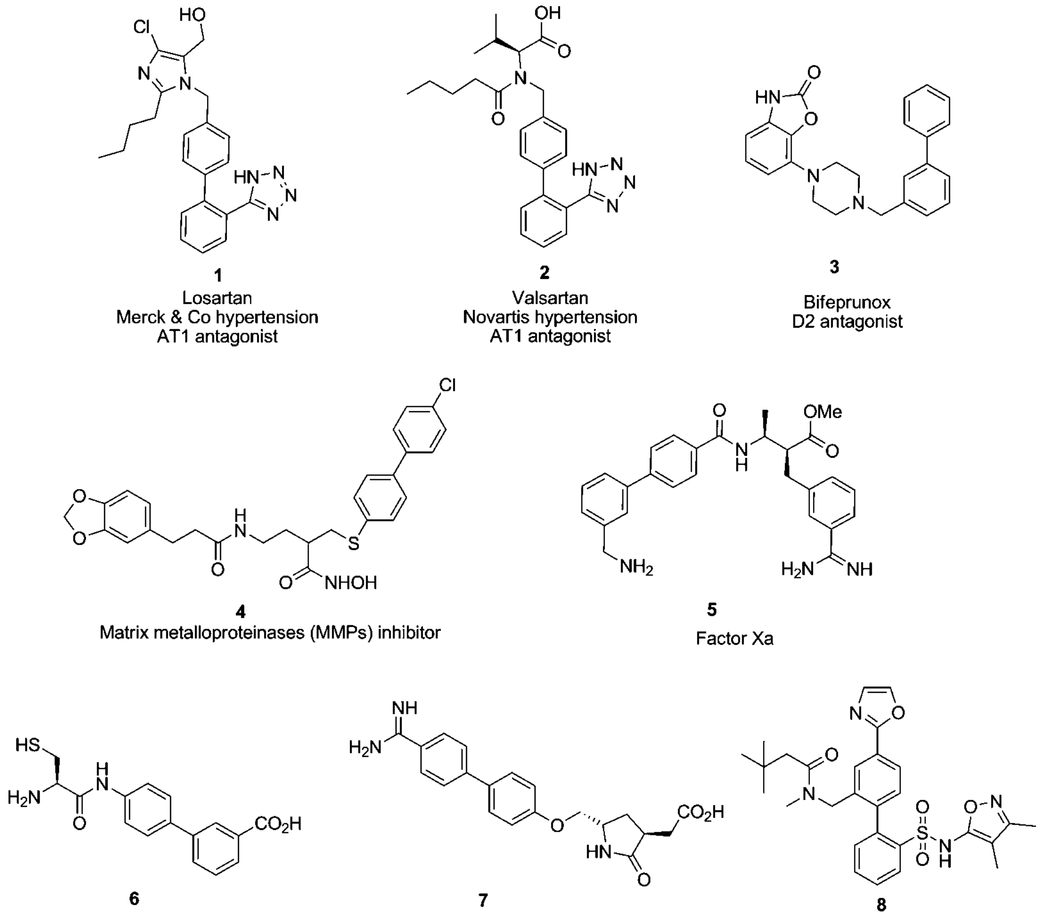


1 Losartan Merck & Co hypertension AT1 antagonist

2 Valsartan Novartis hypertension AT1 antagonist

3 Bifeprunox D2 antagonist

4 Matrix metalloproteinases (MMPs) inhibitor

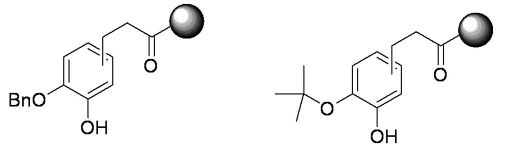
5 Factor Xa

6 Ras farnesyl transferase

7 Fradafiban (BIBU-52), Boehringer, αIIβ3 antagonists

8 BMS207940 ETA receptor anatgonist

Figure 1. Selected compounds in the clinic or in preclinical studies that have the biphenyl as a core template.



9 **10**

Figure 2. Structure of the safety catch linkers.

development of a dithiane "safety catch" linker.[27] Other well-known examples of safety-catch linkers includes Scal linker by Lebl and co-workers,[28] the dithiane-protected benzoin photolabile safety catch (BPSC) linker by Chan and co-workers,[29] a selenium-based linker by Nickalou[7,30] and the acylsulfonamide linker of Kenner.[31,32]

We decided upon the catechol linker developed in our laboratory.[23,24] Unlike most other safety catch linkers that usually require oxidation or alkylation for activation, the catechol safety catch linker **10** only requires simple acid treatment (TFA) for elimination of the *t*-butyl protecting group. This allows the possible incorporation of thiols, thioureas, and other reactive moieties onto the biphenyl framework. A similar linker has previously been reported by Beech et al. for small molecule synthesis.[33]

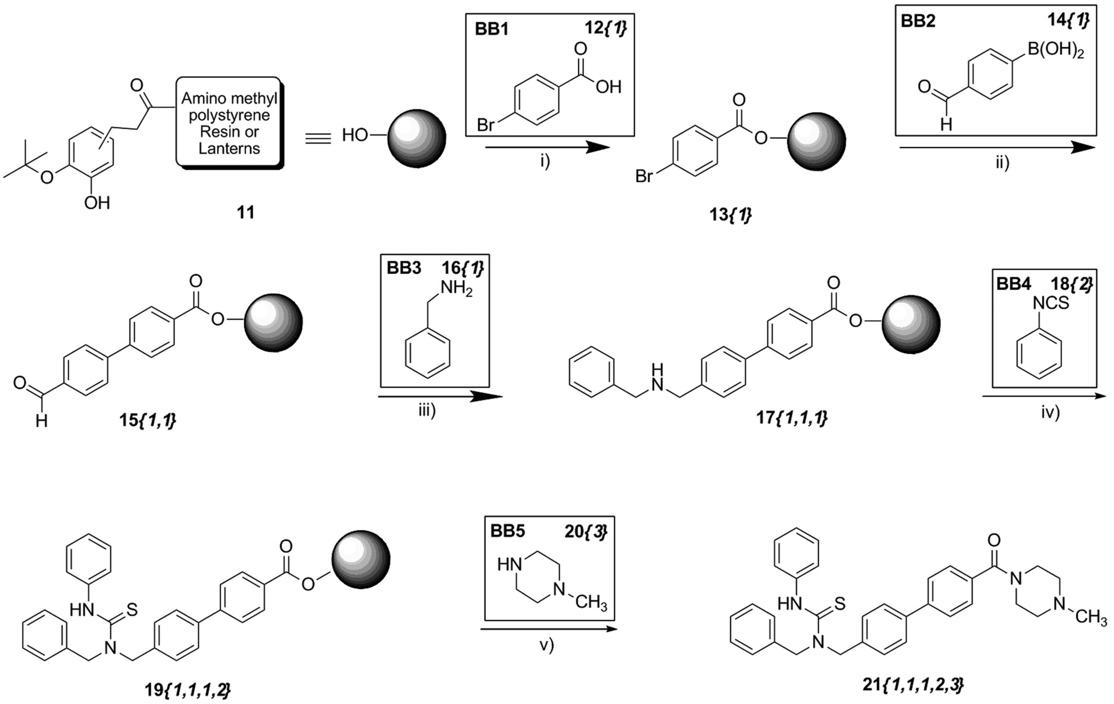
Results and Discussion

Our aim was to develop chemistry that sampled both the topological and chemical elements of diversity about a privileged substructure. Topological diversity is achieved by variations within the scaffold itself and attachment points of functionality to the scaffold. Chemical diversity is achieved by robust chemistry allowing the attachments of multiple functional groups to the scaffold. Ideally this process would use parallel processes and allow the efficient formation of large numbers of discrete molecules. The advantage of using the safety catch linkers **9** or **10** is that these linkers allow the addition of functionality at the cleavage step.

Our synthetic plan is shown in Scheme 1. Initial fuctionalization of the resin was achieved using the safety catch linker with standard in situ neutralization/HBTU activation protocols for BOC chemistry[34] to form **11**. 4-Bromo benzoic acid was then loaded to the linker through formation of the symmetric anhydride to give the bromide **13**. To improve the solubility properties of the acids, excess DIPEA was added in this step.

Suzuki cross-coupling chemistry was chosen to further functionalize bromide **13** into aldehyde **15**. Suzuki reactions have been reported several times for solid-phase chemistry[16,30,35] but never on the catechol safety-catch linker, and therefore, reaction conditions for this transformation were developed. Suzuki cross couplings on solid phase are typically conducted using solvents like 1,2-dimethoxy ethane (DME), toluene, or tetrahydrofuran (THF), often with ethanol (EtOH) as a cosolvent and bases like $CsCO_3$, K_2CO_3, or NaOH either as

Scheme 1. Reagents and Conditions for Synthesis of Substituted Biaryls Using Suzuki Cross-Coupling Chemistry[a]



[a] Reagents and conditions: (i) **12**{*1*}, (2 equiv BB1, Figure 3), DIC, DIPEA, DMAP, DCM, 20°C, 18 h; (ii) **14**{*1*}, (2 equiv BB2, Figure 3), $Pd(PPh_3)_4$, KF, DME/EtOH (5:1 v/v), 50°C, 12 h; (iii) **16**{*1*}, (2 equiv BB3, Figure 3), $NaBH_3CN$, DMF/MeOH/TMOF/AcOH (30:30:30:10 v/v) 12 h; (iv) **18**{*1*}, (2 equiv BB4, Figure 3), DIPEA, CH_2Cl_2/CH_3CN (1:1 v/v), 20°C, 2 h, (v) (a) TFA/tri-isopropyl silane (97:3 v/v); (b) **20**{*3*}, (2 equiv BB5, Figure 3), DIPEA, MIF.

aqueous solutions or as the neat salt. Our problem was that the safety catch linker was cleaved under these conditions and we therefore required a nonbasic route to **15**.

Wright and co-workers[36] showed that the flouride ion retained a high affinity for boron resulting in excellent yields for suzuki couplings. In addition,the flouirde ion also has relatively weak basicity and poor nucleophilicity. For a similar cross-coupling reaction (the Stille reaction), Baldwin[37] observed that the $PdCl_2/PtBu_3$ catalytic system with copper(I)iodide and cesium fluoride in DMF is most effective for coupling aryl bromides, while palladium catalysts in combination with copper(I)iodide with fluoride ion are optimal when coupling iodides and triflates. We therefore decided to use the flouirde ion to enhance Suzuki couplings and reduce the possibility of hydrolysis.

Initial experiments to investigate this conversion of resin bound bromide **13** to biphenyl aldehyde **15** used several palladium catalysts including $Pd(PPh_3)_4$ and $Pd(P^tBu_3)_2$, several solvent/temperature conditions, and several bases. Entries e and m (Table 1) were the most informative. Entry e resulted in a 12% yield, while entry m gave a 90% yield proving our suspicion that K_2CO_3 was too strong a base for the linker. The conditions from entry m were chosen for the library synthesis.

Immobilized aldehyde **15** was reductively aminated using a range of different primary amines, followed by reduction with $NaBH_3CN$ to form resin-bound amine **17**. Immobilized amine **17** was reacted with various different electrophiles (isocyanates, acid chlorides, or methyl sulfonyl chloride) to form ureas, amides, or sulfone amides with the general structure **19**. As alternative routes to **19,** resin bound amine **17** was activated with triphosgene and subsequently treated with amines. Alternatively, amine **17** could be reacted with carboxylic acids using standard in situ neutralization/HBTU activation protocols for BOC chemistry[34] to yield immobilized amides. After activation of the linker with TFA/triispropylsilane (TIPS), the linker was cleaved by addition of a range of nucleophiles such as hydrazine, primary amines, or secondary amines resulting in cleavage of biphenyl **21** from the resin. For the more sterically hindered amines, hydrolysis to form acids was the major byproduct, but drying the solid support under reduced pressure after linker activation and then performing the cleavage step under inert atmosphere resulted in **21** being formed in good yields and purity.

When mono-Boc-protected ethylene diamine **16**{*3*} was used for reductive amination on **15**{*1*,*1*}, **15**{*1*,*2*}, or **15**{*1*,*3*}, followed by reaction of the secondary amine with phenyl isothiocyanate **18**{*2*}, deprotection of the amine resulted in ring closure to form cyclic guanidines. Activation followed by cleavage with isopropyl amine then gave either **21**{*1*,*1*,*3*,*2*,*2*}, **21**{*1*,*2*,*3*,*2*,*2*}, or **21**{*1*,*3*,*3*,*2*,*2*}, respectively (Figure 4).

In total, a small library of 21 compounds was designed to explore the developed chemistry, using aminomethylated polystyrene resin as the solid support (Figure 4). The library was synthesized in a 24-well Bohdan block by parallel solid-phase chemistry employing a range of the building blocks from Figure 3. The synthesis was efficient having high purity with adequate purified final yields.

Because this chemistry was successful and efficient we explored the synthesis of a larger library. Given the advantages of split and mix synthesis, we transferred the chemistry to the Irori radio frequency AccuTag system[30,38]

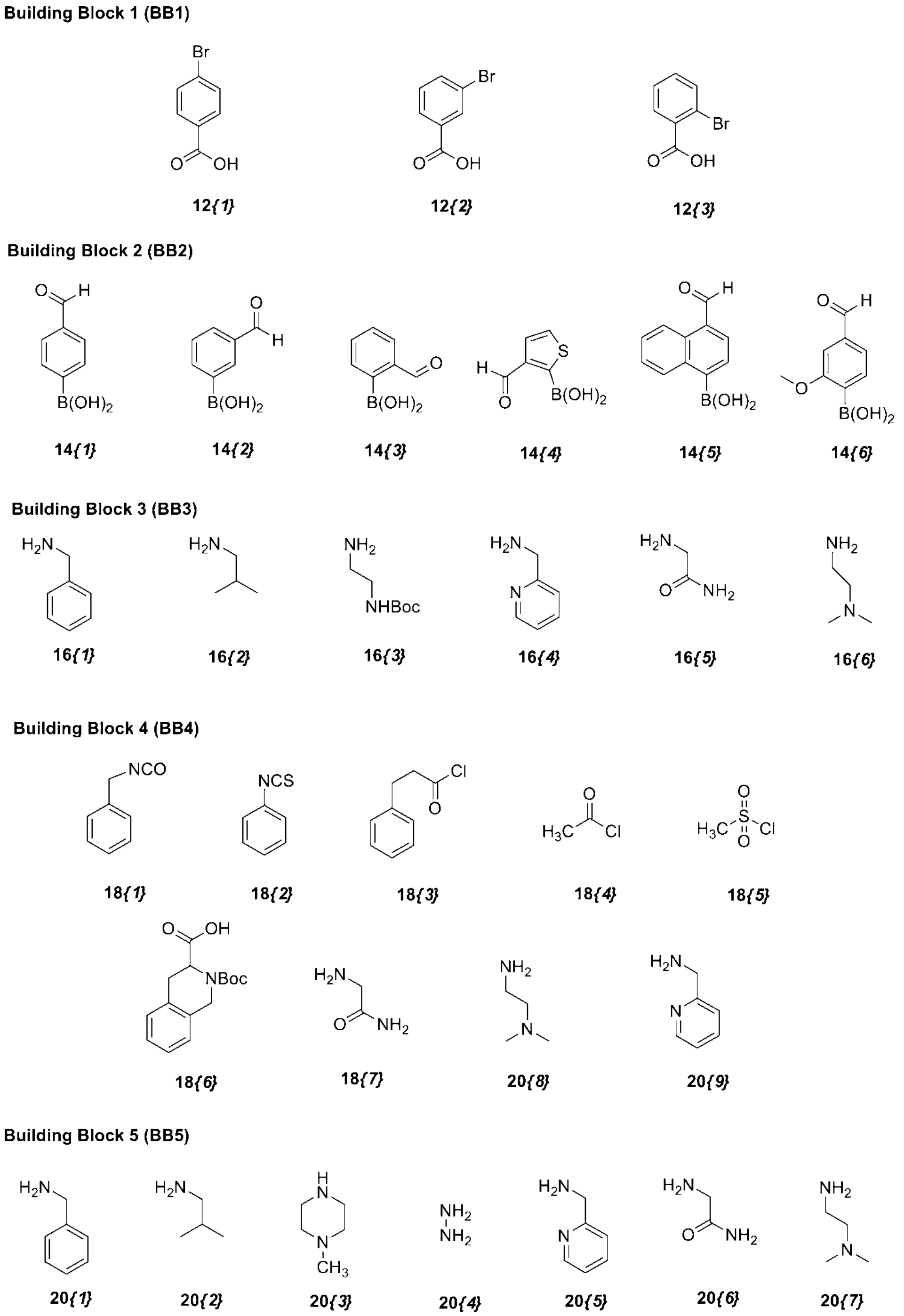


Figure 3. Building blocks for the biphenyl library. Selection was based upon a number of drug-like characteristics.

using the Mimotopes Synphase^{TM} Lanterns.[39] The advantage is that all lanterns that are reacted with a certain building block can be included in the same reaction vessel, and after completion, all the library members were washed in the same funnel. The lanterns were then split again in preperation for derivatization with the next building block.

To sample topological diversity a series of aryl bromides were selected with o-, m-, and p-substituted acids (Figure 3, BB1). Likewise a series of boranes (Figure 3, BB2) were also selected that again contained different o-, m-, and p-substituted aldehydes. Additional chemical and topological diversity can also be achieved by using different aromatics, for example, 5-membered rings would yield different geometry of attached functional groups and naphthyl boranes result in additional chemical diversity. A full combinatorial library using the building blocks depicted in Figure 3 would theoretically yield 6804 different compounds. A diverse set of 199 compounds, comprising a combination of charged, polar, and hydrophobic functionalities arrayed in different topologies was selected. The final products fitted within Lipinski's rule of five.[2]

A 199-membered library was synthesized using the split-and-pool method with directed sorting on Mimotopes Synphase Lanterns.[39] Figure 5 illustrates the purity of the entire library measured using reverse phase LC-MS. Generally the purity of compounds was excellent and in good yields (20−65%). This methodology allows for synthesis of large

Table 1. Selected Results from Suzuki Optimization Using Pd(PPh$_3$)$_4$ As the Catalyst[a]

entry	solvent	time (h)	base	conversion (%)
a	DME	18		5
b	THF	18		5
c	toluene/EtOH/H$_2$O	18		5
d	toluene/EtOH/H$_2$O	5	K$_2$CO$_{3(aq)}$	55
e	toluene/EtOH/H$_2$O	18	K$_2$CO$_{3(aq)}$	12
f	toluene/EtOH/H$_2$O	18	KF	5
g	toluene/EtOH	5	K$_2$CO$_3$	20
h	toluene/EtOH	18	K$_2$CO$_3$	25
i	THF/EtOH	18		5
j	THF/EtOH	18	KF	5
k	DME/EtOH	18		5
l	DME/EtOH	5	KF	60
m	DME/EtOH	18	KF	90
n	DME/EtOH	5	K$_2$CO$_3$	20
o	DME/EtOH	18	K$_2$CO$_3$	20

[a] Conversion was calculated from HPLC of the crude cleavage product at a wavelength $\lambda = 214$ nm. Substitution value for the derivatized resin 0.7 mmol/g. under an atmosphere of argon. Three equivalents of boronic acid was added to the bromide on resin at 1 mmol per 4 mL. All entries were run at at 50 °C.

libraries by taking advantage of a split and pool method with directed sorting.[30,38]

In conclusion, we have developed a solid phase protocol for synthesis of substituted biphenyls. The protocol developed allows for great variation in the biphenyl core and further derivatization employing three different substituents makes it possible to synthesize very diverse compounds using this methodology. Yields for the reactions were high (generally between 20% and 65%), and purity of crude was excellent (generally between 75% to 95%). Finally we have shown that large numbers of compounds could be synthesized using these conditions. Currently we are screening libraries of this nature against a diverse array of receptor targets.

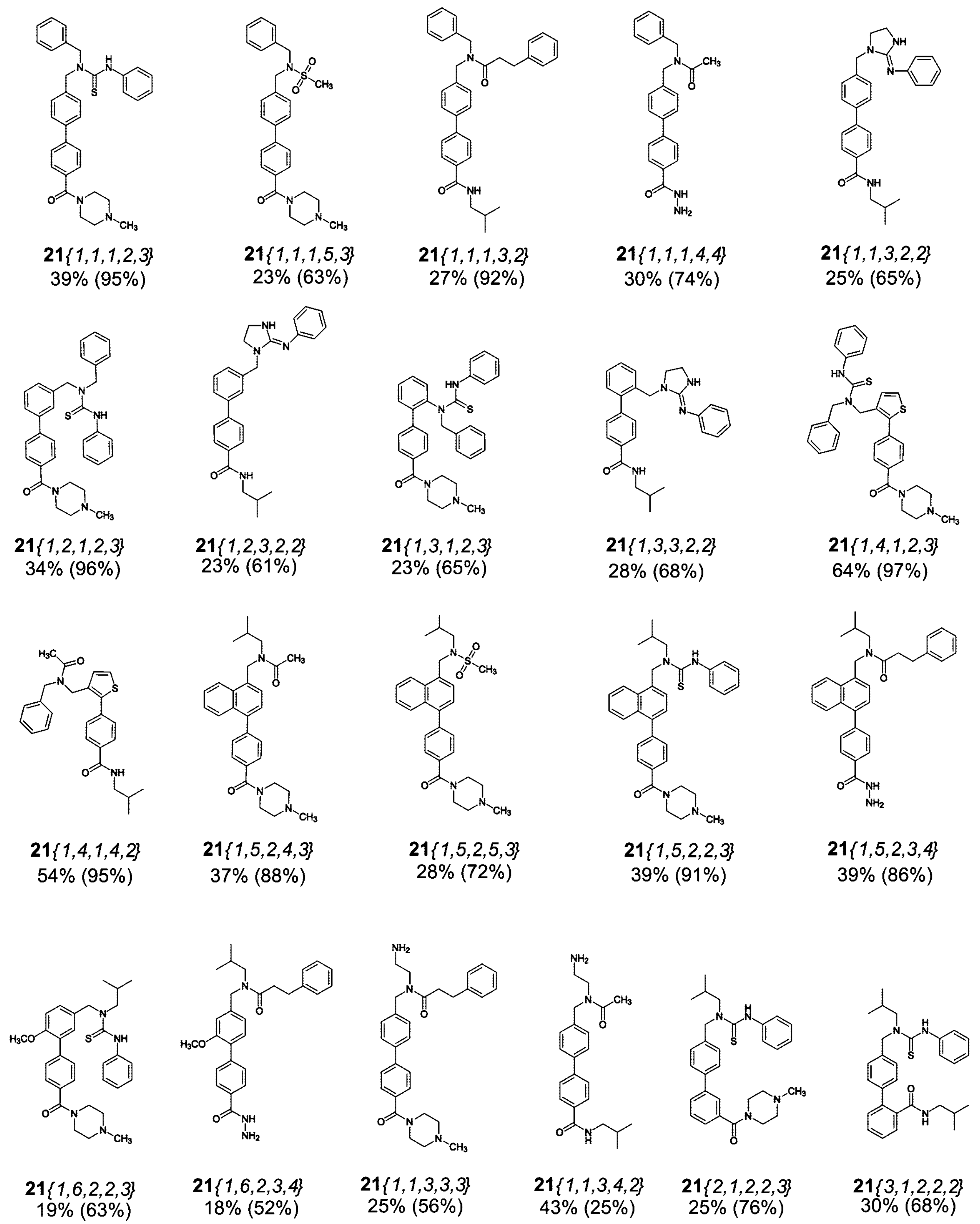
Experimental Section

Nuclear magnetic resonance spectra were recorded at 300 MHz (^{1}H)/75 MHz (^{13}C) or 600 MHz (^{1}H) on a Varian Gemini-300 or a Bruker 600 Ultrashield instrument, respectively. ^{1}H and ^{13}C chemical shifts (δ) are given in parts per million (ppm) using residual protonated solvent as an internal standard. Coupling constants are given in Hertz (Hz). The following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet, dd = double of doublets. Electrospray ionization mass spectra (ESI-MS) and atmospheric pressure chemical ionization mass spectra (APCI-MS) were acquired using either a Waters 2790 Separations Module equipped with a Micromass ZMD mass detector or an Agilent 1100 Series Separations Module equipped with an Agilent 1100 Series LC/MSD mass detector. High resolution mass spectral data was obtained on a PE Sciex API QSTAR Pulsar (ES-QqTOF) instrument using ACP (acyl carrier protein) (65−74) ($C_{47}H_{75}N_{12}O_{16}$ (M+H), 1063.5424) and reserpine ($C_{33}H_{40}N_2O_9$ (M+H), 609.2812) as internal references. Resolution for the instrument was set between 10 000 and 12 000 for all standards. Analytical reversed phase HPLC were run on a Vydac C$_{18}$ column (4.6 × 250 mm) or Phenomonex Luna 5 μm C$_{18}$ column (50 × 2.0 mm), preparative reversed phase HPLC were run on a Vydac C$_{18}$ column (22 × 250 mm) at 8 mL/min or on a Phenomonex Jupiter 10 μm Proteo 90 Å C$_{18}$ column (100 × 21.2 mm). HPLCs were run using an A/B solvent gradient (A: 99.5% H$_2$O, 0.5% TFA; B: 89.75% MeCN, 9.75% H$_2$O, 0.5% TFA). All reactions were optimized using aminomethylpolystyrene resin or trityl chloride polystyrene (TCP) resin. The library was synthesized on Mimotopes Synphase Lanterns using a split and pool method with directed sorting. All 220 library members were purified using reverse-phase HPLC, but only 21 compounds were characterized with NMR and exact mass. Unless stated, all reactions were carried out at 20 °C, and washings were performed at a ratio of 1 mL solvent per 100 mg resin. Unless stated, reactions were monitored by cleaving small portion of the resin and analyzing the crude cleavage product on ESI-MS. The rest of the library was verified using LC-MS. Abbreviations: MeCN, acetonitrile; TFA, trifluoroacetic acid; DCM, dichloromethane; DIC, diisopropylcarbodiimide; DIPEA, diisopropylethyl amine; DMAP, 4-(dimethylamino)pyridine; DME, 1,2-dimethoxy ethane; DMF, *N*,*N*-dimethylformamide; EtOH, ethanol; HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate; MeOH, methanol; TIPS, triisopropylsilane; THF, tetrahydrofuran, TMOF, trimethylorthoformate.

Materials. Boc-L-amino acids, synthesis grade DMF, TFA, and DIPEA were purchased from Auspep (Parkville, Australia). HBTU was purchased from Richelieu Biotechnologies (Montreal, Canada). AR grade MeOH, CH$_2$Cl$_2$, CHCl$_3$, and HPLC grade CH$_3$CN were all obtained from Laboratory Supply (Australia). Aminomethylpolystyrene resins with a substitution value of 0.41 mmol/g were purchased from Novabiochem. Synphase Lanterns were purchased from Mimotopes in Australia. All other reagents were AR grade or better and were obtained from Aldrich or Fluka. The safety-catch linker (3-(3-benzyloxy-4-hydroxyphenyl)propionic acid and 3-(4-benzyloxy-3-hydroxyphenyl)propionic acid) was prepared as a mixture of monoprotected catechols by the procedure of Bourne et al.[23]

General Procedure for the Preparation of Substituted Biaryls (13). Formation of Resin-Bound Bromide (13). Aminomethyl polystyrene resin (1.0 g, 0.7 mmol) was derivatized with H-Gly-Leu-Leu using in situ neutralization/HBTU activation protocols for Boc chemistry. A solution of 1-(3-hydroxy-4-tert-butoxyphenyl)propanoic acid and 1-(4-hydroxy-3-tert-butoxyphenyl)propanoic acid (0.33 g, 1.4 mmol), HBTU (532 mg, 1.4 mmol), and DIPEA (1.8 mmol, 310 μL) in DMF (10 mL) was added to the resin, and the mixture was agitated for 1 h before excess reagents were removed by filtration. The resin was subsequently washed with DMF (3×) and DCM (3×) to give resin **11**. DIC (0.33 mL, 2.1 mmol) was added to a stirred solution of 4-bromobenzoic acid (0.844 g, 4.2 mmol) and DIPEA (0.72 mL, 4.2 mmol) in DCM (10 mL). After it was stirred for 10 min, the mixture was added to resin **2** together with catalytic amount of DMAP (10 mg, 0.08 mmol) and shaken for 16 h. The resin was filtered and washed with DMF (3×) and DCM (5×) and dried under reduced pressure to yield immobilized bromide **13**{*1*}.

Formation of Biaryl Aldehyde (15). Typical procedure: Bromo-functionalized resin **13**{*1*} (1.4 g, 0.7 mmol) was



21{*1,1,1,2,3*} 39% (95%)

21{*1,1,1,5,3*} 23% (63%)

21{*1,1,1,3,2*} 27% (92%)

21{*1,1,1,4,4*} 30% (74%)

21{*1,1,3,2,2*} 25% (65%)

21{*1,2,1,2,3*} 34% (96%)

21{*1,2,3,2,2*} 23% (61%)

21{*1,3,1,2,3*} 23% (65%)

21{*1,3,3,2,2*} 28% (68%)

21{*1,4,1,2,3*} 64% (97%)

21{*1,4,1,4,2*} 54% (95%)

21{*1,5,2,4,3*} 37% (88%)

21{*1,5,2,5,3*} 28% (72%)

21{*1,5,2,2,3*} 39% (91%)

21{*1,5,2,3,4*} 39% (86%)

21{*1,6,2,2,3*} 19% (63%)

21{*1,6,2,3,4*} 18% (52%)

21{*1,1,3,3,3*} 25% (56%)

21{*1,1,3,4,2*} 43% (25%)

21{*2,1,2,2,3*} 25% (76%)

21{*3,1,2,2,2*} 30% (68%)

Figure 4. Selected products from the synthesized biphenyl library. Yields are given below each compound and purity of the crude cleavage products are given in brackets. Purity is calculated from HPLC of the crude cleavage product at 214 nm.

placed in a reaction vessel under nitrogen atmosphere. DME (10 mL) was degassed and added to the resin, followed by addition of neat Pd(PPh$_3$)$_4$ (81 mg, 0.07 mmol). A solution of 4-formyl phenyl boronic acid (315 mg, 2.1 mmol) in degassed EtOH (2 mL) was added to the resin, and the mixture was agitated for 5 min; KF (162 mg, 2.8 mmol) was added neat. The mixture was agitated 16 h at 50 °C before excess reagents were removed by filtration, and the

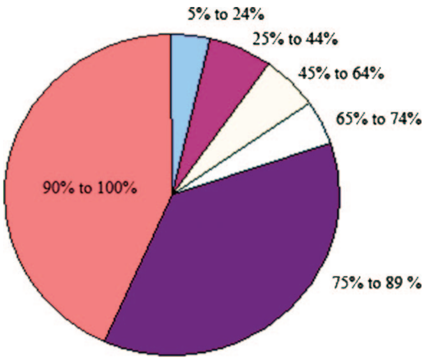


Figure 5. Analytical HPLC purity of the 199-member biphenyl library measured at a wavelength $\lambda = 214$ nm. Purity range of 5−24% (8 compounds), 25−44% (12 compounds), 45−64% (11 compounds), 65−74% (9 compounds), 75–89% (72 compounds), and 90–100% (87 compounds).

resin was washed with DMF (3×) and DCM (3×) to yield resin bound aldehyde **15**{*1*,*1*}.

Formation of Substituted Biaryl Amines (17). Typical procedure: Resin **15**{*1*,*1*} (150 mg, 0.07 mmol) was added benzylamine (75 mg, 0.7 mmol) dissolved in a mixture of DMF/MeOH/TMOF/AcOH (30:30:30:10, v/v, 2 mL) and shaken for 1 h. A solution of $NaBH_3CN$ in MeOH/DMF (1:1 v/v, 2 mL) was added to the resin, and the mixture was agitated 16 h, before excess reagents were removed by filtration. The resin was washed with DMF (3×), MeOH/DCM (1:1 v/v, 2×), and DCM (3×) to yield resin bound amine **17**{*1*,*1*,*1*}.

Reaction with Various Electrophiles Forming Urea or Amide (19). Two general procedures were applied for this step: (1) Reaction of the secondary amine with various electrophiles or (2) preactivation with triphosgene, followed by reaction with amines. (1) Resin **17**{*1*,*1*,*1*} (150 mg, 0.07 mmol) was preswelled in DCM. A solution of phenyl isothiocyanate **18**{*2*} (48.0 mg, 0.35 mmol) and DIPEA (60 μL, 0.35 mmol) in DCM/AcCN (1:1, v/v, 2 mL) was added to the resin, and the mixture was stirred 2 h, before excess reagents were removed by filtration. The resin was subsequently washed with DCM (3×), DCM/MeOH (1:1, v/v, 2×), DMF (2×), and DCM (5×) before it was dried under reduced pressure for 12 h to yield resin **19**{*1*,*1*,*1*,*2*}. (2) Resin **17**{*1*,*1*,*1*} (150 mg, 0.07 mmol) was swollen in a DCM/DIPEA mixture(1.1 mL, 10:1, v/v) and agitated 10 min. DIPEA (25 μL, 0.21 mmol, 3 equiv) was added followed by thionyl chloride **18**{*5*} (15 μL, 0.21 mmol, 3 equiv). The resin was agitated for 3 h before excess reagents were removed by filtration. The resin was washed with DCM (3×), DCM/MeOH (1:1, v/v, 2×), DMF (2×), and DCM (5×) before it was dried under reduced pressure for 12 h to yield resin **19**{*1*,*1*,*1*,*5*}.

Activation of Linker and Cleavage with Amines (21). Typical procedure: Resin **19**{*1*,*1*,*1*,*5*} (150 mg, 0.07 mmol) was placed in a Teflon cleavage vessel under N_2 atmosphere. The resin was treated with a mixture of TFA/TIPS (97:3, v/v, 2×) for 2 × 30 min and washed with DCM (2×), dry DMF (2×), and DCM (2×) before it was dried under reduced pressure for 14 h. A solution of 1-methyl piperazine **20**{*3*} (70 mg, 0.7 mmol) and DIPEA (120 μL, 0.7 mmol) in DMF (2 mL) was added to the resin, and the solution was agitated 4 h at 20 °C. The resin was filtered, and the filtrate was collected. The treatment was repeated with a fresh portion of 1-methyl piperazine/DMF/DIPEA solution for 16 h, and the combined filtrates were concentrated under reduced pressure at 40 °C to give the crude product. Preparative HPLC, followed by freeze-drying, gave the pure product **21**{*1*,*1*,*1*,*5*,*3*} as a white solid material.

1-Benzyl-1-[4′-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-ylmethyl]-3-phenyl-thiourea 21{*1*,*1*,*1*,*2*,*3*}. ^{1}H NMR (600 MHz, DMSO-d_6): δ, 2.80 (s, 3H, NCH_3), 3.61−2.8 (m, 8H, piperazine), 5.09 (s, 2H, PhCH_2), 5.12 (s, 2H, PhCH_2), 7.13 (t, $J = 6.6$ Hz, 1H, Ar*H*), 7.25−7.45 (m, 10H, Ar*H*), 7.54 (d, $J = 7.9$ Hz, 2H, Ar*H*), 7.71 (d, $J = 8.3$ Hz, 2H, Ar*H*), 7.76 (d, $J = 8.3$ Hz, 2H, Ar*H*), 9.42 (s, 1H, N*H*). ES-MS: *m*/*z* 535.2543, calcd for $[C_{33}H_{34}N_4OS + H]^+$ 535.2532.

***N*-Benzyl-*N*-[4′-(4-methyl-piperazine-1-carbonyl)-biphenyl-4-ylmethyl]-methanesulfonamide 21{*1*,*1*,*1*,*5*,*3*}.** ^{1}H NMR (600 MHz, $CDCl_3$): δ, 2.83 (s, 3H, NCH_3), 2.84 (s, 3H, SCH_3), 4.39 (s, 2H, PhCH_2), 4.41 (s, 2H, PhCH_2), 7.33 (m, 4H, Ar*H*), 7.42 (m, 2H, Ar*H*), 7.52 (m, 3H, Ar*H*), 7.57 (d, $J = 8.3$ Hz, 2H, Ar*H*), 7.65 (d, $J = 8.3$ Hz, 2H, Ar*H*). ES-MS: $m/z = 478.2150$, calcd for $[C_{27}H_{31}N_3O_3S + H]^+$ 478.2164.

4′-{[Benzyl-(3-phenyl-propionyl)-amino]-methyl}-biphenyl-4-carboxylic acid isobutyl-amide 21{*1*,*1*,*1*,*3*,*2*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (d, $J = 7.1$, 6H, CH_3), 1.94 (m, 1H, $CH(CH_3)_2$), 2.76 (t, $J = 7.6$ Hz, 2H, $COCH_2$), 3.07 (m, 2H, $NHCH_2CH$), 3.33 (t, $J = 6.6$ Hz, 2H, $COCH_2CH_2$), 4.42 (s, 2H, NCH_2C), 4.54 (d, $J = 4.0$ Hz, 2H, NCH_2C), 6.24 (m, 1H, NH), 7.09 (d, $J = 7.4$ Hz, 1H, ArH), 7.15 (d, $J = 7.9$ Hz, 1H, ArH), 7.20 (m, 4H, ArH), 7.25 (m, 4H, ArH), 7.34 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.65 (d, $J = 8.3$ Hz, 2H, ArH), 7.85 (m, 2H, ArH). ES-MS: *m*/*z* 505.2841, calcd for $[C_{34}H_{36}N_2O_2 + H]^+$ 505.2855.

***N*-Benzyl-*N*-(4′-hydrazinocarbonyl-biphenyl-4-ylmethyl)-acetamide 21{*1*,*1*,*1*,*4*,*4*}.** ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.26 (m, 2H, NH_2), 2.18 (s, 3H, COCH_3), 4.39 (s, 2H, PhCH_2), 4.52 (s, 2H, ArCH_2), 5.5−6.2 (br s, 3H, N*H*), 7.09 (m, 5H, Ar*H*), 7.30 (m, 8H, Ar*H*). ES-MS: *m*/*z* 374.1861, calcd for $[C_{23}H_{23}N_3O_2 + H]^+$ 374.1868.

4′-(2-Phenylimino-imidazolidin-1-ylmethyl)-biphenyl-4-carboxylic Acid Isobutyl-amide 21{*1*,*1*,*3*,*2*,*2*}. ^{1}H NMR (600 MHz, d_6-DMSO): δ 0.91 (d, $J = 6.6$ Hz, 6H, CH(CH_3)$_2$), 1.87 (m, 1H, C*H*(CH$_3$)$_2$), 3.11 (t, $J = 6.6$ Hz, 2H, CH_2CH(CH$_3$)$_2$), 3.65 (m, 4H, NCH_2CH_2NC═N), 4.79 (s, 2H, ArCH_2), 7.38 (m, 4H, Ar*H* + N*H*), 7.52 (m, 3H, Ar*H*), 7.78 (m, 4H, Ar*H*), 7.96 (m, 3H, Ar*H*), 8.53 (s, 1H, CON*H*). ES-MS: *m*/*z* 427.2490, calcd for $[C_{27}H_{30}N_4O + H]^+$ 427.2498.

1-Benzyl-1-[4′-(4-methyl-piperazine-1-carbonyl)-biphenyl-3-ylmethyl]-3-phenyl-thiourea 21{*1*,*2*,*1*,*2*,*3*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.00 (br m, 2H, piperazine) 2.83 (s, 3H, NCH_3), 3.70 (br m, 6H, piperizine), 5.05 (s, 2H, NCH_2), 5.23 (s, 2H, NCH_2), 7.18 (d, $J = 7.0$ Hz, 2H, Ar*H*), 7.22 (s 1H, Ar*H*), 7.30 (t, $J = 7.9$ Hz, 2H, Ar*H*), 7,36 (m 6H, Ar*H*), 7.51 (t, 3H, Ar*H*), 7.58 (m, 2H, Ar*H*), 7.62 (d, $J = 8.3$ Hz, 2H, Ar*H*). ES-MS: $m/z = 535.2539$, calcd for $[C_{33}H_{34}N_4OS + H]^+$ 535.2532.

3′-(2-Phenylimino-imidazolidin-1-ylmethyl)-biphenyl-4-carboxylic acid isobutyl-amide 21{*1,2,3,2,2*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.99 (d, *J* = 7.0 Hz, 6H, $CH(CH_3)_2$), 1.91 (m, 1H, $CH(CH_3)_2$), 3.28 (t, *J* = 6.5 Hz, 2H, $CH_2CH(CH_3)_2$), 3.63 (m, 4H, $NCH_2CH_2NC{=}N$), 4.45 (s, 2H, $ArCH_2$), 6.44 (t, *J* = 5.7 Hz, 1H, N*H*), 7.18 (t, *J* = 8.8 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.30 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.35 (s, 1H, Ar*H*), 7.44 (t, *J* = 7.9 Hz, 1H, Ar*H*), 7.54 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.57 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.82 (d, *J* = 8.7 Hz, 2H, Ar*H*), 9.30 (br s, 1H, CON*H*). ES-MS: *m/z* 427.2501, calcd for $[C_{27}H_{30}N_4O + H]^+$ 427.2498.

1-Benzyl-1-[4′-(4-methyl-piperazine-1-carbonyl)-biphenyl-2-ylmethyl]-3-phenyl-thiourea 21{*1,3,1,2,3*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.50 (br m, 2H, piperazine) 2.78 (s, 3H, NCH_3), 3.62 (br m, 6H, piperazine), 4.79 (s, 2H, $PhCH_2$), 5.12 (s, 2H, $PhCH_2$), 7.03 (s, 1H, N*H*), 7.12 (d, *J* = 7.5 Hz, 2H, Ar*H*), (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.34 (m, 8H, Ar*H*), 7.43 (m, 6H, Ar*H*). ES-MS: *m/z* 535.2520, calcd for $[C_{33}H_{34}N_4OS + H]^+$ 535.2532.

2′-(2-Phenylimino-imidazolidin-1-ylmethyl)-biphenyl-4-carboxylic Acid Isobutyl-amide 21{*1,3,3,2,2*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ, 0.9 (d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$), 0.99 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 1.83 (m, 0.5H, $CH(CH_3)_2$), 2.00 (m, 0.5H, $CH(CH_3)_2$), 3.09 (m, 1H, $CH_2CH(CH_3)_2$), 3.31 (t, *J* = 6,1 Hz, 1H, $NCH_2CH_2NC{=}N$), 3.31 (t, *J* = 6,5 Hz, 1H, $NCH_2CH_2NC{=}N$), 3.46 (t, *J* = 8.3 Hz, 1H, $NCH_2CH_2NC{=}N$), 3.57 (t, *J* = 8.3 Hz, 1H, $NCH_2CH_2NC{=}N$), 4.05 (m, 1H, $CH_2CH(CH_3)_2$), 4.11 (s, 1H, $ArCH_2$), 4.45 (s, 1H, $ArCH_2$), 6.78 (d, *J* = 7.5 Hz, 1H, ArH), 7.08 (d, *J* = 8.4 Hz, 1H, ArH), 7.15 (m, 1H, ArH), 7.24 (m, 3H, ArH), 7.33 (m, 5H, ArH), 7.63 (m 1H, CONH), 7.66 (d, *J* = 7.9 Hz, 1H, ArH), 7.80 (d, *J* = 7.9 Hz, 1H, ArH), 8.30 (br s, 1H, NNH). ES-MS: *m/z* = 427.2504, calcd for $[C_{27}H_{30}N_4O + H]^+$ 427.2498.

1-Benzyl-1-{2-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-thiophen-3-ylmethyl}-3-phenyl-thiourea 21{*1,4,1,2,3*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.65 (br m, 2H, piperazine), 2.81 (s, 3H, NCH_3), 3.53 (br m, 6H, piperizine), 4.76 (s, 2H, NCH_2), 5.44 (s, 2H, NCH_2), 7.05 (d, *J* = 5.1 Hz, 2H, Ar*H*), 7.13 (m, 3H, Ar*H*), 7.17 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.34 (m, 8H, Ar*H*), 7.42 (m, 2H, Ar*H*). ES-MS: *m/z* 541.2080, calcd for $[C_{31}H_{32}N_4OS_2 + H]^+$ 541.2095.

4-{3-[(Acetyl-benzyl-amino)-methyl]-thiophen-2-yl}-*N*-isobutyl-benzamide 21{*1,4,1,4,2*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.94 (m, 1H, $CH(CH_3)_2$), 2.14 (s, 3H, $COCH_3$), 3.32 (m, 2H, $CH_2CH(CH_3)_2$), 4.29 (s, 2H, $PhCH_2$), 4.79 (s, 2H, $ArCH_2$), 6.18 (m, 1H, thiophene), 6.84 (m, 1H, thiophene), 7.00 (d, *J* = 5.4 Hz, 2H, Ar*H*), 7.22 (m, 2H, Ar*H*), 7.29 (m, 3H, Ar*H*), 7.71 (d, *J* = 8.4 Hz, 2H, Ar*H*). ES-MS: *m/z* 421.1936, calcd for $[C_{25}H_{28}N_2O_2 + H]^+$ 421.1950.

***N*-Isobutyl-*N*-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-naphthalen-1-ylmethyl}-acetamide 21{*1,5,2,4,3*}.** ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.90 (d, *J* = 6.6 Hz, 6H, $(CH_3)_2CH$), 2.05 (m, 1H, $(CH_3)_2CH$), 2.17 (br s, 3H, $COCH_3$), 2.85 (s, 3H, NCH_3), 3.09 (m, 4H, $(CH_2)_2NCH_3$ 3.23 (d, *J* = 7.7 Hz, 2H, NCH_2CH), 3.81 (m, 4H, $N(CH_2)_2$), 5.05 (s, 2H, CCH_2), 7.37 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.41 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.56 (m, 3H, Ar*H*), 7.61 (m, 3H, Ar*H*), 7.84 (d, *J* = 8.8 Hz, 1H, Ar*H*), 8.15 (d, *J* = 7.7 Hz, 1H, Ar*H*). ES-MS: *m/z* = 458.2811, calcd for $[C_{29}H_{35}N_3O_2 + H]^+$ 458.2808.

***N*-Isobutyl-*N*-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-naphthalen-1-ylmethyl}-acetamide 21{*1,5,2,4,3*}.** ^{1}H NMR (100 °C) (600 MHz, DMSO-d_6): δ 0.90 (d, *J* = 6.6 Hz, 6H, $(CH_3)_2CH$), 2.05 (m, 1H, $(CH_3)_2CH$), 2.07 (br s, 3H, $COCH_3$), 2.81 (s, 3H, NCH_3), 3.09 (m, 4H, $(CH_2)_2NCH_3$ 3.23 (d, *J* = 7.7 Hz, 2H, NCH_2CH), 3.81 (m, 4H, $N(CH_2)_2$), 5.10 (s, 2H, CCH_2), 7.42 (m, 2H, Ar*H*), 7.56 (d, *J* = 7.7 Hz, 3H, Ar*H*), 7.61 (d, *J* = 7.7 Hz, 3H, Ar*H*), 7.85 (d, *J* = 8.8 Hz, 1H, Ar*H*), 8.17 (d, *J* = 7.7 Hz, 1H, Ar*H*). ES-MS: *m/z* 458.2811, calcd for $[C_{29}H_{35}N_3O_2 + H]^+$ 458.2808.

***N*-Isobutyl-*N*-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-naphthalen-1-ylmethyl}-methanesulfonamide 21{*1,5,2,5,3*}.** ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.61 (m, 1H, $CH(CH_3)_2$), 2.75 (br m, 2H, piperazine) 2.88 (s, 3H, NCH_3), 2.94 (s, 3H, SCH_3), 3.07 (d, *J* = 7.5 Hz, 2H, $CH_2CH(CH_3)_2$), 3.70 (br m, 6H, Piperazine) 4.92 (s, 2H, $ArCH_2$), 7.37 (d, *J* = 7.0 Hz, 1H, Ar*H*), 7.49 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.57 (m, 6H, Ar*H*), 7.85 (d, *J* = 8.3 Hz, 1H, Ar*H*), 8.32 (d, *J* = 8.3 Hz, 2H, Ar*H*), ES-MS: *m/z* 494.2467, calcd for $[C_{28}H_{35}N_3O_3 + H]^+$ 494.2477.

1-Isobutyl-1-{4-[4-(4-methyl-piperazine-1-carbonyl)-phenyl]-naphthalen-1-ylmethyl}-3-phenyl-thiourea 21{*1,5,2,2,3*} . ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.5 Hz, 6H, $CH(CH_3)_2$), 2.05 (m, 1H, $CH(CH_3)_2$), 2.82 (s, 3H, NCH_3), 3.20 (br m, 2H, piperazine), 3.27 (d, *J* = 7.5 Hz, 2H, $CH_2CH(CH_3)_2$), 3.90 (br m, 6H, piperazine), 4.33 (s, 1H, $ArCH_2$), 5.60 (s, 1H, $ArCH_2$), 7.32 (m, 4H, Ar*H*), 7.41 (m, 2H, Ar*H*), 7.55 (m, 5H, Ar*H*), 7.79 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.88 (d, *J* = 8.3 Hz, 1H, Ar*H*), 8.03 (d, *J* = 8.8 Hz, 2H, Ar*H*): ES-MS: *m/z* 551.2830, calcd for $[C_{34}H_{38}N_4OS + H]^+$ 551.2844.

***N*-[4-(4-Hydrazinocarbonyl-phenyl)-naphthalen-1-ylmethyl]-*N*-isobutyl-3-phenyl-propionamide 21{*1,5,2,3,4*}.** ^{1}H NMR (600 MHz, $CDCl_3$): δ, 0.90 (d, *J* = 7.0 Hz, 3H, $CH(CH_3)_2$), 0.95 (d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$), 1.44 (m, 2H, NH_2) 2.06 (m, 1H, $CH(CH_3)_2$), 2.64 (t. *J* = 7.5 Hz, 1H, $COCH_2$), 2.81 (t. *J* = 7.9 Hz, 1H, $COCH_2$), 3.00 (m, 2H, $PhCH_2 + CH_2CH$), 3.08 (t. *J* = 7.5 Hz, 1H, $PhCH_2$), 3.33 (t. *J* = 7.4 Hz, 1H, CH_2CH), 4.94 (s, 1H, $ArCH_2N$), 5.18 (s, 1H, $ArCH_2N$), 7.23 (m, 8H, Ar*H*), 7.55 (m, 4H, Ar*H*), 7,92 (m, 3H, Ar*H*). ES-MS: *m/z* 480.2643, calcd for $[C_{31}H_{33}N_3O_2 + H]^+$ 480.2651.

1-Isobutyl-1-[6-methoxy-4′-(4-methyl-piperazine-1-carbonyl)-biphenyl-3-ylmethyl]-3-phenyl-thiourea 21{*1,6,2,2,3*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ, 1.04 (d, *J* = 5.0 Hz, 6H, $CH(CH_3)_2$), 2.40 (m, 1H, $CH(CH_3)_2$), 2.52 (br m, 2H, piperazine), 2.83 (s, 3H, NCH_3), 3.60 (br m, 6H, piperazine), 3.78 (m, 2H, $CH_2CH(CH_3)_2$), 3.93 (s, 3H, OCH_3), 4.99 (s, 2H, $ArCH_2$), 7.02 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.16 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.23 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.30 (t, *J* = 8.3 Hz, 1H, Ar*H*), 7.45 (m, 2H, Ar*H* + N*H*), 7.49 (d, *J* = 7.9 Hz, 3H, Ar*H*), 7.23 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.60 (d, *J* = 8.3 Hz, 2H, Ar*H*). ES-MS: *m/z* 531.2783, calcd for $[C_{31}H_{38}N_4O_2S + H]^+$ 531.2794.

***N*-(4′-Hydrazinocarbonyl-6-methoxy-biphenyl-3-ylmethyl)-*N*-isobutyl-3-phenyl-propionamide 21{*1,6,2,3,4*}.** ^{1}H NMR (600 MHz, $CDCl_3$): δ, 0.82 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.25 (br s, 2H, N*H*), 1.95 (m, 1H, $CH(CH_3)_2$), 2.57 (m, 2H, $COCH_2$), 2.84 (m, 1H, $PhCH_2$), 2.93 (m, 1H, $PhCH_2$), 3.17 (d, J = 6.6 Hz, 2H, CH_2CH), 3.86 (s, 3H, OCH_3), 3.92 (s, 1H, NCH_2C), 4.42 (s, 1H, NCH_2C), 6.76 (d, J = 8.4, 1H, Ar*H*), 6.88 (s, 1H, Ar*H*), 6.91 (d, J = 8.3, 1H, Ar*H*), 7.03 (d, J = 7.4, 2H, Ar*H*), 7.13 (m, 2H, Ar*H*), 7.17 (m, 2H, Ar*H*), 7.39 (m, 1H, Ar*H*), 7.55 (m, 2H, Ar*H*), 7.73 (br s, 1H, N*H*): ES-MS: *m*/*z* 460.2609, calcd for $[C_{28}H_{33}N_3O_3 + H]^+$ 460.2600.

4′-{[Acetyl-(2-amino-ethyl)-amino]-methyl}-biphenyl-4-carboxylic Acid Isobutyl-amide 21{*1,1,3,4,2*}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.90 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 1.85 (m, 1H, $(CH_3)_2CH$), 2.08 (s, 3H, $COCH_3$), 2.94 (m, 2H, CH_2NH_2), 3.10 (t, J = 6.6 Hz, 2H, $CH_2CH_2NH_2$), 3.43 (m, 2H, NCH_2CH), 4.63 (s, 2H, CCH_2), 7.35 (d, J = 8.8 Hz, 2H, Ar*H*), 7.75 (m, 5H, NH_2 + Ar*H*), 7.93 (t, J = 7.7 Hz, 2H, Ar*H*), 7.85 (d, J = 8.8 Hz, 1H, Ar*H*), 8.17 (t, J = 5.5 Hz, 1H, CON*H*): ES-MS: *m*/*z* 368.2330, calcd for $[C_{22}H_{29}N_3O_2 + H]^+$ 368.2338.

4′-(1-Isobutyl-3-phenyl-thioureidomethyl)-biphenyl-2-carboxylic Acid Isobutyl-amide 21{*3,1,2,2,2*}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 6H, $CH(CH_3)_2$), 2.05 (m, 1H, $CH(CH_3)_2$), 2.82 (s, 3H, NCH_3), 3.20 (br m, 2H, piperazine), 3.27 (d, J = 7.5 Hz, 2H, $CH_2CH(CH_3)_2$), 3.90 (br m, 6H, piperazine), 4.33 (s, 1H, $ArCH_2$), 5.60 (s, 1H, $ArCH_2$), 7.32 (m, 4H, Ar*H*), 7.41 (m, 2H, Ar*H*), 7.55 (m, 5H, Ar*H*), 7.79 (d, J = 8.3 Hz, 1H, Ar*H*), 7.88 (d, J = 8.3 Hz, 1H, Ar*H*), 8.03 (d, J = 8.8 Hz, 2H, Ar*H*). ES-MS: *m*/*z* 474.2584, calcd for $[C_{27}H_{30}N_4O + H]^+$ 474.2579.

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Supporting Information Available. Experimental procedure for the library synthesis of 199 compounds (split and mix method) using the lanterns. This material is available free of charge via the Internet at http://pubs.acs.org.

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