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To be cited as: *ChemMedChem* 10.1002/cmdc.201700082

Link to VoR: http://dx.doi.org/10.1002/cmdc.201700082

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemmedchem.org

Improving non-specific binding and solubility: bicycloalkyls and cubanes as *p*-phenyl bioisosteres

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Abstract: Bicycloalkyl groups have previously been described as phenyl group bioisosteres. This article describes the synthesis of new building blocks allowing their introduction in complex molecules, and explores their use as a means to modify the physicochemical properties of drug candidates and improve the quality of imaging agents. In particular, the replacement of an aromatic ring with a bicyclo[1.1.1]pentane-1,3-diyl group improves solubility by at least 50-fold, and markedly decreases non-specific binding (NSB) as measured using CHI(IAM), the chromatographic hydrophobicity index on immobilized artificial membranes. Structural variations with the bicyclo[2.2.2]octane-1,4-diyl group led to more lipophilic molecules and did not show the same benefits with regard to non-specific binding or solubility, whereas substitutions with cubane-1,4-diyl also showed an improvement in both parameters. These results confirm the potential advantages of both BCP and cubane motifs as bioisosteric replacements for optimizing *para*-phenyl substituted molecules.

Introduction

Non-specific binding (NSB) strongly influences the quality of imaging agents[1, 2], as well as the pharmacological properties of drug candidates[3]. The identification of such molecules often requires extensive optimization efforts. After a medicinal chemistry program has advanced beyond a certain stage, it becomes very challenging to significantly improve the physicochemical properties of advanced candidates without losing desirable pharmacological properties. At this point, the isosteric replacement of detrimental structural elements becomes a valued option, provided such replacements have an advantageous effect on e.g. solubility or non-specific binding without hurting pharmacological properties. We explored the use of the cage-like alkyl motifs bicyclo[1.1.1]pentane-1,3-diyl (BCP), bicyclo[2.2.2]octane-1,4-diyl (BCO) and cubane-1,4-diyl (CUB) as *p*-substituted phenyl bioisosteres (Figure 1), evaluating their effect on physicochemical properties and non-specific binding. Examples of such modifications have been described previously, illustrating the value of replacing a phenyl ring by e.g a BCP group, to balance aqueous solubility, permeability and in vitro metabolic stability.[4]

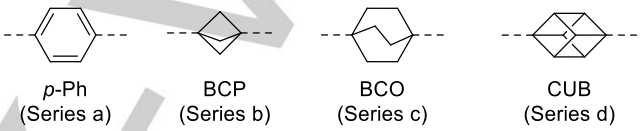


Figure 1. *p*-Ph and bioisosteric series

Despite a number of successful examples, such substitutions are not universally applicable. Their success will strongly depend on the influence of the *p*-substituted arene on the conformation of the molecule, and on its role in the pharmacophore, including possible interactions of the aromatic ring with the target protein (e.g. π-staking). From a geometrical point of view, the distance between connecting atoms in the BCO and CUB groups are very similar to p-Ph, while it is 35% smaller in BCP (Table 1)

Table 1. Distance between bridge heads and percent length compared to a phenyl group.

p-phenyl	BCP	BCO	CUB
2.82Å[4a]	1.85 Å[4a, 5a]	2.60 Å[5b]	2.72 Å[5c]
100%	65%	94%	96%

The experimentally determined chromatographic hydrophobicity index on immobilized artificial membranes, CHI(IAM), is correlated to non-specific binding (NSB).[6] It is a standardized value derived from the retention time in a high-performance liquid chromatography (HPLC) column, and was originally developed to characterize the interactions of drugs with an immobilized artificial membrane.[7] As such, CHI(IAM) can be used to quantify the propensity of a chemical substance for non-specific binding, and allows a direct comparison between pairs of molecules.

Results and Discussion

Chemistry

The synthesis of bicyclopentane and bicyclooctane building blocks has, until recently, been limited to simple manipulations of acid, ester, amine and other functionalities attached to the bridgehead carbons. In order to expand the scope of potential biphenyl bioisosteres, we became interested in the synthesis of arylated BCP, BCO and CUB (Figure 2). These series have very limited precedence in the literature. Ph-BCP's **1b** and **2b** can be prepared by three main methods; (a) by Grignard addition[8] to propellane (tricyclo[1.1.1.0^{1,3}] pentane, **5**);[9] (b) decarboxylation of the BCP-tert-butyl per ester followed by arylation of the bridgehead carbon by heating in benzene [10] and more recently (c) by iron catalysed coupling of redox-active esters with arylzinc reagents.[11] The corresponding Ph-BCO's derivatives **1c** and **2c** can be prepared by two main methods; (a) HgO mediated decarboxylation of the BCO-acid and bromination followed by $AlCl_3$ catalyzed Friedel–Crafts with benzene[12] or (b) Diels alder between 2-oxo-6-phenyl-2H-pyran-3-carboxylates and ethene followed by hydrogenation.[13] To allow for a full comparison of the three *p*-Ph bioisosteres shown in Figure 2, the BCP, BCO and cubane derivatives of their analogues were prepared according to literature procedures, or purchased from commercial sources.

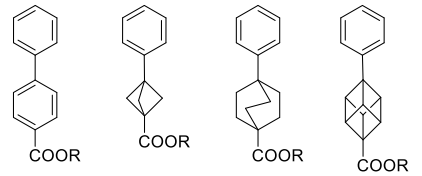
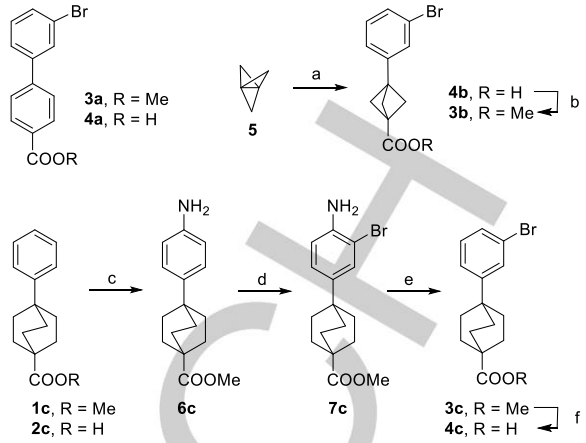


Figure 2. *Arylated BCP, BCO and CUB as p-phenyl bioisosteres*

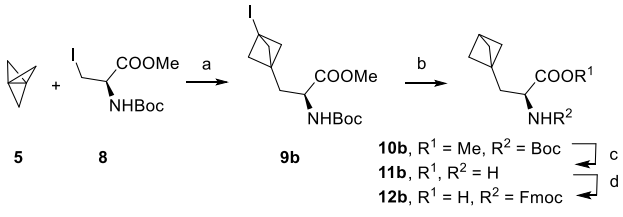
In order to provide a handle for further derivatization, we synthesized the BCP and BCO analogues of methyl 3'-bromo-[1,1'-biphenyl]-4-carboxylate (**3a**) and of its corresponding acid **4a** (Scheme 1). The BCP analogue **4b** was obtained by reacting a solution of **5** with *m*-bromophenyl magnesium bromide and quenching with carbon dioxide. The resulting acid was then esterified with methyl iodide, to yield **3b**. For the BCO analogue, commercially available BCO-ester **1c** was nitrated, and then hydrogenated over palladium to produce aniline **6c**. Reaction with N-bromosuccinimide, and de-amination by heating with *tert*-butyl nitrite yielded **3c**. Hydrolysis with lithium hydroxide produced the corresponding acid **4c**.



Scheme 1. *Reagents and conditions*: a) (i) *m*-bromophenyl magnesium bromide, RT, 6 d, sealed tube, (ii) CO_2 (gas), 0 °C, 20 min, b) MeI, K_2CO_3, DMF, 0 °C to RT, 16 h, 4% (2 steps); c) (i) HNO_3, AcOH, Ac_2O, 5 °C to RT, 2 h, 82% (ii) Pd/C 10%; H_2; EtOH, 1.5 h, RT 96%; d) *N*-bromosuccinimide (NBS), $CHCl_3$, RT 4 h, 73%; e) tBu-nitrite, DMF, 16 h, 65°C, 86% ; f) LiOH·H_2O, THF, H_2O, 16 h, RT, 68%.

BCP analogues of the natural amino acids phenylalanine and tyrosine represent useful building blocks to study conformational and electronic effects in peptides. A related compound, (2*S*)-2-(2'-carboxybicyclo[1.1.1]pentyl)glycine, was synthesized by homologation of a carboxylic acid, followed by a *Strecker* reaction, in 8 steps.[14] Aiming for a short synthesis we envisaged that a desymmetrization reaction of propellane (**5**) would allow the introduction of the stereocenter while installing a handle at the opposite bicyclopentane bridgehead carbon for further derivatization.

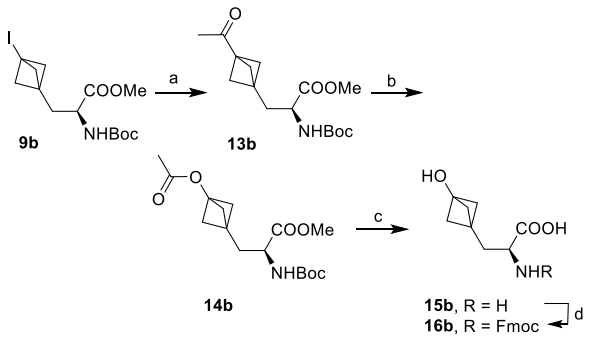
Scheme 2 shows the preparation of **12b**, the BCP analogue of the protected amino acid Fmoc-Phe-OH (**12a**) using photochemistry. Compound **5** was irradiated in the presence of *N*-benzyloxycarbonyl-3-iodo-L-alanine methyl ester **8**, in analogy to a previously described method,[15] yielding the insertion product **9b**. The iodine was removed with tris(trimethylsilyl)silane as reducing agent to yield **10b**,[16] which was hydrolyzed stepwise to **11b**. The amine was finally protected with Fmoc to yield **12b**.



Scheme 2. *Reagents and conditions*: a) 400W Hg medium pressure lamp, pentane, Et_2O, 0°C, 2 mL/min, 69%; b) TTMSS, azobisisobutyronitrile (AIBN), 2-mercaptoethanol, water, 80°C, 3 h, 41%; c) 4N HCl in 1,4-dioxane, RT, 6 h, then 6N aq. HCl, 40°C, 12 h; d) 9-fluorenylmethyl N-succinimidyl carbonate (FmocOSu), aq. $NaHCO_3$, THF, aq. buffer pH 7.0, 22% (2 steps).

Similarly, **16b**, the BCP analogue of the protected amino acid Fmoc-Tyr-OH (**16a**) was prepared from intermediate **9b** (Scheme 3)**.** The introduction of a methyl ketone in place of the

iodine atom by irradiation yielded **13b**,[17] and was followed by Baeyer-Villiger oxidation to give **14b**.[18] One-pot deprotection to the corresponding alcohol **15b** followed by Fmoc protection of the amine yielded **16b**.

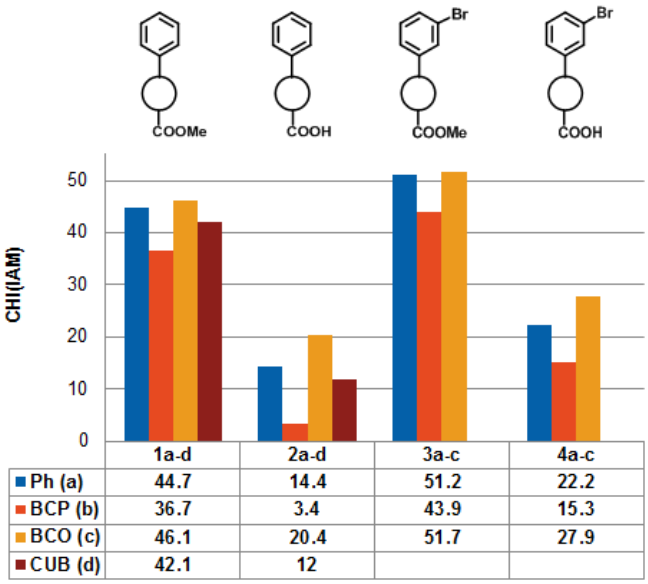


Scheme 3. *Reagents and conditions*: a) biacetyl, tributyltin hydride, MeCN, RT, 400W Hg medium pressure lamp, 68%; b) mCPBA, CH_2Cl_2, RT, 3 d, 67%; c) HCl 4N in 1,4-dioxane, 24 h, RT, then 6N aq. HCl, 24 h, 40°C; d) FmocOSu, aq. $NaHCO_3$, THF/ aq. buffer pH 7.0, 8% (2 steps).

Comparison of *p*-phenyl, BCP, BCO and cubane derivatives

1. Non-specific binding

To get an initial understanding of the effect of replacing *p*-Ph groups by BCP, BCO or CUB, we first compared molecules with simple scaffolds. Our rationale was that the intrinsic effect of the *p*-Ph bioisostere on NSB would have the best chance of being revealed in a molecule with few additional functional groups. Figure 3 reveals systematic changes in CHI(IAM) values across series.



	1a-d	2a-d	3a-c	4a-c
Ph (a)	44.7	14.4	51.2	22.2
BCP (b)	36.7	3.4	43.9	15.3
BCO (c)	46.1	20.4	51.7	27.9
CUB (d)	42.1	12		

Figure 3. CHI(IAM) value of compounds **1a**, **2a**, **3a**, **4a** and their BCP, BCO and CUB analogues

Effect of replacing *p*-phenyl by BCP

The replacement of *p*-Ph by BCP leads to CHI(IAM) values for the four BCP analogues that are decreased by -8.3 units on average. This clearly indicates that the BCP group has a markedly lower propensity for NSB than the *p*-phenyl group. This replacement is therefore of potential interest in the optimization of the physicochemical properties of drugs and imaging tracers.

While this difference appears unambiguous, we wondered whether it would fade when comparing structurally more complex molecules, as this effect might be diluted by additional structural features that offer more potential for interactions with cell membranes. We therefore compared seven pairs of phenyl-containing drug candidates (**A-G,** Table 2) with their BCP bioisosteres, to test whether this principle could be extended to larger, more diverse structures. The molecular weight of the drug candidates in the test set ranged from 337 to 481 (MW= 413 ± 53 g/mol), all chemical scaffolds were different, and their CHI(IAM) values ranged from 22.7 to 48.1 (41.5 ± 8.0).

Table 2. Properties of additional drug candidates tested as pairs (structures not shown). The 13 compounds represent 11 distinct chemotypes.

Compound	MW	clogP	tPSA	HBA	HBD	CHI(IAM) of pair[a]
A	378	3.07	84.6	7	1	43.2, 38.8
B	459	4	84.6	6	1	42.7, 39.5
C	337	4.8	54.2	5	0	47.7, 36.3
D	456	2.13	85.8	7	3	42.5, 35.0
E	481	-0.38	127.6	9	1	22.7, 18.8
F	434	2.14	85	8	1	48.1, 38.0
G	351	5.1	64.6	5	1	43.3, 35.1
H	444	0.62	81.7	7	3	18.8, 22.8
I	430	-0.4	98.7	6	3	29.7, 39.6
J	427	5	40.6	4	0	35.7, 42.8
K	343	1.91	75.6	6	2	35.8, 44.7
L	364	2.84	95.6	7	2	24.3, 15.7
M	358	4.7	75.6	6	0	23.1, 16.4

[a] The first CHI(IAM) value refers to the drug candidate, whereas the second value refers to their BCP. BCO or CUB analogue (details in text).

The characterization of the corresponding BCP analogues systematically indicated a decrease in non-specific binding, with a variation of -7.4 +/- 3.0 CHI(IAM) units. This difference is significant in comparison to a standard deviation of 0.71 units, obtained with a set of 48 independent duplicate measurements. While this effect is in part related to a decrease in lipophilicity (Δ(clogP) = -3.0 +/- 1.8), there was no correlation between changes in CHI(IAM) values and clogP or molecular weight.

Figure 4 illustrates the general lack of correlation between clogP and CHI(IAM) values in a larger set of chemical structures. While lipophilicity influences non-specific binding, it is not the only factor involved and as an experimental measure, CHI(IAM)

provides additional information by measuring the effect of all relevant physicochemical parameters.

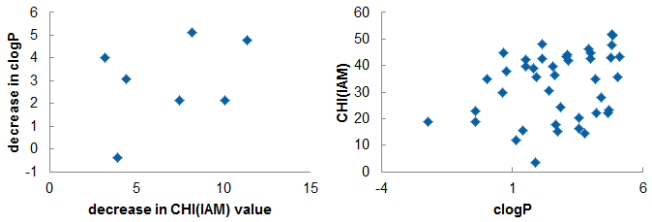


Figure 4. Left panel: graph showing the lack of relationship between the decrease in clogP and decrease in CHI(IAM) values for each pairs based on drug candidates **A**-**G** (R^2 = 0.1442). Right panel: CHI(IAM) and clogP values of all compounds in manuscript, showing the lack of correlation of these parameters (R^2 = 0.0848).

To extend on these observations, we prepared **12b** and **16b**, the BCP analogues of the protected amino acids Fmoc-Phe-OMe (**12a)** and Fmoc-Tyr-OH (**16a**) (Schemes 2 and 3). They were characterized together with additional pairs commercially available from SpiroChem (Figure 5 and 6).

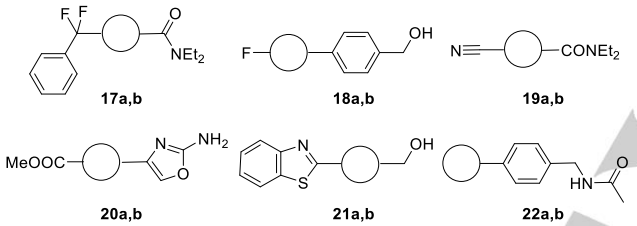
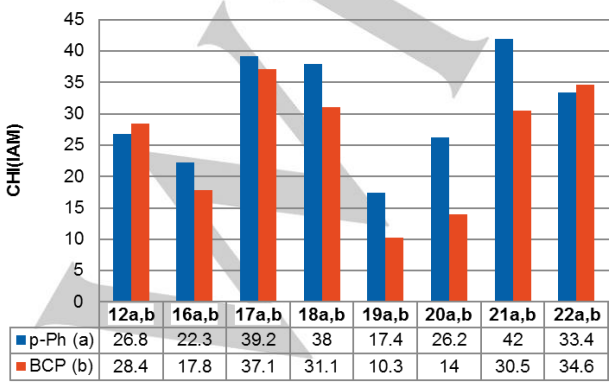


Figure 5. Commercially available pairs included in Figure 6. The circle represents either a *p*-Ph or a BCP group.

Figure 6 confirms previous findings, with most pairs indicating a decrease in CHI(IAM) value upon replacement of the phenyl group. One exception is compound **12b**, where the change in CHI(IAM) value is modestly positive. This is contrary to what is observed with compound **16b** and might have to do with the fact that in **12b**, the BCP group is terminal, exposing additional lipophilic surface compared to a true *p*-Ph analogue. The same observation was made with a second example of a derivative with a terminal BCP, compound **22b**. Across all pairs, the average change for the *p*-Ph to BCP substitution led to a decrease of -7.8 ± 2.8 CHI(IAM) units.



	12a,b	16a,b	17a,b	18a,b	19a,b	20a,b	21a,b	22a,b
p-Ph (a)	26.8	22.3	39.2	38	17.4	26.2	42	33.4
BCP (b)	28.4	17.8	37.1	31.1	10.3	14	30.5	34.6

Figure 6. CHI(IAM) values for eight additional *p*-Ph and BCP pairs.

This supports the conclusion that the replacement of a *p*-Ph group by a BCP decreases non-specific binding in a broad variety of structures, and that this effect, while influenced by a decrease in lipophilicity, is not proportional to it.

Effect of replacing *p*-phenyl by BCO

It has been shown for drug candidates that the replacement of a phenyl group by BCO could maintain pharmacological efficacy, while improving solubility and oral bioavailability.[11] While larger and more lipophilic than BCP, this fragment is potentially of interest as a phenyl bioisostere.

The effect on NSB of replacing *p*-Ph by BCO is also illustrated in Figure 3, indicating CHI(IAM) values for the four BCO analogues that are higher by an average of 3.4 units. In contrast to observations with BCP, replacement of a *p*-substituted phenyl group with BCO increases non-specific binding.

This observation was confirmed in two additional pairs of drug candidates (**H**, **I**, Table 2) where CHI(IAM) values increased by 4 and 9.9 units, respectively.

Effect of replacing *p*-phenyl by cubane

Cubanes are useful structural elements for bioisosteric replacement of aromatic groups. A number of building blocks encompassing a cubane sub-structure have become commercially available,[19a] and some can now be reliably prepared in large scale.[19b] In a number of examples, molecules encompassing a cubane in place of a benzene ring were shown to maintain similar levels of pharmacological efficacy.[20] In these examples a slight increase in lipophilicity was observed, however the most striking difference relates to the increased metabolic stability of the cubane derivatives.

The effect on NSB of replacing *p*-Ph by CUB is illustrated in Figure 3 with two pairs of molecules. Similarly to what was observed with BCP, the CHI(IAM) values of the cubane analogues are lower than for the *p*-Ph derivatives, now by approximately -2.5 units. While the improvement is not as large as with the smaller BCPs, this data confirms that cubanes are attractive bioisosteric alternatives to *para*-substituted phenyl groups. This is nicely recapitulated by an additional series of three compounds (Figure 7), for which the CHI(IAM) values were respectively 42 (**23a**), 30.5 (**23b**) and 37.5 (**23d**).

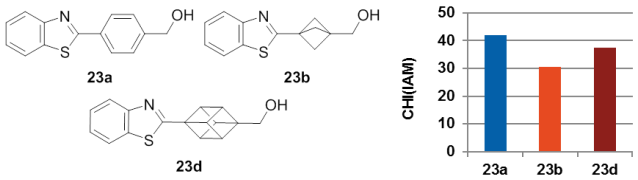


Figure 7. Additional series of *p*-Ph, BCP and CUB analogues.

In analogy to the observation made with terminal BCP derivatives, the replacement of a *p*-Ph with a terminal CUB in a more complex drug candidate (**J**, Table 2), was less favorable and showed an increase of +7.1 CHI(IAM) units. This reinforces the assumption that when a cage-like cycloalkyl group is

terminal, additional lipophilic surface is exposed compared to a true *p*-Ph analogue, allowing further non-specific interactions to take place.

Effect of ionizable groups

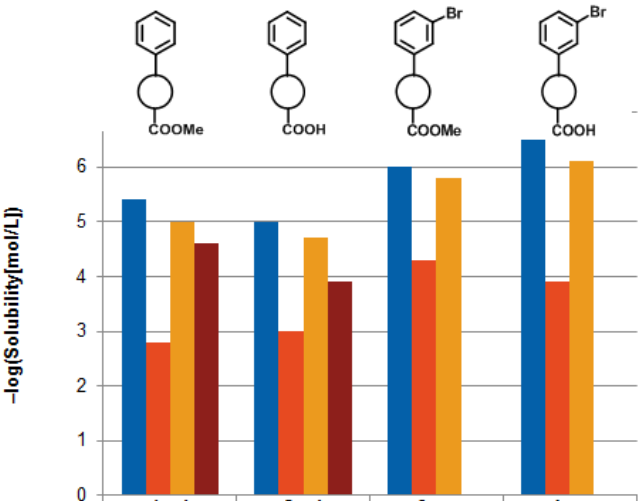
The replacement of an aniline moiety by a bicycloalkylamine strongly influences the basicity of the unsubstituted nitrogen, as expected. The pKa of aniline is 4.6; it increases to 8.6 for BCP-NH_2,[21] and to 10.7 for BCO-NH_2.[22] While pK_a values are not statistically correlated to CHI(IAM), when all else remains equal, basicity influences NSB[7,23] and *p*-substituted anilines are expected to have lower CHI(IAM) values than the corresponding bicycloalkylamines. Accordingly, a drug-like molecule (**K**, Table 2) showed an increase in CHI(IAM) value of +8.9 units upon replacement of the *p*-Ph-NH_2 group by BCP-NH_2.

In contrast to amine derivatives, there was little difference in the acidity of the carboxylic analogues: The pK_a of benzoic acid is 4.2, whereas for BCP-COOH it is 4.1,[21] and 5.1 for BCO-COOH.[24] This does not have a strong influence on CHI(IAM) values and for these compounds, the lipophilicity of the bioisosteric replacement plays a proportionally more important role. Pairs illustrating the *p*-Ph to BCP replacement do not show an effect on NSB directly related to the presence of the carboxylic acid: There was a comparable decrease in CHI(IAM) value for the acid pairs 2a,b/4a,b and for the corresponding esters 1a,b/3a,b. Two additional pairs of drug-like molecules (**L**, **M**, Table 2) led to similar decreases, with differences of -8.6 and -6.7 CHI(IAM) units respectively.

Interestingly, the presence of the carboxylic acid had more effect in the case of the *p*-Ph to BCO substitution. While the ester pairs 1a,c/3a,c only showed differences of +0.5 and +1.4 CHI(IAM) units, the corresponding acid pairs 2a,c/4a,c showed an increase of +6.1 and +6 units. At this point, we do not have an explanation for the difference in behavior between BCP and BCO.

2. Solubility

The change in solubility resulting from the bioisosteric substitutions discussed earlier is illustrated in Figure 8. The crystallinity of all materials was confirmed by polarized light microscopy and DSC, except for compound 3b, which was only available in amorphous form, and for which the solubility value indicated is thus an upper limit. All compounds were tested in aqueous buffer at pH 1 (for acids) or pH 6.8 (for esters), to allow for determination of the intrinsic solubility of the neutral species.



	1a-d	2a-d	3a-c	4a-c
p-Ph (a)	5.4	5	6	6.5
BCP (b)	2.8	3	4.3	3.9
BCO (c)	5	4.7	5.8	6.1
CUB (d)	4.6	3.9		

Figure 8. Shake flask intrinsic solubility values of compounds **1a**, **2a**, **3a**, **4a** and their BCP, BCO and CUB analogues. The solubility is indicated in –log(Solubility[mol/L]) and therefore a lower value indicates a higher solubility.

All replacements of *p*-Ph by BCP led to a large increase in solubility, by a factor of 50 at least. The replacements by BCO only improved solubility by 2 to 3-fold, whereas the two cubane derivatives showed a ten-fold solubility increase. Four additional pairs of *p*-Ph containing drug candidates and their BCP analogues were tested (**A** - **C**, **K**, Table 2). Their solubility ranged from 0.4 μM to 6 mM, or 6.4 to 2.2 in –log(Solubility[mol/L]) units. All BCP analogues showed improved water solubility by factors of 20 to 40 compared to their *p*-Ph analogues, confirming the trend observed with simpler scaffolds.

Conclusions

Recent publications have described a number of cases where BCP, BCO and CUB are valuable bioisosteric replacements for phenyl groups, as well as useful structural elements for increasing the structural diversity of drug candidates. In this report, we have focused on the influence of such isosteric switches on NSB. An increase in this parameter will influence drug pharmacokinetics and distribution, and will occasionally be advantageous in optimizing the drug profile.[25] In the case of positron emission tomography (PET) imaging agents, NSB is always a liability and therefore, any method to decrease NSB during the course of optimization, for instance by using bioisosteric replacements, will facilitate the identification of suitable tracer candidates.

With this work, we show that the replacement of a *p*-Ph group by BCP decreases NSB and markedly increases water solubility. Replacement by BCO has a different effect, slightly increasing NSB, and associated with a much more modest improvement in

solubility. Finally, the replacement of *p*-Ph by CUB has positive effects both on NSB and solubility.

Taking all aspects into account, BCP and CUB thus appear to be *p*-Ph bioisosteres of choice, generally allowing for both an improvement of water solubility and a decrease in NSB. They can be used to modify the physicochemical properties of drug candidates in advanced phases of optimization, as well as to enhance the quality of imaging agents. The examples discussed above provide an encouragement to evaluate BCP and CUB analogues of molecules with *para*-substituted phenyl groups and borderline solubility or binding specificity. They offer an option for improving PET imaging agents that suffer of excessive non-specific binding and do not have the potential to lead to images of sufficient quality.

We therefore believe that these new series of building blocks should be further explored, and become part of the standard toolbox of medicinal chemists in lead optimization programs.

Experimental Section

Chemistry

General methods: All chemicals, reagents and solvents were analytical grade, purchased from commercial sources and used without purification, unless otherwise specified. Compounds **1a** and **2a** were purchased from commercial suppliers; **1b** and **2b** were prepared according to the literature,[10] as well as **1c** and **2c**.[12] **1d** and **2d** were supplied by Spirochem. Propellane solutions were prepared according to literature.[13c]

^{1}H NMR spectra were acquired on a Bruker (400 MHz) or Bruker Advance (600 MHz). δ values are given in parts per million (ppm) relative to the residual solvent peak. Reverse phase Prep HPLC conditions: Column Sunfire C18 (30x250 mm, 5 μM ID); mobile phase: 0.1% aq. formic acid (A) / CH_3CN (B); 60% B for 3 min, then up to 80% B in 5 min + 20 min isocratic; flow rate 30 mL/min. HPLC method for *ee* determination: CHIRALCEL OJ-H column (250 × 4.6 mm, 5 μm). Mobile phase: heptane/EtOH 70:30 + 0.1% TFA, RT, flow rate = 1 mL/min, detection at 210 nm, run time 14 min. LC-HRMS: the analyses were performed by using electrospray ionization in positive ion mode after separation by liquid chromatography (Nexera, Shimadzu). The elemental composition was derived from the mass spectra acquired at the high resolution of about 30'000 on an LTQ Orbitrap XL mass spectrometer (Thermo Scientific). The high mass accuracy below 1 ppm was obtained by using a lock mass.

A modification[6] of the method originally described by Valko et al.[7] was used to measure the CHI(IAM) values of all test compounds on a Regis IAM PC DD2 column (10 cm x 4.6 mm, 10 μm) with immobilized phosphatidylcholine as stationary phase. Mobile phase: MeCN (A) / 50 mM aq. ammonium acetate adjusted at pH=7.4 with 1M aq. NaOH (B); gradient: increase from 0 to 100% B within 6 min, 100% B for 0.5 min, decrease to 0% B over 1 min, 0% B for 2 min; flow rate = 1.0 $mLmin^{-1}$; oven temperature: 40°C. A set of alkylphenone standards (acetophenone, propiophenone, valerophenone and octanophenone) was used to convert the retention time to CHI(IAM) values.

Intrinsic equilibrium solubilities (i.e. the solubilities of the neutral compounds at thermodynamic equilibrium) were determined by a shake flask method, for the acids in aqueous buffer at pH 1, for the esters in aqueous buffer at pH 6.8. Solid material was suspended in the relevant medium with an initial concentration of 2 mg/mL. The samples were equilibrated by shaking at r.t. overnight, then centrifuged twice to obtain particle-free supernatant. The concentrations of the supernatants were quantified by LC-UV (for esters) and LC-HRMS (for acids) using an external calibration curve.

3-(3-Bromophenyl)bicyclo[1.1.1]pentane-1-carboxylic acid (4b).

Freshly prepared 3-bromo-phenylmagnesium bromide (75.6 mmol) in THF (151 mL), was added dropwise at 0 °C to a stirred solution of distilled **5** (75.6 mmol) in ether and pentane (149 mL). The reaction mixture was sealed and stirred at RT for 6 d, after which it was cooled to 0 °C, and CO_2 gas bubbled through for 20 min before acidification with 1N aq. HCl, dilution with water (500 mL) and extraction with EtOAc (500 mL). The organic extracts were combined, concentrated and re-partitioned between saturated $NaHCO_3$ solution (500 mL) and EtOAc (500 mL). The organic layer was separated and the aqueous phase acidified with 1N aq. HCl and extracted with EtOAc (500 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated to give a pale yellow solid. The crude product, approx. 30% pure by HPLC (210 nm), was used in the next step without further purification. A small portion of the crude product was purified by reverse phase prep HPLC to yield the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.5 (s, 1H), 7.47-7.43 (m, 2 H), 7.30 (m, 1 H), 7.25 (m, 1 H), 2.24 (s, 6 H); ^{13}C NMR (151 MHz, DMSO): δ = 171.0, 142.4, 130.5, 129.7, 128.9, 125.2, 121.7, 52.6, 40.4, 36.7; MS: *m/z* = 264.8 $[M-H]^+$.

Methyl 3-(3-bromophenyl)bicyclo[1.1.1]pentane-1-carboxylate (3b).

Methyl iodide (4.19 mL, 67.4 mmol) and potassium carbonate (9.31 g, 67.4 mmol) were added to a stirred solution of crude compound **4b** (6 g) in dimethylformamide (150 mL) at 0 °C, allowed to reach RT and stirred another 16 h. The reaction mixture was diluted with ice cold water and extracted with EtOAc (500 mL). The organic layers were combined, washed with water (250 mL) and brine (250 mL), dried over anhyd Na_2SO_4, concentrated and purified by flash chromatography on silica gel (2-5% EtOAc in petroleum ether) and then by reverse phase prep HPLC to give the title compound as colourless liquid (0.9 g, 4%, 2 steps) in >99% purity (HPLC, 210 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.5 (s, 1H), 7.48-7.45 (m, 2 H), 7.25 (m, 1 H), 7.25 (m, 1 H), 3.65 (s, 3H), 2.29 (s, 12 H); ^{13}C NMR (151 MHz, DMSO): δ = 169.6, 142.1, 130.5, 129.8, 128.9, 125.2, 121.7, 52.8, 51.5, 40.7, 36.4; MS: *m/z* = 281.0 $[M+H]^+$.

Methyl 4-(4-nitrophenyl)bicyclo[2.2.2]octane-1-carboxylate.

Methyl 4-phenylbicyclo[2.2.2]octane-1-carboxylate **1c** (3.4 g, 13.9 mmol) was dissolved in AcOH (68 mL) and acetic anhydride (34 mL). The resulting yellow solution was cooled to 5 °C. A mixture of nitric acid 65% (1.8 mL, 41.1 mmol) in sulfuric acid (16.3 mL, 306 mmol) was added slowly to the reaction mixture and stirred for 45 min at 5 °C, and 2 h at RT before being poured into ice. A yellow solid precipitated. The aqueous mixture was extracted twice with *t*-butylmethylether (TBME, 2 × 200 mL), and the organic layers were combined, washed with brine (200 mL), dried with anhyd Na_2SO_4 and evaporated to give a brown solid, which was purified by flash chromatography on silica gel (2-16% EtOAc in cyclohexane), yielding the title compound as a white solid (3.46 g, 82%) in 95% purity (UPLC, 210-450 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.13 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 3.58 (s, 3H), 1.83 (s, 6 H); MS: *m/z* = 307.3 $[M+NH_4]^+$.

Methyl 4-(4-aminophenyl)bicyclo[2.2.2]octane-1-carboxylate (6c).

Methyl 4-(4-nitrophenyl)bicyclo[2.2.2]octane-1-carboxylate (3.39 g, 11.7 mmol) was hydrogenated at RT with 10% Pd/C (1.2 g) in THF/EtOH (1:1,

70 mL) under 0.5 bar H_2 for 1.5 h until >95% hydrogen uptake. The catalyst was removed by filtration through Hyflo and the filtrate concentrated to give the title compound as a white solid (3.07 g, 96%) in 79% purity (UPLC, 210-450 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.93 (d, *J* = 7.3 Hz, 2H), 6.45 (d, *J* = 7.3 Hz, 2H), 4.79 (s, 2H), 3.57 (s, 3H), 1.79-1.75 (m, 6 H), 1.70-1.66 (m, 6 H); MS: *m/z* = 260.3 $[M+H]^+$.

Methyl 4-(4-amino-3-bromophenyl)bicyclo[2.2.2]octane-1-carboxylate (7c).

Compound **6c** (3.0 g, 11.0 mmol) was dissolved in chloroform (80 mL) under N_2, then NBS (2.0 g, 11.0 mmol) was added and stirred at RT for 4 h. The orange reaction mixture was diluted with brine (200 mL), and the organic layer was separated and dried with anhyd Na_2SO_4, filtered and concentrated to give a red oil, which was purified by flash chromatography on silica gel (4-32% EtOAc in cyclohexane), yielding the title compound as a white solid (3.01 g, 73%) in 90% purity (UPLC, 210-450 nm). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.21 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.10 (d, 2H), 3.59 (s, 3H), 1.82 - 1.73 (m, 6H), 1.74 - 1.68 (m, 6H); MS: *m/z* = 338.1/340.2 $[M+H]^+$.

Methyl 4-(3-bromophenyl)bicyclo[2.2.2]octane-1-carboxylate (3c).

Compound **7c** (3.0 g, 7.98 mmol) was dissolved in DMF (50 mL) under N_2. To the resulting colorless solution was added tert-butyl nitrite (1.58 mL, 12.0 mmol) and the reaction mixture was heated to 65 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and brine (200 mL) and the layers were separated. The organic layer was concentrated and the liquid residue was re-dissolved in EtOAc (200 mL) and washed four times with brine (4 × 100 mL). The organic layer was dried with anhyd Na_2SO_4 before being concentrated to give crude product as an orange solid, which was purified by flash chromatography on silica gel (1-12% EtOAc in cyclohexane) to give the title compound as a white solid (2.21 g, 86%) in >99% purity (UPLC, 210-450 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47 (m, 1H), 7.38-7.34 (m, 2H), 7.27 (m, 1H), 3.60 (s, 3H), 1.81 (d, *J* = 8.0 Hz, 12H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 177.2, 152.0, 130.3, 128.6, 128.4, 124.6, 121.8, 51.5, 38.4, 34.5, 30.9, 28.2.

4-(3-bromophenyl)bicyclo[2.2.2]octane-1-carboxylic acid (4c):

LiOH monohydrate (5.19 mg, 0.12 mmol) was dissolved in water (516 µl) and added dropwise to a solution of **3c** (20 mg, 0.062 mmol) in THF (516 µl) to give a cloudy emulsion which was stirred at room temperature overnight. The yellow solution was diluted with 1N aq. HCl (10 mL) and CH_2Cl_2 (10 ml), the organic layer separated and the aqueous phase washed once more with CH_2Cl_2 (5 mL). The combined organic layers were concentrated under a stream of nitrogen to give the title compound as a white crystalline solid (14.5 mg, 68%) in >99% purity (UPLC, 210-450 nm). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.48 (m, 1H), 7.38-7.35 (m, 2H), 7.26 (m, 1H), 1.79 (s, 12H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 178.7, 152.2, 130.3, 128.5, 128.4, 124.6, 121.7, 37.9, 34.6, 31.1, 28.3.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodobicyclo[1.1.1]-pentan-1-yl)propanoate (9b):

Compound **8** (6 g, 18.23 mmol) was dissolved in a freshly prepared solution of propellane (**5**) in pentane/diethylether (73.5 g, 27.3 mmol) in a 250 mL plastic-coated glass flask, and diluted with pentane/Et_2O 1:1 to a total volume of 150 mL. The solution was kept in an ice bath for 5 minutes while argon was bubbled through it. The flask was closed with a rubber septum through which an overpressure of ca 300 mbar nitrogen was applied, to avoid bubble formation in the pump and an innacurate flow rate. This solution was pumped (Vapourtec R series) at ca 1 mL/min through 7 m of fluorinated ethylene propylene (FEP) tubing (3.1 mm OD, 2.7 mm ID, volume 40 mL) that was wrapped in a single layer around a large quartz immersion well (*Photochemical Reactors Ltd*., article number 3230) equipped with a 400 W medium pressure mercury lamp and a borosilicate filter, followed by 80 mL acetonitrile. The solution left the photo reactor through a back pressure regulator (8 bar) in order to reduce bubble formation. The crude product solution was treated with aq. $NaHSO_3$ (50 mL) and checked for peroxides with test strips (Mquant™ peroxide test from Merck Millipore, product No 1.10011.0001). As soon as this test was negative, the organic phase was dried over sodium sulfate, filtered and concentrated in vacuo at 30°C. The crude material was purified by flash chromatography on 120 g silica gel (EtOAc/heptane 6:94 to 50:50) to give the title compound (6.3 g, 69%) with a purity of ca 80% based on NMR. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.29 (d, *J* = 8.3 Hz, 1H), 5.03 – 4.87 (m, 1H), 3.61 (s, 3H), 2.26 – 2.13 (m, 6H), 1.98 – 1.80 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 172.39, 155.20, 78.37, 60.44, 51.96, 51.70, 32.64, 31.00, 28.22, 7.88 (smaller signals not reported); HRMS (ESI) calcd for $C_{14}H_{23}INO_4$ $[M+H]^+$: *m/z* = 396.06718, found: *m/z* = 396.06705.

Methyl (*S*)-3-(bicyclo[1.1.1]pentan-1-yl)-2-((tert-butoxycarbonyl)-amino)propanoate (10b):

Compound **9b** (3 g, 7.59 mmol) was suspended in 19 mL water in a 50 mL round bottom flask, then treated with tris(trimethylsilyl)silane (5.15 mL, 16.70 mmol). The heterogeneous mixture was stirred for 10 min at RT, then 2-mercaptoethanol (0.053 mL, 0.759 mmol) followed by AIBN (0.031 g, 0.190 mmol) were added. The mixture was stirred for 10 min at RT then heated to 80°C, when a rather exothermic reaction occurred. Care would have to be taken if scaling up. The reaction mixture became clear and colourless, and a LC/MS analysis indicated full conversion. The reaction mixure was diluted with EtOAc (50 mL) and the phases were separated. The aq. phase was extracted one more time with EtOAc (50 mL), the combined organic phases were washed with water (40 mL) and brine (40 mL), dried over anhyd Na_2SO_4, then filtered and concentrated in vacuo to give a clear colourless liquid that was purified by flash chromatography on 120 g silica gel (MeOH/CH_2Cl_2 5:95 to 20:80). The product containing fractions were concentrated and triturated with hexane, filtered and dried to give the title product as a colorless solid (814 mg, 39%) with a purity of >90% (^{1}H NMR). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.20 (d, *J* = 8.2 Hz, 1H), 3.98 (td, *J* = 9.2, 4.2 Hz, 1H), 3.61 (s, 3H), 2.42 (s, 1H), 1.82 – 1.70 (m, 2H), 1.69 – 1.61 (m, 6H), 1.39 (s, 9H). The spectrum shows 10% of a rotamer. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 172.94, 155.15, 78.12, 51.81, 51.76, 50.28, 43.00, 33.24, 28.18, 27.06; HRMS (ESI) calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$: *m/z* =270.16999, found: *m/z* = 270.16998.

(S)-2-amino-3-(bicyclo[1.1.1]pentan-1-yl)propanoic acid (11b):

Compound **10b** (100 mg,0.37 mmol) was placed in a 20 mL round bottom flask and treated with 4N aq. HCl in 1,4-dioxane (8 mL) at RT for 6 h, then 6N aq. HCl (10 mL) was added and the reaction mixture stirred at RT for another 18 h, followed by 19 h at 40°C, by which time LC/MS indicated full deprotection. The crude reaction mixture was concentrated at 40°C in vacuo to give the crude title compound (31 mg) as light orange, oily crystals that were further used without purification.

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(bicyclo[1.1.1]-pentan-1-yl)propanoic acid (12b):

Compound **11b** (31 mg) was mixed in a 50 mL round bottom flask with pH 7.0 phosphate buffer (5 mL), $NaHCO_3$ (17 mg, 0.2 mmol), THF (5 mL) and FmocOSu (67 mg, 0.2 mmol), and stirred at RT for 49 h, concentrated and the residue stirred with 1N aq. HCl (1mL) for 30 min, then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered and concentrated at 30°C to yield 100 mg oily crystals. Purification by flash chromatography on 4 g silica gel (MeOH/EtOAc 1:9 to 3:7) yielded 53 mg colorless solid that was further purified by SFC. The title compound was obtained as a colorless foam (31 mg, 22%) with a purity of >99% (UPLC, 210-450 nm) and enantiopurity >99% *ee* (t_R = 4.33 min (*S*) and 6.53 min (*R*)). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 8.5 Hz, 2H),

7.57 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 4.40 – 4.24 (m, 2H), 4.24 – 4.18 (m, 1H), 3.96 – 3.89 (m, 1H), 2.43 – 2.38 (m, 1H), 1.88 – 1.71 (m, 2H), 1.69 – 1.57 (m, 6H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 173.80, 155.76, 143.85, 143.67, 140.68, 127.56, 126.98, 125.18, 120.05, 65.34, 52.35, 50.33, 46.69, 43.22, 33.09, 27.06; HRMS (ESI) calcd for $C_{23}H_{22}NO_4$ $[M-H]^-$: *m/z* = 376.15543, found: *m/z* = 376.15585.

Methyl (*S*)-3-(3-acetylbicyclo[1.1.1]pentan-1-yl)-2-((tert-butoxycarbonyl)amino)propanoate (13b):

Compound **9b** (2.18 g, 5.52 mmol), biacetyl (1.52 g, 17.6 mmol) and tributyltin hydride (5.24 g,17.6 mmol) were dissolved in acetonitrile (370 mL). The resulting, slightly heterogenous solution was filtered and purged with argon for 5 minutes. This solution was pumped with a Labomatic HD3000 at 100 mL/min through 7 m of FEP tubing (3.1 mm OD, 2.7 mm ID, volume 40 mL) that was wrapped in a single layer around a large quartz immersion well (*Photochemical Reactors Ltd.*, article number 3230) equipped with a 400 W medium pressure mercury lamp in a borosilicate filter. The reaction solution leaving the photoreactor was re-circulated for 2 h until LC/MS indicated full conversion. The reaction mixture was extracted with heptane (3 x 150 mL) and the acetonitrile phase concentrated under vacuo to yield 3.15 g of a yellow oil, which was purified by chromatography on 340 g silica gel (EtOAc/heptane 9:93 to 40:60), to give the title compound (1.16 g, 68%) as a yellow oil with a purity of ca 70% by ^{1}H-NMR, and which was used without further purification. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.26 (d, *J* = 8.2 Hz, 1H), 4.04 – 3.93 (m, 1H), 3.62 (s, 3H), 2.26 (s, 1H), 2.05 (s, 4H), 1.89 – 1.77 (m, 9H), 1.39 (s, 9H), 1.38 – 1.19 (m, 7H); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 210.42, 208.98, 205.43, 172.74, 155.17, 98.07, 82.93, 78.22, 51.83, 51.66, 51.05, 44.07, 36.96, 32.19, 28.17, 26.04, 24.05, 23.86 (major impurities included in spectra); HRMS (ESI) calcd for $C_{16}H_{26}NO_5$ $[M+H]^+$: *m/z* = 312.18055, found: *m/z* = 312.18051.

Methyl (*S*)-3-(3-acetoxybicyclo[1.1.1]pentan-1-yl)-2-((tert-butoxycarbonyl)amino)propanoate (14b):

To a solution of **13b** (640 mg, 2.1 mmol) in CH_2Cl_2 (60 mL) was added mCPBA (816 mg, 4.7 mmol, 2.3 equiv.). The resulting clear, pink solution was stirred at RT for 3 d (the pink color disappeared after 3 h). The light yellow, clear solution was washed with 10% aq. Na_2SO_3 (100 mL) followed by sat. aq. $NaHCO_3$ (100 mL). The organic phase was dried over anhyd Na_2SO_4, filtered and concentrated at 40°C to yield 0.5 g yellow oil that was purified by flash chromatography on 12 g silica gel (EtOAc/heptane 1:9 to 6:4) to give the title compound as a colorless oil (450 mg, 67%) with a purity of >90% (^{1}H NMR). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.26 (d, *J* = 8.4 Hz, 1H), 3.98 (td, *J* = 9.7, 9.2, 4.1 Hz, 1H), 3.62 (s, 3H), 2.04 – 1.85 (m, 11H), 1.39 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.58, 169.70, 155.16, 78.24, 62.34, 53.29, 52.16, 51.85, 31.93, 29.86, 28.16, 20.97; HRMS (ESI) calcd for $C_{16}H_{26}NO_6$ $[M+H]^+$: *m/z* = 328.17547, found: *m/z* = 328.17545.

(S)-2-amino-3-(3-hydroxybicyclo[1.1.1]pentan-1-yl)propanoic acid (15b):

Compound **14b** (400 mg, 1.2 mmol) was dissolved in 4N HCl in 1,4-dioxane (32 mL) and stirred at RT for 24 h in a 50 mL round bottom flask. The reaction mixture was concentrated at 30°C, dissolved in 6N aq. HCl (50 mL) and stirred at RT for 24 h and then at 40°C for 36 h. Concentration of the reaction mixture in vacuo at 40°C resulted in crude title compound as a dark red oil (300 mg), which was used without further purification.

(*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-hydroxybicyclo[1.1.1]pentan-1-yl)propanoic acid (16b):

Crude **15b** (20 mg, 0.12 mmol) was mixed with pH 7.0 phosphate buffer (2 mL), $NaHCO_3$ (16 mg, 0.19 mmol), THF (2 mL) and FmocOSu (39 mg, 0.12 mmol). The reaction mixture was stirred at RT for 20 h, then concentrated under vacuum. The residue was stirred with 1N aq. HCl (1mL) for 30 min at RT, then extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered and concentrated at 30°C to yield 20 mg of turbid oil. Purification by flash chromatography on 4 g silica gel (MeOH/EtOAc 1:9 to 3:7) gave the title compound as colorless crystals (12 mg, 27%) with a purity of >90% (^{1}H-NMR) and enantiopurity >99% *ee* (t_R = 4.86 min (*S*) and 11.37min (*R*)). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.67 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.73 (dd, *J* = 7.4, 4.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (tt, *J* = 7.5, 1.4 Hz, 2H), 6.01 (s, 1H), 4.32 (dd, *J* = 9.6, 6.6 Hz, 1H), 4.28-4.18 (m, 2H), 3.91 (ddd, *J* = 10.3, 8.5, 3.7 Hz, 1H), 2.02 – 1.82 (m, 2H), 1.72-1.58 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.23, 156.30, 144.32, 141.19, 128.14, 127.54, 125.76, 120.60, 66.06, 62.24, 54.48, 53.53, 47.16, 31.02, 30.07; HRMS (ESI) calcd for $C_{23}H_{24}NO_5$ $[M+H]^+$: *m/z* = 394.16490, found: *m/z* = 394.16486.

Acknowledgements

The authors would like to acknowledge the skilled support of Dr. Peter Ertl for his help in identifying pairs in our chemical collection, Caroline Radoch for the CHI(IAM) assay, Daniel Gosling for the solubility measurements, as well as Dominik Wiss, Evelyn Schueller, Thomas Ruppen, Heiner Schuetz and Stephanie Rothe-Poellet for synthetic work.

Keywords: non-specific binding • bicycloalkyl • bioisostere • imaging agent • liquid chromatography

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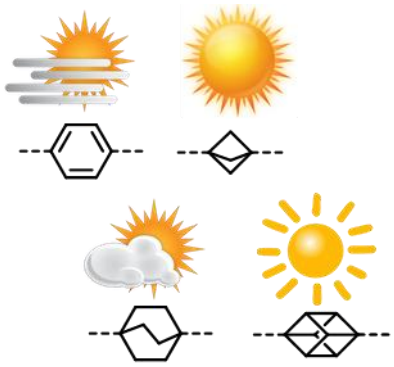
Entry for the Table of Contents



Lifting the fog. Many drug and tracer candidates contain para-substituted phenyl groups, and we show that their physicochemical properties can be improved by bioisosteric substitutions. While bicyclo[2.2.2]octyl has similar properties to p-Ph, the use of bicyclo[1.1.1.]pentyl and cubane-1,4-diyl leads to strongly increased water solubility, and to a marked decrease in non-specific binding (NSB). This is particularly important for PET imaging tracers as the lower the NSB signal, the less “foggy” images will be.