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Medicinal Chemistry Profiling of Monocyclic 1,2-Azaborines

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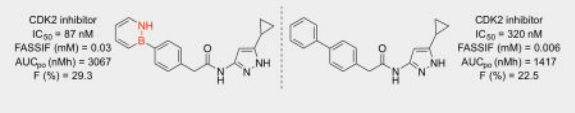
Abstract

The first examples of biologically active monocyclic 1,2-azaborines have been synthesized and demonstrated to exhibit not only improved *in vitro* aqueous solubility in comparison to the corresponding carbonaceous analogues, but in the context of a CDK2 inhibitor, also improved biological activity and better *in vivo* oral bioavailability. This proof-of-concept study establishes the viability of monocyclic 1,2-azaborines as a novel pharmacophore with distinct pharmacological profiles that can help address challenges associated with solubility in drug development research.

COMMUNICATION



BOR-ing? NO!!! Monocyclic 1,2-azaborines can serve as a novel pharmacophore with improved *in vitro* aqueous solubility, improved bioactivity, and better *in vivo* oral availability compared to their carbonaceous analogues.

Keywords

azaborine; BN heterocycle; drug discovery; CDK2 inhibitor; solubility

One of the main goals of synthetic chemistry is to create structural diversity – and as a consequence produce new functions and properties – beyond what Nature can achieve. For instance, a key impetus behind the laboratory syntheses of bioactive natural products is to diversify the original portfolio of structures to systematically investigate structure-function relationships and elucidate mechanism of action.[1] This exploration of new chemical space facilitates the development of reagents that illuminate new biology and the development of therapeutics that can benefit society. BN/CC isosterism[2] (i.e., the replacement of a carbon-carbon unit with a boron-nitrogen (BN) unit) has recently emerged as a strategy to increase

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the chemical space of compounds relevant to biomedical research.[3] When applied to a "privileged" structural motif in medicinal chemistry,[4] this approach can produce a new versatile pharmacophore. Aromatic rings are ubiquitous in medicinal chemistry, and arene-containing compounds prevail among topselling small-molecule drugs.[5] BN/CC isosterism of arenes results in the so-called azaborine heterocycles where specifically 1,2-azaborines are designated as compounds with the boron and nitrogen atoms adjacent to each other (Scheme 1).[6] It has been demonstrated that 1,2-azaborines can bind to aryl recognition pockets[7] in biological targets and engage in hydrogen bonding inside those binding pockets.[8] Furthermore, it has been shown that both the *B*- and *N*-Et BN isosteres of ethylbenzene are inhibitors of ethylbenzene dehydrogenase (EbDH), in contrast to ethylbenzene itself, which is the naturally evolved substrate for the EbDH.[9] Despite the recent advances made in the area of azaborine chemistry,[10] the progress toward evaluating these heterocycles in the context of medicinal chemistry has remained underexplored. BN isosteres of naphthalene have recently been profiled *in vitro* and *in vivo* in terms of biological activity and ADMET (absorption, distribution, metabolism, excretion, toxicity) properties.[11,12] However, to the best of our knowledge, profiling of the arguably more versatile monocyclic 1,2-azaborine motif has not been reported. Thus, essential questions such as stability, biological activity, pharmacological properties of monocyclic 1,2-azaborines have remained unanswered. In our initial exploration in this area, we sought to investigate 1,2-azaborine isosteres of biologically active biphenyl carboxamides, the biphenyl motif being a "privileged" sub-motif of the arene family in drug discovery research.[13,14] In this communication, we establish that 1,2- azaborine-based biphenyl carboxylic acids are compatible with the CDMT/NMM amide coupling conditions, and that the resulting amides 1) are air and water stable, 2) are more soluble in water than their carbonaceous counterparts, 3) exhibit better *in vivo* oral availability, and 4) can exhibit stronger biological activity due to hydrogen bonding.

In 2013, we reported a functional-group tolerant Rh-catalyzed *B*-arylation of *B*-Cl-substituted 1,2-azaborines and as a demonstration synthesized the BN isostere of Felbinac, a nonsteroidal anti-inflammatory drug.[15] Recognizing the versatility of the carboxylic acid functional group present in Felbinac, we sought to develop amide-coupling conditions to access BN isosteres of the ubiquitous biphenyl carboxamide family of biologically active compounds. Gratifyingly, the use of the 2-chloro-4,6-dimethoxy-1,3,5-triazine/N-methylmorpholine (CDMT/NMM) conditions[16] furnished the desired amide coupling products in moderate to good yield (Table 1). We specifically chose three biphenyl carboxamides that inhibit a distinct set of biological targets (dopamine D3 (**BN-1**),[17] PPAR γ and δ (**BN-2**),[18] and CDK2 (**BN-3**)[19] to evaluate the effects of BN/CC isosterism on their pharmacological properties. It is worth noting that the amide coupling can be conducted in air. Furthermore, stability studies reveal no decomposition when **BN-1, BN-2**, and **BN-3** are exposed to air and water at 50 °C for 24 hours, demonstrating the viability of these BN heterocycles in medicinal chemistry applications.[20]

Table 2 shows the ADMET behavior of **BN-1, BN-2**, and **BN-3** in direct comparison to their carbonaceous analogues **CC-1, CC-2**, and **CC-3**.[21] A general trend can be observed in terms of the effect of BN/CC isosterism on aqueous solubility properties: the BN isosteres are

more soluble both under buffered and FASSIF conditions. As a result, they have decreased membrane permeability (more negative PAMPA value) than their carbonaceous analogues. The better aqueous solubility behavior of 1,2-azaborine derivatives is consistent with reported electronic structure analysis that revealed a 2.1 D dipole moment for 1,2-dihydro-1,2-azaborine in contrast to benzene's dipole moment of 0 D.[22] Thus, the incorporation of the 1,2-azaborine motif renders the relatively hydrophobic biphenyl motif more hydrophilic. A majority of currently marketed drugs are poorly soluble.[23] Thus, BN/CC isosterism can potentially be used as a design strategy to produce more soluble active pharmaceutical ingredients. No general trend can be discerned from the RLM Cl, CYP3A4, and hERG data. It appears that functional groups unrelated to BN/CC isosterism may be more responsible for the observed data. Overall, our ADMET data indicate that there is no particular red flag associated with the use of 1,2-azaborines as a pharmacophore in medicinal chemistry.

We then turned our attention to evaluating the biological activity of our BN isosteres in comparison to their all-carbon derivatives. Compound **CC-1** was reported as a selective dopamine D3 antagonist,[17] and in our analysis **CC-1** exhibited an IC_{50} value of 1 nM (Scheme 2). Its BN isostere **BN-1** is also biologically active although the activity is slightly attenuated with an IC_{50} value of 3 nM. **CC-2** has been investigated as antagonists of PPAR γ and δ[18] and in our assay we have determined IC_{50} values of 1 and 2 μM, respectively. Similarly, the corresponding BN isostere **BN-2** also exhibits low micromolar activity against PPAR γ and δ (Scheme 2). Compound **CC-3** was reported as a potent nanomolar antiproliferative agent in a CDK2 kinase assay.[19] In our CDK2 assay **CC-3** showed an IC_{50} of 320 nM. Interestingly, the BN derivative **BN-3** (IC_{50} = 87 nM) showed improved potency than **CC-3**. Compound **BN-3** is selective for CDK2. When tested against a panel of 29 kinases, **BN-3** was found to be a more selective inhbitor of CDK2 than CDK1 (IC_{50} = 460 nM).

The improved biological activity of **BN-3** vs. **CC-3** was intriguing. To understand this improvement in potency, **BN-3** and **CC-3** were analyzed by docking[24,25] in a high resolution crystal structure of CDK2/cyclin A (PDB entry 1VYW).[19] Shown in Figure 1 is one of the three docking poses obtained for **BN-3** in the active site of CDK2. In addition to the hydrogen bonding interaction between the pyrazole amide fragment and hinge residues Leu83, Glu81, an additional hydrogen bonding interaction was observed between the NH of the azaborine and the backbone carbonyl of Ile10. The 3–4 fold improvement in binding of **BN-3** vs. **CC-3** may be attributed to this NH…O=C(amide) hydrogen bonding which we have recently quantified to be ~ 1 kcal/mol in strength (in the context of binding to T4 Lysozymes).[8]

Finally, we asked the question whether the observed improved *in vitro* solubility for **BN-3** vs. **CC-3** would translate into *in vivo* pharmacokinetic behavior. Gratifyingly, we determined that **BN-3** exhibits pharmacokinetic properties that are superior to **CC-3** in male Sprague Dawley Rat models (Table 3). When dosed intravenously, **BN-3** showed lower clearance and a longer terminal half-life ($t_{1/2}$) than **CC-3**. Additionally, **BN-3** gave a two-fold increase in AUC_{po} (area under the curve per oral administration) relative to **CC-3**. This results from a combination of lower clearance and greater bioavailability. The maximum

concentration (C_{max}) of **CC-3**, 692 nM, is observed at 0.5 hour after oral dosing. **BN-3** on the other hand, has maximum concentration of 746 nM at 1.5 hours after dosing, probably due to the increased solubility prolonging the precipitation time and allowing **BN-3** to be absorbed further down the intestine than **CC-3**. Despite the slightly lower permeability of **BN-3** relative to **CC-3** *in vitro*, the improved solubility and lower clearance of **BN-3** *in vivo* enabled an increase in oral exposure for **BN-3** compared to **CC-3**.

In summary, we have synthesized the first examples of biologically active monocyclic 1,2-azaborines and demonstrated that BN/CC isosterism in the context of biphenyl carboxamides leads to improvement *in vitro* aqueous solubility and better *in vivo* oral availability. The BN isosteres of biologically active biphenyl carboxamides are air and moisture stable, and they exhibit biological activity that is comparable to their carbonaceous counterparts. Furthermore, in the context of a CDK2 inhibitor, we have demonstrated that the presence of a 1,2-azaborine motif can lead to improved biological activity likely from an additional hydrogen bonding interaction associated with the NH of the 1,2-azaborine moiety. Overall, we have demonstrated the viability of the monocyclic 1,2-azaborine motif serving as a novel pharmacophore with a distinct pharmacological profile. In view of the solubility challenges associated with many aryl-based drug candidates, BN/CC isosterism may represent a new design principle in medicinal chemistry to address this challenge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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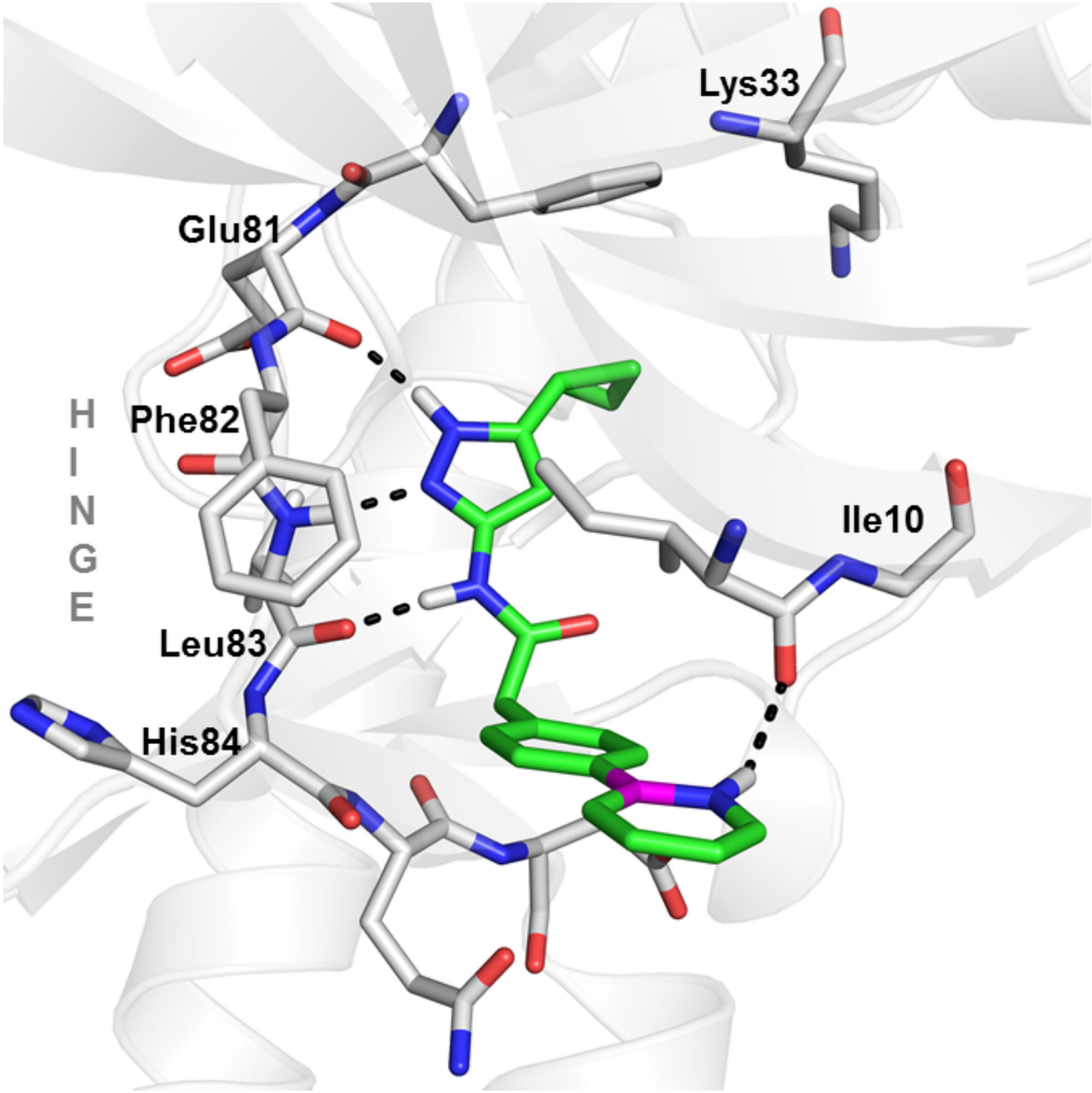
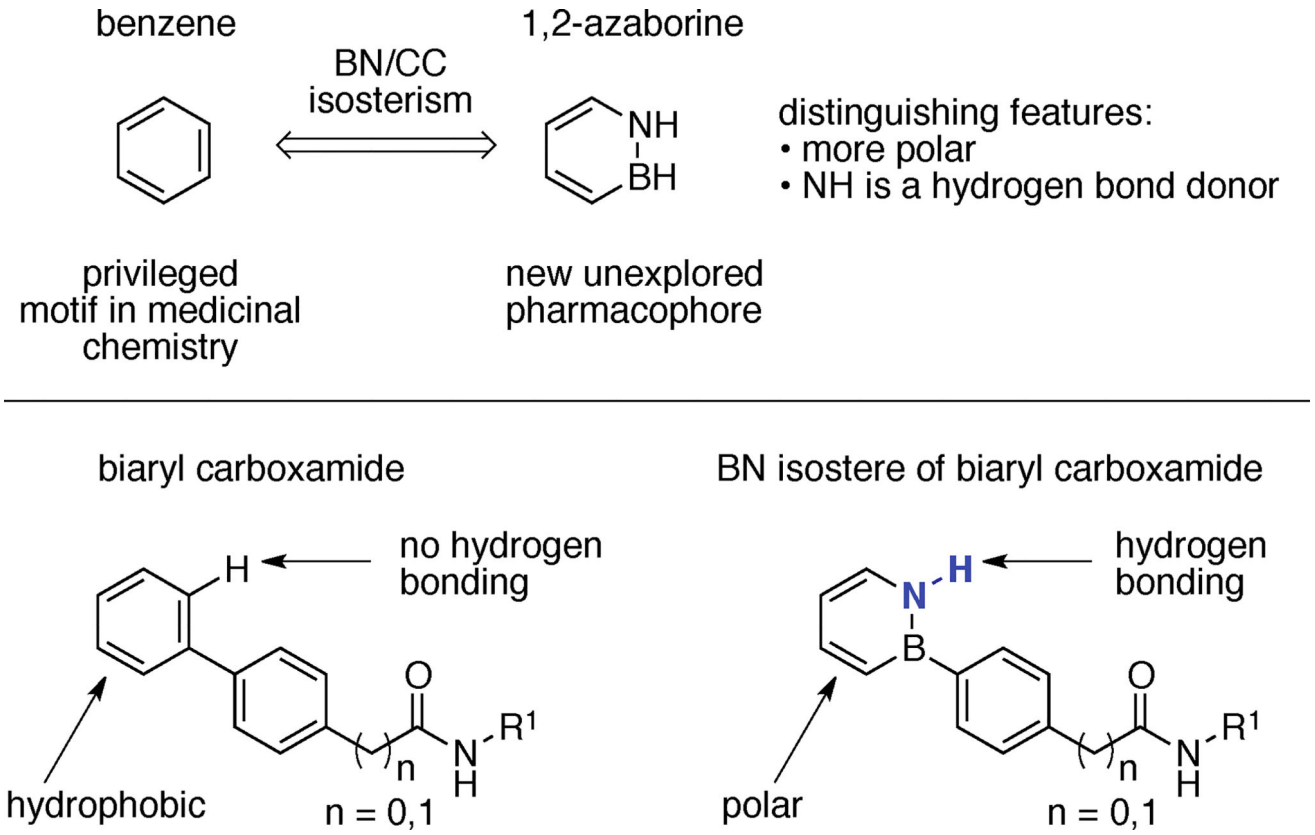
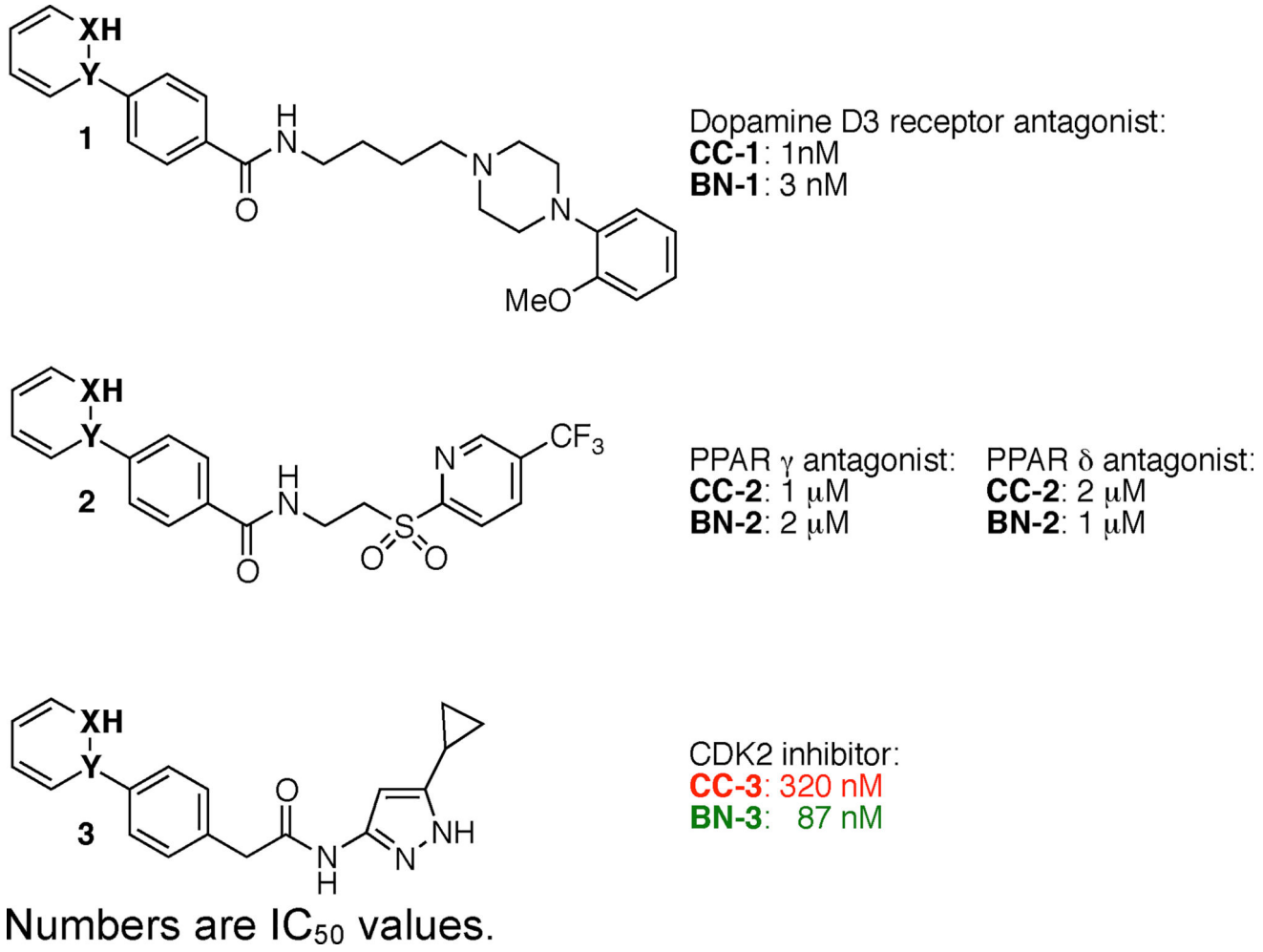


Figure 1.

Modeled binding mode of **BN-3** (green) in the ATP binding site of CDK2 (white). Hydrogen bonding interactions are shown as black dotted lines. Boron in **BN-3** is in magenta color.



Scheme 1.
BN/CC isosterism in the context of biologically active biphenyl carboxamides.

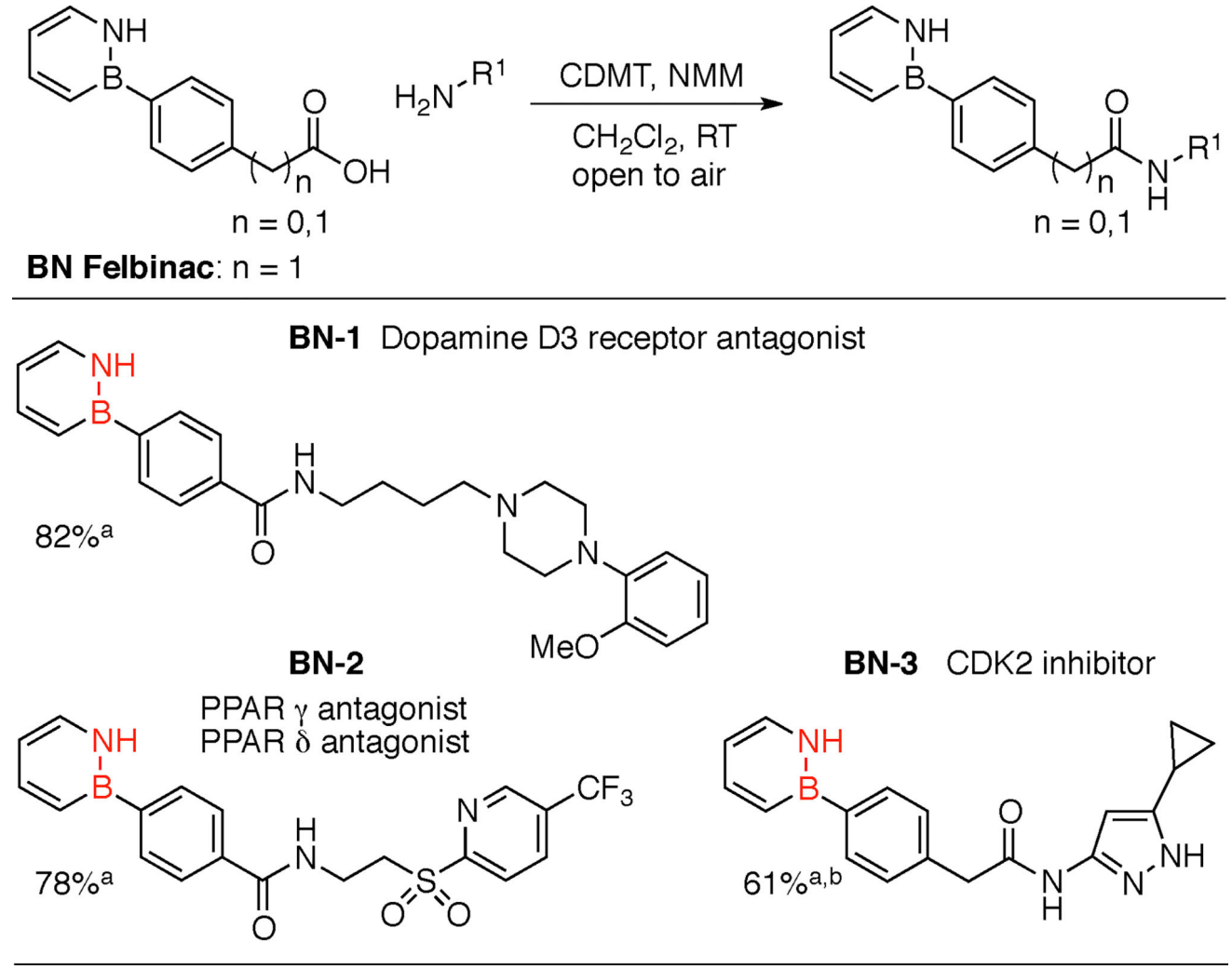


Scheme 2.

Effect of BN/CC isosterism on biological activity. Numbers are IC_{50} values.

Table 1

Synthesis of BN isosteres of biologically active biphenyl carboxamides



[a]Yields are isolated yields.

[b]Yield after amide coupling followed by *N*-BOC removal from the pyrazole group.

Table 2

ADMET study of biphenyl carboxamides and BN-biphenyl carboxamides.

cmpd	solubility pH 6.8 (mM)	FASSIF (mM)	logD	PAMPA	RLM CL (mL min−1 kg−1)	CYP3A4 IC_{50} (mM)	hERG IC_{50} (mM)
CC-1			4.2	−3.9	51	>20	0.042
BN-1			4.1	−4.3	53	11	0.17
CC-2	<0.004		3.5	−4.2	39	>20	>30
BN-2	<0.004		3.5	−4.5	53	>20	>30
CC-3			4.4	−3.9	48	>20	>30
BN-3			3.9	−4.5	48	>20	>30

FASSIF: Fasted and Fed State Simulated Stomach and Intestinal Fluids.
PAMPA: Parallel Artificial Membrane Permeability Assay.
RLM Cl: Rat Liver Microsome Clearance.
CYP3A4: Cytochrome P450 3A4 inhibition.
hERG: Human Ether-a-go-go Related Gene ion channel inhibition.

Table 3

Pharmacokinetic Parameters of **CC-3** and **BN-3** after Intravenous and Oral Administration to Male Sprague Dawley Rats.

cmpd	IV dose (mg/kg)	PO dose (mg/kg)	AUC_{iv} (nMh)	AUC_{po} (nMh)	F (%)	Clearance (mL min^{-1} kg^{-1})	$t_{1/2}$ (h)	t_{max} (h)	MRT (h)	C_{max} (nM)
CC-3	0.5	5.0	1261			39.2	10.5	0.5	0.8	692
BN-3	1.0	5.0	2092			**23.7**	**11.6**	**1.5**	2.7	**746**

PO dose: *per os* dose (oral). F: bioavailability. MRT: mean residence time.

AUC_{iV}: area under the curve (intraveneous) normalized to 1 mg/kg dose.

AUC_{po}: area under the curve (oral) normalized to 1 mg/kg dose.