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2-Aminobenzoxazole ligands of the hepatitis C virus internal ribosome entry site

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ABSTRACT

2-Aminobenzoxazoles have been synthesized as ligands for the hepatitis C virus (HCV) internal ribosome entry site (IRES) RNA. The compounds were designed to explore the less basic benzoxazole system as a replacement for the core scaffold in previously discovered benzimidazole viral translation inhibitors. Structure-activity relationships in the target binding of substituted benzoxazole ligands were investigated.

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The highly conserved internal ribosome entry site (IRES) in the 5' untranslated region of the hepatitis C virus (HCV) RNA genome has previously been exploited as a target for 2-aminobenzimidazole translation inhibitors which selectively suppress the synthesis of viral proteins in infected human host cells (Figure 1).[1] These compounds bind to an internal loop in the IRES subdomain IIa to capture an extended conformation of the RNA and prevent viral translation initiation.[2] Conformational capture of the IIa target had been investigated by a FRET-based assay which also served as a tool for measuring ligand affinity.[3] From crystal structure determination of the RNA target in complex with benzimidazole **1** a detailed picture emerged of the interactions involved in ligand binding (Figure 1C).[4] The 2-aminobenzimidazole scaffold plays a key role in target recognition, by engaging in base stacking interactions with the benzene ring and providing two hydrogen bonds to the Hoogsteen edge of a guanosine residue (G110). While beneficial for RNA target binding, the 2-amino-imidazole system, whose electronic structure resembles guanidine, confers high basicity to the benzimidazole translation inhibitors. The basic pK_a value of 2-aminobenzimidazole is around 7.5.[5] Therefore, compounds such as **1** carry three positive charges under physiological conditions.

Here, we have explored replacement of the benzimidazole system in IIa RNA-targeted ligands by the less basic benzoxazole whose pK_a value is around 4.5 (Figure 1B).[5] Since the significant reduction in basicity of the core scaffold would affect the ability of benzoxazole ligands to engage in a key hydrogen bond involving the protonated N3 position (Figure 1C), we synthesized and evaluated substituted benzoxazole derivatives for IIa RNA target binding. Introduction of the oxazole ring necessitated relocation of the N1-linked polar side chain, which engages in hydrogen bonding with the RNA backbone in the compound **1** complex (Figure 1C).

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Corresponding substituents were moved to the exocyclic 2-amino group of the benzoxazoles **2**. In the following, we describe the synthesis and target affinity testing of several chemical series of substituted 2-aminobenzoxazoles **2** which were designed to explore the impact of various polar substituents attached at either the benzene or oxazole rings.

The impact of structural variations in the substitution pattern of the exocyclic 2-amino group was investigated in compounds **2-1** to **2-13** (Table 1) which were prepared as outlined in Scheme 1. The benzoxazole scaffold was obtained from base-catalyzed condensation of amino-nitrophenols **3** with carbon disulfide, furnishing nitrothiobenzoxazoles **4** as a common precursor.[6-8] Installation of alkylamino substituents at the 2-position proceeded through conversion of **4** with oxalyl chloride to the 2-chloroxazole and *in situ* reaction with the desired primary amine **5**. Dilute reaction conditions were used to disfavor the formation of benzoxazole dimers. Higher yields were obtained for coupling of the aminopropyl reagents likely due to less sterical hindrance as compared to the aminoethyl group. Finally, 2-amino substituted aniline products **2-1** to **2-7**, **2-9**, **2-10** and **2-12** were prepared through nitro reduction, with best yields achieved by using Adam's catalyst.[9]

For the exploration of modifications of the benzene ring, compounds substituted at the 6- or 7-position of the benzoxazole scaffold (**2-14** to **2-27**) were synthesized as outlined in Schemes 2 and 3 (Tables 2, 3). Installation of secondary and tertiary amino functionalities commenced with aromatic substitution of 5-fluoro-2-nitrophenol **6** with amine reagents **7**. Nearly quantitative yields were achieved in most cases, facilitated by the activating nitro group in the substrate.[10] Nitrophenols **8** were then reduced to the diaminophenols which were sensitive to oxidation.[11] Since the electron-rich substituted aminophenol scaffold readily decomposes when exposed to air, the intermediates were immediately cyclized with di(imidazole-1-yl)methanimine[12] which

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provided expedient access to the desired 6-substituted aminobenzoxazoles **2-14** to **2-21** (Scheme 2).

Benzoxazoles carrying benzylic tertiary amine modifications at the 7-position were synthesized starting from reductive amination of 3-nitrosalicylaldehyde **9** with various amines **10** to furnish near quantitative yields of nitrophenols **11** (Scheme 3).[13-15] The use of primary amines **10** in the reductive amination resulted in secondary amines which required the installation of a methyl group to obtain the desired tertiary amines (Table 3). This was accomplished by a second reductive amination step with formaldehyde.[16] Reduction of nitrophenols **11** to air-sensitive aminophenols followed by immediate *in situ* cyclization was performed as outlined before to furnish the substituted 7-methylene-2-aminobenzoxazole products **2-22** to **2-27**.

Combinations of polar substituents at both the exocyclic 2-amino group and the benzene ring were explored preliminarily by syntheses of two representative compounds including **2-28** and **2-29** (Table 4). The disubstituted 2-aminobenzoxazole **2-28** was obtained from **2-14** (Table 2) by nucleophilic substitution with *N,N*-dimethylaminopropyl chloride which proceeded in the presence of potassium bicarbonate at 75°C. Similarly, **2-23** was reacted by nucleophilic substitution with the same reagent in the presence of cesium carbonate at 60°C to furnish compound **2-29**.

The identity of the synthesized benzoxazole derivatives **2** was established after column chromatographic purification by mass- and NMR spectra. See the Supporting Information for experimental procedures and spectra. Crystal structures were determined for selected derivatives. The activity of compounds was assessed by testing binding affinity for the IRES IIa RNA in a FRET assay as previously described.[3] Target affinity expressed as EC_{50} value was determined

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from fitting single-site binding dose response curves to data obtained by averaging triplicate compound titration experiments (Tables 1-4).

Substitution at the excocylic 2-position of the amino-benzoxazole scaffold installed propyl- or ethyl-linked tertiary amines to furnish compounds that in addition carried an amino group at the benzene ring (Table 1). A few nitro derivatives (**2-8**, **2-13**) and one unsubstituted representative (**2-11**) were synthesized as well. In general, propyl-linked substituents conferred higher binding affinity to the IIa RNA target than ethyl-linked homologues (**2-6**, **2-7**). Among compounds carrying the *N,N*-dimethylaminopropyl group, which is found in the original benzimidazole inhibitor **1**, derivatives with 5- and 7-amino substituents (**2-9**, **2-10**, EC_{50}=52μM, 31μM) were two- to fourfold more active than the 6-amino analog (**2-1**, EC_{50}=120μM). While an *N,N*-dimethylaminopropyl-substituted compound without an amino group at the benzene ring retained binding (**2-11**, EC_{50}=110μM), absence of the 2-amino modification led to complete loss of activity (**2-12**). Similarly, a 6-nitro substituent abolished binding whether or not a *N,N*-dimethylaminopropyl modification was present at the 2-position (**2-8**, **2-13**). Apparently, the electron withdrawing effect of the nitro group further reduces the basicity of the benzoxazole N3 position which is detrimental for hydrogen bonding to the RNA target (Figure 1C).

Similar affinity as for the *N,N*-dimethylaminopropyl derivatives was observed with six-membered ring substituents in **2-3** (EC_{50}=47μM) and **2-4** (EC_{50}=43μM), however, surprisingly not with the smaller pyrrolidine modification in **2-2** or the bulkier methylpiperazine in **2-5** neither of which bound the IIa RNA target. In combination with the weaker affinity measured for derivatives which carried shorter ethyl-linked amines (**2-6**, **2-7**, EC_{50}=500μM, 88μM), these observations suggest that benzoxazole ligand binding may benefit from the proper occupancy by the 2-amino-substituent of a spatially restricted site of the IIa RNA target. In agreement with this

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hypothesis is the finding that the fourfold loss of affinity determined for the *N,N*-dimethylaminoethyl derivative (**2-6**, EC_{50}=500μM) compared to the propyl analog (**2-1**, EC_{50}=120μM) is restored by addition of the bulkier piperidine in **2-7** (EC_{50}=88μM).

Modification at the 6-position furnished active compounds only for primary amine substituents while secondary amines gave derivatives that did not bind the IIa RNA target (Table 2). The rigidly attached bulky groups in the latter compounds (**2-17** to **2-21**) might lead to steric clashes in the binding pocket while more flexible substituents as in **2-14**, **2-15** and **2-16** might be accommodated. Extended groups at the 6-position increase binding affinity as attested by derivatives **2-14** and **2-16** which were the most potent benzoxazole derivatives discovered in this study (EC_{50}=25μM, 27μM). Based on the crystal structure of the IIa RNA target in complex with translation inhibitor **1** and structure-activity relationship data of benzimidazole derivatives,[17] we had previously concluded that extended flexible substituents at the 5- and 6-position are directed towards a cleft lined by the sugar phosphate backbone of residues A54-U56 in the IIa RNA internal loop (Figure 1C). Comparison of the crystal structures for the RNA target free and in complex with **1** shows that this region undergoes a large conformational change upon ligand binding.[4, 18] This adaptive binding might benefit accommodation of flexible substituents at the 6-position which, in turn, might increase the binding affinity of benzoxazole ligands such as **2-14** and **2-16**. Rigid bulky groups attached at the same position, for example in derivatives **2-17** to **2-21**, might not be reconciled with target adaptation.

The 7-position of the benzoxazole scaffold was accessible to modification by reductive amination of a benzaldehyde precursor **9**, furnishing tertiary amino substituents attached at a benzylic position in 7-methylene-benzoxazoles (Scheme 3 and Table 3). Only two of the derivatives synthesized in this series showed IIa RNA target binding, albeit with weak affinity

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(**2-23**, **2-25**, EC_{50}=190μM, 600μM), while three other compounds were inactive (**2-22**, **2-24**, **2-26**). The lack of an electron donating amino group attached directly to the benzene in the benzylic amino derivatives, which reduces the basicity and ability of the N3 position to participate in hydrogen bonding to the RNA target, might explain the lower activity of the 7-methylene-benzoxazole derivatives. Flexibility of the substituent and polarity of the terminal functional group were important for binding, as indicated by the inactivity observed for the rigid piperazine in **2-24** or the less polar nitrile in **2-26**. The primary benzylamine itself in **2-27** was not sufficient to confer RNA target binding, in agreement with the inactivity of the unsubstituted compound **2-12** which we discussed above.

While the primary goal of the current study was the initial exploration of structure-binding activity relationship trends of monosubstituted 2-aminobenzoxazoles as ligands of the IIa RNA target, we included two disubstituted derivatives, **2-28** and **2-29** (Table 4), which were designed to combine beneficial modification patterns observed in the monosubstituted compounds. Surprisingly, both disubstituted benzoxazoles showed weaker than expected target binding. Two *N,N*-dimethylaminopropyl groups at the 2- and 6-position each were combined in compound **2-28**, which had a target affinity (EC_{50}=63μM) superior to the 2-monosubstituted **2-1** (EC_{50}=120μM) but weaker than the 6-monosubstituted **2-14** (EC_{50}=25μM) derivative. The 2,7-disubstituted compound **2-29** was a marginal ligand of the IIa RNA target (EC_{50}=310μM), showing an even lower affinity than the monosubstituted **2-23** (EC_{50}=190μM) and a tenfold loss in activity compared to the homolog **2-10** (EC_{50}=31μM) which, however, had an electron donating amino group attached directly at the benzene. As was discussed above, increase of the electron density in the benzoxazole system strengthens the basicity of the N3 position which is a key participant in hydrogen bonding to the RNA target. For both disubstituted derivatives, **2-28**

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and **2-29**, the reduced affinity as compared to the monosubstituted analogs could be rooted in the entropic penalty associated with preorganization of many rotatable bonds of the side chains disfavoring interaction with the RNA. Arrangement of the side chains for binding to the IIa RNA target that avoids steric clashes, specifically involving the substituent at the 2-position, could be further disfavored by electrostatic repulsion of the *N,N*-dimethylamino terminal groups which are protonated under the assay conditions.

In the current study, we have studied 2-aminobenzoxazoles (**2**) as ligands for the IIa RNA target in the HCV IRES element. The goal was to explore if the benzoxazole scaffold is a viable replacement for the more basic benzimidazole system found in previously discovered HCV translation inhibitors. Synthesis and affinity testing of monosubstituted 2-aminobenzoxazole derivatives allowed us to establish structure-binding activity relationships of the ligands. The observed pattern of compound activity in the FRET target binding assay were explained in the context of an earlier determined crystal structure of a benzimidazole translation inhibitor (**1**) bound to the IIa RNA. The most active benzoxazole ligands were binding the target at EC_{50} values around 25–45μM which was inferior to the benzimidazole compounds. While the lower basicity of the benzoxazole scaffold might confer superior drug-like properties to inhibitors, a detrimental effect on target affinity was observed in the compounds studied here. Future studies will focus on benzoxazole derivatives in which the basicity of the N3 position, a key interaction site for RNA target binding, is modulated by the addition of electron donating substituents at the benzene ring.

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Figure and Scheme Legends

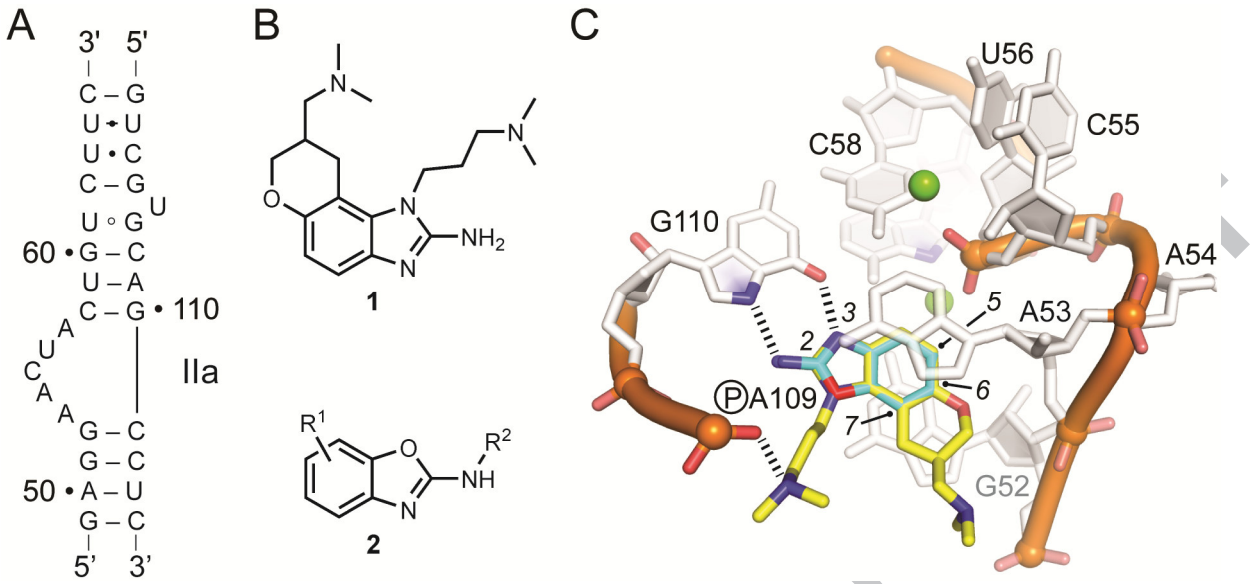
Figure 1. A) Secondary structure of the HCV IRES subdomain IIa RNA target. B) Structures of a 2-aminobenzimidazole translation inhibitor **1** which was previously co-crystallized in complex with the subdomain IIa, and 2-aminobenzoxazoles **2** which were designed here as less basic ligands for the RNA target. C) Superposition of the benzoxazole scaffold (light blue) on the benzimidazole inhibitor **1** (yellow) in the crystal structure of the IIa RNA complex.[4] Hydrogen bonds are shown as dashed lines. Residues G52 and A53, which stack below and above the ligand are shown transparent. Numbering of substitution positions in the benzoxazole is indicated.

Scheme 1. Synthesis of 2-amino-substituted 2-aminobenzoxazoles **2-1** to **2-13** (R=NO_2 or H; R^1=NO_2, H or NH_2) (Table 1). Reagents and conditions: *a*) KOH, CS_2, H_2O, EtOH, 80°C, 77% yield; b) oxalyl chloride, DCM, DMF, then addition of TEA and **5**, 0°C to 23°C, 46–88% yield; compounds **2-8**, **2-11** and **2-13** were isolated after this step; anilines were obtained through reduction by either method outlined in *c* or *d* with generally higher yields obtained using Adam's catalyst in *d*; *c*) $SnCl_2$, HCl, EtOH, 50°C, 53-64% yield; *d*) PtO_2, H_2, 23°C, 68-82% yield.

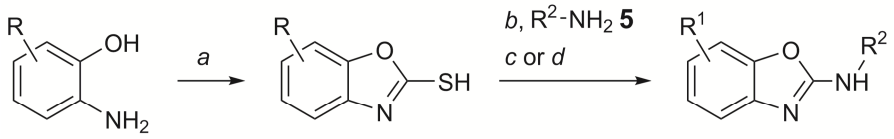
Scheme 2. Synthesis of 6-substituted 2-aminobenzoxazoles **2-14** to **2-21** (Table 2). Reagents and conditions: *e*) **7**, ACN, reflux, 80%-quantitative yield; *f*) 10% Pd/C, H_2, MeOH; *g*) di(imidazole-1-yl)methanimine, ACN, reflux, 41–86% yield over 2 steps.

Scheme 3. Synthesis of substituted 7-methylene-2-aminobenzoxazoles **2-22** to **2-27** (Table 3). Reagents and conditions: *h*) **10**, $NaBH(OAc)_3$, THF, 92%-quantitative yield; *f*) Pd/C, H_2, MeOH; *g*) di(imidazole-1-yl)methanimine, ACN, reflux, 51–77% yield over 2 steps.

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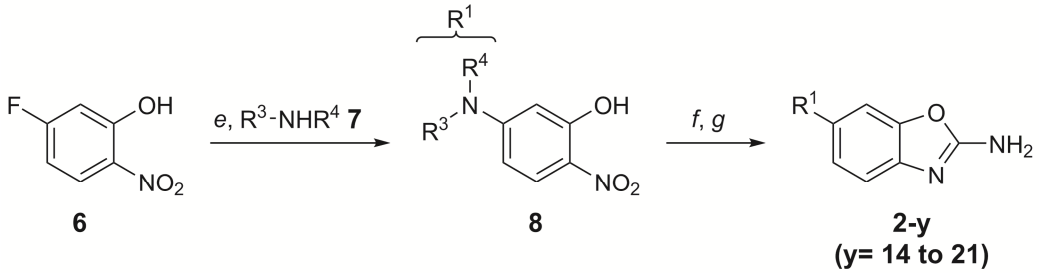
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3 **4** **2-x (x= 1 to 13)**

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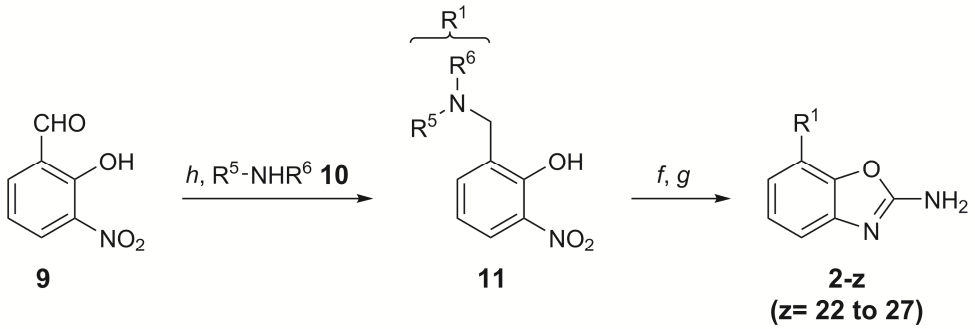
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6 **8** **2-y (y= 14 to 21)**

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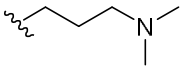
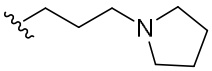
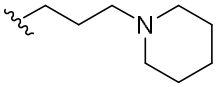
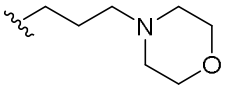
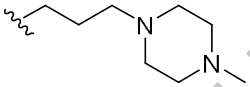
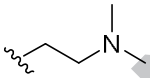
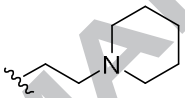
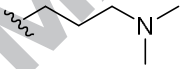
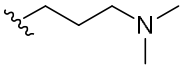
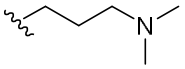
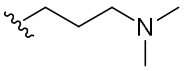


9 **11** **2-z (z= 22 to 27)**

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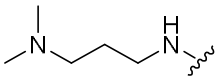
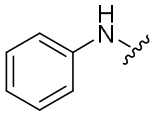
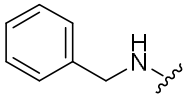
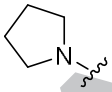
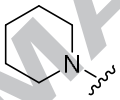
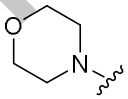
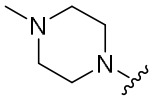
Table 1. Activity of 2-amino-substituted 2-aminobenzoxazoles **2-1** to **2-13** in the FRET assay.

Compound	R^1	R^2	EC_{50} [μM]
2-1	6-NH_2		120
2-2	6-NH_2		n.a.
2-3	6-NH_2		47
2-4	6-NH_2		43
2-5	6-NH_2		n.a.
2-6	6-NH_2		500
2-7	6-NH_2		88
2-8	6-NO_2		n.a.
2-9	5-NH_2		52
2-10	7-NH_2		31
2-11	H		110
2-12	6-NH_2	H	n.a.
2-13	6-NO_2	H	n.a.

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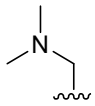
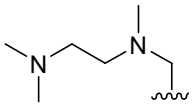
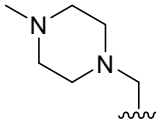
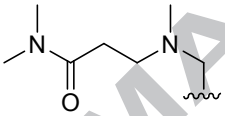
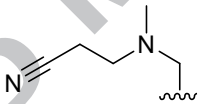
Table 2. Activity of 6-substituted 2-aminobenzoxazoles **2-14** to **2-21** in the FRET assay.

Compound	R^1	EC_{50} [μM]
2-14		25
2-15		90
2-16		27
2-17		n.a.
2-18		n.a.
2-19		n.a.
2-20		n.a.
2-21		n.a.

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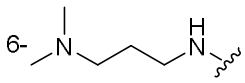
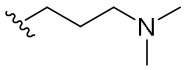
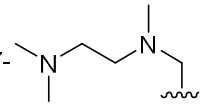
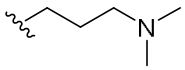
Table 3. Activity of substituted 7-methylene-2-aminobenzoxazoles **2-22** to **2-27** in the FRET assay.

Compound	R^1	EC_{50} [μM]
2-22		n.a.
2-23		190
2-24		n.a.
2-25		600
2-26		n.a.
2-27		n.a.

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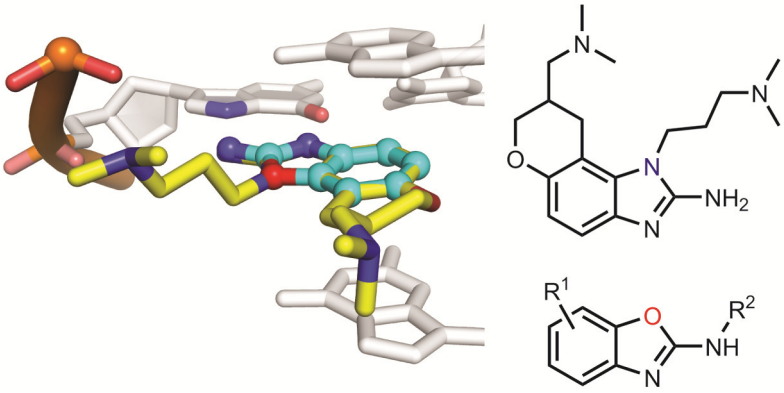
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Table 4. Activity of disubstituted 2-aminobenzoxazoles **2-28** and **2-29** in the FRET assay.

Compound	R^1	R^2	EC_{50} [μM]
2-28			63
2-29			310

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