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Substituted benzoxazinones as potent positive allosteric AMPA receptor modulators: Part II

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ABSTRACT

AMPA receptors (AMPARs) are an important therapeutic target in the CNS. A series of substituted benzoxazinone derivatives with good to very good in vitro activity as positive allosteric AMPAR modulators was synthesized and evaluated. The appropriate substituent choice on the benzoxazinone fragment improved the affinity towards the AMPA receptor significantly in comparison to our lead molecule **CX614**.

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(L)-Glutamic acid, the main excitatory neurotransmitter in the CNS, operates through two main groups of postsynaptic receptors: metabotropic Glu receptors (mGluRs) and ionotropic Glu receptors (iGluRs). Each of these is further divided into subgroups, with the iGluRs consisting of *N*-methyl-D-aspartic acid (NMDA), kainic acid (KA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. The AMPA subtype mediates fast excitatory neurotransmission in the mammalian central nervous system.

Positive allosteric modulators of these AMPA receptors (AMPARs) have been the subject of a wealth of studies and reviews.[1–24] The therapeutic potential of these compounds for a range of psychiatric and neurologic disorders such as attention deficit hyperactivity disorder (ADHD), Schizophrenia, Huntington's, Parkinson's and Alzheimer's disease or mood disorders is significant.[25–32] In the search for drug candidates to treat these diseases, a range of positive AMPAR modulators (AMPAKINE®s) have been synthesized in our laboratories. During optimization studies, we discovered that benzoxazines which have appropriately substituted side-chains are potent AMPAR modulators.[33,34] Instead of affecting glutamate binding itself, these molecules modulate the rate constants for transmitter binding, channel opening and/or desensitisation. It was shown, that AMPAKINE®s facilitate the induction of long term potentiation (LTP), which is considered a key element in learning and memory formation and therefore might allow the development of cognitive enhancers.[35–43] AMPAKINE®s can also upregulate the production of brain derived neurotrophic factor[44–47] (BDNF), promoting synaptic plasticity and neuronal survival in animal models of brain injury.

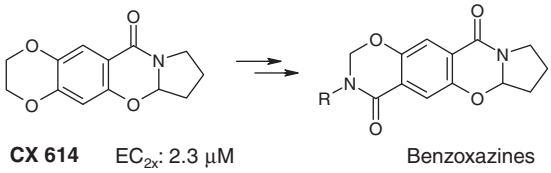

Figure 1. Modification of the lead **CX614** into benzoxazinones.

We wish to report the optimization of a series of benzoxazinone derivatives based on our lead molecule **CX614** (Fig. 1), which has been studied extensively.[1–5] As shown previously,[34] replacement of the 1,4-dioxine unit with a 1,3-oxazin-4-one ring, substituted with simple alkyl sidechains, allowed us to rapidly modify and investigate the role of substituents (R) in regard to their influence on AMPAR activity. In this study, we describe the investigation of more complex alkyl sidechains, substituted with heteroatoms, aryl- and heteroaryl groups.

The affinity of these compounds to displace a Cortex tritated AMPAKINE radioligand from the cyclothiazide AMPAR binding site in rat forebrain cell membranes was measured. In addition the potency and efficacy of the compounds on cultured rat embryonic hippocampal neurons in a patch clamp electrophysiology assay (measured as EC_{2x}) was used as a guideline to optimize this class of AMPAR modulators.[34] The general synthetic route for the synthesis of the benzoxazinones was performed as outlined in Scheme 1.

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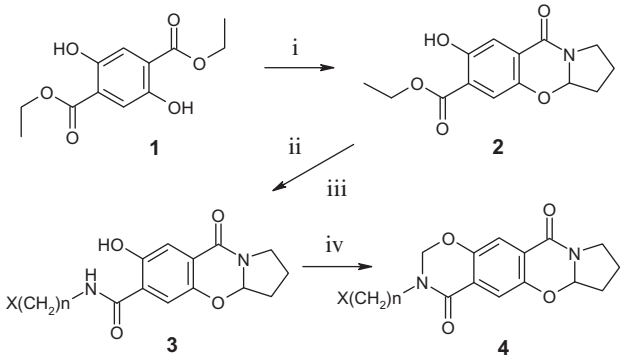


Scheme 1. Synthesis of benzoxazinones: Reagents and conditions: (i) 1.0 equiv **1**, 1.6 equiv 4-aminobutyraldehyde diethylacetal, 120 °C, 7 min; HCl, 20 °C, 60 min, 64–71% **2**; (ii) 15 equiv KOH, MeOH/water, 1.5 h, 50 °C; (iii) 1.0 equiv DMAP, 1.0 equiv HOBT, 2.5 equiv NEt_3, 2.0 equiv EDCI, 1.3 equiv amine, DMF, 20 °C, 4 h; (iv) $CHCl_3$, excess trioxane, cat. H_2SO_4, 2 h, 70 °C 20–90% **4a**–**4s** (three steps).

The commercially available diethyl 2,5-dihydroxy-terephthalate **1** was transformed into the benzoxazinone **2**, simply by heating it together with 4-aminobutyraldehyde diethylacetal, followed by ringclosure under acidic conditions. This versatile starting material was prepared in larger quantities (~50 g) and was easily transformed into the amides **3** by ester hydrolysis, followed by standard amide formation, using the appropriate amine. Ring closure under acidic conditions, using trioxane as a formaldehyde source yielded the target compounds **4a**–**4r** in acceptable to good yields (20–90%, Table 1).

Since simple alkyl substituents (**4a**), attached to the benzoxazinone scaffold, exhibited improved activity in comparison to **CX614**, we investigated a series of similar derivatives with hetero atoms incorporated in the side chain. Groups with increased polarity, as exemplified in compounds **4b**, **4h** and **4s**, had a detrimental effect on AMPAR activity. In contrast, the unsaturated, nitrogen containing analogs, the thiocyanate (**4g**), the azide (**4i**) and the nitrile (**4p**) exhibit higher potency in the EC_{2x} assay and increased amplitude of the excitatory postsynaptic potential (EPSP) in the slice assay.[34] These substituents were introduced into the side-chain, because they are small and allowed us to rapidly determine the effect of heteroatoms and unsaturation, despite the potential safety issues introducing these groups.

This led to other changes, such as phenyl rings, attached through alkyl linkers, which were also explored (Fig. 2). Although the phenyl analogue **5** was inactive, incorporating an alkyl linker significantly improved activity, with the 2 carbon linked analogue **7a** having the highest potency. Since the phenethyl derivative **7a** exhibited 10-fold higher activity compared to **CX614** and was equal to **4a**, we investigated substituents on the aromatic system in order to optimize binding to the receptor (Table 2).

The investigational drugs **7a**–**7r** were synthesized in acceptable to good yields (38–90%), using the appropriately substituted phenethylamine derivatives, following the reaction sequence shown before (Scheme 1). Based on derivatives **7b–7g**, it became clear, that a substituent in the 3-position is favorable, whereas in the 2- and 4-positions it is detrimental for activity. It can also be seen, that polar derivatives such as the amide **7m**, do not work well, whereas the less polar thioamide **7n** is 12 times more active and the least polar nitrile **7o** is the most active in this group.

Small electron withdrawing substituents in the 3-position are preferable (**7c, f, o, p**), compared to electron donating groups (**7i**). This lead to the 3,5-difluoro derivative **7r**, which exhibited a 460-fold higher activity in comparison to **CX614**.

Based on the enhanced activity of some of the phenethyl derivatives we anticipated that heteroaromatic substituents as shown in Table 3 would also work well. The synthesis of these derivatives was accomplished following the procedures outlined in Scheme 1, using the appropriately substituted ethylamine derivative, or following an alternative route, introducing the heterocycle at the end of the synthesis (Scheme 2). In this procedure ethanolamine was incorporated into the molecule, to form **9** and subsequently **10**. This route has the advantage, that the alcohol function could now be transformed into a leaving group followed by substitution with a heterocycle of our choice. In some cases, depending on the heterocycle, Mitsunobu conditions worked as well. This approach allowed us to quickly synthesize a variety of interesting derivatives.

All three pyridyl isomers **11a–11c** have comparable activity to the phenyl derivative **7a**, however the position of the nitrogen is not as relevant as substituents in the phenyl series (compare to **7b–7d**). A series of five-membered heterocyclic systems was also investigated. The isoxazolyl derivative **11f** is slightly less active than **7a**, whereas the thiophene isomers **11d** and **11e** are some of the most potent AMPAR potentiators identified.

Comparison of the imidazoles **11o** and **11p** demonstrates, that the position of attachment of the imidazole ring is important for activity, with the nitrogen linked analogue **11p** being 100-fold more active than the carbon liked derivative **11o**, most likely due

Table 1
Influence of O, S and N-substituents on AMPAR activity

	Substituent	EC_{2x}[a] (μM)	Slice Ampl.[b]% (μM)	K_i[c] (μM)
4a	CH_3CH_2–	0.2	17[10]	20
4b	$HO(CH_2)_2$–	1.3	—	33
4c	$MeO(CH_2)_2$–	1.2	14[10]	41
4d	$MeS(CH_2)_2$–	0.29	12[3]	17
4e	$MeSO(CH_2)_2$–	0.11	14[3]	13
4f	$MeSO_2(CH_2)_2$–	0.32	6[3]	20
4g	$NCS(CH_2)_2$–	0.06	7[3]	1
4h	$NCNH(CH_2)_2$–	1.8	2[10]	51
4i	$N_3(CH_2)_2$–	0.08	16[3]	5.9
4k	$MeSO_2NH(CH_2)_2$–	0.33	10[3]	8.4
4l	$MeSO_2NMe(CH_2)_2$–	0.38	8[10]	31
4m	$MeSO_2NMe(CH_2)_3$–	0.33	9[10]	34
4n	$NC(CH_2)$–	0.5	10[10]	17
4o	$NC(CH_2)_2$–	0.6	19[10]	11
4p	$NC(CH_2)_3$–	0.05	11[3]	6.8
4r	$NC(CH_2)_4$–	0.11	22[10]	4.5
4s	$H_2NCO(CH_2)_2$–	1.1	6[30]	51

[a] EC_{2x} values[34] are defined as the concentration of compound required to double the steady-state current induced by glutamate.

[b] In vitro slice assay[34]: percentage increases in the amplitude of fEPSP, recorded at indicated concentration (— = no data available).

[c] Displacement of tritiated AMPAKINE radioligand in cell membrane preparations from adult rat forebrain.[34]

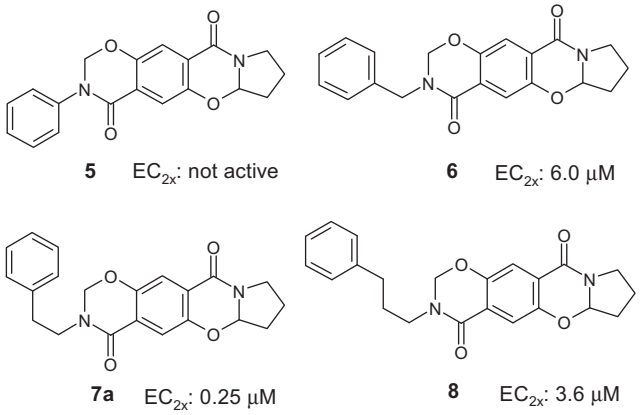


Figure 2. Optimal chain length for aryl-alkyl substituted benzoxazinones.

Table 2
Influence of aromatic substitution on AMPAR activity

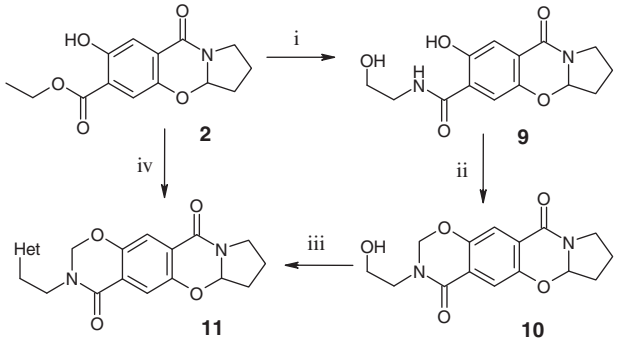
	Substituent	EC_{2x}[a] (μM)	Slice ampl.[b] % (μM)	K_i[c] (μM)
7a	H-Ph	0.25	3[3], 19[30]	7.9
7b	2-F-Ph	5.4	—	36
7c	3-F-Ph	0.011	16[3]	0.5
7d	4-F-Ph	1.2	6[30]	—
7e	2-Cl-Ph	7.1	—	—
7f	3-Cl-Ph	0.02	7[30]	1.8
7g	4-Cl-Ph	>40	—	—
7h	3-Br-Ph	1.6	—	150
7i	3-MeO-Ph	14	—	69
7k	3-CF_3O-Ph	3.0	—	13
7l	3-CF_3-Ph	0.2	1[30]	2.5
7m	3-H_2NCO-Ph	5.0	—	620
7n	3-H_2NCS-Ph	0.4	5[10]	—
7o	3-CN-Ph	0.027	16[3]	3
7p	3-NO_2-Ph	0.015	8[3]	3.6
7r	3,5-F_2-Ph	0.005	16[3]	0.3

[a,b,c] See Table 1.

Table 3
Influence of hetero aromatic substituents on AMPAR activity

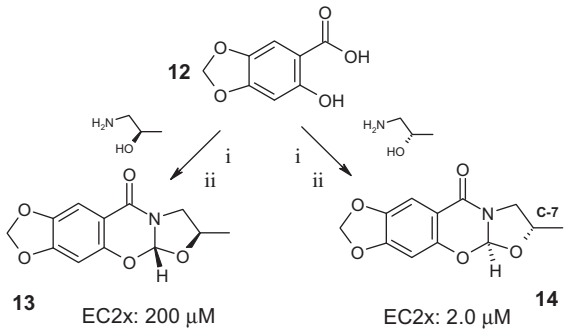
	Substituent	EC_{2x}[a] (μM)	Slice Ampl.[b] % (μM)	K_i[c] (μM)
11a	2-Pyridyl	0.6	15[30]	130
11b	3-Pyridyl	0.2	15[3]	6.6
11c	4-Pyridyl	0.24	3[3], 15[10]	43
11d	Thiophen-2-yl	0.032	—	2
11e	Thiophen-3-yl	0.02	15[3]	0.27
11f	Isoxazol-3-yl	0.4	4[3]	41
11g	Pyrazol-1-yl	0.064	15[3]	5.1
11h	3-Cyanopyrazol-1-yl	0.1	10[3]	18
11i	4-Cyanopyrazol-1-yl	0.04	29[3]	1
11k	5-Cyanopyrazol-1-yl	0.045	16[3]	22
11l	4-Bromopyrazol-1-yl	0.02	32[3]	2.5
11m	4-Chloropyrazol-1-yl	0.0037	23[1]	0.33
11n	4-Nitropyrazol-1-yl	0.0065	29[1]	0.24
11o	Imidazol-4-yl	5.1	—	225
11p	Imidazol-1-yl	0.05	38[10]	6.6
11r	4-Nitroimidazol-1-yl	0.0007	19[0.3]	0.06
11s	2-Methylimidazol-1-yl	1.8	—	227
11t	1,2,4-Triazol-1-yl	0.063	31[3]	2.1
11u	3-Nitro-1,2,4-triazol-1-yl	0.01	14[3]	4.2
11v	Triazol-1-yl	0.16	8[1]	5.1
11w	Triazol-2-yl	0.8	7[3]	62

[a,b,c] See Table 1.



Scheme 2. Synthesis of benzoxazinones: Reagents: (i) 1..0 equiv **2**, 3 equiv ethanolamine, 140 °C, 60 min, 93% **9**; (ii) (a)isobutyric anhydride; (b) $CHCl_3$, excess trioxane, cat. H_2SO_4, 1 h, 70 °C; (c) KOH, MeOH 62% **10**; (iii) MesCl, NEt_3 then heterocycle/NaH/DMF; (iv) conditions: see Scheme 1.

to the negative influence of the polar NH. The position of substitution on the pyrazole system seems to have almost no effect, comparing **11g**–**11k**, however the nature of the substituent (**11g, 11i, 11l**–**11n**) is important, similar to the substituent effect in the phenyl series. This effect is more pronounced in the imidazole series (**11p**–**11s**), which clearly shows, that small electron withdrawing substituents improve the affinity to the receptor, with the 4-nitroimidazole **11r** being the most active AMPAR positive modulator identified to date.



Scheme 3. Synthesis of oxazolo benzoxazinones **13** and **14**: Reagents and conditions: (i) 1.0 equiv DMAP, 1.0 equiv HOBT, 2.5 equiv NEt_3, 2.0 equiv EDCI, 1.3 equiv amine; (ii) $CHCl_3$, excess $HC(OMe)_3$, cat. TosOH, 20 min, 110 °C, (main isomers shown).

The 1,2,4-triazol derivative **11t** exhibits higher in vitro activity compared to the 1,2,3-triazolyl derivatives **11v** and **11w.**

In order to validate the findings based on EC_{2x} (single cell recordings[34]) and binding data, we also generated rat hippocampal slice data[34] to measure the effect of these experimental drugs on a network of neurons. In general, for example when **7c**, **7o** and **7r** are compared, the different datasets are in agreement with each other. However we also noticed inconsistencies, for example comparing **7d** and **7f**. The artificial environment used in these in vitro experiments may explain these differences.

When some pyrrolo benzoxazine derivatives were separated into enantiomers (by chiral HPLC), they exhibited a clear difference in affinity, with the active isomer being approximately 100-fold more potent than the inactive. Unfortunately, we were not able to obtain suitable crystals for X-ray analysis of the 3D structure of these compounds.

A very similar series of oxazolo benzoxazinones was synthesized, starting with salicylic acid **12**, utilising the chiral 1-aminopropan-2-ols as shown in Scheme 3. The main isomers of each reaction (**13** and **14**) had therefore a fixed stereocenter at C-7 and enabled determination of stereochemistry at the newly formed stereocenter using NMR spectroscopy (NOE). Isomer **14** (Scheme 3) is the more active enantiomer, which led to the inference, that the active enantiomer in the pyrrolo benzoxazinone series is the R-isomer, based on the fact, that the 3-dimensional shape of the corresponding molecules is essentially the same (we found that methyl substituents attached to C-7 minimally influence affinity).

In summary, the introduction of a heterocyclic system in combination with small electron withdrawing substituents and the 2 carbon spacer, leads to significant improvements in activity. The nitroimidazole **11r**, exhibits 3000-fold higher activity compared to our starting lead compound **CX614**, and is one of the most potent potentiators of the AMPAR reported to date. When the in vitro binding data, EC2x and slice data are compared, we found that the datasets are generally in agreement which each other.

Acknowledgments

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