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Benzobistriazinones and related heterocyclic ring systems as potent, orally bioavailable positive allosteric AMPA receptor modulators

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ABSTRACT

AMPA receptors (AMPARs) are an important therapeutic target in the CNS. A series of substituted benzobistriazinone, benzobispyrimidinone and related derivatives have been prepared with high potency and selectivity for the allosteric binding site of AMPARs. Further improvements have been made to previously reported series of positive AMPAR modulators and these compounds exhibit excellent in vivo activity and improved in vivo metabolic stability with up to 100% oral bioavailability in rat.

(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 receptor families 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. Multiple series of small molecules (AMPAKINE®s) have been identified that positively modulate the activity of AMPA receptors (AMPARs).[1–7] Instead of affecting glutamate binding itself, these molecules modulate the rate constants for transmitter binding, channel opening and/or deactivation and desensitisation. The therapeutic potential of positive allosteric modulators of AMPARs is considered to be significant.[8–15] Psychiatric and neurologic disorders such as attention deficit hyperactivity disorder (ADHD), schizophrenia, Huntington's disease, Parkinson's disease, and Alzheimer's disease have been targeted by positive AMPAR modulators. AMPAKINE®s have also been shown to upregulate the production of brain derived neurotrophic factor[16–19] (BDNF), promoting synaptic plasticity and neuronal survival in animal models of brain injury and neurodegeneration. Several series of positive allosteric AMPAR modulators[20–23] have been synthesized as potential drug candidates in our laboratories. AMPAKINE® compounds of general structure **1** were previously shown to have good activity in an in vivo electrophysiology assay.[23] The triazinone ring in these compounds improved metabolic stability and plasma half-life over a similar series of bisbenzoxazinone based AMPAKINE®s.[23] We now report on the further optimization of these compounds by replacement of the second oxazinone ring with the metabolically more favourable triazinone and pyrimidinone rings (Fig. 1) resulting in compounds with the general structure **2**.

In our preceding paper, we demonstrated that the lead compound (**3**) is able to facilitate the induction of long term potentiation (LTP) in vivo, which is considered to be a key element in learning and memory formation, and therefore might allow the development of a treatment for disorders with cognitive deficits.[24–32] A summary of the AMPAR activity of the lead compounds **3** and **4** from the previously reported triazinonebenzoxazinone

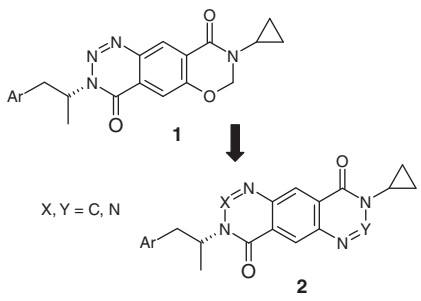

Figure 1. Benzobistriazinone and related heterocycles as AMPAR modulators.

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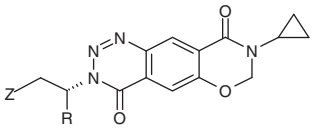
Table 1
Influence of triazinone substitution on AMPAR activity



	Z	$T_{1/2}$ (rat)	R	EC_{2x}[a] [μM]	A(%) [concn][b]
3	Tetrazol-2-yl	0.27 h	Methyl	0.46	33 [5]
4	Tetrazol-1-yl	NT	Methyl	0.19	7 [5]

[a] EC_{2x} values[21] are defined as the concentration of compound required to double the steady-state current induced by glutamate.
[b] In vivo amplitude increase (%) from baseline, using [x] mg/Kg ip.

series[23] is shown in Table 1. The 2-tetrazole **3** was the first analogue from the series to show good activity in the in vivo electrophysiology assay[23] following intraperitoneal (ip) dosing, suggesting some improvement in oral availability. However, since compound **3** has a short plasma half-life in rat (0.27 h), our goal was to further improve metabolic stability in the series. The 1-tetrazole, compound **4**, has poor in vivo activity following both ip and iv dosing, even though it is more potent in vitro than **3**, likely due to lower brain penetration. Analogues of compound **3** were therefore targeted for further optimization studies.

We envisioned that potentially four new scaffolds could be generated by replacement of the oxazinone ring of **3**, and the pyrimidinone analogue thereof, with either a triazinone or a pyrimidinone ring (Fig. 2). To our surprise, only the synthesis of a bispyrimidinone scaffold, required to prepare derivatives **7**, has been reported in the literature.[33,34]

In order to synthesize all four possible combinations of these tricyclic heterocyclic ring systems we needed a partially protected intermediate, for example the bisester **5**, which would allow us to selectively close one ring independent from the other in a controlled way to generate the structures **6**, **7**, **8** and **9** as shown in Figure 2. The synthesis of intermediate **5** was accomplished by protecting the nitrogen of the commercially available dimethyl amino terephthalate **10**, as formate **11**, followed by nitration, which resulted in a 9:1 mixture of nitration products (Scheme 1). The main isomer **12** could be crystallized as a single isomer. The reduction of the nitro group to the aniline **5** was accomplished using Zn/Cu on a smaller scale or H_2/Pd on a larger scale.

In order to prepare the bistriazinone compounds, aniline **5** was diazotized and the crude solution quenched with cyclopropylamine (or any amine of choice) to give the cyclopropyltriazinone derivative **13**, as a mixture of components with the aniline partially

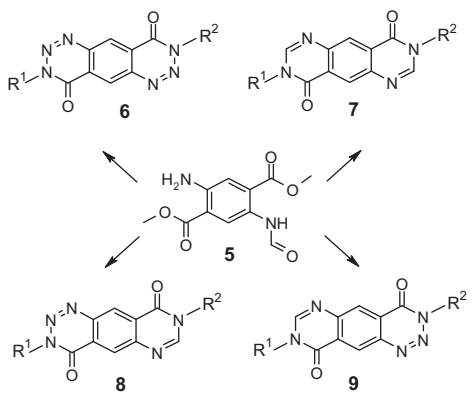
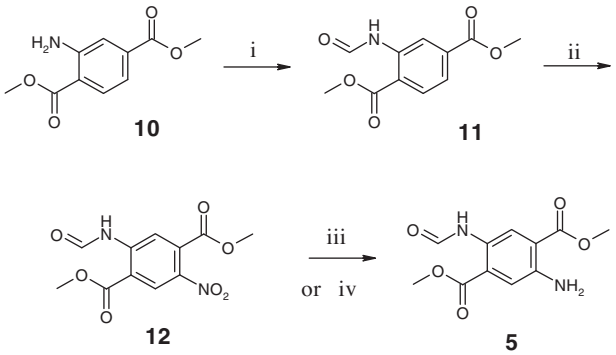


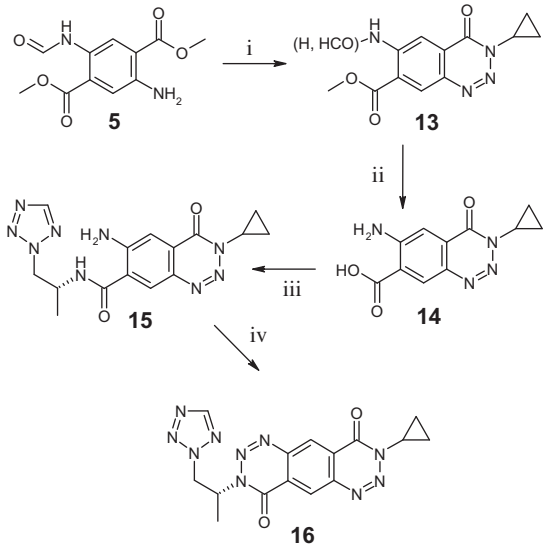
Figure 2. The versatile intermediate **5** allows the selective synthesis of the heterocyclic ring systems **6**–**9**.



Scheme 1. Synthesis of intermediate **5**. Reagents and conditions: (i) 100 ml Ac_2O/30 mL HCOOH, 10 min, rt, 150 mL $CHCl_3$, 25 g **10**, 20 min, 20 °C, **11** quant.; (ii) 150 mL H_2SO_4, −10 °C, 15 mL 90% HNO_3, 2.5 h ~90% 9:1 mixture, cryst CH_2Cl_2/MTBE ~60–70% **12**; (iii) CH_2Cl_2/MeOH, Pd/C 10%, H_2, 50 PSI, 20 °C, 30 min (90%); (iv) THF/MeOH 1:1, excess Zn/Cu, excess HCOOH, 15 min, 20 °C (90%) **5**.

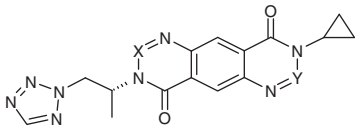
deprotected (Scheme 2). Treatment of **13** with potassium hydroxide yielded acid **14** which was coupled to an enantiomerically pure tetrazole substituted prop-2-ylamine[35] using standard conditions to give the amide **15**. Treatment of this aniline derivative with iso-amyl nitrite yielded the bistriazinone **16** in good overall yield. We were delighted to see that **16** maintained excellent AMPAR activity (see Table 2) demonstrating that both oxazinone rings can be replaced with triazinone rings without loss in activity. A rat pharmacokinetic study with **16** showed it has 100% oral bioavailability and a plasma half-life of 1.7 hours. In cynomolgus monkey **16** has 100% oral bioavailability and a plasma half-life of 9.5 h. Thus, compound **16** has significantly improved pharmacokinetic stability over compound **3**, achieved by replacing the metabolically unstable oxazinone ring with a triazinone ring.

Based on the results with **16**, the pyrimidinone analogues **19** and **20** were also prepared from compound **5** (Scheme 3). Heating **5** with commercially available (*R*)-2-amino propanol gave the pyrimidinone analogue **17**. Ester hydrolysis, followed by standard amide formation and ring closure produced the bisazinone



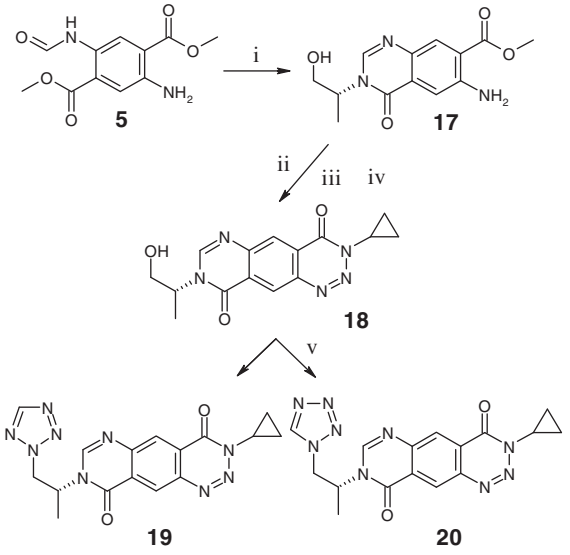
Scheme 2. Synthesis of bistriazinones. Reagents and conditions: (i) THF/H_2O, $NaNO_2$, HCl, 0 °C, 2 equiv amine, NEt_3, 20 °C, **13** (76–86%); (ii) KOH, THF/MeOH/H_2O, 30–60 min, 20 °C **14**; (iii) 1 equiv amine, 3 equiv EDCI, 1 equiv HOBT, 1 equiv DMAP, NEt_3, DMF, 20–50 °C, **15** (50–72%); (iv) DMF, excess *i*-Amyl nitrite, AcOH, 20 °C, 3–18 h, **16** 60%.

Table 2
Influence of triazinone and pyrimidinone units on AMPAR activity

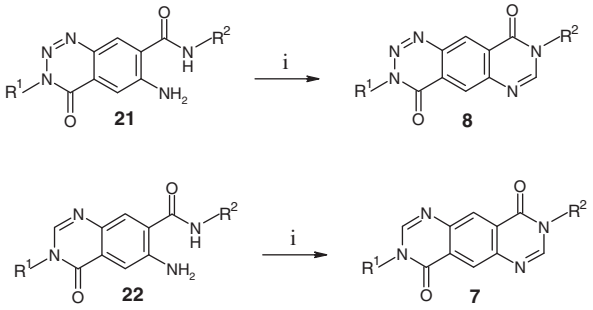


	X	Y	$T_{1/2}$ (rat)	F (rat)	$T_{1/2}$ (dog)	$T_{1/2}$ (monkey)	EC_{2x}[a] [μM]	A(%) [concn][b]
16	N	N	1.7 h	100%	3 h	9.5 h	0.28	37[5]
19	C	N	1.6 h	100%	4.8 h	NT	0.6	33 [5]
23	N	C	NT	NT	NT	NT	1.0	16 [5]
24	C	C	NT	NT	NT	NT	1.4	2 [5]

NT = not tested.
[a] See Table 1.
[b] In vivo amplitude increase (%) from baseline, using [x] mg/Kg ip.



Scheme 3. Synthesis of pyrimidinones/triazinones. Reagents and conditions: (i) 1 equiv **5**, 1.8 equiv (*R*)-2-amino propanol, 0.3 equiv NaCN, 110 °C, 30 min, 59% **17**, (ii) 2.1 equiv KOH, MeOH/H_2O, 1 h, 65 °C; (iii) 3.3 equiv cyclopropylamine, 2.7 equiv EDCI, 1 equiv HOBT, 2 equiv DMAP, 2 equiv NEt_3, DMF, 40 °C, 6 h; (iv) DMF, excess iso-butyl nitrite, AcOH, 22 °C, 16 h, **18**; (v) 4.1 equiv tetrazole, 1.65 equiv Ph_3P, 2 equiv DIAD, THF, 20 °C, 14 h, **19** (less polar) and **20**.



Scheme 4. Synthesis of triazinone–pyrimidinone derivatives and bispyrimidinones. Reagents and conditions: (i) Toluene, TosOH, excess $HC(OMe)_3$ or $CH(OMe)_2N(Me)_2$ 110 °C (40–70%).

derivative **18**. The hydroxyl group of **18** could be replaced by a range of N-linked heterocycles.

For example, replacement with tetrazole under Mitsunobu conditions generated a mixture of tetrazoles **19** and **20** which could be easily separated by column chromatography. We were pleased to see that compound **19** exhibited similar in vitro and in vivo AMPAR activity to compound **16** (Table 2). A rat pharmacokinetic study with **19** showed it to have excellent oral bioavailability, similar to **16** (see Table 2).

In the preceding examples the triazinone ring was closed as the last step to form the tricyclic scaffold. The final step can also be ring closure to form a pyrimidinone ring. This route gave us access to the two remaining bisazinone scaffolds (Scheme 4). From intermediate **21** we were able to make the derivatives **8**, and from intermediate **22** we were able to form the bispyrimidinone derivatives **7**.

Using these routes, the additional analogues of **16** and **19**, compounds **23** and **24**, were prepared[35,36] for comparison studies (see Table 2).

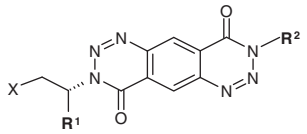
A comparison of this short series of bisazinones shows that the bistriazinone **16** is the most active positive allosteric AMPAR modulator both in vitro and in vivo, whereas the bispyrimidinone **24** is 5 times weaker in vitro and is essentially inactive in the in vivo electrophysiology assay. When only one pyrimidinone unit is present, the compounds are active in vitro and in vivo, however analogue **19** exhibits better properties, compared to **23**. Based on the SAR results of our preceding work[20–23] we prepared a series of compounds based on the lead compounds **16** and **19** incorporating a range of side-chains (Tables 3 and 4).

It is apparent from the data in Tables 3 and 4 that R^1 = methyl is the best group for AMPAR activity. Variation of R^2 on the triazinone ring is tolerated, but small substituents are preferred, for example, methyl and cyclopropyl. All the tetrazol-1-yl substituted compounds are more active in vitro than the tetrazol-2-yl derivatives, but are less active in vivo which may be due to lower CNS penetration of the more polar tetrazol-1-yl derivatives. In general, the bistriazinone and pyrimidinone/triazinone derivatives in Tables 3 and 4 exhibit similar in vivo activities, when compounds with the same substitution pattern are compared. Compound **16** was tested in a large series (~100 targets) of in vitro CNS and nonCNS receptor binding and enzymatic assays (NovaScreen®, Caliper Life Sciences) and showed no 'off target' activity up to 10 μM suggesting good selectivity for the AMPA receptor.

The improvement made in these newer series of compounds is best demonstrated by comparing compounds **3** and **16** (see Figs. 3 and 4) in our in vivo electrophysiology model. The effect of both compounds on evoked EPSP in the dentate gyrus of anesthetized rats after ip dosing is similar, comparing the increase in amplitude. However the duration of the effect is significantly prolonged with **16**, and this correlates with the longer plasma half-life of this compound.

Since the azole side-chains of the compounds in Tables 3 and 4 contribute significantly to the AMPAR activity, we wanted to see if

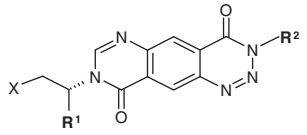
Table 3
AMPAR activity of a series of substituted bistriazinones



	X	R^1	R^2	EC_{2x}[a] [μM]	A(%) [concn][b]
25	3-F-Phenyl	Ethynyl	Cyclopropyl	0.45	1 [5]
26	Tetrazol-2-yl	Ethynyl	Cyclopropyl	NT	4 [5]
27	Tetrazol-2-yl	H	Cyclopropyl	NT	1 [5]
16	Tetrazol-2-yl	Methyl	Cyclopropyl	0.28	37 [5]
28	Tetrazol-1-yl	Methyl	Cyclopropyl	0.07	11 [5]
29	Triazol-2-yl	Methyl	Cyclopropyl	1.3	12 [10]
30	Triazol-1-yl	Methyl	Cyclopropyl	0.37	24 [10]
31	1,2,4-Triazol-1-yl	Methyl	Cyclopropyl	1.1	7 [5]
32	4-Cyano-triazol-2-yl	Methyl	Cyclopropyl	NT	17 [5]
33	Methyltetrazol-2-yl	Methyl	Cyclopropyl	3.1	7 [5]
34	Methyltetrazol-1-yl	Methyl	Cyclopropyl	0.25	8 [5]
35	Methanesulfonamide	Methyl	Cyclopropyl	0.7	NA
36	Tetrazol-2-yl	Methyl	Methyl	0.28	46 [5]
37	Tetrazol-1-yl	Methyl	Methyl	0.08	19 [5]
38	Triazol-2-yl	Methyl	Methyl	2.1	7 [5]
39	Triazol-1-yl	Methyl	Methyl	0.09	7 [5]
40	Tetrazol-2-yl	Methyl	Ethyl	0.3	34 [5]
41	Tetrazol-2-yl	Methyl	2-Propyl	0.44	26 [5]
42	Tetrazol-2-yl	Methyl	Allyl	NT	12 [5]
43	Tetrazol-2-yl	Methyl	Propargyl	0.57	20 [5]
44	Tetrazol-2-yl	Methyl	But-2-ynyl	NT	43 [5]
45	Tetrazol-2-yl	Methyl	Methoxyethyl	NT	34 [5]

NT = not tested; NA = not active.
[a] See Table 1.
[b] In vivo amplitude increase (%) from baseline, using [x] mg/Kg, ip.

Table 4
AMPAR activity of a series of pyrimidinone/triazinones



	X	R^1	R^2	EC_{2x}[a] [μM]	A(%) [concn][b]
46	Tetrazol-2-yl	H	Cyclopropyl	NT	7 [5]
19	Tetrazol-2-yl	Methyl	Cyclopropyl	0.6	33 [5]
20	Tetrazol-1-yl	Methyl	Cyclopropyl	0.07	2 [5]
47	Triazol-2-yl	Methyl	Cyclopropyl	NT	9 [10]
48	4-Cyano-triazol-2-yl	Methyl	Cyclopropyl	NT	3 [10]
49	Pyrazolyl	Methyl	Cyclopropyl	NT	20 [10]
50	4-Cyanopyrazolyl	Methyl	Cyclopropyl	NT	2 [5]
51	Tetrazol-2-yl	Methyl	Methyl	NT	63 [5]
52	Triazol-2-yl	Methyl	Methyl	NT	30 [20]
53	Triazol-1-yl	Methyl	Methyl	NT	5 [20]
54	Tetrazol-2-yl	Methyl	Propargyl	0.5	11 [5]
55	Tetrazol-1-yl	Methyl	Propargyl	0.25	1 [5]
56	Tetrazol-2-yl	Methyl	Fluoroethyl	NT	32 [10]
57	Tetrazol-2-yl	Methyl	Difluoroethyl	NT	16 [20]
58	Tetrazol-2-yl	Methyl	Trifluoroethyl	NT	7 [10]

NT = not tested.
[a] See Table 1.
[b] In vivo amplitude increase (%) from baseline, using [x] mg/Kg, ip.

activity could be enhanced even further by the incorporation of two azole substituted side-chains as shown by the compounds in Table 5. These compounds were prepared using the routes described in Schemes 1–4. As anticipated, potency was enhanced by this modification and the compounds in this series are some of the most potent allosteric AMPAR modulators described to date. As in the preceding series, the most potent compound in vivo is the bistriazinone compound **59** with two tetrazol-2-yl units in the side-chains.

In summary, by replacing both oxazinone rings in previously reported AMPAKINE series with either a triazinone or a pyrimidinone ring removed the metabolic liability and resulted in compounds having good in vivo activity, excellent oral bioavailability and increased pharmacokinetic stability in rat and higher species. The incorporation of two tetrazol-2-yl side-chains on to the bistriazinone scaffold gave the symmetrical compound **59**, the most potent AMPAKINE molecule in the in vivo electrophysiology assay

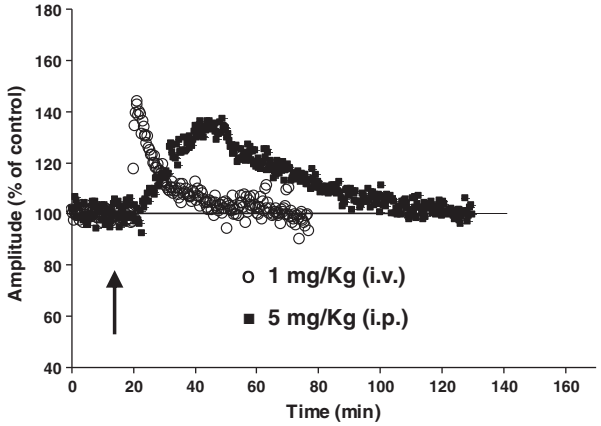


Figure 3. In vivo activity of **3** on the amplitude of the f-EPSP in rat dentate gyrus.

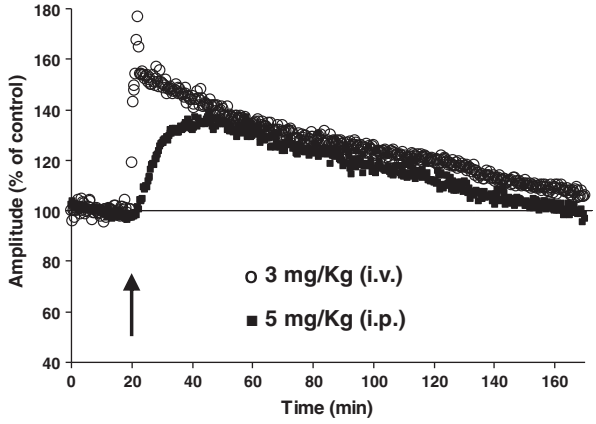
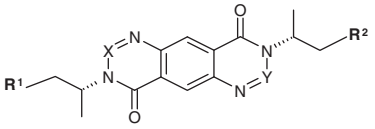


Figure 4. In vivo activity of **16** on the amplitude of the f-EPSP in rat dentate gyrus.

Table 5
Effect of 2 chiral sidechains on AMPAR activity



	R^1	X	Y	R^2	EC_{2x}[a] [μM]	A(%) [concn][b]
59	Tetrazol-2-yl	N	N	Tetrazol-2-yl	0.016	59 [1]
60	Tetrazol-2-yl	N	N	Triazol-2-yl	0.07	26 [3]
61	Triazol-2-yl	N	N	Triazol-2-yl	0.40	9 [5]
62	Triazol-1-yl	N	N	Triazol-1-yl	0.06	0 [3]
63	Tetrazol-2-yl	C	N	Tetrazol-2-yl	0.008	43 [1]
64	Tetrazol-2-yl	C	N	Tetrazol-1-yl	0.02	1 [5]
65	Tetrazol-2-yl	C	C	Tetrazol-2-yl	0.03	0 [5]
66	Pyrazolyl	C	C	Pyrazolyl	0.09	2 [5]

[a] See Table 1.
[b] In vivo amplitude increase (%) from baseline, using [x] mg/Kg, ip.

reported to date. The further biological evaluation of these compounds will be reported in a separate publication.

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