Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1953–1956

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 3-ARYL-5*H*-2,3-BENZODIAZEPINE AMPA ANTAGONISTS

Benjamin A. Anderson,* Nancy K. Harn, Marvin M. Hansen, Allen R. Harkness, David Lodge,† and J. David Leander†

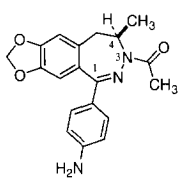
Lilly Research Laboratories, A Division of Eli Lilly and Company, Chemical Process Research and Development Division, †Neuroscience Research Division, Lilly Corporate Center, Indianapolis, IN 46285, U.S.A.

Received 9 March 1999; accepted 26 May 1999

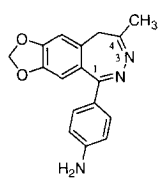
Abstract: A novel series of 3-aryl-5*H*-2,3-benzodiazepines with *N*-3 aromatic substituents has been synthesized. Good *in vivo* anticonvulsant activity of the new compounds has been demonstrated employing the maximal electroshock seizure test in mice. Evaluation of a subset of the compounds in the cortical wedge assay confirmed the new structures to be AMPA antagonists.

Excessive activation of *L*-glutamate receptors has been implicated as a causative factor in the pathology of several acute and chronic neurological disorders.[1] This relationship has focused attention on the identification of selective antagonists of the ionotropic glutamate receptors for which several subtypes have been characterized in the mammalian CNS.[2] These subtypes are pharmacologically distinguished through their selective activation by exogenous ligands which include *N*-methyl-*D*-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA), and kainic acid (KA). Several contemporary clinical and preclinical studies have focused on selective AMPA antagonists.[3] Among these, noncompetitive agents that operate by allosteric modulation of the receptor site are of particular interest since they present the theoretical advantage of effecting antagonist activity at moderate concentrations in the presence of high levels of glutamate.[3]

To date, talampanel (LY300164) represents one of the most clinically advanced agents from a class of highly selective, orally active, noncompetitive AMPA antagonists.[4] The structure-activity study from which talampanel emerged was enabled by the discovery that the 3,4-double bond of the *para*-nitro analog of the series progenitor, GYKI 52466, could be selectively reduced and acylated at nitrogen.[5] While the synthetic



Talampanel
(LY300164)



GYKI 52466

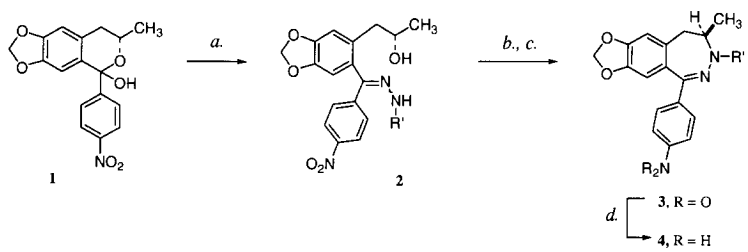
0960-894X/99/$ - see front matter
PII: S0960-894X(99)00315-7

approach proved quite productive, the protocol limited the variability at the nitrogen since only functionalization by acylation or alkylation could be readily accomplished. We report herein the general application of an alternative synthetic approach to the 5*H*-2,3-benzodiazepine nucleus, which has yielded heretofore inaccessible *N*-3 aryl derivatives. The compounds were evaluated in a standard *in vivo* convulsion model in which good activity was demonstrated for several of the new structures.

Variation of the 5*H*-2,3-benzodiazepine nucleus was primarily limited to the modification of the *N*-3 functionality. Structural features that were held constant with the prototype compound, talampanel, included the 2,3-methylenedioxy-aromatic group and the *C*-4 methyl substituent. Evaluation of each enantiomer from the lead series has confirmed that greater potency is associated with the (*R*) enantiomer.[6] The present study was therefore limited to evaluation of optically pure substrates containing the preferred configuration.

Our synthetic approach was adapted from a manufacturing process specifically designed for production of talampanel.[7] The strategy is generally described in Scheme 1. Introduction of the benzodiazepine nitrogen constituents as a modular unit was envisioned to provide a flexible method for variation of the *N*-3 substituent. This was accomplished by production of a hydrazone **2** formed upon treatment of the optically pure hemiketal[7] **1** with the selected hydrazine derivative. The resulting hydrazones **2** were isolated as ~1:1 *E*:*Z* mixtures about the carbon-nitrogen double bond. Base-mediated cyclization of the methanesulfonate esters of **2** delivered the desired 5*H*-2,3-benzodiazepine ring system **3**. In some cases, the corresponding β-styrenyl elimination product was also generated. Competitive elimination appeared to be exacerbated by increased steric bulk of R' (*e.g.*, <1% R' = 2-py; 6% R' = 2-quinoline; 21% R' = 2-phthalazine). Reduction of the aromatic nitro group of **3** was accomplished under palladium-catalyzed transfer hydrogenation conditions.[8]

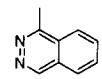
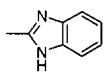
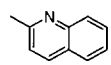
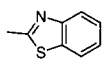
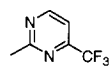
Scheme 1



a. H_2NNHR', EtOH, cat. HCl; *b.* MsCl, Et_3N, CH_2Cl_2; *c.* NaOH, EtOH; *d.* Pd/C, KO_2CH, *i*-PrOH

The *in vivo* structure-activity relationship in this new series was characterized by evaluation of the benzodiazepines in the maximal electroshock seizure (MES) test.[9] This test measures the ability of anticonvulsants to abolish the hindlimb tonic extensor components of a maximal electroshock-induced seizure. Parameters of the study involved *iv* administration of the compound 5 min prior to application of a 50 mA alternating current delivered for 0.2 s through corneal electrodes. Mice that did not exhibit a tonic extensor response after the challenge were considered protected. All compounds were tested at 10 mg/kg. If an anticonvulsant effect was observed, lower doses (5, 2.5, 1.25 mg/kg) were tested in order to determine an ED_{50} value. Anticonvulsant activity is expressed as an ED_{50} value and is summarized in the Table.

Table. *In vivo* activity of *N*-3 derivatives of **4**[a]

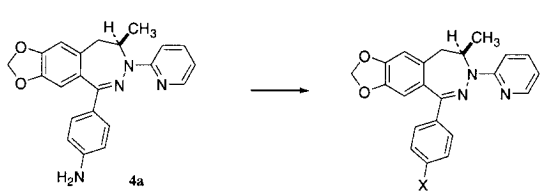
entry	*R'*	**4**	ED_{50}	entry	*R'*	**4**	ED_{50}
1	$COCH_3$	**a**	0.48	6		**f**	7.8
2		**b**	0.76	7		**g**	10 [c]
3		**c**	1.47	8		**h**	NA[d]
4		**d**	3.2	9		**i**	NA
5		**e**	5 [b]	10		**j**	NA

[a] Protection in 50% mice; values expressed in mg/kg. [b] 80% mice protected at 10 mg/kg, none at 5 mg/kg. [c] 40% mice protected at 10 mg/kg. [d] NA indicates not active at 10 mg/kg.

Greater *in vivo* potencies in the MES model were realized for compounds with smaller nitrogen substituents. This trend was also recognized for *N*-3 acylated derivatives.[5u] However, the activity of the *N*-3 aromatic derivatives was particularly surprising given the complete lack of activity reported for the corresponding R' = benzoyl compound (**4**, R' = COPh).[5a] Incorporation of a heteroatom adjacent to the point of attachment increased the anticonvulsant activity of the aromatic derivatives (entry 2 vs 3; entry 6 vs 8). Increased basicity of the heteroatom also improved activity (entry 4 vs. 5). Consistent with this observation was the deleterious effect of incorporation of electron withdrawing groups on the R' heterocycle (entries 7 and 10). Although the mechanism of the anticonvulsant activity of the new structures was not unequivocally established, selective interaction with the AMPA receptor without significant effect on responses to NMDA receptors was demonstrated by evaluation of a subset of the compounds (**4b** and **4f**). Both compounds at 10 μM blocked responses to AMPA (40 μM) on cortical wedges by 50% or more.[10]

Further refinement of the SAR was pursued by modification of the *C*-1 aniline moiety of the most potent agent from this series, **4b**. *N*-acetylation of talampanel (**4a**) is the primary clearance route in monkeys.[11] It

Scheme 2



4a

5a, X = Cl, NA at 10 mg/kg
5b, X = I, NA at 10 mg/kg
5c, X = H, NA at 10 mg/kg

conditions: X = Cl, *t*-BuONO, $CuCl_2$, MeCN (37%); X = I, *t*-BuONO, CuI, MeCN (49%); X = H, (*i*) $NaNO_2$, HCl, H_2O (*ii*) H_3PO_2 (73%).

would therefore be valuable to establish the structural requirements of the *C*-1 constituent. Diazotization of the aniline **4b** allowed conversion to the chloro (**5a**), iodo (**5b**) and proteo (**5c**) analogs (Scheme 2). However, none of the new compounds proved active in the standard MES model. The *para*-nitro analog **3b** was also inactive.

In summary, the synthesis of a novel class of 5*H*-3,4-benzodiazepines has been described. The synthetic approach has been demonstrated to be sufficiently flexible to afford production of a variety of *N*-3 aromatic species which were inaccessible by existing strategies. Furthermore, several new compounds were shown to have surprising *in vivo* activity in the MES anticonvulsant model. The *N*-3-(2-pyridyl) derivative **4b** was the most active compound studied and approached the *in vivo* potency of the clinical candidate talampanel (**4a**, Table). Reaction chemistry of the series was further probed by derivations of the *para*-aniline group through the intermediacy of the corresponding diazonium species. These transformations further established the importance of the aromatic amine to the anticonvulsant activity of the series.

References and Notes

1. Pelletier, J. C.; Hesson, D. P.; Jones, K. A.; Costa, A. M. *J. Med. Chem.* **1996**, *39*, 343 and references cited therein.
2. Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187.
3. (a) Parsons, C. G.; Danysz, W.; Quack, G. *Drug News Perspect.* **1998**, *11*, 523. (b) Rogawski, M. A. *Trends Pharmacol. Sci.* **1993**, *14*, 325.
4. Jewell, H.; Lucas, R.; Schaefer, H.; Mant, T. 99th Annual Meeting of the American Society for Clinical Pharmacology an Therapeutics. New Orleans, Louisiana, March 30, 1998. PII-69.
5. (a) Tarnawa, I.; Berzsenyi, F.; Andrási, F.; Botka, P.; Hámori, T.; Ling, I.; Körösi, J. *Biorg. Med. Chem. Lett.* **1993**, *14*, 325. (b) Ling, I.; Podányi, B.; Hámori, T.; Sólyom, S. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1423.
6. Lodge, D.; Bond, A.; O'Neill, M. J.; Hicks, C. A.; Jones, M. G. *Neuropharmacology* **1997**, *35*, 1681.
7. Anderson, B. A.; Hansen, M. M.; Harkness, A. R.; Henry, C. L.; Vicenzi, J. T.; Zmijewski, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 12358.
8. All new structures were confirmed by ^{1}H NMR, ^{13}C NMR, infrared and mass spectroscopy. Acceptable combustion analyses were obtained for all samples (±0.4%). Representative spectral data is given for compound **4b**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.17 (m, 1H), 7.61 (d, 2H, *J* = 6.8 Hz), 7.46 (m, 1H), 6.97 (d, 1H, *J* = 8.5 Hz), 6.80 (s, 1H), 6.75 (d, 2H, *J* = 9.0 Hz), 6.68 (m, 2H), 5.98 (d, 1H, *J* = 1.3 Hz), 5.92 (d, 1H, *J* = 1.3 Hz), 5.50 (m, 1H), 3.92 (br s, 2H), 2.78 (m, 2H), 1.26 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 167.1, 159.4, 148.6, 148.4, 147.2, 145.8, 137.0, 136.0, 130.9, 128.2, 127.8, 114.4, 113.7, 110.5, 109.4, 108.5, 101.3, 63.0, 39.6, 17.3; MS *m/z* 372 (FD^+). Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.76; H, 5.71; N, 14.93.
9. (a) Swinyard, E. A.; Woodhead, J. H. *"Antiepileptic Drugs"*, 2nd ed.; Woodbury, D. M.; Penry, J. K.; Pippenger, C. E. Eds.; Raven: New York, 1992; pp 111-126. (b) Leander, D. J. *Epilepsia* **1992**, *33*, 573.
10. Palmer, A. J.; Lodge, D. *Eur. J. Pharmacol.* **1993**, *244*, 193.
11. Eckstein, J. A.; Swanson, S. P. *J. Chromatogr., B: Biomed. Appl.* **1995**, *668*, 153.