Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2723–2726

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Substituted 3-(2-Benzoxazyl)-benzimidazol-2-(1*H*)-ones: A New Class of $GABA_A$ Brain Receptor Ligands

Robert W. DeSimone and Charles A. Blum*

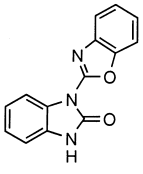
Neurogen Corporation, 35 Northeast Industrial Road, Branford, CT 06405, USA

Received 12 June 2000; accepted 25 September 2000

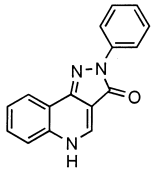
Abstract—A novel class of potent benzodiazepine receptor (BZR) ligands has been designed and synthesized aided by molecular modeling of known benzodiazepine ligands such as CGS-8216 and the use of known pharmacophore models.

Introduction

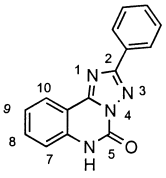
GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter of the brain and the actions of several classes of clinically important drugs, including the benzodiazepines (BZs) and barbiturates, are mediated through the $GABA_A$ receptor complex.[1] Benzodiazepines, which allosterically modulate the actions of GABA, have found widespread use as anxiolytics, sedative/hypnotics, and anticonvulsants.[2] The 'classical' 1,4-benzodiazepines such as diazepam, however, tend to be rather full agonists producing not only the desired anxiolytic, hypnotic, or muscle relaxant effects but also numerous side effects including sedation, developement of tolerance and dependence, rebound symptoms at withdrawal, amnestic effects and potentiation of alcohol actions.[3]



1



CGS-8216



CGS-13767

In the 1980s several benzodiazepine receptor (BZR) ligands with distinct chemical structure were identified that interacted differentially with BZ sites in various brain regions thus supporting the existence of at least two distinct BZR subtypes associated with the $GABA_A$ complex.[3] It was also recognized that BZ-receptor ligands within a chemical series (e.g., the β-carbolines) are capable of exhibiting a wide range of intrinsic activities from full positive or partial positive modulation (agonism) to neutral modulation (antagonism) to partial or full negative modulation (inverse agonism) of the effects of GABA.[4a] Along this continuum lie partial agonists that may have a reduced side effect profile relative to the full agonists while maintaining good efficacy as anxiolytics.[3] More recently, molecular biology studies have shown that the $GABA_A$ receptor complex is even more heterogenous than once thought with several different receptor subunits (α, β, γ, and δ) combining to form the receptor allowing for different $GABA_A$ receptor isoforms depending on which subunits are involved. Several native receptor subtypes have been identified so far and as many as 21 recombinant receptor subtypes are now known.[4b] Along with this rich heterogeneity has come the realization that activation of specific $GABA_A$ receptor subtypes (by BZR ligands) may mediate specific behavioral responses.[4] The promise of discovering BZ-receptor ligands with partial agonist and/or subtype selective properties has prompted scientists to continue their search for anxiolytics, cognition enhancers, and hypnotics devoid of the side effects usually associated with the classical BZs.

The goal of the present study was to design a potent and novel series of BZR ligands that could be evaluated with regard to efficacy and side effect liability.

Design and Synthesis

The design of compounds of formula **1** as potential high affinity ligands for the benzodiazepine (BZ) site of the $GABA_A$ receptor complex, was based on ligands such as

*Corresponding author. Tel.: +1-203-488-8201; fax: +1-203-481-5290; e-mail: cblum@nrgn.com

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00550-3

CGS-8216[5] and CGS-13767[6] as well as pharmacophore models developed to understand the binding of these and other ligands (e.g., the β-carbolines) to the BZR (Fig. 1).[7]

Molecular modeling[8] suggested that **1** had all the requisite functionality in three-dimensional space to interact with the BZR in a manner consistent with the CGS series of ligands, as shown in Figure 1, and conformed to the inclusive pharmacophore model described in the literature.[7] Specifically, **1** has two heteroatoms capable of interacting with the hydrogen-bond donor site (represented by the receptor descriptor H1) present on the BZR. The importance of the benzimidazolone carbonyl oxygen is suggested by the SAR observed with CGS-13767 in which the carbonyl at C-5 was necessary for binding to the BZR.[6] Additionally, the interaction of this carbonyl oxygen with H1 may occur in concert with the benzoxazole oxygen (or nitrogen) to form a three centered hydrogen bond. This type of interaction has been used to explain the high binding affinities observed for other BZR ligands such as certain benzodiazepines and β-carbolines that are thought to interact with the same donor site (H1).[9] The heteroatom contained within the benzoxazole moiety, which is oriented away from H1, is then available to interact with the other H-bond donor site, H2, present on the receptor (Fig. 1). There is some evidence in the literature to suggest that compounds such as CGS-8216 and CGS-13767 can interact with H2 via the imine nitrogen at position 1.[6,9] Furthermore, the N–H bond in **1** is situated to allow favorable interaction with the hydrogen-bond acceptor site (A1) present on the protein. The orientation of aryl ring D in **1** allows for interaction with the lipophilic pocket L1 which is located at the centroid of the D-ring with compounds in the CGS-8216 series.[7a] Although the D-ring of **1** overlaps partially with L1, interaction with the L2 pocket (normally associated with substituents at the 4 position of the D-ring in the CGS-8216 series) appears less likely.

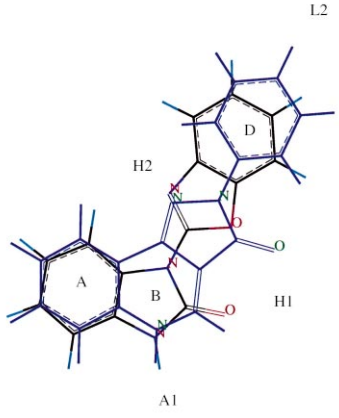
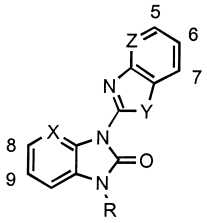


Figure 1. Overlay of **1** and CGS-8216.

Compounds of type **1** (Table 1) were readily prepared by treating 2(3*H*)-benzimidazolone **2** with 2.2 equivalents of LDA followed by the addition of either substituted 2-chlorobenzoxazoles[10] **3** or substituted 2-(methylthio)-benzoxazoles **4**[11,12] (Scheme 1). When the reaction was carried out using 1 equivalent of LDA, bis-alkylation was the predominant reaction outcome, possibly due to either the increased acidity or increased solubility of **1** relative to starting material **2**. Substituted 2-chlorobenzoxazoles (**3**) and substituted

Table 1. Substituted 3-(2-benzoxazyl)-benzimidazol-2-(1*H*)-ones (**1**)



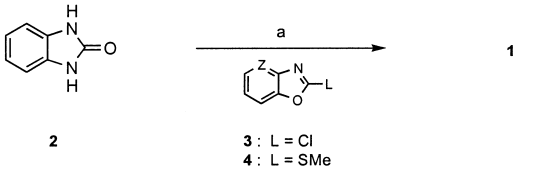
1a - q

Entry	R	X	Y	Z	5	6	7	8	9	K_i (nM)[14]
1a	H	C–H	O	C–H	H	H	H	H	H	54
1b	Me	C–H	O	C–H	H	H	H	H	H	>10,000
1c	H	C–H	S	C–H	H	H	H	H	H	>10,000
1d	H	C–H	O	C–H	F	H	H	H	H	162
1e	H	C–H	O	C–H	H	F	H	H	H	89
1f	H	C–H	O	C–H	H	H	F	H	H	39
1g	H	C–H	O	C–H	H	F	F	H	H	20
1h	H	C–H	O	C–H	OMe	H	H	H	H	91
1i	H	C–H	O	C–H	H	OMe	H	H	H	610
1j	H	C–H	O	C–H	H	Me	H	H	H	303
1k	H	C–H	O	N	H	H	H	H	H	44
1l	H	C–H	O	C–H	H	H	H	F	H	58
1m	H	C–H	O	C–H	H	H	H	H	F	32
1n	H	C–H	O	C–H	H	F	H	H	F	25
1o	H	C–H	O	C–H	H	H	F	H	F	14
1p	H	C–H	O	C–H	H	H	F	F	H	15
1q	H	N	O	C–H	H	H	H	H	H	723
CGS-8216										IC_{50} = 0.4 nM[15]
CGS-13767										IC_{50} = 4 nM[16]

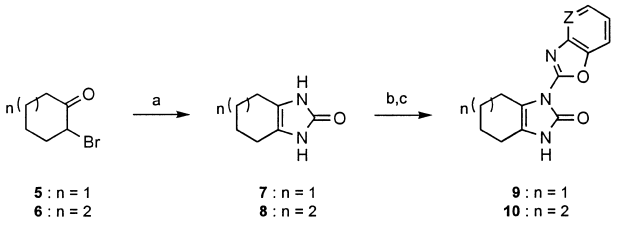
2-(methylthio)-benzoxazoles (**4**) were prepared from the corresponding substituted 2-aminophenols by treatment with the potassium salt of *O*-ethylxanthic acid in refluxing aqueous ethanol.[13] The resulting 2-thiolbenzoxazoles were then treated with thionyl chloride or methyl iodide to give the 2-chloro- and 2-(methylthio)-derivatives, **3** and **4**, respectively.[10,11]

Compound **1m** (Table 1) was prepared by treating 4-fluoro-2-nitroaniline with 2-chlorobenzoxazole followed by reduction of the nitro group and cyclization with carbonyldiimidazole. Compound **1l** was prepared by reaction of 5-fluorobenzimidazolone with **3** followed by chromatographic separation of the resulting regioisomers (**1l** and **1m**).

In similar fashion, 4,5,6,7-tetrahydro-2-benzimidazolone **7** and 3,4,5,6,7,8-hexahydro-2(1*H*)-cycloheptimidazolone **8** were treated with substituted benzoxazoles (**3** or **4**) to give the corresponding A-ring variants **9** and **10**, respectively (Scheme 2). Imidazolones **7** and **8** were prepared from bromoketones **5** and **6** using modifications of literature procedures (Scheme 2).[14]



Scheme 1. (a) 2.2 equiv LDA, THF, rt, 15 min, then **3** or **4** in THF, 0.5–2 h.



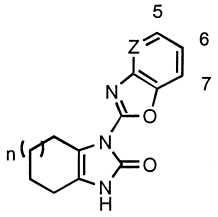
Scheme 2. (a) 1 equiv urea, H_2O, HOAc, NH_4OAc, reflux 4 h; (b) 2.2 equiv LDA, THF, rt, 15 min; (c) 1 equiv **3** or **4** in THF, 0.5–2 h.

Discussion

The pharmacophore model[7] described above was supported by the structure–activity relationship (SAR) of the benzimidazolone (**1**) series as shown in Table 1. Thus, when **1a** was methylated, thereby removing possible H-bonding interactions with A_1, the resulting compound (**1b**) had no affinity for the BZR. Furthermore, when one of the hydrogen bond acceptors present in **1a** (the oxygen atom of the benzoxazole group) is replaced by sulfur, the resulting compound (**1c**) exhibited a marked loss of affinity for the BZR.

Placing fluorine substituents on the benzoxazole group (D-ring) did not significantly change the affinity of this series although the difluoro compound (**1g**) displayed a modest improvement in potency relative to the parent compound (**1a**). In an attempt to maximize interactions with the lipophilic cavity (L2) of the receptor, larger

Table 2. Substituted imidazolones (**9** and **10**)



Entry	n	Z	5	6	7	K_i (nM)[14]
9a	1	C–H	H	H	H	56
9b	1	C–H	F	H	H	26
9c	1	C–H	H	F	H	47
9d	1	C–H	H	H	F	52
9e	1	C–H	H	F	F	21
9f	1	C–H	OMe	H	H	81
9g	1	C–H	H	OMe	H	239
9h	1	N	H	H	H	>1000
10a	2	C–H	H	H	H	8
10b	2	C–H	F	H	H	5
10c	2	C–H	H	F	H	5
10d	2	C–H	H	H	F	5
10e	2	C–H	OMe	H	H	25
10f	2	C–H	H	OMe	H	254
10g	2	N	H	H	H	137
10h	2	C–H	Me	H	H	15
10i	2	C–H	H	Me	H	158
10j	2	C–H	F	F	H	87
10k	2	C–H	F	H	F	7
10l	2	C–H	H	F	F	3
10m	2	C–F	H	F	H	65
10n	2	C–H	Cl	H	H	140

substituents were placed at positions 5 and 6 of **1a** (Fig. 1). However, substitution of a methoxy group at the 5 position (**1h**) produced a deleterious effect on affinity while substitution with methyl or methoxy at the 6 position (**1i** and **1j**) had an even greater negative impact on receptor binding. Close examination of Figure 1 indicates that there is no position on **1** that is ideally suited to project a substituent into the area of space corresponding to the *para* position of CGS-8216 (where interactions with L2 are maximized). It is plausible that substituents at positions 5 or 6 of **1** encounter steric repulsions from regions (S1 or S2) present on the receptor.[7]

As with the D-ring, substitution of fluorine at positions 8 or 9 (**1l** and **1m**) of the A-ring produced only modest effects on receptor affinity. It has been reported that electron withdrawing substituents (e.g., Cl) at the 5-position (position 8 of compound **1**) of indolic BZR ligands can enhance binding affinity.[16] However, placement of a fluorine at position 8 (compound **1l**) did not improve receptor affinity. Combining the best fluorine substituents from the A-ring and the D-ring yielded **1o**, which showed about a 4-fold gain in potency relative to **1a**. Incorporation of a nitrogen into the A-ring of **1a** yielded a compound (**1q**) with a more than 10-fold decrease in potency at the BZR.

The SAR of the corresponding tetrahydrobenzimidazolone series (**9**) closely paralleled that of the aromatic series (**1**) with the former having a slightly greater affinity for the BZR (Table 2). Previous observations suggest that a more three-dimensional A-ring or one bearing substituents capable of forming lipophilic interactions in this area of space (e.g., placement of Cl at position 9 of CGS-13767)[6a] can have a positive influence on binding affinity. Indeed, this is the case when moving to the more lipophilic seven-membered ring homologues of the present series (**10a**–**10n**) with several compounds having K_is of less than 10 nM at the BZR (Table 2). Compounds **10a**–**n** exhibited as much as a 30-fold increase in affinity relative to the analogous benzimidazolones (**1**) reflecting a more favorable interaction with the receptor. In the case of compounds such as CGS-13767, which are thought to bind in a similar fashion to those of the present series, an increased interaction with this lipophilic pocket is often accompanied by an increase in agonist function.

The compounds of the present series are structurally unique and display good to moderate affinity for the BZR. The pharmacology of this series and its potential to produce anxiolytic or sedative/hypnotic effects devoid of the adverse side-effects frequently associated with other BZ ligands, will be reported in due course.

References and Notes

1. (a) Sieghart, W. *Pharmacol. Rev.* **1995**, *47*, 181. (b) Teuber, L.; Watjen, F.; Jensen, L. H. *Curr. Pharmaceut. Des.* **1999**, *5*, 317.
2. (a) Bowery, N. G. In *The GABA Receptors*; Enna, S. J., Bowery, N. G., Eds.; Humana: NJ, 1997; pp 209–236. (b) Gupta, S. P. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1995; Vol. 45, pp 67–106.
3. Costa, E.; Guidotti, A. *Trends Pharmacol. Sci.* **1996**, *17*, 192, and references therein.
4. (a) Rudolph, U.; Crestani, F.; Benke, D.; Brunig, I.; Benson, J.; Fritschy, J.-M.; Martin, J. R.; Bluethmann, H.; Mohler, H. *Nature* **1999**, *401*, 796. (b) Mehta, A. K.; Ticku, M. K. *Brain Res. Rev.*, **1999**, *29*, 196.
5. Yokoyama, N.; Ritter, B.; Neubert, A. D. *J. Med. Chem.* **1982**, *25*, 337.
6. (a) Francis, J. E.; Cash, W. D.; Barbaz, B. S.; Bernard, P. S.; Lovell, R. A.; Mazzenga, G. C.; Friedmann, R. C.; Hyun, J. L.; Braunwalder, A. F.; Loo, P. S.; Bennett, D. A. *J. Med. Chem.* **1991**, *34*, 281. (b) Francis, J. E.; Bennett, D. A.; Hyun, J. L.; Rovinski, S. L.; Amrick, C. L.; Loo, P. S.; Murphy, D.; Neale, R. F.; Wilson, D. E. *J. Med. Chem.* **1991**, *34*, 2899.
7. (a) Liu, R.; Hu, R. J.; Zhang, P.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1996**, *39,* 1928. (b) Zhang, W.; Koehler, K. F.; Zhang, P.; Cook, J. M. *Drug Des. Discov.* **1995**, *12*, 193. (c) Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B.; McKernan, R.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1998**, *41*, 2537.
8. Structures shown in Figure 1 were minimized on a Silicon Graphics Indigo 2 Personal workstation using SYBYL (Tripos Associates, St. Louis, MO).
9. Allen, M. S.; Tan, Y.-C.; Trudell, M. L.; Narayanan, K.; Schindler, L. R.; Martin, M. J.; Schultz, C.; Hagen, T. J.; Koehler, K. F.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 2343.
10. Forster, H.; Boehm, S.; Marhold, A.; Santel, H.; Luerssen, K.; Schmidt, R. R. Eur. Patent 0 572 893, 1993; *Chem. Abstr.* **1993**, *120*, 164158.
11. (a) Yamato, M.; Takeuchi, Y.; Hashigaki, K.; Hirota, T. *Chem. Pharm. Bull.* **1983**, *31*, 733. (b) Chu-Moyer, M. Y.; Berger, R. *J. Org. Chem.* **1995**, *60*, 5721.
12. Compounds gave correct mass spectral analysis and had NMR spectroscopic data consistent with the structures given.
13. Van Allan, J. A.; Deacon, B. D. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 569–570.
14. Zav'yalov, S. I.; Sitkareva, I. V.; Ezhova, G. I.; Dorofeeva, O. V.; Zavozin, A. G. *Khim. Geterotsikl. Soedin.* **1990**, *6*, 847; *Chem. Abstr.* **1991**, *114*, 23873.
15. Compounds were assayed for their ability to displace ^{3}H-RO15-1788 (^{3}H-Flumazenil) from rat cortical tissue. For conditions see: (a) Thomas, J. W.; Tallman, J. F. *J. Neurosci.* **1983**, *3*, 433. (b) Thomas, J.; Tallman, J. *J. Biol. Chem.* **1981**, *256*, 9838. (c) DeSimone, R. W.; Blum, C. A. US Patents 5 637 724, 1997; 5 637 725, 1997; 5 936 095, 1999.
16. Primofiore, G.; Marini, A. M.; DaSettimo, F.; Martini, C.; Bardellini, A.; Giannacchini, G.; Lucacchini, A. *J. Med. Chem.* **1989**, *32*, 2514.