Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 2145–2148
Bioorganic & Medicinal Chemistry Letters

Quinazolines revisited: search for novel anxiolytic and GABAergic agents

R. K. Goel,[a,*] Vipan Kumar[b] and M. P. Mahajan[b,*]

[a]Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, India
[b]Department of Applied Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

Received 9 December 2004; revised 4 February 2005; accepted 5 February 2005
Available online 18 March 2005

Abstract—A systematic approach through computer assisted design to identify novel quinazolines having anxiolytic and GABAergic activity has been reported.

1. Introduction

The γ-amino butyric acid (GABA) mediates the inhibitory neurotransmission in brain via $GABA_A$ and the $GABA_B$ receptors.[1–3] $GABA_A$ receptor has been implicated in a number of neurological diseases and ligands associated with it have been identified as potential therapeutic agents.[4] Hence, the pharmacotherapy of various neurological and psychiatric diseases such as generalized anxiety disorders, sleep disturbances, muscle spasms and seizure disorders involves the modulation of GABA-mediated synaptic transmission in CNS.[5–8] The pharmacological effects of the benzodiazepines (anxiolytic, anticonvulsant, muscle relaxant and sedative–hypnotic) make them the most important $GABA_A$ receptor-modulating drugs in clinical use.[9] As such the benzodiazepines were accidentally discovered during the pharmacological investigation of a series of quinazolines which themselves were shown to be inactive.[10] Subsequently, numerous studies were carried out on the refinement of anxiolytic activity of benzodiazepines and anticonvulsant activity of quinazolones. However, the GABAergic potential of substituted quinazolines has remained largely unexplored.

In the present study an attempt has been made to design, synthesize and evaluate some novel quinazolines as CNS depressants. The design of the title compounds was based on the biological activity predictions made by the computer software PASS (prediction of activity spectra for substances). This software illustrates the predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i) with the accuracy of prediction reported to be as high as 85%.[11,12] The design was initiated with unsubstituted quinazolines followed by the introduction of substituents at C-4 position on the basis of literary rationale. The PASS predictions for thirty variedly substituted quinazolines exhibited a favorable anxiolytic and GABA agonistic activity with aryl substituents at C-4 position. The phenyl substituent at C-4 still showed a better potential as compared to the other aryl substituents viz *p*-methoxyphenyl, *p*-chlorophenyl, *p*-*N*,*N*-dimethylamino phenyl and *p*-nitrophenyl. Therefore based on these predictions three title compounds (**3a**–**c**) have been selected for their synthesis and evaluation (Table 1).

2. Chemistry

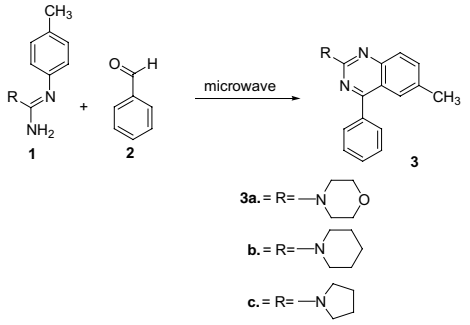
The desired quinazoline derivatives **3** were synthesized by the exposure of microwave radiations to a mixture

Table 1. The PASS prediction score compounds **3a**–**c**

Compound no.	Anxiolytic activity		$GABA_A$ receptor agonist	
	P_a	P_i	P_a	P_i
3a	0.693	0.010	0.458	0.075
3b	0.706	0.009	0.642	0.009
3c	0.708	0.009	0.411	0.068

Keywords: Quinazolines; Anxiolytic; GABAergic; Microwave.
* Corresponding authors. Fax: +91 183 2258819; e-mail: goelrk_us@yahoo.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.02.023



Scheme 1.

of *N*-*p*-tolyl guanidines **1**[13] and aldehyde **2** (power of 200 W for 13–15 min in 6–7 cycles of 2 min each) (Scheme 1). This method[14] is an improvization of our previously reported method,[15] that involved the microwave assisted aza-Wittig reaction of *N*-imidoylimino-phosphoranes with aldehyde. The present methodology bears the merits of reduced number of steps and better yields. The quinazolines so obtained were characterized on the basis of analytical data and spectral evidences.[16]

3. Pharmacology

3.1. Evaluation of anti-anxiety activity

The anxiety behavior was induced and assessed in albino mice using elevated plus maze. Group-housed mice were brought into the testing room and allowed to acclimate to the new environment for 30 min. The mice were placed in the center of elevated plus maze (EPM) and were allowed to explore EPM for 5 min. The parameters recorded are the number of entries and the average time spent in seconds in open arm of EPM during the test. Diazepam was used as reference standard. Animals were given the test compound (10, 25, and 50 mg/kg, i.p.) and diazepam (2.0 mg/kg i.p.) 30 min before the test. The significant increase in time spent and no of entries in the open arm was considered as anxiolytic activity.[17]

3.2. Evaluation of GABA agonistic activity

GABA agonistic activity of the test compounds has been evaluated as the protection offered by the test compounds in picrotoxin-induced chemo-convulsions in mice. Picrotoxin, a $GABA_A$ receptor antagonist was used to induce convulsions at a dose of 20 mg/kg, i.p. The delay in onset and reduction of severity of convulsions was considered as significant GABAergic activity. Animals were given the test compounds (50, 100 and 200 mg/kg, i.p.) and diazepam (8 mg/kg i.p.) 30 min before the picrotoxin challenge.[18]

3.3. Statistical analysis

The experimental data was analyzed using one way ANOVA followed by Dunnet test and $p < 0.05$ was considered significant.[17]

4. Experimental

Melting points were determined by open capillary using veego precision digital melting point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker AC-E 200 (200 MHz) spectrometers using TMS as an internal standard. Chemical shift values are expressed in parts per million downfield from TMS and *J* values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C NMR spectra were also recorded on a Bruker AC-200E (50.4 MHz) spectrometer in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-rapid elemental analyzer. The reactions were performed in a domestic microwave oven manufactured by National Panasonic model No. NN-S650WF.

5. Results and discussion

5.1. Anti anxiety activity

The compounds (**3a**–**b** and **c**) showed a dose dependent anxiolytic effect by increasing the number of entries and

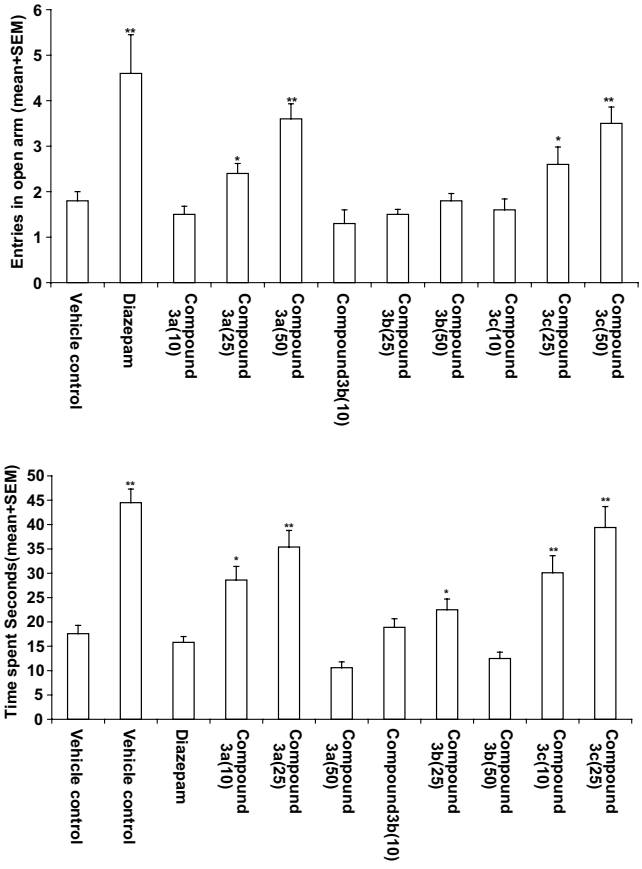


Figure 1. The comparative effect on the number of entries and average time spent in the open arm of the elevated plus maze. $*p < 0.05$ versus control, $**p < 0.01$ versus control (Dunnet's test).

average time spent in the open arms of the elevated plus maze. The significant effect was observed at a 50 mg/kg dose. The order of efficacy of the compounds was **3c** > **a** > **b** (Fig. 1).

5.2. GABAergic activity

The reversal of picrotoxin antagonism at $GABA_A$ receptor by the test compounds was utilized to evaluate the GABAergic activity. The test compounds **3a** and **c** showed a GABAergic activity by delaying the onset and decreasing the severity of picrotoxin-induced convulsions. The observed effect was dose dependent. The order of efficacy of the compounds was **3c** > **a** > **b** (Fig. 2).

Thus the PASS assisted design yielded quinazolines with refined structures over those tested earlier by Sternbach.[10] The inactivity of quinazolines tested earlier by Sternbach was further confirmed by PASS. The structures (**3a**–**b** and **c**) strongly predicted for the desired activity were synthesized. Pharmacological evaluation validated the predictions as the test compounds and showed a significant anxiolytic and GABAergic activity in elevated plus maze and Picrotoxin induced convulsions respectively. However the order of GABAergic activity was observed to be invariant with the PASS predictions in experimental results. The quinazoline having a C-2 pyrrolidine group proved to be more potent as compared to those possessing the morpholino and piperidino groups. Since most of the anxiolytic and GABAergic compounds showed increased exploration in the open arm in EPM and delay in the onset of picrotoxin induced convulsions, it is proposed that the test compounds may be acting via increasing GABA neurotransmission either directly or indirectly. Further investigations are underway to reveal the exact mechanism of action.

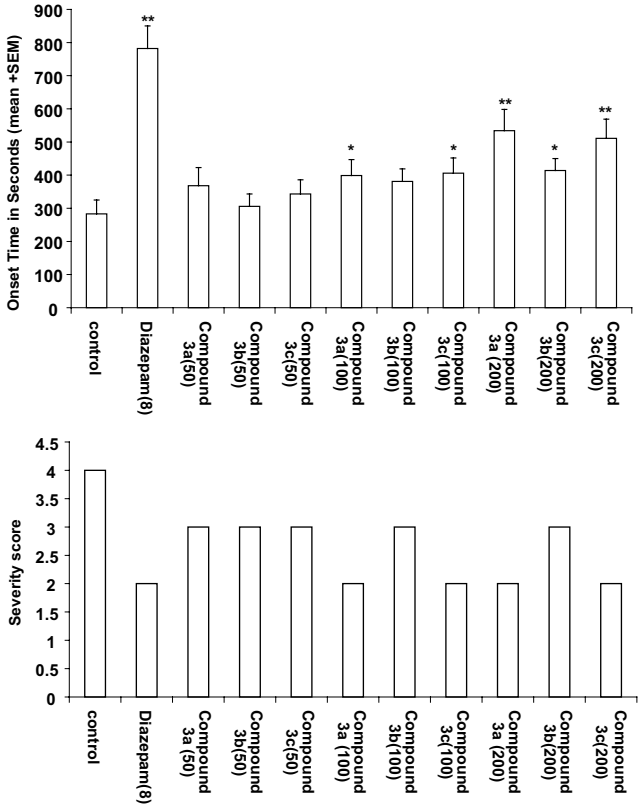


Figure 2. The comparative effect on the onset and severity of convulsions: severity score: 1 = jerks, 2 = jerks + straub tail, 3 = jerks + straub tail + tonic clonic convulsions, 4 = jerks + straub tail + tonic clonic convulsions + hind limb extension. $*p < 0.05$ versus control, $**p < 0.01$ versus control (Dunnet's test).

References and notes

1. Sieghart, W. *Trends Pharmacol. Sci.* **1992**, *13*, 446.
2. Sigel, E.; Barnard, E. A. *J. Biol. Chem.* **1984**, *259*, 7219.
3. Stephenson, F. A. *Biochem. J.* **1995**, *310*, 1.
4. (a) Frølund, B.; Ebert, B.; Kristiansen, U.; Liljefors, T.; Larsen, P. K. *Curr. Top. Med. Chem.* **2002**, *2*, 817; (b) Tsang, S. Y.; Xue, H. *Curr. Pharm. Des.* **2004**, *10*, 1035.
5. Johnston, G. A. *Pharmacol. Ther.* **1996**, *69*, 173.
6. Haefely, W. E. *Eur. Arch. Psychiatry Neurol. Sci.* **1989**, *238*, 294.
7. Olsen, R. W. *J. Neurochem.* **1981**, *37*, 1.
8. Sieghart, W. *Pharmacol. Rev.* **1995**, *47*, 181.
9. Doble, A.; Martin, I. L. *The $GABA_A$/Benzodiazepine Receptor as Target for Psychoactive Drugs*; Springer: Heidelberg, Germany, 1996.
10. Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
11. www.ibmh.msk.su.
12. Poroikov, V.; Filimonov, D.; Borodina, Yu.; Lagunin, A.; Kos, A. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1349.
13. McNeil Lab.; GB 1573532; **1976**; DE 2711757; *Chem. Abstr.*; EN; 88; 37603.
14. Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533.
15. Kumar, V.; Sharma, A. K.; Mahajan, M. P. *Synth. Commun.* **2004**, *34*, 49.
16. *6-Methyl-4-phenyl-2-morpholino-4-yl-quinazoline* (**3a**): yield 78%, mp 147–148 °C, IR (KBr) ν 1595 and 1568 cm^{-1} (C=N). Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.97; H, 6.38; N, 13.48 δ_H (200 MHz): 2.41 (s, 3H, $-CH_3$); 3.81–3.86 (m, 4H, $-CH_2-N-CH_2-$); 3.98–4.02 (m, 4H, $-CH_2-O-CH_2-$); 7.54–7.62 (m, 6H, ArH); 7.74–7.76 (m, 2H, ArH): δ_c (50.4 MHz) 21.37 ($-CH_3$); 44.56 ($-CH_2-N-CH_2-$); 66.97 ($-CH_2-O-CH_2-$); 117.7, 126.0, 128.3, 128.5, 129.5, 129.7, 130.0, 131.3, 135.7, 137.9, 160.9, 168.7. *m/z* 305 (M^+).
6-Methyl-4-phenyl-2-piperidin-1-yl-quinazoline (**3b**): yield 80%, mp 137–138 °C, IR (KBr) ν 1593 and 1570 cm^{-1} (C=N). Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.28; H, 6.83; N, 13.89 δ_H (200 MHz): 1.72–1.77 (m, 6H, $-CH_2-CH_2-CH_2-$); 2.38 (s, 3H, $-CH_3$); 3.97–4.02 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH); 7.70–7.74 (m, 2H, ArH) δ_c (50.4 MHz): 19.3 ($-CH_3$); 25.2 ($-CH_2$); 26.0 ($-CH_2-CH_2-$); 44.4 ($-CH_2-N-CH_2-$); 117.0, 118.3, 120.4, 122.7, 123.4, 125.2, 127.9, 130.0, 135.3, 145.3, 157.7, 166.3. *m/z* 303 (M^+).
6-Methyl-4-phenyl-2-pyrrolidin-1-yl-quinazoline (**3c**): yield 80%, mp 140–141 °C, IR (KBr) ν 1596 and 1565 cm^{-1} (C=N). Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 79.02; H, 6.68; N, 14.28 δ_H (200 MHz): 2.01–2.07 (m, 4H, $-CH_2-CH_2-$); 2.37 (s, 3H, $-CH_3$); 3.70–3.76 (m, 4H, $-CH_2-N-CH_2-$); 7.50–7.58 (m, 6H, ArH);

7.70–7.73 (m, 2H, ArH); δ_c (50.4 MHz): 21.1 ($-CH_3$); 24.9 ($-CH_2-CH_2-$); 45.7 ($-CH_2-N-CH_2$); 117.3, 118.2, 120.1, 122.5, 123.3, 125.4, 127.7, 130.2, 135.6, 145.1, 157.9, 166.6. *m/z* 289 (M^+).

17. Fernandes, C.; File, S. E. *Pharmacol. Biochem. Behav.* **1996**, *54*, 31.
18. Kenji, Y.; Youko, W.; Yutaka, A.; Akihiro, O. *Biol. Pharm. Bull.* **2001**, *24*, 1068.