Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 5179–5181
Bioorganic & Medicinal Chemistry Letters

Microwave assisted synthesis of 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile as a new class of serotonin 5-HT$_3$ receptor antagonists

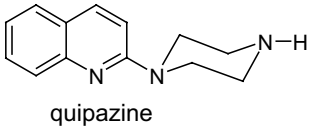
Radhakrishnan Mahesh,* Ramachandran Venkatesha Perumal and Pandi Vijaya Pandi

Pharmacy Group, Birla Institute of Technology and Science, Pilani 333 031, Rajasthan, India

Received 19 June 2004; revised 24 July 2004; accepted 26 July 2004
Available online 1 September 2004

Abstract—A series of novel 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile **6** were prepared by microwave irradiation and conventional heating. The intermediate, 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile **3**, was prepared from 2-aminonicotinaldehyde **1** and ethyl cyanoacetate **2** in the presence of piperidine under solvent free condition. The synthesized compounds were evaluated for 5-HT$_3$ antagonisms in longitudinal muscle-myenteric plexus (LMMP) preparation from Guinea pig ileum against 5-HT$_3$ agonist, 2-methyl-5-HT. Among the compounds tested, 2-(4-allylpiperazin-1-yl)-1,8-naphthyridine-3-carbonitrile **6d** showed most favorable 5-HT$_3$ receptor antagonism in the Guinea pig ileum.

Among the serotonin (5-Hydroxytryptamine, 5-HT) family, 5-HT$_3$ receptor subtype has gained much attention because of the clinical use of 5-HT$_3$ receptor antagonists (RAs) in the treatment of cancer chemotherapy-induced nausea and vomiting (CNIV)[1] and also in postoperative nausea and vomiting (PONV).[2] Moreover, a number of preclinical studies suggest that 5-HT$_3$ RAs can be used in the treatment of various CNS disorders.[3] Hibert et al.[4] proposed the pharmacophore of 5-HT$_3$ RAs, which consists of three components: an aromatic ring, a carbonyl-containing linking moiety and a basic center in a specific spatial arrangement. Based on this pharmacophore, a number of molecules have been reported so far.[5,6] Rosen et al.[7] hypothesized that the carbonyl moiety is not essential for high affinity. This component could serve as a hydrogen-bonding region. One of the 5-HT$_3$ ligand that proved this concept is quipazine (Fig. 1) which exhibits 5-HT$_3$ antagonistic property[8] as well as agonist character in some preparations.[9] Although quipazine lacks a carbonyl group, the negative electrostatic potential energy field generated by the quinoline nitrogen may resemble that generated by a carbonyl group.[10] Indeed, Hibert et al.[4] anticipated that the lone pair of the quipazine nitrogen may play a role equivalent to the carbonyl oxygen. Based on this hypothesis, different heteroaryl piperazines viz., piperazinylquinoxaline,[11] piperazinylbenzothiazole,[12] piperazinylbenzoxazole,[12] and piperazinylbenzimidazole[13] have been reported so far. Among these derivatives piperazinylquinoxaline showed good 5-HT$_3$ antagonistic activities in the isolated Guinea pig ileum as well as in radio ligand binding studies.[11] Most of the 5-HT$_3$ RAs, which were prepared on the basis of the pharmacophore proposed by Hibert et al.,[4] contains chiral centers, so the synthetic cost is high. Only limited work has been done on heteroaryl piperazines as 5-HT$_3$ RAs. As a result, we undertook a study to prepare the title compounds (heteroaryl piperazines), which could serve as better 5-HT$_3$ RAs than the currently available ones.



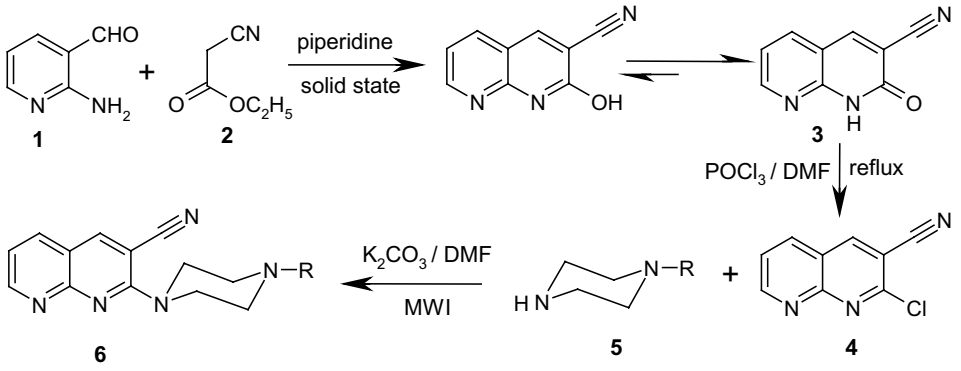
quipazine

Figure 1.

The starting material, 2-aminonicotinaldehyde **1**, was prepared according to the reported method.[14] The intermediate, 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile **3**, was prepared by triturating a mixture of 2-aminonicotinaldehyde **1**, ethyl cyanoacetate **2**, and

Keywords: 1,8-Naphthyridine; Serotonin 5-HT3 antagonists.
* Corresponding author. Tel.: +91 1596 245073; fax: +91 1596 244183; e-mail: rmahesh@bits-pilani.ac.in

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.07.060



Scheme 1.

piperidine in a mortar and pestle at room temperature for about 10 min. Completion of reaction was marked by the change of state from solid to semi solid and reconversion to solid, which was also confirmed by TLC. The solid thus obtained was treated with water, filtered, and recrystallized from DMF–water mixture to give **3**.[15] The compound **3**, was refluxed with phosphorus oxychloride in the presence of catalytic amount of DMF for 1 h. It was then cooled to room temperature and treated with ice water. The resulting solution was basified slowly under cooling with aqueous NaOH (40%). The separated product was filtered, washed with water, dried, and recrystallized from DMF–water mixture to give **4**.[16] Microwave irradiation of **4**, with appropriate piperazines in the presence of K_2CO_3 in DMF for about 5 min. gave the corresponding nucleophilic substituted product **5** (Scheme 1). When this reaction was carried out by conventional heating (oil bath), the reaction was complete (monitored by TLC) in 8–10 h. The product obtained by both the methods was identical in all aspects (mp, mixed mp, co-TLC and super imposable IR). Almost similar yields were obtained by both the methods. It was observed that the reaction was simple and accelerated greatly when carried out in microwave environment. All the synthesized compounds were characterized by spectral (IR, ^{1}H NMR, and mass) and elemental analysis data. IR spectral analysis of the final compounds (**6a–l**) showed strong absorption bands at $\sim$2200 cm^{-1} and $\sim$1600 cm^{-1} due to C=N and C=N functions, respectively. In ^{1}H NMR spectra, methylene protons (cyclic) adjacent to N^1 nitrogen of piperazine showed triplet at δ 3.87–4.13 whereas methylene protons (cyclic) adjacent to N^4 nitrogen of piperazine showed triplet in the range of δ 2.62–3.79. The final compounds (**6a–l**) showed the following ^{1}H NMR signals for 1,8-naphthyridinyl moiety; C_4–H: $\delta \sim 8.4$ (s), C_5–H: $\delta \sim 8.00$ (d), C_6–H: $\delta \sim 7.3$ (dd) C_7–H: $\delta \sim 9.00$ (d). Elemental (CHN) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). Physical data of the final compounds is represented in Table 1.

The Institutional Animal Ethics Committee of the Birla Institute of Technology and Science, Pilani, India, approved experimentation on animals (Protocol No. IAEC/RES/6, dated 21.04.03). Male Dunkin Hartley Guinea pigs (250–300 g; Hissar Agricultural University, Hissar, Haryana, India) were sacrificed by cervical dislocation. The abdomen was cut open and a length of ileum was excised about 2 cm from the ileo–caecal junction. The longitudinal muscle-myenteric plexus (LMMP), 3–4 cm in length was prepared and mounted as described

Table 1. Physical and pharmacological data of compounds **6a–l**

Compd no.	R	Yield (%)	Mp °C (Recryst. solvent[a])	Mol. formula[b]	Mol. wt.[c]	Antagonism to 2-methyl-5-HT pA_2[d]
6a	–H	74	226–227 (E)	$C_{13}H_{13}N_5$	239	6.5
6b	$-CH_3$	82	152–154 (E)	$C_{14}H_{15}N_5$	253	7.4
6c	$-C_2H_5$	76	130–132 (E)	$C_{15}H_{17}N_5$	267	7.1
6d	$-CH_2-CH=CH_2$	75	176–178 (E)	$C_{16}H_{17}N_5$	279	8.2
6e	$-C_6H_5$	75	158–160 (E–A)	$C_{19}H_{17}N_5$	315	5.7
6f	$-CH_2C_6H_5$	81	151–152 (E)	$C_{20}H_{19}N_5$	329	5.1
6g	*o*-OCH_3–C_6H_4	74	223–225 (E–A)	$C_{20}H_{19}N_5O$	345	5.4
6h	*m*-OCH_3–C_6H_4	82	150–152 (A–W)	$C_{20}H_{19}N_5O$	345	6.0
6i	*p*-OCH_3–C_6H_4	77	142–143 (E)	$C_{20}H_{19}N_5O$	345	4.9
6j	*p*-NO_2–C_6H_4	84	239–240 (A–C)	$C_{19}H_{16}N_6O_2$	360	3.8
6k	*p*-Cl–C_6H_4	76	169–171 (E–A)	$C_{19}H_{16}N_5Cl$	349	2.9
6l	2-Pyridyl	80	172–174 (E)	$C_{18}H_{16}N_6$	316	3.9
Ondansetron						6.9

[a] Abbreviations for the solvents used are as follows: A = acetone, C = chloroform, E = ethanol, and W = water.
[b] Elemental (C, H, and N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%).
[c] Molecular weight determination by mass spectral analysis.
[d] Values are the means from three separate experiments. SE was less than 10% of the mean.

by the literature method.[17] The tissue was equilibrated for 30 min. under a resting tension of 500 mg and constant aeration in a 40 mL organ bath containing Tyrode solution maintained at ca. 37 °C. Noncumulative concentrations of 2-methyl-5-HT (Tocris, UK) were added with a 15 min. dosing cycle (to prevent desensitization) and left in contact with the tissue until the maximal contraction had developed. To study the antagonist effect of the test compounds on the response evoked by 2-methyl-5-HT, the compounds were added to the organ bath and left in contact with the tissue for at least 10 min prior to the addition of 2-methyl-5-HT. The contractions were recorded using a T-305 Force transducer coupled to a Student's physiograph (Bio Devices, Ambala, India). Antagonism was expressed in the form of pA_2 values, which were graphically determined.[18] The pA_2 values of the test compounds were compared with the standard antagonist Ondansetron (Natco Pharma, Hyderabad, India). The observed pharmacological data is represented in the Table 1.

In the present study, we have demonstrated the synthesis and 5-HT_3 receptor antagonistic activity of novel 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile in the isolated Guinea pig ileum. All the test compounds showed 5-HT_3 receptor antagonistic activities. Compound **6a** (with no substitution at N^4 piperazine) showed good antagonism (pA_2 6.5); with increased liphophilicity (i.e., methyl group, **6b**) activity increased (pA_2 7.4). Further increase in liphophilicity (i.e., ethyl group, **6c**) decreased the activity (pA_2 7.1), whereas substitution with allyl group (compound **6d**) showed most favorable antagonism (pA_2 8.2). Placement of bulkier groups like aryl/substituted aryl at N^4 piperazine (compounds **6e–l**) decreased the activity. In addition, electron withdrawing substituents at aryl group of N^4 piperazine (compounds **6j–l**) showed the least activity among the aryl derivatives. Compounds **6b**, **6c**, and **6d** showed higher antagonism than Ondansetron (pA_2 6.9) in the isolated Guinea pig ileum. Hence further studies in these compounds are planned to obtain clinically useful agents.

Acknowledgements

This research was supported by grants from the University Grants Commission, New Delhi, India. We are thankful to the CSIR, New Delhi, India for awarding SRF to one of the authors (R.V.P.). We are grateful to the Birla Institute of Technology and Science, Pilani, for providing necessary infrastructure to carry out this research and the RSIC, Punjab University, Chandigarh, India, for providing spectral and analytical data.

References and notes

1. Karim, F.; Roerig, S. C.; Saphier, D. *Biochem. Pharmacol.* **1996**, *52*, 685.
2. Negus, B.; Markocic, S. *Acute Pain* **2003**, *5*(2), 63.
3. Jones, B. J.; Blackburn, T. P. *Pharmacol. Biochem. Behav.* **2002**, *71*, 555.
4. Hibert, M. F.; Hoffmann, R.; Miller, R. C.; Carr, A. A. *J. Med. Chem.* **1990**, *33*, 1594.
5. Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.
6. Ohta, M.; Suzuki, T.; Koide, T.; Matsuhisa, A.; Furuya, T.; Miyata, K.; Yanagisawa, I. *Chem. Pharm. Bull.* **1996**, *44*(5), 991.
7. Rosen, T.; Nagel, A. A.; Rizzi, J. P.; Ives, J. L.; Daffeh, J. B.; Ganong, A. H.; Guarino, K.; Heym, J.; McLean, S.; Nawadowski, J. T.; Schmidt, A. W.; Seeger, T. F.; Siok, C. J.; Vincent, L. A. *J. Med. Chem.* **1990**, *33*, 2715.
8. Round, A.; Wallis, D. I. *Neuropharmacology* **1987**, *26*, 39.
9. Emerit, M. B.; Riad, M.; Fattaccini, C. M.; Hammon, M. *J. Neurochem.* **1993**, *60*, 2059.
10. Laguerre, M.; Dubost, J.-P.; Kummer, E.; Carpy, A. *Drug Des. Discov.* **1994**, *11*, 205.
11. Monge, A.; Palop, J. A.; DelCastillo, C.; Caldero, J. M.; Roca, J.; Romero, G.; Del Rio, J.; Lasheras, B. *J. Med. Chem.* **1993**, *36*, 2745.
12. Monge, A.; Pena, M. D. C.; Palop, J. A.; Caldero, J. M.; Roca, J.; Romero, G.; DelRio, J.; Lasheras, B. *J. Med. Chem.* **1994**, *37*, 1320.
13. Orjales, A.; Mosquera, R.; Rabeaga, L.; Rodes, R. *J. Med. Chem.* **1997**, *40*, 586.
14. Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1974**, *39*(5), 720.
15. 90% Yield; mp > 300 °C. IR (KBr) (cm^{-1}): 3335 (NH), 2216 (C≡N), 1671 (C=O), 1593 (C=N). ^1H NMR (300 MHz) (DMSO-d_6) (δ) ppm: 7.29 (dd, 1H, J=7.5, 8.5 Hz, C_6–H), 7.98 (d, 1H, J = 7.5 Hz, C_5–H), 8.39 (s, 1H, C_4–H), 8.95 (d, 1H, J = 8.5 Hz, C_7–H), 12.01 (s, 1H, NH). Anal. Calcd for $C_9H_5N_3O$: C, 63.16; H, 2.92; N, 24.56. Found C, 63.08; H, 2.76; N, 24.68.
16. 79% Yield; mp > 300 °C. IR (KBr) (cm^{-1}): 2222 (C≡N), 1601 (C=N), 810 (C–Cl). ^1H NMR (300 MHz) (DMSO-d_6) (δ) ppm: 7.31 (dd, 1H, J = 7.5, 8.5 Hz, C_6–H), 7.80 (d, 1H, J = 7.5 Hz, C_5–H), 8.36 (s, 1H, C_4–H), 9.01 (d, 1H, J = 8.5 Hz, C_7–H). Anal. Calcd for $C_9H_4N_3Cl$: C, 56.99; H, 2.11; N, 22.16. Found. C, 56.63; H, 1.91; N, 22.41.
17. Paton, W. D. M.; Zar, A. M. *J. Physiol.* **1968**, *194*, 13.
18. Mac Kay, D. *J. Pharm. Pharmacol.* **1978**, *30*, 312.