Bioorganic & Medicinal Chemistry Letters, Vol.1, No.11, pp. 571-574, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

STUDIES ON QUINAZOLINONES. 3: [1] NOVEL AND EFFICIENT ROUTE TO THE SYNTHESIS OF CONFORMATIONALLY RESTRICTED ANALOGUES OF KETANSERIN AND SGB-1534 AS ANTIHYPERTENSIVE AGENTS

Ji-Wang Chern*, Chia-Yang Shiau and Guan-Yu Lu

Institute of Pharmacy and Medical Laboratories, National Defense Medical Center, P. O. Box 90048-512, Taipei, Taiwan, Republic of China (100)

(*Received* 5 *August* 1991)

Abstract: Bromocyclization of N-allyl quinazoline derivatives with N-bromosuccinimide results in the formation of 2,3-dihydroimidazo[1,2-c]quinazoline derivatives. Substitution reactions of the resulting angularly tricycles led to discover a novel potent antihypertensive agent.

Quinazoline ring system constitutes a class of important antihypertensive agents. Recently, SGB-1534 [2] and ketanserin[3,4] have been proved effective in lowering blood pressure acting as a α_1-antagonist and serotonin-S_2 antagonist respectively. This draws us much attention to the fact that such a small chemically structural change in the side chain between ketanserin and SGB-1534 causes a quite different pharmacological mode of action. During the course of our synthetic studies on fused quinazoline ring system, it is of our considerable interest to synthesize the angularly tricyclic condensed quinazoline derivatives of the general structure shown in figure 1 which would possess a rigid structural feature necessary to elicit the biological activities of both ketanserin and SGB-1534 and might provide a better binding to the receptor site. To our best knowle, these types of compounds have not been investigated. This paper would like to describe our efforts towards the synthesis of the conformationally restricted analogues of these two compounds.

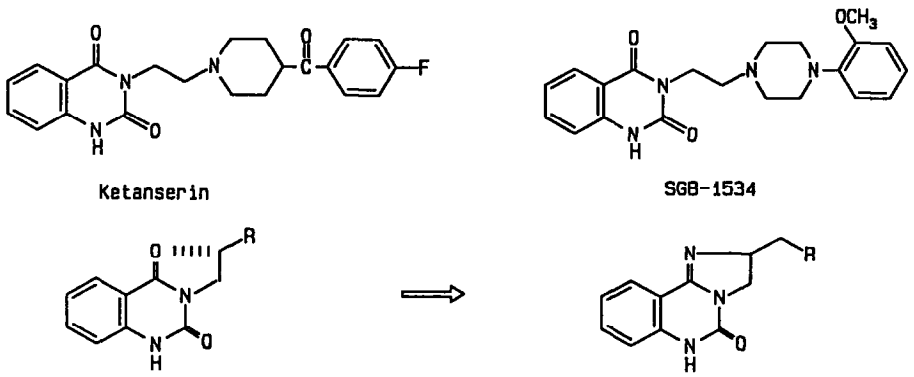
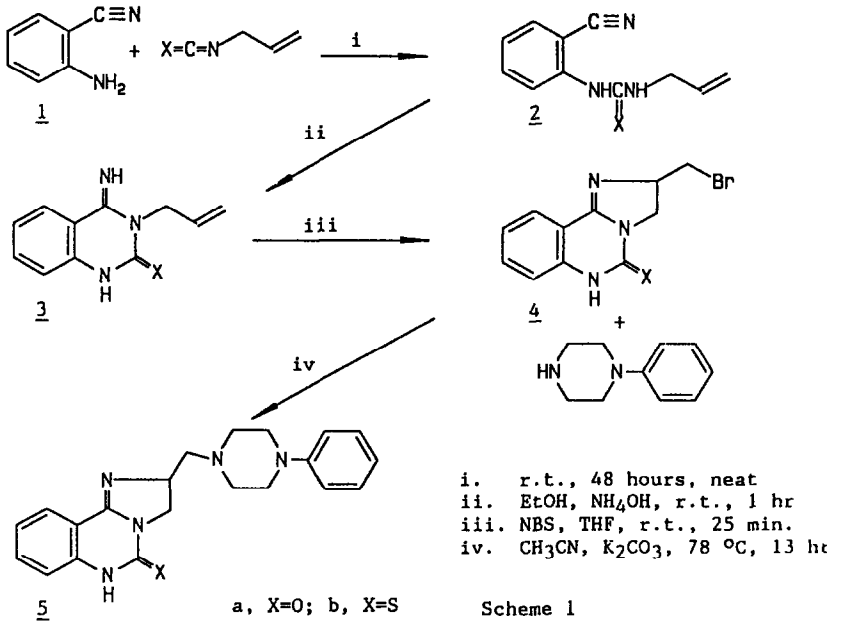


Figure 1: Conformationally rigid analogues of ketanserin and SGB-1534

We thought that compound 4 are the key intermediates toward the synthesis of target compound 5. It has been well documented that the halocyclization of the remote functional group of the alkene lead to various heterocycles.[5] For example, halocyclizations to lactams[6], lactones[7], imidazolines[8] and dihydrothiazoles[9] have been studied. We reasoned that in the case of N-allyl heterocycles such as 3-allyl-4-imino-quinazolin-2(1H)-one (3a), halocyclization can occur either with nitrogen of 4-imino group participation to afford angular 2-bromomethyl-2,3-dihydro-imidazo[1,2-c]quinazolin-5(6H)-one (4a) or with oxygen participation to form linear 2-bromo-methyl-5-imino-2,3-dihydro-oxazolo[2,3-b]quinazoline. Thus, compound 3a was prepared in 84 %

yield by an initial condensation of anthranilonitrile (1) with allyl isocyanate and then ring closure of the resulting urea 2a was effected by using ammonia hydroxide. Compound 3a was subjected to bromocyclization with NBS in acetonitrile at room temperature and the solid was collected by



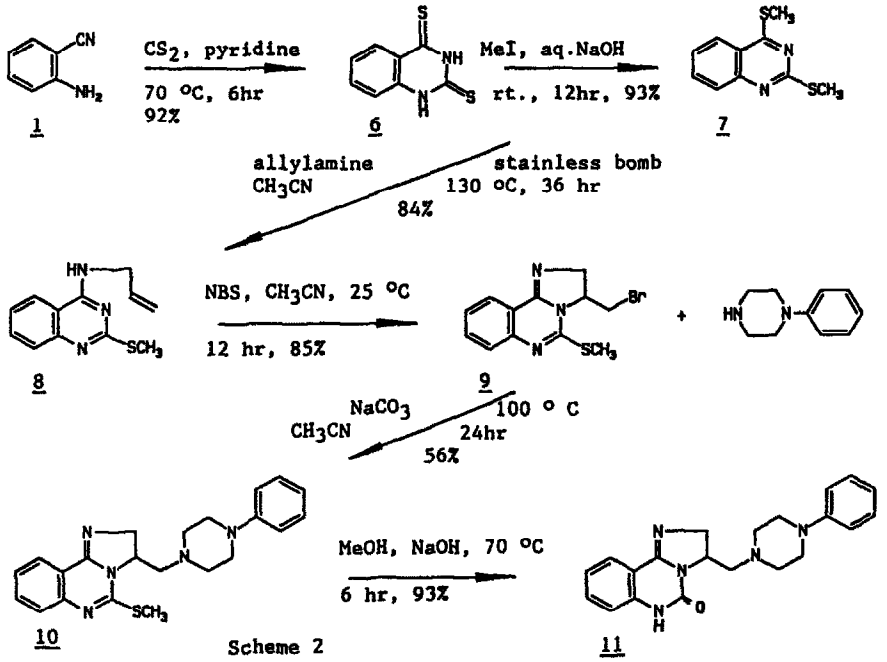
a, X=O; b, X=S

Scheme 1

filtration. The infrared spectrum of the product illustrated a strong absorption peak at 1687 (C=O) cm^{-1}, indicating a carbonyl group exisiting in the molecule. Thus the structure of the product was assigned to be the angular 4a[10] instead of the linear tricycle. Subsequent treatment of 4a with 1-phenylpiperazine in acetonitrile in the presence of sodium carbonate afforded 2-(4-phenyl-1-piperazinyl)methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one (5a)[11] in 76% yield (scheme 1). Similarly, 3-allyl-4-imino-quinazolin-2(1H)-thione (3b) was prepared in 44% yield by a treatment of 1 with allyl isothiocyanate and then ring closure of the resulting thioureido 2b with ammonia hydroxide. A treatment of 3b with N-bromosuccinimide afforded 3-bromomethyl-2,3-dihydro-imidazo[1,2-c]quinazolin-5(6H)-thione hydrobromide (4b)[12] in 40% yield. No linear sulfur tricycle was observed neither. Although the early literature[9] described that iodocyclization of N-allyl thioureas led efficiently to the formation of dihydrothiazoles, however, the synthesis of 4b was achieved through the 4-imino nitrogen addition to the allyl group instead of the participation of neighbouring 2-sulfur atom and the structure of 4b was confirmed by elemental analysis, ^{13}C-NMR and Mass spectral data. Substitution reaction of compound 4b with 1-phenylpiperazine under above condition furnished 2-(4-phenyl-1-piperazinyl)methyl-2,3-dihydroimidazo[1,2-c] quinazolin-5(6H)-thione (5b)[13] in 76% yield.

To elaborate and study the hypotensive effect of the side chain at 3-position of 2,3-

dihydroimidazo[1,2-c]quinazolin-5(6H)-one, N-allyl amidine such as 4-allylamino-2-methylthio-quinazoline (8) was subjected to perform a bromocyclization with NBS as well. To test this possibility, 1 was treated with carbon disulfide in pyridine, following by methylation with methyl iodide and then reacting with allylamine in stainless bomb at 130 °C to give 4-allylamino-2-methyl-thioquinazoline (8). Compound 8 was then treated with NBS under similar condition affording 3-



Scheme 2

bromomethyl-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazoline (9)[14] in 85% yield. 3-(4-Phenyl-1-piperazinyl)methyl-5-methylthio-2,3-dihydro-imidazo[1,2-c]quinazoline (10)[15] was obtained by reacting 9 with 4-phenyl-1-piperazine.(scheme 2) When compound 10 was heated to reflux in methanol in the presence of sodium hydroxide for 6 hours, 3-(4-phenyl-1-piperazinyl)-methyl-2,3-dihydro-imidazo[1,2-c]quinazolin-5(6H)-one (11)[16] was obtained in 93% yield.

In conclusion, a novel and efficient route to the synthesis of conformationally restricted analogues of ketanserin and SGB-1534 was developed. These compounds showed very potent anihypertensive activity through mediating the α_1-adrenoreceptor. Compound 5a is the most potent antihypertensive agent with ED_{50} about 0.25 mg/Kg and lasted more than 4 hours after intravenious administration to anesthetized rat. [17] The synthesis of various heterocycles by this approach is under active investigation in our laboratories and the detailed SAR and pharmacological results will be published elsewhere.

Acknowledgement: This investigation was supported by a research grant from National Science Council of the Republic of China (grant No. NSC79-0412-B016-143).

References and notes:

1. Previous paper in this series : Shiau, C.-Y.; Chern, J.-W.; Liu, K.-C.; Chan, C.-H.; Yen, M.-H.; Cheng, M.-C.; Wang, Y. *J. Heterocyclic Chem.*, **1990**, *27*, 1467.
2. Nagano, H. et al. Eur. Pat. 89 065, 1983, Chugai Pharmaceutical Co., Ltd; *Chem. Abstr.*, **1984**, *100*, 6547p.
3. De Cree , J. ; Verhaegen, H. ; Symoens, J. *Lancet I*, **1981**, 1161.
4. Janssen, P.A. J. *J. Cardiovasc. Pharmacol.*, **1985**, *7* (suppl. 7), S2 .
5. Bartlett, P. A. *"Asymmetric Synthesis"* Ed. J. D. Morrison, Academic Press, Orlando, **1984**, Vol. *3*, Part B, P. 411.
6. Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233.
7. Toshimitsu, A.; Terao, K.; Uemura, S. *Tetrahedron Lett.* **1984**, *25*, 5917.
8. a) Bruni, E.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron Lett.* **1989**, *30*, 1679. b) Hunt, P. A.; May, C.; Moody, C. J. *Tetrahedron Lett.* **1988**, *29*, 3001.
9. Creeke, P. I.; Mellor, J. M. *Tetrahedron Lett.* **1989**, *30*, 4435.
10. Compound 4a: mp 213-214 °C. IR (KBr): 1687 (C=O), 1625 (C=N/C=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.67(m, 2H, CH_2), 3.74 (q, 1H, CH), 3.94 (t, 1H, CH), 4.57 (m, 1H, =CH), 7.07 (q, 2H, Ar-H), 7.51 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.65 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 47.80, 64.16, 110.27, 115.13, 122.23, 125.80, 133.59, 139.97, 147.47, 153.98, 206.07. Anal. Calcd for $C_{11}H_{10}N_3OBr$: C, 47.16; H, 3.59; N, 15.00. Found: C, 47.09; H, 3.41; N, 14.90.
11. Compound 5a: mp 257-258 °C. ms:m/z 361 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ 2.43-2.73 (m, 7H, CH_2), 3.11 (t, 3H, CH_2), 3.65 (q, 1H, CH), 3.91 (t, 1H, CH), 4.41 (m, 1H, CH), 6.75 (t, 1H, Ar-H), 6.91 (d, 2H, Ar-H), 7.06 (q, 2H, Ar-H), 7.17 (q, 2H, Ar-H), 7.48 (p, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.53 (s, 1H, NH). Anal. Calcd for $C_{21}H_{23}N_5O$: C, 69.78; H, 6.41; N, 19.38. Found: C, 69.79; H, 6.45; N, 19.37.
12. Compound 4b: mp >300 °C. IR (KBr): 1660 (C=S), 1599, 1568 cm^{-1};^1H NMR (300 MHz, DMSO-d_6): δ 3.87-4.03(m, 2H, CH_2), 4.54-4.73(m, 3H, CH & CH_2), 7.66-7.71 (t, 2H, Ar-H), 7.97-8.02 (m, 1H, Ar-H), 8.54 (d, 1H, Ar-H), 9.80 (s, 1H, NH), 10.50 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.42, 42.58, 54.27, 112.08, 125.11, 126.85, 127.55, 137.00, 146.89, 155.25, 157.61.; ms:m/z, 297 (M^++1), 295 (M^+-1), 216(M^+-80), 202(M^+-94). Anal. Calcd for $C_{11}H_{10}N_3SBr{\cdot}HBr$ (377.10): C, 35.04; H, 2.94; N, 11.14. Found: C, 35.14; H, 3.01; N, 10.94.
13. Compound 5b: mp 257-258 °C. ms:m/z 361 (M^+). ^1H NMR (300 MHz, DMSO-d_6): δ 2.55-2.79 (m, 6H, 3 CH_2), 3.11-3.12 (m, 4H, 2 CH_2), 4.12-4.16 (m, 1H, CH), 4.30-4.42 (m, 2H, CH_2), 6.77 (t, 1H, J=7.2 Hz, Ar-H), 6.92 (d, 2H, J=8.0 Hz, Ar-H), 7.17-7.30 (m, 4H, Ar-H), 7.53 (t, 1H, J=7.4 Hz, Ar-H), 8.12 (d, 1H, J=8.2 Hz, Ar-H), 11.04 (s, 1H, NH).^{13}C NMR (75 MHz, DMSO-d_6): δ 29.43, 48.14, 51.91, 52.67, 61.18, 115.33, 118.75, 124.75, 124.92, 125.60, 128.81, 132.41, 145.39, 150.86, 159.50, 179.22 (C=S).
14. Compound 9: mp 162-163 °C; ^1H NMR (300 MHz, DMSO-d_6): 2.78 (s, 3H, CH_3), 4.00-4.43 (m, 4H, 2 CH_2), 5.45-5.49 (m, 1H, CH), 7.68-7.73 (m, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 8.06 (t, 1H, Ar-H), 8.38 (d, 1H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6): 13.02, 35.80, 57.37, 59.08, 116.77, 124.98, 125.36, 125.48, 133.06, 145.75, 152.63, 153.69. ms: m/z 310 (M^+), 309 (M^+-1). Anal. Calcd for $C_{12}H_{12}N_3BrS$ (310.21): C, 46.46; H, 3.90; N, 13.55. Found: C, 46.60; H, 3.88; N, 13.70.
15. Compound 10: mp 133-134 °C; ^1H NMR (300 MHz, DMSO-d_6): 2.48-2.52 (m, 2H, CH_2), 2.58 (s, 3H, CH3), 2.68-2.72 (m, 4H, 2 CH2), 3.04-3.16 (m, 4H, 2 CH_2), 3.89-4.08 (m, 2H, CH_2), 4.48-4.55 (m, 1H, CH), 6.75 (t, 1H, Ar-H), 6.73-7.84 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6): 13.13, 48.13, 53.11, 55.87, 58.81, 59.25, 115.35, 116.85, 118.79, 124.81, 125.18, 125.46, 128.87, 132.91, 145.99, 150.91, 152.42. 154.11; ms: m/z 391 (M^+). Anal. Calcd for $C_{22}H_{25}N_5S$ (391.51): C, 67.49; H, 6.43; N, 17.89. Found: C, 67.44; H, 6.48; N, 17.72.
16. Compound 11: mp 252-253 °C; ^1H NMR (300 MHz, DMSO-d_6): 2.49-2.84 (m, 6H, 3 CH_2), 3.10 (m, 4H, 2 CH_2), 3.84-4.08 (m, 2H, CH_2), 4.48 (m, 1H, CH), 6.75 (t, 1H, Ar-H), 6.90 (m, 1H, Ar-H), 7.03-7.10 (m, 2H, Ar-H), 7.16-7.21 (m, 2H, Ar-H), 7.47 (t, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 10.50 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 48.18, 53.25, 53.68, 58.44, 59.16, 111.54, 115.03, 115.29, 118.71, 122.15, 125.56, 128.83, 132.99, 139.71, 148.10, 150.95, 152.49.; ms: m/z 361 (M^+). Anal. Calcd for $C_{21}H_{23}N_5O$ (361.45): C, 69.78; H, 6.41; N, 19.38. Found: C, 69.78; H, 6.43; N, 19.33.
17. Yen, M.-H. et. al. (private communication).