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Synthesis and Anticonvulsant Properties of BW A78U Structurally-Related Compounds

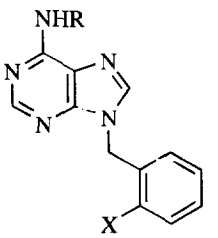
Laurent Désaubry[1], Camille G. Wermuth[1], Annie Boehrer[2], Christian Marescaux[2] and Jean-Jacques Bourguignon[1]*.

[1] Laboratoire de Pharmacochimie Moléculaire
[2] Laboratoire de Neurophysiologie et Biologie des Comportements
Centre de Neurochimie, 5, rue Blaise Pascal, 67084 Strasbourg Cedex, France.

Abstract: Several analogues of the anticonvulsant BW A78U **1** have been synthesized and tested for their anticonvulsant properties, providing preliminary data concerning the structural requirements for this family of drugs.

Currently marketed antiepileptic drugs do not often provide complete control of seizures and are associated with a wide range of side effects[1]. Due to the need for better antiepileptic drugs, a program was initiated to discover and develop improved antiepileptic agents. The potent anticonvulsant purine BW A78U **1** (Figure I) emerged from this program[2-6]. It was reported to exhibit very potent anticonvulsant properties in the rat even when administered orally with a very low toxicity . It exhibits also potent anxiolytic effects in mice at doses lacking in sedative effects[7]. Compared with commonly used anticonvulsants, BW A78U has a unique structure that provides a novel lead for the development of improved agents for the treatment of seizure disorders and anxiety The mechanism of action of BW A78U is yet unknown, however, its action is not mediated through central benzodiazepine, nor adenosine receptors[7].

A first evaluation of the effects of substituents in the purine ring of BW A78U **1** showed that the anticonvulsant properties are associated with the presence in its structure of 9-benzyl and 6-methylamino groups[3-6]. However the N(6)-unsubstituted **2** showed significant anticonvulsant properties and the non-fluorinated derivative **3** was found to be almost equiactive with BW A78U[3]. Among the non-purine analogues of BW A78U, only the 3-deaza compound **4** has been described and it exhibited potent anticonvulsant properties similar to the one of BW A78U[6].



1: R = Me, X = F (BW A78U)
2: R = H, X = F
3: R = Me, X = H

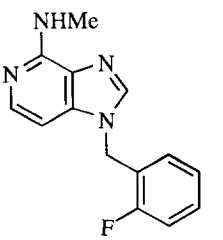


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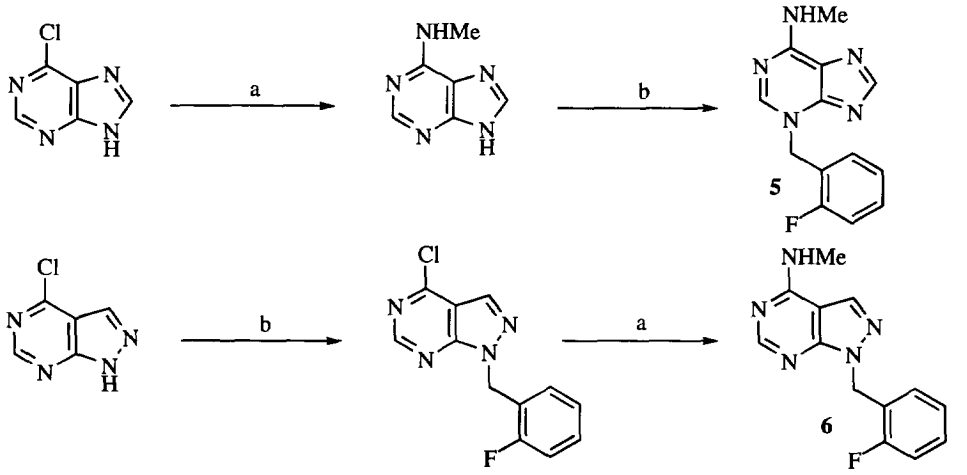
Figure I

The present work describes the synthesis and anticonvulsant properties of others analogues of BW A78U and structurally related compounds.

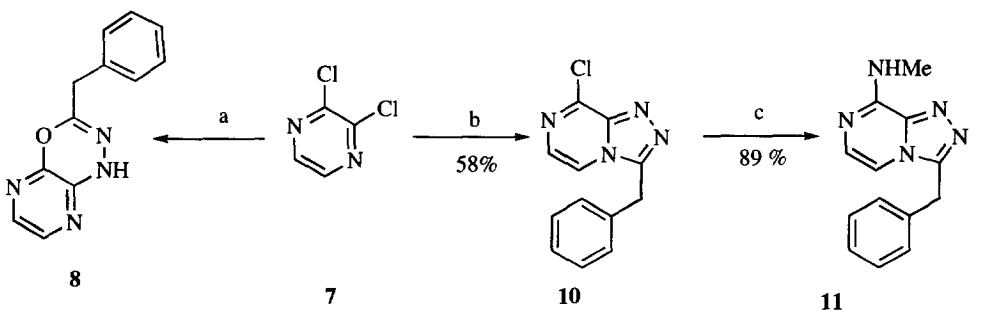
The N(3)-substituted adenine **5** and the aminopyrazolo [3,4-d] pyrimidine **6** were prepared in two steps by alkylation and amination of their corresponding iminochloride in the appropriate order (scheme I).[8,9]



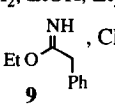
a) $MeNH_2$, EtOH, reflux ; b) $(C_6H_4F)CH_2Br$, K_2CO_3, DMF , rt.

Scheme I

The triazolo[4,3-a] pyrazine **11** was prepared following a modified procedure (scheme II)[9]. The condensation of 2,3-dichloropyrazine **7** with phenylacetic acid hydrazide yielded the cyclized compound **8**, whereas the formation of the awaited product **10** was not observed . In order to avoid this unexpected cyclization, dichloropyrazine **7** was first treated with hydrazine, affording a monoadduct[10], which was condensed with benzyliminoether **9** to give the triazolopyrazine **10**. The chloropyrazine **10** was then reacted with methylamine giving the awaited triazolo [4,3-a] pyrazine **11**.



a) i: $PhCH_2CONHNH_2$, EtOH, Et_3N; ii: $PhPOCl_2$, 180°C;

b) i: N_2H_4, EtOH; ii:  , CH_3CN, reflux, 10 min; c) $MeNH_2$, EtOH.

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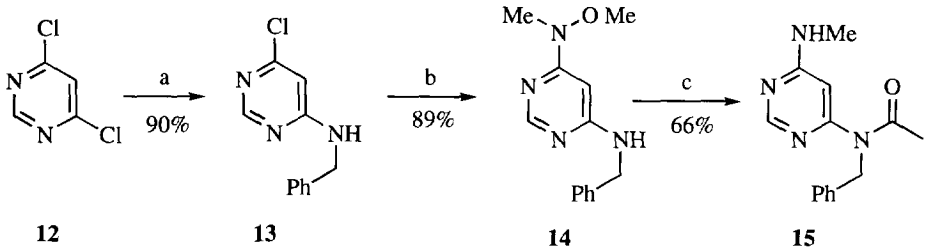
Scheme II

4,6-Dichloropyrimidine **12** reacted with benzylamine to give monoadduct **13** that reacted successfully with the very nucleophilic N,O-dimethylhydroxylamine under drastic conditions (153°C) to afford **14**. This compound was successively acylated and reduced to give the expected pyrimidine **15** (scheme III).

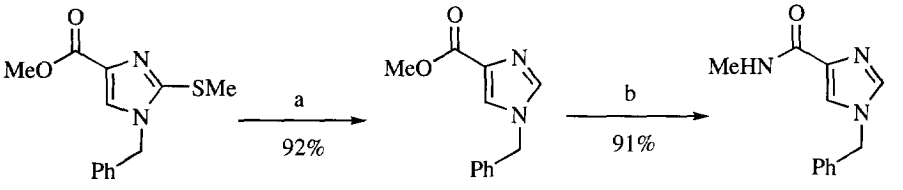


12 **13** **14** **15**

a) $BnNH_2$, Et_3N, EtOH, reflux; b) MeNHOMe, HCl, Et_3N, DMF, reflux, 1h;
c) i: Ac_2O, DMAP, EtOH, reflux, 2h; ii: Zn, AcOH, H_2O, rt, 12h.

Scheme III

The imidazocarboxamide **17** was prepared from the described imidazoester **16**[13] by desulfuration with nickel boride[14], generated in situ from $NiCl_2$ and $NaBH_4$, followed by aminolysis (scheme IV).

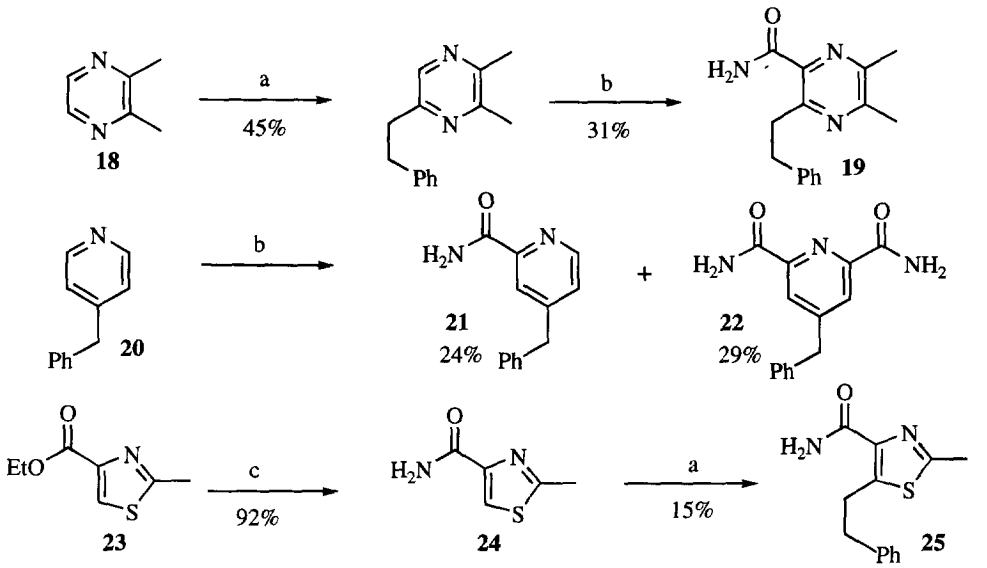


16 **17**

a) $NaBH_4$, $NiCl_2$, MeOH, rt, 12h ; b) NH_2Me, MeOH, rt, 10 days.

Scheme IV

The carboxamidoheterocycles **19**, **21** and **25** were synthesized by radical reactions developed by Minisci and coll.[15] (scheme V). These reactions involved the substitution of protonated nitrogen heterocycle by a free radical in the presence of an oxidizing agent. Dimethylpyrazine **18** reacted successively with the phenethyl radical generated by decarboxylative oxidation of 3-phenylpropionic acid and with the more reactive carbamoyl radical generated by hydrogen abstraction from formamide. Similarly, carbamoylation of 4-benzylpyridine **20** provided a mixture of mono- and di-adducts **21** and **22**. The thiazolecarboxamide **25** was prepared in two steps by first an aminolysis of the corresponding ethyl ester **23**[16] followed by a substitution with the phenethyle radical as above. The Minisci's reaction generally occurs in α or γ position of the protonated nitrogen, however it has also been reported to occur in β[17]. It is noteworthy that this is the first time that such a reaction is reported to occur on this position of the thiazole ring, however the yield was low (15%).



a) $Ph(CH_2)_2COOH$, H_2SO_4, $AgNO_3$, $(NH_4)_2S_2O_8$, H_2O, 90-100°C

b) H_2SO_4, tBuOOH, $FeSO_4$, $HCONH_2$, H_2O,10°C; c) NH_3, MeOH, rt, 24h.

Scheme V

Pharmacological Results.

BW A78U **1** and analogues were tested for their anticonvulsant activity with the model of audiogenic seizures in Wistar rats described by Kiesmann *et al.*[18] The rats were treated by intraperitoneal administration 30 minutes before the test. In this model, BW A78U exhibited a potent anticonvulsant effect with a ID_{50} of 4 mg/kg and protected 100 % of the rats at a dose of 10 mg/kg. All the structural modifications of BW A78U **1** led to less active compounds (Table I).[19] However these results presented here suggest several comments. The N(3)-substituted isomer **5** exhibited good activity (ID_{50}= 10 mg/kg) almost similar to that of BW A78U. The pyrazolopyrimidine **6** was found to be inactive at 10 mg/kg, whereas the triazolopyrazine **11** showed potent anticonvulsant properties. These results suggest that the sp^2 N(7) nitrogen is important for activity, and that the N(9)-benzyl-imidazole moiety in structure of BW A78U can be replaced efficiently by another heterocyclic amidine, *e.g.* a C(5) benzyl triazole as in **11**. It is noteworthy that in the structure of **11**, the sp^2 nitrogen equivalent to N(3) of adenine is missing. Thus, the good activity of the triazolopyrazine **11** has to be compared with that observed for **4**, the 3-deaza isoster of BW A78U. Compound **15** can be considered a more flexible "seco analogue"of BW A78U: the N-acetyl moiety being regarded as a bioisostere of the imidazole ring. However, its poor anticonvulsant activity may be associated with its relatively higher flexibility.

Compound	1 BW A78U	5	6	11	15	17	19	21	25
10 mg/kg	100[a] (6/6)[b]	50 (3/6)	0 (0/6)	65 (6/9)	20 (2/9)	20 (2/9)	0 (0/6)	50 (4/8)	30 (2/6)
40 mg/kg	-	100 (6/6)	65 (4/6)	100 (8/8)	55 (5/9)	90 (7/8)	30 (3/9)	100 (8/8)	65 (6/9)

a. percent of rats protected from tonic seizure.

b. number of rats protected from tonic seizure/ number of rats tested.

Table I : Protection against audiogenic seizures in rats at 10 and 40 mg/kg.

In the same manner, the imidazocarboxamide **17**, which can be considered another "seco analogue"with regard to the carboxamide-amidine bioisosterism, was also found to be less potent than BW A78U. However, the pyridyl-2-carboxamide **21** showed more potent anticonvulsant properties (ID_{50}= 10 mg/kg), even if it strongly resembles the less active N-benzylimidazolecarboxamide **17**. Thus, the difference in their *in vivo* efficacies may result from a better central bioavailability of the pyridyl carboxamide **21**. The other heterocyclic carboxamides **19** and **25** were significantly less active.

These results emphasize the main structural requirements for the anticonvulsant effects of BW A78U-like compounds (figure II):

-a and b) a large hydrophilic zone containing dipoles involved in H-bonding with the target (MeNH-amidine) that is coplanar with an sp^2nitrogen incorporated in an heterocycle (imidazole, triazole, pyridine).

-c) an aromatic ring borne by the aza-heterocycle and correctly located.

We believe that the present data may help to bring together BW A78U with other anticonvulsant agents into a single family of drugs showing original[7] pharmacological properties in the nervous central system.

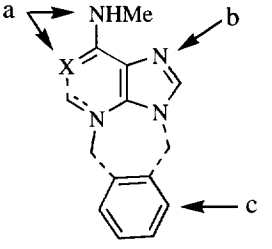


Figure II

References and notes.

1. Davies-Jones, G.A.B. Anticonvulsants. In *Meyler's Side effect of drugs*, 11th ed.; Dukes, M.N.G., Ed.; Elsevier Sciences Publishers B.V.: New-York, 1988; pp 120-136.
2. Kelley, J.L.; Soroko, F.E. *J. Med. Chem.* **1986**, *29*, 1133.
3. Kelley, J.L.; Krochmal, M.P.; Linn, J.A; McLean, E.D.; Soroko, F.E. *J. Med. Chem.* **1988**, *31*, 606.
4. Kelley, J.L.; Krochmal, M.P.; Linn, J.A; McLean, E.D.; Soroko, F.E. *J. Med. Chem* **1988**, *31*, 1005.
5. Kelley, J.L.; McLean, E.D.; Ferris, R.M.; Howard, J.L. *J. Med. Chem.* **1990**, *25*, 1910.
6. Kelley, J.L.; Linn, J.A; McLean, E.D.; Rideout, J.E.; Soroko, F.E. *J. Heterocycl. Chem.* **1988**, *31*, 1255.
7. Willard, M.; Misslin, R.; Vogel, E.; Désaubry, L.; Wermuth, C.G.; Bourguignon, J.-J. *Pharmacol. Biochem. Behav.* **1990**, *35*, 85.
8. Beasley, A.E.; Rasmussen, M. *Austr. J. Chem.* **1981**, *34*, 1107.
9. Robins, R.K.: *J. Am. Chem. Soc.* **1956**, *78*, 784.
10. Huynh-Dinh, T.; Sarfati, R.S.; Gouyette, C.; Igolen, J.; Bisagni, E.; Lhoste, J.M.; Civier, A. *J. Org. Chem.* **1979**, *44*, 1028.
11. Keir, W.F.; Wood, H.C.S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1847.
12. Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* **1984**, *101*, 2548.
13. Gamper, R.; Heinemann, U. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 296.
14. Ewerly, M.R.; Waigh, R.D. *Synth. Commun.* **1986**, *16*, 779.
15. Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489.
16. Jones, E.R.H.; Robinson, F.A.; Stracman, M.N. *J. Chem. Soc.* **1946**, 87.
17. Rao, C. Janakiram; Agosta, William C. *Tetrahedron Lett.***1992**, *33*, 4133.
18. Kiesmann, M.; Marescaux, C.; Vergnes, M.; Micheletti, G.; Depaulis, A.; Warter, J.M. *J. Neural. Transm.* **1988**, *72*, 235.
19. All tested compounds exhibited proper ^1H NMR spectra and satisfactory elemental analyses.

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