J. Pharm. Pharmacol. 1996, 48: 718–722
Received November 14, 1995
Accepted March 22, 1996

Kinetic Studies of *N*-Allenic Analogues of Tryptamine as Monoamine Oxidase Inhibitors

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Abstract

A series of *N*-allenic analogues of tryptamine in which the side chain is located at the 2 position of the indole ring, but which differed in the ring and side-chain nitrogen substituents, were assayed kinetically as MAO A and MAO B inhibitors.

All the compounds studied were mechanism-based inhibitors. The kinetic constants of each inhibition step K_i and k_i, were determined for both MAO A and B. The data obtained indicated that these allenic derivatives show a greater selectivity and potency towards MAO A as inhibitors than the corresponding acetylenic derivatives.

The mitochondrial enzyme monoamine oxidase is responsible for the deamination of biogenic amines, including those that function as neurotransmitters. The importance of monoamine oxidase inhibitors as antidepressants has been recognized since the mood-elevating actions of iproniazid were observed while testing this drug as a potential tuberculostatic agent. Johnston reported the existence of two MAO forms (Johnston 1968), and defined monoamine oxidase-A (MAO A) as being sensitive to inhibition by clorgyline and deaminating 5-hydroxytryptamine (5-HT) as a preferred substrate, whereas monoamine oxidase-B (MAO B) is sensitive to inhibition by l-deprenyl and has benzylamine and 2-phenylethylamine (PEA) as preferred substrates. Inhibitors selective towards MAO A have been shown to be effective antidepressants. MAO B inhibitors have been shown to be of value in the treatment of Parkinson's disease (Dostert et al 1989), although apparently devoid of antidepressant action. This has stimulated the research into the development of new compounds with greater potency and more selectivity towards one or the other form of MAO (Tipton 1989).

The structural features of inhibitors that are responsible for a greater potency and selectivity towards either of the MAOs, are still not completely clear, despite the large number of MAO inhibitors that have been described (Knoll 1979; Kalir et al 1981; Dostert et al 1989).

In our previous studies (Balsa et al 1990, 1991; Avila et al 1993; Tipton et al 1993) we have shown some acetylenic derivatives of tryptamine are effective and selective MAO inhibitors. As part of a project aimed at determining the structural features that lead to inhibitor potency and selectivity, we have now studied the inhibitory behaviour of the corresponding series in which the acetylenic group has been replaced by an allenic moeity (Fig.1). The results obtained are compared with the behaviour of the corresponding acetylenic derivatives.

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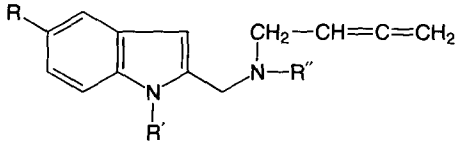
FIG. 1. Structural formulae for *N*-allenic indolalkylamine derivatives.



Compound	R	R′	R″
FA32	H	CH_3	H
FA47	CH_3O	CH_3	H
FA33	H	CH_3	CH_3
FA71	OH	CH_3	CH_3
FA93	OH	H	CH_3
FA57	CH_3O	H	H
FA63	CH_3O	H	CH_3
FA44	CH_3O	CH_3	CH_3

Materials and Methods

5-Hydroxy-(side chain-2-^{14}C)tryptamine creatinine sulphate 55 mCi mmol^{-1}, 50 μCi mL^{-1} was purchased from Amersham (UK). [ethyl-1-^{14}C])-Phenylethylamine HCl 50 mCi mmol^{-1} 0·1 mCi mL^{-1} was purchased from NEN (New England Nuclear). Kynuramine dihydrobromide and benzylamine HCl were obtained from Sigma (London). Deprenyl was a generous gift of Professor J. Knoll of Semmelweis University (Hungary).

The series of *N*-allenic analogues of tryptamine (Fig. 1) was synthesized according to Cruces et al 1988. Rat (Sprague–Dawley) liver homogenates were prepared from male rats, 200–250 g, which had previously fasted overnight, in 10 volumes (w/v) of a 50 mM-potassium phosphate buffer, pH 7·2, using a Dounce homogenizer. Mitochondria were prepared by a standard differential centrifugation method (Gomez et al 1988). The pellets were suspended in the same buffer and frozen as small aliquots at −20°C until required.

Kynuramine is a substrate for both monoamine oxidases. To use this substrate for the determination of MAO A activity,

MAO B was previously inhibited by preincubation with 0·3 μM l-deprenyl at 37°C for 60 min. After this incubation, the free inhibitor was removed by centrifugation at 4°C and 20 000 *g* for 15 min. The pellet was washed by resuspension and centrifugation three times before it was finally resuspended in a 50 mM-potassium phosphate buffer, pH 7·2, and separate samples were frozen at −20°C until used.

MAO activity was determined radiochemically at 37°C (Fowler & Tipton 1981). PEA (22·2 μM) or 5-HT (100 μM) were used as substrates for MAO B and MAO A, respectively. The reaction was carried out in a final volume of 225 μL of a 50 mM-potassium phosphate buffer, pH 7·2 containing 200–400 μg of protein, and was stopped by the addition of 100 μL 2 M citric acid. The products were extracted into toluene/ethyl acetate 1 : 1 (v/v) containing 0·6% (w/v) 2,5-diphenyloxazole and radioactivity was measured in a scintillation counter.

Protein concentration was determined (Hartree 1972) with bovine serum albumin as standard.

To test whether reversible or irreversible inhibition was produced by these allenic tryptamine derivatives, 200-μL samples of the mitochondria (8·5 mg mL^{-1}) from rat liver was preincubated for 30 min at 37°C with 100 μL of the inhibitor at a concentration near to its IC50 value (the inhibitor concentration necessary to give 50% inhibition under the incubation and assay conditions used), in a final volume of 1 mL of a 50 mM potassium phosphate buffer, pH 7·2. After this time the activities remaining were determined. The mixture was then centrifuged and the pellet was washed by resuspension in the same volume of buffer and centrifuged three times. Regain of the activity was determined after each washing. Controls in which the inhibitor was replaced by an identical volume of a buffer were taken through the same procedure.

IC50 values were determined with and without preincubation of the inhibitor with the enzyme for 30 min at 37°C and at inhibitor concentrations ranging for $10^{-2} - 10^{-12}$ M. The MAO A and MAO B activities remaining were measured radiochemically with 5-HT and PEA, respectively, as substrates and expressed as percentages of the control value.

The time-dependence of the inhibitory process was determined at an inhibitor concentration that gave essentially complete inhibition after 30 min of incubation. After different periods of time of preincubation of the inhibitor (400 μL), with the enzyme (800 μL (8·5 mg mL^{-1})) in a total volume of 2 mL of 50 mM-potassium phosphate buffer, pH 7·2, 50-μL samples of the mixture were assayed radiochemically for MAO A and MAO B activities.

Spectrophotometric assays for MAO B activity were performed at 37°C using benzylamine as the substrate by measuring the appearance of the product at 250 nm by a modification (Avila et al 1993) of the Tabor method (Tabor et al 1954), which allowed determination with six samples to be performed simultaneously. MAO A activity was determined spectrophotometrically with kynuramine as the substrate (Weissbach et al 1960), but, measuring the appearance of the product at 324 nm (Avila et al 1993).

The mechanism-based inhibition process of these allenic derivatives of the tryptamine, was quantified by a modification of the Walker and Elmore method (Walker & Elmore 1984), previously reported (Avila et al 1993). The kinetic parameters were determined by direct analysis of the progress curves of the reaction between an enzyme and a fixed amount of substrate in the presence of varying amounts of inhibitor.

The inhibition progress curves were fitted to a first order rate equation by non-linear regression analysis using computer program ENZFITTER (Elsevier-Biosoft) to get the apparent first-order rate constant k_{app}.

The K_m values of MAO A and MAO B for kynuramine and benzylamine as substrates were 35 and 300 μM, respectively, under the conditions used in these experiments. The kinetic parameter K_i which defines the affinity of the reversible step and k_i the velocity constant corresponding to the covalent step of the total inhibitory process were determined according to the mechanism:

$$E + I \overset{K_i}{\rightleftharpoons} E.I \overset{k_i}{\rightarrow} E - I$$

by non-linear regression analysis of the k_{app} versus [I]. The catalytic efficacy of the inhibitory process, was defined as the k_i/K_i ratio.

Results

Fig. 1 shows the structures of the compounds examined. These compounds have in common an allenic group located at the side chain, and differ in the substituents (CH_3, CH_3O- and OH), at different positions of the indole ring.

Fig. 2 shows the concentration-dependence of MAO inhibition by compound FA 93, taken as an example, after 0 and 30 min preincubation with the enzyme. The activity remaining was determined towards 5-HT and PEA as substrates.

The IC50 values were determined from such curves for each inhibitor after either 0 or 30 minutes pre-incubation. Table 1 shows the IC50 values of the different allenic derivatives of the tryptamine studied. These data showed that inhibition was time dependent in all cases. Substitution of a H group (FA 32) for a methoxy-group (FA 47) in the 5- position of the tryptamine ring (position R in Fig. 1) gave aproximately 5-fold and 100-fold increases in the inhibitory potencies towards MAO A and B, respectively, as calculated from the ratio of the IC50 values for these two compounds determined after 30 min enzyme-inhibitor preincubation (Table 1). Despite the increased potency of FA 47 as an inhibitor of both monoamine oxidases, the changes in inhibitory potencies resulted in it having less selectivity towards MAO B than FA 32. This compound

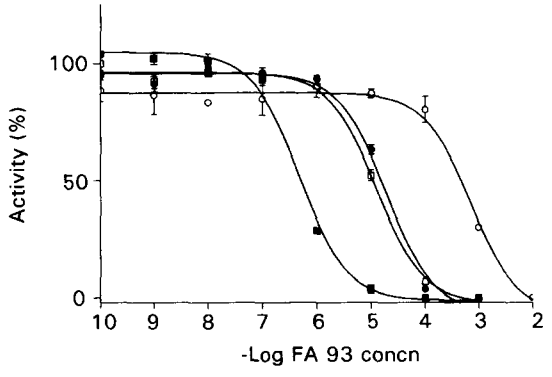


FIG. 2. MAO inhibition by different concentrations of compound FA 93 measuring the remaining activity towards 5-HT and PEA as substrate after 0 and 30 min pre-incubation. (○) MAO B 0 min, (●) MAO B 30 min, (□) MAO A 0 min, (■) MAO A 30 min.

Table 1. IC50 values for MAO inhibition by *N*-allenic indolalquilamine derivatives.

Compound	IC50 (μM) at 0 min		IC50 (μM) at 30 min		B/A at 30 min**
	MAO A	MAO B	MAO A	MAO B	
FA32	5·6 ±0·2	63·0±9·8	0·012±0·0014	2·5±0·05	208·3±12·1
*FA26	1·2±0·05	1·3±0·002	0·2± 0·07	0·30±0·02	1·5±0·96
FA47	0·015±0·003	2·5±0·07	0·0025±0·0008	0·025±0·003	10·0±0·47
*FA42	0·4±015	30·0±1·72	0·03±0·003	3·0±0·17	100·0±17·4
FA33	0·39±0·07	25·0±1·2	0·019±0·002	0·25±0·01	13·1±9·1
*FA27	0·5±0·005	12·0±0·97	0·003±0·0002	0·1±0·006	33·3±4·5
FA71	1·2±0·08	250·0±9·32	0·025±0·0016	3·9±0·005	156·0±10·4
*FA09	5·2±0·067	50·0±0·92	0·3±0·041	3·0±0·005	10·0±1·56
FA93	10·0±0·095	250·0±12·0	0·310±0·022	15·0±0·9	48·38±6·82
FA57	0·250±0·025	15·0±0·84	0.019±0·0016	0·31±0·004	16·3±1·3
FA03	0·250±0·046	150·0±5·67	0·025±0·002	1·5±0·008	6·0±0·17
FA44	5·62±0·29	250·0±8·15	1·7±0·08	25±1·1	14·7±1·4
*FA43	0·003±0·006	15·0±0·72	0·0003±0·00001	0·10±0·002	333·3±18·4

*Data taken for comparative purposes on the corresponding acetylenic derivatives from the results published previously for the MAO inhibition from rat liver. **IC50 ratio between both MAO forms indicating the selectivity of the inhibition process, after 30-min pre-incubation. The values represent the mean ± s.d. of three separate experiments in duplicate.

showed more potency and selectivity towards MAO A when compared with the corresponding acetylenic derivatives (FA 26) taken for comparative purposes (Balsa et al 1991). The structural analogue of FA 47, but containing an acetylenic group in the side chain (FA 42), showed a loss of potency towards both MAO forms but the selectivity increased 10 times.

When comparing the effect of the same structural alteration in the derivatives with a methyl group on the side nitrogen (R″ Fig. 1) (FA 33 and FA 44), the inhibitory potency for both forms of MAO diminished aproximately 90 times, and consequently the selectivity was not affected. When FA 33 is compared with the acetylenic derivative (FA 27), the potency and selectivity increased significantly in the latest case.

The substitution of an H at the 5 position of the indole (FA 33) by an hydroxy group (FA 71), apparently did not affect the inhibitory potency towards MAO A (Table 1), but considerably altered that of MAO B and consequently the selectivity towards MAO A increased 12 times. The corresponding acetylenic derivative FA 69 showed less potency towards MAO A whereas the potency towards MAO B did not alter. The substitution of an H (FA 93, FA 57), by a methyl group at the *N* of the indole ring (R′) (FA 71, FA 47), resulted in all cases in an increase of the inhibitory potency towards both MAO forms. In the case of the 5-hydroxyindol derivatives, (FA 93 and FA 71), the IC50 values for MAO A disminshed 10-fold, whereas in the case of MAO B it decreased 4-fold. Thus the selectivity towards MAO A expressed by IC50 B/IC50 A, diminished 3 times. When the 5-methoxyindol derivatives (FA 57 and FA 47) were compared, the IC50 values for MAO A diminished about 10 times and 12 times in the case of MAO B.

The substitution of an H at the *N* in the side chain (R″) (FA 32 and FA 57) by a methyl group (FA 33 and FA 63), did not affect the inhibitory potency towards MAO A in any case, but the inhibitory potency towards MAO B, was increased between two- and tenfold. Consequently, the selectivity towards MAO A was diminished about 80 times in the case of FA 32 and FA 33, and about 3 times in the case of FA 57 and FA 63. In general terms the selectivity towards MAO A increased in the allenic derivatives compared with the acetylenic ones, but when a CH_3O group is located at the 5 position of the indole ring, the acetylenic derivatives are more selective toward MAO A than the allenic.

MAO A and MAO B were preincubated with each inhibitor at concentrations that resulted in complete inhibition after 30 min preincubation for each case. All the inhibitors assayed, showed a time-dependent increase in inhibition. Fig. 3 showed the time-dependent inhibition, towards each form of MAO, by the compound FA 93 at a concentration of 10^{-5} M for MAO A and 10^{-3} M for MAO B. In both cases the inhibition increased with the preincubation time, becoming complete after 15 min for MAO B and 20 min for MAO A.

The reversibility of the inhibition process, was checked by incubation of mitochondria with an inhibitor concentration that give 40 % inhibition for MAO A and 85 % inhibition for MAO B, after 30 min incubation. Samples were then washed by repeated centrifugation and resuspension in a 50 mM-potassium phosphate buffer, pH 7·2. After three successives washings and resuspensions, no significant recovery of MAO A and MAO B activity, was obtained in any case, indicating an irreversible inhibition process. Table 2 shows the reversibility test for compound FA 93. Dialysis overnight at either 4°C or 37°C against 10 volumes of 50 mM-potassium phosphate buffer pH 7·2, was performed to exclude the possibility of slow

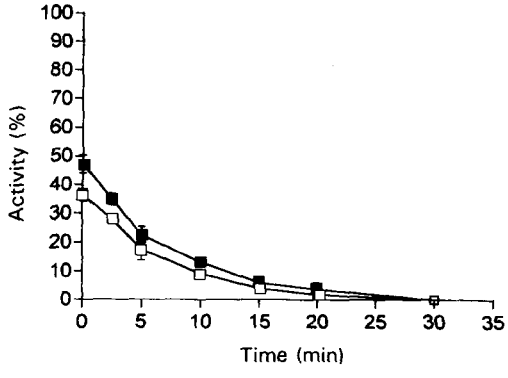


FIG. 3. Time dependence inhibition of MAO A and MAO B by compound FA 93. (■) MAO A activity (5-HT), (□) MAO B activity (PEA).

Table 2. Reversibility test of MAO A and MAO B inhibition by compound FA 93.

Number of washes	Percent MAO activity		
	Control	MAO A	MAO B
0	100 ± 3	60 ± 2	12 ± 1
1	100 ± 2	62 ± 3	12 ± 1
2	100 ± 1	60 ± 3	10 ± 1
3	100 ± 1	60 ± 1	10 ± 0

dissociation of a tight-binding inhibitor. No recovery of activity occurred (data not shown).

The time-dependent inhibition curves of MAO B by compound FA 93, in which the activity towards benzylamine as substrate was measured resulted in an increasing curvature of the reaction progress curves when the inhibitor concentration was increased. The first-order rate-constant k_{app} was calculated at each inhibitor concentration, fitting this data to a first-order rate equation (Balsa et al 1992) and the corresponding kinetic parameters K_i and k_i, were then determined by non linear-regression analysis of k_{app} versus inhibitor concentration.

Table 3 presents the kinetic parameters towards MAO A and MAO B of all the allenic derivatives of the tryptamine studied. The substitution of an H at the 5 position (R) of the indole ring (FA 32) by a methoxy group (FA 47), produced a 25-fold increase in the affinity towards MAO A and a 10-fold increase for MAO B. This substitution doubled the k_i value towards MAO A but this value did not change significantly in the case of MAO B. The catalytic efficacy k_i/K_i increased 15- and 75-fold for MAO B and MAO A respectively.

The substitution of an H at the 5-position (R) of the indole ring (FA 33) by an OH group (FA 71) did not affect the affinity towards MAO A but diminished that for MAO B by about 23-fold. The velocity constant k_i was similar for both MAO forms and did not alter in spite of this structural change.

The same structural change was studied but in this case a methyl group was present on the nitrogen position (R″) of the side chain (FA 33 and FA 44). In this case the kinetic parameters did not change with the exception of the velocity constant k_i for MAO A which diminished as a consequence of this, the catalytic efficacy towards MAO A increased 3-fold.

The substitution of the H at the indole nitrogen (R′ position) (FA 93 and FA 57) by a methyl group (FA 71 and FA 47) diminished the affinity constant K_i 10-fold for MAO A, in the case of FA 93 compared with FA 71, and increased it about 20-fold for MAO B. This structural alteration did not affect the kinetic constant of the second step of the inhibition process. The 130-fold decrease of the catalytic efficacy towards MAO A is explained in terms of the alteration of the corresponding affinity. For MAO B this ratio did not change.

An opposite effect was observed with the series of analogues that contained a methoxy group at the 5 position of the indole ring (FA 57 compared with FA 47). In this case the affinity towards both MAO A and MAO B was increased about 10-fold, and the velocity constant k_i was doubled for both MAO forms. Consequently, the catalytic efficacy increased 8-fold for MAO A and 24-fold for MAO B.

The substitution of the H at the N of the side chain (FA 32) by a methyl group (FA 33), resulted in a 3-fold increase in the affinity towards MAO A, and a 2-fold increase towards MAO B. This effect was counteracted by a 3-fold decrease in the k_i values for both MAO A and MAO B. Consequently, the catalytic efficacy did not change greatly for either enzyme. In the cases of FA 57 and FA 63, this structural modification had no significant effect on the affinity for either MAO forms, while the velocity constant, k_i of the second step of the mechanism-based inhibition, was unaffected.

Discussion

Rando reported that the allylamines behaved as a pseudo-irreversible inhibitor of monoamine oxidase (Rando & Eigner 1977) in which the time-dependent inhibition was reversed by the presence of substrate. The in vivo response of such inhibitors to tyramine challenge might be of particular interest in relation to the cheese effect. This behaviour contrasts with the simple mechanism-based inhibition of MAO A and MAO B by acetylenic amine derivatives. Since we have previously examined the behaviour of a series of substituents of acetylenic derivatives of tryptamine (Balsa et al 1990, 1991; Avila et al 1993) it was of particular interest to examine the corresponding allenic derivatives in terms of their mechanism of MAO inhibition and to establish the comparison between them.

This is the first time that the behaviour of a series of allenic derivatives of tryptamine as MAO A and B inhibitors is reported.

All the compounds are true irreversible inhibitors in which there was no apparent recovery of activity of the dialysed enzyme on incubation with the substrate, and behaved as mechanism-based inhibitors of both enzymes.

The introduction of a methoxy group at the R position of the

Table 3. Kinetic parameters of MAO inhibition by *N*-allenic indolalkylamine derivatives.

Compound	K_i(nM)		k_i (min^{-1})		k_i/K_i (10^{-3})	
	MAO A	MAO B	MAO A	MAO B	MAO A	MAO B
FA 32	54·6 ± 1·1	248·0 ± 8·7	0·124 ± 0·002	0·235 ± 0·005	2·02 ± 0·33	0·94 ± 0·06
FA 47	2·2 ± 0·06	21·5 ± 1·1	0·329 ± 0·007	0·317 ± 0·008	149·5 ± 7·5	14·7 ± 0·44
FA 33	19·3 ± 1·01	153 ± 6·4	0·097 ± 0·006	0·098 ± 0·004	5·02 ± 0·6	0·64 ± 0·05
FA 71	35·0 ± 1·1	3560 ± 140	0·091 ± 0·010	0·054 ± 0·002	2·6 ± 0·37	0·01 ± 0·006
FA 93	348 ± 7·6	1910 ± 15·3	0·062 ± 0·003	0·110 ± 0·008	0·17 ± 0·02	0·05 ± 0·012
FA 57	26·9 ± 1·0	62320 ± 84·0	0·082 ± 0·002	0·144 ± 0·010	3·04 ± 0·21	0·06 ± 0·008
FA 63	14·8 ± 0·89	398 ± 7·1	0·048 ± 0·005	0·098 ± 0·002	3·24 ± 0·6	0·24 ± 0·005
FA 44	33·8 ± 1·0	225 ± 6·3	0·503 ± 0·013	0·127 ± 0·006	14·9 ± 0·8	0·56 ± 0·04

The values represent the mean ± s.d. of three separate experiments in duplicate.

indole ring of the allenic derivatives of the tryptamine (FA 47 and FA 44), resulted in a significant increase of the catalytic efficacy k_i/K_i towards MAO A whereas those values for MAO B, were little affected. These results are in agreement with those obtained in the case of the acetylenic derivatives of tryptamine reported before (Balsa et al 1990, 1991).

The introduction of a methyl group at the R′ position of the indole ring (FA 47 – FA 71), resulted in an increase of the affinity towards MAO A and a decrease of the same parameter towards MAO B. The catalytic efficacy also increased towards the MAO A form as a consequence of this structural alteration. Similar behaviour has been previously described in the case of acetylenic derivatives (Balsa et al 1992).

The introduction of a methyl group at the R″ position (FA 33) did not alter significantly the kinetic inhibitory parameters or the catalytic efficacy of either MAO forms. Nevertheless when this substitution was done in an analogue with a methoxy group at the R position, (FA 44 and FA 63) the catalytic efficacy for MAO A decreased significantly for MAO A but it was not altered for MAO B. Nevertheless the same structural alterations in the case of the acetylenic derivatives (Balsa et al 1992), gave opposite effects to that observed with the allenic derivatives.

The most potent and selective MAO A inhibitor reported was the compound FA 47. This compound has a methoxy group substituted at the 5 position of the indole ring, and a methyl group at the R′ position. When comparing this allenic derivative of tryptamine with the corresponding acetylenic derivative previously reported (Balsa et al 1990), we observed that the catalytic efficacy is aproximately 100 times higher. This parameter for compound FA 47, is of the same order as that of clorgyline ($k_i/K_i = 66{\cdot}6\ min^{-1}\ nM^{-1}$), calculated by the same method. These results allowed us to conclude that replacement of the acetylenic groups on the side chain of tryptamine by an allenic group increased the selectivity and inhibitory potency of all the studied compounds towards MAO A. However, this was not true if some substituents (a methoxy group at the 5 position of the indole ring (FA 47) and a methyl group at the R′ position (FA 44)) were present. In this case the resulting behaviour is affected by these substituents and the corresponding acetylenic derivatives are more selective as MAO A inhibitors.

Acknowledgements

This work has been supported in part by the DGR grant QFN 93-4428 from the Comissionat per a Universitats i Recerca of Generalitat de Catalunya.

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