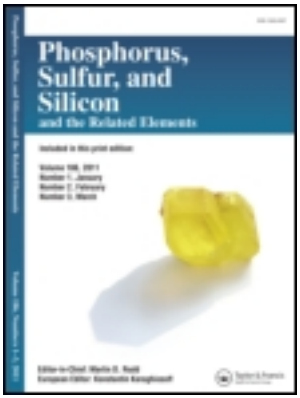

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Synthesis and Biological Activities of Novel 1,4-Bridged Bis-1,2,4-Triazoles, Bis-1,3,4-Thiadiazoles and Bis-1,3,4-Oxadiazoles

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Synthesis and Biological Activities of Novel 1,4-Bridged Bis-1,2,4-Triazoles, Bis-1,3,4-Thiadiazoles and Bis-1,3,4-Oxadiazoles

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*The terephthalic acid hydrazide (**1**) reacted with phenyl / benzyl isothiocyanate **2a**,**b** to yield the corresponding bis-thiosemicarbazides **4a**,**b**, via acid hydrolysis of the intermediate **3** whereas cyclization of **4** gave the bis-1,2,4-triazoles **5**,**6** and bis-1,3,4-thiadiazoles **7**,**8**. Similarly, compound **1** reacted with phenyl isocyanate **9** to give the bis-semicarbazide **10**, which was cyclized to the bis-oxadiazole **11** and / or bis-1,2,4-triazole **12** in $POCl_3$ and NaOH respectively.*

Keywords Bis-1,2,4-triazoles; bis-1,3,4-oxadiazoles; bis-1,3,4-thiadiazoles; bis-thiosemicarbazides; terephthalic acid hydrazide

INTRODUCTION

Certain 1,4-disubstituted thiosemicarbazide, 1,2.4-triazoline-3-thione, and 1,2,4-triazole-3-thiole derivatives are of interest due to their bioactivity, including antibacterial,[1–3] antifungal,[4,5] antitubercular,[6] antimycobacterial[7] and anticancer[8] properties. Moreover, 1,3,4-oxadiazoles are becoming an important member in the heterocyclic family not only because of their wide usage as dyes, and photosensitive and electrical materials,[9] but also because of their broad spectrum in biological activities such as HIV-activity and antibacterial and antifungal activities.[10,11] In recent years, attention has been increasingly paid to the synthesis of bisheterocyclic compounds, which exhibit various biological activities[12–15]. Keeping these observations

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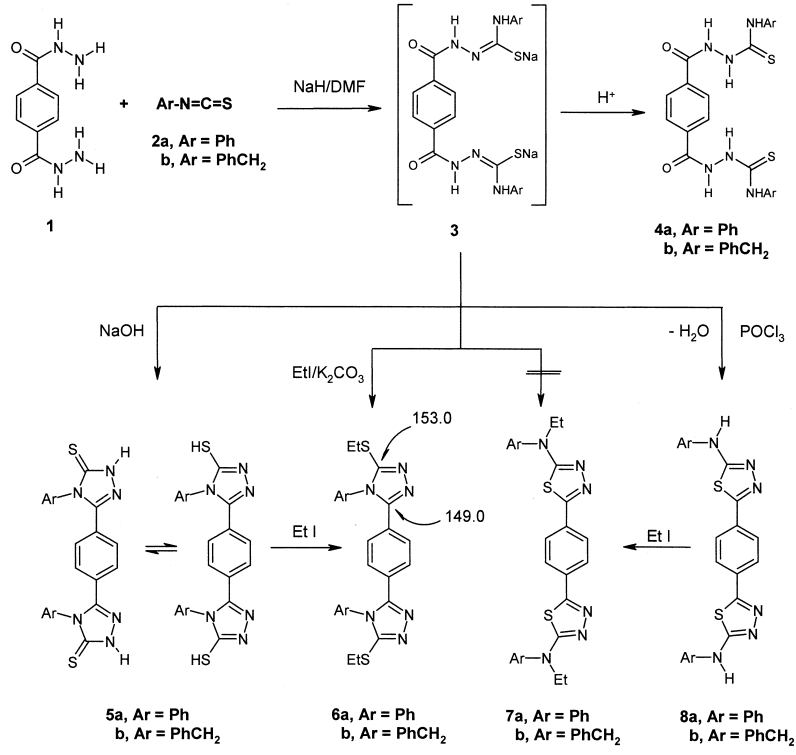
in mind and in continuation of our work on the synthesis of heterocyclic compounds containing nitrogen and sulphur[16,17] and bisheterocyclic compounds[18–21] with expected biological activity, we report herein the synthesis of the versatile and hitherto unreported bis thiosemicarbazides **4a**,**b** and its utility as a building block in the synthesis of several new bisheterocyclic compounds.

RESULTS AND DISCUSSION

Thus, the key intermediate in the present study is the terephthalic acid hydrazide (**1**) which was prepared according to a previously described procedure.[22,23] The reaction of **1** with phenyl/benzyl isothiocyanate **2a**,**b** in DMF in the presence of sodium hydride gave the non-isolable intermediate **3** which was converted into the corresponding thiosemicarbazide **4a**,**b** upon treatment with concentrated hydrochloric acid (Scheme 1). The structural assignments of compounds **4a**,**b**



SCHEME 1

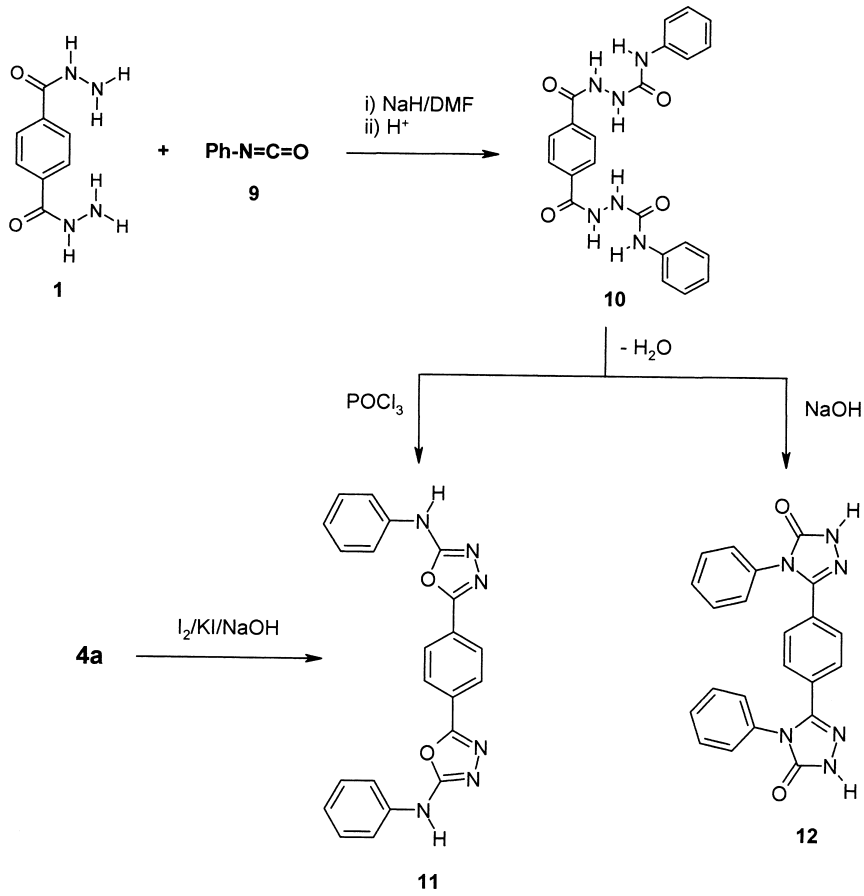
were established by spectroscopic studies and elemental analysis. In its ^{1}H NMR spectra signals of the thiosemicarbazide group protons NHCS (9.30 ppm) and CONH (9.50 ppm) are observed. Also, in the IR spectra, the absorption of the thiosemicarbazide NH (3160–3285 cm^{-1}) and C=O (1670–1665 cm^{-1}) due to fragments are observed. The C=S absorption appears at 1345–1350 cm^{-1} (see Experimental Section).

The bis-thiosemicarbazides **4a**,**b** on treatment with sodium hydroxide underwent cyclization to the bis-1,2,4-triazoles **5a**,**b** (Scheme 1). The spectral data are in good agreement with the proposed structures. Thus, the IR spectra of **5** showed N—H bands in the region of 3080–3285 cm,$^{-1}$ C=S absorption bands at 1340–1350 cm^{-1}, and the absence of any absorption about in 2600–2550 cm^{-1} region cited for S—H group confirmed that these compounds were in the thionic form in the solid state. Also, in its ^{1}H NMR spectra the NH group chemical shifts characteristic of 1,2,4-triazole-2-thiones are observed in the down field region at 10.85–11.20 ppm which also supports the proposed thione structure.[3,5]

Furthermore, the reaction of **4a** with ethyl iodide in DMF at room temperature and in the presence of anhydrous potassium carbonate gave a solid product of molecular formula $C_{26}H_{24}N_6S_2$ ($M^+ = 484$) which may be formulated as **6a** or its isomer **7a** (Scheme 1). The structure of **6a** was indicated by the ^{13}C NMR spectra of the product which gave conclusive evidence for the triazole structure. The spectrum reveals low-field signals at 153.0 ppm (triazole C-3) and 149.0 ppm (triazole C-5). If this product is the isomeric thiadiazole **7a**, the C-2 and C-5 thiadiazole signals should have appeared at a higher field.[24,25] Structural proof was obtained through another synthetic route by the treatment of **5a** with ethyl iodide (Scheme 1).

In addition, the structure of **6a** was confirmed further by an alternative synthesis of its isomer bis-thiadiazoles **7a**. Thus, compound **4a** reacted with phosphoryl chloride at reflux to give bis-thiadiazoles **8a** which was ethylated with ethyl iodide to yield **7a**. Comparison of the data of **7a** with those of **6a** showed differences in mp, IR, and ^{1}H NMR data which indicated the structure of **7a** for our product (See Experimental Section). Similarly, compounds **6b**, **7b**, and **8b** were prepared in a similar way (Scheme 1).

When terephthalic acid hydrazide (**1**) was refluxed with phenyl isocyanate **9** using the procedure described for the synthesis of compounds **4a**,**b**, the bis-semicarbazide **10** was formed (Scheme 2). The structure of compounds **10** was confirmed by analytical and spectral data (See Experimental Section). The compound **10** on treatment with $POCl_3$ and/or NaOH underwent cyclization to the corresponding 5,5′-(1,4-phenylene)bis(2-phenylamino-1,3,4-oxadiazole) (**11**) and 5,5′-(1,4-phenylene)bis (4-phenyl-3-oxo-1,2,4-triazole) (**12**) respectively and



SCHEME 2

their structures were deduced on the basis of analytical and spectral data (Scheme 2 and Experimental Section). Alternatively, compound **11** could also be prepared by boiling **4a** with iodine and potassium iodide in the presence of ethanolic sodium hydroxide solution (Scheme 2).

BIOLOGICAL ACTIVITY

Some of the prepared compounds were tested for antibacterial and fungicidal activity. Gram-negative bacteria (*Seratia*), gram-positive bacteria (*Bacillus cereus*), as well as two different fungi, *Fusarium monoiliforum* and *Aspergillus flavus*, were used for this purpose. The

TABLE I

Compound	*Seratia*	*Bacillus cereus*	*Fusarium monoiliforum*	*Aspergillus flavus*
5a	−	−	−	++
6b	+++	++	−	−
7b	+	+	−	++
8a	−	−	−	−
11	−	+	−	+
12	−	+	−	+

Diameter of the zone of inhibition: 1 cm; + = 1 to 1.5 cm; ++ = 1.5 to 2 cm; +++ = 2 cm; The solvent was DMF.

biological assay was determined according to the filter paper disc method. Assay plates were incubated at 25°C one day for the bacteria and four days for the fungi used.[26] The test results are shown in Table I.

EXPERIMENTAL

All mps. were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^1H NMR spectra were measured in DMSO-d_6 with a Bruker AM 400 (400 MHz) spectrometer using TMS as an internal standard; the ^{13}C NMR spectra were recorded at 100 MHz. The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan Mat 8430 mass spectrometer operating at 70 eV. Microanalytical data were obtained from Microanalytical unit at Cairo University.

General Procedure for the Synthesis of Bis Thiosemicarbazides 4a,b and Bis Semicarbazide 10

Sodium hydride (25 mmol) [50% pentane washed] was added in portions to a solution of terephthalic acid dihydrazide**1** (12.5 mmol) in absolute DMF (10 ml) at 0°C. The aryl isothiocyanate **2a**,**b** and/or phenyl isocyanate **9** (25 mmol) was added dropwise to this stirred mixture while the temperature of the reaction mixture was maintained at 25°C. The whole mixture was stirred at room temperature for 3 h to give **3** which was poured onto cold water and acidified with conc. HCl to pH 3. The resulting solid product was collected by filtration, washed with water, dried, and recrystallized from an appropriate solvent.

1,4-Phenylene bis (4-phenylthiosemicarbazido) (4a)

Obtained in 90% yield, m.p. 200–202°C (from EtOH); (found: C, 56.80; H, 4.40; N, 18.10; S, 13.90. $C_{22}H_{20}N_6O_2S_2$ requires C, 56.88; H, 4.34; N, 18.09; S, 13.80%); υ_{max}/cm^{-1} 3165–3285 (NH), 3050 (Ar-CH), 1670 (CO) and 1345 (C=S); δ_H 7.60–8.20 (m, 14H, Ar-H), 9.30 (s, br, 4H, 4NH), 9.50 (s, br, 2H, 2NH); m/z 464 (M^+, 16%).

1,4-Phenylene bis (4-benzylthiosemicarbazido) (4b)

Obtained in 92% yield, m.p. 236–238°C (from Dioxane); (found: C, 58.30; H, 4.90; N, 17.10; S, 13.10. $C_{24}H_{24}N_6O_2S_2$ requires C, 58.52; H, 4.91; N, 17.06; S, 13.02%); υ_{max}/cm^{-1} 3160–3285 (NH), 3054 (Ar-CH), 2900 (aliph-CH.), 1665 (CO) and 1350 (C=S); δ_H 5.40 (s, 4H, $2CH_2$), 7.40–8.20 (m, 14H, Ar-H), 8.34 (s, br, 2H, 2 CSNH-CH_2), 9.30 (s, br, 2H, 2 NHNHCS), 9.50 (s, br, 2H, 2 CONHNHCS).

1,4-Phenylene bis (4-phenyl-semicarbazido) (10)

Obtained in 95% yield, m.p. 220–222°C (from EtOH); (found: C, 61.20; H, 4.70; N, 19.50. $C_{22}H_{20}N_6O_4$ requires C, 61.11; H, 4.66; N, 19.43%); υ_{max}/cm^{-1} 3350–3160 (NH), 3050 (Ar-CH), 1670 (CO); δ_H 7.60–8.20 (m, 14H, Ar-H), 9.20–9.50 (m, 6H, NH).

Synthesis of Bis-1,2,4-triazoles 5a,b and 12

To a suspension of **4a**,**b** or **10** (10 mmol) in ethanol (20 ml), aqueous NaOH (4 *N*, 10 ml) was added and the solution was refluxed for 4 hr, cooled, and filtered. The filtrate was neutralized to pH = 6 using dilute HCl acid and was kept aside for 1 hr. The separated solid product was filtered, washed with water, dried, and recrystallized from DMF.

5,5′-(1,4-Phenylene)bis(4-phenyl-3-mercapto-1,2,4-triazole) (5a)

Obtained in 65% yield, m.p. >370°C; (found: C, 61.70; H, 3.80; N, 19.60; S, 14.90. $C_{22}H_{16}N_6S_2$ requires C, 61.66; H, 3.76; N, 19.61; S, 14.96%); υ_{max}/cm^{-1} 3285–3080 (NH), 3050 (Ar-CH), 1620 (C=N), 1350 (C=S); δ_H 7.60–8.20 (m, 14H, Ar-H), 11.20 (s, 2H, 2NH).

5,5′-(1,4-Phenylene)bis(4-benzyl-3-mercapto-1,2,4-triazole) (5b)

Obtained in 69% yield, m.p. 360–362°C; (found: C, 63.10; H, 4.40; N, 18.40; S, 14.10. $C_{24}H_{20}N_6S_2$ requires C, 63.13; H, 4.42; N, 18.41; S, 14.04%); υ_{max}/cm^{-1} 3285–3080 (NH), 3050 (Ar-CH), 2900 (aliph-CH.), 1620 (C=N), 1340 (C=S); δ_H 5.40 (S, 4H, $2CH_2$), 7.60–8.20 (m, 14H, Ar-H), 10.85 (s, 2H, 2NH); m/z 456 (M^+, 21%).

5,5′-(1,4-Phenylene)bis(4-phenyl-3-oxo-1,2,4-triazole) (12)

Obtained in 64% yield, m.p. >370°C; (found: C, 66.70; H, 4.10; N, 21.10. $C_{22}H_{16}N_6O_2$ requires C, 66.66; H, 4.07; N, 21.20%); υ_{max}/cm^{-1} 3300–3100 (NH), 3050 (Ar-CH), 1680 (C=O), 1620 (C=N); δ_H 7.60-8.20 (m, 14H, Ar-H), 10.90 (s, br, 2H, 2NH).

General Procedure for the Synthesis of Bis-(3-ethylthio-1,2,4-triazoles) 6a,b

Method A

Ethyl iodide (10 mmol) was added to a mixture of **4a** or **4b** (5 mmol) and anhydrous potassium carbonate (10 mmol) in DMF (5 mL). The reaction mixture was stirred for 1 hr at room temperature and then poured into cold water. After stirring for 10 min the precipitated product was collected by filtration, washed with water, dried, and recrystallized from DMF.

Method B

A solution of **5a** or **5b** (5 mmol) in 8% aqueous sodium hydroxide was treated with ethyl iodide (10 mmol) and stirred for 2–3 hr at room temperature. During this period, the precipitate thus obtained was filtered, washed with water, dried, and recrystallized from DMF.

5,5′-(1,4-Phenylene)bis(3-ethylthio-4-phenyl-1,2,4-triazole) (6a)

Obtained in 58% yield, m.p. 310–312°C; (found: C, 64.40; H, 5.10; N, 17.30; S, 13.20. $C_{26}H_{24}N_6S_2$ requires C, 64.44; H, 4.99; N, 17.34; S, 13.23%); υ_{max}/cm^{-1} 3050 (Ar-CH), 2900 (aliph-CH.); 1620 (C=N); δ_H 1.15 (t, 6H, J = 7 Hz, $2CH_3$), 4.25 (q, 4H, J = 7 Hz, $2CH_2$), 8.20 (m, 14H, Ar-H); δ_C 15.85 (CH_3 carbon), 28.0 (CH_2 carbon), 127.0–137.0 (Ar-C), 149.0 (C-5), 153.0 (C-3); m/z 484 (M^+, 61%).

5,5′-(1,4-Phenylene)bis(3-ethylthio-4-benzyl-1,2,4-triazole) (6b)

Obtained in 62% yield, m.p. 324–326°C; (found: C, 65.50; H, 5.60; N, 16.40; S, 12.50. $C_{28}H_{28}N_6S_2$ requires C, 65.60; H, 5.50; N, 16.39; S, 12.51%); υ_{max}/cm^{-1} 3050 (Ar-CH), 2900 (aliph-CH.); 1620 (C=N); δ_H 1.10 (t, 6H, J = 7Hz, $2CH_3$), 4.20 (q, 4H, J = 7 Hz, $2CH_2$), 5.40 (S, 4H, $2CH_2$), 7.40-8.20 (m, 14H, Ar-H).

General Procedure for the Synthesis of Bis-(2-Arylamino-1,3,4-thiadiazole) 8a, b and bis-(2-phenylamino-1,3,4-oxadiazole) 11

A solution of **4a** or **4b** or **10** (5 mmol) in $POCl_3$ (5 ml) was refluxed for 2 hr. The excess of $POCl_3$ was removed under reduced pressure and the residue was poured into cold water. After stirring for 10 min the precipitated product was collected by filtration, washed with water, dried, and recrystallized from DMF/EtOH.

5,5′-(1,4-Phenylene)bis(2-phenylamino-1,3,4-thiadiazole) (8a)

Obtained in 87% yield, m.p. 345–347°C; (found: C, 61.70; H, 3.80; N, 19.60; S, 14.90. $C_{22}H_{16}N_6S_2$ requires C, 61.66; H, 3.76; N, 19.61; S, 14.96%); υ_{max}/cm^{-1} 3200 (NH), 3050 (Ar-CH), 1620 (C=N); δ_H 6.90–7.30 (m, 14H, Ar-H), 11.25 (s, 2H, 2NH); m/z 428 (M^+, 69%).

5,5′-(1,4-Phenylene)bis(2-benzylamino-1,3,4-thiadiazole) (8b)

Obtained in 92% yield, m.p. 276–278°C; (found: C, 63.20; H, 4.40; N, 18.40; S, 14.00. $C_{24}H_{20}N_6S_2$ requires C, 63.13; H, 4.42; N, 18.41; S, 14.04%); υ_{max}/cm^{-1} 3150 (NH), 3050 (Ar-CH), 2900 (aliph-CH.); 1620 (C=N); δ_H 4.5 (s, 4H, $2CH_2$), 7.00–7.40 (m, 14H, Ar-H), 11.20 (s, 2H, 2NH).

5,5′-(1,4-Phenylene)bis(2-phenylamino-1,3,4-oxadiazole) (11)

Obtained in 73% yield, m.p. 264–266°C; (found: C, 66.70; H, 4.00; N, 21.30. $C_{22}H_{16}N_6O_2$ requires C, 66.66; H, 4.07; N, 21.20%); υ_{max}/cm^{-1} 3200 (NH), 3050 (Ar-CH), 1620 (C=N); δ_H 7.00–7.40 (m, 14H, Ar-H), 11.30 (s, 2H, 2NH).

Alternative Synthesis of 11

Compound **4a** (5 mmol) was suspended in ethanol (20 ml). 5 ml of 4 N sodium hydroxide and iodine in potassium iodide solution (5 ml, 5%) were added gradually with stirring and cooling until the color of iodine

persisted. The precipitated product was filtered, dried, and crystallized from DMF/EtOH to afford **11**, m.p. 264–266°C, mixed m.p. 262–264°C.

Synthesis of Bis-(2-(N-ethyl)-arylamino-1,3,4-thiadiazole) 7a,b

Ethyl iodide (10 mmol) was added to a solution of **8a**,**b** (5 mmol) in DMF. The reaction mixture was heated at 60–65°C for 30 h (monitored by tlc) Thereafter, the mixture was poured into cold water. After stirring over night the precipitated product was collected by filtration, washed with water, dried, and recrystallized from DMF.

5,5′-(1,4-Phenylene)bis(2-(N-ethyl)-phenylamino-1,3,4-thiadiazole) (7a)

Obtained in 65% yield, m.p. 356–358°C; (found: C, 64.40; H, 5.00; N, 17.40; S, 13.20. $C_{26}H_{24}N_6S_2$ requires C, 64.44; H,4.99; N, 17.34; S, 13.23%); υ_{max}/cm^{-1} 3050 (Ar-CH), 2900 (aliph-CH.); 1620 (C=N); δ_H 1.40 (t, 6H, J = 7Hz, $2CH_3$), 4.12 (q, 4H, J = 7 Hz, $2CH_2$), 7.30–7.80 (m, 14H, Ar-H).

5,5′-(1,4-Phenylene)bis(2-(N-ethyl)-benzylamino-1,3,4-thiadiazole) (7b)

Obtained in 69% yield, m.p. >360°C; (found: C, 65.50; H, 5.60; N, 16.40; S, 12.50. $C_{28}H_{28}N_6S_2$ requires C, 65.60; H, 5.50; N, 16.39; S, 12.51%); υ_{max}/cm^{-1} 3050 (Ar-CH), 2900 (aliph-CH); δ_H 1.35 (t, 6H, J = 7 Hz, $2CH_3$), 4.15 (q, 4H, J = 7 Hz, $2CH_2$), 4.5 (s, 4H, $2CH_2$), 7.10–8.00 (m, 14H, Ar-H).

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