One-pot, three-component synthesis of polyfunctionalized benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridine and benzo[*g*]pyrazolo[3,4-*b*]quinoline derivatives in the presence of silver nanoparticles (AgNPs)

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Abstract

An efficient and straightforward protocol for one-pot, three-component reaction of aryl glyoxal monohydrates **1a-h**, 5-amino-1-aryl-3-methylpyrazoles **2a,b** and 4-hydroxyquinoline-2(1*H*)-one **3** or 2-hydroxy-1,4-naphthoquinone **4** using AgNPs as a high performance nanocatalyst in H_2O/EtOH at 60 ^oC afforded the corresponding polyfunctionalized benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines **5a-h** and benzo[*g*]pyrazolo[3,4-*b*]quinolines **6a-i**, respectively. Excellent catalytic activity, high yields, employing green media and green nanocatalyst, cost-effective and simple procedure are some notable advantages of using AgNPs as a noble metal nanocatalyst in this synthetic strategy. The structures of fused heterocycles were confirmed by their FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectral data and microanalysis.

1. INTRODUCTION

According to researchers, the heterocycles containing at least one nitrogen atom generally, have exhibited biological and pharmaceutical properties. Hence, contriving and synthesis of such aza-heterocycles and aza-aromatic compounds have been recognized worthwhile, and have become a major challenge in organic synthesis. Among these, polyfunctionalized heterocycles have considered as magic structures due to appearance of several hetero rings with wide medicinal and clinical applications. Polyfunctionalized fused heterocyclic scaffolds due to the appearance of diverse *N* containing rings simultaneously, have supposed to create a versatile bioactive compound so we faced an increasing prevalence of research in this field.[1-3] As mentioned, pyrazoloquinoline derivatives are highly regarded due to their pharmaceutical and biological properties.[4-8]

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4105

One of the most prominent and facile strategies in organic synthesis and specially, synthesis of heterocyclic compounds and natural products is multicomponent reactions (MCRs); which undoubtedly, has provided a compatible path in the synthesis by breaking or making multiple bonds through environmentally and economically useful one-pot procedures avoiding separation of intermediates or changing the solvent.[9-16]

During recent years, chemists have organized sustainable MCRs, using green solvents alongside novel nanocatalysts have altered this strategy to a conspicuous tool. High catalytic activity, selectivity, stability, reusability and moving along green chemistry are notable features of nanocatalysts. Among them, noble metal nanocatalyst such as AgNPs due to superior physicochemical, and biological properties, environmentally benign, and low-cost have extensively investigated.[17]

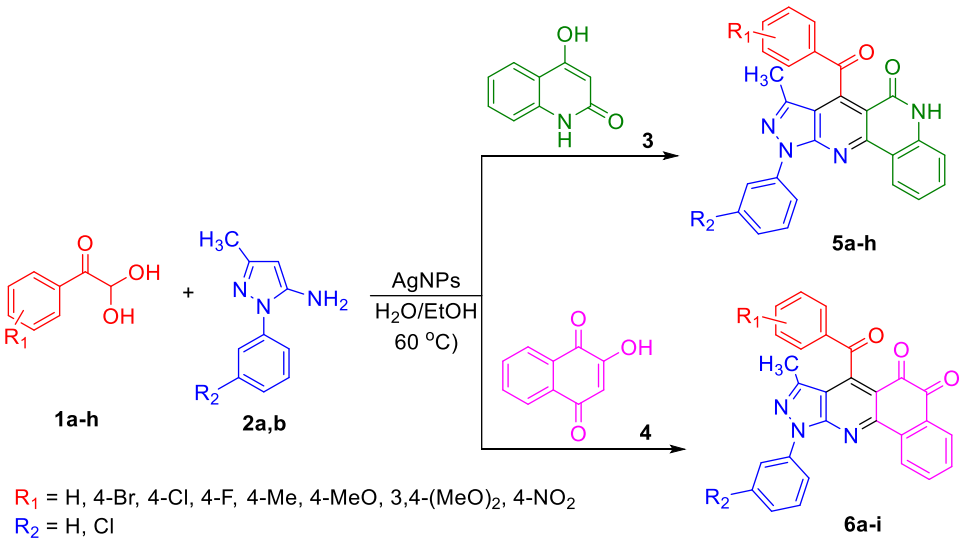
Afterwards, synthesis of heterocycles containing bioactive core framework with diverse biological and pharmaceutical activities is noteworthy and contriving economical, simple and efficient methods to achieve such compounds is much more various. Aryl glyoxals are known as an important synthon in the preparation of complex hetero scaffolds due to the presence of two active sites that has made it as 1,2-biacceptor which could be attacked by nucleophilic reagents.[18-21]

In continuation of our previous studies on the application of aryl glyoxals in the synthesis of heterocyclic compounds,[22-29] herein, we report a one-pot, three-component reaction of aryl glyoxal monohydrates, 5-amino-1-aryl-3-methylpyrazoles and 4-hydroxyquinoline-2(1*H*)-one or 2-hydroxy-1,4-naphthoquinone (lawsone) using AgNPs as nanocatalyst in H_2O/EtOH under mild conditions to afford the corresponding pyrazolonaphthyridines and pyrazoloquinolines respectively in good to high yields.

2. RESULTS AND DISCUSSION

It was found that the reaction of aryl glyoxal monohydrates **1a-h**, 5-amino-1-aryl-3-methylpyrazoles **2a,b** and 4-hydroxyquinoline-2(1*H*)-one (**3**) or 2-hydroxy-1,4-naphthoquinone (**4**) using AgNPs as nanocatalyst in H_2O/EtOH (1:1) at 60 ^oC gave the desired benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines **5a-h** and benzo[*g*]pyrazolo[3,4-*b*]quinolines **6a-i** in

good to high yields (Scheme 1). The products were fully characterized by their FT-IR and ^{1}H-NMR and ^{13}C-NMR spectral data and microanalysis.



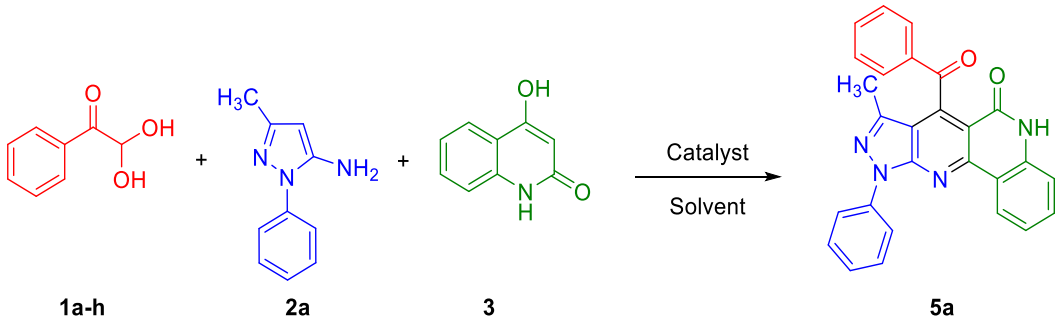
SCHEME 1 Synthesis of benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines **5a-h** and benzo[*g*]pyrazolo[3,4-*b*]quinolines **6a-i**

In our initial studies, we evaluated one-pot, three-component reaction of pheyl glyoxal monohydrates **1a**, 5-amino-1-phenyl-3-methylpyrazole **2a**, and 4-hydroxyquinoline-2(1*H*)-one **3**. The equimolar mixture, of **1a**, **2a**, and **3**, was tested under various conditions. The effects of solvent, catalyst and temperature were appraised for model reaction, and the results are summarized in Table 1.

Firstly, the reaction was carried out under catalyst-free conditions at room temperature but, no product was observed even after 24 h (Table 1, entry 1). Increasing the temperature of reaction up to 60 ^{o}C under catalyst-free condition in H_2O/EtOH (1:1) for 1 h, also did not give any product (Table 1**,** entry 2). Using 5 and 10 ppm of AgNPs as nanocatalyst, the desired products achieved in good yields (Table 1, entries 11-12). The best result was obtained in terms of yield 87% and reaction time 1 h, while 10 ppm of AgNPs were utilized (Table 1, entry 13). Employing 20 ppm of AgNPs, the yield of reaction was not improved so much (Table 1**,** entry 14). The model reaction was carried out using various solvents such as ethanol, acetic acid, and water to find the best solvent system. Among these solvents, H_2O/EtOH (1:1) evaluated as the best

solvent system (Table 1, entry 13). Based on achieved results, we shifted our attention toward using various ordinary catalysts for the same model reaction in H_2O/EtOH (1:1) at 60 ^oC. Other catalysts such as DBU, Et_3N, *p*-TSA, and *L*-proline were tested under similar reaction conditions to obtain the maximum yield and minimum reaction time. The results are mentioned in (Table 1, entries 7-10). In conclusion, the reaction was performed in the presence of catalytic amount of AgNPs in H_2O/EtOH at 60 ^oC, the smooth progress of reaction was clear, by monitoring the reaction completion *via* TLC. High yield of 7-benzoyl-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one was obtained within 1 h.

TABLE 1 Optimization of the reaction conditions for synthesis of **5a**



1a-h **2a** **3** **5a**

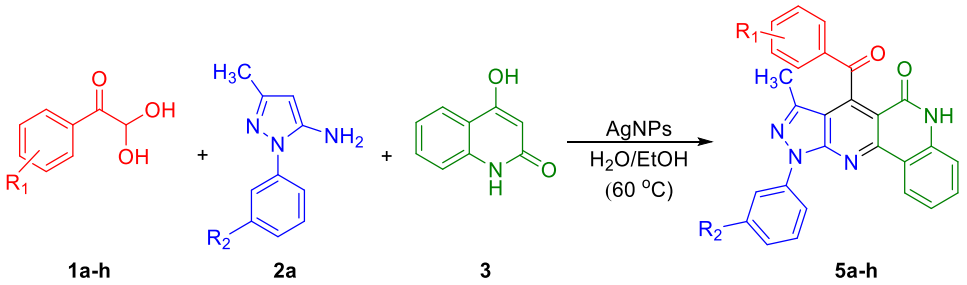
Entry	Catalyst (mol%)	Solvent	Temperature (^oC)	Time (h)	Yield (%)
1	-	H_2O/EtOH (1:1)	r.t.	24	-
2	-	H_2O/EtOH (1:1)	60	1	-
3	-	H_2O/EtOH (2:1)	60	1	-
4	-	H_2O	60	1	-
5	-	EtOH	60	1	-
6	-	AcOH	60	1	-
7	DBU (10 mol%)	H_2O/EtOH (1:1)	60	1	35
8	Et_3N (10 mol%)	H_2O/EtOH (1:1)	60	1	31
9	*p*-TSA (10 mol%)	H_2O/EtOH (1:1)	60	1	32
10	*L*-proline (10 mol%)	H_2O/EtOH (1:1)	60	1	40
11	Ag bulk	H_2O/EtOH (1:1)	60	1	37
12	AgNPs (5 ppm)	H_2O/EtOH (1:1)	60	1	68
13	**AgNPs (10 ppm)**	**H_2O/EtOH (1:1)**	60	1	**87**
14	AgNPs (20 ppm)	H_2O/EtOH (1:1)	60	1	87

15	AgNPs (10 ppm)	H_2O/EtOH (1:2)	60	1	68
16	AgNPs (10 ppm)	H_2O	60	1	56
17	AgNPs (10 ppm)	EtOH	60	1	64
18	AgNPs (10 ppm)	AcOH	60	1	70

The optimized conditions are shown in bold text.

The reaction conditions were then applied to a range of different aryl glyoxal monohydrates, to synthesize a series of products. The reaction times, melting points, and yields of the synthesized polyfunctional benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines **5a-h** are shown in Table 2.

TABLE 2 The yields, reaction times and melting points of compounds **5a-h**



1a-h 2a 3 5a-h

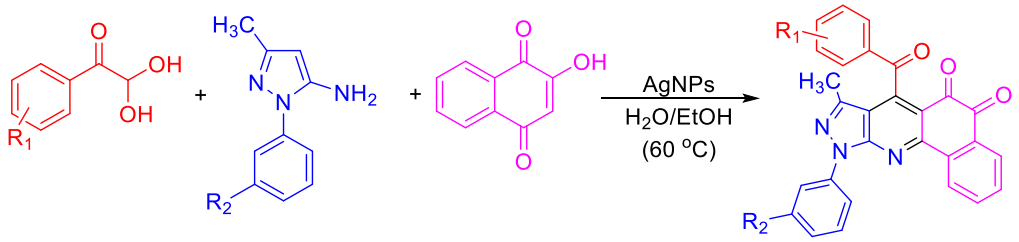
Entry	Products	R_1	R_2	Time (h)	Mp (°C)	Yield[a] (%)
1	**5a**	H	H	1	310-311	87
2	**5b**	4-Br	H	2	300-302	68
3	**5c**	4-Cl	H	2	305-307	86
4	**5d**	4-F	H	1.5	298-300	75
5	**5e**	4-Me	H	1.5	304-306	77
6	**5f**	4-MeO	H	1.5	303-305	79
7	**5g**	3,4-$(MeO)_2$	H	1.5	268-270	81
8	**5h**	4-NO_2	H	2	298-300	65

[a]Isolated yield.

Further investigations, we tried to extend the scope of reactions so, 2-hydroxy-1,4-naphthoquinone **4** as dicarbonyl compound (active methylene) was employed. Interestingly, 2-hydroxy-1,4-naphthoquinone **4** in combination with aryl glyoxal monohydrates **1a-h** and 5-amino-1-aryl-3-methylpyrazoles **2a,b** provided the corresponding fused products **6a-i** in high

yields under the optimized reaction conditions as shown in Table 3. The reaction times, melting points, and yields of the synthesized benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones **6a-i** are listed in Table 3.

TABLE 3 The yields, reaction times and melting points of compounds **6a-i**

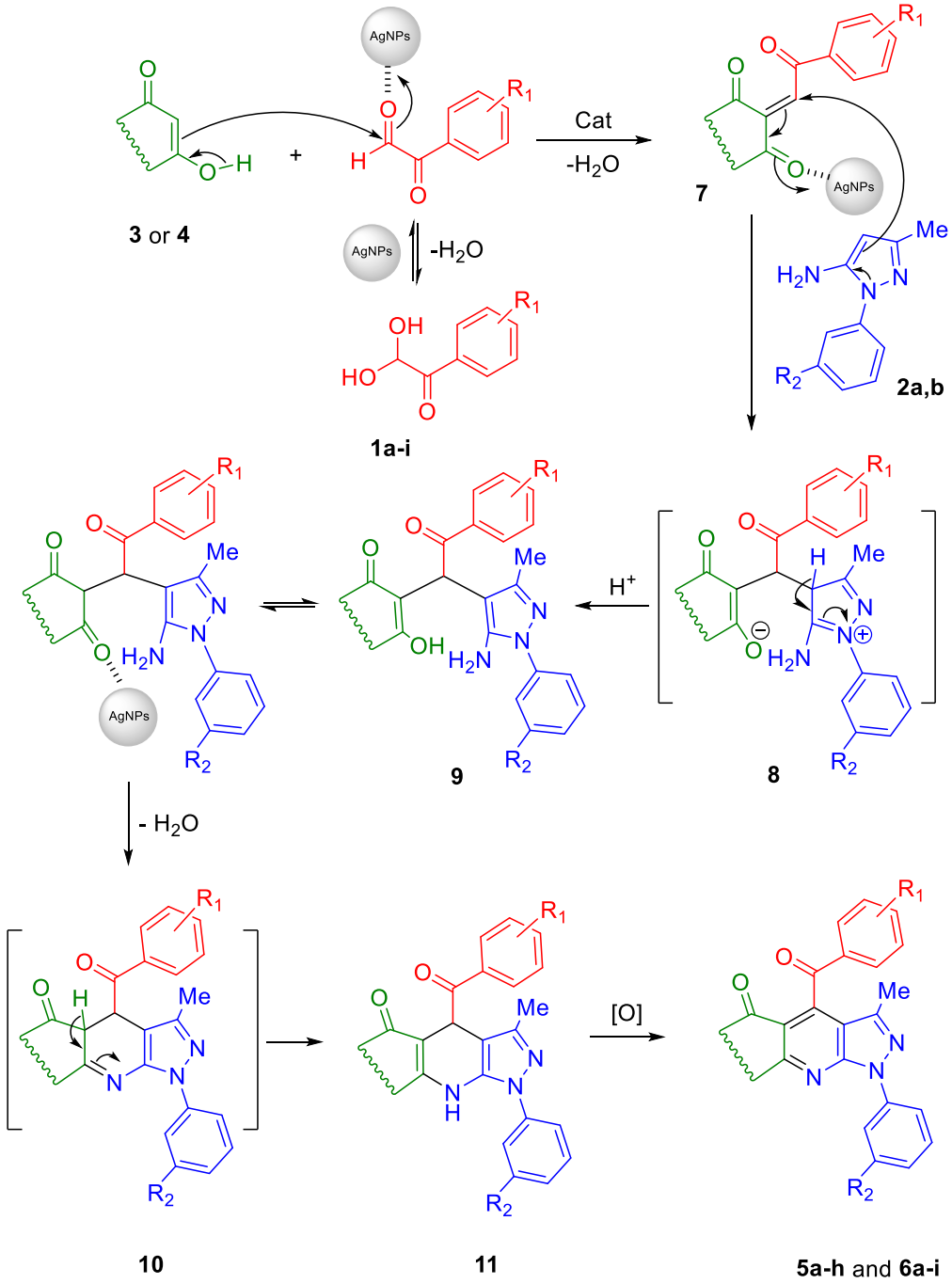


1a-i **2a,b** **4** **6a-i**

Entry	Products	R_1	R_2	Time (h)	Mp (°C)	Yield[a] (%)
1	**6a**	H	H	1	283-285	89
2	**6b**	4-Cl	H	2	279-282	85
3	**6c**	4-F	H	1.5	272-274	88
4	**6d**	4-MeO	H	1.5	284-286	90
5	**6e**	4-NO_2	H	2	275-277	93
6	**6f**	4-Cl	3-Cl	1.5	295-298	89
7	**6g**	4-F	3-Cl	2	272-274	88
8	**6h**	4-MeO	3-Cl	1	263-265	93
9	**6i**	4-NO_2	3-Cl	1.5	248-251	87

[a]Isolated yield.

The proposed mechanism for this reaction, involves the *Knoevenage*l condensation of aryl glyoxals **1a-h** with 4-hydroxyquinolin-2(1*H*)-one **3** or 2-hydroxy-1,4-naphthoquinone **4** by loss of a water molecule to form the corresponding intermediate **7**. Following *Michael* addition of 3-methyl-1-aryl-1*H*-pyrazol-5-one **2a,b** to this intermediate will form the final products benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines **5a-h** and benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones **6a-i**, through protonation to **9**, loss of a water molecule by intramolecular cyclization to **10**, followed by tautomerization to **11**, and final oxidation along with aromatization. (Scheme 2)



SCHEME 2 The proposed mechanism for synthesis of final products **5a-h** and **6a-i**

In the ^{1}H NMR spectra of products **5a-h** and **6a-i,** the characteristic broad singlets at around δ = 11.66-11.75 ppm, ascribed to the NH groups, and singlets at δ = 2.11-2.23 ppm are attributed to the methyl groups of pyrazole ring, which were present in all new products. In the ^{13}C NMR

spectra, signals located around δ = 160.8-194.2 were attributed to three different carbonyl groups. In the FT-IR (KBr) spectra, the characteristic absorptions bands at 3327-3411 cm^{-1} and 1565-1680 cm^{-1} could be assigned to the vibrations of NH and different carbonyl groups, respectively.

3. CONCLUSIONS

We have reported an efficient method for the synthesis of pyrazolonaphthyridines and pyrazoloquinolines through one-pot, three-component condensation reaction of aryl glyoxals, 5-amino-1-aryl-3-methylpyrazoles and 4-hydroxyquinoline-2(1*H*)-one or 2-hydroxy-1,4-naphthoquinone (lawsone) in the presence of AgNPs as a nobel metal nanocatalyst in EtOH/H_2O at 60 ^oC. The products **5a-h**, **6a**, **6d**, **6f**, **6h** and **6i** have been fully characterized by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectral data and microanalysis, products **6b**, **6c** and **6e** have been confirmed by FT-IR and ^{1}H-NMR spectral data and microanalysis and also compound **6g**, characterized by FT-IR spectrum and microanalysis. The simplicity of the method, ease of product isolation, green reaction condition, and short reaction times are the advantages of this procedure. The synthesized pyrazolonaphthyridines and pyrazoloquinolines may have biological and pharmacological activities.

Experimental Section

The chemicals used in this work were purchased from Acros and Merck companies and were used without purification. Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. FT-IR (KBr) spectra were recorded on a Thermo-Nicolet (Nexus 670) spectrometer using KBr discs. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer in DMSO-d_6 with TMS as the internal reference. Elemental analyses were performed using a Leco Analyzer 932. The aryl glyoxals were prepared as their hydrates by oxidation of the corresponding acetophenones with SeO_2.[30] The AgNPs as nanocatalyst was prepared according to the literature.[31, 32]

General procedure for synthesis of benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridines 5a-h and benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones 6a-i

A mixture of 5-amino-1-aryl-3-methylpyrazoles (1 mmol), 4-hydroxyquinoline-2(1*H*)-one (1 mmol) or 2-hydroxy-1,4-naphthoquinone (1 mmol) and various aryl glyoxal monohydrates (1 mmol), in the presence of AgNPs (10 ppm) in H_2O/EtOH (1:1) (5 mL) was heated at 60^oC for the appropriate time. The progress of the reaction was monitored by TLC (chloroform:*n*-hexane / 1:2). Upon the completion of the reaction, the mixture was cooled, and the precipitate was easily isolated by simple filtration and then rinsed with distilled cold water and ethanol. The pure products were obtained by recrystallization from EtOH.

The physical and spectral data for all new products as well as their elemental analyses are reported.

7-Benzoyl-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5a)

Yellow powder; mp: 310-312 ºC; yield: 87% (375 mg). IR (KBr) ν_{max}: 3327, 3036, 2984, 2863, 1667, 1570, 1498, 1433, 1350, 128, 1169, 1125, 750 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.71 (s, exchanged by D_2O addition, 1H, NH), 8.76 (d, J = 7.8 Hz, 1H, Ar), 8.39 (d, J = 7.8 Hz, 2H, Ar), 7.81 (d, J = 7.2 Hz, 2H, Ar), 7.72-7.54 (m, 4H, Ar), 7.51 (t, J = 7.5 Hz, 2H, Ar), 7.40 (t, J = 7.5 Hz, 3H, Ar), 2.19 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 193.2, 160.9, 151.9, 151.6, 146.2, 143.5, 139.1, 139.1, 137.1, 130.1, 129.8, 129.4, 129.0, 128.7, 122.0, 121.7, 120.1, 119.3, 114.7, 114.3, 14.2 ppm. Anal. Calcd for $C_{27}H_{18}N_4O_2$: C, 75.34; H, 4.21; N, 13.02. Found: C, 75.40; H, 4.15; N, 13.12.

7-(4-Bromobenzoyl)-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5b)

Yellow powder; mp: 300-301 ºC; yield: 68% (347 mg). IR (KBr) ν_{max}: 3339, 2981, 2859, 1666, 1571, 1351, 1261, 1223, 1168, 1123, 1068, 756 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.75 (s, exchanged by D_2O addition, 1H, NH), 8.74 (d, J = 7.8 Hz, 1H, Ar), 8.39 (d, J = 8.1 Hz, 2H, Ar), 7.70-7.55 (m, 7H, Ar), 7.43-7.30 (m, 3H, Ar), 2.21 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 193.1, 160.9, 151.9, 151.6, 145.4, 143.5, 139.1, 139.0, 136.1, 132.5, 131.1, 129.8, 128.3, 127.1, 122.6, 122.0, 120.1, 119.3, 114.7, 114.3, 14.2 ppm. Anal. Calcd for $C_{27}H_{17}BrN_4O_2$: C, 63.67; H, 3.36; N, 11.00. Found: C, 63.72; H, 3.42; N, 10.92.

7-(4-Chlorobenzoyl)-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5c)

White powder; mp: 305-306 ºC; yield: 86% (400 mg). IR (KBr) ν_{max}: 3311, 2982, 2860, 1666, 1566, 1348, 1224, 1096, 1021, 758 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.75 (s, exchanged by D_2O addition, 1H, NH), 8.74 (d, J = 7.8 Hz, 1H, Ar), 8.39 (d, J = 7.8 Hz, 2H, Ar), 7.83 (d, J = 8.1 Hz, 2H, Ar), 7.75-7.60 (m, 3H, Ar), 7.56 (d, J = 8.1 Hz, 2H, Ar), 7.44-7.30 (m, 3H, Ar), 2.21 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.9, 160.9, 151.9, 151.6, 145.5, 143.5, 139.1, 139.0, 135.8, 131.0, 129.9, 129.6, 128.5, 122.1, 121.9, 120.1, 119.9, 119.2, 114.7, 114.3, 14.2 ppm. Anal. Calcd for $C_{27}H_{17}ClN_4O_2$: C, 69.75; H, 3.69; N, 12.05. Found: C, 69.70; H, 3.72; N, 12.02.

7-(4-Fluorobenzoyl)-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5d)

Yellow powder; mp: 298-299 ºC; yield: 75% (336 mg). IR (KBr) ν_{max}: 3313, 3178, 3032, 2978, 2856, 1664, 1564, 1502, 1430, 1350, 1232, 1151, 1025, 853, 760 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.73 (s, exchanged by D_2O addition, 1H, NH), 8.75 (d, J = 6.9 Hz, 1H, Ar), 8.39 (d, J = 6.6 Hz, 2H, Ar), 7.90 (bs, 2H, Ar), 7.65 (bs, 3H, Ar), 7.45-7.30 (m, 5H, Ar), 2.20 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.5, 160.9, 151.9, 151.6, 145.8, 143.5, 139.0, 133.9, 133.2, 131.0, 129.8, 128.7, 122.1, 121.9, 120.4, 120.0, 119.2, 116.6, 114.6, 114.3, 14.2 ppm. Anal. Calcd for $C_{27}H_{17}FN_4O_2$: C, 72.31; H, 3.82; N, 12.49. Found: C, 72.40; H, 3.72; N, 12.52.

8-Methyl-7-(4-methylbenzoyl)-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5e)

White powder; mp: 304-306 ºC; yield: 77% (342 mg). IR (KBr) ν_{max}: 3327, 3037, 2982, 2861, 1666, 1568, 1499, 1428, 1351, 1262, 1170, 1124, 1027, 760 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.69 (s, exchanged by D_2O addition, 1H, NH), 8.75 (d, J = 7.8 Hz, 1H, Ar), 8.39 (d, J = 8.1 Hz, 2H, Ar), 7.72-7.60 (m, 5H, Ar), 7.41 (d, J = 7.8 Hz, 2H, Ar), 7.40 (t, J = 6.9 Hz, 1H, Ar), 7.31 (d, J = 8.1 Hz, 2H, Ar), 2.38 (s, 3H, CH_3), 2.23 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 193.5, 160.9, 151.9, 151.6, 146.5, 144.6, 143.6, 139.1, 139.1, 134.8, 130.6,

130.3, 129.8, 129.4, 129.1, 128.8, 122.0, 120.1, 119.2, 114.6, 114.4, 21.9, 14.2 ppm. Anal. Calcd for $C_{28}H_{20}N_4O_2$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.60; H, 4.62; N, 12.65.

7-(4-Methoxybenzoyl)-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5f)

Yellow powder; mp: 303-304 ºC; yield: 79% (364 mg). IR (KBr) ν_{max}: 3411, 2980, 2857, 1670, 1566, 1502, 1358, 1255, 1168, 1023, 756 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.69 (s, exchanged by D_2O addition, 1H, NH), 8.75 (d, J = 7.8 Hz, 1H, Ar), 8.39 (d, J = 7.8 Hz, 2H, Ar), 7.76 (d, J = 8.4 Hz, 2H, Ar), 7.66 (bt, J = 7.8 Hz, 3H, Ar), 7.45-7.32 (m, 3H, Ar), 7.02 (d, J = 8.7 Hz, 2H, Ar), 3.83 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.4, 163.9, 160.8, 151.9, 151.5, 146.7, 143.7, 139.1, 132.6, 131.4, 131.0, 130.3, 122.1, 121.9, 121.7, 120.1, 119.9, 119.2, 114.7, 114.5, 114.3, 56.6, 14.2 ppm. Anal. Calcd for $C_{28}H_{20}N_4O_3$: C, 73.01; H, 4.38; N, 12.17. Found: C, 73.10; H, 4.42; N, 12.12.

7-(3,4-Dimethoxybenzoyl)-8-methyl-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5g)

Yellow powder; mp: 263-265 ºC; yield: 81% (397 mg). IR (KBr) ν_{max}: 3330, 2987, 2917, 1667, 1589, 1504, 1430, 1349, 1267, 1131, 1024, 758 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.66 (s, exchanged by D_2O addition, 1H, NH), 8.75 (d, J = 7.5 Hz, 1H, Ar), 8.40 (d, J = 7.8 Hz, 2H, Ar), 7.75-7.30 (m, 7H, Ar), 7.12 (bd, J = 6.9 Hz, 1H, Ar), 6.92 (d, J = 8.1 Hz, 1H, Ar), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.21 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.4, 163.8, 160.8, 154.0, 151.9, 151.5, 149.5, 146.7, 143.7, 139.2, 131.0, 130.3, 129.8, 128.6, 125.2, 121.9, 120.1, 119.2, 114.5, 56.8, 56.3, 14.2 ppm. Anal. Calcd for $C_{29}H_{22}N_4O_4$: C, 71.01; H, 4.52; N, 11.42. Found: C, 71.10; H, 4.52; N, 11.38.

8-Methyl-7-(4-nitrobenzoyl)-10-phenyl-5,10-dihydro-6*H*-benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridin-6-one (5h)

Yellow powder; mp: 298-300 ºC; yield: 65% (309 mg). IR (KBr) ν_{max}: 3366, 3040, 2993, 2916, 1663, 1569, 1498, 1433, 1346, 1225, 756 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 11.81 (s, exchanged by D_2O addition, 1H, NH), 8.76 (d, J = 7.8 Hz, 1H, Ar), 8.40 (d, J = 7.8 Hz, 2H, Ar), 8.30 (d, J = 7.8 Hz, 2H, Ar), 8.08 (d, J = 8.4 Hz, 2H, Ar), 7.67 (t, J = 7.2 Hz, 3H, Ar), 7.45-7.30

(m, 3H, Ar), 2.23 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.8, 161.1, 151.9, 151.7, 150.6, 144.7, 143.4, 141.3, 139.0, 139.0, 131.1, 129.9, 129.6, 125.7, 125.5, 123.7, 122.0, 120.2, 119.3, 114.8, 114.3, 14.3 ppm. Anal. Calcd for $C_{27}H_{17}N_5O_4$: C, 68.21; H, 3.60; N, 14.73. Found: C, 68.15; H, 3.65; N, 14.62.

7-Benzoyl-8-methyl-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10H)-dione (6a)

Orange powder; mp: 283-286 °C; yield: 89% (396 mg). IR (KBr) ν_{max}: 3064, 1675, 1566, 1446, 1282, 1221, 753, 383 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.71 (d, J = 7.5 Hz, 1H, Ar), 8.27 (d, J = 7.8 Hz, 2H, Ar), 8.06 (d, J = 7.2 Hz, 1H, Ar), 7.92-7.73 (m, 3H, Ar), 7.70 (t, J = 7.5 Hz, 2H, Ar), 7.65 (t, J = 7.8 Hz, 2H, Ar), 7.54 (t, J = 7.5 Hz, 2H, Ar), 7.42 (t, J = 7.5 Hz, 1H, Ar), 2.13 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 194.2, 178.2, 177.5, 162.3, 153.8, 151.0, 147.2, 144.4, 138.6, 136.4, 135.9, 135.7, 134.7, 133.2, 132.1, 129.9, 129.5, 129.3, 128.8, 127.2, 121.4, 120.7, 113.9, 13.8 ppm. Anal. Calcd for $C_{28}H_{17}N_3O_3$: C, 75.84; H, 3.86; N, 9.48. Found: C, 75.75; H, 3.82; N, 9.35.

7-(4-Chlorobenzoyl)-8-methyl-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6b)

Yellow powder; mp: 279-282 °C; yield: 85% (391 mg). IR (KBr) ν_{max}: 3078, 1673, 1565, 1493, 1426, 1283, 1220, 1090, 759 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.71 (d, J = 8.1 Hz, 1H, Ar), 8.28 (d, J = 7.8 Hz, 2H, Ar), 8.07 (d, J = 7.5 Hz, 1H, Ar), 7.99 (t, J = 7.8 Hz, 1H, Ar), 7.91 (d, J = 7.8 Hz, 2H, Ar), 7.71 (t, J = 7.8 Hz, 1H, Ar), 7.65 (t, J = 7.5 Hz, 2H, Ar), 7.60 (d, J = 8.1 Hz, 2H, Ar), 7.43 (t, J = 6.9 Hz, 1H, Ar), 2.15 (s, 3H, CH_3) ppm. Anal. Calcd for $C_{28}H_{16}ClN_3O_3$: C, 70.37; H, 3.37; N, 8.79. Found: C, 70.30; H, 3.32; N, 8.85.

7-(4-Fluorobenzoyl)-8-methyl-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6c)

Yellow powder; mp: 272-274 °C; yield: 88% (408 mg). IR (KBr) ν_{max}: 3076, 2926, 1680, 1576, 1498, 1426, 1285, 1230, 1156, 761 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.72 (d, J = 7.8 Hz, 1H, Ar), 8.28 (d, J = 8.4 Hz, 2H, Ar), 8.07 (d, J = 7.5 Hz, 1H, Ar), 7.99 (t, J = 6.9 Hz, 1H, Ar), 7.90 (d, J = 7.8 Hz, 2H, Ar), 7.71 (t, J = 8.1 Hz, 1H, Ar), 7.66 (t, J = 8.1 Hz, 2H, Ar), 7.44 (d, J =

7.5 Hz, 2H, Ar), 7.36 (t, *J* = 8.4 Hz, 1H, Ar), 2.15 (s, 3H, CH_3) ppm. Anal. Calcd for $C_{28}H_{16}FN_3O_3$: C, 72.88; H, 3.50; N, 9.11. Found: C, 72.75; H, 3.60; N, 9.15.

7-(4-Methoxybenzoyl)-8-methyl-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6d)

Yellow powder; mp: 284-286 °C; yield: 90% (428 mg). IR (KBr) ν_{max}: 3068, 2932, 1672, 1586, 1497, 1450, 1266, 1162, 762 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.71 (d, *J* = 7.8 Hz, 1H, Ar), 8.27 (d, *J* = 7.8 Hz, 2H, Ar), 8.05 (t, *J* = 7.5 Hz, 1H, Ar), 7.92 (d, *J* = 7.5 Hz, 1H, Ar), 7.85 (t, *J* = 7.8 Hz, 2H, Ar), 7.70 (t, *J* = 7.5 Hz, 1H, Ar), 7.65 (t, *J* = 7.5 Hz, 2H, Ar), 7.42 (d, *J* = 7.2 Hz, 1H, Ar), 7.04 (d, *J* = 9 Hz, 2H, Ar), 3.84 (s, 3H, OCH_3), 2.14 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.5, 178.3, 177.5, 164.3, 159.2, 158.1, 153.8, 147.5, 144.6, 138.6, 137.6, 136.5, 135.7, 133.1, 132.0, 131.7, 129.9, 129.0, 128.7, 127.1, 121.4, 120.5, 114.8, 56.1, 13.8 ppm. Anal. Calcd for $C_{29}H_{19}N_3O_4$: C, 73.56; H, 4.04; N, 8.87. Found: C, 73.65; H, 4.02; N, 8.80.

8-Methyl-7-(4-nitrobenzoyl)-10-phenyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6e)

Yellow powder; mp: 275-277 °C; yield: 93% (456 mg). IR (KBr) ν_{max}: 3071, 2926, 1678, 1530, 1431, 1346, 1284, 1218, 757, 687 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.74 (d, *J* = 6 Hz, 1H, Ar), 8.32 (d, *J* = 9 Hz, 2H, Ar), 8.29 (d, *J* = 8.1 Hz, 2H, Ar), 8.15 (d, *J* = 8.7 Hz, 2H, Ar), 8.08 (d, *J* = 8.4 Hz, 1H, Ar), 7.94 (bt, *J* = 8.4 Hz, 1H, Ar), 7.72 (t, *J* = 7.5 Hz, 1H, Ar), 7.67 (t, *J* = 7.5 Hz, 2H, Ar), 7.45 (bt, *J* = 7.8 Hz, 1H, Ar), 2.17 (s, 3H, CH_3) ppm. Anal. Calcd for $C_{28}H_{16}N_4O_5$: C, 68.85; H, 3.30; N, 11.47. Found: C, 68.93; H, 3.32; N, 11.52.

7-(4-Chlorobenzoyl)-10-(3-chlorophenyl)-8-methyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6f)

Yellow powder; mp: 295-298 °C; yield: 89% (458 mg). IR (KBr) ν_{max}: 3081, 2926, 1678, 1575, 1477, 1455, 1277, 1223, 1162, 1091, 772 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.62 (d, *J* = 7.8 Hz, 1H, Ar), 8.32 (t, *J* = 8.7 Hz, 1H, Ar), 8.24 (d, *J* = 7.8 Hz, 1H, Ar), 8.05 (d, *J* = 7.8 Hz, 1H, Ar), 7.89 (bd, *J* = 7.8 Hz, 2H, Ar), 7.70 (t, *J* = 7.5 Hz, 1H, Ar), 7.64 (d, *J* = 8.4 Hz, 1H, Ar), 7.64 (t, *J* = 8.4 Hz, 1H, Ar), 7.60 (d, *J* = 8.4 Hz, 2H, Ar), 7.43 (bd, *J* = 8.1 Hz, 1H, Ar), 2.12 (s,

3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.9, 177.9, 177.4, 162.3, 153.9, 151.2, 146.3, 145.0, 139.7, 136.1, 135.6, 134.5, 134.1, 133.1, 132.2, 131.6, 131.1, 129.8, 129.7, 128.8, 126.6, 126.4, 120.9, 120.5, 114.2, 13.8 ppm. Anal. Calcd for $C_{28}H_{15}Cl_2N_3O_3$: C, 65.64; H, 2.95; N, 8.20. Found: C, 65.68; H, 2.90; N, 8.25.

10-(3-Chlorophenyl)-7-(4-fluorobenzoyl)-8-methyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6g)

Yellow powder; mp: 288-290 °C; yield: 88% (438 mg). IR (KBr) ν_{max}: 3109, 2927, 1675, 1564, 1477, 1443, 1279, 1226, 774 cm^{-1}. Anal. Calcd for $C_{28}H_{15}ClFN_3O_3$: C, 67.82; H, 3.05; N, 8.47. Found: C, 67.87; H, 3.02; N, 7.35.

10-(3-Chlorophenyl)-7-(4-methoxybenzoyl)-8-methyl-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6h)

Yellow powder; mp: 263-265 °C; yield: 93% (474 mg). IR (KBr) ν_{max}: 3058, 2929, 1670, 1583, 1448, 1258, 1165, 1022, 770 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.63 (d, J = 7.8 Hz, 1H, Ar), 8.32 (d, J = 8.1 Hz, 1H, Ar), 8.29 (s, 1H, Ar), 8.04 (d, J = 7.8 Hz, 1H, Ar), 7.90 (t, J = 7.5 Hz, 1H, Ar), 7.84 (d, J = 8.7 Hz, 2H, Ar), 7.69 (t, J = 7.5 Hz, 1H, Ar), 7.64 (t, J = 8.1 Hz, 1H, Ar), 7.43 (d, J = 8.7 Hz, 1H, Ar), 7.03 (d, J = 8.7 Hz, 2H, Ar), 3.32 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.3, 178.1, 177.4, 164.4, 162.3, 153.9, 151.2, 147.5, 145.1, 139.7, 136.3, 135.7, 134.1, 133.1, 132.1, 131.6, 129.0, 128.8, 126.6, 126.4, 120.6, 120.4, 119.2, 114.8, 114.3, 56.1, 13.7 ppm. Anal. Calcd for $C_{29}H_{18}ClN_3O_4$: C, 68.58; H, 3.57; N, 8.27. Found: C, 68.65; H, 3.62; N, 8.25.

10-(3-Chlorophenyl)-8-methyl-7-(4-nitrobenzoyl)-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione (6i)

Yellow powder; mp: 248-251 °C; yield: 87% (457 mg). IR (KBr) ν_{max}: 3093, 1675, 1571, 1531, 1452, 1344, 1218, 771 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.67 (d, J = 7.8 Hz, 1H, Ar), 8.63 (s, 1H, Ar), 8.32 (bd, J = 8.4 Hz, 3H, Ar), 8.14 (t, J = 8.7 Hz, 2H, Ar), 7.93 (t, J = 8.1 Hz, 1H, Ar), 7.92 (d, J = 7.8 Hz, 1H, Ar), 7.72 (t, J = 7.5 Hz, 1H, Ar), 7.67 (d, J = 7.8 Hz, 1H, Ar), 7.47 (d, J = 7.2 Hz, 1H, Ar), 2.15 (s, 3H, CH_3) ppm. ^{13}C-NMR (75.5 MHz, DMSO-d_6) δ: 192.9, 177.8, 177.5, 162.3, 154.0, 151.0, 145.6, 144.9, 139.9, 136.0, 135.7, 134.1, 133.2, 132.3, 131.7,

130.6, 128.8, 126.8, 124.7, 121.1, 120.6, 120.6, 119.3, 114.1, 13.91 ppm. Anal. Calcd for $C_{28}H_{15}ClN_4O_5$: C, 64.32; H, 2.89; N, 10.71. Found: C, 64.29; H, 2.82; N, 10.75.

The compounds **6b, 6c, 6e** and **6g** did not show either ^{1}H-NMR and ^{13}C-NMR or both due to very low solubilities in DMSO-d_6.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial assistance from Urmia University.

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