A Rapid Combinatorial Library Synthesis of Benzazolo[2,1-*b*]quinazolinones and Triazolo[2,1-*b*]quinazolinones

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ABSTRACT: *Benzazolo [2,1-b]quinazolinones and triazolo[2,1-b]quinazolinones were synthesized in high yields by the condensation reaction of an aldehyde and a cyclic β-diketone with 2 - aminobenzimidazole, 2 - aminobenzothiazole or 1, 2, 4 - triazole derivatives in 1 - butyl - 3 - methylimidazolium bromide as an ionic liquid under classic heating conditions within 5-60 minutes.*

KEY WORDS: *2-Aminobenzimidazole, 2-Aminobenzothiazole, 3-Amino-1,2,4-triazole, 3,5-Diamino-1, 2,4-triazole, 3-Amino-5-thiomethoxy-1,2,4-triazole, Ionic liquid.*

INTRODUCTION

Quinazolines are reported to have a broad spectra of biological activities such as propyl hydroxylase inhibitor [1], antidiabetics [2], anti-inflammatory [3], antiviral [4], antimicrobial [5], antineoplastic [6], and potent immunosuppressive agents [7]. They also emerged as an integral backbones of calcium channel blockers[8]. So, the analogs of these heterocycles show potent antitumor activity[9,10]. Quinazoline heterocycles are the subunit of several natural alkaloids and active pharmaceuticals [1,11,12] (Scheme 1).

The useful methods, have been reported for synthesis of tetrahydrobenzimidazo [2,1-*b*] quinazolin-1(2*H*)-ones and tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones ring system skeletons, are the condensation of aminoazoles with benzilidene compounds[13-16] or three-component condensation of 2-aminobenzothiazole or 2-aminobenzimidazole and an aldehyde with cyclic *β*-diketone [17-18]. However, these synthetic protocols suffer from one or more disadvantages such as harsh reaction conditions, prolonged reaction times, or use of hazardous and often expensive acid catalysts. Moreover, the synthesis of these heterocycles is usually carried out in polar solvents such as methanol, acetic acid, THF and DMF leading to complex isolation and recovery procedures. These processes also generate waste containing both catalyst and solvent, which have to be recovered, treated, and disposed off.

Recently, Room-Temperature Ionic Liquids (RTILs) have attracted much attention as promising alternative 'green' solvents to hazardous traditional organic solvents, due to their properties such as non-flammability, negligible vapor pressure, high thermal stability, solvating ability and easy recyclability. They have the potential to be highly polar yet non-coordinating [19-23]. In addition to the above-mentioned salient features of Ionic Liquids (ILs) as reaction media, we have also

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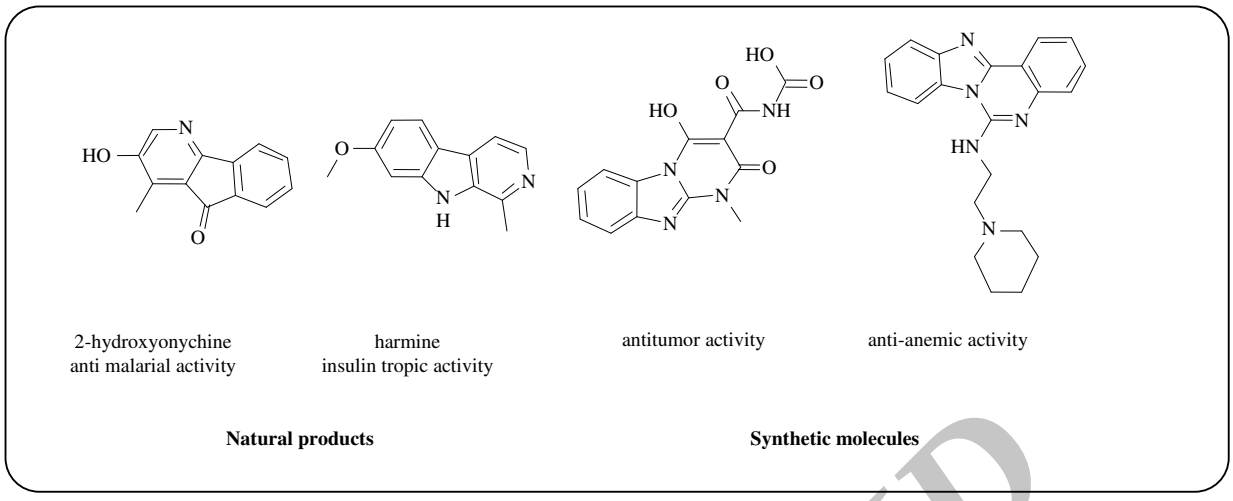
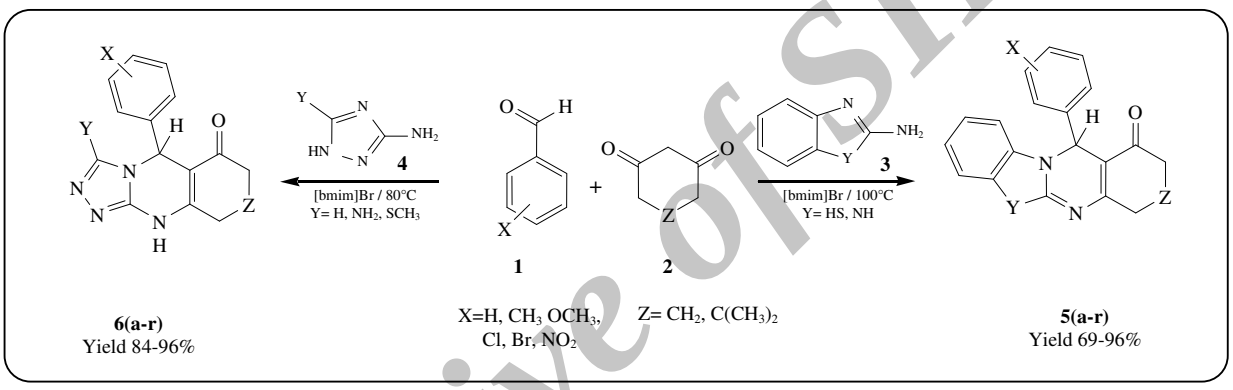


Scheme 1: Quinazoline ring containing bioactive natural products and synthetic molecules.



Scheme 2: Synthesis of tetrahydrobenzimidazo[2,1-b]quinazolin-1(2H)-ones (5a-r) and tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8(4H)-ones (6a-r)

recently shown that they can promote and catalyze important organic transformations under ambient conditions without the need for any added catalysts or ligands. The reactions investigated by us are Biginelli and Biginelli-like reaction [24,25], as well as the Groebke reaction [26], and Hantzch reaction [27], which proceeded with significantly enhanced reaction rates and excellent isolated yields.

Due to the biological properties of quinazolinones and quinazolines and the occurrence of the quinazoline skeleton in various natural products [1,11,12,28-30] and our interest in Multi-Component Reactions(MCRs) [31-38], we developed a rapid combinatorial approach for the synthesis of tetrahydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones ring systems **5** or tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones ring systems **6** by a one-pot three-component condensation reaction of an aldehyde **1** and a cyclic *β*-diketone **2** with 2-aminobenzimidazole, 2-aminobenzothiazole **3** or with various triazole derivatives **4** such as 3-amino-1,2,4-triazole, 3,5-diamino-1,2,4-triazole, 3-amino-5-thiomethoxy-1,2,4-triazole under conventional heating conditions without using any catalyst in 1-butyl-3-methylimidazolium bromide ([bmim]Br) (Scheme2).

EXPERIMENTAL SECTION

Apparatus

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-300 spectrometer at 300.13, and 75.47MHz. NMR spectra

Table 1: Solvent effects on the reaction of dimedone and p-methylbenzaldehyde with 2-aminobezimidazole on the synthesis of 3,3-dimethyl-12-(4-methyl-phenyl)-3,4,5,12-tetrahydrobenz imidazo[2,1-b]quinazolin-1(2H)-one 5b[a].

Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	CH_2Cl_2	2	Reflux	0
2	$CHCl_3$	2	Reflux	0
3	CH_3COOEt	2	Reflux	0
4	$CH_3C_6H_5$	2	Reflux	0
5	CH_3CN	2	Reflux	25
6	CH_3OH	2	Reflux	43
7	CH_3CH_2OH	2	Reflux	66
8	Water	6	80	trace
9	[Bmim]Br	2	80	81
10	[Bmim]Br	1	80	79
11	[Bmim]Br	0.5	80	79
12	-	2	80	trace

a) 2-Aminobenzimidazole (1 mmol), dimedone (1 mmol) and p-methylbenzaldehyde (3 mmol).

were obtained on solutions in DMSO-d[6]. The elemental analysis was performed with an Elementar Analysensysteme GmbH VarioEL CHNS mode. All the products are known compounds, and were characterized by melting points, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. In some cases we used CHNS for compounds which because of low solubility we could not obtain ^{13}C NMR.

General procedure for synthesis of 3,4,5,12-tetrahydrobenzimidazo [2,1-b]quinazolin-1(2H)-one (5a-r)

A mixture of cyclic *β*-diketones (1 mmol), aldehydes (3 mmol), and 2-aminobenzazoles (1 mmol) was successively added to a screw-capped vial containing [bmim]Br (0.3 g) and a magnetic stirring bar. The mixture was heated at 100 °C in a preheated oil bath for 5-60 min. Then, the reaction mixture was washed with cold water and filtered. The solid residue was washed with acetone (3×5 mL) to produce **5** as a white powder in high yield.

General procedure for synthesis of tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8(4H)-ones(6a-r)

A mixture of cyclic *β*-diketones (1 mmol), aldehydes (1 mmol), and amino-1,2,4-triazoles (1 mmol) was added to a screw-capped vial containing [bmim]Br (0.3 g) and a magnetic stirring bar. The reaction mixture was heated at 80 °C in a preheated oil bath for 15-30 min. Then, the reaction mixture was washed with cold water and filtered. The solid residue was washed with acetone (3×5 mL) to produce **6a-r** as a white powder in high yields.

RESULTS AND DISCUSSION

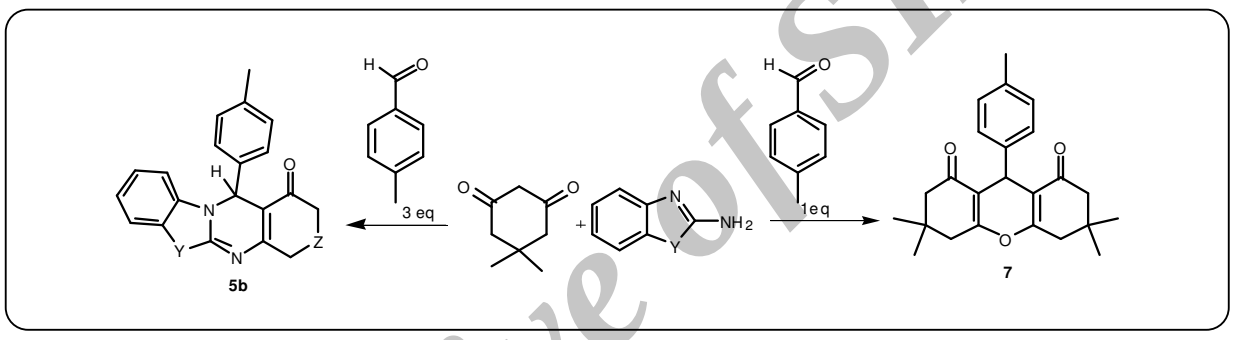
The one-pot method involves the classical heating of an aldehyde **1** and a cyclic *β*-diketone **2** with 2-aminobenzothiazole or 2-aminobezimidazole **3** or 3-amino-1,2,4-triazole or 3,5-diamino-1,2,4-triazole or 3-amino-5-thiomethoxy-1,2,4-triazole **4** without using any catalyst in [bmim]Br to give a family of tetraheterocyclicte trahydrobenzimidazo[2,1-*b*]quinazolin-1(2*H*)-ones **5** and triheterocyclic tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4*H*)-ones **6** in high yields.

To achieve suitable conditions for the above transformations, series of experiments were carried out (Tables 1 and 2). First we investigated the reaction of dimedone and *p*-methylbenzaldehyde with 2-aminobezimidazole under solvent-free conditions, various solvents, water and ionic liquids under classic heating conditions. In the absence of solvent, the reaction was very slow and the yield of the product was trace at 80 °C after 2 h (Table 1, Entriy 12). The reaction did not proceed in aprotic organic solvents even under reflux conditions after 2 h (Table 1, Entries 1-5). The yield of product was improved in protic organic solvents (Table 1, Entries 6-7), but we

Table 2: One-pot synthesis of tetrahydrobenzimidazo[2,1-b]quinazolin-1(2H)-one 5b at different ionic liquid at 30 min[a].

Entry	Ionic liquid	Temperature (°C)	Yield (%)
1	BPB	80	48
2	TMGT	80	43
3	TMGA	80	57
4	TBAB	80	81
5	TBAC	80	79
6	MIT	80	64
7	[bmim]Br	80	89
8	[bmim]Br	100	96
9	[bmim]Br	120	96
10	[bmim]PF_6	80	82
11	-	80	trace

a) 2-Aminobenzimidazole (1 mmol), dimedon (1 mmol) and p-methylbenzaldehyde (3 mmol).



Scheme 3: Reaction optimization for the synthesis of 5b

found the reaction yield was trace in water after 6 h at 80 °C (Table 1, Entry 8). The best solvent was found to be TetraButyl Ammonium Bromide (TBAB) and the reaction yield was 79% after heating 30 min at 80°C (Table 1, Entry 11).

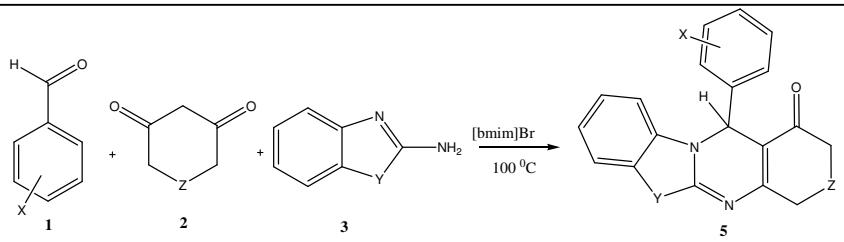
In order to examine the best ionic liquid, different ionic liquids such as Butyl Pyridinium Bromide (BPB), Tetra Methyl Guanidinium Triflouroacetate(TMGT), Tetra Methyl Guanidinium Acetate (TMGA), TetraButyl Ammonium Bromide (TBAB), TetraButyl Ammonium Chloride (TBAC), MethylImidazoliumTriflouroacetate (MIT), 1-butyl-3-methylimidazolium bromide ([bmim]Br), 1-butyl-3-methylimidazolium hexaflouroposphate ([bmim]PF_6) in this condensation reaction were applied (Table 2). In the course of this study it was found that 1-butyl-3-methylimidazolium bromide was the best ionic liquid for this reaction in terms of yield, price and easy at work-up.

To illustrate the need for [bmim]Br in these reactions, the reaction of aldehyde **1**, cyclic *β*-diketone **2** and 2-aminobenzimidazole **3** was studied in the absence of [bmim]Br. The yield of product was trace at 80 ˚C after 2 h (Table 2, Entry 11).

In order to improve the yields, we performed reaction using different quantities of reagents. The best result was obtained with 3:1:1 molar ratios of aldehyde, cyclic *β*-diketone and 2-aminobenzimidazole or 2-aminobenzothiazole. However, the 1:1:1 molar ratios of these reagents gave the compound **7** (Scheme 3). In the case of 3-amino-1,2,4-triazole or 3,5-diamino-1,2,4-triazole or 3-amino-5-thiomethoxy-1,2,4-triazole, the optimum molar ratio was 1:1:1.

One of the advantages of Ionic Liquids (ILs) is the ability to be recyclable as reaction medium. We were able to separate [bmim]Br from reaction medium easily by washing with water and evaporating the solvent

Table 3: One-pot synthesis of tetraheterocyclic tetrahydrobenzimidazo[2,1-b]quinazolin-1(2H)-ones by the condensation reaction of an aldehyde, a cyclic β-diketone and 2-aminobenzothiazole or 2-aminobenzimidazole in [bmim]Br at 100 °C after 5-60 min.



1 X= H, CH_3, OCH_3, Cl, Br, NO_2 **2** Z= CH_2, $C(CH_3)_2$ **3** Y= S, NH **5**

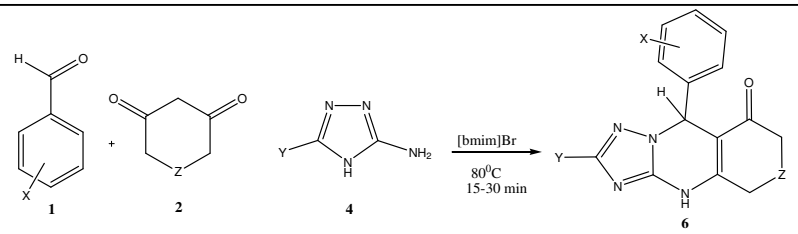
Product	Y	Z	X	Yield (%)	Time(min)
5a	NH	$C(CH_3)_2$	H	94	5
5b	NH	$C(CH_3)_2$	4-CH_3	96(94,93,92,93)[a]	10
5c	NH	$C(CH_3)_2$	4-OCH_3	89	15
5d	NH	$C(CH_3)_2$	4-Cl	91	10
5e	NH	$C(CH_3)_2$	4-Br	93	10
5f	NH	$C(CH_3)_2$	3-OCH_3	85	15
5g	NH	$C(CH_3)_2$	3-Cl	89	5
5h	NH	$C(CH_3)_2$	3-Br	91	15
5i	NH	$C(CH_3)_2$	3-NO_2	88	15
5j	NH	$C(CH_3)_2$	2-CH_3	94	5
5k	NH	$C(CH_3)_2$	2-Cl	91	10
5l	NH	CH_2	H	86	20
5m	NH	CH_2	4-CH_3	91	15
5n	NH	CH_2	4-OCH_3	88	20
5o	NH	CH_2	3-NO_2	90	15
5p	S	$C(CH_3)_2$	H	73	60
5q	S	$C(CH_3)_2$	2-OCH_3	69	60
5r	S	$C(CH_3)_2$	3-OCH_3	72	60

a) The same ionic liquid runs for four times.

under vacuum, and reuse it for subsequent reactions (Table 3, Product **5b**).

To explore the scope and limitations of this reaction, we have extended it to various *ortho*-, *meta*- and *para*-substituted benzaldehydes in the presence of 2-aminobenzimidazole, 2-aminobenzothiazole, 3-amino-1,2,4-triazole and 3,5-diamino-1,2,4-triazole or 3-amino-5-thiomethoxy-1,2,4-triazole. As indicated in Tables 3 and 4, the reaction proceeded efficiently with benzaldehyde and electron-withdrawing and electron-donating *ortho*-, *meta*- and *para*-substituted benzaldehydes.

Table 4: One-pot synthesis of tetrahydro-1,2,4-triazolo[5,1-b]quinazolin-8(4H)-ones by the condensation reaction of an aldehyde, a cyclic β-diketone and 3-amino-1,2,4-triazole, 3,5-diamino-1,2,4-triazole, 3-amino-5-thiomethoxy-1,2,4-triazole in [bmim]Br at 80 °C after 15-30 min.



1 X= H, CH_3, OCH_3, Cl, Br, NO_2 **2** Y= CH_2, $C(CH_3)_2$ **4** Z= H, NH_2, SCH_3 **6** yield 84-96 %

Product	Y	Z	X	Yield (%)	Time(min)
6a	H	$C(CH_3)_2$	H	93	20
6b	H	$C(CH_3)_2$	4-CH_3	96	15
6c	H	$C(CH_3)_2$	4-OCH_3	86	20
6d	H	$C(CH_3)_2$	4-Cl	87	20
6e	H	$C(CH_3)_2$	3-OCH_3	89	20
6f	H	$C(CH_3)_2$	3-NO_2	91	30
6g	H	$C(CH_3)_2$	2-CH_3	93	20
6h	H	CH_2	H	90	30
6i	H	CH_2	4-CH_3	94	20
6j	H	CH_2	4-OCH_3	85	20
6k	H	CH_2	4-Cl	87	30
6l	H	CH_2	3-NO_2	89	30
6m	NH_2	$C(CH_3)_2$	H	93	20
6n	NH_2	$C(CH_3)_2$	4-CH_3	87	20
6o	NH_2	$C(CH_3)_2$	4-OCH_3	84	20
6p	NH_2	$C(CH_3)_2$	4-Cl	90	30
6q	SCH_3	$C(CH_3)_2$	H	85	20
6r	SCH_3	$C(CH_3)_2$	4-OCH_3	84	20

CONCLUSIONS

Three - component condensation of 2-aminobenzimidazole, 2-aminobenzothiazole or various 3-amino-1,2,4-triazoles, aldehydes, and 1,3-diones in ionic liquid afforded the novel library of quinazoline molecules. It has been demonstrated that the ionic liquids are very effective in speeding up both the soluble supported multistep synthesis, as well as accelerating the rate of subsequent multicomponent reaction. Great substrate scope, high yields, short reaction time, pure products and easy work up are advantages of this procedure in comparison to other methods.

This approach provides a high speed path for the rapid synthesis of molecular libraries with high degree of structural diversity.

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