Efficient One-Pot Synthesis of Quinazoline and Benzopyrano[2,3-*d*] pyrimidine Derivatives Catalyzed by *N*-Bromosulfonamides

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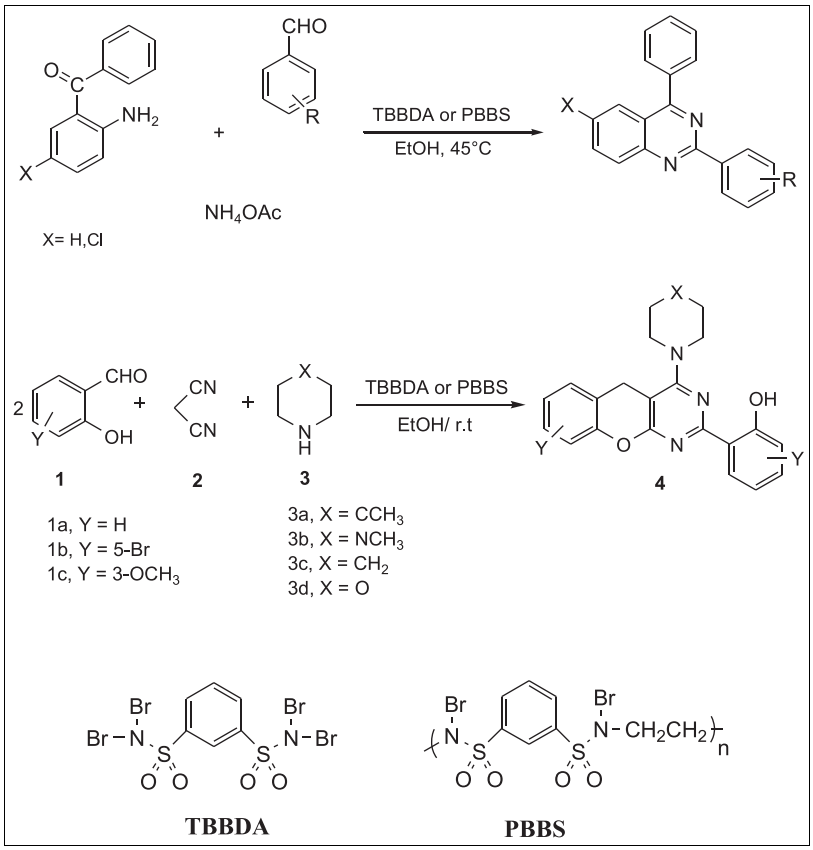

N,N,N',N'-tetrabromobenzene-1,3-disulfonamide and poly(*N,N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) were used as efficient catalysts for one-pot synthesis of new quinazoline derivatives from various aldehydes, 2-amino-benzophenone, and ammonium acetate in good to excellent yields and new benzopyrano[2,3-*d*]pyrimidine derivatives from salicylic aldehydes, various cyclic amines, and malononitrile in good to high yields.

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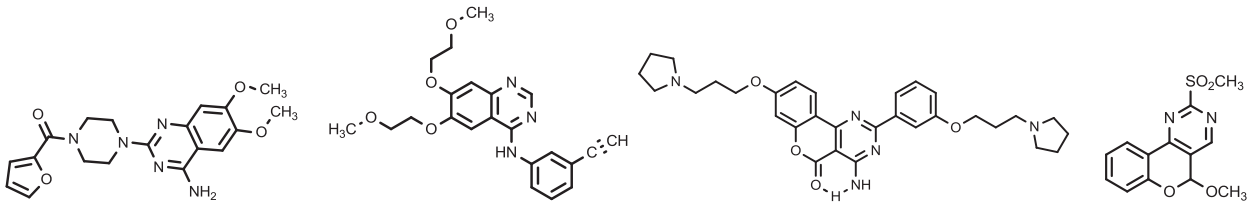
INTRODUCTION

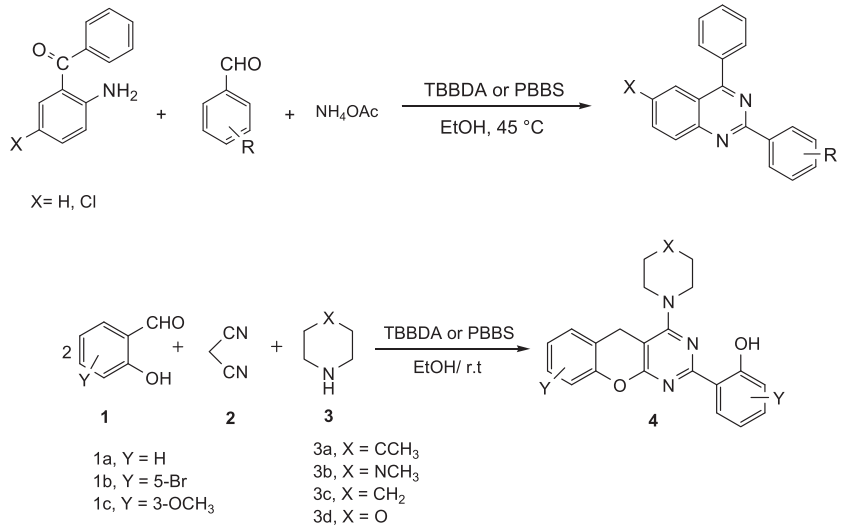
One of the most important and pliable routes for the preparation of heterocyclic compounds with significant biological activities is multicomponent reactions (MCRs). High selectivity, high atom-economy, rapid, and facility are central issues in MCRs. Quinazoline and their fused-ring derivatives, which belong to the *N*-containing heterocyclic compounds, are one of the most prevalent class of compounds in medicinal chemistry. A large number of quinazolines and their condensed derivatives possess broad spectrum of biological and pharmacological activities such as, anti-histaminic [1], anti-hypertensive [2], antiplas modial [3], anti-diabetes [4], antibacterial [5], antiviral [6], anticarcinogen [7], and antimalarial [8]. Also, soporific and sedative actions of some of quinazoline derivatives have been reported [9]. Pyrimidines and their derivatives are well-known heterocyclic compounds, which have been studied for over a century because of a variety of chemical and biological properties. Particularly, benzopyranopyrimidines are important pharmacophores that exhibit anti-inflammatory, anti-aggregating, anti-platelet, analgesic, and anti-thrombotic activities [10–13]. *In vivo* activity by benzopyranopyrimidines have been shown in mice with

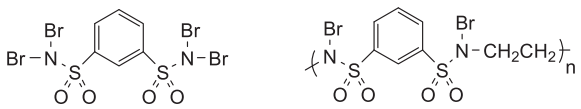


Anti-hypertensive **Anti-cancer** **Anti-cancer** **Anti-platelet**

Figure 1. Bioactive compounds with quinazoline and benzopyranopyrimidine core skeleton.

Scheme 1. Synthesis of quinazoline and benzopyrano[2,3-*d*]pyrimidine derivatives.





TBBDA **PBBS**

Table 1

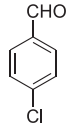
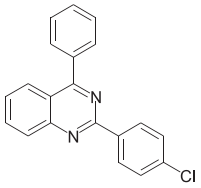
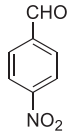
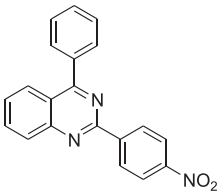
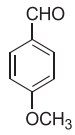
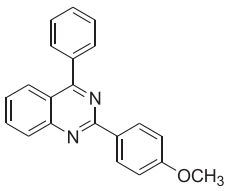
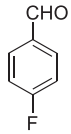
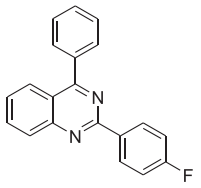
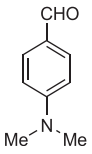
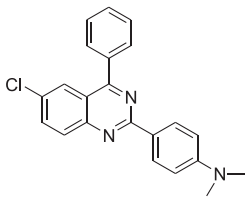
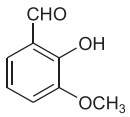
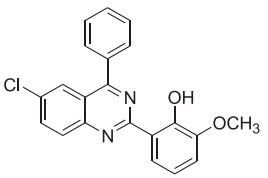
Reaction times and yields in various conditions.

Entry	Solvent	Amount of catalyst [TBBDA (g)]	Temperature (°C)	Time (h)	Yield (%)[b]
1	Solvent-free	0.08	rt	24	0
2	Solvent-free	0.08	45	20	11
3	Solvent-free	0.08	100	15	23
4	CH_3CN	0.08	45	3	0
5	H_2O	0.08	45	5	0.9
6	Ethanol/ H_2O	0.05	45	7	17
7	Ethanol/ H_2O	0.08	45	5	33
8	Ethanol/ H_2O	0.1	45	3	27
9	Ethanol	0.03	45	6	10
10	Ethanol	0.05	45	5	48
11	Ethanol	0.08	45	3	85
12	Ethanol	0.1	45	4	73

[a]Experimental conditions: 4-chlorobenzaldehyde (1 m*M*), ammonium acetate (2.5 m*M*) and 2-amino-benzophenone (1 m*M*).
[b]Isolated yield.
TBBDA, tetrabromobenzene-1,3-disulfonamide.

Table 2

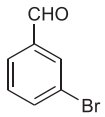
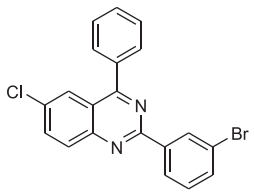
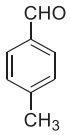
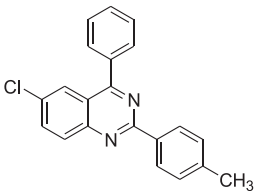
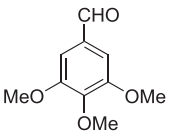
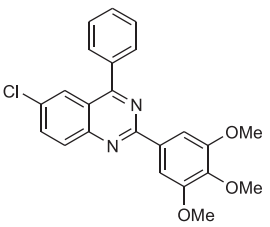
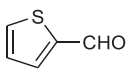
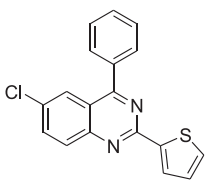
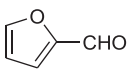
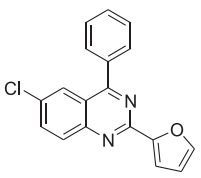
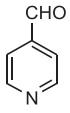
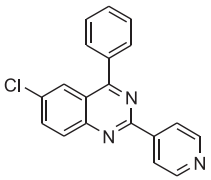
Synthesis of quinazoline derivatives using TBBDA or PBBS as catalysts.

Entry	Aldehyde	Product[a]	TBBDA Time (h)/yield (%)[b]	PBBS Time (h)/yield (%)[b]	Ref.
1			3/85	5/65	[11]
2			3/85	5/58	[11]
3			3/90	5/53	[18]
4			3/65	5/42	[18]
5			3/85	5/65	—
6			3/95	5/45	—

(*Continued*)

Table 2

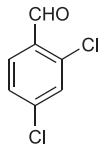
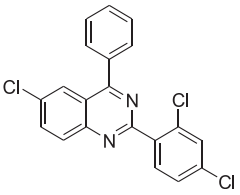
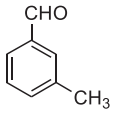
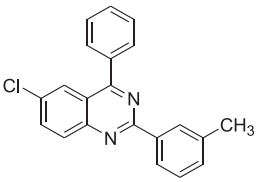
(Continued)

Entry	Aldehyde	Product[a]	TBBDA Time (h)/yield (%)[b]	PBBS Time (h)/yield (%)[b]	Ref.
7			4/82	7/69	—
8			3/75	5/45	[11]
9			3/93	5/72	—
10			7/72	9/55	—
11			7/93	9/75	—
12			3/94	5/70	—

(*Continued*)

Table 2

(Continued)

Entry	Aldehyde	Product[a]	TBBDA Time (h)/yield (%)[b]	PBBS Time (h)/yield (%)[b]	Ref.
13			3/75	5/40	—
14			3/77	5/52	—

[a]The known compounds were characterized from their physical properties, by comparing them with authentic samples, and using spectroscopic methods
[b]Isolated yield.
TBBDA, tetrabromobenzene-1,3-disulfonamide; PBBS, poly(*N*,*N*'-dibromo-*N*-ethyl-benzene-1,3-disulfonamide).

P388 lymphocytic leukemia [14]. In recent years, $LiClO_4$, ionic liquid, and microwave irradiation have been utilized for synthesis of these compounds [15–17]. Because of very diverse pharmacological significance exhibited by the quinazoline and pyrimidine systems (Fig. 1), we hereby report one-pot synthesis of some new quinazoline and benzopyrano[2,3-*d*]pyrimidine derivatives *via* MCRs under various conditions.

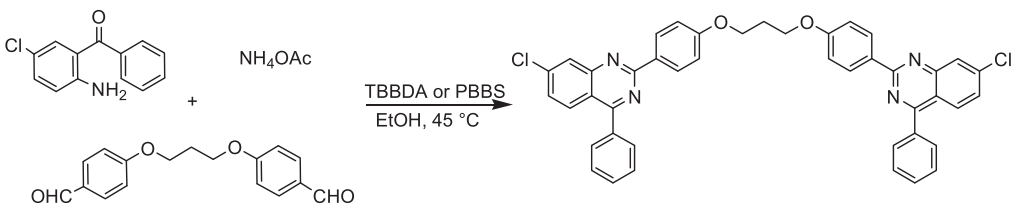
RESULTS AND DISCUSSION

As a part of our research in organic synthesis catalyzed by *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*,*N'*-dibromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS) [18–27], hereby, we report simple, green, and efficient method for synthesis of quinazoline derivatives *via* one-pot, three-component reaction of substituted *o*-aminoaryl ketones, various aldehydes and ammonium acetate in ethanol and synthesis of benzopyrano[2,3-*d*]pyrimidine derivatives from salicylic aldehydes, malononitrile, and various cyclic amines *via* one-pot and pseudo four-component reaction in the presence of TBBDA or PBBS as catalysts under mild conditions (Scheme 1).

Initial efforts focused on optimizing conditions for synthesis of 2-(4-chlorophenyl)-4-phenylquinazoline from 4-chlorobenzaldehyde, ammonium acetate, and 2-aminobenzophenone as a model reaction under various conditions. We examined various solvents and solvent-free conditions with different temperatures and variety amount of catalyst for this model reaction and behold that TBBDA (0.08 g) with ethanol under 45°C can be increased rate of reaction and yield of product (3 h, 85%, Table 1, entry 11). The results are summarized in Table 1.

To establish the scope and generality of this protocol, we examined variety of aldehydes containing either

Scheme 2. Synthesis of *bis*-quinazoline.



Scheme 3. Suggested mechanism for the synthesis of quinazoline derivatives.

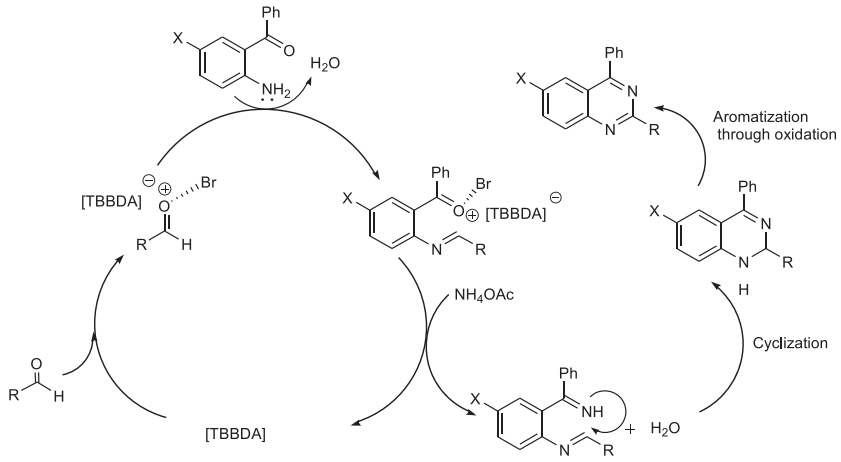


Table 3

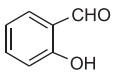
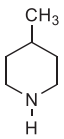
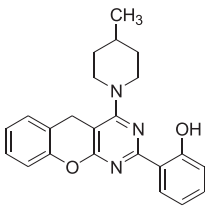
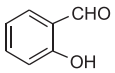
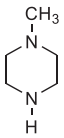
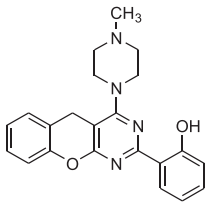
Optimization of reaction in various conditions

Entry	Solvent	Catalyst amount [TBBDA (g)]	Time (h)	Yield (%)[b]
1	Ethylacetate	0.06	24	39
2	Dichloromethane	0.06	24	27
3	Acetonitrile	0.06	24	32
4	H_2O	0.06	10	-
5	EtOH/H_2O	0.06	24	25
6	EtOH	No catalyst	24	29
7	EtOH	0.01	24	67
8	EtOH	0.03	24	78
9	EtOH	0.06	24	85

[a]Experimental conditions: 2-hydroxybenzaldehyde (2.3 m*M*), morpholine (1 m*M*) and malononitrile (1 m*M*).
[b]Isolated yield.
TBBDA, tetrabromobenzene-1,3-disulfonamide.

Table 4

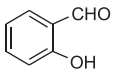
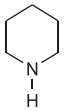
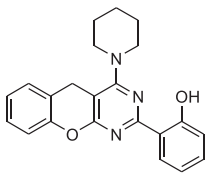
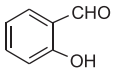
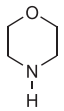
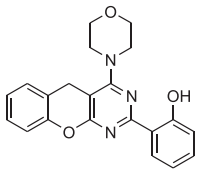
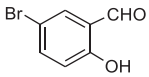
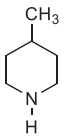
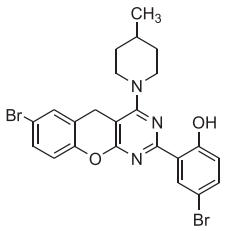
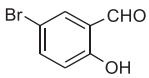
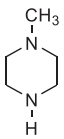
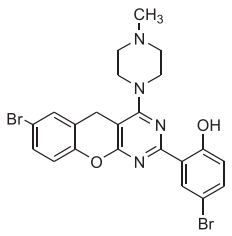
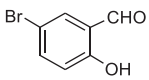
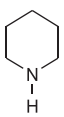
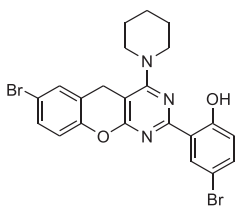
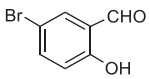
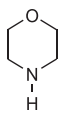
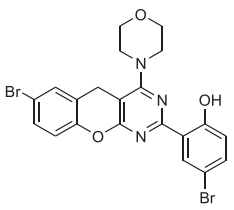
Synthesis of benzopyrano[2,3-*d*]pyrimidine derivatives in the presence of TBBDA or PBBS

Entry	Aldehyde	Amine	Product	Yield (%)[b] TBBDA	Yield (%)[b] PBBS	Ref.
1				87	54	-
2				82	51	-

(*Continued*)

Table 4

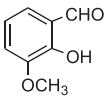
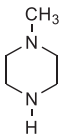
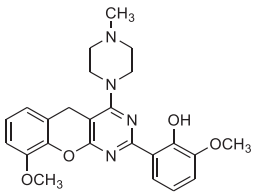
(Continued)

Entry	Aldehyde	Amine	Product	Yield (%)[b] TBBDA	Yield (%)[b] PBBS	Ref.
3				90	58	[15]
4				85	50	[15]
5				83	52	-
6				82	48	-
7				92	53	[15]
8				81	53	[15]

(*Continued*)

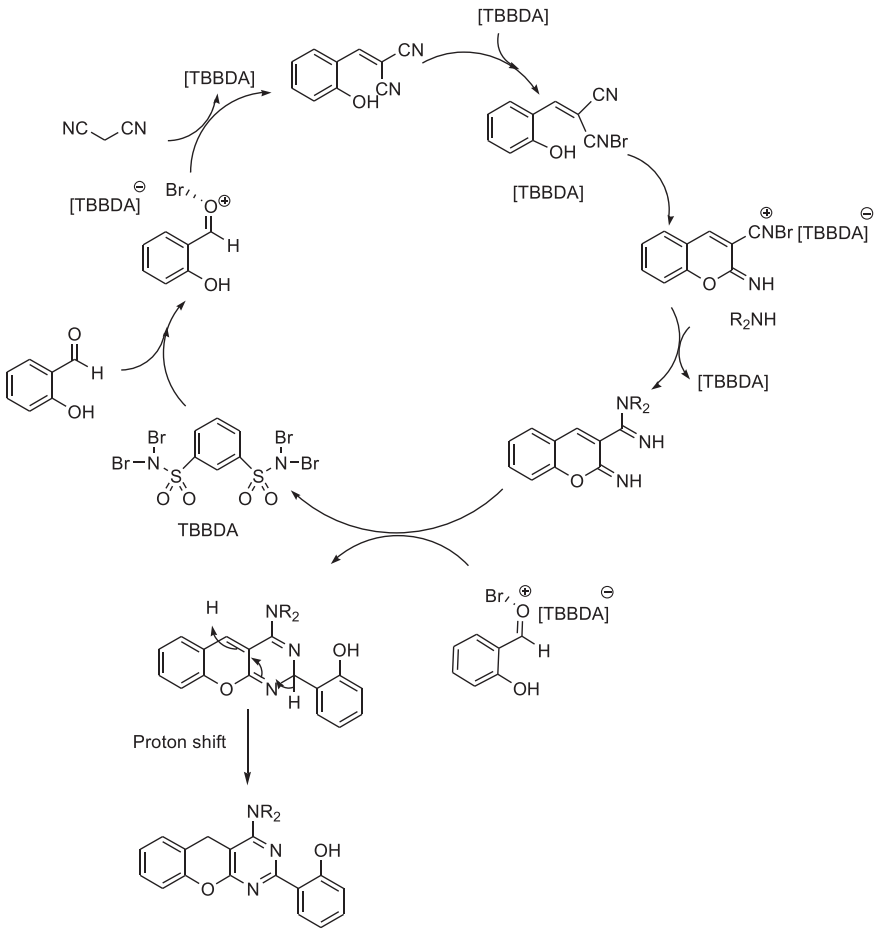
Table 4

(Continued)

Entry	Aldehyde	Amine	Product	Yield (%)[b] TBBDA	Yield (%)[b] PBBS	Ref.
9				78	45	-

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.
[b]Isolated yield.
TBBDA, tetrabromobenzene-1,3-disulfonamide; PBBS, poly(*N*,*N*'-dibromo-*N*-ethyl-benzene-1,3-disulfonamide).

Scheme 4. Suggested mechanism for the synthesis of benzopyrano[2,3-*d*]pyrimidine derivatives.



electron-withdrawing or electron-donating substituents, which successfully reacted with *o*-aminoarylketone and ammonium acetate and gave corresponding products with good to high yields. The results are shown in Table 2.

Also, we synthesized *bis*-quinazoline with good yield *via* one-pot reaction between 4,4'-(propane-1,3-diylbis(oxy)) dibenzaldehyde, *o*-aminoarylketone (2 m*M*), and ammonium acetate (2 m*M*) under optimal reaction condition (Scheme 2).

In the Scheme 3, we suggested a mechanism for the conversion of the *o*-aminoaryl ketones, various aldehydes, and ammonium acetate to quinazoline derivatives. According to this mechanism, TBBDA can be releases Br^+ as electrophilic species and the carbonyl groups activated by this catalyst and gave products [24,28].

Also, in another study, we synthesized benzopyrano [2,3-*d*]pyrimidine derivatives *via* one-pot, pseudo four-component reaction with good to high yield. So, for optimization of reaction conditions, we applied 2-hydroxybenzaldehyde, morpholine, and malononitrile as a model reaction. Various solvents and amounts of TBBDA were used, and the best result was achieved by ethanol and TBBDA (0.06 g, 85%, Table 3, entry 9). Also, this model reaction was carried out by HBr (48%) and the yield of product (24 h, 50%) less because TBBDA was used. The results are summarized in Table 3.

In order to study the scope and generality of these catalysts in MCR, we carried out the efficacy of TBBDA and PBBS in the synthesis of benzopyrano[2,3-*d*]pyrimidine derivatives. Various cyclic amines and salicylic aldehydes were used, and the corresponding products were obtained with good to high yields. The results are presented in Table 4.

Mechanistically, it is likely that TBBDA or PBBS releases Br^+ *in situ*, which acts as an electrophilic species [18]. The mechanism shown in (Scheme 4) is proposed for the synthesis of benzopyrano[2,3-*d*]pyrimidine derivatives [16].

CONCLUSION

In summary, we have developed efficient, green, simple, and one-pot procedure for synthesis of remarkable biologically substituted quinazoline and benzopyrano[2,3-*d*]pyrimidine derivatives using TBBDA and PBBS as catalysts. Inexpensive catalysts, simple method, high yields, and easy work up are advantages of this method.

EXPERIMENTAL

All commercially available chemicals were purchased from Merck (Kenilworth, NJ,) and Fluka (Buchs, Switzerland) companies and used without further purification unless otherwise stated. Infrared (IR) spectroscopy was conducted on a Perkin Elmer GX FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 and $CDCl_3$ on Bruker Avance 400 MHz FT spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm). Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Elemental analyses (C, H, N) were performed with a 4010 CHNS-O Analyzer.

Typical procedure for the preparation of 2-(4-chlorophenyl)-4-phenylquinazoline (Table 2, entry 1). A mixture of 4-chlorobenzaldehyde (1 m*M*), 2-aminobenzophenone (1 m*M*), ammonium acetate (2.5 m*M*), and TBBDA (0.08 g, 0.16 m*M*) or PBBS (0.1 g) was stirred under 45°C for appropriate time. After completion of the reaction, which was monitored by thin-layer chromatography [acetone/*n*-hexane (4:14)], the mixture was cooled to room temperature. Then, ethanol (5 mL) was added to the mixture. The solid product was collected by filtration, washed with ethanol, and purified by recrystallization from ethanol. After evaporation of the ethanol, cool methylene dichloride (2 mL) was added, and catalyst was recovered.

Typical procedure for the synthesis of 2-(2-hydroxyphenyl)-4-(4-methylpiperidine-1-yl)-5*H*-benzopyrano[2,3-*d*]pyrimidine (Table 4, entry 1). A mixture of salicylaldehyde (2.3 m*M*), malononitrile (1 m*M*), 4-methylpiperidine (1 m*M*), ethanol (5 mL), and TBBDA (0.11 m*M*, 0.06 g) were stirred at room temperature for 24 h. The progress of reaction was monitored by thin-layer chromatography [*n*-hexane/acetone (10:3)]. After completion of the reaction, the precipitate product was collected, washed with ethanol. Removal of the solvent under reduced pressure gave the catalyst. The crude product was recrystallized from ethyl acetate to afford the pure product.

Physical and spectroscopic data. ***6-Chloro-2-(4-(dimethylamino)phenyl)-4-phenylquinazoline:*** Yellow solid, mp: 159–161°C. IR (KBr, ν_{max}, cm^{-1}): 1162, 1184, 1364, 1389, 1418, 1528, 1559, 1601. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 3.092 (s, CH_3, 6H), 6.81–8.59 (m, Ar-H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 40.2 ($2CH_3$), 111.6, 121.6, 125.4, 125.7 (C Ar), 128.6, 129.9, 130.03, 130.06, 131.4, 134.1, 137.4, 150.7, 152.2, 160.9, 167.1. MS: m/z 359.2. *Anal.* Calcd for $C_{22}H_{18}ClN_3$: C, 77.74; H, 5.04; N, 11.68. Found: C, 77.00; H, 4.68; N, 11.33 (Table 2, entry 5).

6-Chloro-2-(3-methoxyphenol)-4-phenylquinazoline: Yellow solid, mp: 249–250°C. IR (KBr, ν_{max}, cm^{-1}): 800, 1381, 1479, 1534, 1558. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 3.9 (s, CH_3, 3H), 6.9–8.3 (m, Ar-H, 11H), 14.04 (s, OH, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 56.1 (OCH_3), 114.5, 118.2, 119.1, 121.3 (C Ar), 121.6, 126.1, 128.9, 129.4, 130.0, 130.7, 133.0, 135.3, 136.2, 148.2, 148.9, 151.2, 161.1, 167.4. MS: m/z 362. *Anal.* Calcd for $C_{21}H_{15}ClN_2O_2$: C, 69.52; H, 4.17; N, 7.72. Found: C, 69.09; H, 4.01; N, 7.69 (Table 2, entry 6).

6-Chloro-4-phenyl-2-(3-bromophenyl)quinazoline: White solid, mp: 190–191°C. IR (KBr, ν_{max}, cm^{-1}): 800, 1382, 1480, 1534, 1557. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.3–8.8 (m, Ar-H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 122.3 (C Ar), 122.9, 125.8, 127.2, 128.8, 130.0, 130.1, 130.3, 130.9, 131.6, 133.0, 133.6, 134.7, 136.8, 139.8, 150.3, 158.9, 167.7. MS: m/z 395. *Anal.* Calcd for $C_{20}H_{12}BrClN_2$: C, 60.71; H, 3.06; N, 7.08. Found: C, 60.44; H, 2.89; N, 6.66 (Table 2, entry 7).

6-Chloro-4-phenyl-2-(3,4,5-trimethoxyphenyl)quinazoline: Pale-yellow solid, mp: 164–165°C. IR (KBr, ν_{max}, cm^{-1}): 1123, 1386, 1413, 1506, 1536, 1555, 1590. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 3.96–4.03 (m, $3OCH_3$, 9H), 7.28–8.10 (m, Ar-H, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 40.9 (OCH_3), 56.2 (OCH_3), 60.9 (OCH_3), 105.8, 122.0 (C Ar), 125.8, 128.7, 130.0, 130.2, 130.7, 132.4, 133.2, 134.5, 137.0, 140.5, 150.4, 153.3, 159.9, 167.4. MS: m/z 406.2. *Anal.* Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.9; H, 4.71; N, 6.89. Found: C, 67.16; H, 4.53; N, 6.69 (Table 2, entry 9).

6-Chloro-4-phenyl-2-(thiophen-2-yl)quinazoline: White solid, mp: 219–220°C. IR (KBr, ν_{max}, cm^{-1}): 703, 844, 1384, 1436, 1477, 1540. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.19–8.21 (m, Ar-H, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 122.0, 125.9, 128.3, 128.7, 129.6, 130.0, 130.2, 130.3, 130.4, 132.3, 134.6, 136.7, 143.7, 150.3, 157.4, 167.6. MS: m/z 322 (Table 2, entry 10).

6-Chloro-2-(furan-2-yl)-4-phenylquinazoline: Pale-brown solid, mp: 198–199°C. IR (KBr, ν_{max}, cm^{-1}): 1379, 1470, 1536, 1586. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 6.6 (q, Ar-O, 1H), 7.50–8.11 (m, Ar-H, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 112.3, 114.7, 122.0, 125.9, 128.7, 129.9, 130.3, 132.6, 134.8, 136.2, 145.5, 150.0, 152.4, 153.6, 168.0**.** MS: m/z 306. *Anal.* Calcd for $C_{18}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.23; H, 3.20; N, 9.09 (Table 2, entry 11).

6-Chloro-4-phenyl-2-(pyridine-4-yl)quinazoline: White solid, mp: 194–195°C. IR (KBr, ν_{max}, cm^{-1}): 695, 833, 1413, 1478, 1529, 1555, 1595. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.40–8.19 (m, Ar-H, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 122.3, 122.7, 125.8, 128.8, 130.0, 130.5, 131.0, 133.8, 134.9, 136.6, 145.0, 150.2, 150.4, 158.3, 167.9. MS: m/z 318. *Anal.* Calcd for $C_{19}H_{12}ClN_3$: C, 71.81; H, 3.81; N, 13.22. Found: C, 71.51; H, 3.61; N, 13.20 (Table 2, entry 12)**.**

6-Chloro-2-(2,4-dichlorophenyl)-4-phenylquinazoline: Pale-yellow solid, mp: 149–150°C. IR (KBr, ν_{max}, cm^{-1}): 697, 824, 1384, 1481, 1527, 1555, 1586. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 8.81–7.84 (m, Ar-H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 127.2, 128.4, 128.9, 129.0, 130.0, 130.1, 130.5, 130.6, 130.8, 132.8, 133.7, 134.0, 134.9, 135.0, 135.8, 136.4, 136.5, 150.0, 160.5, 167.6. MS: m/z 385 (Table 2, entry 13).

6-Chloro-2-(3-methylphenyl)-4-phenylquinazoline: Milky solid, mp: 181–182°C. IR (KBr, ν_{max}, cm^{-1}): ^{1}HNMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.5 (s, CH_3, 3H), 7.3–8.5 (m, Ar-H, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 21.5 (CH_3), 122.1, 125.8, 125.7, 129.1, 130.0, 130.2, 130.8, 131.6, 132.5, 134.5, 137.1, 137.7, 138.2, 150.5, 160.6, 167.5. MS: m/z 330. *Anal.* Calcd for $C_{19}H_{12}ClN_3$: C, 76.24; H, 4.57; N, 8.47. Found: C, 75.70; H, 4.31; N, 8.07 (Table 2, entry 14).

2-(2-Hydroxyphenyl)-4-(4-methylpiperidin-1-yl)-5H-benzopyrano[2,3-d]pyrimidine: Yellow solid, mp: 158–159°C. IR (KBr, ν_{max}, cm^{-1}): 3059, 2950, 2808, 1599, 1183. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 1.02–1.04 (d, $J = 8.0$ Hz, 3H, CH_3), 1.34–1.44 (m, 2H, CH_2), 1.64–1.74 (m, 1H, CH_2), 1.80–1.82 (m, 1H, CH_2), 1.84–1.86 (m, 1H, CH), 2.98–3.05 (m, 2H, CH_2), 3.85–3.87 (m, 2H, CH_2), 3.88–3.90 (m, 1H, CH_2), 3.92 (s, 2H, CH_2), 6.89–6.98 (m, 2H, Ar H), 7.08–7.12 (m, 1H, Ar H), 7.17–7.26 (m, 3H, Ar H), 7.36–7.32 (m, 1H, Ar H), 8.42 (dd, $J_a = 7.0$ Hz , $J_b = 2.0$ Hz, 1H, Ar H), 13.45 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 21.8 (CH_3), 25.6 (CH_2CH_2), 30.9 (CH), 34.1 ($2CH_2$), 48.8 (CH_2), 97.4 (C6'), 117.1, 117.5, 118.6, 118.8, 119.5, 124.3 (C Ar), 128.2 , 128.5, 129.2, 132.8, 150.6, 160.4, 162.0, 164.4, 165.0. MS: m/z 373. *Anal.* Calcd for $C_{23}H_{23}N_3O_2$: C, 73.95; H, 6.21; N, 11.25. Found: C, 73.49; H, 6.18; N, 11.11 (Table 4, entry 1).

2-(2-Hydroxyphenyl)-4-(4-methylpiperazin-1-yl)-5H-benzopyrano[2,3-d]pyrimidine: Yellow solid, mp: 179–181°C. IR (KBr, ν_{max}, cm^{-1}): 3057, 2963, 2842,1598, 1186. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.39 (s, 3H, CH_3), 2.61–2.64 (t, $J = 4.8$ Hz, 4H, $2CH_2$), 3.54–3.56 (t, $J = 4.8$ Hz, 4H, $2CH_2$), 3.90 (s, 2H, CH_2), 6.90–6.99 (m, 2H, Ar-H), 7.09–7.13 (m, 1H, Ar-H), 7.18–7.28 (m, 3H, Ar-H), 7.33–7.38 (m, 1H, Ar-H), 8.40–8.42 (dd, $J_a = 8.0$ Hz, $J_b = 2.0$ Hz, 1H, Ar-H), 13.24 (s, 1H, OH).^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 25.7 (CH_2), 46.1 (N-CH_3), 48.1 ($2CH_2$), 54.8 ($2CH_2$), 97.4, 117.1, 117.6, 118.5, 118.8, 119.3, 124.4, 128.3, 128.5, 129.2, 132.9, 150.5, 160.3, 162, 164.6, 164.6. MS: m/z 374. *Anal.* Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C,70.41; H, 5.93; N, 15.08 (Table 4, entry 2).

7-Bromo-2-(5-bromo-2-hydroxyphenyl)-4-(4-methylpiperidin-1-yl)-5H-benzopyrano[2,3 d]pyrimidine: Yellow solid, mp: 233–235°C. IR (KBr, ν_{max}, cm^{-1}): 2949, 2838, 1596, 1221. ^1H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 1.03–1.05 (d, $J = 6.4$ Hz, 3H, CH_3), 1.33–1.43 (m, 2H, CH_2), 1.64–1.77 (m, 1H, CH_2), 1.81–1.83 (m, 1H, CH_2), 1.83–1.86 (m, 1H, CH), 3–3.07 (m, 2H, CH_2), 3.85 (m, 1H, CH_2), 3.88 (m, 1H, CH_2), 3.90 (s, 2H, CH_2), 6.85–6.88 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.06–7.08 (d, $J = 8.4$ Hz, 1H, Ar--H), 7.35–7.38 (m, 2H, Ar-H), 7.40–7.43 (dd, $J = 2.8$ Hz, 1H, ArH), 8.51 (d, $J = 2.4$ Hz, 1H, Ar-H), 13.16 (s,1H, OH).^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 21.8 (CH_3), 25.5 (CH_2), 30.8 (CH_2), 34.1 ($2CH_2$), 48.8 ($2CH_2$), 112.4, 116.8, 118.8, 119.5, 121.5 (C Ar), 131.3, 131.4, 131.5, 134.3, 134.5, 134.9, 135.5, 159.5. MS: m/z 531. *Anal.* Calcd for $C_{23}H_{21}Br_2N_3O_2$: C, 52.00; H, 3.98; N, 7.91. Found: C, 51.71; H, 4; N, 7.86 (Table 4, entry 5).

7-Bromo-2-(5-bromo-2-hydroxyphenyl)-4-(4-methylpiperazin-1-yl)-5H-benzopyrano[2,3-d]pyrimidine: Yellow solid, mp: 229–231°C. IR (KBr, ν_{max}, cm^{-1}): 3074,

2936, 2843, 1596, 1150. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.39 (s, 3H, CH_3), 2.60–2.63 (t, J = 4.8 Hz, 4H, $2CH_2$), 3.53–3.55 (t, J = 4.8 Hz, 4H, $2CH_2$), 3.90 (s, 2H, CH_2), 6.85–6.87 (d, J = 8.8 Hz, 1H, ArH), 7.07–7.09 (d, J = 8.4 Hz, 1H, ArH), 7.35–7.37 (m, 2H, ArH), 7.40–7.43 (dd, J = 6.0 Hz, 1H, ArH), 8.50 (d, J = 2.4 Hz, 1H, ArH), 13.36 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 25.5 (CH), 46.1 (CH_3), 48.1 ($2CH_2$), 54.8 ($2CH_2$), 116.9, 118.8, 119.6, 119.9, 121.2 (C Ar), 131.2, 131.3, 131.4, 135.6, 149.5, 159.4. MS: m/z 532. *Anal.* Calcd for $C_{22}H_{20}Br_2N_4O_2$: C, 49.65; H, 3.79; N, 10.53. Found: C, 49.64; H, 3.81; N, 10.55 (Table 4, entry 6).

2-(2-Hydroxy-3-methoxyphenyl)-9-methoxy-4-(4-methylpiperazin-1-yl)-5H-benzopyrano[2,3-d]pyrimidine: Yellow solid, mp: 179–181°C. IR (KBr, ν_{max}, cm^{-1}): 3052, 2928, 2840, 1581. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.37 (s, 3H, CH_3), 2.60–2.62 (t, J = 4.4 Hz, 4H, $2CH_2$), 3.53–3.55 (t, J = 4.8 Hz, 4H, $2CH_2$), 3.92 (s, 2H, CH_2), 3.93 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.70–6.80 (m, 3H, Ar-H), 6.95–7.05 (m, 2H, Ar-H), 8.09–8.11 (dd, J_a = 8.0 s Hz, J_b = 1.6 Hz, 1H, Ar-H), 13.76 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 25.8 (CH), 46.1 (CH_3), 48.1 ($2CH_2$), 54.8 ($2CH_2$), 56.05 (OCH_3), 56.06 (OCH_3), 97.3, 110.6, 113.9, 117.8, 118.6, 119.7, 120.1 (C Ar), 121.1, 124.2, 140.1, 148.2, 148.6, 150.6, 162.2, 164.2, 164.5. MS: m/z 434. *Anal.* Calcd for $C_{22}H_{20}Br_2N_4O_2$: C, 66.34; H, 6.03; N, 12.89. Found: C, 65.80; H, 6.01; N; 12.90 (Table 4, entry 9).

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