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ORIGINAL PAPER

Microwave-induced preparation of biologically important benzothiazolo[2,3-*b*]quinazolines, and comparison with ultrasonic and classical heating

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Abstract Synthesis of substituted tetrahydro-3,3-dimethyl-1*H*-benzothiazolo[2,3-*b*]quinazolin-1-ones, well established medicinally important compounds, has been achieved by multicomponent condensation reaction of 2-amino-6-chlorobenzothiazole, substituted benzaldehydes, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) under different reaction conditions and using different energy sources, e.g., microwave irradiation, sonication, and classical heating, for comparison purposes. Use of a monomode oven enabled accurate monitoring of the temperature distribution in the microwave reaction vessel, and revealed a very strong and unexpected thermal heterogeneity. The reaction was facilitated by the presence of DMF, the catalytic role of which is demonstrated.

Keywords Monomode reactor · Sonication · Benzothiazolo[2,3-*b*]quinazolines · DMF

Introduction

Organic reactions accelerated by the effect of microwaves [1–4] have attracted much attention in the past decade and their application to multi-component reactions [5–8] can be adapted for high-speed parallel synthesis of a library of biologically active molecules. Chemists now commonly use microwave heating in order to accelerate thermal reactions or to control the kinetics of such syntheses. The weak microwave absorption of most organic chemicals has been circumvented by use of solid supports [9–12] which strongly absorb hyperfrequency beams and also act as catalysts. As a consequence of their double properties, it was difficult to assess the specific role of the hyperfrequency beam in such applications [13–15]. Moreover, the use of domestic microwave ovens was impeded by possible heterogeneity of the magnetic field, sometimes inducing insufficient reproducibility. (*Warning: Use of a domestic microwave oven in a laboratory for organic reactions is a serious safety risk. Such ovens should not be used for preparative work*).

In contrast, use of monomode systems enabled the microwave beam to be focused on the sample. However, accurate comparison of microwave and classical heating could not be achieved without temperature control [16]. For this reason, the most recent work has been performed using infrared pyrometry [17] or optical fluorescence (thermometers fitted with fiber optic cables) [18]; the first technique gives the surface temperature of the reaction mixture whereas the second enabled estimation of local temperatures.

Thiazolo[2,3-*b*]quinazolines are medicinally and pharmaceutically important compounds, because of their diverse range of biological activity [19–22]. Although conventional syntheses of the biologically important benzothiazoloquinazoline ring system [23–26] have their own merit, they are plagued by poor yields and difficult work-up, because of multi-step, long, tedious procedures, and effluent pollution. Consequently, there is need for further

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exploration of mild conditions, operational simplicity, and cost of reagents, with increased variation of the substitutions in the components and better yields.

Our experience in microwave-assisted chemistry of heterocycles [27–34] encouraged us to establish an efficient synthesis of benzothiazolo[2,3-*b*]quinazolines (Scheme 1). In all cases, besides resulting in good to excellent yields, our method results in much faster reactions compared with earlier published procedures at atmospheric pressure. In addition to using a better energy source and better reaction conditions, we have also taken into account all the conditions that could affect this microwave-assisted syntheses. Our work included comparison with classical heating and ultrasonic irradiation [35–37], because sonication as a non-conventional energy source for activation of reactions has now become a very popular and useful technique in organic chemistry.

Results and discussion

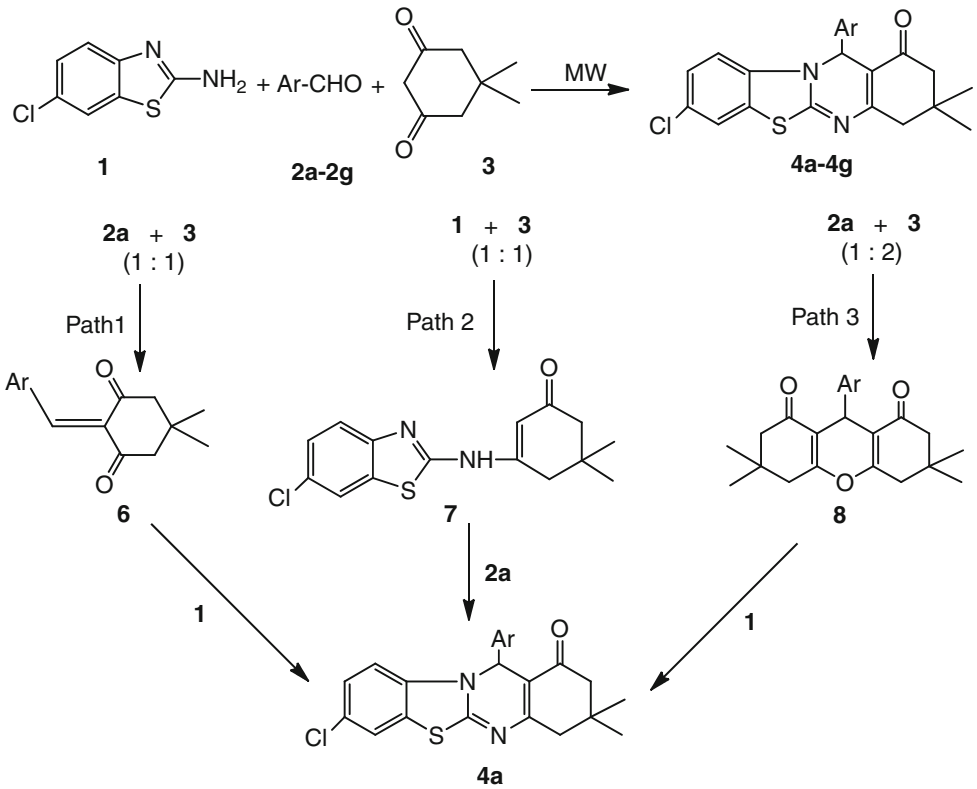
In a multi-component condensation of 2-amino-6-chlorobenzothiazole, substituted benzaldehyde, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) under different conditions, exclusive formation of benzothiazolo[2,3-*b*]quinazolines was observed as depicted in Scheme 1 and listed in Table 1.

The irradiation was performed in parallel using two kinds of reactor—a conventional, 1,000 W power, microwave multimode reactor (National Panasonic oven) (Fig. 1) in which the microwaves are not focused, and a monomode reactor (Prolabo Synthewave 402^{TM}, $\nu =$ 2,450 MHz, $0 \leq P \leq 300$ W) with focused rays and a much more homogenous electromagnetic field (Fig. 2).

In comparison, the reaction was also tried with sonication at different frequencies and with classical heating for the same time and at the same temperature. It was found that with the monomode oven reaction time was reduced drastically with higher yield. We also monitored the effect of different irradiation frequencies on the reaction under sonication and found that with a frequency of 25 kHz the yield of benzothiazolo[2,3-*b*]quinazolines **4** was 80% (Table 1, entry H) within 10 min. Under 40 and 59 kHz irradiation conditions, the yield was 68 and 56%, respectively (Table 1, entries I, J). It seems that use of ultrasound irradiation of lower frequency can improve the yield of quinazoline because at lower frequency the product precipitates and is, therefore, not easily converted into byproducts.

Table 1 shows results from synthesis of **4a** by various methods. To increase the efficiency it was decided to

Scheme 1



4a: Ar = 4-Cl-C_6H_4; **4b**: Ar = 2-NO_2- C_6H_4; **4c**: Ar = 3-NO_2-C_6H_4; **4d**: Ar = C_6H_5; **4e**: Ar = 2-Cl-C_6H_4; **4f**: Ar = 4-OCH_3-C_6H_4; **4g**: Ar = 2-F-C_6H_4

Table 1 Comparative study for the synthesis of **4a**

(A) Multicomponent synthesis

Entry	Reaction medium	Reaction temperature (°C)	Reaction time (min)/yield (%)			
			Δ	US[a]	MW	
					Monomode	Multimode
A	*n*-Butanol	100	2,400/50	20/48	11/68	18/55
B	Isopropanol	76	2,520/45	25/58	18/38	15/60
C	DMF	120	900/60	20/65	10/86	12/75
D	DMF	100	1,200/54	30/48	15/78	18/65
E	DMF	130	1,100/53	25/55	13/80	15/68
F	Neat	120	No reaction	30/40	12/80	18/68
G	Water	120	420/34	24/62	15/59	16/62
H	Water + PTC	120	360/58	18/67	13/76	14/70
I	Toluene	120	18/48	–	14/62	15/58
J	Ethanol	60	10/52	10/80	5/75	5/90
K	Reaction performed in ultrasonic bath at frequency 40 kHz			18/68	–	–
L	Reaction performed in ultrasonic bath at frequency 59 kHz			20/56	–	–

(B) By stepwise reaction with microwave heating[b]

Reactants	Reaction temperature (°C)	Medium	Time (min)	Yield (%)	M.p. (°C)
6 + 1	120	DMF	6	72	190–192
6 + 1	120	Ethanol	8	67	190–192
8 + 1	120	DMF	6	75	190–192
8 + 1	120	Ethanol	6	68	190–192
7 + 2a	120	DMF	5	70	190–192
7 + 2a	120	Ethanol	6	65	190–192

[a] Ultrasound

[b] Monomode reactor

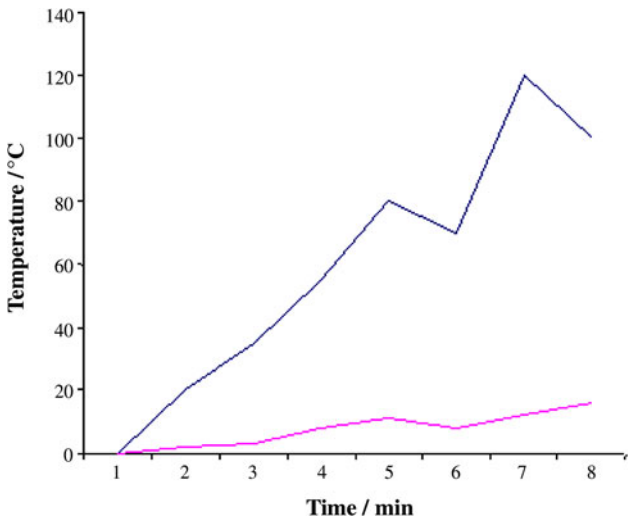


Fig. 1 Temperature profile diagram in multimode oven at 300 W: neat + DMF (*upper zig zag line*); neat (*lower straight line*)

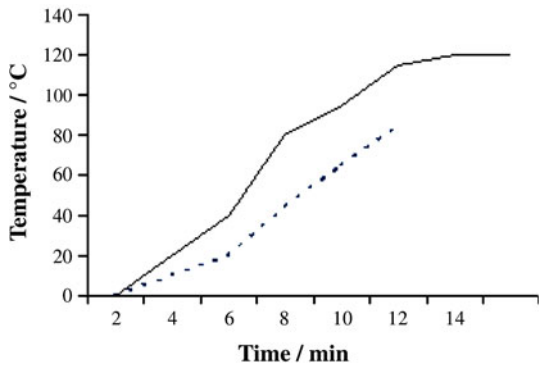


Fig. 2 Temperature profile diagram in monomode oven at 300 W: neat + DMF (*full line*); neat (*dotted line*)

perform this multi-component reaction in polar, highly microwave-absorbing solvents, for example DMF, ethanol, or water. Unfortunately, with water as solvent the reaction time required was longer and the yield obtained was less,

because of the low solubility of the organic substrates in water [38]. However, under neat conditions the reaction took longer than in DMF as energy-transfer agent (Table 1).

As usual in catalytic reactions, increasing the reaction temperature accelerated the conversion of the substrate. It was also observed (Table 1) that increasing the reaction temperature yielded less product, because of decomposition of the reaction substrate at high temperature. For comparison we tried the reaction at a suitable reaction temperature (120 °C) in three different reaction media and found DMF was the best reaction medium for synthesis of benzothiazolo[2,3-*b*]quinazolinones **4** (Table 2).

Thus DMF was found to be most suitable medium, because higher yield of pure product was achieved compared with reactions in ethanol, water, and under neat conditions (Table 2).

The identity of benzothiazolo[2,3-*b*]quinazolinone **4a** was established on the basis of chemical, spectral, and analytical data. The ^{1}H NMR spectrum of **4a** contained two singlets at $\delta = 1.03$ and 1.23 ppm because of two methyl groups, four signals at $\delta = 1.57$, 1.78, 2.28, and 2.42 ppm from two CH_2 groups (forming AB patterns), one methine proton at $\delta = 4.68$ ppm, and aryl protons at $\delta = 6.98$–7.28 ppm.

Table 2 Comparative study of synthesis of **4** at fixed temperature in a monomode reactor

Compd.	Reaction medium	Temp. (°C)	Time (min)	M.p. (°C)	Yield (%)
4a	DMF	120	10	189–192	86
	Neat	120	12		74
	Water	120	16		62
4b	DMF	120	15	163–165	78
	Neat	120	18		52
	Water	120	22		45
4c	DMF	120	9	124–126	82
	Neat	120	13		70
	Water	120	18		60
4d	DMF	120	11	178–182	68
	Neat	120	10		55
	Water	120	15		48
4e	DMF	120	12	222–224	72
	Neat	120	16		50
	Water	120	20		42
4f	DMF	120	15	212–214	83
	Neat	120	18		74
	Water	120	25		68
4g	DMF	120	15	209–211	85
	Neat	120	13		68
	Water	120	22		55

Further confirmation was based on the ^{13}C NMR and mass spectra. In the ^{13}C NMR, sharp signals were observed at $\delta = 17.10$ (C–$(CH_3)_2$), 27.82 (–CH_3), 29.21 (–CH_3), 45.24 (–CH_2), 47.38 (–CH_2), 50.08 (methine carbon), 116.02–127.09 (aromatic carbons), 162.09 (C=N), and 191.22 (C=O) ppm. The appearance of the molecular ion peak at $m/z = 428$ also showed the formation of benzothiazoloquinazoline **4a**.

The formation of product **4** may proceed via three pathways (Scheme 1). Path 1 involves the initial formation of arylidene derivative **6** followed by its reaction with 2-amino-6-chlorobenzothiazole (**1**). Path 2 entails the formation of an enaminoketone followed by its cyclocondensation with 4-chlorobenzaldehyde (**2**). The third possible route may involve the initial formation of intermediate **8** [39, 40] followed by reaction with **1** as shown in Scheme 1. Although the possibility of all these routes was confirmed by the stepwise reaction of pre-synthesized intermediates **6**, **7**, and **8** with **1**, **2**, and **1**, respectively, under microwave conditions these multi-component reactions proceed via path 1, as confirmed by TLC monitoring during the course of reaction and comparison with pre-synthesized intermediates which indicated the formation of intermediate **6**.

Conclusion

In conclusion, we have developed a practical and novel procedure for synthesis of substituted tetrahydro-3,3-dimethyl-1*H*-benzothiazolo[2,3-*b*]quinazolin-1-ones using a monomode microwave reactor, and have compared different energy sources and reactions conditions. In the monomode reactor the temperature is more homogeneous and changes in the activation reactor are more efficient than in the multimode reactor because of the better yield of energy obtained by microwave fascicle focalization and the more homogeneous electromagnetic field. The significant advantages offered by this procedure are operational simplicity, fast reaction, high selectivity, excellent yields of products, no reduction of other reducible functionality, and use of no organic solvent or toxic reagent in the reaction. We believe this reaction will find suitable applications in organic synthesis and will lead to further useful chemistry. The biological activity of synthetic libraries will be reported in due course.

Experimental

Melting points were determined in open glass capillaries. IR spectra (KBr) were recorded on a Shimadzu FT IR-8400S spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300, at 300.15 and

75.47 MHz, respectively, using $CDCl_3$ as solvent. TMS was used as internal reference. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 system using sector double focus and an electron-impact source with an ionizing voltage of 70 eV, and with a Bruker Daltonics Apex II, 3 tesla, FT-ICR-MS with ESI source or EI/CI source. DIPMS (direct insertion probe mass spectrum) values are reported in *m/z*. The purity of all compounds was checked by TLC using silica gel G-coated glass plates and benzene–ethyl acetate (8:2) as eluent. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology operating at 1,000 W generating 2,450 MHz frequency. (*Warning: Use of a domestic microwave oven in a laboratory for organic reactions is a serious safety risk. Such ovens should not be used for preparative work*).

The monomode system was purchased from Prolabo (Synthewave 402^{TM}, $\nu = 2{,}450$ MHz, $0 \leq P \leq 300$ W) and coupled with a microcomputer. For comparison purposes some reactions were repeated in a different monomode microwave reactor (Discover, CEM Corporation and Biotage initiator). The temperature of the reagents was measured by infrared pyrometry and the power of the magnetron was automatically controlled to maintain the set temperature with a proportional integral corrector. Uniform irradiation of reagents was achieved by the regular and automatic rotation of the reaction vessel. The reactors (quartz or borosilicate glass) had the dimensions: inside diameter 15 mm, glass thickness 1.2 mm, maximum content 10 cm^3. Sonication was performed in a Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power of 250 W) and an SK 250 LH ultrasonic cleaner (with a frequency of 40 or 59 kHz and a nominal power of 250 W; Shanghai Kudos Ultrasonic Instrument). The reaction flask was located in the cleaner; the surface of the reactants was slightly lower than the level of water. 2-Amino-6-chlorobenzothiazole was prepared by a literature method [41].

*Multi-component synthesis of compound **4a***

By conventional heating

Equimolar quantities (0.01 mol) of 2-amino-6-chlorobenzothiazole (**1**, 1.84 g), 4-chlorobenzaldehyde (**2**, 1.40 g), and dimedone (**3**, 1.40 g) in isopropanol or *n*-butanol or DMF were heated under reflux for 42, 40, or 15 h. At the end of the reaction (monitored by TLC), the product formed in reactions in isopropanol or *n*-butanol was isolated by column chromatography on silica gel (60–120 mesh), using a 1:1 mixture of chloroform and ethyl acetate as eluent. For the product formed in reactions in DMF, 5 cm^3 2-propanol was added to the reaction mixture and the precipitate was collected to give product **4a**, which was recrystallized from ethanol.

By microwave-assisted reaction

In DMF: An equimolar mixture (0.01 mol) **1**, **2**, and **3** with 5 cm^3 DMF in a 10 cm^3 pressure vial was placed inside the monomode reactor for 10 min (TLC) at 300 W. The reaction mixture was cooled, extracted with 15 cm^3 methanol, and the extract was poured on to crushed ice. The precipitate thus obtained was filtered, washed with water, and found to be pure with no need for further purification.

In ethanol: An equimolar mixture (0.01 mol) **1**, **2**, and **3** was placed in a beaker and the minimum quantity of ethanol (sufficient to make a slurry) was added. The mixture was placed in the microwave oven and irradiated at power output 300 W. The product started to precipitate immediately after cooling the reaction mixture to room temperature (or in some cases during the course of the reaction), was collected, washed with cold aqueous ethanol, and found to be pure by TLC, with no need of further recrystallization.

By ultrasonic irradiation

An equimolar mixture (0.01 mol) **1**, **2**, and **3** was placed in a conical flask with 10 cm^3 ethanol. The reaction mixture was irradiated in an ultrasonic bath for an appropriate time (monitored by TLC) at room temperature/60 °C at different frequency (Table 1). The product started to precipitate during the course of the reaction. Work-up similar to that after the microwave reaction gave pure crystalline solid (TLC). For analytical and spectral analysis the solid was recrystallized from ethanol.

*Stepwise synthesis of compound **4a***

2-[(4-Chlorophenyl)methylene]-5,5-dimethylcyclohexane-1,3-dione (**6a**)

An equimolar mixture (0.01 mol) of 4-chlorobenzaldehyde (**2a**) and dimedone (**3**) was dissolved in the minimum quantity of ethanol and irradiated under microwaves at 300 W until completion of the reaction (4 min, monitored by TLC). On cooling, crystals precipitated which were collected and found to be pure. M.p.: 114 °C (Ref. [42] 114 °C).

3-[(6-Chloro-1,3-benzothiazol-2-yl)amino]-5,5-dimethylcyclohex-2-en-1-one (**7**, $C_{15}H_{15}ClN_2OS$)

An equimolar mixture (0.01 mol) of 2-amino-6-chlorobenzothiazole (**1**) and **3** was dissolved in the minimum quantity of ethanol and irradiated intermittently in the microwave oven at 300 W for 7 min. On cooling pure crystalline product precipitated. M.p.: 122 °C; IR (KBr):

$\bar{\nu}$ = 3,350, 2,935, 1,690, 1,620, 1,580, 1,490, 745 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$ (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.59 (1H, s, 2,4-H_A), 1.75 (1H, s, 2,4-H_A), 2.38 (1H, s, 2,4-H_B), 2.62 (1H, s, 2,4-H_B), 5.48 (1H, s, CH), 6.98–7.69 (3H, m, Ar–H), 12.69 (1H, bs, NH, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.65$, 40.23, 43.56, 103.23, 108.20, 124.80, 128.60, 135.40, 152.32, 154.80 ppm; DIPMS: $m/z = 306.05$ $(M)^+$, 307.05 $(M + 1)^+$; HRMS (EI): calcd. 306.0594, found 306.0601.

9-(4-Chlorophenyl)-3,4,5,6,7,9-hexahydro-3,3,6,6-tetramethyl-1H-xanthene-1,8(2H)-dione (**8**)

A mixture of **2** (0.01 mol) and **3** (0.02 mol) in the minimum quantity of ethanol was irradiated under microwaves (300 W) intermittently until completion of the reaction (5 min, TLC), and after cooling pure product **8** was obtained. M.p.: 231 °C (Refs. [43] 228–230 °C, [44] 230–232 °C (EtOH)).

*Synthesis of **4a** from the intermediates*

Equimolar mixtures of intermediates **6a**, **7**, and **8** with **1**, **2a**, and **1**, respectively (Table 1) in the minimum quantity of ethanol required to form a slurry were irradiated in the microwave oven for an appropriate time (monitored by TLC, Table 1). Crystals of **4a** separated on cooling in every case.

The same reactions were also performed using DMF instead of ethanol under microwaves. Isolation of product in a manner similar to that after the multicomponent reaction gave identical product in all cases.

8-Chloro-12-(4-chlorophenyl)-2,3,4,12-tetrahydro-3,3-dimethyl-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4a**, $C_{22}H_{18}Cl_2N_2OS$)

M.p.: 192 °C; IR (KBr): $\bar{\nu}$ = 2,930–2,875, 1,680, 1,625, 1,580, 1,485, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.57 (1H, s, 2,4-H_A), 1.78 (1H, s, 2,4-H_A), 2.28 (1H, s, 2,4-H_B), 2.42 (1H, s, 2,4-H_B), 4.68 (1H, s, CH), 6.98–7.28 (7H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.10$, 27.82, 29.21, 45.24, 47.38, 50.08, 116.02, 120.60, 124.30, 128.60, 131.50, 135.80, 138.60, 141.30, 148.50, 158.20, 159.60, 162.09, 191.22 ppm; DIPMS: $m/z = 428.05$ $(M)^+$, 429.02 $(M + 1)^+$; HRMS (EI): calcd. 428.0517, found 428.0524.

8-Chloro-2,3,4,12-tetrahydro-3,3-dimethyl-12-(2-nitrophenyl)-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4b**, $C_{22}H_{18}ClN_3O_3S$)

M.p.: 172 °C; IR (KBr): $\bar{\nu}$ = 2,935– 2,885, 1,675, 1,615, 1,570, 1,510, 1,360, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.09$ (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.61 (1H, s, 2,4-H_A), 1.75 (1H, s, 2,4-H_A), 2.32 (1H, s, 2,4-H_B), 2.50 (1H, s, 2,4-H_B), 4.69 (1H, s, CH), 7.15-8.05 (7H, m, Ar- H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.90$, 28.21, 29.81, 45.63, 47.55, 50.02, 119.04, 121.80, 125.60, 129.40, 130.90, 134.80, 139.40, 144.80, 147.90, 164.00, 192.50 ppm; DIPMS: $m/z = 439.07$ $(M)^+$, 440.07 $(M + 1)^+$; HRMS (EI): calcd. 439.0757, found 439.0789.

8-Chloro-2,3,4,12-tetrahydro-3,3-dimethyl-12-(3-nitrophenyl)-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4c**, $C_{22}H_{18}ClN_3O_3S$)

M.p.: 127 °C; IR (KBr): $\bar{\nu}$ = 2,936–2,876, 1,678, 1,620, 1,560, 1,520, 1,370, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.62 (1H, s, 2,4-H_A), 1.78 (1H, s, 2,4-H_A), 2.33 (1H, s, 2,4-H_B), 2.56 (1H, s, 2,4-H_B), 4.69 (1H, s, CH), 7.15–8.10 (7H, m, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.86$, 28.41, 29.93, 45.79, 47.91, 50.22, 120.01, 124.70, 128.90, 132.40, 133.80, 138.60, 143.50, 148.90, 163.01, 190.85 ppm; DIPMS: $m/z = 439.07$ $(M)^+$, 440.07 $(M + 1)^+$; HRMS (EI): calcd. 439.0757, found 439.0790.

8-Chloro-2,3,4,12-tetrahydro-3,3-dimethyl-12-phenyl-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4d**, $C_{22}H_{19}ClN_2OS$)

M.p.: 187 °C; IR (KBr): $\bar{\nu}$ = 2,928–2,879, 1,678, 1,630, 1,540, 1,480, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.05$ (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.58 (1H, s, 2,4-H_A), 1.72 (1H, s, 2,4-H_A), 2.29 (1H, s, 2,4-H_B), 2.43 (1H, s, 2,4-H_B), 4.66 (1H, s, CH), 6.97–7.28 (8H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.68$, 28.52, 29.89, 45.92, 47.84, 50.18, 121.02, 122.30, 124.60, 130.70, 132.60, 138.70, 140.50, 143.90, 149.40, 162.04, 190.02 ppm; DIPMS: $m/z = 394.09$ $(M)^+$, 395.09 $(M + 1)^+$; HRMS (EI): calcd. 394.0907, found 394.1009 .

8-Chloro-12-(2-chlorophenyl)-2,3,4,12-tetrahydro-3,3-dimethyl-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4e**, $C_{22}H_{18}Cl_2N_2OS$)

M.p.: 226 °C; IR (KBr): $\bar{\nu}$ =2,930– 2,880, 1,685, 1,625, 1,560, 1,490, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.56 (1H, s, 2,4-H_A), 1.78 (1H, s, 2,4-H_A), 2.30 (1H, s, 2,4-H_B), 2.53 (1H, s, 2,4-H_B), 4.69 (1H, s, CH), 6.89–7.21 (7H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.45$, 28.51, 29.79, 45.3, 47.59, 50.19, 122.03, 125.60, 128.70, 131.70, 133.40, 139.20, 142.30, 143.80, 149.60, 167.03, 192.30 ppm; DIPMS: $m/z = 428.05$ $(M)^+$, 429.05 $(M + 1)^+$; HRMS (EI): calcd. 428.0517, found 429.0530.

8-Chloro-2,3,4,12-tetrahydro-12-(4-methoxyphenyl)-3,3-dimethyl-1H-benzothiazolo[2,3-b]quinazolin-1-one
(**4f**, $C_{22}H_{18}Cl_2N_2OS$)

M.p.: 207 °C; IR (KBr): $\bar{\nu}$ = 2,928– 2,878, 1,680, 1,632, 1,530, 1,480, 1,130, 760 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): $\delta = 1.07$ (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.62 (1H, s, 2,4-H_A), 1.75 (1H, s, 2,4-H_A), 2.33 (1H, s, 2,4-H_B)*, 2.58 (1H, s, 2,4-H_B)*, 4.66 (1H, s, CH), 6.88–7.23 (7H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.50$, 28.90, 29.20, 45.80, 50.26, 120.02, 122.80, 127.40, 131.50, 133.70, 138.90, 140.90, 145.30, 149.70, 162.06, 190.08 ppm; DIPMS: $m/z = 424.10$ $(M)^+$, 425.10 $(M + 1)^+$; HRMS (EI): calcd. 424.1012, found 424.1030.

8-Chloro-12-(2-fluorophenyl)-2,3,4,12-tetrahydro-3,3-dimethyl-1H-benzothiazolo[2,3-b]quinazolin-1-one (**4g**, $C_{22}H_{18}ClFN_2OS$)

M.p.: 215 °C; IR (KBr): $\bar{\nu}$ = 2,925–2,875, 1,675, 1,625, 1,560, 1,490, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.61 (1H, s, 2,4-H_A), 1.78 (1H, s, 2,4-H_A), 2.29 (1H, s, 2,4-H_B), 2.38 (1H, s, 2,4-H_B), 4.67 (1H, s, CH), 6.95–7.24 (7H, m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.92$, 28.52, 29.81, 45.91, 50.06, 121.04, 123.40, 126.70, 130.40, 133.90, 137.60, 140.80, 144.20, 149.30, 161.05, 191.03 ppm; DIPMS: $m/z = 412.08$ $(M)^+$, 413.08 $(M + 1)^+$; HRMS (EI): calcd. 412.0812, found 412.0825.

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