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Benzo[*h*]thiazolo[2,3-*b*]quinazolines by an efficient *p*-toluenesulfonic acid-catalyzed one-pot two-step tandem reaction

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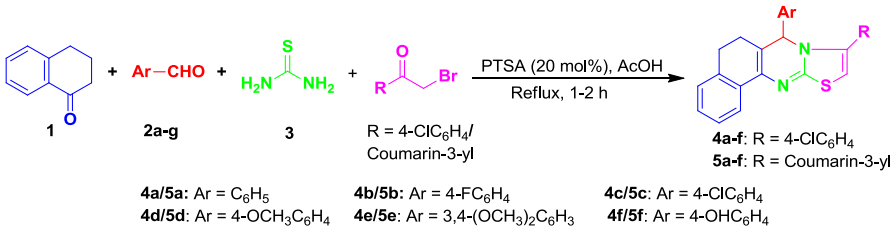
Abstract A highly efficient method has been developed for synthesis of 7,9-disubstituted-6,7-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolines via multicomponent one-pot two-step tandem reaction involving 1-tetralone, arylaldehydes, thiourea, and 4-chlorophenacyl bromide/(3-bromoacetyl)coumarin utilizing *p*-toluenesulfonic acid as catalyst in glacial acetic acid under reflux conditions. Analytically pure products are formed with excellent yield and short reaction time. All the synthesized compounds were confirmed by their spectral and elemental analyses.

Graphical abstract



Keywords Benzo[*h*]thiazolo[2,3-*b*]quinazoline · Coumarin · Multicomponent reaction · Phenacyl bromide · 1-Tetralone

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Introduction

In recent years, increasing interest has been focused on synthesis of thiazolopyrimidine and thiazoloquinazoline derivatives owing to their significant biological activities that include antimicrobial [1, 2], antiviral [3], antioxidant [4], anticancer [5], antiinflammatory [6], antihypertensive [7], antiparkinsonian [8], anti-human immunodeficiency virus (HIV) [9], and antibiofilm [10] properties. They have also been reported as calcium antagonists [11], group 2 metabotropic glutamate receptor antagonists [12], 5-HT2 receptor antagonists [13, 14], and inhibitors of enzymes such as xanthine oxidase [15], acetylcholinesterase [16], and CDC25B phosphatise [17]. Some of the biologically potent thiazolopyrimidine and thiazoloquinazoline derivatives are given in Fig. 1.

A variety of synthetic methods have been reported for preparation of thiazolopyrimidine and thiazoloquinazoline derivatives. One of the commonest methods involves cyclization of dihydropyrimidinethiones with 1,2-dielectrophiles such as 2-bromoketones [18, 19], chloroacetyl chloride [17], chloroacetic acid [3, 6, 10], methyl chloroacetate [20], and *N*-aryl-2-chloroacetamides [21]. Most of these methods involve two steps: Biginelli reaction as well as cyclization. To the best of our knowledge, there is no direct route for construction of the thiazolopyrimidine scaffold in a one-pot procedure. Nowadays, multicomponent reactions have emerged as an efficient and powerful tool in modern organic chemistry towards generation of highly diverse and complex products in a single operation without isolation of intermediates in minimal time with maximum selectivity [22, 23]. Therefore, we envisaged a novel one-pot two-step tandem reaction for construction of thiazoloquinazoline derivatives involving 1-tetralone, arylaldehyde, thiourea, and 4-chlorophenacyl bromide/(3-bromoacetyl)coumarin in presence of *p*-toluenesulfonic acid as catalyst.

Experimental

Materials and methods

All the reagents and solvents were procured from Aldrich/Merck and used without further purification. Melting points were recorded using a Cintex melting point apparatus and are uncorrected. Reaction progress as well as compound purity were monitored with F_{254} silica-gel precoated thin-layer chromatography (TLC) plates using hexane:ethyl acetate (8:3) as eluent, and the developed chromatogram was

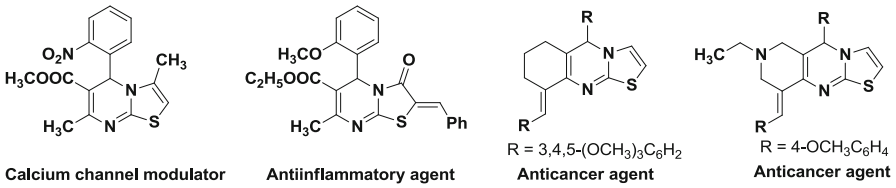


Fig. 1 Biologically active thiazolopyrimidine and thiazoloquinazoline derivatives

visualized under ultraviolet (UV) light and iodine vapors. Infrared (IR) spectra were recorded on a Bruker Tensor 27 series Fourier-transform (FT)-IR spectrophotometer using KBr pellets. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 400-MHz spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Jeol JMSD-400 spectrometer. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit, and the values are within ±0.4 % of theoretical values.

General procedure for synthesis of 7,9-disubstituted-6,7-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolines (4a–f, 5a–f)

p-Toluenesulfonic acid (20 mol%) was added to a mixture of 1-tetralone (1 mmol), aryl aldehyde (**2a–f**, 1 mmol), and thiourea (1 mmol) in glacial acetic acid (10 mL), and refluxed for 30 min. Subsequently, 4-chlorophenacyl bromide/3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) was added to the mixture and further refluxed for 1–2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold water. The solid separated out was filtered, washed with water, and recrystallized from ethanol.

Spectral data of representative compounds

*9-(4-Chlorophenyl)-7-phenyl-6,7-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazoline (**4a**)*

White solid; IR (KBr, ν_{max}, cm^{-1}): 1605 (C=N), 825 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.76 (t, 1H, J = 7.6 Hz), 2.33 (t, 1H, J = 8.0 Hz), 2.57–2.79 (m, 2H), 6.16 (s, 1H), 6.84 (d, 2H, J = 6.4 Hz), 7.17–7.46 (m, 11H), 7.65 (d, 1H, J = 6.8 Hz); Mass (ESI) *m/z*: 426 $[M]^+$; Anal. calcd. for $C_{26}H_{19}ClN_2S$: C, 73.14; H, 4.49; N, 6.56; Found: C, 73.34; H, 4.62; N, 6.37.

*9-(4-Chlorophenyl)-7-(4-methoxyphenyl)-6,7-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazoline (**4d**)*

Pale-yellow solid; IR (KBr, ν_{max}, cm^{-1}): 1608 (C = N), 1245 (C–O–C), 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.75–1.82 (m, 1H), 2.28–2.35 (m, 1H), 2.60 (t, 1H, J = 8.4 Hz), 2.75–2.83 (m, 1H), 3.67 (s, 3H), 6.09 (s, 1H), 6.69–6.75 (m, 4H), 7.26–7.40 (m, 6H), 7.49 (d, 2H, J = 8.4 Hz), 7.63 (d, 1H, J = 7.6 Hz); Mass (ESI) *m/z*: 457 $[M + H]^+$; Anal. calcd. for $C_{27}H_{21}ClN_2OS$: C, 70.96; H, 4.63; N, 6.13; Found: C, 70.71; H, 4.80; N, 6.29.

*3-(7-(4-Chlorophenyl)-6,7-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9-yl)-2H-chromen-2-one (**5c**)*

White solid; IR (KBr, ν_{max}, cm^{-1}): 1741 (C=O), 1635 (C=N), 840 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.73–1.78 (m, 1H), 2.27–2.35 (m, 1H), 2.60–2.66

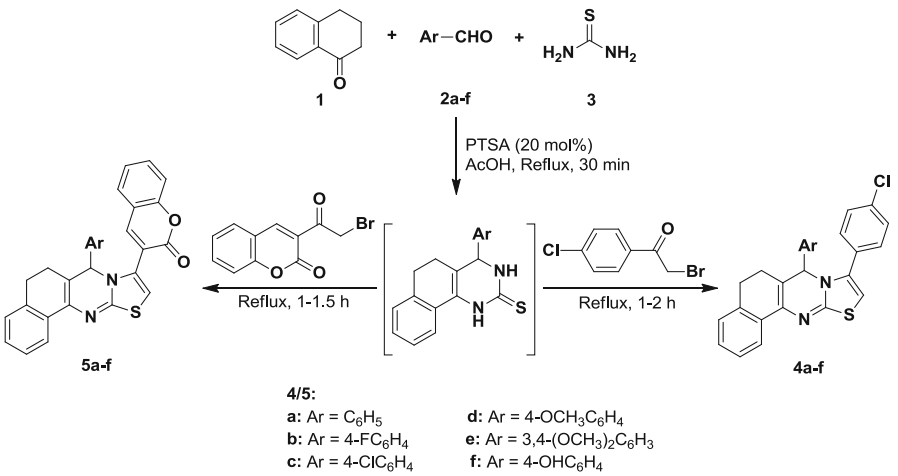
(m, 1H), 2.76–2.81 (m, 1H), 6.26 (s, 1H), 7.23–7.27 (m, 5H), 7.34–7.51 (m, 5H), 7.64–7.75 (m, 3H), 7.94 (s, 1H); Mass (ESI) *m/z*: 495 $[M + H]^+$; Anal. calcd. for $C_{29}H_{19}ClN_2O_2S$: C, 70.37; H, 3.87; N, 5.66; Found: C, 70.61; H, 3.66; N, 5.89.

*3-(7-(3,4-Dimethoxyphenyl)-6,7-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9-yl)-2H-chromen-2-one (**5e**)*

White solid; IR (KBr, ν_{max}, cm^{-1}): 1734 (C=O), 1636 (C=N), 1261 (C–O–C); ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.76–1.83 (m, 1H), 2.29 (t, 1H, $J = 8.0$ Hz), 2.61–2.66 (m, 1H), 2.76–2.80 (m, 1H), 3.26 (s, 3H), 3.59 (s, 3H), 6.15 (s, 1H), 6.68 (s, 1H), 6.75 (s, 2H), 7.25–7.50 (m, 6H), 7.66–7.65 (m, 3H), 7.88 (s, 1H); Mass (ESI) *m/z*: 521 $[M + H]^+$; Anal. calcd. for $C_{31}H_{24}N_2O_4S$: C, 71.52; H, 4.65; N, 5.38; Found: C, 71.35; H, 4.80; N, 5.51.

Results and discussion

A schematic for the formation of 7,9-disubstituted-6,7-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazoline derivatives (**4a–f**, **5a–f**) via one-pot two-step tandem reaction catalyzed by *p*-toluenesulfonic acid is shown in Scheme 1. 4-Aryl-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thiones, which were obtained in situ by reaction of 1-tetralone (**1**), aromatic aldehydes (**2a–f**), and thiourea (**3**) in glacial acetic acid in presence of catalytic *p*-toluenesulfonic acid under reflux conditions, on condensation with 4-chlorophenacyl bromide/3-(2-bromoacetyl)-2*H*-chromen-2-one resulted in the formation of desired products **4a–f**, **5a–f** in good yields (86–94 %). One of the starting materials, 3-(2-bromoacetyl)-2*H*-chromen-2-one, was prepared following the literature procedure [24].



Scheme 1 Synthesis of 7,9-disubstituted-6,7-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolines

Table 1 Optimizing the reaction conditions[a]

Entry	Amount of PTSA (mol%)	Solvent	Time (h)	Yield[b] (%)
1	–	Ethanol	12	–
2	–	Acetic acid	12	14
3	–	Acetonitrile	12	–
4	10	Ethanol	6	19
5	10	Acetic acid	3	46
6	10	Acetonitrile	6	21
7	15	Acetic acid	2	78
8	20	Acetic acid	1.5	93
9	25	Acetic acid	1.5	93

[a] 1-Tetralone (1 mmol), benzaldehyde (1 mmol), thiourea (1 mmol), 4-chlorophenacyl bromide (1 mmol), solvent (10 mL), reflux

[b] Isolated yields

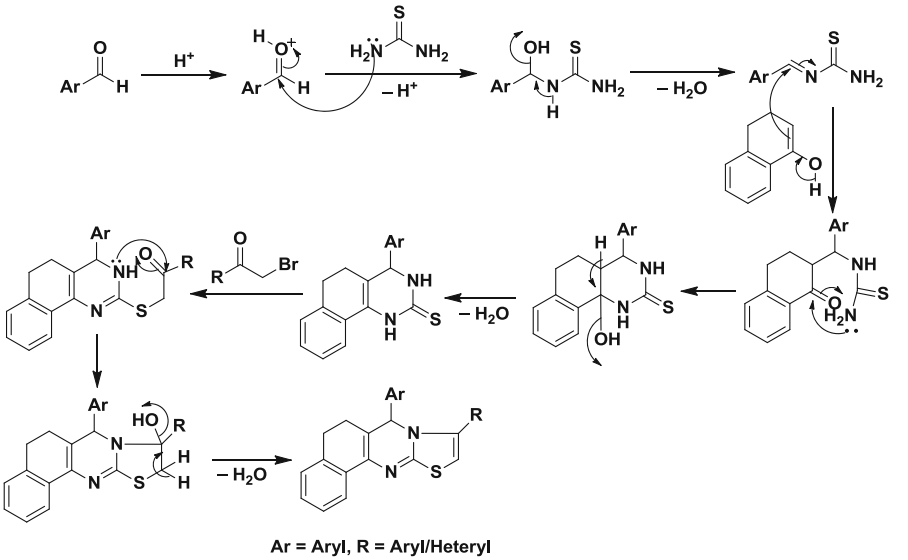
Table 2 Synthesis of benzo[*h*]thiazolo[2,3-*b*]quinazoline derivatives (**4a–f**, **5a–f**)

Product[a]	Aldehyde	Time (h)	Yield[b] (%)	Melting point (°C)	
				Observed	Literature [19]
4a	Benzaldehyde	1.5	93	320–322	319–320
4b	4-Fluorobenzaldehyde	1.5	89	300–302	301–303
4c	4-Chlorobenzaldehyde	1.0	94	319–321	317–318
4d	4-Methoxybenzaldehyde	1.5	91	260–262	260–262
4e	3,4-Dimethoxybenzaldehyde	1.5	92	231–232	233–236
4f	4-Hydroxybenzaldehyde	2.0	86	290–293	292–294
5a	Benzaldehyde	1.5	92	290–292	290–291
5b	4-Fluorobenzaldehyde	1.5	92	280–281	277–279
5c	4-Chlorobenzaldehyde	1.0	93	282–283	280–282
5d	4-Methoxybenzaldehyde	1.0	90	275–276	275–277
5e	3,4-Dimethoxybenzaldehyde	1.5	91	270–272	267–269
5f	4-Hydroxybenzaldehyde	1.5	88	294–296	293–294

[a] Reaction conditions: 1-tetralone (**1**, 1 mmol), arylaldehyde (**2a–f**, 1 mmol), thiourea (**3**, 1 mmol), 4-chlorophenacyl bromide/(3-bromoacetyl)coumarin (1 mmol), glacial acetic acid (10 mL), PTSA (20 mol%), reflux

[b] Isolated yields

Recently, Janardhan et al. [19] reported synthesis of thiazolopyrimidines in a two-step manner, in which the first step is the formation of Biginelli product and the second step is cyclization with various 2-bromoketones. To develop a one-pot method, we carried out the model reaction of 1-tetralone (**1**), benzaldehyde (**2a**), thiourea (**3**), and 4-chlorophenacyl bromide (**4**) in different solvents such as ethanol, acetic acid, and acetonitrile under reflux conditions. Without catalyst, product formation (**4a**) was not observed in ethanol or acetonitrile, whereas only 14 % was



Scheme 2 Plausible mechanism for formation of benzo[*h*]thiazolo[2,3-*b*]quinazolines

observed in acetic acid even after 12 h. Later, the same reaction was carried out in presence of 10 mol% *p*-toluenesulfonic acid (PTSA), observing maximum yield (46 %) of the product (**4a**) in acetic acid within 3 h. To improve the yield of the product and to reduce the reaction time, we tested the reaction with 15, 20, and 25 mol% PTSA, and observed the maximum yield (93 %) of the product with 20 mol% PTSA in shorter reaction time (Table 1). Under these reaction conditions (PTSA 20 mol%, acetic acid, reflux), we synthesized a series of substituted benzo[*h*]thiazolo[2,3-*b*]quinazolines (**4a–f**, **5a–f**) by varying the aromatic aldehyde (**2a–f**) and 2-bromoketone in good to excellent yields (Table 2).

All the synthesized compounds were confirmed by IR, ^{1}H NMR, and mass spectral data as well as elemental analysis studies (Electronic Supplementary Material). The melting points were also compared with literature values, showing good agreement. The proposed mechanism for formation of the title compounds is shown in Scheme 2. In the presence of PTSA, 4-aryl-3,4,5,6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thiones were obtained through Biginelli reaction, which on cyclization with 4-chlorophenacyl bromide/(3-bromoacetyl)coumarin resulted in formation of corresponding benzo[*h*]thiazolo[2,3-*b*]quinazoline derivatives (**4a–f**, **5a–f**).

Conclusions

A novel and efficient method is described for construction of benzo[*h*]thiazolo[2,3-*b*]quinazoline derivatives in a one-pot two-step manner without isolating the Biginelli product. This methodology is high yielding in shorter reaction times and

applicable for industrial preparation of various thiazoloquinazoline derivatives in a single step.

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Conflict of interest The authors report no conflicts of interest. The authors alone hereby stand responsible for the contents of this scientific paper.

Ethical standard This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. S.A. Abdel-Mohsen, J. Chin. Chem. Soc. **50**, 1085 (2003)
2. A.C. Robert, A.G. Richard, F.C. Zdzislaw, J. Med. Chem. **17**, 1025 (1974)
3. S.F. Mohamed, E.M. Flefel, A.E. Amr, D.N. Abd El-Shafy, Eur. J. Med. Chem. **45**, 1494 (2010)
4. S. Maddila, G.L.V. Damu, E.O. Oseghe, O.A. Abafe, C. Venakata Rao, P. Lavanya, J. Korean Chem. Soc. **56**, 334 (2012)
5. E.E. Flefel, M.A. Salama, M. El-Shahat, M.A. El-Hashash, A.F. El-Farargy, Phosphorus Sulfur Silicon Relat. Elem. **182**, 1739 (2007)
6. B. Tozkoparan, M. Ertan, P. Kelicen, R. Demirdamar, Farmaco **54**, 588 (1999)
7. E. Jeanneau-Nicolle, M. Benoit-Guyod, A. Namil, G. Leclerc, Eur. J. Med. Chem. **27**, 115 (1992)
8. E.A. Abd El-Galil, S.S. Maigali, M.M. Abdulla, Monatsh. Chem. **139**, 1409 (2008)
9. K. Danel, E.B. Pedersen, C. Nielsen, J. Med. Chem. **41**, 191 (1998)
10. B. Pan, R. Huang, L. Zheng, C. Chen, S. Han, D. Qu, M. Zhu, P. Wei, Eur. J. Med. Chem. **46**, 819 (2011)
11. A. Balkan, S. Uma, M. Ertan, W. Wiegrebe, Pharmazie **47**, 687 (1992)
12. J. Wichmann, G. Adam, S. Kolczewski, V. Mutel, T. Woltering, Bioorg. Med. Chem. Lett. **9**, 1573 (1999)
13. S. Ruiu, G. Marchese, P.L. Saba, G.L. Gessa, L. Pani, Mol. Psychiatr. **5**, 673 (2000)
14. M.A. Fadi, Sci. Pharm. **76**, 415 (2008)
15. C.N. Khobragade, R.G. Bodade, B.S. Dawane, S.G. Konda, N.T. Khandare, J. Enzyme Inhib. Med. Chem. **25**, 615 (2010)
16. H. Zhi, L.M. Chen, L.L. Zhang, S.J. Liu, D.C.C. Wan, H.Q. Lin, C. Hu, Arkivoc **xiii**, 266 (2008)
17. S. Kolb, O. Mondesert, M.-L. Goddard, D. Jullien, B.O. Villoutreix, B. Ducommun, C. Garbay, E. Braud, Chem. Med. Chem. **4**, 633 (2009)
18. M.M. Ghorab, S.M. Abdel-Gawad, M.S. El-Gaby, Farmaco **55**, 249 (2000)
19. B. Janardhan, K. Manjulatha, B. Srinivas, B. Rajitha, N. Muralikrishna, A. Sadanandam, RSC Adv. **4**, 22866 (2014)
20. A.A. Abu-Hashem, M.M. Youssef, H.A.R. Hussein, J. Chin. Chem. Soc. **58**, 41 (2011)
21. B. Janardhan, B. Srinivas, B. Rajitha, A.C. Peter, Tetrahedron Lett. **55**, 224 (2014)
22. J. Zhu, H. Bienayme, *Multicomponent Reactions* (Wiley-VCH, Weinheim, 2005)
23. A. Domling, I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
24. A. Gursoy, N. Karali, Turk. J. Chem. **27**, 545 (2003)