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ORIGINAL PAPER

An efficient ultrasonic-assisted synthesis of the thiazolo[2,3-*b*] quinazoline and thiazolo[3,2-*a*] pyrimidine derivatives

Ali Darehkordi · Jabber Reentan · Mahin Ramezani

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Abstract Treatment of cyclohexanone or cyclopentanone (**2**) with aromatic aldehyde (**1**) and thiourea (**3**) in the presence of modified montmorinollite nanostructure or HCl as a catalyst under heating and solvent-free conditions produced 7-benzylidene-4-aryl-3,4,6,7-tetrahydro-1*H* cyclopenta[*d*]pyrimidine-2(5*H*)-thione or 8-benzylidene-4-aryl-3,4,5,6,7,8 hexahydroquinazoline-2(1*H*)-thione (**4**). Compound **4** was utilized as a key intermediate for the synthesis of new thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*] pyrimidine derivatives (**5a–5o**) via the reaction with diethyl and dimethyl acetylene dicarboxylate by two different methods: (a) in methanol as a solvent under ultrasonic irradiation at ambient temperature; (b) in methanol as a solvent at ambient temperature (conventional magnetic stirring). Ultrasound-assisted synthesis provides excellent yields (87–95 %) in short reaction times (30–50 min) at room temperature. The chemical structures of the newly synthesized compounds were characterized by UV–Vis, IR and NMR spectral and elemental analysis.

Keywords Dihydropyrimidinone · Thiazolo[2,3-*b*]quinazoline · Thiazolo[3,2-*a*]pyrimidine · Ultrasound assisted · Dialkyl acetylene dicarboxylate

Introduction

The wide occurrence of the heterocycles in bioactive natural products made them important synthetic targets. Thiazoles represent a class of heterocyclic compounds of great importance in biological chemistry. They exist in many condensed fused systems that were found to possess a wide range of activity [1]. Moreover, fused pyrimidines have drawn the attention of medicinal chemists as chemotherapeutic agents, where several members of this class have earned valued places in chemotherapy as effective agents. Various literature reports displayed numerous fused pyrimidine ring systems and their chemotherapeutic activities as anticancer [2], antibacterial [3], antifungal [4], and antiviral [5] agents. Also, substituted thiazolopyrimidine ring systems were reported to possess antitumor activity [6].

It is evident from the literature that quinazolines and condensed quinazolines exhibit potent central nervous system (CNS) activities, e.g., analgesic and anti-inflammatory [7]. Azolopyrimidoquinolines and pyrimidoquinazolines exhibited good anti-oxidant, anti-inflammatory and analgesic activities [8]. Literature reports show that thienopyrimidines (bioisostere of quinazoline and condensed quinazoline) possess CNS and antibacterial activities [9]. On the other hand, thiazoles and their derivatives are found to be associated with various biological activities [10, 11], such as antibacterial, antifungal and anti-inflammatory activities. Furthermore, organic compounds bearing thiazolopyrimidine and pyrimidothiazolo quinoxaline nuclei were found to possess potent anti-cancer activity [12, 13].

Also, thienopyrimidine derivatives have been reported to possess useful molluscicidal and larvicidal activities against *Biomphalaria alexendra* and *Schistosoma mansoni* snails [14].

Previously, synthesis and characterization of pyrimidinone–peptoid hybrid molecules that modulate Hsp70 activity in vitro and, in some cases, prevent cancer cell proliferation have been reported [15–18].

A. Darehkordi (✉) · J. Reentan · M. Ramezani
Department of Chemistry, Faculty of Science, Vali-e-asr University of Rafsanjan, 77176 Rafsanjan, Iran
e-mail: adarehkordi@yahoo.com; darehkordi@mail.vru.ac.ir

Sonochemistry is a unique method in chemical reactions, because of cavitations, a physical process that creates, enlarges and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitations induce very high local temperatures and pressures inside the bubbles (cavities), leading to turbulent flow of the liquid and enhanced mass transfer [19].

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades [20–22]. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation compared with traditional methods [23–25].

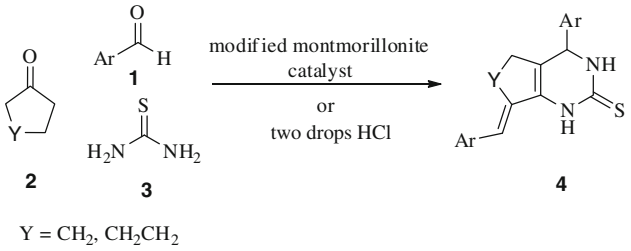
Several methods are reported for the preparation of thiazolo quinoxaline and thiazolo quinazolinone derivatives [26–29].

As our continuous endeavor dealing with the design and preparation of thiazoline compounds [30], we wish to describe herein a simple and efficient method for synthesis of ethyl-5-(aryl)-2-(2-alkoxy-2-oxoethylidene)-7-methyl-3-oxo-3, 5-dihydro-2*H*-thiazolo[3,2-*a*] pyrimidine-6-carboxylate derivatives from reaction of dihydropyrimidinone derivatives with dimethyl and diethyl acetylenedicarboxylate using both ultrasonic irradiation method and a more conventional magnetic stirring method.

Experimental section

A multivalve ultrasonic generator (Bandlin Sonopuls Gerate-Typ: UW 3200, Germany) equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 50 kHz with a maximum power output of 780 W, was used for ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. Melting points were determined in open capillary tubes by an Electrothermal IA 9000 melting point apparatus. IR spectra (KBr) were obtained on a Matson-1000 FT-IR spectrometer. The ^{1}H and ^{13}C-NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.7 MHz, respectively, with Me_4Si as an internal standard (chemical shifts in δ, ppm). Element analyses (C, H, N and S) were performed with a EURO-VECTOR EuroEA3000 CHNSO analyzer. UV–Vis spectra were recorded with a CARY 100 CONC spectrophotometer. Their results corresponded to the calculated values within experimental error. TLC was performed on silica gel Poly-Gram SIL G/UV 254 plates. The starting materials were purchased from Merck and used without further purification. All yields refer to isolated products. Pyrimidinethione derivatives were synthesized by the following procedure.

A mixture of cyclopentanone or cyclohexanone **2** (1 mmol), appropriate aldehyde **1** (2 mmol), thiourea **3** (1.2 mmol) and montmorillonite catalyst (0.6 g) or a few drops of HCl was placed in a test tube and heated in oil bath at 80 °C under solvent-free conditions, for 60–90 min (Scheme 1). After cooling the reaction mixture, ethanol was added and the catalyst was removed by filtration. The filtrate was poured into crushed ice water and the resulting precipitate recrystallized from hot ethanol to yield the pure product. All the compounds were characterized by MP, FT-IR, ^{13}C and ^{1}H-NMR, UV–Vis spectrophotometer and elements analysis.



Scheme 1 Synthesis of pyrimidinethione derivatives under solvent-free conditions

General procedure for synthesis of the thiazolo [2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives

A solution of DMAD (0.001 mol, 0.140 g) or DEAD (0.001 mol, 0.172 g) in 3 ml methanol was added to a solution of pyrimidinethione (0.001 mol) in methanol (10 cc) dropwise. The mixture was stirred at ambient temperature for 2 h. The resulting yellow precipitate was filtered and washed with cold methanol or ethanol and recrystallized with ethanol. The product was obtained as yellow powder.

General procedure for synthesis of the thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives under ultrasonic irradiation

A solution of DMAD (0.001 mol, 0.140 g) or DEAD (0.001 mol, 0.172 g) in 3 ml methanol was added to a solution of pyrimidinethione derivatives (0.001 mol) in methanol (4 ml) in small portions. This reaction mixture was sonicated at 45 kHz. After the completion of reaction (35–45 min, Table 1) as indicated by TLC, the resulting yellow precipitate was filtered and recrystallized with ethanol. The product was obtained as yellow powder.

(*Z*)-methyl 2-((*E*)-9-(3-chlorobenzylidene)-5-(3-chlorophenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5a)

Yellow powder. IR KBr (υ_{max}, cm^{-1}): 3,067 (C–H, aromatic), 1,723, 1,696 (C=O), 1,606, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.55–1.57 (m, 2H, H_7),

Table 1 Structures, yield and conditions of synthesis of thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives (**5a–5o**)

Entry	Y	R	R′O	Product	m.p (°C)	Time (min) Method		Yield % Method	
						A	B	A	B
1	CH_2CH_2	3-Cl	Me	**5a**	167–170	150	45	84	89
2	CH_2CH_2	3-Cl	Et	**5b**	138–140	150	44	81	87
3	CH_2CH_2	3,4-OMe	Me	**5c**	148–150	130	40	91	94
4	CH_2CH_2	3,4-OMe	Et	**5d**	157–160	130	45	92	95
5	CH_2CH_2	2,4-Cl_2	Me	**5e**	155–156	160	55	87	92
6	CH_2CH_2	4-OMe	Me	**5f**	179–182	140	40	89	94
7	CH_2CH_2	4-OMe	Et	**5g**	115–118	140	43	90	93
8	CH_2CH_2	3-NO_2	Me	**5h**	216–219	155	52	87	91
9	CH_2CH_2	3-NO_2	Et	**5i**	225–228	160	56	84	89
10	CH_2CH_2	4-Me	Me	**5j**	145–147	145	50	86	90
11	CH_2CH_2	2-Cl	Me	**5k**	167–170	150	55	88	92
12	CH_2	4-Cl	Me	**5l**	178–181	150	57	84	87
13	CH_2	4-OMe	Me	**5m**	208–210	140	50	87	92
14	CH_2	4-Me	Me	**5n**	154–157	145	45	88	94
15	CH_2	3,4-OMe	Me	**5o**	167–171	135	35	91	95

1.79–1.83 (m, 1H, H_6), 2.21–2.24 (m, 1H, H'_6), 2.49–2.57 (m, 1H, H_8), 2.62–2.66 (m, 1H, H'_8), 3.78 (s, 3H, OCH_3), 5.75 (s, 1H, CH-methine), 6.75 (s, 1H, CH-thiazol ring), 7.29-7.44 (m, 8H, Ar–H), 7.47 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.1 (CH_2), 22.2 (CH_2), 27.3 (CH_2), 53.5 (OCH_3), 59.6 (CH–N), 116.3 (CH), 121.2, 124.2, 126.8, 127.3, 128.4, 128.7, 129.5, 130.9, 131.8, 133.8, 133.9, 134.2, 135.4, 140.3, 141.1, 142.3, 150.4 (C=N), 163.8, 166.8 (C=O). Anal. Calcd. For $C_{26}H_{20}Cl_2N_2O_3S$: C, 61.06; H, 3.94; N, 5.48, S, 6.27. Found: C, 60.96; H, 4.02; N, 5.66; S, 6.12 %.

(*Z*)-ethyl 2-((*E*)-9-(3-chlorobenzylidene)-5-(3-chlorophenyl)-3-oxo-3,5,6,7,8,9-hexa hydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5b)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,066 (C–H, aromatic), 1,721, 1,693 (C=O), 1,605, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 1.57–1.58 (m, 2H, H_7), 1.77–1.84 (m, 1H, H_6), 2.20–2.24 (m, 1H, H'_6), 2.50–2.59 (m, 1H, H_8), 2.62–2.68 (m, 1H, H'_8), 4.25 (q, J = 7.0 Hz, 2H, OCH_2), 5.75 (s, 1H, CH-methine), 6.71 (s, 1H, CH-thiazol ring), 7.21–7.44 (m, 8H, Ar–H), 7.46 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 14.93 (CH_3), 22.2 (CH_2), 22.3 (CH_2), 27.3 (CH_2), 59.6 (CH–N), 62.6 (OCH_2),116.5 (CH), 121.2, 124.2, 126.8, 127.3, 128.4, 128.7, 129.5, 130.9, 131.7, 133.8, 133.9, 134.3, 135.4, 141.1, 141.2, 142.4, 150.5 (C=N), 163.9, 166.9 (C=O). Anal. Calcd. For $C_{27}H_{22}Cl_2N_2O_3S$: C, 61.72; H, 4.22; N, 5.33, S, 6.10. Found: C, 61.88; H, 4.31; N, 5.41; S, 6.14 %.

(*Z*)-methyl 2-((*E*)-9-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5c)

Orange powder, IR KBr (υ_{max}, cm^{-1}): 2,999 (C–H, aromatic), 1,718, 1,629 (C=O), 1,605 (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.54–1.59 (m, 2H, H_7), 1.84–1.90 (m, 1H, H_6), 2.17–2.21 (m, 1H, H'_6) 2.55–2.59 (m, H, H_8), 2.62–2.68 (m, 1H, H'_8), 3.74 (s, 6H, 2OCH_3), 3.77–3.79 (m, 9H, 3OCH_3), 5.63 (s, 1H, CH-methine), 6.75 (s, 1H, CH-thiazol ring), 6.80–6.95 (m, 6H, Ar–H), 7.36 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 21.8 (CH_2), 22.2 (CH_2), 27.7 (CH_2), 57.2, 57.3, 57.5, 57.5, 59.6, (OCH_3) 59.1 (CH–N), 116.3, 121.2, 124.2, 126.9, 127.3, 128.4, 128.7, 129.5, 130.7, 131.8, 133.8, 133.9, 134.2, 135.4, 140.3, 141.1, 142.3, 150.4 (C=N), 163.8, 166.8 (C=O). Anal. Calcd. For $C_{30}H_{30}N_2O_7S$: C, 64.04; H, 5.37; N, 4.98, S, 5.70. Found: C, 64.23; H, 5.18; N, 5.06; S, 5.46 %.

(*Z*)-ethyl 2-((*E*)-9-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5d)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,071 (C–H, aromatic), 1,717, 1,693 (C=O), 1,604 (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 1.56–1.60 (m, 2H, H_7), 1.85–1.89 (m, 1H, H_6), 2.17–2.21 (m, 1H, H'_6) 2.57–2.63 (m, 1H, H_8), 2.66–2.70 (m, 1H, H'_8), 3.73 (s, 6H, 2OCH_3), 3.76 (s, 6H, 2OCH_3), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 5.61 (s, 1H, CH-methine), 6.71 (s, 1H, CH-thiazol ring), 6.80–6.95 (m, 6H, Ar–H),

7.35 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 14.9 (CH_3), 22.4 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 56.2, 56.3, 56.3, 56.5 (OCH_3), 56.9 (CH–N), 62.43 (OCH_2), 112.4, 112.9, 114.1, 116.3, 120.4, 122.6, 130.9, 132.6, 134.0, 141.2, 148.5, 149.2, 149.5, 149.8, 163.8, 166.3 (C=O). Anal. Calcd. For $C_{31}H_{32}N_2O_7S$: C, 64.57; H, 5.59; N, 4.86, S, 5.56. Found: C, 64.15; H, 5.71; N, 4.97; S, 5, 42 %.

(*Z*)-methyl 2-((*E*)-9-(2,4-dichlorobenzylidene)-5-(2,4-dichlorophenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5e)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,067 (C–H, aromatic), 1,724, 1,695 (C=O), 1,604, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.56–164 (m, 2H, H_7), 1.75–1.78 (m, 1H, H_6), 2.15–2.18 (m, 1H, H'_6) 2.54, 2.59 (m, H, H_8), 2.64–2.67(m, 1H, H'_8), 3.77 (s, 3H, OCH_3), 6.10 (s, 1H, CH-methine), 6.75 (s, 1H, CH-thiazol ring), 7.33–7.59 (m, 6H, Ar–H), 7.65 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.1 (CH_2), 22.3 (CH_2), 27.3 (CH_2), 55.4 (OCH_3), 59.6 (CH–N), 116.8, 121.2, 124.2, 126.8, 127.3, 128.5, 128.8, 129.4, 131.0, 132.1, 133.9, 133.9, 134.3, 135.4, 141.1, 141.2, 142.4, 151.1(C=N), 163.9, 167.1 (C=O). Anal. Calcd. For $C_{26}H_{18}Cl_4N_2O_3S$: C, 53.81; H, 3.13; N, 4.83, S, 5.53. Found: C, 53.61; H, 3.39; N, 5.11; S, 5.67 %.

(*Z*)-methyl 2-((*E*)-9-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5f)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,001 (C–H, aromatic), 1,719, 1,698 (C=O), 1,605, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.57–1.63 (m, 2H, H_7), 1.78, 1.80 (m, H, H_6), 2.20–2.24 (m, 1H, H'_6), 2.56–2.67 (m, 1H, H_8), 2.69–2.72 (m, 1H, H'_8), 3.73 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 5.63 (s, 1H, CH-methine), 6.76 (s, 1H, CH-thiazol ring), 6.95–7.45 (m, 8H, Ar–H), 7.62 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.4 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 55.8, 55.9, 56.0 (OCH_3), 59.6 (CH–N), 115.1, 115.9, 117.3, 120.7, 125.0, 129.7, 130.9, 131.4, 132.4, 132.5, 134.2, 142.1, 150.0, 158.9, 161.1, 163.9, 167.2 (C=O). Anal. Calcd. For $C_{28}H_{26}N_2O_5S$: C, 66.91; H, 5.21; N, 5.57, S, 6.38. Found: C, 70.14; H, 5.09; N, 5.45; S, 6.22 %.

(*Z*)-ethyl 2-((*E*)-9-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5g)

Orange powder, IR KBr (υ_{max}, cm^{-1}): 3,064 (C–H, aromatic), 1,693 (C=O), 1,606, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.53–1.59 (m, 2H, H_7), 1.80–1.86 (m, 1H, H_6), 2.15–2.20 (m, 1H, H'_6), 2.51–2.55 (m, 1H, H_8), 2.66–2.69 (m, 1H, H'_8), 3.74 (s, 3H, OCH3), 3.75 (s, 3H, OCH_3), 4.26 (q, J = 7.1 Hz, 2H, OCH_2), 5.63 (s, 1H, CH-methine), 6.71 (s, 1H, CH-thiazol ring), 6.92–6.95 (m, 4H, Ar–H), 7.23–7.26 (m, 2H, Ar–H), 7.30–7.32 (m, 2H, Ar–H),7.35 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 14.9 (CH_3), 22.3 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 55.9, 56.0 (OCH_3), 59.6 (CH–N), 62.4 (OCH_2), 114.6, 115.0, 116.3, 120.4, 124.9, 129.7, 130.6, 131.4, 132.1, 132.3, 134.1, 141.1, 149.9, 158.8, 160.2, 163.8, 166.3 (C=O). Anal. Calcd. For $C_{29}H_{28}N_2O_5S$: C, 67.42; H, 5.46; N, 5.42, S, 6.21. Found: C, 67.63; H, 4.57; N, 5.87; S, 6.33 %.

(*Z*)-methyl 2-((*E*)-9-(3-nitrobenzylidene)-5-(3-nitrophenyl)-3-oxo-3,5,6,7,8,9-hexa hydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5h)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,069 (C–H, aromatic), 1,725, 1,690 (C=O), 1,607, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.58 (br, 2H, H_7), 1.79–1.83 (m, 1H, H_6) 2.26–2.29 (m, 1H, H'_6), 2.51–2.54 (m, 1H, H_8), 2.70–2.73 (m, 1H, H'_8), 3.78 (s, 3H, OCH_3), 5.75 (s, 1H, CH-methine), 6.68 (s, 1H, CH-thiazol ring), 7.51 (s, 1H, H_{10} vinylic), 7.63-7.91 (m, 8H, Ar–H). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.2 (CH_2), 26.2 (CH_2), 27.65 (CH_2), 58.2 (OCH_3) 59.5 (CH–N), 116.9, 122.4, 122.7, 123.3, 123.7, 124.5, 124.5, 129.9, 132.5, 134.2, 135.3, 139.3, 140.2, 142.7, 148.8, 149.7, 150.2, 164.1, 167.2 (C=O). Anal. Calcd. For $C_{26}H_{20}N_4O_7S$: C, 58.64; H, 3.79; N, 10.52, S, 6.02. Found: C, 58.35; H, 3.44; N, 10.68; S, 6.19 %.

(*Z*)-ethyl 2-((*E*)-9-(3-nitrobenzylidene)-5-(3-nitrophenyl)-3-oxo-3,5,6,7,8,9-hexa hydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5i)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,086 (C–H, aromatic), 1,722, 1,691 (C=O), 1,608, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.25 (t, J = 7.0 Hz, 3H, CH_3), 1.59 (br, 2H, H_7), 1.79–1.83 (m, 1H, H_6), 2.27–2.30 (m, 1H, H'_6), 2.55–2.57 (m, 1H, H_8), 2.71–2.74 (m, 1H, H'_8), 4.25 (q, J = 7.0 Hz, 2H, OCH_2), 6.00 (s, 1H, CH-methine), 6.72 (s, 1H, CH-thiazol ring), 7.52 (s, 1H, H_{10} vinylic), 7.52 (s, 1H, H_{10} vinylic), 7.67 (t, J = 5.0 Hz, 1H, Ar–H) 7.71 (t, J = 5.0 Hz, 1H, Ar–H), 7.82 (t, J = 5.0 Hz, 1H, Ar–H), 8.10 (d, J = 7.9, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 8.21 (d, J = 8.0 Hz, 1H, Ar–H), 8.23 (s, 1H, Ar–H). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 14.9 (CH_3), 22.1 (CH_2), 27.1 (CH_2), 27.2 (CH_2), 59.3 (CH–N), 62.5 (OCH_2), 116.7, 121.4, 122.2, 123.5, 123.6, 124.2,

124.5, 130.6, 131.5, 134.1, 134.9, 139.4, 140.9, 141.8, 148.7, 148.8, 150.7, 163.9, 166.3 (2C, C=O). Anal. Calcd. For $C_{27}H_{22}N_4O_7S$: C, 59.33; H, 4.06; N, 10.25, S, 5.87. Found: C, 59.07; H, 4.16; N, 10.42; S, 6.02 %.

(*Z*)-methyl 2-((*E*)-9-(4-methylbenzylidene)-3-oxo-5-p-tolyl-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5j)

Orange powder, IR KBr (υ_{max}, cm^{-1}): 3,001, 3,063 (C–H, aromatic), 1,717 (2C=O), 1,605, (C=C). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.55–158 (m, 2H, H_7), 1.82–1.86 (m, 1H, H_6), 2.10–2.17 (m, 1H, H'_6), 2.53–2.54 (m, 1H, H_8), 2.68–2.71 (m, 1H, H'_8), 3.78 (s, 6H, CH_3), 3.81 (s, 3H, OCH_3), 5.63 (s, 1H, CH-methine), 6.74 (s, 1H, CH-thiazol ring), 6.93 (d, J = 7.0 Hz, 2H, Ar–H), 6.94 (d, J = 7.0 Hz, 2H, Ar–H), 7.24 (d, J = 8.7 Hz, 2H, Ar–H), 7.31 (d, J = 8.7 Hz, 2H, Ar–H), 7.35 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.2 (CH_2), 27.1 (CH_2), 27.5 (CH_2), 55.9 (CH_3), 56.0 (CH_2, OCH_3), 59.6 (CH–N), 114.6, 115.1, 116.1, 124.9, 129.7, 130.5, 131.4, 141.3, 149.8, 158.8, 160.2, 166.8 (C=O). Anal. Calcd. For $C_{28}H_{26}N_2O_3S$: C, 71.46; H, 5.57; N, 5.95, S, 6.81. Found: C, 71.67; H, 5.69; N, 6.22; S, 6.70 %.

(*Z*)-methyl 2-((*E*)-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-3-oxo-3,5,6,7,8,9-hexahydro-2*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetate (5k)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,066 (C–H, aromatic), 1,723, 1,699 (2C=O), 1,605, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 1.57 (br, 2H, H_7), 1.79–1.82 (m, 1H, H_6) 2.20–2.24 (m, 1H, H′6), 2.52–2.55 (m, 1H, H_8), 2.66–2.69 (m, 1H, H'_8), 3.78 (s, 3H, OCH_3), 5.74 (s, 1H, CH-methine), 6.74 (s, 1H, CH-thiazol ring), 7.29–7.31 (m, 4H, Ar–H), 7.38–7.39 (m, 2H, Ar–H), 7.40–7.42 (m, 2H, Ar–H), 7.47 (s, 1H, H_{10} vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.2 (CH_2), 22.3 (CH_2), 27.4 (CH_2), 55.9 (OCH_3), 59.6 (CH–N), 117.4 (CH), 122.1, 124.3, 126.8, 127.2, 128.7, 128.8, 129.6, 130.8, 131.9, 133.6, 133.9, 134.5, 135.4, 141.1, 141.14, 142.6, 151.1 (C=N), 164.7, 166.9 (2C=O). Anal. Calcd. For $C_{26}H_{20}Cl_2N_2O_3S$: C, 61.06; H, 3.94; N, 5.48, S, 6.27. Found: C, 61.33; H, 3.79; N, 5.64; S, 6.13 %.

(*Z*)-methyl 2-((*E*)-8-(4-chlorobenzylidene)-5-(4-chlorophenyl)-7,8-dihydro cyclopenta[*d*] thiazolo[3,2-a]pyrimidin-2(3*H*,5*H*,6*H*)-ylidene)acetate (5l)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,036 (C–H, aromatic), 1,732, 1,700 (2C=O), 1,609, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 2.76–2.83 (m, 2H, H_6), 2.89–294 (m, 2H, H_7), 3.80 (s, 3H, OCH_3), 6.06 (s, 1H, CH-methine), 6.77 (s, 1H, CH-thiazol ring), 7.37–7.73 (m, 8H, Ar–H), 7.74 (s, 1H, H_9 vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.9 (CH_2), 28.9 (CH_2), 53.4 (OCH_3), 57.6 (CH–N), 124.8, 126.9, 128.7, 129.5, 130.9, 132.6, 133.8, 133.8, 134.3, 135.5, 140.2, 141.3, 142.6, 157.0 (C=N), 165.9, 167.7 (C=O). Anal. Calcd. For $C_{26}H_{20}Cl_2N_2O_3S$: C, 61.06; H, 3.94; N, 5.48, S, 6.27. Found: C, 60.89; H, 4.03; N, 5.67; S, 6.30 %.

(*Z*)-methyl 2-((*E*)-8-(4-methylbenzylidene)-5-p-tolyl-7,8-dihydrocyclopenta[*d*] thiazolo[3,2-*a*]pyrimidin-2(3*H*,5*H*,6*H*)-ylidene)acetate (5n)

Orange powder, IR KBr (υ_{max}, cm^{-1}): 3,020 (C–H, aromatic), 1,720, 1,673 (2C=O), 1,607, (C=N). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 21.1 (CH_3) 22.9 (CH_2), 29.1 (CH_2), 53.6 (OCH_3), 56.9 (CH–N), 124.7, 127.2, 128.7, 129.6, 131.2, 132.8, 133.5, 133.6, 134.2, 135.4, 140.1, 141.3, 142.7, 156.1 (C=N), 165.8, 167.7 (C=O). Anal. Calcd. For $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14, S, 7.02. Found: C, 70.97; H, 5.17; N, 6, 38; S, 7.13 %.

(*Z*)-methyl 2-((*E*)-8-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-7,8-dihydro cyclopenta[*d*]thiazolo[3,2-a]pyrimidin-2(3*H*,5*H*,6*H*)-ylidene)acetate(5o)

Yellow powder, IR KBr (υ_{max}, cm^{-1}): 3,057, 3,067 (C–H, aromatic), 1,721 (2C=O), 1,612, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 2.23–2.29 (m, 2H, H_6), 2.37–2.40 (m, 2H, H_7), 3.77–3.79 (s, 15H, OCH_3), 5.96 (s, 1H, CH-methine), 6.85 (s, 1H, CH-thiazol ring), 7.16–7.43 (m, 6H, Ar–H), 7.48 (s, 1H, H_9 vinylic). ^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.0 (CH_2), 28.5 (CH_2), 53.6 (OCH_3), 55.3, 56.7 (OCH_3) 56.9 (CH–N), 111.1, 112.7, 112.9, 119.7, 120.4, 122.6, 131.7, 132.8, 134.5, 141.4, 148.3, 149.7, 149.7, 158.3, 160.5 (C=N), 164.6, 167.7 (C=O). Anal. Calcd. For $C_{29}H_{28}N_2O_7S$: C, 63.49; H, 5.14; N, 5.11, S, 5.84. Found: C, 63.24; H, 5.17; N, 5.23; S, 5.78 %.

(*Z*)-methyl 2-((*E*)-8-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-7,8-dihydro cyclopenta-[*d*]thiazolo[3,2-*a*]pyrimidin-2(3*H*,5*H*,6*H*)-ylidene)acetate (5m)

Orange powder, IR KBr (υ_{max}, cm^{-1}): 3,043 (C–H, aromatic), 1,722, 1,670 (2C=O), 1,606, (C=N). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ (ppm) = 2.20–2.24 (m, 2H, H_6), 2.34–2.38 (m, 2H, H_7), 3.75 (s, 6H, 2OCH3), 3.82 (s, H, OCH_3), 5.94 (s, 1H, CH-methine), 6.87 (s, 1H, CH-thiazol ring), 7.12–7.52 (m, 8H, Ar–H), 7.51 (s, 1H, H_9 vinylic).

^{13}C-NMR (DMSO-d_6, 125.77 MHz): δ (ppm) = 22.1 (CH_2), 28.7 (CH_2), 53.2 (OCH_3), 56.1, 56.1 (OCH_3) 56.93 (CH–N), 114.1, 114.5, 124.4, 131.8, 132.9, 134.4, 137.9, 139.2, 140.3, 158.3, 159.5, 159.8, 160.5 (C=N), 165.1, 167.2 (C=O). Anal. Calcd. For $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73, S, 6.56. Found: C, 66.15; H, 5.02; N, 5.83; S, 6.47 %.

Results and discussion

The preparation of quinazoline and pyrimidine compounds has been developed over the years. Continuing from our synthesis of five-membered S, N-heterocyclic thiazoline [30], we wish to report another heterocyclic compound from pyrimidinone derivatives. In our earlier studies, we have reported the reaction of thiosemicarbazone derivatives with DAMAD and DEAD at ambient temperature. Herein, we have reacted DMAD and DEAD with a different dihydropyrimidinethione using both ultrasonic irradiation method and a conventional method. In this pursuit, we examined the reaction of pyrimidinone derivative **4a** with dialkyl acetylenedicarboxylate in methanol at ambient temperature. This led to excellent yield (84–92 %) of thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives **5a–o** at 130–160 min (Scheme 2).

The structures of target compounds were appropriately characterized by spectral data. For example, the ^{1}H-NMR of spectra of thiazolo[2,3-*b*]quinazoline derivatives show that these compounds are chiral.

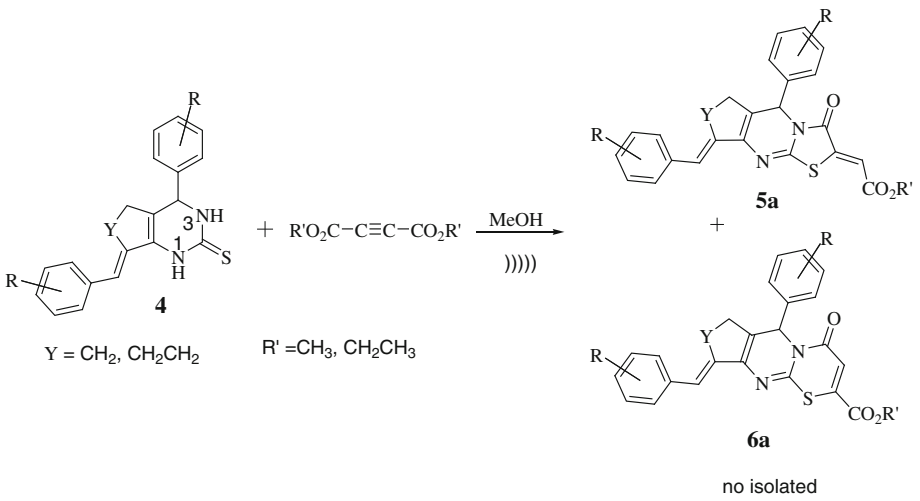
For example, the 1H-NMR spectrum of compound **5a** shows two multiple signals at 2.48 and 2.66 ppm, which belong to H_1 and H_2 of C_8, and two multiples at 1.81, 2.22 ppm, which belong to H_1 and H_2 of C_6 in compound **5a**. The other methylene group appeared at 1.56 ppm in the ^{1}H-NMR spectrum.

The formation of compound **5a** was confirmed by the absence of amino group absorptions in the IR spectra, absence of the signals one of the COOR and the (N1), (N3) protons, which were present in the spectra of the starting materials in the 1H-NMR spectra and appear as signals of the protons of the C=CH unit in the thiazol ring as a singlet around 6.70 ppm in the 1H-NMR spectra.

Compound **5a** also reveals C–H absorption of the aromatic ring at 3,067 cm^{-1}, carbonyl groups at 1,723, 1,696 cm^{-1} and C=N, C=C at 1,606, 1,474 cm^{-1} respectively, in the FT-IR spectra. The ^{1}H-NMR spectrum of **5a** indicates one singlet at δ 7.46 ppm, related to the protons of HC=C H9 vinylic, (δ 5.75) which is related to CH-methaine, (δ 3.78) which in turn is related to the protons of the –CH3 methoxy group. The ^{13}C-NMR spectrum of **5a** indicates carbonyl group carbons (C=O, NC=O) and imino group (C=N) at 166.85 and 163.83 ppm. The mass spectral data and elemental analyses are also in accordance with the proposed structure. In general, all of the spectral data support the structures for all of the compounds (**5a–5o**). The structure of all the thiazole derivatives, reaction conditions and product yields are given in Table 1.

To improve our studies, the synthesis of the same compounds **5a–o** was performed using ultrasound irradiation at room temperature for short reaction times. We examined the reaction of pyrimidinethione derivative **4** with dialkyl acetylenedicarboxylate promoted by ultrasound in methanol to give the corresponding thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives **5a–o** in excellent yield (87–95 %) only in 35–57 min (Table 1). Ultrasonic irradiation displays dramatically reduced reaction times compared to conventional magnetic stirring method and also affords the desired products in high yields and purity (Scheme 2; Table 1).

The UV–visible absorption of **5a–5n** demonstrates major absorption in wavelength ranges of 272.15–362.19 nm



Scheme 2 Synthesis of the thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine derivatives under ultrasonic irradiation

Table 2 UV–Vis absorption of **5a–5i** in DMSO at 25 °C

Entry	Product	λ_{max} (nm)
1	**5a**	314.86
2	**5b**	315.44
3	**5c**	326.41
4	**5d**	323.52
5	**2e**	279.07, 313.71
6	**5f**	362.19
7	**5g**	317.17
8	**5h**	272.15
9	**5i**	275.61
10	**5j**	317.17
11	**5k**	313.70, 317.17
12	**5n**	335.64

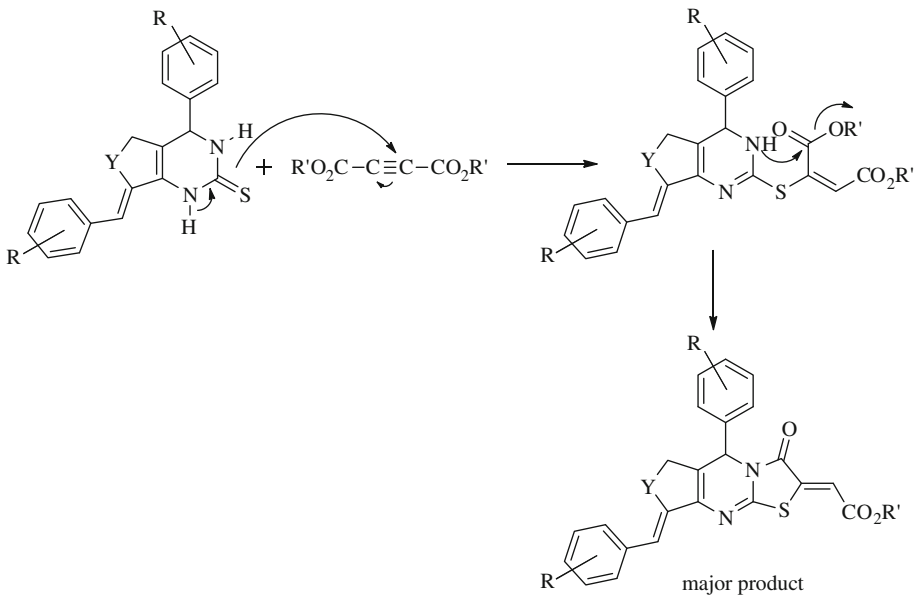
in DMSO solvent at room temperature, as indicated in Table 2.

As revealed therein, using conventional magnetic stirring, the resulting product was obtained with 84–92 % yield after 130–160 min (Table 1). However, under ultrasonic irradiation, with the power 360 W, irradiation frequency of 47 kHz and reaction temperature of 30–35 °C, excellent product yield (87–95 %) was obtained after only 35–57 min (Table 1).

In these reactions, compound **4** contains two nucleophile nitrogens. Because of the more nucleophilic nature of N3 compared to N1 (Scheme 2), compound **5a** (N3 regioisomers) were isolated as the main product, whereas other products (N3 regioisomers) were not isolated. Therefore in each of the examples studied, the formation of products of N3 or N1 cyclization was possible [31–34], but in all cases only the desired products of cyclization **5a** were isolated in 87–95 % yield.

Two types of cyclic products could be obtained in the reaction media (**5 and 6**, Scheme 2). As a result of the conjugate addition of the sulfur center and intermolecular N-acylation, the corresponding thiazolone (**5a**) was isolated as a major product, stabilized by S–O and S–N close contact interactions involving the other carbomethoxy group in a double conjugate addition, followed by spontaneous dehydrogenation. Methyl-[1, 3]thiazin-4-one-6-carboxylate (**6a**) can be interpreted to be formed by the conjugate addition of the sulfur center and alternative N-acylation, presumably furnishing a six-membered ring. As the product ratio **5a**/**6a** increases with longer reaction time, thiazinone (**6a**) seems to be an unstable kinetic product undergoing ring isomerization to **5a**, catalyzed by methanol, which is released in the reaction mixture and can cleave the six-membered lactame at elevated temperature [35, 36]. The recyclization of the resulting intermediate, involving the methoxycarbonyl group separated by one carbon from the sulfur atom, leads to the final product.

The reaction is mainly condensation, followed by cyclization. Initially, the sulfur atom from pyrimidinethione attacks the carbon triplet bond of acetylenic ester compound, which is prone to nucleophilic attack. Then cyclization proceeds on to the esteric (CO_2R) function to give products **5** and **6** in excellent yield (Scheme 3). A plausible mechanism has been proposed for the reactions of pyrimidinone derivatives with DMAD and DEAD to yield ethyl-5-(aryl)-2-(2-alkoxy-2-oxoethylidene)-7-methyl-3-oxo-3, 5-dihydro-2*H* thiazolo[3,2*a*]pyrimidine-6-carboxylate derivatives as shown in Scheme 3.



Scheme 3 Suggested mechanism for synthesis of the thiazolo[2,3-*b*]quinazoline and thiazolo [3,2-*a*]pyrimidine derivatives

Conclusion

This successful synthesis of thiazolo[2,3-*b*]quinazoline and thiazolo[3,2-*a*]pyrimidine demonstrated that addition of pyrimidinone to alkylacetylenic ester and then cyclization of intermediate compounds is a feasible method for the synthesis of fused oxo-thiazoles.

The synthesized thiazolo[2,3-*b*]quinazoline and pyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidine analogs could be considered as useful templates in future to obtain more potent antitumor agents.

In conclusion, we have developed two different simple synthetic methods to prepare thiazolo[2,3-b]quinazoline and thiazolo[3,2-a]pyrimidine derivatives, conventional magnetic stirring and ultrasonic irradiation. Both the methods led to excellent yield. Ultrasonic irradiation displays dramatically reduced reaction times compared to conventional magnetic stirring method and also provides the desired products in high yields and purity.

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