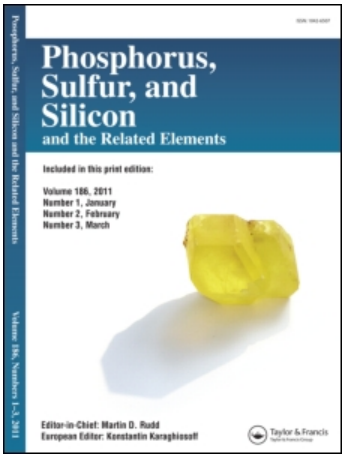

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Synthesis, Characterization, and Antiproliferative Activity of 2-(2-Bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2*b*][1,2,4]triazoles

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SYNTHESIS, CHARACTERIZATION, AND ANTIPROLIFERATIVE ACTIVITY OF 2-(2-BROMO-5-METHOXYPHENYL)-6-ARYL-1,3-THIAZOLO[3,2*b*][1,2,4]TRIAZOLES

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Eight new 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-b][1,2,4]triazoles were synthesized by treating 5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazole-3-thiol with phenacyl bromides. The new products were characterized by spectroscopic and analytical methods. Five of the new compounds were evaluated for their antiproliferative activity. 2-(2-Bromo-5-methoxyphenyl)-6-(3,4-dihydroxyphenyl)-1,3-thiazolo[3,2-b] [1,2,4]triazole exhibited promising activity.

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Keywords Antiproliferative activities; *N*-bridged heterocycles; characterization; synthesis; thiazolotriazoles

INTRODUCTION

The synthesis of heterocyclic systems containing bridgehead nitrogen atom gained considerable attention due to their wide range of biological activities. Many of the thiazolo[3,2-b]-1,2,4-triazoles have been reported as anthelmintics,[1] bactericides,[2] medicinal fungicides,[3] cardiotonics, and bronchodilators.[4] In continuation of our research work on thiazolotriazoles[5] and compounds containing a 2-bromo-5-methoxyphenyl moiety,[6] we aimed to synthesize new 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles and investigate their antiproliferative activity.

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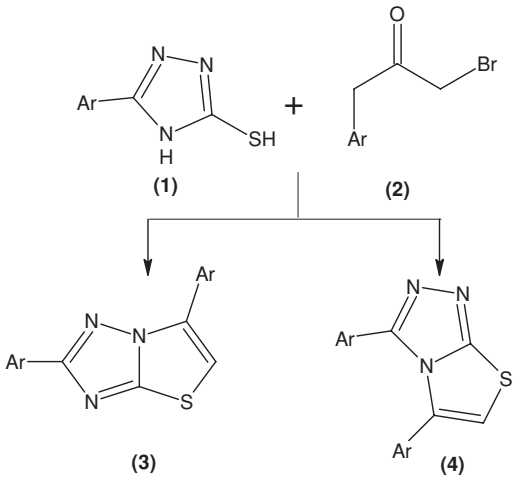
The reaction of α-haloketones (**2**) with 2-substituted 5-mercapto-1,2,4-triazoles (**1**) is expected to result in the formation of either 2,5-disubstituted thiazolo[3,2-*b*]-1,2,4-triazoles (**3**) or 3,5-disubstituted thiazolo[2,3-*c*]-1,2,4-triazoles (**4**), or both,[7–10] as given in Scheme 1. Jag Mohan[11] reported that the reaction of 3-(4-tolyl)-5-mercapto-1,2,4-triazole with 4-substituted phenacyl bromides in dry methanol gives thiazolo[3,2-*b*][1,2,4]triazoles in one step and not the isomeric thiazolo[2,3-*c*]-1,2,4-triazoles. This was also supported by the synthesis of thiazolo[3,2-*b*]-1,2,4-triazoles reported by Narayana et al.[12] Reaction of mercaptotriazole (**5**) (R=H) with bromoketones (**6**) in ethanol followed by cyclization in polyphosphoric acid yielded the thiazolo[3,2-*b*]-1,2,4-triazoles (**7**) and not the isomeric thiazolo[2,3-*c*]-1,2,4-triazoles (**8**), which was established by comparison with an authentic sample of **8** ($R^1 = 4\text{-}MeC_6H_4$) obtained by cyclization of 2-(4-bromobenzoyl)hydrazino-4-(4-tolyl)thiazole-hydrobromide (**9**) (Scheme 2).[11] The melting point, IR spectrum, and thin-layer chromatographic behavior were used to identify this product. The reaction of **5** (R=H) with **6** in methanol led, however, directly to the cyclized products **7** (Scheme 3). In view of these observations, we decided to synthesize further new 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles by treating 5-(2-bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol with phenacyl bromides in methanol. With the help of a single crystal X-ray study,[13] we have established that the cyclization resulted in the formation of 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles only, and not the isomeric thiazolo[2,3-*c*][1,2,4]triazoles.

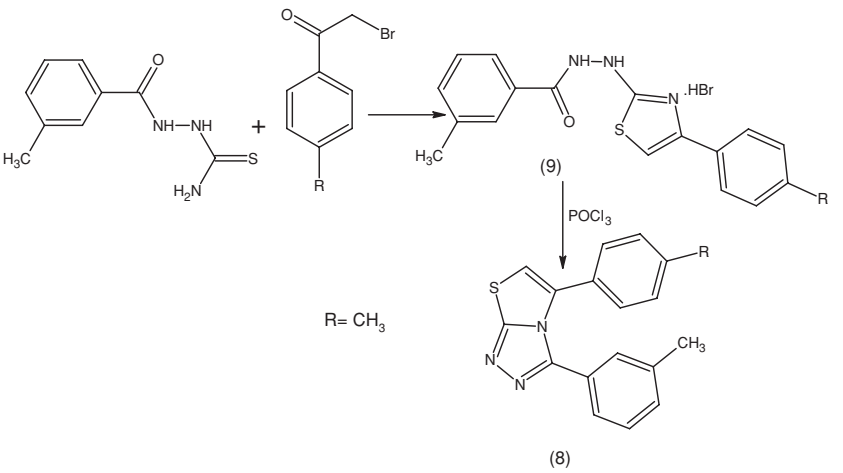


Scheme 1

RESULTS AND DISCUSSION

Chemistry

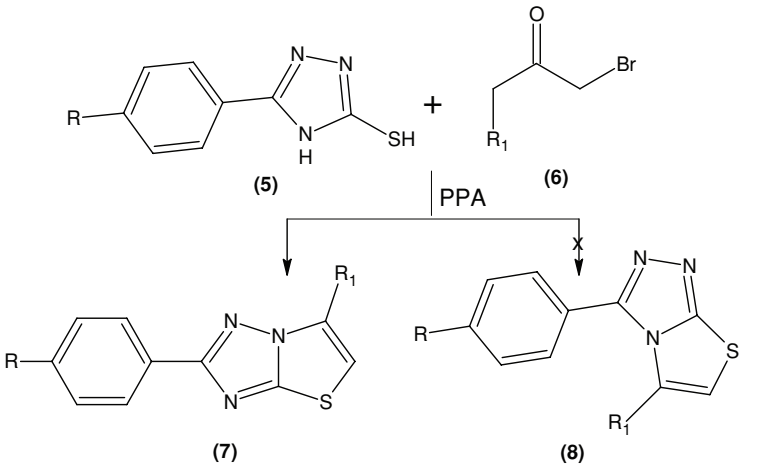
The compound 5-(2-bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol (**10**) was synthesized by the reaction of 2-bromo-5-methoxybenzhydrazide with potassium thiocyanate and concentrated aqueous hydrogen chloride, followed by cyclization of the resulting 1-(2-bromo-5-methoxybenzoyl)thiosemicarbazide with sodium hydroxide.[5] The



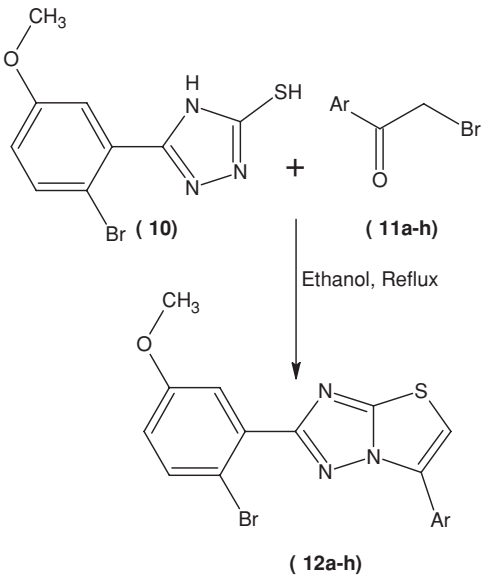
Scheme 2

structure of the starting compound (**10**) was confirmed by recording ^{1}H NMR in DMSO-d_6 and mass spectra. A singlet at $\delta = 3.82$ was due to three protons of the OCH_3 group. A doublet of doublet observed at $\delta = 7.07$ ($J = 3.1$, 8.8 Hz), a doublet at $\delta = 7.23$ ($J = 2.9$ Hz), and another doublet at $\delta = 7.68$ ($J = 8.8$ Hz) accounts for the three aromatic protons. The SH and NH protons appeared as two downfield singlets at $\delta = 13.66$ and $\delta = 13.75$, respectively. The mass spectrum displayed the molecular ion peaks at $m/z = 286$ (80% ^{79}Br-**10**) and 288 (90% ^{81}Br-**10**). Further fragment peaks appeared at $m/z = 254$ (10%, M^+—SH), $m/z = 176$ (45%, phenyl mercaptotriazole radical cation), and $m/z = 136$ (70%, $MeOC_6H_4CNH^+$).

The 1,2,4-triazole (**10**) was then refluxed in ethanol with the phenacyl bromides (**11a–h**) to get 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles (**12a–h**) (Scheme 4).

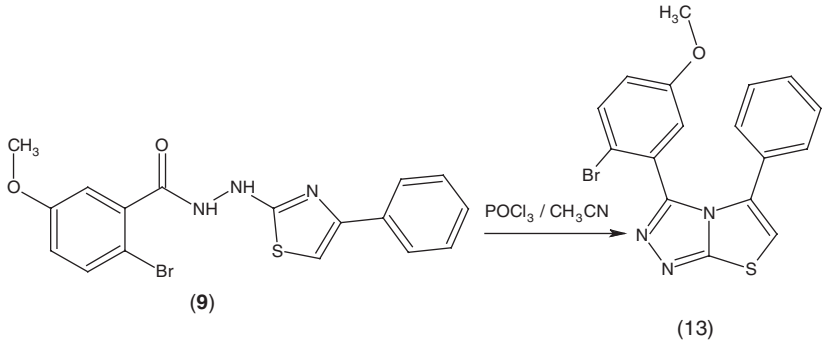


Scheme 3



Scheme 4

The isomeric thiazolo[2,3-*c*][1,2,4]triazoles were not formed in this reaction. This was confirmed by the synthesis of 3-(2-bromo-5-methoxyphenyl)-5-phenyl-1,3-thiazolo[2,3-*c*]-1,2,4-triazole (**13**) by the cyclization of 2-bromo-5-methoxy-*N*′-[4-phenyl-1,3-thiazol-2-yl]benzohydrazide (**9**) (Scheme 5).



Scheme 5

The melting point, IR spectrum, and thin-layer chromatographic behavior were used to differentiate this product from 2-(2-bromo-5-methoxyphenyl)-6-phenyl-1,3-thiazolo[3,2-*b*]-1,2,4-triazole (**12a**). A single crystal X-ray study[13] of (**12a**), formed according to Scheme 4, unequivocally revealed its structure. In a few cases, acyclic products were isolated and identified by IR and mass spectra. These acyclic compounds were then cyclized by refluxing in methanol.

The new 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*]1,2,4-triazoles (**12a–h**) were also well characterized by analytical and spectroscopic analyses to prove their assigned structure. Characterization data are given in Table I.

Table I Experimental data of the 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles (**12a–h**) and 3-(2-bromo-5-methoxyphenyl)-5-phenyl-1,3-thiazolo[3,2-*b*][1,2,4]triazole (**13**)

Nr.	Ar	Molecular formula	Melting point°C	Yield %	Color	Elemental analysis (%) Found (Calcd.)		
						C	H	N
12a	Phenyl	$C_{17}H_{12}BrN_3OS$	208–210	48	Cream	52.78 (52.86)	3.05 (3.13)	10.80 (10.88)
12b	3-Chloro-pyridyl	$C_{16}H_{10}BrClN_4OS$	226–228	46	Dark yellow	45.49 (45.57)	2.31 (2.39)	13.21 (13.29)
12c	3,4-Dihy-droxyphenyl	$C_{17}H_{12}BrN_3O_3S$	210–212	68	Light yellow	48.74 (48.82)	2.81 (2.89)	9.97 (10.05)
12d	3-Carbamo-yl-4-hy-droxyphenyl	$C_{18}H_{13}BrN_4O_3S$	245–248	55	Cream	48.47 (48.55)	2.86 (2.94)	12.50 (12.58)
12e	2-Oxo-chrom-en-3-yl	$C_{20}H_{12}BrN_3O_3S$	220–222	51	Off white	52.80 (52.88)	2.58 (2.66)	9.17 (9.25)
12f	6-Bromo-2-oxochrom-en-3-yl	$C_{20}H_{11}Br_2N_3O_3S$	196–198	88	Yellow	44.97 (45.05)	2.00 (2.08)	7.80 (7.88)
12g	4-Chloro-phenyl	$C_{17}H_{11}BrClN_3OS$	238–241	59	Yellow	48.45 (48.53)	2.58 (2.64)	9.91 (9.99)
12h	4-Methoxy-phenyl	$C_{18}H_{14}BrN_3O_2S$	168–170	78	Yellow	51.87 (51.93)	3.31 (3.39)	10.01 (10.09)
13	Phenyl	$C_{17}H_{12}BrN_3OS$	162–164	58	White	52.88 (52.86)	3.15 (3.13)	10.82 (10.88)

Antiproliferative Activity

Five of the new compounds (**12b–d**, **12g**, and **12h**) were screened for their antiproliferative activity at The National Institutes of Health (NIH), Bethesda, Maryland, USA, under the Drug Discovery Programme of NCI as per the procedure suggested by Boyd and Paull[14] in a primary, three-cell, line-one dose antitumor assay against NCI-H (lung), MCF-7 (breast), and SF 268 (CNS). Further experimental details and Table II-S are available in the Supplemental Materials online.

CONCLUSION

Nine new 2-(2-bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles were synthesized and evaluated for their antiproliferative activity. The compound 2-(2-bromo-5-methoxyphenyl)-6-(3,4-dihydroxyphenyl)-1,3-thiazolo[3,2-*b*][1,2,4]triazole (**12c**) emerged as the most active one and can be recommended for further studies. As the selection of the compound was done by NCI, the prediction of structure–activity relationship is difficult to determine at this point of time.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminum plates. IR spectra were recorded on a Shimadzu-FTIR spectrometer in KBr (ν in cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as internal standard, and ^{13}C NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (75 MHz) spectrometer. FABMS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer (6 kV, 10mA) using argon/xenon as the FAB gas.

5-(2-Bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol (10)

1-(2-Bromo-5-methoxybenzoyl)thiosemicarbazide (50 g, 0.164 mol) was refluxed with 500 mL of 5% sodium hydroxide solution for 4 h and was cooled and filtered. The clear solution was acidified with conc. HCl to pH 5–6. The solid obtained was filtered and recrystallized (MeOH) to give white crystals; yield, 42 g (89%), mp $>250^\circ C$

2-(2-Bromo-5-methoxyphenyl)-6-aryl-1,3-thiazolo[3,2-*b*][1,2,4]triazoles (12a–h)

5-(2-Bromo-5-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol (**10**) (0.01 mol) and the appropriate phenacyl bromide (**11**) (0.01 mol) were refluxed in ethanol for 4 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled and the precipitated solid was filtered off. The solid was recrystallized from MeOH/DMF. The compounds were obtained in 40–88% yield (see Table I).

Spectroscopic Data

2-(2-Bromo-5-methoxyphenyl)-6-phenyl-1,3-thiazolo[3,2-*b*][1,2,4]triazole (12a)[13]. IR: 3118, 3070 (CH), 1560 (C=N), 734 (C−Br); ^{1}H NMR (DMSO-d_6): δ 3.8 (s, 3H, OCH_3), 7.03 (dd, J = 3.3, 8.7 Hz, 1H, ArH), 7.44 (s, 1H, ArH), 7.55 (m, 3H, ArH), 7.67 (d, J = 8.7 Hz, 1H, ArH), 8.01 (s, 1H, ArH), 8.27 (d, J = 7.8 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 55.62, 111.14, 111.47, 116.96, 117.31, 126.27, 127.57, 129.00, 129.69, 131.52, 132.57, 134.66, 158.43; DEPT: 55.64, 111.16, 116.98, 117.34, 126.29, 129.04, 129.73, 134.68. FABMS: *m/z* 388 (95%, $M^+ + 1$), 387 (20%, $M^+ + 1$), 386 (100%, $M^+ + 1$), 307 (12%, M^+—Br), 136 (40%, $MeOC_6H_4CNH^+$).

2-(2-Bromo-5-methoxyphenyl)-6-(3,4-dihydroxyphenyl)-1,3-thiazolo[3,2-*b*][1,2,4]triazole (12c). IR: 3400 (OH), 3109 (CH), 1562 (C=N), 734 (C−Br); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.87 (dd, J = 2.9, 8.7 Hz, 1H, ArH), 7.02 (s, 2H, ArH), 7.26 (s, 5H, 2-OH + H_2O), 7.45 (d, J = 3.0 Hz, 1H, ArH), 7.61 (d, J = 8.7 Hz, 2H, ArH), 7.82 (s, 1H, ArH). FABMS: *m/z* 420 (75%, $M^+ + 1$), 419 (45%, $M^+ + 1$), 418 (73%, $M^+ + 1$), 136 (98%, $MeOC_6H_4CNH^+$).

2-(2-Bromo-5-methoxyphenyl)-6-(3-carbamoyl-4-hydroxyphenyl)-1,3-thiazolo-[3,2-*b*][1,2,4]triazole (12d). IR: 3411 (OH), 3336 (NH_2), 1595 (C=N), 821 (C−Br); FABMS: *m/z* 447 (80%, $M^+ + 1$) 446 (60%, M^+), 445 (70%, $M^+ + 1$), 136 (90%, $MeOC_6H_4CNH^+$).

2-(2-Bromo-5-methoxyphenyl)-6-(4-methoxyphenyl)-1,3-thiazolo[3,2-*b*][1,2,4]-triazole (12h). IR: 3114, 2898 (CH), 1560 (C=N), 1022, 812 (C−Br); ^{1}H NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.86 (dd, J = 3.4, 8.8 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 7.00 (dd, J = 1.8, 6.9 Hz, 2H, ArH), 7.49 (d, J = 3.0 Hz, 1H, ArH), 7.60 (d, J = 8.8 Hz, 1H, ArH), 8.11 (dd, J = 2.04, 8.7 Hz, 2H, ArH); FABMS: *m/z* 418 (100%, $M^+ + 1$), 417 (60%, $M^+ + 1$), 416 (98%, $M^+ + 1$), 136 (60%, $MeOC_6H_4CNH^+$).

3-(2-Bromo-5-methoxyphenyl)-5-phenyl-1,3-thiazolo[2,3-*c*][1,2,4]triazole (13). IR: 3114, 2898 (CH), 1560 (C=N), 1022, 812 (C−Br); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.99 (dd, J = 3.6, 9.0 Hz, 1H, ArH), 7.37–7.48 (m, 4H, ArH), 7.63 (d, J = 8.7 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 8.0 (d J = 7.2 Hz, 2H, ArH).

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