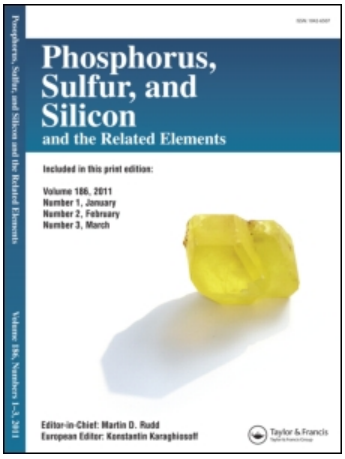

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NOVEL THREE COMPONENT SYNTHESIS OF 1,2,4-TRIAZOLO[3,4-b]THIAZOLES AND THEIR ANTIMICROBIAL ACTIVITY

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1,2,4-Triazolo[3,4-b]thiazole derivatives ***5a–j*** *have been synthesized by novel multi-component reaction of 2,4-dichloro-5-fluorophenacyl bromide (**1**), thiosemicarbazide (**2**), and aromatic carboxylic acids (**4**) using phosphorous oxychloride as the cyclizing agent. This reaction protocol is simple, efficient, and requires shorter reaction times in comparison to the conventional multi-step synthesis. The products were identified to be same by an alternate synthesis. All the compounds were screened for their antimicrobial activity against some of bacterial and fungal strains.*

Keywords: 1,2,4-Triazolo[3,4-b]thiazoles; antimicrobial activity; multicomponent reaction

1,2,4-Triazole derivatives have been of great interest in the medicinal and agricultural fields due to their profound antibacterial, herbicidal, insecticidal, and fungicidal activities.[1–5] Similarly, thiazole derivatives are reported to possess diverse pharmacological activities.[6–7] It is therefore thought of interest to combine these two potential biologically active units to give fused derivatives. Further, it is reported to increase the biological activity profile of a molecule by substitution of hydrogen by fluorine or trifluromethyl group.[8] In this point of view, 2,4-dichloro-5-fluoro moiety is interesting due to its influence over the activity of ciprofloxacin, a broad spectrum antibacterial agent.[9] Recently, multicomponent reactions (MCRs) are employed over conventional synthesis

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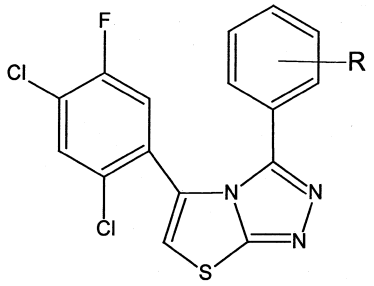
for generating molecules for combinatorial libraries.[10–12] In MCRs the sequence of irreversible reactions all proceeds toward the product.[13] In this article, we report the novel three component reaction of 2,4-dichloro-5-fluoro phenacyl bromide (**1**), thiosemicarbazide (**2**), and aryl carboxylic acid (**4**) to yield triazolothiazoles (**5**) in good to excellent yields (Scheme 1). All the compounds were screened for their antimicrobial activities against bacterial and fungal strains.



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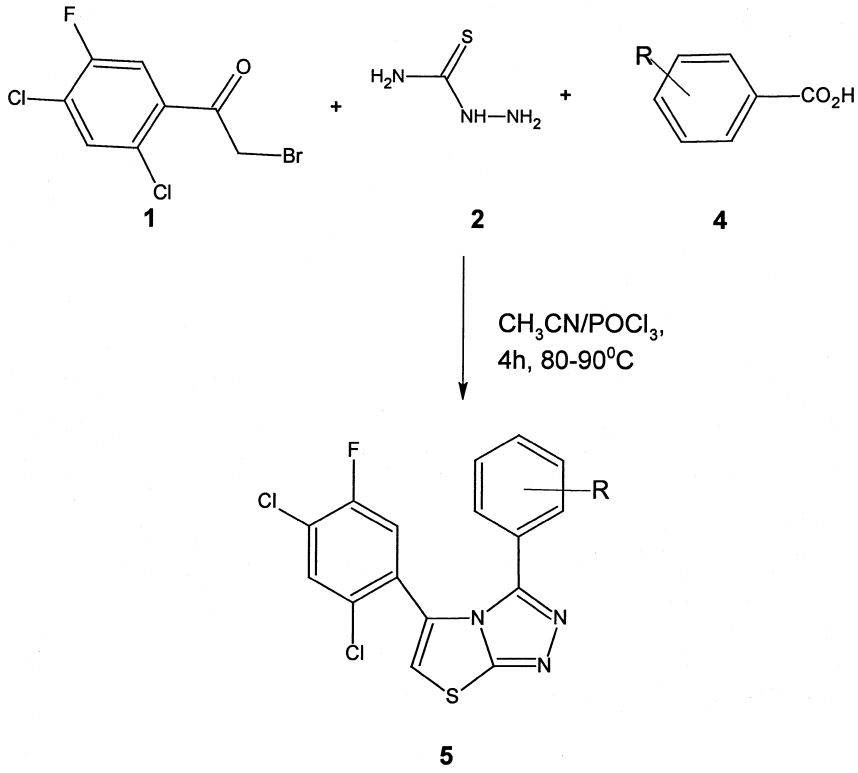
RESULTS AND DISCUSSION

2,4-Dichloro-5-fluoroacetophenone obtained from a commercial source was brominated in the presence of dry aluminium chloride and diethyl ether to give 2,4-dichloro-5-fluoro phenacyl bromide (**1**). The compound (**1**) in acetonitrile was added slowly into thiosemicarbazide (**2**). To this aryl carboxylic acids (**4**) and phosphorous oxychloride were added in drops (Scheme 1). The formation of triazolothiazoles (**5**) was confirmed on the basis of elemental analysis and spectroscopic studies. It is believed that the reaction proceeds through the initial formation of hydrazinothiazoles by nucleophilic attack of thiosemicarbazide on phenacyl bromide. Hydrazinothiazole then undergoes cyclization with carboxylic acids to give triazolthiazoles (**5**). The syntheses of the same compounds were carried out by an alternate two-step reaction (Scheme 2). In the ^{1}H NMR spectrum of compound **3**, showed a doublet at δ 7.63 due to ortho H-F coupling with J value of 8Hz. Two sharp singlets observed at δ 7.3 & 7.2 were assigned to protons of the 2,4-dichloro-5-fluorophenyl moiety and that of thiazole ring. The hydrazino protons appeared at δ 2.5 to 3. In the IR spectrum of compound **5b** peaks for NH and NH_2 were absent indicating the formation of cyclized product. The ^{1}H NMR spectrum of compound **5b**, showed a doublet at

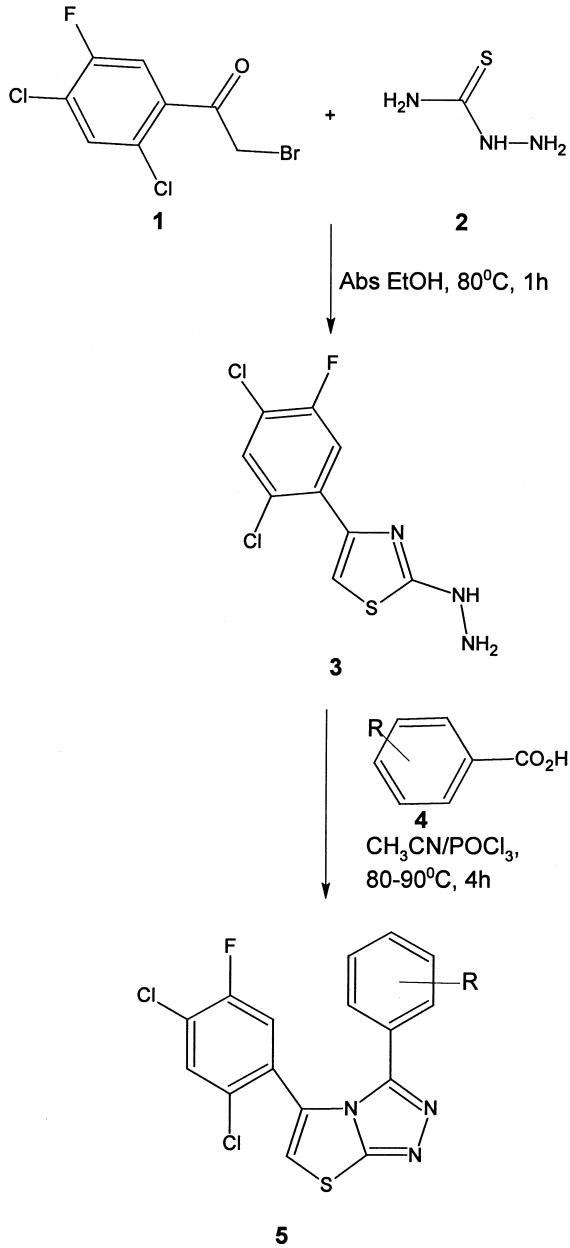


SCHEME 1 Synthesis of triazothiazoles.

δ 8.06 due to ortho H-F coupling with J value of 8.2 Hz. Two sharp singlets observed at δ 8.05 & 7.15 were assigned to protons of the 2,4-dichloro-5-fluorophenyl moiety and that of thiazole ring. Two distinct doublet of doublets observed at δ 7.0–6.9 was due to the presence of protons 4-methoxyphenyl moiety. Methoxy protons appeared as singlet at δ 4. The mass spectrum of compound **5b** did not show molecular ion peak. The major fragmentations in the mass spectra were indicated in Table II. The physical data of these compounds are given in Table I. Spectral data for some of the compounds are given in Table II.

ANTIMICROBIAL ACTIVITY

All the newly synthesized compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli ESS 2231* and *Staphylococcus aureus 209p*. Antifungal activity studies were carried out against *Aspergillus fumigatus*, *Candida albicans*, *Candida albicans*



SCHEME 2 Alternate synthesis of triazothiazoles.

TABLE I Characterization Data of 1,2,4-Triazolo[3,2-a]thiazoles (**3, 5a–j**)

Comp. No.	R	m.p (°C)	Yield (%)[a,b]	Mol. formula[c]
3	—	194–196	95	$C_9H_6Cl_2FN_3S$
5a	—H	174–175	65	$C_{16}H_8Cl_2FN_3S$
5b	—OCH_3	202–203	60	$C_{17}H_{10}Cl_2FN_3OS$
5c	-2—Cl	146–148	68	$C_{16}H_7Cl_3FN_3S$
5d	4—Cl	166	72	$C_{16}H_7Cl_3FN_3S$
5e	2,4—Cl_2—	178–180	78	$C_{16}H_6Cl_4FN_3S$
5f	2,4—Cl_2—5—F—	204–205	60	$C_{16}H_5Cl_4F_2N_3S$
5g	4—F—3—(OC_6H_5)—	138–139	55	$C_{22}H_{11}Cl_2F_2N_3OS$
5h	2—NO_2—	188	66	$C_{16}H_7Cl_2FN_4O_2S$
5i	4—NO_2—	198–200	63	$C_{16}H_7Cl_2FN_4O_2S$
5j	3,5—(NO_2)—	225–227	68	$C_{16}H_6Cl_2FN_5O_4S$

[a]Reported yields are after recrystallization.
[b]The compounds were crystallized from ethanol + dioxan mixture.
[c]Compounds showed satisfactory microanalysis.

ATCC 10231, *Candida krusei GO3*, and *Candida glabrata HO5* according to literature method.[14] Fluconazole, an antifungal drug was used as the standard for comparison. It is interesting to note that all the compounds are moderately active against *Candida albicans* and *Candida albicans ATCC 10231* (Table III). None of the compounds is active against *Candida krusei GO3* and *Candida glabrata HO5*. However, with respect to antibacterial activity only compound **5c** containing 2-chlorophenyl moiety is active.

TABLE II Spectral Characterization Data of the Compounds (**3**, **5b**, and **5f**)

Comp. No.	IR (υ cm^{-1})	^1H NMR (δ, ppm)	Mass (EIMS, *m/z*)
3	3250(NH str.), 3025(Ar—CH str.), 1580(C=N str.), 1180(C—F str.), 890(C—Cl str.)	7.63(d, 1H, $J_{H—F}$ = 8 Hz), 7.3 (s, 1H, thiazole H), 7.2(s, 1H, Ar—H), 3(s, b, NH), .6(s, b, NH_2)	—
5b	3050(Ar—CH str.), 2980(OCH_3 str.), 1585(C=N str.), 1210(C—F str.), 895(C—Cl str.)	8.06(d, 1H, Ar—H, J = 8.2 Hz), 8.04(s, 1H, Ar—H), 7.15(s, 1H, thiazole H), 7.0 -6.9(dd, 4H, Ar—H, J = 8.6 Hz), 3.9(s, 3H, OCH_3)	393(M^+, not observed), 342, 256, 206(4%), 135(100%), 107(9%)
5f	3075(Ar—CH str.), 1590(C=N str.), 1178(C—F str.), 890(C—Cl str.)	8.0-7.5(m, 4H, ArHs), 7.3(s, 1H, thiazole H)	453(M^+, 6%), 418(2%), 261(12%), 204(58%), 191(100%), 163(45%)

TABLE III Antimicrobial Activity Data of Triazolothiazole Derivatives (MIC in μg/ml) (**3** and **5a–j**)

	Bacterial strains tested		Fungal strains tested		
Comp. No.	*E. coli 2231*	*S. aureus 209p*	*A. fumigatus*	*C. albicans*	*C. albicans ATCC 10231*
3	—	—	50	20	20
5a	—	—	—	15	15
5b	—	—	50	20	20
5c	40	40	—	20	20
5d	—	—	—	20	20
5e	—	—	—	15	15
5f	—	—	—	15	15
5g	—	—	—	15	15
5h	—	—	—	25	25
5i	—	—	—	25	25
5j	—	—	—	20	20
Fluconazole (standard drug)	—	—	—	<10	<10

MIC: Minimum inhibitory concentration.
— indicates the compounds are inactive.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. The IR spectra in KBr disc were recorded on a Shimadzu FT IR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker AC-300F (300 MHz) NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a JEOL-JMS D-300 mass spectrometer operating at 70eV. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using a hexane: chloroform (4:1) solvent system. Iodine was used as the visualizing agent.

General Procedure for the Preparation of 2,4-Dichloro-5-fluorophenacyl Bromide (1)

2,4-dichloro-5-fluoro acetophenone (0.01 mmol) was dissolved in minimum amount of dry diethyl ether. To it catalytic amount of aluminum chloride was added (about 50 mg). The reaction mixture was cooled to 0–5°C. Pure bromine (0.01 mmol) was added drop wise with stirring. The mixture was stirred for 2 h. The ether was removed by distillation. The yield of 2,4-dichloro-5-fluorophenacyl bromide was nearly quantitative and proceeded to next step without purification.

General Procedure for the Synthesis of 1,2,4-Triazolo[3,4-b]thiazoles (5)

A mixture of 2,4-dichloro-5-fluorophenacyl bromide (1 mmol) (**1**), thiosemicarbazide (1 mmol) (**2**), and aryl carboxylic acid (1.2 mmol) (**4**) were taken in 20 ml of dry acetonitrile/toluene. To it was added 5 ml of phosphorous oxychloride dropwise, with stirring. The reaction mixture was refluxed on an oil bath for 4 h. Excess of solvent and phosphorous oxychloride were removed by distillation under reduced pressure. The reaction mixture was cooled and poured onto crushed ice. The resulting solid product was filtered, washed with sodium bicarbonate solution (2%), followed by cold water. It was dried and recrystallized from dioxan and ethanol mixture. The yield and characterization data of triazolothiazoles (**5**) prepared according to this method are given in Table I.

Synthesis of 4-(2,4-Dichloro-5-fluorophenyl)-2-hydrazinothiazole (3)

2,4-Dichloro-5-fluorophenacyl bromide (**1**) (1 mmol) and thiosemicarbazide (**2**) in ethanol were refluxed on a waterbath for 30 min. The excess of solvent was distilled off. The solid product obtained was purified by recrystallization from ethanol. m.p: 194-96; Yield: 86%.

Synthesis of 1,2,4-Triazolo[3,4-b]thiazoles (5)

A mixture of 4-(2,4-dichloro-5-fluorophenyl)-2-hydrazinothiazole (1 mmol) (**3**) and aryl carboxylic acid (1.2 mmol) (**4**) were refluxed with 5 mL of phosphorous oxychloride for 4 h (Scheme 2). The reaction mixture was cooled, distilled off excess of phosphorous oxychloride, and poured onto crushed ice. The solid product separated was filtered out and purified by repeated crystallization. The products were identified to be same as that of prepared by three component reaction.

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