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Preliminary communication

Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents☆

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Abstract

A series of arylthioureas (**1**), aromatic aldehyde thiosemicarbazones (**2**) and 5-aryl-2-furfuraldehyde thiosemicarbazones (**3**) were condensed with 2,4-dichloro-5-fluorophenacyl bromide to yield respective arylaminothiazoles, arylidene/5-aryl-2-furfurylidene hydrazinothiazoles (**4**). The newly synthesized compounds were characterized by IR, ^{1}H-NMR and mass spectral studies. These compounds were also screened for their antibacterial and anti-inflammatory activities. Two of the newly synthesized compounds showed anti-inflammatory activity comparable with that of Ibuprofen.

Keywords: Thiazoles; Arylthiourea; Arylaldehydethiosemicarbazone; Arylfurfuraldehyde thiosemicarbazone; Antibacterial activity; Anti-inflammatory activity

1. Introduction

Thiazoles and their derivatives are found to be associated with various biological activities [1–3] such as antibacterial, antifungal, anti-inflammatory activities. Organic compounds bearing thiazoles of different pharmacodynamic nuclei were found to possess potent anti-inflammatory activities [4]. Incorporation of fluorine into a heterocyclic molecule is reported to increase drug persistence by increasing its solubility in lipid material and fat deposits in the body [5]. Prompted by these reports and in continuation of our search for bioactive molecules[6] it was contemplated to synthesize some newer congeners of 2-substituted-4-(2,4-dichloro-5-fluorophenyl)-thiazoles starting from substituted thioureas (**1**), araldehydethiosemicarbazones (**2**), 5-aryl-2-furfuraldehydethiosemicarbazones (**3**) and 2,4-dichloro-5 fluorophenacyl bromide.

2. Chemistry

Substituted thioureas (**1**) were synthesized by the reaction of benzoyl chloride and ammonium thiocyanate with appropriate aniline. Araldehydethiosemicarbazones (**2**) were synthesized by the condensation of appropriate aldehydes with thiosemicarbazide in the presence of concentrated sulphuric acid. 5-Aryl-2-furfuraldehyde thiosemicarbazones (**3**) were prepared by the condensation of substituted 5-aryl-2-furfuraldehyde with thiosemicarbazides in the presence of concentrated sulphuric acid. Compounds **1**, **2** and **3** were then treated with 2,4-dichloro-5-fluorophenacyl bromide to yield 2-substituted-4-(2,4-dichloro-5-fluorophenyl) thiazoles (**4**) (Figs. 1–3).

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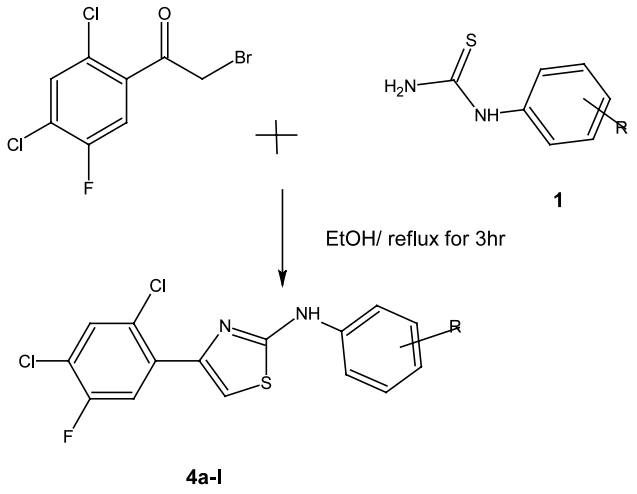


Fig. 1.

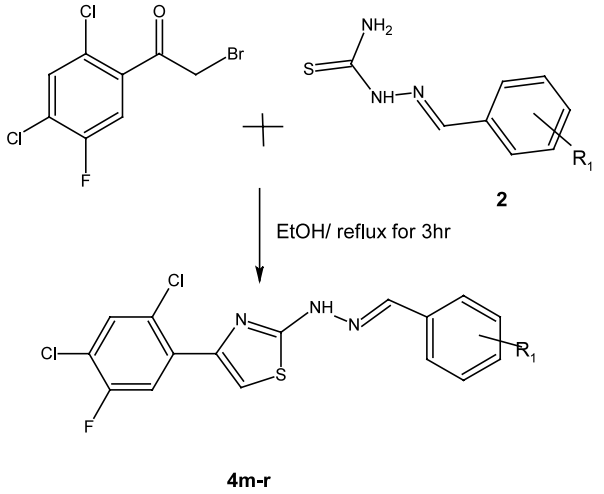


Fig. 2.

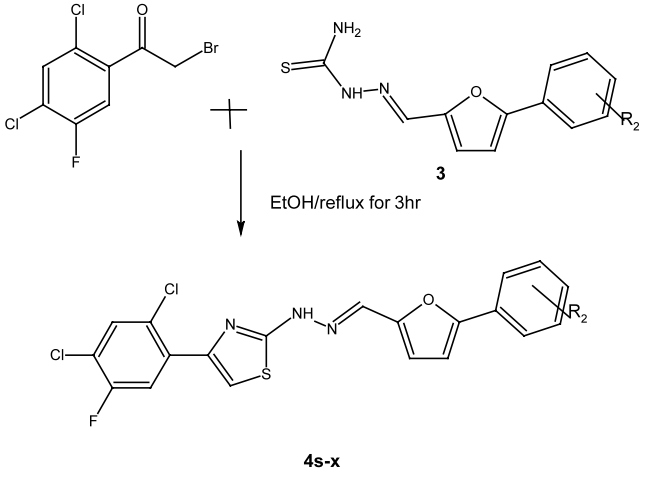


Fig. 3.

3. Results and discussion

The characterization data of thiazoles 4**a**–**x** are given in Tables 1–3. The formation of thiazoles was confirmed by recording the IR, ^{1}H-NMR and mass spectra of a few selected compounds. IR spectrum of **4a** showed absorption bands at 3294, 1594, 1092, 1068 and 767 cm^{-1} due to NH, C=N, C–F, C=S and C–Cl groups, respectively. The absence of the absorption band corresponding to carbonyl stretching frequency of the parent phenacyl bromide clearly confirmed the formation of 2-substituted aminothiazoles **4a**–**x**. The IR spectra of other aminothiazoles of the series showed similar absorption bands and the data are listed in Table 1.

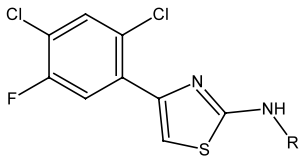
The ^{1}H-NMR spectrum of **4m** showed a singlet at δ 7.96 corresponding to NH proton. A sharp singlet at δ 7.6 is attributed to the C-5 proton of the thiazole ring. The aromatic protons of the 2, 4-dichloro-5-fluorophenyl ring resonated as two doublets at δ 7.5 ($J = 6.7$ Hz, *meta* H–F coupling) and δ 7.85 ($J = 10.6$ Hz, *ortho* H–F coupling) integrating for one proton, respectively. The aromatic protons of the phenyl ring resonated as a doublet at δ 7.64 ($J = 8$ Hz) integrating for two protons and as a multiplet in the region δ 7.33–7.41 integrating for three protons. The N=CH proton resonated as a singlet at δ 11.6. The ^{1}H-NMR spectra of **4e**, **4h**, **4l**, **4u**, **4q** and **4t** were also recorded and their spectral data are given in Tables 1–3. Mass spectra of compounds **4h**, **4l**, **4m**, **4n** and **4t** showed intense molecular ion peaks at *m*/*z* 352, 339, 365, 399 and 476, respectively, in agreement with their respective molecular formulae.

4. Pharmacology

4.1. Antibacterial activity

The newly synthesized thiazoles (**4**) were screened for their antibacterial activity against *Escherichia coli*, *Staphyllococcus aureus* (Smith), *Psuedomonus aeruginosa* (Gessard) and *Klebsiella pneumoniae* (Friedlader) bacterial strains by disc diffusion method [7]. The discs measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using dimethyl formamide. One millilitre containing 100 times the amount of chemical required in each disc was added to each bottle which contain 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Nitrofurazone was used as a standard drug. Solvent and growth controls were kept. The zone of inhibition and minimum

Table 1
Characterization data of 2-arylamino-4-(2,4-dichloro-5-fluorophenyl) thiazoles (**4a–l**)

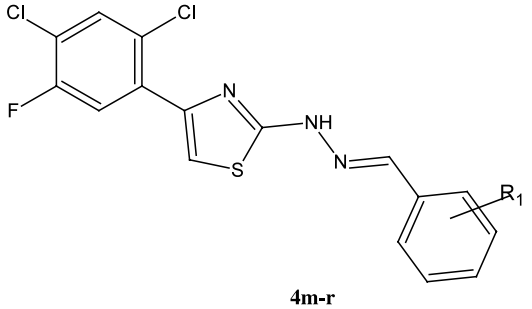


4a-l

Compound no.	Ar	M.p. (°C)	Yield(%)	Nature of the compound	Molecular formula
4a	C_6H_5	110	73	pale yellow micro crystals	$C_{15}H_9Cl_2FN_2S$
4b	4-Cl–C_6H_4	158	82	greenish white micro crystals	$C_{15}H_8Cl_3FN_2S$
4c	2,4-$Cl_2C_6H_3$	176	70	white flakes	$C_{15}H_7Cl_4FN_2S$
4d	4-BrC_6H_4	178	78	white flakes	$C_{15}H_8BrCl_2FN_2S$
4e	3-Cl–4-BrC_6H_3	240	63	white flakes	$C_{15}H_7BrCl_3FN_2S$
4f	2-Br–4-$CH_3C_6H_3$	132	55	white flakes	$C_{16}H_{10}BrCl_2FN_2S$
4g	2-$CH_3C_6H_4$	146	70	bright yellow micro needles	$C_{16}H_{11}Cl_2FN_2S$
4h	4-$CH_3C_6H_4$	144	78	bright yellow micro needles	$C_{16}H_{11}Cl_2FN_2S$
4i	2-$OCH_3C_6H_4$	124	54	pale yellow micro needles	$C_{16}H_{11}Cl_2FN_2OS$
4j	4-$OCH_3C_6H_4$	210	60	greenish yellow micro needles	$C_{16}H_{11}Cl_2FN_2OS$
4k	3-Cl–4-F–C_6H_3	110	79	white flakes	$C_{15}H_7Cl_3F_2N_2S$
4l	2-pyridyl	262	69	pale yellow micro needles	$C_{14}H_8Cl_2FN_3S$

IR (KBr, γ_{max} cm^{-1})—**4a**: 3294 (NH), 1539 (C=C), 1594 (C=N), 1092 (C–F), 1068 (C=S), 767 (C–C1) ; **4f**: 3352 (NH), 1612 (C=N), 1549 (C=C), 1091 (C–F), 1077 (C=S), 784 (C–C1) ; **4h**: 3230 (NH), 2924 (C–H), 1564 (C=C), 1599 (C=N), 1095 (C–F), 722 (C–C1). ^{1}H-NMR (DMSO-d_6)—**4f**: δ 2.32 (s 3H CH_3), 7.16 (d, 1H, Ar–H, $J = 8.5$Hz), 7.36 (s, 1H, thiazole H), 7.41 (s, 1H, Ar–H), 7.50 (d, 1H, Ar–$H_{H-F\ meta}$, $J = 6.7$ Hz), 7.86 (d, 1H, Ar–$H_{H-F\ ortho}$, $J = 10.2$ Hz), 7.97(d, 1H, Ar–H, $J = 8.5$Hz), **4h**: δ 2.33 (s, 3H, CH_3), 7.11 (s, 1H, thiazole H), 7.17 (m, 4H, Ar–H); 7.44 (d, 1H, Ar–$H_{H-F\ meta}$, $J = 6$ Hz), 7.46 (d, 1H, Ar–$H_{H-F\ ortho}$, $J = 9.6$ Hz), 7.62 (d, 1H, Ar–$H_{H-F\ meta}$, $J = 6$ Hz), 7.74 (d, 1H, Ar–$H_{H-F\ ortho}$, $J = 10.2$ Hz), 7.9 (s, 1H, NH), **4l**: δ 7.26 (s, 1H, thiazole H), 7.35–7.48 (m, 2H, Ar–H), 8.2 (s, 1H, NH), 8.15 (d, 1H, Ar–H, $J = 5.9$Hz). MS—**4h**: m/z 352 (100%, M^+); 163 (15.6%, 2,4-dichloro-5-fluoro-phenyl cation); 91 (14%, 4-methyl phenyl cation); **4l**: m/z 339 (100% M^+), 304 (38.5%, ($M^+ - Cl$).

Table 2
Characterization of data (2-arylidenehydrazino)-4-(2.4-dichloro-5-fluorophenyl) thiazoles (**4m–4r**)

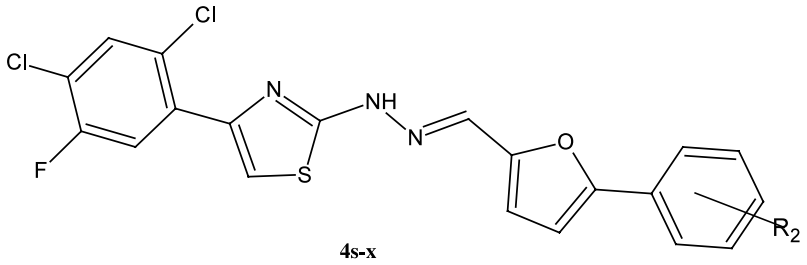


4m-r

Compound no.	R_1	M.p (°C)	Yield (%)	Nature of the compound	Molecular formula
4m	H	190	82	shining yellow micro-needles	$C_{16}H_{10}Cl_2FN_3S$
4n	4-Cl	212	86	light pale yellow micro-needles	$C_{16}H_9Cl_3FN_3S$
4o	2,4-Cl_2	210	78	light pale yellow flakes	$C_{16}H_8Cl_4FN_3S$
4p	3,4-O–CH_2–O	220	76	bright yellow micro-needles	$C_{17}H_{10}Cl_2FN_3O_2S$
4v	4-OCH_3	188	58	shining pink micro-needles	$C_{17}H_{12}Cl_2FN_3OS$
4r	3,4-O–CH_2–O–5-Br	190	52	reddish brown micro-needles	$C_{17}H_9BrCl_2FN_3O_2S$

IR (KBr, γ_{max} cm^{-1})—**4m**: 3294 (NH), 1574 (C=N), 1554 (C=C), 1092 (C–F), 1068 (C=S), 767 (C–C1): **4p**: 3313 (NH), 1573 (C=N), 1452 (C=C), 1069 (C–F), 1035 (C=S), 730 (C–C1). ^{1}H-NMR (DMSO-d_6)—**4m**: δ 7.33–741 (m, 3H, Ar–H), 7.6 (s, 1H, thiazole H), 7.5 (d, 1H, Ar–$H_{H-F\ meta}$, $J = 6.7$ Hz), 7.85 (d, 1H, Ar–$H_{H-F\ ortho}$, $J = 10.6$ Hz), 7.64 (d, 2H, Ar–H, $J = 6.8$ Hz), 7.96 (s, 1H, NH), 11.68 (s, 1H, –N=CH); **4q**: δ 3.85 (s, 3H, –OCH_3), 6.91–6.94 (m, 2H, Ar–H), 7.3 (s, 1H, thiazole H), 7.59 (s, 1H, NH), 7.76 (d, 1H, Ar–$H_{H-F\ ortho}$, $J = 10.2$ Hz) 9.58 (s, 1H, –N=CH). MS—**4m**: m/z 365 (42.2%, M^+); 262 (100%, $M^+ - N{\equiv}CC_6H_5$); 227 [60.2%, (262–Cl)]; **4n**: m/z 399 [56.7%, M^+]; 262 [100%, $M^+ - N{\equiv}C{-}C_6H_4Cl$]; 138 [14.5%, $-N{=}CHC_6H_4Cl$].

Table 3
2-(5-Aryl-2-furfurylidenehydrazino)-4-(2,4-dichloro-5-fluoro phenyl)thiazoles (**4s–x**)



4s-x

Compound no.	R_2	M.p. (°C)	Yield (%)	Nature of the compound	Molecular formula
4s	2-NO_2	115	68	reddish brown microcrystals	$C_{20}H_{11}Cl_2FN_4O_3S$
4t	4-NO_2	230	76	reddish brown microcrystals	$C_{20}H_{11}Cl_2FN_4O_3S$
4u	4-Br	242	74	reddish brown microcrystals	$C_{20}H_{11}BrCl_2FN_3OS$
4v	2,4-Cl_2	175	70	greenish yellow microcrystals	$C_{20}H_{10}Cl_4FN_3OS$
4w	2-NO_2–4-OCH_3	186	58	greenish yellow microcrystals	$C_{21}H_{13}Cl_2FN_4O_4S$
4x	2–CH_3–4-NO_2	170	62	reddish brown microcrystals	$C_{21}H_{13}Cl_2FN_4O_3S$

IR (KBr, γ_{max} cm^{-1})—**4u**: 3200 (NH), 1620 (C=N), 1264 (cyclic C–O), 1096 (C–F), 813 (Ar–H-bending), 756 (C–Cl), 534 (C–Br). ^{1}H-NMR (DMSO-d_6)—**4u**: δ 6.75 (d, 1H, Furan 3-H, $J = 3.6$ Hz), 6.79–6.82 (m, 2H, 1 Ar–H and Furan 4–H), 7.26 (s, 1H, thiazole H), 7.53–7.64 (m, 5H, Ar–H) 7.9 (s, 1H, NH), 8.07 (s, 1H, –N=CH). MS—**4t**: *m/z* 476 [23.2%, M^+], 189 [12.4% 2,4-dichloro- 5-fluoro benzonitrile].

inhibitory concentrations [MIC] were noted. The results of such studies are given in Table 4. Interestingly almost all the compounds showed moderate to good antibacterial activity. Among the compounds tested **4k**, **4s** and **4x** thiazoles carrying 3-chloro-4-fluoro, 2-nitrophenylfurfuryl and 4-nitro-2-methylphenylfurfuryl substituents showed excellent antibacterial activity against *S. aureus* (Smith) and *P. aeruginosa* (Gessard).

Table 4
Antibacterial screening data

Compound no.	Zone of inhibition (mm) (minimum inhibitory concentration in μg ml^{-1})			
	S. aureus	*E. coli*	*Klebsiella* sp.	*P. aeruginosa*
4a	5 (50)	6 (60)	2 (40)	6 (100)
4b	5 (50)	8 (80)	4 (100)	5 (100)
4c	7 (80)	8 (100)	3 (100)	6 (100)
4d	10 (20)	7 (80)	6 (90)	5 (100)
4c	5 (100)	10 (80)	7 (30)	2 (100)
4f	7 (40)	8 (40)	6 (60)	8 (90)
4g	8 (60)	4 (50)	3 (80)	4 (100)
4h	5 (20)	6 (40)	8 (30)	8 (100)
4I	2 (30)	4.5 (50)	3.5 (70)	4.5 (80)
4j	1.5 (20)	6.0 (40)	5.5 (40)	4 (80)
4k	13 (10)	6 (80)	5 (50)	12 (10)
4l	8 (30)	7.5 (50)	6.5 (40)	7 (100)
4m	6.5 (40)	4.0 (30)	6.5 (50)	3.5 (80)
4n	5.5 (30)	5.5 (50)	7.5 (80)	6.5 (100)
4o	3.5 (20)	3.5 (20)	7.5 (40)	6.5 (80)
4p	1.5 (20)	5.5 (40)	7 (60)	3.5 (100)
4q	2.0 (30)	3.0 (40)	5.5 (90)	4.5 (90)
4r	4.5 (30)	2.5 (30)	3.0 (40)	1.5 (40)
4s	12.75 (10)	9 (100)	5 (80)	11.30 (10)
4t	8 (30)	6 (40)	5 (60)	3.5 (80)
4u	5. (20)	4 (60)	1.5 (40)	2 (60)
4v	7.00 (50)	6 (40)	5.5 (50)	6 (90)
4w	2.5 (40)	6.5 (60)	5.5 (40)	7.5 (90)
4x	12.00 (10)	10 (50)	9 (80)	11.30 (10)
Nitrofurazone	12.65 $<$ 10.00	14.45 $<$ 10.00	10.20 $<$ 10.00	11.25 $<$ 10.00

4.2. Anti-inflammatory activity

The thiazoles (**4**) were also screened for their anti-inflammatory activity. The screening was conducted in two models, acute inflammatory model and chronic inflammatory model. In acute inflammatory model, carrageenan induced rat paw oedema method [8] was used. Carrageenan (an irritant) at a concentration of 1 mg ml^{-1} was injected subcutaneously into the hind paw of the rat to produce oedema. Different groups of animals were administered a standard drug Ibuprofen, the test samples and the vehicle used for the preparation of samples .The increase in the paw volume was measured before and after three hours of administration and the results were compared.

Fifty-four healthy albino rats of body weight 100–200 g were selected and made into nine groups of six animals each. All the animals were kept on fasting for 18 h. One group of animals was kept as control which received 2% w/v acacia mucilage which was used to suspend the sample. Another group received the standard drug ibuprofen 20 mg kg^{-1} body weight intraperitonially. Remaining seven groups of animals received seven different test compounds (20 mg kg^{-1} body weight) intraperitonially. After 30 min 0.1 ml of w/v carrageenan was injected subcutaneously into the right hind paw of the rats. A mark was made at the lateral maleous of the right hind paw which was dipped in the plethismograph up to the mark and the volume was measured immediately and after 3 h. The change in paw volume was compared with that in the vehicle treated control animals. The percentage inhibition of oedema was calculated using the formula,

$$\%\text{Oedemainhibition} = 100 - (V_{\text{test}}/V_{\text{control}}) \times 100.$$

In chronic inflammatory model, cotton pellet Granuloma method [9] was used. Granuloma represents the exudative and proliferative phases of inflammation. The inflammation is measured by weighing the capsular granuloma together with the cotton pellet. The results of such studies are given in Tables 5 and 6. In both the cases, the percentage of inhibition was compared with that of the standard drug Ibuprofen. Interestingly five compounds **4d**, **4g**, **4k**, **4n** and **4s** carrying 4-bromophenyl, 4-methylphenyl, 3-chloro-4-fluorophenyl, 4-chlorobenzylideneamino and 2-nitrophenylfurylideneamino substituents showed acute anti-inflammatory activity. Compounds **4d** and **4p** carrying 4-bromophenyl and 3,4-methylenedioxybenzylidene amino substituents showed excellent chronic anti-inflammatory activity comparable with that of ibuprofen.

Table 5
Chronic inflammation

Group	Net wt. of granulation tissue, mean ± S.E.	Percentage of Inhibition, mean ± S.E. [P]
Control	131.5 ± 0	–
Ibuprofen	72.0 ± 1.25	45.10
4d	72.25 ± 33	45.5 ± 25.5
4g	86.25 ± 3.25	34.5 ± 2.5
4k	110.50 ± 11.25	15.5 ± 8.5
4l	85.75 ± 0.5	34.5 ± 0.5
4n	92.50 ± 13.0	30 ± 10
4p	71.0 ± 1.0	45.5 ± 0.5
4s	81.87 ± 3.62	37.5 ± 0.5

Table 6
Anti-inflammatory activity screening of compounds **4d**, **4g**, **4k**, **4l**, **4n**, **4p** and **4s**: acute inflammation

Group	Paw oedema volume, mean + S.E. (ml)	Percentage of inhibition, mean − S.E. [P]
Control	0.27 ± 0.02	–
Ibuprofen	0.0	100%
4d	0.05 ± 0.05	79.75 ± 20.25
4g	0.03 ± 0.03	89.0 ± 11
4k	0.015 ± 0.01	94.5 ± 5.5
4n	0.04 ± 0.02	63.75 ± 16.80
4s	0.02 ± 0.02	92.75 ± 7.25

$P < 0.05$ vs. ibuprofen.

5. Experimental

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr pellets were recorded on JASCO FT-IR 5300 Infrared spectrophotometer. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as an internal standard and the mass spectra were recorded on a VG-s-70 micro mass, mass spectrometer operating at 70 eV.

5.1. General procedure for the synthesis of N-substituted thioureas (*1*)

Benzoyl chloride (0.01 mol) was added over 5 min to a freshly prepared solution of ammonium isothiocyanate (0.012 mol) in reagent grade acetone and the mixture was heated under reflux for about 15 min. Heating was stopped and appropriate aniline in acetone was added. The mixture was heated under reflux for 30 min and then poured on to crushed ice. The resulting solid was collected, washed with water, followed by cold mixture of water and methanol (1:1). Suitably substituted benzoylthioureas were added to a preheated solution of aqueous sodium hydroxide (5%) and stirred. The mixture was then poured onto crushed ice containing hydrochloric acid (5%). The benzoic acid separated was removed by treating the reaction mixture with sodium

carbonate. The product was collected, washed with water and dried.

5.2. General procedure for the synthesis of arylidene thiosemicarbazone, 5-aryl-2-furfurylidene thiosemicarbazone (**3**)

An equimolar mixture of the appropriate aldehyde–5-aryl-2-furfurals (0.01 mol), thiosemicarbazide (0.01 mol.) in ethanol (25 ml) and concentrated sulphuric acid (0.005 mol) was refluxed on a water bath for 2 h. The solid mass that separated on cooling was collected by filtration, dried and recrystallized from ethanol.

5.3. General procedure for the synthesis of 2, 4-dichloro-5-fluorophenacyl bromide

Bromine (0.01 mol) was added gradually to a cold solution of 2, 4-dichloro-5-fluoroacetophenone (0.01 mol) in carbon tetrachloride (10 ml) (ca. 30 min) with continuous stirring and maintaining the temperature of the reaction mixture at 0–5 °C. After the addition was complete, the reaction mixture was slowly brought to room temperature (r.t.) and stirring was continued for another 60 min until the evolution of hydrogen bromide gas ceased. The solvent was removed under reduced pressure. The precipitated solid was filtered, dried and recrystallized from methanol, m.p. 60–62 °C.

5.4. General procedure for the synthesis of 2-substituted 4-(2,4-dichloro-5-fluorophenyl) thiazoles (**4**)

2,4-Dichloro-5-fluorophenacyl bromide (0.01 mol) and an appropriate thiourea/arylidenethiosemicarbazone/5-aryl-2-furfurylidenethiosemicarbazone (0.01 mol) in ethanol was refluxed on a water bath for 3 h. The solid which separated on cooling was collected by filtration, dried and recrystallized from ethanol.

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