

Synthesis and biological screening of some halogenated thiadiazoles and triazoles

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Acid hydrazide **1** is treated with aryl isothiocyanates to get corresponding thiosemicarbazides **2**. Compounds **2** in acidic medium give thiadiazoles **3** and in basic medium give triazoles **4**. These compounds are synthesized by conventional method and ultra sound irradiation method. Some of the synthesized compounds are tested for their antimicrobial, antiviral and antioxidant activities.

Keywords: Ultrasonication, fluorine, chlorine, thiosemicarbazides, thiadiazoles, triazoles

In recent days active research has been initiated on halogen containing heterocycles. A number of fluoro and perfluoroalkyl substituted pharmaceuticals, agrochemicals, dyes and polymers have been commercialized. Fluorine containing heterocycles are very fascinating targets for synthetic organic chemists because of their potentially high physiological activities¹. Fluorine containing organic compounds are associated with antimicrobial², antitumor³, antibacterial⁴ and anticancer⁵ activities. They also act as selective inhibitors of biosynthesis of aminergic neurotransmitters⁶.

Activity of all agrochemicals depends on their toxicity. The toxicity of chemical entity is related to substitutions like halogen, sulfur, phosphorus and nitrile groups. Nowadays number of herbicides and insecticides⁷⁻¹⁰ are commercially available which proves the above fact. The chlorinated organic compounds like picloram, pyrichlor, erbon, chlorpyrifos etc are proved to be good herbicides and insecticides. The chlorine containing heterocycles are associated with antibacterial and insecticidal activities¹¹. Chloro-pyridines are used in pharmaceutical and agrochemical industries¹².

Thiosemicarbazides are associated with important biological activities and industrial applications. Thiosemicarbazides are found to show antibacterial, antifungal¹³, plant growth promoting¹⁴, anti-convulsant¹⁵ and antiviral¹⁶ activities.

Compounds containing 1,3,4-thiadiazole nucleus has been reported with variety of biological activities such as antimicrobial^{17,18}, antitubercular^{17,19} and anti-cancer activity¹⁷.

Triazoles are an important class of heterocyclic compounds. Triazoles are known for their fungicidal²⁰, pesticidal²¹ and antimycotic²² activities.

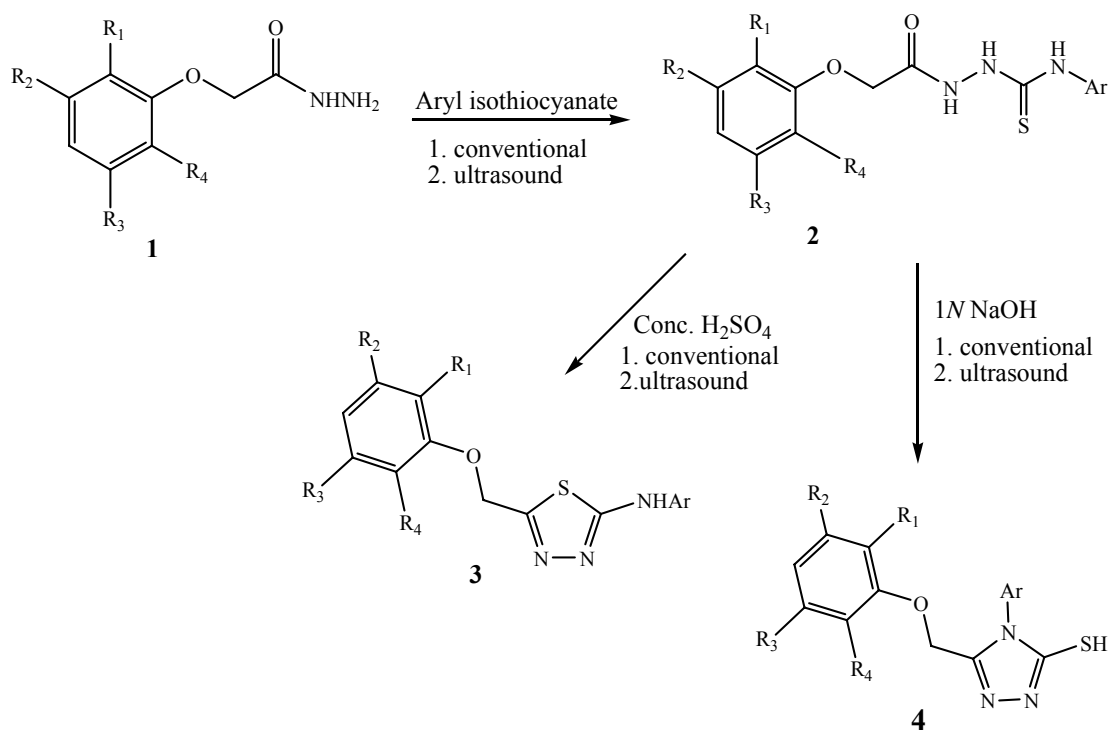
Holla *et al.* have reported the synthesis of thiadiazoles and triazoles by conventional method²³⁻²⁵. Now-a-days one pot reactions²⁶ are gaining prominence due to their environmental advantages and cost effectiveness. Similarly, application of ultrasound²⁷ in chemistry is reaching a stage of importance because of its proven ability to accelerate even very robust transformations²⁸.

Biological activities associated with fluorine, chlorine and azoles prompted us to synthesize these compounds by conventional and non-conventional method (**Scheme I, Table I**) and to screen them for various biological activities.

Biological activities

Antimicrobial activity

Synthesized compounds were screened for their antifungal and antibacterial activities. The *in vitro* antimicrobial activities of the synthesized compounds were assessed against fungi and bacteria. The fungi used were *C. albicans* and *A. fumigatus*. The bacteria used were *S. aureus* and *E. coli*.

**Table I** — Characterization data for compounds **2a-j**, **3a-j** and **4a-j**

Compd	R ₁	R ₂	R ₃	R ₄	Ar	m.p. (°C)	Conventional		Ultrasound	
							Time (min)	Yield (%)	Time (min)	Yield (%)
2a	H	Cl	Cl	H	Phenyl	159	45	78	22	90
2b	H	Cl	Cl	H	2-methylphenyl	105	45	79	18	91
2c	H	Cl	Cl	H	3-methylphenyl	164	45	75	18	89
2d	H	Cl	Cl	H	4-methylphenyl	182	45	77	20	88
2e	H	Cl	Cl	H	3-methoxyphenyl	160	45	70	22	85
2f	F	F	F	F	Phenyl	170	45	70	22	86
2g	F	F	F	F	2-methylphenyl	129	45	73	19	85
2h	F	F	F	F	3-methoxyphenyl	149	45	69	22	82
2i	F	F	F	F	4-methylphenyl	187	45	78	21	89
2j	F	F	F	F	4-methoxyphenyl	169	45	76	22	87
3a	H	Cl	Cl	H	Phenyl	179	180	55	20	78
3b	H	Cl	Cl	H	2-methylphenyl	148	180	70	18	80
3c	H	Cl	Cl	H	3-methylphenyl	156	180	65	22	88
3d	H	Cl	Cl	H	4-methylphenyl	192	180	68	20	86
3e	H	Cl	Cl	H	3-methoxyphenyl	172	180	71	22	85
3f	F	F	F	F	Phenyl	300	180	58	20	75
3g	F	F	F	F	2-methylphenyl	284	180	65	24	80
3h	F	F	F	F	3-methoxyphenyl	265	180	68	20	79
3i	F	F	F	F	4-methylphenyl	283	180	66	18	85
3j	F	F	F	F	4-methoxyphenyl	255	180	58	22	89

—Contd

Table I — Characterization data for compounds **2a-j**, **3a-j** and **4a-j**—*Contd*

Compd	R ₁	R ₂	R ₃	R ₄	Ar	m.p. (°C)	Conventional		Ultrasound	
							Time (min)	Yield (%)	Time (min)	Yield (%)
4a	H	Cl	Cl	H	Phenyl	169	90	58	30	78
4b	H	Cl	Cl	H	2-methylphenyl	200	90	60	29	80
4c	H	Cl	Cl	H	3-methylphenyl	181	90	57	28	83
4d	H	Cl	Cl	H	4-methylphenyl	185	90	48	32	85
4e	H	Cl	Cl	H	3-methoxyphenyl	177	90	55	35	88
4f	F	F	F	F	Phenyl	300	90	50	32	75
4g	F	F	F	F	2-methylphenyl	284	90	51	35	78
4h	F	F	F	F	3-methoxyphenyl	265	90	54	34	79
4i	F	F	F	F	4-methylphenyl	283	90	57	35	86
4j	F	F	F	F	4-methoxyphenyl	255	90	58	32	84

Table II — Antimicrobial activity of **2a-e** and **4a-d** – Zone of inhibition in mm

Compd	Conc. (µg/mL)	Antifungal Test		Antibacterial Test		Remark
		<i>C. albicans</i> ATCC 14503	<i>A. fumigatus</i> ATCC 16424	<i>S. aureus</i> 209P	<i>E. coli</i> ATCC 25922	
2a	100	-	-	-	-	inactive
	1000	-	14hr	15	-	activity in both indication
2b	100	-	-	-	-	inactive
	1000	-	13hr	17	-	activity in both indication
2c	100	-	-	9	-	poor antibacterial spectrum
	1000	-	-	16	-	poor antibacterial spectrum
2d	100	-	10hr	10	-	activity in both indication
	1000	-	11hr	15	-	activity in both indication
2e	100	-	-	-	-	inactive
	1000	-	12hr	11hr	-	activity in both indication
4a	100	-	-	-	-	inactive
	1000	-	-	13	-	poor antibacterial spectrum
4b	100	-	-	9	-	poor antibacterial spectrum
	1000	-	-	18	-	poor antibacterial spectrum
4c	100	-	-	51hr	-	poor antibacterial spectrum
	1000	-	-	18hr	-	poor antibacterial spectrum
4d	100	-	-	9	-	poor antibacterial spectrum
	1000	-	-	18hr	-	poor antibacterial spectrum
Vancomycin (10 µg/mL)		NT	NT	15	14	-
Amphotericin B (20 µg/mL)		22	24	NT	NT	-

NT: Not tested, h: hazy, slh: slightly hazy. Compounds **2g-j** and **3a-j** are inactive.

Amphotericin B and vancomycin were used as standards for comparison for antifungal and antibacterial activities respectively. The activities were determined by measuring the diameter of the inhibition zone in mm.

None of the compounds is a suitable candidate for antifungal and antibacterial indication as shown in **Table II**.

Antiviral activity

The antiviral activity of some of the compounds was determined against *Herpes Simplex virus-2* by CPE inhibition assay. Vero cells (African green monkey kidney cell line-ATCC CCL-81) were cultivated as monolayers in 5% carbon dioxide at 37°C, in Dulbecco's modified Eagle medium (MEM) with 5% fetal bovine serum (FBS).

Table III — Antiviral activity of **2a-e**, **2g-j**, **3a-g**, **3i-j** and **4a-e**

Compd	% CPE inhibition	Compd	% CPE inhibition	Compd	% CPE inhibition
2a	-	2j	-	3j	-
2b	-	3a	-	4a	-
2c	-	3b	-	4b	-
2d	-	3d	-	4c	-
2e	-	3e	-	4d	-
2g	+	3f	-	4e	+
2h	-	3g	-		
2i	+	3i	-		

Standard Famciclovir (10 µg/mL)

Scoring: - 0-25%, ++ 26-50%, +++ 51-75%, ++++ 76-100%

Samples **2g**, **2i** and **4e** were considered as positive and selected for dose response study.**Table IIIa** — Evaluation of primary positives by dose dependent study

Compd	Anti-HSV-2 activity (%CPE inhibition)							
	1.56 µg/mL	3.12 µg/mL	6.25 µg/mL	12.5 µg/mL	25 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL
2g	-	-	-	-	-	+	-	-
2i	-	-	-	-	-	+	-	-
4e	-	-	-	-	-	+	+	+

Scoring: - 0-25%, ++ 26-50%, +++ 51-75%, ++++ 76-100%

Compound **4e** get precipitated at higher concentrations. Compounds **2g** and **2i** showed no dose dependent activity.

The diluted extracts (100 g/mL) were transferred to the aspirated Vero cell monolayers. Cultures were incubated at 37°C for 60 minutes. 100 µL of virus (100 TCID₅₀) was added to each well. The tray was transferred to an environmental chamber (37°C).

Cultures were inspected periodically for virus-induced cytopathic effect (viral CPE). Absence of CPE indicated complete inactivation of the virus. Partial inhibition was considered to be a negative result. Some of the synthesized compounds were found to be active as shown in **Table III** and **Table IIIa**.

Antioxidant activity

The antioxidant activity of some of the synthesized compounds was determined by DPPH method using Trolox as a reference standard. Amongst the compounds screened for antioxidant activity, some of the synthesized compounds were found to be active as shown in **Tables IV**, **IVa** and **IVb**.

Results and Discussion

To prepare the targeted compounds, the required acid hydrazides **1** were prepared from corresponding phenoxy esters by treating them with hydrazine

hydrate. Acid hydrazides **1** were treated with aryl isothiocyanates to get corresponding thiosemicarbazides **2**. Compounds **2** under acidic condition get cyclised to give thiadiazoles **3** and under basic condition to give triazoles **4**. The structures of the synthesized compounds were confirmed by spectral analysis (IR, ¹H NMR and mass). The IR spectrum of compound **2a** showed a peak at 3331 cm⁻¹ due to -NH stretch. In ¹H NMR spectrum it exhibited three singlets, one at δ 4.72 due to -CH₂, second at 9.65 due to two -NH protons and third at 10.25 due to one -NH proton. Mass spectrum was consistent with the assigned structure.

As expected the ¹H NMR spectrum of compound **3a** showed singlet at δ 10.40 due to -NH proton while another singlet at δ 9.65 due to two -NH protons get disappeared due to the cyclisation of thiosemicarbazide into thiadiazole. Similarly, the ¹H NMR spectrum of compound **4a** showed deshielded singlet at δ 11.23 attributed to -SH proton. The IR and mass spectral data of **3a** and **4a** were consistent with the assigned structures.

Some of the synthesized compounds were tested for their antimicrobial, antiviral and antioxidant

Table IV — Antioxidant activity of **2a-e**, **2g-j**, **3a-g**, **3i-j** and **4a-e**
 (Primary screening data of DPPH assay with test Conc. 125 µg/mL)

Compd	% AO activity	Compd	% AO activity	Compd	% AO activity
2a	92.52	2j	90.60	3j	-9.23
2b	92.71	3a	-3.08	4a	73.29
2c	92.66	3b	-2.22	4b	70.76
2d	92.55	3d	11.85	4c	90.88
2e	92.52	3e	3.87	4d	76.60
2g	92.24	3f	-14.10	4e	87.80
2h	92.38	3g	-12.39		
2i	92.40	3i	-13.87		

Compounds **2a-j** and **4a-e** were found to be active in primary screening and were further tested in a dose dependent manner using DPPH assay

Table IVa — Evaluation of primary positives by dose dependent DPPH assay

Compd	Test Conc. (µg/mL)				Compd	Test Conc. (µg/mL)			
	62.5	31.25	15.6	7.3		62.5	31.25	15.6	7.3
2a	91.95	90.60	65.62	35.35	2i	91.74	90.18	63.78	35.80
2b	89.94	80.66	53.69	43.48	2j	90.39	89.40	61.26	8.98
2c	91.62	89.46	61.08	32.13	4a	61.67	45.31	27.62	16.11
2d	91.79	90.60	67.65	36.64	4b	55.19	39.72	26.48	17.13
2e	91.64	90.03	65.22	36.08	4c	61.67	45.31	27.62	16.11
2g	90.72	81.98	45.02	29.16	4d	55.19	39.74	26.54	16.12
2h	91.59	89.82	58.62	23.90	4e	64.66	46.51	27.81	16.39

Compounds **2a**, **2c**, **2d**, **2e**, **2h**, **2i**, **2j**, were found active in dose dependent DPPH assay. These were further tested using riboflavin-methionine assay.

Table IVb — Evaluation by riboflavin-methionine assay. (% SOD activity)

Compd	Test Conc. (µg/mL)			
	250	125	62.5	31.25
2a	37.943	32.933	37.742	25.785
2c	14.896	18.570	16.900	12.759
2d	-40.080	8.016	29.125	33.667
2e	55.716	46.631	43.141	41.276
2h	35.003	51.503	36.273	29.593
2i	20.174	26.186	26.987	23.046
2j	40.347	48.965	42.218	28.257

None of the screened compounds showed high % superoxide dismutase (SOD) activity.

activities. Some derivatives of thiosemicarbazides and triazoles showed poor antimicrobial activity. In primary screening of antiviral activity, compounds **2g**, **2i** and **4e** were found to be active. Hence they were selected for dose dependent study but compound **4e** get precipitated at higher concentration while **2g** and **2i** showed no dose dependent activity. These compounds were also tested for

antioxidant activity. In primary screening, compounds **2a-j** and **4a-e** were found to be active and were further tested for dose dependent study. Compounds **2a**, **2c**, **2d**, **2e**, **2h**, **2i**, **2j** were found active in dose dependent study and were further tested for percent superoxide dismutase activity. But none of the compound showed high percentage of SOD activity.

Experimental Section

Melting points were recorded in open capillaries in liquid paraffin-bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR spectrometer in KBr disc. ^1H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer using $\text{DMSO}-d_6$ as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on Finnigan mass spectrometer.

1-(2-(3,5-Dichlorophenoxy)acetyl)-4-phenylthiosemicarbazide and 1-(2-(2,3,5,6-tetrafluorophenoxy)acetyl)-4-phenylthiosemicarbazide, 2a-j

Conventional method

A mixture of compound **1** (0.01 mole) and aryl isothiocyanate (0.01 mole) in 15 mL of ethanol was heated under reflux for 45 minutes. The progress of reaction was monitored by TLC. After completion of reaction the contents were cooled and the solid obtained was filtered and crystallized from ethanol to get compound **2**. The compounds synthesized by above procedure are listed in **Table I**.

Ultrasound method

A mixture of compound **1** (0.01 mole) and aryl isothiocyanate (0.01 mole) in 15 mL ethanol was subjected to ultrasound irradiation for 18-22 minutes. The progress of reaction was monitored by TLC. After completion of reaction the product obtained was filtered and crystallized from ethanol. Formation of compound **2** was confirmed by melting point, mixed melting point, TLC and spectral analysis. The data of synthesized compounds is given in **Table I**.

2a: IR (KBr): 3331, 3221, 1690 and 1043 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 4.72 (s, 2H), 7.12 (m, 4H), 7.32 (m, 4H), 9.65 (s, 2H), 10.25 (s, 1H); MS: m/z 370 (M^+) with isotopic peaks.

2e: IR (KBr): 3320, 3203, 1699 and 1055 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 3.81 (s, 3H), 4.53 (s, 2H), 6.85 (d, 1H), 6.96 (m, 3H), 7.04 (d, 2H), 7.30 (d, 1H), 9.48 (s, 2H), 10.21 (s, 1H); MS: m/z 400 (M^+) with isotopic peaks.

2f: IR (KBr): 3354, 3267, 1694 and 1131 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 4.92 (s, 2H), 7.08 (m, 1H), 7.38 (m, 4H), 7.61 (m, 1H), 9.75 (s, 2H), 10.26 (s, 1H); MS: m/z 373 (M^+).

2g: IR (KBr): 3350, 3263, 1698 and 1137 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 2.27 (s, 3H), 4.89 (s, 2H), 6.94 (m, 1H), 7.22 (m, 3H), 7.52 (m, 1H), 9.12 (s, 2H), 10.15 (s, 1H); MS: m/z 387 (M^+).

5-[(3,5-Dichlorophenoxy)methyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine and 5-[(2,3,5,6-tetrafluorophenoxy)methyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine, 3a-j

Conventional method

Thiosemicarbazide **2** (0.001 mole) was dissolved in 3 mL of conc. H_2SO_4 in 50 mL beaker and stirred at RT for 3 hr. After completion of reaction 10 g of crushed ice was added in it. The solid obtained was separated by filtration and crystallized from 1:1 mixture of DMF and water to afford thiadiazole **3**. The data of synthesized compounds is given in **Table I**.

Ultrasound method

Thiosemicarbazide **2** (0.001 mole) was dissolved in 3 mL of conc. H_2SO_4 and subjected to ultrasound irradiation for 18-25 minutes. The progress of reaction was monitored with the help of TLC. After completion of reaction 10 g of crushed ice was added in it. The solid obtained was separated by filtration and crystallized from 1:1 mixture of DMF and water to afford thiadiazole **3**. Formation of compound **3** was confirmed by melting point, mixed melting point, TLC and spectral analysis. The data of synthesized compounds is given in **Table I**.

3a: IR (KBr): 3359, 1590 and 1055 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 5.48 (s, 2H), 7.01 (t, 1H), 7.22 (d, 3H), 7.35 (t, 2H), 7.61 (d, 2H), 10.40 (s, 1H); MS: m/z 352 (M^+) with isotopic peaks.

3e: IR (KBr): 3368, 1587 and 1053 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 3.80 (s, 3H), 5.27 (s, 2H), 6.89 (m, 3H), 6.98 (d, 1H), 7.26 (m, 3H), 8.78 (s, 1H); MS: m/z 382 (M^+) with isotopic peaks.

3f: IR (KBr): 3370, 1584 and 1172 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 5.59 (s, 2H), 7.02 (m, 1H), 7.35 (t, 2H), 7.60 (m, 3H), 10.50 (s, 1H); MS: m/z 355 (M^+).

3g: IR (KBr): 3368, 1581 and 1173 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 2.29 (s, 3H), 5.59 (s, 2H), 6.97 (m, 1H), 7.22 (m, 3H), 7.31 (m, 1H), 10.42 (s, 1H); MS: m/z 369 (M^+).

5-[(3,5-Dichlorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-thiol and 5-[(2,3,5,6-tetrafluorophenoxy)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-thiol, 4a-j

Conventional method

A mixture of thiosemicarbazide **2** and 10 mL of 1*N* NaOH was heated under mild reflux for 1.5 hr. The progress of reaction was monitored by TLC. After completion of reaction the contents were cooled and poured into crushed ice. Then it was acidified with gl.

acetic acid. The product was separated by filtration and crystallized from the mixture (1:1) of DMF and water to get corresponding triazole **4**. The data of synthesized compounds is given in **Table I**.

Ultrasound method

A mixture of thiosemicarbazide **2** and 10 mL of 1N NaOH in 100 mL RBF was subjected to ultrasound irradiation for 25-35 minutes. The progress of reaction was monitored by TLC. After completion of reaction the contents were cooled and poured into crushed ice. Then it was acidified with gl. acetic acid. The product was separated by filtration and crystallized from the mixture (1:1) of DMF and water to get corresponding triazole **4**. The data of synthesized compounds is given in **Table I**.

4a: IR (KBr): 3440, 1582, 1578 and 1050 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 4.98 (s, 2H), 6.95 (d, 2H), 7.18 (d, 1H), 7.5 (m, 5H), 11.23 (s, 1H); MS: m/z 353 (M+H) with isotopic peaks.

4e: IR (KBr): 3444, 1588, 1574 and 1041 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 3.85 (s, 3H), 4.84 (s, 2H), 6.71 (d, 1H), 6.98 (m, 3H), 7.26 (m, 3H), 11.55 (s, 1H); MS: m/z 383 (M+H) with isotopic peaks.

References

- Niccolai D, Tarsi L & Thomas R T, *Chem Commun*, 24, **1997**, 2333.
- Shelke S N, Dalvi N R, Kale S B, More M S, Gill C H & Karale B K, *Indian J Chem*, 46B, **2007**, 1174.
- Lucey N M & McElhinney R S, *J Chem Res*, **1985**, 240.
- Patel V M & Desai K R, *Indian J Chem*, 44B, **2005**, 1084.
- Hammam A E G, El-Salam O I A, Mohamed A M & Hafez N A, *Indian J Chem*, 44B, **2005**, 1887.
- Kollonitsch J, Patchet A A, Marburg S, Maycock A L, Perkins L M, Doldouras G A, Duggan D E & Aster S D, *Nature*, 274, **1978**, 906.
- Ashton F M, Penner D & Hoffman S, *Weed Sci*, 16, **1968**, 169.
- Alsh G E & Grow T E, *Weed Sci*, 22, **1971**, 64.
- Chang I K & Foy C L, *Weed Sci*, 19, **1971**, 1.
- Kirkwood R C, Dalziel J, Matlib M A & Somerville L, *Pestic Sci*, 3, **1972**, 307.
- Holla B S, Prasanna C S, Poojary Boja, Rao K S & Shridhara K, *Indian J Chem*, 45B, **2006**, 2071.
- Shi W, Qian X, Zhang R & Song G, *J Agric Food Chem*, 49, **2001**, 124.
- Brousse B N, Massa R, Moglioni A G, Alho M M, Accorso N D, Gutkhind G & Moltrasio G Y, *J Chil Chem Soc*, 49, **2004**, 1.
- Ali S & Alm M, *Arch Pharm Res*, 17, **1994**, 131.
- Vereshchagin L I & Kuznestova I N, *Khim Geterotskil Scedin*, **1986**, 932.
- Turk S R, Shipman Ch Jr & Drach J C, *Biochem Pharm*, 35, **1986**, 1539.
- Hirpara S B, Parikh K A, Merja B C & Parekh H H, *Indian J Chem*, 42B, **2003**, 1172.
- Kilcigil G A, Kus C, Altanlar N & Ozbey S, *Turk J Chem*, 29, **2005**, 153.
- Thaker K M & Joshi H S, *Indian J Chem*, 44B, **2005**, 410.
- Gil-Lamagnere C, Roilides E, Mosquera J, Maloukon A & Walsh T J, *Antimicrob Agents Chemother*, 46(7), **2002**, 2234.
- Webb M A & Parsons J H, *Chem Abstr*, 86, **1977**, 117870w.
- Wujec M, Pitucha M, Dobosz M, Kosikowska U & Malm A, *Actapharm*, 54, **2004**, 251.
- Holla B S, Prasanna C S, Poojary Boja, Rao K S, Shridhara K & Bhat U G, *Indian J Chem*, 43B, **2004**, 2170.
- Sudha B S, Shashikanth S & Khanum S A, *Indian J Chem*, 42B, **2003**, 2652.
- Desai N C, Bhavsar A M, Shah M D & Saxena A K, *Indian J Chem*, 47B, **2008**, 579.
- Ugi I, Domling A & Horl W, *Endeavour*, 18, **1994**, 115.
- Mason T, *J Chem Soc Rev*, 26, **1997**, 443.
- Chandrasekhar S, Narsihmulu Ch & Jagadeshwar V, *Syn Lett*, 5, **2002**, 771.