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Synthesis and Antimicrobial Activity of Some 2-[(4-Substituted-Phenyl-3-Chloro-Azetidin-2-One)-5-(2'-Methylamino-4-Phenyl-1', 3'-Thiazolyl-]-1, 3,4-Thiadiazoles

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Abstract

A new 2-[(4-substituted-phenyl-3-chloroazetidin-2-one)-5-(2'-methylamino 4-phenyl-1', 3'-thiazolyl-]-1, 3, 4-thiadiazoles, **5(a-n)** were synthesized from 2-substituted-benzylideneamino-5-[2'-methylamino-4'-phenyl-1',3'-thiazolyl]-1,3, 4-thiadiazole, **4(a-n**) using 2-amino-4phenyl-1, 3-thiazole as a starting material. The synthesised compounds have been screened *in vitro* for their antimicrobial activity against *Bacillus subtilis, Escherichia coli. Klebsiella pneumoniae* and *Streptococcus aureus* bacteria and *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* fungi respectively. Some of the compounds displayed pronounced biological activity.

Keywords: 2-Amino-4-phenyl-1,3-thiazole; Thiadiazole; Arylidene; 2-Azetidinone; Antimicrobial activity

Introduction

2-Azetidinone skeleton is well established as the key pharmacophores of -lactam antibiotics, the most widely employed class of antibacterial agents [1]. The important and structural diversity of biologically active -lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted 2-azetidinones with attendant control of functional group and stereochemistry. Tricycle -lactam antibiotics, generally referred to as trinems, are a new class of synthetic antibacterial agent featuring good resistance of -lactomases and dehydropeptidases [2]. Recently, some other type of biological activity besides the antibacterial [3,4], antifungal [5,6], antitubercular [7], antitumur [8], cholesterol absorption inhibition and enzyme inhibition activity [9] have been reported in compounds containing 2-azetidinone ring. 2-Amino-4-phenyl-1,3-thiazole is among the most important classes of heterocyclic azoles compound with pharmacological and versatile type biological activity [10]. Some 2-amino thiazole derivatives are known for their inhibition of kinurenine-3-dydroxylase and cyclin-dependent kinase enzyme [11]. Thiazole derivative are reported to show a variety of biological activity depending on the substituent, this heterocycles can induce different pharmacological properties such as anti-inflammatory [12], antibacterial [13], antifungal [14]. It has been established that the introduction of 1,3,4-thiadiazole moieties at position-2 of the thiazole ring enhanced

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antimicrobial activity [15]. In the present study in view of the antimicrobial property of the above pharmacophore, some novel thiadiazolo-thiazolyl derivatives that contain 4-substituted-aryl-3-chloro-2-azetidinone moiety were synthesized.

Materials and Methods

Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel "G" coated TLC plates. All instrumental analysis was performed in the Central Drugs Research Institute Lucknow (India). IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer ($_{max}$ in cm^{-1}) and ^{1}HNMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 MHz using TMS as an internal standard. All chemical shifts were reported as (ppm) values. The FAB mass spectra were recorded on a Jeol SX–102 mass spectrometer. Elemental analysis were performed on a Carlo Erba–1108 analyzer. The analytical data of all the compounds were highly satisfactory. For chromatographic purification Merck silica Gel 60 (230-400 Mesh) was used. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallization before use.

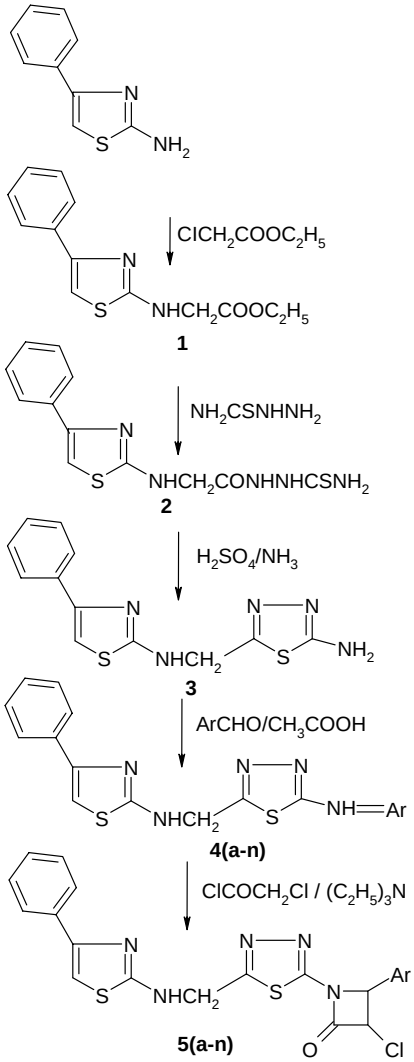
General Procedure for the Synthesis of Compounds

Preparation of 2-(Ethylaminoacetate)-4-Phenyl-1,3-Thiazole (1)

A mixture of 2-amino-4-phenyl-1,3-thiazole (0.35 mole, 61.68 g) and ethyl-chloroacetate (0.35 mole, 42.87 g) with K_2CO_3 (6.168 g) in methanol (300 ml) was kept overnight at room temperature. The reaction mixture was refluxed on a steam bath for about 1 hr. It was cooled, filtered and solvent was distilled off under reduced pressure. The solid thus obtained, dried over $CaCl_2$, recrystallised with ethanol to furnish colourless needles of compound **1**. Yield 74%, m.p. 159-61°C; Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.54, H, 5.34, N, 10.68%; found C, 59.51, H, 3.32, N, 10.63%; IR: 3358 (-NH), 1720 (C=O), 3022, 2846, 1593, 1418, 740 (thiazole with aromatic ring); ^{1}HNMR: 1.90 (t, 3H, J=7Hz, -$COOCH_2\underline{CH_3}$), 4.42 (q, *J=3.5Hz*, 2H, -CH_2), 7.82 (t, *J=2.8Hz*, 1H, -NH), 6.66 (s, 1H, -CH, C-5 of thiazole), 6.86-7.72 (m, 5H, Ar-H); Mass(FAB): 262(M^+), 217, 189, 175, 134, 133, 77, 56, 45.

Preparation of 2-Acetylamino-Thiosemicarbazide-4-Phenyl-1,3-Thiazole (2)

The compound **1** (0.17 mole, 44.54 g) and thiosemicarbezide (0.17 mole, 15.49) in methanol (250 ml) was refluxed on a steam bath for about 10 hr. It was filtered, cooled and purified over the column of silica gel using acetone: methanol (6:4v/v) mixture as an eluant. The eluate was concentrated and the product was recrystallised with ethanol to give compound **2**. Yield 87%, m.p. 131-33°C. Anal. Calcd for $C_{12}H_{13}N_5OS_2$: C, 46.90, H, 4.23, N, 22.80%; found C, 46.83, H, 4.16, N, 22.71%; IR: 3400, 3275 (-NH_2), 3352 (-NH),; ^{1}HNMR: 8.12 - 8.35 (m, 4H, -$NHNHCSNH_2$), 7.80 (t, *J=5.0 Hz*, 1H, -NH), 4.44 (d, *J=5.0Hz*, 2H, -CH_2), 6.62 (s, 1H, -CH, C-5 of thiazole), 6.89-7.76 (m, 5H, Ar-H); Mass(FAB): 307(M^+), 291, 232, 217, 189, 175, 134, 133, 77, 59, 56.



Scheme 1.
Ar = Substituted aryl groups

Table 1. Characterization data of the compounds 4(b-n) and 5(b-n)

Comp	Ar	Yield (%)	M.P. (°C)	Molecular formula	Found% (Calcd)		
					C	H	N
4b	2-ClC_6H_4	74	145-47	$C_{19}H_{14}N_5S_2Cl$	55.33 (55.40)	3.32 (3.40)	16.91 (17.01)
4c	3-ClC_6H_4	75	148-50	$C_{19}H_{14}N_5S_2Cl$	55.34 (55.40)	3.31 (3.40)	16.93 (17.01)
4d	4-ClC_6H_4	72	143-45	$C_{19}H_{14}N_5S_2Cl$	55.32 (55.40)	3.34 (3.40)	16.87 (17.01)
4e	2-BrC_6H_4	81	218-20	$C_{19}H_{14}N_5S_2Br$	49.89 (50.60)	2.98 (3.07)	15.29 (15.35)
4f	3-BrC_6H_4	84	208-10	$C_{19}H_{14}N_5S_2Br$	49.87 (50.60)	2.94 (3.07)	15.28 (15.35)
4g	4-BrC_6H_4	79	227-29	$C_{19}H_{14}N_5S_2Br$	49.86 (50.60)	2.97 (3.07)	15.27 (15.35)
4h	2-$OCH_3C_6H_4$	67	107-09	$C_{20}H_{17}N_5OS_2$	58.86 (58.96)	4.13 (4.17)	17.11 (17.19)
4i	3-$OCH_3C_6H_4$	68	96-98	$C_{20}H_{17}N_5OS_2$	58.89 (58.96)	4.12 (4.17)	17.10 (17.19)
4j	4-$OCH_3C_6H_4$	65	176-78	$C_{20}H_{17}N_5OS_2$	58.87 (58.96)	4.11 (4.17)	17.13 (17.19)
4k	2-$NO_2C_6H_4$	79	168-70	$C_{19}H_{14}N_6O_2S_2$	53.97 (54.02)	3.26 (3.31)	19.84 (19.90)
4l	3-$NO_2C_6H_4$	76	176-78	$C_{19}H_{14}N_6O_2S_2$	53.96 (54.02)	3.24 (3.31)	19.82 (19.90)
4m	4-$NO_2C_6H_4$	78	173-75	$C_{19}H_{14}N_6O_2S_2$	53.92 (54.02)	3.29 (3.31)	19.79 (19.90)
4n	4,4-$(CH_3)_2NC_6H_4$	91	123-25	$C_{21}H_{20}N_6S_2$	59.89 (60.00)	4.69 (4.76)	19.93 (20.00)
5b	2-ClC_6H_4	66	188-90	$C_{21}H_{15}N_5OS_2Cl_2$	51.69 (51.74)	2.93 (3.06)	14.29 (14.37)
5c	3-ClC_6H_4	54	179-81	$C_{21}H_{15}N_5OS_2Cl_2$	51.68 (51.74)	2.91 (3.06)	14.26 (14.37)
5d	4-ClC_6H_4	58	183-85	$C_{21}H_{15}N_5OS_2Cl_2$	51.67 (51.74)	2.94 (3.06)	14.27 (14.37)
5e	2-BrC_6H_4	65	167-69	$C_{21}H_{15}N_5OS_2ClBr$	47.29 (47.33)	2.78 (2.81)	13.09 (13.14)
5f	3-BrC_6H_4	68	141-43	$C_{21}H_{15}N_5OS_2ClBr$	47.30 (47.33)	2.77 (2.81)	13.08 (13.14)
5g	4-BrC_6H_4	70	149-51	$C_{21}H_{15}N_5OS_2ClBr$	47.31 (47.33)	2.80 (2.81)	13.10 (13.14)
5h	2-$OCH_3C_6H_4$	59	95-97	$C_{22}H_{18}N_5O_2S_2Cl$	56.79 (56.82)	3.58 (3.62)	11.67 (11.69)
5i	3-$OCH_3C_6H_4$	60	80-82	$C_{22}H_{18}N_5O_2S_2Cl$	56.80 (56.82)	3.60 (3.62)	11.66 (11.69)
5j	4-$OCH_3C_6H_4$	61	76-78	$C_{22}H_{18}N_5O_2S_2Cl$	56.78 (56.82)	3.59 (3.62)	11.64 (11.69)
5k	2-$NO_2C_6H_4$	67	118-20	$C_{21}H_{15}N_6O_3S_2Cl$	50.49 (50.55)	2.91 (3.00)	16.82 (16.85)
5l	3-$NO_2C_6H_4$	65	111-13	$C_{21}H_{15}N_6O_3S_2Cl$	50.51 (50.55)	2.93 (3.00)	16.84 (16.85)
5m	4-$NO_2C_6H_4$	70	114-16	$C_{21}H_{15}N_6O_3S_2Cl$	50.50 (50.55)	2.95 (3.00)	16.81 (16.85)
5n	4, 4-$(CH_3)_2NC_6H_4$	82	158-60	$C_{18}H_{17}N_4SCl$	55.62 (55.65)	4.19 (4.22)	16.87 (16.91)

Preparation of 2-Amino-[5-(2'-Methylamino - 4'-Phenyl-1',3'-Thiazolyl)]-1,3,4-Thiadiazole (3)

The equimolar solution of compound **2** (0.125 mole, 38.37 g) and con. H_2SO_4 (0.125 mole, 12.25 g, AR grade) in methanol (150 ml) was kept overnight at room temperature. It was refluxed on a steam bath for about 8 hr. After cooling the reaction mixture, it was neutralized with concentrated liq.ammonia and filtered. The solvent was removed *in vacvo*, solid thus obtained was dried and purified over the column of silica gel using chloroform: methanol (5:5 v/v) mixture as eluant. The eluate was concentrated and the product was recrystallised from ethanol to give compound **3**. Yield, 90%, m.p. 162-64°C. Anal. Calcd. for $C_{12}H_{11}N_5S_2$: C, 49.82, H, 3.80, N, 24.22%, found: C, 49.76, H, 3.72, N, 24.16%; IR: 3410, 3268 (-NH_2), 3356 (-NH), 2970 (-CH_2), 1627 (-N=C-S); ^{1}HNMR: 4.81 (s, 1H, -NH_2), 7.94 (t, *J=5.0 Hz*, 1H, -NH), 4.41 (d, *J=5.0 Hz*, 2H, -CH_2), 6.68 (s, 1H, -CH of thiazole), 6.95-7.84 (m, 5H, Ar-H). Mass(FAB): 289(M^+), 273, 215, 189, 175, 134, 133, 77, 58, 56.

Preparation of 2-Substituted-Benzylidene-Imino-5{2'methylamino-(4'-Phenyl-1',3'-Thiazolyl }-1,3,4-Thiadiazole] (4a-N)

The equimolar solution of compound **3** (0.0085 mole, 2.450 g) and benzaldehyde (0.0085 mole, 0.902 g) in methanol (50 ml) with 4-5 drops glacial acetic acid was refluxed on a water bath for about 2 hr. The solvent was distilled off under reduced pressure and the solid thus obtained was purified over the column of silica gel using chloroform: methanol (6:4 v/v) mixture as eluent.

Table 2. Antibacterial activity of the compounds **4(a-n)** and **5(a-n)** against various bacteria at different concentrations (ppm)

Comp.	*B. subtilis*		*E. coli*		*K. pneumoniae*		*S. aureus*	
	50	100	50	100	50	100	50	100
4a	-	-	-	-	-	-	-	-
4b	+	+	-	-	+	+	-	-
4c	+	+		-	+	+	-	-
4d	-	-	+	+ +	-	-	+	+ +
4e	+	+	+	+ +	-	+	-	+
4f	+	++	-	-	+	+ +	-	+
4g	+	-	+	++	-	-	-	+
4h	+	+ +	+	+ +	-	-	-	++
4i	-	+	-	+	+	+ +	+	+
4j	-	+	-	+	+	+ +	+	+
4k	+	+	-	-	+	+	-	-
4l	-	+	-	-	-	+	+	+
4m	+	+	-	+	+	+	-	+
4n	-	-	+	+	-	+	-	+
5a	-	+	-	-	-	-	-	+
5b	+ +	+ +	+	+ +	+ +	+ +	+ +	+ +
5c	+	+	+ +	+ +	+	+ +	+ +	+ +
5d	+	+	+	+ +	+ +	+ +	+ + +	+ + +
5e	+ +	+ +	+	+	+ +	+ +	+ +	+ +
5f	+ +	+ +	+ +	+ +	+ + +	+ + +	+ +	+ +
5g	+	+	+ +	+ +	+ + +	+ + +	+ +	+ +
5h	+	+	-	+	+ +	+ +	+	+
5i	+	+	+	+ +	+ +	+ +	+	+ +
5j	-	+	-	+	+	+	+	+ +
5k	+	+	+	+ +	+	+	-	-
5l	+	+	+	+	+	+	-	+
5m	+	+	-	+	+	+	-	+
5n	+	+	+	+	+ +	+ +	+	+ +
SM	+ + +	+ + + +	+ + +	+ + + +	+ + +	+ + + +	+ + +	+ + + +

SM = Streptomycin, inhibition diameter in mm (-) < 6, (+) 6-10, (++) 10-16, (+++) 16-25, (++++) 25-30.

The elute was concentrated and the product was recrystallised with ethanol to give crystals of compound **4a.** Yield 75%, m.p. 176-78°C Anal. Calcd. for $C_{19}H_{15}N_5S_2$: C, 60.47, H, 3.97, N, 18.56%, found: C, 60.36, H, 3.86, N, 18.42%; IR: 3357 (-NH), 2960 (-CH_2), 1546 (-N=CH); ^{1}HNMR: 6.92-7.88 (m, 10 H, Ar-H), 4.91 (s, 1H, -N=CH), 4.46 *(d, J = 5Hz, 2H, -CH_2)*, 7.93 (t, *J = 5.0Hz*, 1H, -NH), 6.63 (s, 1H, -CH, C-5 of thiazole). Mass (FAB); 289(M^+), 273, 215, 189, 175, 134, 133, 101, 77, 56.

Other compound **4(b-n)** were synthesized in the similar manner using compound **3** and various selected aromatic aldehydes. Characterization data are presented in Table 1.

Preparation of 2-[(4-Substituted-Phenyl-3-Chloro-Azetidin-2-One)-5-(2'-Methylamino-4-Phenyl-1',3'-Thiazolyl-]-1,3,4-Thiadiazoles 5(A-N)

The compound **4a** (0.004 mole, 1.508g) and triethylamine (0.004 mole, 0.40g) in methanol (20 ml) with chloroacetyl chloride (0.004 mole, 0.45g) was first stirred for about 2 hr. followed by refuxing on a steam

Table 3. Antifungal activity of the compounds **4(a-n)** and **5(a-n)** against various fungi at different concentrations (ppm)

Comp.	*A. niger*		*A. flavus*		*F. oxisporium*		*T. viride*	
	50	100	50	100	50	100	50	100
4a	-	+	-	-	+	+	-	+
4b	-	-	+	+	-	-	+	+
4c	+	+	-	-	+	+	-	+
4d	-	-	+	+	-	-	+	+
4e	+	+	+	+	+	+	+	+
4f	-	+	+	+ +	+	+	+ +	+ +
4g	+ +	+ +	+	+	+	+	-	-
4h	-	+	-	-	-	-	-	-
4i	-	+	-	-	+	+	-	+
4j	-	-	-	-	+	+	-	+
4k	+	+	-	+	-	-	-	+
4l	+	+	-	+	-	+	+	+
4m	-	+	+	+	-	-	-	-
4n	+	+	+	+	+	++	+	+
5a	+	+ +	+	+	+	+	+	+ +
5b	-	+	+	+	+	+	+ +	+ +
5c	+	+	+	+ +	+ +	+ +	-	+
5d	+	+ +	-	+	-	+	+	+
5e	++	+ +	+	+	+	++	++	++
5f	+	+ +	++	+++	+	++	++	++
5g	++	++	+	++	++	+ + +	+ +	+ +
5h	+	+	+ +	+ +	+ +	+ +	+ +	+ + +
5i	+	+ +	+ +	+ +	+	+	+	+
5j	+	+ +	+ +	+ +	-	-	-	-
5k	+	+ +	+ +	+ +	-	+	-	+
5l	+ +	+ +	+	+	-	+	+	+
5m	+ +	+ +	+	+	+	+	+	+
5n	+	+ +	+	+	-	+	+	+ +
GF	+ + +	+ + + +	+ + +	+ + + +	+ + +	+ + + +	+ + +	+ + + +

GF = Griseofulvin, inhibition diameter in mm (-) < 4, (+) 4-12, (+ +) 12-18, (+ + +) 18-27, (+ + + +) 27-30.

bath for about 9 hr. It was cooled, filtered and passed through a column of silica gel using chloroform: methanol (7:3 v/v) mixture as eluant. The eluate was concentrated and dried. The product was recrystallised from etharol to give compound **5a.** Yield 70%, m.p. 131-32°C. Anal. caled. for $C_{21}H_{16}N_5OS_2Cl$: C, 55.56, H, 3.52, N 15.43% found: C,55.48, H, 3.50, N 15.39%; IR: 3353(-NH), 2963(-CH_2), 1775 (>C=O); ^{1}HNMR 4.49(d, *J*=5Hz, 2H,-CH_2), 7.96(t, *J*=5Hz,-NH), 6.67(s, 1H, C-H, C-5 of thiazole), 6.90-7.82(m, 10H Ar-H), 5.16(d *J*=5. Hz, 1H,-CHCl), 4.18 (d *J*=5Hz, 1H, -NCHAr); Mass(FAB): 453(M^+) 425, 273, 215, 189, 175, 152, 134, 133, 77, 56.

Other compounds **5(b-n)** were synthesized in the similar manner using compounds **4(b-n)**. Characterization data are presented in Table 1.

Antimicrobial Activity

Antibacterial Activity

All the compounds were evaluated *in vitro* for antibacterial activity by using filter paper disc method against different strains of bacteria *viz*. *B. subtilis, E. coli,*

S. aureus and *K. pneumoniae*. All the compounds along with standard antibacterial Streptomycin were used at 50 and 100 ppm concentrations. Results are present in Table 2.

Antifungal Activity

All the compounds were assayed *in vitro* for antifungal activity against *A. niger, A. flavus, F. oxisporium and T. viride* fungi employing the filter paper disc method by measuring inhibition zone in mm. All the tested compounds along with standard fungicide Griseofulvin were used at 50 and 100 ppm concentrations. Results are presented in Table 3.

Results and Discussion

Reaction of ethylchloroacetate with 2-amino-4-phenyl-1,3-thiazole yieled 2-(ethyaminoacetate)-4-phenyl-1,3-thiazole, **(1)** followed by thiosemicarbazide resulted in the formation of 2-(acetylamino-thiosemicarbazide-4-phenyl-1,3-thiazole, **(2)**. The compound **(2)** on dehydrative annulation by mineral acid afforded the thiadiazole **(3)** which on condensation with various substituted aromatic aldehydes furnished 2 Substituted-benzylidene-amino-5-[2'-methyl-amino 4'-phenyl-1',3'-thiazolyl]-1,3,4-thiadiazoles, **4(a-n**). The compounds **4(a-n)** on reaction with chloroacetyl chloride in the presence of triethyl amine afforded 2-[(4-Substituted-phenyl-3-chloro-azetidin-2-one)-5-(2'-methylamino-4-phenyl-1', 3'-thiazolyl-]-1,3,4-thiadiazoles, **5(a-n**). The structures of new compounds were confirmed by elemental analysis IR, ^{1}HNMR and Mass spectral data.

All the synthesized compounds **4(a-n)** and **5(a-n)** have been screened *in vitro* for their antibacterial activity against *B. subtilis* (Bs), *E. coli* (Ec), *S. aureus* (Sa) and *K. pneumoniae* (Kp) at two concentrations (50 and 100 ppm) and antifungal activity against *A. niger* (An), *A. flavus* (Af), *F. oxisporium* (Fo) and *T. viride* (Tv) at two concentrations (50 and 100 ppm). Standard antibacterial Streptomycin and fungicide Griseofulvin were also screened under the similar conditions for comparison. The following compounds were found active against the tested becteria: 4d(Ec, Sa), 4f(Bs, Kp), 4g(Ec), 4h(Bs, Ec, Sa), 4i, 4j(Kp), 5b, 5c, 5d, 5e, 5f, 5g(Bs, Ec, Kp, Sa), 5i(Ec, Kp, Sa), 5h(Kp), 5k (Ec), 5n(Kp, Sa) and fungi: 5f(Af, Tv), 5g(An), 4n(Fo), 5b(Tv), 5c(Af, Fo), 5d(An), 5e, 5f, 5g(An, Af, Fo, Tv), 5i(Af, Fo), 5j(An, Af), 5h(Fo, Tv), 5k(An, Af), 5l, 3m, 5n(An). On the basis of structural activity relationship it has been observed that among the substituents present on the phenyl ring, halo derivatives were found to be highly active against in the series. Further study reveals that bromo derivatives are highly active.

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