Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2013, 5(2):75-81
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antimicrobial activity of some novel 4-oxo-1,3-thiazolidines tethered to phthalimido moiety

A. Cendil Kumar[1], R. Vidhya[2], Rishikesh Vilas Antre[3] and V. Sivajothi[4]

[1]Acharya & B. M. Reddy College of Pharmacy, Bangalore, Karnataka, India
[2]Mandya Institute of Medical Sciences, Mandya, Karnataka, India
[3]Medicinal Chemistry Research Laboratory, JSPM`s Charak College of Pharmacy & Research, Pune, Maharashtra, India
[4]The Oxford College of Pharmacy, Bangalore, Karnataka, India

---

ABSTRACT

In present research work, phthalimide is esterified with chloro ethylacetate followed by amination using hydrazine hydrate. Thus formed phthalimido acetohydrazide (2) was condensed with various substituted aldehydes to yield Arylidene phthalimido acetohydazides (Schiff bases) (3a-3j) which on cycloaddition with thioglycollic acid yield arylidene 4-oxo-1,3-thiazolidine phthalimido acetohydrazides (4a-4j). Structures of all the synthesized compounds were identified and characterized by melting point determination, TLC, FT-IR, ^{1}H NMR and Mass spectral analysis. Compounds (3a-3j) & (4a-4j) were screened for their antimicrobial activity viz., antibacterial and antifungal activity using Ciprofloxacin and Ampicillin as standard drugs for antibacterial activity; Fluconazole and Amphotericin B as standard for antifungal activity.

Keywords: 4-oxo-1,3-thiazolidine, Schiff base, antimicrobial activity.

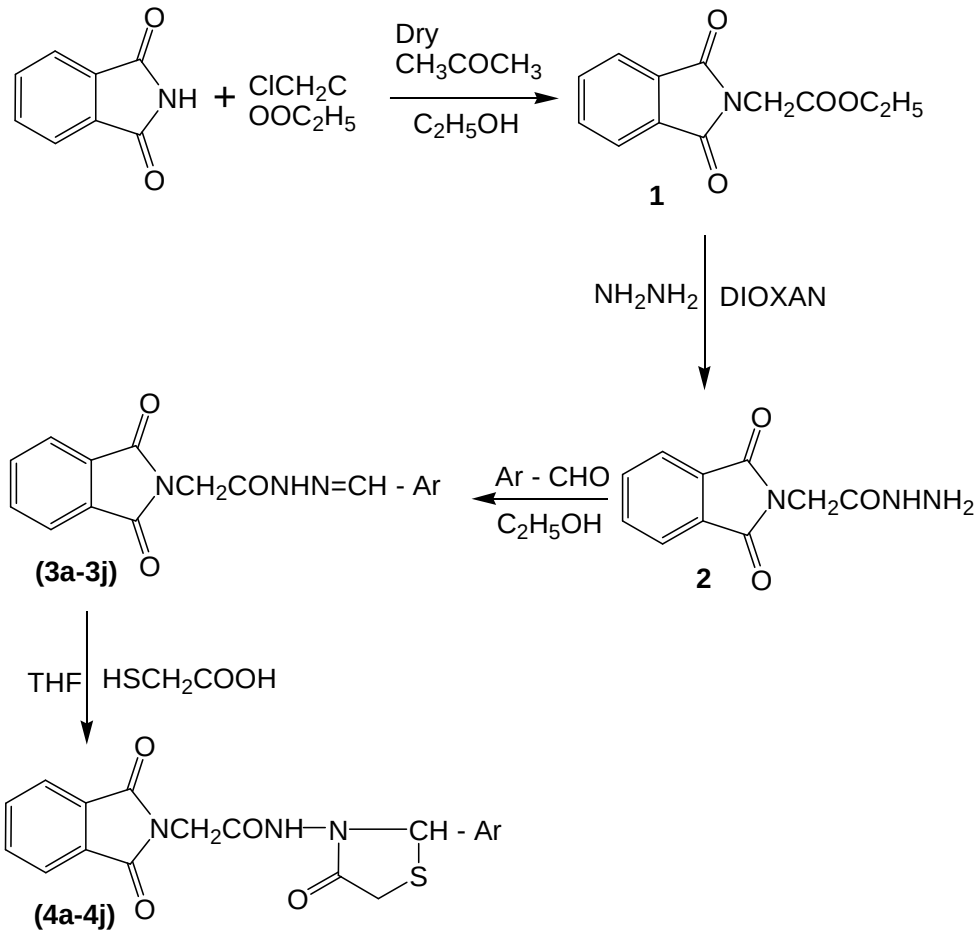
INTRODUCTION

Thiazolidines particularly thiazolidine-2,4-dione and 2-thioxothiazolidin-4-one acquired importance because of their pharmacological activities such as antidiabetic [1,2], antimicrobial [3], antimalarials [4], antiviral [5], anticonvulsant [6], anti-inflammatory [7] and also as thyroid hormone receptor antagonist [8]. Additionally, these derivatives are popular as small molecule inhibitors of numerous targets such as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [9], HIV-1 [10], aldose reductase [11], tyrosinase [12]. Spiro(indole-thiazolidines) are one of the most studied 3-spiroindole derivatives with broad spectrum of pharmacological activities like antimicrobial [13], antifungal [14], antileukemic [15], and anticonvulsant [16] activities.

In contrast, thiazolidine compounds have emerged as antineoplastic agents with broad spectrum of antitumour activity against human cancer cells [17,18]. They are agonists of peroxisome proliferator-activated receptor c (PPARc), which is expressed in many human tumours, including lung, breast, colon, prostate and bladder [19], they modulate the proliferation and apoptosis of many cancer cell types. Arylidene-thiazolidine-2,4-diones were also synthesised and screened as anti-inflammatory compounds, showing considerable biological efficacy, when compared to rosiglitazone, agonist of proliferator-activated receptor and used as a reference drug [20-22].

1,3-Thiazolidines are the new class of antimicrobial agents with broad spectrum of activity against Grampositive pathogens including Staphylococci, Streptococci, and Enterococci [23]. The presence of arylidene moiety in different positions of the thiazolidine ring enhanced the antimicrobial activity [24,25]. Organic compounds bearing thiazoles of different pharmacodynamic nuclei were found to possess potent antibacterial [26] and antifungal [27] activities.

Scheme: Synthesis scheme for compounds (4a-4j)



MATERIALS AND METHODS

All the reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Melting points are uncorrected, determined by open capillary on Thermonik precision apparatus (Model-C-PMP-2, Mumbai, India). FT-IR spectra of the compounds were recorded on a Tensor 27 spectrophotometer, Bruker optik (Germany) using KBr method. ^{1}H NMR spectra were recorded on a Bruker spectrometer using TMS as internal reference (chemical shift represented in δ ppm). Mass spectra were recorded on LC–MS QP5050A System (benchtop quadrupole mass spectrophotometer). Purity of the compounds was monitored on (10x10cm) precoated silica gel GF $_{254}$ TLC plates (E.Merck Darmstadt, Germany).

Synthesis of Phthalimido Ethylacetate (1)

Phthalimide (0.05 mol, 6 g) was taken in 500 ml round bottom flask added chloroethyl acetate (0.05 mol, 7.6 ml), dry acetone (60 ml) and ethanol (40 ml). The mixture was refluxed for about 7-8 hours in water bath, cooled and poured into ice-cold water; phthalimido ethylacetate precipitated out, was filtered and dried in oven at 125 ˚C.

Synthesis of Phthalimido Acetohydrazide (2)

Phthalimido ethylacetate (0.05 mol, 11 g) was taken in round bottom flask added hydrazine hydrate (0.05 mol, 1.6 ml), 1,4-dioxan (50 ml) and refluxed for about 5 hrs, the temperature maintained at 60-70˚C. The Soft solid mass appeared was filtered, dried and recrystalized with ethanol, Phthalimido acetohydrazide was obtained as a white crystalline powder.

Synthesis of Arylidene Phthalimido Acetohydrazide (3a-3j)

Phthalimido acetohydrazide (0.05 mol, 12.95 g) was taken in round bottom flask along with 30 ml ethanol. The aromatic aldehyde was dissolved in 30 ml ethanol and added slowly for about 20 min with vigorous stirring, maintaining the temperature at 40-50˚C. Added four drops of glacial acetic acid and allowed to reflux for further 3 hrs. Poured the mixture into 250 ml ice-cold water and stirred. Precipitate obtained was filtered, dried and recrystalized from ethanol, yellow colored crystalline product formed.

Synthesis of Arylidene 4-oxo-1, 3-thiazolidine phthalimido acetohydrazide (4a-4j)

Arylidene phthalimido acetohydrazide (0.01 mol) was taken in round bottom flask, added thioglycollic acid (0.01 mol), a pinch of anhydrous zinc chloride and THF (60 ml). The mixture was refluxed for about 10-11 hrs in a heating mantle and allowed to cool. Filtered, product obtained was dried and recrystallized from chloroform. The product formed as a White crystalline powder.

Table 1: Physical data of synthesized compounds

Compound	Ar	Molecular Formula	Molecular Weight	M.P. (°C)	% Yield
1	-	$C_{12}H_{11}O_4N$	233	180˚C	67%
2	-	$C_{10}H_9O_3N_3$	259	291˚C	87%
3a	-H	$C_{17}H_{13}N_3O_3$	307	252˚C	53%
3b	2-OH	$C_{19}H_{15}N_3O_4$	323	182˚C	26%
3c	2-NO_2	$C_{17}H_{13}N_4O_5$	353	226˚C	35%
3d	2,4-dichloro	$C_{17}H_{11}N_3O_3Cl_2$	375	248˚C	46%
3e	3,4,5-trimethoxy	$C_{20}H_{18}N_3O_6$	396	268˚C	44%
3f	4-chloro	$C_{17}H_{12}N_3O_3Cl$	341	222˚C	45%
3g	3-methoxy, 4-hydroxy	$C_{18}H_{15}N_3O_5$	353	246˚C	46%
3h	4-N,N-dimethylamine	$C_{19}H_{18}N_4O_3$	350	288˚C	58%
3i	3,4-dimethoxy	$C_{19}H_{17}N_3O_5$	373	224˚C	37%
3j	3-methoxy	$C_{18}H_{15}N_3O_4$	337	204˚C	43%
4a	-H	$C_{19}H_{15}N_3O_4$	381	198˚C	60%
4b	2-OH	$C_{19}H_{15}N_3O_5S$	397	202˚C	80%
4c	2-NO_2	$C_{19}H_{14}N_4O_6S$	426	190˚C	79%
4d	2,4-dichloro	$C_{19}H_{13}N_3O_4SCl_2$	450	224˚C	80%
4e	3,4,5-trimethoxy	$C_{22}H_{21}N_3O_7S$	471	188˚C	70%
4f	4-chloro	$C_{19}H_{12}N_3O_4ClS$	415	194˚C	70%
4g	3-methoxy, 4-hydroxy	$C_{19}H_{17}N_3O_6S$	427	166˚C	78%
4h	4-N,N-dimethylamine	$C_{21}H_{20}N_4O_4S$	424	230˚C	69 %
4i	3,4-dimethoxy	$C_{21}H_{29}N_3O_6S$	442	178˚C	72 %
4j	3-methoxy	$C_{20}H_{17}N_3O_5S$	411	162˚C	87 %

Table 2: Spectral data of synthesized compounds

Compound	IR (KBr) cm^{-1}	^1H NMR	MS m/z
1	2862 (-CH_2-C str), 1622 (-CO-N-CO), 1276 (-N-CH_2-), 1210 (O=C-$COOC_2H_5$)	7.51-7.8 (4H (Ar-H)), 3.1 (2H, N-CH_2), 2.7 (5H, C_2H_5)	233 (M^+), 234 (M^{+1}), 235 (M^{+2})
2	3163 (NH-NH_2), 2858 (-CH_2-C), 1658 (CONH), 1521, 1230	7.4-7.6 (4H (Ar-H)), 2.9 (2H, N-CH_2), 9.75 (3H, $NHNH_2$)	259 (M^+), 260 (M^{+1})
3a	3183 (-NH-str), 2887 (CH_2-C), 1664 (CONH), 1600 (-CO-N-CO), 1623 (CH=N), 1210 (-N-CH_2-)	11.5 (1H, N=CH), 8.7(1H, CONH), 7.51-7.8 (9H (Ar-H)), 2.5 (2H -CO-CH_2-)	307 (M^+), 308 (M^{+1}), 309 (M^{+2})
3b	3200 (C-OH), 3186 (-NH-str), 2880 (CH_2-C), 1674 (CONH), 1620 (-CO-N-CO), 1629 (CH=N), 1220 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (8H (Ar-H)), 4.2 (1H, OH), 2.3 (2H -CO-CH_2-)	323 (M^+), 334 (M^{+1}), 335 (M^{+2})
3c	3180 (-NH-str), 2870 (CH_2-C), 1654 (CONH), 1610 (-CO-N-CO), 1640 (CH=N), 1334 (NO_2), 1205 (-N-CH_2-)	11.2 (1H, N=CH), 8.7 (1H, CONH), 7.40-7.85 (8H (Ar-H)), 2.2 (2H -CO-CH_2-)	353 (M^+), 354 (M^{+1})
3d	3170 (-NH-str), 2870 (CH_2-C), 1623 (CH=N), 1210 (-N-CH_2-), 1100 (Cl)	11.2 (1H, N=CH), 8.8 (1H, CONH), 7.50-7.70 (7H (Ar-H)), 2.2 (2H -CO-CH_2-)	374 (M^{-1}), 375 (M^+), 376 (M^{+1})
3e	3180 (-NH-str), 2880 (CH_2-C), 1660 (CONH), 1600 (-CO-N-CO), 1620 (CH=N), 1210 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.5-7.8 (6H (Ar-H)), 2.3 (2H -CO-CH_2-), 2.1 (9H, OCH_3)	396 (M^+), 397 (M^{+1})
3f	3183 (-NH-str), 2887 (CH_2-C), 1664 (CONH), 1600 (-CO-N-CO), 1623 (CH=N), 1210 (-N-CH_2-), 1093 (Cl)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (8H (Ar-H)), 2.3 (2H -CO-CH_2-)	341 (M^+), 342 (M^{+1}), 343 (M^{+2}), 344 (M^{+3})
3g	3342 (OH), 3173 (-NH-str), 2887 (CH_2-C), 1694 (CONH), 1630 (-CO-N-CO), 1643 (CH=N), 1220 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (7H (Ar-H)), 4.2 (1H, OH) 2.3 (2H -CO-CH_2-), 2.2 (1H, OCH_3)	353 (M^+), 354 (M^{+1}), 355 (M^{+2})
3h	3164 (-N-$(CH_3)_2$), 3183 (-NH-str), 2887 (CH_2-C), 1664 (CONH), 1600 (-CO-N-CO), 1623 (CH=N), 1210 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (8H (Ar-H)), 2.3 (2H -CO-CH_2-), 2.1 (6H, N-$(CH_3)_2$)	350 (M^+), 351 (M^{+1}), 552 (M^{+2})
3i	2887 (CH_2-C), 1668 (CONH), 1615 (-CO-N-CO), 1635 (CH=N), 1250 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (7H (Ar-H)), 2.3 (2H -CO-CH_2-), 2.2 (6H, OCH_3)	373 (M^+), 374 (M^{+1})
3j	3180 (-NH-str), 2880 (CH_2-C), 1660 (CONH), 1615 (-CO-N-CO), 1630 (CH=N), 1225 (-N-CH_2-)	11.3 (1H, N=CH), 8.8 (1H, CONH), 7.51-7.89 (7H (Ar-H)), 2.3 (2H -CO-CH_2-), 2.2 (3H, OCH_3)	337 (M^+), 338 (M^{+1})
4a	3360 (-NH- str), 2879 (-N-CH_2-S), 1720 (C=O cyclic), 1600 (-CO-N-CO), 1685 (CONH), 1552 (-C=C-), 690 (-CH_2-S-CH)	8.6 (1H, CONH), 7.1-7.8 (9H (Ar-H)), 6.1(1H (N-CH-Ar)), 3.6-3.7(2H (S-CH_2)), 3.8-3.9(2H N-CH_2), 1.2 (2H CO-CH_2)	381 (M^+), 382 (M^{+1}), 384 (M^{+2})
4b	3200 (C-OH), 2868(-N-CH_2-S), 1732 (C=O cyclic), 1604(-CO-N-CO), 1642(CONH), 1542(-C=C-), 678(-CH_2-S-CH)	8.5 (1H, CONH), 7.3-7.9 (8H (Ar-H)), 6.2 (1H (N-CH-Ar)), 3.4-3.6 (2H (S-CH_2)), 3.6-3.8 (2H N-CH_2), 1.1 (2H CO-CH_2)	397 (M^+), 398 (M^{+1})
4c	2887(-N-CH_2-S), 1682 (C=O cyclic), 1600(-CO-N-CO), 1558(-C=C-), 1328(NO_2-C), 684(-CH_2-S-CH)	8.7 (1H, CONH), 7.2-7.8 (8H (Ar-H)), 6.2 (1H (N-CH-Ar)), 3.6-3.7 (2H (S-CH_2)), 3.4-3.8 (2H N-CH_2), 1.1 (2H CO-CH_2)	426 (M^+), 427 (M^{+1}), 428 (M^{+2})
4d	2923(-N-CH_2-S), 1680(C=O), 1616(-CO-N-CO), 1220(-NCH_2-),1103(-C-C-Cl), 692(-CH_2-S-CH)	8.7 (1H, CONH), 7.3-7.7 (7H (Ar-H)), 6.2 (1H (N-CH-Ar)), 3.5-3.8 (2H (S-CH_2)), 3.6-3.8 (2H N-CH_2), 1.3 (2H CO-CH_2)	450 (M^+), 451 (M^{+1})
4e	2839(-N-CH_2-S), 1710 (C=O cyclic), 1619(-CO-N-CO), 1579(-C=C-),1233(-NCH_2-), 690(-CH_2-S-CH)	8.6 (1H, CONH), 7.1-7.8 (6H (Ar-H)), 6.1 (1H (N-CH-Ar)), 3.6-3.7 (2H (S-CH_2)), 3.8-3.9(2H N-CH_2), 2.1 (9H, OCH_3), 1.2 (2H CO-CH_2)	471 (M^+), 472 (M^{+1})
4f	2877(-N-CH_2-S), 1718 (C=O cyclic), 1604(-CO-N-CO), 1544(-C=C-), 1093(Cl-C), 688(-CH_2-S-CH)	8.5 (1H, CONH), 7.2-7.8 (8H (Ar-H)), 6.3 (1H (N-CH-Ar)), 3.5-3.9 (2H (S-CH_2)), 3.9-3.95 (2H N-CH_2), 1.3 (2H CO-CH_2)	415 (M^+), 416 (M^{+1}), 417 (M^{+2})
4g	3342(OH-C), 2879(-N-CH_2-S), 1720(C=O cyclic), 1600(-CO-N-CO), 1685(CONH), 1546(-C=C-), 688(-CH_2-S-CH)	8.4 (1H, CONH), 7.1-7.8 (7H (Ar-H)), 6.1 (1H (N-CH-Ar)), 4.1 (1H, OH), 3.6-3.7 (2H (S-CH_2)), 3.7-3.9(2H N-CH_2), 2.9 (3H, OCH_3), 1.3 (2H CO-CH_2)	427 (M^+), 428 (M^{+1}), 429 (M^{+2})
4h	3164(-N-$(CH_3)_2$), 2896(-N-CH_2-S), 1600(-CO-N-CO), 1660(CONH), 1554(-C=C-), 688(-CH_2-S-CH)	8.5 (1H, CONH), 7.1-7.8 (8H (Ar-H)), 6.1 (1H (N-CH-Ar)), 3.6-3.7 (2H (S-CH_2)), 3.8-3.9 (2H N-CH_2), 2.8 (6H, (N-$CH_3)_2$), 1.2 (2H CO-CH_2)	424 (M^+), 425 (M^{+1})
4i	2880(-N-CH_2-S), 1720(C=O), 1610(-CO-N-CO), 1480(-C=C-), 692(-CH_2-S-CH)	8.3 (1H, CONH), 7.1-7.8 (7H (Ar-H)), 6.1 (1H (N-CH-Ar)), 3.6-3.7 (2H (S-CH_2)), 3.8-3.9 (2H N-CH_2), 2.9 (6H, OCH_3), 1.2 (2H CO-CH_2)	442 (M^+), 443 (M^{+1})
4j	2935(-N-CH_2-S), 1770 (C=O), 1622(-CONH), 1604(-CO-N-CO), 1573(-C=C-),1245(-NCH_2-),692(-CH_2-S-CH)	8.5 (1H, CONH), 7.2-7.9 (8H (Ar-H)), 6.2 (1H (N-CH-Ar)), 3.5-3.7 (2H (S-CH_2)), 3.8-3.95 (2H N-CH_2), 2.7 (3H, OCH_3), 1.2 (2H CO-CH_2)	411 (M^+), 412 (M^{+1})

Table 3: Antibacterial activity of newly synthesized compounds (3a-3j) and (4a-4j)

Compound	Zone of Inhibition (in mm)									
	Gram Positive				Gram Negative					
	B. subtilis		*S. aureus*		*Shigella*		*E. coli*		*P. aeruginosa*	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
3a	06	08	09	12	02	04	04	04	05	08
3b	09	10	07	08	03	05	04	06	09	10
3c	05	06	04	06	NI	NI	03	05	06	07
3d	11	13	10	13	05	06	05	07	07	09
3e	08	12	10	11	05	08	07	09	09	11
3f	09	11	07	09	06	07	08	09	06	08
3g	11	12	09	11	12	13	10	11	09	10
3h	06	07	07	08	06	07	06	07	09	10
3i	02	03	02	04	03	03	04	04	04	05
3j	05	07	04	05	02	05	02	03	04	05
4a	06	08	05	07	NI	03	03	03	04	07
4b	08	08	08	10	03	05	04	05	07	09
4c	09	10	08	11	03	05	06	06	09	10
4d	08	11	09	10	05	08	06	07	09	12
4e	05	05	06	08	04	04	04	06	05	06
4f	09	12	07	10	05	07	05	05	08	10
4g	10	14	09	11	04	06	07	08	08	09
4h	07	08	09	12	03	03	06	08	09	11
4i	03	05	02	04	NI	NI	NI	03	03	05
4j	06	08	05	05	02	04	03	03	05	08
Ciprofloxacin	12	15	13	16	09	10	12	14	11	13
Ampicillin	08	10	07	10	06	07	08	11	07	09
Control	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

NI: No Inhibition

Table 4: Antifungal activity of newly synthesized compounds (3a-3j) and (4a-4j)

Compound	Zone of inhibition (in mm)			
	A. niger		*C. albicans*	
	50 µg	100 µg	50 µg	100 µg
3a	4	5	3	3
3b	3	3	NI	NI
3c	NI	NI	NI	NI
3d	5	5	4	6
3e	4	6	4	5
3f	3	5	4	5
3g	4	5	4	5
3h	5	6	6	6
3i	2	3	1	3
3j	NI	NI	NI	NI
4a	NI	2	NI	NI
4b	3	3	NI	3
4c	5	6	3	4
4d	4	4	3	3
4e	NI	NI	NI	2
4f	3	4	5	5
4g	4	6	4	6
4h	5	6	5	6
4i	NI	3	NI	3
4j	NI	NI	NI	NI
Amphotericin B	5	7	7	8
Clotrimazole	6	8	7	9
Control	NI	NI	NI	NI

NI: No Inhibition

RESULTS AND DISCUSSION

The twenty compounds synthesized were screened for antimicrobial activity studies viz., antibacterial and antifungal activities, at concentrations of 50µg/ml and 100µg/ml using DMSO as a control against *B. subtilis, Shigella,*

S.aureus, E. coli and P. aeruginosa (bacterial strains) and *A. niger* and *C. albicans* (fungal strains) by disc-diffusion method on nutrient agar media and sabouraud dextrose media respectively. The standard drugs like Ciprofloxacin and Ampicillin (for antibacterial activity) and Amphotericin B and Clotrimazole (for antifungal activity) were used for comparison of the antimicrobial activity at the concentration 50 µg/ml and 100 µg/ml against Gram positive and Gram negative bacteria as well as fungal strains for the present study. The data of the antimicrobial studies is given in the Table 3 (antibacterial studies) and Table 4 (antifungal studies). The zone of inhibition of all the synthesized compounds was found to be in the range 2-11 mm at concentration of 50 µg/ml and 3-14 mm at concentration of 100 µg/ml, whereas the zone of inhibition for standard drugs was between 9-11 mm at concentration of 50 µg/ml and 12-16 mm at concentration of 100 µg/ml (for Ciprofloxacin), between 6-8 mm at concentration of 50µg/ml and 7-11 mm at concentration of 100µg/ml (for Ampicillin), between 6-7 mm at concentration of 50µg/ml and 8-9 mm at concentration of 100µg/ml (for Fluconazole) and between 5-7 mm at concentration of 50µg/ml concentration and 6-7 mm at concentration of 100µg/ml (for Amphotericin B). The results reveal that all the synthesized compounds exhibited good antibacterial activity, but at the same time, none of them exhibited antifungal activity.

CONCLUSION

Among all the synthesized compounds, total ten compounds viz., 3c, 3d 3f, 3g, 3h and 4c, 4d, 4f, 4g, 4h exhibited good antibacterial activity showing a zone of inhibition and activity ranges in decreasing order 3c > 3d >3g >3f >3h and 4c >4d > 4g > 4f >4h respectively. Hence, it may be concluded that antimicrobial activity was found to be in decreasing order, 2-$NO_2C_6H_4$ > 2,4$(Cl)_2C_6H_3$> 4-OH, 3-$OCH_3C_6H_3$ > 4-ClC_6H_4 > 4-N,N$(CH_3)_2C_6H_4$ derivatives respectively. The series of arylidene 4-oxo-1,3-thiazolidine phthalimido acetohydrazides (4a-4j) were prepared by reaction of Arylidene phthalimido acetohydazides (Schiff bases) (3a-3j) With thioglycollic acid.

REFERENCES

[1] F. W. A. Barros, T. G. Silva, M. G. R. Pitta, D. P. Bezerra, L. V. C. Lotufo, M. O. Moraes, C. Pessoa, M. A. Moura, et. al., *Bioorg. Med. Chem.*, **2012,** 20, 3533.
[2] R. T. Carroll, D. E. Dluzen, H. Stinnett, P. S. Awale, M. O. Funk, W. J. Geldenhuys, *Bioorg. Med. Chem. Lett.*, **2011,** 21, 4798;
[3] X. F. Liu, C. J. Zheng, L. P. Sun, X. F. Liu, H. R. Piao, *Eur. J. Med. Chem.*, **2011,** 46, 3469.
[4] N. Sunduru, K. Srivastava, S. Rajakumar, S. K. Puri, J. K. Saxena, P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.*, **2009,** 19, 2570.
[5] T. Tomasic, L. P. Masic, *Curr. Med. Chem.*, **2009,** 16, 1596.
[6] G. Captan, N. Ulusoy, N. Ergenc, A. C. Ekinic, A. Vidin, *II Farmaco*, **1996,** 51, 729.
[7] M. W. Irvine, G. L. Patrick, J. Kewney, S. F. Hastings, S. J. MacKenzie, *Bioorg. Med. Chem. Lett.*, **2008,** 18, 2032.
[8]T. Komatsu, T. Hirano, C. Songkram, E. K. H. Kagechika, *Bioorg. Med. Chem.*, **2007,** 15, 3115.
[9] Y. Wu, H. H. Tai, H. Cho, *Bioorg. Med. Chem.*, **2010,** 18, 1428.
[10] S. Kamila, H. Ankati, E. R. Biehl, *Tetrahedron Lett.*, **2011,** 52, 4375.
[11] H. Fujishima, K. Tuboto, *Br. J. Ophthalmol.*, **2002,** 86, 860.
[12] J. Liu, F. Wu, L. Chen, J. Hu, L. Zhao, C. Chen, L. Peng, *Bioorg. Med. Chem. Lett.*, **2011,** 21, 2376.
[13] P. C. Mhaske, S. H. Shelke, R. P. Jadhav, H. N. Raundal, S. V. Patil, A. A. Patil, V. D. Bobade, *J. Heterocycl. Chem.*, **2010,** 47, 1415.
[14] A. Dandia, R. Singh, S. Khaturia, C. Merienne, G. Morgant, A. Loupy, *Bioorg. Med. Chem.*, **2006,** 14, 2409.
[15] M. Rajopadhye, F. D. Popp, *J. Heterocycl. Chem.*, **1987,** 24, 1637.
[16] M. Rajopadhye, F. D. Popp, *J. Heterocycl. Chem.*, **1984,** 21, 289.
[17] J. O. Ban, D. H. Kwak, J. H. Oh, E. J. Park, M. C. Cho, H. S. Song, M. J. Song, S. B. Han, D. C. Moon, K. W. Kang, J. T. Hong, *Chem. Biol. Interact.*, **2010,** 188, 75.
[18] Z. Beharry, M. Zemskova, S. Mahajan, F. Zhang, J. Ma, Z. Xia, M. Lilly, C. D. Smith, A. S. Kraft, *Mol. Cancer Ther.*, **2009**, 8, 1473.
[19] S. Chandrappa, P. S. B. Benaka, K. Vinaya, K. C. S. Ananda, N. R. Thimmegowda, K. S. Rangappa, *Invest. New Drugs*, **2008,** 26, 437.
[20] W. Li, Y. Lu, Z. Wang, J. T. Dalton, D. D. Miller, *Bioorg. Med. Chem. Lett.*, **2007,** 17, 4113.
[21] C. W. Shiau, C. C. Yang, S. K. Kulp, K. F. Chen, C. S. Chen, J. W. Huang, C. S. Chen, *Cancer Res.*, **2005,** 65, 1561.

[22] C. D. Barros, A. A. Amato, T. B. de Oliveira, K. B. Iannini, A. L. Silva, T. G. Silva, E. S. Leite,M. Z. Hernandes, M. do C. Alves de Lima, S. L. Galdino, F. de A. Neves, R. Pitta, *Bioorg. Med. Chem.*, **2010,** 18, 3805.
[23] M. N. Nasr, M. M. Gineinah, E. R. El-Bendary, *Arch. Pharm.*, **2003,** 336, 560.
[24] M. C. A. DeLima, D. L. B. Costa, A. J. S. Goes, S. L. Galdino, I. R. Pitta, C. Luu-Duc, *Pharmazie*, **1992,** 47, 182.
[25] I. M. Labouta, H. M. Salama, N. H. Eshba, O. Kader, E. El-Chrbini, *Eur. J. Med. Chem.*, **1987,** 22, 485.
[26] R. C. Sup, R. Y. Sup, C. W. Bang, *Korean J. Med. Chem.*, **1995,** 5, 72.
[27] N. Agarwal, S. Kumar, A. K. Srivastava, P. C. Sarkar, *Ind. J. Het. Chem.*, **1997,** 6, 291.