Synthesis, Characterization and Pharmacological Studies of Some Ethoxyphthalimido Thiazolo[4,5-d] Pyrimidines and Ethoxy-phthalimido Thiazolo [4,5-c] Isoxazoles

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Abstract- A number of 3-*N*-ethoxyphthalimido-5-amino-2-oxo- 7-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl) -1,3-thiazolo[4,5-d]pyrimidines [5a-f] and 6-*N*-ethoxyphthalimido-5-oxo 3-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl)- 3,3a-dihydro[1,3] thiazole [4,5-c]isoxazoles [7a-f] derivatives have been proposed to synthesize from the condensation of phthalimidoxyethyl bromide with [4a-f] and [6a-f], respectively. The compounds [4a-f] and [6a-f] in turn have been prepared by the reaction of 5-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl)-1,3 thiazolidine -2,4-dione [3a-f] with guanidine nitrate and hydroxylamine hydrochloride, respectively. All the synthesized compounds were characterized by carbon and nitrogen elemental analysis and IR, 1H, NMR and mass spectral studies. All the final derivatives of titled compounds have been tested for their antifungal activities against Candida albicans and Aspergillus fumigatus and antibacterial activities against Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli and Proteus mirabilis comparing with standard drugs.

Keywords- Iminothiazolidinone; Cyclisation; Condensation; Alkoxyphthalimides.

1. INTRODUCTION

The importance of various five & six-membered and fused heterocyclic derivatives is very well established in the world of organic synthesis and medicinal chemistry. It is well known that a number of thiazolidinone and respective compounds are indulged in a broad range of biological activities, i.e., anticonvulsant [1], anti-inflammatory [2,3], hypnotic [4], amoebicidal [5], analgesic [6], anti-AIDS [7] properties etc. Nitrogen-containing heterocyclic compounds i.e. pyrimidine play an important role in the living process. Besides the naturally occurring pyrimidines, a variety of synthetic pyrimidine derivatives are of clinical importance and are used in treating a range of diseases i.e., anticancer [8-10], anti- HIV [11,12], anti-viral against herpes simplex virus (HSV) [13], analgesic, anticonvulsant and antiparkinsonian [14]. Isoxazole derivatives have been found to show anticancer [15], antibacterial [16], and beneficial effects on neuronal disorders [17-20]. Various alkoxyphthalimide derivatized heterocycles are also found to hold anticonvulsant [21], anticancer [22], antimalarial [23,24] and anti-microbial [25-27] activities.

By reviewing above-mentioned potent activities of these combinational heterocycles, it was planned to design a complex molecular framework. In this paper, we have synthesized various ethoxyphthalimide derivatives by first combining the thiazolidinone moiety with pyrimidine and isoxazole through separate pathways.

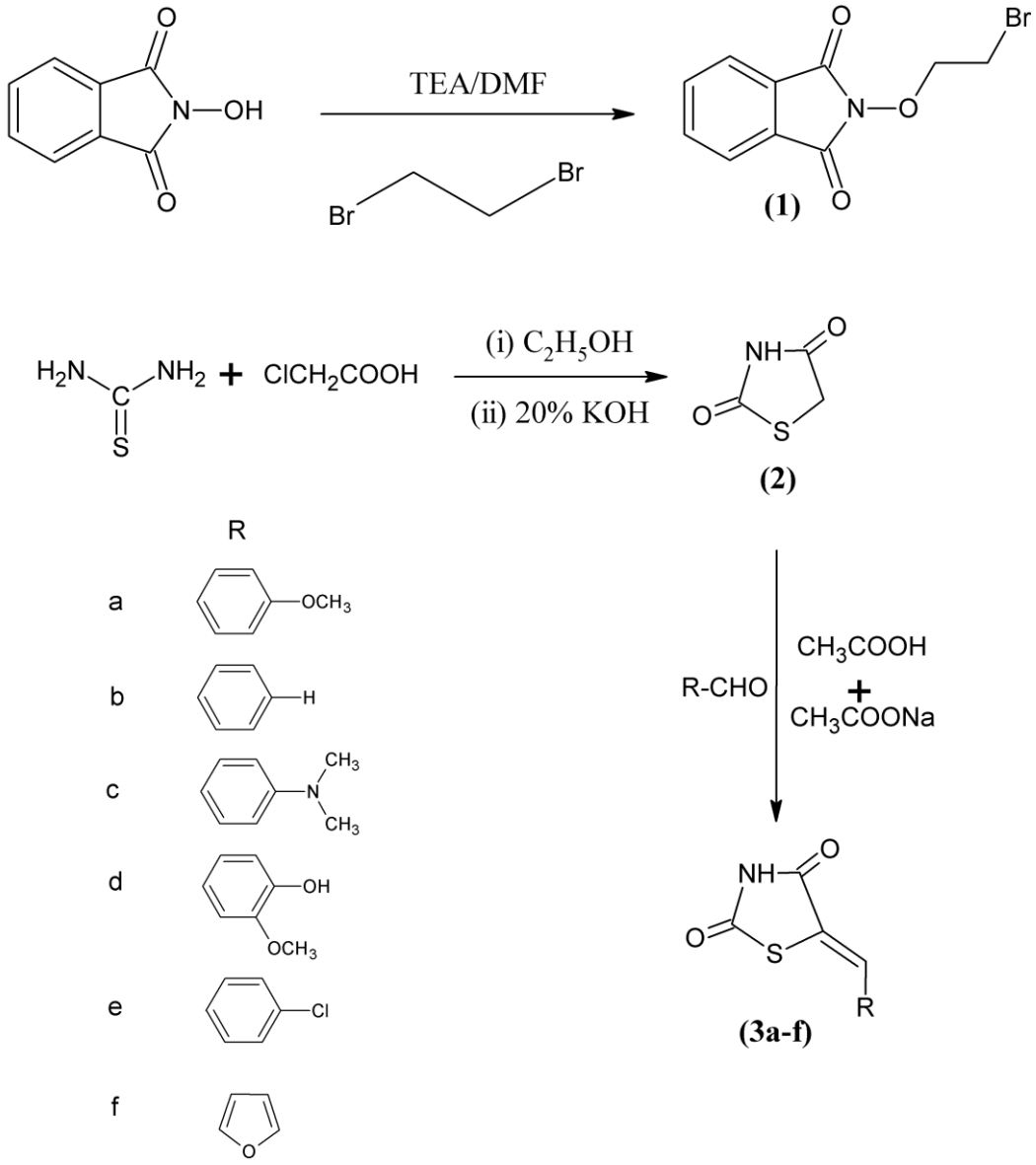

Figure 1. Reaction scheme showing the synthesis of 1,3-Thiazolidin-2,4-dione and its derivatives.

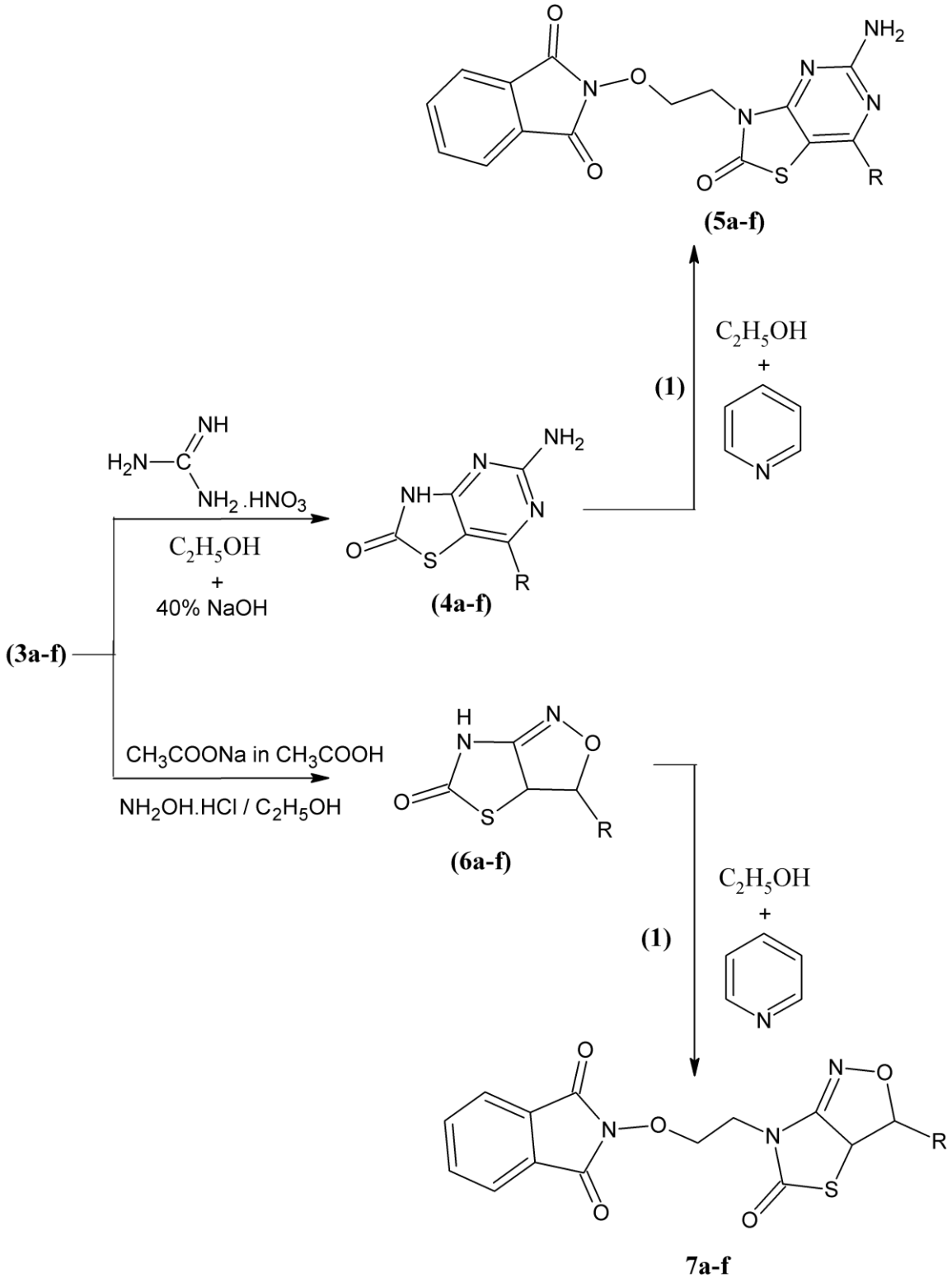

Figure 2. Reaction Scheme showing the synthesis of the titled compounds.

2. RESULT AND DISCUSSION

1,3-Thiazolidin-2, 4-dione **[2]** was prepared utilizing the reported method. It was prepared by the reaction between thiourea and 2-chloroacetic acid in absolute alcohol, here 20% KOH was used to achieve the imino group hydrolysis. Formation of compound **[2]** was confirmed by IR spectral data in which peak of C=O at 1695 cm^{-1}

and peak of N-H showed at 3425.9 cm^{-1}. The reaction of the compound **[2]** with various 4-substituted phenyl/2-furyl/3,4-disubstituted phenyl aldehydes in the presence of acetic acid produced α, β-unsaturated moiety in the resulting 5-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl)-1,3-thiazolidin-2,4-dione **[3a-f]** in basic media of sodium acetate. Compound formation for example **[3a]** was characterized by the shift in carbonyl peak at 1690 cm^{-1}, because of α,β-unsaturated moiety of carbonyl group. In NMR spectra, compound **3a** exhibited the new singlet at δ 6.0 (C=CH-Ar) and disappearance of singlet at δ 3.5 (active CH_2) as was present in the precursor, also confirmed its formation.

In the first reaction route, compounds 5-amino-2-oxo-7-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl)-[1,3] thiazolo [4,5-d]pyrimidine [4a-f] have been synthesized by the cycloaddition of [3a-f] in the presence of alcoholic sodium hydroxide with guanidine nitrate (Figure 2). Formation of the expected compound was confirmed by ^{1}HNMR signal of the NH_2 and NH group at δ 5.42 (s) and δ 9.5, respectively. The furnished compounds [4a-f] were condensed with ω-bromoalkoxyphthalimide **[1]** in presence of pyridine to give titled compound. Synthesis of 3-*N*-ethoxyphthalimido-5-amino-2-oxo-7-(4-substituted phenyl)-2-oxo [1,3] thiazolo [4,5-d] pyrimidine **[5a-f].** Characteristic IR peak for N-O and C-O appeared at 1382 and 1087 cm^{-1} while ^{1}HNMR peak of NH at δ 9.5 disappeared in the final compound, confirming the formation of **[5a-f].**

In the second reaction route, the compounds **[3a-f]** underwent cycloaddition reaction with hydroxylamine hydrochloride to afford 3-(4-substituted phenyl/2-furyl/3,4-disubstituted phenyl)-3,3a-dihydro [1,3] thiazolo [4,5-*c*] isoxazol-5(6*H*)-one **[6a-f].** The structure assignment of compound **[6a]** was supported by the appearance of a new band at 1593 cm^{-1} for N-O group and at 1640 cm^{-1} for C=N str in the IR region. The structure of compound **[6a-f]** was further established by ^{1}HNMR spectral data. The ^{1}HNMR spectra of compound [6a-f] in the region δ 6.53 showed the absence of a C=CH-Ar proton shifting, thereby suggesting a cycloid structure for compound **[6a-f].** Treatment of **[6a-f]** with ω-bromoethoxyphthalimide **[1]** afforded the corresponding condensed product 6-*N*-ethoxyphthalimido-5-oxo-3-(4-substituted phenyl/2 -furyl/3,4-disubstituted phenyl)- 3,3a-dihydro [1,3] thiazolo [4,5-c] isoxazole **[7a-f]**. Structure elucidation of compound **[7a]** was done on the basis of IR and proton NMR studies. In IR, new bands appeared at 1733 cm^{-1} and 1204 cm^{-1} because of CO-N-CO and C-N stretching, and a band at 3422 cm^{-1} disappeared corresponding to the N-H str as was present in **[6a]**. The ^{1}HNMR spectrum of compound **[7a]** showed a doublet at δ 3.59 for NCH_2 proton and disappearance of singlet at 9.76 δ for NH proton.

Physical, analytical and elemental analysis data of all the newly synthesized compounds are depicted in Table 1 Characterization data in the form of IR, Proton NMR and Mass spectra of the synthesized compounds are tabulated in Table 2.

Table 1 Physical, analytical and elemental analysis of synthesized compounds

Compound	Mol. Formula	Mol. wt.	m.p. °C	Yield %	Calcd. (found) %		
					C	H	N
4a	$C_{12}H_{10}N_4O_2S$	274	280	68	52.54 (52.30)	3.67 (3.40)	20.43 (20.21)
4b	$C_{11}H_8N_4OS$	244	274	72	54.09 (53.99)	3.30 (3.01)	22.94 22.70)
4c	$C_{13}H_{13}N_5OS$	287	270	66	54.34 (54.15)	4.56 (4.20)	24.37 (24.30)
4d	$C_{12}H_{10}N_4O_3S$	290	285	64	49.65 (49.55)	3.47 (3.21)	19.30 (19.10)
4e	$C_{11}H_7ClN_4OS$	278	282	60	47.40 (47.09)	2.53 (2.31)	20.10 (19.85)
4f	$C_9H_6N_4O_2S$	234	240	68	46.15 (46.01)	2.58 (2.46)	23.92 (23.72)
5a	$C_{22}H_{17}N_5O_5S$	463	>300	63	57.01 (56.95)	3.70 (3.52)	15.11 (15.02)
5b	$C_{21}H_{15}N_5O_4S$	433	290	75	58.19 (58.09)	3.49 (3.28)	16.16 (16.09)
5c	$C_{23}H_{20}N_6O_4S$	476	288	68	57.97 (57.81)	4.23 (4.15)	17.64 (17.53)
5d	$C_{22}H_{17}N_5O_6S$	479	298	63	55.11 (55.02)	3.57 (3.48)	14.61 (14.49)
5e	$C_{21}H_{14}N_5O_4SCl$	467	>300	69	53.91 (53.80)	3.02 (2.95)	14.97 (14.89)

5f	$C_{19}H_{13}N_5O_5S$	423	267	72	53.90 (53.83)	3.09 (2.94)	16.54 (16.37)
6a	$C_{11}H_{10}N_2O_3S$	250	200	68	52.79 (52.75)	4.03 (3.98)	11.19 (11.02)
6b	$C_{10}H_8N_2O_2S$	220	180	72	54.53 (54.52)	3.66 (3.61)	12.72 12.65)
6c	$C_{12}H_{13}N_3O_2S$	263	195	66	54.74 (54.71)	4.98 (4.90)	15.96 (15.81)
6d	$C_{12}H_{10}N_4O_3S$	266	210	64	49.62 (49.60)	3.79 (3.75)	10.52 (10.42)
6e	$C_{10}H_7ClN_2O_2S$	254	199	60	47.16 (47.18)	2.77 (2.71)	13.92 (13.80)
6f	$C_8H_6N_2O_3S$	210	185	68	45.71 (45.61)	2.88 (2.83)	13.13 (13.02)
7a	$C_{21}H_{17}N_3O_6S$	439	190	72	58.67 (58.64)	3.69 (3.64)	10.26 (10.15)
7b	$C_{20}H_{15}N_3O_5S$	409	174	77	57.40 (57.35)	3.90 (3.88)	9.56 (9.41)
7c	$C_{22}H_{20}N_4O_5S$	452	190	64	58.40 (58.34)	4.46 (4.40)	12.38 (12.25)
7d	$C_{21}H_{17}N_3O_7S$	455	192	67	55.38 (55.31)	3.76 (3.72)	9.23 ((9.15)
7e	$C_{20}H_{14}N_3O_5SCl$	443	194	62	54.12 (54.08)	3.18 (3.15)	9.47 (9.35)
7f	$C_{18}H_{13}N_3O_6S$	399	180	71	54.13 (54.10)	3.28 (3.21)	10.52 (10.40)

Table 2 IR, Proton NMR and Mass spectra of the newly synthesized compounds

Comp		Characterization
1	IR cm^{-1}	3425 [N-H str.], 1695 [C=O str], 1595.3 [C=N str], 672 [C-S-C bend]
	^{1}HNMR δ_H	10.2 [s,1H, NH], 3.50 [s,2H,CH_2]
3a	IR cm^{-1}	3375 [N-H], 2830.9 [C-H asymm. str., CH_3], 1690 [C=O str], 1595 [C=N str], 773 [C-S-C bend], 1302.9 [O-CH_3 str]
	^{1}HNMRδ_H	9.9 [s, 1H, NH], 7.9-7.6 [m, 4H, Ar-H], 6.0 [s, 1H, C=CH-Ar] 3.80 [s, 2H, CH_2]
3f	IR cm^{-1}	3457 [N-H str], 1691 [C=O str], 1384.6 [C-N str], 799 [C-S-C]
	^{1}HNMRδ_H	9.8 [s, 1H, NH], 7.4-6.6 [m, 3H, Ar-H], 6.2 [s, 1H, C=CH-Ar], 3.7 [s, 2H, CH_2]
4a	IR cm^{-1}	3408.7 [N-H str], 3021.7 [Ar-H str], 2833.9 [C-H, CH_3 str], 1735 [C=O str], 1673.9 [NH_2 bend], 1603.1 [C=N str], 1254.1 [O-CH_3 str], 1148.1-1208.6 [C-N, C-NH_2], 1033 [C-S], 811.1 [C-H (para)subs benz.], 711.6 [C-S-C]
	^{1}HNMRδ_H	9.6 [s, 1H, NH], 8.03-6.63 [m, 4H, Ar-H], 6.47 [s, br., 2H, NH_2],3.82 [s, 3 H, OCH_3]
4b	IR cm^{-1}	3415.0 [N-H], 3025.0 [Ar-H], 1740 [C=O], 1670 [NH_2 bend], 1570 [C=N], 1160 [C-N], 1040 [C-S], 715 [C-S-C]
	^{1}HNMRδ_H	9.73 [s, 1H, NH], 07-7.00 [m, 5H, Ar-H], 6.49 [s, br., 2H, NH_2]
4c	IR cm^{-1}	3430 [N-H], 3032 [Ar-H], 1724 [C=O], 1672-1603 [NH_2 bend], 1572 [C=N], 1030 [C-S], 709 [C-S-C]
	^{1}HNMRδ_H	9.57 [s, 1H, NH], 8.3-7.25 [m, 4H, Ar-H], 6.47 [s, br., 2H, NH_2], 3.15 [s, 6H, N (CH_3)$_2$]
4d	IR cm^{-1}	3502 [Br, OH], 3409 [N-H], 3028 [Ar-H], 2840 [C-H, CH_3], 1716 [C=O], 1676 [NH_2], 1573 [C=N], 1023 [C-S], 699 [C-S-C]
	^{1}HNMRδ_H	9.70 [s, 1H, NH], 8.05-6.55 [m, 3H, Ar-H], 6.43 [s, br., 2H, NH_2], 4.79 [br.1H, OH], 3.87 [s, 3H, OCH_3]
4e	IR cm^{-1}	3402 [N-H], 3023 [Ar-H], 1710 [C=O], 1664 [NH_2 bend], 1580 [C=N], 1019 [C-S], 750 [Ar-Cl], 697 [C-S-C]
	^{1}HNMRδ_H	9.55 [s, 1H, NH], 8.01-6.61 [m, 4H, Ar-H], 6.43 [s, br., 2H, NH_2]
4f	IR cm^{-1}	3463 [N-H], 3033 [C-H, CH=CH cyclic], 1778 [C=O], 1682 [NH_2 bend], 1542 [C=N], 1285 [C-N], 1018 [C-O], 755 [C-S-C]
	^{1}HNMRδ_H	9.51 [s, 1H, NH], 7.03-6.34 [m, 3H, Ar-H], 6.41 [s,br., 2H, NH_2]
5a	IR cm^{-1}	3433 [N-H], 3021 [C-H, Ar-H], 2945-2840 [C-H, CH_3, $CH_{2=}$], 1731,1698 [C=O str], 1565 [C=N str], 1380 [N-O str], 1082 [C-O str], 683 [C-S-C]
	^{1}HNMRδ_H	7.95-6.58 [m, 8H, Ar-H], 6.43 [s, br., 2H, NH_2], 3.48 [t, 2H, NCH_2], 2.39 [t, 2H, OCH_2], 3.80 [t, 3H, OCH_3]
	Mass	463 $[M]^{+\cdot}$, 273, 236, 190, 177, 136, 132, 107, 92.
5b	IR cm^{-1}	3443 [N-H], 3025 [C-H, Ar-H], 2951 [C-H, CH_3],1735,1698[C=O str], 1590 [C=N str], 1385 [N-O str], 1085 [C-O str], 690 [C-S-C]
	^{1}HNMRδ_H	7.95-6.95 [m, 9H, Ar-H], 6.48 [s, br., 2H, NH_2], 3.50 [t, 2H, NCH_2], 2.43 [t, 2H, OCH_2]
	Mass	433 $[M]^{+\cdot}$, 273l 236, 223, 190, 177, 132, 106, 77.
5c	IR cm^{-1}	3430 [N-H], 3017 [C-H, Ar-H], 2940,2845 [C-H, CH_3], 1732,1683 [C=O str], 1560 [C=N str], 1383 [N-O str], 1076 [C-O str], 673 [C-S-C]
	^{1}HNMRδ_H	8.18-7.20 [m, 8H, Ar-H], 6.45 [s, br., 2H, NH_2], 3.40 [t, 2H, NCH_2], 2.33 [t, 2H, OCH_2], 2.19 [s, 6H, $N(CH_3)_2$]
	Mass	476 $[M]^{+\cdot}$, 273, 236, 177, 148, 132, 120.
5d	IR cm^{-1}	3499 [O-H, br.], 3428 [N-H], 3019 [C-H, Ar-H], 2945-2842 [C-H, CH_3], 1722,1681 [C=O str], 1563 [C=N str], 1380 [N-O str], 1080 [C-O str], 680 [C-S-C]

	^{1}HNMRδ_H	7.93-6.39 [m, 7H, Ar-H], 6.43 [s, br., 2H, NH_2], 4.73 [br., 1H, OH], 3.31 [t, 2H, NCH_2], 2.80 [t, 2H, OCH_2]
	Mass	479 $[M]^{+\cdot}$, 273, 236, 190, 162, 151, 132, 123.
5e	IR cm^{-1}	3417 [N-H], 3025 [C-H, Ar-H], 2951 [C-H, CH_3],1719,1673 [C=O str], 1590 [C=N str], 1376 [N-O str], 1079 [C-O str], 671 [C-S-C]
	^{1}HNMRδ_H	7.79-7.03 [m, 8H, Ar-H],6.40 [s, br., 2H, NH_2], 3.30 [t, 2H, NCH_2], 2.78 [t, 2H, OCH_2]
	Mass	469 $[M+2]^{+\cdot}$, 467 $[M]^{+\cdot}$, 273, 236, 190, 177, 137, 132, 111.
5f	IRcm^{-1}	3440 [N-H], 3022 [C-H, Ar-H], 2930.8 [C-H, CH_3], 1700,1690 [C=O str], 1597 [C=N str], 1382 [N-O str], 1087 [C-O str], 680 [C-S-C]
	^{1}HNMRδ_H	8.59-7.53 [m, 7H, Ar-H], 5.39 [s, br., 2H, NH_2], 4.45 [t, 2H, OCH_2] 4.14 [t, 2H, NCH_2],
	Mass	423 $[M]^{+\cdot}$, 273, 246, 236, 190, 162, 95, 67.
6a	IR cm^{-1}	3422 [N-H str.], 3030 [Ar-H str.], 2830 [C-H str in CH3], 1690 [C=O str.], 1640 [C=N str.], 1514 [N-Ostr.], 1284 [O-CH3 str.], 813.1 [C-H (para) subs benz.], 683 [C-S-C str.]
	^{1}HNMRδ_H	10.80 [s, 1H, NH], 6.92-7.71 [m, 4H, Ar-H], 5.58 [d, 1H, OCH_2], 5.22 [d, 1H, SCH_2], 3.82 [s, 3H, OCH3]
6b	IR cm^{-1}	3430 [N-H str.], 3032 [Ar-H str.], 1695 [C=O str.], 1641 [C=N str.], 1521 [N-O str.], 817 [C-H (para)subs benz.], 687 [C-S-C str.]
	^{1}HNMRδ_H	10.2 [s, 1H, NH], 7.46-7.16 [m, 4H, Ar-H], 5.62 [d, 1H, OCH_2], 5.25[d, 1H, SCH_2]
6c	IR cm^{-1}	3028 [Ar-H str.], 3421 [N-H str.], 2845 [C-H str in CH3], 1686 [C=O str.], 1634 [C=N str.], 1512 [N-Ostr.], 1284 [O-CH3 str.], 811 [C-H (para)subs. benz.], 681 [C-S-C str.]
	^{1}HNMRδ_H	9.96[s, 1H, NH], 7.39-6.87 [m, 4H, Ar-H], 5.59 [d, 1H, OCH_2], 5.19[d, 1H, SCH_2], 2.89 [s, 6H, $N(CH_3)2$]
6d	IR cm^{-1}	3510[br.O-H str.], 3421 [N-H str.], 3025 [Ar-H str.], 2840 [C-H str in CH3],1683 [C=O str.], 1631 [C=N str.], 1510.2 [N-O str.], 1284 [O-CH3 str.],680 [C-S-C str.]
	^{1}HNMRδ_H	9.8[s, 1H, NH], 7.11-6.89 [m, 3H, Ar-H], 6.45 [s, 1H, OH], 5.56 [d, 1H, OCH_2], 5.14[d, 1H, SCH_2], 3.78 [s, 3H, OCH 3]
6e	IR cm^{-1}	3417 [N-H str.], 3021 [Ar-H str.], 1681 [C=O str.], 1631 [C=N str.], 1510.2 [N-O str.], 737[C-Cl str.], 681 [C-S-C str.]
	^{1}HNMRδ_H	9.76[s, 1H, NH], 7.44-7.40 [m, 4H, Ar-H], 5.67 [d, 1H, OCH_2], 5.22 [d, 1H, SCH_2]
6f	IR cm^{-1}	3426 [N-H str.], 3031 [Ar-H str.], 1679 [C=O str.], 1634 [C=N str.], 1509 [N-O str.], 1018[C-O-C str.], 683 [C-S-C str]
	^{1}HNMRδ_H	9.94[s, 1H, NH], 7.43-6.35 [m, 3H, Ar-H], 5.64 [d, 1H, OCH_2], 5.31 [d, 1H, SCH_2]
7a	IR cm^{-1}	3043 [Ar-H], 2830 [C-H, CH_2], 1751,1696 [C=O str], 1634 [C=N str], 1511 [N-O str], 1207 [C-N str], 1179 [C-O str], 805 [C-H (para)subs benz.], 681 [C-S-C]
	^{1}HNMRδ_H	7.79-7.04 [m, 8H, Ar-H], 5.17 [d, 1H, OCH_2], 5.12 [d, 1H, SCH_2], 4.09 [t, 2H, OCH_2], 3.67 [t, 2H, NCH_2], 3.43 [s, 3H, OCH_3]
	Mass	439 $[M]^{+\cdot}$, 371 ,289 ,236, 203, 190, 162, 136, 132, 118.
7b	IR cm^{-1}	3048 [Ar-H], 2837 [C-H, CH_2], 1752,1710 [C=O str], 1639 [C=N str], 1516 [N-O str], 1208 [C-N str], 1188 [C-O str], 682 [C-S-C]
	^{1}HNMRδ_H	7.84-7.00 [m, 9H, Ar-H], 5.18 [d, 1H, OCH_2], 5.14 [d, 1H, SCH_2], 4.13 [t, 2H, OCH_2], 3.76 [t, 2H, NCH_2]
	Mass	409 $[M]^{+\cdot}$, 289, 203,190, 162, 132,106, 77.
7c	IR cm^{-1}	3041 [Ar-H], 2835 [C-H, CH_3], 1748,1690 [C=O str], 1630 [C=N str], 1510 [N-O str], 1206 [C-N str], 1175 [C-O str], 803 [C-H (para)subs benz.], 681 [C-S-C]
	^{1}HNMRδ_H	7.79-7.89 [m, 8H, Ar-H], 5.15 [d, 1H, OCH_2], 5.10 [d,1H, SCH_2], 4.07 [t, 2H, OCH_2], 3.42 [t, 2H, NCH_2], 2.83 [t, 2H, $N(CH_3)_2$]
	Mass	452 $[M]^{+\cdot}$, 289, 203, 190, 162, 149, 132, 120.
7d	IR cm^{-1}	3503 [br.O-H], 3041 [Ar-H], 2831 [C-H, CH_3], 1747,1690 [C=O str], 1631 [C=N str], 1506 [N-O str], 1282 [O-CH_3 str], 1204 [C-N str], 1171 [C-O str], 681 [C-S-C]
	^{1}HNMRδ_H	7.79-6.84 [m, 7H, Ar-H], 6.45 [s, br, 1H, OH], 5.13 [d, 1H, OCH_2], 5.09 [d, 1H, SCH_2], 4.05 [s, 3H, OCH_3], 3.51 [t, 2H, OCH_2], 2.88 [t, 2H, NCH_2]
	Mass	455 $[M]^{+\cdot}$, 289, 203, 190, 162,152, 132, 123.
7e	IR cm^{-1}	3040 [Ar-H], 1743,1681 [C=O str], 1629 [C=N str], 1505 [N-O str], 1201 [C-N str], 1168 [C-O str], 731[C-Cl], 680 [C-S-C]
	^{1}HNMRδ_H	7.09-8.18 [m, 8H, Ar-H], 5.09 [d, 1H, OCH_2], 4.95 [d, 1H, SCH_2], 4.04 [t, 2H, OCH_2], 3.59 [t, 2H, NCH_2]
	Mass	445 $[M+2]^{+\cdot}$, 443 $[M]^{+\cdot}$, 289, 203, 190, 162, 140, 132, 111.
7f	IR cm^{-1}	3041 [Ar-H], 1748,1678 [C=O], 1629 [C=N str], 1509 [N-O str], 1203 [C-N str], 1170 [C-O str], 1012 [C-O-C str], 682 [C-S-C]
	^{1}HNMRδ_H	7.79-6.35 [m, 7H, Ar-H], 5.05 [d, 1H, OCH_2], 4.92 [d, 1H, SCH_2], 4.01 [t, 2H, OCH_2], 3.42 [t, 2H, NCH_2]
	Mass	399 $[M]^{+\cdot}$, 259, 203 ,190, 162, 132, 96, 80.

3. EXPERIMENT

3.1. Materials and Instruments

For characterization of compounds FTIR IR RX1 Perkin Elmer spectrophotometers (for IR) and Bruker DRX-300 MHz spectrometer ($CDCl_3$) (for NMR) and a MICROMASS QUATTRO II triple quadrupole mass spectrometer having a JASCOPU-980 HPLC pump (for mass) connected was used.

Phthalimidoxy ethyl bromide [1] was prepared by the literature method using ω,ω'-dibromoethane and N-hydroxyphthalimide in the solvent Dimethyl formamide and triethylamine was used as base [28].

3.2. Synthesis of 1,3-thiazolidin-2,4-dione (2)

A reaction mixture was made by mixing chloroacetic acid (0.01 mole) and thiourea (0.01mole) in absolute alcohol and refluxed for 3-4 hr on heating metal. After this, the reaction substance was cooled, resulting in a solid. After filtration, the residue was dissolved in boiling water, thus separated from HCl (a bi-product). After 24hr, the white shining crystals formed were filtered refluxed in aqueous KOH (20%) for 2-3 hr. The reaction product was further kept at room temperature for some time and then poured into dilute acetic acid (1:1). The final product was dried and recrystallized by absolute alcohol.

3.3. Synthesis of 5-(4-methoxybenzylidene)-1,3-thiazolidin-2,4-dione (3a*)*

4-Methoxybenzylidene (0.01 mole) was dissolved in glacial acetic acid with compound [2] (0.01 mole) and sodium acetate was used as a base. This reaction mixture was refluxed for 6-8 hrs. After the completion of the reaction, the reaction substance was transferred into crushed ice and filtered, resulting into a yellow colored solid. This solid was then washed and recrystallized by absolute alcohol Compounds [3b-f] were synthesized in a similar way.

3.4. Synthesis of 5-amino-2-oxo-7-(4-methoxyphenyl)- [1,3] thiazolo [4,5-d] pyrimidine (4a)

Compound 5-(4-methoxybenzylidene)-1,3-thiazolidin-2,4-dione [3a] (0.01 mole) was dissolved in absolute ethanol and teated with guanidine nitrate (0.01 mole). During the reflux, 40% aqueous NaOH solution was added to it. The reaction mixture was kept on reflux for 6-7 hrs. Afterwards, the solution is poured into ice-cold water. The orange yellow coloured product was filtered, dried washed and recrystallized from absolute ethanol. Compounds [4b-f] were prepared with minor modification in reaction time.

3.5. Synthesis of 3-N-ethoxyphthalimido- 5-amino-2-oxo-7-(4-methoxyphenyl)-2-oxo [1,3] thiazolo [4,5-d] pyrimidine (5a)

To a solution of compound 5-amino-2-oxo-7-(4-methoxyphenyl)- [1,3] thiazolo [4,5-d] pyrimidine [4a] (0.01 mole) in absolute ethanol, pyridine (0.02 mole) as base was added portion-wise with constant stirring. Further, phthalimidoxyethyl bromide [1] (0.01 mole) was added and reflux is continued for 12-13 hrs. A solid was obtained upon cooling, which was treated with DMF and recrystallized from ethanol. In a similar way, other derivatives [5b-f] were synthesized using appropriate reactants.

3.6. Synthesis of 3-(4-methoxyphenyl)-3,3a-dihydro [1,3] thiazolo [4,5-c] isoxazol-5(6H)-one (6b)

To a boiling solution of compound [3a] (0.01 mole) in absolute ethanol, hydroxylamine hydrochloride (0.01 mole) was added. In a separate flask sodium acetate (0.02 mole) is dissolved in acetic acid. Both the solutions are mixed together and refluxed for 7-8 hr. The resultant mixture was added into ice cold water with stirring. The colored solid obtained was filtered and recrystallized from absolute ethanol. Utilizing proper reactants and slight changes in the refluxed time, compounds [6b-f] were synthesized in a similar method.

3.7. Synthesis of 6-N-ethoxyphthalimido-5-oxo-3-(4-methoxyphenyl)- 3,3a-dihydro [1,3] thiazolo [4,5-c] isoxazole (7a)

To a magnetically stirred solution of 3-(4-methoxyphenyl)-3,3a-dihydro [1,3] thiazolo[4,5-c] isoxazol-5(6H)-one [6a] (0.01 mole) in abs. ethanol, phthalimidoxy ethyl bromide [1] (0.01) and pyridine (0.02) as base was added and refluxed for 14-15 hr. The solid thus obtained after cooling was filtered with vacuum pump, dried and recrystallized from absolute alcohol. Compounds [7b-f] were synthesized in an analogous way by utilizing minor changes in reflux time.

4. PHARMACOLOGICAL SCREENING

All compounds were tested *in vitro* for antibacterial and antifungal activities using 500 µg/mL concentrations in DMF using cup or well method with respect to standard drug i.e. Ciprofloxacin and Amphotericin B respectively. Antibacterial testing was carried out against, gram +ve Bacterial strain *Bacillus subtilis* and gram –ve strains *Klebsiella pneumoniae*, *Proteus mirabilis* and *Escherichia coli*. Compounds were assayed for their antifungal activities against fungal species of *Aspergillus fumigatus* (MTCC 2550) and *Candida albicans* (MTCC 227). Comparative study was carried out in the form of measurement of zone of inhibition (in mm) along with activity index calculation between tested compounds and standard drugs. Compound 5e and 7e showed promising activity against *B. subtilis*, whereas activity of 5a, 5e and 5f was comparable with ciprofloxacin against *E. coli*. Compound **7e** exhibited highest activity amongst all the other derivatives of pyrimidines and isoxazoles against *P. mirabilis*. All the final compounds showed moderate to high activity against both the fungal strains. Moreover, the result of antifungal activity for *A. fumigatus* was 2-3 folds higher than that of the standard drug.

Compounds have been tested for antiviral screening in CRFK, Hel, HeLa and Vero cell

cultures. On the basis of MIC values compounds show no significant activity, all the screened compounds showed activity but rather on high concentration. Therefore, any of the compounds at a concentration of the standard compound did not demonstrate significant antiviral activity.

Antimicrobial testing results of all the final derivatives have been depicted in Compounds have shown less to moderate activity, but it can be concluded that synthesized compounds are better antifungal agents

Table 3 Antimicrobial assay of final derivatives

Compound	Antibacterial Assay				Antifungal Assay	
	B. subtilis	***E. coli***	***K. pneumoniae***	***P. mirabilis***	***C. albicans***	***A. fumigatus***
5a	2 (0.181)	12 (1.00)	6 (0.50)	7 (0.50)	10 (0.83)	26 (4.33)
5b	3 (0.272)	10 (0.83)	5 (0.41)	9 (0.64)	8 (0.66)	23 (3.83)
5c	4 (0.363)	9 (0.75)	7 (0.58)	10 (0.71)	6 (0.50)	20 (3.33)
5d	5 (0.454)	11 (0.92)	4 (0.33)	4 (0.28)	6 (0.50)	17 (2.83)
5e	9 (0.818)	13 (1.08)	13 (1.08)	13 (0.92)	9 (0.75)	14 (2.33)
5f	4 (0.363)	12 (1.00)	12 (1.00)	8 (0.57)	12 (1.00)	13 (2.16)
7a	6 (0.545)	9 (0.75)	8 (0.72)	10 (0.71)	11 (0.91)	20 (3.33)
7b	5 (0.454)	8 (0.66)	6 (0.50)	11 (0.78)	10 (0.83)	15 (2.50)
7c	4 (0.363)	5 (0.41)	9 (0.75)	8 (0.57)	13 (1.08)	10 (1.66)
7d	6 (0.545)	7 (0.58)	3 (0.25)	12 (0.85)	12 (1.00)	11 (1.83)
7e	9 (0.818)	10 (0.83)	12 (1.00)	14 (1.00)	12 (1.00)	17 (2.83)
7f	8 (0.727)	10 (0.83)	7 (0.58)	11 (0.78)	11 (0.91)	21 (3.50)
Standard	11	12	12	14	12	6
Standard used: Antibacterial = **Ciprofloxacin**; Antifungal = **Amphotericin B**,						

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