Ethoxyphathalimide linked some 2, 4, 8-Triphenyl-4*H*-9-thia-1, 4a, 5, 7-tetraaza-fluoren-6-ylamine derivatives: Synthesis and Pharmacological Evaluation from Chalcone

Prajapat Prakash[1,2,3]*, Kherodiya Bhawana[1*] and Talesara Ganpat L.[1]
1. Department of Chemistry, M. L. Sukhadia University, Udaipur-313001, Rajasthan, INDIA
2. Shree K. V. Parekh Science College, M. K. Bhavnagar University, Mahuva-364290, Gujarat, INDIA
3. Department of Chemistry, Ganpat University-MUIS, Mehsana-384012, Gujarat, INDIA
*prajapatprakash321@gmail.com; jainbhawana1989@gmail.com

Abstract

Synthesis of benzalacetophenones (1a-c) has been achieved by the aldol condensation of substituted acetophenone with benzaldehyde. These were treated with thiourea by utilizing HCl to give substituted dihydropyrimidine-thiones (2a-c). Cyclization of these compounds with DMF and chloroacetic acid yielded pyrimidothiazolidinone moieties (3a-c). Reaction of benzaldehyde with 3a-c produced corresponding chalcone derivatives (4a-c). These chalcone derivatives when treated with guanidine nitrate in presence of a base gave (5a-c). Condensation of 5a-c with bromoethoxyphthalimide afforded titled compounds (6a-c).

Structures of prepared scaffolds were established by the spectral studies, elemental analysis and chemical tests. Subsequently, heterocyclic hybrids (5a-c, 6a-c) were assayed to their in vitro anti-microbial activity against a variety of infectious strains of bacteria and fungi.

Keywords: Pyrimidine, Thiazolidinone, Ethoxyphthalimide, Anti-microbial activity.

Introduction

Pyrimidines are a significant class of heterocycles and their structural framework is a crucial component of many pharmacophores with potent biological effects including alkaloids, nucleic bases and several pharmacophores. In medicine, pyrimidines have a special and unique role because a wide range of their non-nucleoside derivatives has different pharmacological properties[10,28,29,32]. Since uracil[34] and thymine[23] are components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) respectively and since cytosine[24] is a component of ribonucleic acid (DNA), pyrimidines are by far the most significant of the diazine family physiologically.

Depending upon many natural products and medications include this heterocyclic component, the synthesis of thiazoles and their derivatives has gained substantial attention[20]. A number of thiazole derivatives have been found to have significant and varied biological activities including those that are antimicrobial[19], antioxidant[16], anti-HIV[17], anti-inflammatory[36], antiallergic[3], analgesic[4], anti-bacterial[38], hypertension[26], schizophrenia[14], cardiotonic[2], fungicidal[11] and those that treat children's mental retardation[9], as well as age-related and neurodegenerative brain damage (Alzheimer's disease, Parkinson's disease) and as new inhibitors of bacterial DNA gyrase[18], anti-convulsant[1], cytotoxic[15], anti-tubercular[8], anticancer [12, 25, 35], antithrombotic[5] etc.

Thiazoles are quickly metabolized in regular metabolic processes and do not naturally cause cancer[29]. The biological activities of various combinations of heterocyclic rings connected to alkoxyphthalimide groups have been investigated[13,21,22,27,30,31]. Based on the findings discussed above and continuing our interest in creating novel ethoxyphthalimide-plugged heterocyclic frameworks beginning with chalcone, our plan was to create a new class of heterocyclic hybrids that contain all the moieties with increased biological activities.

Material and Methods

All melting points were established using the electro thermal technique in uncorrected open capillary tubes. The 1H-NMR spectra of the compounds were recorded on a Bruker DRX-300 MHz spectrometer in $CDCl_3$ solvent using TMS as an internal standard. The IR spectra of the compounds were recorded on a 4000-450 cm-1 range using KBr discs on FTIR RX1 Perkin Elmer spectrophotometer. A Jeol SX-102 (FAB) mass spectrometer was used to record the mass spectra. On silica gel G TLC plates of 2 mm thickness, the purity of the produced compounds was examined using the appropriate solvent. In an iodine chamber, spot visualization was performed. Based on their chemical analyses as well as analytical and spectral data, the observed physical properties are shown in table 1.

Synthesis of benzalacetophenone (1a)[7]: To a stirred mixture of p-substituted acetophenone (10 mmol) and benzaldehyde (10 mmol) in ethanol (10 mL), sodium hydroxide (10 mL) was added dropwise with vigorous stirring to the reaction mixture for 30 min. till the solution becomes cloudy. The reaction temperature was maintained between 20 and 25°C using a cold-water bath on the magnetic stirrer. After vigorous stirring for 4-5 hours, the reaction mixture was neutralized with HCl whereupon a

precipitate was formed. After filtration, the crude product is recrystallized from ethanol. Likewise, all compounds (1b-c) were synthesized by the above method with little change in reaction conditions.

Synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione (2a): A mixture of 1a (0.01 mol) and thiourea (0.02 mol) was dissolved in dry ethanol (50 mL) and 10 mL conc. HCl was added. It was refluxed for 18 hours. The contents were filtered while hot and allowed to cool. It was then neutralized with 5N sodium hydroxide solution. The resulting solid was washed with water and recrystallized from acetic acid. Likewise, all compounds (2b-c) were synthesized by the above method with a small change in the reaction conditions.

Synthesis of 5,7-diphenyl-5H-[1,3]thiazolo[3,2-a] pyrimidine-3(2H)-one (3a): A mixture of 2a (0.01 mol) and chloroacetic acid (0.011 mol) in DMF was refluxed for 4 hours. The resulting solution was left at room temperature for one hour and cooled to 0 °C. The separated solid was filtered, washed with cooled water and recrystallized from ethanol. Likewise, all compounds (3b-c) were synthesized by the above method with a small change in the reaction conditions.

Synthesis of 2-benzylidene-5,7-diphenyl-5H-[1,3]thiazolo [3,2-a]pyrimidin-3(2H)-one (4a): Compound 3a (0.01 mol), sodium acetate (0.02 mol) and benzaldehyde (0.01 mol) in glacial acetic acid were added under reflux for 16-18 hours. After the reaction was complete, ice water was gradually added to the reaction mixture with constant stirring to give a crude product. The product was recrystallized from ethanol. Similarly, all compounds (4b-c) were synthesized by the above method with slight changes in reaction conditions.

Synthesis of 2,4,8-Triphenyl-4H-9-thia-1,4a,5,7-tetraaza -fluoren-6-ylamine(5a): Compound 4a (0.01 mol) and guanidine nitrate (0.01 mol) were dissolved in absolute alcohol (20 mL) and stirred for 1 hour. 10% NaOH solution was added to the reaction mixture and reflux was continued for 8-9 hours. The reaction mixture was cooled and poured into crushed ice to give a solid product. It was purified by filtration, dried and recrystallized from ethanol. Other substrates (5b-c) were synthesized with slight changes in reflux time.

Synthesis of 2-[2-(2,4,8-triphenyl-4H-9thia -1,4a,5,7-tetraaza-fluoren-6-ylamino)-ethoxy]-isoindole-1,3-dione (6a): A mixture of 5a (0.005 mol) and bromethoxyphthalimide (0.005 mol) in absolute ethanol (15 ml) was refluxed for 16-18 hours using pyridine (0.01 mol) as a base. The solvent was removed and concentrated under reduced pressure and the resulting filtrate was poured into crushed ice and stirred to give a solid product, which was filtered, dried and recrystallized from alcohol. Similarly, all compounds (6b-c) were synthesized by the above method with slight changes in reaction conditions. The spectral data are presented in tables 2 and 3.

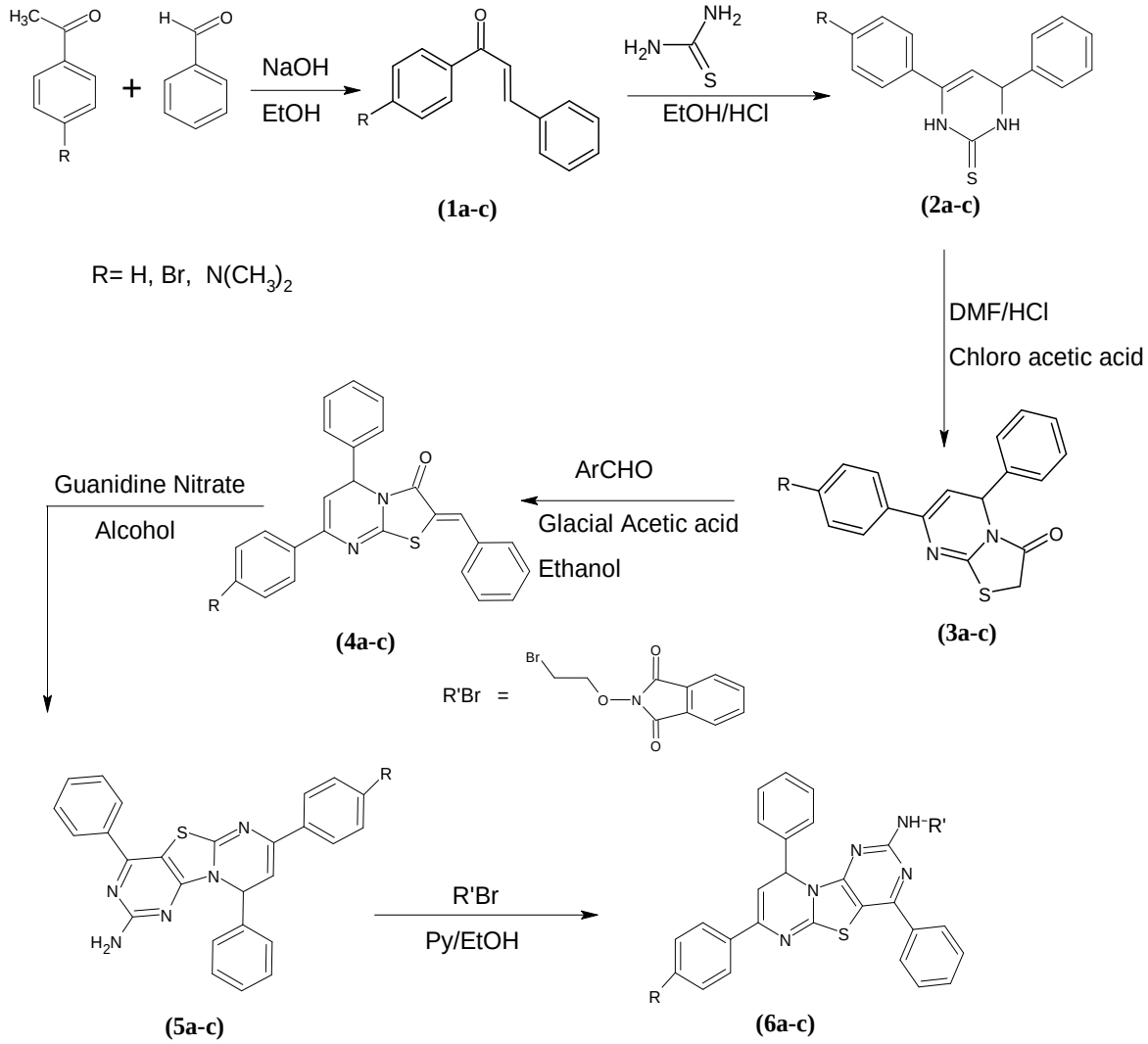
Antimicrobial Screening: By using ampicillin as the standard (S_1) antibacterial drug, compounds 5a-c and 6a-c were investigated for their *in vitro* antibacterial activity against two Gram-positive bacteria, *Staphylococcs aureus* MTCC 96 and *S. pyogenes* MTCC 443 and two gram-negative bacteria, *Escherichia coli* MTCC 442 and *Pseudomonas aeruginosa* MTCC 441. The conventional antifungal reference griseofulvin (S_2) was utilized in studies of *in vitro* antifungal activity against three different fungi, including *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323. The synthesized compounds' minimal inhibitory concentrations (MICs, g/mL) were measured using the broth micro-dilution technique in accordance with National Committee for Clinical Laboratory Standards[33]. The results of this investigation are presented in table 4.

Results and Discussion

In the present investigation, bromoethoxyphthalimide was prepared by reported method[6]. Compounds (1a-c) were synthesized by reported method which on cyclization with thiourea and catalytic amount of acid gave (2a-c). IR and 1H-NMR spectral data established the structure of these compounds. IR absorption band at 1286 cm^{-1} and 3478 cm^{-1} indicated the presence of C=S and -NH functionality respectively and confirmed by doublet at δ = 6.47 (-CH=C-Ar) observed in 1H-NMR. These compounds were converted into (3a-c) by cyclization with DMF and chloroacetic acid. Formation of thiazolidinone ring was characterized by an intense band observed at 659 cm^{-1} due to C-S-C linkage, at 1693 cm^{-1} for C=O linkage and disappearance of band at 1286 cm^{-1} of C=S str.

Compounds (3a-c) were condensed with benzaldehyde in ethanolic media by using catalytic amount of glacial acetic acid yielding corresponding chalcone derivatives (4a-c). Their structures were corroborated by 1H-NMR spectral studies in which a singlet was observed at δ = 7.87. When compounds (4a-c) were subjected to react with guanidine nitrate, a cyclocondensation reaction gave 2,4,8-triphenyl-4H-9-thia-1,4a,5,7-tetraaza-fluoren-6-ylamine (5a-c). The IR spectra of compound showed an absorption band at 3447 cm-1 corresponds to $–NH_2$ group, confirming the occurrence of ring closer in the form of amino pyrimidine.

1H-NMR spectrum of compound (5a-c) revealed a singlet at 5.78 attributed to NH_2 proton. Treatment of (5a-c) with bromoethoxyphthalimide in ethanol using pyridine as a base gave titled compounds (6a-c). Structures of these were characterized by strong band at 1339, 1079 cm^{-1} for –N-O, -C-O str. respectively. The mass spectrum also supported the structures of these compounds by viewing molecular ion peak. Further confirmation of ethoxyphthalimide group attachment was provided by a standard fluorescence assay. All these reactions are shown in the reaction scheme.



Scheme 1: Synthesis of ethoxyphthalimide linked pyrimidothiazolidinone derivatives

Table 1
Physical and analytical data of all synthesized compounds

Compd. No.	Mol. Formula	Mol. Weight	R	m.p. (ºC)	Yield (%)	Found (Calcd.) % N
1a	$C_{15}H_{12}O$	208	H	59-61	92	-
1b	$C_{15}H_{11}OBr$	287	Br	50-53	96	-
1c	$C_{17}H_{17}NO$	251	$N(CH_3)_2$	54-58	89	5.12(5.57)
2a	$C_{16}H_{14}N_2S$	266	H	87-90	72	9.87(10.52)
2b	$C_{16}H_{13}N_2BrS$	345	Br	83-85	75	7.34 (8.10)
2c	$C_{18}H_{19}N_3S$	309	$N(CH_3)_2$	91-95	65	11.27(13.58)
3a	$C_{18}H_{14}N_2OS$	306	H	72-75	68	7.90 (9.14)
3b	$C_{18}H_{13}N_2BrOS$	385	Br	64-67	71	6.32 (7.27)
3c	$C_{20}H_{19}N_3OS$	349	$N(CH_3)_2$	66-68	63	11.21(12.02)
4a	$C_{25}H_{18}N_2OS$	394	H	88-90	82	6.02(7.10)
4b	$C_{25}H_{17}N_2BrOS$	473	Br	91-94	76	3.89(5.92)
4c	$C_{27}H_{23}N_3OS$	437	$N(CH_3)_2$	97-99	71	7.23(9.60)
5a	$C_{26}H_{19}N_5S$	433	H	128-132	59	15.87(16.15)
5b	$C_{26}H_{18}N_5BrS$	512	Br	135-140	67	12.34(13.67)
5c	$C_{28}H_{24}N_6S$	476	$N(CH_3)_2$	139-142	54	16.29(17.63)
6a	$C_{36}H_{26}N_6O_3S$	622	H	105-107	52	11.09(13.50)
6b	$C_{36}H_{25}N_6O_3SBr$	761	Br	109-112	56	11.17(11.98)
6c	$C_{38}H_{31}N_7O_3S$	665	$N(CH_3)_2$	103-106	48	13.78(14.73)

Table 2
IR and ^{1}H-NMR Spectral data of compounds (2a-c), (3a-c), (4a-c), (5a-c)

Compd. No.	IR (cm^{-1})	^{1}H-NMR (δ)
2a	3128 (Ar-CH str.), 1238 (C-N str.), 1286 (C=S), 3478 (N-H str.)	7.27-7.93 (m, 10H, Ar-H), 6.47 (d, 1H, -CH=C-Ar), 4.68 (d, 1H, -CH-Ar), 3.86 (s, 1H, -CH=C-NH-), 3.47(d, 1H, N-H proton of –CH-CH-NH-Ar)
2b	3165 (Ar-CH str.), 1253 (C-N str.), 1293 (C=S), 3485(N-H str.), 654 (C-Br str.)	7.31-8.06 (m, 9H, Ar-H), 6.84 (d, 1H, -CH=C-Ar), 4.85 (d, 1H, -CH-Ar), 3.95 (s, 1H, -CH=C-NH-), 3.78 (d, 1H, N-H proton of –CH-CH-NH-Ar)
2c	3105 (Ar-CH str.), 1217 (C-N str.), 1242 (C=S), 3447 (N-H str.)	7.07-7.57 (m, 9H, Ar-H), 6.21 (d, 1H, -CH=C-Ar), 4.25 (d, 1H, -CH-Ar), 3.59 (s, 1H, -CH=C-NH-), 3.27(d, 1H, N-H proton of –CH-CH-NH-Ar), 3.13 (s, 6H, $N(CH_3)_2$)
3a	3152 (Ar-CH str.), 1249 (C-N str.), 659 (C-S-C), 1693 (C=O str.), 1632 (C=N str.)	7.14-7.84 (m, 10H, Ar-H), 6.53 (d, 1H, -CH=C-Ar), 5.42 (d, 1H, -CH-Ar), 3.83 (s, 2H, S-CH_2)
3b	3175 (Ar-CH str.), 1273 (C-N str.), 685 (C-S-C), 1712 (C=O str.), 1654 (C=N str.), 689(C-Br str.)	7.31-8.26 (m, 9H, Ar-H), 6.65 (d, 1H, -CH=C-Ar), 5.59 (d, 1H, -CH-Ar), 4.03 (s, 2H, S-CH_2)
3c	3117 (Ar-CH str.), 1221 (C-N str.), 634 (C-S-C), 1668 (C=O str.), 1612 (C=N str.)	6.96-7.48 (m, 9H, Ar-H), 6.24 (d, 1H, -CH=C-Ar), 5.15 (d, 1H, -CH-Ar), 3.65 (s, 2H, S-CH_2), 2.89 (s, 6H, $N(CH_3)_2$)
4a	3133 (Ar-CH str.), 1256 (C-N str.), 645 (C-S-C), 1717 (C=O str.), 1607 (C=N str.)	7.20-8.10 (m, 15H, Ar-H), 7.87 (s, 1H, -C-CH=Ar), 5.64 (d, 1H, -CH-Ar),
4b	3165 (Ar-CH str.), 1276 (C-N str.), 692 (C-S-C), 1728 (C=O str.), 1627 (C=N str.), 718 (C-Br str.)	7.37-8.18(m, 14H, Ar-H), 7.94 (s, 1H, -C-CH=Ar), 5.85 (d, 1H, -CH-Ar),
4c	3078 (Ar-CH str.), 1229 (C-N str.), 639 (C-S-C), 1703 (C=O str.), 1579 (C=N str.)	7.34-7.85 (m, 14H, Ar-H), 7.36 (s, 1H, -C-CH=Ar), 5.32 (d, 1H, -CH-Ar), 3.01 (s, 6H, $N(CH_3)_2$)
5a	3098 (Ar-CH str.), 1243 (C-N str.), 1642 (C=N str.), 3447 (-NH_2 str.)	7.23-7.78 (m, 15H, Ar-H), 6.45 (d, 1H, -CH=C-Ar), 5.34 (d, 1H, -CH-Ar), 5.78 (s, 2H, -NH_2)
5b	3125(Ar-CH str.), 1263 (C-N str.), 1659 (C=N str.), 3476 (-NH_2 str.), 716 (C-Br str.)	7.21-7.89 (m, 14H, Ar-H), 6.76 (d, 1H, -CH=C-Ar), 5.51 (d, 1H, -CH-Ar), 6.10 (s, 2H, -NH_2)
5c	3029 (Ar-CH str.), 1225 (C-N str.), 1619 (C=N str.), 3428(-NH_2 str.)	7.01-7.59 (m, 14H, Ar-H), 6.23 (d, 1H, -CH=C-Ar), 5.04 (d, 1H, -CH-Ar), 5.38 (s, 2H, -NH_2), 3.34 (s, 6H, $N(CH_3)_2$)

Table 3
IR, ^{1}H-NMR and Mass Spectral data of compounds (6a-c)

Compd. No.	IR (cm^{-1})	^{1}H-NMR (δ)	Mass (m/z)
6a	3072 (Ar-CH str.), 1339 (-N-O str.), 1079 (-C-O str.), 3374 (-NH str.), 1705 (-C=O str.)	7.38-7.76 (m, 19H, Ar-H), 6.19 (d, 1H, -CH=C-Ar), 5.23 (d, 1H, -CH-Ar), 5.45 (t, 2H, -OCH_2), 4.67 (t, 2H, N-CH_2)	622[M]+· 544[M-C_6H_6]+· 475[M-$C_8H_5NO_2$]+· 416[M-$C_{10}H_{10}N_2O_3$]+· 206[M-$C_{26}H_{16}N_4S$]+· 191[M-$C_{26}H_{17}N_5S$]+· 177[M-$C_{27}H_{19}N_5S$]+· 147[M-$C_{28}H_{21}N_5OS$]+·
6b	3117 (Ar-CH str.), 1354 (-N-O str.), 1114 (-C-O str.), 3427 (-NH str.), 1722 (-C=O str.), 746(C-Br str.)	7.23-8.11 (m, 18H, Ar-H), 6.59 (d, 1H, -CH=C-Ar), 5.74 (d, 1H, -CH-Ar), 8.89 (s, 1H, -NH), 5.76 (t, 2H, -OCH_2), 4.90 (t, 2H, N-CH_2)	700[M] +· 702[M+2] +· 622[M-C_6H_6]+· 553[M-$C_8H_5NO_2$]+· 537[M-$C_8H_5NO_3$]+· 509[M-$C_{10}H_9NO_3$]+· 206[M-$C_{26}H_{15}N_4SBr$]+· 156[M-$C_{30}H_{20}N_6O_3S$]+· 147[M-$C_{28}H_{20}N_5OSBr$]+·
6c	3038 (Ar-CH str.), 1324 (-N-O str.), 1058 (-C-O str.), 3334(-NH str.), 1686 (-C=O str.)	7.02-7.88 (m, 18H, Ar-H), 5.89 (d, 1H, -CH=C-Ar), 8.12 (s, 1H, -NH), 3.27 (s, 6H, $N(CH_3)_2$), 5.22 (t, 2H, -OCH_2), 4.18 (t, 2H, N-CH_2)	665[M] +· 502[M-$C_8H_5NO_3$]+· 488[M-$C_9H_7NO_3$]+· 459[M-$C_{10}H_{10}N_2O_3$]+· 191[M-$C_{28}H_{22}N_6S$]+· 147[M-$C_{30}H_{26}N_6OS$]+· 121[M-$C_{30}H_{20}N_6O_3S$]+·

Table 4
***In vitro* anti-microbial activity (MICs, µg/mL) of compounds 5a-c and 6a-c.**

Com.	Antibacterial activity				Antifungal activity		
	Gram +ve		Gram –ve				
	S. aureus **MTCC *96***	***S. pyogenes*** **MTCC 443**	***E. coli*** **MTCC 442**	***P. aeruginosa*** **MTCC 441**	***C. albicans*** **MTCC 227**	***A. niger*** **MTCC 282**	***A. clavatus*** **MTCC 1323**
5a	500	500	100	250	500	200	125
5b	>1000	250	500	1000	>1000	250	200
5c	250	100	62.5	100	500	100	100
6a	500	1000	500	125	500	125	125
6b	500	200	250	200	>1000	250	62.5
6c	>1000	125	125	250	1000	200	250
S_1	250	100	100	--	-	-	-
S_2	-	-	-	-	500	100	100

S_1- Ampicillin, S_2- Griseofulvin

When compared to conventional medications, all the test substances demonstrated appreciable activity. It was found that several of the heterocycles were equivalent to or stronger than the common medications.

The compounds 5c and 6b can be developed into powerful chemotherapeutic drugs since they have substantial antibacterial activity against the bacteria *E. coli* and *P. aeruginosa* as well as the fungi *C. albicans*, *A. niger* and *A. clavatus*.

Conclusion

In this study, spectroscopic and analytical analyses were used to characterize a series of pyrimidothiazolidinones from chalcone that were coupled by ethoxyphthalimides. *In vitro* anti-microbial activity of the compounds was assayed against a panel of infectious bacterial and fungal strains.

When compared to traditional medications, anti-microbial data showed that the compounds 5c and 6b significantly exhibited activity against all bacterial and fungal strains.

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