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REVIEW: ANTI-MICROBIAL IMPORTANCE OF 1,3-THIAZOLE DERIVATIVES

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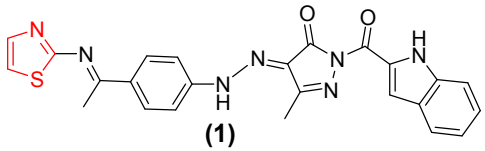
Abstract: Heterocyclic compounds were the major family of organic compounds. These are enormously essential with wide range of synthetic, pharmaceutical and industrial applications and are famous for their biological activities. These five membered heterocyclic compounds have broadened scope in remedying various dispositions in clinical medicines. Thiazoles have been reported to show pharmacological activities. Data on the synthesis of thiazoles systems from thioamide, thiourea, thiosemicarbazide, and labile sulfur was reviewed. This articles aims to review the work reported, their chemistry and biological activities of thiazole during past years as anti-microbial agent.

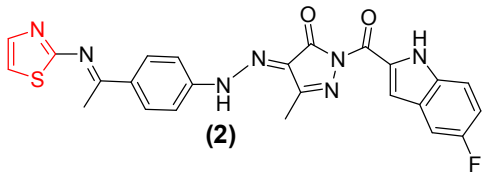
Key words: Thiazoles, Anti-bacterial agent, Anti-fungal agent, Anti-microbial study, Pharmacological activities.

Introduction: Thiazole derivatives are important class of sulfur containing heterocyclic compounds, found in many potent biologically active molecules such as Cefdinir (antibacterial drug, semisynthetic third generation cephalosporin drug), flucloxacillin (androgenic steroid danazol), Pramipexole (The dopamine D_2-agonist), Sulfathiazol (antimicrobial drug), Ritonavir (The HIV-1 protease inhibitor, antiretroviral drug), Famotidine (H2-receptor antagonist), Febuxostat (Xanthine oxidase inhibitor), Ziprasidone (Antipsychotic agent), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug), Fanetizole (anti-inflammatory), Combendazole (fungicidal), Niridazole (Schistozomicidal), Carurnonaml (monobactam antibiotic), Cefditoren pivoxil (cephalosporin), Amiphenazol (respiratory stimulant), Aztreonam (monobactam antibiotic), tiazofurin (anticancer), Nizatidine (Histamine H2-receptor antagonist), Nitazoxanide (antiprotozoal). 2-Aminothiazole derivatives are mainly known as biologically active compounds with a broad range of activities and used as intermediates in the synthesis of antibiotics, such as the well known sulfa drugs such as sulfathiazole. The chemistry and pharmacology of thiazole derivative have been of great interest to medicinal chemistry because thiazole derivatives have wide range of pharmacological properties. It has been noticed continuously over the years that interesting biological activities [1-2] were associated with thiazole derivatives. Recently the applications of thiazoles were found in drug development for the treatment of allergies [3], hypertension [4], inflammation [5], schizophrenia [6], bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain [10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B. [12] A brief review of thiazoles associated with antimicrobial activity is presented below.

Antimicrobial activity: A variety of 3-methyl-1-[(5-substituted-1H-indol-2-yl)carbonyl]-4-{[4-(substitutedthiazol-2-yl)iminoethyl)phenyl]hydrazono}-2-pyrazolin-5-one derivatives were synthesized from 4-aminoacetophenone and 2-aminothiazols by conventional and microwave method [13]. All the synthesized compounds were tested for their antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*), Gram-negative bacteria ((*Pseudomonas aurignosa*, *Echerichia coli*, *Enterobacter aerogenes*), as well as fungi (*Aspergillus niger*, *Penicillium italicum*, *Fusarium oxysporum*) with reference to standard drugs, ampicillin. The compounds (**1,2**) showing potent antimicrobial activity.

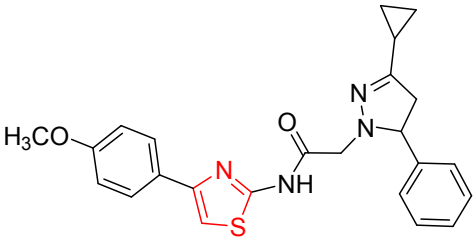


(1)

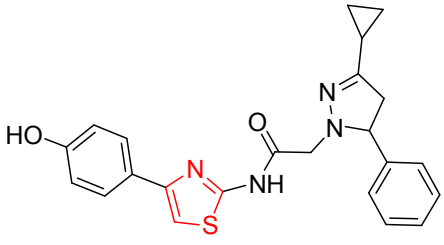


(2)

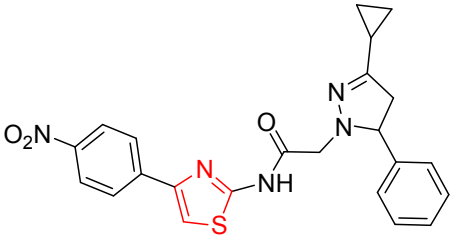
A series of thiazoles containing pyrazoline derivatives at position 2 (e.g. **3a-b, 4**) were synthesized from 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide and chalcones. The *in vitro* antimicrobial activities of the synthesized compounds were investigated against four pathogenic representative microorganism *Staphylococcus aureus* ATCC6538P, *Pseudomonas aeruginosa* ATCC9027, *Es-cherichia coli* ATCC8739 and *Candida albicans* ATCC2091 using Ampicillin, Imipenam and Clotrimazole as standard drugs by agar well-diffusion method [14]. Also same sequence of the reaction followed to obtain 2-substituted pyrazoline derivatives and for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique [15]. Most of the compounds showed a moderate degree of potent antimicrobial activity. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl) acetamide (**5**) was the showing highest anti-bacterial activity while 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetami-de (**6**) exhibited highest antifungal activity.



(3a)



(3b)



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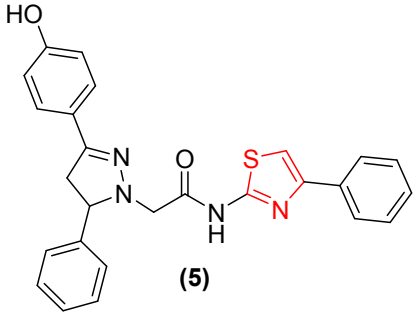
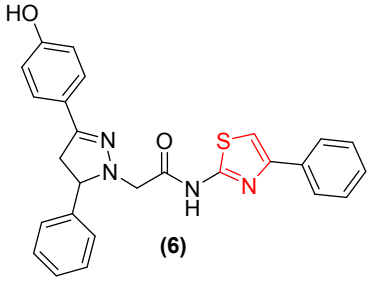


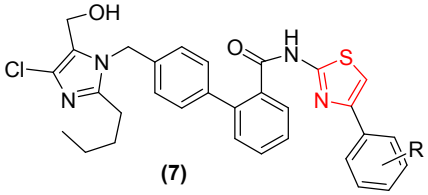
(5)

A series of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-caboxylic acid-(4-phenyl/substitutedphenyl thiazole)-amide (**7**) were synthesized from substituted acetophenone by series of reactions. The synthesized compounds were screened for their *in vitro* antibacterial activity against *S. aureus* and *B. subtilis* and also for in-vitro antifungal activity against C. *albicans and A. Niger* [16]. It has been observed that all the compounds exhibited the activity against all the organisms employed.

The 1-(5-(4-chlorophenyl)thiazol-2-yl)hydrazine hydrobromide (**8**) was synthesized by condensation of 2-bromo-1-(4-chlorophenyl)ethanone with thiosemicarbazide and screened for *in vitro* antibacterial screening by agar well diffusion method against ten different Gram positive and Gram negative bacteria and it exhibited strong efficacy against *B. subtilis* and *S. aureus* [17].

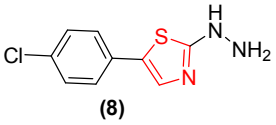


(6)



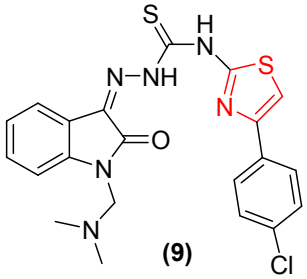
(7)

R = Cl, F, p-OCH3, 2,4-(OCH3)2, 2,4-(OEt)2



(8)

A series of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'chloropheyl) thiazol-2-yl]thiosemicarbazide synthesized from and studied antimicrobial activity by agar dilution method against 28 pathogenic bacteria, 8 pathogenic fungi and anti-HIV-1 (IIIB) in MT-4 cells [18]. The compound (**9**) showed the most favorable antimicrobial activity. A series of N-{4-[(4-amino-5-sulphanyl-4H-1, 2, 4-triazol-3-yl) methyl]-1, 3-thiazol-2-yl}-2-substituted amide derivatives were reported and tested for their preliminary in vitro antibacterial activity against S. aureus, E. coli, P. aeroginosa and S. typhosa and then were screened for antitubercular activity against M. tuberculae H37Rv strain [19]. Among the all compound (**10**) and (**11**) showed best activity. The various novel oxazolidinone analogue containing substituted thiazole/fused bicyclic [imidazo[1,2-b] pyradazine/imidazo [2,1-b] thiazole groups were designed and synthesized and evaluated their in vitro antibacterial activity against S. aureus [20]. Among them compound (**12**) displayed promising antibacterial activity comparable to that of standard linezolid. The new set of 2-thiazolylimino-5-arylidene-4-thiazolidinones were synthesized and assayed in vitro for their antimicrobial activity against Gram positive and Gram negative bacteria, yeast and mould [21]. All the compounds especially compound (**13**) exhibited potent against Gram positive bacteria. They have studied the SAR study and it has been observed that the 5-arylidene derivatives showed a significant antibacterial efficacy greater than that of the parent compound which indicates that the unsubstituted and substituted 5-arylidene moiety plays an important role in enhancing the antimicrobial properties of this class of compounds.



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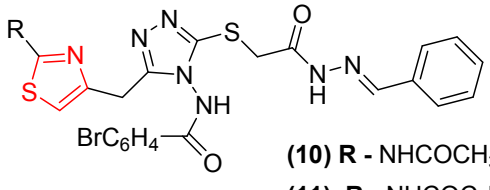
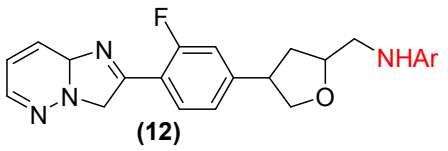
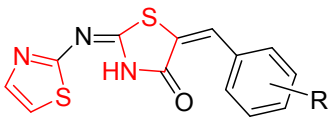


(10) R - $NHCOCH_3$

(11) R - $NHCOC_6H_5$



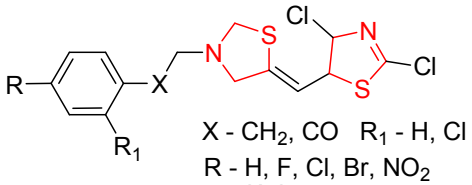
(12)



R - H, OH, OCH_3, NO_2, Cl

(13)

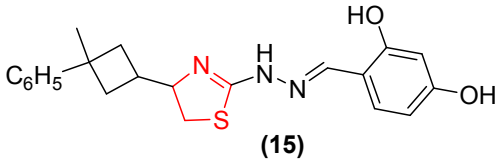
The thiazolyl thiazolidine-2,4-dione derivatives were reported and screened them for their antibacterial and antifungal activities against methicillin resistant S. aureus, E. coli and C. albicans [22]. From the all reported series of compounds (**14**) were found to be moderately potent against screened microorganisms. The SAR study showed that the anti-fungal activity of the substituents at the phenyl ring of thiazolyl thiazolidine-2,4-dione is H, Cl, Br, o,p-diCl > F, NO_2 for benzylic 2,4-TZD compounds. As for phenacyl 2,4-TZD compounds, it is Cl, Br > H, F, o,p-di-Cl, NO_2. The series of Schiff bases containing 2, 4-disubstituted thiazole, cyclobutane rings and hydrazones moieties in the same molecule were synthesized and evaluated them for antibacterial and antifungal activities [23]. Among the tested compounds, the most effective compound providing a MIC value of 16 µg ml-1 was found to be (**15**) against C. tropicalis and B. subtilis. The new thiazole derivatives of triazoles were reported and evaluated for antifungal and antibacterial activity [24]. Their antimicrobial activities against Candida albicans (two strains), C. glabrata, E. coli, S. aureus, P. aeruginosa were investigated and results showed that out of the reported compounds (**16**) have very strong antifungal activity.



X - CH_2, CO R_1 - H, Cl

R - H, F, Cl, Br, NO_2

(14)



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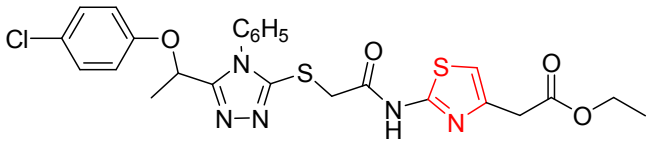
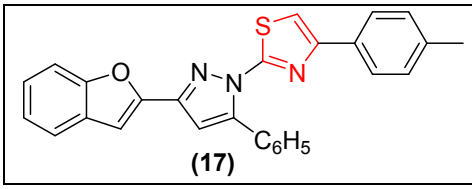
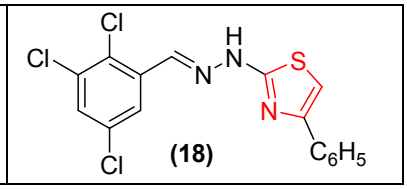


(16)

The series of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles were synthesized and all were screened for their antibacterial and antifungal activities [25]. The compound (**17**) showed a significant activity against E. coli higher than that of the control drug, whereas antifungal activity against Aspergillus niger was exhibited equal to that of the reference drug. The novel 4-aryl-2-(2, 3, 5-trichlorophenylidenehydrazino)-1, 3-thiazoles were synthesized in good yield and screened for their antibacterial and antifungal activities [26]. Preliminary results reveal that derivatives of synthesized compound (**18**) are showing promising antimicrobial activity.



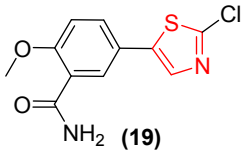
(17)



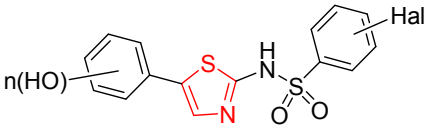
(18)

The series of 5-{2-[(N-substituted aryl) amino]-1, 3-thiazol-5-yl}-2-hydroxy benzamides were synthesized by reacting 5-(bromoacetyl) salicylamide with thiourea, thioformamide, thioalkylamide and substituted thioureas in absolute ethanol which were further converted to

5-(2-substituted–1, 3-thiazol-5-yl)-2-alkoxybenzamides and 5-(2-N-(substituted aryl)-1, 3-thiazol-5-yl)-2-alkoxy benzamides by reacting with n-alkylbromides in presence of a base [27]. The newly synthesized compounds were screened for their antifungal activity among which compound (**19**) exhibited significant activity. The synthesized polymethoxylated and polyhydroxylated derivatives of 2-amino-4-arylthiazoles bearing a halogenobenzenesulfonamide moiety (**20**) at position 2 as azole and in vitro assays against various pathogenic fungal strains (Candida and Trichophyton species) showed no activity in comparison to econazole as reference [28]. A novel series of 2-thiazolylhydrazone derivatives [29] were synthesized and screened for their in vitro activities against 22 clinical isolates of Candida sp., representing six different species, compared to clotrimazole as a reference compound. The compound (**21**) exhibited higher potency against most of the Candida sp. considered.



(19)



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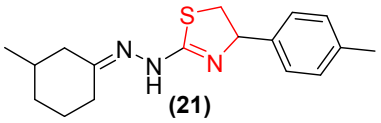
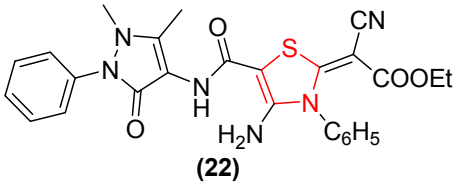


(21)

A series of thiazolylantipyrine and thiadiazolylantipyrine were synthesized and screened their antibacterial activity [30]. From these series of compounds, the molecules belonging to the thiazolylantipyrine series exhibited better antibacterial potencies than members of the thiadiazolylantipyrine one. Among these, compounds (**22**) and (**23a,b**) are most active antimicrobial members identified in this study with a broad spectrum of antibacterial activity against both Gram positive and Gram negative bacteria. These were also showing anti-inflammatory anti analgesic profile.



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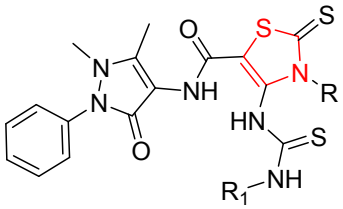
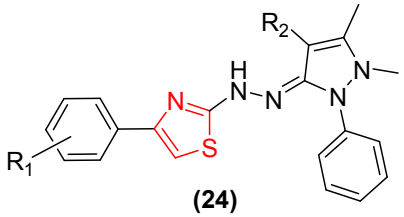


(23a) - R = R_1 = C_6H_5

(23b) - R = C_6H_5, R_1 = $4ClC_6H_4$

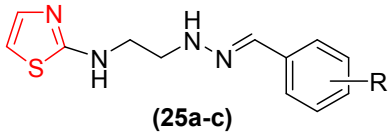
A novel series of thiazole derivatives (**24**) were synthesized and screened for their anti-bacterial and anti-fungal activity [31]. The antibacterial activities were evaluated against gram positive bacteria and gram negative bacteria, all the compounds had shown moderate to significant anti-bacterial activity with respect to standard.



(24)

A new series of 3-chloro-4-(substituted phenyl)-1-{[2-(2-thiazolylamino)ethyl]amino}-2-azetidinone, compounds, were synthesized from 2-aminothiazole [32]. All the synthesized compounds were screened for their antibacterial and antifungal activities against some selected bacteria and fungi and for their antitubercular activity against *Mycobacterium tuberculosis*, and their minimum inhibitory concentration (*MIC*) values were determined. All the synthesized compounds have a SAR activity because the activity of the compounds varied with substitution. The nitro group-containing compounds (**25a-c**) showed higher activity than

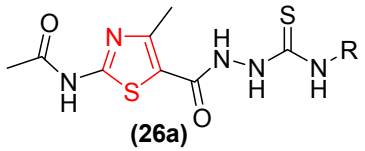
the chloro and bromo group containing compounds. The SAR activity can be concluded that the activity of the compounds depends on electron withdrawing nature of the substituent groups. The sequence of the activity was in the following order: NO_2 > Cl > Br > OH > > OCH_3 > CH_3.



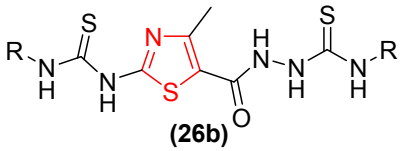
(25a-c)

a - R = 2-NO_2
b - R = 3-NO_2
c - R = 4-NO_2

Two newly synthesized series of 2,4,5-polysubstituted thiazoles compounds were subjected to in-vitro antibacterial and antifungal screening [33]. Thirteen derivatives displayed inhibitory effect on the growth of three Gram-positive strains while they lack activity against Gram-negative bacteria. Four derivatives were able to exert antifungal activity against C. albicans. Potential antibacterial and antifungal activities were linked to the thiosemicarbazide function and those substituted with both the thioureido and thiosemicarbazide moieties. Compounds **26a-b** (R = 4-F-C_6H_4) could be considered as the most active members in this investigation with a broad spectrum of antibacterial activity against three types of Gram-positive bacteria, together with an appreciable antifungal activity against C. albicans. Seventeen compounds were selected and tested for their preliminary in-vitro anticancer activity according to the current one-dose protocol of the NCI. Three cell lines, non-small cell lung cancer Hop-92, ovarian cancer IGROV1, and melanoma SK-MEL-2, were used for testing. Compound **26b** proved to be the most active anticancer member with a broad spectrum of activity against most of the tested subpanel tumor cell lines.

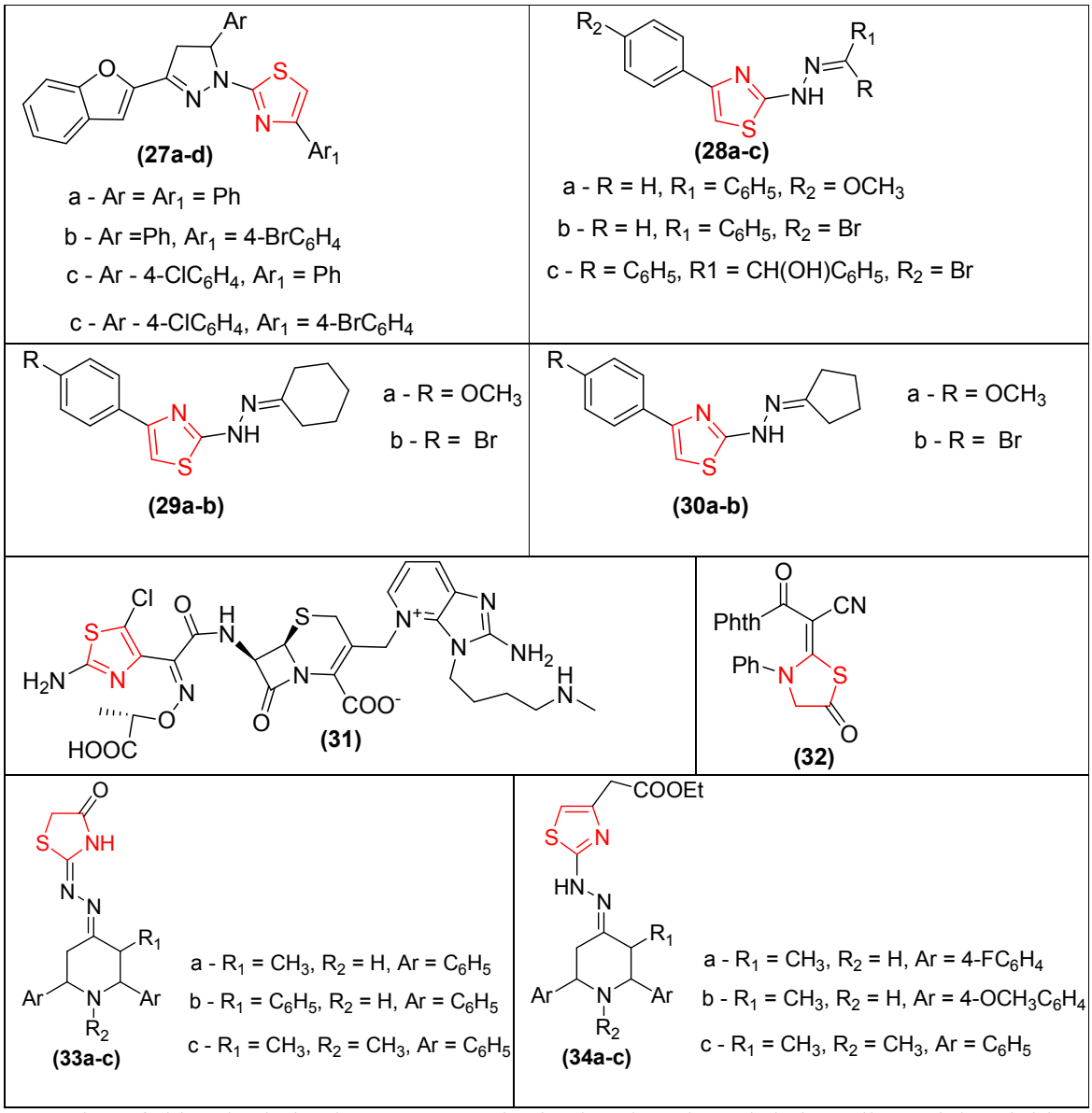


(26a)



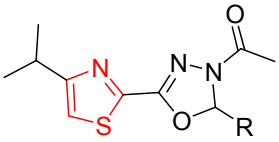
(26b)

Various derivatives of thiazoles were synthesized such as pyrazoline incorporated thiazole derivatives [34] (**27a-d**) (screened for antibacterial and antifungal activity against Escherichia coli and Aspergillus niger), A series of arylidene-2-(4-(4-methoxy/bromophenyl)thiazol-2-yl)hydrazine and 1-(4-(4-methoxy/bromophenyl)-thiazol-2-yl)-2-cyclohexylidene/ cyclopentylidene hydrazine were synthesized and screened for antifungal and anti-bacterial activity with with MIC values [35]. Among all the compounds screened showed moderate to good anti-bacterial activity while ten of the newly synthesized compounds displayed good to excellent anti-fungal activity. Among the tested compounds, the most effective compounds with MIC value in the range of 6.25–25 μg/ml are **28a-c, 29a-b,** and **30a-b** against three fungal strains viz. *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus flavus* than standard drug (Fluconazole).7β-[2-(2-amino-5-chlorothiazol-4-yl)-2(Z)-((S)-1-carboxyethoxyimino)acetamido] cephalosporins bearing various pyridinium groups at the C-3′ position [36] (cephalosporins, 2-amino-1-(3-methylamino-propyl)-1H-imidazo-[4,5-b]-pyridinium group at the C-3’ position (**31**) showed potent and well-balanced antibacterial activities against P. aeruginosa and other Gram-negative pathogens), 3-oxopropiononitrile and thioamide derivatives for new thiazole [37] (compound **32**) showed potent antibacterial activity, thiazolidinones and thiazoles [38] (tested against Mycobacterium tuberculosis, compounds (**33a-c**) and (**34a-c**) exhibited two fold activity than Rifampicin).



A series of thiazole derivatives were synthesized and evaluated their antibacterial activities such as 4-isopropylthiazole-2-carbohydrazide analogs derived clubbed oxadiazole-thiazole and triazole-thiazole derivatives and evaluated them for in vitro antibacterial, antifungal and antitubercular activity against Mycobacterium tuberculosis H37Rv strain [39] (compounds **35a-c** showed potent antitubercular efficacy), 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)-2-pyrazoline derivatives [40] and tested for antibacterial and antifungal activity (compounds **36a-e** exhibited stronger antifungal and antibacterial activities), 5-((3-oxoisothiazol-2(3H)-yl)methyl)-3-phenyloxazolidin-2-ones and analogous 2-(4-substituted phenyl)-3(2H)-isothiazolones [41] (compounds **37a-c** showed potent activity), thiazolylcoumarin derivatives [42] and screened in vitro for antibacterial activity against Mycobacterium tuberculosis and Candida albicans (compounds **38a-b** and **39** exhibited very good activity), 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(4-methoxyphenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones [43] and screened for antifungal and antibacterial activities (compounds **40a-c** showed excellent activity against fungi, whereas compounds **40d-f** displayed against bacteria), and

oxovanadium (IV) complexes of Schiff's bases **41** and evaluated their antibacterial activity [44].

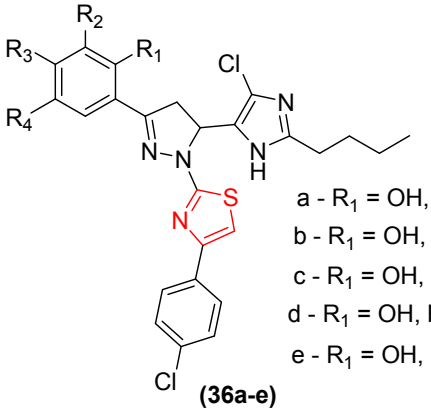


(35a-c)

a - R = C_6H_5

b - R = 3,4,5-$(OCH_3)C_6H_5$

c - R = 4-OHC_6H_5



(36a-e)

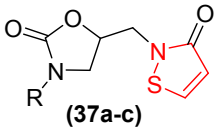
a - R_1 = OH, R_2 = I, R_3 = H, R_4 = Cl

b - R_1 = OH, R_2 = Br, R_3 = H, R_4 = Cl

c - R_1 = OH, R_2 = Cl, R_3 = H, R_4 = Cl

d - R_1 = OH, R_2 = Br, R_3 = H, R_4 = Br

e - R_1 = OH, R_2 = Cl, R_3 = H, R_4 = Cl

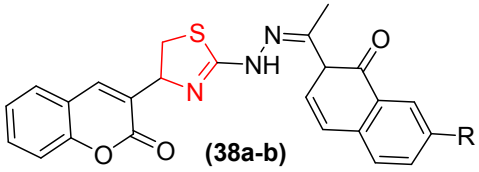


(37a-c)

a - R = C_6H_5

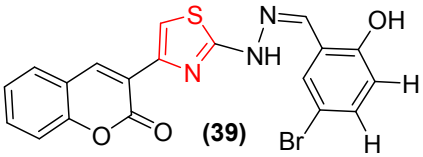
b - R = 4-FC_6H_4

c - R = $CH_2C_6H_5$

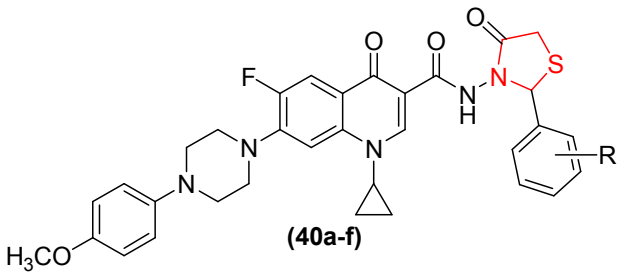


(38a-b)

a - R = Br, b - R = OH



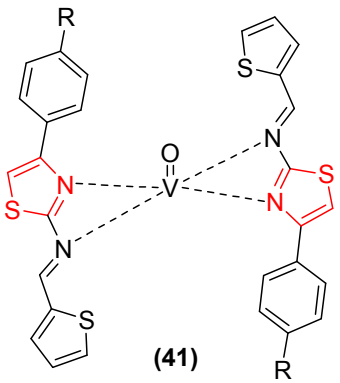
(39)



(40a-f)

a - R = 3-OCH_3, b - R = 4-OH, c - R = 3-OH

d - R = 2-NO_2, e - R = 2-Cl, f - R = 4-Cl

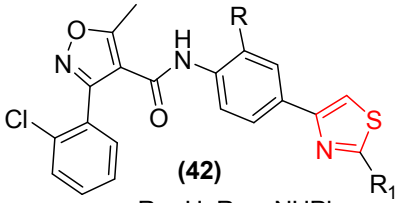


(41)

R = H, OH, OCH_3, NO_2, Cl, Br, CH_3

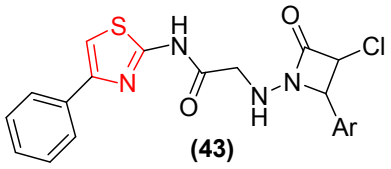
A variety of 2-substituted anilino/phenyl/benzyl/-5-substituted-4-phenylamido-(3-*o*-chlorophenyl-5-methylisoxazolyl) thiazoles were synthesized [45] and scanned their *in vitro* antitubercular activity and anti-microbial activity. The compound (**42**) exhibited potent *in vitro* antitubercular activity against $H_{37}RV$ strain and anti-microbial activity against *S.aureus* and *E.coli*. 2-(2'-arylidine-hydrazino-acetyl-amino)-4-phenyl-1,3-thiazoles and 2-[2'-{4"-substuted-aryl-3"-chloro-2"-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles were synthesized from 2-(2'hydrazino-acetyl)-amino-4-phenyl-1,3-thiazole and studied for their

antifungal activity against *Aspergilllus niger, Aspergilllus flavus, Fusarium oxisporium and Trichoderma viride* and antimicrobial activity against *E. coli, Bacillus substils, Klebsiella pneumoneae* and *Staphylococcus aureus* [46]. The halo-substituted phenyl derivatives (**43**) show good activity against the bacteria and fungi as compared to reference compounds.



(42)

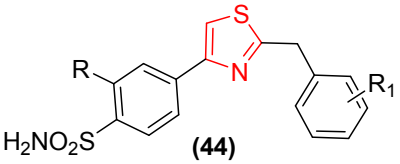
R = H, R_1 = NHPh



(43)

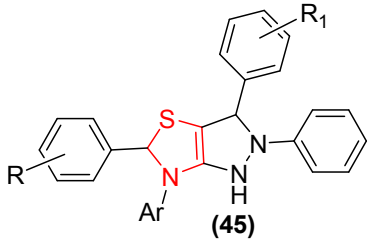
(Ar - halosub. phenyl group)

A series of 2-substituted benzyl-4-(*p*-phenylsulphonamido)-5-unsubstituted/methyl thiazoles were synthesized by treating 4-(*α*-bromoacetyl/2-bromopropionyl)phenyl sulphonamides with appropriate 2-substituted phenyl-thioacetamides in ethanol and evaluated for antibacterial activity against *S.aureus*, *S.typhi* and *E.coli* [47]. The compound (**44**) shows moderate antibacterial activity against EA and EC. 2-Phenyl-3,5-diphenyl(substituted)-6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo(3,4-d)thiazoles were synthesized by series of reactions from Schiff's bases of substituted benzaldehydes with primary arylamines and evaluated for its antibacterial activity against *S.aureus, E.coli, Actinmomyces pyogene* [48]. The results of antibacterial activity study revealed promising inhibitory activity for 2,3,5,6-tetrahydro-2H-pyrazolo[3,4-d] thiazole derivatives (**45**) with 4-chloro and 4-nitro phenyl substitutions at 5-position against all the tested strains.



(44)

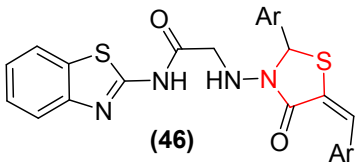
(R = H, R_1 = Cl)



(45)

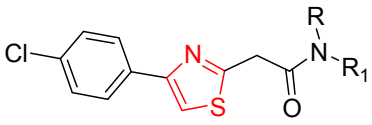
R = 4-Cl, 4-NO_2

A biologically active compounds of 2-amino benzthiazole derivative, some new [(2''-substituted aryl)-4"-oxo-1",3"-thiazolidine-3"-iminoacetyl]-2-aminobenzothiazole and [(5''-arylidene-2"-substitutedaryl-4"-oxo-1",3"-thiazolidine)-3"-iminoacetyl]-2-aminobenzothiazole [49] were synthesized from 2-amino benzothiazole which evaluated for their anti bacterial activity against *E.coli*, *S.aureus, K. pneumonia* and *B.substilis* and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxxisporum* and *Trichoderma niger*. The derivative (**46**) shows good activity. Some new substituted mercaptothiazoles and their derivatives were synthesized [50] and evaluated for their biological activity against *S. aureus* and *E. coli*. As compared to the reference standard drug norfloxacin, the compound (**47**) shows moderate activity at concentration range 100 – 150 µg/ml.



(46)

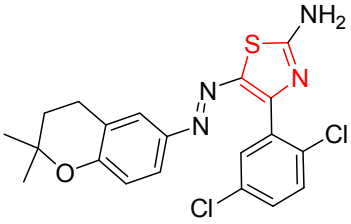
Ar - C_6H_5, Br, Cl, NO_2, $N(CH_3)_2$ derivatives



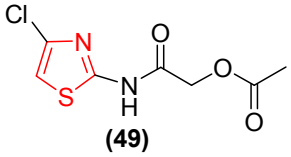
(47)

R = H, R_1 = C_6H_5

Some 2-Amino-4-aryl-5-chromannylazoles derivatives were synthesized by the condensation of diazotised 6-amino-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran with different 2-amino-4-arylthiazoles synthesized and studied anti microbial activity [51]. These compounds have been tested for their antifungal and antibacterial activities, the compound (**48**) shows good activity as compared the reference compounds. Some substituted amino thiazoles [52] were synthesized and evaluated for various biological activities like Anti-diabetic, anti-inflammatory,anti-fungal activity. The compound was tested *in vitro* for their anti-bacterial activity against two microorganisms viz. *E.coli, S. aureus* by disc diffusion method using Mullar-Hinton agar. The compound (**49**) shows good activity as compared the reference compounds.

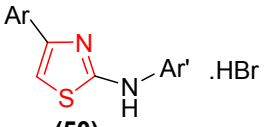


(48)

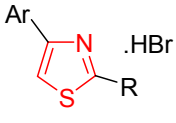


(49)

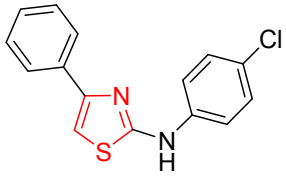
The Novel 16 flourine containing 2-(N-arylamino)- (**50**) / 2-methyl-4-arylthiazoles **(51)** were synthesized from appropriate fluorinated arylketones [53] and screened for their bactericidal activity on the standard bacterium (Staph. aureus strain NCTC 6571). Some of the screened compounds were sensitive. Remarkably high-speed syntheses of 2-amino-4-arylthiazoles were reported in polar solvent without use of any catalyst [54] and studied their antibacterial properties. The *in vitro* biological tests of some of the thiazoles showed good activity towards gram-positive bacteria, gram-negative bacteria and fungi comparable with the standard drugs, nitrofurantoin and griseofulvin, for their antibacterial and antifungal activities, respectively. Among them compound (**52**) and (**53**) showed good activity than standard drug (Nitrofurantoin).



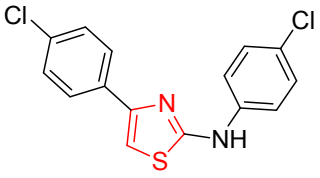
(50)



(51)

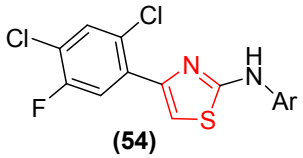


(52)

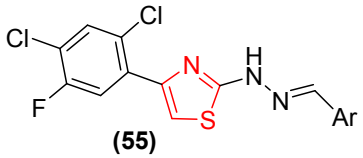


(53)

A series of arylaminothiazoles **(54)** and arylidine/5-aryl-2-furfurylidinehydrazinothiazole **(55)** were synthesized by condensing arylthioureas, aromatic aldehyde thiosemicarbazones and 5-aryl-2-furfuraldehyde thiosemicarbazones and were screened for antibacterial activity and anti-inflammatory activities [55]. The newly synthesized compounds showed moderate to good anti-inflammatory activity as compared with that of Ibuprofen.



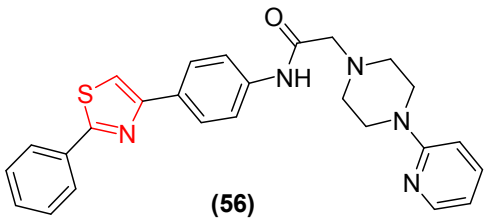
(54)



(55)

New 2-(4-arylpiperazine-1-yl)-N-[4-(2-(4-substitutedphenyl)thiazol-4-yl)phenyl]acetamide derivatives were synthesized [56]. These products were tested for their in vitro growth inhibitory activity against human pathogenic microorganisms as Gram-positive bacteria, Enterococcus faecalis (ATCC 29212) and as Gram-negative bacteria, Pseudomonas aeruginosa (ATCC 27853), Klebsiella pneumoniae (ATCC 700603), Escherichia coli (ATCC

35218), and E. coli (ATCC 25922) and yeast as Candida albicans (90028), Candida glabrata (ATCC 90030), Candida krusei (ATCC 6258), and Candida parapsilosis (ATCC 7330) by using Chloramphenicol and ketoconazole as control drugs and anti-cholinesterase activity was studied by using acetylcholinesterase enzyme, AChE using spectrophotometer. Acetylcholinesterase inhibitory activities of the compounds were found weak while that of antifungal activity of the compounds was found significant, especially against Candida parapsilosis. Compounds (**56**, **57**, and **58**) exhibited two-fold anticandidal activity compared with ketoconazole against C. parapsilosis.



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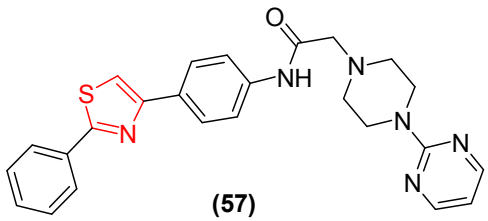

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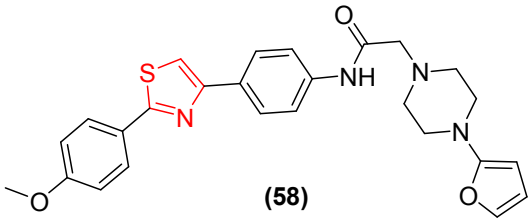
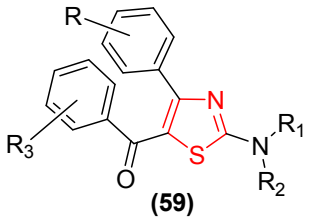


(58)

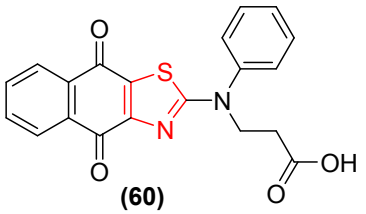
A series of 2, 4, 5-Trisubstituted thiazole derivatives [57] were synthesized from N-(Substituted benzoyl)morpholine/piperidine/pyrrolidine carbothioamide which was synthesized by condensing substituted benzoyl isothiocyanate with different secondary heterocyclic amines, like morpholine/piperidine/pyrrolidine. The newly synthesized thiazole derivatives were screened for in vitro anti bacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa* bacterial strains by paper disc diffusion method. All the synthesized compounds show moderate to good anti bacterial activity as compared to ciprofloxacin. Among the tested compounds (**59**) thiazole carrying 2-piperidino, 4-phenyl, 4-nitrobenzoyl is showing good activity against all the tested species.



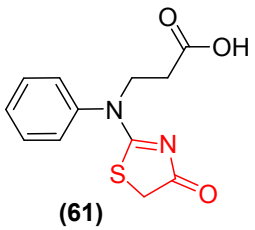
(59)

R = H
$R_1 = R_2 = (CH_2)_5$
R_3 = 4-NO_2

New derivatives of *N*,*N*-disubstituted β-amino acids with thiazole, aromatic, and heterocyclic substituents were synthesized [58] from *N*-phenyl-*N*-thiocarbamoyl-β-alanine by the Hantzsch method and derivatives with hydrazone fragments were also synthesized. These compounds was screened for antibacterial activity against Gram-positive spore-forming rods of *Bacillus cereus* (ATCC 11778), Gram-positive cocci of *Staphylococcus* (ATCC 9144), Gram-negative rods of *E. coli* (ATCC 8739) and *Pseudomonas aeruginosa* (NCTC 6750) by the broth and spread-plate methods. Among the all synthesized compounds, the highest antibacterial activity was exhibited by thiazole compound **(60)** containing a naphthoquinone ring and 3-[(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(phenyl)amino]propanoic acid **(61)** was found to promote rapeseed growth and to increase seed yield and oil content.

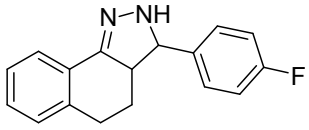


(60)



(61)

A new series of 3-(4-fluorophenyl)benzo[*g*]indazoles derivatives were synthesized by the reaction of α-tetralone with 4-fluorobenzaldehyde followed by reaction with hydrazine or thiosemicarbazide high yielding routes [59]. All the synthesized compounds were screened for their antibacterial and antifungal activities against four *Gram positive bacteria* (*Staphelococcus Aureus* ATCC 29213; *B. subtilis ATCC6633*; *B. megaterium ATCC* 9885 and *Sarcinalutea*), three *Gram negative bacteria* (*Klebseillapeneumoniae*ATCC13883; *Pseudomonas. Aeroginosa* ATCC27953; *E. coli ATCC 25922*) and two yeast (*Saccharomyces cervesia* and *Candida Albicans* NRRL Y-477). The newly synthesized compounds were evaluated for their antimicrobial activity and compounds **(62)**, **(63)**, **(64)** and **(65)** demonstrated inhibitory effects on the growth of a wide range of microbes.



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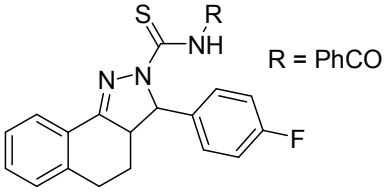
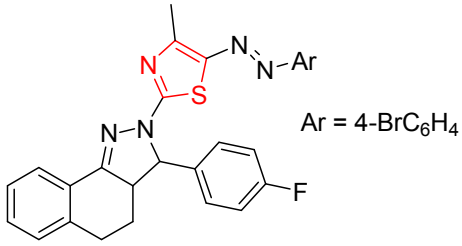


(63)



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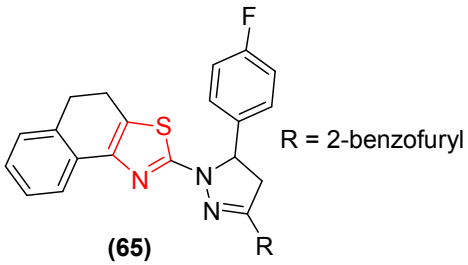
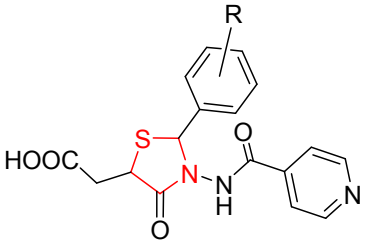


(65)

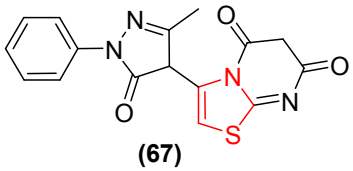
A series of Isoninicotinic acid hydrazide (INH) incorporated derivatives of thiazolidin-4-one (**66**), azetidin-2-one and 1,3,4-oxadiazole were synthesized from isonicotinic acid Hydrazide and pharmacologically evaluated for their *in vitro* antimicrobial activity [60]. A majority of the tested compounds showed good to moderate antimicrobial activity against all tested pathogenic bacterial and fungal strains.



(66)

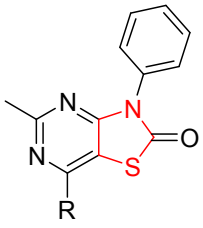
A series of 4- (2-Aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline were synthesized by the reaction of 4-bromoacetyl-3-methyl-5-oxo-1-phenyl-2-pyrazoline with thiourea and was transformed to related fused heterocyclic systems [61]. They evaluated these compounds for their antimicrobial activity (antifungal and antibacterial studies) against six fungal strains such as *Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis, Aspergillus*

flavus, Aspergillus niger and *Trichophyton rubrum* and five bacterial species *Bacillus cereus (Gram positive), Staphylococcus aureus (Gram positive), Pseudomonas aeruginosa (Gram negative), Serratia marcescens (Gram negative)* and *Escherichia coli (Gram negative)*. Compound 3- (4,5-dihydro-3-methyl-5-oxo-1-phenyl-1H-pyrazol-4-yl)-6H-thia- -zolo[3,2-a]pyrimidine-5,7-dione **(67)** showed a wide spectrum of antifungal activity but a narrow spectrum of antibacterial activity with minimum inhibitory concentrations (MIC = 5-50 mg/cm^3). They also reported that Gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens* were generally resistant to the test compounds.

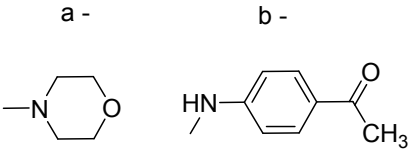


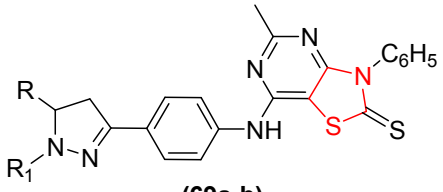
(67)

The synthesis of a series of new thiazolo[4,5-d] pyrimidine derivatives, such as 7- substituted amino-5-methyl-3-phenylthiazolo[4,5-d] pyrimidine - 2(3H)-thiones, ethyl 2-cyano-2-(7-substituted-5-methyl-3- phenylthiazolo[4,5-d]-pyrimidin-2(3H)-ylidene)acetates, 2-(7-substituted-5-methyl-3-phenylthiazolo [4,5-d] pyrimidin 2(3H)- ylidene)malononitriles, 5-methyl-7-morpholino-3-phenylthiazolo [4,5-d] pyrimidine-2(3H)-one, and 7-[4-(1-substituted-5-phenyl- 4,5-dihydro-lH-pyrazolin-3-yl)anUino]-5-methyl-3-phenyl thiazolo [4,5-d]pyrimidine-2(3H)-thiones were reported *via* the reaction of 4-(2-aminothiazol-4-yl)-3-methyl-1-phenyl-2-pyrazolin-5-one with benzylidene malononitrile and was then transformed to related fused heterocyclic systems [62]. They were screened for their antimicrobial activity against *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* using cup diffusion technique. Compounds (**68a, 69a-b**) showed both antimicrobial and antifungal activities. Compounds (**68a, 69a, 70a-b**) possess antimicrobial activity against *Escherichia coli* with inhibition zone (IZ) 18 – 20 mm and with minimum inhibitory concentration (MIC) 62.5 µg/ml while compounds (**68a, 68b, 69b**) showed the most antifungal activity against *Candida albicans* with IZ= 20- 25mm and MIC 31.25 µg/ml which is one sixth of the activity of clotrimazole.

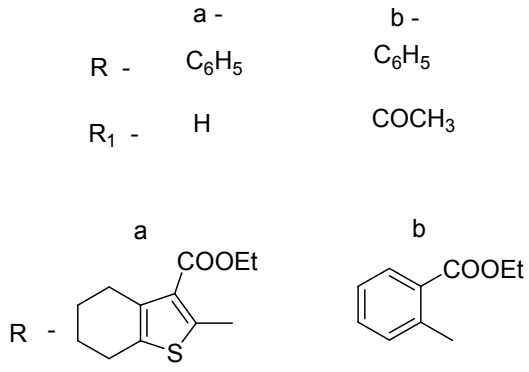


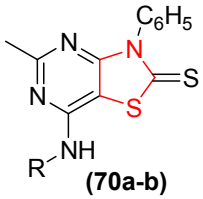
(68a-b)





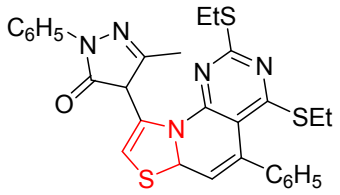
(69a-b)



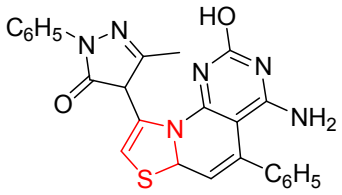


(70a-b)

A series of novel thiazolo[3,2-a]pyrimidine derivatives such as 2,4-Bis(ethylthio)-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4-e]thiazolo[3,2-a]pyrimidine and 4-Amino-2-hydroxy-9-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-phenyl-5H-pyrimido[5,4e]-thiazolo[3,2-a]-Pyrimidine were synthesized by using 5-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile [63]. All the synthesized compounds were tested for their antimicrobial activity against six fungal such as *Aspergillus flavus, Aspergillus niger, Candida albicans, Geotrichum candidum*, *Scopulariopsis brevicaulis* and *Trichophyton rubrum* and against five bacterial strains such as *Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens* and *Escherichia coli*. Comparing the minimum inhibitory concentration (MIC) of all tested compounds with their reference drugs such as chlotrimazole as antifungal agent and chloramphenical as antibacterial agent. Compounds **(71)** and **(72)** showed a wide spectrum of antifungal action but narrow spectrum of antibacterial effect with MIC ranging from 5 -50 mg/cm^3.

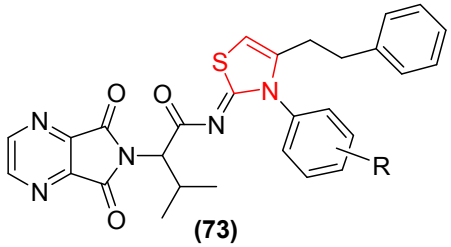


(71)



(72)

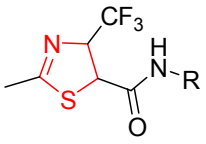
A series of the 6[1-oxo-1-(N-2-imino-3-substitutedphenyl-4-phenyl thiazole)-3-methyl-butane-2-yl]-5,7-dioxo pyrolo[2,3b] pyrazine derivatives (**73**) were synthesized by the series of reaction or one pot synthesis by using ammonium thiocyanate, water, acyl chloride, aryl amine and α-bromoacetone or α-bromoacetophenone [64]. All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli, P aeruginosa, gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method.



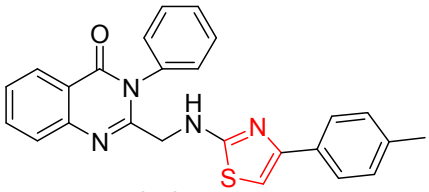
(73)

A novel series of 2-methyl-4-triflurомethyl-thiazole-5-carboxamide derivatives were synthesized from ethyl 4,4,4-trifluoroacetoacetate [65] and evaluated for fungicidal and insecticidal activity. All of the tested compounds have some fungicidal and insecticidal activity but no herbicidal activity. Compound **(74)** has fungicidal activity with 90% control of tomato late blight at 375 g ai/ha. A series of 3-aryl-2-(4'-aryl thiazole-2'-ylaminomethyl) quinazol-4(3H)-ones (**75**) have been synthesized by condensing 3-aryl-2-chloromethylquinazol-4(3H)-ones with 2-amino-4-substituted phenylthiazoles [66] and characterized by spectral data and evaluate their antifungal activity. Five derivatives of 2-imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones (**76**) and a series of their 5-arylidine derivatives were synthesized [67] and synthesized compounds antifungal activity was screened against seven agricultural fungi. 2-Imino-3-(2,4-dichloro-5-fluorophenylthiazol-2-yl)-4-thiazolidi-none and 2-imino-3-(2,4-dichlorophenylthiazol-2-yl)-4-thiazolidione, both of

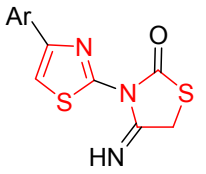
them new compounds, exhibited higher fungicidal effects than the other compounds prepared.



(74)



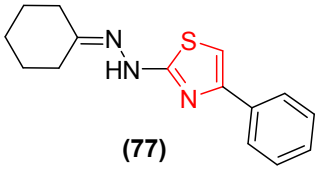
(75)



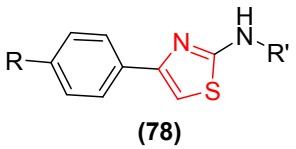
Ar - 2,4(Cl)$_2$C$_6$H$_3$

(76)

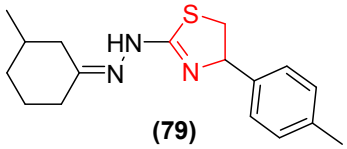
The *in vitro* antifungal activity cyclohexylidenehydrazo-4-phenylthiazole (EM-01D2) (**77**) was studied against 114 clinical isolates of *Candida* species including fluconazole-resistant *candida albicans*, representing five different species, by microdilution [68]. Toxicity *in vitro* was evaluated by MTT reduction assay. EM-01D2 demonstrated low toxicity, broad spectrum, fungicidal activity and was active against *C. albicans* and *Candida krusei* at concentrations lower than those shown by amphotericin B and fluconazole. It maintained potent *in vitro* activity against fluconazole-resistant *C. albicans* isolates. However, when *C. albicans* biofilms were pre-exposed to subinhibitory concentrations of EM-01D2, a reduction of MIC_{50} of amphotericin B was observed. Based on these results, EM-01D2 could represent a template for the development of novel fungicidal agents. 2-Arylamino-4-fluoroarylthiazoles, 2-Arylideneamino-4-fluoroarylthiazoles (**78**), 2-arylsulfonamido-4-fluoroaryl-5-H/alkyl thiazoles, 2-Acetamido-4-fluoroaryl-5-aryloxythiazoles were synthesized by the reaction of various fluorinated phenacyl bromides with arylthioureas [69]. In all sixty two new fluorinated heterocyclic compounds have been prepared. Out of these thirty six were screened against *Aspergillus niger* and *Aspergillus flavus* for their antifungal activity. Among the synthesized compounds many showed good antifungal activity. A novel series of 2-sulfonamidothiazoles derivatives [70] were synthesized and screened for their in vitro activities against 22 clinical isolates of Candida species, representing six different species, compared to clotrimazole as a reference compound. In this series, some of the compounds posses significant activity as compared to clotrimazole, compound **(79)** showed good activity against variety of candida species. The compounds that were most active as anti-Candida agents were also submitted to cytotoxic screening by the Trypan Blue dye exclusion assay and in general they were shown to induce low cytotoxic effects.



(77)

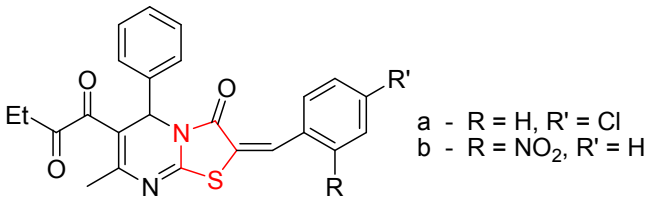


(78)



(79)

Various substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-*5H*-[1,3]-thiazolo[3,2-a]pyrimidie-6-carboxylate derivatives were synthesized by reaction of Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-a]pyrimidine-6-carboxylate with different aromatic aldehydes in ethanol:dioxane (2:1) medium [71]. All the compounds were screened for antifungal activity against *Aspergillus niger*, *Candida albicans* and Aspergillus flavus by using agar cup disk method. Evaluation of antifungal activity showed that almost all the compounds exhibited promising activity and thus could be promising novel drug candidates. Out of all the synthesize compounds, **(80a)** shows the excellent antifungal activity against *A. niger* and *A. flavus* and the compounds **(80b)** were promising antifungal activity against *Aspergillus Niger* and *Aspergillus flavus* as compared to the standard drug.



(80a-b)

References:

1. Quiroga J, Hernandez P, Insuasty B, Abonia R, Cobo J, Sanchez A, Nogueras M, Low JN. Control of the Reaction Between 2-Aminobenzothiazoles and Mannich Bases: Synthesis of pyrido[2,1-b][1,3]benzothiazoles versus [1,3]benzothiazolo[2,3-b]quinazolines. J Chem Soc Perkin Trans1. 2002; 4:555-559.
2. Hutchinson I, Jennings SA, Vishnuvajjala BR, Westwell AD, Stevens MFG. Antitumor Benzothiazoles. 16 Synthesis and Pharmaceutical Properties of Antitumor 2-(4-Aminophenyl)benzothiazole Amino Acid Prodrugs. J Med Chem. 2002; 45:744-747.
3. Hargrave KD, Hess FK, Oliver JT. N-(4-Substituted-thiazolyl)oxamic acid Derivatives, New Series of Potent, Orally Active Antiallergy Agents. J Med Chem. 1983; 26:1158-1163.
4. Patt WC, Hamilton HW, Taylor MD, Ryan MJ, Taylor Jr. DG, Connolly CJC, Doherty AM, Klutchko SR, Sircar I, Steinbaugh BA, Batley BL, Painchaud CA, Rapundalo ST, Michniewicz BM, Olson SCJ. Structure-activity relationships of a Series of 2-Amino-4-thiazole Containing Renin Inhibitors. J Med Chem. 1992; 35:2562-2572.
5. Sharma RN, Xavier FP, Vasu KK, Chaturvedi SC, Pancholi SS. Synthesis of 4-Benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: An Analogue-based Drug Design Approach. J Enz Inhib Med Chem. 2009; 24:890 – 897.
6. Jaen JC, Wise LD, Caprathe BW, Tecle H, Bergmeier S, Humblet CC, Heffner TG, Meltzner LT, Pugsley TA. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-Thiazolamines: A Novel Class of Compounds With Central Dopamine Agonist Properties. J Med Chem. 1990; 33:311-317.
7. Tsuji K, Ishikawa H. Synthesis and Anti-pseudomonal Activity of New 2-Isocephems with a Dihydroxypyridone Moiety at C-7. Bioorg Med Chem Lett. 1994; 4:1601-1606.
8. Bell FW, Cantrell AS, Hogberg M, Jaskunas SR, Johansson NG, Jordon CL, Kinnick MD, Lind P, Morin Jr. JM, Noreen R, Oberg B, Palkowitz JA, Parrish CA, Pranc P, Sahlberg C, Ternansky RJ, Vasileff RT, Vrang L, West SJ, Zhang H, Zhou XX. Phenethylthiazolethiourea (PETT) Compounds, a New Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs. J Med Chem. 1995; 38:4929-4936.
9. Ergenc N, Capan G, Gunay NS, Ozkirimli S, Gungor M, Ozbey S, Kendi E. Synthesis and Hypnotic Activity of New 4-Thiazolidinone and 2-Thioxo- 4,5-Imidazolidinedione Derivatives. Arch Pharm Pharm Med Chem. 1999; 332:343-347.
10. Carter JS, Kramer S, Talley JJ, Penning T, Collins P, Graneto MJ, Seibert K, Koboldt C, Masferrer J, Zweifel B. Synthesis and Activity of Sulfonamide-Substituted 4,5-Diaryl Thiazoles as Selective Cyclooxygenase-2 Inhibitors. Bioorg Med Chem Lett. 1999; 9:1171-1174.
11. Badorc A, Bordes MF, De Cointet P, Savi P, Bernat A, Lale A, Petitou M, Maffrand

JP, Herbert JM. New Orally Active Non-Peptide Fibrinogen Receptor (GpIIb-IIIa) Antagonists: Identification of Ethyl 3-[N-[4-[4-Amino[(ethoxycarbonyl)imino] methyl]phenyl]-1,3-thiazol-2-yl]-N-[1-(ethoxycarbonyl)methyl]piperid-4-yl]amino] propionate (SR 121787) as a Potent and Long-Acting Antithrombotic Agent. J Med Chem. 1997; 40:3393-3401.

12. Rudolph J, Theis H, Hanke R, Endermann R, Johannsen L, Geschke FU. seco-Cyclothialidines: New Concise Synthesis, Inhibitory Activity toward Bacterial and Human DNA Topoisomerases, and Antibacterial Properties. J Med Chem. 2001; 44:619-626.
13. Mostafa, M.S. and N.M. Abd El-Salam, Synthesis and biological evaluation of 3-methyl- 2-pyrazolin-5-one derivatives containing thiazole and indole moieties. *Der. Pharma. Chemica*, **2013,** 5: 1-7.
14. Sharshira, E.M. and N.M.M. Hamada, Synthesis, characterization and antimicrobial activities of some thiazole derivatives. *Am. J. Organ. Chem*., **2012,** 2: 69-73
15. Saravanan, G., V. Alagarsamy, T.G.V. Pavitra, G.C. Kumar and Y. Savithri et al., Synthesis, characterization and anti-microbial activities of novel thiazole derivatives. *Int. J. Pharma Bio Sci.,* **2010,** 1: 1-8.
16. Shreenivas, M.T., B.E. Kumara Swamy, G.R. Srinivasa and B.S. Sherigara, Synthesis and antibacterial evaluation of some novel aminothiazole derivatives. *Der. Pharma. Chemica*, **2011.** 3: 156-161.
17. Khan, I., A. Ibrar, M. Waqas and J.M. White, Synthesis, X-ray crystallographic studies and antibacterial screening of 1-(5-(4-Chlorophenyl) thiazol-2-yl) hydrazine hydrobromide. *Phys. Rev. Res. Int.,* **2013,** 3: 10-17.
18. Pandeya SN, Sriram D, Nath G, DeClerq E. Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl) thiazol-2-yl] thiosemicarbazide. *Eur J Pharm Sci.* **1999**; 9:25-31.
19. Shiradkar MR, Murahari KK, Gangadasu HR, Suresh T, Kalyan CA, Panchal D, Kaur R, Burange P, Ghogare J, Mokale V, Raut M. Synthesis of new S-derivatives of clubbed triazole as anti-Mycobacterium tuberculosis agents. *Bioorg Med Chem.* **2007**; 15:3997-4008.
20. Xin Z, Yang-fang Z, Jia W, Wei J, Liang H, Ping G. Synthesis and antibacterial activity of novel oxazolidinone analogues containing substituted thiazole/fused bicyclic groups. *Chem Res Chinese U.* **2006**; 22:459-464.
21. Vicini P, Geronikaki A, Anastasia K, Incerti M, Zani F. Synthesis and antimicrobial activity of novel 2-thiazolyl imino-5-arylidene-4-thiazolidinones. *Bioorg Med Chem.* **2006**; 14:3859-3864.
22. Dundar OB, Ozgen O, Mentese A, Altanlar N, Ath O, Kendj E, Ertan R. Synthesis and antimicrobial activity of some new thiazolyl thiazolidine-2,4- dione derivatives. *Bioorg Med Chem.* **2007**; 15:6012-6017.
23. Cukurovali A, Yilmaz I, Gur S, Kazaz C. Synthesis antibacterial and antifungal activity of some new thiazolylhydrazone derivatives containing 3-substituted cyclobutane ring. *Eur J Med Chem.* **2006**; 41:201-207.
24. Zitouni GT, Kaplancıklı ZA, Yıldız MT, Chevallet P, Kaya D. Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole derivatives. *Eur J Med Chem.* **2005**; 40:607–613.
25. Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM. Synthesis and antimicrobial

evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles. *Eur J Med Chem.* **2009**; 44:2632-2635.

26. Karegoudar P, Karthikeyan MS, Prasad DJ, Mahalinga M, Holla BS, Kumari NS. Synthesis of some novel 2,4-disubstituted thiazoles as possible antimicrobial agents. *Eur J Med Chem.* **2008**; 43:261-267.
27. Narayana B, Vijaya Raj KK, Ashalatha BV, Kumari NS, Sarojini BK. Synthesis of some new 5-(2-substituted-1,3-thiazol-5-yl)-2-hydroxy benzamides and their 2-alkoxy derivatives as possible antifungal agents. *Eur J Med Chem.* **2004**; 39:867–872.
28. Beuchet P, Varache-Lembège M, Neveu A, Léger JM, Vercauteren J, Larrouture S, Deffieux G, Nuhrich A. New 2-sulfonamidothiazoles substituted at C-4: synthesis of polyoxygenated aryl derivatives and in vitro evaluation of antifungal activity. *Eur J Med Chem.* **1999**; 34:773−779.
29. Chimenti F, Bizzarri B, Maccioni E, Secci D, Bolasco A, Fioravanti R, Chimenti P, Granese A, Carradori S, Rivanera D, Lilli D, Zicari A, Distinto S. Synthesis and *in vitro* activity of 2-thiazolylhydrazone derivatives compared with the activity of clotrimazole against clinical isolates of Candida spp. *Bioorg Med Chem Lett*. **2007**; 17:4635–4640.
30. Sherif A F R, Ibrahim M El-A, Heba A A El*, Bioorg. Med. Chem. Lett.,* 17, 882, **2009.**
31. R. Sumathi, A Sultan, S Syed Shafi, Anti-microbial evaluation of novel thiazole, *J. Pharm Sci Innov*. **2014**, 3(2), 139-142. Doi.org/10.7897/2277-4572.032125.
32. PUSHKAL SAMADHIYA*, RITU SHARMA, SANTOSH K. SRIVASTAVA and SAVITRI D. SRIVASTAVA, Synthesis of 2-oxoazetidine derivatives of 2-aminothiazole and their biological activity, *J. Serb. Chem. Soc. 77* (5) 599–605 (**2012**), doi: 10.2298/JSC110616002S.
33. Mohammed S. Al-Saadi, Hassan M. Faidallah, and Sherif A. F. Rostom, Synthesis and Biological Evaluation of Some 2,4,5-Trisubstituted Thiazole Derivatives as Potential Antimicrobial and Anticancer Agents *Arch. Pharm. Chem. Life Sci.* **2008**, 341, 424 – 434, DOI 10.1002/ardp.200800026.
34. Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM. Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles. *Eur J Med Chem* **2009**; 44: 2632-2635.
35. Bharti SK, Nath G, Tilak R, Singh SK. Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring. *Eur J Med Chem* **2010**; 45: 651-660.
36. Yamawaki K, Nomura T, Yasukata T, Tanimoto N, Uotani K, Miwa H, Yamano Y, Takeda K, Nishitani Y. A novel series of parenteral cephalosporins exhibiting potent activities against both Pseudomonas aeruginosa and other Gram-negative pathogens. Part 2: Synthesis and structure–activity relationships. *Bioorg Med Chem* **2008**; 16: 1632-1647.
37. Khalil AM, Berghot MA, Gouda MA. Synthesis and antibacterial activity of some new thiazole and thiophene derivatives. *Eur J Med Chem* **2009**; 44: 4434-4440.
38. Aridoss G, Amirthaganesan S, Kim MS, Kim JT, Jeong YT. Synthesis, spectral and biological evaluation of some new thiazolidinones and thiazoles based on t-3-alkyl-r-2, c-6-diarylpiperidin-4-ones. *Eur J Med Chem* **2009**; 44: 4199-4210.
39. Mallikarjuna BP, Sastry BS, Kumar GVS, Prasad RY, Chandrashekar SM, Sathisha

K. Synthesis of new 4-isopropylthiazole hydrazide analogs and some derived clubbed triazole, oxadiazole ring systems-A novel class of potential antibacterial, antifungal and antitubercular agents. *Eur J Med Chem* **2009**; 44: 4739-4746.

40. Dawane BS, Konda SG, Mandawad GG, Shaikh BM. Poly(ethylene glycol) (PEG-400) as an alternative reaction solvent for the synthesis of some new 1-(4-(4-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)-2-pyrazolines and their in vitro antimicrobial evaluation. *Eur J Med Chem* **2010**; 45: 387-392.
41. Adibpour N, Khalaj A, Rajabalian S. Synthesis and antibacterial activity of isothiazolyloxazolidinones and analogous 3(2H)-isothiazolones. *Eur J Med Chem* **2010**; 45: 19-24.
42. Arshad A, Osman H, Bagiey MC, Lan CK, Mohamad S, Safirah A, Zahariluddin M. Synthesis and antimicrobial properties of some new thiazolyl coumarin derivatives. *Eur J Med Chem* **2011**; 1-7.
43. Patel NB and Patel SD. Synthesis and antimicrobial study of fluoroquinolone based thiazolidinones. *Med Chem Res* **2010**; 19: 757–770.
44. Sindhu Y, Athira CJ, Sujamol MS, Mohanan K. Synthesis, characterization and antibacterial studies of oxavanadium (IV) complexs with thiazole derived Schiff Bases. *Phosphorus Sulphur and Silicon* **2010**; 185: 1955-1963.
45. Manian A.K., Khadse B.G., Sengupta S.R., Synthesis of 2- substituted-anilino/phenyl/benzyl-5-substituted-4-phenyalamido-(3-o-chlorophenyl-5-methylisoxazol-yl)thiazoles as potential antitubercular and antimicrobial agents, *Indian Drugs*, **1994**; 31(9): 442-444.
46. Sonawne SK, Shrivastava SD, Shrivastava SK. Synthesis and antimicrobial activity of 2-(2'-arylidine-hydrazino-acetyl-amino)-4-phenyl-1,3-thiazoles and 2-[2'-{4"-substuted-aryl-3"-chloro-2"-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles *Ind J Chem* **2008**; 47B: 633-636.
47. Arulmoli T, Khadse BG. Synthesis and antibacterial activity of 2-substituted benzyl-4-(p Phenylsulphonamido)-5-Unsubstituted/Methyl Thiazoles. *Ind J Pharm Sci* **1994**:192-195.
48. Sahu SK, Mishra SK, Mohanta NK, Panda PK, Azam AM. Synthesis and antimicrobial activity of 2-phenyl-3,5-diphenyl(substituted)-6-aryl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles. *Ind J Pharm Sci* **2007**: 689-692.
49. Srivastva SD, Sen JP. Synthesis and Biological evaluation of 2-amino-benzothiazole derivatives. *Ind J Chem* **2008**; 47B:1583-1586.
50. Pattan S, Sirajunasia T, Pattan J. Synthesis and evaluation of some substituted mercaptothiazoles and their derivatives of biological interest, *Ind J Chem* **2004**; 43B: 439-441.
51. Ahluwalia V, Raj S, Rishi S. 1987; Synthesis and anti-microbial activity of some 2-amino-4-aryl-5-chromanylazothiazoles. *Ind J Chem* **26B**: 287-289.
52. Pattan S, Dighe N, Nirmal S, Merekar A, Laware R, Shinde H, Musmade D. 2009; Synthesis *and* biological evaluation of some substituted amino thiazole derivatives, *Asian J Research Chem* **2**(2):196-201.
53. K.C. Joshi, V.N. Pathak, P. Arya, Synthesis of Some New Fluorine Containing 2-(*N*-Arylamino)/2-methyl-4-aryl Thiazoles and Their Bactericidal Activity, *Agri. Chem. Soc. Japan*, **1979**, *43*, 199-201.
54. S. N. Dighe, P. K. Chaskar, K. S. Jain, M. S. Phoujdar, K. V. Srinivasan, A Remarkably High-Speed Solution-Phase Combinatorial Synthesis of 2-Substituted-Amino-4-Aryl Thiazoles in Polar Solvents in the Absence of a Catalyst under

Ambient Conditions and Study of Their Antimicrobial Activities, *ISRN Organic Chemistry*, **2011**, doi:10.5402/2011/434613.

55. B.S. Holla, K.V. Malini, S. B. Rao, B.K. Sarojini, S.N. Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, *Eur. J. Med. Chem.*, **2003**, 38 (3), 313-318.
56. Leyla Yurttaş,1 Yusuf Özkay,1 Hülya Karaca Gençer,2 and Ulviye Acar, Synthesis of Some New Thiazole Derivatives and Their Biological Activity Evaluation, *Journal of Chemistry*, Volume 2015 (**2015**), Article ID 464379, 7 pages.
57. Dharmesh N. Darji, T. Y. Pasha, Anil Bhandari, K. I. Molvi, Sarav A. Desai and Mehul V. Makwana, Synthesis of some novel 2, 4, 5 –trisubstituted thiazoles as possible antibacterial agents, *J. Chem. Pharm. Res*., **2012**, 4(4):2148-2152.
58. Vytautas Mickevičius, Aušra Voskienė, Ilona Jonuškienė, Ramūnė Kolosej, Jūratė Šiugždaitė, Petras Rimantas Venskutonis, Rita Kazernavičiūtė, Zita Brazienė and Elena Jakienė, Synthesis and Biological Activity of 3-[Phenyl(1,3-thiazol-2-yl)-amino]propanoic Acids and Their Derivatives *Molecules* **2013**, 18, 15000-15018; doi:10.3390/molecules181215000.
59. Bakr F. Abdel-Wahab, Hanan A. Mohamed and Ghada E. A. Awad, Synthesis and Antimicrobial activity of some new 3-(4-fluorophenyl)benzo[*g*]indazoles and 1-pyrazolylthiazoles, *Eur. Chem. Bull.,* **2014***,* 3(11), 1069-1074.
60. Gilani SJ, Nagarajan K, Katiyar D, Goel R, Khan SA. Synthesis of some derived thiazolidin-4-one, azetidin-2-one and 1,3,4-oxadiazole ring systems from Isoninicotinic acid hydrazide: A novel class of potential antibacterial agents. *Int J Pharmacol Pharm Sci.* **2014**; 1(1) 6-10.
61. Youssef MSK, Ahmed RA, Abbady MS, Abdel-Mohsen SA, Omar AA. Reactions of 4-(2-aminothiazole-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline. Synthesis of thiazolo[3,2-*a*]pyrimidine and imidazo[2,1-*b*]thiazole derivatives *Monatsh Chem*. **2008**; 139 (4): 553–559.
62. Youssef MSK, Omar AA. Synthesis and Reactions of 5-Amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-7-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile, *Monatshefte fur Chemie*. **2007**; 138 (10): 989–995.
63. EI-Tombary AA, Nargues S, Habib RS, EI-Hawash SA, Shaaban OG. Synthesis of thiazolo[4,5-d]pyrimidine derivatives as potential antimicrobial agents *Arch Pharm Res*. **2007**; 30: 1511-1520.
64. Vijay V. Dabholkar*, Navnath Shinde and Sunil Rajaram Patil, Chemistry of novel piprazine-thiazole derivatives- their synthesis and microbial evaluation, *Der Pharma Chemica*, **2013**, 5(4):116-119.
65. Chang Ling Liu, Zheng Ming Li, Bin Zhong. Synthesis and biological activity of novel 2-methyl-4-trifluoromethyl-thiazole-5-carboxamide derivatives, *J Flu Chem* **2004**; 125: 1287-1290.
66. Pattanaik J, Pattanaik M, Bhatta D. Synthesis and fungicidal activity of 3-aryl-2-4-aryl thazol-2'- ylaminomethyl) quinazol-4(3H)-ones. *Ind J Chem* **1998**; 37B: 1304-1306.
67. Liu, H.-L.; Lieberzeit, Z.; Anthonsen, T. Synthesis and Fungicidal Activity of 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and Their 5-Arylidene Derivatives. *Molecules* **2000**, *5*, 1055-1061.
68. A.D. Logu, M. Saddi, M.C. Cardia, R. Borgna, C. Sanna, B. Saddi, E. Maccioni, *In vitro* activity of 2-cyclohexylidenhydrazo-4-phenyl-thiazole compared with those of amphotericin B and fluconazole against clinical isolates of *Candida* spp. and fluconazole-resistant *Candida albicans J. Antimicro. Chem.,* **2005**, 55(5), 692-698.

69. R.H. Khan, S.C. Bahl, Synthesis of Fluoroarylthiazoles and Related Compounds as Possible Fungicides**,** *Agr. Biol. Chem.,* **1976**, *40*, 1129-1135.
70. F. Chimenti, B. Bizzarri, E. Maccioni, D. Secci, A. Bolasco, R. Fioravanti, P. Chimenti, A. Granese, S. Carradori, D. Rivanera, D. Lilli, A. Zicari, S. Distinto, Synthesis and in vitro activity of 2-thiazolylhydrazone derivatives compared with the activity of clotrimazole against clinical isolates of Candida spp. *Bioorg. Med. Chem. Lett.*, **2007**, 17 (16), 4635–4640.
71. Vishant Patel and Vaibhav Patel, Synthesis, characterization and antifungal activity of substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-*5H*-[1,3]-thiazolo[3,2-a]pyrimidie-6-carboxylate derivatives, *Der Pharmacia Sinica,* **2013**, 4(5): 72-78.

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