



A SYSTEMIC REVIEW: MICROWAVE SYNTHESIS AS A PART OF GREEN CHEMISTRY FOR THE SYNTHESIS OF NOVEL 1, 2, 4- TRIAZOLE DERIVATIVES

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ABSTRACT

Microwave reactions are based on the basic principles of green chemistry, basically involve "Go Green" concept. Purpose of green synthesis is to proceed with all the synthetic procedures which are ecofriendly and economic. Great deal of better yield in lesser time than conventional methods are observed. In medicinal chemistry, 1,2,4- triazoles are the source for potent medicaments for different pharmacological activities. In connection with this, literature is being compiled up for the sake of synthesis of 1,2,4- triazoles derivatives by using microwave irradiations.

Keywords: Microwave synthesis, green chemistry, triazoles, pharmacology, synthesis.

INTRODUCTION

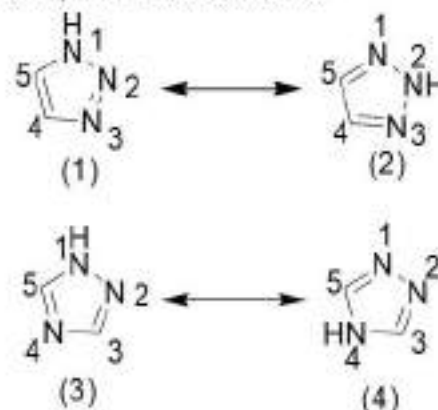
Organic synthesis is the preparation of a desired organic compound from available starting materials. The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic areas, because it is a new enabling technology for drug discovery and development. Microwave technology is an emerging alternative energy source powerful enough to accomplish chemical transformations in minutes, instead of hours or even days. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. A growing number of investigators are adopting microwave-assisted synthesis as a means to increase their productivity. Microwave assisted organic synthesis has been the foremost and one of the most researched applications of Microwaves in chemical reactions is an important part of green chemistry. Green chemistry is the design and implementation of processes and products that minimize or eliminate the use and generation of hazardous chemicals and solvents and other substances which may have an adverse effect on the environment and on human health. Green chemistry is a more eco-friendly green alternative to conventional chemistry practices. The green chemistry movement is part of a larger movement ultimately leading to a green economy- namely sustainable development, sustainable business and sustainable living practices. Green Chemistry encourages environmentally conscious behaviour, such as reducing and preventing pollution and the destruction of the planet.

The term green chemistry was first used in 1990 by P. T. Anastas. Green chemistry incorporates a new approach to the synthesis, processing and application of chemical substances in such a manner as to reduce threats to health and the environment. Green chemistry is also known as:

- Environmentally benign chemistry
- Clean chemistry
- Atom economy
- Benign-by-design chemistry¹

In, inorganic chemistry, microwave technology was used since the late 1970s, while it has only implemented in organic chemistry since the mid-1980s. The first microwave-assisted organic syntheses, reported in 1986 by groups of Richard Gedy² and Raymond J. Giguere/George Majetich³ attracted our attention. Considerably shorter reaction times than

normal had been obtained for common organic transformations such as esterification, hydrolysis, etherification, addition, and rearrangement. This suggested that microwave heating could be advantageous for synthesis if it could be conducted safely. Scientists have demonstrated the potential of microwave -assisted organic synthesis using ionic liquids as solvent, cosolvent, additives and/or catalyst⁴. Triazoles are 5-membered rings, which contain two carbon and three nitrogen atoms. According to the position of nitrogen atoms, triazoles exist in isomeric forms i.e. 1,2,3- triazole and 1,2,4-triazole⁵. Two structural isomeric triazoles exists in two dissimilar tautomeric forms, are known the 1*H*-1,2,3-triazole (1) or 2*H*-1,2,3-triazole (2) and the 1*H*-1,2,4-triazole (3) or 4*H*-1,2,4-triazole (4) the former being known as *oxotriazole*, and the latter as *triazole*⁶.

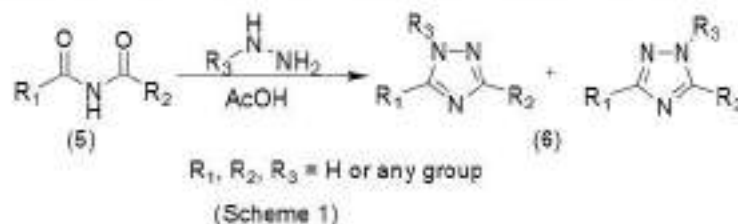


Out of the two triazoles, 1,2,4- triazole have drawn great attention to medicinal chemists from two decades due to its wide variety of activity⁷, low toxicity and good pharmacokinetic and pharmacodynamic profiles. 1,2,4-triazole derivatives exhibit wide range of biological activities including antibacterial⁸⁻¹⁰, antifungal^{11,12}, hypoglycaemic^{13,14}, antidepressant¹⁵, analgesic¹⁶, antitumor¹⁷, anti-proliferative¹⁸, antitubercular¹⁹, anticonvulsant²⁰ activities.

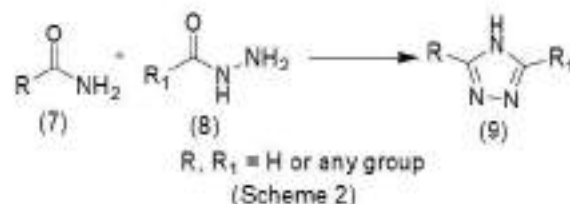
GENERAL METHOD OF SYNTHESIS

1,2,4-Triazoles are usually prepared using either of two reactions, i.e. the Einhorn-Brunner reaction or Pellizzari reaction²¹.

The **Einhorn-Brunner reaction** occurs between an alkyl hydrazine and an imide (5) that give a mixture of isomeric 1,2,4-triazoles (6). This cyclization reaction is catalyzed by an organic acid, such as acetic acid (Scheme 1).



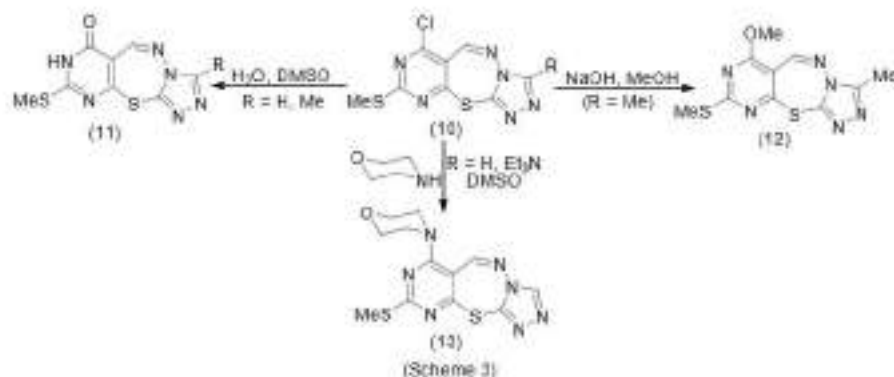
In the **Pellizzari reaction**, an acyl hydrazide (8) is condensed with an amide (7) at high temperature and give substituted 1,2,4-triazole (9) (Scheme 2).



CHEMISTRY OF THE 1,2,4-TRIAZOLES

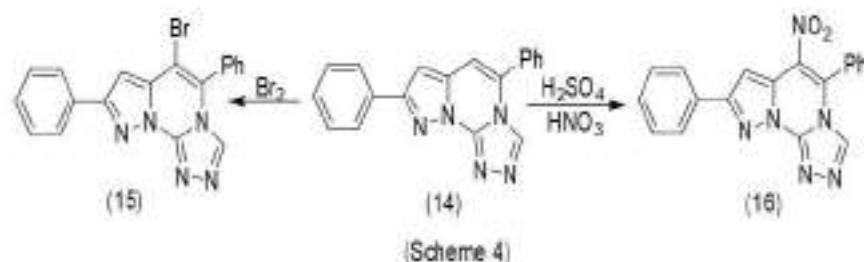
Nucleophilic substitution and Rearrangement reaction

Nucleophilic substitution of 7-chloro-9-methylthio-3-substitutedpyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepines (10) with water gives 3-substituted 9-methylthio-7,8-dihydropyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepin-7-ones (11). sodium methoxide gives 7-Methoxy-3-methyl-9-methylthiopyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepines (12) and amines occurs with the formation of the corresponding 3-Substituted 7-(substituted amino)-9-methylthiopyrimido[5,4-*f*][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepines (13)²² (Scheme 3).

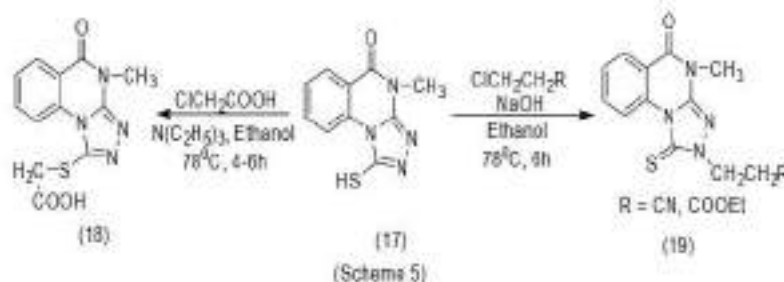


Electrophilic substitution reaction

The electrophilic substitution reactions of 5,8-Diphenylpyrazolo[1,5-*c*]-1,2,4-triazolo[4,3-*a*]pyrimidine (14) such as bromination with bromine and nitration with nitric and sulfuric acids in glacial acetic acid gave the respective 6-Bromo-5,8-diphenylpyrazolo[1,5-*c*]-1,2,4-triazolo[4,3-*a*]pyrimidine (15) and 6-Nitro-5,8-diphenylpyrazolo[1,5-*c*]-1,2,4-triazolo[4,3-*a*]pyrimidine (16) compound²³ (Scheme 4).

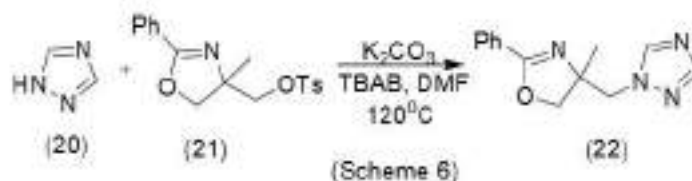


4-Methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (17) reacts with alkyl halides under basic conditions (K_2CO_3 , NEt_3) in presence of ethanol to produce the *S*-substituted products 2-[(4-Methyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-1-yl)sulfanyl]acetic acid (18) via an SN_2 reaction mechanism. On the other hand, when either 3-chloropropanenitrile or methyl-3-chloropropionate were used, the reaction gave the *N* (2)-substituted products (19)²⁴ (Scheme 5).

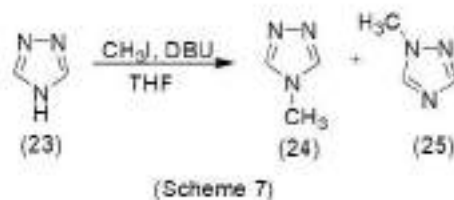


Alkylation reaction

Alkylation of 1,2,4-triazole with alkyl halides and a variety of bases afforded the corresponding 1- and 4-alkylated isomers, with prevalence of the N1-isomer, but reaction of 1*H*-1,2,4-triazole (20) with *O*-tosyloxazoline derivative (21) and K_2CO_3 was carried out in the presence of a catalytic amount of tetra-*n*-butylammonium bromide (TBAB) in *N,N'*-dimethylformamide at $120^\circ C$ for 12 hours afforded only the 1-substituted product, 4-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-methyl-2-phenyl-4,5-dihydrooxazole (22)²⁵ (Scheme 6).

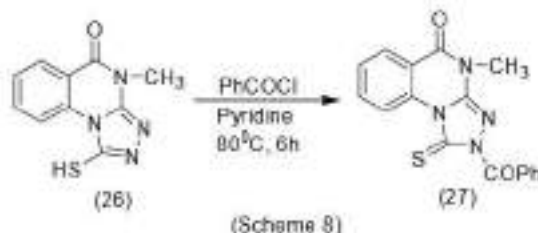


The alkylation of 1,2,4-triazole with the help of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base synthetically allows for a convenient and high yielding synthesis of 1-substituted-1,2,4-triazoles. Hence, by applying these conditions to a range of alkylating agents like methyl iodide good yields of 4-methyl 1,2,4-triazole (24) was obtained as compared to 1-methyl 1,2,4-triazole (25) with the regioselectivity of 86:14 up to 94:6 from 4*H*-1,2,4-triazole (23)²⁶ (Scheme 7).



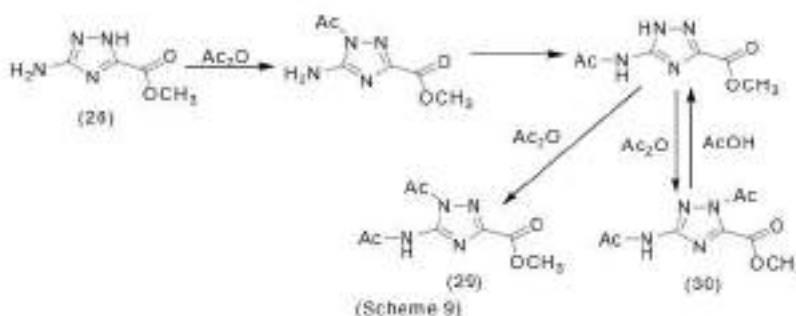
Acylation reaction

4-Methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (26) with benzoyl chloride gave only the *N*-acyl derivative i.e. 2-benzoyl-4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (27)²⁴ (Scheme 8).

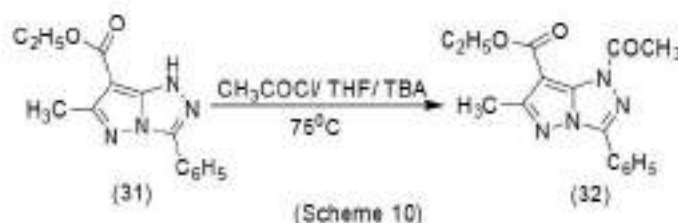


Acetylation reactions

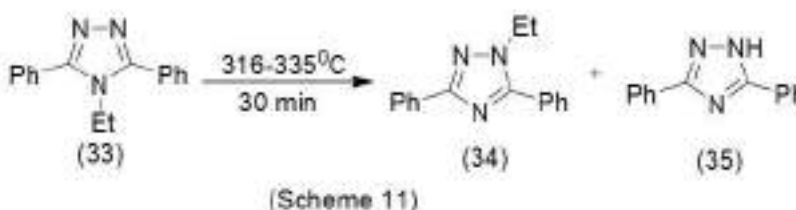
Methyl 5-amino-1*H*-[1, 2, 4] triazole-3-carboxylate (28) undergoes acetylation with acetic anhydride to form two isomeric diacetylated products (29) and (30)²⁷ (Scheme 9).



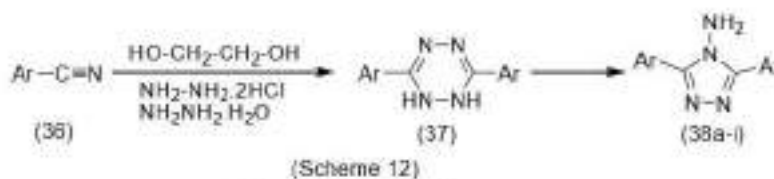
Acetylation of 7-ethoxycarbonyl-6-methyl-3-phenyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole (31) with acetyl chloride in the presence of THF/ tributylamine, has led to the 1-acetyl-7-ethoxycarbonyl-6-methyl-3-phenyl-pyrazolo[5,1-*c*][1,2,4]triazole (32)²⁸ (Scheme 10)

**Thermolysis**

3,4,5-substituted-1,2,4-triazole (33) undergo thermolysis when heated at 316-335°C for 30 min and rearranged to yield 1-ethyl-3,5-diphenyl-1*H*-1,2,4-triazole (34) together with elimination of small amount of 3,5-diphenyl-1*H*-1,2,4-triazole derivative (35)²⁹ (Scheme 11).

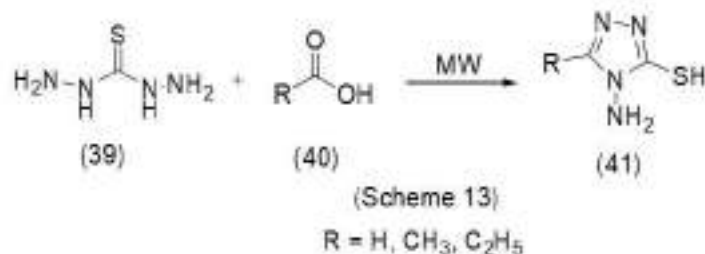
**Synthesis of novel 1,2,4 triazole derivatives**

3,5-disubstituted 4-amino-1,2,4-triazoles (38a-i) was synthesized by the reaction of aromatic nitriles (36) on hydrazine dihydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol under microwave irradiation *via* formation of 1,2-dihydro-1,2,4,5-tetrazine (37)³⁰ (Scheme 12).

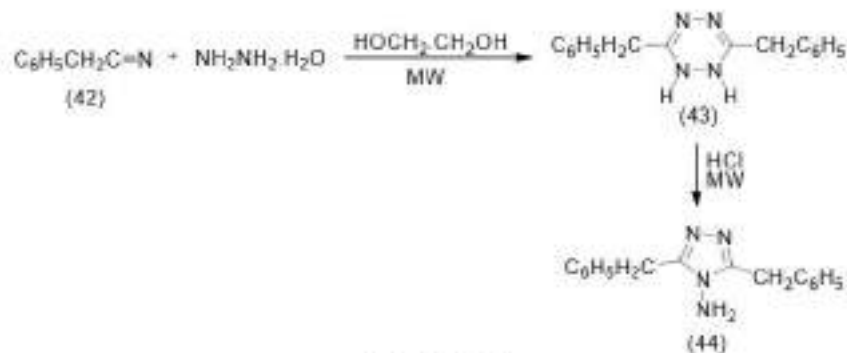


Compound	Ar
38a	C ₆ H ₅
38b	4-CH ₃ C ₆ H ₄
38c	4-NH ₂ C ₆ H ₄
38d	4-OHC ₆ H ₄
38e	3-CH ₃ O, 4-OHC ₆ H ₃
38f	4-CH ₃ OC ₆ H ₄
38g	4-ClC ₆ H ₄
38h	2-pyridyl
38i	4-pyridyl

3-substituted-4-amino-5-mercapto-1,2,4-triazole (41) derivatives was synthesized by condensation of thiocarbonylhydrazide (39) with different alkanolic acids (40) under microwave irradiation³¹ (Scheme 13).

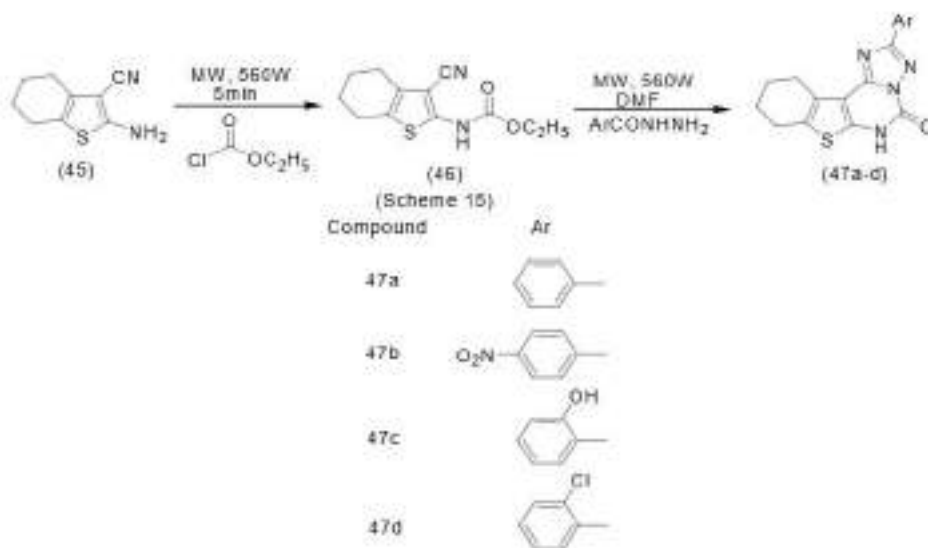


3,5-dibenzyl-4-amino-1,2,4-triazole (44) was synthesised from benzyl cyanide (42) in the presence of hydrazine hydrate and ethylene glycol *via* dihydro-1,2,4,5-tetrazine (43) which rearranged on treatment under acidic conditions into the product³² (Scheme 14).

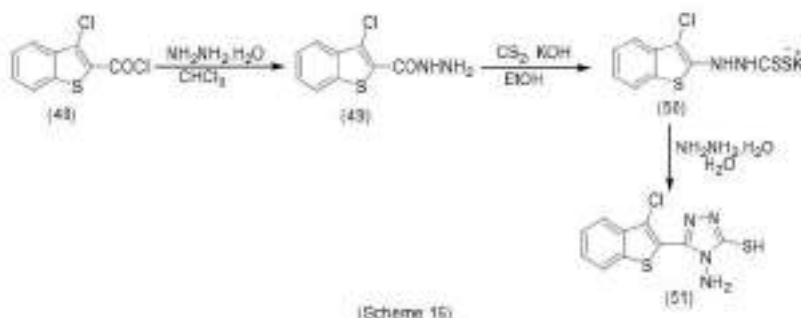


(Scheme 14)

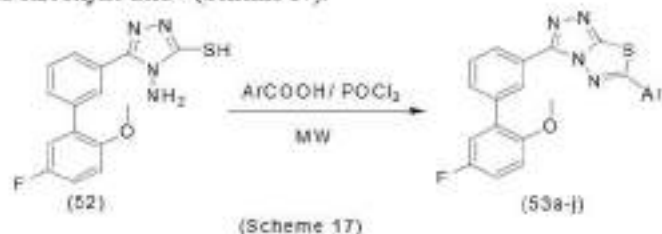
8,9-cycloalkathieno[3,2-*c*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones (47a-d) was synthesized from 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (45) in ethyl chloroformate gives ethyl-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-yl carbamate (46) which on condensation with aryl acid hydrazides under microwave-assisted conditions yield the final product³³ (Scheme 15).



4-amino-5-(3-chlorobenzo[*b*]thien-2-yl)-3-mercapto-1,2,4-triazole (51) was synthesized from potassium dithiocarbazate (50) under microwave irradiation from 3-chloro-2-chlorocarbonylbenzo[*b*]thiophene (48) through an corresponding hydrazide intermediate (49), which on cyclisation with hydrazide gives the product³⁴ (Scheme 16).

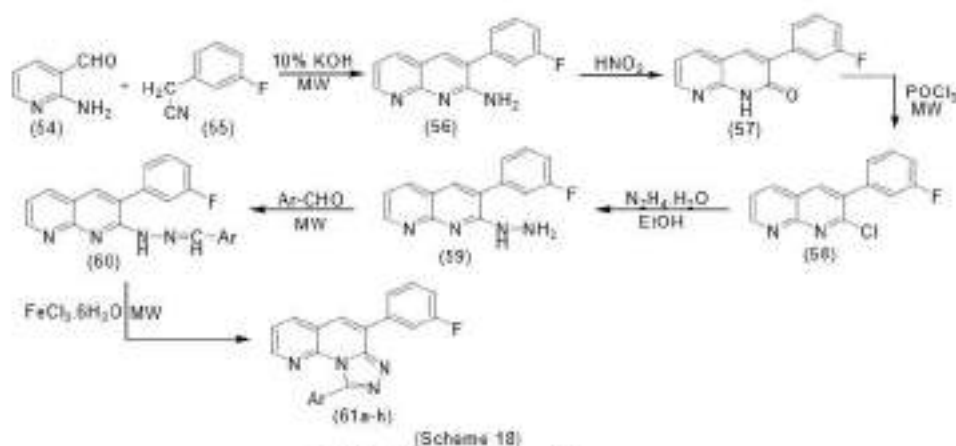


3-(5'-fluoro-2'-methoxybiphenyl-3-yl)-6-(substituted)[1,2,4]-triazolo[3,4-*b*][1,3,4] thiadiazole (53a-j) was synthesized from 4-amino-5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-4*H*-1,2,4-triazole-3-thiol (52) subjected to MW irradiation using dry phosphorous oxychloride and carboxylic acid³⁵ (Scheme 17).



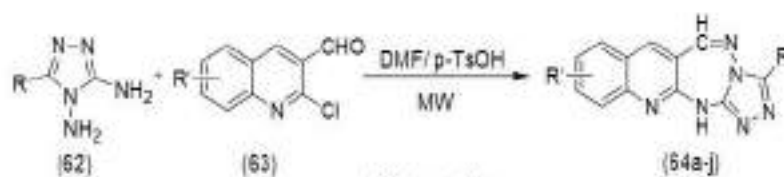
Compound	Ar	Compound	Ar
53a	2-FC ₆ H ₄	53f	2-Cl, 6-FC ₆ H ₄
53b	4-F, 3-CF ₃ C ₆ H ₃	53g	2-F, 5-NO ₂ C ₆ H ₃
53c	4-IC ₆ H ₄	53h	4-F, 3-NO ₂ C ₆ H ₃
53d		53i	2,4-Cl ₂ , 5-FC ₆ H ₃
53e		53j	

9-aryl-6-(3-fluorophenyl)-1,2,4-triazolo[4,3-*a*][1,8]naphthyridines (61a-h) was synthesized from aryl aldehyde 3-(3-fluorophenyl)-1,8-naphthyridine-2-ylhydrazones (60) using FeCl₃.6H₂O under microwave irradiation³⁶ (Scheme 18).



Compound	Ar
61a	C ₆ H ₅
61b	4-CH ₃ C ₆ H ₄
61c	4-CH ₃ OC ₆ H ₄
61d	2-ClC ₆ H ₄
61e	4-ClC ₆ H ₄
61f	3-NO ₂ C ₆ H ₄
61g	4-NO ₂ C ₆ H ₄
61h	3,4-(CH ₃ O) ₂ C ₆ H ₃

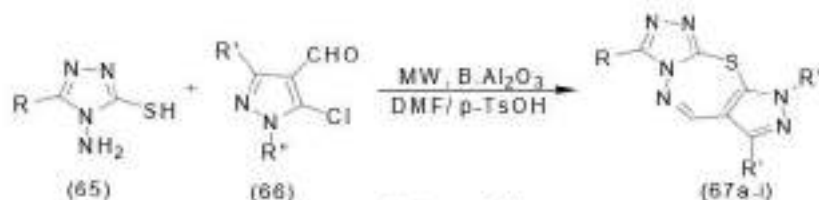
9-substituted-3-aryl-5*H*,13*aH*-quinolino[3,2-*f*][1,2,4]triazolo[4,3-*b*][1,2,4]triazepine (64a-j) was synthesized from 5-aryl-3,4-diamino-1,2,4-triazoles (62) and 2-chloro-3-formylquinoline (63) using catalytic amount of *p*-TsOH and *N,N*-dimethylformamide as an energy transfer medium using MW heating³⁷ (Scheme 19).



(Scheme 19)

Compound	R	R'
64a	C ₆ H ₅	H
64b	4-NO ₂ -C ₆ H ₄	H
64c	2-Cl-C ₆ H ₄	3-CH ₃
64d	4-NO ₂ -C ₆ H ₄	3-CH ₃
64e	2-Cl-C ₆ H ₄	4-OCH ₃
64f	CH ₃ -C ₆ H ₅	4-CH ₃
64g	C ₆ H ₅	4-CH ₃
64h	4-Cl-C ₆ H ₄	4-OCH ₃
64i	4-NO ₂ -C ₆ H ₄	4-OCH ₃
64j	4-NO ₂ -C ₆ H ₄	4-CH ₃

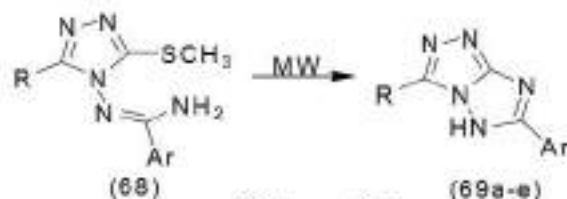
1-substituted-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*]-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines (67a-i) were synthesized by condensation of 1-amino-2-mercapto-1,3,4-triazoles (65) and 5-chloro-4-formyl-1,2-pyrazoles (66) in the presence of *N,N*-dimethylformamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation³⁸ (Scheme 20).



(Scheme 20)

Compound	R	R'	R''
67a	CH ₃	CH ₃	H
67b	C ₂ H ₅	CH ₃	H
67c	n-C ₃ H ₇	CH ₃	H
67d	4-OCH ₃ -C ₆ H ₄	CH ₃	H
67e	CH ₃	4-NO ₂ -C ₆ H ₄	C ₆ H ₅
67f	n-C ₃ H ₇	4-NO ₂ -C ₆ H ₄	C ₆ H ₅
67g	C ₆ H ₅	4-Br-C ₆ H ₄	C ₆ H ₅
67h	4-OCH ₃ -C ₆ H ₄	4-NO ₂ -C ₆ H ₄	C ₆ H ₅
67i	4-Cl-C ₆ H ₄	4-NO ₂ -C ₆ H ₄	C ₆ H ₅

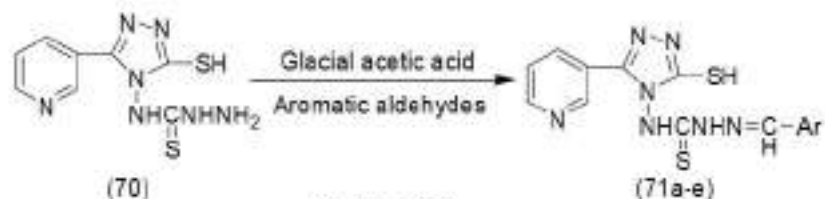
6-aryl-3-substituted-5*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles (69a-e) was synthesized by microwave assisted cyclization of *N*-(3-methylthio-5-substituted-4*H*-1,2,4-triazol-4-yl)benzenecarboximidamides (68)³⁹ (Scheme 21).



(Scheme 21)

Compound	R	Ar
69a	CH ₃	C ₆ H ₅
69b	CH ₃	4-Cl-C ₆ H ₄
69c	CH ₃	4-Br-C ₆ H ₄
69d	CH ₃	4-CH ₃ -C ₆ H ₄
69e	H	C ₆ H ₅

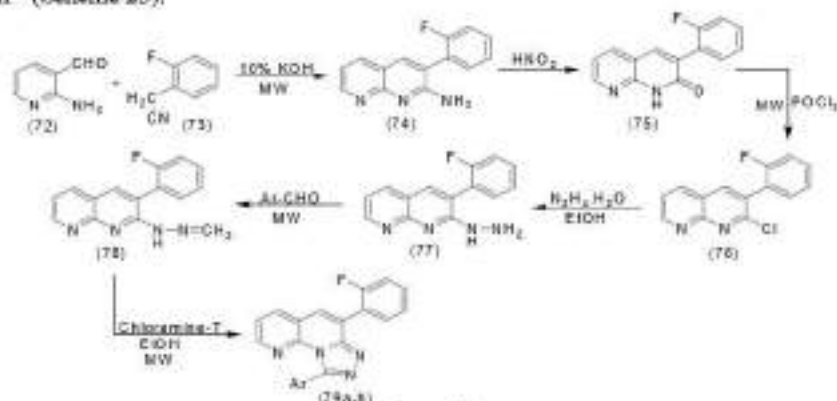
Schiff's bases of 5-mercapto-3-(3'-pyridyl)-4H-1,2,4-triazole-4-yl-thiosemicarbazide (70) was synthesized by reacting with different aromatic aldehyde to yield (71a-e)⁴⁰ (Scheme 22).



(Scheme 22)

Compound	Ar
71a	phenyl
71b	2-furyl
71c	2-hydroxyphenyl
71d	2-chlorophenyl
71e	4-methoxyphenyl

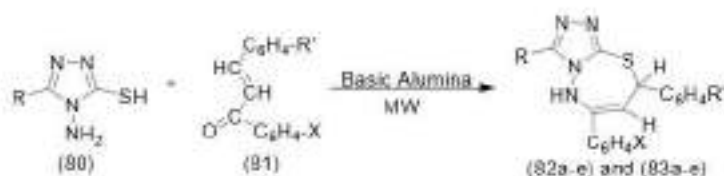
9-aryl-6-(2-fluorophenyl)-1,2,4-triazolo[4,3-*a*][1,8]naphthyridines (79a-h) was synthesized by oxidation of the corresponding aryl aldehyde 3-(2-fluorophenyl)-1,8-naphthyridin-2-ylhydrazones (78) with chloramines-T in ethanol under microwave irradiation⁴¹ (Scheme 23).



(Scheme 23)

Compound	Ar
79a	C ₆ H ₅
79b	4-CH ₃ C ₆ H ₄
79c	4-CH ₃ OCC ₆ H ₄
79d	2-ClC ₆ H ₄
79e	4-ClC ₆ H ₄
79f	3-NO ₂ C ₆ H ₄
79g	4-NO ₂ C ₆ H ₄
79h	3,4-(CH ₃ O) ₂ C ₆ H ₃

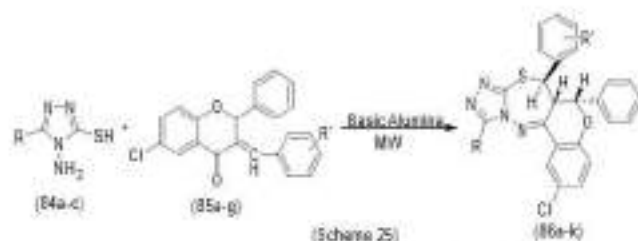
5-substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines (82a-e) and (83a-e) was synthesized from the reaction of 1-amino-2-mercapto-5-substituted triazoles (80) and substituted chalcones (81) on basic alumina under microwave irradiation⁴² (Scheme 24).



(Scheme 24)

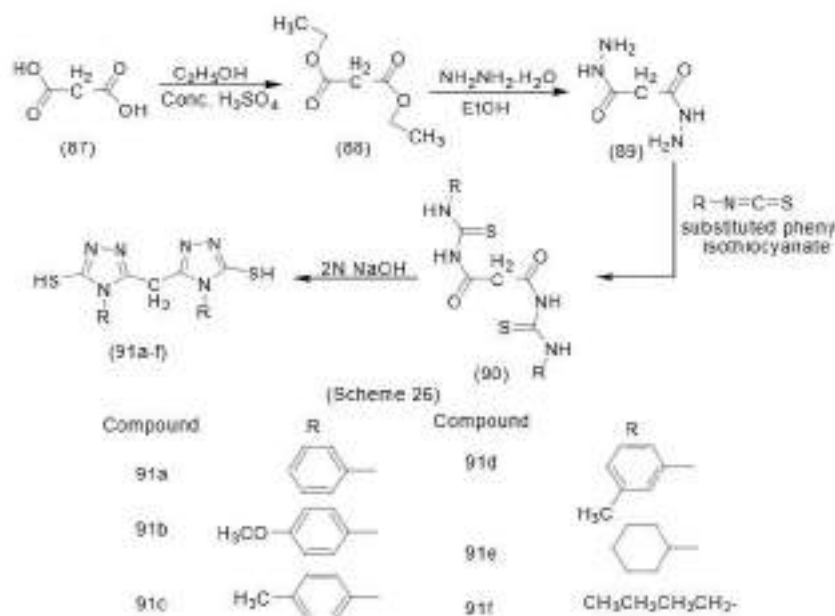
Compound	a	b	c	d	e
R =					
(82a-e) =	R'	X	CH ₃	OCH ₃	H ₃ C
(83a-e) =	4-OCH ₃	H	3,4-OCH ₂ O-	4-Br	

Fluorine containing 3-alkyl-7-chloro-11a,12-dihydro-11-phenyl-12-(substituted aryl)-11H-benzopyrano[4,3-e][1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazepines (**86a-k**) was synthesized using basic alumina as solid support from 4-Amino-5-alkyl-3-mercaptoptriazoles (**84a-c**) and 6-chloro-3-(substituted-arylidene)-flavanones (**85a-g**) under microwaves irradiation⁴³ (Scheme 25).

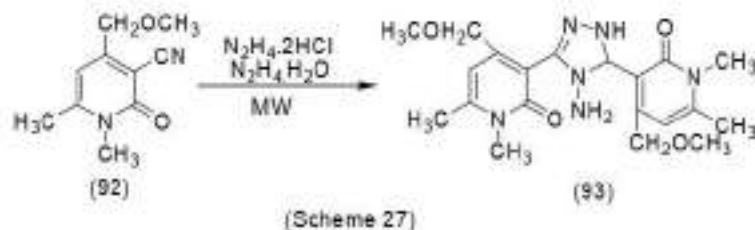


Compound	R	Compound	R'	Compound	R	R'
84a	CH ₃	85a	2-F	86a	CH ₃	2-F
84b	C ₂ H ₅	85b	4-OCF ₃	86b	CH ₃	4-OCF ₃
84c	C ₃ H ₇	85c	2-Cl	86c	CH ₃	2-Cl
		85d	H	86d	CH ₃	H
		85e	4-F	86e	C ₂ H ₅	4-F
		85f	2-Cl, 4-F	86f	C ₂ H ₅	2-Cl, 4-F
		85g	3,4-dF	86g	C ₂ H ₅	2-F
				86h	C ₂ H ₅	3,4-dF
				86i	C ₂ H ₅	2-F
				86j	C ₂ H ₅	4-OCF ₃
				86k	C ₂ H ₅	2-Cl, 4-F

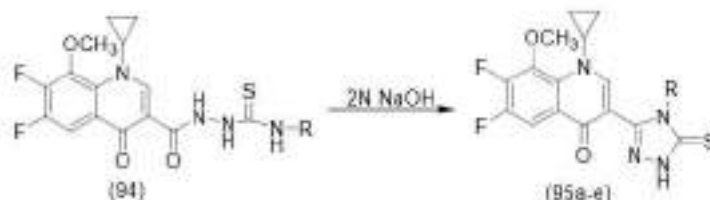
5, 5-methylenebis (4-substituted phenyl/alkyl-4H-1,2,4-triazole-3-thiol) (**91a-f**) was synthesized from malonic acid bisester (**88**) through malonic acid bis hydrazide (**89**), yield substituted bis thiosemicarbazide (**90**) which on addition of 2M sodium hydroxide solution gives series of bis-triazole derivatives⁴⁴ (Scheme 26).



4-amino-3,5-bis[6-(methoxymethyl)-3,4-dimethyl-2-oxo-1,2 dihydropyridine-1-yl]-1,2,4-triazole-2(H) (**93**) was synthesised by subjecting a mixture of 4-(methoxymethyl)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3- carbonitrile (**92**), hydrazine dihydrochloride and hydrazine hydrate in ethylene glycol in microwave reactor⁴⁵ (Scheme 27).



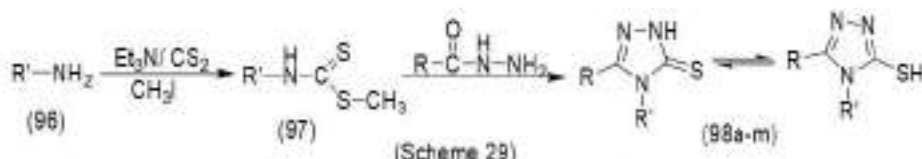
1-cyclopropyl-6,7-difluoro-8-methoxy-3-(4-substitutedphenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl) quinolin-4(1H)-one (95a-e) was synthesized from 1-(1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonyl)-4-substitutedphenylthiosemi-carbazides (94) in 2N NaOH under microwave irradiation⁴⁶ (Scheme 28).



(Scheme 28)

Compound	R
95a	3-OCH ₃ C ₆ H ₄
95b	3-ClC ₆ H ₄
95c	C ₆ H ₅
95d	1-CH ₃ C ₆ H ₄
95e	2-CH ₃ C ₆ H ₄

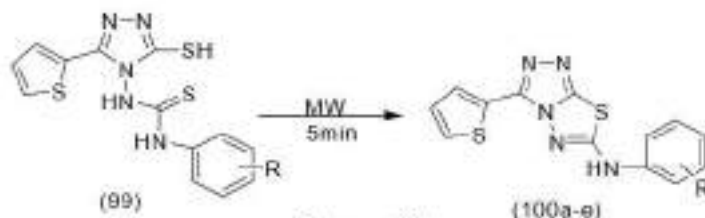
4-N, N-Dimethylamino/ 4-Cycloamino-Substituted 1,2,4-Triazole-3-thiones (98a-m) was synthesized from substituted methyl dithiocarbazates (97) and benzhydrazides under microwave irradiations. Methyl dithiocarbazates were obtained by the treatment of N,Ndimethylhydrazine, N-aminopiperidine, N-aminomorpholine, and N-methyl-1-aminopiperazine with carbon disulfide in the presence of triethylamine, followed by methylation with methyl iodide⁴⁷ (Scheme 29).



(Scheme 29)

Compound	R	R'
98a	C ₆ H ₅	N(CH ₃) ₂
98b	C ₆ H ₅	Piperidine
98c	C ₆ H ₅	Morpholine
98d	4-ClC ₆ H ₄	N(CH ₃) ₂
98e	4-ClC ₆ H ₄	Piperidine
98f	4-ClC ₆ H ₄	Morpholine
98g	4-FC ₆ H ₄	Morpholine
98h	4-NH ₂ C ₆ H ₄	N(CH ₃) ₂
98i	4-NH ₂ C ₆ H ₄	Piperidine
98j	4-NH ₂ C ₆ H ₄	Morpholine
98k	4-OCH ₃ C ₆ H ₄	Morpholine
98l	3,4-Cl ₂ C ₆ H ₃	N(CH ₃) ₂
98m	3,5-(OCH ₃) ₂ C ₆ H ₃	4-Methylpiperazine

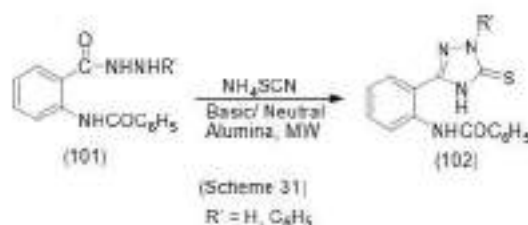
2-Arylamino-5-(2-thienyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles derivatives (100a-e) was synthesized from dehydrosulphurization of N-[3-Mercapto-5-(2-thienyl)-1,2,4-triazol-4-yl]-N' arylthiourcas (99) via exposure to microwave irradiation for 5 min⁴⁸ (Scheme 30).



(Scheme 30)

Compound	R
100a	H
100b	3-F
100c	4-F
100d	4-Cl
100e	4-Br

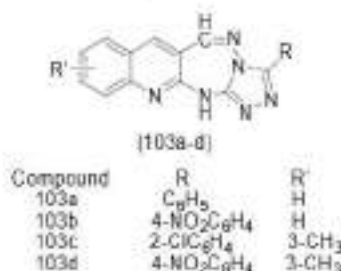
3-[(2-benzoylamino) phenyl]-1,2,4-triazolin-5-thione (102) was synthesized from 2-(benzoylamino) benzoic hydrazide/ 2-benzoylamino benzoic phenylhydrazide (101) and ammonium thiocyanate in ethanol using different solid supports under microwave irradiation⁴⁰ (Scheme 31).



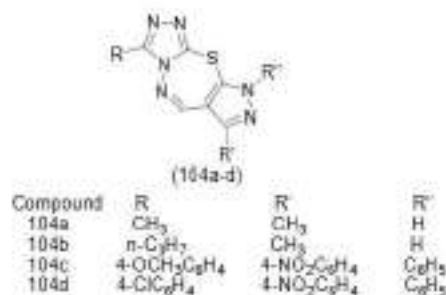
PHARMACOLOGICAL ACTIVITIES

Antifungal Activity

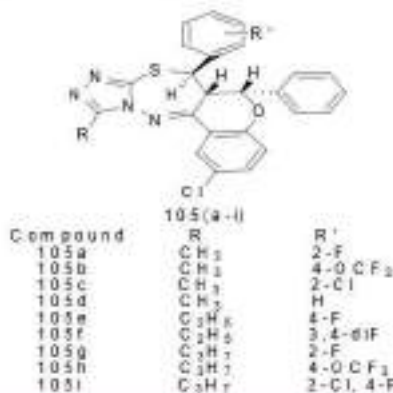
9-substituted -3-aryl-5H, 13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepine (103a-d) were screened for anti-fungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus* species and *Penicillium notatum* species by paper disc method at conc. 500 µg/ml and 1000 µg/ml using fluconazole as standard. Compounds showed excellent activity against *Aspergillus niger* at 1000 µg conc. and *Penicillium notatum* at 500 µg as well as 1000µg/ml conc whereas they showed good to moderate activity against *Aspergillus flavus* and *Rhizopus* species at both conc³⁷.



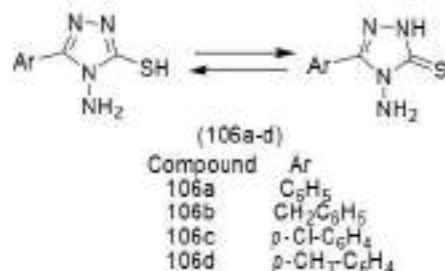
1-substituted-3,7-dialkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[3,4-b][1,3,4]thiadiazepines (104a-d) were evaluated for anti-fungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Rhizopus* species and *Penicillium* species by paper disc method at concentrations 500µg/ml and 1000µg/ml using fluconazole as standard. Compounds showed good to moderate activity except *penicillium* species³⁸.



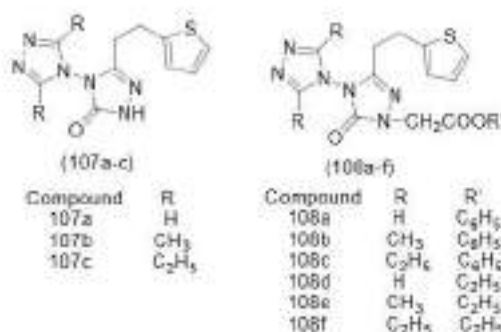
Fluorine containing 3-alkyl- 7-chloro-11a,12-dihydro-11-phenyl-12-(substituted aryl)-11H-benzopyrano[4,3-e][1,2,4]-triazolo[3,4-b][1,3,4]-thiadiazepines (105a-i) were screened for *in vitro* anti-fungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Colletotrichum capsici*. Compounds have shown good activity against these pathogens⁴³.



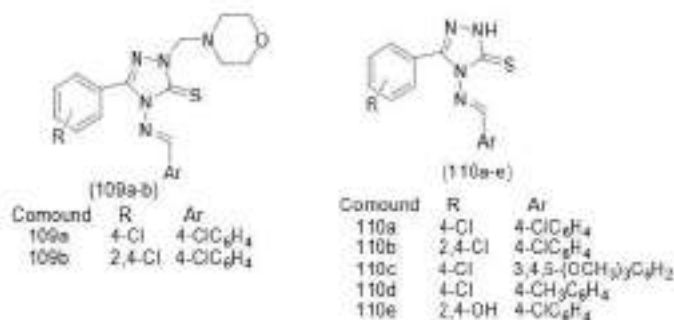
4-amino-3-mercapto-1,2,4 triazoles (106a-d) was evaluated as antifungal agents against *Candida albicans* and *Candida tropicalis* by the disk diffusion method. Compounds exhibit high activity against *Candida albicans* and *Candida tropicalis*³⁰.



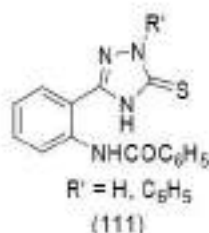
4-(3,5-disubstitue-4*H*-1,2,4-triazol-4-yl)-5-(thiophen-2-yl-methyl)-2*H*-1,2,4-triazol-3(4*H*)- ones (107a-c) and 4-(3,5-disubstitue-4*H*-1,2,4-triazol-4-yl)-2-(2-oxo-2-arylethyl)-5-(thiophen-2-ylmethyl)-2*H*-1,2,4-triazol-3(4*H*)-ones (108a-f) were evaluated for antifungal activity against *Penicillium* spp., and *Aspergillus* spp. by agar-well diffusion method using fluconazole (5 µg) as standard drug. Compounds showed potent activity³¹.



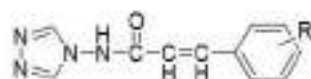
4-(4-substituted benzylideneamino)-2-(morpholinomethyl)-5(substitutedphenyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (109a-b) and 4-(4-substitutedbenzylideneamino)-5(substitutedphenyl)-2*H*-1,2,4-triazole-3(4*H*)thione (110a-e) were evaluated for anti-fungal activity against *Candida albicans*, *Candida tropicalis* and *Aspergillus niger* by tube dilution/turbidity method using fluconazole as standard. All compounds showed very good activity³².



3-[(2-benzoylamino)phenyl]-1,2,4-triazolin-5-thione (111) were screened for their antifungal activity against *Aspergillus niger* and *Aspergillus flavus* by the paper disc diffusion method and compared to standard salicylic acid. Both compounds have shown good activity against both fungi³³.



3-(substitutedphenyl)-N-(4H-1,2,4-triazol-4-yl)acrylamide (112a-c) were studied for their in-vitro antifungal activity against *Mucor*, *Aspergillus niger* and *Penicillium* strains by the turbidometry method. Compounds 112a and 112c gives comparable activity of fluconazole⁵⁴.

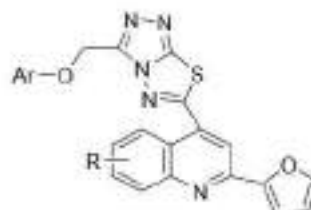


(112a-c)

Compound	R
112a	4-N(CH ₃) ₂
112d	3-OCH ₃
112c	2-OH

Antibacterial Activity

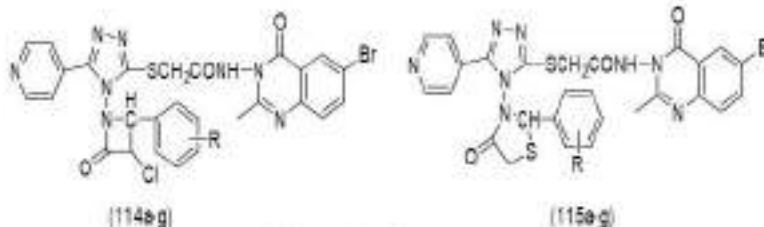
2-(2-furyl)-4-(3-aryloxymethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl)quinolines (113a-k) were screened for their antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa* using furacin as standard by serial dilution method. All the compounds showed moderate to excellent activity compared with the standard drug, furacin⁵⁵.



(113a-k)

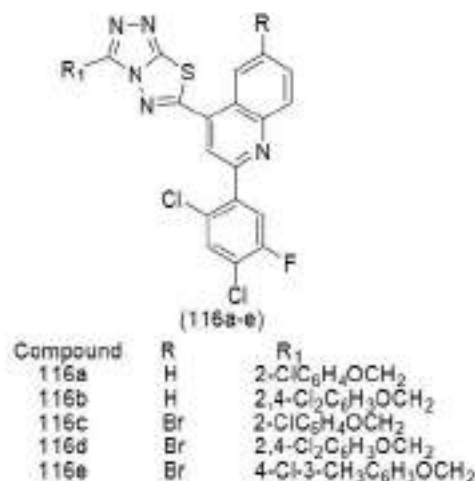
Compound	R	Ar
113a	Br	4-ClC ₆ H ₄
113b	Br	3-ClC ₆ H ₄
113c	Br	4-CH ₃ C ₆ H ₄
113d	Br	3-CH ₃ C ₆ H ₄
113e	CH ₃	4-ClC ₆ H ₄
113f	CH ₃	3-ClC ₆ H ₄
113g	CH ₃	4-CH ₃ C ₆ H ₄
113h	CH ₃	3-CH ₃ C ₆ H ₄
113i	H	4-ClC ₆ H ₄
113j	H	4-CH ₃ C ₆ H ₄
113k	H	3-CH ₃ C ₆ H ₄

N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl)-5-(pyridin-4-yl)-5-thio)acetamido-1,2,4-triazoles (114a-g), N-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-2-(4-(2-(substitutedphenyl)-4-oxothiazolidin-3-yl)-5-(pyridin-4-yl)-3-thio)acetamido-1,2,4-triazoles (115a-g) were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas vulgaris* and *Klebsilla pneumoniae*. Among azetidinones 114a-g, compound 114b exhibited promising antibacterial activity. Among the compounds 115a-g, compounds 115b and 115c showed better activity against *S. aureus*, *E. coli* and *P. vulgaris*, 115e exhibited equipotent while 115a, 115d, 115f and 115g showed good antibacterial activity compared to that standard drugs ampicillin and gatifloxacin⁵⁶.

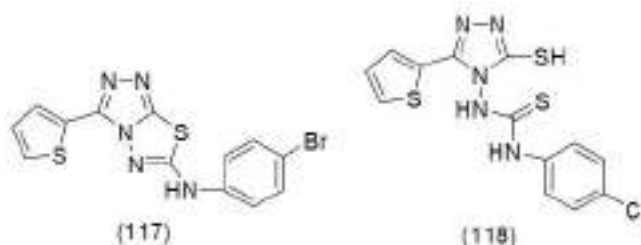


Compound	R
a	4-OH, 3-OCH ₃
b	2,4-Cl
c	2,6-Cl
d	2,4-Br
e	2,6-Br
f	2-OH
g	N(CH ₃) ₂

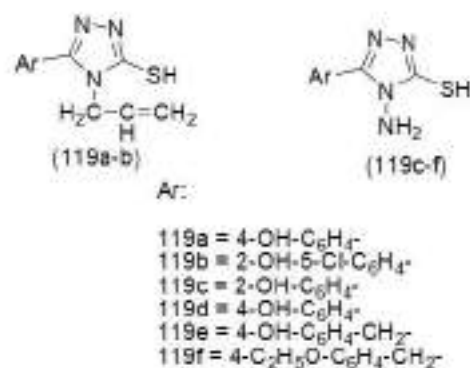
3-Substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl-2-(2,4-dichloro-5-fluorophenyl) quinolines (116a-e) were screened for their in-vitro anti-bacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis* by serial dilution method using Nitrofurazone (furacin) as standard drug. All compounds showed very good activity⁵¹.



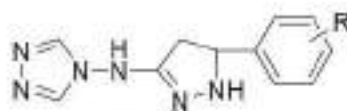
N-(4-bromophenyl)-3-(thiophen-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine (117) and 1-(4-chlorophenyl)-3-(3-mercapto-5-(thiophen-2-yl)-4*H*-1,2,4-triazol-4-yl)thiourea (118) was tested for their *in vitro* anti-bacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* using Ampicillin trihydrate antibiotic as standard by the agar disc-diffusion method. Compound display marked activity⁴⁶.



4-allyl/amino-5-aryl-1,2,4-triazoles (119a-f) was tested for anti-bacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Salmonella enteritidis* and *Staphylococcus aureus* by filter paper disc method. Free NH₂ groups in the 4 position (119e-f) showed the greatest inhibitory activity. The 4-amino-5-(4-hydroxyphenyl)-1,2,4-triazole (119d) showed the highest inhibition zone diameter against *Staphylococcus aureus* (28 mm), than all the other tested organisms and compounds³⁵.



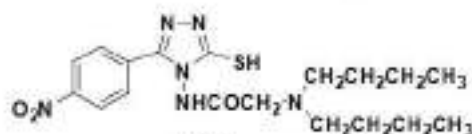
N-(5-(substitutedphenyl)-4,5-dihydro-1H-pyrazol-3-yl)-4H-1,2,4-triazol-4-amine (120a-c) were screened for their *in-vitro* antibacterial activity against *Bacillus megaterium*, *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter*, *Proteus vulgaris* and *Pseudomonas aeruginosa* by the agar well diffusion method using standard antibiotic chloramphenicol. All compounds showed significant activity⁵⁹.



(120a-c)

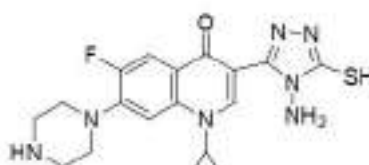
Compound	R
120a	4-N(CH ₃) ₂
120b	3-OCH ₃
120c	2-OH

4-[N-dibutylamine]acetylamino-3-mercapto-5-(4-nitro)phenyl-1,2,4-triazole (121) were screened for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* by disc diffusion method using vancomycin and amikacin as standard. The compound display very good activity⁶⁰.



(121)

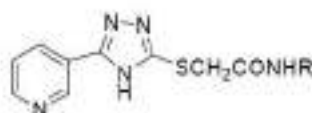
3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-1-cyclopropyl-6-fluoro-7-(piperazin-1-yl) quinolin-4(1H)-one (122) was screened for their antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* by cup plate method. The compound exhibited good effect towards *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* but moderate activity against *Bacillus subtilis*⁶¹.



(122)

Anti-tubercular Activity

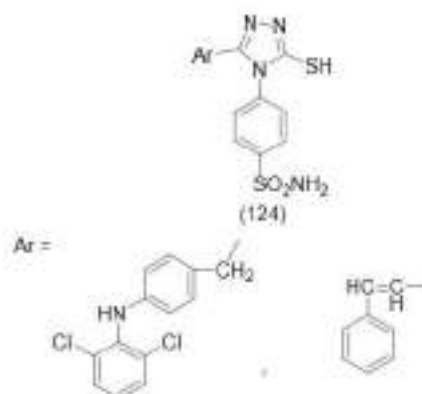
5-(N-substituted carboxamidomethylthio)-3-(3'-pyridyl)-1,2,4-triazoles (123a-f) were evaluated for *in-vitro* anti-tubercular activity at 50 µg/mL against *Mycobacterium tuberculosis* H₃₇ Rv using rifampicin as standard. All compound exhibited excellent anti-TB activity⁶².



(123a-f)

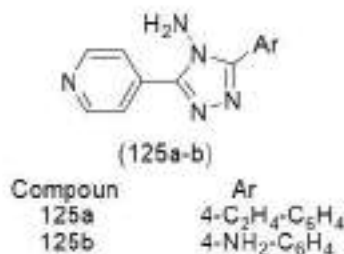
Compound	R
123a	4-BrC ₆ H ₄
123b	4-ClC ₆ H ₄
123c	4-NO ₂ C ₆ H ₄
123d	3-NO ₂ C ₆ H ₄
123e	2,6-Cl ₂ C ₆ H ₃
123f	2,6-CH ₃ C ₆ H ₃

4-(3-mercapto-5-substituted-4H-1,2,4-triazol-4-yl)benzenesulfonamide (124) was evaluated for anti-tubercular activity against *Mycobacterium tuberculosis* H₃₇Rv strain at 25µg/ml, 50µg/ml, 100µg/ml by Middlebrook 7H9 agar medium using Streptomycin as standard drug. Both compound have shown significant activity at all concentrations⁶³.

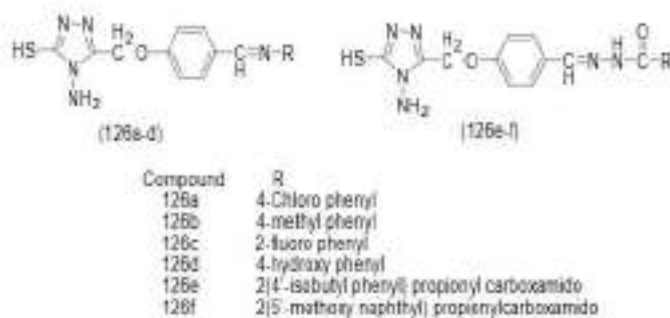


Anti-inflammatory Activity

5-substituted-3-pyridine-1,2,4-triazole (125a-b) was studied for *in-vivo* anti-inflammatory activity using indomethacin as control by Carrageenan- induced hind paw edema model in rat. Compounds have shown good activity⁶⁴.

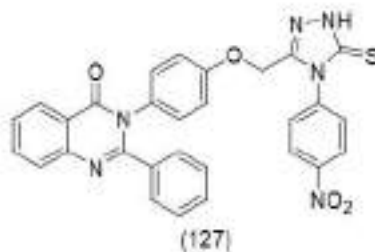


Schiff bases of 4-amino-3-substituted-5-mercapto-1,2,4-triazoles (126a-f) were investigated for anti-inflammatory activity by carrageenan induced rat paw oedema method and showed significant activity comparable to standard drug (Ibuprofen)⁶⁵.



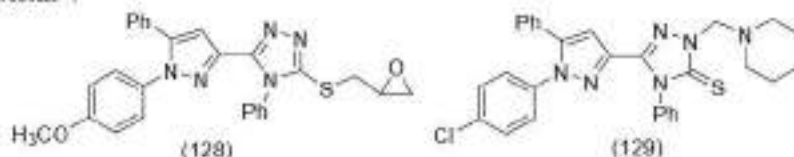
Antimalarial Activity

3-[4-[4-(4-fluoro-phenyl)-4H-1,2,4-triazol-3-yl-methoxy]-phenyl]-2-phenyl-3H-quinazolin-4-one (127) was evaluated against chloroquine-resistant *Plasmodium falciparum* malarial parasite using the tritiated Hypoxanthine incorporation assay. The compound was found to be most active against *Plasmodium falciparum* strains⁶⁶.

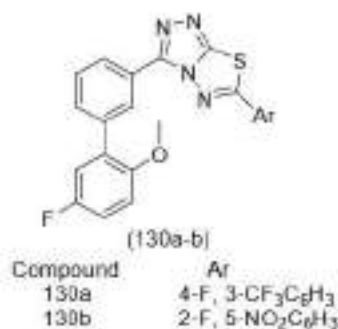


Anticancer Activity

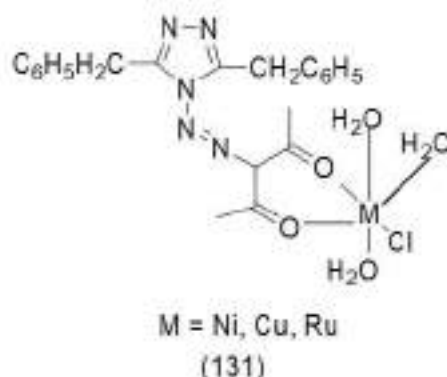
3-(1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazol-3-yl)-5-(oxiran-2-ylmethylthio)-4-phenyl-4*H*-1,2,4-triazole (128), 5-(1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl)-4-phenyl-2-(piperidin-1-yl)methyl-2*H*-1,2,4-triazole-3(4*H*)-thione (129) were screened for their anticancer activities against breast carcinoma (MCF7) and cervix carcinoma (HELA) human cell lines compared with Doxorubicin positive control. Compounds showed good activity against both types of carcinoma cell lines than that obtained by doxorubicin⁶⁷.



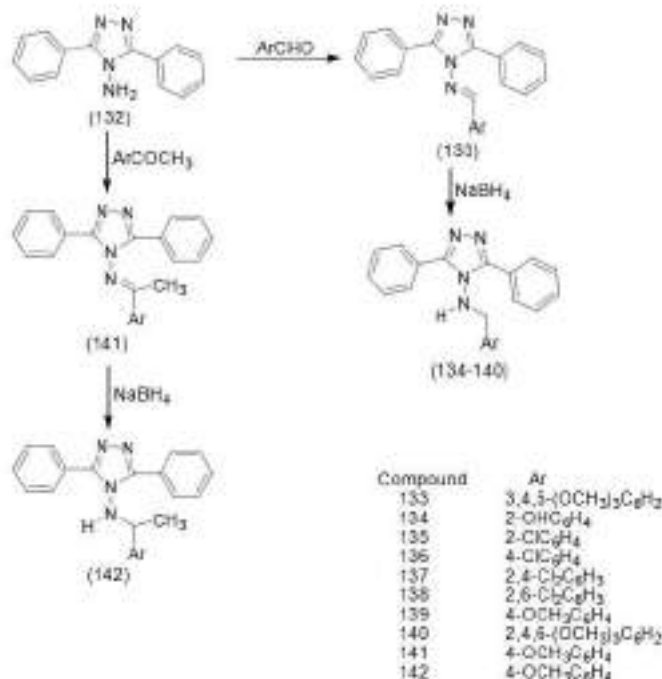
3-(5'-fluoro-2'-methoxybiphenyl-3-yl)-6-(substituted)[1,2,4]-triazolo[3,4-*b*][1,3,4]-thiadiazole (130) were screened for their anticancer activity against cancer cell lines HT29 (human adenocarcinoma), K293 (human kidney cancer) and MDA231 (human breast cancer) by using the MTT assay. Compounds exhibited significant activity comparable to 5-fluorouracil³⁵.



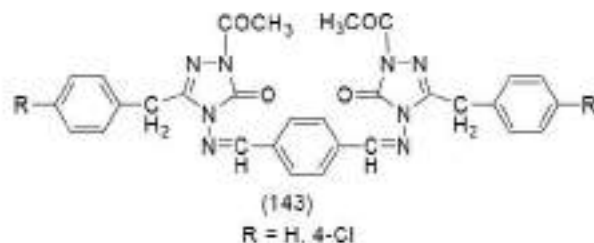
3,5-dibenzyl-4-amino-1,2,4-triazole (131) was screened for anticancer activity on Jurkat, Raji & PBMC cell lines. Ruthenium complexes showed potential anticancer activities³².



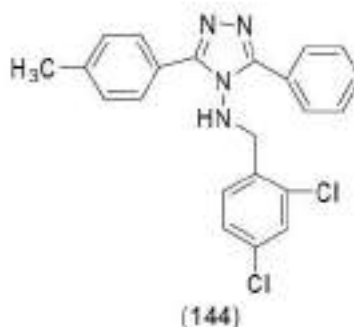
4-arylidenamino-4*H*-1,2,4-triazoles (133), 4-arylmethylamino-4*H*-1,2,4-triazoles (134-140), 4-(1-aryl) ethylidenamino-4*H*-1,2,4-triazoles (141) and 4-(1-aryl)ethylamino-4*H*-1,2,4-triazoles (142) were screened on three human tumor cell lines, breast cancer (MCF7), non small cell lung cancer (NCI-H460) and CNS cancer (SF-268) at National Cancer Institute (NIH), USA. The compounds showed low antiproliferative activity in the anticancer tests⁶⁸.



N,N'-bis(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-1,4-xylenediimines (143) were screened for antitumor activities using cell lines derived from human solid tumors (lung, colon, melanoma, renal, ovarian, CNS, prostate, breast and leukemia). Compound showed weak cytostatic activity⁶⁹.

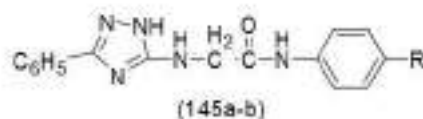


3-Phenyl-5-p-tolyl-4-(2,6-dichlorobenzylamino)-4*H*-1,2,4-triazole (144) was tested for anticancer activity. Compound showed higher anticancer activity in the preliminary tests with the cancer cell lines of breast cancer (MCF7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) and exhibited remarkable anticancer potential in screening tests with 60 human cancer cell lines⁷⁰.



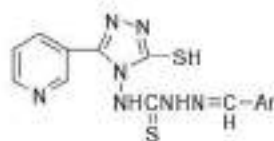
Anticonvulsant Activity

N-(substituted phenyl)-2-[5-phenyl-2*H*-1,2,4-triazol-3-ylamino] acetamide (145) was tested for anticonvulsant activity by MES method using phenytoin as standard anticonvulsant drug in screening. The compounds were found to be active as they reduced the time of extensor phase compared to control⁷¹.



Compound	R
145a	NO ₂
145b	Cl

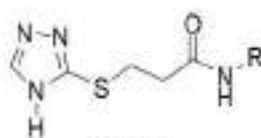
Thiosemicarbazide derivatives of 5-mercapto-3-(3'-pyridyl)-4*H*-1,2,4-triazole (146a-e) were screened for anticonvulsant activity by Maximum Electroshock (MES) method. The compounds have shown good activity⁴⁰.



Compound	Ar
146a	phenyl
146b	2-furyl
146c	2-hydroxyphenyl
146d	2-chlorophenyl
146e	4-methoxyphenyl

Anxiolytic Activity

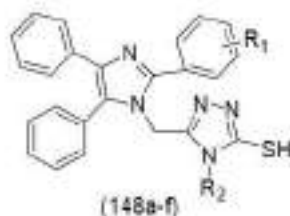
3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazoles (147a-h) were screened for anxiolytic activity by Elevated plus maze, using diazepam at the dose of 2mg/kg as standard. All compounds showed significant activity⁷².



Compound	R
147a	C ₆ H ₅
147b	4-ClC ₆ H ₄
147c	4-NO ₂ C ₆ H ₄
147d	3-ClC ₆ H ₄
147e	3-NO ₂ C ₆ H ₄
147f	2-CH ₃ C ₆ H ₄
147g	4-OCH ₃ C ₆ H ₄
147h	CH ₂ C ₆ H ₅

Anthelmintic Activity

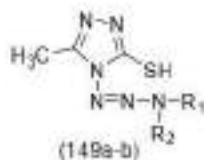
Imidazole containing triazole derivatives (148a-f) were screened for their anthelmintic activity against Indian adult earthworms (*pheretima posthuma*) at different concentrations of 0.150% and 0.300% w/v by using albendazole as standard drug. Compound 148d was found to be the most potent, whereas compounds like 148b and 148f showed high activity, while 148a, 148c and 148e showed moderate athelmintic activity when compared with standard drug albendazole⁷³.



Compound	R ₁	R ₂
148a	4-F	C ₆ H ₅
148b	4-NO ₂	C ₆ H ₅
148c	4-F	4-ClC ₆ H ₄
148d	4-NO ₂	4-ClC ₆ H ₄
148e	4-F	4-CH ₃ C ₆ H ₄
148f	4-NO ₂	4-CH ₃ C ₆ H ₄

Analgesic Activity

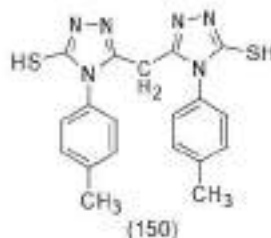
3-substituted -4H-1, 2, 4- triazoles (149a-b) were evaluated for their analgesic activity using hot plate method. The compound were exhibit higher activity than the standard drug (aspirin)⁷⁴.



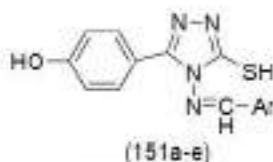
Compound	R ₁	R ₂
149a	H	4-OCH ₃ C ₆ H ₄
149b	C ₆ H ₅	C ₆ H ₅

Antioxidant Activity

5, 5-methylene bis [4-(4-methylphenyl)-4H-1, 2, 4-triazole-3-thiol (150) was for their antioxidant activity by DPPH method. The compound was found to having potent antioxidant activity⁷⁵.



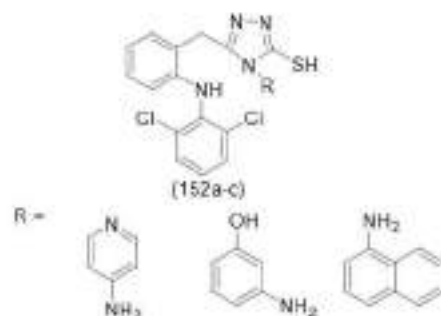
Schiff's bases of 3-substituted 1,2,4-triazo -5 thione (151a-e) were evaluated for its antioxidant activity by hydrogen peroxide scavenging method. All compounds have significant antioxidant activity⁷⁶.



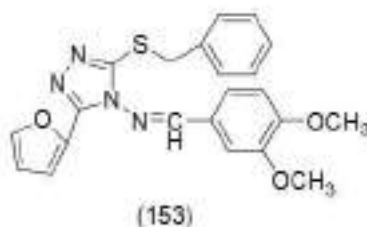
Compound	Ar
151a	C ₆ H ₅
151b	3-OHC ₆ H ₄
151c	2-ClC ₆ H ₄
151d	2-NO ₂ C ₆ H ₄
151e	3-NO ₂ C ₆ H ₄

Anticancer Activity

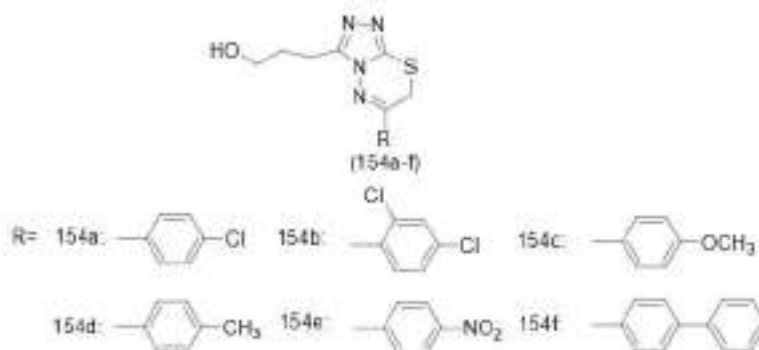
3-mercapto-1,2,4-triazole derivatives (152a-c) were screened for their ulcerogenic activity using diclofenac potassium as standard. Gastro intestinal tolerance of these compounds is better than that of Diclofenac potassium at 10mg/kg therapeutic dose⁷⁶.

**Antiviral Activity**

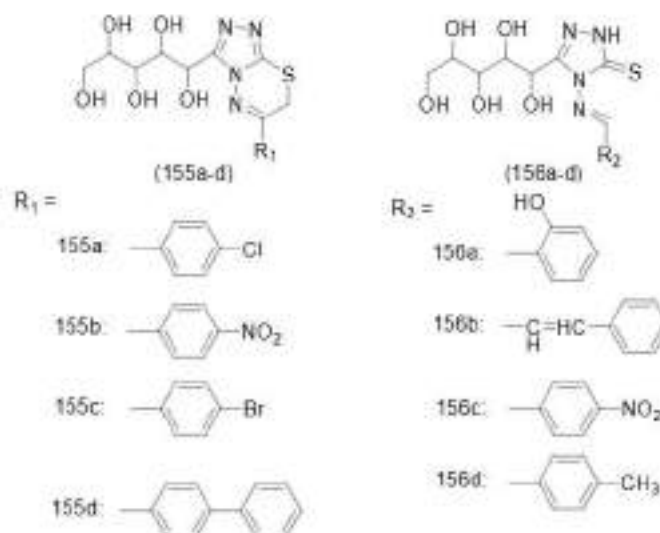
4-(3,4-Dimethoxyphenylidene)amino-3-(2-furyl)-5-benzylthio-4H-1,2,4-triazole (153) was assayed for anti-HIV-1 activity by examination of their inhibition of HIV-1-induced cytopathogenicity in MT-4 cells and by determination of their inhibitory effect on HIV-1 reverse transcriptase. Compound was found to be the most active inhibitor against HIV-1 replication in cell culture ($EC_{50} = 12 \mu M$) and against HIV-1 reverse transcriptase ($IC_{50} = 43.5 \mu M$)⁷⁷.

**Plant Growth Regulating Activity**

6-aryl-3-(3-hydroxypropyl)-7H-1,2,4-triazolo[3,4-b][1,3,4]-thiadiazines (154a-f) was investigated on sprouting of wheat and radish seeds. All compounds display remarkable inhibitory activities on the growth of radish and wheat⁷⁸.



6-aryl-3-(D-galactopentitol-1-yl)-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (155a-d) and 4-(arylmethylidene)amino-5-(D-galactopentitol-1-yl)-3-mercapto-4H-1,2,4-triazoles (156a-d) was investigated on sprouting of wheat and radish seeds. These compounds have remarkable effects on the growth of radish and wheat¹⁹.



CONCLUSION

The literature survey reveals that 1,2,4-triazole is a unique template that is associated with several biological activities, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The dynamic microwave power system employed offered an efficient heating of the material, thus reduced chemical reactions times and increased reaction yields were observed in most of the most of the literature quoted in this paper. In this respect, it can be concluded that 1,2,4-triazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents which are undisclosed till date.

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