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Thiazolopyrimidines without bridge-head nitrogen: thiazolo [4,5-*d*] pyrimidines

Khairy A. M. El-Bayouki[a]; Wahid M. Basyouni[a]
[a] Department of Chemistry, National Research Center, Cairo, Egypt

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REVIEW ARTICLE

Thiazolopyrimidines without bridge-head nitrogen: thiazolo [4,5-*d*] pyrimidines

Khairy A.M. El-Bayouki* and Wahid M. Basyouni

Department of Chemistry, National Research Center, Tahrir Street, Dokki, 11111 Cairo, Egypt

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This review article is an attempt to cover a literature survey about thiazolopyrimidine ring system without the bridge-head nitrogen: thiazolo[4,5-*d*]pyrimidines, preparation of the ring system via azines, azoles and other miscellaneous approaches, reactions, biological activity, application and spectroscopic and crystal X-ray determinations.

Keywords: thiazolo[4,5-*d*]pyrimidines; azines; azoles; reactions; biological activity; applications; spectroscopy

1. Introduction

The thiazole nucleus plays a vital role in many biological activities making it one of the most extensively studied heterocycles. The thiazole nucleus is known, chemically, as the active center in the important co-enzyme "thymine." Numerous researches have directed their attention for the preparation of *ortho*-substituted thiazole systems on the basis of their utilization as synthetic intermediates for the biologically valuable purine analogs: thiazolopyrimidines.

Pyrimidine compounds are the smaller of the two kinds of nitrogenous base found in DNA and RNA, the larger being purines. Fused pyrimidines are an important class of heterocyclic compounds and are well known to have numerous biological activities in several useful applications.

Thiazolo-pyrimidines as purine antagonists are known to have potential biological importance (*e.g.* anti-tumor, bronchodilators, central nervous system (CNS) depressants, analgesics, psychotropes, anti-human immunodeficiency virus (HIV)-1, anti-inflammatory, anti-microbial, anti-diuretic and CNS-active agents). In general, they are widely used in the fields of medicine and pesticides (*1–5*). The [4,5-*d*] isomer of thiazolopyrimidines can be considered as 7-thio analogs of guanine and adenine due to the replacement of a nitrogen by a sulfur atom at position 7 of the purine ring. Retro synthetic analysis of the thiazolo[4,5-*d*]pyrimidine scaffold shows that the synthesis can proceed via either: (i) a pyrimidine onto which a thiazole ring can be annulated

*Corresponding author. Email: khelbayouki@yahoo.com

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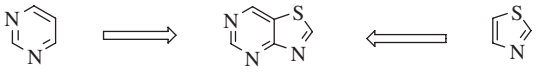
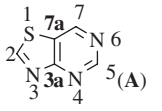
(*i.e.* azine approaches) or (ii) a thiazole bearing substituent which allows the formation of the pyrimidine ring (*i.e.* azole approaches) or (iii) by other miscellaneous reaction approaches.



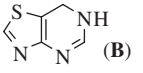
2. Atom numbering and parent ring systems

The way of atom numbering for thiazolo[4,5-*d*]pyrimidine ring system as well as the parent ring system and structural isomers is illustrated in structures A–D.



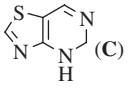
(**A**)

Thiazolo[4,5-*d*]pyrimidine



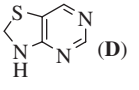
(**B**)

6,7-dihydrothiazolo[4,5-*d*]pyrimidine



(**C**)

4,5-dihydrothiazolo[4,5-*d*]pyrimidine



(**D**)

2,3-dihydrothiazolo[4,5-*d*]pyrimidine

3. Abbreviations

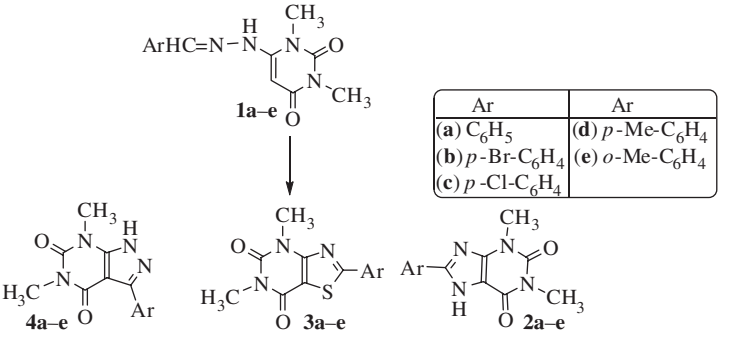
CNS	Central nervous system	HIV	Human immunodeficiency virus
NBS	*N*-Bromosuccinimide	BMMA	*N*-[bis(methylthio)methylene] amino
HMPA	Hexamethylphosphoramide	LDA	Lithium diisopropyl amide
PMB	*p*-metoxy benzyl	CAN	Ceric ammonium nitrate
THF	Tetrahydrofuran	TEA	Triethylamine
rt	Room temperature	TFA	Trifluoroacetic acid
DMAP	Dimethylaminopyridine	PPh_3	Triphenylphosphine
Ph_3PBr_2	Triphenylphosphine dibromide	Ac	Acetyl
Ac_2O	Acetic anhydride	DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide	*m*-CPBA	*m*-Chloroperoxybenzoic acid
Mont. KSF	Montmorillonite KSF as solid support	PTSA	*p*-Toluene sulfonic acid
CRH	Corticotrophin-releasing hormone	EGFR	Epidermal growth factor receptor
CXCR2	CXC chemokine receptor	HCMV	Human cytomegalovirus
TNF-α	Tumor necrosis factor-alpha	CRF	Corticotrophin-releasing factor
EMCV	Encephalomyocarditis virus	MCMV	Murine cytomegalovirus
SFV	Semliki Forest virus	DHPG	Di-hydroxy propoxymethyl guanine (anti-viral drug)

4. Preparation of thiazolo[4,5-*d*]pyrimidines

4.1. *Azine approaches*

4.1.1. *Reaction of arylidenehydrazino-1,3-dimethyluracils and thionyl chloride*

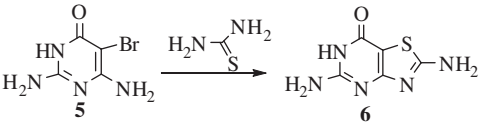
Reaction of 6-arylidenehydrazino-1,3-dimethyluracile derivatives **1a**–**e** with three equivalents of thionyl chloride in dry benzene at 95 °C for 2 h afforded purines **2a**–**e**, thiazolo[4,5-*d*]pyrimidines **3a**–**e** along with the pyrazolo[3,4-*d*]pyrimidines **4a**–**e**. In general, the purines were readily precipitated out from the reaction mixture, while the other products were isolated by the fractional recrystallization of the filtrate. Plausible mechanisms for the reaction of **1** with thionyl chloride leading to the formation of various fused pyrimidines, including the preparation of thiazolo[4,5-*d*]pyrimidines in fair yield, were described (*6*).



Scheme 1.

4.1.2. *Reaction of 2,6-diamino-5-bromopyrimidin-4(3H)-one with thiourea*

2,5-Diaminothiazolo[4,5-*d*]pyrimidin-7-(6*H*)-one **6** was synthesized (in moderate yield) from 2,6-diamino-5-bromopyrimidin-4(3*H*)-one **5** by reaction with thiourea in absolute ethanol (*7*).

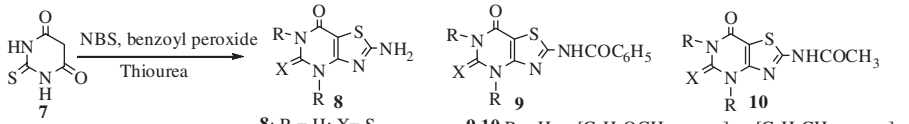


Scheme 2.

4.1.3. *One-step synthesis: reaction of thiobarbituric acids with N-bromosuccinimide, benzoyl peroxide and thiourea*

2-Thiobarbituric acid **7** upon reaction with *N*-bromosuccinimide (NBS), benzoyl peroxide and thiourea at reflux temperature in benzene gave 5-amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-*d*]pyrimidine **8** (80% yield). Benzoylation of **8** gave **9** (70–80% yield), while the acetylation of **8** afforded **10** (80–86% yield). Similar condensation of 1,3-diarylthiobarbituric

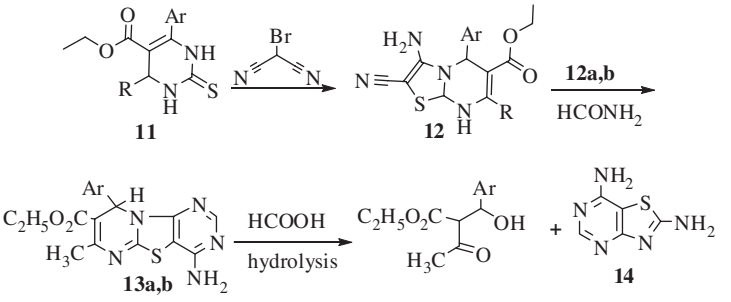
acids afforded 1,3-diaryl-5-amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-*d*]pyrimidines (*8*).



Scheme 3.

4.1.4. *Reaction of tetrahydropyrimidin-5-carboxylate derivatives and bromomalononitrile*

Pyrimidine **11** was reacted with bromomalononitrile to give ethyl 3-amino-5-aryl-2-cyano-7-substituted-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates **12a**–**d** (88–92% yield). When **12a** and **b** were heated with formamide in the presence of formic acid and dimethylformamide (DMF) to afford the expected thiazolo[3,2-*a*:4,5-*b*]dipyrimidine derivatives **13**, only 2,7-diaminothiazolo[4,5-*d*]pyrimidine **14** was obtained (*9*).



11	R	Ar
(**a**)	CH_3	C_6H_5
(**b**)	CH_3	C_6H_4-OCH_3-*p*
(**c**)	CH_3	C_6H_4-Cl-*p*
(**d**)	CH_3	C_6H_4-$N(CH_3)_2$-*p*
(**e**)	C_6H_5	

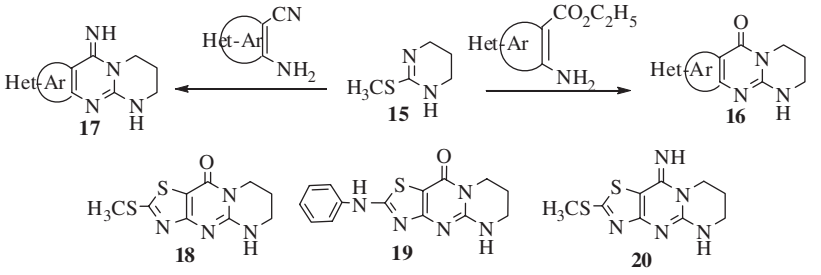
12	R	Ar
(**a**)	CH_3	C_6H_5
(**b**)	CH_3	C_6H_4-OCH_3-*p*
(**c**)	CH_3	C_6H_4-Cl-*p*
(**d**)	C_6H_5	C_6H_5

Scheme 4.

4.1.5. *Reactions of 2-(methylsulfanyl)-1,4,5,6-tetrahydropyrimidine*

In continuation of the previous investigations (*10a*, *b*) dealing with cyclic reagents; utilization of 2-(methylsulfanyl)-1,4,5,6-tetrahydropyrimidine **15** within the versatile *N*-[bis(methylthio)methylene]amino (BMMA) strategy was described to expand these investigations toward the annelation of a primido[1,2-*a*] unit. Accordingly, the reaction of the pyrimidine **15** with a number of monocyclic heterocycles with vicinal amino and ester functionalities, *e.g.* ethyl 4-amino-2-(methylsulfanyl)thiazole-5-carboxylate, ethyl 4-amino-2(phenylamino)-thiazole-5-carboxylate and 4-amino-2-(methylsulfanyl)-thiazole-5-carbonitrile,

gave the tricyclic oxo compounds of type **16**. Examples of the synthesized compounds are: 5,6,7,8-tetrahydro-2-(methylsulfanyl)-10*H*-pyrimido[1,2-*a*]thiazolo[4,5-*d*]pyrimidin-10-one **18** (69% yield) and 5,6,7,8-tetrahydro-2-(phenylamino)-10*H*-pyrimido[1,2-*a*]thiazolo[4,5-*d*]pyrimidin-10-one **19** (62% yield) which were obtained from the reaction of pyrimidine **15** in hexamethylphosphoramide (HMPA) at 150 °C for 5 h with ethyl 4-amino-2-(methylsulfanyl)thiazole-5-carboxylate and ethyl 4-amino-2(phenylamino)-thiazole-5-carboxylate, respectively. The reaction of pyrimidine **15** with substituted heterocyclic amino nitriles gave the imino derivatives of type **17**. For example, **20** was obtained (60% yield) from the reaction of **15** and 4-amino-2-(methylsulfanyl)thiazole-5-carbonitrile in HMPA at 150 °C for 4 h (*10c*).



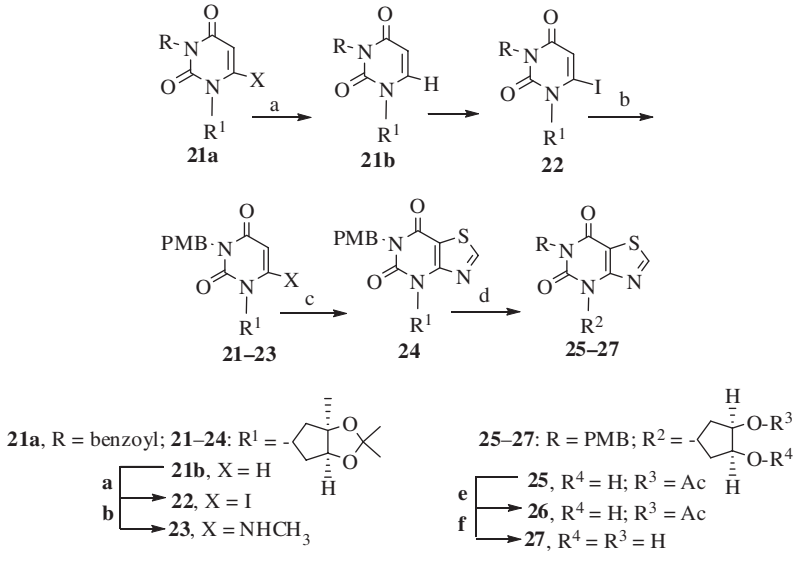
Scheme 5.

4.1.6. *Synthesis of fused pyrimidine-thiazole ring system from pyrimidine-dione nucleoside*

When treating pyrimidine-dione **21a** with lithium diisopropyl amide (LDA) and iodine, iodination occurred at multiple sites, including on the benzoyl group. Turning next to the Bn group, iodination proceeded with no problems, and the ring closure to give the desired fused pyrimidine–thiazole ring system was accomplished in good yield, but the removal of the Bn group proved difficult. Treatment of **21b** with LDA and iodine provided the 6-iodo intermediate **22** (78% yield) which is converted to **23** (94% yield) upon treatment with CH_3NH_2. Iodination, followed by displacement with methylamine, and subsequent ring closure by adding $SOCl_2$ while refluxing in pyridine gave *p*-metoxy benzyl (PMB)-protected 2,2-dimethyltetrahydro-3aH-cyclopenta[*d*][1,3]dioxol-4-yl)-6-(4methoxy-benzyl)thiazole[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione **24** (80% yield). Reprotection of the unmasked hydroxyls of **24** gave 5,7-dioxo-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-4(5*H*)yl)cyclo-pentane-1,2-diyldiacetate **25** (92% yield). Deprotection of the PMB group with ceric ammonium nitrate (CAN) afforded 5,7-dioxo-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-4(5*H*)-yl)cyclopentane diacetate **26** (86% yield), followed by the removal of acetates, provided 2,3-dihydroxycyclopentyl)thiazole[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **27** in a 75% yield (*11*).

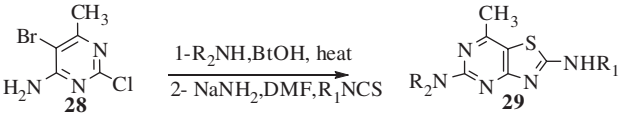
4.1.7. *Access to thiazolo[4,5-d]pyrimidine derivatives from 5-bromo-6-methylpyrimidin-4-amine*

5-Bromo-2-chloro-6-methylpyrimidin-4-amine **28** was readily obtained from 5-bromo-2,4-dichloro-6-methylpyrimidine by sequential treatment with ethanolic ammonia. Compound **28** was successfully reacted with various isothiocyanates in the presence of sodamide in DMF to form the new thiazolo[4,5-*d*] pyrimidine derivatives **29** (*12*).



Reagents and conditions (and yield %): (a) LDA, THF, I2, 78°C, 3 h, (58%); (b) 33% NH_2Me, EtOH,rt, 1.5 h, (94%); (c) $SOCl_2$, pyridine, reflux, 3 h, (80%); (d) (i) TFA/H_2O(2:1), rt, 18 h; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 12 h, (82%) for two steps; (e) 10:1CH_3CN/H_2O, CAN, 55°C, 3 h, (86%); (f) NH_3, MeOH, rt 15 h, (65%).

Scheme 6.



29	R_1	R_2	29	R_1	R_2
(**a**)	C_6H_5	mor.	(**d**)	ethyl	pyrro.
(**b**)	C_6H_5	pyrro.	(**e**)	butyl	mor.
(**c**)	ethyl	mor.	(**f**)	butyl	pyrro.

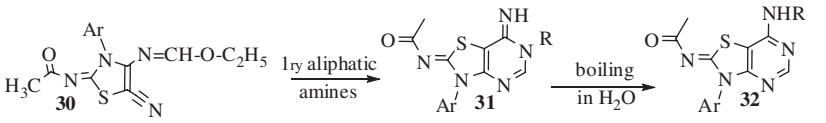
mor. = morpholine; pyrro. = pyrrolidine

Scheme 7.

4.2. *Azoles approaches*

4.2.1. *Reactions of 2-acetylimino-3-aryl-4-ethoxymethyleneamino-5-cyano-thiazolines with primary amines*

Upon reaction of 2-acetylimino-3-aryl-4-ethoxymethyleneamino-5-cyano-thiazolines **30** with primary amines, *e.g.* methyl- or *n*-propyl amine, at room temperature (rt) afforded the thiazolo[4,5-*d*]pyrimidines **31a**–**e** (70–80% yield). The Dimroth rearrangement was successfully attempted by heating in water for a long time (40 h) and the products were the 7-alkyl-aminothiazolo[4,5-*d*]pyrimidines **32a**–**e** (*13*).

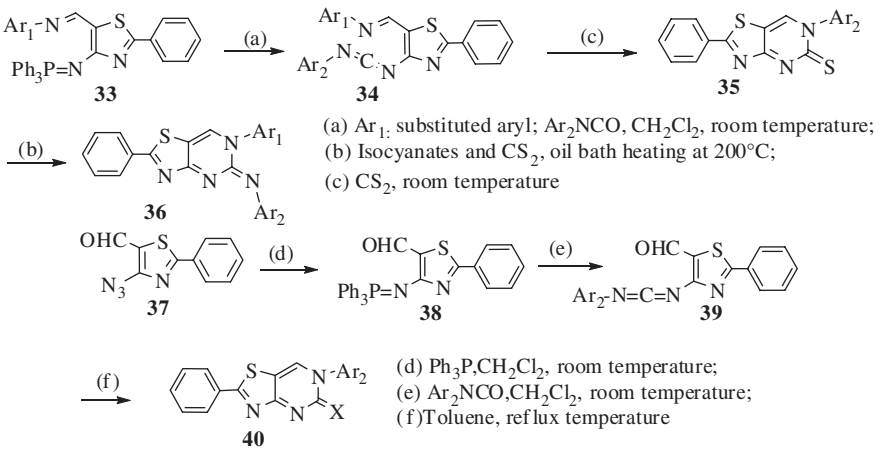


31, 32	Ar	R	31, 32	Ar	R
(**a**)	phenyl	methyl	(**d**)	*p*-tolyl	*n*-propyl
(**b**)	*p*-tolyl	methyl	(**e**)	*o*-tolyl	*n*-propyl
(**c**)	phenyl	*n*-propyl			

Scheme 8.

4.2.2. *Aza-Wittig reaction: reaction of iminophosphoranes with isocyanates and carbon disulfide*

2-Phenyl-5-((arylimino)methyl)-*N*-((aryllimino)methylene)thiazol-4-amines **34** derived from iminophosphoranes **33** were reacted with isocyanates and carbon disulfide to form thiazolo[4,5-*d*]pyrimidines **35** (50–54% yield) and **36** (60–65% yield). 5-Formyl-2-phenyl-4-[(triphenylphosphoranylidene)amino]thiazole **38** obtained from 4-azido-2-phenylthiazole-5-carbaldehyde **37** (Staudinger reaction) when treated with aromatic isocyanates afforded 2-phenyl-4-(phenylimino)methyleneamino)thiazole-5-carbaldehyde **39** which cyclized when refluxed in toluene to afford 6-aryl-5-oxo-5,6-dihydrothiazolo[4,5-*d*]pyrimidines **40** (69–73% yield) (*14*).



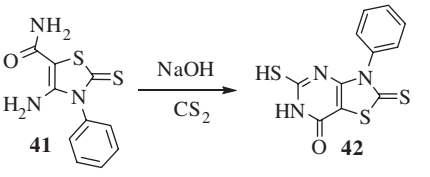
Comp.	Ar_1	Ar_2
36a	C_6H_5	*p*-$CH_3.C_4H_4N$
b	C_6H_5	*p*-$CH_3OC_6H_4N$
c	*p*-$CH_3.C_6H_4$	*p*-$CH_3.C_6H_4N$
d	*p*-$CH_3.C_6H_4$	*p*-$CH_3OC_6H_4N$

Comp.	Ar_2	X
39	C_6H_5	–
40a	C_6H_5	O
b	*p*-$CH_3.C_6H_4$	O
c	*p*-$CH_3OC_6H_4$	O

Scheme 9.

4.2.3. *Cyclization of 4-amino-5-carbamoyl-3-phenylthiazole-2(3H)-thione with carbon disulfide*

Cyclization of 4-amino-5-carbamoyl-3-phenylthiazole-2(3*H*)-thione **41** with carbon disulfide in the presence of sodium hydroxide gave 2,3-dihydro-5-mercapto-3-phenyl-2-thioxothiazololo[4,5-*d*]pyrimidin-7(6*H*)-one **42** (60% yield) (*15*).

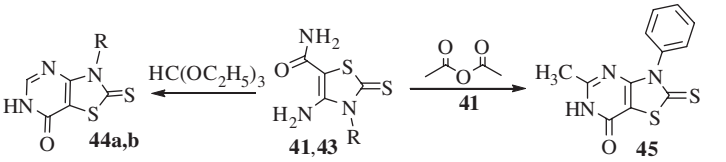


41 **42**

Scheme 10.

4.2.4. *Cyclization of 4-amino-5-carbamoylthiazole-2(3H)thione derivatives with either triethylorthoformate or Ac_2O*

Cyclization of 4-amino-5-carbamoylthiazole-2(3*H*)thiones **41** (*16*), **43** with either triethylorthoformate *or* acetic anhydride (Ac_2O) afforded thiazolo[4,5-*d*]pyrimidines **44a** and **b** (90% and 70% yield) and **45** (*16*).



44a,b **41**,**43** **41** **45**

41: R = C_6H_5 , **43**: R = $CH_2CH{=}CH_2$, **44** : (**a**) R = C_6H_5 , (**b**) R = $CH_2CH{=}CH_2$

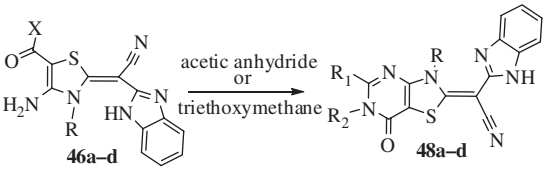
Scheme 11.

4.2.5. *Cyclization of substituted-thiazolyl-benzimidazole derivatives with either triethylorthoformate or Ac_2O*

Thiazolyl-benzimidazoles **46a**–**d** were cyclized with either triethoxymethane or Ac_2O to the corresponding thiazolo[4,5-*d*]pyrimidines **48a**–**d** (65–72% yield). Compound **48e** was prepared by the reaction of 3-allyl-2,3-dihydro-6-methyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one **47** with dimethyl sulfate and 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (*17*).

4.2.6. *Reactions of N-substituted 4-amino-thioxothiazole-5-carboxylates and isothiocyanates*

The reaction of aminothiazoles **49a**–**d** with isothiocyanates yielded 2,3-dihydro-3,6-diaryl-5-mercapto-2-thioxothiazolo[4,5-*d*]pyrimidine-7-(6*H*)-ones **50a**–**d** (60–68% yield). 5-Alkylmercapto-2,3-dihydro-3,6-diaryl-2-thioxothiazolo[4,5-*d*]pyrimidin-7-(6*H*)ones **51a** and **b** were obtained (83% and 85% yield) upon reacting **50a** or **b** with the appropriate alkyl

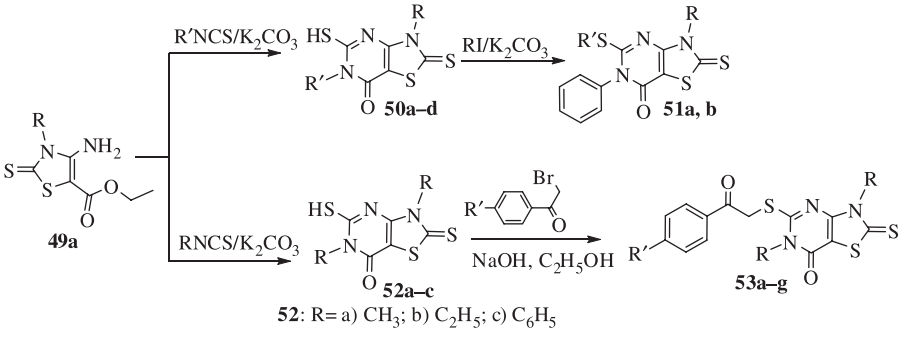


46	R	X
a	$CH_2CH{=}CH_2$	NH_2
b	C_6H_5	NH_2
c	*m*-$CH_3C_6H_4$	NH_2
d	C_6H_5	OC_2H_5

48	R	R_1	R_2
a	$CH_2CH{=}CH_2$	H	H
b	C_6H_5	H	H
c	*m*-$CH_2C_6H_4$	H	H
d	C_6H_5	CH_3	H
e	$CH_2CH{=}CH_2$	H	CH_3

Scheme 12.

iodide in the presence of anhydrous potassium carbonate in acetone (*18*). Also, the reaction of **49a** with isothiocyanates and K_2CO_3 afforded 2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6*H*)-one derivatives **52a–c** (70–79% yield). Further reaction of products **52a** and **b** with 2-bromo-1-(*p*-substituted-phenyl)ethanone derivatives in ethanol/NaOH gave 5-(4′-nonsubtituted/-substituted benzoylmethyl)-thio derivatives **53a–g** (70–97% yield) (*19*). Moreover, the synthesis of 2,3-dihydro-3-methyl-5-mercapto-6-methyl/ethyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **54a** and **b** was accomplished (65% and 58% yield, respectively) via cyclization of **49e** with methy/ethyl isothiocyanate in the presence of potassium carbonate.



49	R
a	C_6H_5
b	$CH_2C_6H_4$-*o*
c	$CH_2C_6H_4$-*m*
d	ClC_6H_4-*p*
e	CH_3

50	R, R′
a	C_6H_5
b	$CH_2C_6H_4$-*o*
c	$CH_2C_6H_4$-*m*
d	ClC_6H_4-*p*

51	R	R′
a	C_6H_5	CH_3
b	$CH_3C_6H_4$-*o*	C_2H_5

53	R	R′		R	R′
a	CH_3	H	**e**	C_2H_5	H
b	CH_3	Cl	**f**	C_2H_5	Cl
c	CH_3	Br	**g**	C_2H_5	Br
d	CH_3	CH_3			

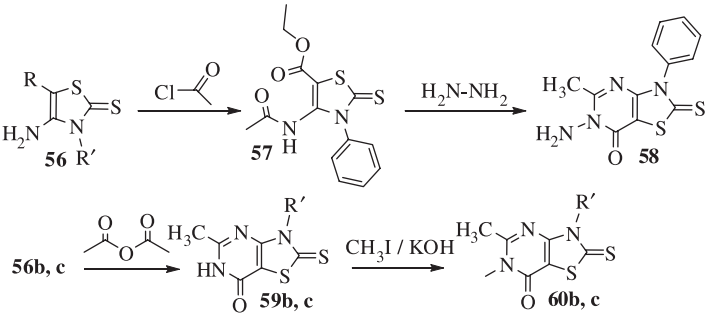
55	R	R_1	yield %	55	R	R_1	yield %
a	CH_3	H	78	**e**	C_2H_5	H	88
b	CH_3	Cl	84	**f**	C_2H_5	Cl	74
c	CH_3	Br	91	**g**	C_2H_5	Br	75
d	CH_3	CH_3	90	**h**	C_2H_5	CH_3	94

Scheme 13.

2,3-Dihydro-3-methyl-5-(4′-nonsubstituted/-substituted benzoyl methyl)thio-6-methyl/-ethyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **55a**–**h** were obtained (74–94% yield) upon reaction of **54** with 2-bromo-1-(*p*-substitutedphenyl)ethanones (*18–20*).

4.2.7. *Reactions of N-substituted-thioxothiazole-5-carboxylate with acetyl chloride then hydrazine hydrate or with Ac_2O*

The reaction of ethyl 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate **56a** with acetyl chloride gave the corresponding 4-acetamido derivative **57**. The latter product when treated with hydrazine hydrate gave 6-amino-2,3-dihydro-5-methyl-3-phenyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6H)-one **58** (30% yield). 3-(Substituted)-5-methyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin7(6H)-ones **59b** and **c** were afforded upon heating **56b** or **c** in Ac_2O. Methylation of **59** with methyl iodide gave 2,3-dihydro-5,6-dimethyl-3-substituted-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **60b** and **c** (75% yield) (*21*).



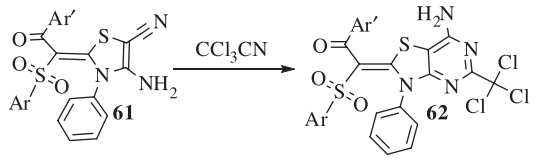
56	R	R′
a	$CO_2C_2H_5$	C_6H_5
b	$CONH_2$	CH_2=$CHCH_2$
c	$CONH_2$	*p*-ClC_6H_5

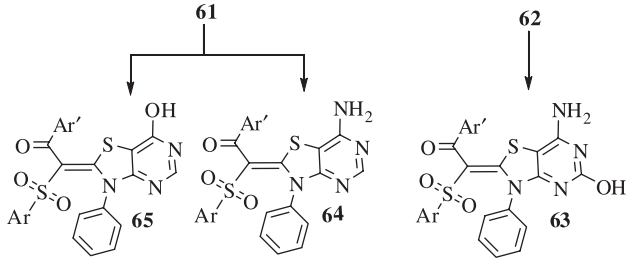
59,60	R′
b	CH_2=$CHCH_2$
c	*p*-ClC_6H_5

Scheme 14.

4.2.8. *Reaction of the β-enaminonitrile moiety of 4-amino-thiazole-5-carboxylate (or -5-carbonitrile) derivatives with trichloroacetonitrile*

The β-enaminonitrile moiety in 4-amino-2,3-dihydro-1,3-thiazole-5-carbonitrile derivatives **61** proved to be highly reactive toward a variety of chemical reagents. For example, cyanoaminothiazoles **61a** and **b** were reacted with equimolar amounts of trichloroacetonitrile in dioxane/Et_3N to yield 1:1 adducts: thiazolo[4,5-*d*]pyrimidine structure **62a** and **b**. The trichloromethyl moiety in products **62** was readily attacked by nucleophilic reagents. For example, compound **62a** upon heating in EtOH/KOH afforded the corresponding 5-hydroxy-thiazolo[4,5-*d*]pyrimindine derivatives **63** (46% yield). Compounds **61a** and **b** upon treating with formamide in the presence of formic acid and DMF afforded the corresponding 7-aminothiazolo[4,5-*d*]pyrimidines **64a** and **b** (54% and 49% yield, respectively). Similarly, prolonged heating of compounds **61a** and **b** with formic acid gave the 7-hydroxythiazolo[4,5-*d*]pyrimidines **65a** and **b** (52% and 55% yield, respectively) (*22*).





61,62	Ar	Ar′
a	C_6H_5	C_6H_5
b	C_6H_5	*p*-C_6H_4-Br
c	*p*-C_6H_4-CH_3	C_6H_5
d	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br

63,64,65	Ar	Ar′
a	C_6H_5	C_6H_5
b	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br

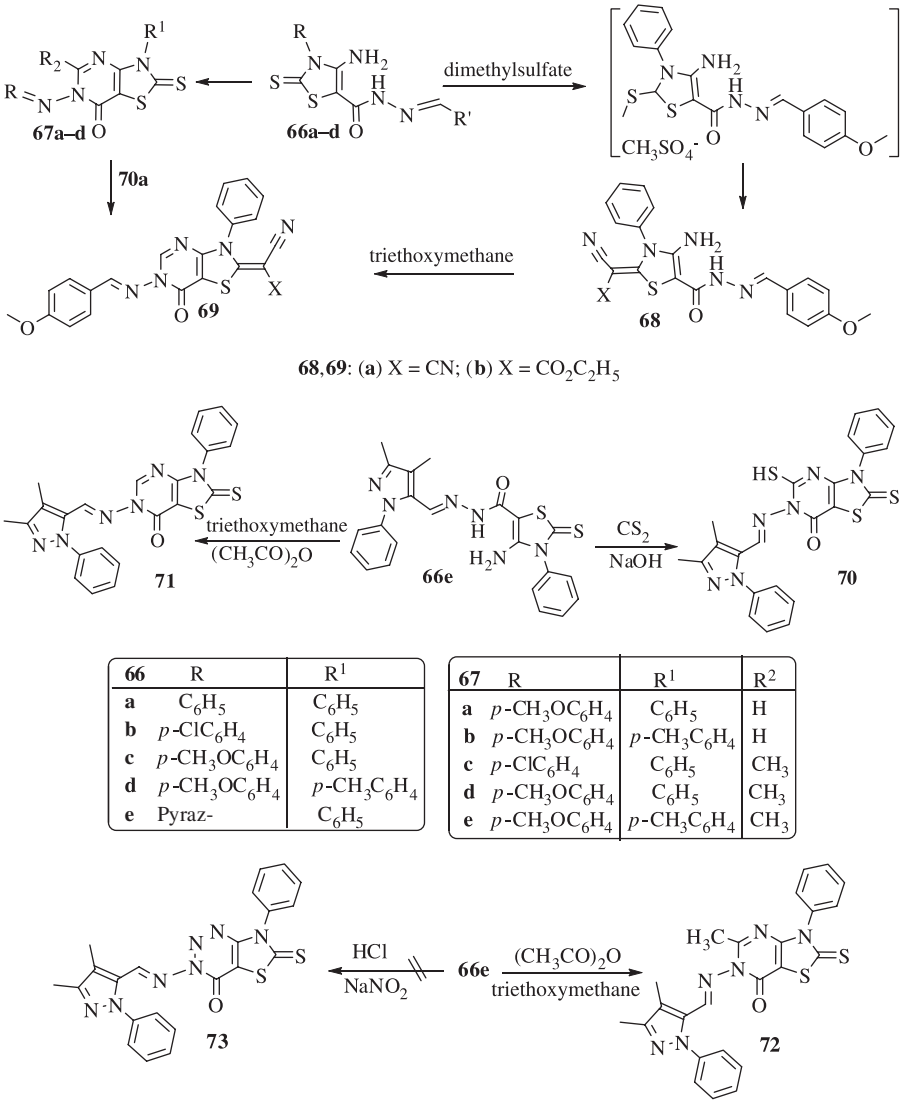
Scheme 15.

4.2.9. *Cyclization of 3-substituted 4-amino-5-arylidenehydrazinocarbonylthiazole-2(3H)-thiones with either trimethylorthoformate or Ac_2O*

3-Substituted 4-amino-5-arylidenehydrazinocarbonylthiazole-2(3*H*)-thiones **66a**–**d** were cyclized by either using triethylorthoformate or Ac_2O to give the corresponding thiazolo[4,5-*d*]pyrimidines **67a**–**e**. 2-Dicyanomethylidene or 2-(cyano, ethoxycarbonyl)methylidene thiazolo derivatives **68a** and **b** (*23a*) were cyclized with triethyl orthoformate or Ac_2O to give 2-dicyanomethylidene and 2-(cyano, ethoxycarbonyl)methylidenethiazolo[4,5-*d*]pyrimidine derivatives **69a** and **b** (70–80% yield, respectively). The latter thiazolopyrimidine derivatives could be synthesized (68–69% yield) from **67a** through the subsequent action of dimethyl sulfate and malononitrile or ethyl cyanoacetate (*23b*). Cyclization of 3-phenyl-4-amino-5-(3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-methylidenehydrazinocarbonyl)thiazolo-2-(3*H*)-thione **66e** with carbon disulfide in the presence of sodium hydroxide at rt followed by dilute hydrochloric acid afforded 6-(3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-methylideneamino)-5-mercapto-3-phenyl-thioxo-2,3-dihydrothiazolo-[4,5-*d*]pyrimidin-7-(6*H*)one **70** (75.3% yield). The polysubstituted thiazolo[4,5-*d*]pyrimidinone derivatives **71** and **72** were prepared by heating **66e** with a mixture of triethylorthoformate and Ac_2O (1:1) or with Ac_2O (60% and 53% yield). Trials to synthesize thiazolo[4,5-*d*]triazine of type **73** failed upon reacting **66e** with $NaNO_2$/HCl (*24*, p. 12).

4.2.10. *Cyclization of N-(5-acetyl-2-(methylthio)thiazole-2-chloroacetamide derivatives with potassium thiocyanate*

N-Chloroacetyl derivatives of five-membered heterocycles with enaminocarbonyl structure **74** and **76** reacted with potassium thiocyanate to yield thiazolo[4,5-*d*]pyrimidines **75** and **77** (73% and 70% yield). Other substituted products of type **77** when stirred in ethanol for 7 h at rt with hydrazine hydrate *or* when heated in ethanol with morpholine afforded the corresponding hydrazino- and morpholino-thiazolopyrimidine derivatives **78a** and **b** (*25*).



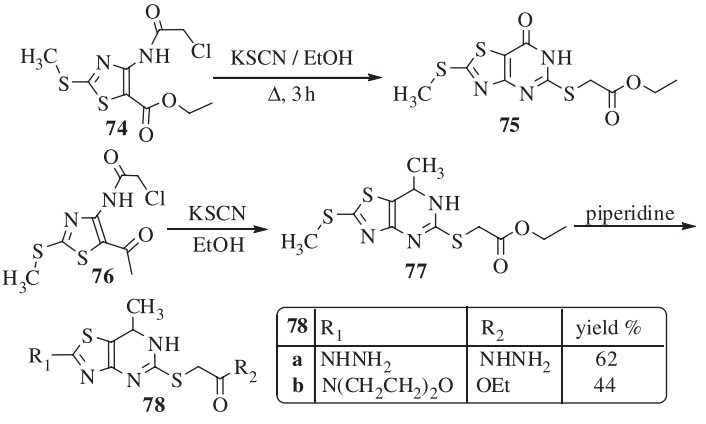
66	R	R^1
a	C_6H_5	C_6H_5
b	*p*-ClC_6H_4	C_6H_5
c	*p*-$CH_3OC_6H_4$	C_6H_5
d	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$
e	Pyraz-	C_6H_5

67	R	R^1	R^2
a	*p*-$CH_3OC_6H_4$	C_6H_5	H
b	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	H
c	*p*-ClC_6H_4	C_6H_5	CH_3
d	*p*-$CH_3OC_6H_4$	C_6H_5	CH_3
e	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	CH_3

Scheme 16.

4.2.11. *Intermolecular [2 + 2] cycloaddition reaction: a new synthetic method for new azeto[1,2-α][1,3]thiazolo[4,5-d]pyrimidine ring system*

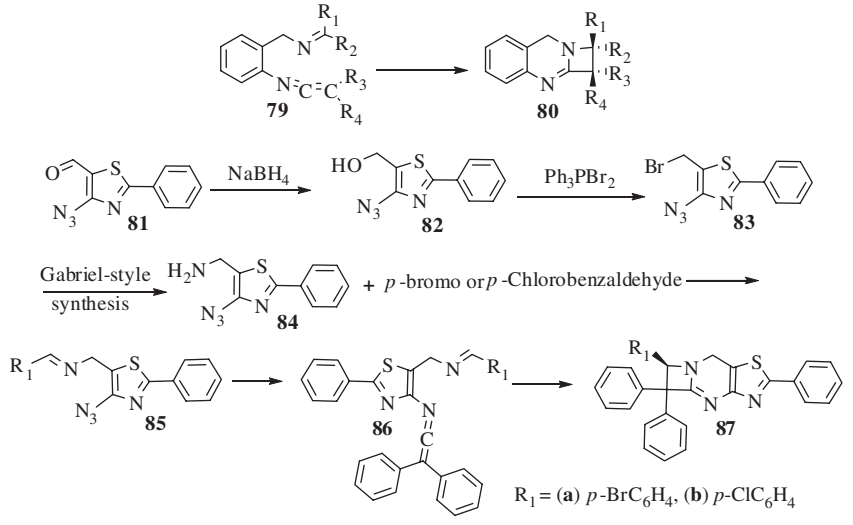
The intramolecular [2 + 2] cycloaddition reaction between ketene-imine and imine functions **79** afforded azeto[2,1-*b*]-quinazolines **80** in a highly stereo-controlled manner. The synthetic sequence resulting in azeto[1,2-α][1,3]thiazolo[4,5-*d*]pyrimidines **87** started with 5-(amino-methyl)thiazole **84**, which was obtained in four steps by standard procedures in 35% overall yield starting from the known azido aldehyde **81** involved: (i) sodium borohydride reduction to alcohol **82**; (ii) conversion into the bromide **83** with triphenylphosphine dibromide (Ph_3PBr_2) and (iii) the Gabriel-style synthesis of amine **84**. Treatment of **84** with *p*-bromo- or *p*-chlorobenzaldehyde yielded the expected aldimines **86**. Sequential treatment of toluene solutions of aldimines **86** with



78	R_1	R_2	yield %
a	$NHNH_2$	$NHNH_2$	62
b	$N(CH_2CH_2)_2O$	OEt	44

Scheme 17.

trimethylphosphane and diphenyl ketene provided imino-ketenimines **86**. Compounds **86** were relatively stable at rt. Intermolecular [2 + 2] cycloaddition of imino-ketenimines **86** took place upon heating the reaction mixture at reflux for 1 h. Azeto[1,2-α][1,3]thiazolo[4,5-*d*]pyrimidines **87** were obtained in moderate yields (51% and 64%, respectively) after column chromatography(*26*).

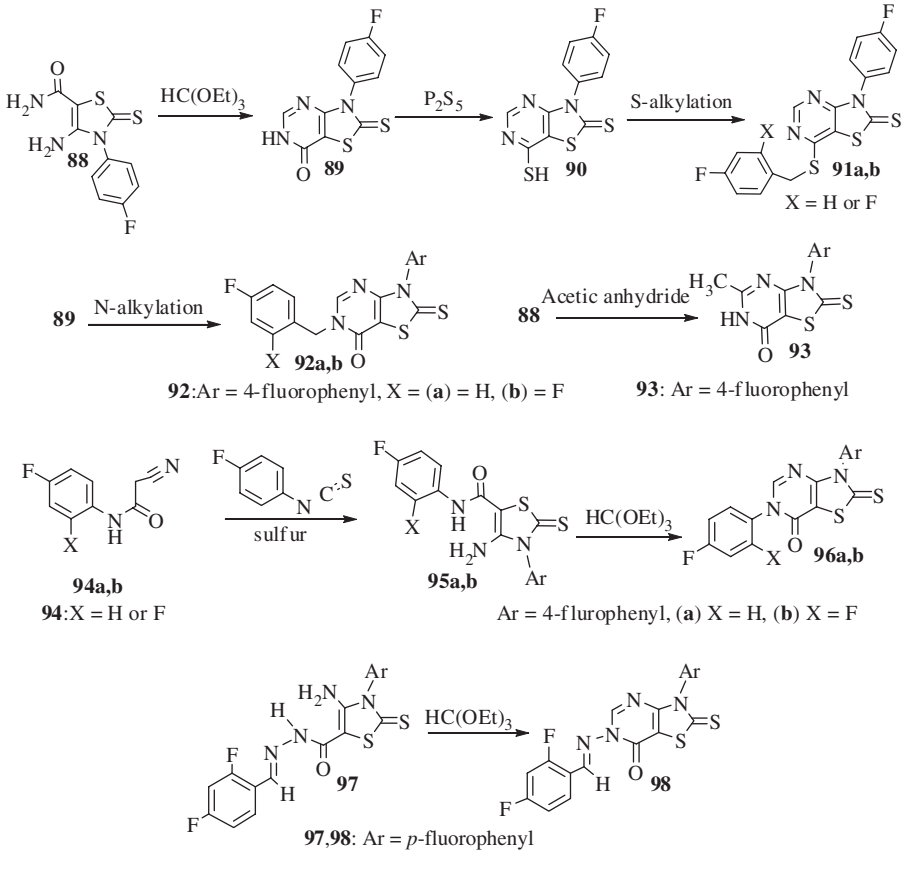


Scheme 18.

4.2.12. *Cyclization of 4-amino-3-(substituted-fluorophenyl)-2,3-dihydro-2-thioxothiazole-5-carboxamide derivatives using triethylorthoformate/Ac_2O mixture*

4-Amino-5-carboxamido-2,3-dihydrothiazole-2-thione **88** was cyclized to afford the thiazolo[4,5-*d*]pyrimidine **89** (85% yield) using triethylorthoformate/Ac_2O mixture. 7-Mercapto-thiazolo [4,5-*d*]pyrimidine **90** was obtained in 80% yield through the reaction of **89** with phosphorus pentasulfide. S-Alkylation of **90** yielded the 7-fluorobenzylthio derivatives **91a** and **b** (87% and 82% yield). N-Alkylation of **89** gave the 6-fluorobenzyl derivatives **92a** and **b** (77% and 74%

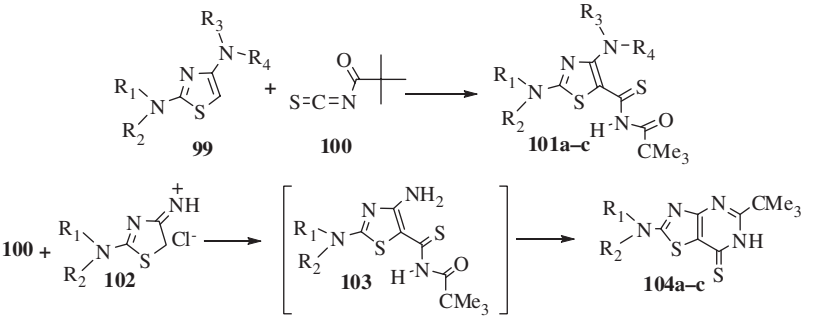
yield, respectively). Thiazolo[4,5-*d*]pyrimidine **93** was prepared in 88% yield by cyclization of the starting thiazole **88** with Ac_2O. 4-Amino-5-fluorophenylaminocarbonyl-2,3-dihydrothiazole-2-thione **95** was prepared from 2-cyano-*N*-(4-fluorophenyl or 4-fluoro-2-methylphenyl)acetamides **94a** and **b**, sulfur and 4-fluorophenyl isocyanate. When **95a** and **b** were reacted with ortho-formate, 3,6-fluoro phenylthiazolo[4,5-*d*]pyrimidines **96a** and **b** were obtained (74% and 72% yield). 6-(2,4-Difluorobenzylidene-amino)thiazolo[4,5-*d*]pyrimidine **98** was prepared in 83% yield from 4-amino-3-(4-fluorophenyl)-6-(2,4-difluorobenzylidene-hydrazinecarbonyl)thiazole-2(3H)-thione **97** via a cyclization reaction with triethylorthoformate (*27*).



Scheme 19.

4.2.13. *Reactions of thiazole-2,4-diamines with isothiocyanates (e.g. pivaloyl isothiocyanates)*

Reaction of N^2,N^2,N^4,N^4-tetrasubstituted thiazole-2,4-diamines **99** with acylisothiocyanates (*e.g.* pivaloyl isothiocyanates **100**) afforded N^5-pivaloyl-substituted-2,4-diaminothiazole-5-carbothioamides **101**. When N^4-unsubstituted thiazole-2,4-diamines (**103**) (generated *in situ* from the corresponding hydrochlorides **102**) were used for this reaction, fused thiazolo[4,5-*d*]pyrimidin-7-(6*H*)-thiones **104a**–**c** were obtained (71%, 69% and 62% yield) instead of N^5-pivaloyl-substituted-2,4-diamino-thiazole carbo-thioamides **103** (*28*).



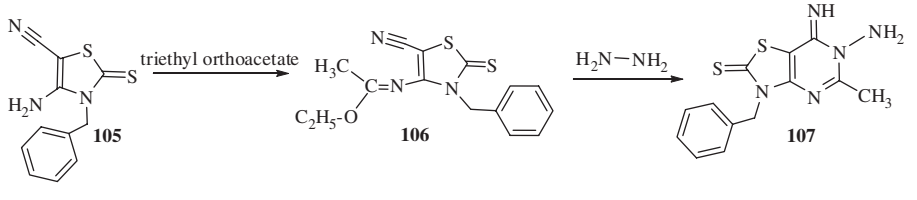
99, 101, 102	R_1R_2N	R_3R_4N
a	mor.	mor.
b	pip.	pip.
c	pyr.	pyr.

104	R_1R_2N	yield %
a	mor.	71
b	pip.	69
c	pyr.	62

Scheme 20.

4.2.14. *Cyclocondensation of 3-benzyl-5-cyano-4-(α-ethoxyethylideneamino)thiazolin-2-thione with hydrazine hydrate*

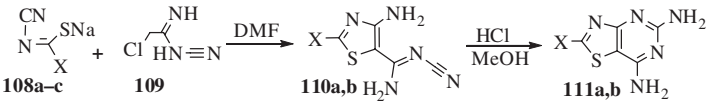
4-Amino-3-benzyl-5-cyano-2,3-dihydrothiazol-2-thione **105** when reacted with triethyl orthoacetate in Ac_2O yielded 3-benzyl-5-cyano-4-(α-ethoxyethylideneamino)thiazolin-2-thione **106**. The latter product when treated with hydrazine hydrate afforded 6-amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thione **107** (61% yield) (*29*).



Scheme 21.

4.2.15. *Ring closure of 4-amino-N'-cyano-2-(methylthio)thiazole-5-carboxamidine derivatives with HCl/methanol*

The sodium salt of 1-alkyl-3-cyanothiourea **108a** (obtained from cyanamide and alkylisothiocyanate) reacted with *N*-cyanochloroacetamidine **109** in DMF at rt forming the substituted thiazole **110a**. Cyaniminomethylthiocarbothiolate **108b** obtained *in situ* from sodium cyaniminocarbodithiolate **108c** and methyl iodide reacted to yield the thiazole **108b**. Upon treatment with HCl in MeOH, thiazoles **110** close the diaminopyrimidine ring with the formation of thiazolo[4,5-*d*]pyrimidines **111a** and **b** (87–84% yield, respectively) which are of significant interest, because they are thio-analogs of purines (*30*).



108a–c **109** **110a,b** **111a,b**

108, **110** and **111**: (**a**) X = $NHCH_2CH{=}CH_2$, (**b**) X = SCH_3; **108c**: X = SNa

Scheme 22.

4.2.16. *Synthesis of thiazolo[4,5-d]pyrimidines from 4-amino-2,5-substituted thioxo thiazoles*

Reactions of 2-cyano-*N′*-((1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)methylene)-acetohydrazide or (1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde and 4-amino-2-hydrazono-3-(*p*-substituted aryl)-2,3-dihydrothiazole-5-carboxamide) or *N′*-(1-(benzofuran-2-yl)ethylidene)-2-cyanoacetohydrazide with sulfur and the appropriate aryl isothiocyantes in the presence of a catalytic amount of piperidine gave the corresponding thiazolyl hydrazones **112**, **113** and **114**, respectively. Cyclization of **112a** and **b** with triethyl orthoformate/acetic acid anhydride mixture yielded the thiazolo[4,5-*d*]pyrimidinones **115a** and **b**. Heating **112a** and **b** with excess Ac_2O yielded the corresponding thiazolo[4,5-*d*]pyrimidinones **116a** and **b**. The dithio-thiazolo[4,5-*d*]pyrimidinones **117a** and **b** were synthesized by cyclization of **112a** and **b** with carbon disulfide in the presence of sodium hydroxide solution at rt followed by acidification with dilute HCl. Thiazoles **113a** and **b** were used to synthesize thiazolo[4,5-*d*]pyrimidines **118a** and **b**, **119a** and **b** and **120a** and **b** (*31*). Cyclization of 4-amino-*N′*-(1-(benzofuran-2-yl)ethylidene)-3-(*p*-substituted-phenyl)-2-thioxo-2,3dihydrothiazole-5-carbohydrazide **114** with either Ac_2O or with a mixture of Ac_2O and triethyl orthoformate (1:1 by volume) gave the corresponding 6-(1-benzofuran-2-yl-ethylideneamino)-3-substituted-2-thioxo-2,3-dihydro-6*H*-thiazolo-[4,5-*d*]pyrimidin-7-ones **121a**–**c** and **122a**–**c**, respectively (*32*).

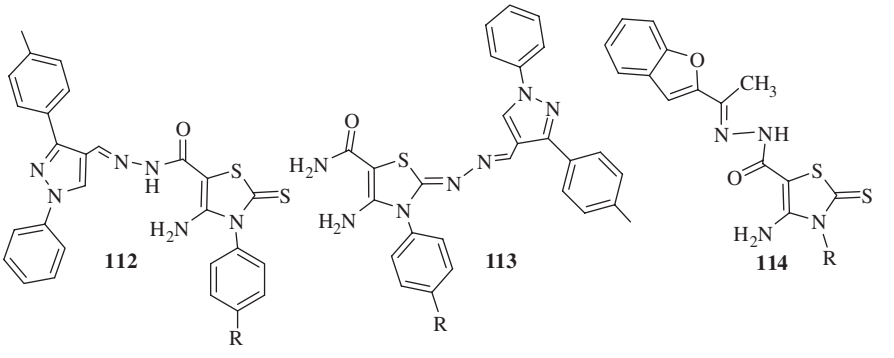
4.2.17. *Synthesis of fluorine-containing thiazolo[4,5-d]pyrimidin-7(6H)-ones via ring closure of 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate iminophosphoran derivatives*

5-Alkylamino-6-aryl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **126a**–**r** were designed and easily synthesized *via* a tandem Aza-Wittig reaction. Treatment of iminophosphorane **123** (prepared from **56a** (*21*) and triphenylphosphine (PPh_3)) with aromatic isocyanates gave carbo-diimide **124**, which reacted with fluoro-substituted alkyl amines to provide the thiazolo[4,5-*d*]pyrimidine derivatives **126a**–**r** (*via* the intermediate **125**) using sodium ethoxide as a catalyst; without the formation of **127** (*33*).

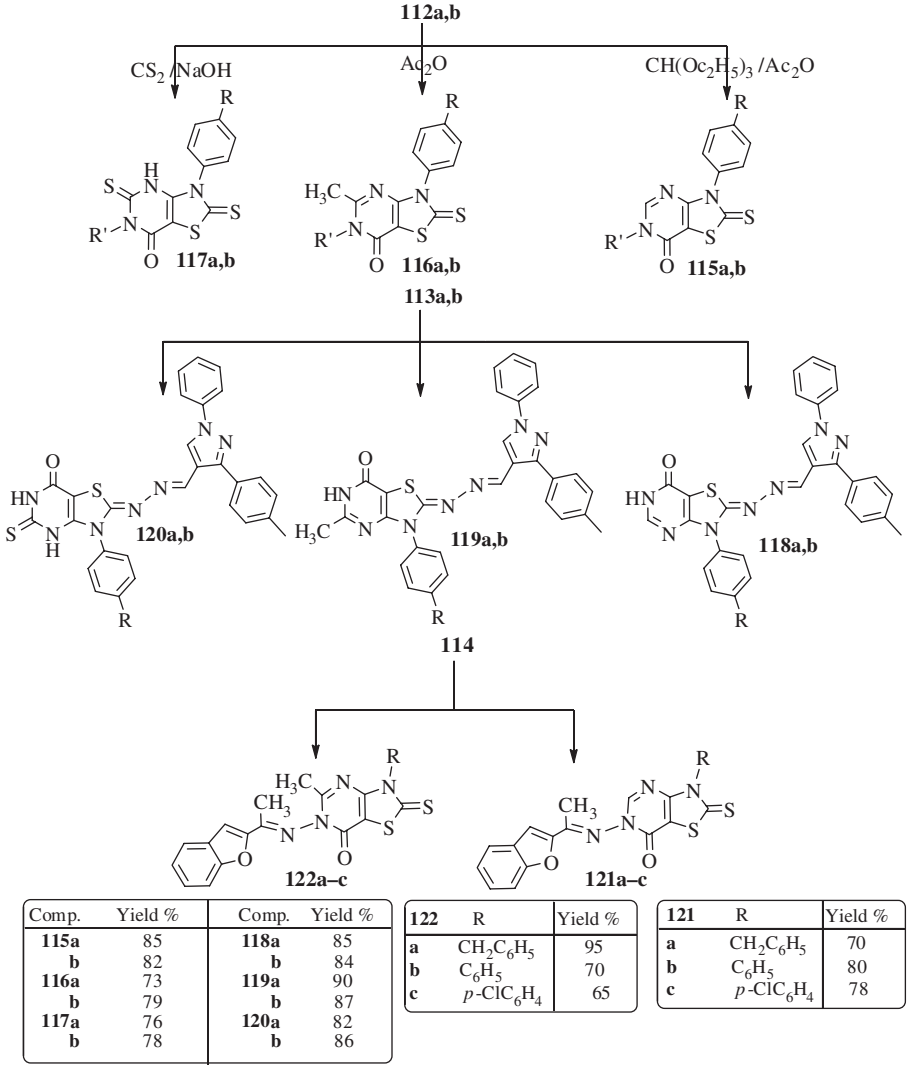
4.2.18. *Synthesis of 2-phenylamino-6H-thiazolo- and 2-methylsulfanyl-6H-thiazolo[4,5-d]-pyrimidin-7-one derivatives*

Reaction of phenyl isothiocyanates **128** (obtained from substituted phenyl amines and thiophosgene in the presence of concentrated hydrochloric acid provided intermediates (**129**) which reacted with methyl chloroacetate to afford substituted 4-amino-2-phenylamino-thiazole-5-carboxylic acid methyl esters **130**. Compounds **130** when treated with Ac_2O in formamide gave substituted 2-phenylamino-6*H*-thiazolo[4,5-*d*]pyrimidin-7-ones **131**.

When chloro acetonitrile was reacted with potassium methyl *N*-cyanodithioimido carbonate **132**, followed by treatment with triethylamine (TEA) gave 4-amino-2-methylsulfanyl-thiazole-5-carbonitrile **133**. The thiazole **133** when heated with formic acid gave 2-methylsulfanyl-6*H*-thiazolo[4,5-*d*]pyrimidin-7-one **134** (*34*).



112, **113**: (**a**) R = H; (**b**) R = CH_3; **114**: (**a**) R = $CH_2C_6H_5$; (**b**) R = C_6H5; (**c**) R = *p*-ClC_6H_5

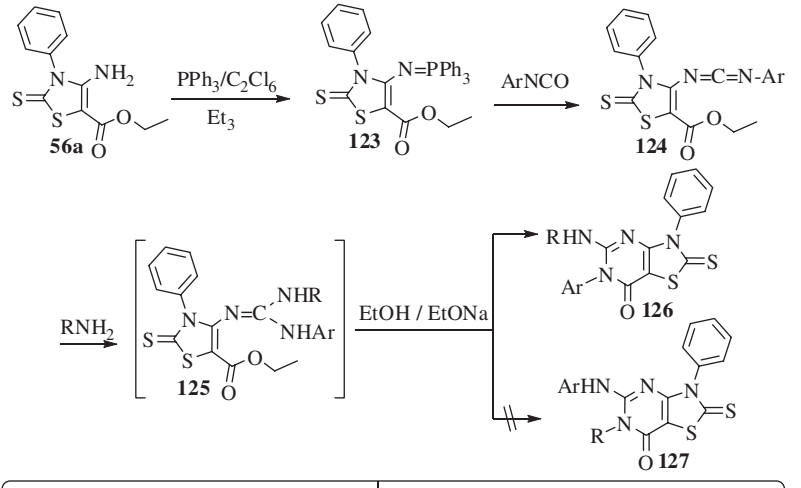


Comp.	Yield %	Comp.	Yield %
115a	85	**118a**	85
b	82	**b**	84
116a	73	**119a**	90
b	79	**b**	87
117a	76	**120a**	82
b	78	**b**	86

122	R	Yield %
a	$CH_2C_6H_5$	95
b	C_6H_5	70
c	*p*-ClC_6H_4	65

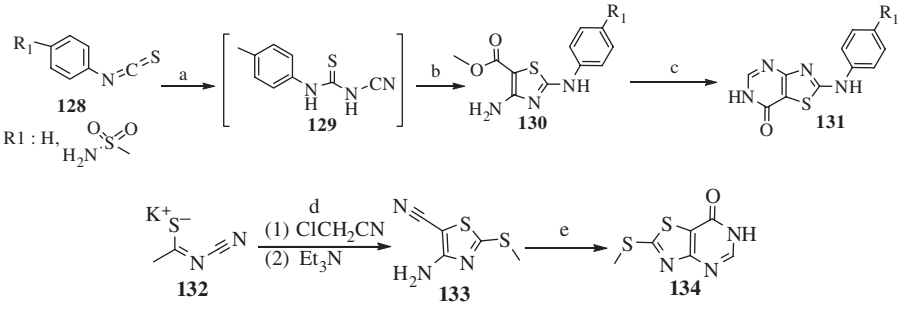
121	R	Yield %
a	$CH_2C_6H_5$	70
b	C_6H_5	80
c	*p*-ClC_6H_4	78

Scheme 23.



Comp.No.	Ar	R	Yield %	Comp. No.	Ar	R	Yield %
126a	Ph	*n*-Pr	82.6	**126j**	4-FPh	*t*-Bu	65.3
b	Ph	*n*-Bu	80.9	**k**	4-FPh	2-MePhCH$_2$	77.2
c	Ph	*i*-Bu	79.3	**l**	4-FPh	3-MePhCH$_2$	73.8
d	Ph	2-FPhCH$_2$	77.5	**m**	4-FPh	4-MePhCH$_2$	76.5
e	Ph	3-FPhCH$_2$	80.4	**n**	4-FPh	4-MeOPhCH$_2$	69.8
f	Ph	4-FPhCH$_2$	78.3	**o**	4-FPh	4-ClPhCH$_2$	87.7
g	4-FPh	*n*-Pr	82.4	**p**	4-FPh	2-FPhCH$_2$	76.4
h	4-FPh	*n*-Bu	78.6	**q**	4-FPh	3-FPhCH$_2$	74.1
i	4-FPh	*i*-Bu	71.6	**r**	4-FPh	4-FPhCH$_2$	74.9

Scheme 24.



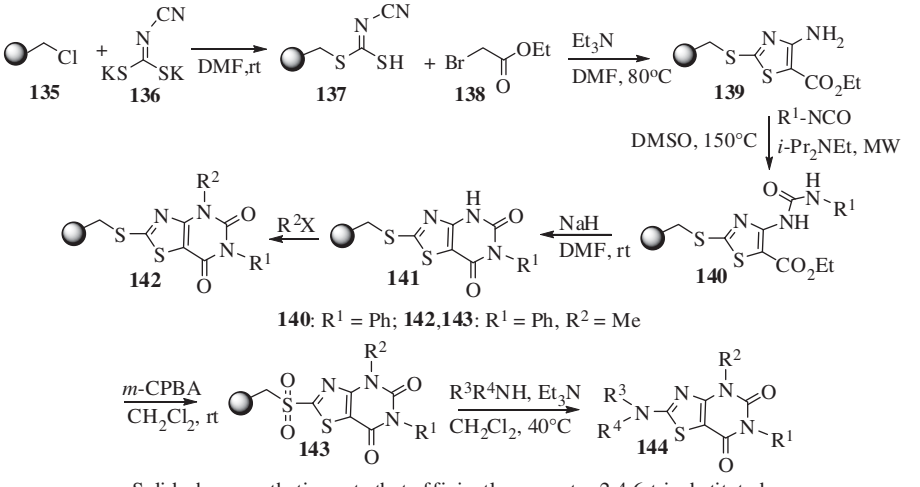
Reagents and conditions (and yield %): (a) cyanamide, sodium methoxide, rt, 3 h, (82%); (b)methyl chloroacetate, 50–60°C, 12 h, (95%); (c) acetic anhydride, formamide, 150–180°C, 7 h, (57–88%); (d) (1) chloro acetonitrile, acetone, rt, 1 h; (2) triethylamine, rt, 72 h, (82%); (e) Fomic acid, water, reflux, 4 h, (95%).

Scheme 25.

4.2.19. *Traceless solid-phase synthesis of 2,4,6-trisubstituted thiazolo[4,5-d]pyrimidine-5,7-dione derivatives*

Thiazole amino ester resin **139** was synthesized through reaction of the solid-supported cyanocarbonimidodithioate **137** with ethyl 2-bromoacetate **138**. The resin **137** was derived from the Merrifield resin **135** by reaction with dipotassium cyanodithioimidocarbonate **136**. The amino ester resin **139** was first swollen in dimethyl sulfoxide (DMSO) and then treated under MW irradiation conditions with isocyanates (the first diversity element) to give the corresponding

thiazolourea resin **140**. The one-pot cyclization/N-alkylation of thiazolourea resin **140**, using NaH/alkyl halide (the second diversity element), was carried out in DMF at rt. Treatment of the resin **140** with NaH in DMF provided the intermediate **141**, which undergoes *in situ* N-alkylation with methyl iodide to provide the desired thiazolo[4,5-*d*]pyrimidine-5,7-dione resin **142** (R^1 = Ph, R^2 = Me). Treatment of the resin **142** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 provided the resin-bound sulfone intermediate resin **143**. Finally, the sulfone group in resin **143** was displaced by desulfonative substitution reaction with the corresponding amines (benzyl amine for **144**), serving as a third diversity element in CH_2Cl_2. This process, which was accompanied by concurrent cleavage from the resin, furnished the final traceless 2,4,6-trisubstituted thiazolo[4,5-*d*]pyrimidine-5,7-dione **144** (29–34% yield) (*35*).



140: R^1 = Ph; **142**,**143**: R^1 = Ph, R^2 = Me

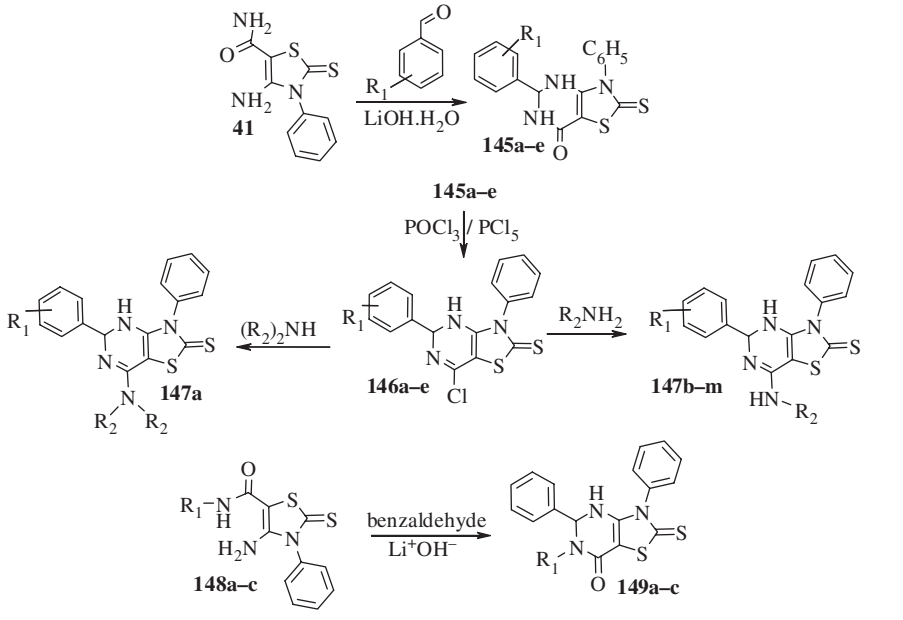
Solid-phase synthetic route that efficiently generates 2,4,6-trisubstituted thiazolo[4,5-d]pyrimidine-5,7-dione derivatives

144	R^1	R^2	R^3R^4N		R^1	R^2	R^3R^4N
a	Ph	Me	NHBn	**e**	Ph	Me	Et_2N
b	Ph	Me	4-MeO-BnNH	**f**	Ph	Me	Pyrrolidine
c	Ph	Me	*n*-PrNH	**g**	Ph	Me	Piperidine
d	Ph	Me	$C_6H_{11}CH_2NH$	**h**	Ph	Me	pyran

Scheme 26.

4.2.20. *Synthesis of novel 3-phenylthiazolo[4,5-d]pyrimidin-2-thione derivatives*

Thiazolo[4,5-*d*]pyrimidine derivatives **145a**–**e** were prepared (54.3–70.0% yield) by heating 4-amino-5-carboxamido-2,3-dihydrothiazole-2-thione 41 (*15*) with the appropriate substituted aromatic aldehyde in the presence of a basic catalyst such as lithium hydroxide. An excess of aromatic aldehyde was used as the medium of the reaction. Chlorination of **145a**–**e** with a mixture of phosphorus oxychloride and phosphorus pentachloride gave the 7-chloro derivatives **146a**–**e** (62.0–77.3% yield). Treatment of compounds **146** with amines and hydrazine hydrate gave 7-amino derivatives **147** (64.5–75.2% yield). The reaction required the presence of bases and an excess of the appropriate amine. The thiazole derivatives **148a**–**c** underwent cyclo-condensation with benzaldehyde to yield the target bicyclic thiazole[4,5-*d*]pyrimidines **149a**–**c** (56.7–59.5% yield) (*36*).



145,146	R_1
a	C_6H_5
b	C_6H_4-*p*-Cl
c	C_6H_4-*o*-Cl
d	C_6H_4-*p*-F
e	C_6H_4-*o*-OCH_3

147	R_1	R_2
a	C_6H_5	--
b	C_6H_5	C_4H_9
c	C_6H_5	NH_2
d	C_6H_5	CH_3
e	C_6H_5	*p*-F-Phenyl
f	C_6H_5	benzyl

147	R_1	R_2
g	*o*-Cl-Phenyl	*o*-Cl-benzyl
h	*o*-Cl-Phenyl	CH_3
i	*o*-Cl-Phenyl	*p*-F-Phenyl
j	*p*-F-Phenyl	*p*-F-benzyl
k	*p*-F-Phenyl	NH_2
l	*p*-F-Phenyl	CH_3
m	o-CH_3-C_6H_4	*p*-F-benzyl

148,149	R_1
a	CH_3
b	C_6H_5
c	benzyl

Scheme 27.

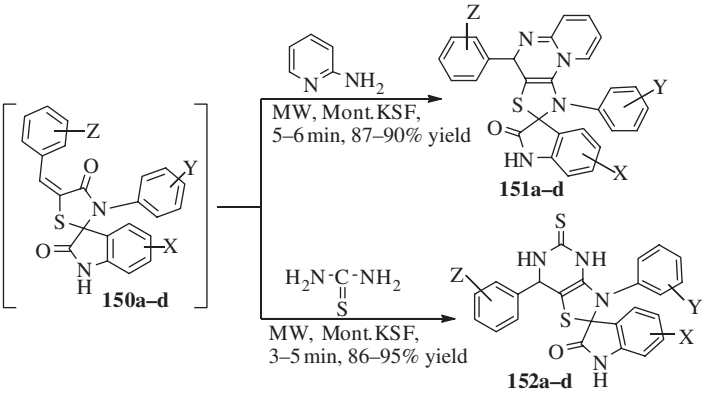
4.3. *Miscellaneous syntheses*

4.3.1. *Improved synthetic method for affording fluorinated spiro[indole-3,2′-thiazolo[4,5-d] pyrimidines under microwaves in the presence of montmorillonite KSF as solid support*

The arylidene of fluorinated spiro thiazolidines **150** containing α,β-unsaturated function (−CH=CH−CO−) in their structure have been used as Michael acceptor with 2-aminopyridine to give spiro[indole-3,2′-pyrido[1,2-*a*]thiazolo[5,4-*e*]pyrimidines] **151** (87–90% yield) in a single step under microwaves in the presence of montmorillonite KSF (mont. KSF) as solid support. An improved synthetic method for obtaining fluorinated spiro[indole-3,2-thiazolo[4,5-*d*]pyrimidines **152** in 86–95% yield was developed involving the reaction of **150** with thiourea under mono-mode microwave reactor. Conventionally, **150**–**152** were synthesized by long refluxing in glacial AcOH and fused sodium acetate in volatile solvents such as dioxane and dry toluene using Dean Strak apparatus with a tedious work-up process and purification by a chromatographic technique with further need of solvent yielding the desired compounds in lower yield (*37*).

4.3.2. *Synthesis of some new fused thiazolo[4,5-d]pyrimidine derivatives from 2,4-thiazolidine, urea and different aromatic aldehydes*

The fused ring system 3-isopropyl-4-aryl-1,4,5,7-tetrahydropyrazolo[3,4-*d*] pyrimidin-6-ones **154a**–**d** have been synthesized (32–47% yield) by the reaction of 5-isopropyl-2,



150a–d

151a–d

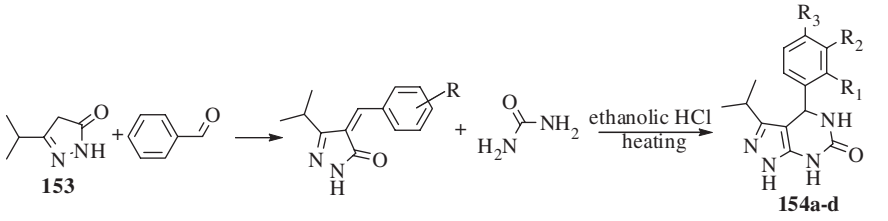
152a–d

	X	Y	Z
150a	5-F	H	4-N(CH_3)$_2$
b	7-F	H	4-OCH_3
c	5-CF_3	H	3-OCH_3
d	7-CF_3	4-OCH_3	CH_3

	X	Y	Z
151a	5-F	H	4-N(CH_3)$_2$
b	7-F	H	4-OCH_3
c	5-CF_3	H	3-OCH_3
152a	5-F	H	4-N(CH_3)$_2$
b	7-F	H	4-OCH_3
c	5-CF_3	H	3-OCH_3
d	7-CF	4-OCH_3	CH_3

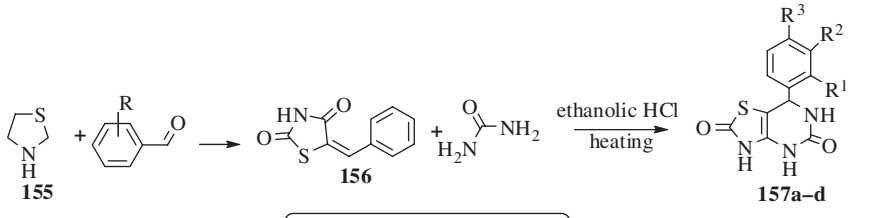
Scheme 28.

4-dihydro-3-pyrazolone **153**, urea and different aromatic aldehydes, while 7-aryl-6,7-dihydro-3*H*,4*H*-thiazolo[4,5-*d*)pyrimidine-2,5-diones **157** have been synthesized by using 2,4-thiazolidine **155** to give 5-substituted-benzylidenethiazolidine-2,4-dione **156**, which upon heating with ethanolic HCl afforded **157a**–**d** in 40–50% yield (*38*).



153

154a-d



155

156

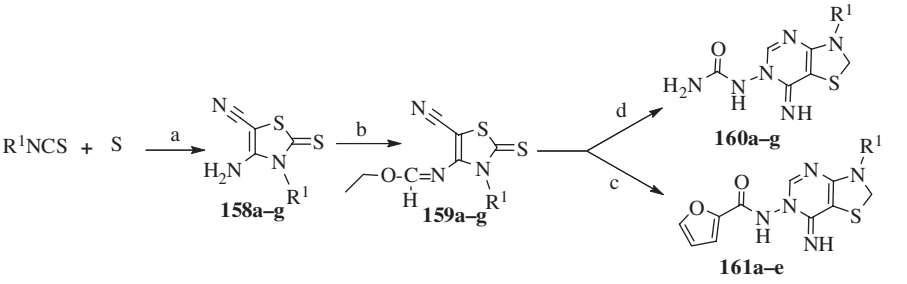
157a–d

154,157	R^1	R^2	R^3
a	H	H	H
b	H	OCH_3	H
c	H	OCH_3	OCH_3
d	H	H	OCH_3

Scheme 29.

4.3.3. *Synthesis of novel 7-imino-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidine derivatives via the reaction of isothiocyanate, malononitrile and sulfur powder*

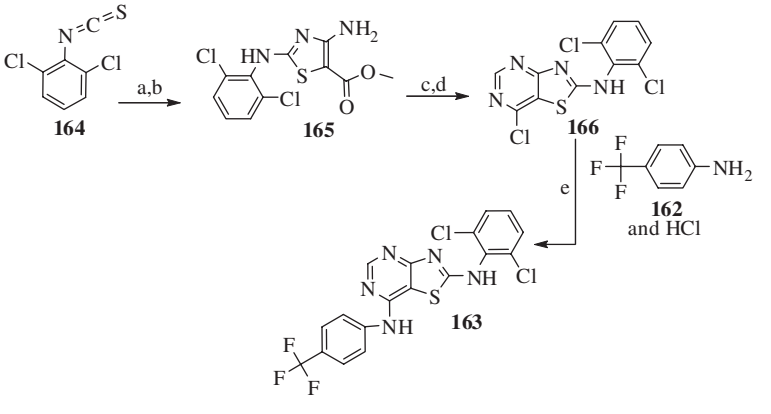
Synthesis of the thiazolo[4,5-*d*]pyrimidine derivatives **160a**–**g** was afforded by adding equimolar mixture of isothiocyanate, malononitrile and sulfur powder in DMF. The reaction mixture was stirred in an ice bath. After 15 min, TEA was added dropwise to the mixture, and the reaction was continued for 4 h to give 4-amino-3-substituted-2-thioxo-2,3-dihydrothiazole-5-carbonitrile derivatives **158a**–**g**. The carbonitrile derivatives **158a**–**g** were refluxed in toluene with triethylorthoformate (equimolar ratio) and *p*-toluene sulfonic acid (catalytic amount) for 6 h to yield imino-ether derivatives **159a**–**g**. Mixture of **159a**–**g**, semicarbazide hydrochloride/furoic acid hydrazide (equal mol) and TEA (catalyst) in ethanol was stirred at rt for 12 h to give 3-substituted-7-imino-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-6(7*H*)-amine **160a**–**g** or *N*-(3-substituted-7-imino-2,3-dihydrothiazolo-[4,5-*d*]pyrimidin-6(7*H*)-yl)furan-2-carboxamide **161a**–**e** (*39*).



158, 159, 160: R^1=(a) -C_2H_5, (b) -C_3H_7, (c) -C_4H_9, (d) -C_3H_5, (e) -C_6H_5, (f) -C_6H_4I, (g) -$CH_2C_6H_5$.
161 :R^1=(a) -C_2H_5, (b) -C_3H_7, (c) -C_4H_9.

Reagents and conditions: (a) triethyl amine (TEA), rt; (b) triethylorthoformate ,*p*-toluene sulfonic acid (PTSA), reflux; (c) furoic acid hydrazide, TEA, rt; (d) semi-carbazide HCl, TEA, rt.

Scheme 30.



Reagents and conditions: (a) NH_2CN, sodium methoxide, rt; (b) chloroacetic acid methyl ester, 50°C, 24 h (77% over two steps); (c) formamide, Ac_2O (cat),170°C, sealed tube, 18 h; (d) $POCl_3$, 90°C, 6 h (26% over two steps); (e) 1 equiv 4-trifluoromethyl-phenyl amine, 2.2 equiv HCl in IPA (1.25M), IPA, 90°C, 6 h (40%).

Scheme 31.

4.3.4. *Synthesis of N^2-(2,6-dichlorophenyl)-N^7-(4-(trifluoromethyl)phenyl)thiazolo[4,5-d]pyrimidine-2,7-diamine*

The thiazolo[4,5-d]pyrimidine **163** was synthesized in five steps using an improved version of a previously published procedure (*40b*). Formation of the 4-amino-thiazole-5-methyl ester **165** was accomplished in two steps from commercially available 2,6-dichlorophenyl isothiocyanate **164**. Exposure of 4-amino-thiazole-5-methyl ester **165** to formamide at 170 °C followed by chlorination in the presence of $POCl_3$ afforded the 7-chloro-thiazolo[4,5-d]-pyrimidine **166** in 26% yield over two steps. Amination of 7-chlorothiazolo[4,5-d]pyrimidine **166** in the presence of HCl and 4-trifluoromethyl-phenyl amine **162** provided compound N^2-(2,6-dichlorophenyl)-N^7-(4-(trifluoromethyl)phenyl)thiazolo[4,5-*d*]pyrimidine-2,7-diamine **163** in 40% yield (*40a*, *b*).

5. Some selected reactions

5.1. *Reactions of 2-substituted thiazolo[4,5-d]pyrimidin-7-ones with some substituted aryl amines*

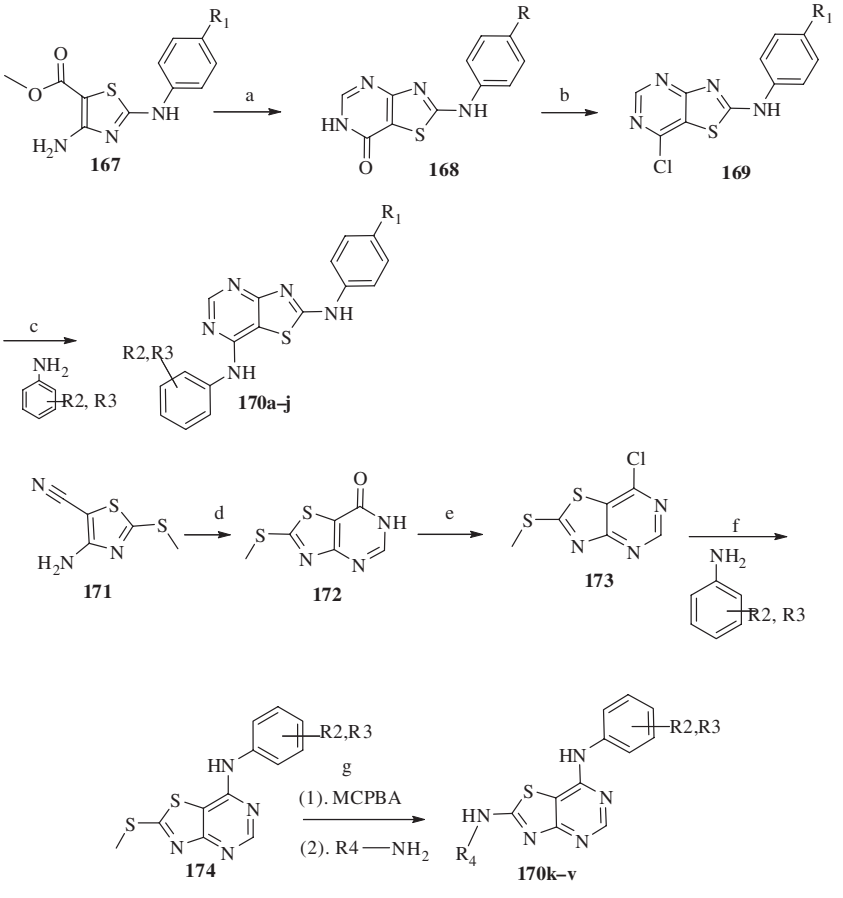
Substituted 2-phenylamino-6*H*-thiazolo[4,5-*d*]pyrimidin-7-ones **168** were synthesized from the starting substituted 4-amino-2-phenylamino-thiazole-5-carboxylic acid methyl esters **167**. Chlorination of **168** in the presence of HMPA afforded the thiazolo[4,5-*d*]pyrimidin-2-yl)-phenyl amines **169**. Reaction of **169** and substituted phenylamines in isopropanol, diglyme or butoxyethanol provided substituted N^2,N^7-diphenyl thiazolo[4,5-*d*]pyrimidine-2,7-diamines **170a–j** in 20–65% yield.

4-Amino-2-(methylthio)thiazole-5-carbonitrile **171** when heated with formic acid gave 2-methylsulfanyl-6*H*-thiazolo[4,5-*d*]pyrimidin-7-one **172**. Chlorination of **172** provided 7-chloro-2-methylsulfanyl-thiazolo[4,5-*d*]pyrimidine **173**. Reaction of **173** with substituted phenyl amines, upon heating in diglyme, provided substituted (3-phenyl)-(2-methylsulfanyl-thiazolo[4,5-*d*]pyrimidin-7-yl)-amines **174** (53–92% yield). Compounds **174** were oxidized by *m*-CPBA, followed by treatment with primary amines, in glacial acetic acid to provide thiazolo[4,5-*d*]pyrimidines **170k–v** (55–78% yield) (*34*).

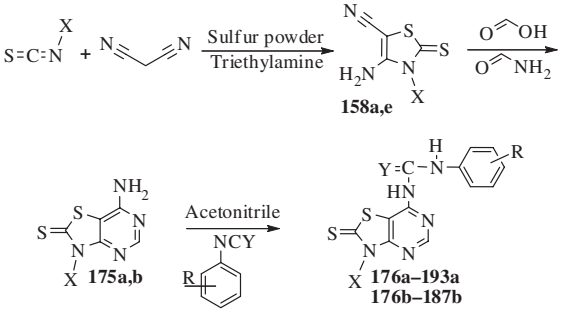
4-Amino-3-phenyl/ethyl-2-thioxo-2,3-dihydro-thiazole-5-carbonitriles **158a** and **e** (*39*) were prepared from a mixture of malononitrile, phenyl/ethyl isothiocyanate and finely divided sulfur in DMF in the presence of TEA (added very slowly with constant stirring at rt). Upon treatment of **158a** and **e** with formamide and formic acid with heating yielded 7-amino-3-phenyl/ethyl thiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione **175a** and **b**. The urea and thiourea derivatives **176a–193a** and **176b–187b** were obtained (59–91% and 55–90% yield, respectively) when **175a** or **b** and appropriate aryl isocyanate/isothiocyanate were heated under reflux with stirring in dry acetonitrile (*41*).

5.2. *Reaction of 3-aryl-7-oxothiazolo[4,5-d]pyrimidin-2(3H)-thiones with ω-bromoacetophenones and 2-chloro-N-(2-thiazolyl)acetamides*

3-Aryl-6-substituted thiazolo[4,5-*d*]pyrimidin-2(3*H*)-thione derivatives **195a–l** (61–78% yield) or **196a–f** (54–86% yield) have been synthesized by reacting thiazolo[4,5-*d*]pyrimidines **44a** (*16*) and **194a** and **b** with ω-bromo-acetophenones or 2-chloro-*N*-(2-thiazolyl) acetamides (*42*).

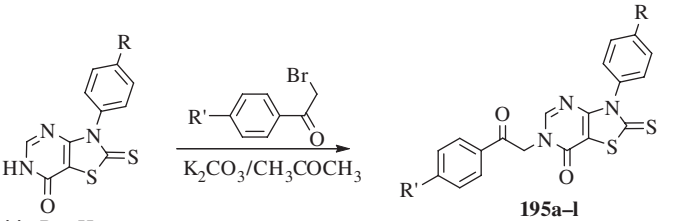


Reagents and conditions (and yield %): (a) aceticanhydride, formamide, 150–180°C, 7 h, (57–88%); (b) $POCl_3$ in HMPA, 70–80°C, overnight, (53–69%); (c) 2-butoxyethanol, 150–180°C, 4–7 h, (20–65%); (d) Fomic acid, water, reflux, 4 h, (95%); (e) phosphorus oxytrichloride, reflux, 1 h, (57%); (f) Substituted aniline, diglyme, 140°C, 3–6 h, (53–92%); (g)(1) MCPBA, DCM, water, $NaHCO_3$, 5°C, 2 h, (2) primary amine, 40°C, 4 h, (55–78%).

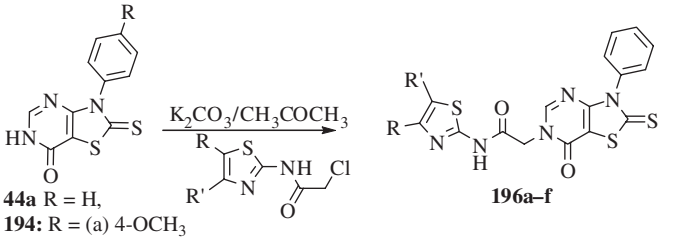


(a) X=Ph, (b) X=Et for all cases and Y=O or S		
176a,b; 185a,b (R=H)	**179a,b**; **188a** (R=2-F)	**182a**; **191a** (R=4-Cl)
177a,b; 186a,b (R=4-OCH_3)	**180a,b**; **189a** (R=4-F)	**183a,b**; **192a** (R=2-NO_2)
178a,b; 187a,b (R=2-OCH_3)	**181a,b**; **190a** (R=2-Cl)	**184,b**; **193a** (R=4-NO_2)

Scheme 32.



44a R = H,
194: R = (a) 4-OCH_3
(b) 4-Cl



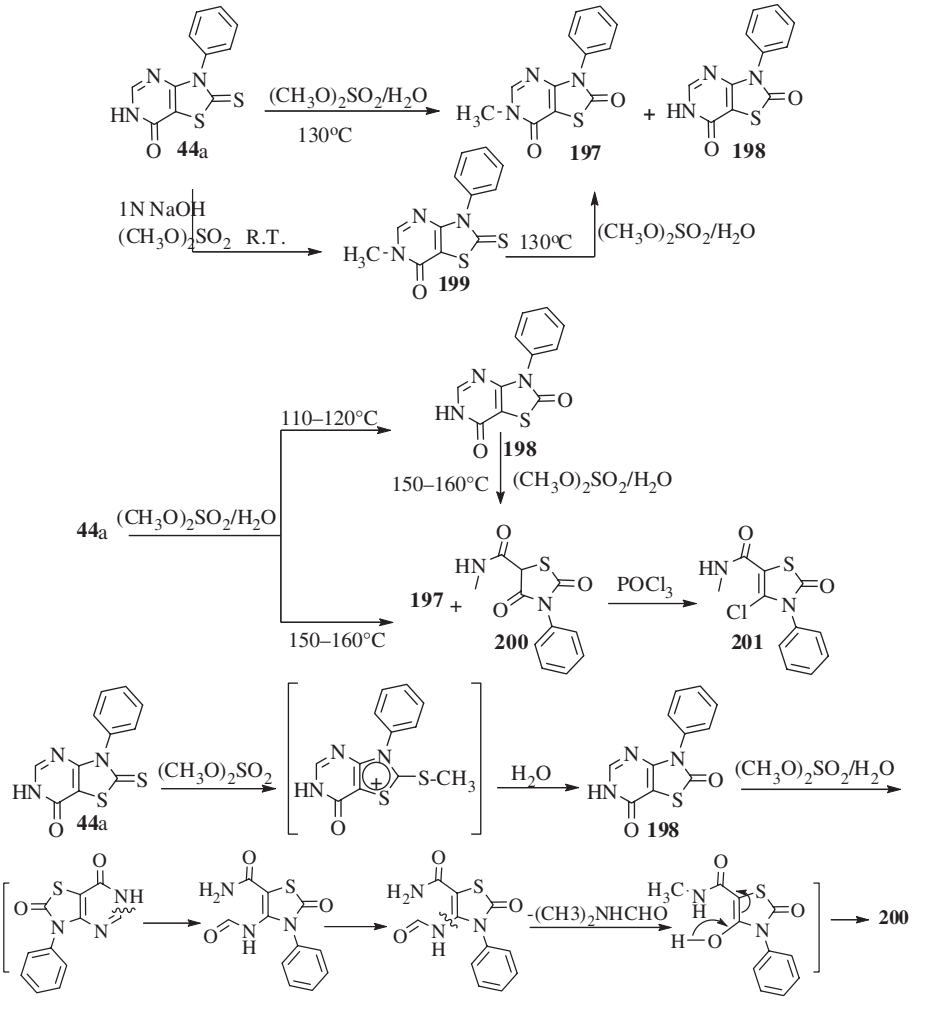
44a R = H,
194: R = (a) 4-OCH_3
(b) 4-Cl

195	R	R'	**195**	R	R'
a	H	H	**j**	Cl	CH_3
b	H	CH_3	**k**	Cl	OCH_3
c	H	OCH_3	**l**	Cl	Cl
d	H	Cl	**196a**	H	H
e	OCH_3	H	**b**	CH_3	H
f	OCH_3	CH_3	**c**	CH_3	H
g	OCH_3	OCH_3	**d**	$-CH_2-CH_2$	$-CH_2-CH_2$
h	OCH_3	Cl	**e**	C_6H_5	H
i	Cl	H	**f**	-CH=CH	-CH=CH

Scheme 33.

5.3. *Reaction of 7-oxo-3-phenylthiazolo[4,5-d]pyrimidin-2(6H)thione with dimethyl sulfate leading to a novel ring closure*

Treatment of 2,3-dihydro-3-phenyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one **44a** (*16*) with dimethyl sulfate at 130 °C afforded the corresponding 6-methyl-3-phenylthiazolo[4,5-*d*]pyrimidine-2,7-dione **197** (25% yield) and 3-phenylthiazolo[4,5-*d*]pyrimidine2,7(6*H*)-dione **198** (27% yield), respectively. Stirring **44a** with dimethyl sulfate in an aqueous solution of NaOH at rt gave 6-methyl-2-thioxo-3-phenyl-thiazolo[4,5-*d*]pyrimidin-7-one **199**. Reaction of **44a** with dimethyl sulfate at 110–120 °C gave **198** (93% yield). Heating of **198** with dimethyl sulfate at 150–160 °C afforded **197** (43% yield) and 5-*N*-methylcarbamoyl-3-phenyl-2,4-thiazolidinedione **200** (8% yield), respectively. The reaction of **198** with dimethyl sulfate at 150–160 °C for 1 h caused the ring opening to give **200**. Treatment of **200** with phosphorus oxychloride and *N*,*N*-dimethylaniline at 130 °C afforded 4-chloro-2-oxo-3-phenylthiazolidine-5-*N*-methylcarboxamide **201** (49% yield). The ring cleavage of **44a** to **200** probably proceeds through the initial hydrolysis of the thione moiety in compound **44a**, followed by the ring opening of the pyrimidine ring, methylation and loss of *N*,*N*-DMF by hydrolysis (*43*).

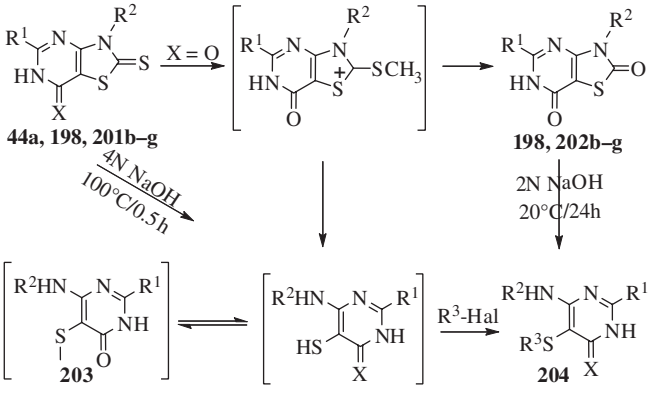


Scheme 34.

5.4. *Ring cleavage of 2-oxo-, 2-thioxo and 7-amino-thiazolo[4,5-d]-pyrimidin-ones and thiones*

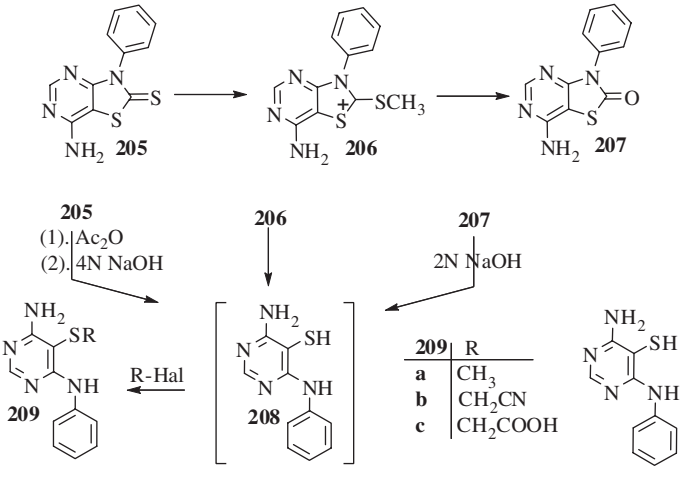
The 2-thioxo- and 2-oxo-thiazolo[4,5-*d*]pyrimidin-7-ones and -thiones **44a** (*16*), **198** (*43*), **202b**–**g** and **203b**–**g** undergo ring opening by hydrolysis to give the substituted 4-amino-6-oxo- and 4-amino-6-thioxo-pyrimidine-5-thiols. They have been isolated as their disulfides *or* 5-alkyl derivatives, *i.e.* the substituted 4-amino-5-alkylthiopyrimidin-6-ones and -thiones **203** *or* **204** (31–85% yield).

In analogy, the 7-amino-thiazolo[4,5-*d*]-pyrimidin-2-thione **205**, its 2-methyl thio **206** and its 2-one derivative **207** react by ring cleavage to yield 4,6-diamino-pyrimidin-5-thiole derivative, respectively, isolated as their disulfides **208** or alkylthio-derivatives **209** (67–21% yield) (*44*).



201–203	R^1	R^2	X	201–203	R^1	R^2	X
b	H	CH_3	O	**e**	H	C_6H_5	S
c	H	CH_2=CH-CH_2	O	**f**	H	CH_3	S
d	CH_3	C_6H_5	O	**g**	H	CH_2=CH-CH	S

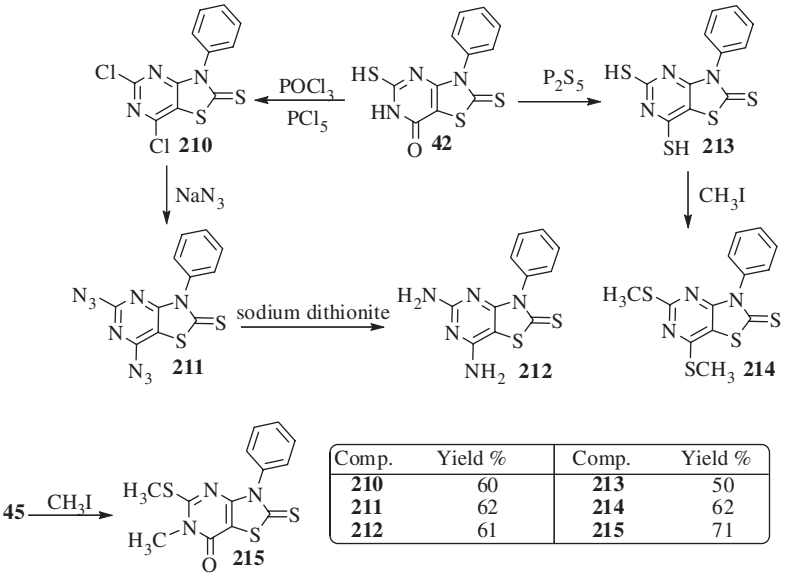
204: R^1= H or CH_3; R^2 = CH_3, or C_6H_5 or CH_2=CH-CH_2;
R^3 = CH_3 or CH_2COOH or CH_2COOEt or CH_2CN or CH_2CONH_2
or $CH_2COC_6H_5$ and X = O or S



Scheme 35.

5.5. *Chlorination, thiation and methylation of 2,3-dihydro-5-mercapto-3-phenyl-2-thioxothiazololo[4,5-d]pyrimidin-7(6H)-one*

Chlorination of 5-mercapto-thiazolopyrimidine **42** (*15*) with a mixture of phosphorous pentachloride and phosphorous oxychloride gave 5,7-dichloro compound **210**. Displacement of the chlorine atoms in the latter compound with sodium azide gave 5,7-diazido derivative **211** which, upon reduction with sodium dithionite, gave 5,7-diamino analog **212**. Thiation of **42** with phosphorous pentasulfide yielded 5,7-dimercapto derivative **213** which, upon methylation with methyl iodide, gave 5,7-dimethythio compound **214**. Methylation of the parent compound **42** with CH_3I yielded the*N*-methyl-*S*-methyl derivative **215** (*15*).



Comp.	Yield %	Comp.	Yield %
210	60	**213**	50
211	62	**214**	62
212	61	**215**	71

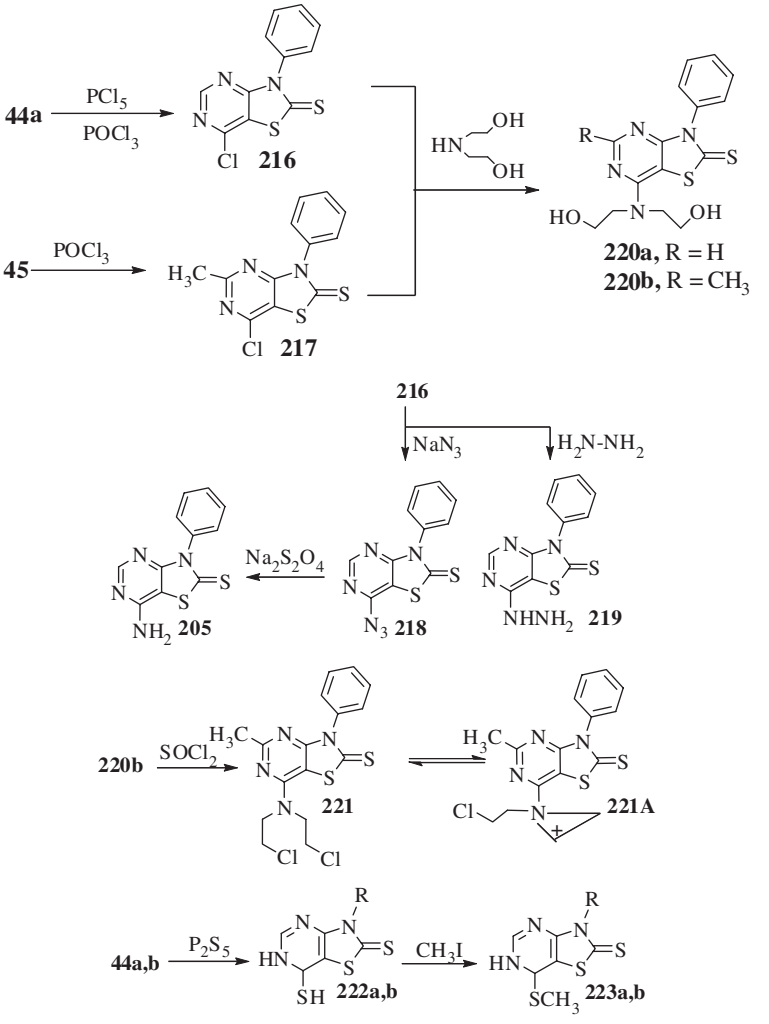
Scheme 36.

5.6. *Chlorination, thiation of 2,3-dihydro-5-substituted/unsubstituted-3-arylthioxothiazolo [4,5-d]pyrimidines*

Chlorination of **44a** and **45** (*16*) afforded the 7-chloro derivatives **216** and **217**, respectively. Treatment of **216** with sodium azide gave the 7-azido derivative **218** which, upon reduction with sodium dithionite, afforded the 7-amino analog **205** (*44*). Substitution of the chlorine atom of **216** with hydrazine hydrate resulted in the formation of 7-hydrazino derivative **219**. Chloro compounds **216** and **217** were also utilized for the synthesis of the 7-diethanolamino derivatives **220a** and **b**. Reaction of **220b** with thionyl chloride gave the 7-bis(2-chloroethyl) amino derivative **221** which exists in the aziridinium form **221a** in DMSO-d_6. Thiation of **44a** and **b** with phosphorous pentasulfide gave the 7-mercapto compounds **222a** and **b** which upon methylation produced the 7-methylthio analogs **223a** and **b** (*16*).

5.7. *Reactions of 7-chloro-5-methyl-3-phenylthiazolo[4,5-d]pyrimidine-2(3H)-thione with secondary amines, 4-aminoacetophenone and with either ethyl 2-amino-4,5,6,7-tetrahydro[1]benzo-thiophene-3-carboxylate or ethyl anthranilate*

Nucleophilic substitution of the chlorine atom of **217** with the appropriate amine gave 7-(substituted amino)-5-methyl-3-phenylthiazolo[4,5-*d*]pyrimidine-2(3*H*)thiones **224a**–**e**. Treatment of **224a** and **b** with dimethyl sulfate, followed by the reaction of the produced 2-methylthiothiazolium salt with malononitrile or ethyl cyanoacetate, gave ethyl 2-cyano-2-(7-substituted-5-methyl-3-phenylthiazolo[4,5-*d*]pyrimidin-2(3*H*)ylidene)-acetates **225a** and **b** or 2-(7-substituted-5-methyl-3-phenyl-thiazolo[4,5-*d*]pyrimidin-2(3*H*)-ylidene)malononitrile derivatives **226a** and **b**. 5-Methyl-7-morpholino-3-phenylthiazolo[4,5-*d*]pyrimidine2(3*H*)one **227** was prepared from **224a** through the subsequent action of dimethyl sulfate and TEA in the presence of few drops of water. Refluxing **217** with 4-amino-acetophenone gave 7-(4-acetylanilino)-5-methy-3-phenylthiazolo[4,5-*d*]pyrimidine-2(3*H*)-thione **228**. Condensation of **228** with benzaldehyde under the Claisen–Schmidt reaction conditions gave 5-methyl-3-phenyl-7-[4-(1-phenyl-3-oxopropenyl) anilino]thiazolo[4,5−*d*]pyrimidine-2-(3*H*)thione **229**.

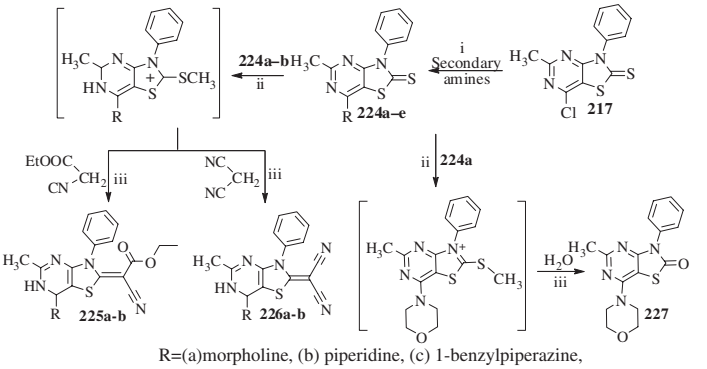


44; **222**; **223**: (a) R = C_6H_5; (b) R = $CH_2CH=CH_2$

Comp.	Yield %	Comp.	Yield %
216	70	**222a**	73
218	71	**b**	75
219	60	**223a**	70
220a	62	**b**	73
b	75		

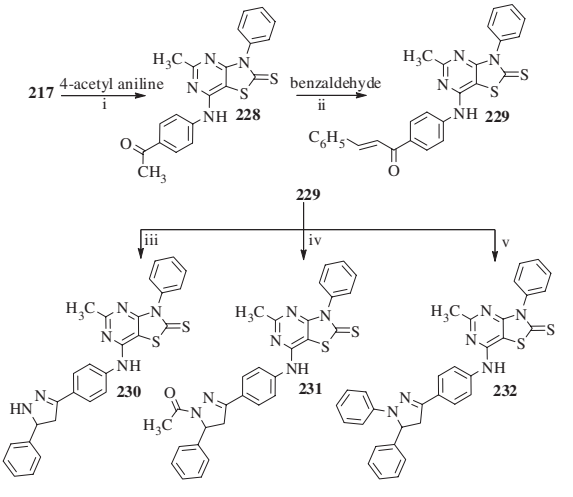
Scheme 37.

Alternatively, **228** condensed with benzaldehyde to afford the same chalcone **229** in the same yield but with a shorter reaction time. Cyclization of the chalcone **229** by heating with hydrazine hydrate *or* with phenyl hydrazine gave the corresponding 5-phenylpyrazoline **230**, 1-acetyl-5-phenylpyrazoline **231** *or* 1,5-diphenylpyrazoline derivative **232,** respectively (*45a–d*). Fusion of **217** with either ethyl 2-amino-4,5,6,7-tetrahydro[1]benzo-thiophene-3-carboxylate or ethyl anthraxnilate afforded [3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thieno-2-yl]amino derivative **233** or 2-(ethoxycarbonyl) aniline derivative **235**, respectively, instead of the cyclized products **234** and **236** (*44*).

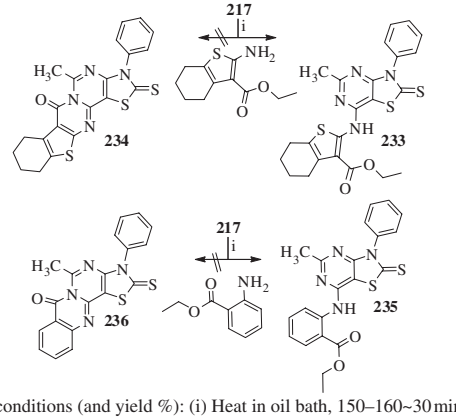


R=(a)morpholine, (b) piperidine, (c) 1-benzylpiperazine,
(d) 1-methylpiperazine, (e) 4-benzylpiperidine

Reaction conditions (and yield %): (i) dryacetone, reflux, 3 h, (65–73%); (ii) $(CH_3)2SO_4$, acetonitrile, reflux, 1h; (iii) $N(C_2H_5)_3$ stir, boiling water bath, 30 min (61–65%).



Reaction conditions (and yield %): (i) *n*-butanol, reflux, 5 h, (61%); (ii) two methods: (a): anhydrous. K_2CO_3, dry dioxane, reflux 10 h, (64%); (b): $(CH_3OO)_2O$, reflux, 3 h, (66%); (iii) NH_2NH_2 (99%), EtOH(absolute), reflux, 3–4 h, 75%; (iv) NH_2NH_2 (99%), HAc(glacial), reflux, 3 h, (67%); (v) $C_6H_5NHNH_2$, HAc(glacial), reflux, 4–5 h (61%).

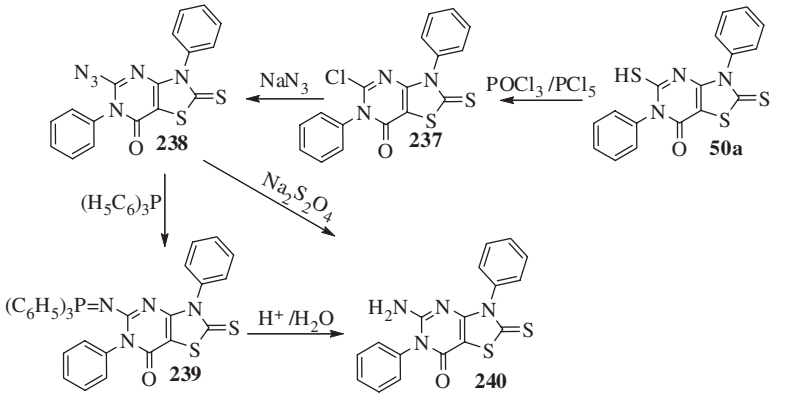


Reaction conditions (and yield %): (i) Heat in oil bath, 150–160~30 min (76 and 78%).

Scheme 38.

5.8. *Reactions of 5-chloro-2,3-dihydro-3,6-diphenyl-2-thioxothiazolo[4,5-d]pyrimidin-7(6H)-one with sodium azide, triphenylphosphine*

Chlorination of thiazolopyrimidine **50a** (*19*) with phosphorus oxychloride in the presence of phosphorus pentachloride afforded the 5-chloro-2,3-dihydro-3,6-diphenyl-2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-one **237** (59% yield). Displacement of the 5-chloro with sodium azide gave the 5-azido derivative **238** in 66% yield, which was converted into the imino-phosphorane **239** (65% yield) upon treatment with PPh_3. The 5-amino thiazolo[4,5-*d*]pyrimidine derivative **240** was prepared by hydrolyzing **239** with hydrochloric acid or by reducing the 5-azido analogue **238** with sodium dithionite (*18*, *19*).



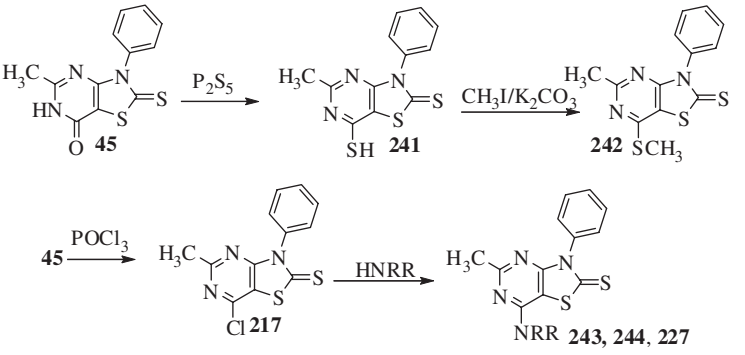
Scheme 39.

5.9. *Thiation of 2,3-dihydro-5-methyl-3-phenyl-2-thioxothiazolo[4,5-d]pyrimidin-7-(6H)-one and nucleophilic displacement of its 7-chloro derivative with 2ry amines*

5-Methyl-7-methylmercapto-3-phenyl-thiazolo[4,5-*d*]pyrimidin-2-(3*H*)-thione **242** was obtained by direct thiation of **45** (*16*) with phosphorus pentasulfide followed by treatment of the formed 7-mercapto derivative **241** with methyl iodide. Chlorination of **45** yielded 7-chloro-5-methyl-3-phenyl-thiazolo[4,5-*d*]pyrimidin-2-(3*H*)thione **217** in excellent yield. Nucleophilic displacement of the 7-chloro substituent with dimethyl amine, diethyl amine or morpholine gave the 7-dialkyl amino **243**, **244** or 7-morpholino **227** (*44*) derivatives, respectively. The 7-amino compound **246** was prepared by sodium dithionite reduction of the 7-azido analog **245**, which is readily accessible from **217** and sodium azide (*44*).

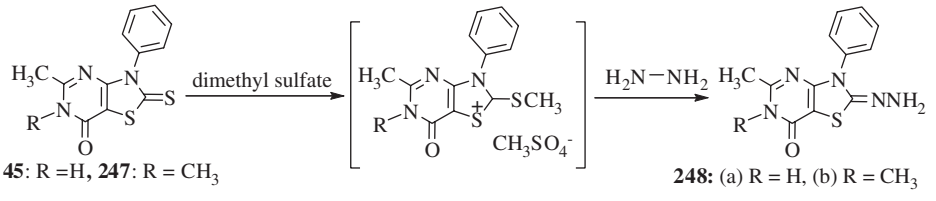
5.10. *Reaction of 5-methyl-3-phenyl-2-thioxothiazolo[4,5-d]pyrimidin-7(6H)-one derivatives with dimethyl sulfate*

The 2-hydrazono compounds **248a** and **b** were prepared in 73% and 78% yield, respectively, from the 2-thioxothiazolo[4,5-*d*]pyrimidin-7(6*H*)-ones **45** (*16*) and **247** *via* reaction with dimethyl sulfate and hydrazine hydrate (*16*).



Comp.	Yield %	Comp.	Yield %
45	78	**244**	70
241	77	**227**	85
242	70	**245**	80
243	90	**246**	60

Scheme 40.

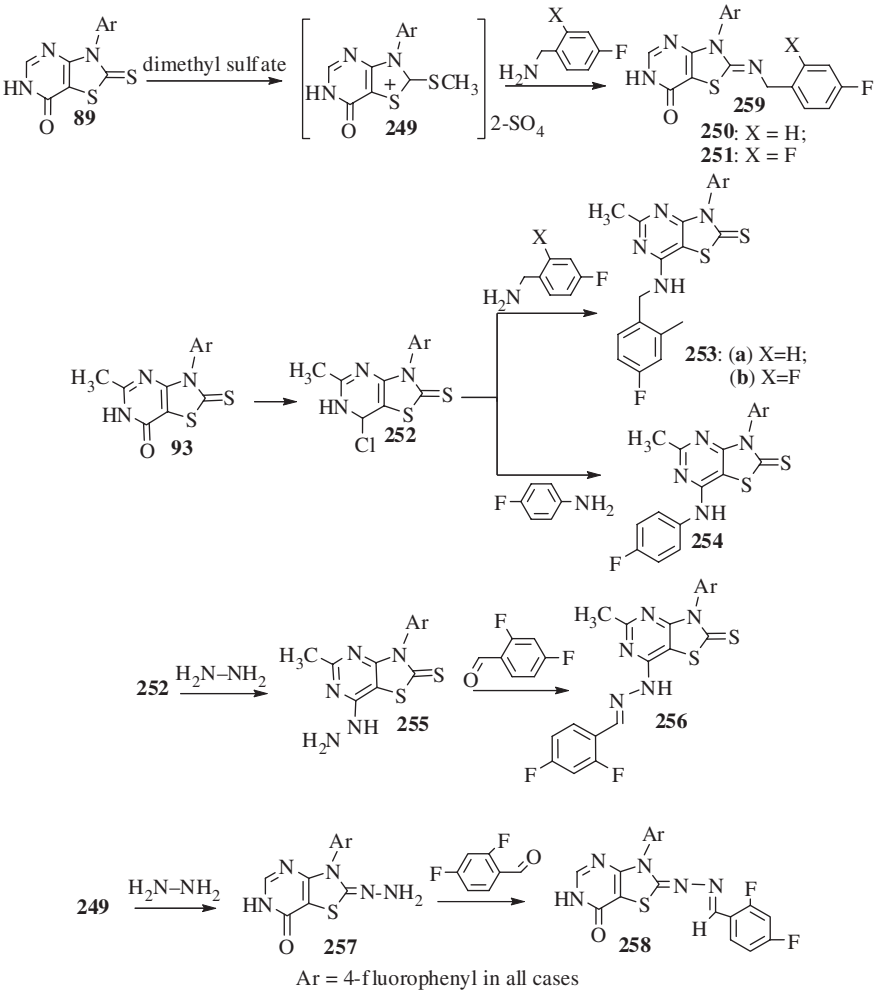


Scheme 41.

5.11. *Structural modifications of the thiazolo[4,5-d]pyrimidine ring system to introduce a fluorophenyl moiety into different positions of the molecule using various bridges*

Reaction of thiazolo[4,5-*d*]pyrimidine **89** (*27*) with dimethyl sulfate produced 2-methylthiothiazolium salt **249** which upon treatment with fluorobenzyl amines gave the 2-fluorobenzyl derivatives **250** and **251** (72% and 70% yield, respectively). Chlorination of the thiazolo[4,5-*d*]pyrimidine **93** (*27*) gave the 7-chloro derivative **252** (78% yield) which when treated with fluorobenzyl amines gave the 7-fluorobenzylamines **253a** and **b** (72% and 70% yield, respectively). Compound **252** with 4-fluoroaniline in the presence of TEA gave the 7-(4-fluorophenyl)amino derivative **254** (73% yield). The 2,4-difluorophenyl-anilines failed to react even in the presence of strong bases. This may be attributed to its poor nucleophilicity due to the electron withdrawing effects of the 2-fluorine atoms. The chloro compound **252** when reacted with

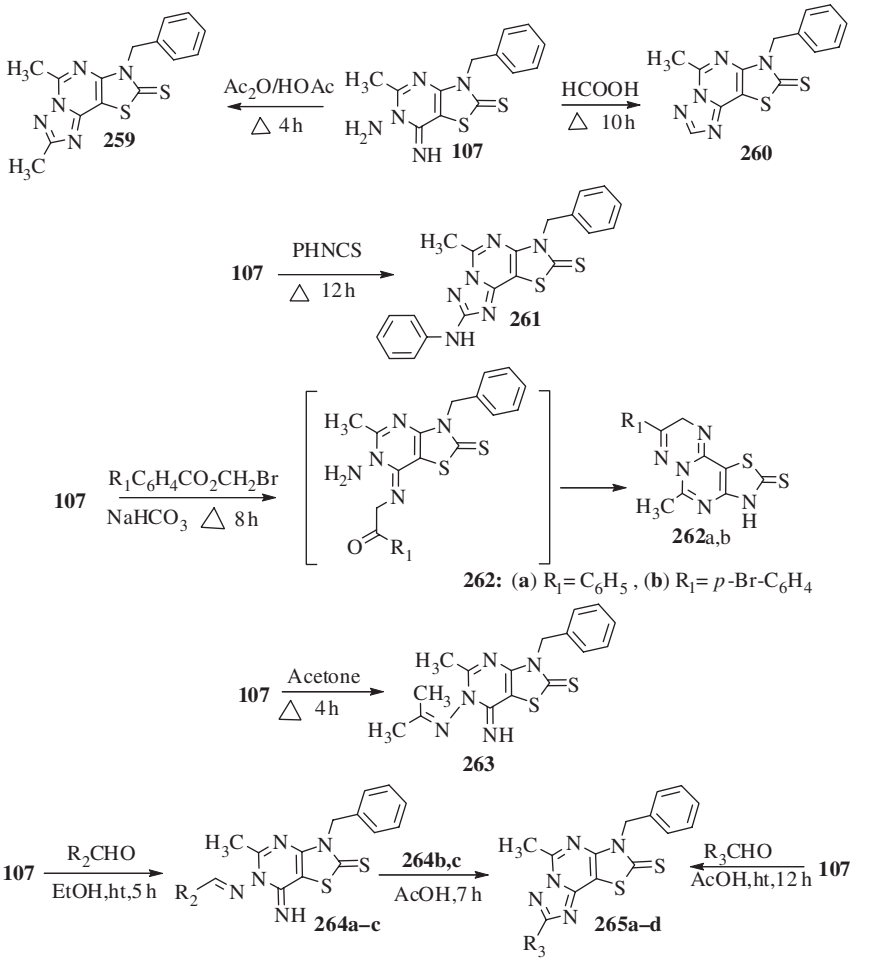
hydrazine hydrate gave the 7-hydrazino derivative **255** in 70% yield; which when condensed with 2,4-difluorobenzaldehyde gave 7-(2,4-difluorobenzylidene-hydrazinothiazolo[4,5-*d*]pyrimidine **256** (80% yield). 2-Methylthio thiazolium salt **249** with hydrazine hydrate gave the 2-hydrazono compound **257** (72% yield); which then underwent condensation with 2,4-difluorobenzaldehyde to give 2-(2,4-difluorobenzylidene-hydrazonothiazolo[4,5-*d*]pyrimidine **258** (83% yield) (*27*).



Scheme 42.

5.12. *Preparation of triazolo and triazinopyrimidine derivatives of 6-amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-2-thione*

6-Amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thione **107** (*29*) reacted with several reagents to yield the corresponding new series of triazolo- and triazino-pyrimidine derivatives **259**–**265** (*29*).



Comp.	Yield %	Comp.	Yield %
250	57	**264b**	85
260	64	**264c**	79
261	64	**265a**	60
262a	61	**265b**	64
262b	60	**265c**	62
263	76	**265d**	60
264a	80		

264a R_2= *p*-Br-C_6H_4
b R_2= *p*-Cl-C_6H_4
c R_2= *p*-NO_2-C_6H_4

265a R_3= *p*-Cl-C_6H_4
b R_3= *p*-F-C_6H_4
c R_3= *p*-NO_2-C_6H_4
d R_3= *o*-Thienyl

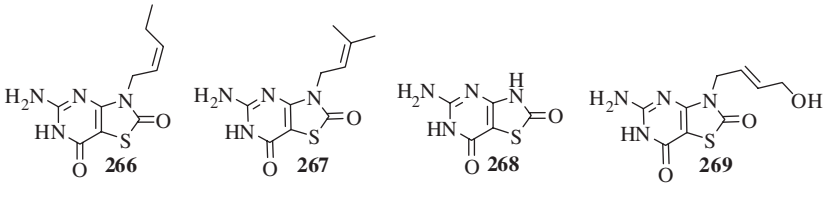
Scheme 43.

6. Biological activity

Numerous thiazolo[4,5-*d*]pyrimidine derivatives have been reported for their interesting biological and pharmaceutical activities, *e.g.* many derivatives of this ring system were found to have CNS-depressant properties (*13*) and antifungal (*15, 22*), antimicrobial (*31b, 39, 42*), anti-HIV (*17*), antituberculosis (*42*) and herbicidal (*33*) activities. Other derivatives were also investigated

to have good binding affinity to the corticotrophin-releasing hormone (CRH-RI) receptor (potential anxiolytics) (*46*), have good anti-tumor activity against many cancer tumor cell lines (*27*), be screened as anti-tumor epidermal growth factor receptor (EGFR) (*41*) and have antagonistic effects on haloperidol-induced catalepsy (anti-parkinsonian) and oxidative stress in mice (*35*). Also, some derivatives of the ring system were screened for their *in vivo* anti-inflammatory activity and the data compared with those of indomethacin as a reference drug and showed no or minimal ulcerogenic effects (*31a*), and some others were evaluated *in vivo* for their analgesic and anti-inflammatory and were of similar potencies as acetylsalicylic acid in terms of analgesic activity and were much potent as phenylbutazone in terms of anti-inflammatory activity (*45*). Moreover, a series of compounds based on a thiazolo[4,5-*d*]pyrimidine-2(3*H*)-one core was surveyed and discovered to possess a high affinity for chemokine receptor (CCR2), and the favorable pharmacokinetic and physicochemical properties of this series render them excellent investigative tools for the *in vivo* assessment of combined CXC chemokine receptor (CXCR)2 and CCR2 antagonism (*47*).

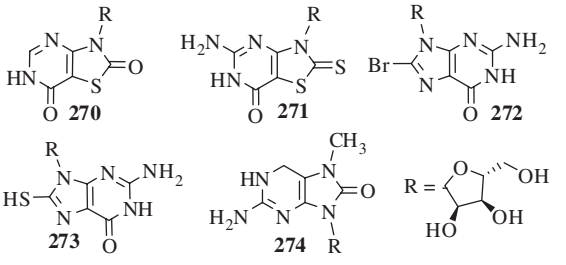
Some guanine analogs containing a thiazolo[4,5-*d*]pyrimidine ring were tested against laboratory strains activity of both human cytomegalovirus (HCMV) and herpes simplex Forest virus (SFV) types 1 and 2. For example, compounds **266** and **267** were evaluated for anti-HCMV activity and the obtained data suggested that the antiviral activity of alkenyl-substituted thiazolopyrimidine derivatives may represent a mechanism of action against herpes virus's alternative to that of classical nucleoside analogs such as acyclovir or ganciclovir di-hydroxy propoxymethyl guanine (antiviral drug) (DHPG) (*48*, *49*). Also, the *in vitro* antiviral activity of certain hydroxyalkoxymethyl, hydroxyalkyl, hydroxyalkenyl and phosphonoalkenyl thiazolo[4,5-*d*]pyrimidine derivatives of the guanine congener 5-amino-thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione **268** were reported. 5-Amino-3-(4-hydroxybut-2-enyl)thiazolo[4,5-*d*]pyrimidine2,7-(3*H*,6*H*)dione **269** showed significant *in vitro* activity against (HCMV) and was also found to have a cytotoxicity profile similar to that of ganciclovir (DHPG) (*50*).



6.1. *Biological activity of some thiazolo[4,5-d]pyrimidine nucleosides*

The thiazolo[4,5-*d*]pyrimidine nucleoside **270** has been evaluated for antiviral activity in rodent models and proved to be effective against an intranasal challenge of rat corona virus in suckling rats. Protection was observed against herpes type 1 and murine cytomegalovirus (MCMV) infections and encephalitis induced by intracerebral inoculation of a human corona virus in mice (*51*). The same nucleoside **270** was found to have a broad spectrum of antiviral activities and activates natural killer cells, macrophages and B lymphocytes (*52b*). Also, the thiazolo[4,5-*d*]pyrimidine nucleosides **270** and **271** were reported to exhibit significant immuno activity relative to the positive control purine nucleosides **272**, **273** and **274**. Furthermore, nucleoside **270** exhibited greater immuno activity than any of the other guanosine analogs and was about twice as potent as the nucleoside **274** in the murine spleen cell mutogenecity assay and provided excellent protection

(92% survivors compared with 0% for placebo controls) against SFV in mice (*51*, *53*).



7. Applications

Numerous thiazolo[4,5-*d*]pyrimidine ring system patents have been reported for their probable uses in therapeutic application and pharmaceutical areas, in the treatment of disorders, asthma and allergic diseases, also as modulators of chemokine receptor activity wherein the disease is psoriasis and rheumatoid arthritis. Other patents were reported as modulators of chemokine receptor activity, as inhibitors of tumor necrosis factor (TNF-α) release and can be used for treating other diseases such as rheumatoid arthritis, multiple sclerosis, asthma, psoriasis, congestive heart failure and insulin-resistant diabetes. Moreover, many other patents of the ring system were registered for their uses as corticotrophin-releasing factor (CRF) antagonists, *e.g.* in the treatment of psychiatric disorders and neurological diseases including affective disorders, anxiety, depressions, headache, irritable bowel syndrome, posttraumatic stress disorder and progressive supranuclear palsy. Furthermore, other patents were published and can be useful for treating infections and/or diseases, *e.g.* Alzheimer's, gastrointestinal, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol-withdrawal symptoms, inflammatory, cardiovascular or heart-related, fertility, human immunodeficiency virus, hemorrhagic stress, stroke, ulcers, obesity, head and spinal cord traumas and epilepsy problems (*54–61*).

8. IR, UV, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy

8.1. *Infrared*

Infrared absorption spectra of numerous thiazolo[4,5-*d*]pyrimidine derivatives are generally characterized by the presence of two bands around 1260–1215 and 1090–1020 cm^{-1} corresponding to C–S–C moiety (*14*, *18*, *23b*, *20*, *29*, *30*, *37*, *43*).

8.2. *Ultra violet*

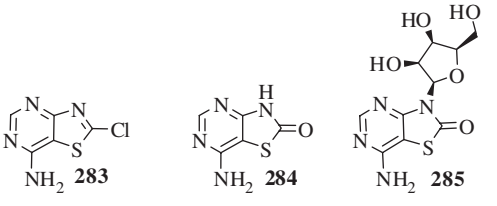
Compounds with thiazole ring are characterized by electronic bands in 220–300 nm regions. Table 1 shows UV spectra of the thiazolo[4,5-*d*]pyrimidine derivatives **283**, **284** and **285** [λ_{max}, nm (ε) values] carried out at different pH values, *e.g.* 2-chlorothiazolo[4,5-d]pyrimidin-7-amine **283**,

Table 1. Ultra-violet spectra for some thiazolo[4,5-*d*]pyrimidine derivatives at different pH values.

Reference	Solvent	λ_{max} (ε), nm	Compound no.
(*62*)	(pH 1)	220(22400); 266(8600); 290(8300)	**283**
	(pH 7,11)	232(33800); 286(9700)	
(*62*)	(pH 1)	220(20400); 267(7600); 290(6.900)	**284**
	(pH 7,11)	231(24200); 285(8100)	
(*62*)	(pH 1)	222(35100); 265(14300) 290(11400)	**285**[a]
	(pH 7,11)	215(45000); 262(13200).	

Note: [a]Nucleoside derivative.

7-aminothiazolo[4,5d]pyrimidin2(3*H*)-one **284** and 7-amino-4-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)thiazolo[4,5-*d*]pyrimidin-2(4*H*)-one **285** (*62*).



8.3. *^{1}H NMR*

Proton NMR spectra of numerous substituted thiazolo[4,5-*d*]pyrimidines reveal C7-H *or* C5-H and/*or* C2-H. The positions of these signals are slightly altered by changing the solvent and nature of ring substitution. Table 2 shows the theoretical values of C7-H, C5-H (pyrimidine) and C2-H (thiazole) for the parent thiazolo[4,5-*d*]pyrimidine ring system and some other of its substituted derivatives **14**, **55a** and **e**, **48e**, **69a** and **b, 91a** and **b**, **118a** and **b**, **198** and **270** at C7-H and C2-H in different solvents.

8.4. *^{13}C NMR*

The chemical shifts for non-bridge-head nitrogen thiazolo[4,5-*d*]pyrimidine derivatives were extensively reported. Table 3 shows the chemical shift (δ) values for some selected thiazolo[4,5-*d*]pyrimidine derivatives **50c**, **69a** and **b**, **122b**, **237** and **234**.

Table 2. ^{1}H NMR spectra for thiazolo[4,5-*d*]pyrimidine and some of its substituted derivatives.

Ref.	Solvent	C2-H	C5-H	C7-H	Comp. name (or no.)
Theoretical	DMSO-d_6	8.88	9.26	8.7	Thiazolo[4,5-*d*]pyrimidine
(*9*)	DMSO-d_6	–	10.4	–	**14**
(*20*)	$CDCl_3$	–	7.45-8.19	–	**55a**
(*20*)	$CDCl_3$	–	7.55-8.09	–	**55e**
(*17*)	CF_3COOH	–	8.4	–	**48e**
(*24*)	CF_3COOH	–	8.70-8.75	–	**69a**,**b**
(*27*)	$CDCl_3$	–	8.70-8.65	–	**91a**,**b**
(*32*)	$CDCl_3$	–	8.77	–	**118a**,**b**
(*43*)	DMSO-d_6	–	8.16	–	**198**
(*51*, *53*)	DMSO-d_6	–	8.30	–	**270**[a]

Note: [a]Nucleoside derivative.

Table 3. ^{13}C NMR chemical shifts δ (ppm; DMSO-d_6) relative to TMS.

Ref.	(C-2)	C-5	C-3a	C-7	C-7a	Comp. no.
(*20*)	189.88	158.88	154.13	154.64	103.55	**50**c
(*24*)	189.82	154.58	151.99	168.29	106.61	**69**a
(*24*)	190.96	154.39	149.36	163.55	108.42	**69**b[a]
(*32*)	167.00	156.00	157.00	165.00	149.00	**122b**[a]
(*18, 19, 44*)	189.37	133.95	136.55	151.25	133.70	**237**
(*18, 44*)	191.13	156.28	152.09	155.99	107.35	**243**

Note: [a]$CDCl_3$.

Table 4. ^{19}F NMR (chemical shifts) for some thiazolo[4,5-*d*]pyrimidine derivatives (δ), ($CDCl_3$).

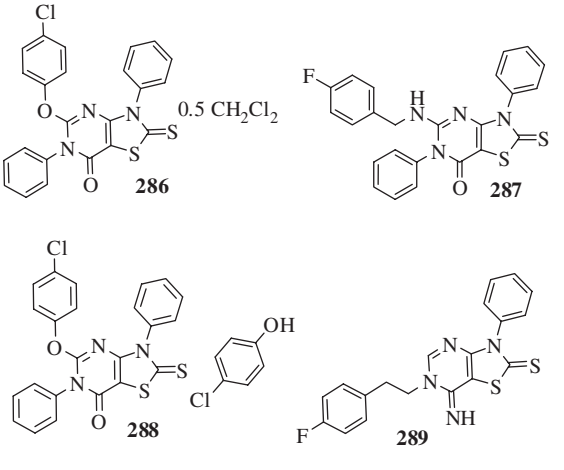
Ref.	^{19}F (δ)	Comp. no.
(*37*)	−120.36 (s, F)	**152a**
(*37*)	−119.08 (s, F)	**152b**
(*37*)	−64.36 (s, CF_3)	**152c**
(*37*)	−63.94 (s, CF_3)	**152d**

8.5. *^{19}F NMR*

Many thiazolo[4,5-*d*]pyrimidine derivatives were reported for their ^{19}F NMR spectroscopy. For example, in compounds **152a–d** (*38*), the presence of fluorine was confirmed by ^{19}F, and differences between C–F and CF_3 chemical shifts (δ) are shown in Table 4.

8.6. *X-ray crystallography*

Single-crystal X-ray crystal analyses for the selected derivatives **278** (*53*), **285** (*62*), **286** (*63*), **287** (*64*), **288** (*65*) and **289** (*66*) have been reported and their structural assignment has been confirmed.



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