Pyrano[2,3-*D*]Thiazole: Synthesis, Reactions And Biological Applications

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Abstract

This Review Describes The Synthesis And Reactions Of Pyrano[2,3-*D*]Thiazole Derivatives And To Highlight The Effects Of Compounds Containing The Pyrano[2,3-*D*]Thiazole Moiety In Important Biological Applications.

Keywords: Thiazolidinones, Pyrano[2,3-*D*]Thiazole, Michael Addition , Anti-Cancer, Anti-Inflammatory, Anti-Microbial.

Introduction

Various Pyran-2-One Derivatives Act As Nonpeptidic HIV Protease Inhibitors [1], Anticancer Agents [2] And Potent PPAR Activator [3]. Thiazoles Have Been Reported To Exhibit A Wide Range Of Applications In Drug Development Against Inflammation [4], Bacterial [5], And HIV Infections [6]. Literature Records That Incorporation Of A Thiol Function In Heterocycles Imparts Interesting Biological And Therapeutic Properties [7,8]. Pyrano[2,3-*D*]Thiazoles Have Been Reported To Exhibit A Wide Range Of Applications In Drug Development Against Obesity, Hyperlipidemia, And Atherosclerotic Diseases, Anticancer [9]. Thus, Pyrano[2,3-*D*]Thiazoles Are Expected To Possess High Pharmacological Potential And Could Be Attractive Scaffolds For Exploiting Chemical Diversity And Generating A Drug-Like Library To Screen For Lead Candidates.

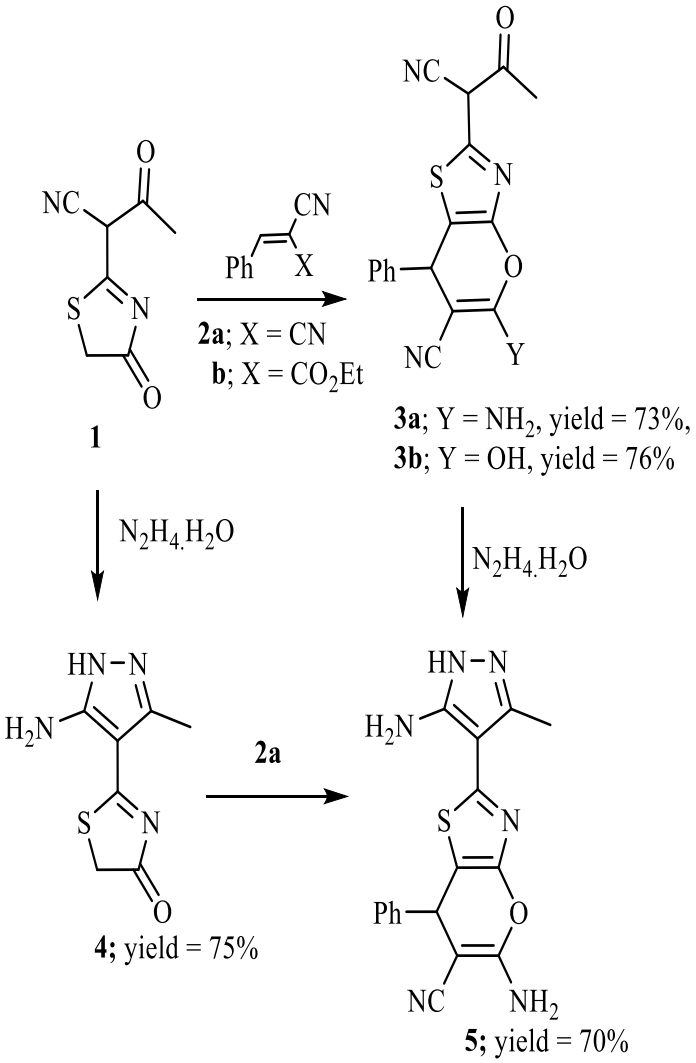
Synthesis

1- From Thiazolidinones

Reaction With Arylidene

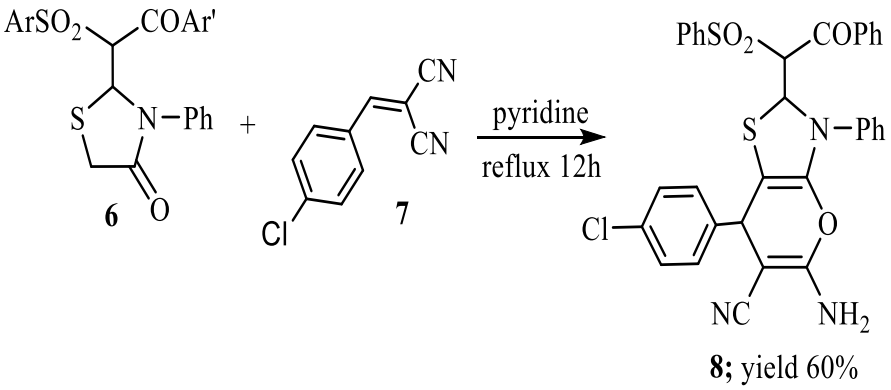
Several Pyrano[2,3-*D*]Thiazoles Have Been Reported Based On Michael Addition Of Active Methylene Of Thiazolidinones To The Activated Double Bond Of A-Cinnamonitriles In Different Conditions.

In 1992, Ismail Et Al. [10] Reported The Reaction Of 2-A-Cyanoacetonyl-2-Thiazolin-4-One **1** With A-Cinnamonitriles **2**a,B By Refluxing In N-Butanol In The Presence Of A Catalytic Amount Of Triethylamine To Afford Pyrano[2,3-*D*]Thiazoles **3**a,B. Moreover, 4-(2-Thiazolin-4'-On)-2'-Ylpyrazole Derivatives **4** (Prepared By Treatment Of 2-A-Cyanoacetonyl-2-Thiazolin-4-One (**1)** With Hydrazine Hydrate) Was Allowed To React With A-Cinnamonitrile **2**a And Pyrano[2,3-*D*]Thiazoles **5** Was Obtained. Compound **5** Could Also Be Synthesised Via The Reaction Of **3**a With Hydrazine Hydrate.



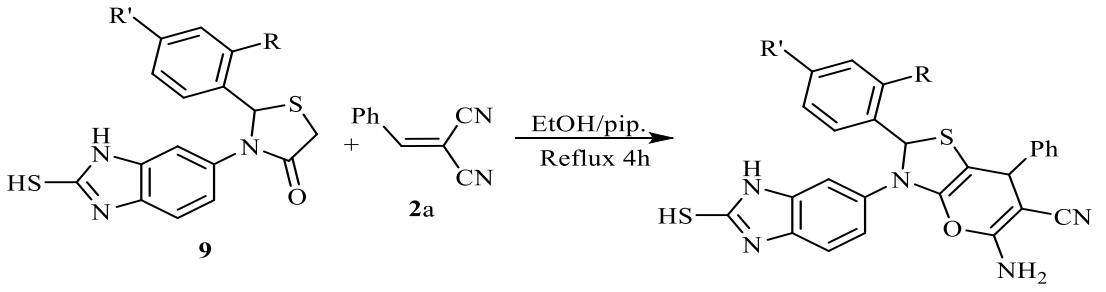
Scheme 1:

Also, Tratment Of Thiazolin-4-One **6** With *P*-Chlorobenzylidenemalono-Nitrile **7** In Pyridine Solution Under Reflux Furnished Pyrano[2,3-*D*]Thiazole **8** [11].



Scheme 2:

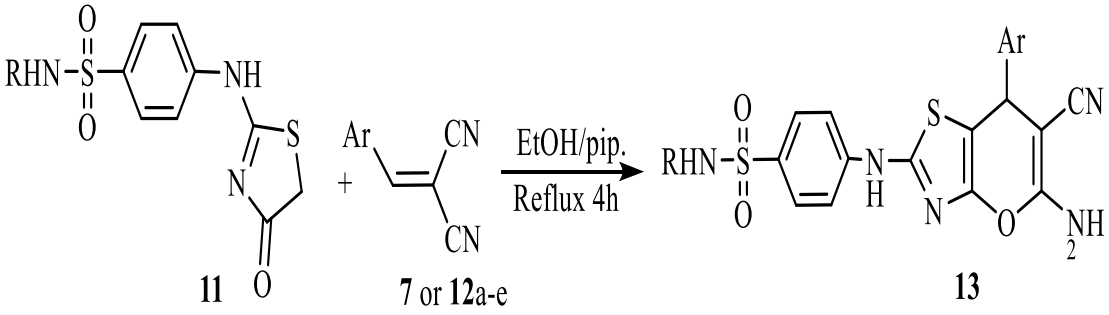
Malladi Et Al.[12] Found That Benzimidazolylpyrano[2,3-*D*][1,3]Thiazolo-Carbonitriles (**10**a-J) Were Synthesized And Evaluated *In Vitro* As Anti-Inflammatory Reagent. Compounds **10**a-J Were Achieved By Reaction Of Benzimidazolyl-1,3-Thiazolan-4-Ones (**9**) With 2-(Phenylmethylene)-Malononitrile (**2**a) In Boiling Ethanol Contining Catalytic Amount Of Piperidine.



10a; R = R' = H, yield = 73%,
b; R = H, R' = NO_2, yield = 71%,
c; R = H, R' = Cl, yield = 70%,
d; R = H, R' = OCH_3, yield = 74%,
e; R = H, R' = $N(CH_3)_2$, yield = 69%,
f; R = H, R' = Br, yield = 70%,
g; R = OH, R' = H, yield = 73%,
h; R = OH, R' = Br, yield = 69%,
i; R = OH, R' = OCH_3, yield = 74%,
j; R = OH, R' = Cl, yield = 75%,

Scheme 3:

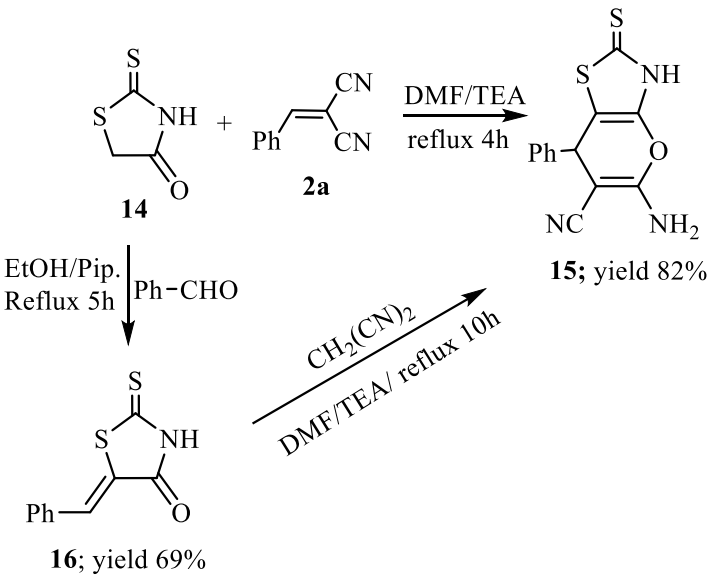
Additionally, It Has Been Found That 5-Amino-6-Cyano-7H-Pyrano[2,3-*D*]Thiazoles **13**a-F Were Obtained By Heating Thiazolidinone Derivatives **11** With Benzylidenemalononitriles **7** Or **12**a-E In Ethanol Containing A Catalytic Amount Of Piperidine, As A Base Catalyst [13-15]. Pyrano[2,3-D]Thiazole Derivative **13**b Showed Promising Anticancer Activity Against Human Breast Cancer Cell Line [MCF7][14].



13a; R = pyridin-2-yl, Ar = C_6H_4Cl-p yield = 86%,
b; R = H, Ar = $C_6H_4OCH_3$-p, yield = 70%,
c; R = H, Ar = $C_6H_4NO_2$-p, yield = 67%,
d; R = H, Ar = $C_6H_3(OCH_3)$-3,4, yield = 64%,
e; R = H, Ar = C_6H_4Cl-o, yield = 65%,
f; R = H, Ar = C_6H_4Br-m, yield = 61%,

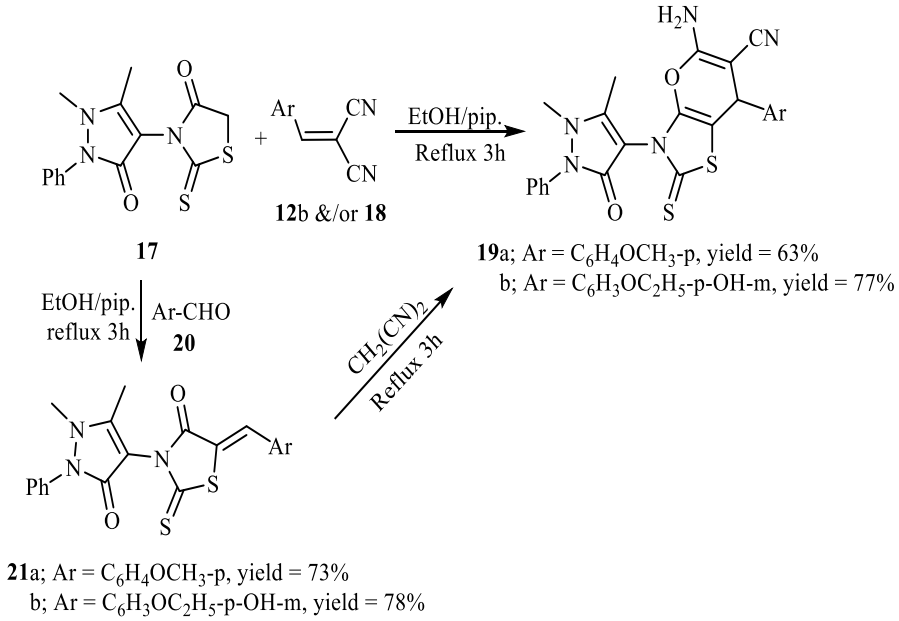
Scheme 4

In 1995, Mohareb Et Al. [16] Reported That Pyrano[2,3-*D*]Thiazole **15** Derivative Was Achieved Upon The Reacting Of 4-Thiazole-2-Thione (**14)** With Benzalmalononitrile **2a** In DMF And In Presence Of TEA. Furthermore, The Reaction Of Compound **14** With Benzaldehyde In Refluxing DMF Containing A Catalytic Amount Of Piperidine Afforded The Benzal Derivative **16** Which Subsequently Reacted With Malononitrile To Give The Pyrano[2,3-D]Thiazole Derivative **15**.



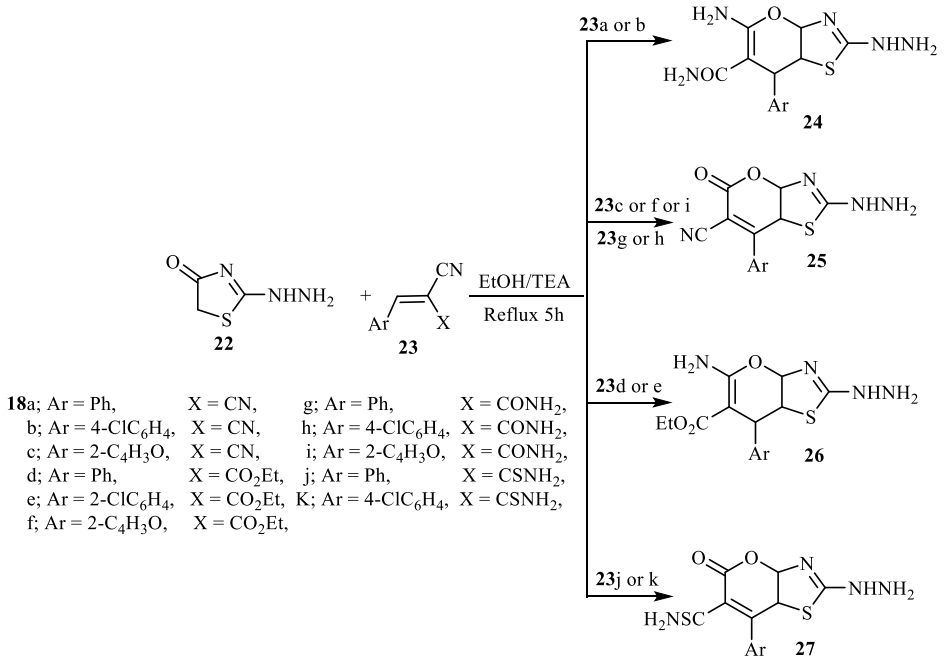
Scheme 5:

Similarly, Reaction Of 3- (1,5-Dimethyl-3-Oxo-2-Phenyl-2,3-Dihydro-1H-Pyrazol-4-Yl)-2-Thioxo-1,3-Thiazolidin-4-One (**17**) With Cinnamonitrile **12**b &/Or **18** In Ethanol In The Presence Of Piperidine As Catalyst Afforded Pyrano[2,3-*D*]Thiazole Derivative **19**a,B. Moreover, The Reaction Of Rhodanine **17** With The Aromatic Aldehydes **20** Namely (P-Methoxy-Benzaldehyde And Ethyl Vanillin) In Ethanol Containing A Catalytic Amount Of Piperidine Afforded The Arylidine Derivatives **21**a,B, Followed By Its Treatment With Malononitrile To Give Pyrano[2,3-D]Thiazoles **19**[17].



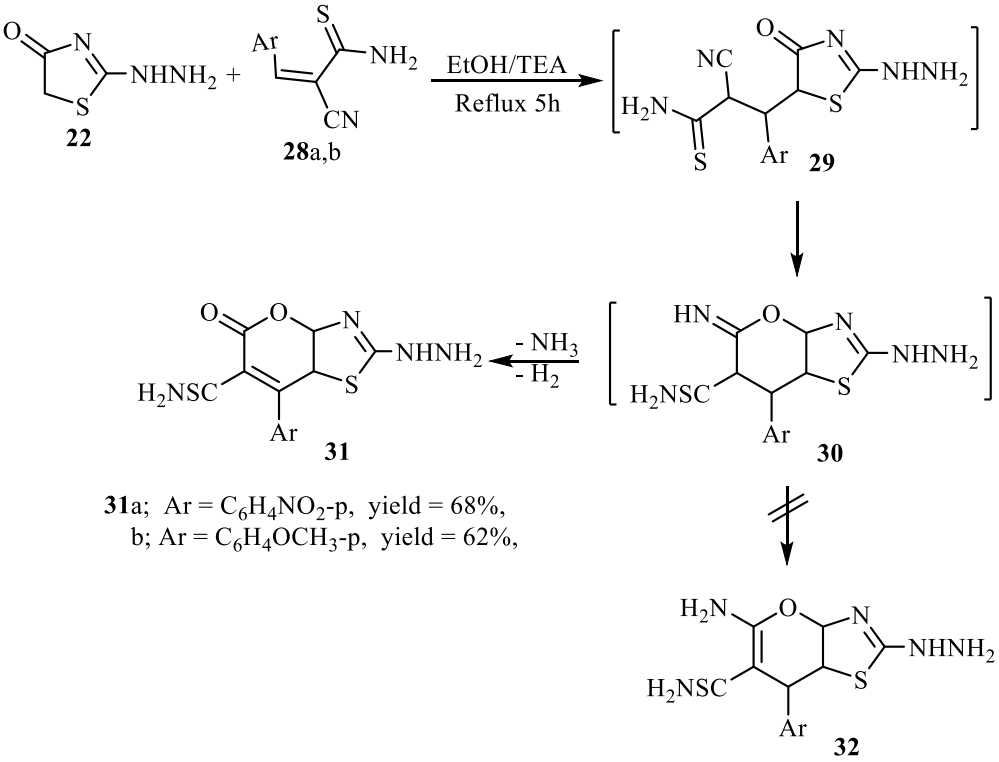
Scheme 6:

In 1998, Sanaa M. Eldin [18] Found That Various Novel Pyrano[2,3-*D*]Thiazole Derivatives **24**-**27** Have Been Synthesized Upon Refluxing Of 2-Hydrazinothiazol-4(5H)-One (**22**) With A Variety Of Cinnamonitriles **23** In The Presence Of A Base Catalyst.



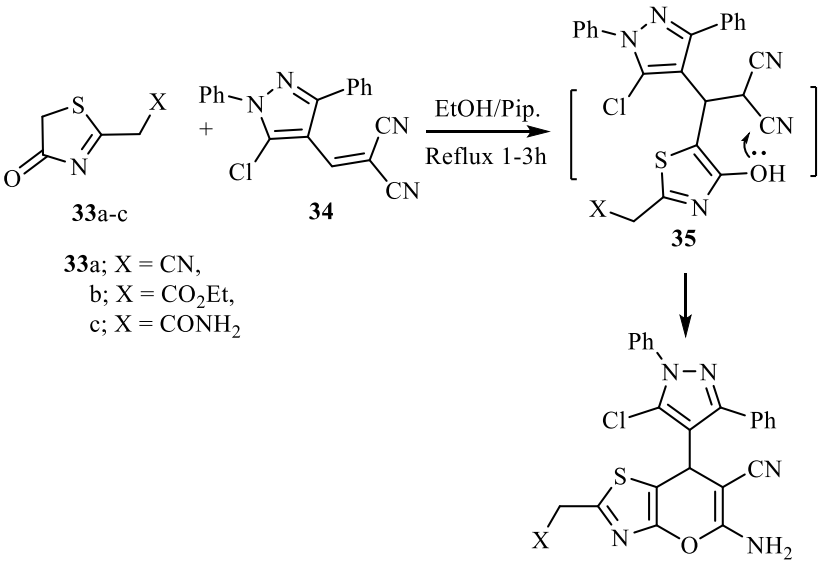
Scheme 7:

In The Next Year, Sanaa M. Eldin [19] Reported That 2-Hydrazinothiazol-4(5H)-One (**22**) Was Allowed To React With Thiocarboxamidocinnamonitrile Derivatives **28**a,B By Refluxing In Absolute Ethanol Containing A Catalytic Amount Of Trimethylamine To Yield The Corresponding 5-Oxopyrano[2,3-*D*]Thiazole **31**a,B. The Formation Of **29**a In This Reaction Is Assumed To Proceed Via Initial Formation Of The Intermediate Michael Adduct **29** Which Is Then Cyclized Via Addition To The Nitrile Function To Give The Non-Isolable Intermediate **30**. Compound **30** Is Then Autoxidized And Hydrolyzed Under The Applied Reaction Conditions To Give The Pyrano[2,3-*D*]Thiazole **31**a Rather Than Tautomerization To Give **32** (Scheme 8).



Scheme 8:

Michael Addition Of The Methyl Group In 2-Substituted 2-Thiazolin-4-Ones **33** To The Activated Double Bond In Arylidene **34** In Refluxing Ethanol Catalyzed By Piperidine Was Achieved To Afford Pyrano[2,3-*D*]Thiazole Derivatives **36** Through Formation Of Michael Adduct **35** [20](Scheme 9).



33a-c

34

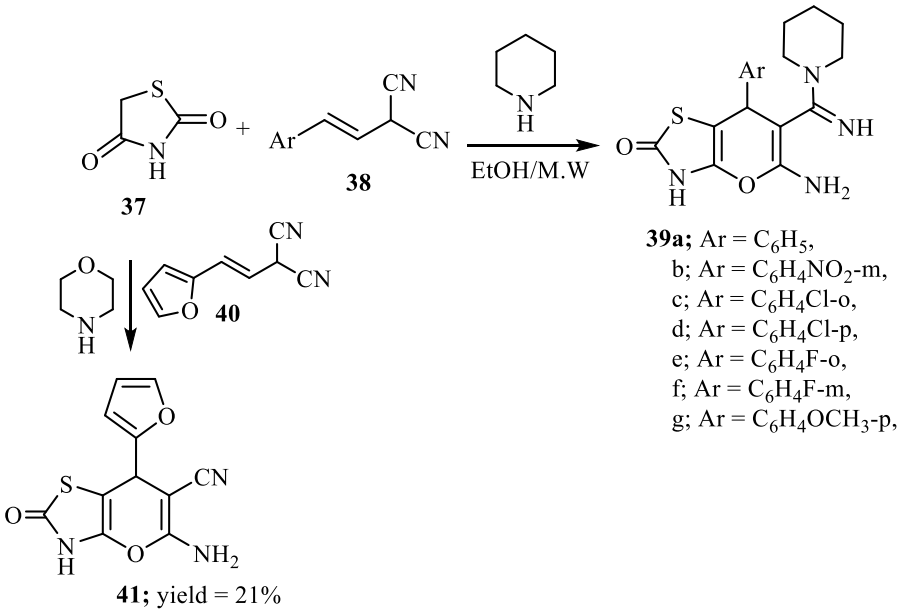
35

33a; X = CN,
b; X = CO_2Et,
c; X = $CONH_2$

36a; X = CN, yield = 72%,
b; X = CO_2Et, yield = 70%,
c; X = $CONH_2$, yield = 75%,

Scheme 9

In Addition, 1,3-Thiazolidin-2,5-Dione (**37**) Are Found To React Smoothly Under Microwave Irradiation With Arylidenemalononitriles **38** And Piperidine To Give The Corresponding Pyrano[2,3-*D*]Thiazoles **39**a-G [21](Table 1). In This Reaction, Piperidine Behaves Both As A Base Catalyst And As A Nucleophile. But, When 1,3-Thiazolidin-2,5-Dione (**37**) Was Allowed To React With Furilydenemalononitrile **40** In The Presence Of Morpholin Under Thermal Condition The Corresponding Pyrano[2,3-*D*]Thiazole **41** [22] Was Obtained.



37

38

39a; Ar = C_6H_5,
b; Ar = $C_6H_4NO_2$-m,
c; Ar = C_6H_4Cl-o,
d; Ar = C_6H_4Cl-p,
e; Ar = C_6H_4F-o,
f; Ar = C_6H_4F-m,
g; Ar = $C_6H_4OCH_3$-p,

40

41; yield = 21%

Scheme 10:

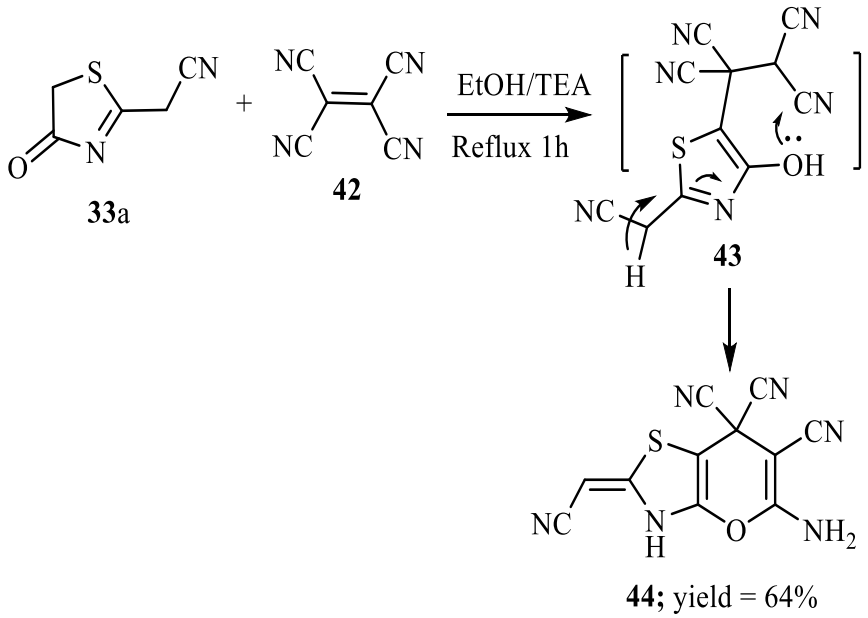
Table 1: Results Of The Domino Synthesis Under MW Of Compound **39**a-G

Compound No.	Ar	Solvent	Time (Min.)	Yield(%)

39a	C_6H_5	Etoh	10	65
39b	$C_6H_4NO_2$-M	Etoh	10	75
39c	C_6H_4Cl-O	Etoh	10	68
39d	C_6H_4Cl-P	Etoh	10	70
39e	C_6H_4F-O	Etoh	10	73
39f	C_6H_4F-M	Etoh	10	71
39g	C_6H_4-OCH_3	Etoh	10	62

Reaction With Tetracyanoethylene

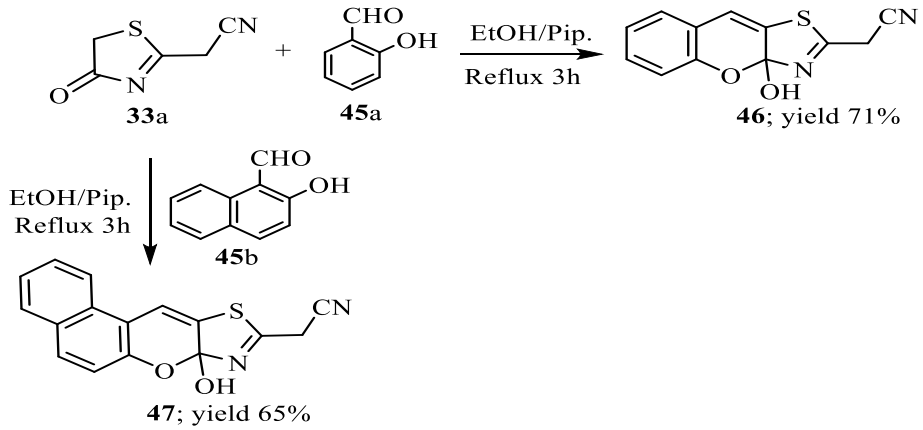
In 2008, El-Hag Ali Et Al. [23] Were Found That, Reaction Of 2-Cyanometh-Yl-4-Thiazolinone (**33**a) With Tetracyanoethylene (**42**) In Refluxing Ethanol Containing A Catalytic Amount Of Triethylamine Furnished Pyrano[2,3-*D*]Thiazole Derivative **44** Through The Formation Of Michael Adduct **43** (Scheme 11).



Scheme 11:

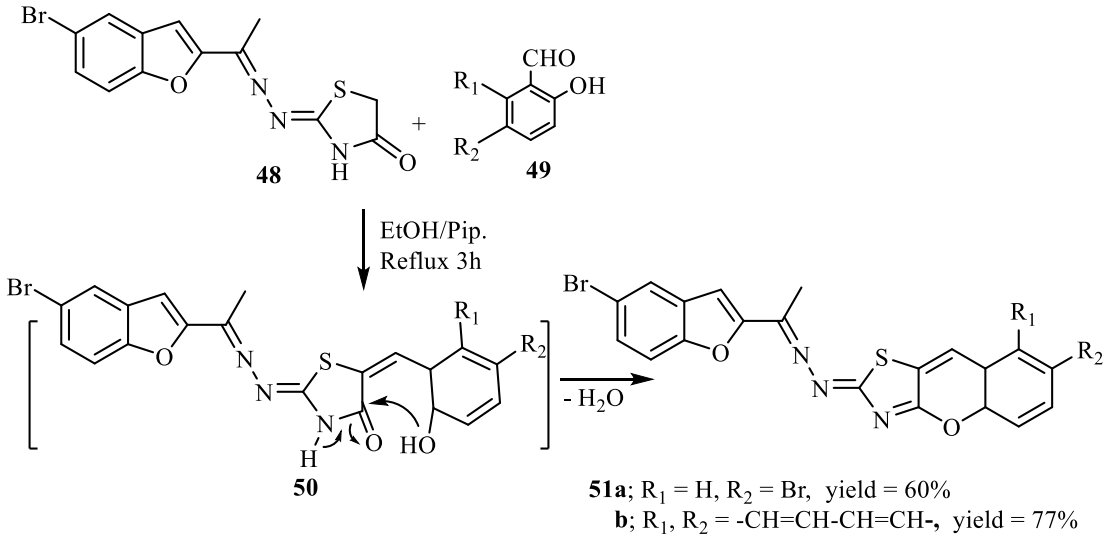
Reaction With O-Hydroxyaldehydes

It Has Been Found That Benzo[E]Pyrano[2,3-*D*]Thiazole **46** And Naphtho[E]Pyrano[2,3-*D*]-Thiazole **47** Were Achieved By Cycloconden-Sation Of 2-Cyanometh-Yl-4-Thiazolinone (**33**a) With Salicylaldehyde And /Or 2-Hydroxy1naphthaaldehyde **45**a,B Under Reflux In Ethanol Solution Containing Catalytic Amount Of Piperidine [23](Scheme 12).



Scheme 12:

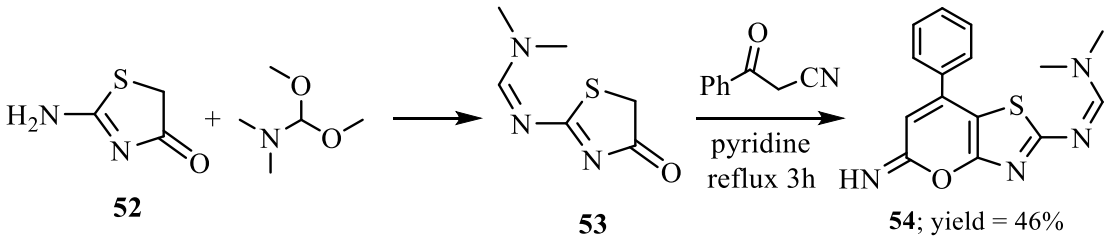
On The Other Hand, Halawa Et Al. [24] Reported That Reaction Of (2-((1-(5-Bromobenzofuran-2yl)Ethylidene)Hydrazono)Thiazolidin-4-One) (**48**) With Salicylaldehyde Derivatives **49** In Ethanolic Piperidine Solution Under Reflux Condition Afforded Benzo[E]Pyrano[2,3-*D*]Thiazole Derivatives **51** Through Acyclic Intermediate **50** (Scheme 13).



Scheme 13:

Reaction With Benzoylacetonitrile

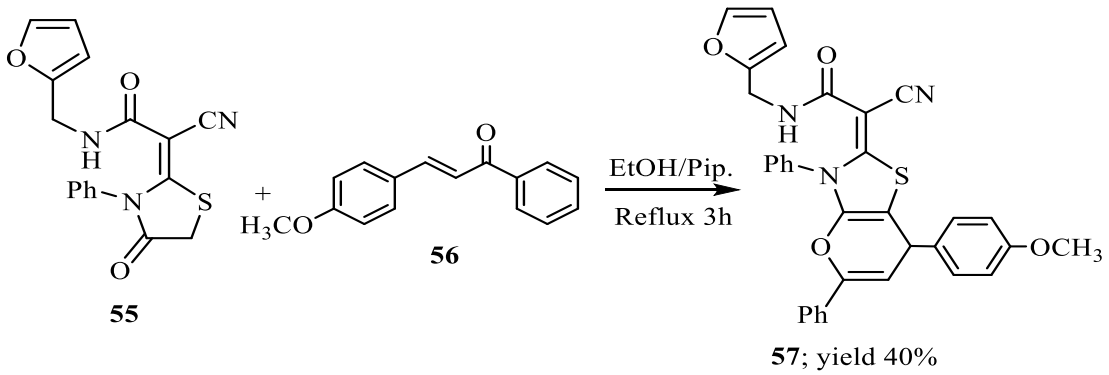
Manhi And Coworkers [25] Reported That Reacting Of N,N-Dimethyl-N'-(4-Oxo-4,5-Dihydrothiazol-2yl)Imidoformamide (**53**) [Prepared By Treatment Of 2-Aminothiazl-4-One (**52**) With N,N-Dimethyl Formamide Dimethyl-Acetal] With Benzoylacetonitrile Has Resulted In Only The Formation Of The Condensed Isomeric Pyranothiazol Product **54** (Scheme 14).



Scheme 14:

Reaction With A,B-Unsaturated Ketone

In 2017, Salem Et Al.[26] Found That Pyrano[2,3-*D*]Thiazole Derivative **57** Was Synthesized And Evaluated *In Vitro* For Potential Antimicrobial Agent. Compound **57** Was Synthesized Via Cycloaddition Of 4-Thiazoldinone **55** With Chalcone Derivative **56** In The Presence Of A Catalytic Amount Of Piperidine (Scheme 15).

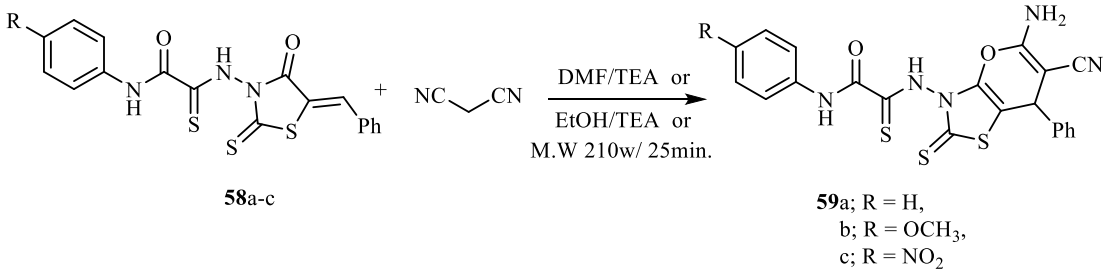


Scheme 15:

2- From 5-Ylidenethiazol-4-Ones

Deferent Type Of 5-Arylmethylidenethiazole-4-One Derivatives (Were Prepared From Reaction Of 4-Thiazoldinones With Aromatic Aldehyde) Having A Conjugated Carbonyl Group Reacted With Such Different Nucleophiles To Give Pyrano[2,3-*D*]Thiazoles.

In 2007, Yarovenko Et Al. [27] Reported That 5-Amino-2-Thioxo-3,7-Dihydro-2H-Pyrano[2,3-*D*][1,3]Thiazole-6-Carbonitriles **59**a-C Were Found To Be Obtained When 5-Benzylidenerhodanine Derivatives **58**a-C Were Heated With Malononitrile In DMF In The Presence Of Triethylamine For 10h Or In Anhydrous Ethanol For 3h (Yield 30-35%; Scheme 16). But When This Reaction Activated By Microwave Irradiation Were As Follows: MW Power 210 W, Reaction Time 45 Min; In This Case, The Yields Of Pyranothiazoles **59**a-C Were 85-87%, Scheme 16.

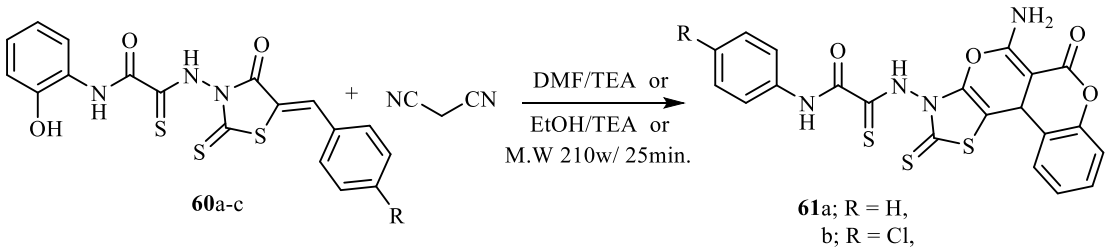


58a-c

59a; R = H,
b; R = OCH_3,
c; R = NO_2

Scheme 16

Under The Same Reaction Condition, The Presence Of A Reactive Substituent In The Ortho Position Of The Benzene Ring In The Arylmethylidene Fragment Of Molecule Provides The Possibility For Subsequent Heterocyclization. Thus, 2-Hydroxybenzylidene Derivatives **60**a-C (Ar = 2-HOC_6H_4) Reacted With Malononitrile To Give Fused Chromeno[4′,3′:4,5]Pyrano [2,3-*D*]Thiazol-6-Ones **61**a-C[27].

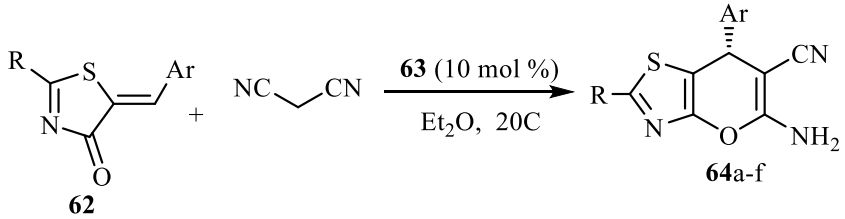


60a-c

61a; R = H,
b; R = Cl,
c; R = OCH_3

Scheme 17:

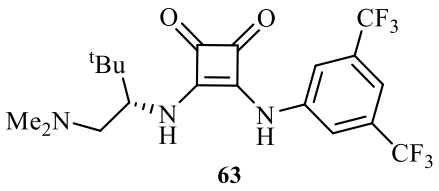
Also, An Efficient Catalytic Asymmetric Synthesis Of 7H-Pyrano[2,3-*D*]Thiazoles Has Been Developed By Cui Et Al. [28] On The Basis Of The Organocatalyzed [4+2] Annulation Of Malononitrile And 5-Ylidenethiazol-4-Ones. Under The Catalysis Of An Enantiopure Bifunctional Squaramide **63** Derived From L-Tertleucine (Figure 1), A Wide Range Of 5-Ylidenethiazol-4-Ones **62** Were Well Tolerated In This Cascade Reaction To Furnish Structurally Diverse 7H-Pyrano[2,3-*D*]Thiazoles **64** In Good Yields (Table 2) And With Moderate To Excellent Enantioselectivities.



62

64a-f

Scheme 18:



63

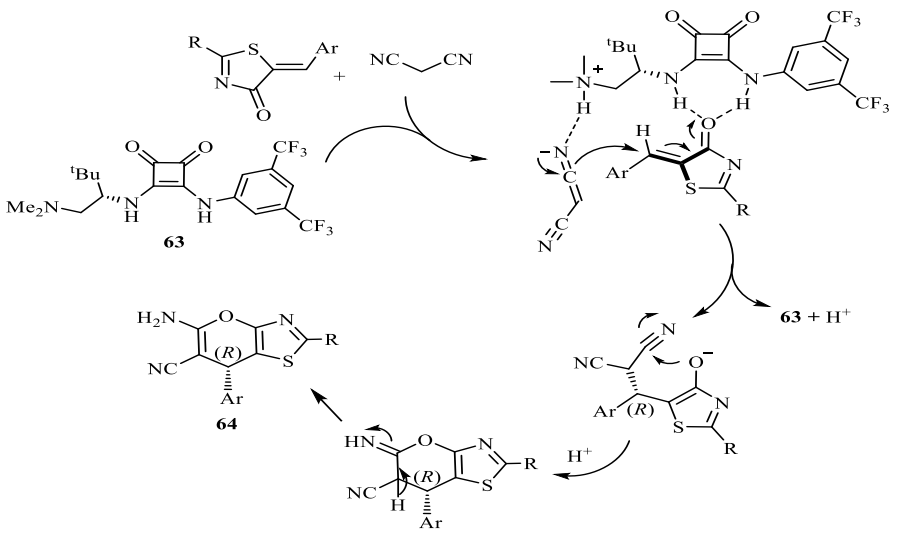
Figure 1: Screened Double Hydrogen Bond Donor Catalysts.

Table 2:**63**-Catalyzed Asymmetric [4+2] Annulation Of 5-Ylidenethiazol-4-Ones **62** And Malononitrile

Comp. No.	R	Ar	Time (H)	Yield (%)[B]	Ee (%)[C]
64a	Ph	Ph	3	92	> 99
64b	4-FC_6H_4	Ph	70	74	55
64c	2-FC_6H_4	Ph	24	76	77
64d	4-Clc_6h_4	Ph	4	78	98
64e	3-Clc_6h_4	Ph	78	82	94
64f	2-Clc_6h_4	Ph	30	82	98
64g	4-Brc_6h_4	Ph	36	70	98
64h	3-Brc_6h_4	Ph	40	72	98
64i	2-Brc_6h_4	Ph	20	77	74
64j	4-$CH_3C_6H_4$	Ph	30	72	91
64k	2-$CH_3C_6H_4$	Ph	72	79	92
64l	3- CH_3-4-Clc_6h_3	Ph	78	93	93
64m	4-$OCH_3C_6H_4$	Ph	30	75	56
64n	3,5-$(OCH_3)_2FC_6H_3$	Ph	76	76	45
64o	CH_3S	Ph	94	54	26
64p	Ph	3-Clc_6h_4	30	94	58
64q	Ph	2-$OCH_3C_6H_4$	72	75	43
64r	Ph	2-Thienyl	12	75	70

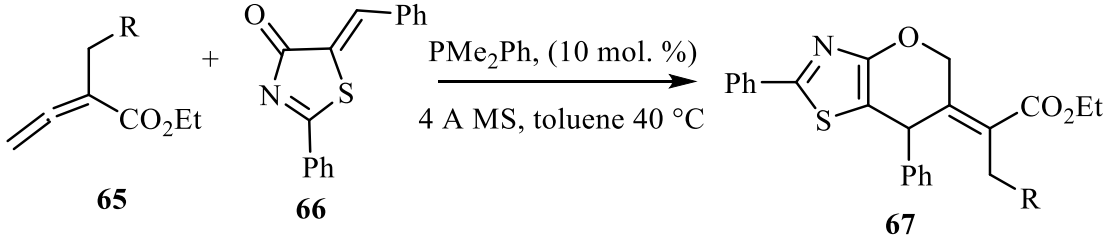
[A] All Reactions Were Carried Out With 1 (0.11 Mmol), 2 (0.10 Mmol) And Catalyst III (10 Mol %) In Diethyl Ether (1 Ml) At 20 C. [B] Isolated Yield. [C] Determined By HPLC Analysis With A Chiral Stationary Phase.

A Possible Mechanism For This [4+2] Cyclization Reaction Is Proposed On The Basis Of The Observed Results As Follow [28](Scheme 19):



Scheme 19: Proposed Reaction Mechanism For Formation Of 64.

Similarly, Wang Et Al.[29] Were Furnished The Synthesis Of Biologically Important Functionalized 6,7-Dihydro-5H-Pyrano[2,3-*D*]Thiazoles **67** In High To Excellent Yields (Table 3) When Phosphine-Catalyzed [2 + 4] Annulation Of A-Substituted Allenoates **65** As C_2 Synthons With 5-Benzylidene-2-Phenylthiazol-4(5H)-One (**66**) As C_4 Synthons Has Been Achieved Under Mild Conditions (Scheme 20).



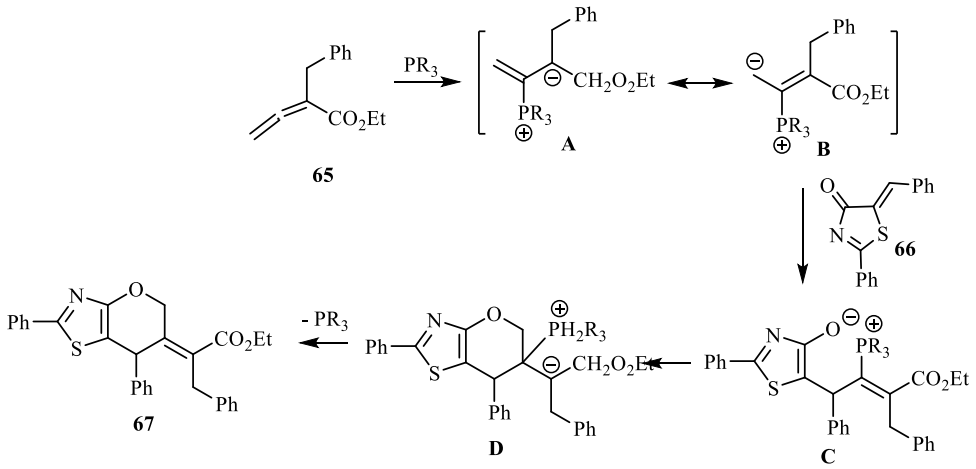
Scheme 20:

Table 3: Scope Of Allenoates **65**[a]

Comp. No.	R In 66	Time	Yield (%)[B]
67a	Ph	40 Min	80
67b	3-Mec$_6$h$_4$	1.5 H	62
67c	4-Mec$_6$h$_4$	1 H	67
67d	4-T-Buc$_6$h$_4$	1 H	71
67e	3,5-Ome$_2$c$_6$h$_3$	1.5 H	70
67f	2-FC$_6$H$_4$	1 H	71
67g	3-FC$_6$H$_4$	1 H	72
67h	4-FC$_6$H$_4$	1 H	75
67i	2-Clc$_6$h$_4$	30 Min	70
67j	3-Clc$_6$h$_4$	1 H	72
67k	4-Clc$_6$h$_4$	30 Min	72
67l	2-Brc$_6$h$_4$	1 H	70

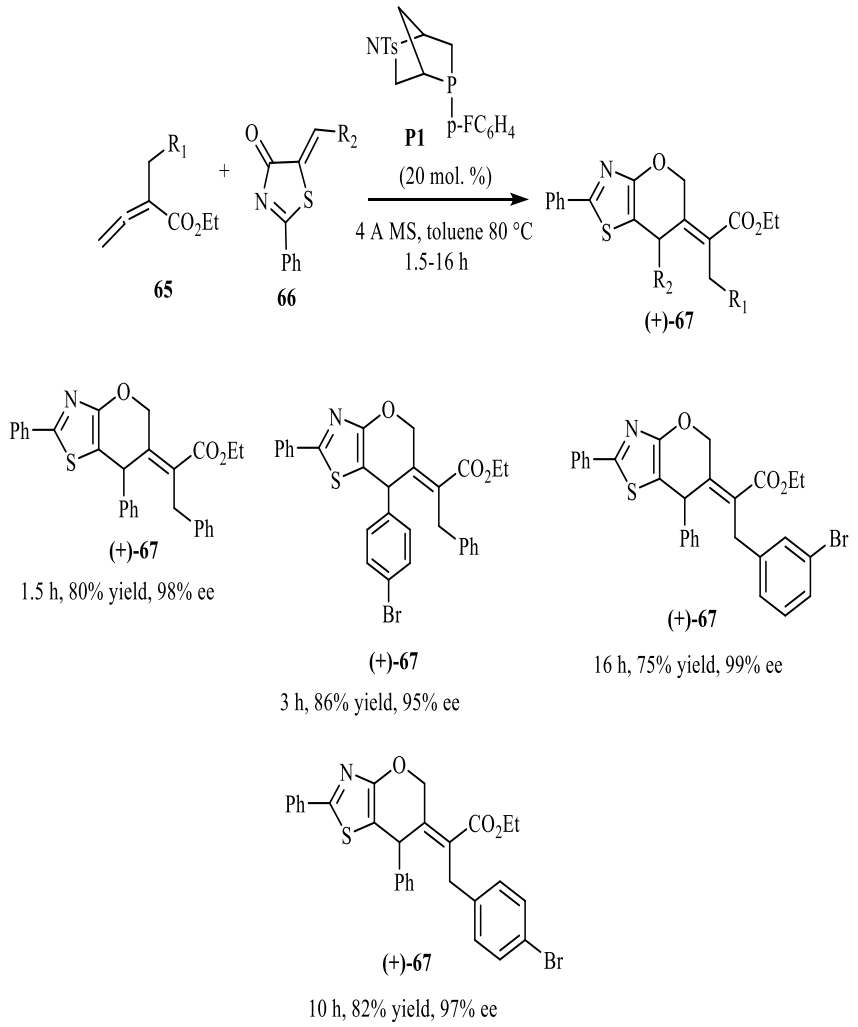
67m	3-Brc_6h_4	50 Min	71
67n	4-Brc_6h_4	30 Min	72
67o	3-$CF_3C_6H_3$	1 H	70
67p	4-$CF_3C_6H_3$	1 H	70
67q	4-$CO_2MeC_6H_4$	3 H	69
67r	2-Naphthyl	2 H	63
67s	H	24 H	Trace

[A]all Reactions Were Performed With **65** (0.15 Mmol), **66** (0.1 Mmol), 4 Å MS (100 Mg), And Pme_2ph (0.01 Mmol) In Toluene (1 Ml) At 40°C. [B] Isolated Yield.



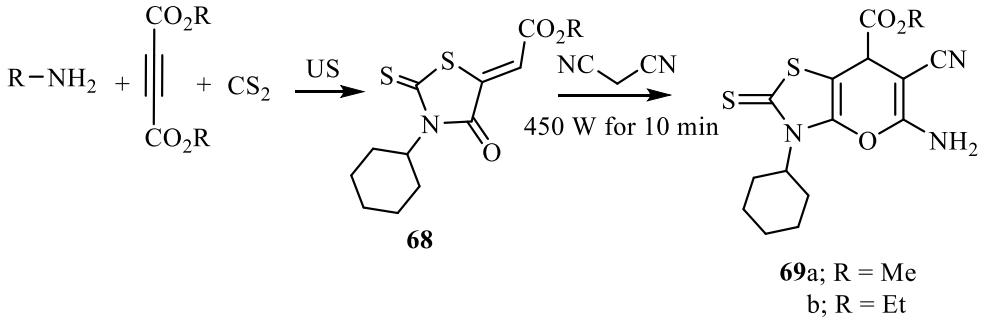
Scheme 21: A Plausible Reaction Mechanism For Formation Of **67**.

When The Authors Attempted To Develop The Asymmetric Variant Of This Phosphine-Catalyzed [2 + 4] Annulation Of A-Substituted Allenoates **65** With 5-Argiomethylene Substituted Thiazolones **66**. The Commercially Available Kwon's Phosphine P1[30] Was Found To Be An Excellent Chiral Catalyst For This Reaction, Affording The Chiral Product (+)-**67** In Good Yields With Excellent 95-99% (Scheme 22) [29].



Scheme 22:

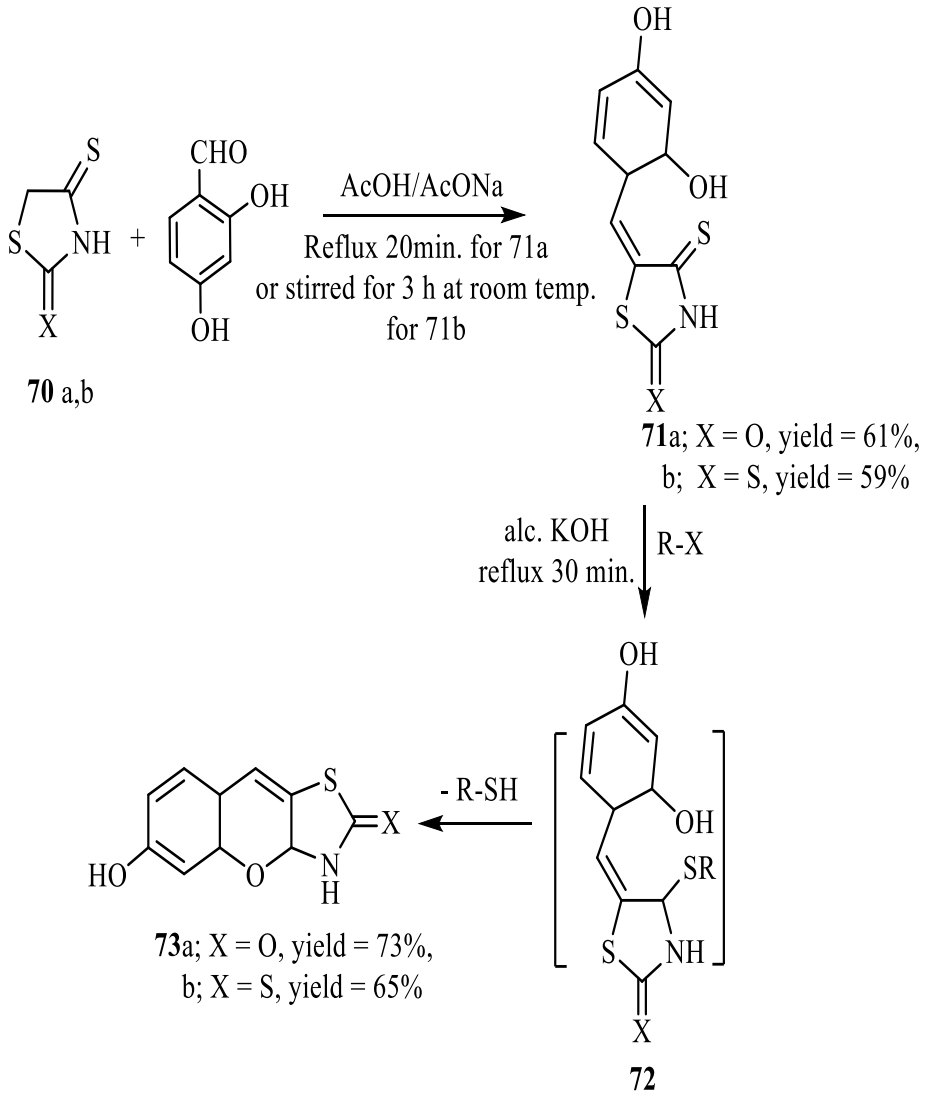
Moreover, The Pyrano[2,3-*D*]Thiazoles **69** Were Prepared From The Corresponding Rhodanines **68** (Synthesized Via A Three-Component Reaction Of Carbon Disulfide, Amines, And Dialkyl Acetylenedicarboxylate In Polyethylene Glycol Under Conventional Stirring Or Ultrasound Irradiation) And Malononitrile Under Microwave Condition [31](Scheme 23).



Scheme 23:

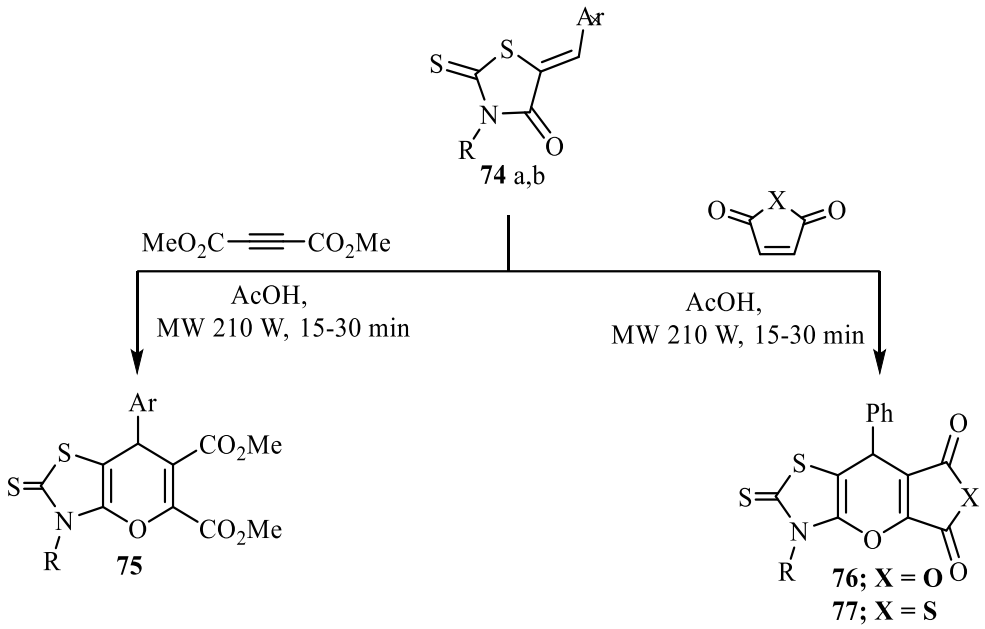
In 2007, Metwally Et Al. [32] Reported That Knoevenagel Condensation Of Thiazolidin-2-Ones **70**a,B With 2,4-Dihydroxybenzaldehyde Afforded The Highly Colored 5-(2,4-Dihydroxy-Benzylidene)Thiazolidines **71**a.B, Which Was Treated With Methyl Iodide, Ethyl Bromoacetate And/Or Phenacyl Bromide In Alcoholic Potassium Hydroxide To Afford Benzo[B]Pyrano[2,3-*D*]Thiazoles **73**. The Reaction Seems To Take Place Via *S*-Alkylation To

Form Non-Isolable Product **72** Followed By Cyclization Through Elimination Of Alkane Thiol (R-SH), (Scheme 24).



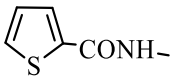
Scheme 24:

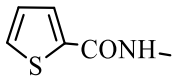
In 2008, Yarovenko And Coworkers [33] Reported That Diels-Alder Reactions Of Arylidenerhodanines **74** Are A Convenient Route To Pyrano[2,3-*D*]Thiazole. The Reactions Of Arylidenerhodanines **74a**-E With DMAD, Maleic Anhydride And N-Phenylmaleimide Under 210 W Microwave Radiations Smoothly Formed The Respective Cycloaddition Products **75**, **76** And **77** Within 15-30 Min In 72-90% Yield (Scheme 25).



75	R Ar = Ph
a	PhNHC(S)C(O)NH, yield = 81%
b	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 76%
c	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 72%
d	Ph, yield = 78%

75	Ar R = 
e	Ph, yield = 82%
f	2-HOC$_6$H$_4$-, yield = 62%
g	2-O$_2$NC$_6$H$_4$-, yield = 57%
h	4-MeOC$_6$H$_4$-, yield = 68%

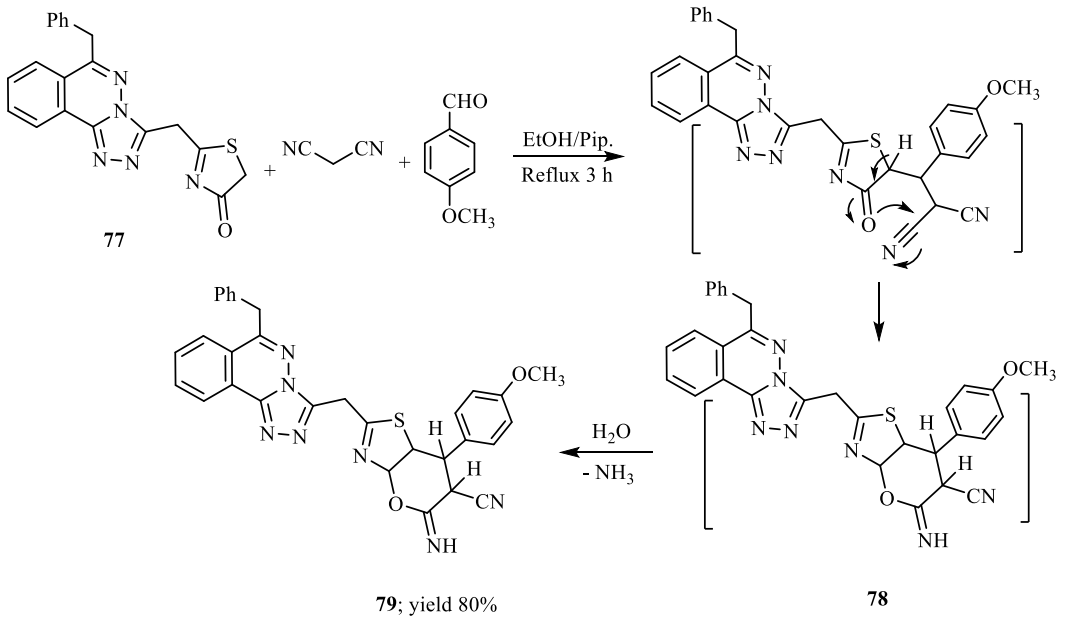
76	R
a	PhNHC(S)C(O)NH, yield = 82%
b	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 74%
c	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 89%
d	Ph, yield = 90%
e	 , yield = 83%

77	R
a	PhNHC(S)C(O)NH, yield = 86%
b	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 80%
c	4-ClC$_6$H$_4$NHC(S)C(O)NH, yield = 78%
d	Ph, yield = 86%
e	 , yield = 79%

Scheme 25

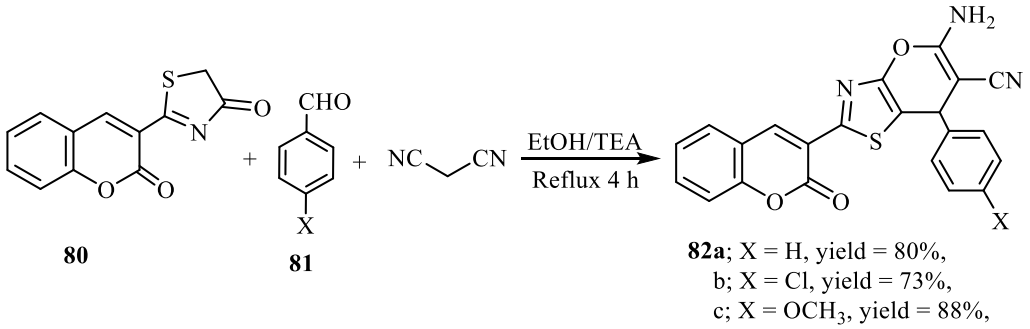
3- One Pot Synthesis

5H-Pyrano[2,3-*D*]Thiazole-6-Carbonitrile **79** Was Found To Be Obtained By One Pot Reaction Of An Equimolar Mixture Of 2-(6-Benzyl[1,2,4]Triazolo-[3,4-*A*]Phthalazin-3-Ylmeth-Yl)Thiazol-4-One (**77**), Malononitrile And P-Anisaladehyde In Boiling Ethanol Containing A Catalytic Amount Of Piperidine Under Reflux [34]. The Formation Of Compound **79** Can Be Rationalized By Michael Addition Of Active Methylene Group Of 4-Thiazolinone **77** At The Activated Ethylenic Double Bond Of Benzylidene Malononitrile Forming An Adduct To Form **78** Which Undergoes Intramolecular Cyclization And Spontaneous Hydrolysis Of The Imino Function Into The Carbonyl Group Under The Experimental Reaction Conditions Employed (Scheme 26).



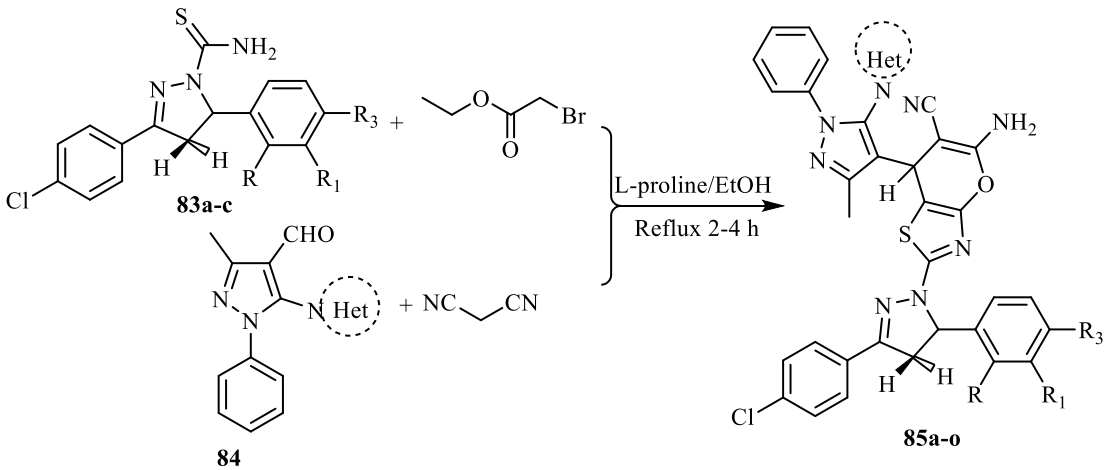
Scheme 26:

Also, The One Pot Synthesis Of 7H-Pyrano[2,3-*D*]Thiazole-6-Carbonitriles **82** Were Achieved Upon The Reaction Of 2-(4-Oxo-4,5-Dihydrothiazol-2-Yl)Acetonitrile (**80**), Malononitrile And Aromatic Aldehyde **81** In Refluxing Ethanol Containing Catalytic Amount Of Trimethylamine [35] (Scheme 27).



Scheme 27:

A New Approach For The Synthesis Of A Pyrano[2,3-*D*]Thiazole **85** Has Been Claimed By Kalaria Et Al. [36] Through A One-Pot Four-Component Tandem Type Reaction. Substituted Carbothioamide **83**a-C, Pyrazolyl Aldehydes **84**, A-Bromoethylacetate And Malononitrile In The Presence Of L-Proline As The Catalyst Yielded The Targeted Products In High Yields Over A Short Reaction Time(Table 4).

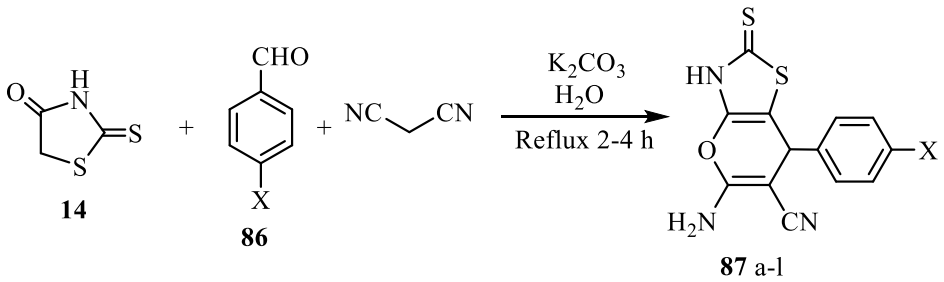


Scheme 28:

Table 4: Substituents Pattern For The Synthesized Compounds **85**a-O.

Compound No.	R1	R2	R3	Het.	Yield(%)
85a	-	-	$-CF_3$	Triazole	84
85b	-	-	$-CF_3$	4-Methylimidazole	76
85c	-	-	$-CF_3$	Imidazole	81
85d	-	-	$-CF_3$	Benzimidazole	71
85e	-	-	$-CF_3$	Benzotriazole	72
85f	-	$-CF_3$	-	Triazole	88
85g	-	$-CF_3$	-	4-Methylimidazole	75
85h	-	$-CF_3$	-	Imidazole	79
85i	-	$-CF_3$	-	Benzimidazole	73
85j	-	$-CF_3$	-	Benzotriazole	76
85k	$-CF_3$	-	-	Triazole	83
85l	$-CF_3$	-	-	4-Methylimidazole	76
85m	$-CF_3$	-	-	Imidazole	80
85n	$-CF_3$	-	-	Benzimidazole	74
85o	$-CF_3$	-	-	Benzotriazole	71

Shelke Et Al. [37] Were Reported A One-Pot Efficient, Green And Environ-Mentally Friendly Multicomponent Synthesis Of Novel 2H-Pyrano[2,3-*D*]Thiazole-6-Carbonitrile Derivatives **87** In The Presence Of Green, Low Cost, Mild, Effcient And Commercially Available K_2CO_3 As The Catalyst With Water. Thus, It Was Found That An Equimolar Mixture Of 2-Thioxothiazoli-Din-4-One (**14**), Aromatic Aldehyde **86** And Malononitrile At Reflux Temperature In The Presence Of K_2CO_3 With Water Afforded 5-Amino-7-(Substituted Phenyl)-2-Thioxo-3,7-Dihydro-2H-Pyrano[2,3-D]Thiazole-6-Carbonitrile **87** In Excellent Yield (Table 5).



Scheme 29:

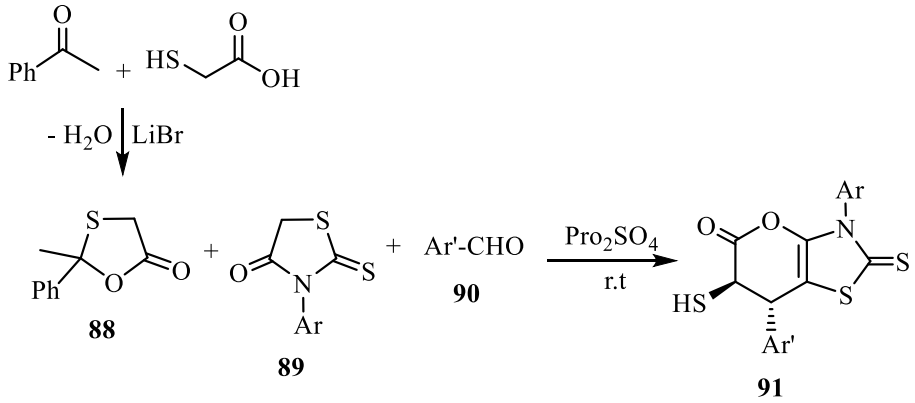
Table 5. Synthesis Of 5-Amino-7-(Substituted Phenyl)-2-Thioxo-3,7-Dihydro-2H-Pyrano[2,3-D]Thiazole-6-Carbonitrile (**84**a-L)[A].

Compound No.	Substituted Aldehyde	Time (H)	Yield(%)
87a	4-Chlorobenzaldehyde	2	98

87b	Benzaldehyde	3	94
87c	2-Chlorobenzaldehyde	2	92
87d	4-Methoxybenzaldehyde	4	94
87e	4-Floroobenzaldehyde	4	92
87f	4-Hydroxybenzaldehyde	3	92
87g	4-Nitrobenzaldehyde	2	94
87h	2,4-Dichlorobenzaldehyde	2	92
87i	3-Fluorobenzaldehyde	4	96
87j	2,4-Dimethoxybenzaldehyde	4	94
87k	2-Fluorobenzaldehyde	2	96
87l	4-Methylbenzaldehyde	3	96

[A] Reaction Condition (4a-L): Potassium Carbonate, Water, Reflux 2-4 H.

In 2008, Yadav Et Al. [38] Were Reported A Low Hazardous, One-Pot, Expeditious Annulation Involving Tandem Knoevenagel, Michael And Ring Transformation Reactions Of 3-Arylrhodanines (**89**), Aromatic Aldehydes **90** And A Mercaptoacetyl Transfer Agent, 2-Methyl-2-Phenyl-1,3-Oxathiolan-5-One (**88**), Diastereoselectively Yields 6-Mercaptopyrano[2,3-*D*]Thiazoles **91** In Good Yield(Table 6). The Annulation Is Performed Using A Chiral Ionic Liquid (Pro_2SO_4) As The Reaction Medium And Catalyst.



Scheme 30:

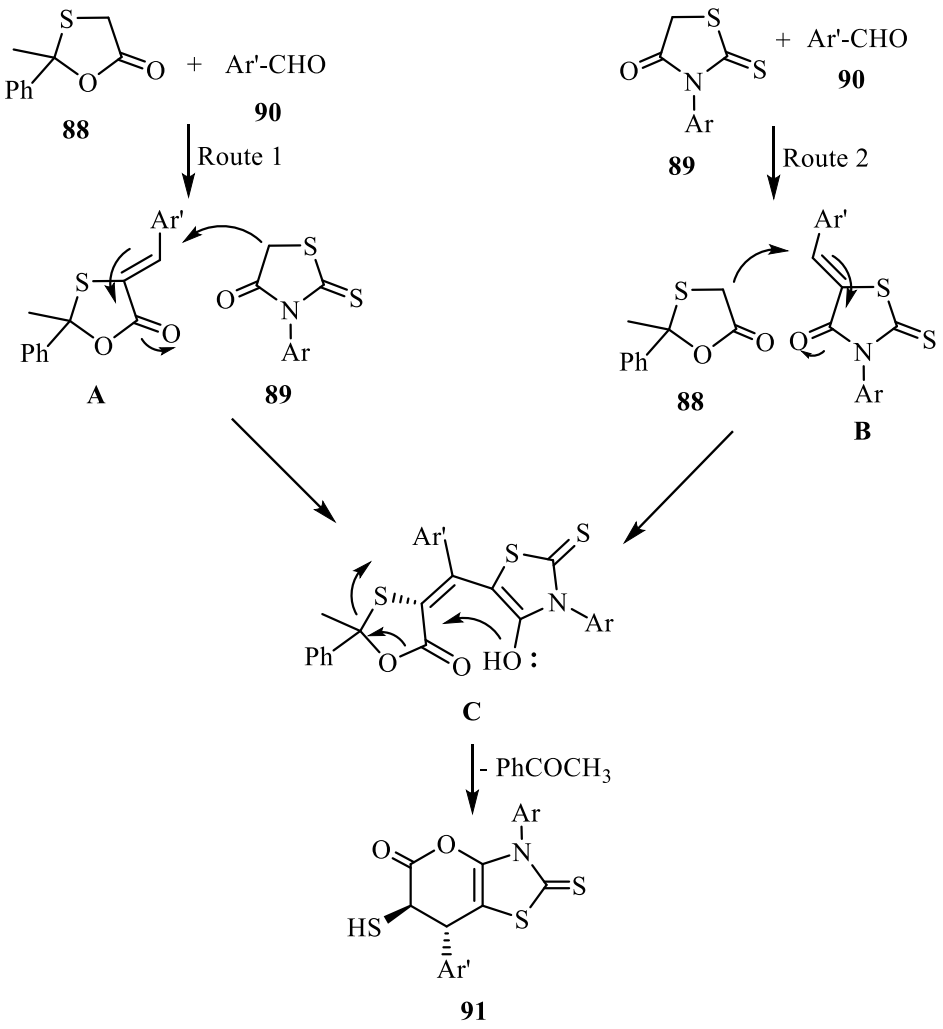
Table 6: Substituents Pattern For The Synthesized Compounds **91**a-L.

Compound No.	**Ar**	**Ar'**	**Time (H)[A]**	**Yield(%)[B,C]**	**(Ee)[D]**
91a	Ph	Ph	27	79	91
91b	Ph	4-Clc_6h_4	25	90	88
91c	Ph	4-$OCH_3C_6H_4$	25	87	88
91d	2-$OCH_3C_6H_4$	Ph	30	88	93
91e	2-$OCH_3C_6H_4$	4-Clc_6h_4	29	85	92
91f	2-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	28	76	95
91g	4-$OCH_3C_6H_4$	Ph	26	84	89

91h	4-$OCH_3C_6H_4$	4-Clc_6h_4	30	78	90
91i	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	27	77	92
91j	2-$CH_3C_6H_4$	Ph	25	82	91
91k	2-$CH_3C_6H_4$	4-Clc_6h_4	28	90	94
91l	2-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	28	85	93

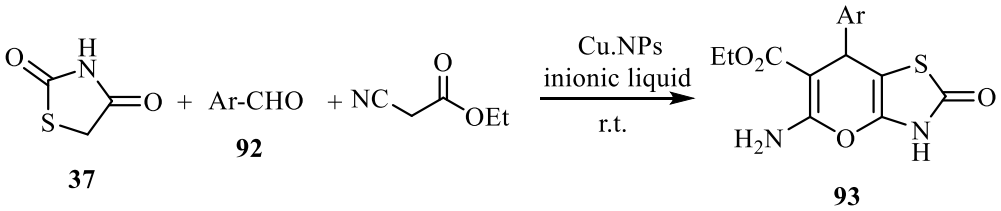
[A] Stirring Time At Room Temperature. [B] Yield Of Isolated And Purified Products. [C] All Compounds Gave C, H And N Analyses Within ± 0.36 % And Satisfactory Spectral (IR, ^{1}H NMR, ^{13}C NMR And EIMS) Data. [E] As Determined By HPLC, Daicel Chiralcel OD-H Column.

The Formation Of **91** Is Rationalized By The Michael Addition Of Rhodanines **89** To Arylidene Of Oxathiolan-5-One **88**, Formed *In Situ*, To Furnish Adducts **C** Which Undergo Intramolecular Nucleophilic Attack Of The Oxygen Atom (Of The OH) At The Carbonyl Carbon (*C*-5) Of The Oxathiolan-5-One Nucleus To Yield **91** With The Elimination Of Acetophenone (Scheme 31, Route 1). This Conclusion Is Based On The Observation That The Representative Intermediate Compounds **C** A**, C** E And **C** H Could Be Isolated In 45-52% Yield With 91-95% Ee, These Could Be Converted Into The Corresponding Annulated Products **91**a**, 91**e And **91**h In Quantitative Yield, And That Acetophenone Was Formed During The Reaction (Scheme 31). The Formation Of Adducts **C** And Their Annulation To **91** Were Highly Diastereoselective In Favour Of *Trans* Isomers. In A Reaction Mixture Containing An Equimolar **88**, **89** And **90**, More Reactive **88** And **89** Exclusively React To Give Arylidene **A** (Scheme 31, Route 1), Instead Of The Reaction Of **89** And **90** To Give **B** (Scheme 31, Route 2) Under The Present Reaction Conditions. This Is Supported By The Observation That The Reaction Of Equimolar Mixture Of **88**, **89** And **90** In Pro_2SO_4 For 10-12 H Afforded Only **A** In 90-94% Yields But Not **B**. Thus, Arylidene **A** Is First Formed Only Then Relatively Slower Michael Addition Of **89** To **A** Takes Place To Afford **91** As The Sole Product Through Isolable Intermediates **C** (Scheme 31, Route 1). However, When A Mixture Of **89** And **90** In Pro_2SO_4 Was Stirred At R.T. For ~15 H, **B** Is Obtained In 80-85% Yields Which On Treatment With **88** Afforded **91** In 71-84% Yields Through **C** (Scheme 31, Route 2)[38].



Scheme 31:

Recently, A One-Pot Practical, Efficient, And Environmentally Benign Multi-Component Synthesis Of Tetrahydropyrano[2,3-*D*]Thiazole **93** Using Copper Nanoparticles In Ionic Liquid Has Been Developed By Chakravarty Et Al [39].This Reaction Was Achieved Via A One-Pot Reaction Of An Thiazolidine-2,4-Dione (**37**), Aldehyde **92** And Cyanoethyl Acetate In The Presence Of Cu Nps In IL As Efficient Catalytic System To Afford Biological Potent Symmetrical And Asymmetrical Thiazolopyrans In High Yield (Table 7).



Scheme 32:

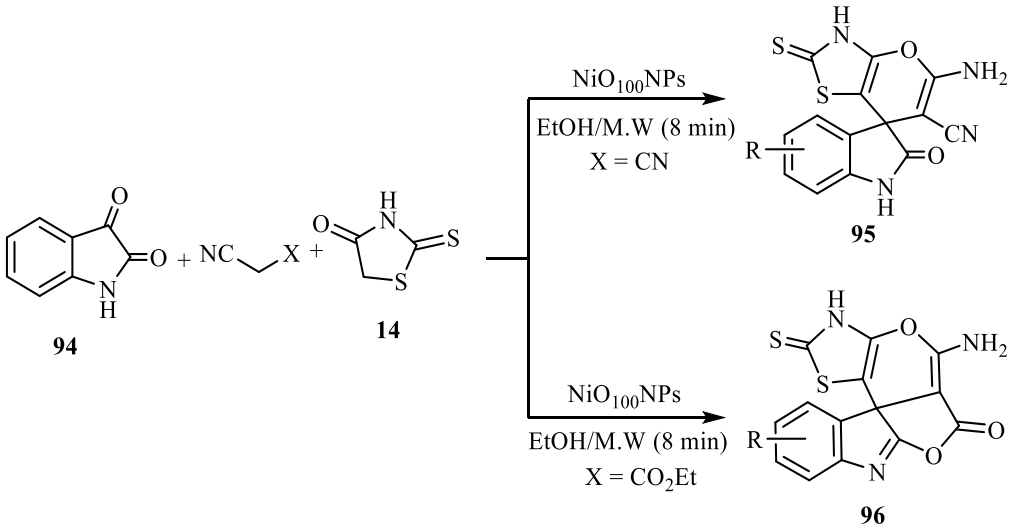
Table 7 Synthesis Of Pyranothiazoles (4) Via One Pot Three Component Reactions Of Thiazolidine-2, 4-Dione, Cyanoethylacetate And Aldehydes Using Cu Nps In IL

Compound No.	Ar	Time (Min)[A]	Yield(%)[B]
93a	C_6H_5	10	95
93b	2,4-$Cl_2C_6H_3$	12	92

93c	2,6-$Cl_2C_6H_3$	14	93
93d	2-Brc_6h_4	15	92
93e	3-$OCH_3C_6H_4$	9	95
93f	2-Clc_6h_4	18	94
93g	4-Clc_6h_4	20	92
93h	4-FC_6H_4	18	90
93i	3-$NO_2C_6H_4$	9	94
93j	4-$N(CH_3)_2C_6H_4$	16	90

[A] Stirring Time At Room Temperature. [B] Yield Of Isolated And Purified Products.

Sachdeva Et Al. [40] Were Developed A Facile And Efficient Catalytic Approach For The Multicomponent One-Pot Synthesis Of Novel Spiro[Indol-Inepyranothiazole]Carbonitriles **95** And **96** (Scheme 33) Through The Reaction Of Hindole-2,3-Dione (**94**) And 2-Thioxo-4-Thiazolidinone (**14**) With Ethylcyanoacetate/Or Malononitrile In Absolute Ethanol In The Presence Of Nio Nanoparticles Under Microwave Irradiation. The Overall Process Involves The Knoevenagel Condensation Of Hindole-2,3-Dione With 2-Thioxo-4-Hiazolidinone Followed "In Situ" Michael Addition Of Ethylcyanoacetate/Or Malononitrile In Single Operation. The Effectiveness Of The Process Was Studied By Comparing The Results Obtained With And Without Catalyst Under Normal Conditions (Table 8).



Scheme 33: Synthesis Of Spiro And Condensed Indole Derivatives **95** & **96**.

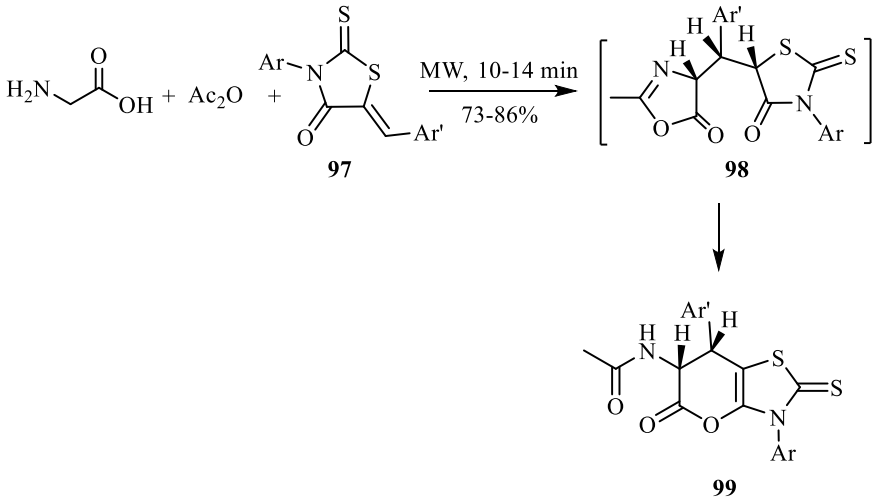
Table 8: Synthesis Of Spiro And Condensed Indole Derivatives Under Microwave Irradiation Using Ni_{100} Nanoparticles.

Compound No.	**R**	**Time** (Min)	**Yield(%)** Ni_{100}	**Yield(%)** Piperidine
95a	H	8	90	75
95b	5-Cl	8	87	72
95c	7-Cl	9	87	74
95d	5-Br	8	88	72

95e	5-NO_2	10	90	72
95f	5-CH_3	8	88	70
96a	H	8	89	74
96b	5-Cl	9	87	73
96c	7-Cl	10	88	73
96d	5-Br	9	88	72
96e	5-NO_2	9	84	74
96f	5-CH_3	10	87	71

Nio_{100} Is The Nanoparticle Calcined At 100°C.

Furthermore, Yadav Et Al. [41] Reported A Three-Component, One-Pot Reaction Of Glycine, Acetic Anhydride, And 5-Arylidenerhodanines **97**a-L Expeditiously And Diastereoselectively Yields 6,7-Dihydro-5H-Pyrano[2,3-*D*]Thiazol-2-Thiones **99**a-L Under Microwave Irradiation And Solvent-Free Conditions In High Yield (Table 9). The Formation Of Pyranothiazoles **99** Is Best Explained By Michael Addition Of Azlactone, Generated In Situ, To Thiazolone **97**, To Afford The Corresponding Michael Adducts **98**, Which Undergo Ring Transformation To Yield The Final Products **99** (Scheme 34). The Formation Of Michael Adducts **98** And Their Ring Transformation To **99** Were Highly Diastereoselective In Favour Of The *Cis (Syn)* Isomers[41].



Scheme 34:

Table 9: Pyranothiazoles **99** Prepared Under Solvent-Free Conditions.

Compound No.	**Ar**	**Ar'**	**Time** (Min)[A]	**Yield(%)** Piperidine
99a	Ph	Ph	12	78
99b	Ph	4-Clc_6h_4	10	82
99c	Ph	4-$OCH_3C_6H_4$	12	80
99d	4-Clc_6h_4	Ph	12	81
99e	4-Clc_6h_4	4-Clc_6h_4	10	86
99f	4-Clc_6h_4	4-$OCH_3C_6H_4$	12	83

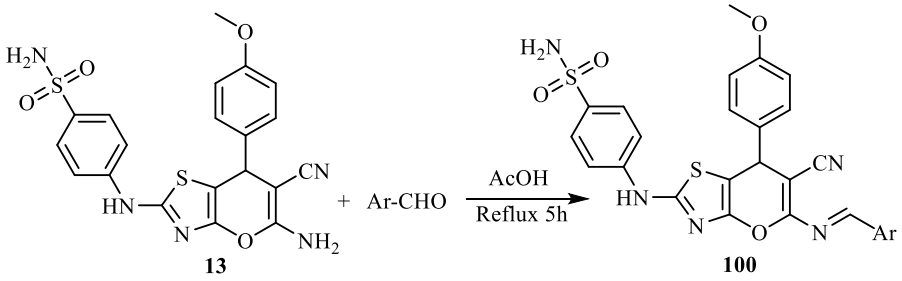
99g	2-$CH_3C_6H_4$	Ph	14	73
99h	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	14	77
99i	2-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	12	75
99j	4-$CH_3C_6H_4$	Ph	14	77
99k	4-$CH_3C_6H_4$	4-Clc_6h_4	12	78
99l	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$	10	81

[A] Microwave Irradiation Time (Power = 560 W). Parentheses Show The Time For Oil-Bath Heating At 90 °C. [B] Yield Of Isolated Product. Parentheses Show Yield Obtained Using Oil-Bath Heating.

Reaction Of Pyrano[2,3-*D*]Thiazoles

It Has Been Found That, Substituted Pyrano[2,3-*D*]Thiazole Derivatives Were Reacted With Some Appropriate Electrophilic Reagents To Find A New Class Of Biologically Active Compounds.

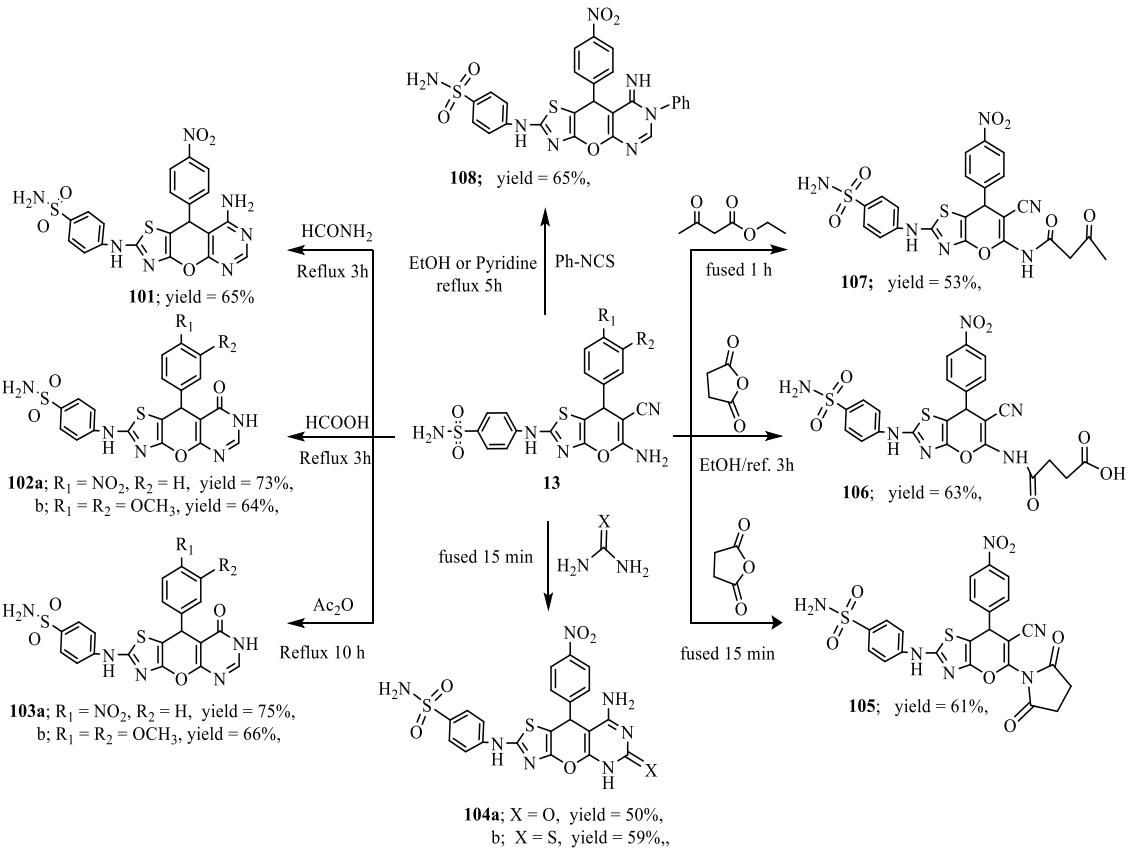
Thus, Ghorab Et Al.[14] Were Reported The Synthesis Of Some New Shiff Bases 5-(Substituted Benzylideneamino-6-Cyano-7H-7-(4-Methoxyphenyl-)-2-Sulphamoylamino)Pyrano[2,3-*D*]Thiazole **100**a-K Via Condensation Of 5-Aminopyrano[2,3-*D*]Thiazole **13**b With Substituted Aromatic Aldehydes In Acetic Acid Under Reflux (Scheme 35).



100a;Ar = C_6H_5, yield = 51%, g; Ar = $C_6H_4NO_2$-4, yield = 75%,
b; Ar = C_6H_4Cl-2, yield = 47%, h; Ar = $C_6H_3N(CH_3)_2$-4, yield = 43%,
c; Ar = C_6H_4Cl-4, yield = 67%, i; Ar = $CH{=}CHC_6H_4$, yield = 39%,
d; Ar = C_6H_4Br-3, yield = 54%, j; Ar = C_6H_4OH-4, yield = 46%,
e; Ar = C_6H_4F-4, yield = 63%, k; Ar = piperonyl, , yield = 71%,
f; Ar = $C_6H_3Cl_2$-2,4, yield = 77%,

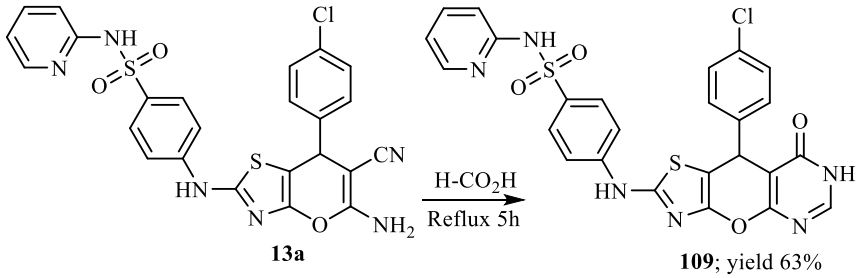
Scheme 35

Also, Ghorab Et Al. [15] Found That Treatment Of Pyrano[2,3-*D*]Thiazole **13**c,D With One-Carbon Cyclizing Agents, Such As Formamide, Formic Acid And Acetic Anhydride Yielded The Corresponding Thiazolopyranopyrimidine Derivatives **101**, **102**a,B, **103**a,B (Scheme 36). The 2-Oxo/Thioxo Pyrimido Derivatives **104**a And **104**b Were Obtained By Fusion Of Compound **13**c With Urea And/Or Thiourea, Respectively. When Compound **13**c Was Fused With Succinic Anhydride, The 2,5-Dioxopyrrolidine Derivative **105** Was Obtained. But, When Compound **13**c Was Allowed To React With Succinic Anhydride In Ethanol Under Reflux, The Oxobutanoic Acid Derivative **106** Was Furnished. Also, The Oxobutanoic Acid Derivative **107** Was Formed By Reaction Of **13**c With Ethylacetoacetate Under Fusion Condition. When Compound **13**d Was Reacted With Phenyl Isothiocyanate Either In Pyridine, Or In Ethanol The Thiazolopyranopyrimidine Derivative **108** Was Isolated Via Dimroth Rearrangement (Scheme 36).



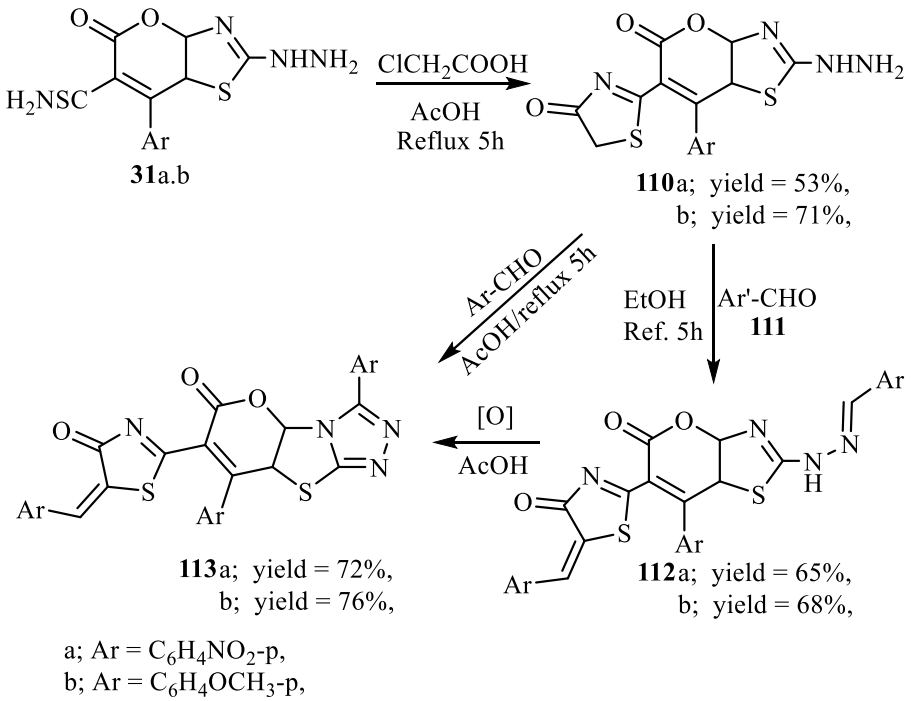
Scheme 36

Furthermore, Ghorab Et Al.[13] Reported That Thiazolo[4,5-*B*]Pyrano[2,3-*D*] Pyrimidine Derivative **109** Was Obtained By Treatment **13**a With Formic Acid Under Reflux Condition (Scheme 37).



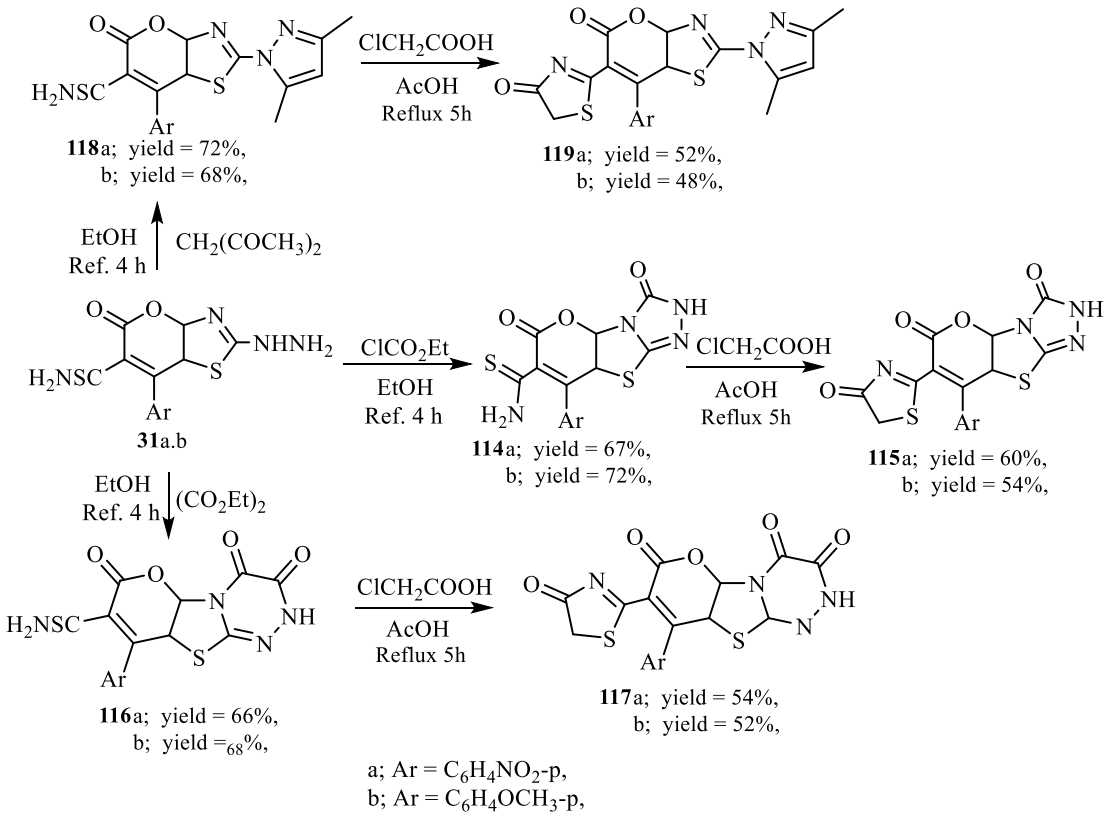
Scheme 37

5H-Pyrano[2,3-*D*]Thiazole-6-Carbothioamides **31**a,B Were Taken As The Starting Materials For The Synthesis Of Antimicrobial Agents And Their Synthetic Potential Was Demonstrated By Their Reactions With A Variety Of Chloroacids, Chloroesters, Diesters And Diketones. Thus, It Has Been Found That **31a** Reacted Via Its Thiocarboxamido Group With Chloroacetic Acid In Glacial Acetic Acid To Give The 5-Oxopyrano[2,3-*D*]Thiazole **110**a,B, Condensation Of **109** With Aromatic Aldehydes **111** In Boiling Ethanol Afforded The Corresponding 7-Aryl-2- Arylhydrazono-6-(2'-Thiazo-Lidin-4'-On-2'-Yl)-5-Oxopyrano[2,3-D]Thiazole Derivatives (**112**a,B), Respectively. When Performing The Above Reaction In Boiling Glacial Acetic Acid The Corresponding 6-Oxopyrano[2',3':4,5]Thiazolo[2,3-C]L,2,4-Triazoles **113**a,B Were Obtained. Moreover, A Solid Evidence For Structure **113**a,B Came From Their Authentication Via Reacting **112**a,B With The Appropriate Aromatic Aldehyde In Boiling Glacial Acetic Acid, Scheme 38 [19].



Scheme 38

Furthermore, Heating Of 5H-Pyrano[2,3-*D*]Thiazole-6-Carbothioamides **31**a,B With Ethyl Chloroformate In Absolute Ethanol Afforded The Corresponding 7-Thiocar-Boxamidopyrano[2',3':4,5]Thiazolo[2,3-*C*]1,2,4-Triazole **114**a,B Which Then Reacted With Chloroacetic Acid In Glacial Acetic Acid To Yield 6-Oxo-7(2'-Thiazolin-4'-On-2'-Yl)-Pyrano[2',3':4,5]Thiazolo-[2,3-*C*]L,2,4-Triazole **115**. Similarly, Reaction Of **31**a,B With Diethyl Oxalate Afforded The Corresponding 9-Aryl-8-Thiocarboxamido-3,4,7-Tri-Oxopyrano [2',3': 4,5]Thiazolo[2,3-*C*]1,2,4-Triazine Derivatives **116a**,B. The Later Was Allowed To React With Chloroacetic Acid In Glacial Acetic Acid To Yield Thiazolonylpyranothiazolo-L,2,4-Triazine Derivatives **117**a,B. Furthermore, Cyclocondensation Of **31**a,B With Acetylacetone Afforded 2-(2',4'-Dimethylp-Yrazol-L'-Yl)-5-Oxo-6-Thiocarboxamidopyrano[2,3-D]Thiazoles **118**a,B Which Then Reacted With Chloroacetic Acid In Glacial Acetic Acid To Give The Corresponding 2'-Di-Methylpyrazolyl-5-Oxo-6-Thiazolinonyl-Pyrano[2,3-*D*]Thiazoles **119**a,B Respectively ,Scheme 39 [19].

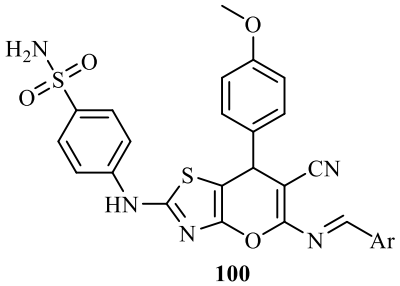


Scheme 39

Biological Activity

Anticancer Activity

Ghorab Et Al. [14] Reported That Various Shiff Bases Derivatives **100**a-K Were Evaluated For Their *In Vitro* Anticancer Activity Against Human Breast Cancer Cell Line (MCF7). Most Of The Screened Derivatives Showed Interesting Cytotoxic Activities Compared To Doxorubicin As A Reference Drug, While Compounds **100**a-D And **100**g (IC_{50}: 27.51, 10.25, 9.55, 9.39 And 9.70 µm, Respectively) Exhibited Higher Cytotoxic Activities Than The Reference Drug Doxorubicin. Also, The Ability Of The Most Five Active Compounds **100**a-D And **100**g To Enhance The Cell Killing Effect Of Γ-Radiation. The IC_{50} Values Were Decreased To 14.76, 9.11, 8.72, 8.72 And 7.55 µm, When The Cell Were Treated With A Single Dose Of Γ-Radiation A Dose Level Of 8 Gy.

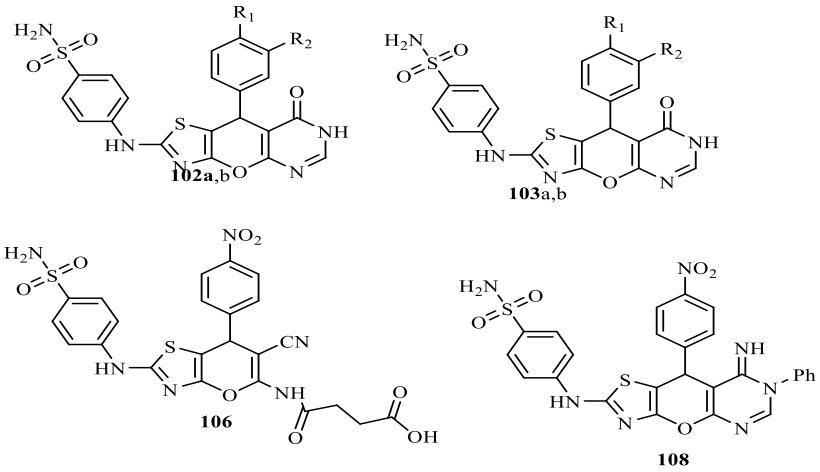


100

100a;Ar = C_6H_5, g; Ar = $C_6H_4NO_2$-4,
b; Ar = C_6H_4Cl-2, h; Ar = $C_6H_3N(CH_3)_2$-4,
c; Ar = C_6H_4Cl-4, i; Ar = $CH{=}CHC_6H_4$,
d; Ar = C_6H_4Br-3, j; Ar = C_6H_4OH-4,
e; Ar = C_6H_4F-4, k; Ar = piperonyl, ,
f; Ar = $C_6H_3Cl_2$-2,4,

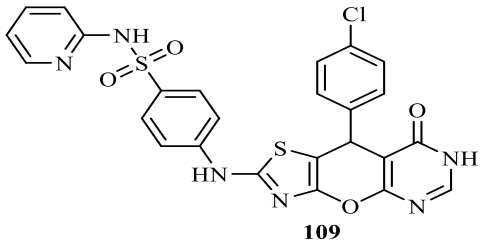
Also, All The Synthesized Compounds **101**-**108** Were Evaluated For Their *In Vitro* Anticancer Activity Against Human Liver Cancer Cell Line In Which Hcaii Is Overexpressed. It Has Been Observed That The Pyrimidine Derivatives **102**b, **103**b, And **108** Were Found To Possess Higher Potency With (IC_{50}: 32, 30, And 31 µm),

Respectively, Followed By The Oxobutanoic Acid Derivative **106** With (IC_{50} = 32 µm), Then The Pyrimidine Derivative **102**a With (IC_{50} = 36 µm) Compared With That Of Doxorubicin (IC_{50} = 32 µm). Also, The Radiosensitizing Ability Of The Promising Compounds **102**a, **103**b, **106**, And **108** Was Studied Which Showed An Increase In The Cell Killing Effect Of Γ-Radiation After Combination With Them [15].



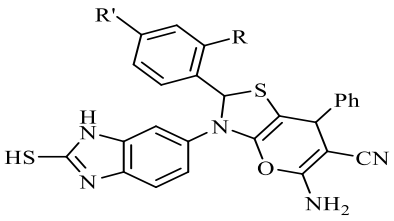
a; $R_1 = NO_2$, R_2 = H, yield = 75%,
b; $R_1 = R_2 = OCH_3$, yield = 66%,

Ghorab Et Al. [13] Reported That 4-[3H-5-(4-Chlorophenyl)-Thiazolo[4,5-*B*]-Pyrano[2,3-*D*]Pyrimidin-4-One]-N-(Pyridin-2-Yl)Benzene-Sulfonamide (**109**) Showed Highly Cytotoxic Against MCF-7 Cells With An IC_{50} Value Of 12.0 µm, Which Was Significantly Better Than Doxorubicin, The Reference Drug (IC50 = 26.1 Mm) [13].



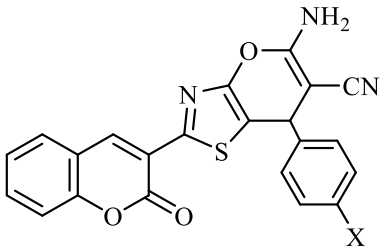
Anti-Inflammatory Activity

In 2014, Malladi, Et Al. [12] Reported That Benzimidazolylpyrano[2,3-*D*][1,3]Thiazolocarbonitriles (**10**a-J) Were Evaluated *In Vitro* Antiinflamm-Atory Activity. Compared To The Standard, Diclofenac Sodium, They Have Shown Adequate Anti-Inflammatory Activity. Among All The Tested Compounds **10**c, **10**e, **10**h And **10**j Possessing Chloro, N,N-Dimethylamine, Hydroxylbromo And Hydroxylchloro Groups As Substituents On The Benzene Ring Showed Potent Activity In The Compound **10** Series. The Compound **10**a Have Showed Moderate Activity Because It Has No Substituent On The Benzene Ring. While Other Compounds Having Weak Activity.



10a; R = R' = H,
b; R = H, R' = NO_2,
c; R = H, R' = Cl,
d; R = H, R' = OCH_3,
e; R = H, R' = $N(CH_3)_2$,
f; R = H, R' = Br,
g; R = OH, R' = H,
h; R = OH, R' = Br,
i; R = OH, R' = OCH_3,
j; R = OH, R' = Cl,

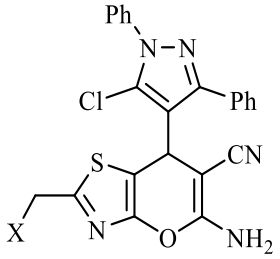
Also, Mohareb Et Al [35] Reported That 7H-Pyrano[2,3-*D*]Thiazole-6-Carbonitriles **82**a-C Showed Marked Anti-Inflammatory Activity Compared To The Standard Drugs Ibuprofen (20 Mg/Kg Body Weight), Mefenamic Acid (100 Mg/Kg Body Weight).



82a; X = H,
b; X = Cl,
c; X = OCH_3,

Molluscicidal Activity

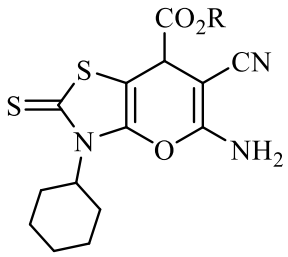
The Toxicity Of Compounds Pyrano[2,3-*D*]Thiazole Derivatives **36**a-C To Biomphalaria Alexandrina Snails Was Evaluated And The Half Lethal Dose (LC_{50}) And The Sublethal Dose (LC_{90}) In Ppm [µm] For Each Compound Was Determined. An Insight Inspection Of The Results, All Compounds Have Generally Moderate To Low Effect On The Snails [20].



36a; X = CN,
b; X = CO_2Et,
c; X = $CONH_2$,

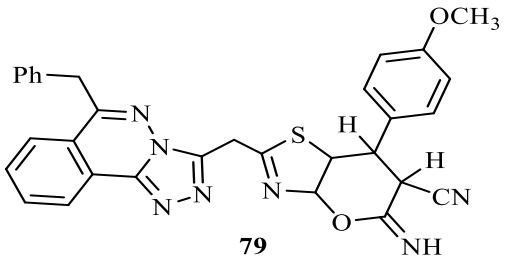
Antimicrobial Activity

Arafa, Et Al. [31] Reported That Pyrano[2,3-*D*]Thiazoles **69**a,B Showed Good Antibacterial Activity Compared To The Parent Drugs. Compounds **69**a,B Were Screened For Their Antibacterial Activity Against Nine Human, Animal And Plant Pathogenic Gram-Positive And Gram-Negative Bacteria Using The Agar Well Diffusion Method.



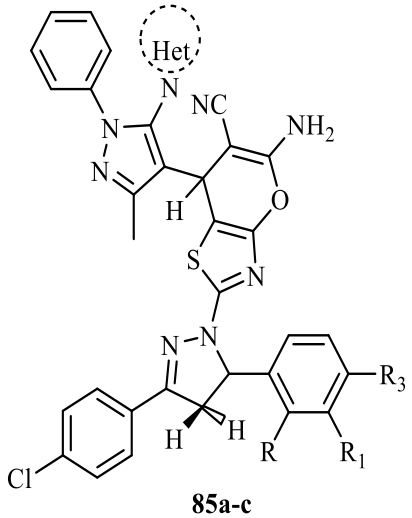
69a; R = Me
b; R = Et

El-Wahab Et Al. [34] Reported That 5H-Pyrano[2,3-*D*]Thiazole-6-Carbonitrile **79** Exhibited Good Activity Against *B. Cereus* And *B. Subtilis* Compared To Standard Drug Ampicillin.



79

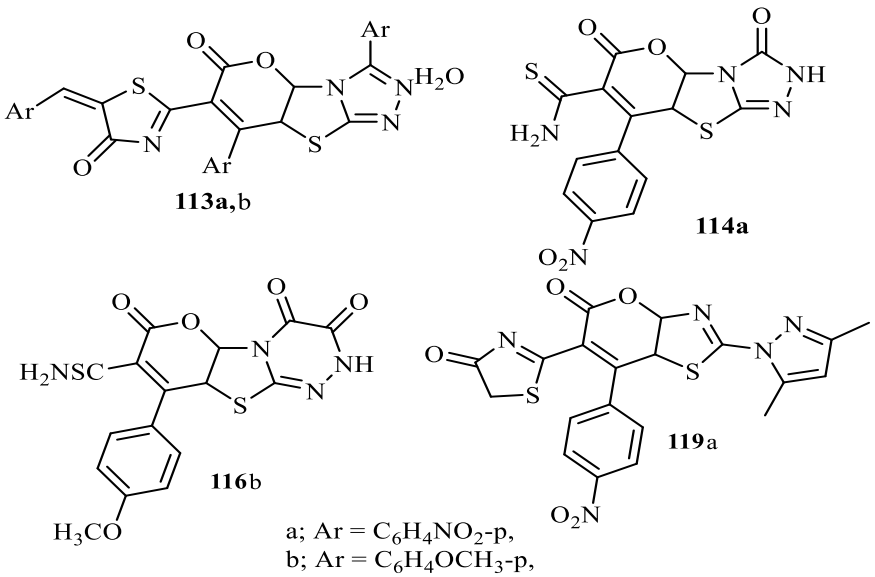
Also, Pyrano[2,3-*D*]Thiazoles **85** Were Screened For Their Preliminary *In Vitro* Antimicrobial Activity Against A Panel Of Pathogenic Strains. It Was Observed That Most Of The Compounds Illustrated Excellent Activity Against Gram Positive Bacteria *B*. *Subtilis* And *C*. *Tetani* As Compared To Ampicillin. Compounds **85**a, **85**d, **85**f And **85**k Were Found To Be More Potent (62.5 µg Ml^{-1}) Compared To Ampicillin (250 µg Ml^{-1}) And Norfloxacin (100 µg Ml^{-1}). While Compounds **85**c, **85**g, **85**j, **85**m, **85**n And **85**l Showed Equivalent Potency Against *B*. *Subtilis* To That Of Norfloxacin And Ampicillin Respectively. Also, They Found That *In Vitro* Antifungal Screening Data For Compounds **85**a, **85**h, 85m And **85**o Were Found To Be Equally Potent Against *C*. *Albicans* As Compared To Griseofulvin. Against *A*. *Niger*, Compounds **85**d And **85**b I.E. 100 µg Ml^{-1}were Found To Be Equally Active As Compared To Nystatin And Griseofulvin [36].



85a-c

a;Triazole
b;4-Methylimidazole
c;Imidazole
d;Benzimidazole
e;Benzotriazole
f;Triazole
g;4-Methylimidazole
h;Imidazole
i;Benzimidazole
j;Benzotriazole
k;Triazole
l;4-Methylimidazole
m;Imidazole
n;Benzimidazole
o;Benzotriazole

Moreover, Pyrano[2,3-*D*]Thiazoles **114**-**119** Were Evaluated For Their *In Vitro* Antimicrobial Activity Against Gram+ Gram- Bacteria, Yeast And Fungi Compared With NA Using The Cup-Plate Method. Compounds **113**b, **116**b And **119**b Showed Strong Activity Of Against *Bacillus Subtilis* And *Staphylococcus Aureus*. Compounds **113**a And **114**a Showed A Moderate Activity Against Aspergillus Niger While The Rest Of The Compounds Showed Only Slight Activity Or Inactivity Against The Tested Organisms [19].



Conclusion

The Data Considered In This Review Evident That Many Of Pyranothiazoles And Fused Pyranothiazoles Possess A Wide Range Of Pharmacological Properties And A 'Drug Candidate' From These Heterocycles Can Be Developed.

References

1. Vara Prasad, V. N.; Tummino, P. J.; Fergusan, D.; Saunders, J.; Vander, R.; Mc Quade, J. J.; Heldsinger, A.; Reyner, E. L.; Stewart, B. H.; Guttendrof, R. J.; Para, K. S.; Lunney, E. A.; Gracheck, S. J.; Oomagala, J. M. *Biochem. Biophy. Research Commun*., **1996**, 221, 815-820.
2. Mizuno, T.; *Int. J. Med. Mushr*., **1999**, 1, 9-29.
3. Sharon, A.; Pratap, R.; Vatsyayan, R.; Maulik, P. R.; Roy, U.; Goel, A.; Ram, V. J. *Bioorg. Med. Chem. Lett*., **2005**, 15, 3356-3360.
4. Haviv, F.; Denet, R. W.; Carter, G. W. *J. Med. Chem*., **1988**, 31, 1719-1728.
5. Tsuji, K.; Ishikawa, H. *Med. Chem. Lett*., **1994**, 4, 1601-1606.
6. Bell, F. W.; Hoberg, M.; Zhou, X-X.; *J. Med. Chem*., **1995**, 38, 4929-4936.
7. Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem*., **2002**, 37, 511-517.
8. Holla, B. S.; Poojary, K. N.; Kalluraya, B.; Gowda, P.V. *Il Farmaco* **1996**, 51, 785-792.
9. Cantin, L.; Choi, S.; Clark, R. B.; Hentemann, M. F.; Ma, X. Rudolph, J. *PCT Int. Appl. WO*. **2004**, *58*, 174; *Chem. Abstr*. **2004**, *141*, 123483x.
10. Ismail, N. A.; Khalifa, F. A.; Fekry, R. M.; Abdel Azim, Y. N. *Phosphorus, Sulfur, And Silicon*, **1992**, 66, 29-35.
11. Sherief, S. M. *Monatshefte Fur Chemie*,, **1996**, 127, 557-568.
12. Malladi, S. R.; Anisetti, R.; Raoi, P. R. *Indian J. Pharm.Sci*., **2014**, 76, 510-518.
13. Ghorab, M. M. ; Ragab, F. A.; Heiba, H. I.; Agha, H. M.; Nissan, Y. M. *Arch. Pharm. Res*., **2012**, 35, 59-68.
14. Ghorab, M. M.; Shaaban, M. A.; Refaat, H. M. ; Heiba, H. I.; Ibrahim, S. S. *Europ. J. Med. Chem*., **2012**, 53, 403-407.
15. Abou El Ella, D. A.; Ghorab, M. M.; Heiba, H. I.; Soliman, A. M.
16. *Med. Chem. Res*., **2012**, 21, 2395-2407.

17. Mohareb, R. M.; Zohdi, H. F.; Wardakhan, W. W. *Monatshefte Fur Chemie.,* **1995**, 126, 1391-1400.
18. Abdelall, M. M. *American J. Heterocyclic Chem*., **2017**; 3, 8-18.
19. Eldin, S. M. J. Chem. Research (S), **1998**, 12, 730-731.
20. Eldin, S. M. *Z. Naturforsch*., **1999**, 54b, 1589-1597.
21. Abdelrazek, F. M.; Michael, F. A.; Mohamed, A. E. *Arch. Pharm. Chem. Life Sci*., **2006**, 339, 305-312.
22. Sun, H. S.; Wang, J. Q.; Gu, Da. W.; Guo, Ch.;Shen, L. J. *I.R.J.P.A.C*, **2016**, 11(4): 1-8.
23. AL-Hazimi, H.M.A.; Al-Alshaikh, M.A. *J. Saudi Chem. Soc*., **2010** 14, 373-382.
24. El-Hag Ali, G. A. M.; Abd El-Rahman, M. T.; Helal, M. H. M.; El-Gaby, M. S. A. *Phosph., Sulfur, And Silicon*, **2008**, 183, 3023-3036.
25. Halawa, A. H. *World J. Organic Chem*., **2014**, 2(1), 9-17.
26. Manhi, F. M.; Mahmoud, M. R. *Heteroatom Chem.*, **2005**, 16, 121-131.
27. Salem, M. A. Croat. Chem. Acta, **2017**, 90(1), 7-15.
28. Yarovenko, V. N. ; Nikitina, A. S.; Zavarzin, I. V.; Krayushkin, M. M.; Kovalenk, L. V. *Russian J. Organic Chem.,* **2007**, 43 (9), 1364-1370.
29. Cui, L.; Wang, Y.; Zhou, Zh. *Tetrahedron: Asymm*., **2016**, 27, 1056-1061.
30. Wang, C.; Gao, Z.; Zhou, L.; Yuan, C.; Sun, Z.; Xiao, Y.; Guo, H. *Org. Lett.*, **2016**, 18 (14), 3418-3421.
31. Henry, C. E.; Xu, Q.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, 136, 11890-11893.
32. Arafa, W. A. A. ; Fareed, M. F. ; Rabeh, S. A.; Shaker, R. M. *Phosph., Sulfur, And Silicon And The Related Elem*., **2016**, 191(8), 1129-1136.
33. Metwally, N. H. *Journal Of Sulfur Chem.,* **2007**, 28(3), 275-284.
34. Yarovenko, V. N.; Nikitina, A. S.; Zayakin, E. S.; Zavarzin, I. V.; Krayushkin, M. M.; Kovalenk, L. V. ARKIVOC., **2008** (Iv) 103-111.
35. Abd El-Wahab, A. H. F.; Mohamed, H. M.; El-Agrody, A. M.; El-Nassag, M. A.; Bedair, A. H. *European J. Chem*., **2013**, 4 (1), 10-19.
36. Mohareb, R. M.; Al-Omran, F.; Abdelaziz, M. A. Ibrahim, R. A. *Acta Chim. Slov***., 2017**, 64, 349-364.
37. Kalaria, P. N.; Satasia, S. P.; Rava, D. K. *RSC Adv*., **2014**, 4, 32353-32362.
38. Shelke, R.N.; Pansare, D.N.; Pawar, C.D.; Shinde, D.B.; Thore, S.N.; Pawar, R.P.; Bembalkar, S.R. *Research & Reviews: J. Chemistry*, **2016**, 5, 29-36.
39. Yadav, L. S.; Yadav, B. S.; Rai, V. K. *J. Heterocyclic Chem.,* **2008**, 45, 1315-1319.
40. Chakravarty, A. K.; Singh, P.; Kumari, K. *International J. Current Advanced Res.,* **2016**, 5, 559-563.
41. Sachdeva, H.; Dwivedi, D.; Bhattacharjee, R. R.; Khaturia, S.; Saroj, R. *J. Chem*., **2013**, 2013,1-10.
42. Yadav, L. S.; Singh, A. *Synthesis* **2003**, 15, 2395-2399.