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Review

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Recent developments in the chemistry of 1*H*-indole-3-carbohydrazides and their role in the synthesis of 3-hetaryl indoles of biological importance

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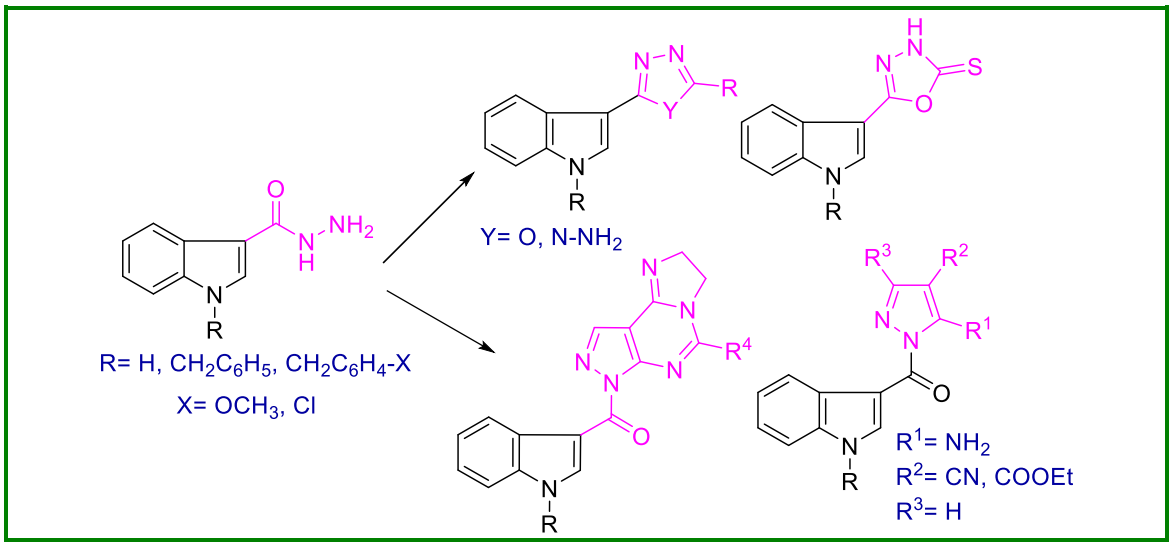
Abstract

1*H*-indole-3-carbohydrazide is a significant class of heterocyclic compounds with several applications in the field of medicinal chemistry. In this review, the synthetic methods and different attempts made in the synthesizing of indole-3-carbohydrazide from various starting materials over the last twenty years are summarized. Additionally, this review focuses on the latest advancements in the different reactions of indole-3-carbohydrazide to produce a variety of nucleuses on C-3 of the indole moiety



Keywords:1*H*-Indole-3-carbohydrazide, indolyl-1,3,4-oxadiazoles, indolyl-1,2,4-triazoles, indolyl-1,2,4-thiazoles

Table of Contents

1. Introduction

Indole-containing natural and synthetic products,[1] including reserpine, vincristine, indolmicine, mitomycine, pindolol, dolasetrone mesylate, indomethacine, or sumatriptan, are used to treat a variety of illnesses, the indole structure represents a highly relevant heterocyclic system. More precisely, according to a number of investigations, indole-2-carbohydrazides and their related compounds have anti-mycobacterial activity,[2] antidepressant,[3] as multifunction neurodegenerative agent,[4] and antmicrobial.[5] According to reports, several 3-substituted indole-based heterocycles have been utilized as biological and pharmacological potential.[6] Additionally, it has been demonstrated that by introducing heterocyclic moieties, such as isothiazoles, to position 3 of the indole nucleus, these biological activities can be enhanced as potent anti-diabetic and anti-alzheimer's medicines.[7] However, a class of heterocycles known as 1,3,4-oxadiazoles has garnered a lot of attention in medicinal chemistry because of its several biological effects, which include antibacterial, antifungal, anti-inflammatory, and antihypertensive action.[8-12] The 1,3,4-oxadiazole system and its derivatives are a significant bio-active class of heterocycles, as evidenced by their extensive use as a scaffold in medicinal chemistry.[8] Their favorable metabolic profile and hydrogen bonding capabilities are also responsible for this. In particular, commercially available antihypertensive drugs like tiodazosin and nesapidil, as well as antibiotics like furamizole, include the oxadiazole nucleus.[13-15] In addition, the anti-angiogenesis and anti-*HIV* integrase medications that contain 1,3,4-oxadiazole are also advantageous,[15, 16] They are also used to combat AIDS-related infections[17] and have antibacterial.[18] Furthermore, 3-substitued indole derivatives showed to possess anticonvulsant,[19] antimicrobial,[20-23] anti-proliferative agents,[24] antioxidant[25] and anticancer properties.[26-29] They are also used as insecticides, fungicides, and herbicides in agriculture.[30] The indole-3-carbohydrizide was used in the synthesis of some indole derivatives containing 1,3,4-oxadiazole, 1,2,4-triazole, imidazole and pyrazole moieties (**I**, **II**, **III** and **IV**).[31-34] Antifungal properties were effectively demonstrated by two series of pimprinine derivatives, **A** and **B**, which contained 1,3,4-oxadiazole-5-thioether moieties **C** and **D**.[35] Combining

the indole nucleus with the triazole and pyrazole or oxadiazole moiety may enhance the biological activities. Due to the 1*H*-indole-3-carbohydrazide is a versatile molecule in the synthesis of intriguing bioactive candidates and in keeping with our earlier publications on the chemistry of pyridazino[4,5-*b*]indole.[36, 37] We have chosen to discuss the recent developments in the chemistry of 1*H*-indole-3-carbohydrazide and their role in the synthesis of 3-hetaryl indoles of biological importance.

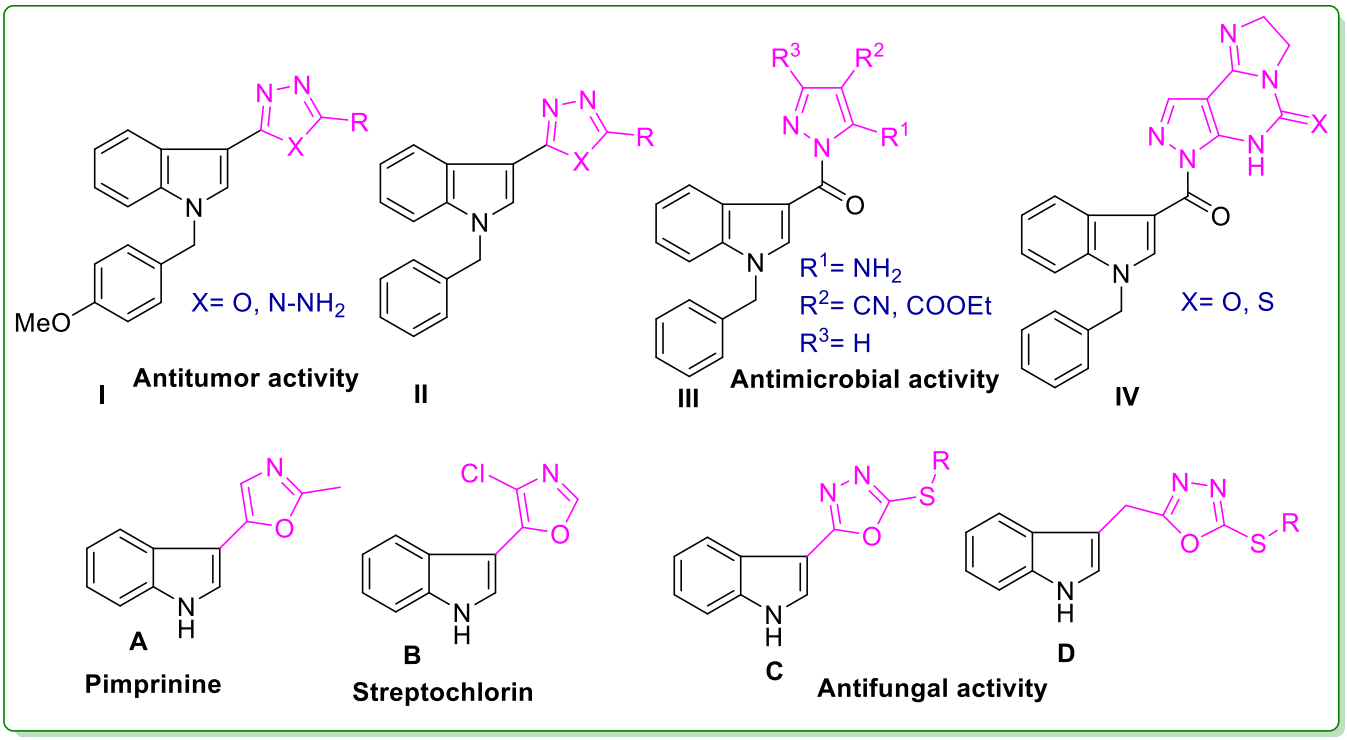


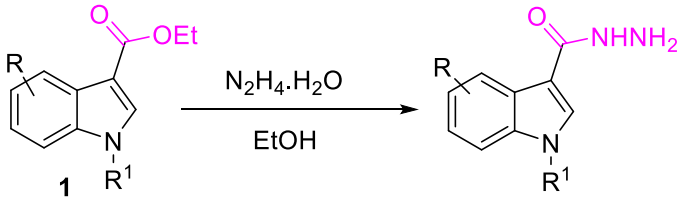
Figure 1. Some selective biologically active 3-substitued indoles

2. Synthesis of 1*H*-Indole-3-carbohydrazide

Indoles-based compounds are a prevalent class of natural and synthetic compounds found to be in abundance in biologically active compounds such as agrochemicals, medicines, and alkaloids. 3-Substituted indoles[38] are an important framework of many drugs, agricultural chemicals, functional materials, and bioactive compounds.

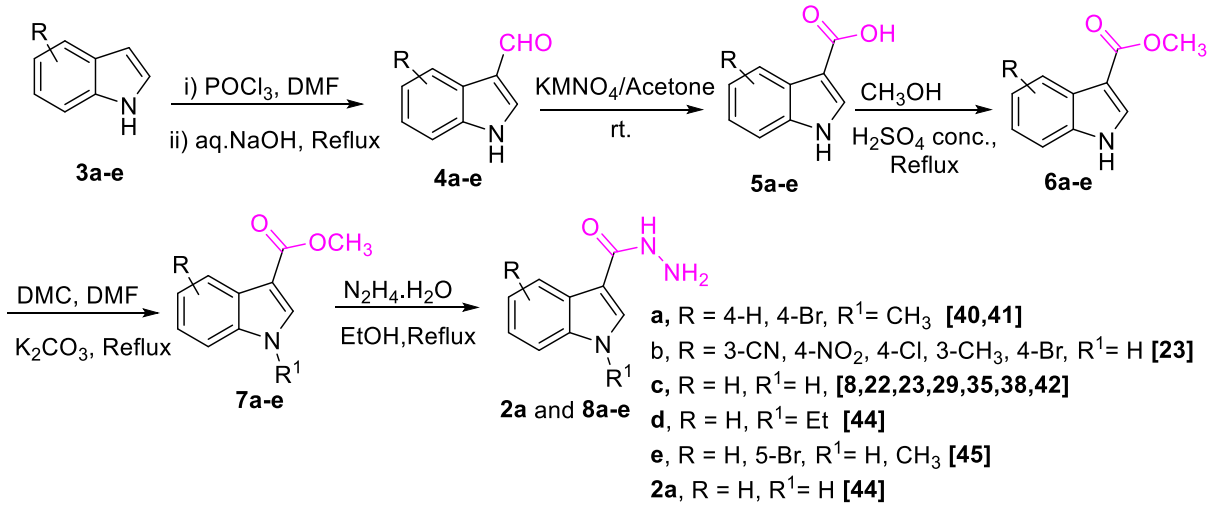
2.1. Synthesis of 2-unsubstitued-1*H*-indole-3-carbohydrazide derivatives

It was mentioned that reaction of compound **1** with hydrazine monohydrate 99% in ethanol gave the carbohydrazide derivative **2a**[39] (Scheme 1).



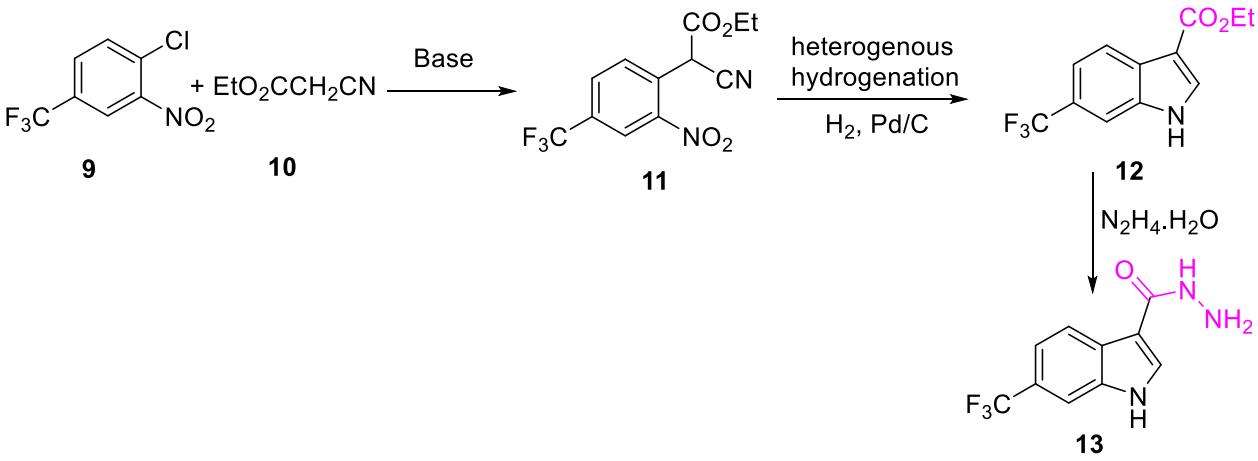
Scheme 1. Synthesis of 1*H*-indole-3-carbohydrazide **2.**

It was described that[40-43] the indole-3-carboxaldehydes **4a-e** were prepared by Vilsmeier-Haack reaction[44] of indole and 5-substituted indole **3a-e**. Oxidation of aldehyde derivatives with potassium permanganate and acetone yielded corresponding carboxylic acid **5a-e** derivatives. The latter derivatives were subjected to simple esterification with conc. H_2SO_4 as a dehydrating agent furnished the corresponding esters **6a-e**.[35, 45] Furthermore, the ring nitrogen was protected via methylation using dimethyl carbonate and K_2CO_3 followed by reflux in DMF for 4 h gave the compounds **7a-e**. Treatment of the ester **7a-e** with ethanolic hydrazine hydrate under reflux resulted in the formation of the carbohydrazide derivatives **2a** and **8a** (Scheme 2).[8, 22, 23, 29, 35, 39, 43, 45, 46]



Scheme 2. Synthesis of 5-substituted-1-methyl-1*H*-indole-3-carbohydrazide **8a-e**.

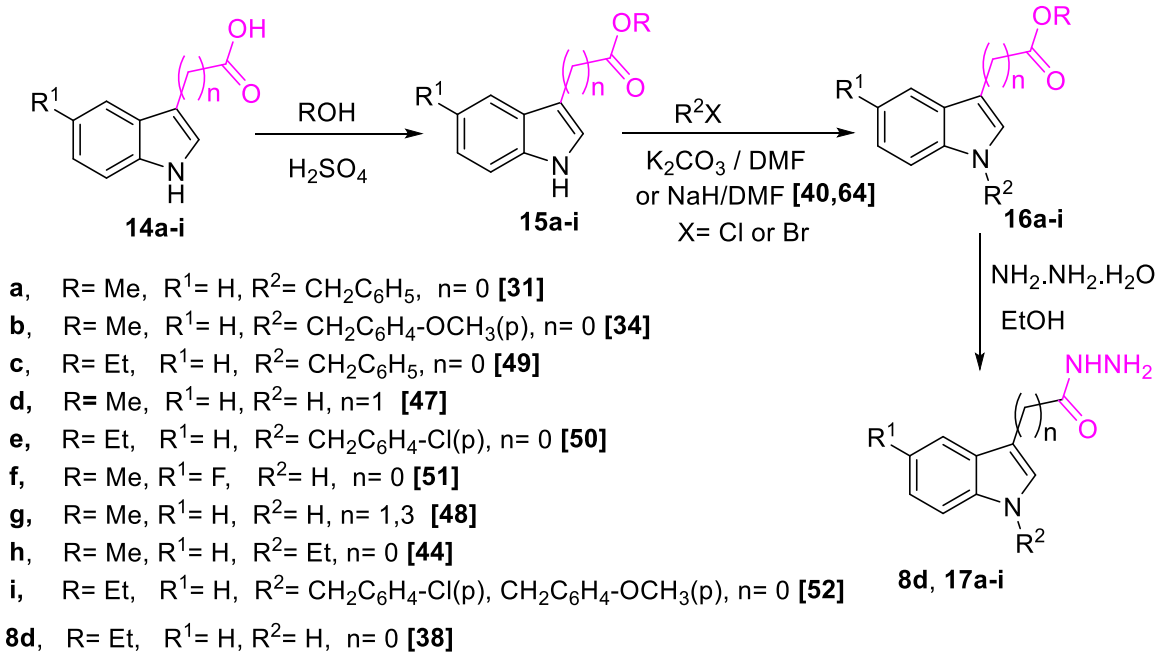
In 2017, Baumann M. *et al* suggested that[47] the reaction of 2-chloronitrobenzene **9** with ethyl cyanoacetate **10** as the nucleophile in a base resulted the product **11.** Reductive cyclisation of compound **11** using heterogeneous hydrogenation produced the indole product **12**. Treatment of the ester **12** with hydrazine hydrate gave the corresponding hydrazide **13** (Scheme 3).



Scheme 3. Synthesis of 6-(trifluoromethyl)-1*H*-indole-3-carbohydrazide **13**.

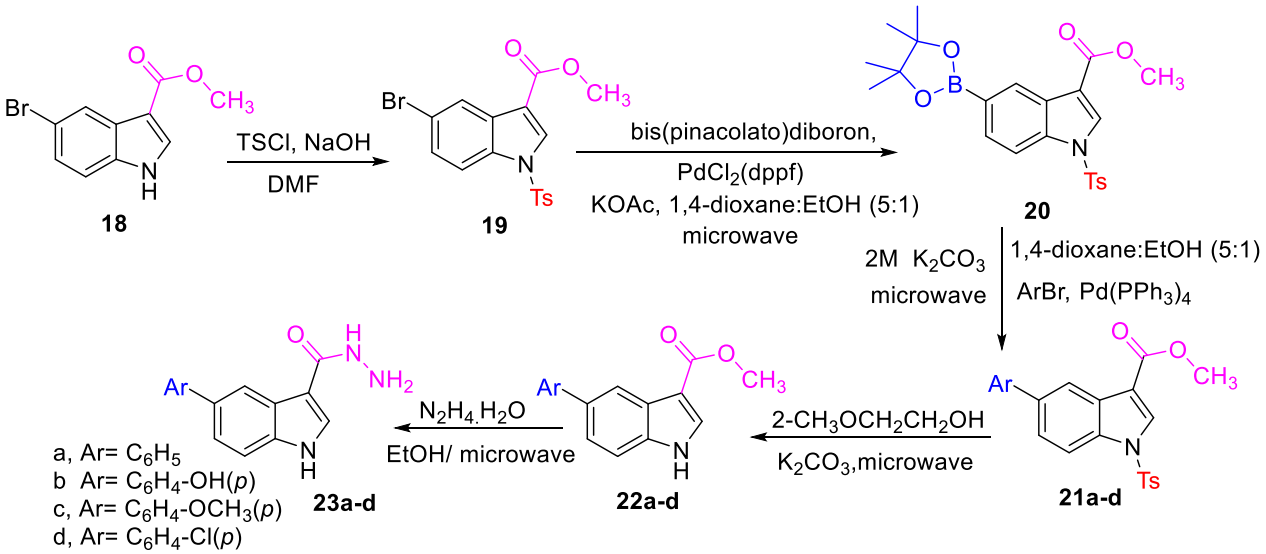
It was described that [48, 49] esterification of indole-3-acetic acid or indole-3-butanoic acid **14** in absolute methanol using conc. H_2SO_4 as a catalyst yielded the ester compounds **15a-i.** Alkylation of the 1*H*-indol-3-

carboxylate **15a-l** with aryl halide or alkyl bromide in DMF and anhydrous potassium carbonate gave the corresponding ethyl 1-substituted-1*H*-indole-3-carboxylate **16a-i**. Treatment of the latter compound **16a-i** with hydrazine hydrate afforded the 1-substituted-1*H*-indole-3-carbohydrazide and **17a-c,e-l** (Scheme 4).[31, 34, 39, 45, 48-53]



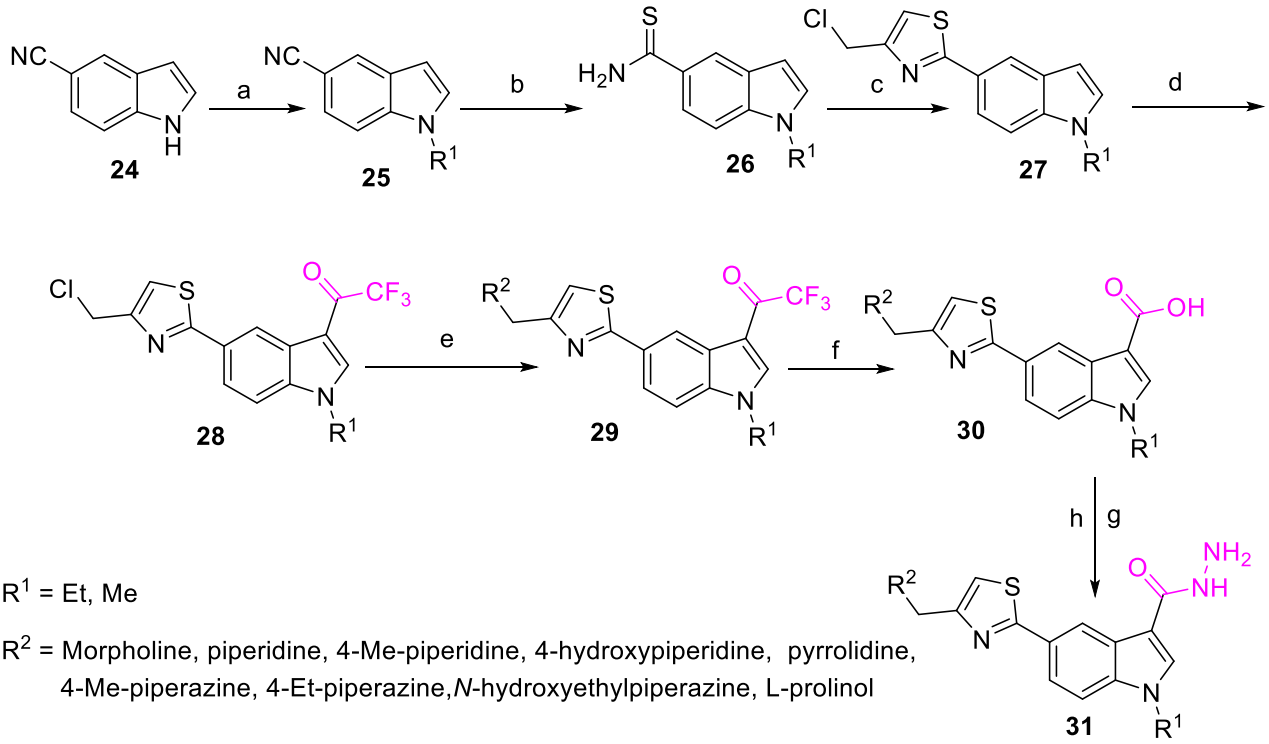
Scheme 4. Synthesis of 1*H*-indole-3-carbohydrazide derivatives **17**.

It was found that[54] interaction of the ester **18** with tosyl chloride in presence of sodium hydride gave the compound **19**. The latter compound was allowed to palladium-catalyzed borylation to give compound **20** which was reacted with aryl halide via Suzuki coupling reaction giving the corresponding derivatives **21**. Deprotection of tosyl group was performed in the presence of the base to afford compound **22**. Hydrazinolysis of compound **22** with hydrazine hydrate afforded the corresponding hydrazide **23** (Scheme 5).



Scheme 5. Synthesis of 5-substistued-1*H*-indole-3-carbohydrazide derivatives **23**.

Lei H. *et al* mentioned that[55] the reaction of indole-5-carbonitrile **24** with alkyl iodide afforded the corresponding **25**. Treatment of **25** with NaHS in the presence of $MgCl_2 \cdot 6H_2O$ as catalyst gave the thioamide derivative **26**.[56] Treatment of **26** with 1,3-dichloroacetone furnished the cyclized thiazole product **27**. Reaction of latter compound **27** with trifluoroacetic anhydride in DMF gave compound **28** with the chloromethyl unchanged.[57] Interaction between **28** and various amines in a mixture of K_2CO_3/MeCN yielded compound **29**. Subsequently, hydrolysis of the latter compound **29** with 6 M NaOH under reflux[58] led to the formation of the corresponding acid derivatives **30**. Esterification reaction followed by a sequential hydrazinolysis of compounds **30** gave rise to the acyl hydrazine products **31** (Scheme 6).



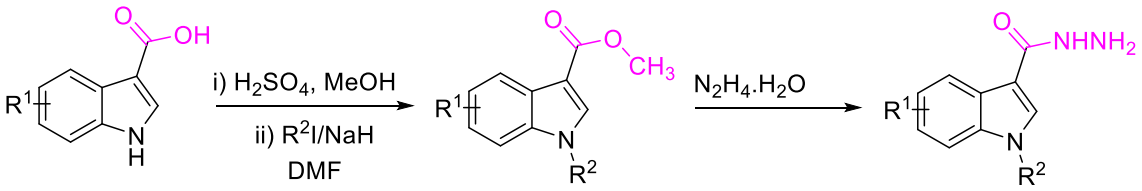
R^1 = Et, Me

R^2 = Morpholine, piperidine, 4-Me-piperidine, 4-hydroxypiperidine, pyrrolidine, 4-Me-piperazine, 4-Et-piperazine, *N*-hydroxyethylpiperazine, L-prolinol

a) MeI or EtI, DMF, 25 ^{0}C; b) NaHS, $MgCl_2.6H_2O$, DMF, 25 ^{0}C, 3h; c) 1,3-dichloropropan-2-one, toluene, reflux, 2.5 h.; d) $(CF_3CO)_2O$, DMF, 55 ^{0}C, 1.5h.; e) amine, K_2CO_3, MeCN, 25 ^{0}C, 2h.; f) 6 N NaOH (aq), 100 ^{0}C, 2h.; g) MeOH, H_2SO_4, 25 ^{0}C, reflux, 2h.; h) $N_2H_4.H_2O$, EtOH, reflux, 2h.

Scheme 6. Synthesis of 5-substistued-1*H*-indole-3-carbohydrazide **31**.

Esterification[59] of indole-3-carboxylic acid **5a** with methanol in the presence of concentrated sulfuric acid at refluxing temperature produce a compound **7d**. Indole-3-carboxylic acid derivatives **32a-h** were methylated by iodomethane using NaH as a base in dry DMF to obtain intermediates **33a-h**. Reaction of **7d** and **33a-h** with hydrazine hydrate afforded intermediates **2a**, **8d** and **34b-h** (Scheme 7).



5d, 32a-h

5d, R^1= H

7d, 33a-h

7d, R^1= H, R^2= Et

2a, 8d, 34b-h

2a, R^1= H, R^2= H

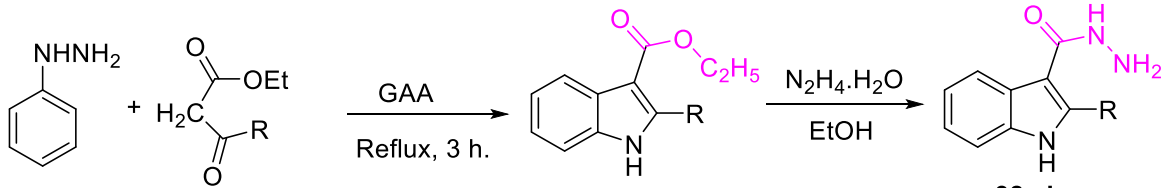
8d, R^1= H, R^2= Et

Cd.	R^1, R^2	Ref	Cd.	R^1, R^2	Ref
32a, 33a, 2a	R^1= H, R^2= H	58	32b, 33b, 34b	R^1= 5-F, R^2= Me	58
32c, 33c, 34c	R^1= 6-F, R^2= Me	58	32d, 33d, 34d	R^1= 5-Cl, R^2= Me	58
32e, 33e, 34e	R^1= 6-Cl, R^2= Me	58	32f, 33f, 34f	R^1= 5-Br, R^2= Me	58
32g, 33g, 34g	R^1= 6-Br, R^2= Me	58	32b, 33b, 34h	R^1= 5-OMe, R^2= Me	58

Scheme 7. Synthesis of the 1*H*-indol-3-carbohydrazides **8d** and **34b-h**.

2.2. Synthesis of 2-methyl (trifluoromethyl)-1*H*-indole-3-carbohydrazide derivatives

It was reported that[60-62] the reaction of phenylhydrazine **35** with ethyl 3-oxobutanoate and/or 4,4,4-trifluoro-3-oxobutanoate **36a,b** in glacial acetic acid (Fischer indole synthesis) under reflux afforded the corresponding ethyl 2-methyl (trifluoromethyl)-1*H*-indole-3-carboxylate (**37a,b**). Treatment of ester **37a,b** with hydrazine hydrate gave the 2-methyl (trifluoromethyl)-1*H*-indole- 3-carbohydrazide (**38a,b**) (Scheme 8).



35

36a,b

37a,b

38a,b

a, R= CH_3 **[59,60]**

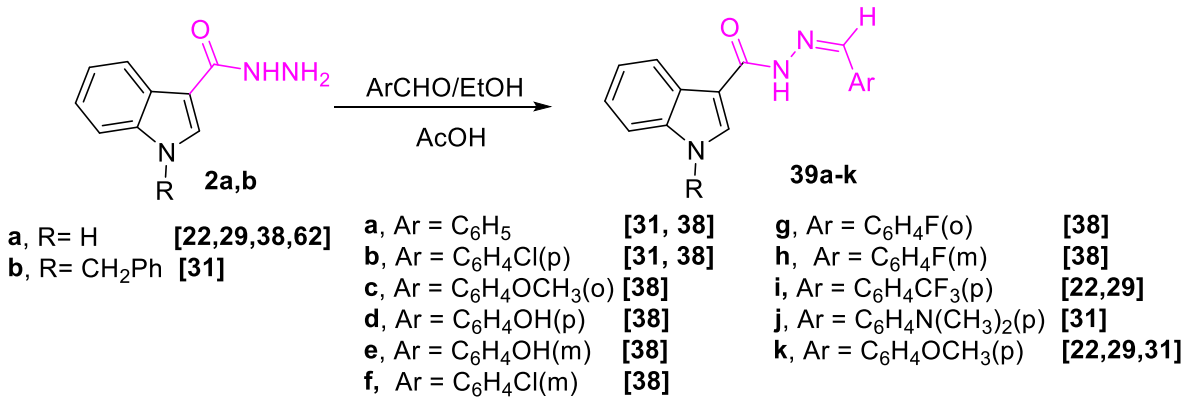
b, R= CF_3 **[61]**

Scheme 8. Synthesis of 2-substituted-1*H*-indole-3-carbohydrazide **38a,b.**

3. Reactions of 1*H*-Indole-3-carbohydrazide

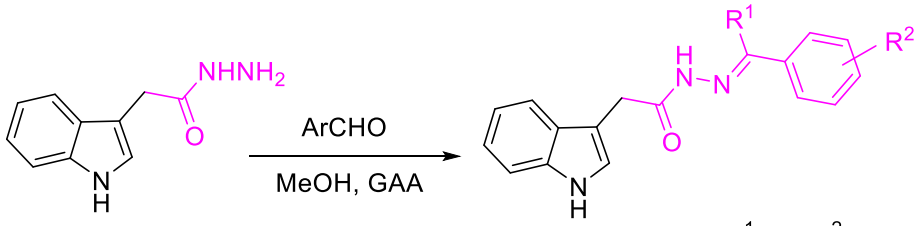
3.1. Synthesis of *N*'-arylilidene-1*H*-indole-3-carbohydrazide derivatives

Condensation[22, 29, 31, 39, 63] of the 3-indolecarbohydrazide **2a,b** with aromatic aldehydes in ethanol and glacial acetic acid afforded the corresponding arylidene derivatives **39a-k** (Scheme 9).



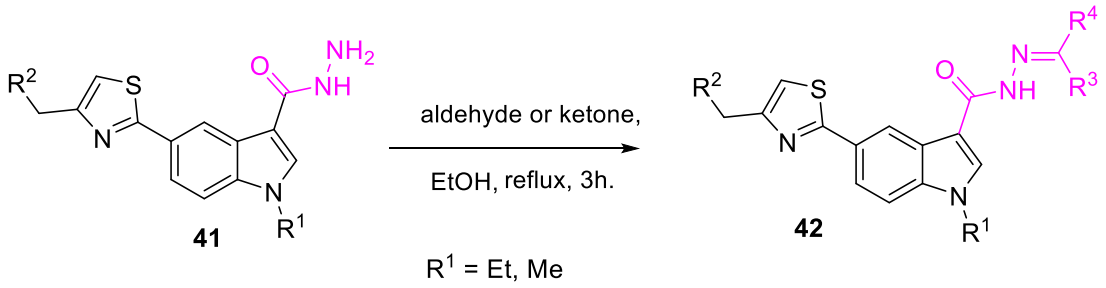
Scheme 9. Synthesis of (Z)-*N'*-(arylidene)-1*H*-indole-3-carbohydrazide **39a-k.**

Yar M. *et al* reported that[48] the treatment of the hydrazide derivative **17d** with selected aldehydes and ketones in methanol in the presence of glacial acetic acid afforded the corresponding Schiff base derivatives **40a-g** (Scheme 10).



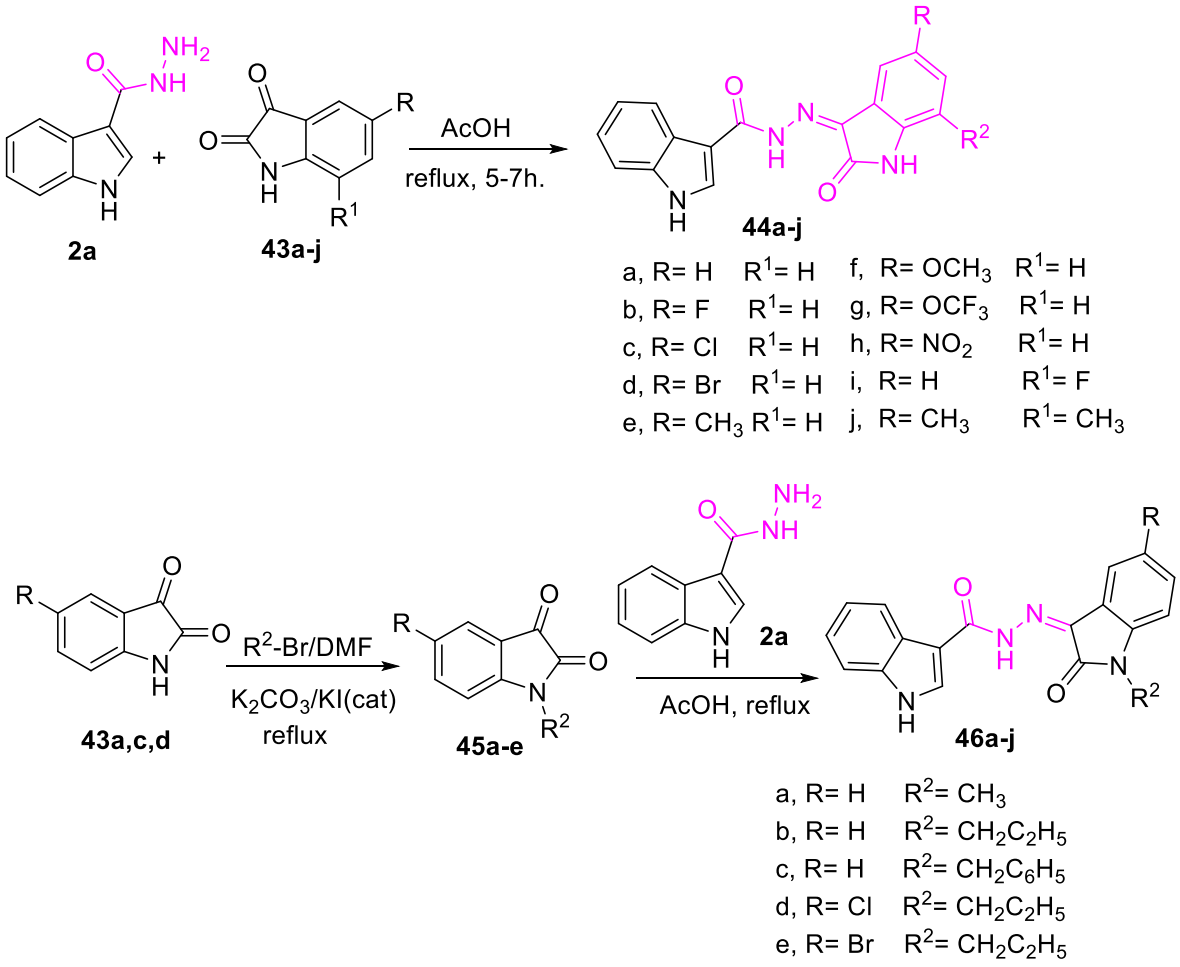
Scheme 10. Synthesis of 3-indolyl -Schiff base derivatives **40a-g.**

In 2020, Lei H. *et al* mentioned that[55] the interaction of hydrazide derivatives **41** with various aldehydes or ketones in ethanol furnished the compounds **42** (Scheme 11).



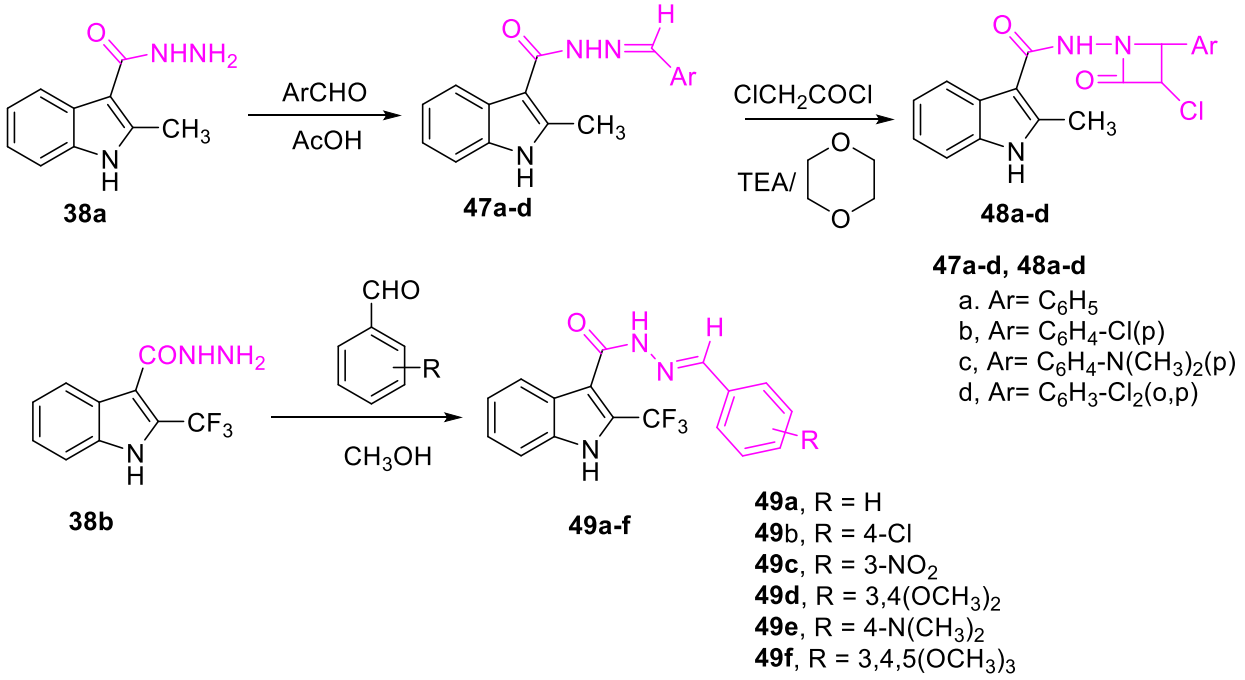
Scheme 11. Synthesis of 3-indolyl-Schiff base derivatives **42.**

Eldehna, W. M. *et al* suggested that[40] the 1*H*-indole-3-carbohydrazide **2a** was condensed with different isatin derivatives **43a-j** in glacial acetic acid to give the 2-oxindolin-3-ylidene-indole-3-carbohydrazide **44a-j**. On the other hand, three isatins **43a, 43c** and **43d** were alkylated with methyl iodide, propyl bromide and benzyl bromide in DMF with the presence of K_2CO_3 and catalytic amount of KI to give the *N*-substituted isatin derivatives **45a-e**, which heated under reflux with the carbohydrazide **2a** in acetic acid to furnish the corresponding **46a-e** (Scheme 12).



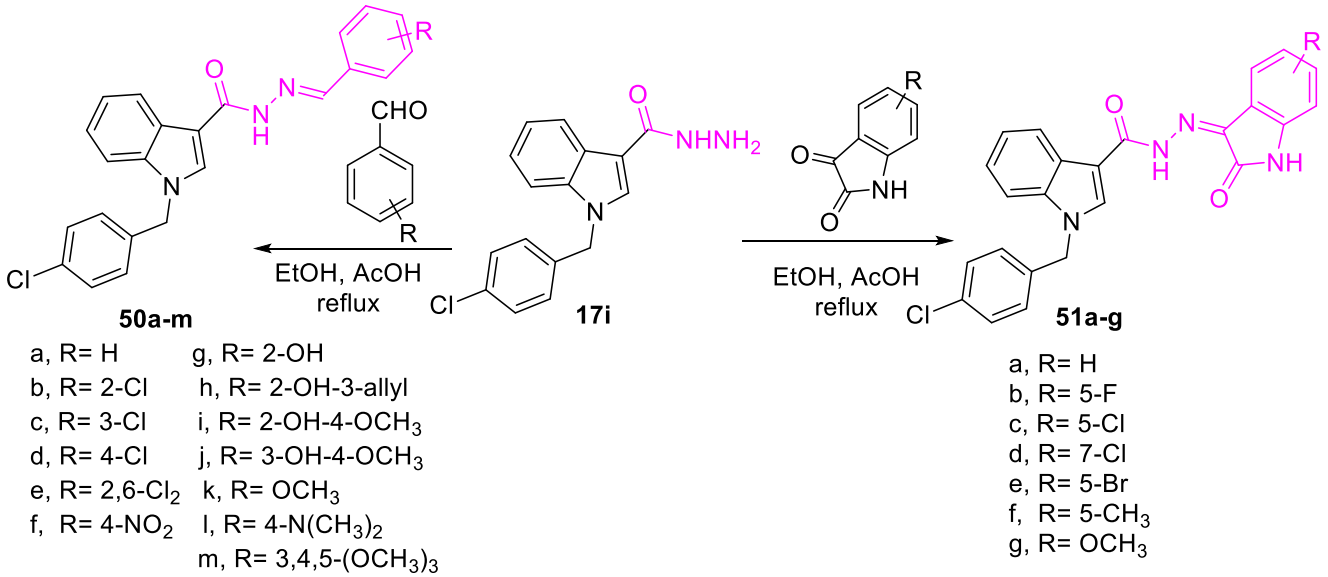
Scheme 12. Synthesis of *N*-substituted -3-ylidene-indole-3-carbohydrazide **46a-e.**

It was reported that[60] the condensation of 2-methyl-1*H*-indole-3-carbohydrazide **38a** and substituted benzaldehyde gave (*Z*)-*N*'-benzylidene-2-methyl-1*H*-indole-3-carbohydrazide derivatives **47a-d**. The addition of triethylamine in dry 1,4-dioxane and chloroacetyl chloride gave *N*-(3- chloro-2-oxo-4-substituted- azetidine-1-yl)2-methyl-1*H*-indole-3-carboxamide derivatives **48a-d**. Similarly, condensation of indole-3-carbohydrazide **38b** with aromatic aldehydes in methanol led to the formation of Schiff's bases **59a-f** [62] (Scheme 13).



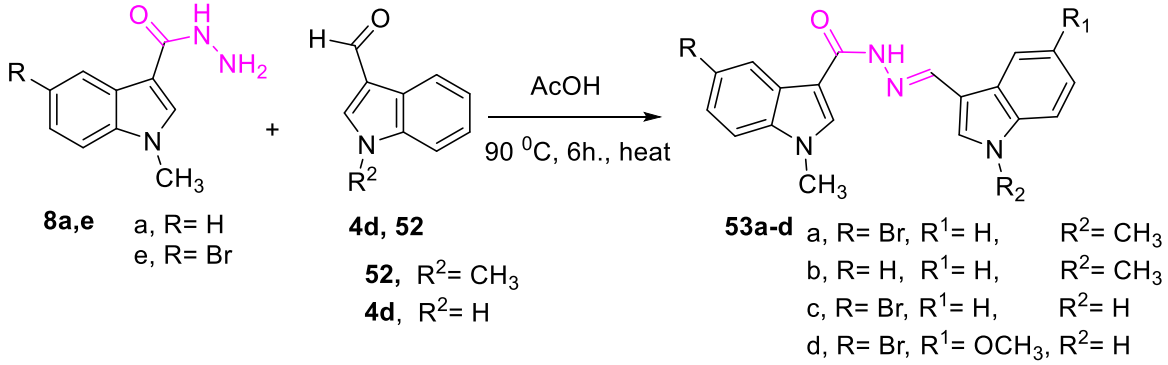
Scheme 13. Synthesis of *N*-substituted -3-ylidene-indole-3-carbohydrazide **47a-d** and (**49a-f**).

It was reported that[51] the condensation of the hydrazide **17i** with respective benzaldehydes or isatins afforded the series **50a-m** and **51a-g** (Scheme 14).



Scheme 14. Synthesis of *N*'-substitued-1-(4-chlorobenzyl)-1*H*-indol-3-carbohydrazides **50a-m** and **51a-g.**

In 2019, it was mentioned that[64] the reaction of *N*-methyl indolyl-3-carbohydrazides **8a,e** with different indole-3-carboxaldehydes **4d** and **52** in the presence of glac. CH_3COOH at 90 °C for 6h afforded *N*-methyl-and *N,N*-dimethyl bis(indolyl) hydrazide-hydrazones **53a-d** in good yields (Scheme 15).



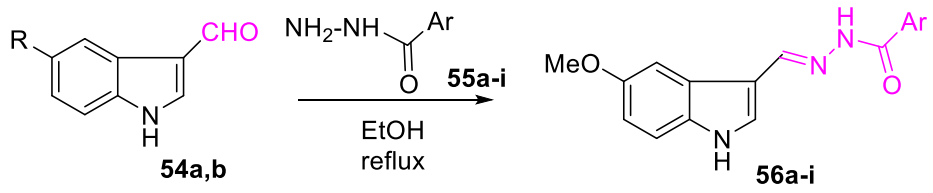
8a,e a, R= H
e, R= Br

4d, 52
52, R^2= CH_3
4d, R^2= H

53a-d a, R= Br, R^1= H, R^2= CH_3
b, R= H, R^1= H, R^2= CH_3
c, R= Br, R^1= H, R^2= H
d, R= Br, R^1= OCH_3, R^2= H

Scheme 15. Synthesis of bis (indolyl)hydrazide-hydrazone derivatives **53a-d.**

Synthesis[65, 66] of a series of indole 3-substituted aroyl hydrazones **56a-i** were achieved by condensation of the hydrazides **55a-i** with corresponding 5-substituted indole-3-carbaldehydes **54a,b** as outlined in (Scheme 16).



54a,b

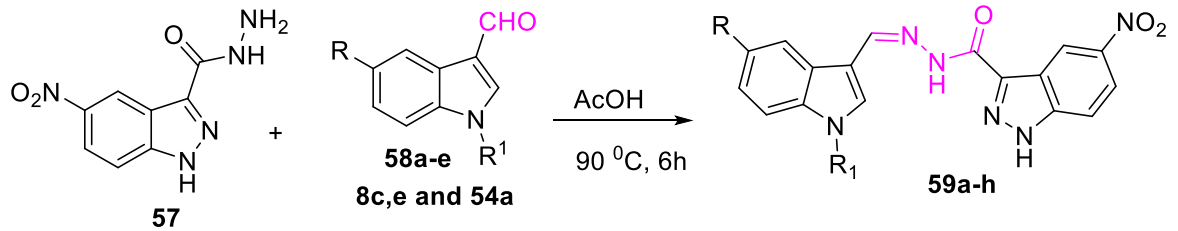
a, R= OMe [64,65]
b, R= Br, OCH_2Ph [65]

56a-i

a, Ar= *P*-OH-C_6H_4
b, Ar= *o*-,*P*-diOH-C_6H_3
c, Ar= *P*-Cl-C_6H_4
d, Ar= *P*-F-C_6H_4
e, Ar= 2-furyl
f, Ar= 2-thienyl
g, Ar= *P*-OH, *m*-OMe-C_6H_3
h, Ar= 5-(4-methyl-1,2,3-thiadiazolyl)
i, Ar= 3-indolyl

Scheme 16. Synthesis of indole C-3 substituted aroyl hydrazones **56a-i.**

Condensation[67] the acid hydrazides **57** was condensed with different indole aldehydes **8c, e**, **54a** and **58a–e** in glacial acetic acid at 90 ^{0}C for 6 h. afforded hydrazide–hydrazones linked between indole and indazole moieties **59a–h** (Scheme 17).



57

8c, R= H, R^1= H
8e, R= Br, R^1= H
54a, R= OCH_3, R^1= H

58a-e
8c,e and 54a

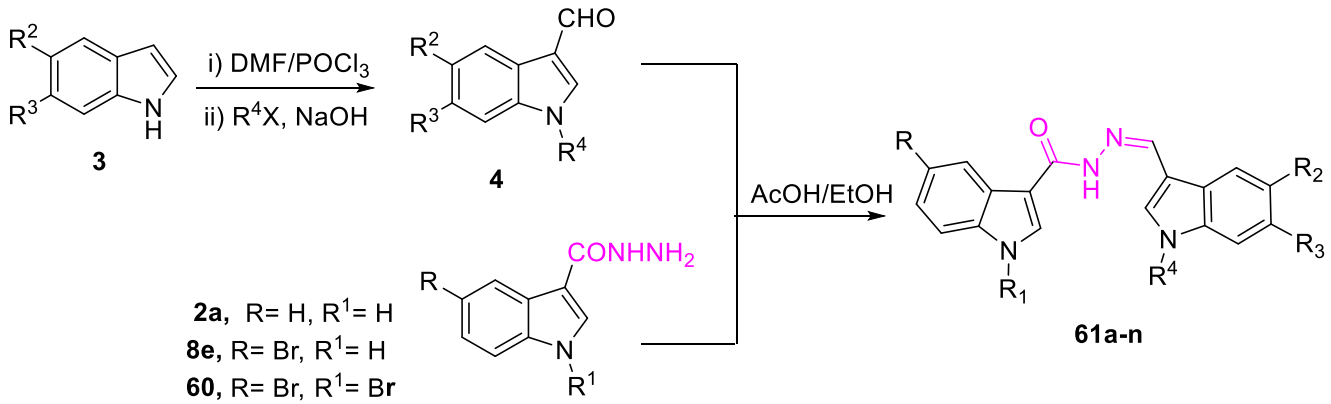
58a, R= H, R^1= CH_3
58b, R= Br, R^1= CH_3
58c, R= NO_2, R^1= H
58d, R= OCH_3, R^1= CH_3
58e, R= NO_2, R^1= H

59a-h

59a, R= H, R^1= H
59b, R= H, R^1= CH_3
59c, R= Br, R^1= H
59d, R= Br, R^1= CH_3
59e, R= NO_2, R^1= H
59f, R= OCH_3, R^1= H
59g, R= OCH_3, R^1= CH_3
59h, R= NO_2, R^1= H

Scheme 17. Synthesis of the indole hydrazide–hydrazones derivatives **59a–h**.

In 2012, it was suggested that[46] the reaction of indole **3** with phosphoryl chloride in presence of dimethylformamide followed by alkylation resulted in the formation of indole-3-carboxaldehydes **4**. The reaction of indole-3-carbohydrazides **2, 8e** and **60** with indole-3-carboxaldehydes **4** in presence of a catalytic amount of acetic acid in ethanol led to formation of bis(indolyl) hydrazide–hydrazones **61a–n** (Scheme 18).

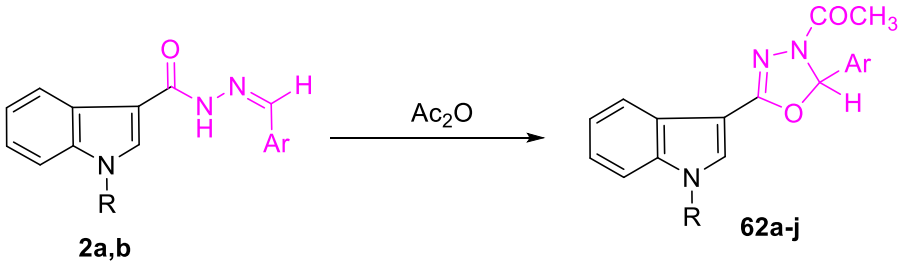


61a-n	R	R^1	R^2	R^3	R^4	61a-n	R	R^1	R^2	R^3	R^4
a	H	H	H	H	4-$ClC_6H_4CH_2$	i	H	H	H	F	4-$OCH_3C_6H_4CH_2$
b	H	H	Br	H	4-$ClC_6H_4CH_2$	j	Br	Br	H	F	4-$OCH_3C_6H_4CH_2$
c	H	H	OMe	H	4-$ClC_6H_4CH_2$	k	Br	Br	OMe	H	4-$OCH_3C_6H_4CH_2$
d	H	H	H	F	4-$ClC_6H_4CH_2$	l	H	H	H	H	4-$OCH_3C_6H_4CH_2$
e	Br	H	OMe	H	4-$ClC_6H_4CH_2$	m	H	Me	H	F	4-$OCH_3C_6H_4CH_2$
f	Br	H	H	F	4-$ClC_6H_4CH_2$	n	H	Me	OMe	F	4-$ClC_6H_4CH_2$
g	H	H	H	H	4-$OCH_3C_6H_4CH_2$	o	H	Me	H	H	4-$ClC_6H_4CH_2$
h	H	H	OMe	H	4-$OCH_3C_6H_4CH_2$						

Scheme 18. Synthesis of bis(indolyl)hydrazide–hydrazones **61a–n**.

3.2. Synthesis of 3-indolyl-1,3,4-oxadiazole derivatives

It was found that the cyclization[31, 39] of the arylidene compounds **2a,b** by its boiling with acetic anhydride afforded the 1,3,4-oxadizole derivatives **62a-j** (Scheme 19).

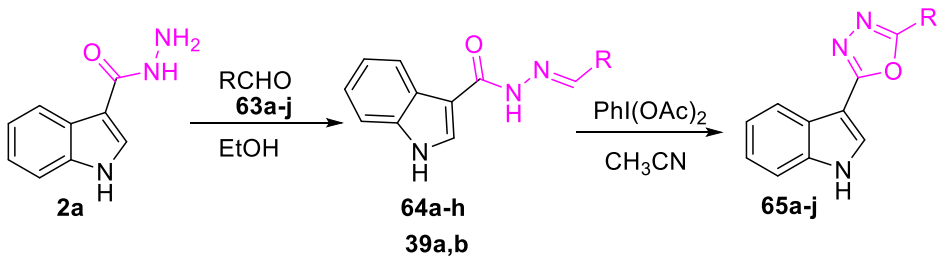


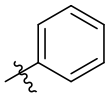
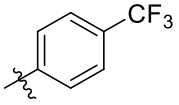
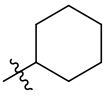
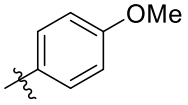
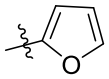
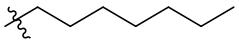
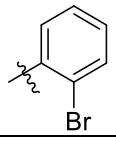
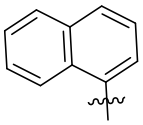
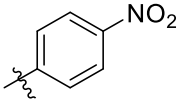
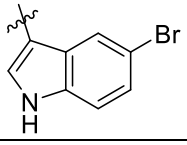
a, R= H **[39]**
b, R= CH_2Ph **[31]**

a, Ar = C_6H_5 **[31, 39]**
b, Ar = C_6H_4Cl(p) **[31, 39]**
c, Ar = $C_6H_4OCH_3$(p) **[31]**
d, Ar = $C_6H_4N(CH_3)_2$(p) **[31]**
e, Ar = $C_6H_4OCH_3$(o) **[39]**
f, Ar = C_6H_4Cl(m) **[39]**
g, Ar = C_6H_4OH(p) **[39]**
h, Ar = C_6H_4F(o) **[39]**
i, Ar = C_6H_4OH(m) **[39]**
j, Ar = C_6H_4F(m) **[39]**

Scheme 19. Synthesis of 1,3,4-oxadiazol derivatives **62a-j**.

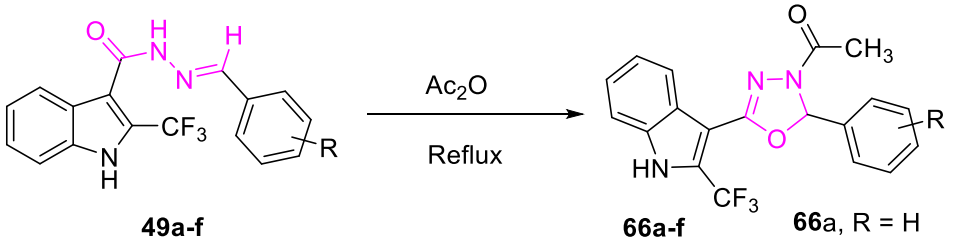
Liu, B. *et al*[68] treatment of hydrazide **2a** with a number of aldehydes **63a–j** gave acylhydrazones **39a,b** and **64a–h**. Treatment of the latter compounds with iodobenzene diacetate afforded the oxadiazoles **65a–j** (Scheme 20).



Cd.	R	Cd.	R	Cd.	R
39a, 65a		64c 65e		64g 65i	
39b 65b		64d 65f		64h 65j	
64a 65c		64e 65g			
64b 65d		64f 65h			

Scheme 20. Synthesis of the 1,3,4-oxadiazole derivatives **65a-j**.

Cyclization of compounds **49a-f** was performed by reaction of **6a** with acetic anhydride under reflux gave the corresponding 1,3,4-oxadiazole derivative **66a-f** [62] (Scheme 21).

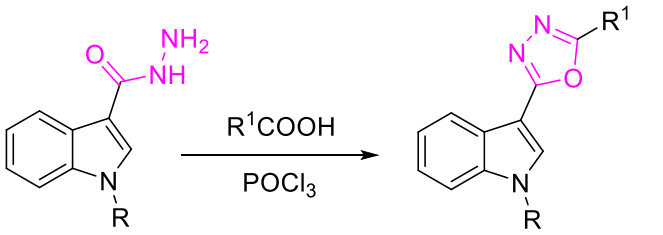


66a, R = H
66b, R = 4-Cl
66c, R = 3-NO_2
66d, R = 3,4$(OCH_3)_2$
66e, R = 4-$N(CH_3)_2$
66f, R = 3,4,5$(OCH_3)_3$

Scheme 21. Synthesis of 3-indolyl-1,3,4-oxadiazole derivatives **66a-f.**

It was reported that[45] treatment of hydrazide **2a**, **8d** and **17d** with a variety of substituted benzoic or aliphatic carboxylic acids followed by dehydrative ring closure in the same pot was achieved by treatment with

phosphoryl chloride at 80 ^{0}C under reflux and led to the formation of the corresponding 1,3,4-oxadiazoles **67-69** (Scheme 22).

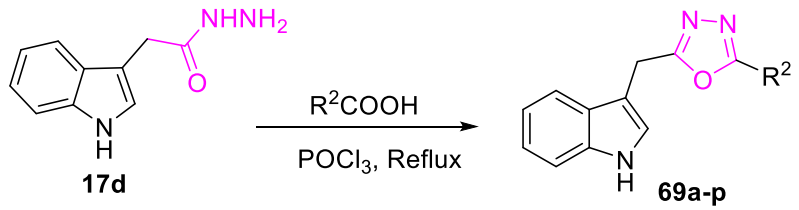


2a, R= H
8d, R= Et

67a-m and **68a-z**

67a-m	**R^1**	**R**	**67-a-m**	**R^1**	**R**
a	CH_3	H	h	CH_2Cl	H
b	CH_3CH_2	H	i	2-F-C_6H_4	H
c	$CH_3CH_2CH_2$	H	j	2-I-C_6H_4	H
d	$(CH_3)_3CCH_2$	H	k	2-Cl-C_6H_4	H
e	$CH_3CH_2(CH_3)_2C$	H	l	3-Cl-C_6H_4	H
f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	H	m	4-Me-C_6H_4	H
g	CF_3	H			H

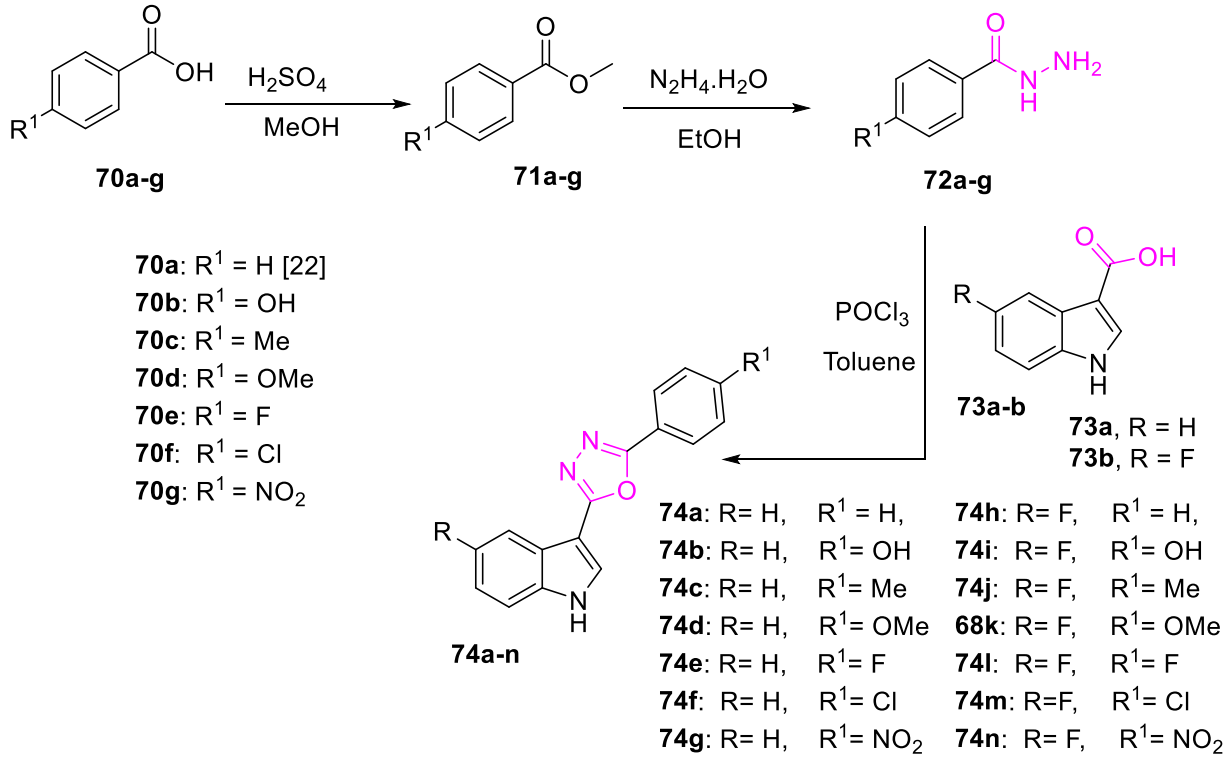
68a-m	**R^1**	**R**	**68n-z**	**R^1**	**R**
a	CH_3	Et	n	3-Cl-C_6H_4	Et
b	CH_3CH_2	Et	o	3-NO_2-C_6H4	Et
c	$CH_3CH_2CH_2$	Et	p	3-Pyridyl	Et
d	$(CH_3)_3CCH_2$	Et	q	4-Cl-C_6H_4	Et
e	$CH_3CH_2(CH_3)_2C$	Et	r	4-Br-C_6H_4	Et
f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	Et	s	4-NO_2-C_6H_4	Et
g	CF_3	Et	t	4-Me-C_6H_4	Et
h	CH_2Cl	Et	u	4-MeO-C_6H_4	Et
i	CCl_3	Et	v	3,5-Di-Me-C_6H_3	Et
j	C_6H_5	Et	w	3,4,5-Tri-MeO-C_6H_2	Et
k	2-F-C_6H_4	Et	x	$C_6H_5CH_2$	Et
l	3-Cl-C_6H_4	Et	y	2-Me-$C_6H_5CH_2$	Et
m	4-I-C_6H_4	Et	z	(E)-C_6H_5CH:CH	Et



69a-p	R^1	R	69a-p	R^1	R
a	CH_3	H	i	CCl_3	H
b	CH_3CH_2	H	j	2-F-C_6H_4	H
c	$CH_3CH_2CH_2$	H	k	3-Cl-C_6H_4	H
d	$(CH_3)_3CCH_2$	H	l	4-Br-C_6H_4	H
e	$CH_3CH_2(CH_3)_2C$	H	m	4-MeO-C_6H_4	H
f	$(CH_3)_3CCH_2(CH_3)CHCH_2$	H	n	4-Me-C_6H4	H
g	CF_3	H	o	3,5-Di-MeO-C_6H_3	H
h	CH_2Cl	H	p	3,4,5-Tri-MeO-C_6H_2	H

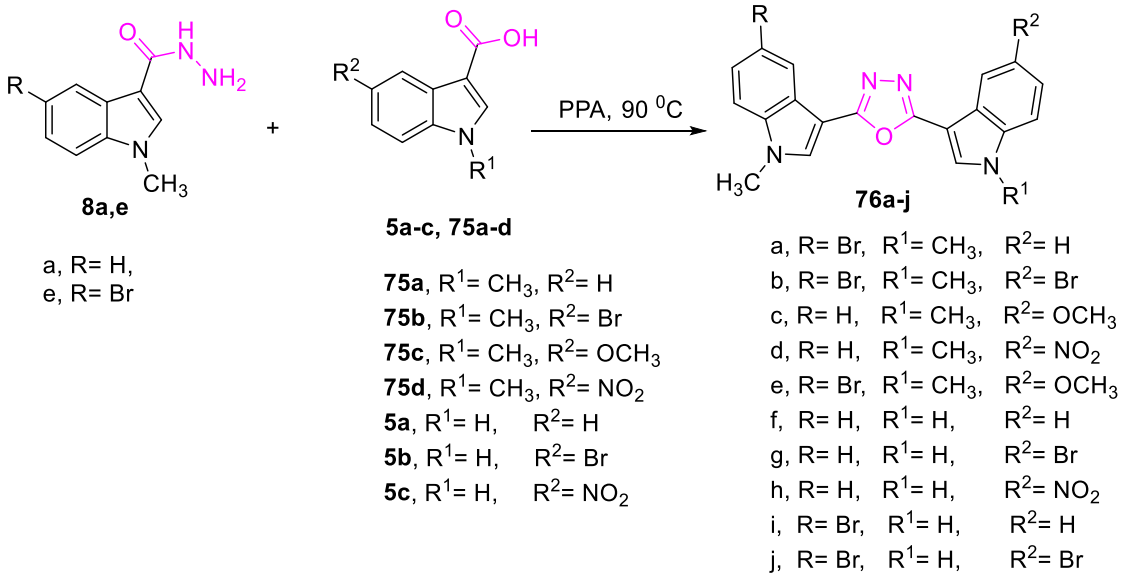
Scheme 22. Synthesis of 3-indolyl-1,3,4-oxadiazoles **67-69**.

Recently, it was found that[88] the reaction of *p*-substituted aromatic carboxylic acids **70a-g** with methanol and concentrated H_2SO_4 produced the corresponding esters **71a-g**. Treatment of the latter esters with hydrazine hydrate in ethanol under reflux yielded the corresponding *p*-substituted benzoic acid hydrazides **72a-g**.[22] Further, reaction of latter hydrazides with substituted indole carboxylic acids **73a-b** in the presence of $POCl_3$ and toluene afforded the indolo-1,3,4-oxadiazoles derivatives (**74a-n**)[8] (Scheme 23).



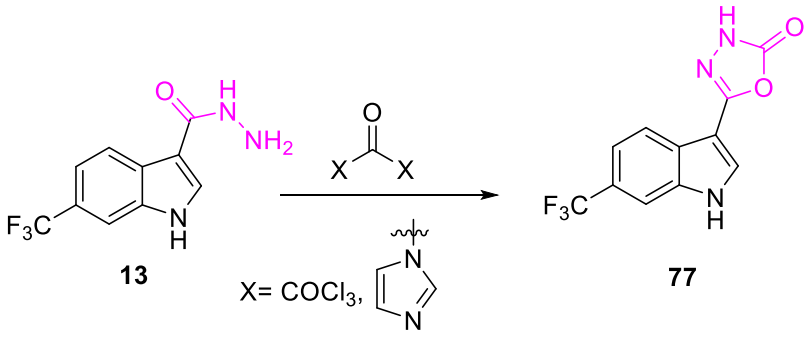
Scheme 23. Synthesis of 3-indolyl-1,3,4-oxadiazole derivatives **74a-n.**

It was mentioned that[41] the interaction of carbohydrazide derivatives **8a,e** with different indole-3-carboxylic acids **5a-c** and **75a-g** in the presence of solid phase catalyst polyphosphoric acid yielded bis(indolyl)oxadiazole derivatives **76a-j** (Scheme 24).



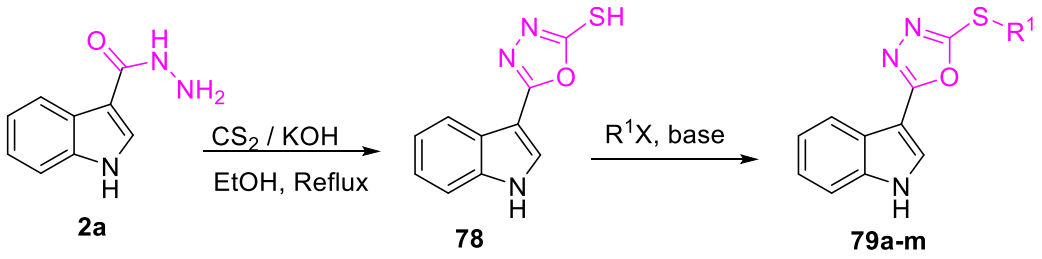
Scheme 24. Synthesis of bis(indolyl)oxadiazole derivatives **76a-j**.

Reaction[45,47] of hydrazide compound **13** with CDI (1,1′-carbonyldiimidazole) or triphosgene (bis(trichloromethyl) carbonate) gave the corresponding 5-(6-(trifluoromethyl)-1*H*-indol-3-yl)-1,3,4-oxadiazol-2(3*H*)-one **77** (Scheme 25).

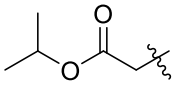
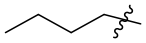
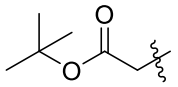
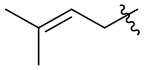
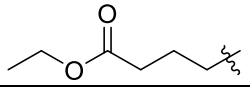
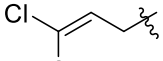
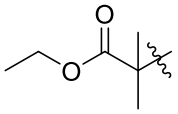
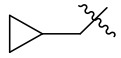
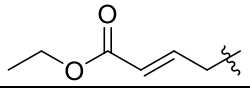
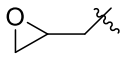
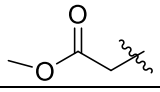


Scheme 25. Synthesis of the 5-(6-(trifluoromethyl)-1*H*-indol-3-yl)-1,3,4-oxadiazol-2(3*H*)-one **77.**

It was found that[35] the treatment of the latter compound **2a** CS_2 in ethanol and KOH gave the 5-(3′-indolyl)-1,3,4-oxadiazole-2-thiol **78**. Alkylation of the thiol **78** with some alkylating agents led to the formation of the corresponding s-alkylated products **79a-j** (Scheme 26).

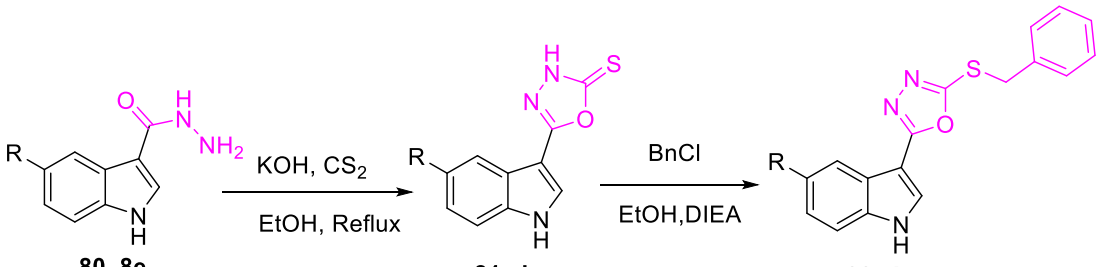


2a **78** **79a-m**

79a-g	R^1	79h-m	R^1
a		h	
b		i	
c		j	
d		k	
e		l	
f		m	CH_2Ph
g			

Scheme 26. Synthesis of 5-(3-indolyl)-1,3,4-oxadiazole-2-thiol derivatives **79a-m.**

Reaction[54] of hydrazide compound **8e** and **80** with CS_2 afforded the corresponding 1,3,4-oxadiazole-2-thione **81a,b**. Reaction of the thione **81a,b** with benzyl chloride in basic medium led to the formation of s-benzylated products **82a,b** (Scheme 27).



80, 8e
80, R=Ph
8e, R= Br

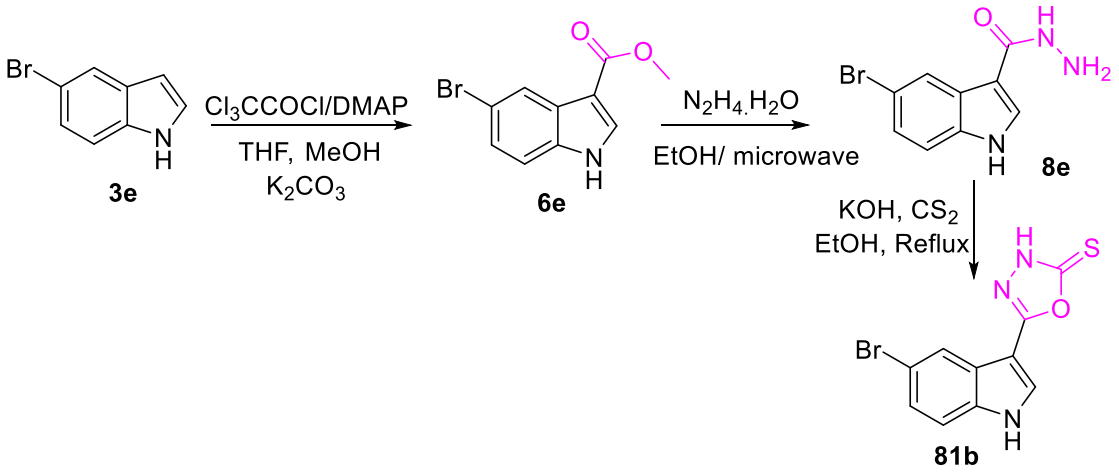
81a,b
a, R=Ph
b, R= Br

82a,b
a, R= ph
b, R= Br

Scheme 27. Synthesis of s-benzylated products **82a,b.**

Acylation[54] of 5-bromo-1*H*-indole **3e** with 2,2,2-trichoroacetyl chloride in MeOH afforded the corresponding ester **6e** which was reacted with hydrazine hydrate to give the hydrazide derivative **8e**.

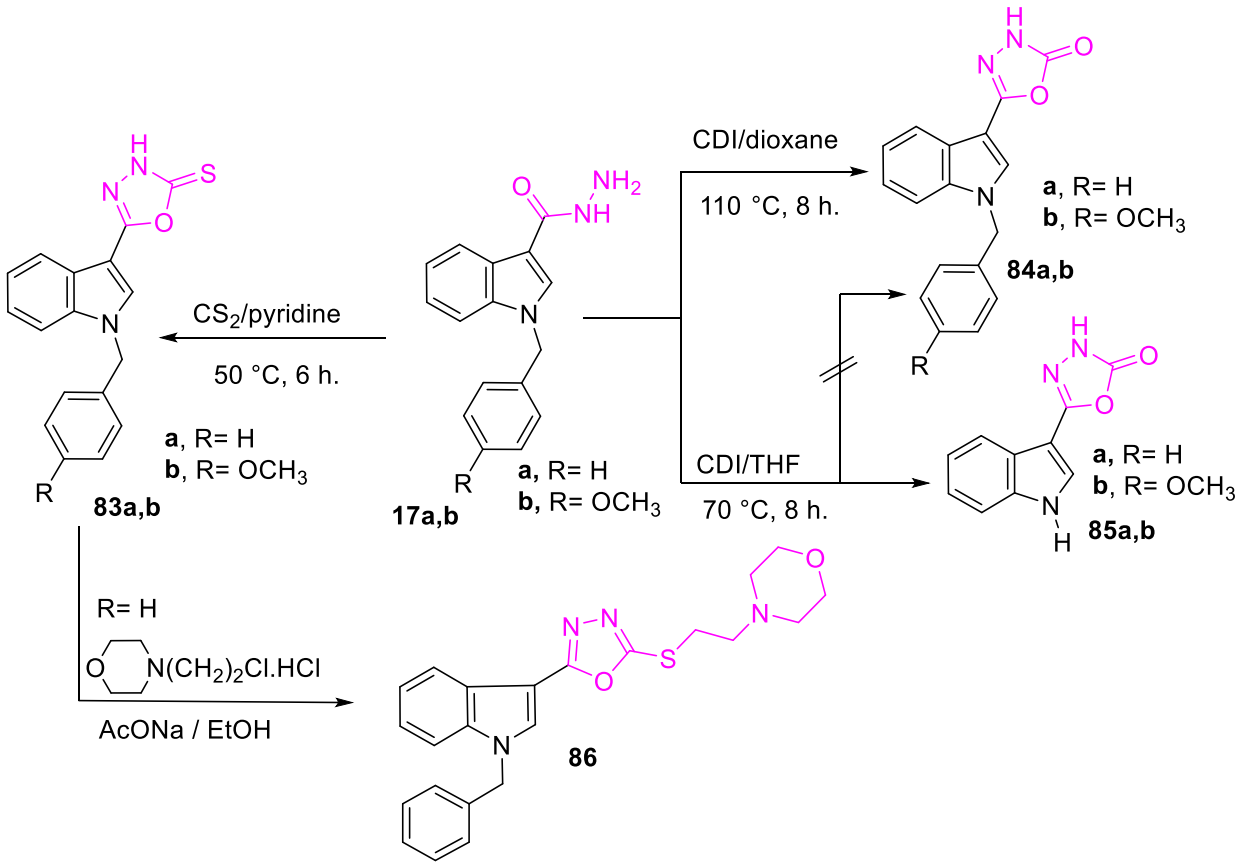
Treatment of latter compound **8e** with CS_2 in ethanol and KOH yielded the corresponding cyclized 1,3,4-oxadiazole thione product **81b** (Scheme 28).



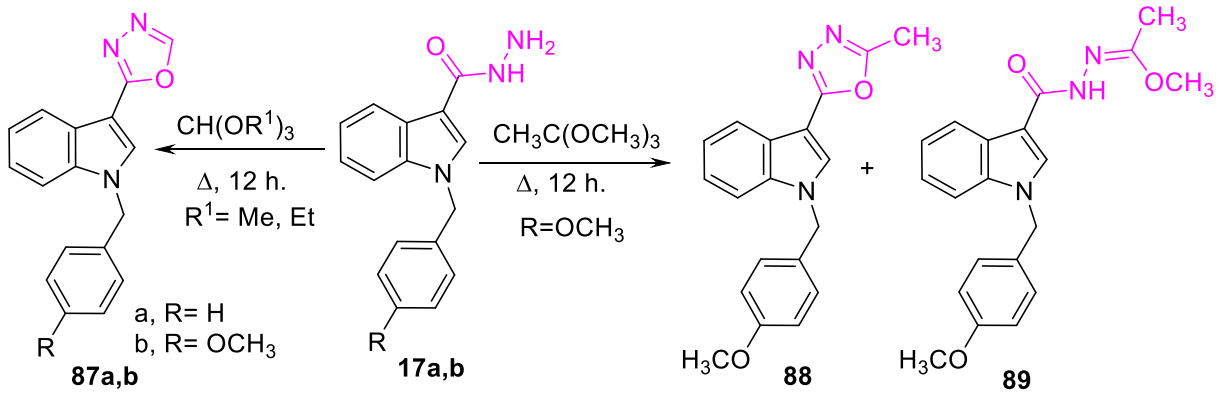
Scheme 28. Synthesis of indolyl-1,3,4-oxadiazole derivatives **81b.**

It was reported that[31, 34] treatment of the acid hydrazide **17a,b** with carbon disulfide in boiling pyridine led to the formation of the corresponding oxadiazole thione **83a,b**. Whereas reaction of **17a,b** with 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran (THF) at 70°C did not afford the expected 5-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazol-2(3*H*)-one (**84a,b**), an unexpected debenzylation occurred and the oxadiazolone **85a,b** [34] was obtained. However, when the reaction was carried out in boiling dioxane, the *N*-substituted analogue **85a,b** was obtained. Interaction[31] of **83a** with 4-(2-chloroethyl) morpholine hydrochloride in refluxing ethanol in the presence of anhydrous sodium acetate gave the S-alkylated product **86** in good yield (Scheme 29).

In continuation to above work,[31, 34] condensation of carbohydrazide **17a,b** with tri(ethyl)methyl orthoformate gave the corresponding 1,3,4-oxadiazole derivative **87a,b** whereas, the reaction of **17b** with trimethyl orthoacetate afforded a mixture of 2-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-5-methyl-1,3,4-oxadiazole (**88**) and methyl methyl (*Z*)-*N*-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl) acetohydrazonate (**89**) respectively (Scheme 30).

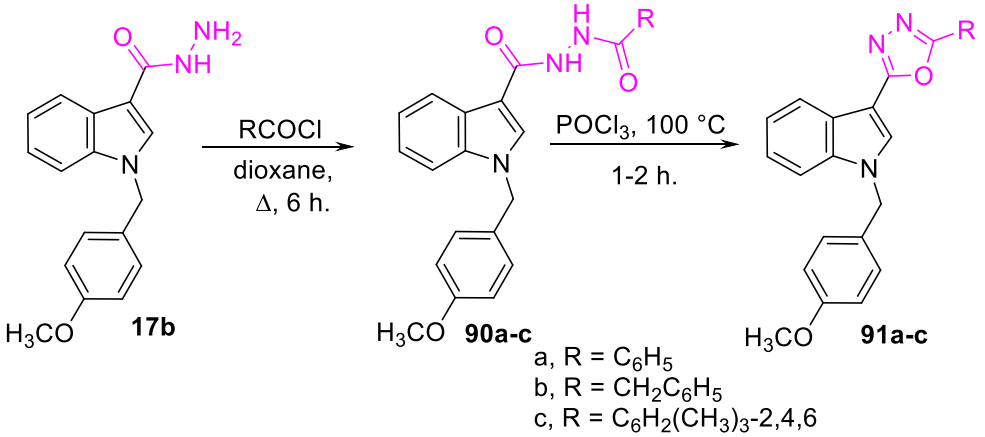


Scheme 29. Synthesis of new PMB-substituted indoles containing 1,3,4-oxadiazole units **83-86**.



Scheme 30. Reaction of hydrazide **17a,b** with tri(ethyl)methyl orthoformate.

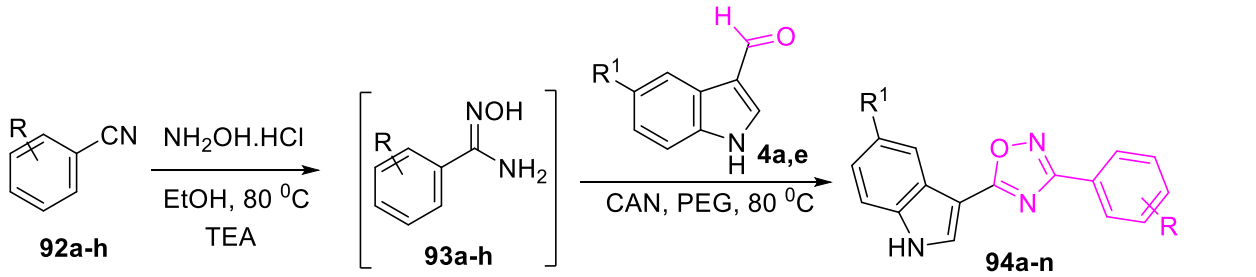
However,[34] the reaction of carbohydrazide **17b** with acid chlorides such as benzoyl chloride, phenylacetyl chloride and 2,4,6-trimethylbenzoyl chloride in refluxing dry dioxane did not lead to cyclized products, but afforded the corresponding substituted carbohydrazide derivatives **90a-c**. The latter compounds then could be cyclized into the oxadiazole derivatives **91a-c** by heating with phosphoryl chloride at 100 °C for 1–2 h. (Scheme 31)



Scheme 31. Synthesis of 3-indolyl-5-substitued-1,3,4-oxadiazole **91a-c.**

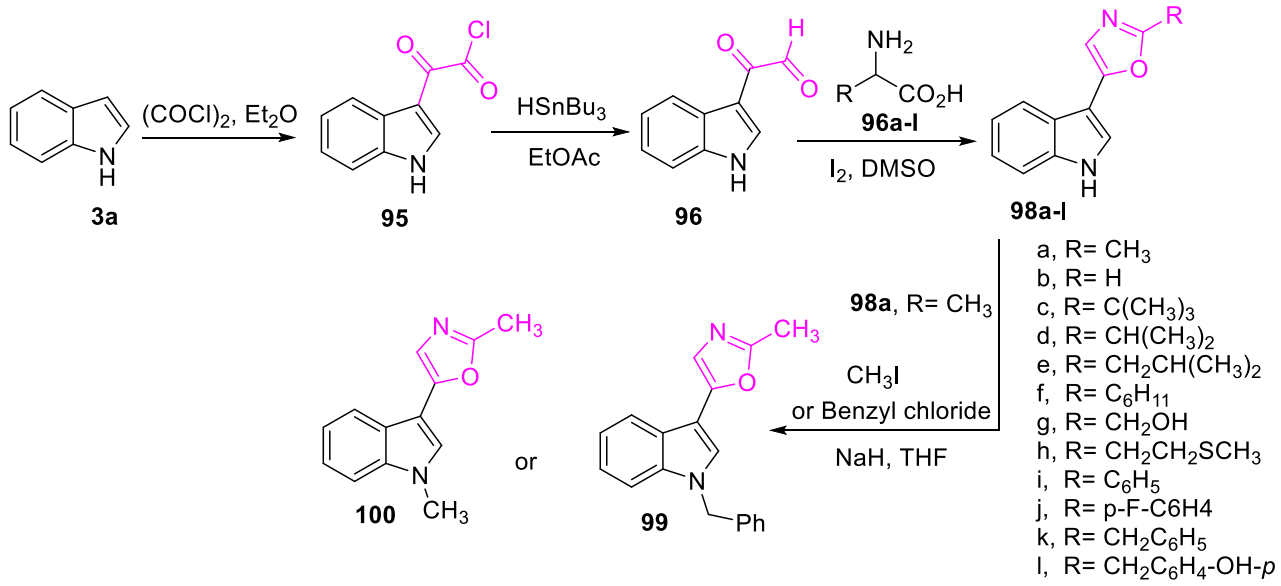
3.3. Synthesis of 3-indolyl-1,2,4-oxadiazole derivatives

In 2024, it was found that the treatment of a series of benzo nitriles **92a-h** with hydroxylamine hydrochloride, TEA, in ethanol under refluxing afforded the corresponding benzamidoxime **93a-h**. Reaction of latter compound with 1*H*-indole-3-carboxaldehyde **4a,e** in the presence of cerium ammonium nitrate (CAN) and polyethylene glycol (PEG) as a solvent provided the 1*H*-(indole-5-yl)-3-substituted-1,2,4-oxadiazoles **94a-n** (Scheme 32).[10]



Scheme 32. Synthesis of 3-indolyl-1,2,4-oxadiazole derivatives **94a-n.**

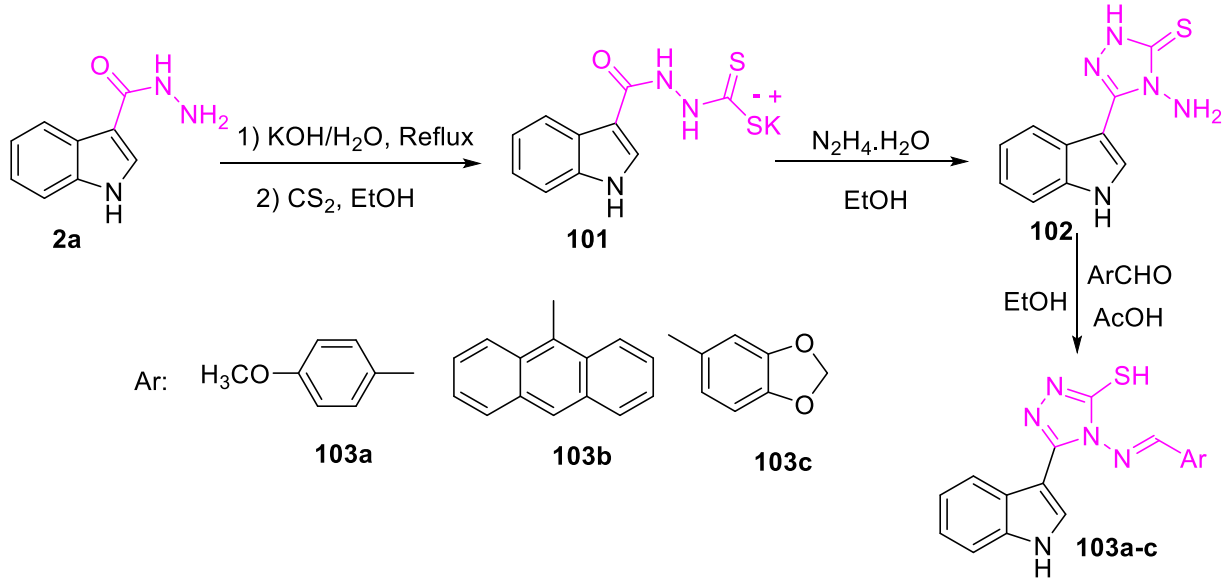
In 2019, Liu, B. *et al*[68] found that the treatment of indole **3a** with oxalyl chloride in ether afforded the 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride **95**. Reaction of compound **95** with ethyl acetate in presence of $HSnBu_3$ yielded the corresponding 2-oxoacetaldehyde **96**. Decarboxylation coupling reaction of latter compound with the amino acids **97a-l** led to the formation of 5-(1*H*-indol-3-yl)-2-substiuted oxazole **98a–l**. Reaction of the 2-methyl oxazole **98a** with methyl iodide or benzyl bromide in the presence of NaH gave the indole nitrogen substituted products **99** and **100** (Scheme 33).



Scheme 33. Synthesis of 5-(1-benzyl(methyl)-1*H*-indol-3-yl)-2-methyloxazole **99** and **100.**

3.4. Synthesis of 3-indolyl-1,2,4-triazole derivatives

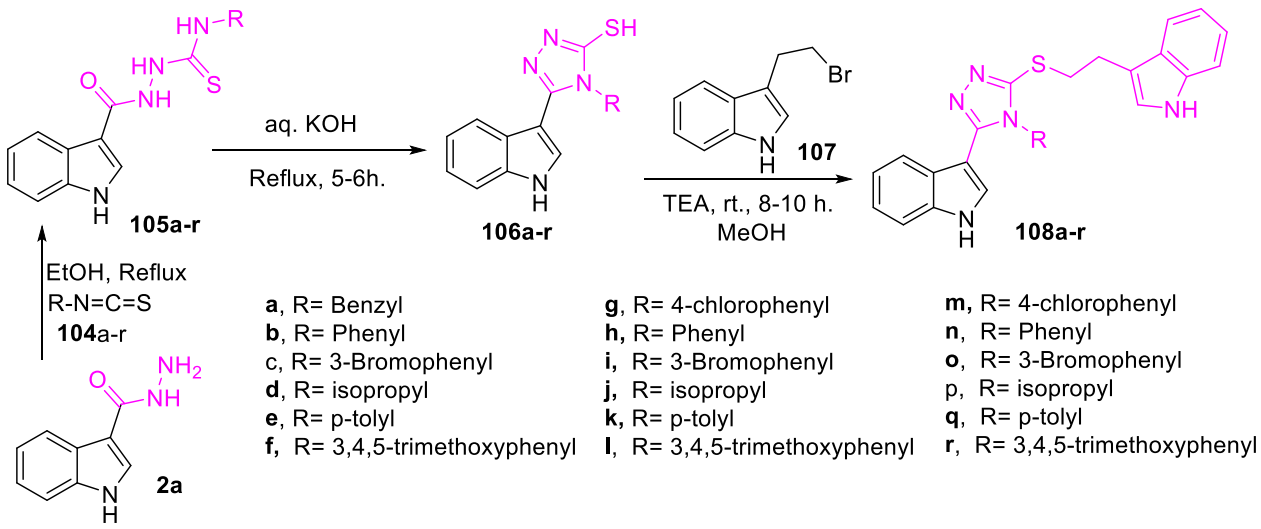
Mahdi et al reported that[24, 29] the interaction of 3-indolecarbohydrazide **2a** with carbon disulfide in KOH afforded the 2-(1*H*-indole-3-carbonyl)hydrazine-1-carbodithioate (**101**). Treatment of compound **2a** with hydrazine hydrate and potassium hydroxide gave the corresponding indole-3-triazole **102**. Condensation of indole-3-triazole **102** with aromatic aldehydes in presence of few drops of acetic acid as a catalyst under reflux yielded the Schiff bases of indole triazole derivatives **103a-c** (Scheme 34).



Scheme 34. Synthesis of (E)-4-(arylideneamino)-5-(1*H*-indol-3-yl)-4*H*-1,2,4-triazole-3-thiol derivatives **103a-c.**

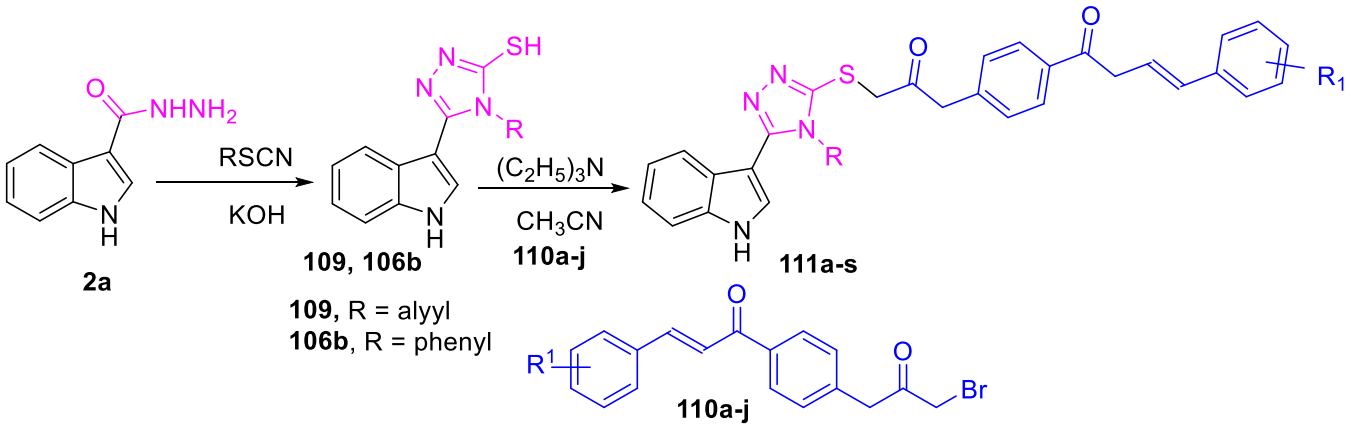
Yakkala *et al* mentioned that[69] treatment of 1*H*-indole-3-carbohydrazide **2a**[70] with different aliphatic and aromatic isothiocyanates[71] (**104a–r**) obtained the corresponding substituted thiosemi-carbazides[72] (**105a–r**). These latter compounds were cyclized by using an excess of aqueous KOH to afford 5-mercapto-1,2,4-

triazoles (**106a–r**). The 1,2,4-triazoles were reacted with 3-(2-bromoethyl)-1*H*-indole (**107**) in the presence of trimethylamine (TEA) to form the corresponding 1,2,4-triazolo-linked bis-indolyl conjugates **108a–r**, as shown in scheme 35.



Scheme 35. Synthesis of 1,2,4-triazolo-linked bis-indolyl conjugates **108a–r**.

Also,[43] reaction of indole-3-carbohydrazide **2a** with phenyl isothiocyanate in a small amount of ethanol under reflux followed by treatment with 2 *N* KOH at reflux in ethanol, then acidification with HCl to yield the 1,3,4-triazole thiol derivatives **106b** and **109**. Alkylation of thiols **109** or **106b** with acylated chalcone derivatives **110a–j** in the presence of triethylamine (TEA) using acetonitrile as a solvent to afford the corresponding compounds **111a–s** (Scheme 36).

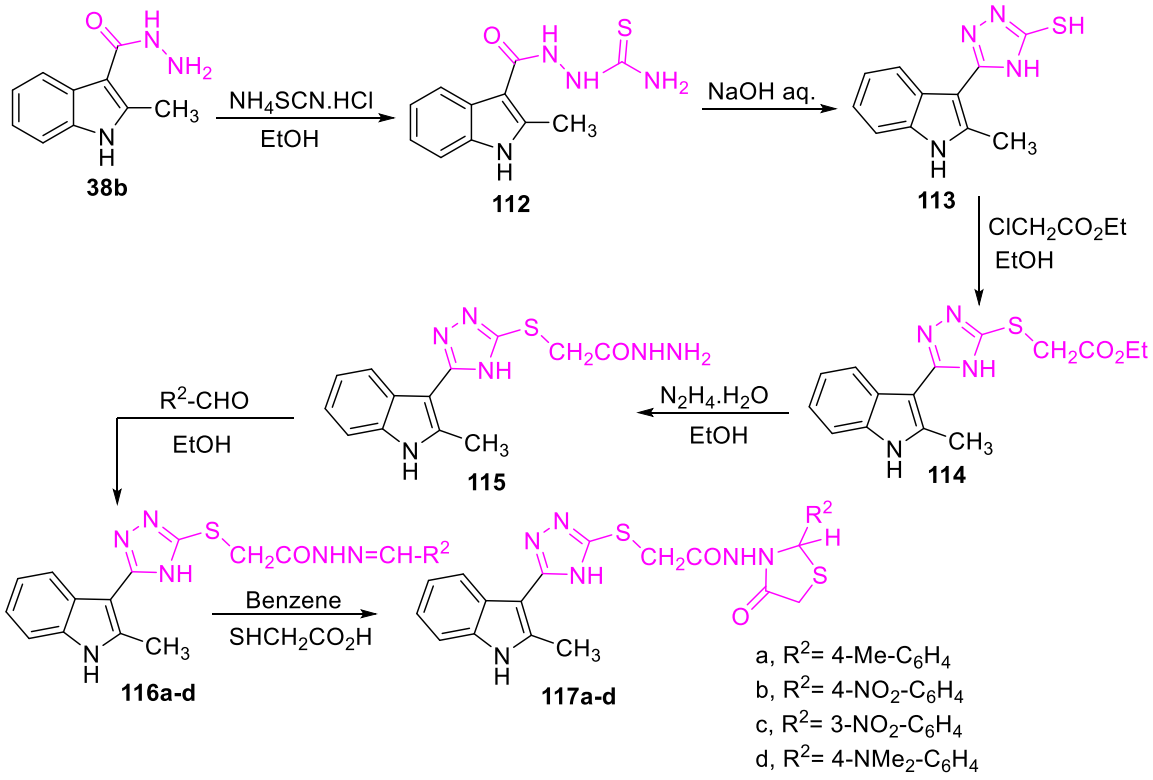


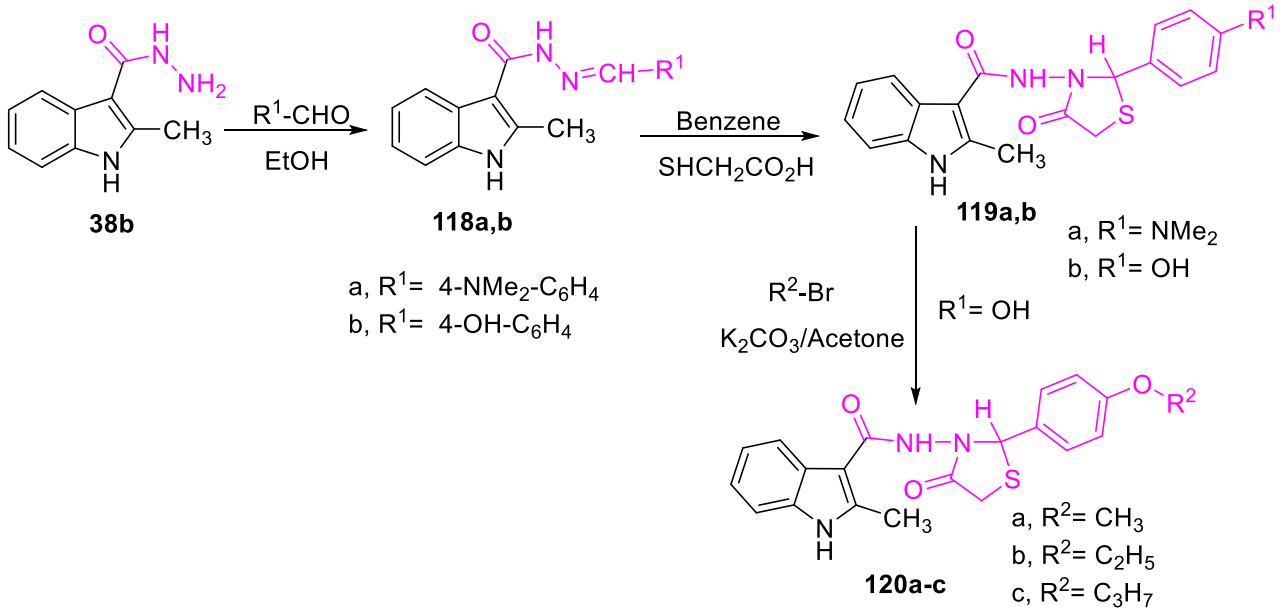
111a-i	R^1	R	111k-s	R^1	R
a	H	Allyl	k	2,4-Dimethyl	Phenyl
b	4-OCH_3	Allyl	l	4-Br	Phenyl
c	4-Cl	Allyl	m	3,4-Dimethoxy	Phenyl
d	3,4-Dimethoxy	Allyl	n	3,4,5-Trimethoxy	Phenyl
e	3,4,5-Trimethoxy	Allyl	o	4-Cl	Phenyl
f	4-Br	Allyl	p	4-OCH_3	Phenyl

g	3-NO_2	Allyl	q	4-CH_3	Phenyl
h	4-CH_3	Allyl	r	2-Cl	Phenyl
i	2-Cl	Allyl	s	3-NO_2	Phenyl
j	2,4-Dimethyl	Allyl	-	-	-

Scheme 36. Synthesis of indole/1,2,4-triazole/chalcone hybrids **111a-s**.

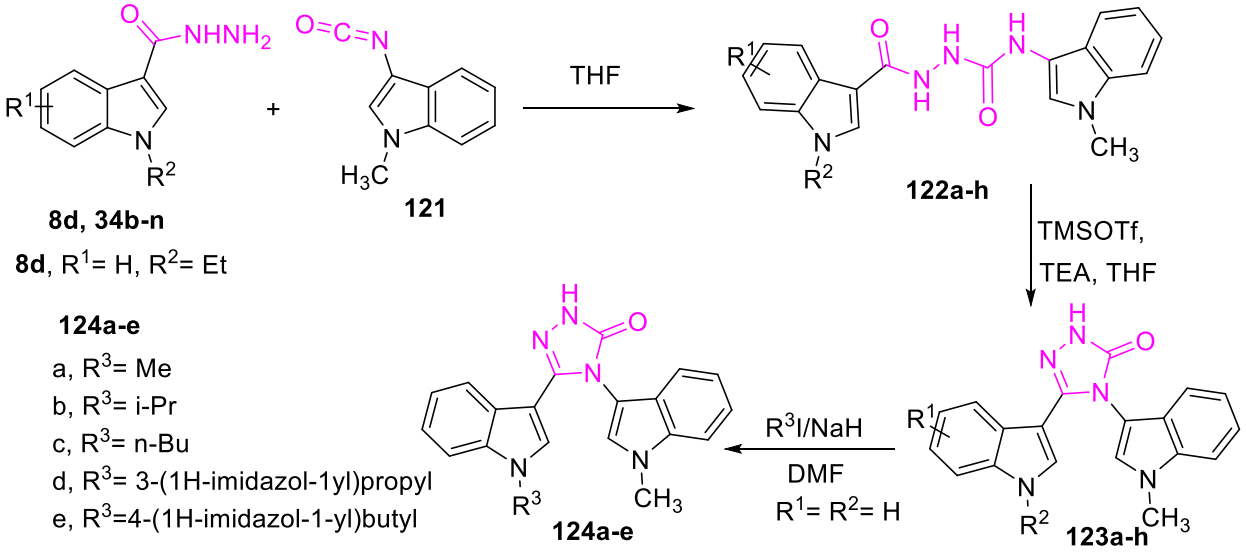
Nucleophilic addition reaction[61] of acid hydrazide **38b** with ammonium thiocyanate in ethanol using hydrochloric acid as the catalyst gave 2-(2-methyl-1*H*-indole-3-carbonyl) hydrazine carbothio-amide **112**. Cyclization reaction of thiosemicarbazides **112** in aqueous sodium hydroxide solution followed by acidification with hydrochloric acid yielded the 1,2,4-triazole derivatives **113.** Reaction of triazole thiol **113** with ethyl chloroacetate gave the ester compound **114** which was reacted with hydrazine hydrate to give the acid hydrazide derivatives **115**. Refluxing of acid hydrazide derivatives **38b** or **115** with different aromatic aldehydes in ethanol afforded the Schiff bases compounds **116a,b** and **118a,b**. Refluxing of the Schiff bases **116a,b** and **118a-d** with thioglycolic acid in dry benzene yielded the thiazolidin-4-ones derivatives **117a-d** and **119a,b**. Reaction of compound **119a** with different alkyl bromide in alkaline medium gave a series of compounds **120a-c** (Scheme 37**)**.





Scheme 37. Synthesis of thiazolidinone derivatives containing indole **117a-d** and **119a,b.**

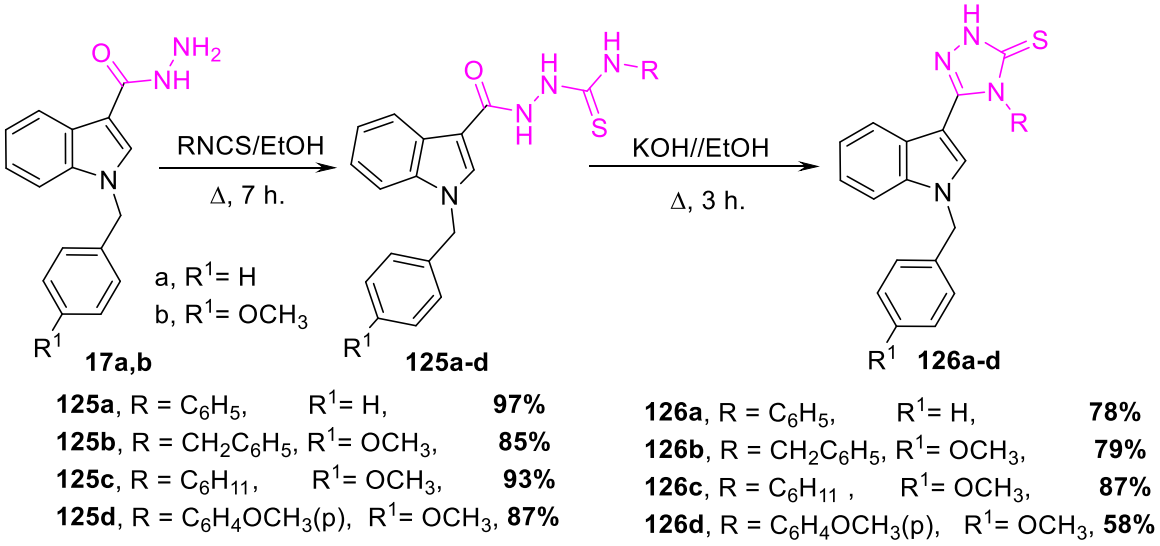
Condensation[59] of **8d** and **34b-h** with 3-isocyanato-1-methyl-1*H*-indole **121** in dry THF afforded intermediates **122a-h**, which were cyclized to afford **123a-h** in the presence of an excess amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine in dry DMF. Compounds **124a-e** were obtained by *N*-alkylation of **123a** with different alkyl halides using NaH as a base in dry DMF (Scheme 38).



Cd.	R^1, R^2	Cd.	R^1, R^2
122a, 123a	R^1= H, R^2= H	34e, 122e, 123e	R^1= 6-Cl, R^2= Me
34b, 122b, 123b	R^1= 5-F, R^2= Me	34f, 122f, 123f	R^1= 6-Br, R^2= Me
34c , 122c, 123c	R^1= 6-F, R^2= Me	34g, 122g, 123g	R^1= 5-Br, R^2= Me
34d, 122d, 123d	R^1= 5-Cl, R^2= Me	34h, 122h, 123h	R^1= 5-OMe, R^2= Me

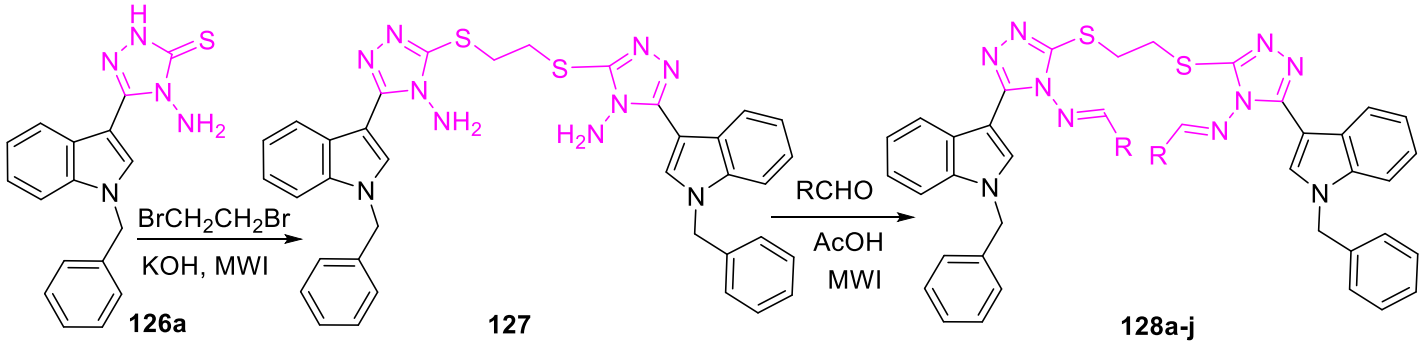
Scheme 38. Synthesis of the 2,4-dihydro-3*H*-1,2,4-triazol-3-one **123a-e**.

Moreover,[31, 34] reaction of compound **17a,b** with isothiocyanates in refluxing ethanol afforded the substituted thiosemicarbazide derivatives **125a-d**, which were transformed into the corresponding 1,2,4-triazole-3-thione derivatives **126a-d** via intramolecular cyclization in boiling ethanolic potassium hydroxide solution (Scheme 39).



Scheme 39. Synthesis of 1,2,4-triazole-3-thione derivatives **126a-d.**

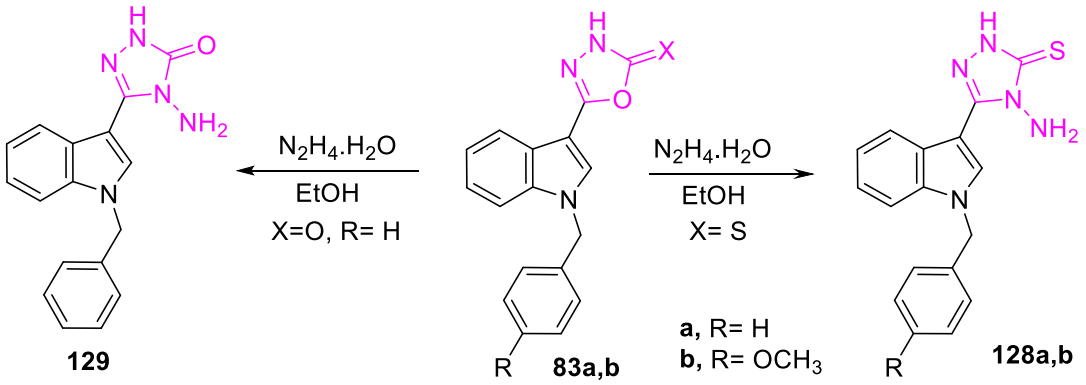
In contuination to what reported previously by farghaly,[31] Peng Y. *et al* reported that treatment of the **126a** with 1,2-dibromoethane in the presence of KOH under microwave irradiation affoded the corresponding the sulfide derivative **127**. Reaction of the latter compound with different aldehydes in acetic acid gave the Schiffbases **128** (Scheme 40).[73]



128a-e	R	128f-j	R
a	C_6H_5	f	3-BrC_6H_4
b	3-FC_6H_4	g	2-$O_2NC_6H_4$
c	2-HOC_6H_4	h	4-BrC_6H_4
d	4-$CH_3OC_6H_4$	i	2-BrC_6H_4
e	4-HOC_6H_4	j	2-furyl

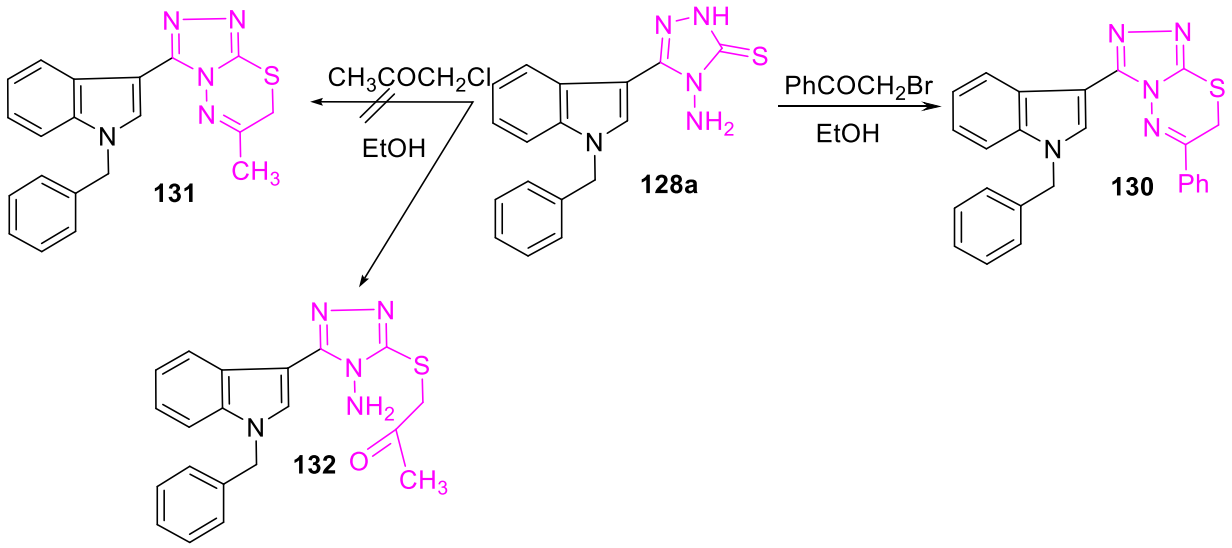
Scheme 40. Synthesis of Schiff bases **128a-j.**

Also, Farghaly *et al* reported that[31, 34] treatment of oxadiazolethione **83a,b** or oxadiazole-3-one **84a** derivatives with hydrazine hydrate in boiling ethanol by a ring opening and ring closure sequence gave the corresponding *N*-amino-substituted 1,2,4-triazole **129** and **130** respectively (Scheme 41).



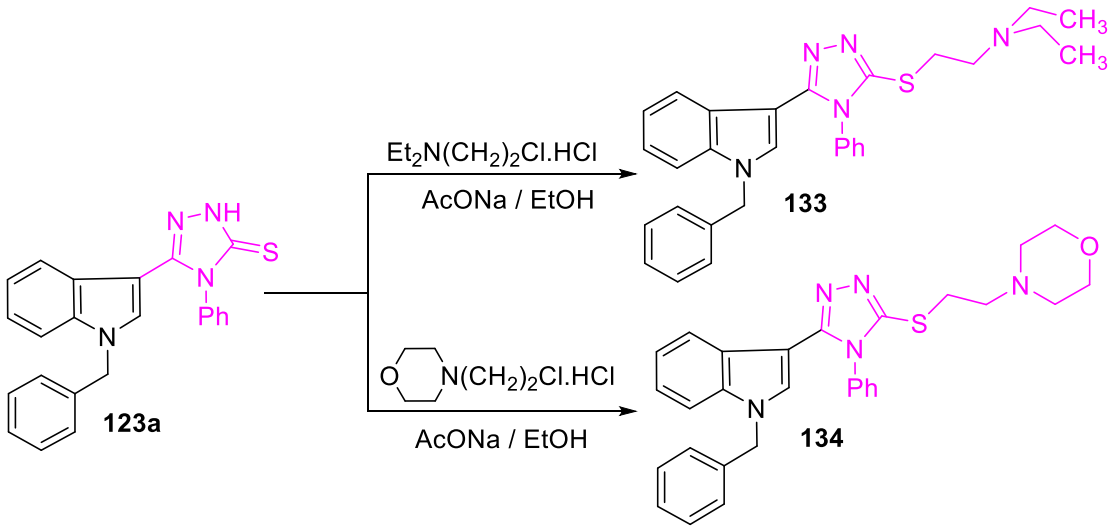
Scheme 41. Synthesis of *N*-amino-substituted 1,2,4-triazole **128a,b** and **129**.

Furthermore, refluxing[31] the triazolthione **128a** with phenacyl bromide in ethanol produced the corresponding 3-(1-benzyl-1*H*-indol-3-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine **130**. Whereas, its reaction with chloro acetone did not give the thiadiazine **131** but gave the corresponding acetonylthio derivative **132** (Scheme 42).



Scheme 42. Synthesis of triazolo[3,4-*b*][1,3,4]thiadiazine derivatives **130**.

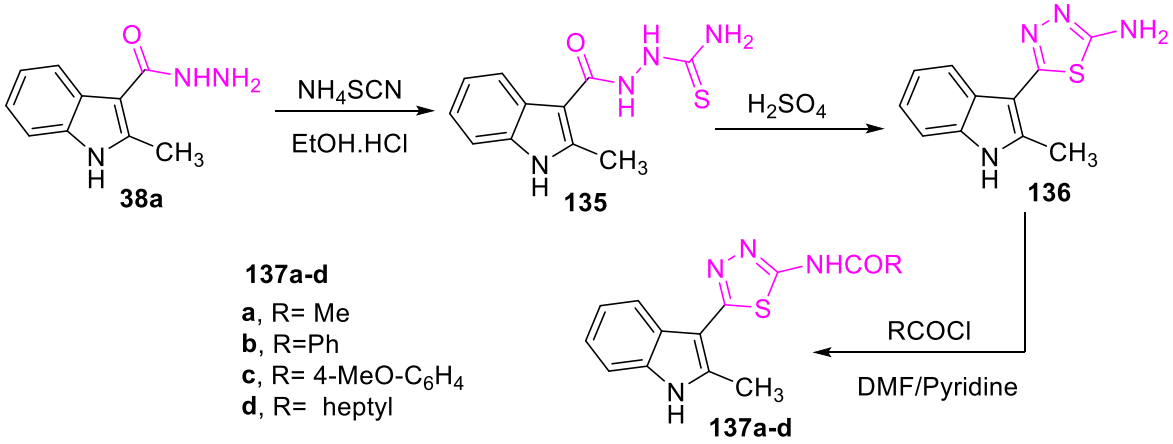
Interestingly,[31] the thione function in compound **123a** should offer the possibility for further elaboration by alkylation reaction, e.g. the introduction of the basic side chains as potentially pharmacophoric substructures. Thus treatment of **123a** with diethylaminoethyl chloride hydrochloride and/or with 4-(2-chloroethyl) morpholine hydrochloride in refluxing ethanol in the presence of anhydrous sodium acetate gave the corresponding s-alkylated products **133** and **134** respectively (Scheme 43).



Scheme 43. Synthesis of s-alkylated products **133** and 1**34**.

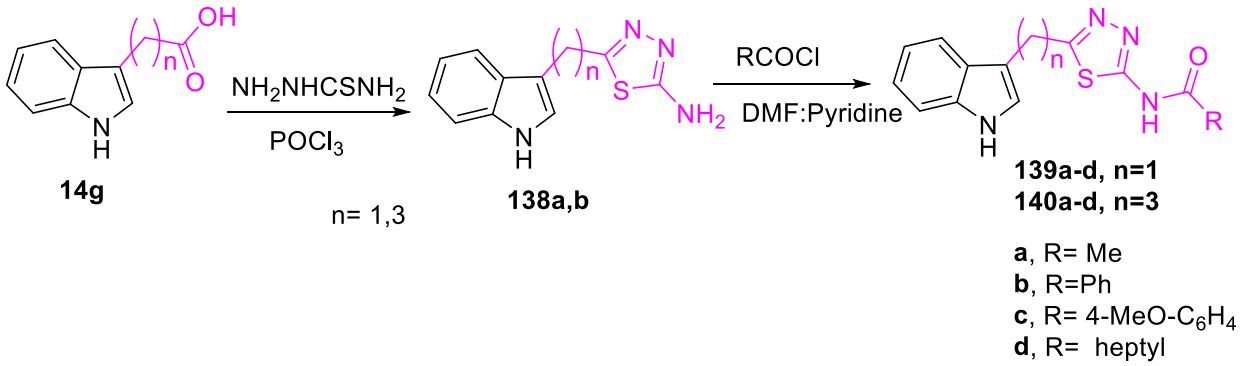
3.5. Synthesis of 3-indolyl-1,3,4-thidiazole derivatives

It was described that[49] the reaction of acid hydrazide **38a** with ammonium thiocyanate in ethanol using hydrochloric acid as a catalyst gave the 2-(2-methyl-1*H*-indole-3-carbonyl) hydrazine carbothioamide **135**. Treatment of latter compound with conc. H_2SO_4 followed by neutralized with liquid ammonia yielded 2-amino-5-(2-methyl-1*H*-indol-3-yl)-1,3,4-thiadiazole **136**. Reaction of amino-1,3,4-thiadiazole **136** with different acid chlorides in DMF and pyridine afforded the amid derivatives **137a-d** (Scheme 44).



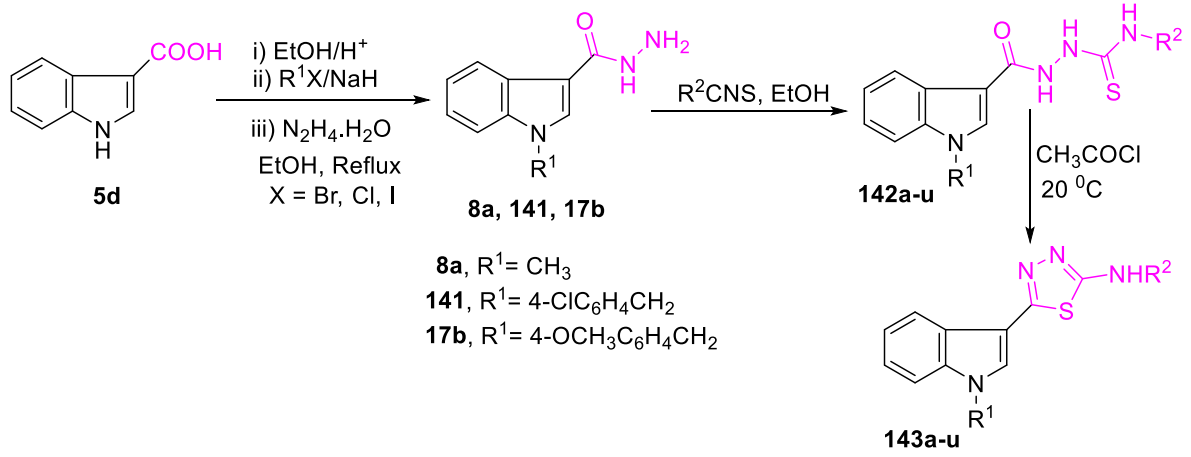
Scheme 44. Synthesis of 3-indolyl-1,3,4-thidiazole derivatives **137a-d.**

Also,[49] the reaction of indole-3-acetic acid or indole-3-butric acid **14g** with thiosemicarbazide in the presence of phosphoryl chloride under reflux formed the corresponding 2-amino-1,3,4-thiadiazole derivatives **138a,b**. The amide derivatives **139a-d, 140a-d** and **141a-d** were synthesized by the reaction of 2-amino-1,3,4-thiadiazoles **138a,b** with different acid chlorides in DMF and pyridine (see Scheme 45).



Scheme 45. Synthesis of 3-indolyl amide derivatives **139** and **140**.

Kumar D. *et al* reported that[53] they used the protocol reported previously.[51, 74] Thus, treatment of indole-3-carboxylic acid **5d** with halo compounds in ethanol and sodium hydride followed by reaction with hydrazine hydrate afforded the corresponding *N*-substited-indole-3-carbohydrazide **8a, 17b** and **141**. Reaction of the latter compounds with aryl isothiocyanates yielded the thiosemi-carbazone **142a-v**. Oxidative cyclization of **142a-v** was accomplished in presence of acetyl chloride to afford **143a-v** (Scheme 46).

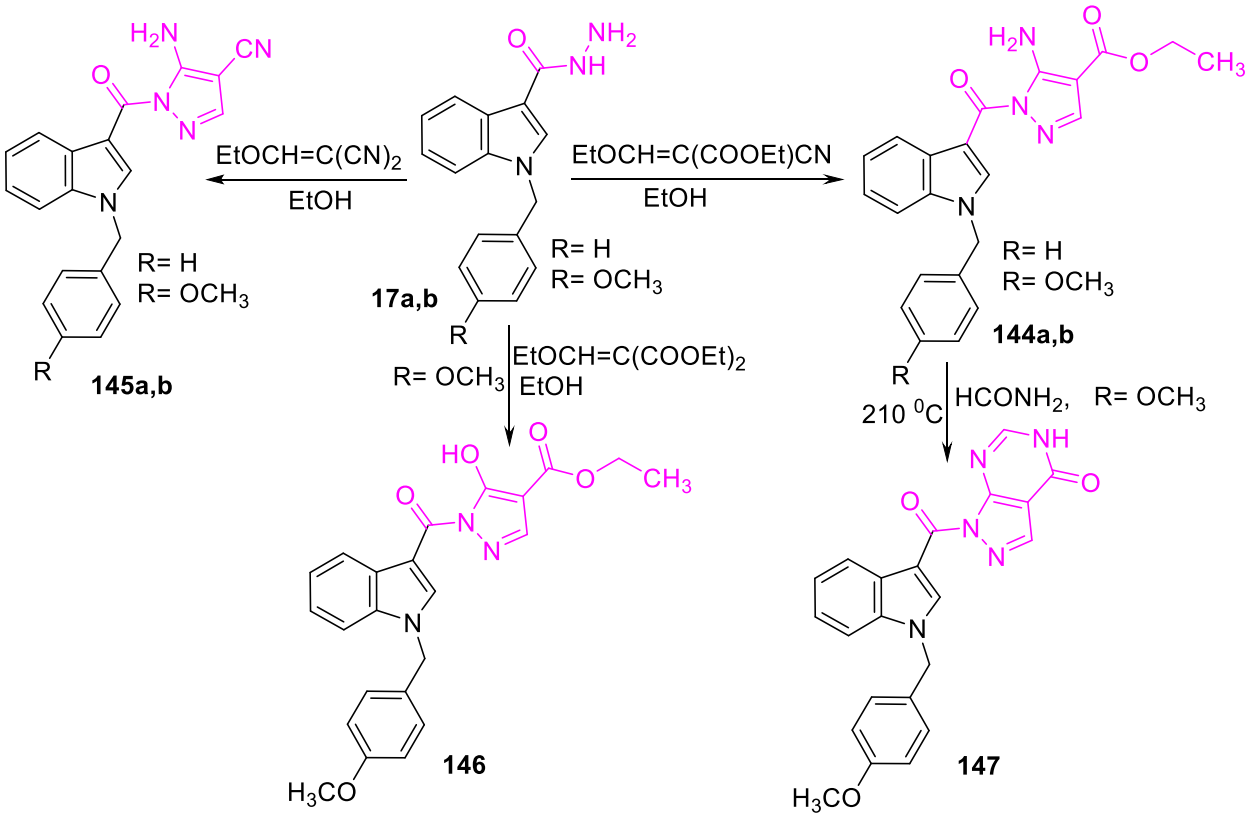


Cd	R	R^1	R^2	Cd	R	R^1	R^2
a	H	H	C_6H_5	**l**	H	4-$OCH_3C_6H_4CH_2$	4-$OCH_3C_6H_4$
b	H	H	4-$CH_3C_6H_4$	**m**	H	H	3,4,5-$(OCH_3)_3C_6H_2$
c	H	H	4-ClC_6H_4	**n**	OCH_3	H	4-$OCH_3C_6H_4$
d	H	H	4-$OCH_3C_6H_4$	**o**	OCH_3	H	4-$OCH_3C_6H_4$
e	H	H	4-$CF_3C_6H_4$	**p**	OCH_3	H	3,4,5-$(OCH_3)_3C_6H_2$
f	H	H	3,4,5-$(OCH_3)_3C_6H_2$	**q**	H	H	4-ClC_6H_4
g	H	H	$CH_2C_6H_4$	**r**	H	H	4-$OCH_3C_6H_4$
h	H	H	C_6H_5	**s**	H	H	3,4,5-$(OCH_3)_3C_6H_2$
i	H	4-$ClC_6H_4CH_2$	4-ClC_6H_4	**t**	H	H	$CH_2C_6H_4$
j	H	4-$ClC_6H_4CH_2$	C_6H_5	**u**	H	H	4-$OCH_3C_6H_4$
k	H	4-$OCH_3C_6H_4CH_2$	3,4,5-$(OCH_3)_3C_6H_2$	**v**	H	H	3,4,5-$(OCH_3)_3C_6H_2$

Scheme 46. Synthesis of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles **143a-u.**

3.6. Synthesis of 3-indolyl-pyrazole hybrids

In 2010, Farghaly at al reported that,[32, 34] the easily accessible 1*H*-indole-3-carbohydrazide **17a,b** was chosen as starting material of the synthesis of the new pyrazole derivatives as well as pyrazolone derivatives. Thus, treatment of carbohydrazide **17a,b** with ethyl ethoxymethylene cyanoacetate or ethoxymethylene-malononitrile in absolute ethanol resulted in the formation of the corresponding ethyl 5-amino-1-(1-(4-sustitutedbenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carboxylate (**144**) and 5-Amino-1-(1-(4-sustituted-benzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carbonitrile (**145**) respectively. Reaction of latter compound **145** with formamide gave the corresponding 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **147**. When **17a** was allowed to react with diethyl ethoxymethylenemalonate in refluxing absolute ethanol, the expected ethyl 5-hydroxy-1-(1-(4-methoxybenzyl)-1*H*-indole-3-carbonyl)-1*H*-pyrazole-4-carboxylate analog **146** was obtained (Scheme 47).

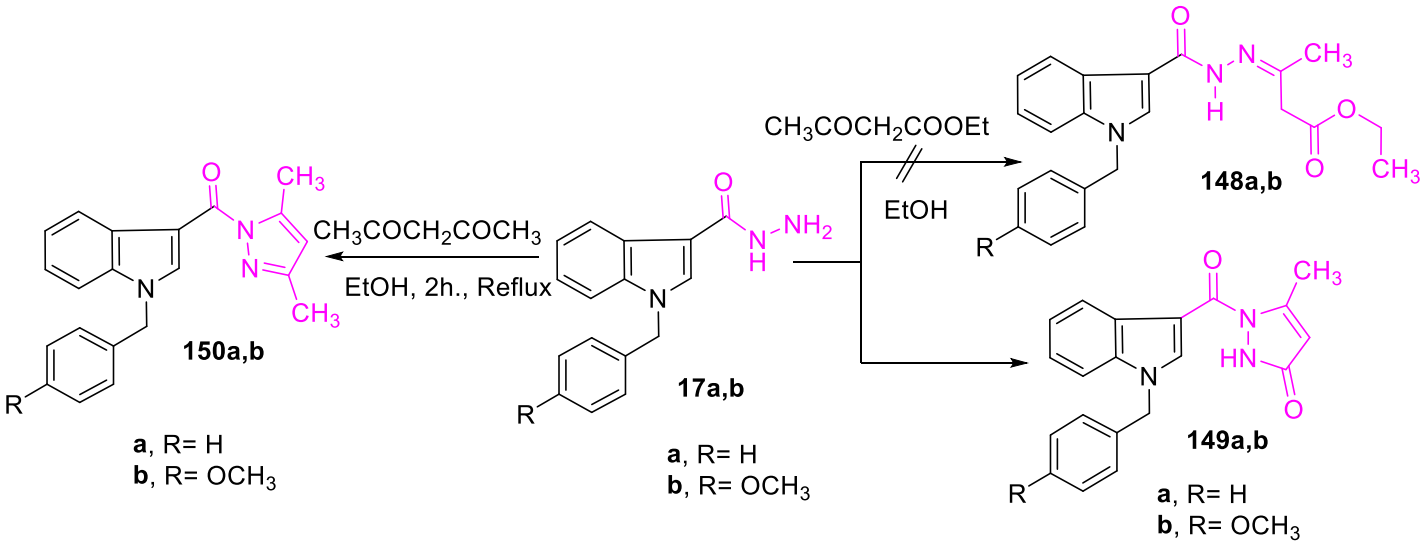


Scheme 47. Synthesis of indole derivatives containing pyrazole moiety **144-147**.

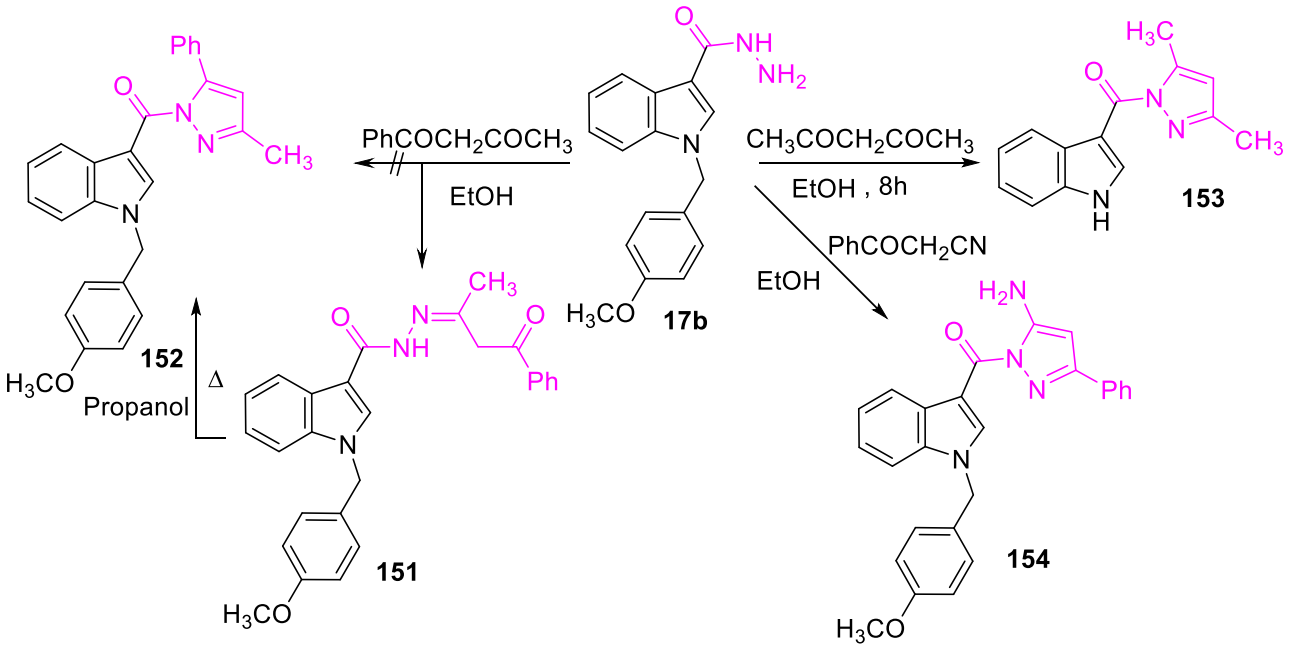
Treatment[31, 32] of **17a,b** with ethyl acetoacetate without solvent did not afford the ester derivative **148a,b** but gave the cyclized product, pyrazolone derivative **149a,b**. On the other hand, condensation of the hydrazide **17a,b** with acetyl acetone in refluxing ethanol gave the corresponding pyrazolyl derivative **150a,b** in 85 % yield (Scheme 48).

Interestingly,[32] when the acid hydrazide **17b** was allowed to react with acetyl acetone in refluxing ethanol for 2 hours afforded directly the cyclized 3,5-dimethy pyrazole derivative **150b** in 64% yield. Whereas, heating the same acid hydrazide with benzoyl acetone under the same reaction conditions led to the formation the open structure **151** which was cyclized via its boiling in propanol to afford the corresponding (1-(4-Methoxybenzyl)-*1H*-indol-3-yl)(3-methyl-5-phenyl-*1H*-pyrazol-1-yl) methanone (**152**). It is worthy to note that, when the carbohydrazide **17b** was allowed to react with acetyl acetone in boiling ethanol for prolonged

time, an unexpected debenzylation occurred and the (3,5-dimethyl-1*H*-pyrazol-1-yl)(1*H*-indol-3-yl)methanone (**153**) was obtained. Treatment of the acid hydrazide with benzolyl acetonitrile in boiling ethanol rise to the formation of the corresponding 5-amino-3-phenyl-1*H*-pyrazole **154** (Scheme 49).

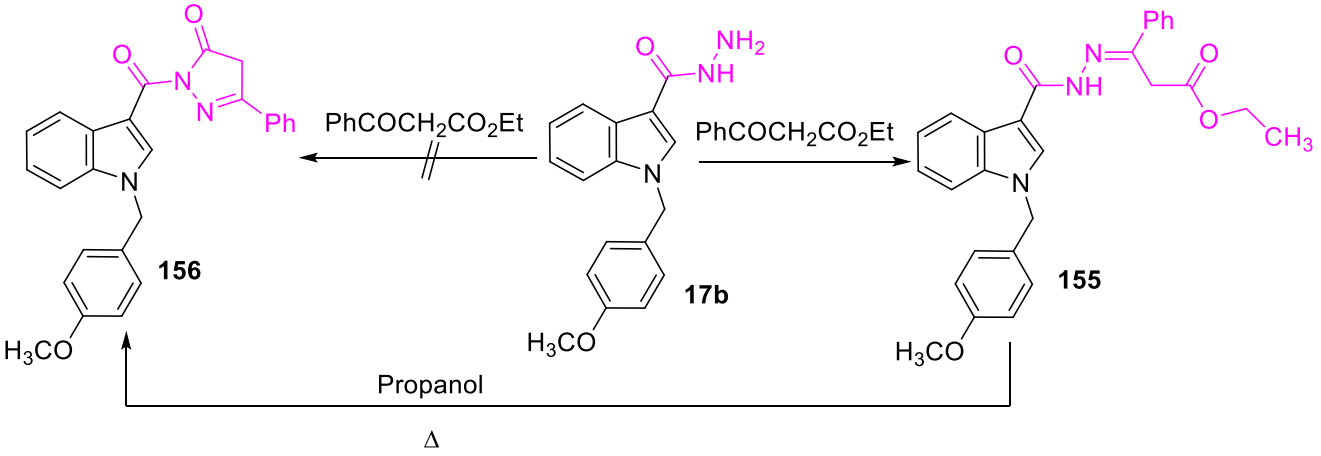


Scheme 48. Synthesis of pyrazolyl derivatives **149a,b** and **150.**



Scheme 49. Reaction of carbohydrazide **17b** with some diketone compounds.

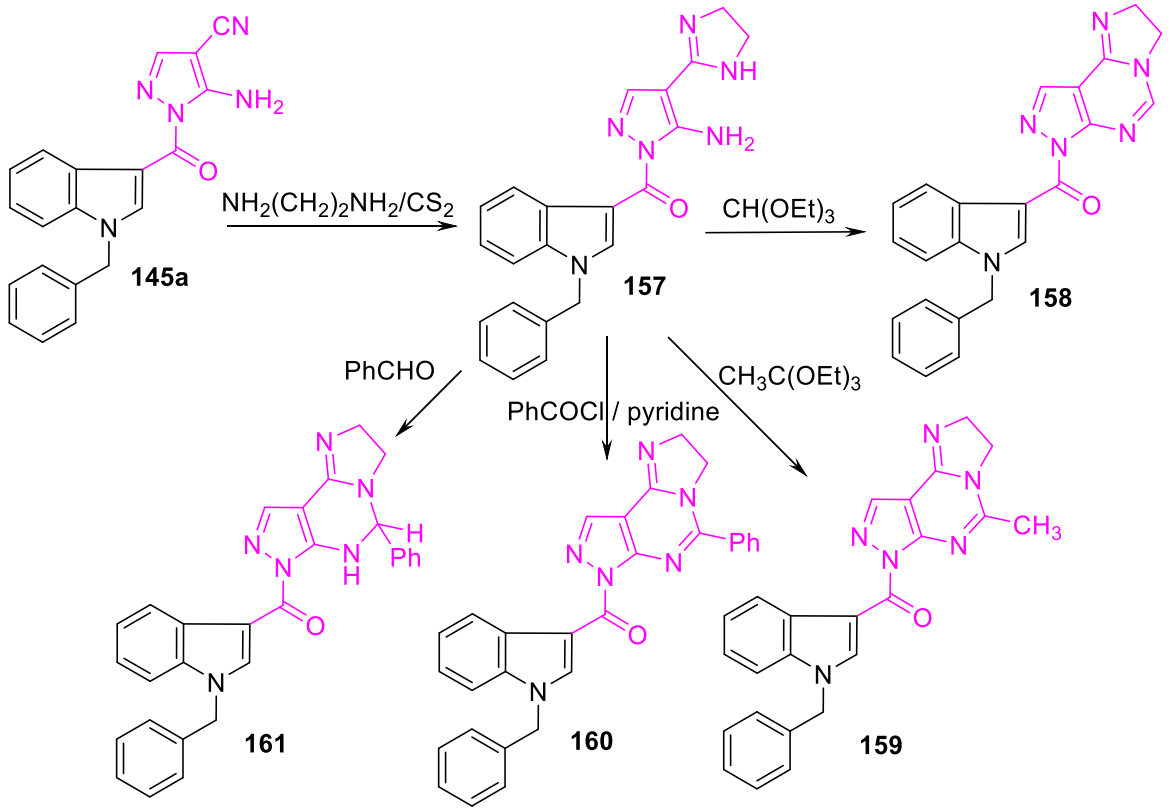
Furthermore, treatment[32] of the acid hydrazide **17b** with ethyl benzoylacetate in ethanol, the open structure **155** was obtained. The latter compound could be cyclized via its boiling with high boiling point solvent (propanol) to afford the corresponding 1*H*-pyrazol-5(4*H*)-one **156** (Scheme 50).



Scheme 50. Synthesis of 5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one based indole **156.**

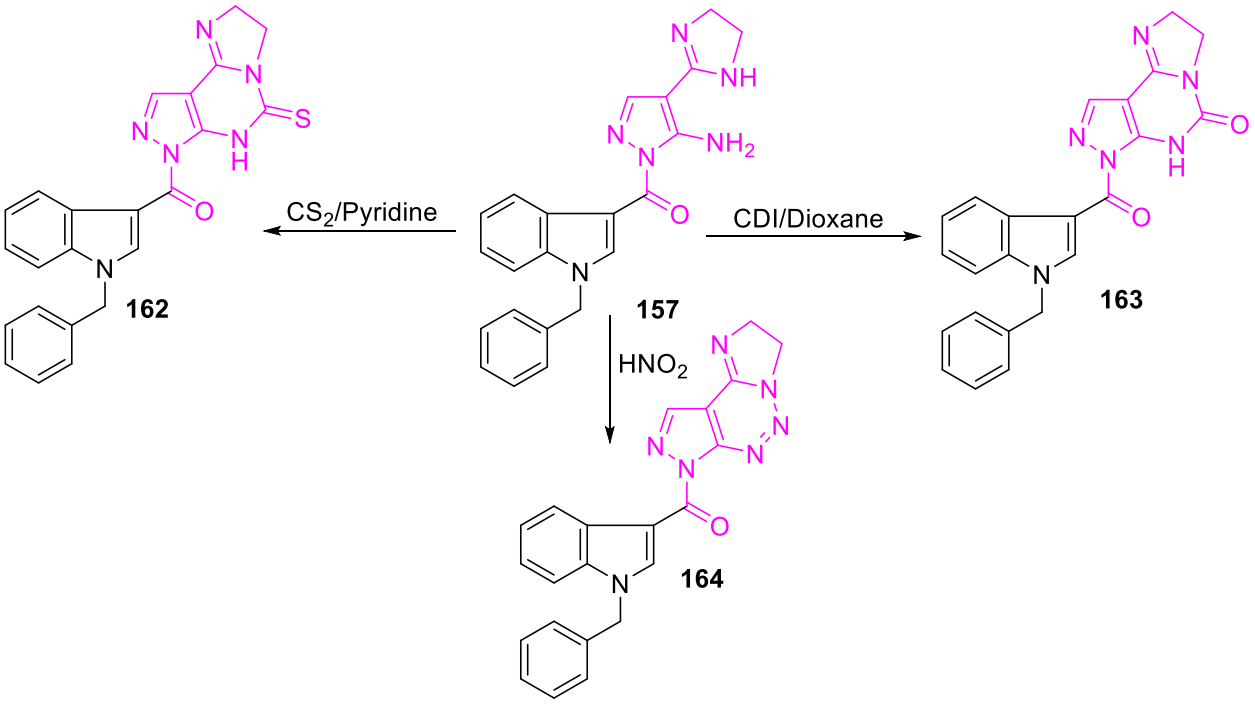
3.6.1. Synthesis of imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines derived from indole and related heterocycles

Farghaly *et al*[33] reported that, the interaction of the aminonitrile **145a**[32] with ethylenediamine in the presence of a catalytic amount of carbon disulfide afforded the corresponding imidazolinylpyrazole **157a.** The latter compound could be ring closed into tricyclic systems in different ways. The tricyclic system **158** was prepared by the reaction of imidazolinylpyrazole **157a** with triethlorthoformate. The methyl analog of imidazopyrazolo-pyrimidine **159** was obtained by the reaction of **157a** with trimethylorthoacetate. Whereas, when compound **157a** was allowed to react with benzoyl chloride in boiling pyridine, the corresponding phenyl analog **160** was formed. Interaction of **157a** with benzaldehyde afforded the corresponding imidazolpyrazolopyrimidine derivative **161** (Scheme 51).



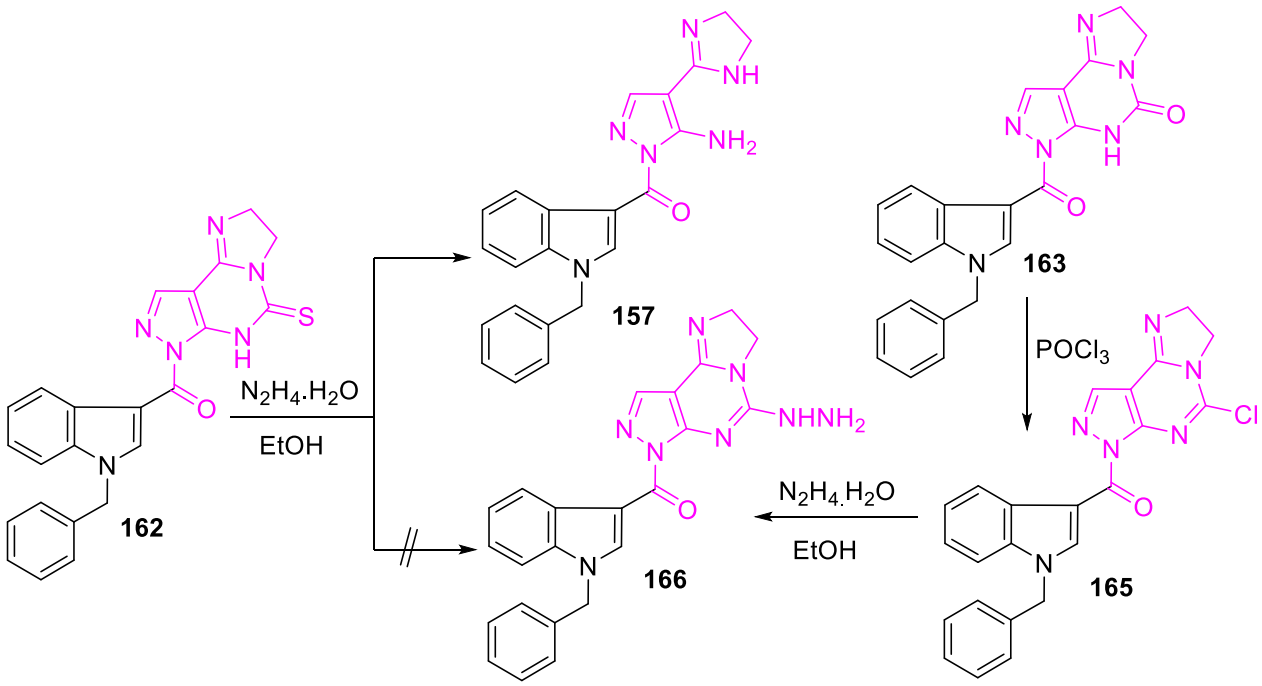
Scheme 51. Synthesis of tricyclic compounds **158-161.**

Treatment[33] of **157** with carbon disulfide led to the formation of the corresponding imidazo-pyrazolopyrimidine thione **162**. Whereas, reaction of **157** with 1,1`-carbonyldi-imidazolyl (CDI) in boiling dioxane gave the oxo-analog **163**. The triazine derivative **164** could be obtained through the interaction of **157** with nitrous acid at room temperature (Scheme 52).



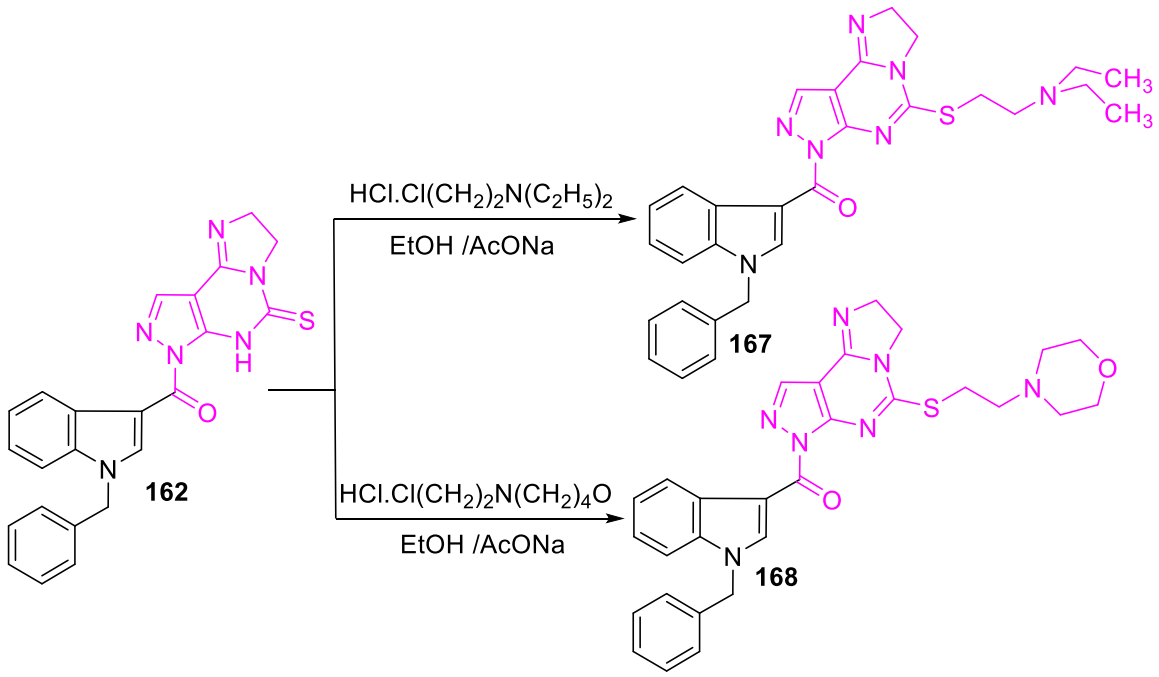
Scheme 52. Synthesis of pyrimidine and triazine derivatives **162-194**.

Interestingly,[33] hydrazinolysis of the thione **162** with hydrazine hydrate did not afford the expected hydrazine product **166** but the ring opining was occurred and the imidazopyrazole **157** was recovered Treatment of the imidazopyrazolopyrimidine-5-one **163** with phosphoryl chloride led to the formation of the corresponding chloro derivative **165**. The latter compound was subjected to the hydrazinolysis to give the corresponding hydrazino compound **166** (Scheme 53).



Scheme 53. Synthesis of hydrazino compound **166.**

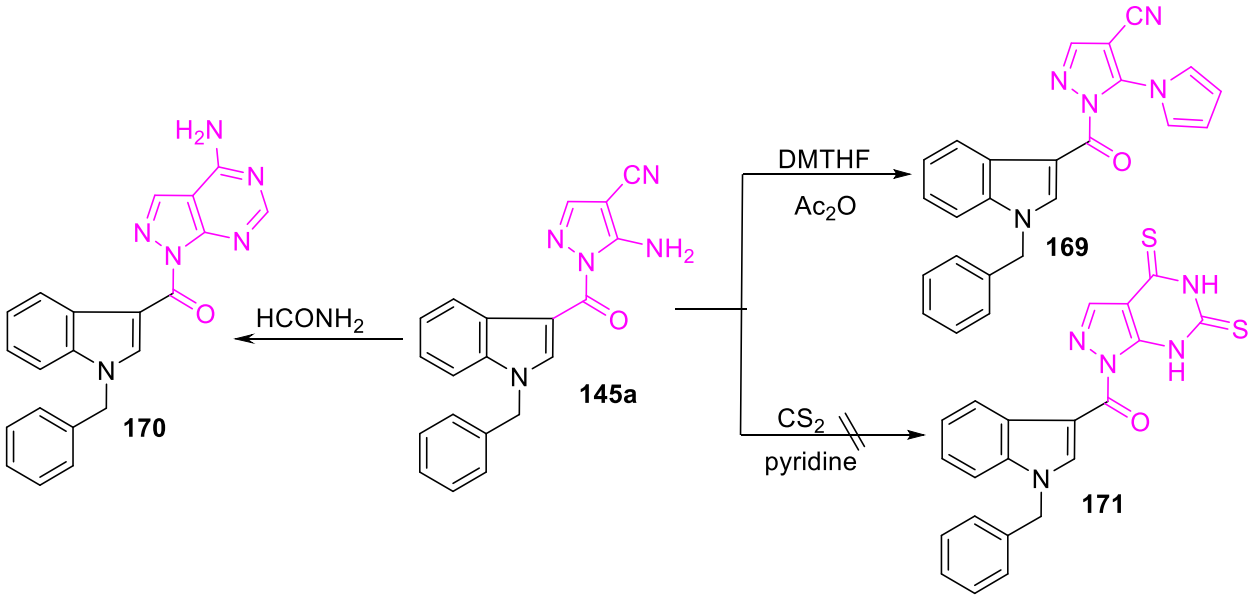
The thione derivative **162**[33] was subjected to the alkylation reactions with some bioactive alkylating agents such as 4-(2-chloroethyl)morpholine hydrochloride and/or 2-dimethyaminopropyl chloride hydrochloride in boiling ethanol in the presence of fused sodium acetate to give the s-alkylated products **167**, **168** (Scheme 54).



Scheme 54. Synthesis of the s-alkylated products **167**, **168**.

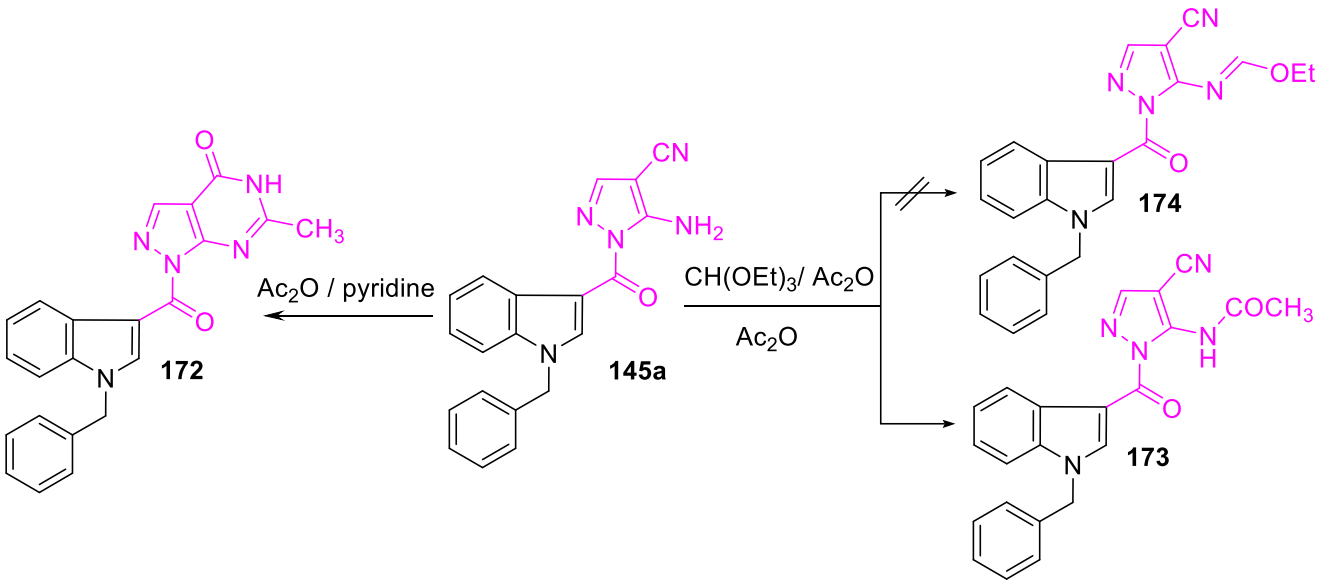
In continuation to was mentioned above,[33] interaction of amino nitrile **145a** with 2,5-dimethoxytetrahydrofurane afforded the pyrrolyl derivative **169**. However, reaction of **145a** with formamide

gave the corresponding pyrazolopyrimidine **170**. An attempt was done to prepare the pyrazolopyrimidine-dithione **171** via the reaction of **145a** with carbon disulfide in boiling pyridine but it was unsuccessful, the starting material was recovered unchanged (Scheme 55).



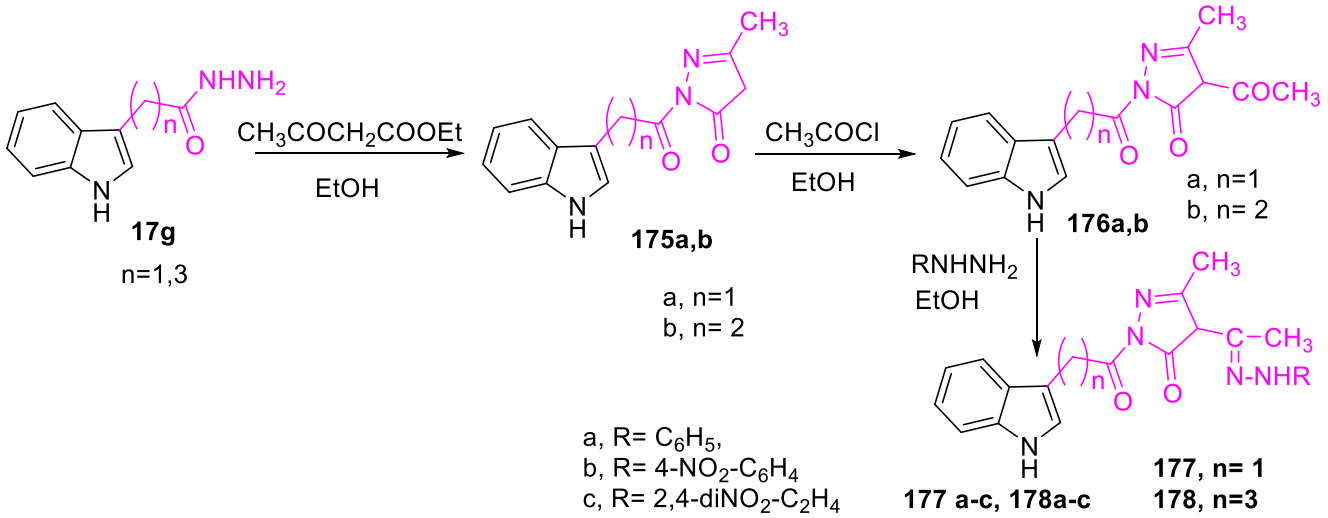
Scheme 55. Synthesis of amino pyrazolopyrimidine **170.**

Treatment[33] of **145a** with acetic anhydride in boiling pyridine led to the formation of the corresponding pyrazolopyrimidine derivative **172** through Dimroth rearmament reaction. However, reaction of **145a** with neat acetic anhydride gave the acetyl amino derivative **173**. Moreover, an attempt to obtain the ethoxymethyleneimino **174** via the reaction of **145a** with neat triethylorthformate, the starting material was recovered unchanged, whereas the reaction was carried out in the presence of acetic anhydride, the product was identified as the acetyl amino derivative **173** (Scheme 56).



Scheme 56. Reaction of amino nitrile **145a** with acetic anhydride

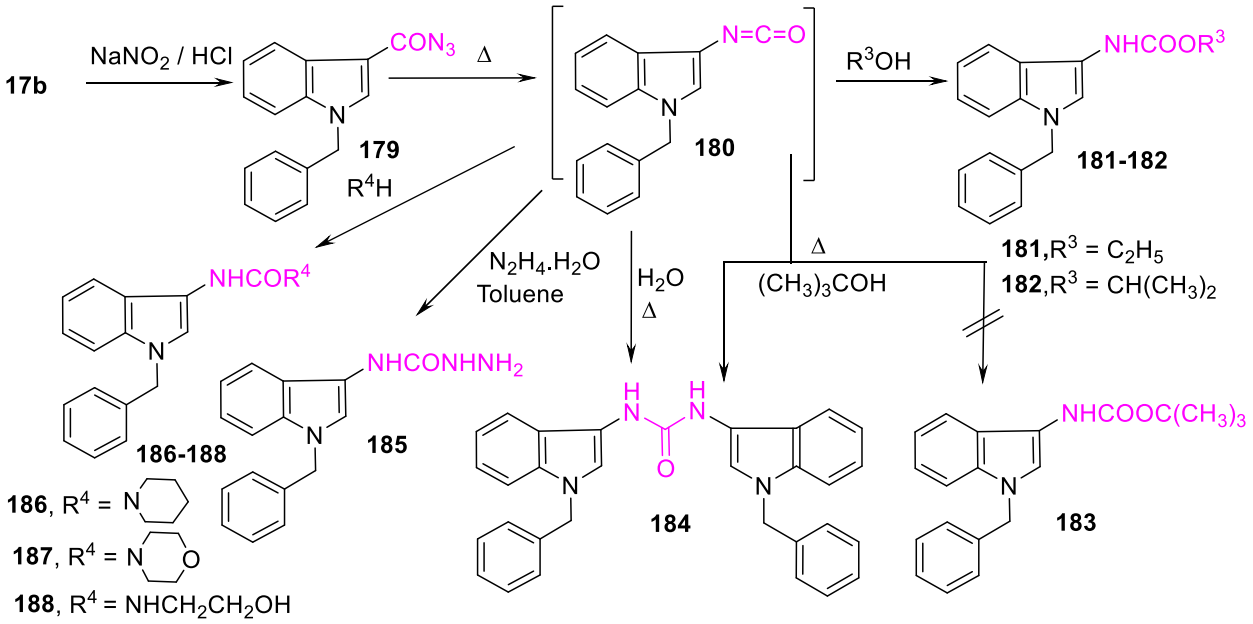
It was suggested that[48, 49] the reaction of hydrazides **17g** with ethylacetoacetate in absolute ethanol yielded the pyrazolone derivatives **175a,b**. Treatment of pyrazolone derivatives **175a,b** with acetyl chloride in 1,4-Dioxane in present of calcium hydroxide led to formation of 4-acetyl pyrazolone compounds **176a,b**. Amide derivatives **177** were synthesized by the reaction equimolar of 2-amino-1,3,4-thiadiazole **176a,b** and different acid chlorides in DMF and pyridine as accepter (Scheme 57).



Scheme 57. Synthesis of 3-indolyl-pyrazole derivatives **175-178.**

3.7. Synthesis of 3-indolyl semicarbazides and urea dcerivatives

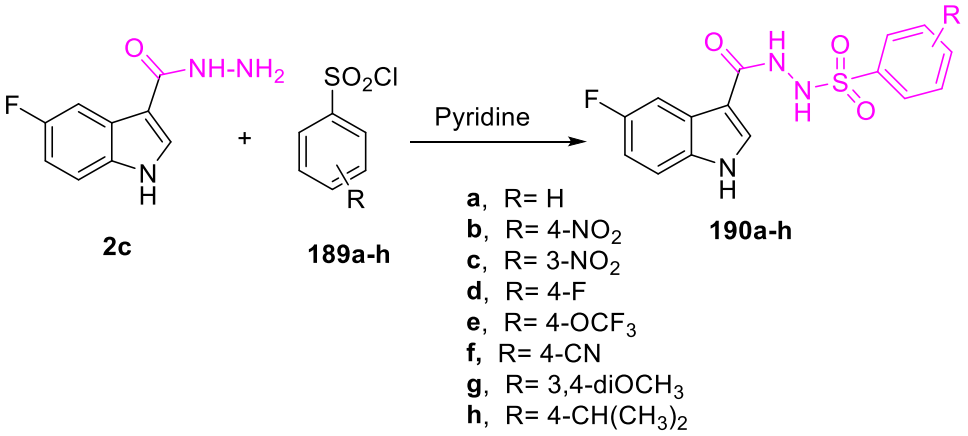
Diazotisation[31] of **17a** with an equimolar quantity of sodium nitrite in glacial acetic acid produced the carboazide compound **179**. On refluxing **179** in ethanol or isopropyl alcohol, it underwent *Curtius* rearrangement where the isocyanate derivative **180** was formed as intermediate The latter intermediate reacted concomitantly with ethanol and isopropyl alcohol, used as a solvent to give the corresponding ethyl and isopropyl carbamate **181** and **182** respectively. Interestingly, refluxing of the carboazide **179** with tertiary butyl alcohol did not give the tertiary butyl carbamate **183** but afforded the urea derivative **184**, which was prepared independently by boiling of **179** with water. When the alcohol was replaced by amines, the corresponding urea derivatives **186-188** were obtained. It is noteworthy that when the acid azide **179** was heated in an excess of hydrazine hydrate, *Curtius* rearrangement did not occur and the product was identified as acid hydrazide **17a**. However, when **179** was boiled first in dry toluene to insure the *Curtius* rearrangement of **179** into the isocyanate **180** followed by addition of an excess of hydrazine hydrate, the expected semicarbazide **30** was obtained (Scheme 58).



Scheme 58. Synthesis of 3-indolyl-semicarbazides and urea dcerivatives

3.8. Synthesis of indole-based sulfonamide derivatives

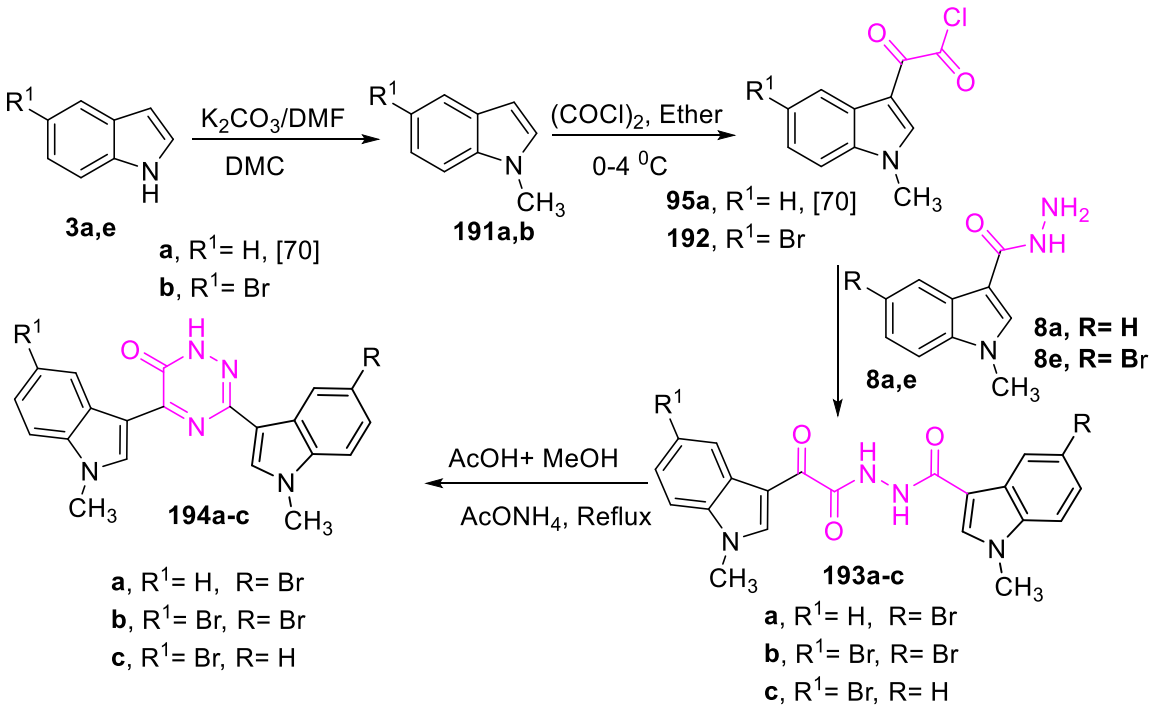
Ibrahim M. *et al*,[52] suggested that the treatment of 5-fluoro-1*H*-indole-3-carbohydrazide **2c** with aryl sulfonyl chloride derivatives **189a-h** in the presence of pyridine gave the corresponding of indole-based-sulfonamide derivatives **190a-h** (Scheme 59).



Scheme 59. Synthesis of indole-based sulfonamide derivatives **190a-h.**

3.8. Synthesis of 3-indolyltriazinones

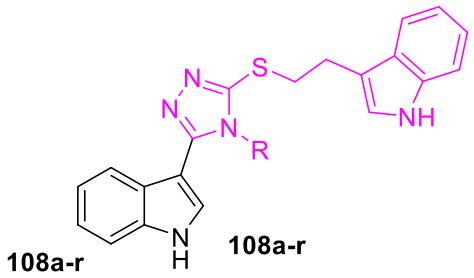
In 2018, Sreenivasulu, R. *et al*[42] mentioned that the reaction of indole derivatives **3a,e** with dimethylcarbonate and K_2CO_3 in DMF solvent afforded the corresponding *N*-methyl derivatives **191a,b**.[75] Treatment of **191a,b** with oxalyl chloride in diethyl ether at 0–4 °C for 4 h. gave *N*-methyl indole-3-glyoxalyl chloride derivatives **95a** and **192**[76] Reaction of latter compounds with *N*-methyl indolyl-3-carbohydrazides **8a,e** in THF and Et_3N under reflux yielded 1,2,5-triketo-3,4-diamino derivatives **193a–c**. Treatment of the tri keto diamino derivatives reacted with Glac. AcOH, methanol and ammonium acetate under reflux afforded the corresponding triazinone **194a–c** (Scheme 60).



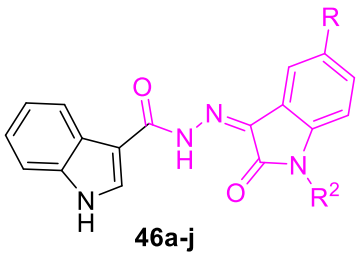
Scheme 60. Synthesis of the triazinone derivatives **194a-c**.

4. Biological Importance

Indole derivatives have a wide range of biological and pharmacological activities.[6] Specifically, 3-substituted indole derivatives exhibit a variety of pharmacological effects, including antibacterial[18] anti-inflammatory,[77] antitumor,[51] anti-cancer,[41, 42] antihypertensive[78] antidepressant,[41] antiviral[79] and anti-*HIV*[15, 16] activities. Oxadiazole and indole containing substances exhibit a diversity of biological roles. Therefore, the linked molecules of 3-substituted indole and oxadiazole frame structures, indole-based oxadiazoles, are useful physiologically active agents. Indole substituted 1,2,4-oxadiazoles exhibit a broad spectrum of biological activities, including anticancer activity.[80] Indole-substituted 1,2,4-oxadiazoles also act as 5-HT3 antagonists.[81] It was mentioned that, the cytotoxic activity of 1,2,4-triazolo-linked bis-indolyl conjugates **108a-r** as dual inhibitors of tankyrase and PI3K.[69] The development of 2-oxindolin-3-ylidene-indole-3-carbohydrazide derivatives **46a-j** were proved as novel apoptotic and anti-proliferative agents[40] towards colorectal cancer cells.



108a-r

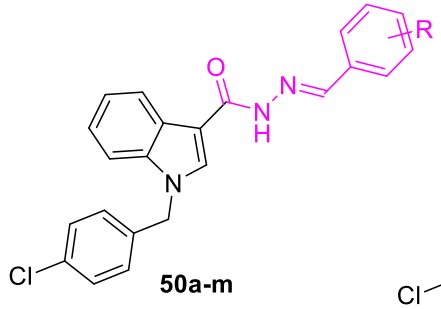


46a-j

46a-j a, R= H R^2= CH_3
b, R= H R^2= $CH_2C_2H_5$
c, R= H R^2= $CH_2C_6H_5$
d, R= Cl R^2= $CH_2C_2H_5$
e, R= Br R^2= $CH_2C_2H_5$

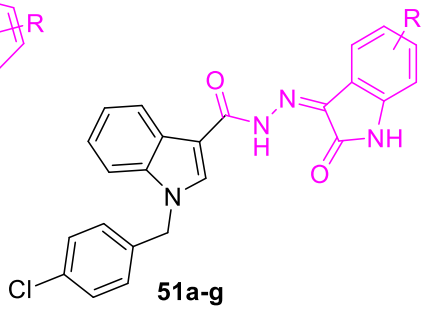
a, R= Benzyl
b, R= Phenyl
c, R= 3-Bromophenyl
d, R= isopropyl
e, R= p-tolyl
f, R= 3,4,5-trimethoxyphenyl
g, R= 4-chlorophenyl
h, R= Phenyl
i, R= 3-Bromophenyl
j, R= isopropyl
k, R= p-tolyl
l, R= 3,4,5-trimethoxyphenyl
m, R= 4-chlorophenyl
n, R= Phenyl
o, R= 3-Bromophenyl
p, R= isopropyl
q, R= p-tolyl
r, R= 3,4,5-trimethoxyphenyl

In 2020, R. Sreenivasulu *et al*. reported that,[41] the 2,5-bis(indolyl)-1,3,4-oxadiazoles **76a-j**, nortopsentin analogues were found to be as anticancer agents. Whereas, Design, synthesis, and evaluation of novel N'-substituted-1-(4-chlorobenzyl)-1Hindol- 3-carbohydrazides **50a-m** and **51a-g** as antitumor agents.[51]



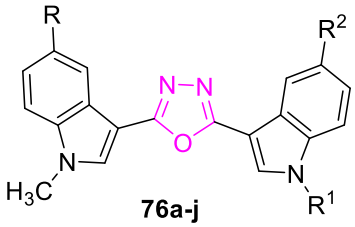
50a-m

a, R= H
b, R= 2-Cl
c, R= 3-Cl
d, R= 4-Cl
e, R= 2,6-Cl_2
f, R= 4-NO_2
g, R= 2-OH
h, R= 2-OH-3-allyl
i, R= 2-OH-4-OCH_3
j, R= 3-OH-4-OCH_3
k, R= OCH_3
l, R= 4-$N(CH_3)_2$
m, R= 3,4,5-$(OCH_3)_3$



51a-g

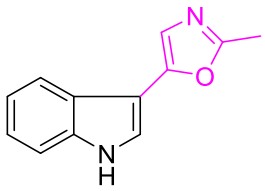
a, R= H
b, R= 5-F
c, R= 5-Cl
d, R= 7-Cl
e, R= 5-Br
f, R= 5-CH_3
g, R= OCH_3



76a-j

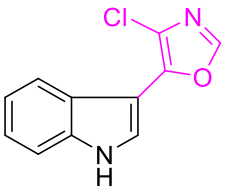
a, R= Br, R^1= CH_3, R^2= H
b, R= Br, R^1= CH_3, R^2= Br
c, R= H, R^1= CH_3, R^2= OCH_3
d, R= H, R^1= CH_3, R^2= NO_2
e, R= Br, R^1= CH_3, R^2= OCH_3
f, R= H, R^1= H, R^2= H
g, R= H, R^1= H, R^2= Br
h, R= H, R^1= H, R^2= NO_2
i, R= Br, R^1= H, R^2= H
j, R= Br, R^1= H, R^2= Br

Two series of pimprinine derivatives **A** and **B** containing 1,3,4-oxadiazole-5-thioether moieties **C** and **D** were efficiently exhibited antifungal activities.[35] The 2-(1*H*-indol-3-yl)-5-substitued-1,3,4-oxadiazoles **65a-j**, 5-(1*H*-indol-3-yl)-2-substiuted oxazole **98a–l** and 5-(1-benzyl-1*H*-indol-3-yl)-2-methyloxazole **99** were discovered as pimprinine alkaloids as novel agents against a plant virus.[68] 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl)methylindoles showed antifungal activity.[45]



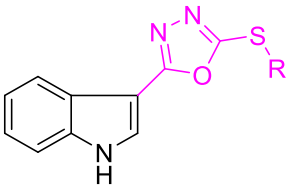
A

Pimprinine

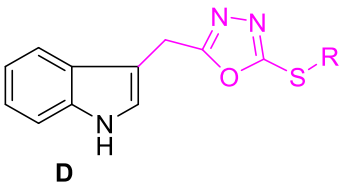


B

Streptochlorin

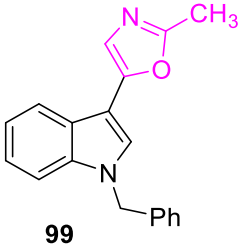


C

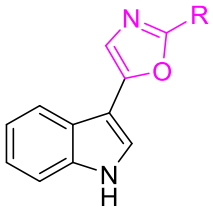


D

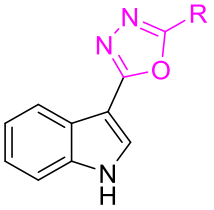
1,3,4-Oxadiazole-5-thioethers, antifungal activities



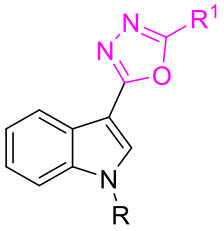
99



98a-l

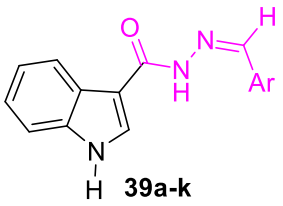


65a-j



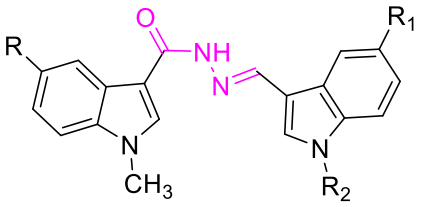
67a-m and **68a-z**

It was mentioned that the bis(indolyl)hydrazide-hydrazone **53a-d** derivatives showed antiproliferative activities[64] and the indole-based aroyl hydrazones **56a-i** were discovered to be as anticonvulsants.[65, 66] The arylidene indoles **39a-k** were proved to be as anti-platelet aggregation inhibitors.[39, 63]

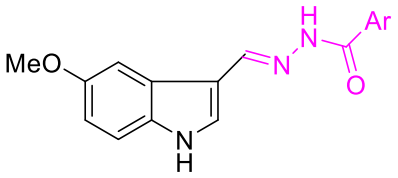


39a-k

a, Ar = C_6H_5 **[31, 39]**
b, Ar = C_6H_4Cl(p) **[31, 39]**
c, Ar = $C_6H_4OCH_3$(o) **[39]**
d, Ar = C_6H_4OH(p) **[39]**
e, Ar = C_6H_4OH(m) **[39]**
f, Ar = C_6H_4Cl(m) **[39]**
g, Ar = C_6H_4F(o) **[39]**
h, Ar = C_6H_4F(m) **[39]**
i, Ar = $C_6H_4CF_3$(p) **[22,29]**
j, Ar = $C_6H_4N(CH_3)_2$(p) **[31]**
k, Ar = $C_6H_4OCH_3$(p) **[22,29,31**

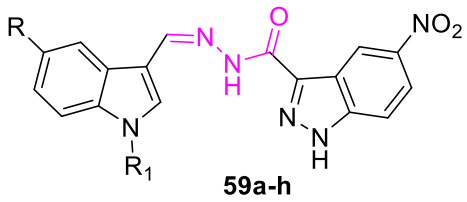


53a-d **a,** R= Br, R^1= H, R^2= CH_3
b, R= H, R^1= H, R^2= CH_3
c, R= Br, R^1= H, R^2= H
d, R= Br, R^1= OCH_3, R^2= H



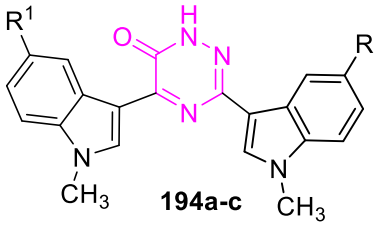
56a-i **a,** Ar= *P*-OH-C_6H_4
b, Ar= *o*-,*P*-diOH-C_6H_3
c, Ar= *P*-Cl-C_6H_4
d, Ar= *P*-F-C_6H_4
e, Ar= 2-furyl
f, Ar= 2-thienyl
g, Ar= *P*-OH, *m*-OMe-C_6H_3
h, Ar= 5-(4-methyl-1,2,3-thiadiazolyl)
i, Ar= 3-indolyl

It was reported that the (Z)-*N*'-((1,5-disubstituted-1*H*-indol-3-yl)methylene)-5-nitro-1*H*-indazole-3-carbohydrazides **59a-h** were evaluated as and the 3,5-bis(1,5-disubstitued-1*H*-indol-3-yl)-1,2,4-triazin-6(1*H*)-one (nortopsentin analogs) **194a-c** were evaluated as antitumor agents.[42, 67]



59a-h

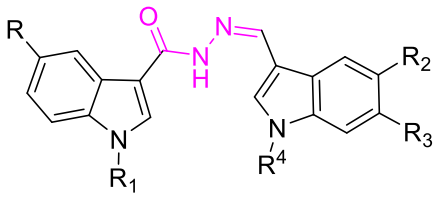
59a, R= H, R^1= H
59b, R= H, R^1= CH_3
59c, R= Br, R^1= H
59d, R= Br, R^1= CH_3
59e, R= NO_2, R^1= H
59f, R= OCH_3, R^1= H
59g, R= OCH_3, R^1= CH_3
59h, R= NO_2, R^1= H



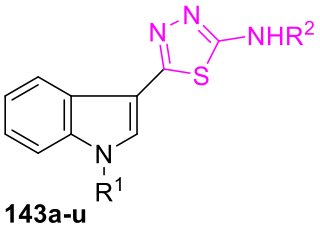
194a-c

a, R^1= H, R= Br
b, R^1= Br, R= Br
c, R^1= Br, R= H

It was mentioned that the bis(indolyl)hydrazide–hydrazones **61a-n** were proved to be as potent cytotoxic agents[46] and a series of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles **143a-u** as potent cytotoxic agents.[53]



61a-n



143a-u

Conclusions

Indole derivatives have a wide range of biological and pharmacological activities. Specifically, 3-substituted indole derivatives have attracted particular attention to scientists due to the high biological and therapeutic importance of these compounds in all fields. All this encouraged us to search for advances in synthetic methods of the 1*H*-indole-3-carbohydrazide derivative and its reactions, in addition to the biological importance of these compounds.

Acknowledgements

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