The Synthesis of Aplysinopsins, Meridianines, and Related Compounds

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Abstract: Aplysinopsins and meridianines have been isolated from various marine organisms. They exhibit interesting biological activity, such as cytotoxicity and neurotransmission effects. Various synthetic approaches towards these two classes of natural products and their synthetic analogs have been developed. Most syntheses of aplysinopsins, meridianines, and their analogs are based either on coupling of two heterocyclic moieties *via* the methylidene bridge, or on heterocyclization of indoles, functionalized at position 3.

Keywords: Aplysinopsins, meridianines, alkaloids, natural products, marine organisms.

1. INTRODUCTION

The range of alkaloids isolated from marine organisms is enormous and, among them, a variety of biologically active metabolites containing the indole nucleus have been identified. 3-Substituted indoles represent an important functional group. The substituent at the 3-position of the indole ring is a formyl group, acetic acid, and frequently, a five or six membered heterocyclic ring, such as maleimide, imidazole, dihydroimidazole, oxazole, oxadiazine, and piperidine.

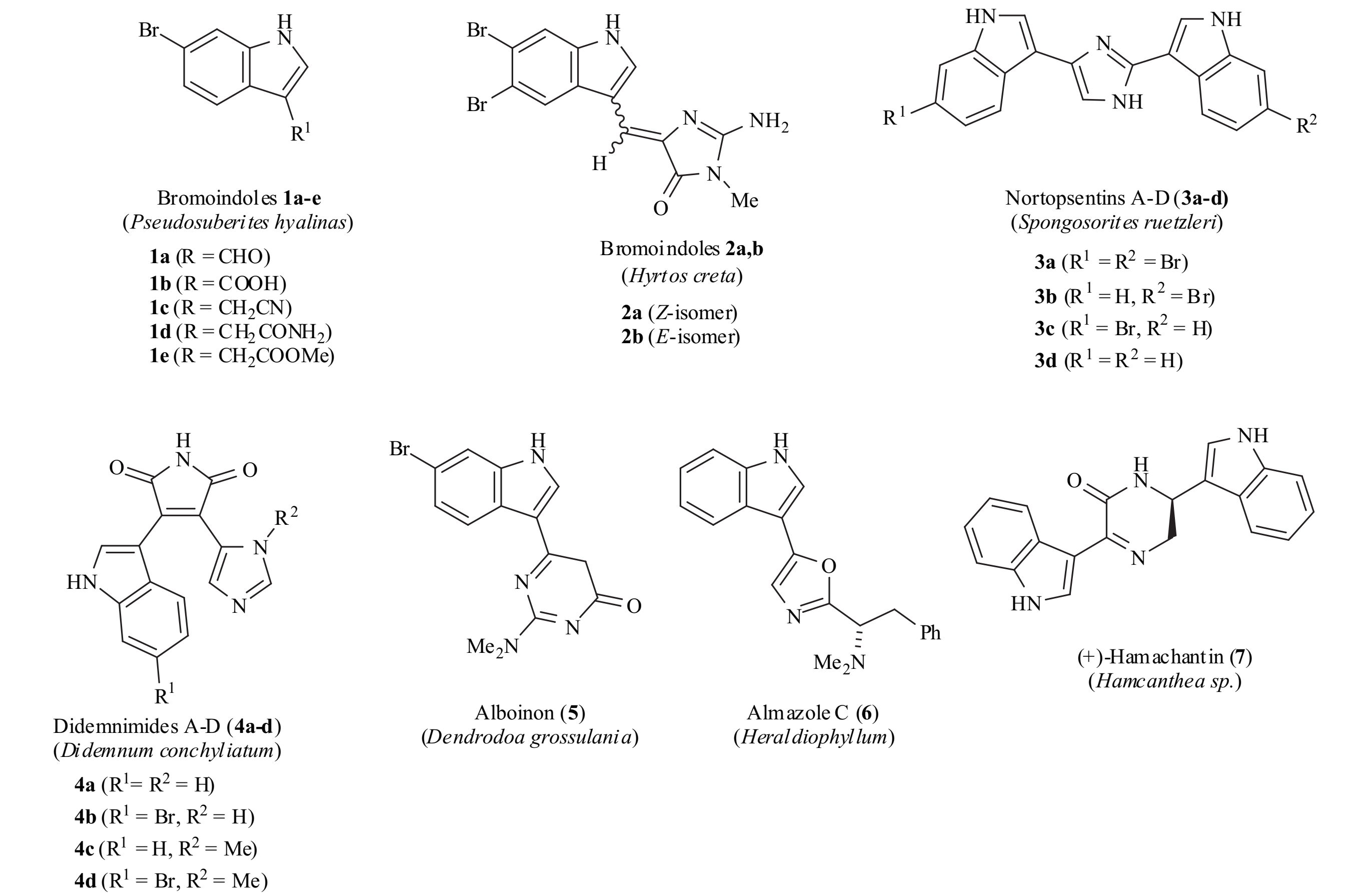

Fig. (1).

Both, the ascidien *Stromozoa murrayi* and an associated bacterium *Acinetobacter sp.* contain 6-bromoindole-3-carboxaldehyde (**1a**), which has previously been isolated from a marine *Pseudomones sp.* [1]. 6-Bromoindole-3-carboxaldehyde (**1a**) inhibited *in vitro* settlement of barnacle

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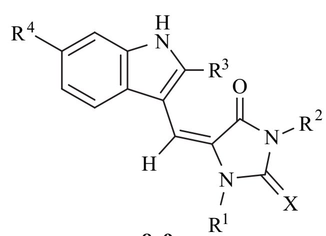
(*Belanus amphitrite*) larvae and showed moderate antibacterial properties [2]. The structures of four bromoindoles **1b–d**, isolated from *Pseudosuberites hyalinas*, were also confirmed by synthesis [3]. *Hyrtos creta* species collected in Okinawa yielded two isomeric selective inhibitors (**2a,b**) of neuronal nitric oxide synthase [4]. Antifungal alkaloids nortopsentins A–C **3a–c** were obtained from *Spongosorites ruetzleri* [5], while the non-brominated derivative nortopsentin D (**3d**) has been synthesized [6]. *Didemnum conchyliatum*, which has been collected from seagrass blades in mangrove habilitats in the Bahamas, contains the indole alkaloids didemnimides A–D **4a–d** that inhibit predation by fish [7]. Alboinon (**5**) is an oxadiazinone alkaloid from *Dendrodoa grossulania* from North Sea [8]. Almazole C (**6**) is an alkaloid from a Senegalese red alga of the genus *Heraldiophyllum* [9,10]. The synthesis of the (–)-enantiomer of the (+)-hamachantin A (**7**), isolated from *Hamacanthea sp.*[11], established the (*S*)-configuration of the stereogenic centre [12]. (Fig. **1**).

2. SYNTHESIS OF APLYSINOPSINS

Aplysinopsin (**8a**) has been isolated from sponge *Aplysinopsis reticulata* of the Australian Great Barrier Reef [13] and *Verongia spengelii* [14]. Some other derivatives, such as 2'-demethyl aplysinopsin **8b**, have been isolated from the marine sponge *Dercitus* sp. [15], 2'-demethyl-3'-methylaplysinopsin **8c** and 3'-deimino-3'-oxoaplysinopsin **8g** from dendrophylliid coral *Tubastraea* sp. [16,17], and 3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin **8h** from *Leptopsammia pruvoti* [16], 6-bromoaplysinopsins derivatives **8d–f** from *Dendrophyllia* sp. [17], **8i** from *Dercitus* [16], and **8j** from *Leptopsammia pruvoti* [16]. Some of these compounds display biological activities, such as specific cytotoxicity against the KB, P388, and L1210 cell cultures [14] and affect neurotransmission [18]. Recently, 5-[(2-phenyl-1*H*-indol-3-yl)methylidene]-2-thio-oxoimidazolidin-4-one (**9a**), a synthetic analog of aplysinopsin (**8a**), has been successfully tested against several cancer cell lines with the most significant activity obtained against leukemia cell lines [19]. (Fig. **2**).

Synthetic approaches towards aplysinopsin-type structures **8** involve base-catalyzed condensation of a 3-formyl indole derivative **1** with a five membered ring containing an α-methylene carbonyl functional element, such as creatinine (**10**) or hydantoin derivatives (**11**). However, poor yields, purification difficulties and formation of mixtures of *Z* and *E* isomers are generally encountered in these procedures [15-17, 20]. (Scheme **1**).

These inconveniences have been circumvented by the introduction of a tandem Staudinger/aza-Wittig reaction followed by electrocyclic ring closure [21]. In this context, the aplysinopsin skeleton has been prepared from



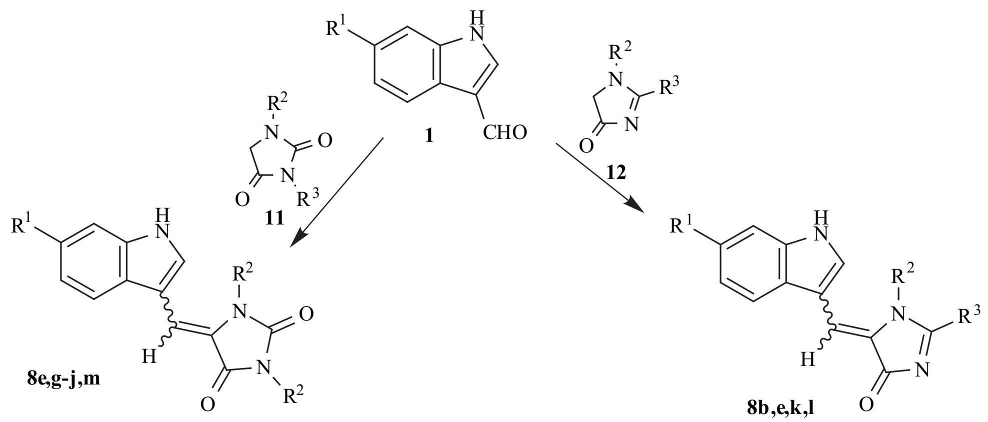
8, 9

	R^1	R^2	R^3	R^4	X	Yield (%)	Lit.
8a	Me	Me	H	H	NH	2.7[a]	15
8b	H	Me	H	H	NH	1.9[a]	15
8c	Me	Me	H	H	NMe		
8d	Me	Me	H	Br	NH		
8e	H	Me	H	Br	NH	1.0[a]	15
8f	H	Me	H	Br	NMe		
8g	Me	Me	H	H	O	*b*	16
8h	H	H	H	H	O		
8i	Me	Me	H	Br	O	*b*	16
8j	H	H	H	Br	O		
9a	H	H	Ph	H	S		

[a] Dry weight.

[b] Not given.

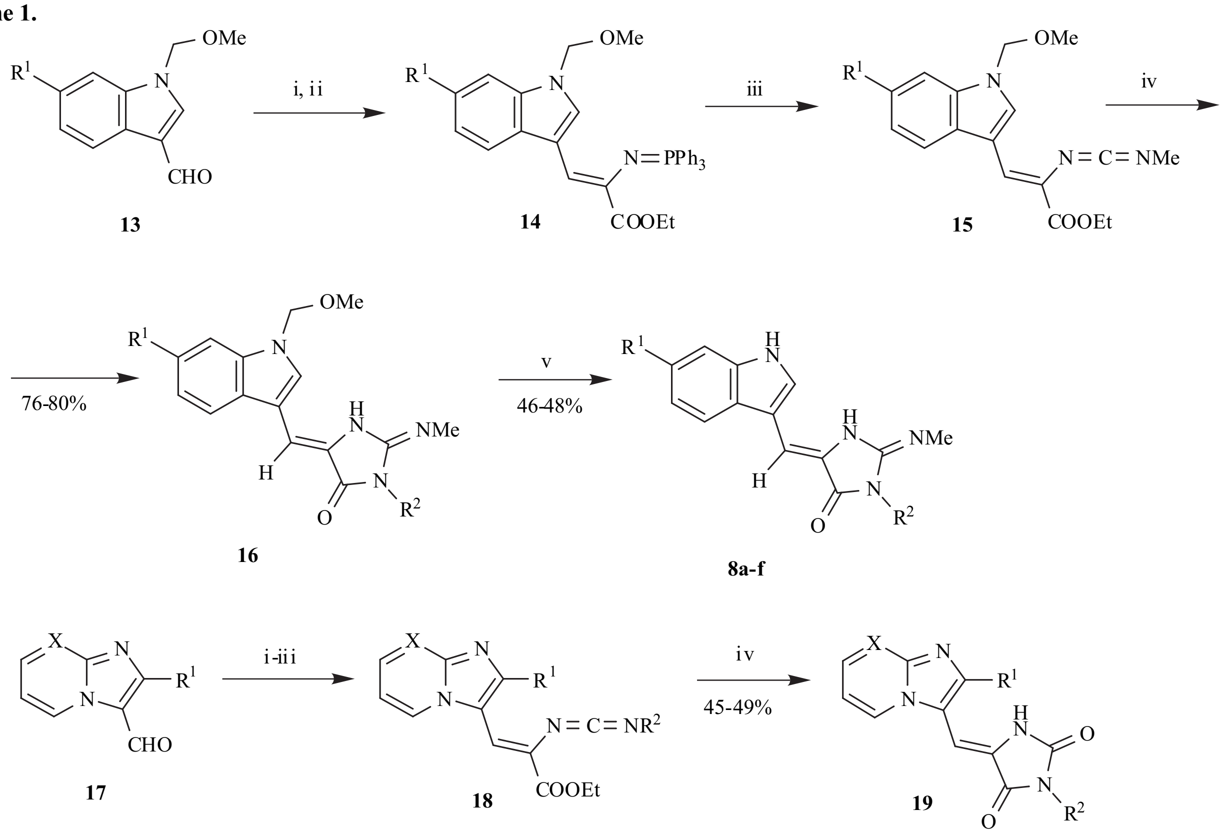
Fig. (2). Aplysinopsin (**8a**), its naturally occurring analogs (**8b–j**), and its synthetic analog (**9a**).



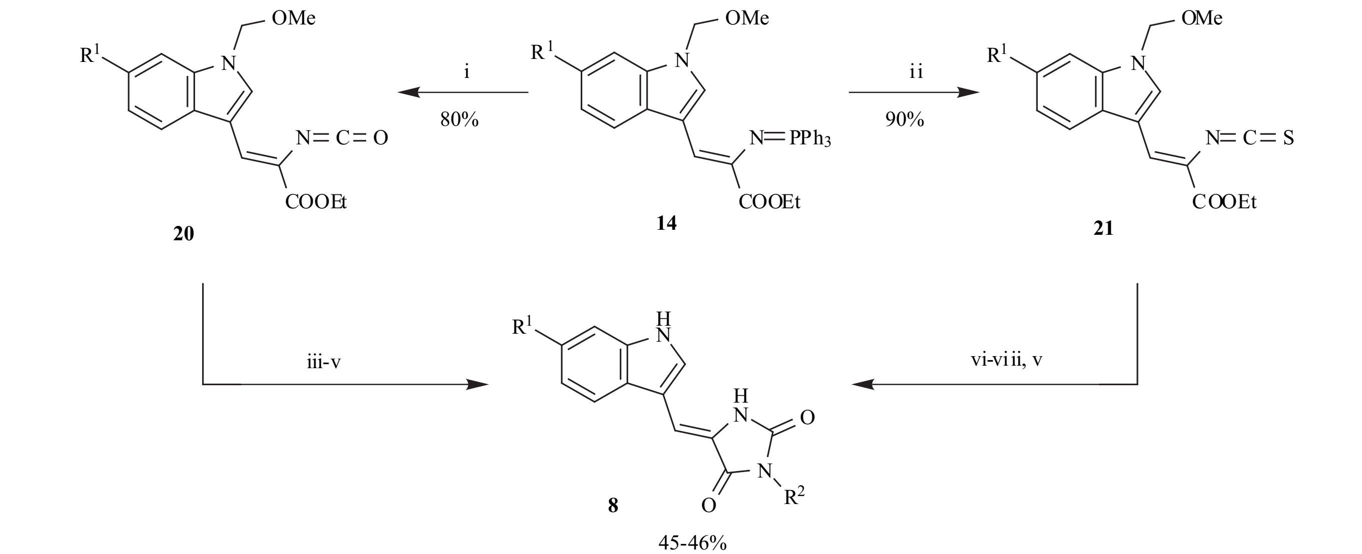
	R^1	R^2	R^3	*E* or *Z*	E:Z	Yield (%)	Lit.
8b	H	Me	NH_2	Z	5:95	84	15
8e	Br	Me	NH_2	Z	5:95	*a*	17
8g	H	Me	Me	E	95:5	*a*	17
8h	H	H	H	Z	5:95	*a*	17
8i	Br	Me	Me	E	95:5	*a*	17
8j	Br	H	H	Z	-	*a*	17
8k	Br	Me	NHMe	E	95:5	*a*	17
8l	H	H	NH_2	Z		*a*	17
8m	H	H	Me	Z		*a*	17

[a] Not given.

Scheme 1.



Scheme 2. Reaction conditions: (i) N_3CH_2COOEt, NaOEt, EtOH; (ii) PPh_3, CH_2Cl_2; (iii) MeNCO, toluene; (iv) RNH_2, toluene; (v) HCOOH, reflux.

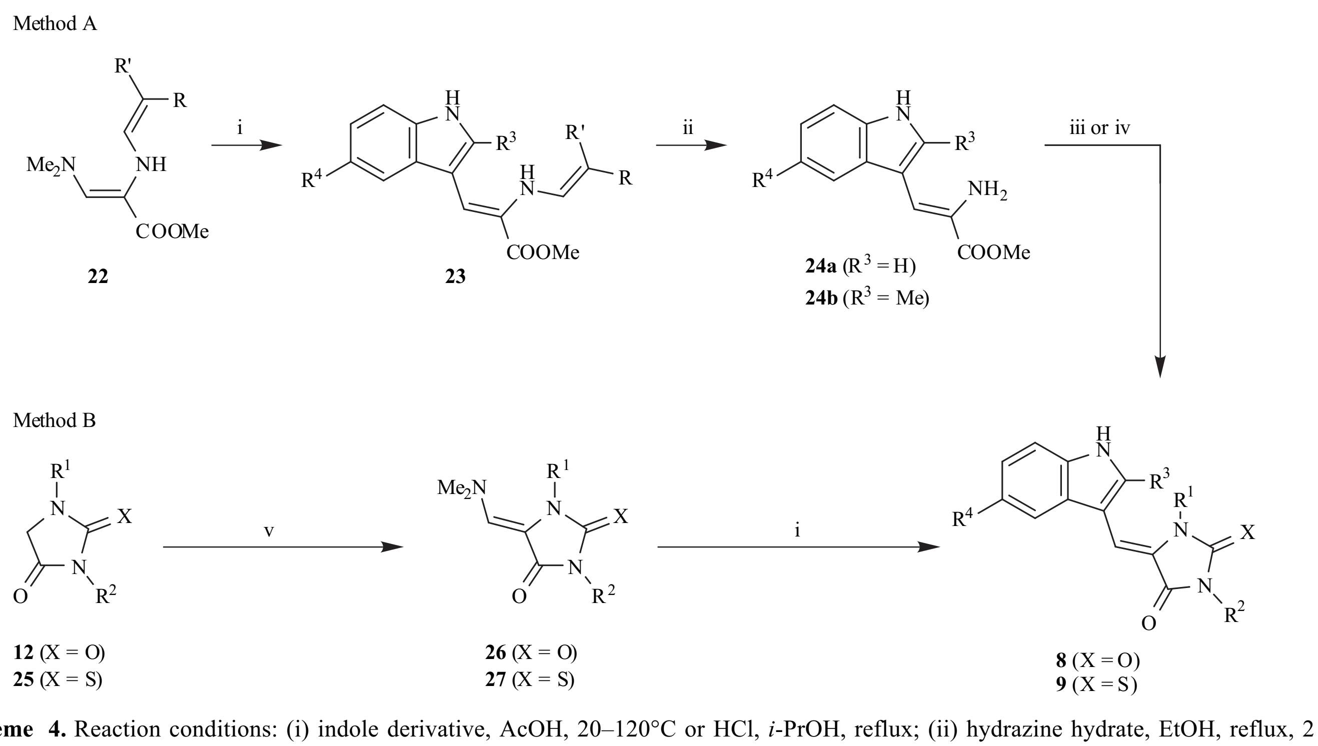


Scheme 3. Reaction conditions: (i) CO_2, toluene; (ii) CS_2, toluene, reflux; (iii) NH_4OAc; (iv) Ac_2O; (v) HCOOH, reflux; (vi) $MeNH_2$, toluene; (vii) Me_2SO_4, EtOH; (viii) KOH, H_2O, reflux.

iminophosphoranes **14**, obtained from 3-formylindole derivative **13** in two steps, followed by the reaction with methyl isocyanate to form the corresponding carbodiimide **15**. Cyclization of carbodiimide **15** into hydantoins **16** was achieved by treatment with primary amines, such as ammonia and aliphatic amines. Deprotection by treatment with formic acid at reflux furnished aplysinopsin derivatives **8** [22]. Using the same synthetic approach, some highly effective methods for the synthesis of azaaplysinopsin mimic structures **19** from aldehydes **17** *via* the heterocumulenes **18** [23,24] have been reported. (Scheme **2**).

Aplysinopsins **8** have also been prepared by treatment of iminophosphoranes **14** with carbon dioxide and carbon disulfide to give the corresponding isocyanates **20** and isothiocyanates **21**, followed by cyclization and deprotection [24a]. (Scheme **3**).

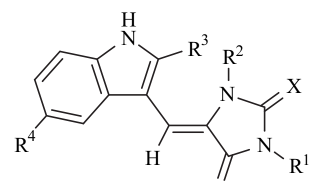
Recently, two simple and efficient approaches toward the aplysinopsin skeleton have been developed. Both methods are stereoselective and can afford various types of aplysinopsin analogs in moderate or good overall yields. The first method (Method A) is a three step synthesis, where methyl 2-(2,2-disubstituted ethenyl)amino-3-(dimethylamino)propenoates **22** first react with indole derivatives to



Scheme 4. Reaction conditions: (i) indole derivative, AcOH, 20–120°C or HCl, *i*-PrOH, reflux; (ii) hydrazine hydrate, EtOH, reflux, 2 h; (iii) urea, DMF, reflux, 2 h, or *N,N′*-diphenylthiourea, pyridine, reflux 2.5–3.5 h; (iv) alkyl, allyl, or aryl isothiocyanate, pyridine, reflux, 3–10 h; (v) bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) or DMFDMA, acetonitrile or DMF, reflux.

give 3-(1*H*-indol-3-yl)propenoates **23**, followed by deprotection of the amino group, which affords methyl 2-amino-3-(1*H*-indol-3-yl)propenoates **24a,b**. Treatment of **24** with urea, *N*,*N*'-diphenylthiourea, or an isothiocyanate affords aplysinopsin **8** and thioaplysinopsin derivatives **9** in 10–96% yields [25]. The second method (Method B) is a two step synthesis. In this case, hydantoin derivatives **12** are transformed with *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) or *N,N*-dimethylformamide dimethyl acetal (DMFDMA) into the corresponding (*Z*)-5-[(dimethylamino) methylidene] imidazo-lidine-2,4-diones **26**, which react further with indole derivatives to give aplysinopsin derivatives **8g–w** in 10–81% yields [25,26]. Similarly, thiooxo analogs of aplysinopsin **9a–k** were prepared in 2 steps from thiohydantoins **25** *via* 3-substituted (*Z*)-5-[(dimethylamino) methylidene]-2-thiooxoimidazolidin-4-ones **27** [26, 27]. (Scheme **4**), (Table **1**).

Table 1. Aplysinopsin Analogs Prepared by Methods A and B



	R^1	R^2	R^3	R^4	X	Method	Yield^a (%)	Z:E	Ref.
8g	Me	Me	H	H	O	A	65	0:100	27
8g	Me	Me	H	H	O	B	78	0:100	26
8h	H	H	H	H	O	A	65	>95:5	25
8h	H	H	H	H	O	B	48	>95:5	25
8i	Me	Me	H	Br	O	B	35	0:100	26
8j	H	H	H	Br	O	B	45	92:8	26
8k	Me	Me	Me	H	O	B	61	28:72	27
8l	Me	Me	Ph	H	O	B	10	0:100	26
8m	Me	H	Me	H	O	B	60	>95:5	25
8n	H	H	Me	H	O	B	65	>99:1	25
8o	H	H	Ph	H	O	B	68	100:0	26
8p	Me	H	H	H	O	B	42	>95:5	25
8q	Me	H	Ph	H	O	B	46	100:0	26
8r	Me	H	H	Br	O	B	40	>95:5	26
8s	H	Me	H	H	O	B	58	0:100	27
8t	H	Me	Me	H	O	B	81	38:62	27
8u	H	Me	H	Br	O	B	38	0:100	27
8v	H	Me	H	F	O	B	69	0:100	27
8w	H	Me	Ph	H	O	B	14	0:100	26
9a	H	H	Ph	H	S	B	55	100:0	26
9b	Me	H	H	H	S	A	42	>95:5	25
9c	Et	H	H	H	S	A	28	92:8	25
9d	allyl	H	H	H	S	A	25	94:6	25
9e	Ph	H	H	H	S	A	61	80:20	25
9f	4-Me-C_6H_4	H	H	H	S	A	10	92:8	25
9g	Me	H	Me	H	S	A	96	>99:1	25

(Table 1)contd.....

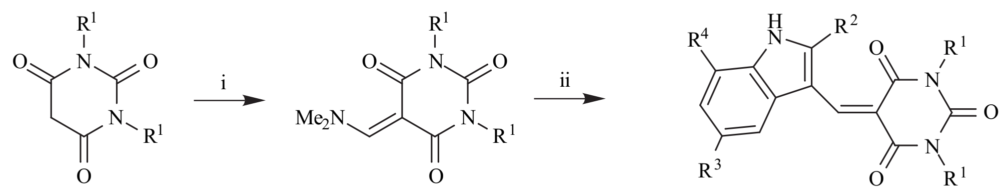
	R^1	R^2	R^3	R^4	X	Method	Yield[a] (%)	Z:E	Ref.
9h	Et	H	Me	H	S	A	39	>99:1	25
9h	Et	H	Me	H	S	B	15	100:0	27
9i	allyl	H	Me	H	S	A	40	>99:1	25
9i	allyl	H	Me	H	S	B	48	100:0	27
9j	Ph	H	Me	H	S	A	78	>99:1	25
9j	Ph	H	Me	H	S	B	79	100:0	27
9k	4-Me-C_6H_4	H	Me	H	S	A	58	>99:1	25
9k	4-Me-C_6H_4	H	Me	H	S	B	77	100:0	27

[a] The yields of the last step are given.

In the same manner, pyrimidinetrione analogs of aplysinopsins **30a–i** were prepared from 5-[(dimethylamino) methylidene]pyrimidine-2,4,6-triones **28a,b** and various substituted indoles [26, 28]. (Scheme **5**), (Table **2**).

Further examples of aplysinopsin analogs **32a–d** and **35** were synthesized in two steps from thiohydantoins **25** and 2-amino-1,3-thiazol-4(5*H*)-one (**33**), respectively. Upon reaction of **25** with excess DMFDMA, S-methylation also occurred to give enaminones **31a–d**. Further treatment with 2-methylindole furnished compounds **32a–d** in 7–65% yields. Similarly, (5Z)-2-methyl-5-[(2-methyl-1*H*-indol-3-yl)methylidene]-1,3-thiazol-4(5*H*)-one hydrobromide (**35**) was obtained upon reaction of 2-amino-1,3-thiazol-4(5*H*)-one (**33**) with Bredereck's reagent followed by treatment of the intermediate (5Z)-2-(dimethylamino)-5-[(dimethylamino) methylidene]-1,3-thiazol-4(5*H*)-one (**34**) with 2-methyl-indole [27]. (Scheme **6**).

As a further extension in this field, the stereoselective synthesis of novel aplysinopsin analogs, where the indole moiety replaced by various carbocyclic and heterocyclic systems, was developed. In this context, compounds **26** and **27** were treated with carbocyclic and heterocyclic *C*-nucleophiles in acetic acid under reflux to give the corresponding substitution products **36–41**, isolated as pure



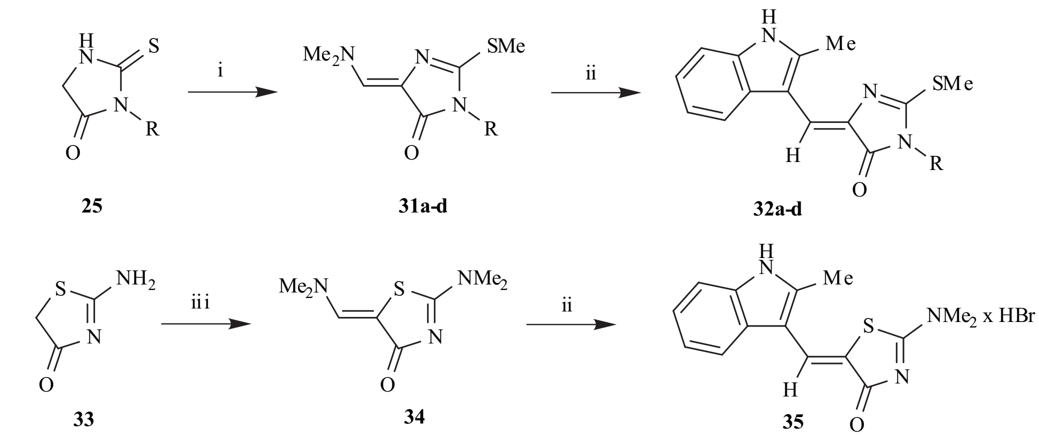
28a (R^1 = H)
28b (R^1 = Me)
29a (R^1 = H)
29b (R^1 = Me)
30a-i

Scheme 5. Reaction conditions: (i) bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) or DMFDMA, acetonitrile or DMSO; (ii) indole derivative, AcOH, 90–100°C (Method A) or 2-phenylindole, HCl, *i*-PrOH, reflux (Method B).

Table 2. Pyrimidinetrione Analogs of Aplysinopsins 30a–i

	R^1	R^2	R^3	R^4	Method	Yield[a] (%)	Ref.
30a	H	H	H	H	A	73	28
30b	H	Me	H	H	A	85	28
30c	H	Ph	H	H	B	76	26
30d	H	H	Br	H	A	69	28
30e	H	H	H	Et	A	56	28
30f	Me	H	H	H	A	73	28
30g	Me	Ph	H	H	B	46	26
30h	Me	H	Br	H	A	29	28
30i	Me	H	H	Et	A	11	28

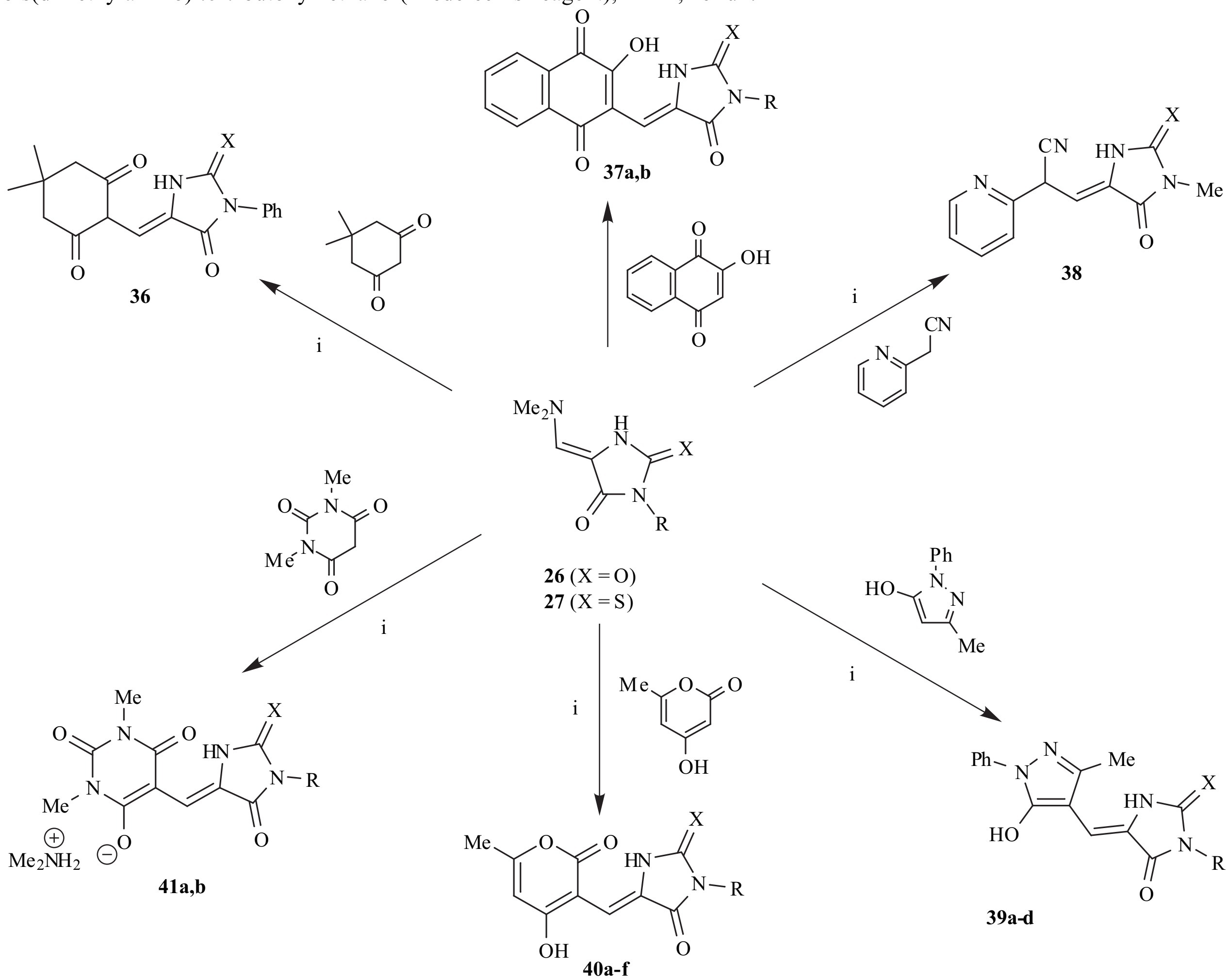
[a] The yields of the last step are given.



	R	Yield[a] (%)
32a	Et	7
32b	allyl	48
32c	Ph	14
32d	4-Me-C_6H_4	65
35	-	48

[a] The yields of the last step are given.

Scheme 6. Reaction conditions: (i) DMFDMA, acetonitrile or DMF, reflux; (ii) 2-methylindole, AcOH, HBr, 20–50°C; (iii) bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent), DMF, reflux.



Scheme 7. Reaction conditions: (i) AcOH, reflux.

(*Z*)-isomers in 36–84% yields. Compounds **41a,b** were obtained as dimethylammonium salts [29]. (Scheme **7**), (Table **3**).

Table 3. Aplysinopsin Analogs 36–41

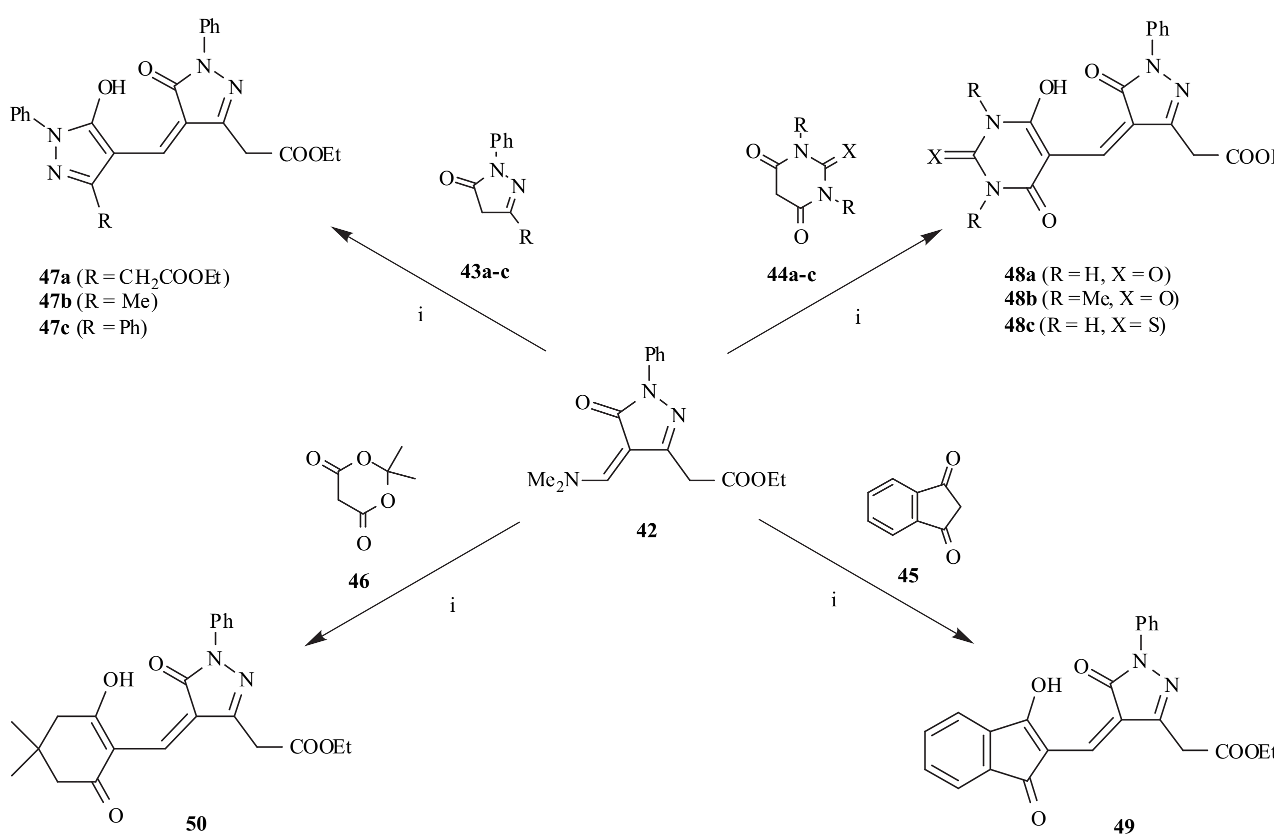
	R	X	Yield (%)
36	-	S	36
37a	H	O	56
37b	Me	O	84
38	Me	O	43
39a	H	O	43
39b	Me	O	50
39c	Et	S	78
39d	Ph	S	50
40a	H	O	51
40b	Me	O	71
40c	Et	S	76
40d	allyl	S	56
40e	Ph	S	82
40f	4-Me-C_6H_4	S	65
41a	H	O	52
41b	Me	O	66

Further structurally related examples of aplysinopsin analogs **47–50** were prepared from ethyl [(*Z*)-4-(dimethylamino)methylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate (**42**) and heterocyclic 1,3-dicarbonyl compounds **43–46** by heating in ethanol in the presence of hydrochloric acid. Interestingly, (*Z*)-[4-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethylidene)-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate (**47a**) was also obtained in 75% yield, when enaminone **42** was heated in ethanol in the presence of hydrochloric acid. This compound was identical with the compound **47a** prepared from **42** and ethyl (5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate (**43a**) in 90% yield. Apparently, partial hydrolysis of the enamine **42** took place to furnish *in situ* the pyrazole derivative **43a** as the *C*-nucleophile, which reacted with the non-hydrolysed enaminone **42** to afford **47a** in 90% yield [30]. (Scheme **8**).

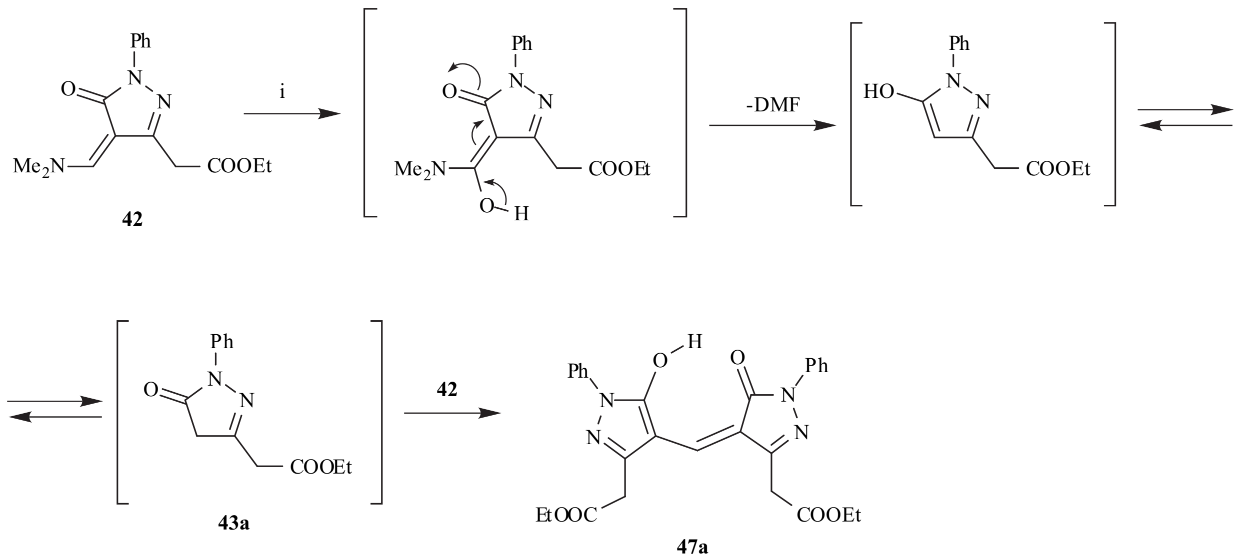
Fused imidazoles with the imidazole ring connected by a methylidene bridge to an oxazolone system were prepared as azaaplysinopsin analogs in three steps from oxazolone **51**, which was first treated with various *N*,*N*-dimethyl-*N*'-heteroarylformamidines in acetonitrile or DMF to afford, *via* the intermediate quarternary salts **52**, the fused imidazoazoles and imidazoazines **53a–g**. Further treatment of oxazolones **53** with sodium methoxide in methanol gave propenoates **54** in 29–95% yields [31]. (Scheme **9**).

3. SYNTHESIS OF MERIDIANINES

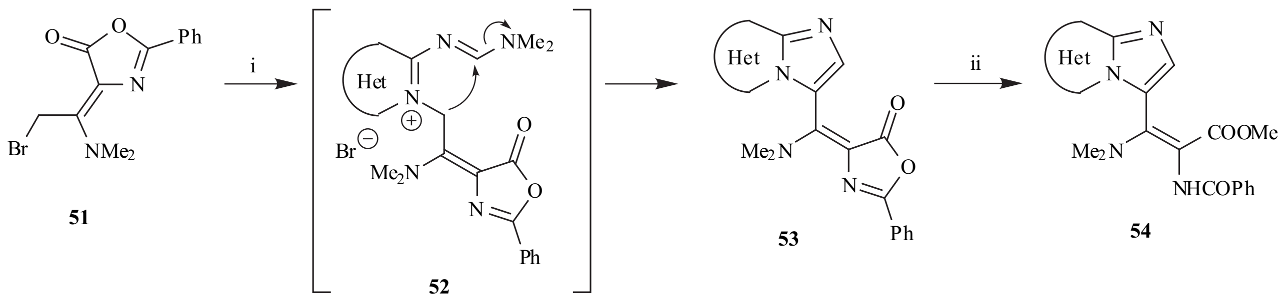
Tunicatae are a particularly rich source of a variety of structurally fascinating bioactive nitrogen containing marine natural products [32]. Recently, the meridianines **55a–d** (Fig. **3**), another series of indole alkaloids showing

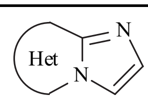


(Scheme 8)contd.....



Scheme 8. Reaction conditions: (i) EtOH, 37% HCl (aq.), reflux.

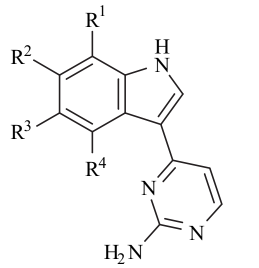


		Yield (%)	
		53	**54**
52a–54a	imidazo[1,2-*a*]pyridin-3-yl	69	70
52b–54b	7-methylimidazo[1,2-*a*]pyridin-3-yl	57	95
52c–54c	8-nitroimidazo[1,2-*a*]pyridin-3-yl	14	
52d–54d	6-chloroimidazo[1,2-*a*]pyridin-3-yl	80	29
52e–54e	imidazo[1,2-*b*]pyridazin-3-yl	25	
52f, 53f	6-chloroimidazo[1,2-*b*]pyridazin-3-yl	81	
54f	6-methoxyimidazo[1,2-*b*]pyridazin-3-yl		82
52g–54g	imidazo[1,2-*b*]thiazol-3-yl	70	84

Scheme 9. Reaction conditions: (i) *N*,*N*-dimethyl-*N*'-heteroarylformamidine, MeCN or DMF, r.t. → reflux; (ii) MeOH/MeONa, r.t.

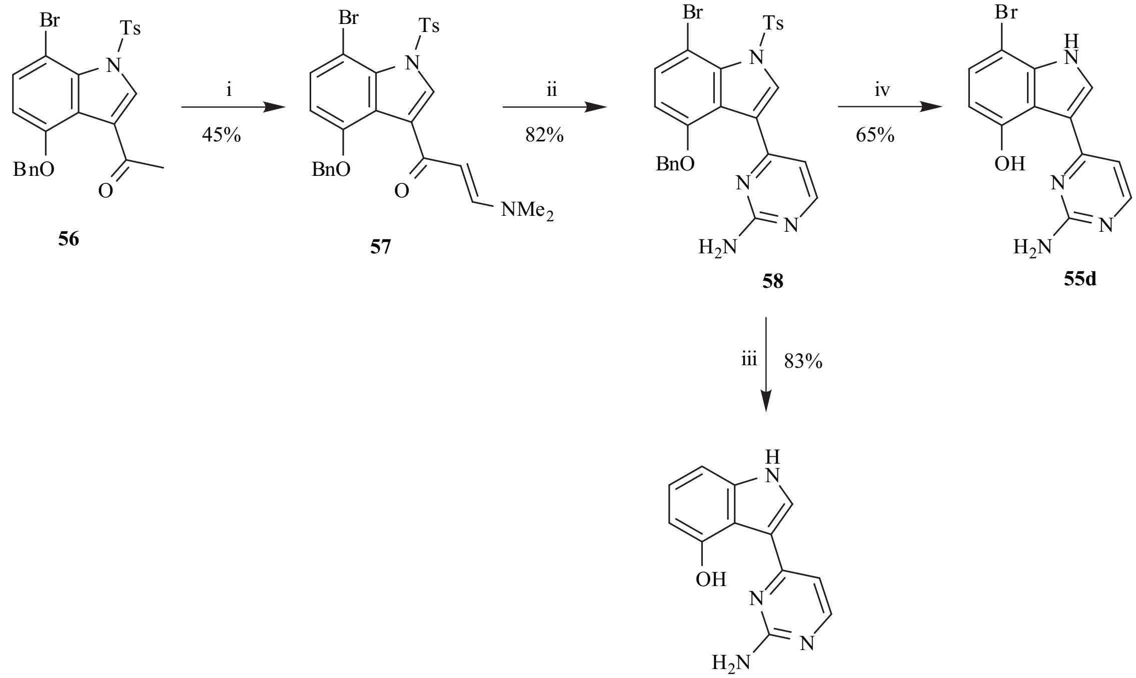
interesting antitumor properties, have been isolated from *Tunicatae Aplidium meridianum* [33,34]. Meridianines A (**55a**) and E (**55d**) have been synthesized in good yields from *N*-tosyl-3-acetylindoles **56** in several steps [35]. (Scheme **10**).

In a similar way, the synthesis of meridianines C (**55b**) and D (**55c**) and the synthesis of the 7-aza analog **65** were achieved starting from the corresponding brominated indoles **59** and 7-azaindole (**62**), respectively [35]. (Scheme **11**).

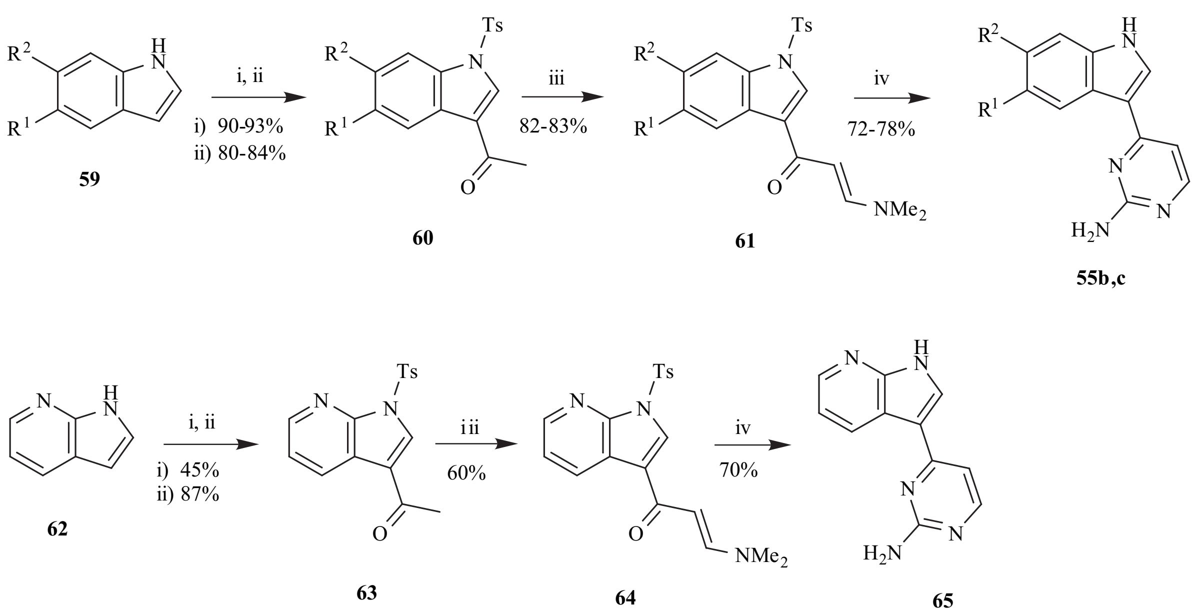


Meridianine A (**55a**): $R^1 = R^2 = R^3 = H$, $R^4 = OH$
Meridianine C (**55b**): $R^1 = R^3 = R^4 = H$, $R^2 = Br$
Meridianine D (**55c**): $R^1 = R^2 = R^4 = H$, $R^3 = Br$
Meridianine E (**55d**): $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Br$

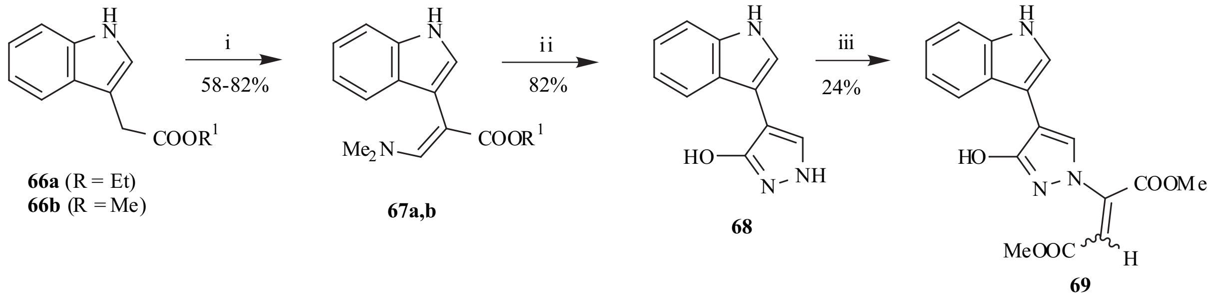
Fig. (3).



Scheme 10. Reaction conditions: (i) DMFDMA, DMF, 110 °C; (ii) guanidine hydrochloride, K_2CO_3, 2-methoxyethanol, reflux; (iii) TFA, thioanisole, r.t.; (iv) H_2, Pd–C, EtOAc.



Scheme 11. Reaction conditions: (i) MeCOCl, $SnCl_4$, benzene; (ii) TsCl, NaH, DMF; (iii) DMFDMA, DMF, 110 °C; (iv) guanidine hydrochloride, K_2CO_3, 2-methoxyethanol, reflux.



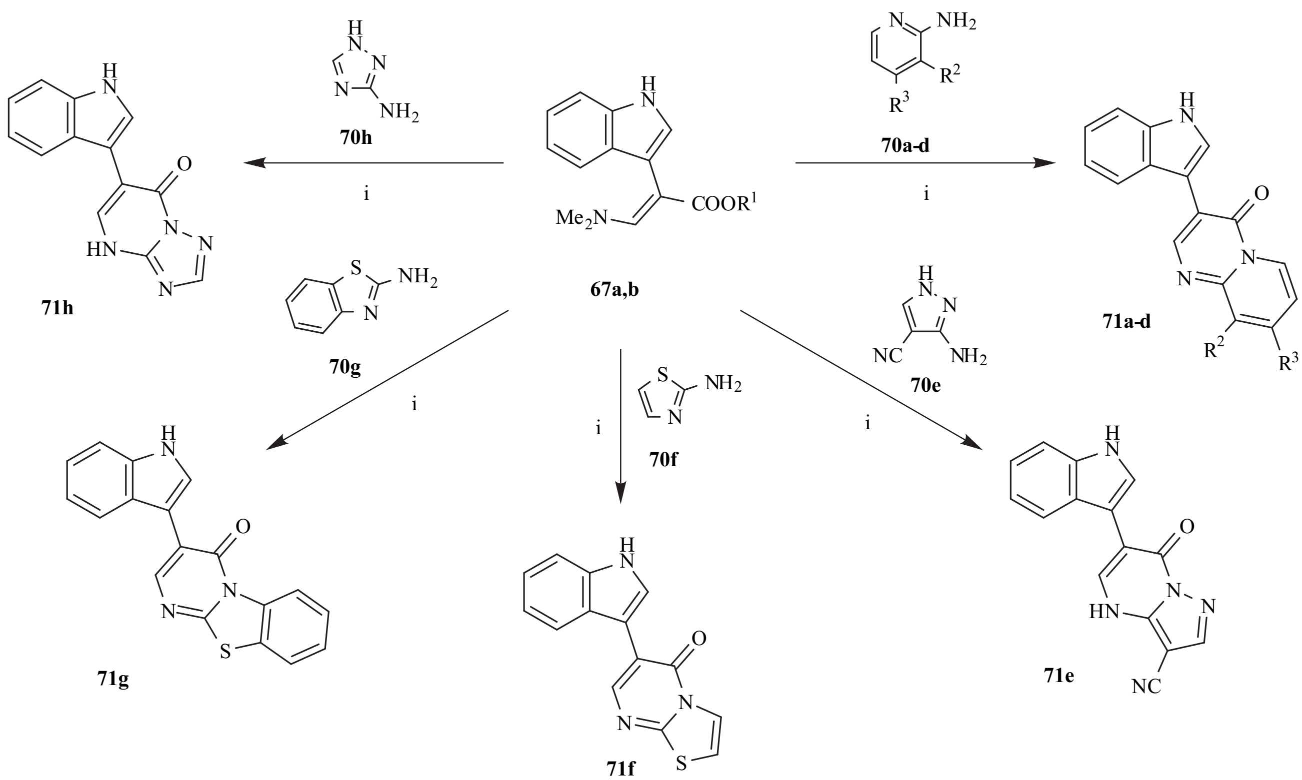
Scheme 12. Reaction conditions: (i) *t*-$BuOCH(NMe_2)_2$, DMF, reflux; (ii) N_2H_4 x HCl, EtOH, reflux; (iii) DMAD, MeOH, reflux.

Preparation of various 3-heteroarylindoles as the meridianine and chromene analogs can be achieved by treatment of alkyl 3-dimethylamino-2-(1*H*-indol-3-yl)propenoates **67a,b** with *N*,*N*- and *C*,*O*-dinucleophiles. Alkyl (2*E*)-3-dimethylamino-2-(1*H*-indol-3-yl)propenoates **67a,b** are available in one step from alkyl 3-indoleacetates **66a,b** and *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent). Enaminones **67a** and **67b** were reacted with hydrazine hydrochloride in ethanol under reflux to afford the pyrazolol **68** in 82 and 58% yield, respectively. Further reaction of **68** with one equivalent of dimethyl acetylenedicarboxylate gave dimethyl 2-[3-hydroxy-4-(1*H*-indol-3-yl)-1*H*-pyrazol-1-yl]but-2-ene-1,4-dioate (**69**) in 24% yield as a mixture of (*E*)- and (*Z*)-isomer in a ratio of 1:1 [36]. (Scheme **12**).

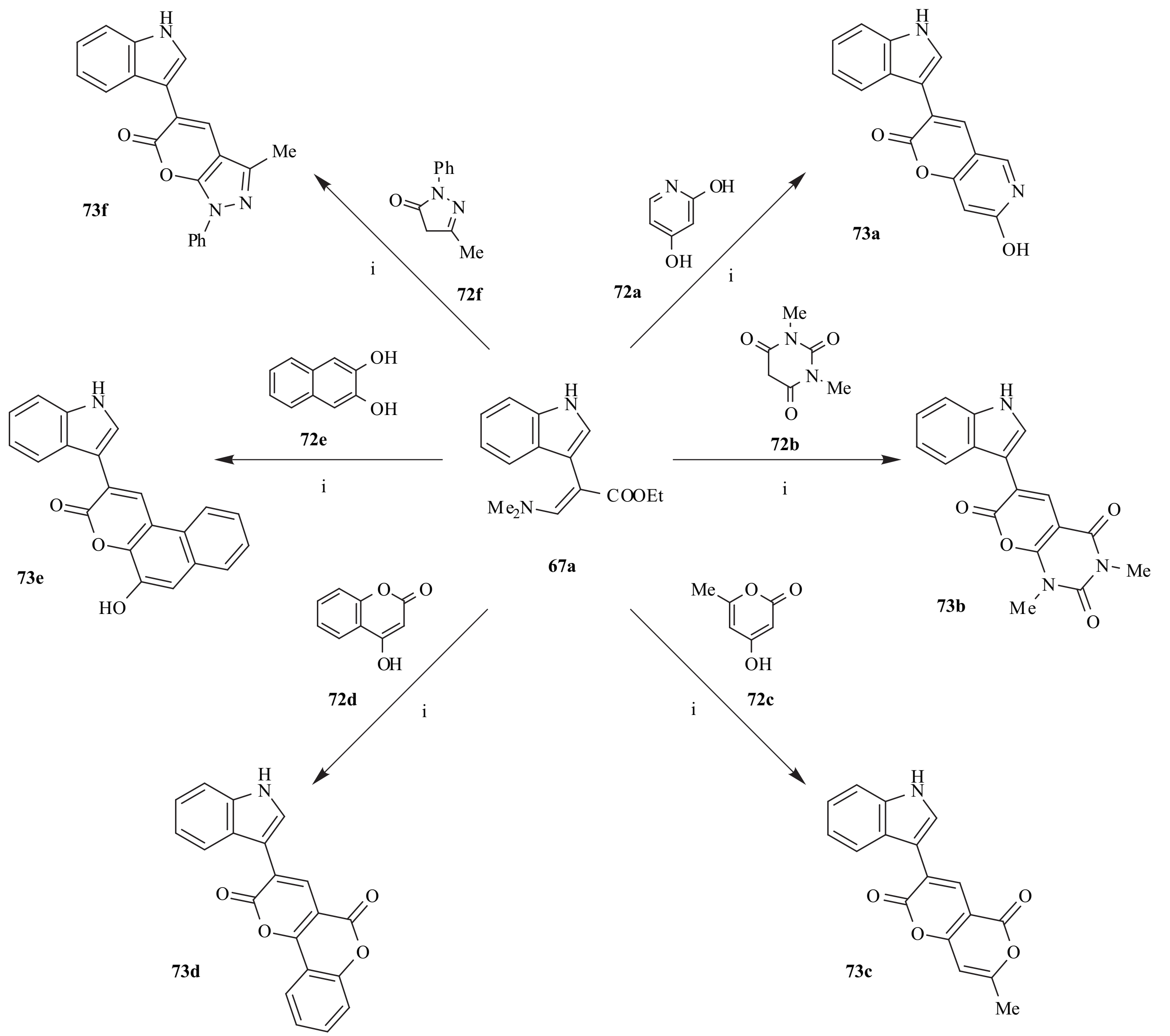
Reactions of **67a,b** with heteroarylamines **70a–h** resulted in formation of the cyclocondensation products **71a–h**, regardless of the heteroaryl moiety. Thus, heating of the propenoates **67a,b** with 2-aminopyridines **70a–d**, 3-amino-1*H*-pyrazole-4-carbonitrile (**70e**), 2-aminothiazole (**70f**), 2-aminobenzothiazole (**70g**), and 3-amino-1,2,4-triazole (**70h**) and in acetic acid for 1.5–7 h furnished the corresponding 3-heteroaryl-1*H*-indoles **71a–h** as the meridianine analogues in 11–95% yields [36]. (Scheme **13**), (Table **4**).

By treatment of **67a** with (hetero)cyclic *C*,*O*-dinucleophiles **72a–f** in acetic acid under reflux for several hours pyrano[3,2–*c*]pyridin-2-one **73a**, pyrano[2,3–*d*]pyrimidine-2,4,7-trione **73b**, pyrano[4,3–*b*]pyran-2,5-dione **73c**, chromene **73d,e**, and pyrano[3,2–*c*]pyrazole derivatives **73f** were obtained in 9–81% yields [36]. (Scheme **14**), (Table **4**).

Formation of 3-heteroarylindoles **68**, **71**, and **73** from **67a,b** and *N*,*N*-dinucleophiles and *C*,*O*-dinucleophiles proceeds by initial substitution of the dimethylamino group followed by cyclization. In the reaction of **67a** with 3-chloro-6-hydrazinopyridazine, the intermediate substitution product **73** was isolated in its hydrazono tautomeric form **74** and further cyclization to **75** did not take place. In all other cases, the intermediate substitution products could not be isolated. Nevertheless, a two step mechanism for formation



Scheme 13. Reaction conditions: (i) AcOH, reflux.



Scheme 14. Reaction conditions: (i) AcOH, reflux.

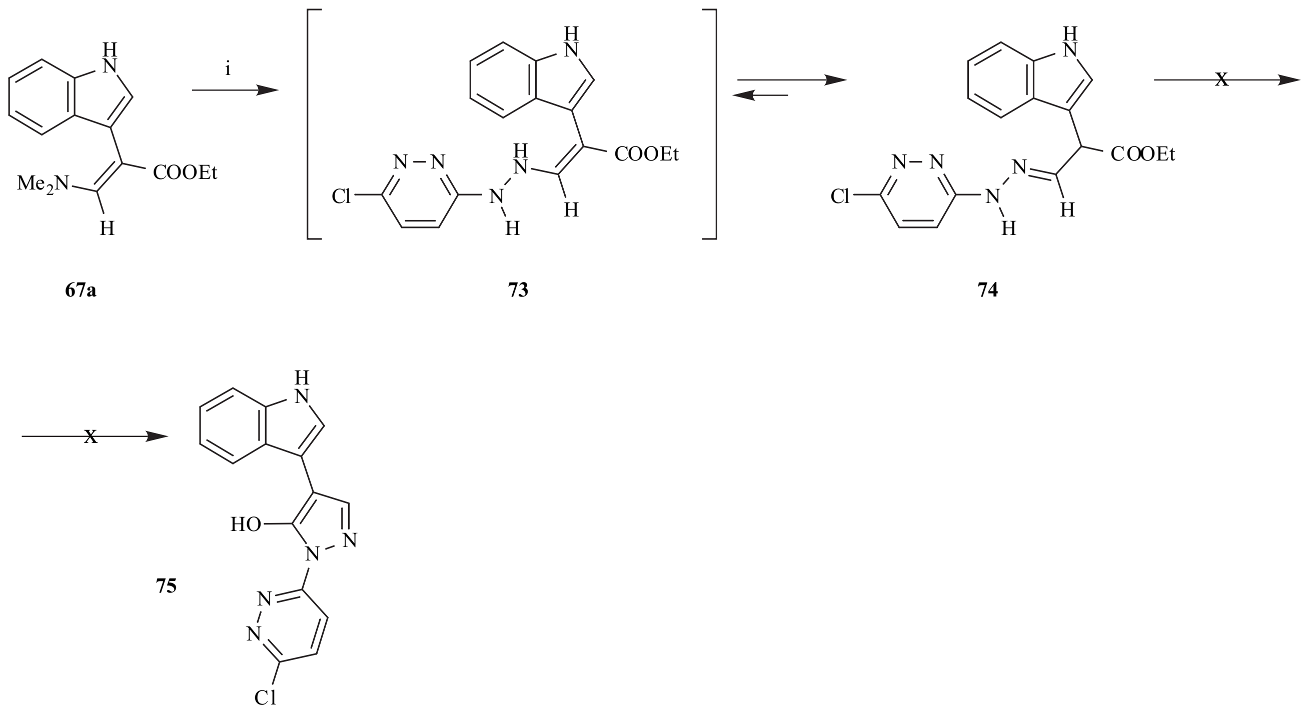
of indolyl substituted pyrazole **68**, pyrimidones **71**, andpyranones **73** is supported by previously described cyclisations between other closely related 3-(dimethylamino)propenoates and ambident nucleophiles [36-42] (Scheme **15**).

Table 4. 3-Heteroaryl-1*H*-indoles 71 and 73

Reaction	R^1	R^2	R^3	Yield [%]
67a + **70a** → **71a**	Et	H	H	39
67a + **70b** → **71b**	Et	Me	H	67
67b + **70b** → **71b**	Me	Me	H	69
67a + **70c** → **71c**	Et	OH	H	35
67a + **70d** → **71d**	Et	H	Cl	95
67b + **70d** → **71d**	Me	H	Cl	88
67a + **70e** → **71e**	Et			68

(Table 4)contd.....

Reaction	R^1	R^2	R^3	Yield [%]
67b + **70e** → **71e**	Me			71
67a + **70f** → **71f**	Et			30
67a + **70g** → **71g**	Et			11
67b + **70g** → **71g**	Me			13
67a + **70h** → **71h**	Et			35
67b + **70h** → **71h**	Me			25
67a + **72a** → **73a**				52
67a + **72b** → **73b**				78
67a + **72c** → **73c**				44
67a + **72d** → **73d**				73
67a + **72e** → **73e**				9
67a + **72f** → **73f**				81



Scheme 15.

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