Meridianins: Marine-Derived Potent Kinase Inhibitors

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Abstract: Marine invertebrates are a rich source of novel, bioactive secondary metabolites and have attracted a great deal of attention from scientists in the fields of chemistry, pharmacology, ecology, and molecular biology. This profilic natural source has produced several antitumor secondary metabolites and amongst these, indole alkaloids are of wide occurrence. Meridianins A-G (**1-7**) are indole alkaloids isolated from tunicate *Aplidium meridianum* and are known to inhibit variety of protein kinases associated with cancer and neurodegenerative diseases. These compounds also exhibited promising antiproliferative activity in several cancer cell lines. Amongst natural meridianins, meridianin E (**5**) showed potent and selective inhibition of CDK-1 and CDK-5. Several synthetic meridianin analogs exhibited potent and selective inhibition of glycogen synthase-3 (GSK-3) and dual-specificity tyrosine-phosphorylation regulated kinase 1A (Dyrk-1A) which are known to be implicated in progression of Alzheimer's disease. The present review provides the critical account of isolation, medicinal chemistry and pharmacology of meridianins. Our analysis of the structure-activity relationships of this family of compounds highlights the existence of various potential leads for the development of novel anticancer and anti-Alzheimer's agents.

Keywords: Anticancer, antimalarial, kinase inhibitors, marine natural product, meridianins.

1. INTRODUCTION

The oceans cover more than 70% of the earth's surface, which represent over 95% of the biosphere. The oceans are therefore an unexplored area of opportunity for the discovery of pharmacologically active compounds. Oceans with their millions of species are a rich source of marine plants and animals. In recent years, number of potential therapeutic agents have been isolated from marine flora and fauna. Several marine natural products are currently in preclinical and clinical evaluation, others show promising biological activity *in vitro* and *in vivo* biological assays and several others are making significant contributions to our understanding of cellular processes at the biochemical level. Although initiated in late 1970's, natural product drug discovery from the world's oceans has been accelerated by the chemical uniqueness of marine organisms and by the need to develop drugs for contemporary, difficult to cure diseases. Although, invertebrates are the subject of interest due to the possible presence of interesting bioactive molecules; however, there is controversy about whether the bioactive molecules originate from invertebrates cell or the micro-organisms contained therein. This sometimes becomes apparent when invertebrates are kept in aquaria and are subsequently found to have lost the potential to produce interesting molecules. However, now there is a growing recognition that microorganisms associated with marine invertebrate hosts play an important role in the biosynthesis of secondary metabolites. The isolation and cultivation of microbial symbionts remains as a significant challenge due to their potential dependence on host supplied factors for growth and secondary metabolite production [1, 2].

Due to presence of distinct biogenetic conditions like high salt content, high pressure and constant temperature, marine organism secondary metabolites possess number of structural differences as compared to terrestrial natural products. Marine metabolites often possess complexities such as halogen substituent's. Their structure elucidation, chemical modification, stereochemistry, synthesis, and pharmacology have received a great deal of interdisciplinary attention from areas of research other than chemistry and include pharmacology, physiology, and medicine [3]. A variety of marine sources including sponges, tunicates, red alga, acorn worms, and symbiotic bacteria have been shown to generate indole alkaloids, which represent the largest number and most complicated of the marine alkaloids.

The indole ring system is probably the most ubiquitous heterocycle in nature. Because of the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. Among a huge diversity of nature-derived structures, indole alkaloids are frequently found in marine invertebrates and are considered as lead compounds for the discovery of new drugs in medicinal chemistry [3, 4]. The biological activity of marine indole alkaloids is clearly a product of the unique functionality and elements involved in the biosynthesis of marine natural products. For instance, bromination of many natural products has the potential to increase biological activity significantly [3]. Indoles with 5-or 6-membered heterocyclic substituent's in the 3-position have aroused considerable attention due to remarkable spectrum of

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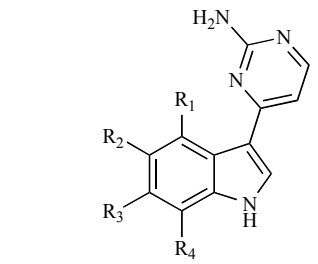
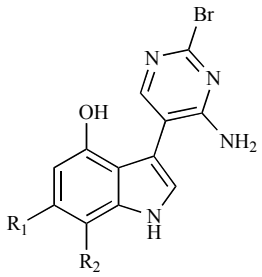
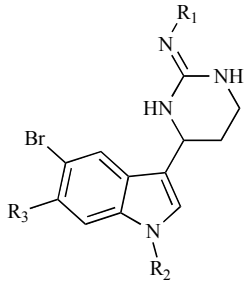


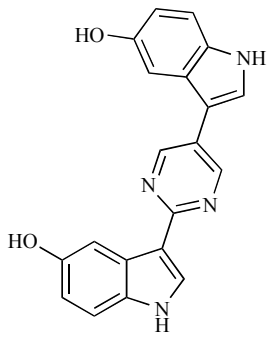
Meridianin A (**1**): R_1 = OH, R_2 = R_3 = R_4 = H
Meridianin B (**2**): R_1 = OH, R_2 = R_4 = H, R_3 = Br
Meridianin C (**3**): R_1 = R_3 = R_4 = H, R_2 = Br
Meridianin D (**4**): R_1 = R_2 = R_4 = H, R_3 = Br
Meridianin E (**5**): R_1 = OH, R_2 = R_3= H, R_4 = Br
Meridianin F (**6**): R_1 = R_4= H, R_2 = R_3 = Br
Meridianin G (**7**): R_1 = R_2 = R_3 = R_4 = H



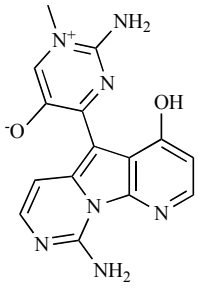
Psammopemmin A (**8**): R_1 = R_2 = H
Psammopemmin B (**9**): R_1 = H, R_2 = Br
Psammopemmin C (**10**): R_1 = Br, R_2 = H



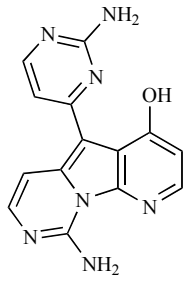
Aplicyanin A (**11**): R_1 = R_2 = R_3 = H
Aplicyanin B (**12**): R_1 = Ac, R_2 = R_3 = H
Aplicyanin C (**13**): R_1 = OMe, R_2 = R_3 = H
Aplicyanin D (**14**): R_1 = Ac, R_2 = OMe, R_3 = H
Aplicyanin E (**15**): R_1 = H, R_2 = OMe, R_3 = Br
Aplicyanin F (**16**): R_1 = Ac, R_2 = OMe, R_3 = Br



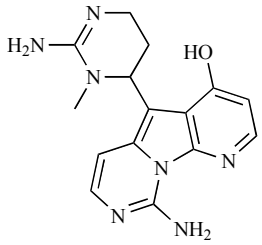
Hyrtinadine A (**17**)



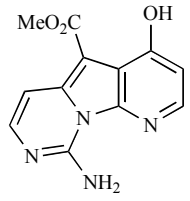
Variolin A (**18**)



Varolin B (**19**)



N(3')-Methyl tetrahydro variolin B (**20**)



Variolin D (**21**)

Fig. (1). Structures of marine derived indoles **1-17** and azaindoles **18-21**.

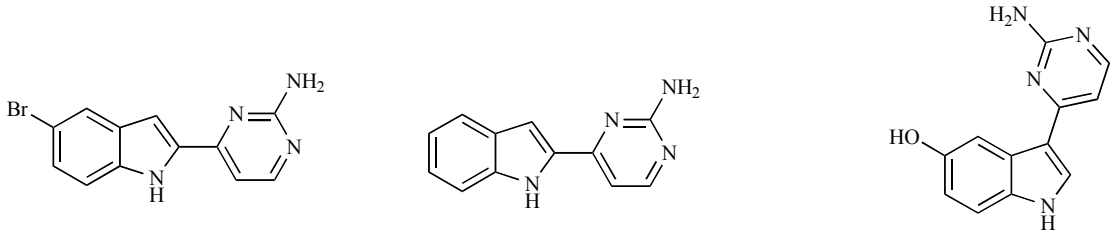
biological activity [5]. For example, meridianins **1-7** [6], psammopemmins **8-10** [7], aplicyanins **11-16** [8, 9], hyrtinadine A **17** [10], variolins **18-21** [11, 12] and meriolins [13, 14] are small marine alkaloids consisting of indole and 7-azaindole frameworks connected to a pyrimidine ring, the essential structural element for the kinase inhibitory activity of these marine natural products. Meriolins are synthetic hybrids of meridianins and variolins. The pyrido[3',2':4,5]pyrrolo[1,2-c]pyrimidine ring system of variolins has not been encountered in any other natural products. The chemical structures of marine-derived indoles/ azaindoles substituted at 3-position are shown in Fig. (**1**).

There are few reviews published earlier on nature-derived indole alkaloids. Pindur and Lemster (2001) [15] discussed chemical and biological aspects of marine-derived indoles and annelated indoles. Hibino and Chosi (2002) [16] discussed chemical aspects of simple indole alkaloids, isoprenoid tryptamines, and bisindole alkaloids with a non-rearranged monoterpenoid unit. Gul and Hamann (2005) [3] reviewed indole alkaloids derived from marine source possessing different therapeutic activities. Stanovnik and Svete (2005) [17] reviewed synthesis of aplysinopsins, meridianins and related compounds. Pauletti *et al.* (2010) [18] reviewed halogenated marine indole alkaloids and have discussed meridianins briefly. Recently, Skropeta *et al* (2011) [19] reviewed kinase inhibitors isolated specifically from marine sponges, thus not covered meridianins.

Several natural as well as synthetic analogs of meridianins are reported in literature with extensive work on kinase inhibitory activity and antiproliferative activity, but no any comprehensive review published on chemistry and pharmacology of these interesting marine derived molecules. The present review provides the critical account on natural product chemistry, synthetic chemistry and pharmacology of meridianins.

2. MERIDIANINS: STRUCTURE-ACTIVITY RELATIONSHIP AMONGST NATURAL ANALOGS

Meridianins A-E (**1-5**) were first isolated in 1998 by Palermo and co-workers [6] from tunicate *Aplidium meridianum* (Family: Ascidiae, Polyclinidae) and later in 2007 same group identified two other meridianins F (**6**) and G (**7**) from same source by tandem mass spectrometry [20]. Recently meridianins A (**1**), B (**2**), C (**3**) and E (**5**) have also been reported from the Antarctic tunicate *Synoicum* sp [21]. Meridianins **1-7** are indole alkaloids substituted at the C-3 position by a 2-aminopyrimidine ring. Isomeridianin C (**22**) and G (**23**) are 2-substituted synthetic analogs of natural meridianins prepared by same group of researchers who isolated meridianins, in order to study structure-activity relationship for this class of compounds [22]. Recently



Isomeridianin C (**22**) Isomeridianin G (**23**) Isomeridianin A (**24**)

Fig. (2). Structures of isomeridianins C (**22**), G (**23**) and A (**24**).

Tasch *et al* (2011) [23] reported a synthesis of another iso-analog called isomeridianin A (**24**), which differs from meridianin A by position of –OH group on indole nucleus. Structures of isomeridianins **22-24** are shown in Fig. (**2**).

Meridianins showed ability to inhibit various protein kinases such as cyclin dependent kinases, glycogen synthase kinase-3, cyclic nucleotide-dependent kinases and casein kinase-1 [24] and also displayed antitumor activity [25]. The kinase inhibitory activities of meridianins are shown in Table **1** [24] and activity of meridianin E (**5**) against a panel of 25 different kinases is shown in Table **2** [24]. All meridianins, except meridianin G (**7**) and isomeridianin **22-23**, exhibited inhibition of CDKs, GSK-3, PKA and other protein kinases at low micromolar concentration. Meridianin B (**2**) and meridianin E (**5**) were most potent inhibitors while meridianin G (**7**), isomeridianin C (**22**) and G (**7**) were essentially inactive [24]. Interesting SAR features were observed from the kinase inhibitory profile of meridianins. From Table **1**, it is evident that, for CDK-1 and CDK-5 inhibition, a bromine substitution on position 7 of the indole [compare meridianins E (**5**) and A (**1**) or B (**2**)] and a hydroxyl group on position 4 [compare meridianins A (**1**) and G (**7**), meridianins B (**2**) and D (**4**)] provide the best inhibitory activity. The removal of both bromine and hydroxyl substitutions [meridianin G (**7**)] essentially inactivates meridianins as CDK inhibitors. A single bromine substitution in position 5 or 6 significantly increases the inhibitory activity [compare meridianins C (**3**) or D (**4**) and G (**7**)]. Two bromine substitutions somewhat reduce the inhibitory potency [compare meridianins C (**3**) or D (**4**) and F (**6**)]. Shifting the 2-amino pyrimidine ring from position 3 to position 2 inactivates the inhibitor [compare meridianin C (**3**) and isomeridianin C (**22**)]. The hydroxyl group in position 4 seems to be important by itself for the inhibitory activity [compare meridianin A (**1**) and G (**7**)], but much less

Table 1. Kinase Inhibition and Antiproliferative Activities of Meridianins A-G (1-7), Isomeridianin C (22) and Isomeridianin G (23)

Protein Kinase[a]	Meridianins (IC_{50} in μM)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**22**	**23**
CDK1/B	2.5	1.5	3.0	13	0.18	20	150	160.00	140
CDK5/p25	3.0	1.0	6.0	5.5	0.15	20	140	300.00	130
PKA	11	0.21	0.7	1.0	0.09	3.2	120	>1000	500
PKG	200	1.0	0.4	0.8	0.6	0.6	400	>1000	1000
GSK3-β	1.3	0.5	2.0	2.5	2.5	2.0	350	>1000	420
CK1	-	1.0	30	100	0.4	nt[b]	nt[b]	nt[b]	nt[b]
Cell line									
PTP	nt[b]	37.2	23.9	42	22	nt[b]	nt[b]	nt[b]	nt[b]
Hep2	na[b]	1.7	9.7	7.3	1.1	1.8	nt[b]	nt[b]	nt[b]
HT29	na[b]	nt[b]	5.5	36.6	nt[b]	nt[b]	nt[b]	nt[b]	nt[b]
RD	nt[b]	nt[b]	6.6	21.7	nt[b]	nt[b]	nt[b]	nt[b]	nt[b]
U937	nt[b]	11.6	2.7	16.9	9.8	0.2	nt[b]	nt[b]	nt[b]
LMM3	na[b]	17.7	9.3	33.9	11.1	1.4	nt[b]	nt[b]	nt[b]

[a]CDK-1/B: cyclin-dependent kinase-1/cyclin B; CDK-5/p25: cyclin- dependent kinase-5/cyclin p25; CK1: casein kinase-1; GSK-3β: glycogen synthase kinase-3β isoform; PTP: a foreskin fibroblast cell line; Hep2: larynx carcinoma; HT29: colon carcinoma; RD: rabdomyocarcinoma; U937: myeloid leukemia; LMM3: murine mammalian adenocarcinoma cell line.

[b]nt, not tested; na, not active.

when a bromine substitution is present [compare meridianin B (**2**) and D (**4**)]. The structure-activity relationship (SAR) of meridianins on cyclic nucleotide-dependent kinases is comparatively similar to other kinases but not identical. A bromine substitution on position 7 and a hydroxyl group on position 4 of indole provides best inhibitory activity. In case of meridianin F (**6**) the presence of two bromine atoms was not able to improve activity; however a decrease in activity against some kinases was observed. It may be hypothesized that the primary amine of the pyrimidine and the hydroxyl group of indole acts as H-bond donors while the nitrogen of the pyrimidine ring could acts as a H-bond acceptor [24]. Since isomeridianins **22-24** were less active, indicates the importance of 3-substituted meridianins for biological activity.

Meridianins A-F (**1-6**) were also evaluated for their anti-proliferative effect on different cancer cell lines. Only meridianins B (**2**) and E (**6**) exhibited effect on proliferating human teratocarcinoma NT2 cells, which suggested that only most kinase active meridianins possess anti-proliferative properties. It was interesting to note that the non-brominated alkaloid meridianin A (**1**) never showed cytotoxicity even at higher concentrations, though it showed relatively good inhibitory profile on various protein kinases. On the other hand, all other meridianins B-F (**2-6**) exhibited an evident cytotoxic activity at low micromolar range (Table **1**). Regarding the relationship between meridianin cellular effects and their pharmacological activity, the capacity to inhibit the kinase activity of cAMP-dependent PK and cGMP-dependent PK seems to correlate best with their antiproliferative action, since only the non-cytotoxic meridianin A showed high IC_{50} values for these enzymes [6, 24].

Meridianin E (**5**) was the most promising natural analog and was therefore evaluated against a panel of 25 different kinases. It exhibited potent inhibition of cyclin dependent kinases – CDK-1, CDK-2 and CDK-5 with IC_{50} values of 180, 800 and 150 nM respectively. Meridianin E (**5**) also showed promising inhibitory activity against c-AMP and c-GMP dependent protein kinases with IC_{50} values of 90 and 600 nM respectively. Two other kinases *viz.* casein kinase-1 and GSK-3 were also inhibited by **5** at nanomolar concentrations. The IC_{50} values of meridianin E (**5**) against different kinases are shown in Table **2**.

Naturally occurring structural analog hyrtinadine A (**17**) exhibited cytotoxicity against murine leukemia L1210 cells (IC_{50} 1 μg/ml) and human epidermoid carcinoma KB cells (IC_{50} 3 μg/ml) *in vitro* [10]. Aplicyanins (**11-16**) also showed cytotoxicity in human cancer cell lines MDA-MB-231 (breast adenocarcinoma), A549 (lung carcinoma) and HT-29 (colorectal carcinoma) and also exhibited antimitotic activity [8, 9]. The presence of bromine at position 5 of the indole nucleus strongly favors antiproliferative activity and acetyl group at imine nitrogen playing key role in the biological activity of the aplicyanin family [26].

3. SYNTHETIC STUDIES ON MERIDIANINS

Due to promising biological activity profile, meridianin syntheses have been extensively explored by several researchers. Fresneda and co-workers (2000) [27] were the first to report the synthesis of meridianins, which was followed by large number of synthetic routes for these molecules. Till now, there exist total 20 reports on the synthesis of meridianins and its analogs/ derivatives. Amongst these, 10 syntheses have been reviewed recently by Walker *et al.* (2007) [28] in his review on variolins and

Table 2. Inhibitory Activities of Meridianin E (5) Towards a Panel of 25 Protein Kinases

Protein Kinase [a]	IC_{50} (μM)	Protein Kinase	IC_{50} (μM)
CDK1/B	0.18	Protein kinase Cβ1	1.50
CDK2/A	0.80	Protein kinase Cβ2	2.00
CDK2/E	1.80	Protein kinase Cγ	2.00
CDK4/D1	3.00	Protein kinase Cδ	1.20
CDK5/p25	0.15	Protein kinase Cε	4.00
Erk1	100	Protein kinase Cη	1.30
Erk2	100	Protein kinase Cζ	4.00
c-Raf	1-10	cAMP-dependent PK	0.09
MAPKK	100	cGMP-dependent PK	0.60
c-Jun N-terminal kinase	1.00	GSK3-α	0.90
Casein kinase 1	0.40	GSK3-β	2.50
Casein kinase 2	100	Insulin Receptor Tyr Kinase	80.00
Protein kinase Cα	1.30		

[a]CDK-1/B: cyclin- dependent kinase-1/cyclin B; CDK-2/A: cyclin- dependent kinase-1/cyclin B; CDK-2/E: cyclin- dependent kinase-1/cyclin B; CDK-4/D1: cyclin- dependent kinase-4/cyclin D1; CDK-5/p25: cyclin-dependent kinase-5/cyclin p25; Erk1 and Erk2: are mitogen-activated protein (MAP) kinases; MAPKK: mitogen-activated protein kinase kinase; GSK-3α: glycogen synthase kinase-3α isoform; GSK-3β: glycogen synthase kinase-3β isoform.

related alkaloids. Remaining 10 syntheses are discussed in the present review. The summary of all reported syntheses is provided in Table **3**.

Simon *et al.* (2007) [36] reported the total synthesis of meridianin C (**3**) and G (**7**) starting from indole derivatives **25a-b** (Fig. **3**). Steps involved in the synthesis of meridianin C (**3**) and G (**7**) involves the protection of indolic nitrogen with tosyl chloride followed by acetylation using acetic anhydride and $AlCl_3$ yielding intermediates **27a-b**. Compounds **27a-b** were further converted into enaminones **28a-b** using dimethyl formamide-dimethylacetal (DMF-DMA) in 53-84% yield followed by a construction of aminopyrimidine ring by treatment with guanidine hydrochloride. Finally deprotection was done using sodium ethoxide under reflux to yield meridianin C (**3**) and G (**7**) in 57 and 62% yield respectively.

Yu and Yu (2009) [37] reported synthesis of meridianin analogs (general structure **33**) starting from substituted indoles **29** and α-oxo ketene dithioacetal **30** (Fig. **4**). Alkenylation of indoles **29** with α-oxo ketene dithioacetal **30** was performed in TFA under refluxing conditions. Further alkenylated indole **31** on treatment with guanidine nitrate led to formation of meridianin skeleton **32** which finally on N-deprotection yielded desired meridianin analogs with general structure **33**.

Radwan *et al.* (2009) [38] synthesized several 3-heteroaryl analogs **37-38** of meridianins involving a base promoted cyclization of indole enaminonitrile **35** as a key step. Treatment of cyanoacetyl indole (**34**) with DMF-DMA led to formation of indole enaminonitrile **35** which on reaction with α -heteroarylamines **36** or phenylhydrazine in presence of base resulted in cyclization forming analogs **37-38** as depicted in Fig. (**5**).

Recently Chen *et al* (2010) [44] synthesized spirooxindole derivatives **41** of meridianins using multi-component one-pot reaction of 3-cyanoacetyl indoles **34**, isatins **39**, and *1H*-pyrazol-5-amines **40** in H_2O/HOAc in good yields (Fig. **6**). Tibiletti *et al.* (2010) [40] synthesized meridianins C (**3**) and G (**7**) *via* indolization of nitrosoarenes as depicted in Fig. (**7**). The synthesis of meridianin G (**7**)

Table 3. List of Syntheses Reported for Meridianins and its Derivatives

Sr. No.	Authors and Reference	Starting Material	Meridianins Synthesized	Figure
1.	Fresneda *et al*. (2000) [27]	N-tosyl-3-acetylindole	Meridianins C (3), D (4), E (5)	†
2.	Jiang and Yang (2000) [29]	N-tosyl-6-bromoindole	D (4), G (7)	†
3.	Fresneda *et al* (2001) [30]	N-tosyl-3-acetylindole	A (1), C (3), E (5)	†
4.	Jiang *et al*. (2001)[31]	N-tosyl-3-boronic acid indole	Indolyl pyrazines	†
5.	Franco and Palermo (2003) [22]	Isocytosine	Isomeridianin C (22) and G (23)	†
6.	Jakse *et al* (2004) [32]	Indole ester	Analogs (pyrimidine replaced with pyrimidinone or fused bicylics)	†
7.	Karpov *et al* (2005) [33]	Substituted indole	C (3), D (4), G (7)	†
8.	Casar *et al* (2005) [34]	Indole ester	Analogs	†
9.	Radwan and El-Sherbiny (2007) [25]	Indole	Meridianin G (7) and few analogs	†
10.	Rossignol *et al* (2007) [35]	3-acetyl indole	Meridianin G (7) and analogs	†
11.	Simon *et al.* (2007) [36]	Indole	Meridianin C (3) and G (7)	Fig. (**3**)
12.	Yu and Yu (2009) [37]	Indole	Analogs 33	Fig. (**4**)
13.	Radwan et al (2009) [38]	Cyanoacetyl indole	Condensed meridianin analogs 37-38	Fig. (**5**)
14.	Akue-Gedu *et al* (2009) [39]	Substituted indole	Analogs 82-84 and their biology	‡
15.	Tibiletti *et al.* (2010) [40]	2,4-dichloro pyrimidine	Meridianins C (3) and G (7)	Fig. (**7**)
16.	Merkul *et al.* (2011) [5]	N-Boc -3-iodoindole	Meridianin A (1) and G (7)	Fig. (**8**)
17.	Parsons *et al.* (2011) [41]	Indole 3-ester	Meridianin F (6)	Fig. (**9**)
18.	Sperry *et al* (2011) [42]	Dibromo-indole-3-carbaxaldehyde	Meridianin F (6)	Fig. (**10**)
19.	Tasch *et al* (2011) [23]	N-Boc -3-iodo- 5-methoxyindole	Isomeridianin A (24)	Fig. (**11**)
20	Giraud *et al.* (2011) [43]	Substituted indole	Analogs 68-81 and their biology	‡

†covered in earlier reviews [28].
‡synthetic route is similar to Simon *et al.* (2007) [36].

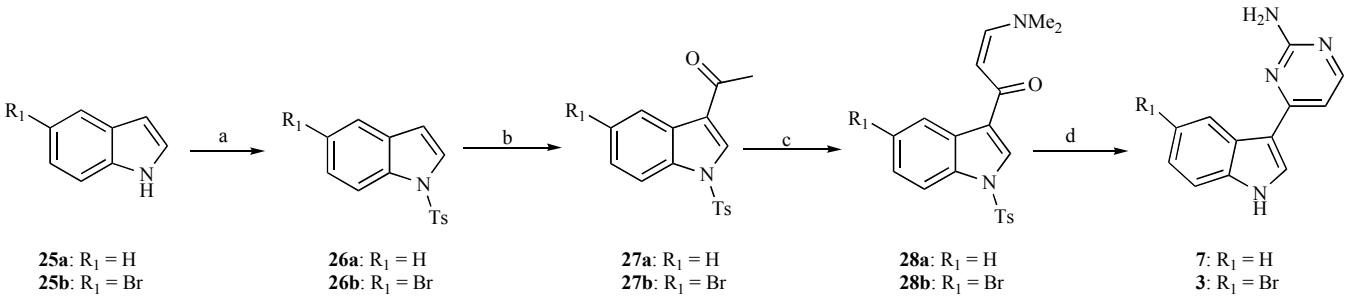


Fig. (3). Total synthesis of meridianin C (**3**) and G (**7**) by Simon *et al.* (2007) [36]. Reagents and conditions: (a) TsCl, NaOH, $Bu_4^+HSO_4^-$, DCM, H_2O, 250 °C, 87-95%; (b). AC_2O, $AlCl_3$, DCM, 250 °C, 88-97%; (c). DMF-DMA, DMF, 110 °C, 53-84%; (d). guanidine HCl, EtONa, EtOH, reflux, 57-62%.

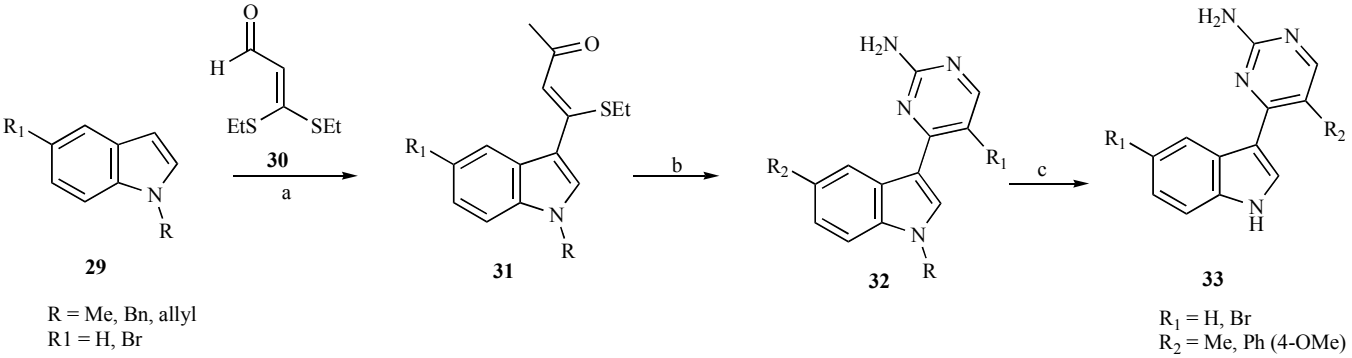


Fig. (4). Synthesis of meridianin analogs **33** (Yu and Yu 2009) [37]. Reagents and conditions: (a). TFA, CH_2Cl_2, reflux, 30 min, 90%; (b). guanidine nitrate, KOH/EtOH, reflux, 63-80%; (c). tBuOK, DMSO, O_2, rt, 76-83%.

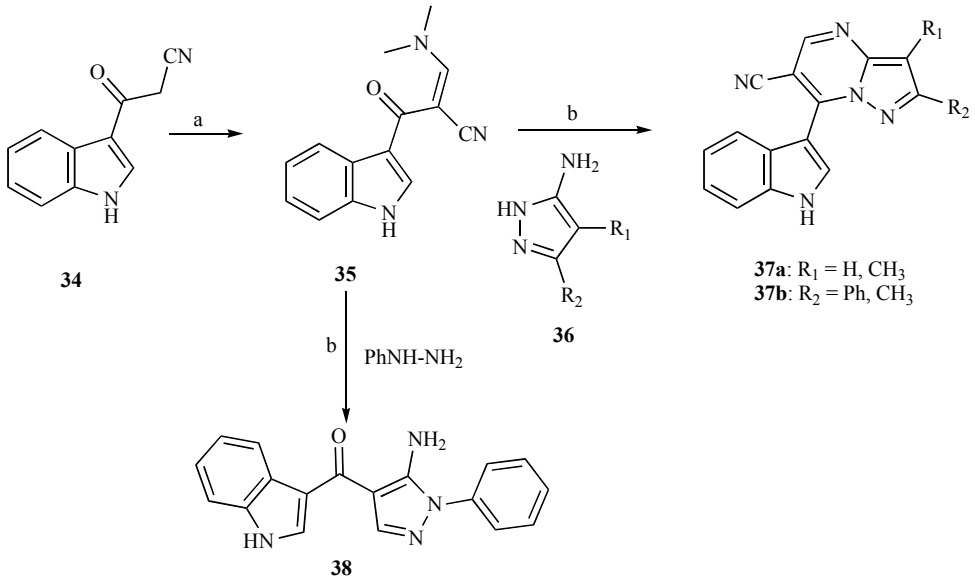
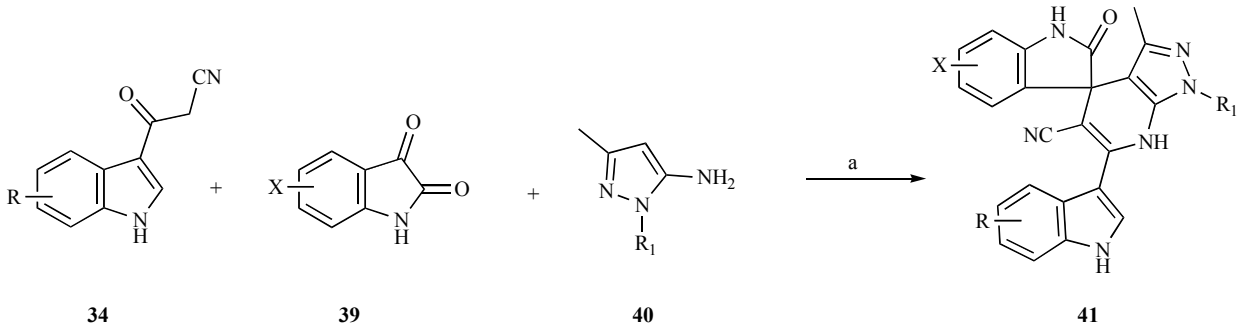


Fig. (5). Synthesis of 3-heteroaryl analogs **37-38** of meridianins (Radwan *et al* 2009) [38]. Reagents and conditions: (a). DMF-DMA, DMF, 110 °C, 82-83%; (b). EtOH, piperidine, reflux, 6 h, 75-87%.

started with 2,4-dichloro pyrimidine (**42**). Sonogashira coupling of **42** with ethynyltrimethylsilane followed by deprotection of trimethylsilyl group with KOH/MeOH resulted in formation of 2-chloro 4-ethynyl pyrimidine (**44**). This on further reaction with nitrosobenzene (**45**) gave 3-(2-chloropyrimidinyl) indole (**46**) which on treatment with aqueous ammonia in sealed tube gave meridianin G (**7**) in 54% yield. Another route to make meridianin G (**7**) along with a meridianin C (**3**) started with thiouracil (**47**). Thiouracil (**47**) on methylation using methyl iodide afforded methylated thiouracil (**48**). Compound **48** on treatment with ammonium acetate gave isocytosine (**49**) which on reflux with $POCl_3$ yielded 2-amino-4-chloropyrimidine (**50**). The key intermediate **50** on sonogashira coupling with



34 **39** **40** **41**

Fig. (6). Synthesis of 3-heteroaryl analogs **41** of meridianins using one-pot multicomponent reaction (Chen *et al* 2010) [44]. Reagents and conditions: (a). H_2O/HOAc (1:1 v/v), 140 °C, 12 h, 80%.

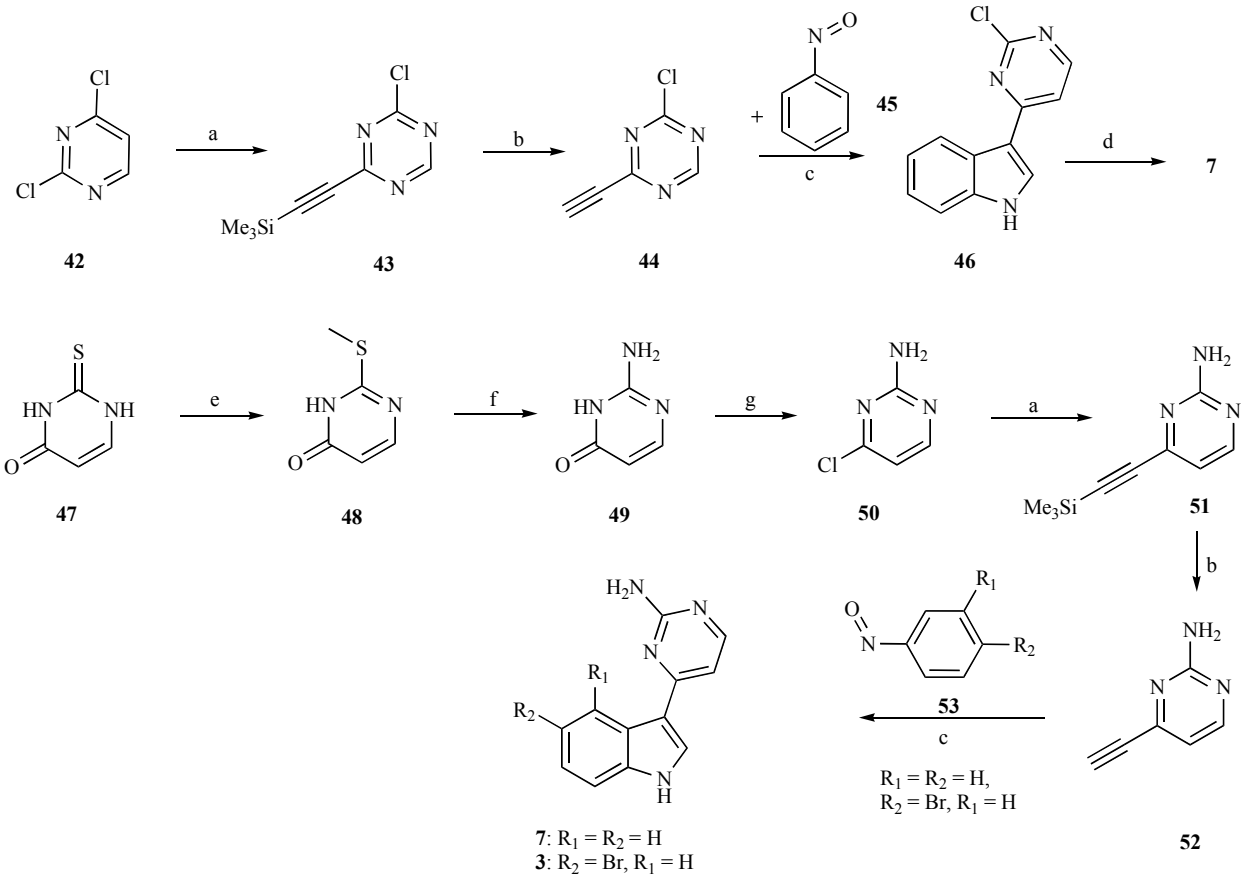


Fig. (7). Total synthesis of meridianin G (**7**) and meridianin C (**3**) by Tibiletti *et al.* (2010) [40]. Reagents and conditions: (a). Ethynyltrimethylsilane, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, 60-70%; (b). KOH, MeOH, 90%; (c). toluene, 80 ^{0}C, 67%; (d). NH_3, 80 ^{0}C, sealed tube, 41%; (e). CH_3I, NaOH, H_2O, quantitative; (f). NH_4OAc, 160 ^{0}C, 52%; (g). $POCl_3$, reflux. 37%.

ethynyltrimethylsilane followed by deprotection of trimethylsilyl group gave 2-amino-4-ethynyl pyrimidine (**52**). Finally the cyclization between amine **52** and nitrosoarenes **53** led to formation of **7** and **3** in 41 and 28% yield respectively.

Merkul *et al.* (2011) [5] reported the total synthesis of meridianin A (**1**) and G (**7**) in 4 steps with 54% overall yield starting from N-Boc protected 3-iodoindole (Fig. **8**). N-Boc-3-iodo indole (**54a**) was converted to N-Boc indole-3-pinacol ester **55a** using Masuda borylation. This was further converted to meridianin G (**7**) using Suzuki cross-coupling reaction with 4-chloro pyrimidin-2-amine (**50**). For the synthesis of meridianin A (**1**), N-Boc protected 3-iodo-4-methoxyindole (**54b**) was used as starting material. Compound **54b** was converted to corresponding pinacol ester **55b** followed by Suzuki cross coupling reaction with 4-chloro pyrimidin-2-amine (**50**) to form O-methyl meridianin A (**56**) which finally on demethylation using pyridine-HCl led to formation of meridianin A (**1**).

Parsons *et al.* (2011) [41] synthesized meridianin F (**6**) in 4 steps starting from indole-3-ester (Fig. **9**). Indole 3-carboxylate **57** on dibromination using bromine in acetic

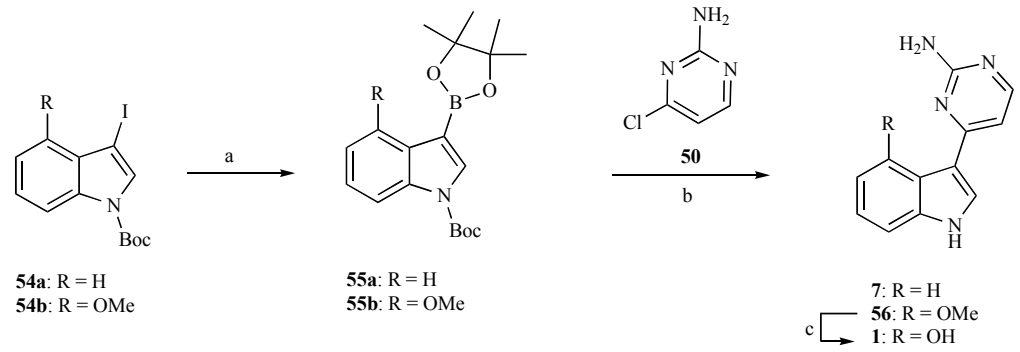


Fig. (8). Total synthesis of meridianin A (**1**) and G (**7**) by Merkul *et al.* (2011) [5]. Reagents and conditions: (a). Masuda borylation $Pd(PPh_3)_4$, HBpin, NEt_3, 1,4-dioxane, 80 ^{0}C, 3 h; (b).Suzuki coupling: Cs_2CO_3, MeOH, 100 ^{0}C, overnight, 77% from **54**; (c). 20% pyridine HCl, 210 ^{0}C, 0.5 h, 85%.

acid at room temperature gave **58** in 70% yield. Dibrominated compound **58** was protected using Boc anhydride and then converted to Weinreb amide **59** using N-methoxymethanamine hydrochloride. Treatment of the Weinreb amide **59** with lithium(trimethylsilyl)acetylide directly gave terminal alkyne derivative **60** which on treatment with guanidine led to formation of **6** in 47% yield.

Sperry *et al* (2011) [42] reported the concise total synthesis of meridianin F (**6**) starting from 5,6-dibromo *1H*-indole-3-carboxaldehyde (**61**). Carboxaldehyde **61** on protection with benzyl bromide followed by Grignard reaction with methyl magnesium bromide led to formation of **62**. Oxidation of secondary alcohol **62** using iodoxy benzoic acid (IBX) resulted in formation of the key intermediate N-benzyl protected 3-acetyl indole **63** with overall yield of 71% (from **61**). Key intermediate **63** was smoothly converted into enaminone by using DMF-DMA followed by immediate treatment with guanidine hydrochloride in the presence of potassium carbonate to get N-benzyl meridianin F (**64**). The deprotection was achieved using potassium tertiary-butoxide in DMSO under an atmosphere of oxygen to give **6** in good yield (Fig. **10**).

Tasch *et al* (2011) [23] recently reported the total synthesis of isomeridianin A (**24**) in 2 steps starting from N-Boc protected 3-iodo-5-methoxyindole (**65**) as depicted in Fig. (**11**). Indole **65** on Masuda borylation followed by Suzuki coupling with 4-chloro pyrimidin-2-amine (**50**) yielded O-methyl isomeridianin A (**67**). This was further demethylated using pyridine-HCl to give isomeridianin A (**24**) in 89% yield.

4. MERIDIANIN-INSPIRED SYNTHETIC ANALOGS AS KINASE INHIBITORS

Moreau *et al*. [39, 43] synthesized series of meridianin derivatives **68-84** using similar synthetic scheme as reported by Simon *et al.* (Fig. **3**) [36] and evaluated their kinase

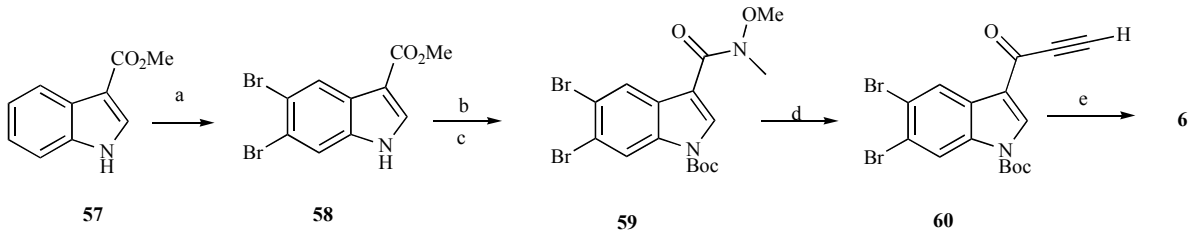


Fig. (9). Total synthesis of meridianin F (**6**) by Parsons *et al.* (2011) [41]. Reagents and conditions: (a). Br_2, AcOH, rt, 70%; (b). Boc_2O, 96%; (c). PhMgCl, MeNHOMe.HCl, THF, 88% (d). lithium(trimethylsilyl) acetylide, THF, 90%; (e). guanidine, Na_2CO_3, t-BuOH, MeCN, H_2O, heat, 47%.

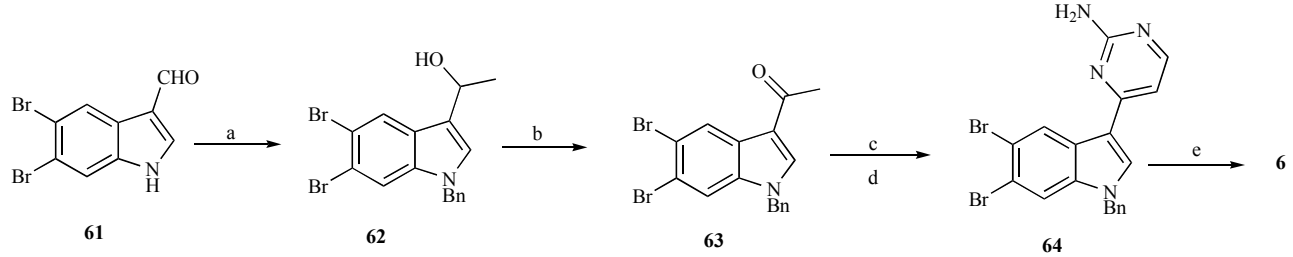


Fig. (10). Total synthesis of meridianin F (**6**) by Sperry *et al.* (2011) [42]. Reagents and conditions: (a). (i). NaH, BnBr, THF, r.t., 2h; (ii). MeMgBr, THF, 0 ^{0}C - r.t., 20 min; (b). IBX, DMSO, 50 ^{0}C, 1 h, 71% from **61**; (c). DMF-DMA, DMF, reflux, 8 h; (d). Guanidine.HCl, K_2CO_3, EtOH, reflux, 36 h, 53% from **63**; (e). O_2, KO^{t}Bu, DMSO, r.t., 15 min, 88%.

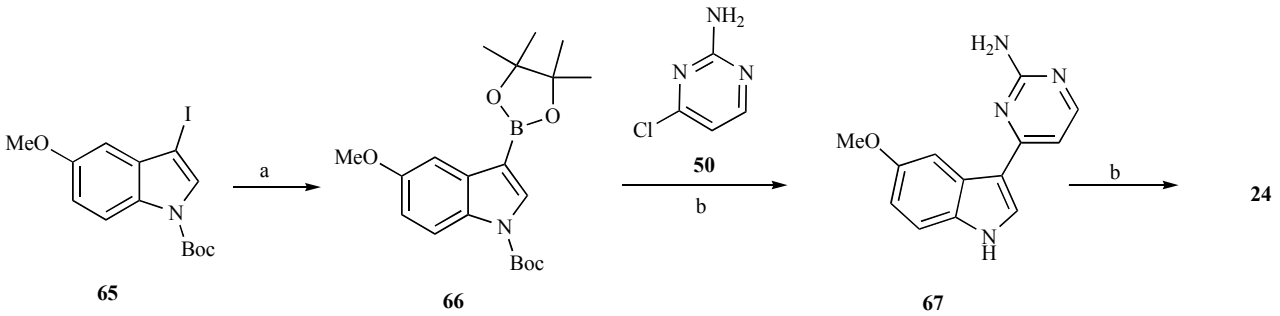
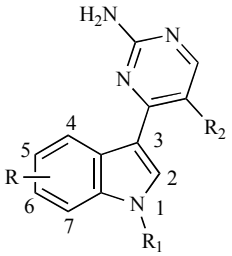


Fig. (11). Synthesis of isomeridianin A (**24**) by Tasch *et al*. (2011) [23]. Reagents and conditions: (a). $Pd(PPh_3)_4$, HBpin, NEt_3, 1,4-dioxane, 80 ^{0}C, 3 h; (b). Cs_2CO_3, MeOH, 100 ^{0}C, 24 h, 86% from **65**; (c). pyridine-HCl, 210 ^{0}C, 0.5 h, 89%.

Table 4. Synthetic Analogs of Meridianin 68-84 and their Kinase Inhibitory Activities

Entry				Kinase[a] IC_{50} (μM)				
	R	**R_1**	**R_2**	**CDK5/p25**	**CK1δ/ε**	**GSK-3α/β**	**CLK1**	**Dyrk1A**
68	7-Br	H	H	3.1	4.2	>10	0.065	0.068
69	6-Br	H	I	0.68	0.7	1.1	0.032	0.034
70	7-Br	H	I	2.1	1.6	4	0.042	0.039
71	6-Br	H	4-acetylphenyl	> 10	>10	2.0	1.8	>10
72	5-Br	H	4-acetamidophenyl	6.8	2.1	0.4	0.75	4.15
73	7-Br	H	4-acetamidophenyl	7.5	>10	2.2	0.087	0.19
74	4-Br	H	3-methoxyphenyl	6	>10	1.4	1.3	0.81
75	7-Br	H	3-methoxyphenyl	>10	4.2	>10	0.87	0.85
76	7-NO_2	H	H	6.3	10	>10	0.07	0.085
77	6-NO_2	H	I	1.6	1	2.6	0.067	0.095
78	H	H	I	1.4	0.9	3.7	0.03	0.066
79	5-NH_2	H	I	>10	0.27	>10	0.61	2.3
80	6-NH_2	H	I	6.2	0.51	4.2	0.08	0.22
81	7-NH_2	H	I	0.66	1.1	4.4	0.026	0.11
82[b]	H	H	4-trifluoromethylphenyl	11	8.3	1.9	nt[c]	2.3
83[b]	H	Me	4-acetylphenyl	> 10	>10	1.4	nt[c]	5.0
84[b]	H	Me	I	2.6	1.1	4.2	nt[c]	0.4

[a] CDK-5/p25: cyclin- dependent kinase-5/cyclin p25; CK1δ/ε: casein kinase-1 δ/ε isoforms; GSK-3α/β: glycogen synthase kinase-3α/β isoforms; CLK1: cdc2-like kinase, is a dual specificity protein kinase encoded by the CLK1 gene; Dyrk1A: Dual specificity tyrosine-phosphorylation-regulated kinase 1A enzyme encoded by Dyrk1A gene.
[b]Compounds **82-84** were also tested against Erk2 kinase and showed IC_{50} of 0.58, >10 and 4 μM respectively.
[c] nt: not tested.

inhibitory activities and antiproliferative activity in different cell lines. Series of meridianin derivatives were prepared by varying substitution mainly on a pyrimidine ring. Most of the compounds were highly active against Dyrk-1A and CLK-1

kinases, the most potent compound **69** showed IC_{50} of 34 and 32 nM respectively. Although number of compounds active towards other tested kinases (CDK-5, CK-1, GSK-3) were less, but few compounds showed good IC_{50} against these kinases as well. These include compounds **81** (CLK-1: 26 nM; CDK-5: 660 nM), **72** (GSK: 400 nM) and **79** (CK-1: 270 nM). The most effective compounds towards Dyrk-1A and CLK-1 kinases were found to be 6- and 7- bromo derivatives **68-70** that showed more than 45-fold selectivity towards Dyrk-1A/CLK-1 kinases over other kinases tested. Chemical structures of selected compounds **68-84** possessing good activity for different kinase are depicted in Table **4**.

Compound **71** which showed activity only against GSK-3 and CLK-1 showed potent antiproliferative activity in all cell lines tested. Other analogs **69** and **70** which showed selective inhibition of Dyrk-1A and CLK-1 also showed good antiproliferative activity in all cell lines. Compounds **82** and **83** showed potent anti-proliferative activity against PA1 cells with IC_{50} values of 90 and 50 nM respectively. Antiproliferative effect of most active compounds are depicted in Table **5**. Compound **71** was the most promising as it showed antiproliferative effect in all cell lines *viz*. SHSY-5Y, IMR-32, MCF-7, HT22, PA1, PC3, DU45 and Fibro with IC_{50} values of 0.1, 0.33, 1, 2.5, <0.6, <0.6, <0.6 and <0.6 μM respectively. Amongst different cell lines evaluated, promising cytotoxic effects were observed in human ovary teratocarcinoma cell line PA1, with all compounds **69-84** showing IC_{50} values < 31 μM. Compounds **82** and **83** which contain 4-trifluoromethylphenyl and 4-acetylphenyl moiety on the pyrimidinyl part showed antiproliferative effect with IC_{50} values of 90 nM and 50 nM in PA1 cell line.

Rossignol *et al* (2008) [45] evaluated series of synthetic analogs **85-90** against different kinases *viz.* KDR, IGFR-1, c-Met, RET, c-SRC, c-Abl, PKA, CDK-2/A and HER-1 and three cell lines *viz*. fibro, MCF7 and PA1. Kinase inhibitory and antiproliferative activities of most active compounds **85-90** are depicted in Table **6**. Same group of researchers also evaluated meridianin G (**7**) and its bromo derivative **85** against several other kinases *viz*. MKK-1, ERK-2, RSK-2, PKCα, GSK-3β, CDK-2/A, CK-2 and MST-2. Meridianin G (**7**) showed 66, 36, 9, 56, 43, 54, 38 and 31% inhibition of these kinases at 10 μM whereas bromo derivative **85** showed 98, 92, 85, 91, 87, 85, 93 and 96% inhibition at 10 μM respectively [35]. Radwan and El-Sherbiny (2007) [25] synthesized 6-debromomeridianin D (**7**) starting from cyanoacetyl indole (**34**). During the same period, this synthetic 6-bromomeridianin D was also isolated as a natural product by Seldes *et al.* [20] and named as meridianin G (**7**). Along with 6-debromomeridianin D (**7**), Radwan and El-Sherbiny also synthesized analogs **91-93** and tested for antiproliferative activity. The cyano meridianin D **91** exhibited a good cytotoxic activity against breast carcinoma cell line (MCF7) and cervix cell line (HeLa) with the IC_{50} values of 0.85 and 2.65 μg, respectively, but carboxylic acid analogue **92** and amidrazone analogue **93** showed high cytotoxicity with IC_{50} values of 0.75 and 0.25 μg, respectively (against MCF7).

Jiang *et al* (2001) [31] reported bis-indolyl pyrimidines **94-95** and indolyl pyrazine analogs **96-97** of meridianins and evaluated for anticancer activities. Bisindolyl pyrimidine compound **94** exhibited significant inhibitory activity against leukemia SR, CNS cancer SF-539, and breast cancer MDA-MB-435 cell lines with the GI_{50} values of 0.22, 0.16 and 0.22 μM respectively. Another bisindolyl pyrimidine **95** displayed strong selective cytotoxic activity against IGROV1 tumor cell line with GI_{50} values below 0.01 μM. Pyrazine analog of meridianin, compound **96** also showed good inhibitory activity against a variety of tumor cell lines with GI_{50} values below 10 μM. Similarly another pyrazine analog **97** exhibited excellent selective inhibition against CCRF-CEM cancer cell lines with GI_{50} value of 0.03 μM.

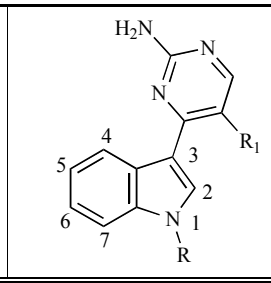
Recently Lebar *et al* (2011) [46] reported antimalarial and CNS activity of series of meridianin analogs. Meridianin A (**1**) and 4-methoxy analog of meridianin A **98** showed inhibition of *Plasmodium falciparum* with IC_{50} of 12 and 40

Table 5. Antiproliferative Acitivities of Meridianin Analogs 69-84

Entry	Cell lines IC_{50} (μM)[a]							
	SHSY-5Y	IMR-32	MCF7	HT22	PA1	PC3	DU45	Fibro
69	3.2	3.8	5.2	5.1	< 1	2.9	< 1	3.5
70	8	7.3	17	12	2	15	4.2	10
71	0.4	0.33	1	2.5	< 0.6	< 0.6	< 0.6	< 0.6
78	7.5	10	17	7.3	3.3	10.6	5	8
81	9	4	20	12	2.5	14	6.1	10.6
82	nt[b]	nt[b]	nt[b]	nt[b]	0.09	nt[b]	nt[b]	nt[b]
83	nt[b]	nt[b]	nt[b]	nt[b]	0.05	nt[b]	nt[b]	nt[b]
84	nt[b]	nt[b]	nt[b]	nt[b]	31	nt[b]	nt[b]	nt[b]

[a]SHSY-5Y and IMR-32: human neuroblastoma cell lines; MCF7: breast cancer cell line; HT22: immortalized mouse hippocampal cell line; PA1: human ovary teratocarcinoma cell line; PC3 and DU45: human prostate cancer cell lines; Fibro: human fibroblast primary culture.
[b]nt: not tested.

Table 6. Synthetic Analogs of Meridianin 85-90 and their Kinase Inhibitory and Antiproliferative Activities

Entry		Kinases[a] IC_{50} in μM							Cell lines[a] IC_{50} in μM		
		KDR	IGFR-1	RET	C-Abl	PKA	CDK-2/A	HER-1	Fibro	MCF7	PA1
85	R = H, R_1 = Br	1.1	3.1	>10	7.8	2.5	5.9	>10	76%[b]	78%[b]	33%[b]
86	R = H, R_1 = 4-acetylphenyl	>10	5.9	5.0	7.1	>10	>10	>10	9.5	22.7	2.0
87	R = CH_3, R_1 = 4-acetylphenyl	>10	3.4	6.0	>10	>10	>10	>10	3.8	1.6	0.05
88	R = CH_3, R_1 = 4-biphenyl	>10	>10	7.8	>10	>10	>10	>10	0.9	0.28	0.08
89	R = H, R_1 = 4-trifluromethylphenyl	>10	>10	>10	>10	>10	>10	8.9	8.7	14.0	0.09
90	R = H, R_1 = 4-trifluromethoxyphenyl	>10	>10	>10	>10	>10	>10	5.2	25.8	0.3	0.08

[a] KDR: kinase domain receptor (also called as vascular endothelial growth factor receptor, VEGF); IGFR-1: insulin-like growth factor receptor-1; RET: is an abbreviation for "rearranged during transfection" and is the receptor for members of the glial cell line-derived neurotrophic factor family of extracellular signalling molecules or ligands; C-Abl: Abelson leukemia oncogen cellular homologue and is the non-receptor tyrosine kinase; PKA: protein kinase-A; CDK-2/A: cyclin dependent kinase-2/cyclin A; HER-1: is the epidermal growth factor receptor, EGFR; Fibro: human fibroblast primary culture; MCF7: breast cancer cell line; PA1: human ovary teratocarcinoma cell line.

[b] Percentage of residual activity at 5 μM.

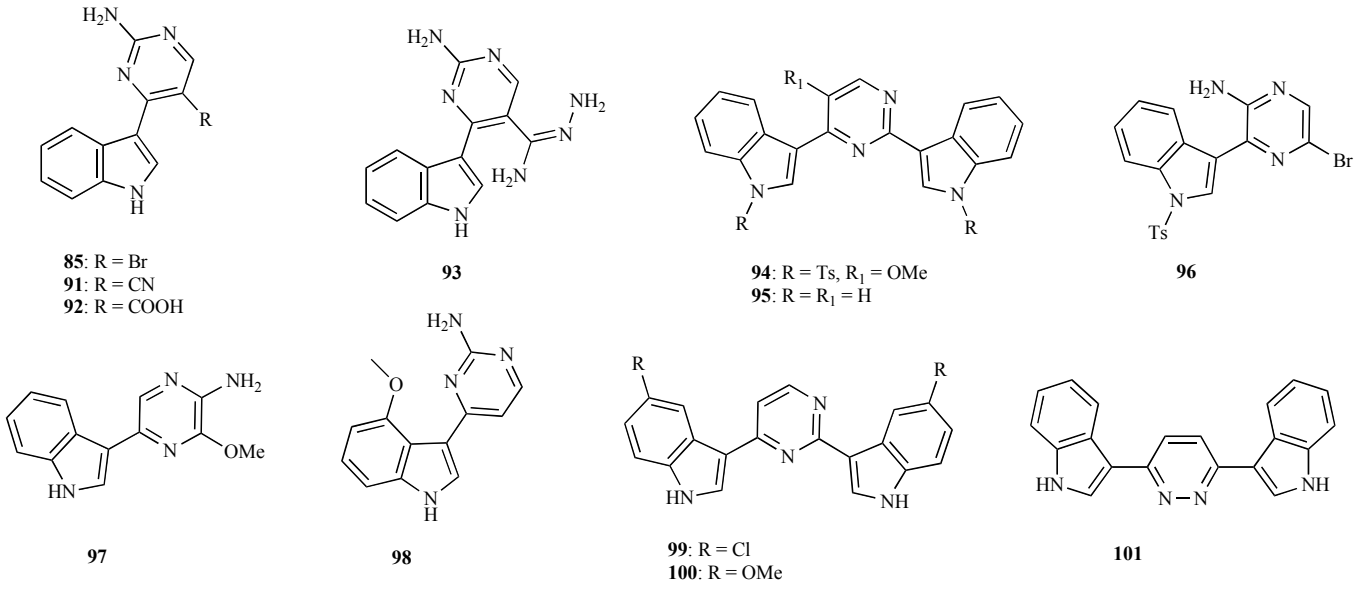


Fig. (12). Structures of meridianin analogs **85** and **91-101**.

μM respectively. Compounds **1** and **98** also showed good binding to 5-HT2B receptor with *ki* values of 0.15 and 0.088 μM respectively. Bisindolic hyrtinadine analogs **99-101** exhibited antiproliferative activity against HCT116 and A2780 cell lines with IC_{50} values of 5.3, 3.7, >10 and 0.9, 4.5, 3. μM respectively [23]. Chemical structures of compounds **85** and **91-101** are shown in Fig. (**12**).

5.COMPUTATIONAL STUDIES

Giraud *et al*. [43] studied the binding mode and orientation of potent meridianin analogs **68-70** against Dyrk1A and CLK-1 using molecular docking studies on available PDB structures, 2WO6 and 1Z57 respectively. In case of Dyrk-1A, meridianin derivatives **68-70** adopt a similar binding mode. The aminopyrimidine moiety is oriented toward the bottom of the pocket making two hydrogen bonds with the ATP binding site. Thus, the amino group is H-bonded with Glu239 backbone carbonyl and the N-1 atom is H-bonded with Leu241 backbone NH (Fig. **13A**). Moreover, the heteroaromatic scaffold of compounds **68-70** is strongly associated to the protein by hydrophobic interactions with Ile165, Val173, Ala186, Leu241, Leu294,

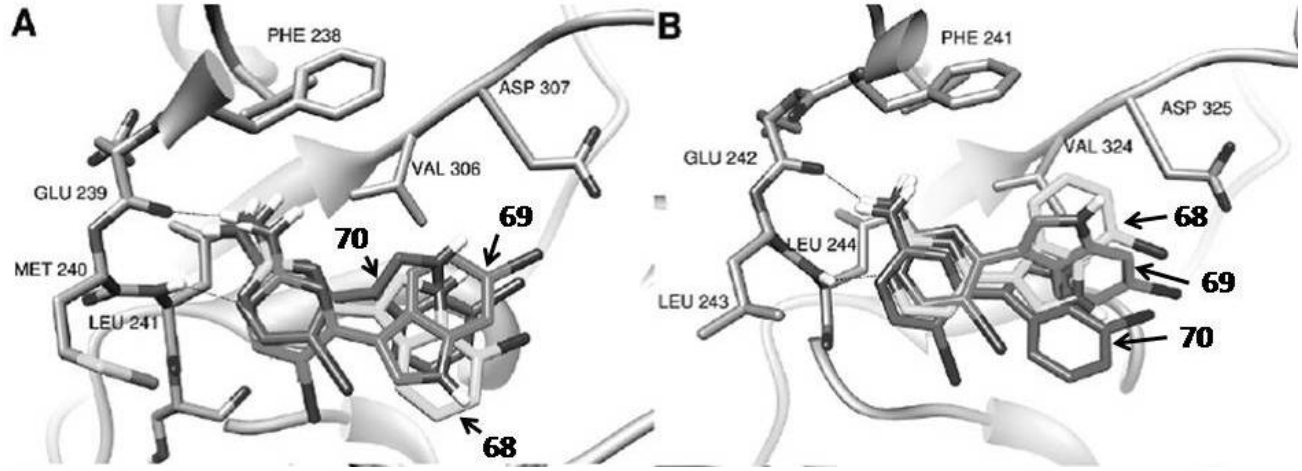


Fig. (13). Docking models of compounds **68** (off white), **69** (medium grey) and **70** (dark grey) into the ATP binding site of Dyrk1A (A, pdb: 2wo6) and CLK1 (B, pdb: 1z57) [43].

and Val306 side chains. The same approach was also used to propose a probable binding mode of meridianin derivatives **68-70** with the CLK-1 ATP binding site by using a X-ray cocrystal structure of CLK-1 (PDB code 1z57). Here as well, three meridianin derivatives adopt the same binding mode. In this case, the amino group of the aminopyrimidine moiety is H-bonded with Glu242 backbone carbonyl and the N-1 atom is H-bonded with Leu244 backbone NH (Fig. **13B**). For this protein kinase, the hydrophobic interactions with compounds **68-70** involve residue side chains of Leu167, Val175, Ala189, Leu244, Leu295, and Val324. In both cases, the interaction between the meridianin derivatives **68-70** and the ATP binding site of the kinase is driven by the H-bonding of the aminopyrimidine moiety and the enzyme as described above. On the other hand, the orientation of the indolic ring system differs from a complex model to another. The preferential positioning of the indole moiety is directed by hydrophobic interactions and steric effects due to the presence of a bromine atom in the 6- or 7-position and/or the one of an iodine atom at the 5-position of the aminopyrimidine ring. Docking models of compounds **68-70** into the ATP binding site of Dyrk-1A and CLK-1 are shown in Fig. (**13**).

CONCLUSIONS

Natural marine compounds represent an interesting source of novel leads with potent chemotherapeutic or chemopreventive activities. Meridianins **1-7** are very promising marine-derived natural product lead compounds with promising kinase inhibitory profile and antiproliferative activities. There exist good SAR amongst natural meridianins indicating the importance of Br substitution and pyrimidine ring at 3-position of indole for kinase inhibition. Meridianin E (**5**) possess potent CDK (mainly CDK-1 and CDK-5) inhibitory properties which assures their potential to produce leads for anticancer or antimalarial drug discovery. There exist several synthetic analogs which could be used as potential leads for new drug discovery for cancer or neurodegenerative diseases. Compounds **68-70** have shown potent and selective inhibition of Dyrk1A with IC_{50} values of 68, 34 and 39 nM indicating potential of these compounds to emerge as lead candidates for neurodegenerative diseases. Most of these compounds exhibit pronounced cytotoxicity and thus should be of interest for further structural synthetic design in the field of antitumor active drugs. Promising biological activities has already led to discovery of few natural as well as synthetic lead molecules and still there is much unexplored medicinal chemistry of this scaffold which may further lead to discovery of novel anticancer/ anti-Alzheimer's lead compounds.

CONFLICT OF INTEREST

Authors declare no any conflict of interest in connection with the present article.

ABBREVIATIONS

Hep2	=	larynx carcinoma
HT29	=	colon carcinoma
RD	=	rabdomyocarcinoma
U937	=	myeloid leukemia
PTP	=	a foreskin fibroblast cell line
LMM3	=	murine mammalian adenocarcinoma cell line
c-Abl	=	Abelson leukemia oncogen cellular homologue
SHSY-5Y and IMR-32	=	human neuroblastoma cell lines
MCF7	=	breast cancer cell line
HT22	=	immortalized mouse hippocampal cell line
PA1	=	human ovary teratocarcinoma cell line
PC3 and DU45	=	human prostate cancer cell lines
Fibro	=	human fibroblast primary culture
LMM3	=	murine mammalian adenocarcinoma cell line

MAPKK	=	mitogen-activated protein kinase kinase
CDK	=	cyclin-dependent protein kinase
CK	=	casein kinase
CLK	=	cdc2-like kinase
DMA	=	dimethylacetal
DYRK	=	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase
Erk	=	extracellular signal regulated kinase
GSK-3	=	glycogen synthase kinase 3
GST	=	glutathione transferase
IGFR-1	=	insulin growth factor receptor-1
KDR	=	kinase domain receptor
PKA	=	cAMP-dependent protein kinase
PKG	=	protein kinase G
Src	=	sarcoma kinase
IBX	=	iodoxy benzoic acid
MKK1	=	mitogen-activated kinase kinase-1
RSK2	=	p90 ribosomal S6 kinase 2
PKC	=	protein kinase C
MST2	=	mammalian STE20 like kinase 2
RET	=	rearranged during transfection.

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