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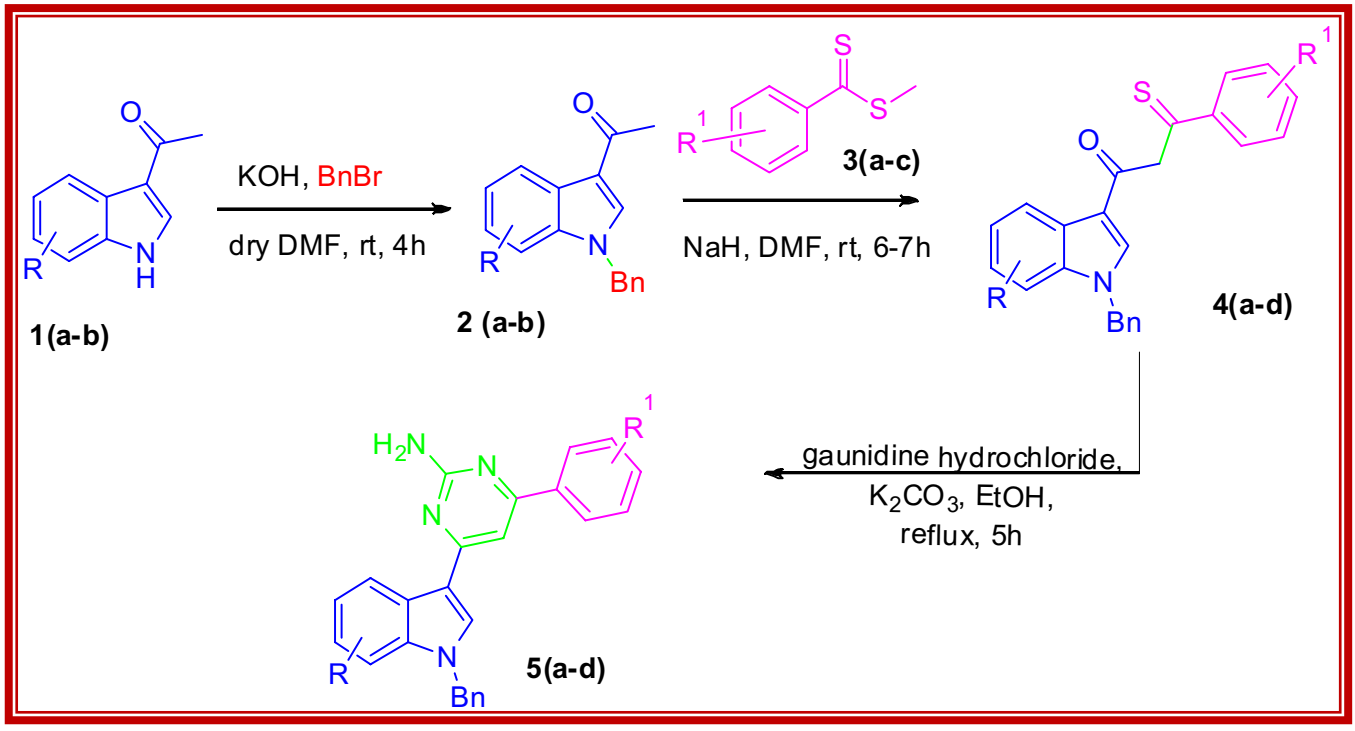

ORGANIC CHEMISTRY | RESEARCH ARTICLE

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Jenifer T.A. Vijay, Nandeesh K. Nagalingaiah, Sandhya C. Nagarakere, G.P. Suresha, Rangappa S. Kanchugarakoppal and Mantelingu Kempegowda

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Concise synthesis of substituted meridianins

Jenifer T.A. Vijay[1], Nandeesh K. Nagalingaiah[1], Sandhya C. Nagarakere[1], G.P. Suresha[1], Rangappa S. Kanchugarakoppal[1*] and Mantelingu Kempegowda[1*]

Abstract: A mild and versatile method for the efficient construction of heterocyclic framework of meridianins from simple precursors has been devised. The strategy involves the assembly of the pyrimidine ring utilizing the nucleophilicitiy of mono-thio-1,3-diketone formed by thioacylation at the C-3 in the indole ring.

Subjects: Medicinal & Pharmaceutical Chemistry; Natural Products; Organic Chemistry

Keywords: meridianin; monothio-1; 3-diketone; thioacylation

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Additional information is available at the end of the article

1. Introduction

Indole happens to be the most interesting molecule which the chemists have explored time and again. Its occurrence in natural products has intensified its scope for application in various fields of research. Through the years, work on indole moiety was mostly concentrated on the variations effected at C-3 position, as indole undergoes readily electrophilic substitution (Sundberg, 2010). Literature reports showed an interesting class of indole-based marine alkaloids with pyrimidine ring at the C-3 position, and these include Variolins (Trimurtulu et al., 1994), Psammopemmins (Butler, Capon, & Lu, 1992), Hyrtinadine A (Endo, Tsuda, Fromont, & Kobayashi, 2007), Aplicyanins (Reyes et al., 2008), and Meridianins (Herna et al., 1998; Seldes, Rodriguez Brasco, Hernandez Franco, & Palermo, 2007) (Figure 1).

Among these tethered biheterocycles, meridianins are being studied for their potent kinase inhibition, as they inhibited CDKs, GSK-3, PKA, and other protein kinases in low micromolar range (Gompel et al., 2004). Meridianins (A–G) are a family of alkaloids isolated from the South Atlantic tunicate

Rangappa S. Kanchugarakoppal

ABOUT THE AUTHORS

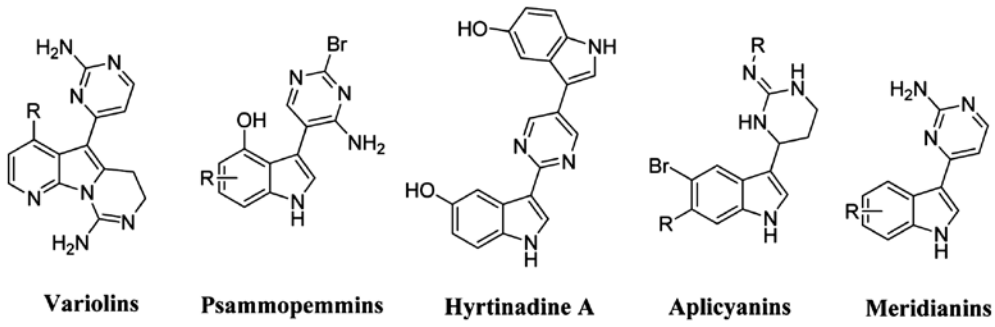
Our research group is headed by Prof. Rangappa S. Kanchugarakoppal, PhD, DSc, FRSC, FNASc, the current Vice-Chancellor of University of Mysore. He is the recipient of several prestigious awards. He has 400 research papers in National and International peer-reviewed journals and has over 2,200 scientific citations as of 2015. He has guided 50 PhD students and 7 are working under him.

Dr. Mantelingu Kempegowda, (Assistant Professor in Chemistry, University of Mysore), one of the PhD students of Prof. Rangappa S. Kanchugarakoppal is the other corresponding author of this paper. He is also the recipient of *Merck Millipore India Innovation Award 2012*. The main focus of our research group is to develop simple and efficient synthetic strategies for heterocyclic compounds. In this work, dithioesters are used as a precursor for the construction of 4-amino pyrimidine ring at the C-3 in the indole ring leading to the synthesis of substituted marine alkaloid, Meridianin.

PUBLIC INTEREST STATEMENT

People have always looked up to Mother Nature for solutions to cure aliments and diseases. Usually, the secondary metabolite, be it plant or animal, are extracted and screened for its medicinal properties. The isolated natural products are chemically analyzed and characterized. To formulate the syntheses of these natural products in the laboratory has been challenging task to the chemists. Interestingly, even marine animals are also exploited and among them is South Atlantic tunicate *Aplidium meridianum*. The alkaloids, Meridianins (A–G), isolated from the tunicate are known for their potent kinase inhibition, inhibiting CDKs, GSK-3, PKA, and other protein kinases in the low micromolar range. In this context, we have devised a route for the synthesis of substituted meridianins from simple dithioesters.

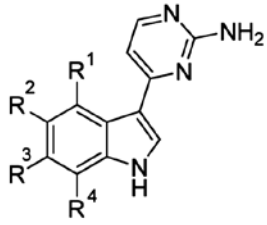
Figure 1. Indole-based marine alkaloids.



Aplidium meridianum, containing a 2-aminopyrimidyl ring at C-3 position with variations at 4-, 5-, 6-, and 7-positions of indole ring (Figure 2).

Owing to its unique structure and biological activity, several methods have been proposed for the synthesis of most of the members of the family as well as syntheses of numerous analogs. Basically, the structure of meridianins could be achieved by three main routes; one is by introducing 2-amino pyrimidine to indole by Suzuki coupling (Jiang & Yang, 2000), and second is by constructing a 2-aminopyrimidine by Bredereck synthesis of indole-enaminone with guanidine (Agarwal, Dathi, Saifuddin, & Kundu, 2012; Fresneda, Molina, & Bleda, 2001; Fresneda, Molina, Delgado, & Bleda, 2000; More, Jang, Hong, & Lee, 2014; Sperry, 2011). The third route being the synthesis from monocyclic alkynes via Sonogashira coupling (Karpov, Merkul, Rominger, & Müller, 2005; Tibiletti et al., 2010) and Cacchi indole synthesis (Walker, Czyz, & Morris, 2014). The acid-mediated direct alkenylation of indoles with α-oxo ketene dithioacetals and subsequent condensation with guanidine is the first and only report to use a sulfur synthon (Yu & Yu, 2009). Furthermore, substitution on C-5 position of the 2-amino pyrimidine ring by various aryl groups has shown significantly lesser cytotoxicity toward PA 1 cells (Akue-Gedu et al., 2009), and substitution on indole ring at C-5, C-6, and C-7 has produced compounds with potent and selective inhibition of Dyrk1A indicating potential of these compounds to emerge as lead candidates for neurodegenerative diseases (Bharate, Yadav, Battula, & Vishwakarma, 2012). Most of the reported methods make use of transition metal, expensive reagents and reactants, and require maintaining certain reaction conditions. Additionally, the variation in the substituent can be decided with dithioester before the formation of meridianin analogs, rather than adding more steps in introducing substituent to meridianin. Inspired to overcome these challenges and also as our research being mainly based on construction of heterocycles using dithioesters and its derived synthons, we attempted to devise a method for the synthesis of meridianin analogs wherein the reactants are easily synthesized and in addition the number of reactants and steps are reduced.

Figure 2. Meridianins (A–G).



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 = 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

2. Result and discussion

The retro synthesis of substituted meridianins **5a–d** is shown in Scheme 1. Since monothio-1,3-diketones are potentially useful 3-carbon 1,3-bielectrophilic synthons for the construction of 5- and 6-membered heterocycles (Kumar et al., 2013), we envisaged the cyclocondensation of monothio-1,3-diketone **4** with guanidine. The monothio-1,3-diketone **4** was to be accessed by thioacylation of dithioesters **3** and 3-acetyl indole **1** which was *N*-benzylated.

With ready availability of 3-acetyl indole **1**, straightforward *N*-benzylation with 78% yield was achieved. As per our previous studies (Jenifer Vijay, Nandeesh, Raghavendra, Rangappa, & Mantelingu, 2013), we synthesized monothio-1,3-diketone **4** using simple dithioester **3** in presence of NaH as base and DMF as solvent. The best result with 80% yield was obtained when 2 equivalences of NaH.

Scheme 1. Retro synthesis of meridianin analog.

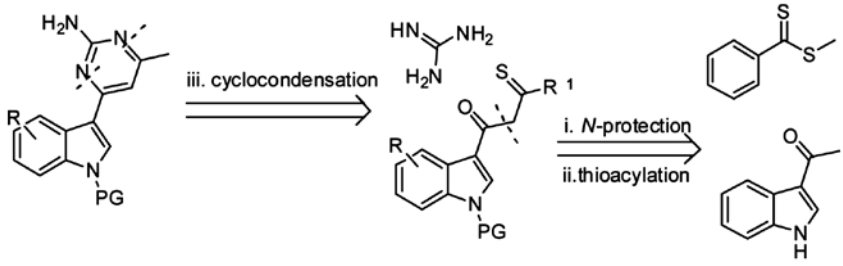
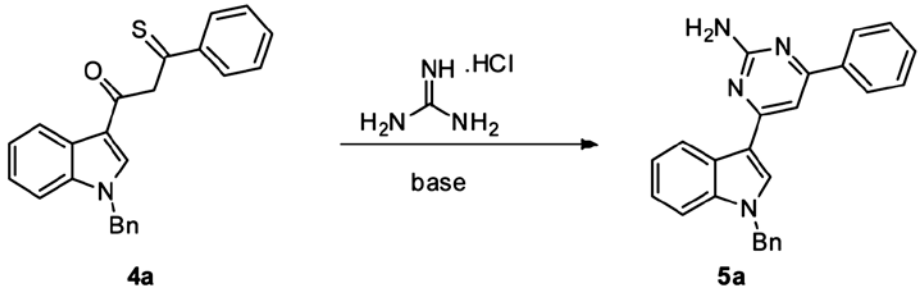


Table 1. Establishment of reaction conditions



4a **5a**

Entry	Base[a]	Solvent (mL)	Time (h)	Yield (%)[b]
1	KOH	EtOH	8–10	20
2	NaOH	EtOH	8–10	22
3	*t*-BuOK	EtOH	8–10	25
4	MeONa	EtOH	8–10	Traces
5	NaH	EtOH	8–10	–
6	NaH	DMF	8–10	–
7	TEA	DMF	8–10	–
8	K_2CO_3(1 equvi)	EtOH	8–10	53
9	K_2CO_3(1.5 equvi)	EtOH	7	57
10	K_2CO_3(2.0 equvi)	EtOH	5	66
11	K_2CO_3(2.5 equvi)	EtOH	5	71
12	K_2CO_3(3.0 equvi)	EtOH	5	68

[a]The mixture of **4a** (1.0 mmol), guanidine hydrochloride (1.5 mmol) and 2 equvi base in 5 mL solvent was stirred in a flask at reflux condition.

[b]Isolated yield.

Finally, the pivotal step that is, the cyclocondensation of the monothio-1,3-diketone **4** with guanidine under suitable base and solvent was attempted. To start with monothio-1,3-diketone **4a** and guanidine hydrochloride was chosen as template reactants; KOH (1 equiv) were chosen as base and ethanol as solvent, and the reaction was carried out under reflux condition (Table 1, entry 1) resulting in 20% yield.

Encouraged by the result, we tried several bases like, NaOH, KOH, *t*-BuOK, MeONa, TEA, NaH (for solvents EtOH and DMF), and K_2CO_3 (for different equivalences) (Table 1, entries 1–12). As K_2CO_3 provided better results (Table 1, entry 8), its loading was optimized. It was found that 2.5 equiv of K_2CO_3 gave a maximum yield of 71% (Table 1, entry 11), but 3.0 equiv of K_2CO_3 gave slightly decreased yield (Table 1, entry 12). Thus establishing an efficient method with simple work-up was achieved by employing 2.5 equiv of K_2CO_3 in ethanol at refluxing condition. Within 5 h, the products were formed in moderate to good yields as pale yellow solids (Scheme 2).

With the optimized reaction conditions, analog of Meridianin G **5a** was synthesized using guanidine hydrochloride and 1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one **4a**, which was readily synthesized by thioacylation of 1-(1-benzyl-1*H*-indol-3-yl)ethanone **2a** and phenyldithioester **3a** (Table 2, entry 1). The formation of Meridianin G **5a** was ascertained by characterization data. The ^{1}H NMR of 4-(1-benzyl-1*H*-indol-3-yl)-6-phenylpyrimidin-2-amine **5a** displayed four singlets at δ 7.93 ppm (2-H of indolyl), δ 7.43 ppm (2-aminopyrimidine CH), δ 5.39 ppm (broad singlet of NH_2), and δ 5.19 ppm (*N*–CH_2). A doublet at δ 8.42 ppm correlates to C-4 of indolyl ring and the aromatic protons is indicated by the multiplets at δ 7.51–7.48 ppm and δ 7.36–7.19 ppm. The ^{13}C NMR of **5a** exhibited seventeen signals with indicative signals at δ 106.6 ppm assigned to the CH of 2-aminopyrimidine ring and 50.8 ppm assigned to *N*–CH_2 group. The IR values also indicate the presence of primary amine with N-H stretching frequency at 3,332 cm^{-1} and bending frequency 1,582 cm^{-1}. In addition, the mass spectrum and analytical data confirm the structure of **5a**. The results indicated the successful synthesis of **5a**.

Thus, Meridianin G was further varied using 4-methoxyphenyldithioester **3b** (Table 2, entry 2) and 2-thiophenedithioester **3c** (Table 2, entry 3). Meridianin C was also synthesized in a similar way using 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one **4d**, which was accessed from 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)ethanone **2d** (Table 2, entry 4). The structures of all the substituted meridianins **4a–d** were characterized by ^{1}H, ^{13}C NMR, and mass spectrometry (see Supplementary material).

It is presumed that the mechanism for cyclocondensation of monothio 1,3-diketones **4** with guanidine is as depicted in Scheme 3. The probable route could be the attack of guanidine on thioenolic form of **4** to give the intermediate **A**. The intermediate **A** on subsequent elimination of mercapto group undergoes intramolecular cyclization with loss of a molecule of water to yield substituted meridianin **5**.

Scheme 2. Facile route for the synthesis of substituted meridianins.

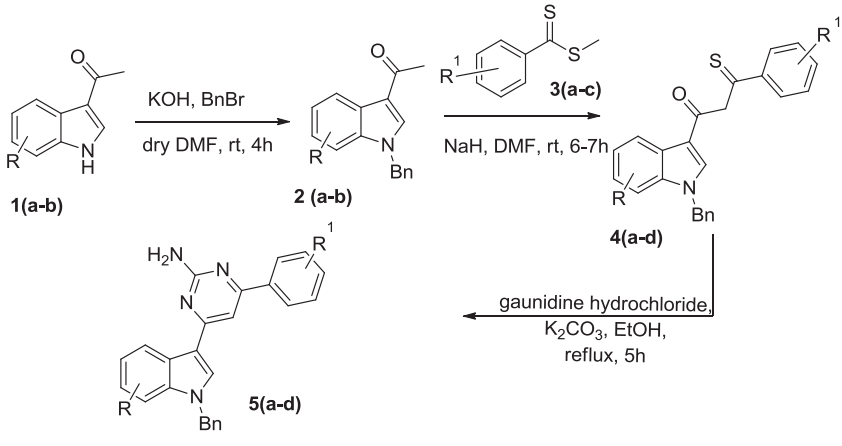
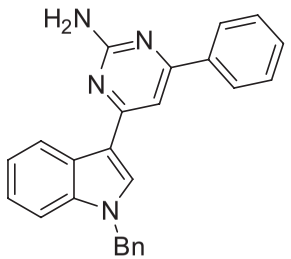
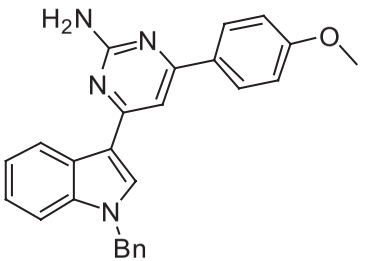
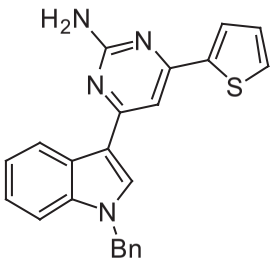
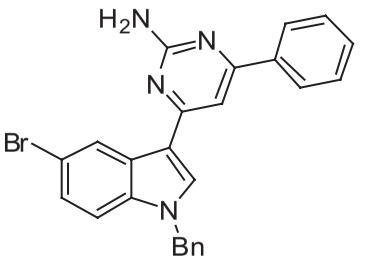


Table 2. Structures of newly synthesized substituted meridianins[a]

			
5a [71%][b]	**5b** [76%][c]	**5c** [78%][b]	**5d** [68%][b]

[a]General conditions for **5a–d: 4a** (1.0 mmol), guanidine hydrochloride (1.5 mmol), K_2CO_3 (2.5 mmol) in ethanol, reflux, 5 h.

[b]Isolated yield.

[c]Reported compounds (Yu & Yu, 2009).

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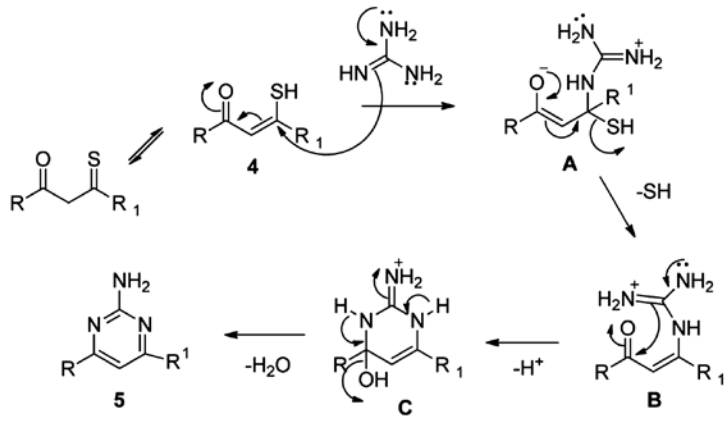
Scheme 3. Plausible mechanism for the synthesis of compounds 5(a–d).



3. Experimental

3.1. Preparation of N-benzyl-3-acetylindole (Corbel et al., 2007)

A mixture of 3-acetyl indole (2.5 g, 15.72 mmol) and potassium hydroxide (1. 25 g, 22.27 mmol) in dry DMF (10 mL) was stirred until solubilization of KOH. Next, benzyl bromide (1.4 mL, 11.77 mmol) was added and stirred at room temperature until 3-acetyl indole disappeared (monitored by TLC). After completion of reaction, the mixture was poured into water and extracted to ethyl acetate, was dried over sodium sulfate. Solvent was removed and half-white solid was recrystallized with diethyl ether.

3.2. Preparation of 1-(1-benzyl-1H-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one derivatives 4(a–d) (Raghava et al., 2014)

To 60% suspension of NaH in mineral oil (0.06 g, 2.5 mmol) in DMF (2 mL) at 0°C was added *N*-benzyl-3-acetylindole (0.249 g, 1.0 mmol) followed by stirring for 10-15 min at room temperature. A solution of dithioester (1.0 mmol) in DMF (2 mL) was added over a period of 10 min at 0°C followed by stirring at room temperature for 6–7 h. The completion of the reaction was monitored by TLC. The mixture was poured into water and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica using hexane/ethyl acetate (9:1) to afford 1-(1-benzyl-1*H*-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one derivatives **4(a–d)**.

3.3. Preparation of substituted meridianin 5(a–d)

Guanidine hydrochloride (0.142 g, 1.5 mmol) was added to a stirred suspension of K_2CO_3 (0.346 g, 2.5 mmol) in EtOH (95%; 10 mL), and then a solution of 1-(1-benzyl-1*H*-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one (1.0 mmol) in ethanol (2 mL) was added. The reaction mixture was heated at reflux with stirring for 5–6 h (monitored by TLC). The mixture was then filtered over Celite® S and the filtrate was concentrated to dryness under reduced pressure and the residue was extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with water (2 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to ge ctrude products, which were purified by column chromatography on silica gel using hexane/ethyl acetate (7:3) to afford substituted meridianins **5(a–d)**.

3.3.1. 4-(1-benzyl-1H-indol-3-yl)-6-phenylpyrimidin-2-amine (5a)

Following the general procedure, compound **5a** was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one (**4a**) and guanidine hydrochloride as a

cream-colored solid with 71% yield; mp 164–166°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, J = 8.0 Hz, 1H, aromatic CH), 8.04 (d, J = 7.4 Hz, 2H, aromatic CH), 7.93 (s, 1H, 2-H of indolyl), 7.51–7.47 (m, 3H, aromatic CH), 7.43 (s, 1H, *N*-heteroaryl CH), 7.36–7.19 (m, 6H, aromatic CH), 7.18 (d, J = 6.4 Hz, 2H, aromatic CH), 5.39 (s, 2H, NH_2), 5.19 (s, 2H, *N*–CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0, 163.2, 158.3, 137.9, 133.3, 131.1, 129.1, 127.6, 127.4, 126.5, 124.0, 123.0, 121.6, 113.7, 111.0, 106.6 (CH), 50.8 (CH_2); IR (KBr): 3,332, 3,089, 2,955, 2,861, 1,582, 1,505, 1,049, 865, 753 cm^{-1}; MS (ESI + ion): m/z = 377.2 (M^+). Anal. Cacld for $C_{25}H_{20}N_4$: C, 79.76; H, 5.35; N, 14.88. Found: C, 79.74; H, 5.34; N, 14.87.

3.3.2. 4-(1-benzyl-1H-indol-3-yl)-6-(4-methoxyphenyl) pyrimidin-2-amine (Yu & Yu, 2009) **(5b)**

Following the general procedure, compound **5b** was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-3-thioxopropan-1-one (**4b**) and guanidine hydrochloride as a half-white-colored solid with 76% yield; mp 195–196°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, J = 6.8 Hz, 1H, aromatic CH), 8.05 (d, J = 6.8 Hz, 2H, aromatic CH), 7.94 (s, 1H, 2-H of indolyl), 7.51–7.48 (m, 3H, aromatic CH), 7.44 (s, 1H, *N*-heteroaryl CH), 7.36–7.28 (m, 7H, aromatic CH), 7.19 (d, J = 8.0 Hz, 2H, aromatic CH), 5.40 (s, 2H, NH_2), 5.20 (s, 2H, *N*–CH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.1, 164.0, 163.2, 158.3, 136.9, 131.1, 130.1, 128.3, 127.5, 127.4, 126.1, 123.0, 122.0, 120.6, 113.8, 110.0, 100.0 (CH), 55.2 (CH_2), 50.7 (OCH_3); IR (KBr): 3,330, 3,150, 2,595, 2,761, 1,573, 1,604, 1,300, 1,150, 765, 642 cm^{-1};MS (ESI + ion): m/z = 407.7 (M^+). Anal. Cacld for $C_{24}H_{17}NOS$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.81; H, 5.45; N, 13.79.

3.3.3. 4-(1-benzyl-1H-indol-3-yl)-6-(thiophen-2-yl)pyrimidin-2-amine **(5c)**

Following the general procedure, compound **5c** was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (**4c**) and guanidine hydrochloride as a pale yellow-colored solid with 78% yield; mp 112–113°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H, 2-H of indolyl), 7.95(s, 1H, *N*-heteroaryl CH), 7.81 (d, J = 8.8 Hz, 2H), 7.58 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.8 Hz, 4H, aromatic CH), 7.40–7.27 (m, 3H, aromatic CH), 7.25 (d, J = 8.8 Hz, 2H, aromatic CH), 5.61 (s, 2H, NH_2), 5.47 (s, 2H, *N*–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 176.3, 143.4, 138.3, 136.0, 129.2, 128.8, 128.0, 126.7, 125.7, 122.2, 122.1, 122.0, 112.9, 109.6, 100.1(CH), 54.1(CH_2); IR (KBr): 3,335, 3,178, 3,025, 2,671, 1,579, 1,516, 1,053, 887, 731 cm^{-1}; MS (ESI + ion): m/z = 382.9 (M^+). Anal. Cacld for $C_{24}H_{17}NOS$: C, 72.22; H, 4.74; N, 14.65. Found: C, 72.21; H, 4.73; N, 14.64.

3.3.4. 4-(1-benzyl-5-bromo-1H-indol-3-yl)-6-phenylpyrimidin-2-amine **(5d)**

Following the general procedure, compound **5d** was obtained from the reaction 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one (**4d**) and guanidine hydrochloride as a pale brown-colored solid with 68% yield; mp 174–176°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H, aromatic CH), 8.33 (s, 1H, 2-H of indolyl), 8.20–8.12 (m, 3H, aromatic CH), 8.06 (d, J = 8.0 Hz, 1H, aromatic CH next to Br), 7.75–7.71 (m, 2H, aromatic CH, *N*-heteroaryl CH), 7.66 (d, J = 7.2 Hz, 1H, aromatic CH), 7.33–7.30 (m, 4H, aromatic CH), 7.14–7.10 (m, 2H, aromatic CH), 5.51 (s, 2H, NH_2), 5.31 (s, 2H, *N*–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 162.8, 162.7, 161.0, 137.3, 135.6, 133.1, 130.0, 128.2, 127.7, 127.1, 125.0, 124.8, 114.9, 113.5, 112.6, 100.2 (CH), 55.3(CH_2); IR (KBr): 3,334, 3,109, 2,975, 2,851, 1,578, 1,512, 1,052, 799, 733, 510 cm^{-1};MS (ESI + ion): m/z = 456.8 (M^+). Anal. Cacld for $C_{24}H_{17}NOS$: C, 65.94; H, 4.21; N, 12.30; Found: C, 65.93; H, 4.18; N, 12.29.

4. Conclusion

In conclusion, we have devised an efficient method for the synthesis of substituted meridianins, especially Meridianin C and Meridianin G. Unlike the earlier reports, our method does not involve the use of transition metal catalysts and drastic conditions. The reaction was reduced to a three-step procedure using readily available reactants. In addition, this method provides a scope to synthesize various derivatives whilst the formation of the final product. As a result, it provides a large spectrum of compounds for biological screening.

Supplementary material
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