Concise synthesis of substituted meridianins

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Cogent Chemistry (2015), 1: 1083068
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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 nucleophilicity of monothio-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

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 Aplidium meridianum.

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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 alkyne 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) \( R^1=\text{OH}, R^2=R^3=R^4=\text{H} \)
Meridianin B (2) \( R^1=\text{OH}, R^2=R^4=\text{H}, R^3=\text{Br} \)
Meridianin C (3) \( R^1=R^3=R^4=\text{H}, R^2=\text{Br} \)
Meridianin D (4) \( R^1=R^2=R^4=\text{H}, R^3=\text{Br} \)
Meridianin E (5) \( R^1=R^2=R^3=R^4=\text{H} \)
Meridianin F (6) \( R^1=R^4=\text{H}, R^2=R^3=\text{Br} \)
Meridianin G (7) \( R^1=R^2=R^3=R^4=\text{H} \)
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 thioacetylation 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 equivalents of NaH.

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**Table 1. Establishment of reaction conditions**

| Entry | Basea | 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     | –          |
| 5     | NaH   | EtOH         | 8–10     | Traces     |
| 6     | NaH   | DMF          | 8–10     | –          |
| 7     | TEA   | DMF          | 8–10     | –          |
| 8     | K₂CO₃(1 equvi) | EtOH | 8–10 | 53         |
| 9     | K₂CO₃(1.5 equvi) | EtOH | 7   | 57         |
| 10    | K₂CO₃(2.0 equvi) | EtOH | 5   | 66         |
| 11    | K₂CO₃(2.5 equvi) | EtOH | 5   | 71         |
| 12    | K₂CO₃(3.0 equvi) | EtOH | 5   | 68         |

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

*bIsolated 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 K2CO3 (for different equivalences) (Table 1, entries 1–12). As K2CO3 provided better results (Table 1, entry 8), its loading was optimized. It was found that 2.5 equiv of K2CO3 gave a maximum yield of 71% (Table 1, entry 11), but 3.0 equiv of K2CO3 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 K2CO3 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-1H-indol-3-yl)-3-phenyl-3-thioxopropan-1-one 4a, which was readily synthesized by thioacylation of 1-(1-benzyl-1H-indol-3-yl)ethanone 2a and phenyldithioester 3a (Table 2, entry 1). The formation of Meridianin G 5a was ascertained by characterization data. The 1H NMR of 4-(1-benzyl-1H-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 NH2), and δ 5.19 ppm (N–CH2). 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 13C 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–CH2 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-methoxyphenylthioethioester 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-1H-indol-3-yl)-3-phenyl-3-thioxopropan-1-one 4d, which was accessed from 1-(1-benzyl-5-bromo-1H-indol-3-yl)ethanone 2d (Table 2, entry 4). The structures of all the substituted meridianins 4a–d were characterized by 1H, 13C 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 thienoenic 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

| Structure | Isolated Yield |
|-----------|----------------|
| ![Structure 5a](image) | 71%b |
| ![Structure 5b](image) | 76%c |
| ![Structure 5c](image) | 78%b |
| ![Structure 5d](image) | 68%b |

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- **General conditions for 5a–d**: 4a (1.0 mmol), guanidine hydrochloride (1.5 mmol), K₂CO₃ (2.5 mmol) in ethanol, reflux, 5 h.
- **Isolated yield.**
- **Reported compounds (Yu & Yu, 2009).**
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-1H-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 K₂CO₃ (0.346 g, 2.5 mmol) in EtOH (95%; 10 mL), and then a solution of 1-(1-benzyl-1H-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 crude product was passed through a small plug of silica using hexane/ethyl acetate (9:1) to afford 1-(1-benzyl-1H-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one derivatives 4(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-1H-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; \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 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\(_2\)); \( ^13C \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta \) 164.0, 163.2, 158.3, 137.9, 133.3, 131.1, 129.1, 127.6, 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\(^{-1}\);

\( m/z = 377.2 \) (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-1H-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; \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): \( \delta \) 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\(_3\)); \( ^13C \) NMR (100 MHz, DMSO-\( d_6 \)): \( \delta \) 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\(^{-1}\);

\( m/z = 407.7 \) (M\(^+\)). Anal. Cacld for C\(_{24}\)H\(_{17}\)N\(_2\)O\(_{5}\): 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-1H-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; \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_2\)); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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\(^{-1}\);

\( m/z = 382.9 \) (M\(^+\)). Anal. Cacld for C\(_{24}\)H\(_{17}\)N\(_2\)S: 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-1H-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; \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_2\)); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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), 53.3 (CH\(_2\)); IR (KBr): 3,334, 3,109, 2,975, 2,851, 1,578, 1,512, 1,052, 799, 733, 510 cm\(^{-1}\);

\( m/z = 456.8 \) (M\(^+\)). Anal. Cacld for C\(_{25}\)H\(_{17}\)N\(_2\)S: 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
Supplementary material for this article can be accessed here http://dx.doi.org/10.1080/23312009.2015.1083068.

Acknowledgements
The Ministry of Human-Resource Development (MHRD) and University Grant Commission (UGC), New Delhi, India, are acknowledged for recognizing University of Mysore as the Institute of Excellence and for the fellowship. We also thank NMR Facility, IOE, University of Mysore, Manasagangotri, Mysore 570 006, India, for spectral data.

Funding
The authors received no direct funding for this research.

Competing interests
The author(s) confirm that the above content has no “Competing Interests”.

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Citation information
Cite this article as: Concise synthesis of substituted Cationic π-cyclization.

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