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A novel synthesis of highly substituted indole derivatives from the reaction of indole, aryl aldehydes and activated CH aides in the presence of $ZnCl_2$, $CuCl_2$ or $AlCl_3$

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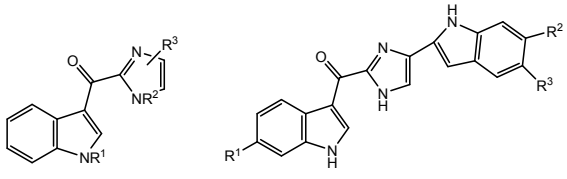
Abstract: An efficient method for the synthesis of highly substituted indole derivatives has been developed from an efficient one-pot or two steps reaction between indole, arylaldehydes activated CH acids such as acetylaceton and dimethylmalonate in the presence of $ZnCl_2$, $CuCl_2$ or $AlCl_3$. The reaction provided 3-[(1*H*-indol-3-yl) (*p*-tolyl) methyl]pentane-2,4-dione **4a**, 3-[(1*H*-indol-3-yl)(4-nitrophenyl)methyl]pentane-2,4-dione **4b**, dimethyl-2-[(1*H*-indol-3yl)(4-nitrophenyl)methyl]malonate **4c**, 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]-1*H*-indole **5a**, 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl]-1*H*-indole **5b** in moderate to good yields.

Keywords: Indole; Arylaldehydes; Dimethylmalonate; $ZnCl_2$; $AlCl_3$.

Introduction

The development of resistance to chemotherapy with exiting anti-cancer drugs has challenged the pharmaceutical industry to rapidly identify and develop new chemical entities able to counteract this unmet medical need. Prolonged treatment of cancer cells with certain drugs can result in an acquired resistance of these cells toward multiple drugs. This phenomenon is known as multidrug resistance (MDR) [1]. While the concise mechanism of MDR is not completely understood, it is known that MDR is often associated with an over expression of ATP-binding cassette (ABC) transporters [2]. The two best-known ABC transporters are P-glycoprotein (P-gp) and multidrug resistance protein 1 (MDR 1) that effectively pump out the anti-cancer drug from MDR-cancer cells. Other mechanisms believed to be associated with MDR in cancer cells include increased expression of anti-apoptotic genes and decreased expression of pro-apoptotic genes [3], over expression of specific tubulin isotypes [4], decreased expression of topoisomerases [5], and over expression of major vault protein [6]. Various strategies have been employed to overcome MDR, the most common being inhibition of P-gp and related proteins to effectively block the efflux of the drug [7] Numerous MDR-reversal agents have been reported but most have undesirable side effects such as toxicity. Other complex natural products such as the epothilones [8], discodermolide [9] and modified taxanes [10] display potent activity against MDR resistance cancer cell lines. The conjugated indole-imidazole derivatives **1** display in vitro cytotoxicity against a range of cancer cell lines, even MDR cancer cell lines [11]. These compounds are structurally related to the bisindole alkaloids which include the topsentins **2** [12]. The topsentins display a rabge of biological activities including anti-tumor activity [13] (Figure **1**).



1 **2**

R^1, R^2, R^3= H, Br or OH

Figure 1: Derivatives of 1 and 2.

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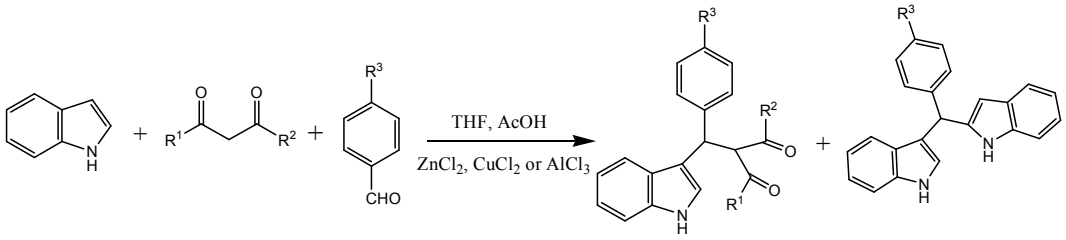
Herein, we wish to report the reaction of indole **1**, activated CH acids such as acetylaceton or Dimethylmalonate **2** and arylaldehydes **3** with indole to provided highly substituted indole derivatives (Scheme **1**).



1 **2** **3** **4a, b** **5a, b**

R^1=Me, OMe
R^2=Me, OMe
R^3=Me,NO_2

Scheme 1: The reaction of **1**, **2** and **3**, leads to the **4** and **5** derivatives.

Results and discussion

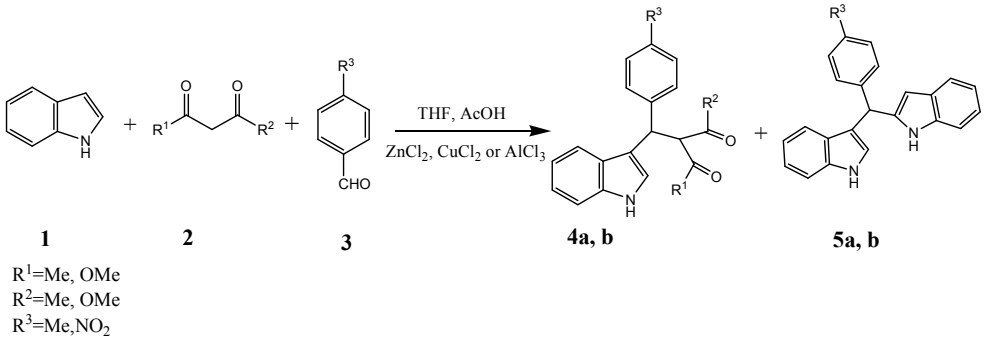
The reaction between indole **1**, acetylaceton **2**, with *p*-methylbenzaldehyde **3**, catalyzed by $ZnCl_2$, under refluxing, leads to highly functionalized 3-[(1*H*-indol-3-yl) (*p*-tolyl)methyl]pentane-2,4-dione **4a** and 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]-1*H*-indole **5a**, in 40% and 60% yield, respectively. The structure of compound **4a** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **4a** showed absorption at 3383 and 1748 cm^{-1} indicating the presence of –NH and C=O groups, respectively. In the ^{1}H NMR spectrum of compounds **4a**, aromatic signals were seen at δ 8.02-7.04 ppm. Three methyl protons were observed at δ 2.26, 2.07 and 1.96 ppm, methine protons were observed at δ 5.09 (d, *J*=12.4 Hz) and 4.67 (d, *J*=12.4 Hz)ppm, and one broad singlet at δ 8.10 showed the presence of –NH group (D_2O exchangeable). In the ^{13}C NMR spectrum, carbonyl carbons resonated at δ 204.3 and 203.7 ppm. The structure of compound **5a** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. In the IR spectrum of **5a** showed absorption at 3483, 3055, 2987, 1796, 1698 and 1620 cm^{-1} indicating the presence of –NH, $CHsp^2$, $CHsp^3$, C=O groups and C=C, respectively. In the ^{1}H NMR spectrum of compound **5a**, proton of NH resonated at δ 7.89 ppm and the aromatic signals were seen at δ 7.44-6.65 ppm, benzyl proton at δ 5.88 and methyl protons at δ 2.35 ppm. In the ^{13}C NMR of compound **5a**, aromatic signals were seen at δ 153.1-111.4 ppm and methyl was observed at δ 27.6 ppm. Similar reaction was carried out under room temperature and afforded only 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl-1*H*-indole **5a** in 40% yield.

When the reaction was carried out between indole and acetylaceton in the presence of *p*-methylbenzaldehyde or *p*-nitrobenzaldehyde from an efficient one-pot reaction under room temperature or refluxing, in the presence of $CuCl_2$, afforded 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]- 1*H*-indole **5a** or 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl-1*H*-indole **5b**, but with low yield. When the reaction was carried out between indole and acetylaceton in the presence of *p*-nitrobenzaldehyde from an efficient one-pot reaction in the presence of $ZnCl_2$ under room temperature afforded 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl-1*H*-indole **5b** in 60% yield. The structure of compound **5b** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. In the IR spectrum of **5b** showed absorption at 3306, 3066, 2925, 1599, 1522 and 1346 cm^{-1}. In the ^{1}H NMR spectrum of compound **5b**, proton of NH resonated at δ 10.12 ppm aromatic signals were seen at δ 8.19-6.91 ppm, and benzylic proton at δ 6.12 ppm. In the ^{13}C NMR of compound **5b**, aromatic signals were seen at δ 153.1-111.4 ppm and benzilic carbon was observed at δ 40.1 ppm (Scheme **2**).

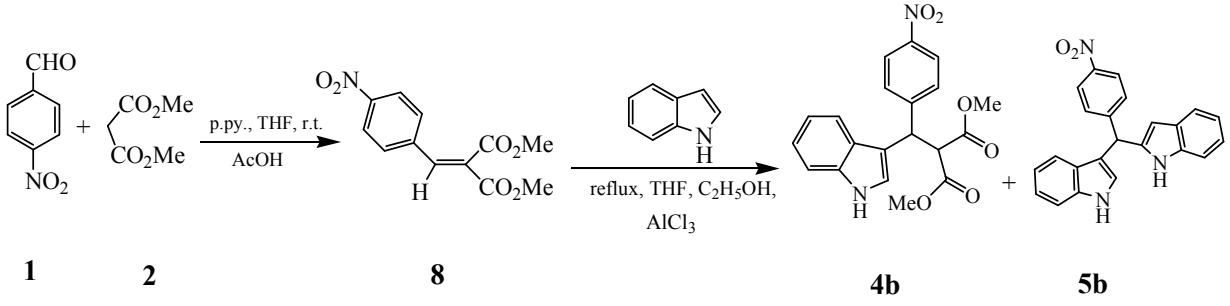
When the two steps reaction was carried out between indole and intermediate **8** from the reaction of *p*-nitrobenzaldehyde **1** and dimethylmalonate **2**, in the presence of $AlCl_3$, under refluxing, afforded dimethyl-2-[(1*H*-indol-3-yl)(4-nitrophenyl)methyl]-malonate **4b** and 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl]-1*H*-indole **5b** in 90% and 10% yield, respectively, in 4h (Scheme **3**).

Similar reaction was carried out between indole and *p*-nitrobenzaldehyde in the presence of dimethylmalonate under one-pot, reflux and $AlCl_3$ and then afforded dimethyl-2-[(1*H*-indol-3-yl)(4-nitrophenyl)methyl]-malonate **4b** and 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl]-1*H*-indole **5b** in 90% and 10% yield, respectively and in 2h.

The structure of compound **4b** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The IR spectrum of **4b** showed absorption at 3383 and 1748 cm^{-1} indicating the presence of –NH and C=O groups, respectively. In the ^{1}H NMR spectrum of compounds **4b**, the broad singlet at δ 8.22 showed the presence of –NH group (D_2O exchangeable) and aromatic signals were seen at δ 8.14-7.05 ppm. Methine protons were observed at δ 5.24 (d, *J*=11.6 Hz) and 4.37(d, *J*=11.6 Hz) ppm.The two methoxy protons were seen at δ 3.60 and 3.58 ppm. In the ^{13}C NMR spectrum, the two carbonyl groups resonated at δ 167.8 and 167.7 ppm, and 14 atoms of carbons sp^2 were seen at 148.9- 111.2 ppm. Two *C*H were resonated at δ 57.4 and 42.4 and two carbons of methoxy were resonated at δ 52.9 and 52.8 ppm.



Scheme 2: One-pot reaction of indole, acetylaceton and *p*-methylbezaldehyde.



Scheme 3: Two steps reaction of indole and intermediate **8.**

Table: a) The one-pot reaction of acetylaceton with p-methylbenzaldehyde or p-nitrobenzaldehyde under r.t. or reflux and indole in the presence of $ZnCl_2$ or $CuCl_2$.
b) The two- step or one-pot reaction of p-nitrobenzaldehyde with methylmalonate and indole in the presence of $AlCl_3$.

Product	R^1	R^2	R^3	Lewis acid	Solvenr	Method	Time	Yield
4a, 5a	Me	Me	Me	$ZnCl_2$	THF, AcOH	reflux, one-pot	48 h	40%, 60%
4b,5b	OMe	OMe	NO_2	$AlCl_3$	THF, C_2H_5OH	reflux, two-step	4 h	90%,10%
5a	Me	Me	Me	$ZnCl_2$	THF, AcOH	r. t., one-pot	48 h	60%
5a	Me	Me	Me	$CuCl_2$	THF, AcOH	r.t.,or reflux one-pot	48 h	20%
5b	Me	Me	NO_2	$CuCl_2$	THF, AcOH	r.t., or reflux one-pot	48 h	20%
4b, 5b	OMe	OMe	NO_2	$AlCl_3$	THF, C_2H_5OH	reflux, one-pot	2 h	90%,10%

The structure of intermediate compound **8** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. In the IR spectrum of **8** showed absorption at 3054, 2987, 1594 (C=C), 1505 and 1335 (NO_2) cm^{-1}. In the

^{1}H NMR spectrum of compounds **8**, the aromatic signals were seen at δ 8.27(d, *J*=8.8 Hz) and 7.61(d, *J*=8.4 Hz) ppm. The benzylic proton was resonated at δ 7.81 ppm. The two methoxy protons were observed at δ 3.89 and 3.85 ppm. In the ^{13}C NMR spectrum of compound **8**, the two carbonyl groups resonated at δ 166.0 and 163.7 ppm and aromatic signals were seen at δ 148.4-124.0 ppm. The two methoxy resonated at δ 53.0 and 52.9 ppm.

Conclusion

In conclusion, when the reaction carried out between indole **1**, acetylaceton **2**, with *p*-methylbenzaldehyde **3**, catalyzed by $ZnCl_2$, under refluxing, leads to highly functionalized3-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]pentane-2,4-dione **4a** and 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]-1*H*-indole **5a** in 40% and 60% yield, respectively. The similar reaction was carried out between indole **1**, acetylaceton **2**, with *p*-nitrobenzaldehyde **3**, catalyzed by $ZnCl_2$, under refluxing or room temperature , leads to highly functionalized only 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl-1*H*-indole **5b**. When the reaction carried out between indole and acetylaceton in presence of *p*-nitrobenzaldehyde or *p*-methylbenzaldehyde from an efficient one-pot reaction in the presence of $CuCl_2$ and under refluxing or room temperature, afforded 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl-1*H*-indole **5b** or 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]-1*H*-indole **5a** respectively, but with low yield. When the reaction was carried out between intermediate **8**, from the reaction of *p*-nitrobenzaldehyde and dimethyl malonate under room temperature, and indole in the presence of $AlCl_3$, under refluxing, afforded dimethyl-2-[(1*H*-indol-3-yl)(4-nitrophenyl)methyl]-malonate **4b** in 80% yield and 2-[(1*H*-indol-3-yl)(4-nitrophenyl]methyl]-1*H*-indole **5b** in 20% yield. According to our investigations, the products obtained from the react of indole between benzaldehyde derivatives and acetylacetone or dimethylmalonat in the presence of Lewis acids are new compounds.

Experimental

All reagents were obtained from Merck and were used without further purification. Mp: Thomas-Hoover capillary. FT-IR spectra: Bruker VERTEX-70. ^{1}H and ^{13}CNMR spectra: Bruker DRX-400Avance instrument; in $CDCl_3$ at 400 and 100.6 MHz, respectively; δ in part per million and *J* in hertz.

Typical experimental procedure:

To a stirred solution of Indole **1** (0.5 g, 1 mmol), methylacetoacetate **2** (0.4 cc, 2 mmol), and *p*-methylbenzaldehyde **3** (0.5 g, 1 mmol) in THF (5 mL), was added $ZnCl_2$ under refluxing in the presence CH_3CO_2H (2 mL). The reaction stirred for about 4 h. The reaction proceeded smoothly and afforded the corresponding 3-[(1*H*-indol-3-yl) (*p*-tolyl) methyl] pentane-2, 4-dione **4a** and 2-[(1*H*-indol-3-yl)(*p*-tolyl)methyl]-1*H*-indole **5a** in 40% and 60% yield, respectively.

*3-[(1H-indol-3-yl) (p-tolyl) methyl] pentane-2, 4-dione (**4a**):*

Brown crystal, (0.17g, 40%), m.p. 100-102 °C, IR (KBr) (ν_{max}/cm^{-1}): 3383 (NH), 3055 (CH, sp^2) 2945-2885 (CH, sp^3), 1748 (C=O), 1620 (C=C), cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ= 8.10 (1H, s, NH), 8.02 (1H, d, *J* = 8.4 Hz, CH_{sp2}), 7.56 (2H, d, *J* = 7.6 Hz CH_{sp2}), 7.33 (2H, d, *J* = 8.0 Hz CH_{sp2}), 7.22 (1H, d, *J* = 8.4 Hz, CH_{sp2}), 7.14 (1H, t, *J* = 8.4 and 8.4 Hz, CH, sp^2), 7.13 (1H, s, CH_{sp2}), 7.04 (1H, t, *J* = 8 and 8.4 Hz, CH_{sp2}), 5.09 (1H, d, *J* = 12.4 Hz, $CH_{benzylic}$), 4.67 (1H, d, CH_{sp3}), 2.26 (3H, s, CH_3C=O), 2.07 (3H, s, CH_3C=O), 1.96 (1H, s, CH_3) ppm. ^{13}C NMR (100.6 MHz, TMS, $CDCl_3$): δ = 204.3 (C=O), 203.7 (C=O), 138.2, 136.3, 136.2, 130.2, 129.3, 129.2, 127.8, 122.5, 121.1, 119.7, 119.1, 116.8. 111.3 (12 CH_{sp^2}), 75.3, 42.7, 31.4, 29.7, and 27.6 (5 C_{sp3}) ppm.

*Dimethyl-2-[(1H-indol-3-yl) (4-nitrophenyl) methyl]-malonate (**4b**):*

Yellow crystal, (0.19 g, 90%), m.p. 160-162 °C, IR (KBr) (ν_{max}/cm^{-1}): 3383 (NH), 3115 (ArCH), 2955 (CHsp^3), 1748 and 1721 (C=O), 1571 (C=C), 1522 and 1345 (NO_2) cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ= 8.22 (1H, s broad NH), 8.13 (2H, d, *J* = 8.4 Hz, ArCH), 7.56 (2H, d, *J* = 8.4 Hz, ArCH), 7.46 (1H, d, *J* = 7.6 Hz, ArCH), 7.36 (1H, d, *J* = 8.4 Hz ArCH), 7.24 (1H, s, ArCH), 7.20 (1H, t, *J* = 7.6 and 7.6 Hz ArCH), 7.09 (1H, t, *J* = 7.4 and 7.6 Hz, ArCH), 5.24 (1H, d, *J* = 11.6 Hz, CH), 4.37 (1H, d, *J* = 11.6 Hz, CH), 3.60 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), ppm. ^{13}C NMR (100.6 MHz, TMS, $CDCl_3$): δ 167.8 (C=O), 167.7 (C=O), 148.9, 146.7, 136.2, 129.1, 126.1, 123.7, 122.7, 121.1, 119.9, 118.8, 115.2 and 111.3 (12 C sp^2) 57.4, 52.9, 52.8 and 42.4 (4 C_{sp3}) ppm.

*2-[(1H-indol-3-yl)(p-tolyl)methyl]- 1H-indole (**5a**):*

Brown crystals, (0.20 g, 60% under one-pot and under two-step 10%), m.p. 84-86 °C, IR (KBr) (ν_{max}/cm^{-1}): 3483 (NH), 3055 (CH, sp^2), 2987 (CH, sp^3), 1796 and 1698 (C=O), 1620 (C=C), cm^{-1}. ^{1}H

NMR (400 MHz, TMS, $CDCl_3$): δ= 7.89 (2H, sbr, NH), 7.44 (2H, d, *J* = 8.0 Hz, ArCH), 7.36 (2H, d, *J* = 7.6 Hz, ArCH), 7.27 (2H, d, *J* = 7.8 Hz, ArCH), 7.21 (2H, t, *J* = 7.8 and 7.4 Hz ArCH), 7.12 (2H, d, *J* = 8.0 Hz ArCH), 7.07 (2H, t, *J*=7.6 and 7.4 Hz ArCH), 6.65 (2H, s, ArCH), 5.88 (1H, s, $CH_{benzylic}$), 2.35 (3H, s, CH_3), ppm. ^{13}C NMR (100.6 MHz, TMS, $CDCl_3$): δ 146.5, 136.6, 130.9, 129.5, 126.6, 123.6, 122.3, 120.9, 119.6, 119.5, 118.1 and 111.2 (12 C, sp^2), 42.7 and 27.6 (2 C, sp^3) ppm.

2-[(1H-indol-3-yl)(4-nitrophenyl]methyl-1H-indole (5b):

Orange crystals, (0.21 g, 60%) m.p. 240-242 °C, IR (KBr) (ν_{max}/cm^{-1}): 3383 (NH), 3054 (CH, aromatic), 2987 ($CHsp^3$), 1592 (C=C), 1505 and 1335 (NO_2) cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ= 10.12 (2H, s broad NH), 8.19 (2H, d, *J* = 8.8 Hz, ArCH), 7.68 (2H, d, *J* = 8.4 Hz, ArCH), 7.45 (2H, d, *J* =8.4 Hz, ArCH), 7.38 (2H, d, *J*=7.6 Hz, ArCH), 7.13 (2H, t, *J*=7.4 and 7.8 Hz, ArCH), 6.96 (2 H, t, *J*=7.6 and 7.4 Hz ArCH), 6.91 (2H, s, ArCH), 6.12 (1 H, s, $CH_{benzylic}$), ppm. ^{13}C NMR (100.6 MHz, TMS, $CDCl_3$): δ 153.1, 146.4, 137.2, 129.6, 126.9, 123.9, 123.2, 121.4, 119.1, 118.7, 117.5 and 111.4 (12 C, sp^2), 40.1 (2 C, sp^3) ppm.

Dimethyl-2-(4-nitrobenylidene) malonate (8):

White crystals, (0.22 g, 87%), m.p. 134-136 °C, IR (KBr) (ν_{max}/cm^{-1}): 3054 (CH, aromatic), 2987 ($CHsp^3$), 1594 (C=C), 1505 and 1335 (NO_2) cm^{-1}. ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ= 8.26 (2H, d, *J* =8.8 Hz, ArCH), 7.81 (1H, s, CH), 7.60 (2H, d, *J* = 8.4 Hz, ArCH), 3.89 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), ppm. ^{13}C NMR (100.6 MHz, TMS, $CDCl_3$): δ 166.1 (C=O), 163.7 (C=O), 148.4, 139.9, 139.1, 129.9, 129.5, 129.2, 124.0 and 123.9 (8 C, sp^2), 53.1 and 52.9 (2 C, 2 OCH_3), ppm.

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