Regioselective Amination of 3-Bromoindolylmaleimide with Amines

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Abstract: 3-Bromoindolylmaleimide and bisindolylmaleimide were synthesized from succinimide in three steps sequnence consisting of bromination, N-methylation and indole addition in the presence of magnesium and bromoethane. They were subjeced to the regioselective amination with substituted amines to provide 3-aminoindolylmaleimides, 3-amino-N-alkylated indolylmaleimides and N-alkylated bisindolylmaleimides in good yields. The resulting indolylmaleimides represent a new class of potentially bioactive compounds.

Keywords: 3-Bromoindolylmaleimide, bisindolylmaleimide, regioselective amination, reaction mechanism.

INTRODUCTION

Protein kinase C (PKC) represents an important family of serine/threonine kinases that is involved in the transduction of signals for cell proliferation and differentiation [1]. The important role of PKC in processes relevant to neoplastic transformation, carcinogenesis and tumour cell invasion renders it a potentially suitable target for anticancer therapy. Furthermore, there is accumulating evidence that selective targeting of PKC may improve the therapeutic efficacy of established neoplastic agents and sensitise cells to ionising radiation [2,3]. The natural product staurosporine, although a potent inhibitor of PKC, has limited selectivity *in vitro* for both ATP-dependent kinases and individual PKC isozymes [4]. Hence, over the past few years there have been significant research activities towards selective inhibitors for PKC. A series of novel indolylmaleimides were developed for clinical trail [5,6], such as Ruboxistaurin [7], Enzastaurin [8] and Sotrastaurin [9]. Structurally related derivatives, in which one indole substitutent was replaced by other (hetero)arenes, have been identified as strong protein kinase C inhibitors as well [9-12]. Ruboxistaurin, a macrocyclic bisindolylmaleimide, was widely known because of its marked PKC β selectivity. More recently Enzastaurin, another bisindolylmaleimide, was reported as PKC β selective inhibitor, which is now evaluated for the treament of B-cell lymphomas[7].

Recently, our research group has been interested in the synthesis and development of indolylmaleimide derivatives as anticancer agents [5,13]. In continuation of this research, we tried to synthesize some water-soluble 3-amino-4-indolylmaleimide derivatives. When 3-bromo-4-indolyl-N-methylmaleimide was treated with substituted amines, we found 3-amino-4-indolyl-N-methylmaleimides and 3-amino-N-alkyl-4-indolylmaleimides were obtained in good yields, respectively. In this paper, we described the regioselective amination of 3-bromoindolyl-N-methylmaleimide and bisindolylmaleimide with different N-substituted amines.

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RESULTS AND DISCUSSION

The general route for the synthesis of 3-amino-4-indolylmaleimides is outlined in the Fig. (**1**). Firstly, 2-bromo-3-(1*H*-indol-3-yl)-N-methymaleimide **4** as the key intermediate could be easily synthesized from succinimide by bromination with bromine, methylation with methyl idodide and by reation of indole with 2,3-dibromo-N-methylmaleimide in the presence of magnesium and ethyl bromide in 39% overall yield in there steps [13,14]. With the compound **4** in hand, we treated this compound (1.0 equiv.) with ethanolamine (1.2 equiv.), in the presence of triethylamine (1.5 equiv.) as a base, in DMF at 100℃ to give 3-(2-hydroxyethylamino)-4-indolyl-N-methylmaleimide **5a** as main product with 78% isolated yield. When treating ethanolamine (2.0 equiv.) with **4** (1.0 equiv.), a new compound was detected by a TLC analysis besides the compound **5a**. With increasing the amount of ethanolamine, the yield of the new compound increased. It was turn to be a main product when ethanolamine was used as a solvent. After the purification with flash column chromatography, a red crystal was isolated and carried out spectral detection. ^{1}H NMR spectrum showed the signal of methyl group at δ 3.0 ppm disappeared, one more signals exhibited in the range of δ 2~4 ppm. Furthermore, the EI mass spectrum of this compound showed a molecular ion at 315 (M^+). On the basis of spectral data, we supposed the ring opening and closing happened in this reaction and assigned to the obtained compound the structure of 1-(2-hydroxylethyl)-3-(2-hydroxyethylamino)-4-indolylmaleimide **6a** (Fig. **1**).

Dodo, K. and co-workers reported that 3-amino-4-indolylmaleimide derivatives were synthesized from 3-bromoindolylmaleimides as starting material by treating with different amines in dichloromethane [15]. Among others, untill recently, Beller M. and co-workers presented the amination of 3-bromoindolylmaleimides [16]. However, limited information was available for this amination, and a detailed reaction process was not discussed in above literature. In order to investigate this reaction, bisindolylmaleimide **7,** prepared by the reaction of indole with 3,4-dibromo-N-methylmaleimide in the presence of magnesium and ethyl bromide, was used as the substrate. Treatment of compound **7** with isopropanolamine gave

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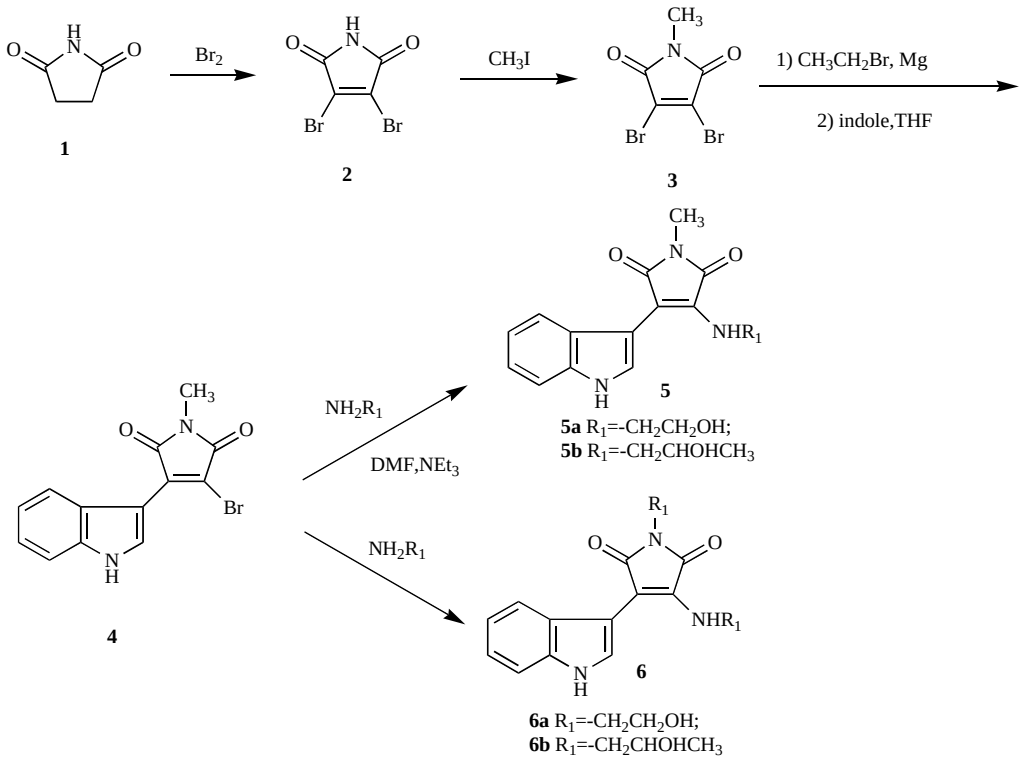


Fig. (1). Synthetic route for compounds **5** and **6**.

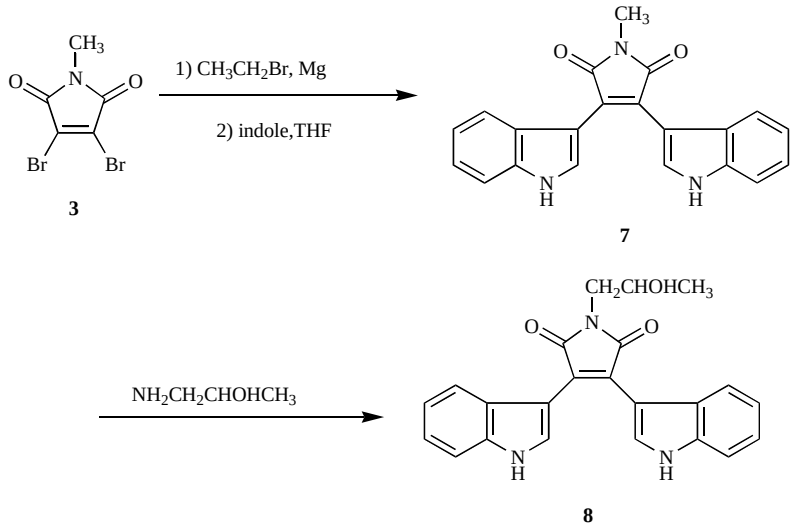
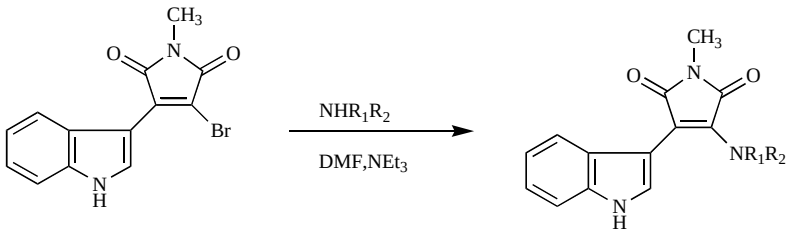


Fig. (2). Regioselective amination of bisindolylmaleimide.

compounds **8** with 80% isolated yield (Fig. **2**). However, when compound **4** was treated with the secondary amines, such as pyrrolidine, or diethanolamine, a main product 3-aminoindolylmaleimides were obtained in 75~86% yield. No other related N-alkylated compounds were isolated from the reaction mixture. These results made we believe maleimide ring can be opened and reclosed under primary amines (Fig. **3**). This reaction proved to be a suitable procedure to prepare N-alkylated indolylmaleimide derivatives. The structures of all new compounds were unambiguously confirmed by spectroscopic methods.

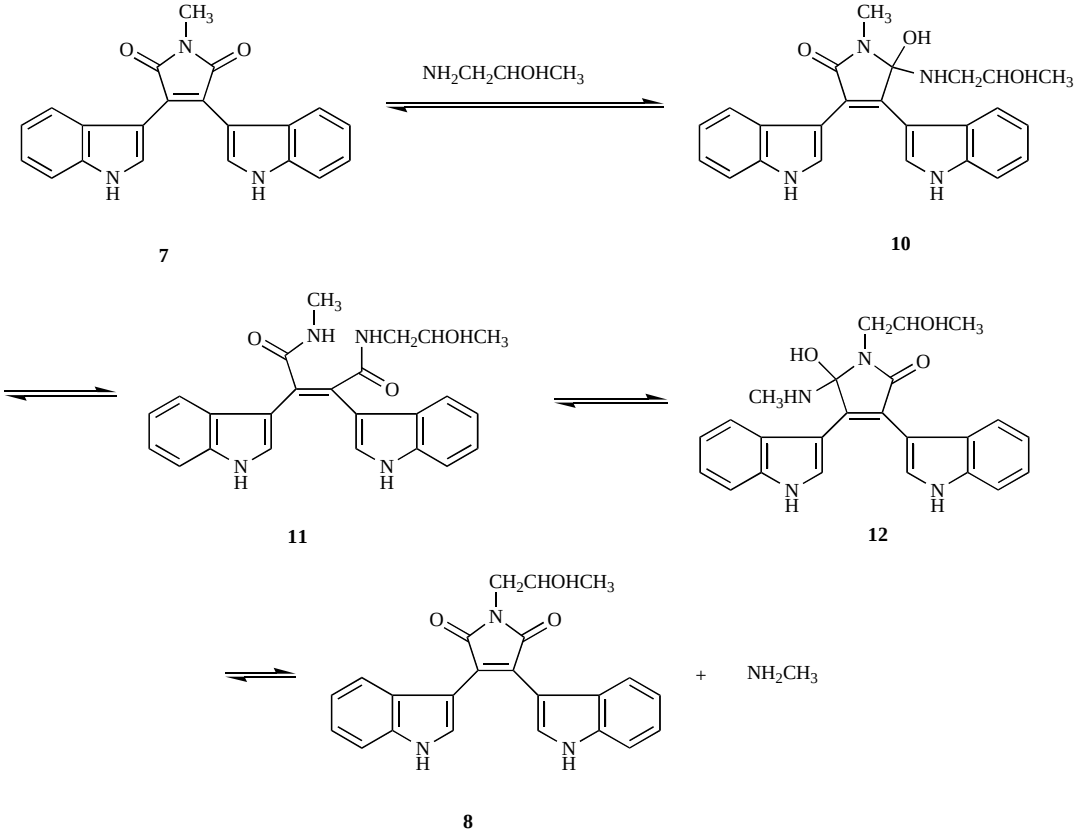
Based on the experimental results, a plausible mechanism can be proposed in Fig. (**4**). Initially, bisindolylmaleimide **7** reacted with isopropanolamine to give the intermediate **10**. Secondly, the intermediate **10** was subjected to ring openning to give compound **11.** Thirdly, nitrogen atom in compound **11** bound to the isopropyl group attacked the carbonyl of the mehlylamide group to provide the intermediate **12**, then subjected to demethylamination to give the compound **8**. Herein, methylamine was released from the nucleophile addition reaction and made this reaction complete. In case of secondary amines, nitrogen atom was unable to attack at the carbonyl group in maleimide ring due



4 **9**

9a R_1=-CH_2CH_2OH,R_2= -CH_2CH_2OH;
9b R_1=-$(CH_2)_3CH_3$,R_2= -$(CH_2)_3CH_3$;
9c R_1,R_2= -$CH_2CH_2CH_2CH_2$-

Fig. (3). Synthetic route for compounds **9**.



7 **10** **11** **12** **8**

Fig. (4). Supposed the mechanism for the regioselective amination.

to steric hindrance. All isolated product are bright coloured crystalline compounds.

In conclusion, we have demonstrated that 3-bromoindolyl-N-methylmaleimide and bisindolylmaleimide can sucessfully be regioselectively aminated with primary amines to provide 3-amino-4-indolylmaleimides, 3-amine-N-alkyl-4-indolylmaleimide, respectivily and N-alklylated bisindolylmaleimide in 70~88% yields. This reaction provided a suitable procedure to prepare N-alkylated indolylmaleimide derivatives. Further biological evaluation of the synthesized compounds are currently in progress.

EXPERIMENTAL

Melting points were determined with RY-1 apparatus, and were uncorrected. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker AV 400 MHz spectrometer in DMSO-d_6, $CDCl_3$ and acetone-d_6 with tetramethylsilane as internal standard. EI mass spectra were recorded on Shimadzu QP-2010 GC-MS system. ESI mass spectra were obtained on Shimadzu 2010A LC-MS instrument. Elemental analyses were performed on a Vario EL Ⅲ elemental analyser. All chemicals and reagents were purchased from known commerical suppliers and were used without further purification. 3,4-Diboromaleimide, 3,4-dibromo-N-methylmaleimide, 2-bromo-3-(1*H*-indol-3-yl)-N-methymaleimide and bisindolyl-N-methylmaleimide were synthesized according to the literature procedures with minor change[13,14]. The target compounds were prepared according to the synthetic routes shown in Figs. (**1**, **3**).

General Procedure for Preparation of Compounds 5

4 (5 mmol) and triethylamine (10 mmol) were mixed thoroughly in DMF (10 mL). To this solution, ethanolamine (6 mmol) was added. The reaction mixture was stirred at 100℃ for 16 h. Water (10 mL) was added. The mixture was extracted with ethyl acetate(40 mL×2), and washed with saturated $NaHCO_3$(40 mL×2) and water(40 mL×2). The solvent was removed and purified by flash column chromatography (dichloromethane / methanol=10:1, v/v) to give a red-yellow solid **5**. Compounds **9** were synthesized from **4** following the procedure given above. Compounds **6** were synthesized from **4** by using amines as solvent. The physical and spectral data of the compounds **5a-5b**、**6a-6b**、**8** and **9a-9c** are as follows.

3-(2-hydroxyethylamino)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (5a)

Red crystalline solid; m.p. 219-222 ℃; yield:78%; IR (cm^{-1}): 1701(C=O), 1638(C=O). ^1H NMR(DMSO-d_6): δ 2.91(s, 3H, CH_3), 3.11(t, *J*=5.8Hz, 2H, CH_2), 3.24(t, *J*=5.8Hz, 2H, CH_2), 4.58(s, 1H, OH), 6.90(s, 1H, NH), 7.00(m, 1H, Ar-H), 7.09(m, 1H, Ar-H), 7.29(m, 1H, Ar-H), 7.37(m, 2H, Ar-H), 11.17(s, 1H, NH); MS(ESI, m/z): 286.2$[(M+H)]^+$, 308.3 $[(M+Na)]^+$. Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.01; N, 14.42%.

3-(2-hydroxypropylamino)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (5b)

Red crystalline solid; m.p. 248-250 ℃; yield: 72%; IR (cm^{-1}): 1704(C=O), 1642 (C=O). ^1H NMR(DMSO-d_6): δ 0.66(d, *J*=6.2Hz, 3H, CH_3), 2.91(s, 3H, CH_3), 2.93(m, 1H, CH_2), 3.47(m, H, CH), 4.63(s, H, OH), 6.86(s, 1H, NH), 7.00(m, 1H, Ar-H), 7.09(m, 1H, Ar-H), 7.28(d, 1H, Ar-H), 7.37(m, 2H, Ar-H), 11.21(s, 1H, NH); MS(EI, m/z):299$[M]^+$. Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.45; H, 5.51; N, 14.39%.

3-(2-hydroxyethylamino)-1-(2-hydroxyethyl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione (6a)

Red crystalline solid; m.p. 232-235ºC; yield:77%; IR (cm^{-1}): 1697(C=O), 1648(C=O). ^1H NMR(DMSO-d_6): δ 3.12(t, *J*=5.8Hz, 2H, CH_2), 3.22(t, *J*=5.8Hz, 2H, CH_2), 3.49(m, 4H, $2CH_2$), 4.60(m, 1H, OH), 4.84(m, 1H, OH), 6.92(m, 1H, Ar-H), 7.01(m, 1H, Ar-H), 7.07(m, 1H, Ar-H), 7.30(s, 1H, NH), 7.39(m, 2H, Ar-H); 11.23(s, 1H, NH); MS(ESI, m/z): 315$[M]^+$. Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.58; H, 5.76; N, 12.99%.

3-(2-hydroxypropylamino)-1-(2-hydroxypropyl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione (6b)

Red crystalline solid; m.p. 258-261 ℃; yield:70%; IR (cm^{-1}): 1703(C=O), 1639(C=O). ^1H NMR(DMSO-d_6): δ 0.67(d, *J*=6.6Hz, 3H, CH_3), 1.04(d, *J*=6.6Hz, 3H, CH_3), 2.91(m, 2H, CH_2), 3.28(m, 2H, CH_2), 3.37(m, 1H, CH), 3.81(m, 1H, CH), 4.64(s, 1H, OH), 4.81(s, 1H, OH), 6.89 (s, 1H, NH), 6.98(m, 1H, Ar-H), 7.07(m, 1H, Ar-H), 7.29(m, 1H, Ar-H), 7.37(m, 2H, Ar-H), 11.21(s, 1H, NH); MS(EI, m/z): 343 $[M]^+$. Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.61; H, 6.12; N, 12.08%.

1-(2-hydroxypropyl)-3,4-di-(1H-indol-3-y)-1H-pyrrole-2,5-dione (8)

Red crystalline solid; m.p. 265-268ºC; yield: 79%; IR (cm^{-1}): 1712(C=O), 1657(C=O). ^1H NMR (DMSO-d_6): δ 0.98(d, *J*=6.8Hz, 3H, CH_3), 3.51(m, 2H, CH_2), 3.94(m, 1H, CH), 4.91(s, 1H, OH), 6.66(m, 2H, Ar-H), 7.81(m, 2H, Ar-H), 6.95(m, 2H, Ar-H), 7.35(m, 2H, Ar-H), 7.75(m, 2H, Ar-H), 11.67(s, 2H, NH); MS(EI) m/e $[M]^+$385. Anal. Calcd. for $C_{23}H_{19}N_3O_3$: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.32; H, 5.81; N, 11.19%.

3-(bis(2-hydroxyethyl)amino)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (9a)

Red crystalline solid; m.p. 260-262ºC; yield: 78%; IR (cm^{-1}): 1710(C=O), 1669(C=O). ^1H NMR(DMSO-d_6): δ 2.89(s, 3H, CH_3), 3.43(m, 4H, $2CH_2$), 3.57 (m, 4H, $2CH_2$), 4.66(s, 2H, 2OH), 6.98(m, 1H, Ar-H), 7.07(m, 1H, Ar-H), 7.29(s, 1H, Ar-H), 7.36(d, 1H, Ar-H), 7.47(d, 1H, Ar-H), 11.24(s, 1H, NH); MS(EI, m/z): 329 $[M]^+$. Anal. Calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.29; H, 5.71; N, 12.96%.

3-dibutylamino-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (9b)

Red crystalline solid; m.p. 197-199ºC; yield: 84%; IR (cm^{-1}):1695(C=O), 1646(C=O). ^1H NMR(acetone-d_6): δ 0.72(m, 6H, $2CH_3$), 1.04(m, 4H, $2CH_2$), 1.48(m, 4H, $2CH_2$), 3.01(s, 3H, CH_3), 3.50(m, 4H, $2CH_2$), 7.04(m, 1H, Ar-H), 7.12(m, 1H, Ar-H), 7.31(s, 1H, Ar-H), 7.42(m, 2H, Ar-H), 10.55(s, 1H, NH); MS(ESI, m/z): 354.3 $[(M+H)]^+$, 376.4 $[M+Na]^+$. Anal. Calcd. for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found: C, 71.02; H, 7.41; N, 11.59%.

3-(1-pyrrolidino)-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione(9c)

Red crystalline solid; m.p. 209-212ºC; yield:88%; IR(cm^{-1}):1683(C=O), 1630(C=O); ^1H NMR($CDCl_3$): δ1.75(m, 4H, $2CH_2$), 3.06(s, 3H, CH_3), 3.55(m, 4H, $2CH_2$), 7.12(m, 2H, Ar-H), 7.20(m, 1H, Ar-H), 7.35(m, 1H, Ar-H), 7.46(m, 1H, Ar-H), 8.28(s, 1H, NH);MS(ESI, m/e):$[M+H]^+$ 296.3, $[M+Na]^+$ 318.1. Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.04; H, 5.57; N, 14.12%.

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