Synthesis of Functionalized 1,2,3-Triazole Derivatives of 2-Indolones from Morita-Baylis-Hillman Adducts of Isatin *via* ''Click Chemistry''

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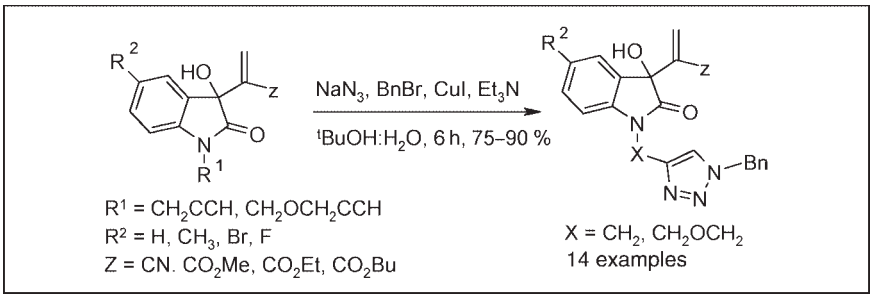

A short and efficient regioselective synthesis of a number of 1,4-disubstituted-1,2,3-triazole derivatives of oxindoles from *N*-terminal alkyne and alkynyl ether derivatives of Morita-Baylis-Hillman (MBH) adducts of isatin with *in situ* generated alkyl azide and copper(I) iodide as a catalyst in 1:1 mixture of *t*-BuOH:water as a solvent system has been achieved. The synthetic procedure tolerates most of the functional groups present in the MBH adducts and circumvents the problems associated with the isolation of potentially toxic and explosive organic azides.

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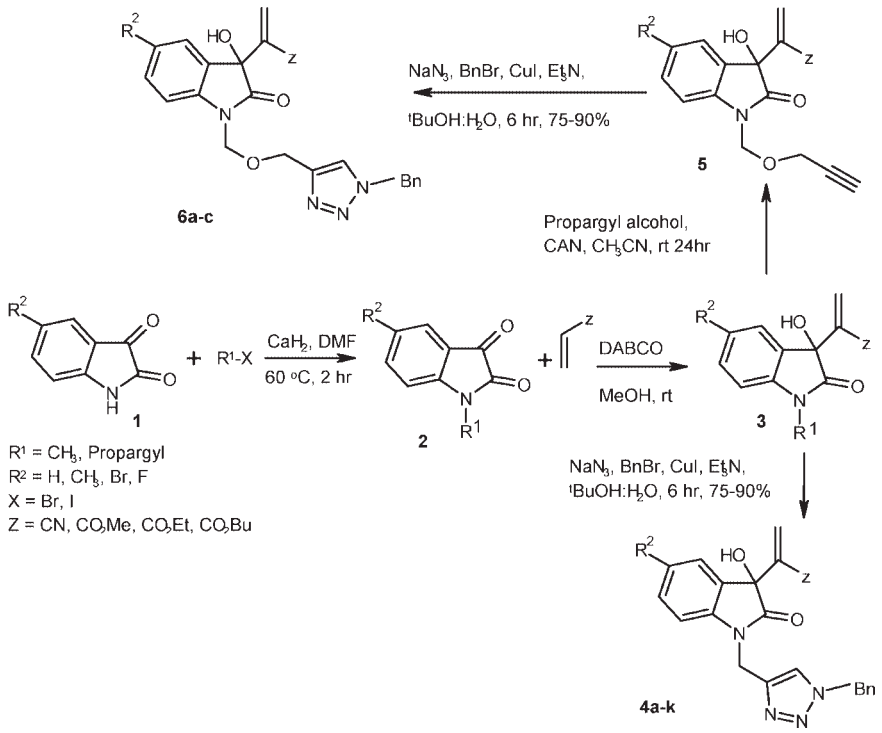
INTRODUCTION

Oxindoles derivatized as 1,2,3-triazole are elegant synthetic targets in organic synthesis due to their significant biological activities [1]. Recently, click chemistry has been emerged as a fast and efficient method for the synthesis of novel diverse chemical entities and the generation of large number of drug-like molecules with triazole scaffolds [2]. The triazole scaffolds are considered as significant synthetic targets due to their significant biological activities, such as antibacterial [3], anti-HIV [4], and anti-allergic [5]. Hence, a number of synthetic routes have been developed for the preparation of these structural frameworks [6–9]. As a result, there has been considerable interest in developing efficient synthetic methods for these compounds with oxindole as core structure. The Morita-Baylis-Hillman (MBH) adduct and their derivatives, such as halides, acetates, ethers, etc. play an important role as synthons for a number of potential synthetic intermediates and natural product syntheses [10]. As part of our on going research on novel synthetic applications of MBH adducts [11–13], particularly for the construction of novel oxindole derivatives [14–18], we were interested to explore the synthesis of title compounds using the versatile ''click chemistry'' reaction methodology. Several methods have been reported for the synthesis of 1,2,3-triazoles and 1,3-dipolar cycloaddition of azides to alkynes [19–21]. Recently, Sharpless and coworkers have reported a high yielding synthesis of triazoles using a Cu(I) catalyst with an excellent 1,4-regioselectivity. The metal-catalyzed reaction discovered simultaneously and independently in the Sharpless and Meldal laboratories [22] constitutes a substantial improvement of the classical Huisgen-type thermal 1,3-dipolar cycloaddition, which usually afford a mixture of 1,4- and 1,5-disubstituted triazoles. Fokin and coworkers have developed a multicomponent variant for the synthesis of trizoles both in conventional [23] and microwave irradiation [24] methods. Although *N*-propargyl isatins obtained from Friedel-Crafts alkylation of 2-napthol with isatin have been used for the 1,3-dipolar cycloaddition with alkyl azides [25], however, the reaction with *N*-alkyne and *N*-alkynyl ether derivatives of MBH adducts of isatin are unknown. Thus, herein, we report an efficient, safe, and one-pot synthesis of 1,4-disubstituted-1,2,3-triazole derivatives of oxindoles from the 1,3-dipolar cycloaddition reaction of *N*-propargyl MBH adduct of isatin with *in situ* generated alkyl azide and copper iodide as catalyst in 1:1 mixture of *t*-BuOH and water as a solvent. The reaction condition was fully compatible and environmentally benign. A detailed study

Scheme 1



on the 1,3-dipolar cycloaddition reaction of *N*-terminal alkynes **3** and **5** with alkyl azides to afford highly functionalized triazole derivatives is the subject matter of this article (Scheme 1).

RESULTS AND DISCUSSION

The starting material *N*-terminal alkynes of isatin were prepared from the alkylation reaction of isatin with propargyl bromide and CaH_2 as a base in DMF at 60°C for 1 hr. Further, the corresponding MBH adducts were prepared following reported procedure [26]. The other substrate namely, *N*-propargyl ether derivative of MBH adduct was prepared from the *N*-methylated MBH adduct of isatin with propargyl alcohol and cerium ammonium nitrate (CAN) in acetonitrile at room temperature [11].

Initially, we carried out a reaction of alkyne **3** with 1.2 equivalents of sodium azide, 2.6 equivalents of triethylamine, and 2.2 equivalents of benzyl bromide in the presence of 2.5 mol % CuI in PEG-400. The reaction did not proceed and attempts to carry out the reaction with other solvent such as H_2O also did not yield fruitful results. However, the use of a mixture of $^tBuOH:H_2O$ (1:1 v/v) as solvent drove the reaction to form the desired 1,4-disubstituted 1,2,3-bistriazole product in excellent yield (Scheme 1, Table 1, entry 1). The click chemistry reaction, under mild conditions, constituted the Cu(I) catalyzed alkyne–azide [3+2]-cycloaddition furnished pharmaceutically important 1,4-disubstituted 1,2,3-triazole indolones in excellent yields (Scheme 1, Table 1). This investigation offers a mild and efficient method for the preparation of 1,2,3-triazoles using CuI as catalyst for the 1,3-dipolar cycloaddition of terminal alkynes with alkyl azides. The copper(I) readily inserts into terminal alkynes in the presence of a base, which proceeds *via* the intriguing six-membered ring [22,27]. The triazole was formed in a regioselective manner, with no contamination of 1,5-regioisomer. To demonstrate the methodology applicable to a variety of substrates having bromo, fluorine, and alkyl substitutions, synthesis of several triazole derivatives of oxindoles have been achieved and the results are collected in Table 1. The structure of 1,4-disubstituted 1,2,3-triazoles obtained is in good agreement with those described in the previous reports on the synthesis of substituted triazoles *via* three component coupling reaction [28]. The results revealed that the reaction was dependent on the nature of substituents on the isatin as evident from the comparison of the yields of products (**4a–k** and **6a–c**) due to electronic effects. The yields of the products decreased when electron donating groups were present on the isatin (entries 3 and 4). The yield of the products increased when electron-withdrawing groups were present on the isatin (entries 5, 6, 9, and 10). The substitution in ester group from Me → Et → Bu (entries 6, 7, 8, 10, and 11) afforded decreased yields.

Table 1

Synthesis of 1,2,3-triazole derivatives of oxindole.

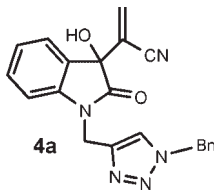
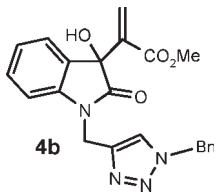
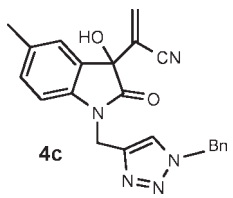
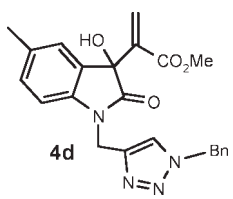
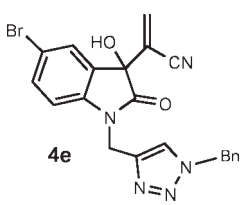
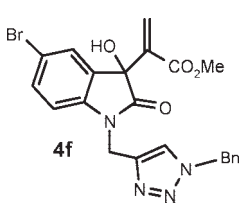
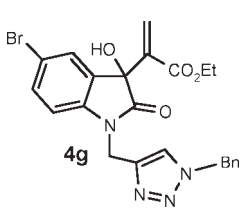
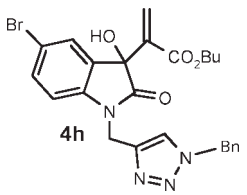
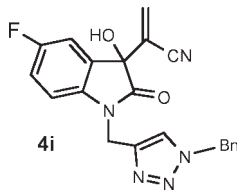
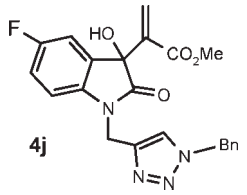
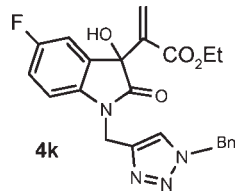
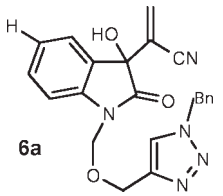
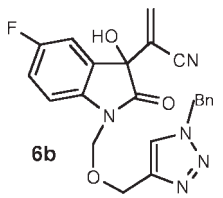
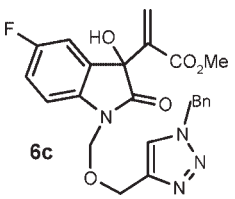
Entry	Substrate (R^2)	Product	Yield (%)[a]
1	H		80
2	H		82
3	Me		73
4	Me		71
5	Br		82
6	Br		84
7	Br		78

Table 1

(*Continued*)

Entry	Substrate (R^2)	Product	Yield (%)[a]
8	Br		75
9	F		86
10	F		88
11	F		77
12	H		79
13	F		82
14	F		80

[a] Isolated yield.

All the new compounds were characterized thoroughly by spectroscopic methods (IR, ^{1}H, ^{13}C NMR, and ESI-mass spectra).

It is noteworthy that these reactions were efficiently performed in a neutral aqueous solution (water:^{t}BuOH) at an ambient temperature (RT). Molar equivalents of the halide, sodium azide, and alkyne were used in the mild 1,3-dipolar cycloaddition reaction. The method avoid the problems associated during the isolation of organic azides, and complements the reported method for the preparation of 1,2,3-triazoles. The operational simplicity of this method makes it attractive for preparative applications as well as a library compounds for drug discovery.

In conclusion, we have demonstrated an efficient synthetic procedure for the synthesis of highly functionalized 1,2,3-triazole derivatives of 2-indolones *via* a copper(I) catalyzed 1,3-dipolar cycloaddition of *N*-terminal alkyne derivative of MBH adduct of isatin with *in situ* generated alkyl azides. Further studies on this reagent system are in progress.

EXPERIMENTAL

General. IR measurements were done as KBr pellets for solids using PerkinElmer Spectrum RXI FTIR. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with, Bruker 500 MHz and Bruker 300.1 MHz high resolution NMR spectrometer. $CDCl_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in ppm with TMS as internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). The mass were analyzed by using a Electrospray Ionization method with Thermo Finnigan Mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2-mm thickness (Macherey-Nagel, Germany).

Typical experimental procedure (4b). A mixture of *N*-propargyl derivative of MBH adduct (100 mg, 0.35 mmol), sodium azide (27 mg, 0.42 mmol), benzyl bromide (66 mg, 0.38 mmol), triethylamine (92 mg, 0.91 mmol), and CuI (2.5 mol %) in 3 mL of *t*-butanol:water (1:1) was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the catalyst was filtered off through a pad of celite® and the product was extracted with ether (2 × 20 mL). The combined organic layer was dried (anhyd. Na_2SO_4), filtered, and removed under vacuum. The crude product was purified by silica gel column chromatography using hexane–ethyl acetate (7:3) solvent mixture to afford pure triazole derivatives.

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4a). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3378, 1612, 1487, 1332, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.39 (brs, 1H), 4.86 (d, J = 15.8 Hz, 1H), 5.10 (d, J = 15.9 Hz, 1H), 5.38 (AB quartet, J = 14.2 Hz, 2H), 6.13 (s, 1H), 6.39 (s, 1H), 6.74–7.13 (m, 4H), 7.26–7.31 (m, 5H), 7.54 (s, 1H). ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 34.9, 52.5, 54.2, 76.2, 108.9, 112.1, 114.3, 122.7, 122.3, 122.6, 124.4, 128.0, 128.2, 128.9, 129.0, 131.0, 141.2, 164.3, 176.1. MS (EI) m/z 372 (M^+).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-y2l)methyl)-3-hydroxy-2-oxoindolin-3-yl) acrylate (4b). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3383, 1718, 1612, 1490, 1327, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.32 (brs, 1H), 3.49 (s, 3H), 4.92 (d, J = 15.8 Hz, 1H), 5.17 (d, J = 15.8 Hz, 1H), 5.45 (AB quartet, J = 13.7 Hz, 2H), 6.46 (s, 1H), 6.57 (s, 1H), 6.97–7.32 (m, 9H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 36.0, 51.8, 54.2, 76.0, 109.8, 122.9, 123.1, 123.7, 128.0, 128.1, 128.7, 129.0, 129.4, 130.2, 134.4, 139.0, 142.9, 143.1, 164.9, 176.0. MS (EI) m/z 405 (M^+).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-ydroxy-5-methyl-2-oxoindolin-3-yl)acrylonitrile (4c). White solid: R_f (60% EtOAc/hexane) 0.34; IR (KBr): 3371, 2221, 1719, 1608, 1483, 1330, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.30 (s, 1H), 4.37 (brs, 1H), 4.88 (d, J = 15.7 Hz, 1H), 5.06 (d, J = 15.7 Hz, 1H), 5.40 (AB quartet, J = 13.8 Hz, 2H), 6.16 (s, 1H), 6.40 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 7.13–7.19 (m, 4H), 7.29–7.34 (m, 3H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 20.9, 33.0, 36.0, 54.2, 54.8, 76.5, 105.3, 110.1, 117.9, 122.6, 122.8, 125.2, 127.0, 128.0, 128.7, 129.0, 131.2, 131.3, 139.5, 142.9, 176.0. MS (EI) m/z 386 (M^+).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-hydroxy-5-methyl-2-oxoindolin-3-yl)acrylate (4d). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3387, 1721, 1612, 1492, 1322, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.03 (brs, 1H), 2.62 (s, 3H), 3.48 (s, 3H), 5.01 (AB quartet, J = 12.4 Hz, 2H), 5.38 (d, J = 14.8 Hz, 1H), 5.45 (d, J = 14.8 Hz, 1H), 6.49 (s, 1H), 6.56 (s, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.95–7.11 (m, 3H), 7.24–7.31 (m, 4H), 7.64 (s, 1H). ^{13}C NMR ($CDCl_3$/TMS, 125 MHz): 20.9, 36.0, 51.8, 54.2, 75.8, 109.5, 122.8, 124.4, 127.8, 127.9, 128.0, 128.3, 128.6, 129.01, 129.2, 130.4, 132.7, 134.4, 138.9, 140.6, 143.0, 164.9, 176.6. MS (EI) m/z 419 (M^+).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4e). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3381, 1614, 1495, 1323, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.00 (brs, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.99 (d, J = 15.7 Hz, 1H), 5.41 (AB quartet, J = 14.3 Hz, 2H), 6.20 (s, 1H), 6.44 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.07–7.14 (m, 2H), 7.30–7.35 (m, 3H), 7.42–7.44 (m, 2H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.3, 52.1, 54.2, 76.1, 112.0, 122.1, 122.6, 126.2, 126.9, 128.0, 128.7, 128.6, 128.9, 130.2, 132.7, 133.9, 138.4, 142.2, 142.7, 175.4. MS (EI) m/z 450 (M^+), 452 (M + 2).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl) acrylate (4f). White solid: R_f (60% EtOAc/hexane) 0.30; IR (KBr): 3371, 2221, 1719, 1608, 1483, 1330, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.03 (s, 1H), 3.51 (s, 1H), 4.85 (d, J = 15.8 Hz, 1H), 5.09 (d, J = 15.9 Hz, 1H), 5.41 (AB quartet, J = 12.5 Hz, 2H), 6.51 (s, 1H), 6.58 (s, 1H), 6.82 (d, J = 8.2 Hz, 1H), 7.26–7.43 (m, 7H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.8, 51.8, 54.2, 76.5, 111.3, 122.1, 122.8, 126.8, 126.9, 128.0, 128.4, 128.6, 128.9, 129.1, 132.7, 134.2, 138.4, 142.0, 142.4, 165.4, 175.4. MS (EI) m/z 483 (M^+), 485 (M + 2).

Ethyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylate (4g). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3369, 1724, 1617, 1484, 1318, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.09

(t, J = 3.24 Hz, 3H), 2.03 (brs, 1H,), 3.95 (q, J = 4.5, 11.8 Hz, 2H), 4.92 (d, J = 15.8 Hz, 1H), 5.09 (d, J = 15.9 Hz, 1H), 5.45 (AB quartet, J = 11.9 Hz, 2H), 6.48 (s, 1H), 6.60 (s, 1H), 6.79–7.01 (m, 3H), 7.26–7.38 (m, 5H), 7.60 (s, 1H). MS (EI) m/z 266 (M^+);^{13}C NMR ($CDCl_3$/TMS, 125 MHz): 13.8, 14.1, 22.6, 22.9, 29.6, 34.6, 52.7, 54.3, 61.1, 75.7, 111.4, 115.7, 122.8, 125.0, 127.0, 128.1, 128.2, 128.7, 129.0, 135.2, 138.4, 142.0, 164.3, 175.4. MS (EI) m/z 497 (M^+), 499 (M + 2).

Butyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-bromo-3-hydroxy-2-oxoindolin-3-yl)acrylate (4h). White solid: R_f (60% EA/hexane) 0.25; IR (KBr): 3383, 1718, 1612, 1490, 1327, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 0.88 (t, J = 7.2 Hz, 3H), 1.19–1.29 (m, 4H), 3.89 (t, J = 6.9 Hz, 2H), 4.08 (brs, 1H), 4.91 (d, J = 15.6 Hz, 1H), 5.08 (d, J = 15.9 Hz, 1H), 5.44 (AB quartet, J = 12.1 Hz, 2H), 6.47 (s, 1H), 6.61 (s, 1H), 6.84 (d, 1H, J = 8.1 Hz), 7.24–7.38 (m, 7H), 7.61 (s, 1H). MS (EI) m/z 266 (M^+);^{13}C NMR ($CDCl_3$/TMS, 125 MHz): 13.6, 18.9, 19.0, 29.6, 30.2, 36.0, 43.3, 54.3, 64.9, 75.7, 111.4, 115.7, 122.8, 127.0, 128.1, 128.2, 128.6, 128.7 (C), 129.0, 129.3, 132.6, 134.3, 138.4, 142.0, 164.4, 175.5. MS (EI) m/z 525 (M^+), 527 (M + 2).

2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro 3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (4i). White solid: R_f (60% EtOAc/hexane) 0.32; IR (KBr): 3386, 2243, 1726, 1619, 1490, 1343, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.02 (brs, 1H), 4.89 (d, J = 15.8 Hz, 1H), 4.99 (d, J = 15.8 Hz, 1H), 5.40 (d AB quartet, J = 13.3 Hz, 2H), 6.17 (s, 1H), 6.43 (s, 1H), 6.96–7.09 (m, 3H), 7.22 (d, J = 3.3 Hz, 1H), 7.26–7.34 (m, 4H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.8, 52.0, 54.2, 76.5, 109.2, 112.4, 115.5, 122.1 122.7, 123.5, 128.0, 128.7, 129.0, 131.9, 134.0, 140.1, 141.8, 142.5, 143.3, 173.8. MS (EI) m/z 390 (M^+).

Methyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylate (4j). White solid: R_f (60% EtOAc/hexane) 0.28; IR (KBr): 3362, 2217, 1722, 1612, 1490, 1334 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.50 (s, 3H), 4.65 (brs, 1H), 4.86 (d, J = 15.9 Hz, 1H), 5.08 (d, J = 15.9 Hz, 1H), 5.41 (AB quartet, J = 10.0 Hz, 2H), 6.46 (s, 1H), 6.51 (s, 1H), 6.83–6.95 (m,3H), 7.21 (d, J = 3.0 Hz, 1H), 7.26–7.39 (m, 3H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.9, 51.8, 54.2, 75.9, 110.1, 122.8, 128.0, 128.3, 128.6, 128.9, 129.2, 129.7, 130.0, 134.3, 138.5, 139.0, 142.5, 143.2, 164.7, 175.7. MS (EI) m/z 423 (M^+).

Ethyl 2-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylate (4k). White solid: R_f (60% EA/hexane) 0.31; IR (KBr): 3371, 1718, 1630, 1469, 1318, 1183 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.07 (t, 3H, J = 7.1 Hz), 2.48 (brs, 1H), 3.92 (q, J = 4.3, 11.2 Hz, 2H), 4.85(d, J = 15.9 Hz, 1H), 5.04 (d, J = 15.9 Hz, 1H), 5.39 (AB quartet, J = 9.3 Hz, 2H), 6.44 (s, 1H), 6.50 (s, 1H), 6.82–6.92 (m, 5H), 7.28–7.34 (m, 3H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 14.2, 22.4, 33.8, 51.8, 53.9, 62.0, 75.5, 96.0, 99.2, 109.6, 113.8, 113.9, 115.4, 122.4, 128.3, 128.6, 128.8, 129.0, 129.4, 134.2, 138.4, 142.0, 164.1, 172.0. MS (EI) m/z 437 (M^+).

2-(1-(((1-benzyl-1H-1,2,3-triazol-4-l)methoxy)methyl)-3-hydroxy-2-oxoindolin-3-yl) acrylonitrile (6a). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3377, 1615, 1473, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.43 (s, 1H, brs), 3.51 (s, 3H), 3.94–5.49 (m, 6H), 6.45 (s, 1H), 6.49 (s, 1H), 6.35–6.98 (m, 9H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 30.1, 52.3, 53.9, 68.1, 74.2, 112.2, 114.9, 116.3, 125.9, 127.6, 128.1, 128.5, 129.4, 133.0, 135.5, 138.3, 138.6, 164.7, 177.1. MS (EI) m/z 402 (M^+).

2-(1-(((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (6b). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3382, 1621, 1486, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 4.63 (d, J = 13.2 Hz, 1H), 4.72 (d, J = 13.1 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 5.36 (AB quartet, J = 9.8 Hz, 2H), 5.53 (d, J = 11.4 Hz, 1H), 5.84 (brs, 1H), 6.25 (s, 1H), 6.58 (s, 1H), 6.78–6.81 (m, 4H), 7.00–7.12 (m, 4H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 35.7, 53.2, 53.9, 69.7, 76.1, 111.5, 113.4, 115.8, 116.1, 123.3, 128.6, 128.1, 128.7, 128.9, 132.4, 134.7, 137.9, 138.3, 144.0, 164.4, 175.6. MS (EI) m/z 420 (M^+).

Methyl2-(1-(((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)-5-fluoro-3-hydroxy-2-oxoindolin-3-yl) acrylate (6c). White solid: R_f (60% EA/hexane) 0.29; IR (KBr): 3386, 1722, 1617, 1483, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.50 (s, 3H), 4.60 (d, J = 12.6 Hz, 1H), 4.68 (d, J = 12.8 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 5.29 (d, J = 11.3 Hz, 1H), 5.40–5.51 (m, 2H), 5.71 (s, 1H, br), 6.61 (s, 1H), 6.83 (s, 1H), 6.83–6.93 (m, 3H), 7.30–7.36 (m, 3H), 7.14–7.17 (s, 2H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 14.8, 35.9, 51.8, 53.9, 69.7, 75.8, 110.5, 111.7, 115.8, 116.1, 123.3, 127.9, 128.4, 128.6, 128.9, 131.4, 134.2, 138.1, 138.3, 144.0, 164.8, 176.9. MS (EI) m/z 453 (M^+).

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REFERENCES AND NOTES

[1] (a) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. J Med Chem 1994, 37, 4185; (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camarasa, M. J. Antivir Chem Chemother 1998, 9, 481.

[2] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew Chem Int Ed Engl 2001, 40, 2004.

[3] Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Babbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. A.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. J Med Chem 2000, 43, 953.

[4] Alvarez, R.; Valazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C. F.; Karlsson, F. A.; Balzarini, J.; Camarasa, M. J. J Med Chem 1994, 37, 4185.

[5] (a) Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; Maclntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. Bioorg Med Chem Lett 2000, 10, 2111; (b) Trybulski, E. J.; Benjamin, L.; Vitone, S.; Walser, A.; Fryer, I. R. J Med Chem 1983, 26, 367.

[6] Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, Ch. Tetrahedron Lett 2000, 42, 5561.

[7] Chandrasekhar, S.; Narsihmulu, Ch.; Jagadeshwar, V. Synlett 2001, 5, 771.

[8] Rostovstev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew Chem Int Ed Engl 2002, 41, 2596.

[9] Tornøe, C. W.; Christensen, C.; Meldal, M. J Org Chem 2002, 67, 3057.

[10] (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem Rev 2003, 103, 811; (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. Chem Soc Rev 2007, 36, 1581; (c) Singh, V.; Batra, S. Tetrahedron 2008, 64, 4511.

[11] Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. Tetrahedron Lett 2006, 47, 6851.

[12] Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B.; Madhavan, S. Tetrahedron Lett 2007, 48, 9190.

[13] Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. Aust J Chem 2007, 60, 296.

[14] Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. Tetrahedron 2006, 62, 4342.

[15] Shanmugam, P.; Viswambharan, B.; Madhavan, S. Org Lett 2007, 9, 4095.

[16] Shanmugam, P.; Viswambharan, B.; Selvakumar, K.; Madhavan, S. Tetrahedron Lett 2008, 49, 2611.

[17] Shanmugam, P.; Vaithiyanathan, V. Tetrahedron 2008, 64, 3322.

[18] Shanmugam, P.; Vaithiyanathan, V.; Selvakumar, K. Tetrahedron Lett 2008, 49, 2119.

[19] Fan, W.-Q.; Katritzky, A. R. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 4, pp 1–126.

[20] Fuks, R.; Viehe, H. G. In Chemistry of Acetylenes; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 425–593.

[21] Bastide, J.; Henri-Rousseau, O. In The Chemistry of the Carbon-Carbon Triple Bond; Patai, S., Ed.; Interscience Publishers: London, 1978; pp 447–552.

[22] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. Angew Chem Int Ed Engl 2002, 41, 2596; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. J Org Chem 2002, 67, 3057; (c) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. J Am Chem Soc 2003, 125, 3192; (d) Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. Org Lett 2003, 5, 1753.

[23] Feldman, A. K.; Colasson, B.; Fokin, V. V. Org Lett 2004, 6, 3897.

[24] Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Eycken, E. V. Org Lett 2004, 6, 4223.

[25] Ramachary, D. B.; Reddy, G. B.; Mondal, R. Tetrahedron Lett 2007, 48, 7618.

[26] Simon, J. G.; Janet, M. S. S. Tetrahedron Lett 2002, 43, 1969.

[27] Odlo, K.; Høydahl, E. A.; Hansen, T. V. Tetrahedron Lett 2007, 48, 2097.

[28] (a) Sreedhar, B.; Reddy, P. S.; Krishna, V. R. Tetrahedron Lett 2007, 48, 5831; (b) Chandrasekhar, S.; Basu, D.; Rambabu, Ch. Tetrahedron Lett 2006, 47, 3059.