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Multicomponent stereo and regioselective reactions of beta lactams in water: Click reaction

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ABSTRACT

Multicomponent reaction in water was used to prepare a series of triazole substituted *trans*-beta-lactams from the corresponding *trans*-4-acetoxy-lactam, sodium azide, and alkynes *via* a Cu(I)-catalyzed click chemistry with base free. This highly stereo and regioselective procedure is simple, clean and efficient. © 2013 Trade Science Inc. - INDIA

KEYWORDS

Multicomponent reaction;
Triazole;
Click reaction;
Quinoxalline;
Azetidinones.

INTRODUCTION

The introduction of beta-lactam antibiotics into the health care system in the latter stages of World War II represents one of the most important contributions to medical science in recent history. Today, beta-lactams remain the most widely utilized antibiotics owing to their comparatively high effectiveness, low cost, ease of delivery and minimal side effects. beta-lactams target transpeptidase enzymes that synthesize the bacterial cell wall. The desirable attributes of this class of antibiotic arise from the facts that these enzymes are localized to the outer leaflet of the bacterial cytoplasmic membrane (i.e. are relatively accessible) and that they are specific to bacteria (with no functional or structural counterpart in the human host)[1,2]. In a practical sense, the low cost of production of beta-lactam antibiotics allows for a wide availability; thus, it is imperative that we preserve the power of this valuable clinical resource. beta-Lactam (azetidinones) derivatives are important compounds that attract significant research interests from both synthetic and pharmaceutical areas[3,4]. The beta-lactam nucleus is considered to be a general lead-structure for the design and synthesis not only of new antibacterial products, such as carbapenems, carbacephems, and monobactams[5], but also of new inhibitors of enzymes containing a serine nucleophile in their active site, like beta-lactamases[6], human leukocyte elastase and cholesterol absorption inhibitors[7,8]. Therefore the search for new functionalized beta-lactam with potential clinical usefulness would be continued. Owing to the presence of several stereocenters whose correct configuration is crucial for pharmacological activity; there is a need for highly stereoselective syntheses of these molecules. The copper catalyzed 1,3-dipolar cycloadditions of organic azides with terminal alkynes for the synthesis of triazoles[9] has been widely used in various fields, ranging from bioorganic and medicinal chemistry to materials science for its remarkable efficiency and high regioselectivity[10,11]. Recently, a novel family of saccharide beta-lactam hybrids for lectin inhibition has been built *via* click reaction which displayed full anomer and configuration control. Nowadays, the multi-

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component reactions (MCRs) involving domino processes with at least three different simple substrates have emerged as a powerful strategy. These methodologies allow molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis. Also, the MCRs are particularly well-adapted for combinatorial synthesis. As a part of our program aiming at new approaches to diverse heterocycles, we developed a stereo- and regioselective method for the synthesis of triazole substituted beta-lactams *via* copper-catalyzed three-component click reaction of 4-acetoxy beta-lactam, sodium azide and alkynes.

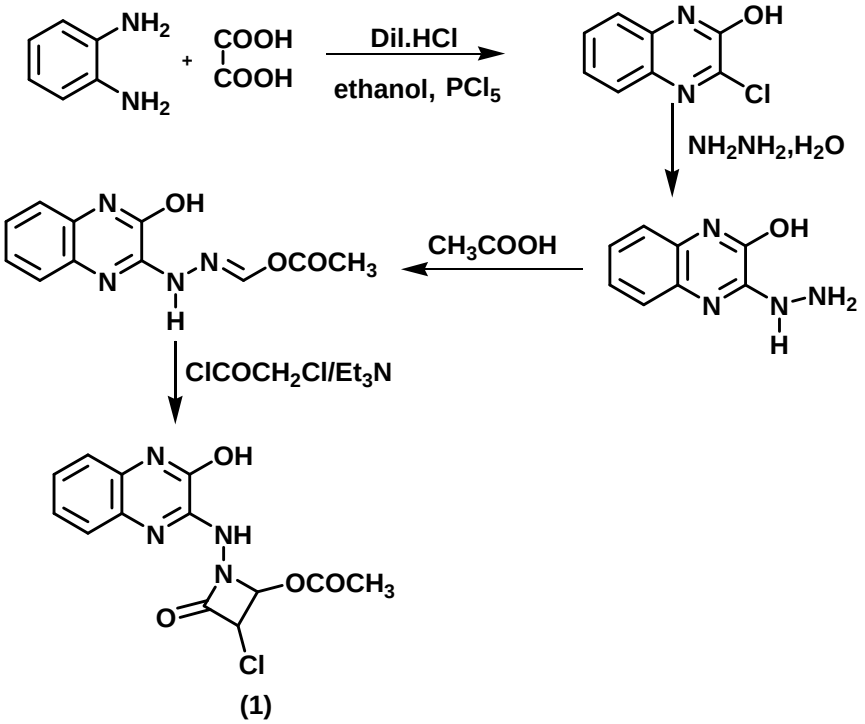
RESULTS AND DISCUSSION

Preparation of (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate:

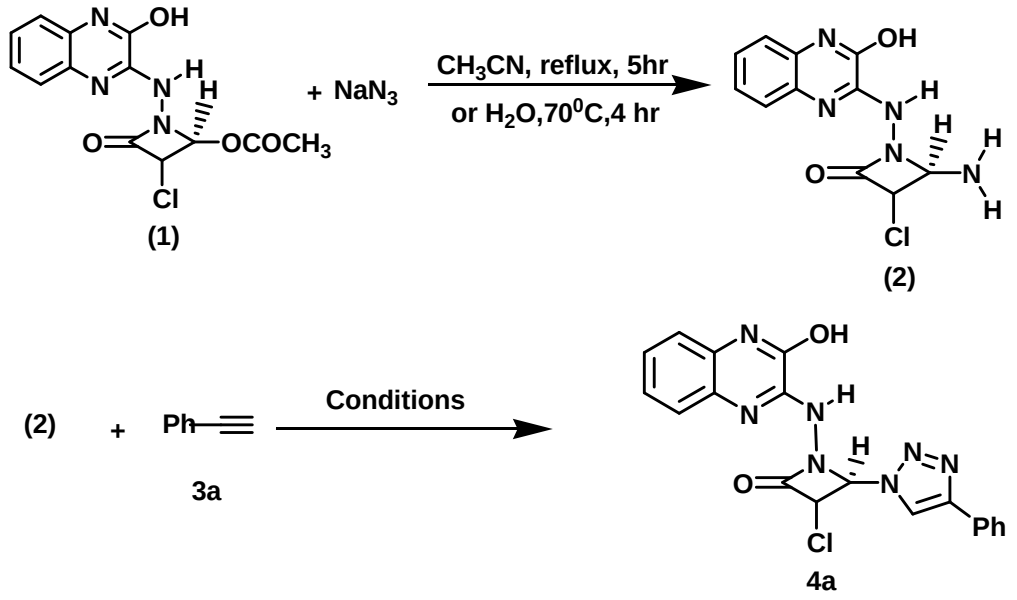
To a solution of 3-hydroxy-2(*p*-methoxy benzylidine hydrazine) quinoxaline (0.01mol) in dry dioxane was added to well stirred mixture of triethylamine (0.012mol) and chloroacetylchloride (0.012mol) and acetic acid at low temperature. The resulting solid was crystallized from chloroform-methanol mixture to give pure (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate.

Yield 60%; m.p. 147°C; IR(KBr, V_{max}, cm^{-1}) 3257(-NH str), 1759(beta-lactam ring C=O str), 1610(C=N str), 1496(-NH def), 1040(-COCH); ^1H NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 4.97 (d, 1H), 3.89 (s, 3H, -OCH_3), 6.92-7.8(m, 4H), 7.0 and 7.22 (d, 2H, quinoxaline ring protons), 8.2 (hr, 1H), 8.4(s, 1H, N=CH-) and 9.11 (s, 1H, -NH-N)ppm.

Initially, (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate (1), a convenient source of a labile azetidinone which has taken part in coupling reactions with nucleophiles leading to many novel systems of biological interest, was used to react with sodium azide in CH_3CN. We were pleased to find that 4-azide substituted *trans*- beta-lactam 2 was formed in nearly quantitative yield (Scheme 2) with 4-position stereo configuration retention. Compared with Kita's method, ZnI_2 catalyzed substitution of *trans*-4-sulfinylazetidin-2-one with 2-hydroxyl quinoxalin-3yl amino, the present method provided a practical and convenient route to (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate, which is the key intermediate of a new class of beta-lactam derivatives bearing 4-heterofunction scaffolds. Fortunately, water could be used to take place of CH_3CN as a clean medium and afforded 2 in 95% yield.



Scheme 1 : Preparation of (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate.



Scheme 2 : Sterioselective synthesis of 4-azide substituted trans beta-lactum

As we envisioned that a Cu(I)-catalyzed click reaction of 2 with terminal alkyne would lead to triazole substituted beta-lactams. Phenylacetylene 3a was used to identify the optimum reaction condition (TABLE 1). The best result was obtained in presence of a catalytic amount of CuI (5 mol%) in CH_3CN at 70°C with 95% yield (TABLE 1, entry 2). At room temperature, the reaction led to slight yield decreasing and time prolonging (TABLE 1, entry 3). Regarding to solvent, EtOH performed fairly well (TABLE 1, entries 4), while THF, CH_2Cl_2 and toluene were less effective (TABLE 1, entries 1, 5 and 6). It was also found that CuI, as the catalyst, was crucial for the reaction while CuCl worked in lower activity. It is noteworthy that the present click reaction proceeded without base addition. Most importantly, in water, the reaction successfully carried out in high yield (95%). Combined with the step for preparation of 2 in water, this result suggests a one-pot two step procedure for the synthesis of triazole substituted beta -lactams.

Although organic azides are stable against most reaction conditions, the compounds of low molecular weight or those containing several azides tend to be explosive and are difficult to handle. Thus, some procedures for the generation of azide in situ followed by azide-alkyne cycloaddition have been reported. With the success in hand, therefore, we probed a modular synthesis of triazoles applying a MCRs protocol (Scheme 3). As expected, in water without isolation of azide 2, the reaction smoothly afforded the corresponding product 4a in excellent yield (95%) in shortened time (TABLE 2, entry 1).

TABLE 1 : Optimization of conditions or click reaction.

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$ZnCl_2$	THF	7	60
2	$ZnCl_2$	DMSO	4.5	90
3	$ZnCl_2$	DMSO	15	92
4	$ZnCl_2$	CH_3CH_2OH	6.5	86
5	$ZnCl_2$	CH_2Cl_2	22	Trace
6	$ZnCl_2$	Toluene	24	Trace
7	$ZnCl_2$	DMSO	25	Trace
8	$ZnCl_2$	DMSO	24	88
9	$ZnCl_2$	H_2O	3.5	90

All reaction were carried out on a 1 mmol scale; 1.1 equiv. of 3a was used in 10 ml solvent at 70°C unless other state.

Furthermore, the crude product could be obtained by simple filtration. Inspired by these excellent results we expanded the scope of the reaction regarding the terminal alkynes which containing various functionalities. As shown in TABLE 2, all of the substrates gave clean reactions under mild conditions and tolerated functional groups, such as hydroxyl, cyclopropyl, ester, ether, amide groups. No significant difference was observed for alkynes substituted with alkyl, phenyl, electron-donating or electron-withdrawing group. The yields remained good to excellent, and regioselectivity was exclusive: only 1,4-regioisomeric products were formed.

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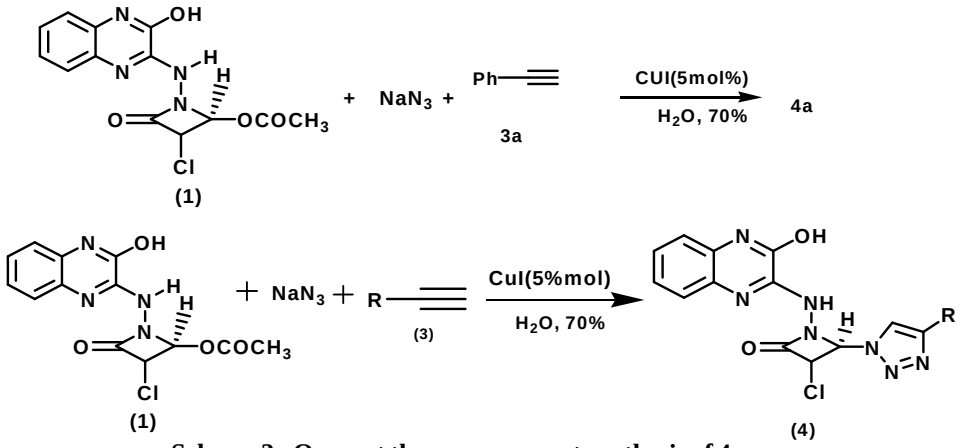
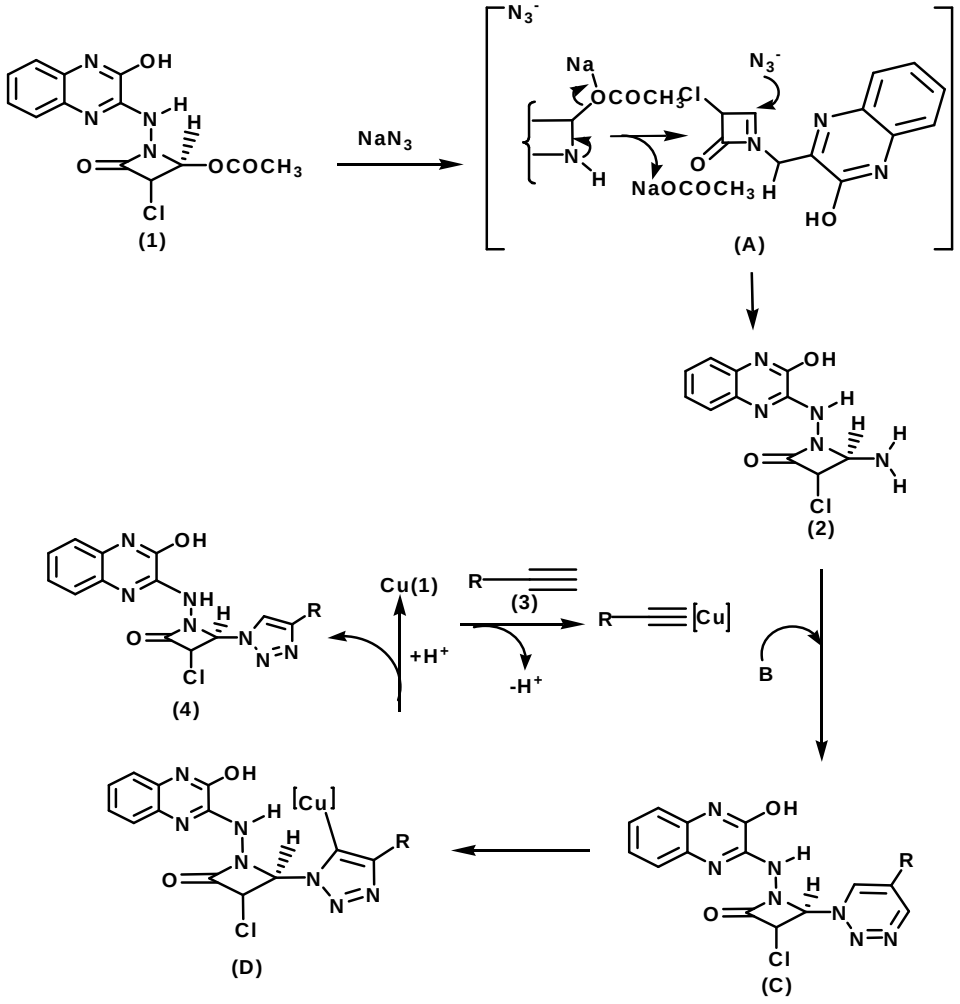
Our mechanistic proposals are depicted in Scheme 4. The nucleophilic component, NaN_3, also as a base, underwent the reaction with 1 to yield 2 *via* acyliminium intermediate (A). Subsequently, a click reaction with Cu(I) acetylide B generated from alkyne 3 in the presence of CuI as catalyst to afford triazolyl copper species D *via* metallocycle C, followed by a protonation to furnish triazole substituted beta-lactams. Herein, water appears to be an ideal solvent capable of supporting Cu(I) acetylide B in its reactive state, especially when it is formed *in situ*. So this three component reaction performed smoothly in water in high yields.

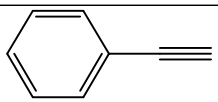
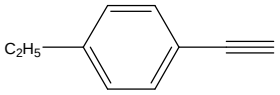
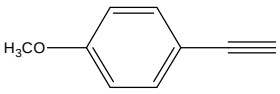
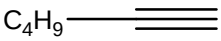
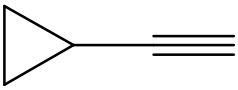
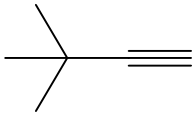
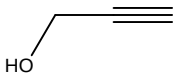
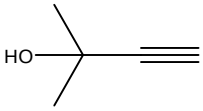
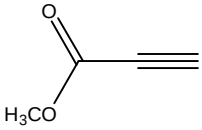
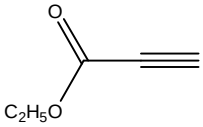
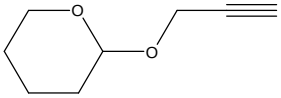
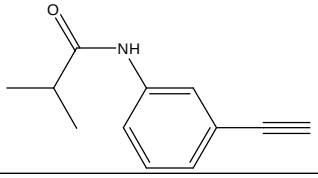


Scheme 3 : One-pot three-component synthesis of 4a.



Scheme 4 : Mechanism or the three component synthesis.

TABLE 2 : One-pot synthesis of triazole substituted beta-lactams in water from 1, sodium azide and alkynes.

Entry	Alkyne	Time (min)	Product	Yield (%)[b]
1		150	4a	93
2		150	4b	95
3		150	4c	94
4		300	4d	87
5		300	4e	85
6		300	4f	80
7		330	4g	94
8		330	4h	86
9		330	4i	83
10		330	4j	86
11		330	4k	90
12		120	4l	92

All reaction were carried out on a 1 mmol scale; equiv molar of 1, sodium azide and alkyne were used with 5 mol% CuI in 10 ml water at 70°C. [b]Isolated yield based on 1.

In conclusion, we have developed a stereo- and regioselective method for the preparation of triazole substituted *trans*- beta-lactams from *trans*-4-acetoxy beta-lactam, sodium azide and alkynes in water in high yields (88~96%). This three component procedure, *via* Cu(I)-catalyzed click reaction with base free, does not require isolation of the azide intermediates and proves to be experimentally simple and efficient.

EXPERIMENTAL

All chemicals were reagent grade and used as purchased. ^{1}H NMR spectra were recorded at 500 MHz. ^{13}C NMR spectra were recorded at 125 MHz. Optical rotations were measured on Perkin Elmer Model 341 with the solvent indicated. Melting points were measured on a WRS-1B digital melting point apparatus. Infrared spectra were recorded as thin film or in KBr. MS spectra were recorded with ESI ionization source.

Preparation of (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate

To a solution of 3-hydroxy-2(*p*-methoxy benzylidine hydrazine) quinoxaline (0.01mol) in dry dioxane was added to well stirred mixture of triethylamine (0.012mol) and chloroacetylchloride (0.012mol) and acetic acid at low temperature. The resulting solid was crystallized frem chloroform-methanol mixture to give pure (2S)-1-(2-hydroxy quinoxalin-3yl amino)-3-chloro-4-oxoazetidin-2yl acetate.

Yield 60%; m.p. 147°C; IR(KBr, V_{max}, cm^{-1})3257(-NH str),1759(beta-lactam ring C=O str), 1610(C=N str), 1496(-NH def), 1040(-COCH); ^{1}H NMR ($CDCl_3$): δ 2.69 (s, 3H, CH_3), 4.97 (d, 1H), 3.89 (s, 3H, -OCH_3), 6.92-7.8(m, 4H), 7.0 and 7.22 (d, 2H, quinoxaline ring protons), 8.2 (hr, 1H), 8.4(s, 1H, N=CH-) and 9.11 (s, 1H, -NH-N)ppm; ^{13}C NMR ($CDCl_2$): δ 165.5, 67.6, 24.1, 22.6, 19.1, -3.9,-4.8.

Representative experimental procedure for the synthesis of compound 2

In a 100ml single necked flask, the mixture of compound 1 (10 mmol, 2.87 g) and sodium azide (15 mmol, 9.75 g) in 30ml CH_3CN was stirred and refluxed for 5h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane (1:3) as eluent. After completion, CH_3CN was removed under vacuum. Then the residue was dissolved in 80ml of ethyl acetate/H_2O (5:3), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 ml). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash silica gel chromatography elut-

ing with EtOAc-ether (1:5) afforded 2.57 g of compound 2 in 95% yield.

White solid; $[\alpha]_D^{20}$: +38.0 (c 0.10, CH_3CN); m.p. 70.9-71.2°C; MS(ESI): *m/z* 292.7 [M+Na^+]; IR (KBr): 3174, 2105; 1770 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.34 (1H, br s,-NH), 5.02 (1H, s, 4-H), 4.23 (1H, m), 3.15 (1H, dd, *J* : 3.7, 1.4 Hz, 3-H), 1.23 (3H, d, *J* : 6.4Hz), 0.88 (9H, s), 0.08 and 0.01 (total 6H, each s); ^{13}C NMR ($CDCl_3$): δ 166.5, 66.7, 65.4, 64.2, 25.6, 22.6, 18.1, -4.1, -4.9.

Representative experimental procedure for the synthesis of compound 4a from compound 2

In a 25ml single necked flask, the mixture of compound 2 (270 mg, 1 mmol), phenylacetylene (112 mg, 1.1 mmol) and CuI (0.05 mmol, 9.6 mg) in 10ml H_2O was stirred at 70°C under N_2 The progress of the reaction was monitored by TLC using ethyl acetate/hexane (1:3) as eluent. After completion the reaction, the crude product was obtained by filtration and was purified by flash silica gel chromatography eluting with EtOAc-ether (1:5) afforded 353mg of compound 4a in 95% yield. m.p. 114.6-115.4°C; MS(ESI): *m/z* 407.09(100%), 409.09(32.9%), 408.09(23.2); IR (KBr): 3315, 1794, 1768, 1646, 1555, 1464cm^{-1}; ^1H NMR: δ 7.68(CH),5.9(H),5(OH); ^{13}C NMR: δ 125.5, 126.6, 137.5, 136.2; Elemental Anal. C,15.96; H,3.46; Cl,8.69; N,24.04; O,7.85.

Representative experimental procedure for one-pot synthesis of compound 4a from compound 1 in water

In a 25ml single necked flask, the mixture of compound 1 (287 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), sodium azide 2 (1 mmol, 65 mg) and CuI (0.05 mmol, 9.6 mg) in 10ml H_2O was stirred at 70°C under N_2. The progress of the reaction was monitored by TLC using ethyl acetate/hexane (1:3) as eluent. After completion the reaction, the crude product was obtained by filtration and was purified by flash silica gel chromatography eluting with EtOAc-ether (1:5) afforded 354mg of 4a in 95% yield.

(a) Compound 4b

Yield 95%; m.p. 51.8°C; MS(ESI): *m/z* 435.12(100%), 437.12(32.6%), 436.12(25.3%); IR (KBr): 3448, 2960, 1786, 1259, 846 cm^{-1}; ^1H NMR: δ 7.68 (CH), 5.9 (H), 5 (OH); ^{13}C NMR: δ 137.5, 125.5, 32.4, 14.6; Elemental Anal. C, 57.87; H, 4.16; N, 22.49; O, 7.34; Cl, 8.13.

(b) Compound 4c

Yield 94%; m.p. 147.6-148.9°C; MS(ESI): *m/z* 437.10(100%), 439.10(33.1%), 438.10 (24.3%); IR (KBr): 3384, 2958, 1778, 1254, 830 cm^{-1}; ^1H NMR: δ 7.71-7.73 (CH), 5.9 (H), 5 (OH), 3.73 (CH_3); ^{13}C NMR: δ 137.5, 125.5, 55.9; Elemental Anal. C, 54.86; H, 3.68; Cl, 8.10; N, 22.39; O, 10.96.

(c) Compound 4d

Yield 87%; m.p. 70.6-71.1°C; MS(ESI): *m/z* 387.12(100%), 389.12(32.5%), 388.12(21.0%); IR (KBr): 3209, 1778, 1750, 1358cm^{-1}; ^1H NMR: δ 7.68-8.07 (CH), 5.9 (H), 5 (OH), 1.33 (CH_2), 0.96 (CH_3); ^{13}C NMR: δ 137.5, 125.5, 32.7, 14.1; Elemental Anal. C, 52.65; H, 4.68; Cl, 9.14; N, 25.28; O, 8.25.

(d) Compound 4e

Yield 85%; m.p. 133.0-133.7°C; MS(ESI): *m/z* 371.09(100%), 373.09(32.8%), 372.09(20.0%). IR (KBr): 3448, 1783, 1652, 1558, 1341cm^{-1}. ^1H NMR: δ 7.68 (CH), 5.9 (H), 5 (OH), 0.63=0.38 (CH_2).^{13}C NMR: δ 137.5, 125.5, 8.2; Elemental Anal. C, 51.69; H, 3.80; N, 26.37; Cl, 9.54; O, 8.61.

(e) Compound 4f

Yield 80%; m.p.133.8-134.5°C; MS(ESI): *m/z* 387.12(100%), 389.12(32.5%), 388.12(21.0%); IR (KBr): 2961, 2936, 1780, 1047, 846 cm^{-1}; ^1H NMR: δ 7.68-8.07 (CH), 5.9 (H), 5 (OH), 1.4(CH_3); ^{13}C NMR: δ 137.5, 125.5, 31.1; Elemental Anal. C, 52.65; H, 4.68; Cl, 9.14; N, 25.68; O, 8.25.

(f) Compound 4g

Yield 94%; m.p. 124.0-125.8°C; MS(ESI): *m/z* 361.07(100%), 363.07(33.0%), 362.07(17.8%); IR (KBr): 3392, 1777, 1445, 1142 cm^{-1}; ^1H NMR: δ 7.68-8.07 (CH), 5.9 (H), 5 (OH), 4.79 (CH_2); ^{13}C NMR: δ 137.5, 125.5, 59.5; Elemental Anal. C, 46.48; H, 3.34; Cl, 9.80; N, 27.10; O, 13.27.

(g) Compound 4h

Yield 86%; m.p. 137.3-137.9°C; MS(ESI): *m/z* 389.10(100%), 391.10(33%), 390.10(20%). IR (KBr): 3217, 1776, 1752 cm^{-1}; ^1H NMR: δ 7.68 (CH), 5.9 (H), 5 (OH), 1.54 (CH_3). ^{13}C NMR: δ 137.5,

125.5, 31.4; Elemental Anal. C, 49.30; H, 4.14; Cl, 9.10; N, 25.15; O, 12.31.

(h) Compound 4i

Yield 83%; m.p. 139.4-140.6°C; MS(ESI): *m/z* 389.06(100%), 391.06(32.4%), 390.07(16.5%); IR (KBr): 2951, 1788, 1745, 1374, 1214, 1042 cm^{-1}; ^1H NMR: δ 7.68 (CH), 5.9 (H), 5 (OH), 3.88 (CH_3); ^{13}C NMR: δ 137.5, 125.5, 51.5; Elemental Anal. C, 46.22; H, 3.10; Cl, 9.10; N, 25.16; O, 16.42.

(i) Compound 4j

Yield 86%; m.p. 142.1-143.9°C; MS(ESI): m/z 403.08(100%), 405.08(33.2%), 404.08(20.0%); IR (KBr): 2936, 1790, 1739, 1209, 1040 cm-1; ^1H NMR: δ 8.07 (CH), 5.9 (H), 5 (OH), 4.29 (CH_2), 1.30 (CH_3). ^{13}C NMR: δ 137.5, 125.5, 60.9, 14.1; Elemental Anal. C, 47.59; H, 3.49; Cl, 8.78; N, 24.28; O, 15.85.

(j) Compound 4k

Yield 90%; m.p. 79.1-80.9°C; MS(ESI): *m/z* 445.13(100%), 447.12(32.0%), 446.13(20.9%); IR: 3262, 2951, 1788, 1462, 1132, 832 cm^{-1}; ^1H NMR: δ 7.68 (CH), 5.9 (H), 5 (OH), 3.60 (CH_2); ^{13}C NMR: δ 137.5, 125.5, 63.2; Elemental Anal. C, 51.18; H, 4.52; Cl, 7.95; N, 21.99; O, 14.35.

(k) Compound 4l

Yield 92%; m.p. 95.1-97.2°C. MS(ESI): *m/z* 492.14(100%), 494.14(32.7%) 493.15(25.2%); IR (KBr): 3317, 2958, 2930, 1775, 1376, 1252cm^{-1}; ^1H NMR: δ 8.0(NH), 7.68(CH), 5.9 (H), 5 (OH), 1.19 (CH_3); ^{13}C NMR: δ 137.5, 125.5, 19.7; Elemental Anal. C, 56.04; H, 4.29; Cl, 7.19, N, 22.73; O, 9.74.

(l) Compound 6

Yield 93%; White solid; $[\alpha]_D^{20}$ +73.5 (c 0.10, CH_3CN); m.p.184.0-184.2°C; MS (ESI): *m/z* 309.2[M+Na^+], 287.2[M+H^+]; IR (KBr): 3448, 2960, 1786, 1259, 846 cm^{-1}; ^1H NMR: (*d*6 -DMSO): δ 9.04 (1H, br s, -NH), 8.87 (1H, s), 7.78 (2H, d, *J* = 7.9), 7.29 (2H, d, *J* = 7.9), 6.15 (1H, s, 4-H), 5.19 (1H, -OH), 4.05 (1H, m), 3.64 (1H, m, 3-H), 2.61-2.66 (q, 2H, *J* = 7.5Hz), 1.17-1.22 (6H, m); ^{13}C NMR: (*d*6-DMSO): δ 167.0, 147.5, 144.2, 128.7, 128.4, 125.7, 119.8, 67.2, 63.5, 63.3, 28.4, 22.1, 15.9; Elemental Anal. C, 62.92; H, 6.34; N, 19.57. Found: C, 62.81; H, 6.38; N 19.61.

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