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Graphical Abstract

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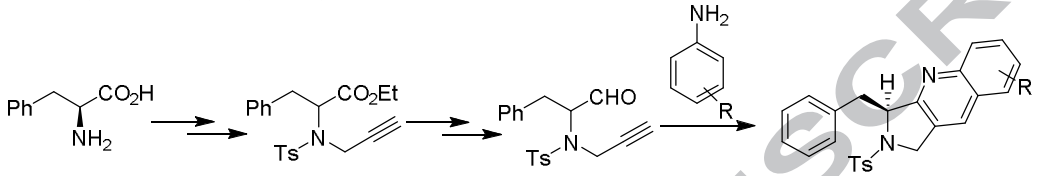

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Straightforward synthesis of pyrrolo[3,4-*b*]quinolines through intramolecular Povarov reactions

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ABSTRACT

A series of novel pyrrolo[3,4-*b*]quinolines have been synthesized from *N*-alkynyl aldehydes and various substituted arylamines in good to excellent yields utilising an intramolecular Povarov reaction catalyzed by boron trifluoride diethyl etherate as the key final step.

The quinoline nucleus is one of the most prevalent heterocyclic scaffolds and is found in several bio-active natural products.[1] Compounds with the quinoline sub-structure play a unique role in drug discovery programs and have been found to exhibit a wide range of pharmaceutical activities such as antimalarial,[2] antiprotozoal,[3] antitubercular,[4] anti-HIV,[5] antibacterial,[6] antifungal[7] and anticancer.[8] Quinoline derivatives also act as fluorophores[9] and have been studied as potential organic semiconductors.[10] Furthermore, its derivatives such as quinine have been reported to exhibit antipyretic activity[11] as well as being found a large number of drugs such as the fluoroquinolone antibacterials *viz*. Ciprofloxacin[12] and levofloxacin.[13]

Owing to its importance in multidisciplinary fields, much effort has been devoted to develop efficient and convenient strategies for the synthesis of quinoline derivatives. Classical methods, such as the Skraup,[14] Combes,[15] Friedlander,[16] Pfitzinger[17] and Doebner-von Miller[18] reactions have been frequently employed. However, they typically do not allow the formation of quinolines with wide diversity.

The Povarov reaction,[19–21] is an inverse electron-demand aza-Diels-Alder (IED-DA) reaction of *N*-aryl imines, derived from aldehydes and anilines, with electron-rich olefins, which has become one of the most efficient protocols for the synthesis of quinolines. _____

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The reaction has gained considerable recent attention as it allows the construction of tetrahydroquinolines using multicomponent reaction methodology in the presence of protic and Lewis acids. 2,4-Disubsititued quinolines have been synthesized by several research groups using alkynes as dienophiles using the Povarov reaction followed by either an aerobic oxidation or by using an additional oxidant. The substrate imines are known to act as an oxidant to produce quinolines from di- and tetra-hydroquinolines, giving the corresponding amine as a byproduct.[22] The synthesis of quinolines *via* the Povarov reaction and a subsequent hydrogen transfer reaction using triflic imide as an auto tandem catalyst has been reported by Takasu and co-workers.[23]

The anticancer alkaloids camptothecin and luotonin A and their semi-synthetic analogs topotecan and irinotecan[24,25] each contain the pyrrolo[3,4-*b*]quinoline moiety (Figure 1). The intramolecular Povarov reaction has been utilized by Stevenson and co-workers for the synthesis of luotonin A[26] and by Batey and co-workers for the syntheses of the pyrrolo[3,4-*b*]quinoline core of camptothecin and the total synthesis of luotonin A.[27] Despite this precedent, the intramolecular Povarov reaction is relatively unexploited in the literature. In recent years, our research group has largely been involved in the synthesis of hybrid bioactive heterocycles using inter/intramolecular cycloaddition methodology.[28-30] With this synthetic background, and our aim for the synthesis of luotonin inspired heterocyclic hybrids, herein we describe the first synthesis of 3-benzyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*] quinolone derivatives, a key

intermediate for the synthesis of D-ring modified luotonin inspired heterocyclic hybrids using the intramolecular Povarov reactions.

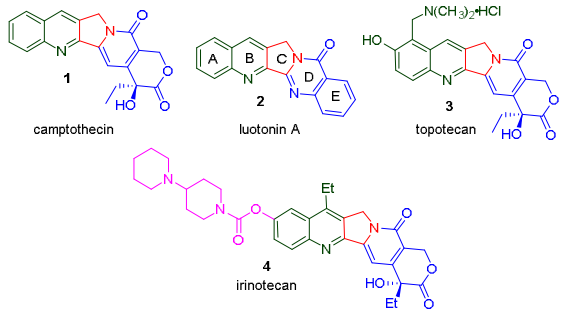
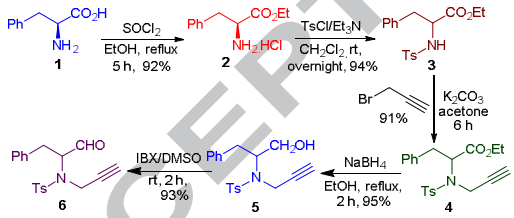


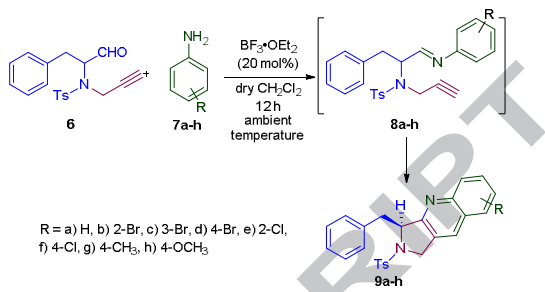
Figure1. Promising anti-cancer leads related to the alkaloids camptothecin and luotonin A

The intramolecular Povarov reaction requires a strategically positioned aldehyde functional group tethered to an alkynyl component. Hence, for the construction of pyrrolo[3,4-*b*] quinolines, an alkynyl-tethered aldehyde is necessary. Consequently, our synthetic work began with the inexpensive, readily available chiral pool precursor (*S*)-phenylalanine **1**, which was subjected to the sequence of transformations outlined in Scheme 1. Thus, (*S*)-phenylalanine **1** was converted into its ethyl ester hydrochloride **2** by treatment with an excess of thionyl chloride in dry ethanol.[31] The hydrochloride salt of the phenylalanine ester was protected as the *N*-sulfonylester **3** in good yield,[32] which was then subjected to *N*-alkylation using propargyl bromide to obtain *N*-propargyl ester **4** in excellent yields (Scheme 1). The structure of *N*-propargyl ester **4** was confirmed from NMR spectroscopic data.[33] A two-step sequence involving reduction of the ester to an alcohol and the subsequent oxidation was adopted to obtain aldehyde **6**. Thus, reduction using 2 equiv. of sodium borohydride in ethanol afforded alcohol **5** in 95% yield, which was converted into cyclisation precursor **6** in quantitative yield using iodoxybenzoic acid (IBX) (Scheme 1). The structures of alcohol **5** and aldehyde **6** were confirmed through spectroscopic analysis.



Scheme 1. Synthesis of *N*-alkynyl aldehyde **6**

Having synthesized aldehyde **6** in good yield, an intermolecular Povarov reaction was performed for the synthesis of a series of hybrid heterocycles **9a-h** (Scheme 2). For optimization studies, this reaction was initially investigated by the reaction of an equimolar mixture of aldehyde **6** and *p*-toluidine **7g** in the presence of Lewis acid catalysts such as $InCl_3$, $InBr_3$, CAN and $Yb(OTf)_3$ in acetonitrile at 70 °C for 12 hours. In all these reactions, less than 5% of product **9g** was obtained along with a mixture of inseparable by-products. Extending the reaction time to 48 hours resulted in a small increase in yield (22%) using $Yb(OTf)_3$, whilst there was no appreciable increase in yield using $InCl_3$, $InBr_3$ and CAN. The reaction was then attempted using boron trifluoride diethyl etherate ($BF_3.OEt_2$, 20 mol%) in dry CH_2Cl_2 containing molecular sieves at ambient temperature for 12 h. Under these conditions, the reaction afforded **9g** in 94% yield,[34] while the same reaction in acetonitrile gave only 68% yield. Thus, $BF_3.OEt_2$ in dry CH_2Cl_2 was selected as the optimal catalyst-solvent combination. Subsequent reactions aimed at expansion of the reaction scope were carried out using the optimized conditions, affording products **9a-h** in excellent yields (92-97%, Table 1).



Scheme 2: Synthesis of pyrrolo[3,4-*b*]quinolines

Table 1. Synthesis of pyrrolo[3, 4-*b*]quinolines (**9a-h**)

Entry	Product	R	Yield (%)[a,b]	mp (°C)
1	**9a**	H	92	164-166
2	**9b**	2-Br	93	188-190
3	**9c**	3-Br	95	176-178
4	**9d**	4-Br	97	189-191
5	**9e**	2-Cl	95	187-189
6	**9f**	4-Cl	96	200-202
7	**9g**	4-CH_3	94	198-200
8	**9h**	4-MeO	92	180-191

[a]Isolated yield after purification by column chromatography. [b]Conditions: $BF_3.OEt_2$, 20 mol%, 12 h, ambient temperature

The structures of compounds **9a-h** were confirmed by ^1H and ^{13}C NMR spectral analysis. Furthermore, the structures of **9e** and **9f** were unambiguously corroborated by single crystal X-ray diffraction analysis[35] and ORTEP diagrams with all atom labels are shown in Figure 1. X-ray analysis yielded a monoclinic, crystal lattice with P21/c and C2/c space groups, respectively. The pyrrolo[3,4-*b*]quinoline ring was almost planar, however the two aryl rings attached to pyrrolo[3,4-*b*]quinoline moiety were tilted. The dihedral angles between the aryl ring (C13-C18) and the pyrrolo[3,4-*b*]quinoline (C1-C9/N2/C10-C11) were found to be 51.13° and 67.38° in compounds **9e** and **9f**, respectively. The methyl-aryl ring (C19-C24) showed a dihedral angle of 88.81° and 88.70° for the pyrrolo[3,4-*b*]quinoline (C1-C9/N2/C10-C11) in the compounds **9e** and **9f**, respectively. The crystal structure in compound **9e** was found to be stabilized by intra/intermolecular hydrogen bonding C12—H12B•••O2, C20—H20A•••O1, C24—H24A•••O2 and C23—H23A•••O1, whereas the crystal structure of compound **9f** was stabilized by C12—H12B•••O2, C24—H24A•••O2 and C25—H25C•••O2 hydrogen bonding.

A plausible mechanism for the formation of compounds **9** is depicted in Scheme 3. The *N*-tethered propargyl aldehyde **6** reacts with the arylamine **7** to form arylimine **8**, which then undergoes a formal [4+2] cycloaddition to form a dihydroquinoline intermediate, which undergoes oxidative aromatisation in air to afford the pyrrolo[3,4-*b*]quinolone **9**.

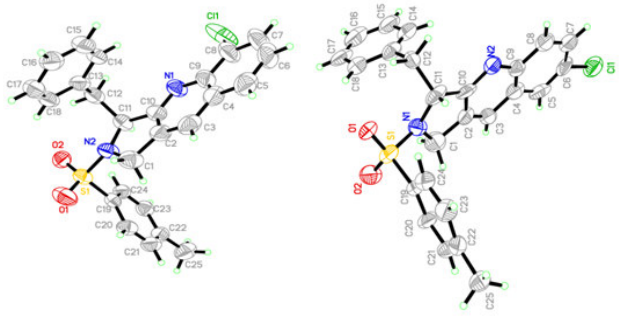
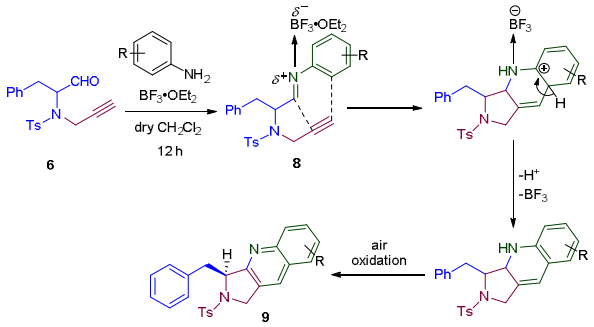


Figure 1. ORTEP diagram of **9e** and **9f**



Scheme 2. Plausible mechanism for the formation of pyrrolo-[3,4-*b*]quinolines **9**

In conclusion, *N*-alkynylaldehyde **6** was obtained in five steps in good yield from readily available (*S*)-phenylalanine. The $BF_3.OEt_2$ catalyzed intramolecular Povarov reaction of **6** with various substituted arylamines afforded a series of pyrrolo[3,4-*b*]quinolines in excellent yields. To the best of our knowledge, this is the first report for the preparation of 3-benzyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*] quinolines, which are key intermediates for the synthesis of D-ring modified luotonin inspired heterocyclic hybrids.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://

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33. Preparation of (*S*)-ethyl 2-(4-methyl-N-(prop-2-yn-1-yl)phenylsulfonamido)-3-phenyl-propanoate, **4** To a solution of (*S*)-ethyl 2-(4-methylphenylsulfonamido)-3-phenylpropanoate (**5 g**, 0.144 mol) in dry acetone (40 mL) under nitrogen atmosphere was added K_2CO_3 (6.95 g, 0.054 mole). To this stirred solution, propargyl bromide (2.57 g, 0.215mol) in dry acetone (10 mL) was added and the stirring was continued for 8–10 h. After completion of the reaction, the solid was filtered and the residue was washed with acetone (3 ×15 mL) and before the filtrate was concentrated in *vacuo* and extracted with CH_2Cl_2 (30 mL) and water (30 mL). The organic extract was washed with a brine solution (50 mL × 2) and concentrated under reduced pressure. The crude product was subjected to flash column chromatography eluting with hexane–ethyl acetate mixture (9:1) to obtain pure. *(S)-ethyl 2-(4-methyl-N-(prop-2-yn-1-yl)phenylsulfonamido)-3-phenylpropanoate*, **4** 5.05 g, 91%, white solid, mp: 112-114 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.06 (t, *J* = 6.96 Hz, 3H), 2.18 (s, 1H), 2.40 (s, 3H), 3.05 (dd, *J* = 13.92, 7.32 Hz, 1H), 3.30 (dd, *J* = 13.96, 8.8 Hz, 1H), 3.94-4.02 (m, 2H), 4.25-4.26 (m, 2H), 4.75 (t, *J* = 8.08 Hz, 1H), 7.19-7.65 (m, Ar-H, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.3, 22.0, 34.6, 37.2, 61.4, 61.8, 73.4, 79.6, 127.3, 128.2, 129.0, 129.7, 129.8, 137.0, 137.2, 143.0, 170.7 ppm. LC/MS (ESI): 386 (M^+); Anal.Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63%. Found: C, 65.54; H, 6.11; N, 3.73%.
34. General procedure for synthesis of pyrrol[3,4-*b*]quinolines, **9a-h** To (*S*)-4-methyl-*N*-(1-oxo-3-phenylpropan-2-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**6**) (100 mg, 0.29 mmol) in dry CH_2Cl_2 was added *p*-toluidine **7g** (27 mg, 0.29 mmol) followed by added $BF_3.OEt_2$ (20 mol%). The reaction mixture was stirred for 12 h at ambient temperature. Upon completion of the reaction as evident by TLC analysis, the solvent was removed under reduced pressure. The crude product was purified by column chromatography eluting with hexane:ethyl acetate mixture (8.5:1.5) to obtain 3-benzyl-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline in good yield. Characterization data for representative compounds *3-benzyl-7-methyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinoline*, **9g**: (118 mg, 94%); Colorless crystals.^1H NMR (400 MHz, $CDCl_3$): δ_H 2.30 (s, 3H), 2.48 (s, 3H), 3.49 (dd, *J* = 13.20, 2.92 Hz, 1H), 3.60 (dd, *J* = 13.20, 5.12 Hz, 1H), 4.05 (d, *J* = 14.68 Hz, 1H), 4.50 (d, *J* =14.64 Hz, 1H), 5.28-5.29 (m, 1H), 6.90-7.97 (m, Ar-H, 13H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.42, 21.48, 41.36, 51.64, 65.95, 126.18, 126.62, 127.21, 127.67, 128.42, 128.54, 128.72, 129.86, 130.11, 130.57, 131.88, 134.77, 135.95, 136.56, 143.69, 146.62, 160.06 ppm. LC/MS (ESI): 429 (M+1); Anal.Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54%. Found: C, 72.96; H, 5.55; N, 6.66%.
35. Crystallographic data (including structure factors) for the compounds **9e** and **9f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1046773-1046776. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].