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Apparent Carbon Monoxide Insertion *via* Double Isocyanide Incorporation during Palladium-Catalyzed Construction of Indoloquinoline Ring in a Single Pot: Synthesis of New Cytotoxic Agents

Suresh Babu Nallapati,[a,b] Bagineni Prasad,[a] B. Yogi Sreenivas,[a] Rajnikanth Sunke,[a] Y. Poornachandra,[c] C. Ganesh Kumar,[c] B. Sridhar,[d] S. Shivashankar,[a] K. Mukkanti,[b] and Manojit Pal[a,*]

[a] Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad – 500 046, India
E-mail: manojitpal@rediffmail.com
[b] Institute of Science and Technology, JNT University Hyderabad, Hyderabad – 500085, India
[c] Chemical Biology Laboratory, Med Chem and Pharmacology Division, CSIR-IICT, Tarnaka, Hyderabad – 500007, India
[d] X-ray Crystallography Division, CSIR-IICT, Tarnaka, Hyderabad – 500007, India

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Abstract: The formation of an amide bond *via* incorporation of two isocyanide units during a palladium-catalyzed construction of the indoloquinoline ring afforded *N*-substituted 6*H*-indolo[2,3-*b*]quinoline-11-carboxamides as new cytotoxic agents. The solvent and base play a key role in the selective and unprecedented synthesis of this class of amides.

Keywords: amides; cytotoxic agents; indoloquinolines; isocyanides; palladium

Due to the carbene-like reactivity of their divalent carbon atom, isocyanides have emerged as remarkably useful building blocks in organic synthesis. Thus, the development of new strategies based on isocyanide insertion that allows the rapid build-up of molecular complexities is of particular interest.[1]

Heteroaryl carboxamides are an attractive class of small molecules because of their interesting pharmacological properties. For example, a series of cyclic amines has been explored as modulators of 11βHSD1 for the potential treatment of diabetes, obesity and other related diseases.[2a] Specifically, the cyclohexyl amide derivatives have been explored as corticotropin releasing factor (CRF-1) receptor antagonists for the treatment or prevention of gastrointestinal disorders including irritable bowel syndrome, inflammatory bowel diseases, etc.[2b] Indeed, the usefulness of the cyclohexyl amide moiety is best represented by the approved drug SB-277,011A (Figure 1) that acts as a potent and selective dopamine D_3 receptor antagonist useful for the treatment of drug addiction.[2c] Notably, recent studies have indicated that dopamine receptor antagonists might be useful for the potential treatment of cancer.[3a,b]

The 11-arylamino-substituted 6*H*-indolo[2,3-*b*]quinolines (**A**, Figure 1) on the other hand showed promising cytotoxic properties against a number of cancer cell lines (breast, lung and CNS).[3c] It was therefore intriguing to know the potential medicinal value of the newly designed framework **B** containing a cyclohexyl amide moiety as well as the structural features of **A** and SB-277,011A (Figure 1).

The preparation of amides[4] based on **B** appeared to be challenging. Moreover, a direct and straightforward strategy leading to **B** was desirable for the quicker access to a library of target compounds. Recently we have reported the construction of the indolo[2,3-*b*]quinoline ring possessing an amine moiety at C-11 (Scheme 1).[5]

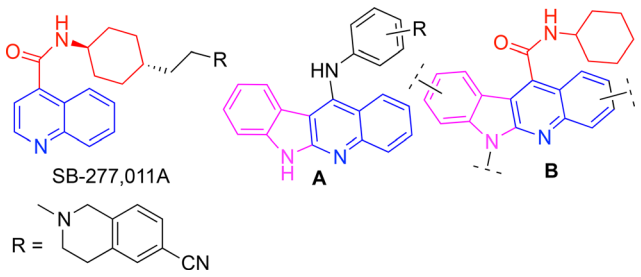
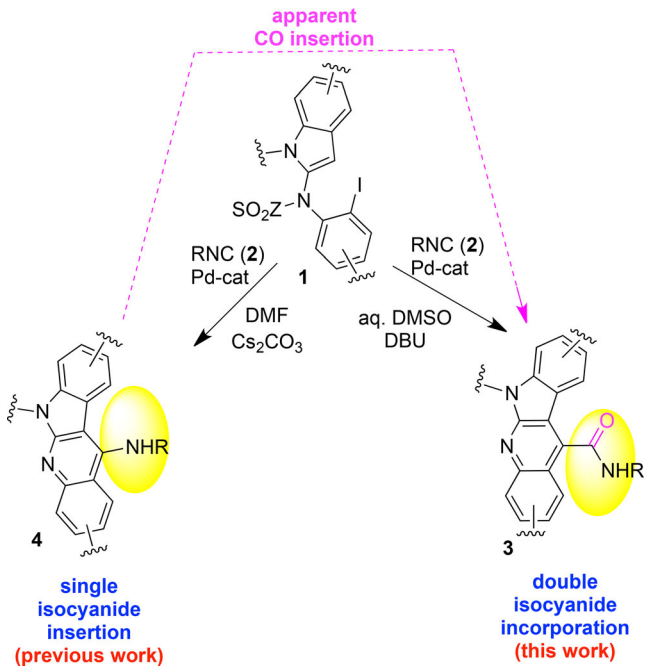


Figure 1. Known drug SB-277,011A, the cytotoxic agent **A** and the proposed new molecules **B**.

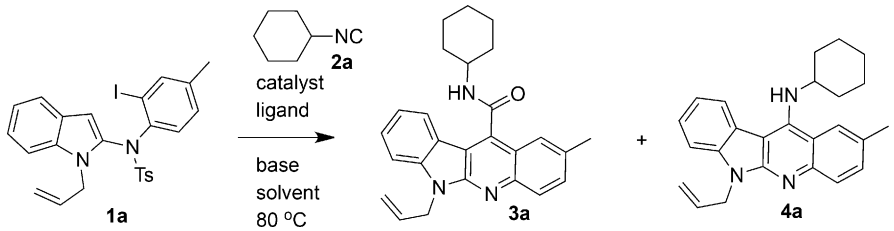


Scheme 1. Pd-catalyzed isocyanide insertion based strategy leading to **3** and **4**.

A Pd-catalyzed isocyanide insertion followed by a nucleophilic attack involving the indole C-3 and *N*-desulfonylation were key steps in this reaction. We wondered if any of these steps could be influenced to alter the product formation. Indeed, we have observed that changes of base and solvent afforded **3** (*cf,* **B**) instead of **4** as the result of a double incorporation of isocyanide units. This was remarkable as apparently a "C=O" group was inserted into the C-11–N bond of **4** without using CO gas or CO-containing agents.[6] While cascade reactions involving double isocyanide insertion[7,8] are known, a similar approach that allows apparent insertion of a "C=O" group into a C–N bond thereby creating an amide moiety is not known. Herein we report an isocyanide insertion-based, unprecedented strategy leading to **3** in a single pot (Scheme 1) along with an *in vitro* pharmacological evaluation of the compounds synthesized.

Our initial challenge was to establish the appropriate reaction conditions for accessing **3** preferentially over **4**. In our previous study,[5] two reactions were performed using isocyanocyclohexane (**2a**) when the desired products belonging to type **4** were obtained (in moderate yields) along with a side product. To study this further, we performed the reaction of **1a**[5]

Table 1. Optimization of the reaction conditions.[a]



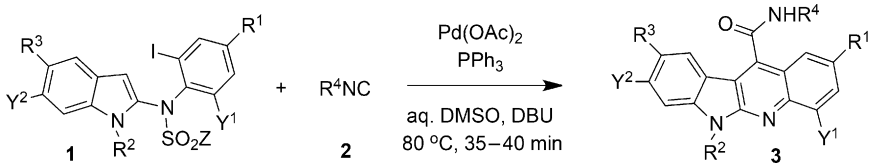
Entry	Catalyst/Ligand	Base	Solvent	Time [h]	Yield [%][b]	
					3a	**4a**
1	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	DMF	5	34	26
2	$Pd(OAc)_2$/Xantphos	Cs_2CO_3	DMF	5	30	18
3	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	DMSO	5	38	24
4	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	MeCN	4	20	14
5	$Pd(OAc)_2/PPh_3$	DIPEA	DMF	6	–	40
6	$Pd(OAc)_2/PPh_3$	K_2CO_3	DMF	5	–	52
7	$Pd(OAc)_2/PPh_3$	K_2CO_3	DMSO[c]	5	40	15
8	$Pd(OAc)_2/PPh_3$	DBU	DMSO[c]	35 min	78	–
9	$Pd(OAc)_2$/X-Phos	DBU	DMSO[c]	2	58	–
10	$Pd(OAc)_2/PPh_3$	DBU	DMF	45 min	62	–
11	$Pd(OAc)_2/PPh_3$	DBU	THF	4	52	–
12	$Pd(OAc)_2/PPh_3$	DBU	MeCN	4	54	–
13	$PdCl_2/PPh_3$	DBU	DMSO[c]	3	62	–
14	$Pd(PPh_3)_2Cl_2/PPh_3$	DBU	DMSO[c]	2	56	–
15	$Pd(OAc)_2/PPh_3$	DBU	DMSO[c]	5[d]	50	–

[a] *Reaction conditions:* **1a** (1 mmol), **2a** (3 mmol), catalyst (5 mol%) ligand (10 mol%) and base in a solvent (2.0 mL) at 80 °C.
[b] Isolated yield.
[c] 5% aqueous DMSO was used.
[d] The reaction was performed at room temperature.

with **2a** under various conditions (Table 1). The reaction carried out in the presence of $Pd(OAc)_2$-PPh_3 or $Pd(OAc)_2$-Xantphos and Cs_2CO_3, at 80 °C in DMF afforded both products **3a** and **4a** in low yields (entries 1 and 2, Table 1). The change of solvent (entries 3 and 4, Table 1) or base (entries 5 and 6, Table 1) did not improve the yield or give better product selectivity. Notably, the use of K_2CO_3 in 5% aqueous DMSO afforded **3a** as a major product albeit in 40% yield (entry 7, Table 1). While **4a** was obtained in 15% yield in this case, its formation was suppressed when K_2CO_3 was replaced by DBU (entry 8, Table 1). Indeed, the reaction was completed within 35 min and the yield of **3a** was increased dramatically. We were delighted with this observation and continued our study to achieve further improvement in product yield. While product selectivity was maintained when DBU was used as a base the yield of **3a** was decreased with the change of ligand (entry 9, Table 1), solvent (entries 10–12, Table 1), Pd catalyst (entries 13 and 14, Table 1) or temperature (entry 15, Table 1). The role of Pd catalyst and DBU was also examined in the absence of which the reaction did not proceed. Indeed, replacing $Pd(OAc)_2$ with $Cu(OAc)_2$ failed to produce any product indicating the need of a Pd catalyst for the reaction to proceed. The role of water was confirmed by performing the reaction in dry DMSO that afforded poor yields of **3a**. Notably, an increase of the water content from 5% to 10% did not improve the yield beyond the 78% of entry 8 (Table 1). Overall, the combination of $Pd(OAc)_2$-PPh_3-DBU in 5% aqueous DMSO at 80 °C (entry 8, Table 1) was found to be optimal for the synthesis of **3a**.

The substrate scope and generality of the present Pd-catalyzed cascade reaction was assessed by synthesizing a large number of *N*-substituted 6*H*-indolo[2,3-*b*]quinoline-11-carboxamide derivatives (**3**) (Table 2). To fulfil our goal, mostly *N*-cyclohexyl analogues

Table 2. Pd-catalyzed synthesis of *N*-substituted 6*H*-indolo[2,3-*b*]quinoline-11-carboxamide derivatives (**3**).[a] (see also Table S-2 in the Supporting Information).

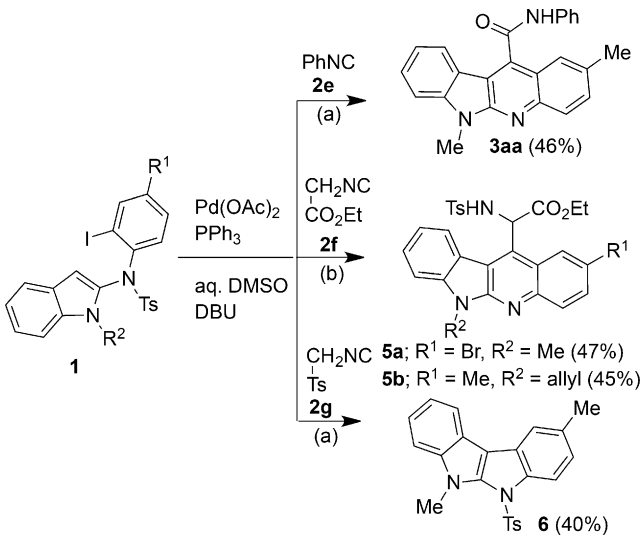


Entry	Compound (**1**): R^1, R^2, R^3, Z, Y^1, Y^2	Compound (**2**): R^4	Product (**3**)	Yield [%][b]
1	(**1a**): Me, allyl, H, *p*-tolyl, H, H	(**2a**): cyclohexyl	**3a**	78
2	(**1b**): Br, allyl, H, *p*-tolyl, H, H	**2a**	**3b**	72
3	(**1c**): Cl, Me, H, Me, H, H	**2a**	**3c**	69
4	(**1d**): Me, Me, H, Me, H, H	**2a**	**3d**	75
5	(**1e**): F, allyl, H, Me, H, H	**2a**	**3e**	70
6	(**1f**): F, allyl, OMe, Me, H, H	**2a**	**3f**	67
7	(**1g**): Cl, allyl, H, Me, H, H	**2a**	**3g**	64
8	(**1h**): Me, allyl, OMe, *p*-tolyl, H, H	**2a**	**3h**	65
9	(**1i**): H, allyl, H, *p*-tolyl, H, H	**2a**	**3i**	68
10	(**1j**): Me, *i*-Pr, H, *p*-tolyl, H, H	**2a**	**3j**	64
11	(**1k**): Cl, allyl, F, *p*-tolyl, H, H	**2a**	**3k**	69
12	**1a**	(**2b**): *n*-pentyl	**3l**	80
13	**1d**	**2b**	**3m**	74
14	(**1l**): F, allyl, H, *p*-tolyl, H, H	**2b**	**3n**	72
15	(**1m**): F, allyl, OMe, *p*-tolyl, H, H	**2b**	**3o**	76
16	**1i**	**2b**	**3p**	66
17	(**1n**): Me, allyl, Cl, *p*-tolyl, H, H	**2b**	**3q**	64
18	(**1o**): Cl, allyl, Br, *p*-tolyl, H, H	**2b**	**3r**	70
19	(**1p**): Me, Me, H, *p*-tolyl, Me, H	**2b**	**3s**	62
20	(**1q**): F, Me, H, *p*-tolyl, H, Cl	**2b**	**3t**	70
21	(**1r**): Me, allyl, F, *p*-tolyl, Me, H	**2b**	**3u**	60
22	**1p**	**2a**	**3v**	64
23	**1q**	**2a**	**3w**	65
24	**1a**	(**2c**): *i*-propyl	**3x**	72
25	(**1s**): Me, Me, H, *p*-tolyl, H, H	**2c**	**3y**	78
26	(**1t**): Cl, Et, H, *p*-tolyl, H, H	(**2d**): $PhCH_2$	**3z**	67

[a] All the reactions were carried out using **1** (1 mmol), **2** (3 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and DBU (2.5 mmol) in 5% aqueous DMSO (2 mL) at 80 °C for 35–40 min under open air.
[b] Isolated yield.

were prepared by using **2a** for *in vitro* assay (entries 1–11, 22 and 23, Table 2). However, the use of other isocyanides, for example, **2b** and **2c** was also successful (entries 12–21, 24 and 25, Table 2). Notably, the use of *t*-butyl isocyanide afforded the corresponding analog of **4a** instead of **3a**. We also employed **1** having a variety of substituents, for example, Me, F, Cl and Br on the benzene ring (entries 1–8, 10–15, 17–26, Table 2) and OMe, F, Cl and Br (entries 6, 8, 11, 15, 17, 18, 20, 21 and 23, Table 2) on the indole ring. The indole nitrogen may be substituted with an allyl (entries 1, 2, 5-9, 11, 12, 14-18, 21, and 24, Table 2), or alkyl group (entries 3, 4, 10, 13, 19, 20, 22, 23, 25 and 26, Table 2). The position of the substituent on the benzene or indole ring was also varied to afford the desired products. Having examined a number of alkyl isocyanides (**2a–d**) we then focused on the use of other types of isocyanides such as PhNC (**2e**), $EtOCOCH_2NC$ (**2f**) and $TsCH_2NC$ (**2g**) (Scheme 2). While the isocyanide **2e** afforded the desired product **3aa** the isocyanide **2f** afforded the product (**5a, b**) that seemed to be formed *via* following a slightly different pathway.[9a] The isocyanide **2g** did not participate in the reaction as the product **6** was formed *via* the known Pd-mediated intramolecular cyclization of the reactant employed.[9b] Notably, all these reactions (except using **2f**) were performed under open air as the methodology was insensitive to aerial oxygen. All the compounds synthesized were characterized by spectral (NMR, IR, MS and HPLC) data and this was supported by the molecular structure of **3t** being confirmed by X-ray analysis (Figure 2).[10]

Based on the fact that (i) the weaker base DBU favoured the formation of **3** over **4** and (ii) water



Scheme 2. Pd-catalyzed reaction of **1** with isocyanides **2e–g**; *conditions:* (a) 80 °C for 35–40 min; (b) 110 °C in a sealed tube for 3–4 h.

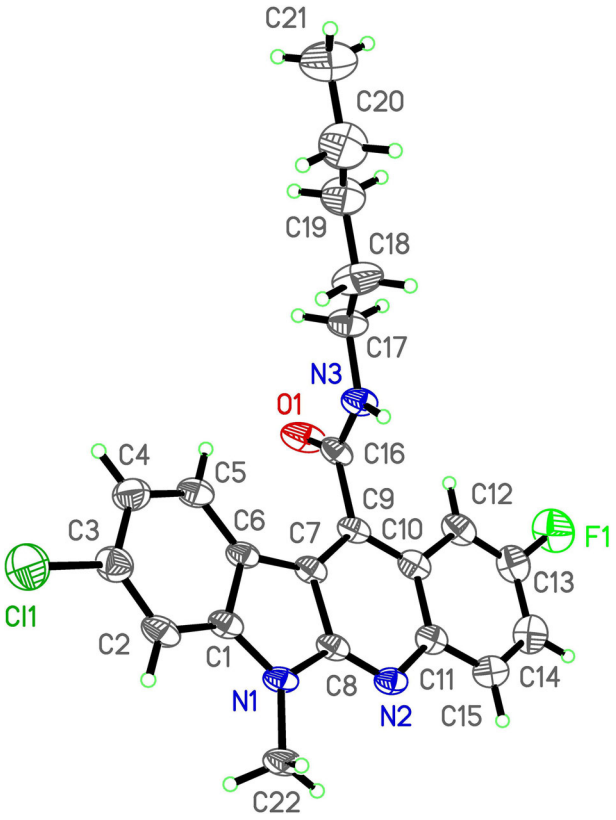
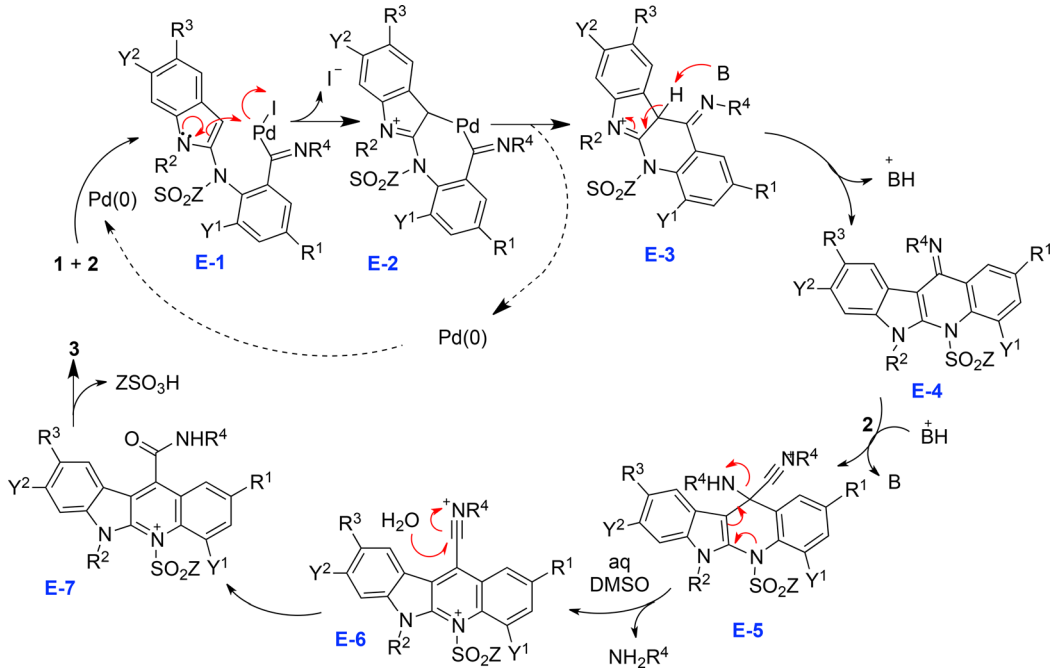


Figure 2. X-ray crystal structure of **3t** (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.

played a key role, a probable reaction mechanism is presented in Scheme 3. While a cleavage of the N–SO_2Z bond of **E-1** by Cs_2CO_3 could afford the product[5] **4** this bond cleavage perhaps was not favoured in the initial stage in the presence of DBU. Thus once formed, **E-1** undergoes an intramolecular attack by C-3 of indole[11a] on Pd to give **E-2**, which on reductive elimination of Pd regenerates Pd(0) and **E-3**. Aromatization of **E-3** affords **E-4** the imine moiety of which on further nucleophilic attack by **2** generates **E-5**.[11b] The release of amine from **E-5** affords **E-6** which on reaction with the water molecule provides **E-7**. Hydrolysis of **E-7** during work-up affords the desired compound **3**. Notably, the formation of **E-7** was indicated by the M^+ signal in the corresponding mass spectra. In the case of **2f**, the corresponding intermediate **E-4** reacted with the carbanion[11c] generated from **2f** *in situ* and followed a somewhat different pathway (see Scheme S-1 in the Supporting Information) presumably involving elimination of ethyl 2-aminoacetate initially and then *p*-tosyl group with the conversion of the isocyanide moiety to a TsNH group affording the product **5a, b**.[11d]

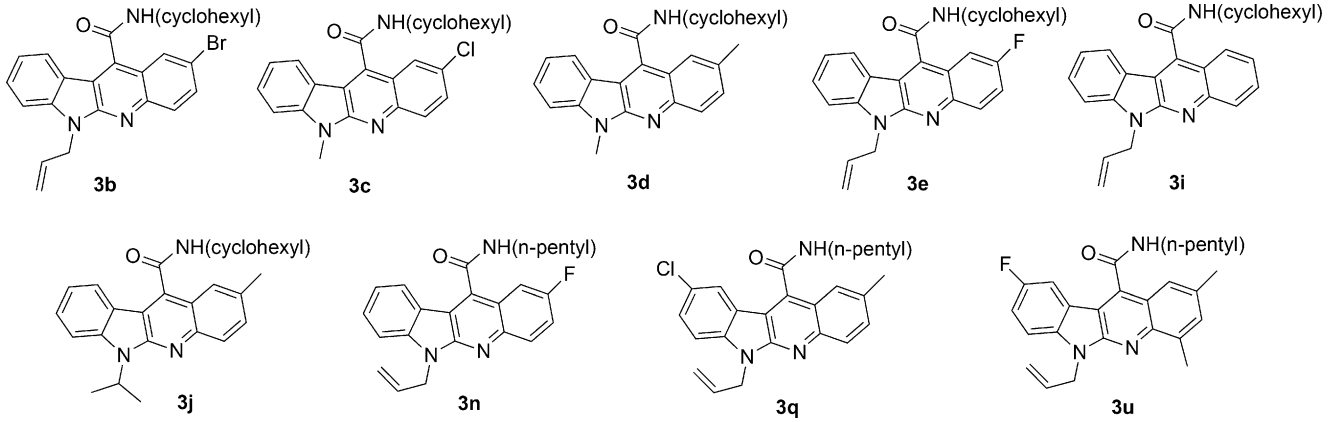
The cytotoxicity of these compounds was determined on the basis of measurement of *in vitro* growth inhibition of four cancer cell lines, for example, HeLa (cervical), DU145 (prostate), MCF7 (breast) and



Scheme 3. The probable reaction mechanism.

A549 (lung) using an MTT assay with doxorubicin as a reference compound. The IC_{50} values of most active compounds are presented in Table 3. Among these compounds, **3c**, **3d**, **3e**, and **3i** were found to be promising ($IC_{50} < 8$ μM) against lung cancer cells, **3e** was active against cervical and prostate cancer cells

Table 3. *In vitro* growth inhibition of cancer cell lines by compounds **3**.



Compound	IC_{50} values[a] (μM)				
	HeLa	DU145	MCF7	A549	HUVEC
3b	14.2 ± 0.2	23.6 ± 0.3	16.7 ± 0.4	8.7 ± 0.2	98.6 ± 0.2
3c	10.3 ± 0.2	20.7 ± 0.1	***9.7 ± 0.4***	***7.2 ± 0.4***	101.2 ± 0.4
3d	12.1 ± 0.3	12.5 ± 0.3	10.6 ± 0.2	***6.9 ± 0.3***	88.5 ± 0.4
3e	***9.9 ± 0.2***	***9.4 ± 0.1***	11.9 ± 0.4	***7.7 ± 0.2***	132.5 ± 0.2
3i	10.6 ± 0.2	39.8 ± 0.2	22.6 ± 0.5	***7.9 ± 0.3***	91.0 ± 0.3
3j	14.7 ± 0.4	15.7 ± 0.3	***9.7 ± 0.1***	18.4 ± 0.3	89.9 ± 0.3
3n	14.3 ± 0.2	***11.3 ± 0.2***	12.8 ± 0.3	8.5 ± 0.3	99.4 ± 0.5
3q	11.1 ± 0.2	17.5 ± 0.2	11.4 ± 0.4	12.3 ± 0.3	92.5 ± 0.4
3u	11.6 ± 0.2	13.6 ± 0.3	12.5 ± 0.1	12.9 ± 0.3	88.2 ± 0.5

[a] All the experiments were performed in triplicate and the IC_{50} values are expressed in mean ± SD.

whereas **3c** and **3j** were active against breast cancer cells. Notably, none of these compounds showed a significant effect ($IC_{50} > 88$ μM) on non-cancerous HUVEC cells indicating their selectivity (>10-fold) towards cancer cells. To understand the mechanism of action, **3c** and **3e** were tested for their inhibitory potential against sirtuins (class III NAD-dependent deacetylases) that are shown to be up-regulated in various types of cancer[12] and their inhibition allows re-expression of silenced tumour suppressor genes leading to reduced growth of cancer cells. In the Sirt1 fluorescence activity assay[13a] **3c**, **3e** and the reference drug suramin showed 71, 67 and 78% inhibition [and no inhibition by doxorubicin (negative control)] at 10 μM (see Figure S-1 in the Supporting Information) indicating that the anticancer properties of **3c** and **3e** are possibly due to their sirtuin inhibiting properties.[13b] Based on encouraging cytotoxicity, selectivity and sirtuin inhibitory properties, the compounds **3c** and **3e** appeared to be of further interest. Overall, our study confirmed that modification of **A** *via* incorporating the structural features of SB-277,011A (Figure 1) afforded compounds based on **B** that maintained the cytotoxic properties of **A**.

In conclusion, the change of solvent and base afforded a new, straightforward and inexpensive yet innovative method to synthesize *N*-substituted 6*H*-indolo[2,3-*b*]quinoline-11-carboxamides. An apparent CO insertion whereby an amide bond formation *via* double isocyanide incorporation during Pd-catalyzed construction of indoloquinoline ring in a single pot is the key feature of this method that was facilitated by the use of DBU in aqueous DMSO. This operationally simple methodology that afforded a new class of promising cytotoxic agents is unprecedented and may find applications in organic/medicinal chemistry.

Experimental Section

General Procedure for the Preparation of Indolo[2,3-*b*]quinolin-11-carboxamides (3)

To a mixture of *N*-(4-substituted-2-iodophenyl)-*N*-(1-alkyl-1*H*-indol-2-yl)methanesulfonamide (**1**) (1 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and DBU (2.5 mmol) in 5% aqueous DMSO (2 mL) was added isocyanide (3 mmol) slowly and then the mixture was stirred at 80 °C for 35-.40 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature, and filtered to remove the solid materials. The filtrate was extracted with ethyl acetate (3×15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using 5–10% ethyl acetate-hexane to give the desired product **3**.

Acknowledgements

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[10] Crystal data for **3t**: $C_{22}H_{21}N_3OFCl$ (M = 397.87): monoclinic, space group $P2_1/n$ (no. 14), $a = 15.627(3)$ Å, $b = 7.9992(13)$ Å, $c = 16.280(3)$ Å, $\beta = 103.130(2)°$, $V =$

1981.8(6) Å^3, $Z=4$, $T=294.15$ K, μ(MoKα)= 0.219 mm^{-1}, $D_{calc}=1.333$ g/mm^3, 15813 reflections measured ($3.262 \leq 2\Theta \leq 47.064$), 2936 unique ($R_{int}=0.0422$) which were used in all calculations. The final R_1 was 0.0923 ($I > 2\sigma(I)$) and wR_2 was 0.2336 (all data). CCDC 1444794 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) J. Peng, L. Liu, Z. Hu, J. Huang, Q. Zhu, *Chem. Commun.* **2012**, *48*, 3772; b) in the case of *t*-butyl isocyanide the corresponding **E-4** generated did not undergo a further nucleophilic attack by **2** (R^4 = *t*-Bu) due to the steric bulk of the *t*-butyl group. Rather it underwent a hydrolytic cleavage of the N–SO_2Z bond (aided by aqueous BH^+) to afford the corresponding analog of **4a**. c) For the generation of the carbanion from **2f** in the presence of DBU, see: M. Suzuki, M. Miyoshi, K. Matsumoto, *J. Org. Chem.* **1974**, *39*, 1980. d) The NMR data indicated that the compound **5a**, **b** predominantly remained in the enol form stabilized by an intramolecular H-bond (for the analysis of NMR data of **5b**, see the Supporting Information).

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