Tetrahedron 70 (2014) 4031–4037

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An alternate route to substituted 6,7-dihydro 5*H*-dibenz[*c*,*e*] azepines from allylbenzamides derived from the Morita–Baylis–Hillman adducts

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ARTICLE INFO

Article history:
Received 18 February 2014
Received in revised form 16 April 2014
Accepted 17 April 2014
Available online 2 May 2014

Keywords:
Morita–Baylis–Hillman
Amides
Polycycles
Cascade
Diastereoselectivity

ABSTRACT

An acid-catalyzed modular synthesis of substituted 5*H*-dibenz[*c*,*e*]azepines from a biaryl allylbenzamides prepared from the MBH adducts via a cascade dearoylation and intramolecular cyclization is described. The utility of the product for preparing 7,9-dihydro-4*bH*-dibenz[*c*,*e*]pyrrolo[1,2-*a*]azepine is also presented.

1. Introduction

The dibenzazepine is a member of the privileged class of biaryl frameworks represented in several pharmaceuticals.[1] Moreover such biaryls offers many opportunities to construct a variety of chiral catalyst systems and atropisomer bioligands (Fig. 1).[2] Analogous tricyclic core is also present in the natural alkaloid allocolchicine.[3] In our sustained efforts toward exploring the potential of the Morita–Baylis–Hillman (MBH) chemistry[4] for the synthesis of heterocycles,[5] natural product mimics,[6] and drug intermediates,[7] we have recently disclosed diastereoselective synthesis of allocolchicine analogs from the allylbenzamides, which were readily prepared from the MBH adducts of 2-bromobenzaldehyde.[8] These compounds were demonstrated to be useful as the insulin disaggregation agents. The success of the one-pot cascade reaction was attributed to the participation of the alkoxyl anion generated from the solvent under basic medium. In order to seek unambiguous support for the mechanism, the reaction was performed in dioxane instead of alkanol to successfully isolate the biaryl intermediate as a mixture of atropisomers in 1:1 ratio. Aiming to extend the utility of this biaryl intermediate, we anticipated it to be the starting material for preparing substituted 5*H*-dibenz[*c*,*e*]azepine. We reasoned that deprotecting the amide functionality of the biaryl allylbenzamide under acidic condition would render a free amino group, which would in situ trigger an intramolecular cyclization via Schiff base formation to furnish the substituted dibenz[*c*,*e*]azepine ring system. Notably literature describes cleavage of the NH-benzoyl group under the acidic condition.[9]

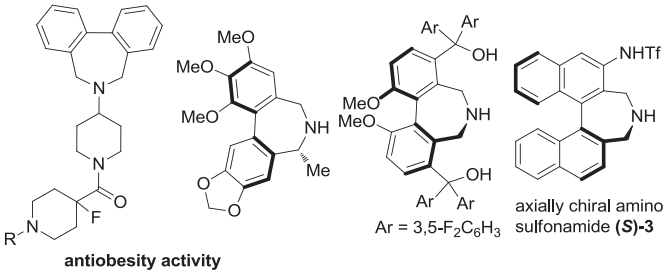

Fig. 1. Biarylazepine core represented by bioactive compounds and chiral catalysts.

It would be pertinent to mention that till date several elegant strategies for the synthesis of substituted 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine have been reported. Kündig et al. were first to report

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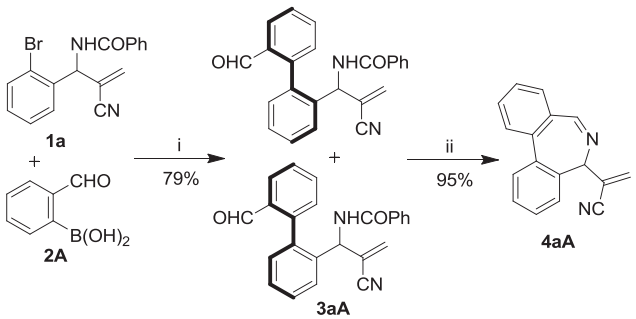
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.04.055

the synthesis of non racemic 5,7-dimethyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines as a chiral lithium amide base precursor.[10] Subsequently Baudoin et al. disclosed the first enantioselective synthesis of 5-methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines.[11] Page et al. described the synthesis of 5-substituted dibenzazepines through a chiral auxillary-based approach.[12] In recent times Eycken's group has successfully achieved the synthesis of dibenzazepine framework either via A^3 coupling or Ugi 3-component reaction.[13] More recently, Levacher et al. described Meyer's lactamization approach to biaryl structures with defined axial chirality.[14] Indeed the Meyer's lactamization process to access axially chiral 7,5-fused lactams was earlier employed by Wallace et al. too.[15] Besides, Heo et al. reported a concise synthesis of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepin-5-one via initial Suzuki coupling of 2-bromobenzylamides with 2-methoxycarbonyl phenyl boronic acid followed by intramolecular reductive cyclization.[16] During the compilation of this work a novel multicomponent approach to one-step synthesis of 5*H*-dibenz[*c*,*e*]azepin-5-one employing joint palladium/norborene organometallic catalyst was reported.[17] Inspite of such enormous development, we considered to investigate the envisaged strategy as it would not only offer an alternate and modular route to the dibenz[*c*,*e*]azepines bearing an allyl chain for further manipulation but would enhance the synthetic versatility of derivatives prepared from MBH adducts toward construction of heterocycles. Working toward this objective we have observed that treating the atropisomeric mixture of allylbenzamides with HCl in ethanol afforded substituted 5*H*-dibenz[*c*,*e*]azepines. Moreover these products are viable precursor to 7,9-dihydro-4*bH*-dibenz[*c*,*e*]pyrrolo[1,2-*a*]azepine. The results of our study are presented herein.

2. Results and discussion

In the first stage of the study we embarked on the synthesis of the biaryl intermediate following the reported procedure.[8] Accordingly, the Suzuki cross coupling reaction between the *N*-(1-(2-bromophenyl)-2-cyanoallyl)benzamide **1a** and 2-formylphenylboronic acid **2A** in the presence of $Pd(PPh_3)_4$ (5 mol %) and aq Na_2CO_3 in dioxane as the medium at 80 °C was performed to obtain the expected *N*-(2-cyano-1-(2′-formyl-[1,1′-biphenyl]-2-yl) allyl)benzamide **3aA** as a mixture of atropisomers (as evident from NMR spectra). With the biaryl allylbenzamide **3aA** in hand, next we set out to explore a suitable condition for the cascade NH-debenzoylation and intramolecular cyclization via an imine formation leading to 5*H*-dibenz[*c*,*e*]azepine. After a short screening of several acidic conditions, we discovered that performing the reaction in a 1:3 mixture of HCl/EtOH at 80 °C led to its completion within 2 h to afford a solid product in more than 95% yield (Scheme 1). The spectroscopic characterization led us to establish the structure of the product as 2-(5*H*-dibenz[*c*,*e*]azepin-5-yl)acrylonitrile **4aA**. It is worthwhile to mention that the reaction failed to yield a product when performed at room temperature.



Scheme 1. Reagents and conditions: (i) $Pd(PPh_3)_4$ (5 mol %), aq Na_2CO_3, dioxane, 80 °C, 2 h; (ii) HCl/EtOH (1:3), 80 °C, 2 h.

The success of the protocol prompted us to investigate the scope of the strategy by preparing a small library of biarylazepines. In this context, initially different allylbenzamides **1**(**b**–**g**) were reacted with 2-formylphenylboronic acid (**2A**) in the presence of $Pd(PPh_3)_4$ to furnish different biaryls **3bA**–**3gA** as a mixture of atropisomers in 1:1 ratio. Treating these biarylbenzamides with HCl in ethanol gave the required products **4bA**–**4gA** in excellent yields (Table 1, entries 1–6). The electronic nature of the substituent on the phenyl ring did not influence the outcome. To enhance the scope subsequently, *N*-(1-(2-bromophenyl)-2-cyanoallyl)benzamide **1a** was treated with different substituted 2-formylphenylboronic acids **2B**–**D** to prepare diverse biaryls **3aB**–**3aD**. These biaryls upon acid-mediated cyclization afforded the respective products **4aB**–**4aD** in 88–94% yields (Table 1, entries 7–9). Next to make the protocol modular **1a**,**b** were treated with 2-formylthiophene boronic acid **2E** to afford the biaryls **3aE** and **3bE**, respectively. The intramolecular cyclization here too was successful to furnish the corresponding biarylazepines **4aE** and **4bE** in 90–93% yields (Table 1, entries 10 and 11). Further we also employed 4-iodo-susbtituted pyrazole-based allylamide (**1h**) for the Suzuki coupling with **2A** to obtain the biaryl **3hA** in 65% yield. Treating **3hA** with HCl/EtOH afforded 2-(1-(4-chlorophenyl)-2-phenyl-2,4-dihydrobenzo[*c*]pyrazolo[4,3-*e*] azepin-4-yl)acrylonitrile (**4hA**) in 58% yield (Table 1, entry 12). Finally to investigate the influence of aroyl group, if any, on the dearoylation reaction the benzoyl group in **1a** was replaced by 2-chlorobenzoyl and 2-furoyl groups to generate **1i** and **1J**, which were subjected to identical sequence of reactions. It was observed that these substrates resulted into the formation of dibenzazepine **4aA** in excellent yields (Table 1, entries 13 and 14). The result inferred that invariably the aroyl group is cleaved during the reaction. Thus it was evident that the protocol for the formation of biarylazepine was modular and is not affected by the substitutions present on the aryl rings. Although straightforward, the mechanism of the reaction is delineated in Fig. 2. A few of the compounds were investigated for their cytotoxicity, but none of the analogs was found to be toxic as compared to podophyllotoxin (see SD).

Having established the scope of the protocol to prepare a variety of biarylazepine frameworks, we turned our attention to investigate the utility of these products for the synthesis of benzpyrroloazepine. It may be noted that benzpyrroloazepine is an important core present in a variety of natural products and pharmaceuticals.[18] Accordingly in a representative set of experiment the imine functionality of **4aA** was reduced with $NaBH_3CN$ in a mixture of glacial AcOH/EtOH (1:9) at room temperature for 1.5 h to prepare the amine **5** in 86% yield. Treating this amine **5** with allyl bromide in the presence of K_2CO_3 in DMF as the medium gave the bisallyl derivative **6** in 81% yield. Finally the ring closing metathesis reaction in the presence of 10 mol % Grubbs second generation catalyst furnished the desired dibenzpyrroloazepine **7** in 62% yield (Scheme 2).

3. Conclusions

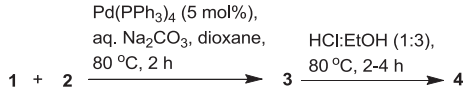
In summary we have disclosed herein an alternate, modular, and efficient route to 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines from allylbenzamides prepared from the MBH adducts. The protocol is compatible to a variety of substrates, which can be readily prepared from easily available starting materials. Further work is underway to study the utility of the reduced product **5** for generating more complex systems.

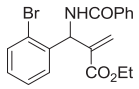
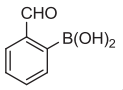
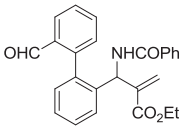
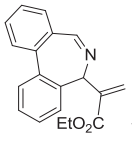
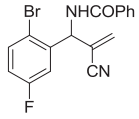
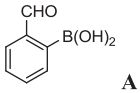
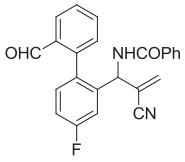
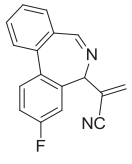
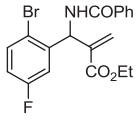
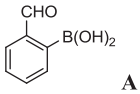
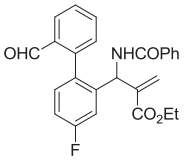
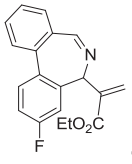
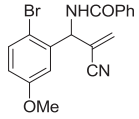
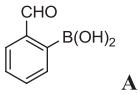
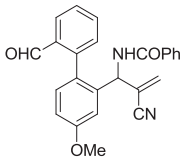
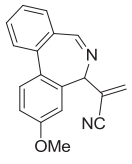
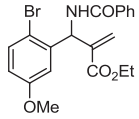
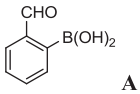
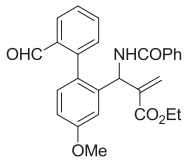
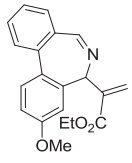
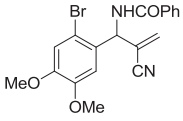
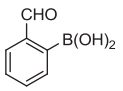
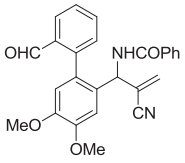
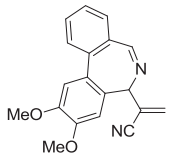
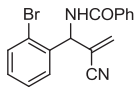
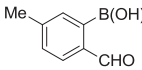
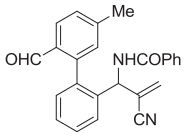
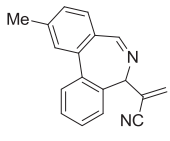
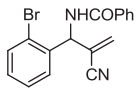
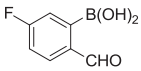
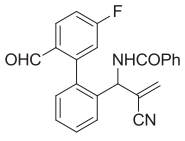
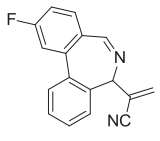
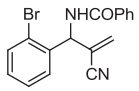
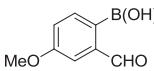
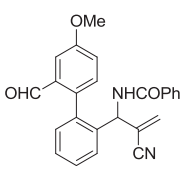
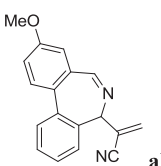
4. Experimental section

4.1. General

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon

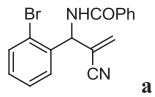
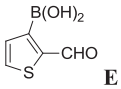
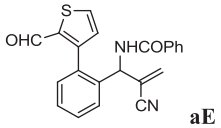
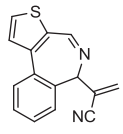
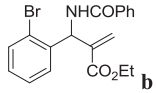
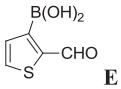
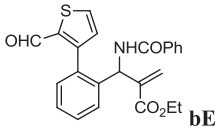
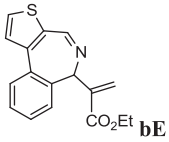
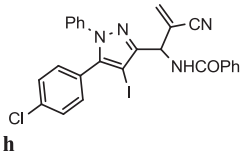
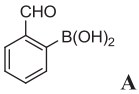
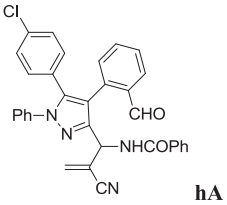
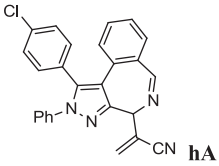
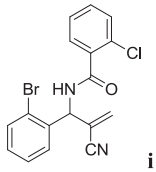
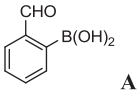
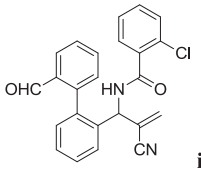
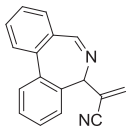
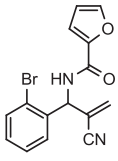
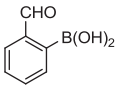
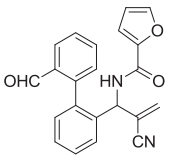
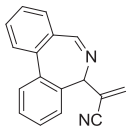
Table 1
Scope of the acid-catalyzed cascade reaction of biaryl allylbenzamides (**3**)[a] for the synthesis of biarylazepines (**4**)



Entry	Allylamide (**1**)	Boronic acid (**2**)	Biaryl (**3**)	Product (**4**)	Yield [%] of **4**[b]
1	 **b**	 **A**	 **bA**	 **bA**	92
2	 **c**	 **A**	 **cA**	 **cA**	96
3	 **d**	 **A**	 **dA**	 **dA**	89
4	 **e**	 **A**	 **eA**	 **eA**	92
5	 **f**	 **A**	 **fA**	 **fA**	90
6	 **g**	 **A**	 **gA**	 **gA**	83
7	 **a**	 **B**	 **aB**	 **aB**	86
8	 **a**	 **C**	 **aC**	 **aC**	94
9	 **a**	 **D**	 **aD**	 **aD**	88

(*continued on next page*)

Table 1 (*continued*)

Entry	Allylamide (**1**)	Boronic acid (**2**)	Biaryl (**3**)	Product (**4**)	Yield [%] of **4**[b]
10	 **a**	 **E**	 **aE**	 **aE**	93
11	 **b**	 **E**	 **bE**	 **bE**	90
12	 **h**	 **A**	 **hA**	 **hA**	58
13	 **i**	 **A**	 **iA**	 **aA**	89
14	 **j**	 **A**	 **jA**	 **aA**	61

[a] Compound **3** (0.3 mmol), HCl/EtOH (4 mL, 1:3 v/v).
[b] Isolated yields.

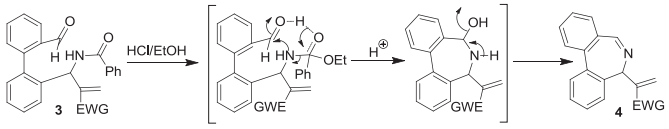
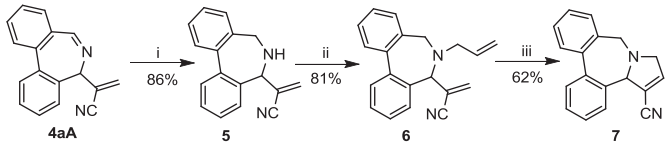


Fig. 2. Plausible mechanism for the formation of the observed product.



Scheme 2. Reagents and conditions: (i) $NaBH_3CN$, glacial AcOH/EtOH (1:9), rt, 1.5 h; (ii) Allyl bromide, K_2CO_3, DMF, rt, 1.5 h; (iii) Grubbs II, CH_2Cl_2, 40 °C, 6 h.

oil. IR spectra were recorded using a Perkin Elmer's RX I FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded either on Bruker Avance DRX-300 or Bruker 400 MHz spectrometers, using TMS as an internal standard. The ESMS were recorded on Thermo Finnigan LCQ Advantage, Ion Trap Mass spectrometer. The HRMS spectra were recorded as EI-HRMS on Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The synthesis of the starting amides was published earlier.[8] The spectroscopic details of unreported amides and the biaryl allylbenzamides are included in the Supplementary data.

4.2. General procedure for the synthesis of 3aA–3jA, 3aB–aE, 3bE as exemplified for 3aA

A suspension of **1a** (0.20 g, 0.59 mmol), 2-formylphenylboronic acid **2A** (0.09 g, 0.65 mmol), 2(M) aq Na_2CO_3 (0.13 g, 1.18 mmol) in dioxane (3 mL) was degassed under N_2 for 15 min. Then a weighed amount of $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol) was added to it and the reaction mixture was transferred to an oil bath and heated at 80 °C until all the starting materials were consumed. The excess 2-propanol was evaporated under reduced pressure and the crude mixture was worked up with EtOAc (3×10 mL). Thereafter the combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to yield the crude product as brown oil, which after chromatographic purification [silica gel, hexane/EtOAc (80:20)] yielded the pure **3aA** (0.18 g, 79%) as a white solid.

4.3. General procedure for the synthesis of 4aA–4hA, 4aB–4aE, 4bE as exemplified for 4aA

To a solution of concd HCl (12 N, 1 mL) and EtOH (3 mL), **3aA** (0.1 g, 0.27 mmol) was added at room temperature and the mixture was heated to reflux for 2 h. After complete consumption of the starting material the solvent was evaporated under vacuum. The resulting oily mixture was then basified to pH 9 with aq $NaHCO_3$ and extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine (25 mL), and dried over anhydrous Na_2SO_4. Evaporation of solvent in vacuo gave a residue, which upon

purification via silica-gel column chromatography (hexane/EtOAc, 85:15) afforded the desired dibenzazepine **4aA** (0.06 g, 95%) as a white solid.

*4.3.1. 2-(5H-Dibenz[c,e]azepin-5-yl)acrylonitrile (**4aA**).* 95% as a white solid (0.06 g from 0.10 g); mp=159–161 °C; R_f=0.52 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1626 (C=N), 2220 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=4.46 (s, 1H, CH), 6.50 (s, 1H, CH_2), 6.82 (s, 1H, CH_2), 7.43–7.64 (m, 7H, ArH), 7.83 (d, 1H, J=7.8 Hz, ArH), 8.46 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=63.1, 118.5, 123.1, 124.6, 127.8, 128.4, 128.9, 129.0, 129.2, 129.5, 130.7, 132.5, 133.8, 137.1, 138.6, 139.5, 160.9; mass (ES^+) m/z=245.1 (M^++H); ES-HRMS calcd for $C_{17}H_{13}N_2$ 245.1079 (M^++H), Found 245.1074.

*4.3.2. Ethyl 2-(5H-dibenz[c,e]azepin-5-yl)acrylate (**4bA**).* 92% as brown oil (0.06 g from 0.10 g); R_f=0.50 (hexanes/EtOAc, 70:30, v/v); ν_{max} (neat) 1627 (C=N), 1711 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.15 (t, 3H, J=7.1 Hz, CH_3), 4.09–4.13 (m, 2H, CH_2), 4.81 (s, 1H, CH), 6.85 (s, 2H, CH_2), 7.35–7.38 (m, 2H, ArH), 7.48–7.61 (m, 5H, ArH), 7.84 (d, 1H, J=7.6 Hz, ArH), 8.47 (d, 1H, J=1.8 Hz, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.1, 60.7, 61.4, 124.2, 127.5, 127.6, 128.4, 128.6, 128.8, 129.0, 129.2, 130.2, 132.8, 137.0, 140.0, 140.2, 141.0, 160.5, 166.6; mass (ES^+) m/z=292.0 (M^++H); ES-HRMS calcd for $C_{19}H_{18}NO_2$ 292.1338 (M^++H), Found 292.1343.

*4.3.3. 2-(3-Fluoro-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4cA**).* 96% as a white solid (0.07 g from 0.10 g); mp=138–140 °C; R_f=0.46 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1621 (C=N), 2217 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=4.44 (s, 1H, CH), 6.52 (s, 1H, CH_2), 6.85 (s, 1H, CH_2), 7.15 (t, 2H, J=6.7 Hz, ArH), 7.52–7.65 (m, 4H, ArH), 7.77 (d, 1H, J=7.6 Hz, ArH), 8.45 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=62.8, 111.9 (d, J=23.1 Hz), 115.5 (d, J=21.6 Hz), 118.2, 122.5, 127.9, 128.9, 129.3, 130.8, 131.0, 132.3, 133.3, 134.4, 138.5, 140.4, 161.4, 163.5 (d, J=247.9 Hz); mass (ES^+) m/z=263.1 (M^++H); ES-HRMS calcd for $C_{17}H_{12}FN_2$ 263.0985 (M^++H), Found 263.0988.

*4.3.4. Ethyl 2-(3-fluoro-5H-dibenz[c,e]azepin-5-yl)acrylate (**4dA**).* 89% as brown oil (0.06 g from 0.10 g); R_f=0.42 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1627 (C=N), 1712 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.18–1.21 (m, 3H, CH_3), 4.11–4.15 (m, 2H, CH_2), 4.80 (s, 1H, CH), 6.86 (s, 2H, CH_2), 6.94–7.06 (m, 2H, ArH), 7.55–7.58 (m, 4H, ArH), 7.77 (d, 1H, J=3.4 Hz, ArH), 8.47 (s, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.2, 60.9, 61.1, 111.5 (d, J=22.1 Hz), 114.6 (d, J=21.4 Hz), 127.6, 128.4, 128.5, 128.7, 129.2, 129.7, 130.3, 132.9, 133.6, 139.0, 139.5, 163.8 (d, J=261.5 Hz), 166.8, 170.9; mass (ES^+) m/z=310.1 (M^++H); ES-HRMS calcd for $C_{19}H_{17}FNO_2$ 310.1243 (M^++H), Found 310.1244.

*4.3.5. 2-(3-Methoxy-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4eA**).* 92% as a white solid (0.06 g from 0.10 g); mp=85–87 °C; R_f=0.39 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1618 (C=N), 2217 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.87 (s, 3H, OCH_3), 4.45 (s, 1H, CH), 6.50 (s, 1H, CH_2), 6.82 (s, 1H, CH_2), 6.95–6.99 (m, 2H, ArH), 7.48–7.62 (m, 4H, ArH), 7.76 (d, 1H, J=7.4 Hz, ArH), 8.44 (s, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=55.6, 63.2, 110.3, 114.0, 118.4, 123.1, 127.2, 128.6, 129.3, 129.9, 130.2, 130.6, 132.2, 134.0, 139.3, 139.7, 160.5, 161.4; mass (ES^+) m/z=275.1 (M^++H); ES-HRMS calcd for $C_{18}H_{15}N_2O$ 275.1184 (M^++H), Found 275.1191.

*4.3.6. Ethyl 2-(3-methoxy-5H-dibenz[c,e]azepin-5-yl)acrylate (**4fA**).* 90% as brown oil (0.07 g from 0.10 g); R_f=0.38 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1624 (C=N), 1711 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.16 (t, 3H, J=7.1 Hz, CH_3), 3.78 (s, 3H, OCH_3), 4.06–4.17 (m, 2H, CH_2), 4.82 (s, 1H, CH), 6.79–6.91 (m, 4H, ArH), 7.41–7.57 (m, 4H, ArH), 7.76 (d, 1H, J=7.7 Hz, ArH), 8.46 (d, 1H, J=1.9 Hz, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.1, 55.4, 60.7, 61.4, 109.9, 113.1, 126.8, 128.4, 128.6, 129.1, 129.6, 129.9, 130.3, 132.5, 139.7, 140.1, 142.2, 160.2, 160.9, 166.5; mass (ES^+) m/z=322.0 (M^++H); ES-HRMS calcd for $C_{20}H_{20}NO_3$ 322.1443 (M^++H), Found 322.1439.

*4.3.7. 2-(2,3-Dimethoxy-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4gA**).* 83% as a white solid (0.06 g from 0.10 g); mp=135–137 °C; R_f=0.36 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1619 (C=N), 2216 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.31 (s, 1H, CH), 6.43 (s, 1H, CH_2), 6.78 (s, 1H, CH_2), 6.85 (s, 1H, ArH), 7.04 (s, 1H, ArH), 7.42–7.58 (m, 3H, ArH), 7.73 (d, 1H, J=7.8 Hz, ArH), 8.37 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.2, 56.3, 62.7, 107.8, 112.3, 114.2, 118.4, 123.2, 127.3, 128.6, 129.4, 129.8, 130.7, 131.3, 132.5, 133.9, 149.1, 149.9, 160.9; mass (ES^+) m/z=305.1 (M^++H); ES-HRMS calcd for $C_{19}H_{17}N_2O_2$ 305.1290 (M^++H), Found 305.1288.

*4.3.8. 2-(10-Methyl-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4aB**).* 86% as a white solid (0.06 g from 0.10 g); mp=128–130 °C; R_f=0.44 (hexanes/EtOAc, 70:30, v/v); ν_{max} (KBr) 1621 (C=N), 2221 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.53 (s, 3H, CH_3), 4.44 (s, 1H, CH), 6.48 (s, 1H, CH_2), 6.80 (s, 1H, CH_2), 7.35 (d, 1H, J=7.9 Hz, ArH), 7.40–7.50 (m, 4H, ArH), 7.62 (d, 2H, J=5.8 Hz, ArH), 8.41 (d, 1H, J=1.9 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.8, 63.2, 118.5, 123.3, 124.5, 128.3, 128.8, 129.2, 129.4, 130.2, 133.7, 137.2, 138.4, 139.5, 141.0, 160.9; mass (ES^+) m/z=259.0 (M^++H); ES-HRMS calcd for $C_{18}H_{15}N_2$ 259.1235 (M^++H), Found 259.1233.

*4.3.9. 2-(10-Fluoro-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4aC**).* 94% as a white solid (0.06 g from 0.10 g); mp=210–212 °C; R_f=0.46 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1621 (C=N), 2216 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=4.46 (d, 1H, J=10.2 Hz, CH), 6.50 (d, 1H, J=10.8 Hz, CH_2), 6.82 (d, 1H, J=10.2 Hz, CH_2), 7.20–7.25 (m, 1H, ArH), 7.43–7.60 (m, 6H, ArH), 8.42 (d, 1H, J=11.2 Hz, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=63.1, 115.5 (d, J=22.1 Hz), 118.4, 122.9, 124.8, 128.6, 129.4, 129.5, 131.7, 131.9, 134.0, 136.1, 138.3, 142.1, 142.3, 160.3 (d, J=44.7 Hz), 165.8; mass (ES^+) m/z=263.1 (M^++H); ES-HRMS calcd for $C_{17}H_{12}FN_2$ 263.0985 (M^++H), Found 263.0989.

*4.3.10. 2-(9-Methoxy-5H-dibenz[c,e]azepin-5-yl)acrylonitrile (**4aD**).* 88% as a white solid (0.07 g from 0.10 g); mp=124–126 °C; R_f=0.38 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1623 (NHCO), 2221 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=3.92 (s, 3H, OCH_3), 4.44 (s, 1H, CH), 6.48 (s, 1H, CH_2), 6.79 (s, 1H, CH_2), 7.03 (s, 1H, ArH), 7.19 (d, 1H, J=8.4 Hz, ArH), 7.43 (d, 3H, J=2.5 Hz, ArH), 7.51 (d, 1H, J=4.8 Hz, ArH), 7.75 (d, 1H, J=8.7 Hz, ArH), 8.39 (s, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=55.7, 63.3, 112.6, 117.8, 118.5, 123.3, 124.6, 128.2, 128.4, 129.0, 130.5, 132.3, 133.7, 137.0, 137.8, 159.0, 160.5; mass (ES^+) m/z=275.1 (M^++H); ES-HRMS calcd for $C_{18}H_{15}N_2O$ 275.1184 (M^++H), Found 275.1187.

4.3.11. 2-(6H-Benz[c]thieno[3,2-e]azepin-6-yl)acrylonitrile (**4aE**). 93% as brown solid (0.06 g from 0.10 g); mp=64–66 °C; R_f=0.43 (hexanes/EtOAc, 80:20, v/v); ν_{max} (neat) 1632 (C=N), 2232 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=4.46 (s, 1H, CH), 6.49 (s, 1H, CH_2), 6.79 (s, 1H, CH_2), 7.42–7.56 (m, 4H, ArH), 7.62–7.68 (m, 2H, ArH), 8.47 (s, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=64.6, 118.5, 123.4, 125.8, 127.4, 127.6, 128.3, 129.5, 129.8, 133.5, 133.7, 134.1, 134.3, 144.3, 153.7; mass (ES^+) m/z=251.0 (M^++H); ES-HRMS calcd for $C_{15}H_{11}N_2S$ 251.0643 (M^++H), Found 251.0644.

*4.3.12. Ethyl 2-(6H-benz[c]thieno[3,2-e]azepin-6-yl)acrylate (**4bE**).* 90% as a white solid (0.06 g from 0.10 g); mp=96–98 °C; R_f=0.42 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1632 (NHCO), 1714 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.15 (t, 3H, J=7.1 Hz, CH_3), 4.03–4.22 (m, 2H, CH_2), 4.79 (s, 1H, CH), 6.84 (d, 2H, J=1.9 Hz, CH_2), 7.28–7.42 (m, 3H, ArH), 7.54–7.58 (m, 2H, ArH), 7.61–7.64 (m,

1H, ArH), 8.47 (d, 1H, J=2.1 Hz, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.2, 60.7, 62.9, 125.4, 127.3, 127.4, 127.5, 128.6, 129.3, 133.4, 134.5, 136.4, 140.7, 144.5, 153.1, 166.7; mass (ES^+) m/z=298.0 (M^++H); ES-HRMS calcd for $C_{17}H_{16}NO_2S$ 298.0902 (M^++H), Found 298.0903.

*4.3.13. 2-(1-(4-Chlorophenyl)-2-phenyl-2,4-dihydrobenz[b]pyrazolo [4,3-d]azepin-4-yl)acrylonitrile (**4hA**).* 58% as a white solid (0.04 g from 0.10 g); mp=190–192 °C; R_f=0.29 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 1633 (C=N), 2210 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=4.84 (s, 1H, CH), 6.39 (s, 1H, CH_2), 6.70 (s, 1H, CH_2), 7.00–7.04 (m, 3H, ArH), 7.12 (d, 2H, J=7.6 Hz, ArH), 7.22–7.31 (m, 7H, ArH), 7.55 (d, 1H, J=7.1 Hz, ArH), 8.59 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=59.4, 117.1, 118.7, 121.9, 125.5, 126.2, 126.7, 127.5, 128.1, 128.2, 128.8, 129.8, 130.1, 130.2, 130.9, 131.9, 132.7, 132.8, 139.2, 139.6, 141.1, 151.0, 163.1; mass (ES^+) m/z=421.1 (M^++H); ES-HRMS calcd for $C_{26}H_{18}ClN_4$ 421.1220 (M^++H), Found 421.1229.

4.4. Typical procedure for the synthesis of 2-(6,7-dihydro-5*H*-dibenz[*c*,*e*]azepin-5-yl)acrylonitrile (5)

To a mixture of **4aA** (0.05 g, 0.20 mmol) in AcOH (0.5 mL) and EtOH (4.5 mL) at 0 °C, $NaBH_3CN$ (0.02 g, 0.30 mmol) was added and the reaction was allowed to continue at room temperature for 1.5 h. Thereafter the solvent was removed and the residue was basified to pH 9 with aq $NaHCO_3$. The resulting mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a residue, which upon purification by column chromatography on silica gel (hexane/EtOAc=75:25) gave **5** (0.04 g, 86%) as a colorless oil. R_f=0.12 (hexanes/EtOAc, 80:20, v/v); ν_{max} (neat) 2219 (CN), 3401 (NH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.27 (br s, 1H, NH), 3.49 (d, 1H, J=13.3 Hz, CH_2), 3.71 (d, 1H, J=13.3 Hz, CH_2), 4.33 (s, 1H, CH), 6.04 (d, 2H, J=7.8 Hz, CH_2), 7.23–7.44 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=48.8, 59.3, 119.5, 121.7, 128.0, 128.1, 128.4, 128.6, 128.7, 129.2, 135.7, 140.4, 136.6, 140.8; mass (ES^+) m/z=247.1 (M^++H); ES-HRMS calcd for $C_{17}H_{15}N_2$ 247.1235 (M^++H), Found 247.1239.

4.5. Typical procedure for the synthesis of 2-(6-allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepin-5-yl)acrylonitrile (6)

To a stirred solution of **5** (0.04 g, 0.16 mmol) in dry DMF (2 mL), K_2CO_3 (0.3 g, 0.24 mmol) was added and cooled to 0 °C. Then allyl bromide (0.02 mL, 0.24 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried, concentrated under reduced pressure, and purified over silica gel column using hexane/EtOAc=90:10 as the eluent to furnish **6** (0.04 g, 81%) as a colorless oil. R_f=0.35 (hexanes/EtOAc, 80:20, v/v); ν_{max} (neat) 2216 (CN) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.14 (d, 2H, J=6.2 Hz, CH_2), 3.23 (d, 1H, J=12.1 Hz, CH_2), 3.52 (d, 1H, J=12.1 Hz, CH_2), 4.06 (s, 1H, CH), 5.17 (d, 1H, J=10.2 Hz, CH_2), 5.25 (d, 1H, J_1=17.2 Hz, J_2=1.6 Hz, CH_2), 5.62 (s, 2H, CH_2), 5.83–5.93 (m, 1H, CH), 7.19–7.26 (m, 3H, ArH), 7.28–7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.1, 61.3, 69.5, 118.8, 121.6, 127.8, 128.2, 128.4, 128.9, 129.0, 129.1, 129.5, 131.7, 134.5, 135.5, 135.9, 138.9, 141.1; mass (ES^+) m/z=287.1 (M^++H); ES-HRMS calcd for $C_{20}H_{19}N_2$ 287.1548 (M^++H), Found 287.1556.

4.6. Typical procedure for the synthesis of 7,9-dihydro-4b*H*-dibenz[*c*,*e*]pyrrolo[1,2-*a*]azepine-5-carbonitrile (7)

A mixture of diene **6** (0.03 g, 0.10 mmol) and Grubbs' second -generation catalyst (1.0 mg, 10 mol %) in degassed methylene chloride (10 mL) was stirred at 40 °C for 6 h. The solvent was evaporated and the crude mixture was purified via column chromatography over silica gel by eluting with hexane/EtOAc (90:10) to afford **7** (0.02 g, 62%) as a brown solid. Mp=173–175 °C; R_f=0.24 (hexanes/EtOAc, 80:20, v/v); ν_{max} (KBr) 2223 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.29–3.41 (m, 2H, CH_2), 3.52–3.66 (m, 2H, CH_2), 5.81 (s, 1H, CH), 7.17 (d, 1H, J=7.2 Hz, CH), 7.31–7.53 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.1, 56.2, 70.1, 114.2, 125.3, 127.8, 127.9, 128.9, 129.3, 129.9, 130.2, 131.6, 132.2, 139.4, 141.0; mass (ES^+) m/z=259.1 (M^++H); ES-HRMS calcd for $C_{18}H_{15}N_2$ 259.1235 (M^++H), Found 259.1244.

Acknowledgements

Two of the authors (S.B., S.B.) acknowledge the financial support in the form of fellowship from Council of Scientific and Industrial Research, New Delhi. The authors acknowledge the SAIF Division of CSIR-CDRI for furnishing the spectroscopic data. The authors acknowledge Dr. Kumkum Srivastava, Parasitology Division, CSIR-CDRI for providing the cytotoxicity data of compounds. This work was carried out under the project funded by Department of Science and Technology, Ministry of Science and Technology (SR/S1/OC-01/2010), New Delhi. The CDRI communication no. for this manuscript is MS. 8664.

Supplementary data

The spectroscopic details of remaining compounds and copies of ^{1}H and ^{13}C NMR spectra of all compounds and HR-EIMS of all final compounds are provided. Result of the cytotoxicity assay of a few analogs is also included. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.055. These data include MOL files and InChiKeys of the most important compounds described in this article.

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