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PAPER

A new approach to construct a fused 2-ylidene chromene ring: highly regioselective synthesis of novel chromeno quinoxalines†

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Regioselective construction of a fused 2-ylidene chromene ring was achieved for the first time by using $AlCl_3$-induced C–C bond formation followed by Pd/C–Cu mediate coupling-cyclization strategy. A number of chromeno[4,3-*b*]quinoxaline derivatives were prepared by using this strategy. Single crystal X-ray diffraction study of a representative compound *e.g.* 6-(2,2-dimethylpropylidene)-4-methyl-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol confirmed the presence of an exocyclic C–C double bond with *Z*-geometry. The crystal structure analysis and hydrogen bonding patterns of the same compound along with its structure elaboration *via* propargylation followed by Sonogashira coupling of the resulting terminal alkyne is presented. A probable mechanism for the formation of 2-ylidene chromene ring is discussed. Some of the compounds synthesized showed anticancer properties when tested *in vitro*.

Introduction

The chromene framework with an exocyclic double bond at C-2 (**A**, Fig. 1) constitutes a unique class of *O*-heterocycles and found to be integral part of progestins **B**. In addition to their uses in many therapeutic areas, progestins are known as effective anticancer agents.[2] Several quinoxalines are also known as anticancer drugs[3] *e.g.* NSC 339004 (**D**, Fig. 1). Thus appropriate combination of structural features of **A** (or **B**) with a quinoxaline nucleus in a single template was expected to provide new chemical space (*e.g.* **C**, Fig. 1) to develop novel anticancer agents.[3] Since cancer is the second leading cause of death[4] worldwide, the search for new anticancer agents is therefore desirable. We now report the evaluation of the anticancer properties of novel small molecules based on **C**, the synthesis of which has been carried out using a newly developed strategy.

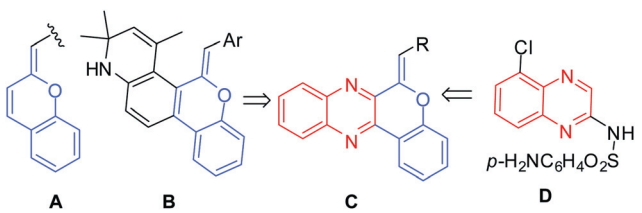

Fig. 1 Design of new and potential anticancer agents **C**.

The only method known for constructing a 2-ylidene chromene ring involves the reaction of a Grignard reagent prepared from the corresponding benzyl bromide or chloride with a lactone *e.g.* 2,2,4-trimethyl-1*H*-chromeno[3,4-*f*]quinolin-5(2*H*)-one followed by treating the resulting hemi-acetal intermediate with *p*-toluenesulfonic acid.[1] Alternatively, the lactone can be reacted with an organo-lithium reagent (prepared *via* lateral lithiation of a 2-methyl thiophene derivative with LDA) to give the hemi-acetal intermediate which under protic acid conditions provides a 2-ylidene chromene derivative.[5] While effective for the preparation a particular class of compounds, *e.g.* benzylidenes or thienyl methylidenes, these methods lack generality and also require cumbersome preparation of moisture sensitive Grignard or organo-lithium reagents. One of the major goals of the present work was therefore to develop a more straightforward and robust methodology for the preparation of our target molecules **C**. Transition metal mediated synthesis of *O*-containing heterocycles *via* intramolecular addition of an *O*-nucleophile across the C–C triple bond has become a powerful tool in organic chemistry.[6] A large variety of structurally diverse compounds has been synthesized by using this strategy and Pd has

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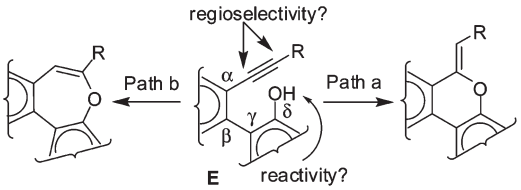
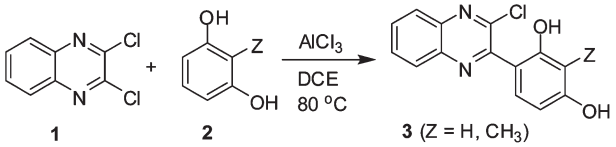
† Electronic supplementary information (ESI) available: Copies of NMR spectra for all new compounds. CCDC 858005. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25416f



Scheme 1 Intramolecular addition of O–H across the C–C triple bond.



Scheme 2 Preparation of 4-(3-chloroquinoxalin-2-yl)benzene-1,3-diol (**3**).

been the most utilized metal in these catalytic processes. Recently, the use of Pd/C as an inexpensive, easily separable and recyclable catalyst has also been explored for the synthesis of *O*-heterocycles.[7] We envisaged that a phenolic OH present at the δ-position to the alkynyl moiety of **E** might undergo an intramolecular cyclization in a regioselective manner under an appropriate reaction conditions (Scheme 1). The challenging issues however to be addressed here were (i) installation of a phenolic OH at the δ-position to the alkynyl moiety, (ii) its reactivity towards transition metal-activated alkynes, (iii) regioselectivity and (iv) the optimal catalyst system.

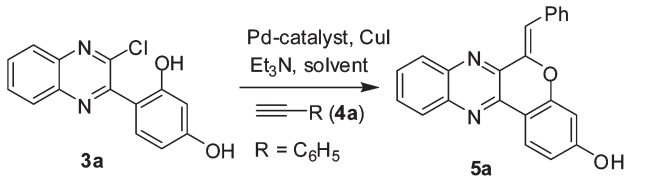
Results and discussion

The $AlCl_3$ induced C–C bond forming reaction, an effective strategy for the introduction of a phenol moiety to an *N*-heterocyclic ring[8] was adopted to generate the key starting material. Thus the chloro compound **3** required for our study, was prepared (Scheme 2) *via* $AlCl_3$ mediated reaction of 2,3-dichloroquinoxaline (**1**) with phenols (**2**) in 1,2-dichloroethane (DCE).

To this end, we initially choose to examine the coupling-cyclization of **3a** (Z = H) with phenylacetylene (**4a**) in the presence of 10% Pd/C-PPh_3-CuI[7] and Et_3N in toluene (Table 1). To our satisfaction, the reaction proceeded smoothly with high regioselectivity affording the compound **5a** as the only product (entry 1, Table 1). The reaction was carried out for 6 h and a longer reaction time did not improve the product yield (entry 2, Table 1). The use of other catalysts, *e.g.* $PdCl_2(PPh_3)_2$ and Pd-$(OAc)_2$-PPh_3, afforded the product **5a** but in inferior yield (entries 3–4, Table 1). The absence of CuI did not provide **5a** indicating the need of CuI for the reaction to proceed. The reaction afforded only traces amount of **5a** in the absence of Pd-catalyst whereas the use of other solvents, *e.g.* 1,4-dioxane, CH_3CN, EtOH or MeOH decreased the product yield (entries 5–8, Table 1). Thus a combination of Pd/C-PPh_3-CuI and Et_3N in toluene was found to be optimum for the present coupling-cyclization reaction.

With the optimized reaction conditions in hand, a variety of terminal alkynes (**4**) were reacted with chloro compound **3** (Table 2). Both aromatic (entries 1–2, 4 Table 2) and aliphatic alkynes (entries 3, 5–12 Table 2) participated well in this reaction, affording the desired products in good yields. All the products isolated were characterized by spectral (NMR, IR and MS) data. Depending on the nature of substituent present a singlet or triplet was observed in the region δ 6.3–6.5 in the ^1H NMR spectra of **5**, indicating the presence of a vinylic proton. Notably, we were able to isolate the 7-membered ring product *i.e.* 6-hexyl-4-methylbenzo[*b*]quinoxalinoxepin-3-ol (**5kk**) in 10% yield along with **5k** when the reaction of **3b** and the alkyne **4k**

Table 1 Effect of reaction conditions on the Pd-catalyzed coupling of 4-(3-chloroquinoxalin-2-yl)benzene-1,3-diol (**3a**) with phenylacetylene (**4a**)[a]



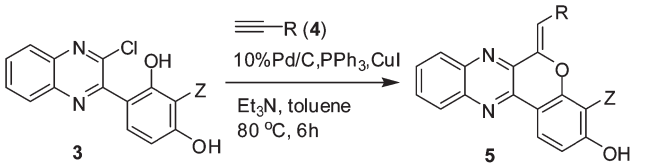
Entry	Catalyst	Solvent	Time (h)	%Yield[b]
1	10% Pd/C-PPh_3	Toluene	6	82
2	10% Pd/C-PPh_3	Toluene	10	80
3	$PdCl_2(PPh_3)_2$	Toluene	8	75[c]
4	$Pd(OAc)_2$-PPh_3	Toluene	8	70
5	10% Pd/C-PPh_3	1,4-Dioxane	6	78
6	10% Pd/C-PPh_3	CH_3CN	7	75
7	10% Pd/C-PPh_3	EtOH	8	70
8	10% Pd/C-PPh_3	MeOH	8	72

[a] All reactions were carried out by using **3a** (1.0 equiv.), **4a** (1.5 equiv.), Pd-catalyst (0.05 equiv.) or Pd/C (0.035 equiv.), PPh_3 (0.35 mmol), CuI (0.06 equiv.), Et_3N (3.0 equiv.) in a solvent (5 mL) at 80 °C under N_2. [b] Isolated yields. [c] PPh_3 was not used.

was conducted in the presence of $PdCl_2(PPh_3)_2$ and CuI in toluene at 80 °C for 8 h (Scheme 3). The presence of a vinylic proton was indicated by a singlet observed at δ 6.25 in the ^1H NMR spectra of **5kk** compared to a triplet at δ 6.31 for **5k**. Nevertheless, the molecular structure of **5f** was established unambiguously by single crystal X-ray diffraction study (Fig. 2)[9a] confirming the presence of an exocyclic C–C double bond with *Z*-geometry.[9b] The compound **5f** crystallizes in the monoclinic $P2_1/c$ space group with one molecule in the asymmetric unit (Z: 4 Z': 1) (Fig. 2). The quinoxaline ring of the molecule in the asymmetric unit is not in coplanar with 2,2-dimethylpropylidene moiety of the molecule. The torsion angle of the quinoxaline ring and neopentane moieties are −174.2(2) (C15–C16–C17–C18). Interestingly, the molecule in the asymmetric unit form strong hydrogen bonding *via* O–H···N synthon (N1···O2 2.874(2), N1···H2 2.06) and are forming the 1D corrugated layers as shown in Fig. 3 and 4 along the ac plane. The free hydrogen of the O–H group interacts with quinoxaline moiety and forms O–H···N intermolecular hydrogen bond and are stabilized by dimer formation through aromatic C–H···π interactions. These interactions propagate in 2D corrugated type layered structure in *bc* plane as shown in Fig. 5.

Further structure elaboration of **5f** was carried out *via* propargylation followed by Sonogashira coupling of the resulting terminal alkyne (**6**) with an iodoarene (**7**) to give

Table 2 Pd/C-mediated synthesis of 6-substituted 6*H*-chromeno[4,3-*b*]-quinoxalin-3-ol (**5**)[a]



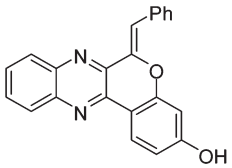
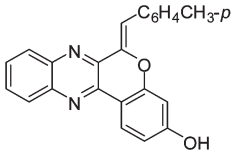
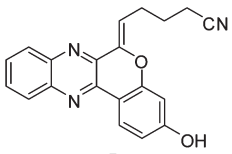
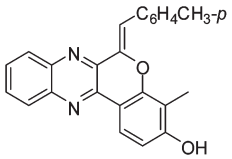
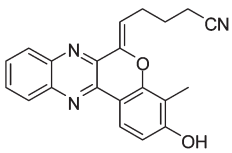
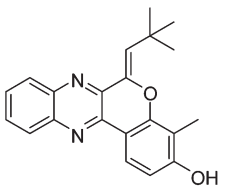
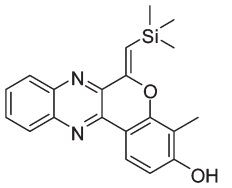
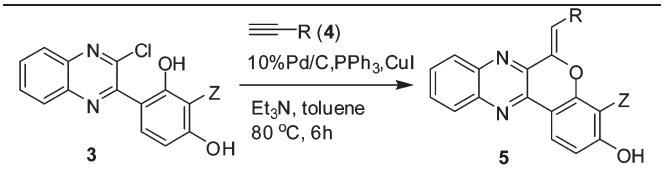
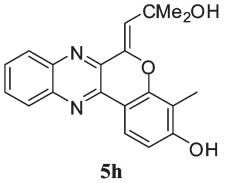
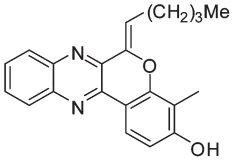
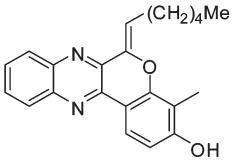
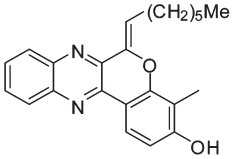
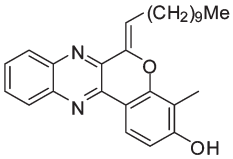
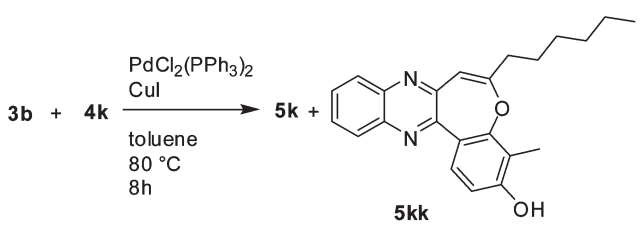
Entry	**3**; Z =	**4**; R =	Products (**5**)	% Yield[b]
1	**3a**; H	**4a**; C_6H_5	 **5a**	82
2	**3a**	**4b**; C_6H_4Me-*p*	 **5b**	80
3	**3a**	**4c**; C_3H_6CN-*p*	 **5c**	80
4	**3b**; Me	**4d**; C_6H_4Me-*p*	 **5d**	80
5	**3b**	**4c**	 **5e**	78
6	**3b**	**4e**; CMe_3	 **5f**	80
7	**3b**	**4f**; $SiMe_3$	 **5g**	82

Table 2 *(Contd.)*



Entry	**3**; Z =	**4**; R =	Products (**5**)	% Yield[b]
8	**3b**	**4g** CMe_2OH	 **5h**	80
9	**3b**	**4h** $(CH_2)_3Me$	 **5i**	78
10	**3b**	**4i** $(CH_2)_4Me$	 **5j**	78
11	**3b**	**4j** $(CH_2)_5Me$	 **5k**	80
12	**3b**	**4k** $(CH_2)_9Me$	 **5l**	80

[a] All reactions were carried out by using **3** (1.0 equiv.), **4** (1.5 equiv.), 10% Pd/C (0.035), PPh_3 (0.35 equiv.), CuI (0.06 equiv.) and Et_3N (3.0 equiv.) in toluene (5 mL) at 80 °C for 6 h under N_2. [b] Isolated yields.



Scheme 3 Preparation of 7-membered ring product **5kk**.

(*Z*)-6-(2,2-dimethylpropylidene)-4-methyl-3-(3-phenyl prop-2-ynyloxy)-6*H*-chromeno[4,3-*b*]quinoxaline (**8**) (Scheme 4). Thus compound **5f** was reacted with propargyl bromide in the

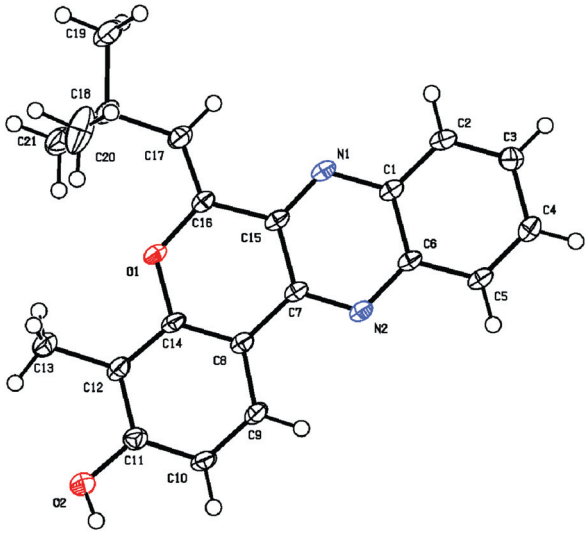


Fig. 2 ORTEP representation of **5f** (thermal ellipsoids are drawn at 50% probability level).

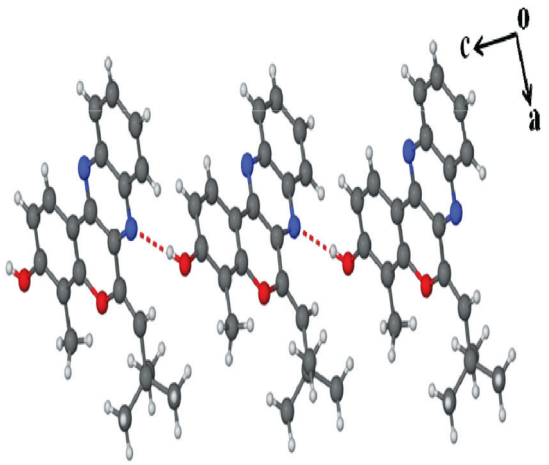


Fig. 3 The formation of O–H···N intermolecular hydrogen bonding in the *ac* plane.

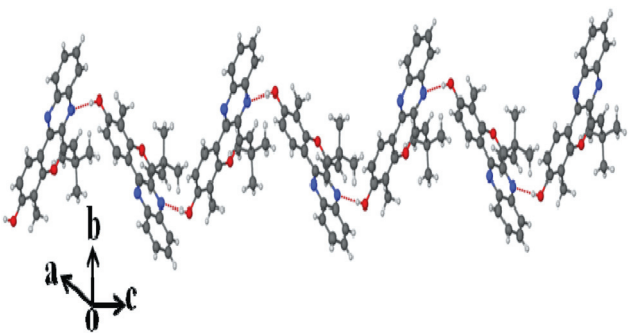


Fig. 4 The formation of corrugated tapes.

presence of K_2CO_3 in DMF to give the corresponding terminal alkyne *i.e.* (*Z*)-6-(2,2-dimethylpropylidene)-4-methyl-3-(prop-2-ynyloxy)-6H-chromeno[4,3-*b*]quinoxaline (**6**) in 80% yield. Subsequent coupling of the alkyne **6** with iodobenzene **7** was

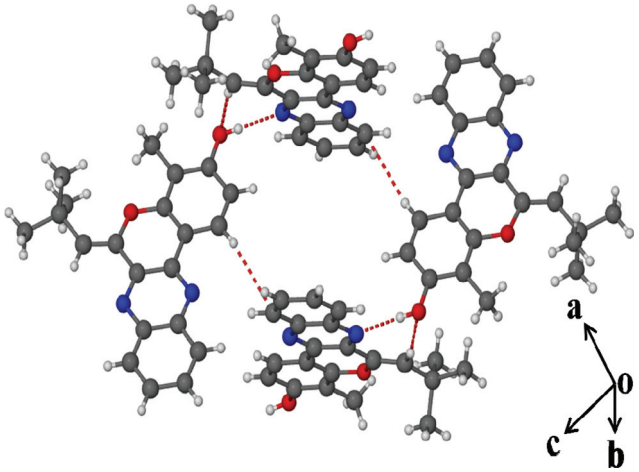
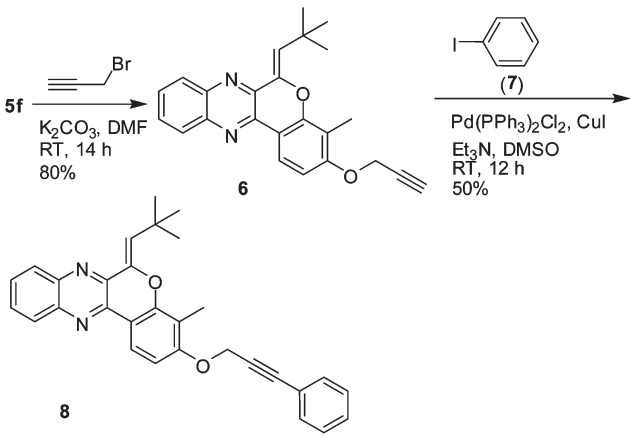
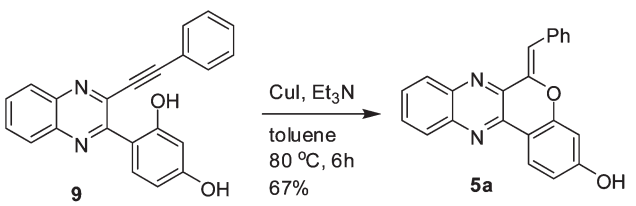


Fig. 5 The formation of 2D corrugated layer with channels via O–H···N intermolecular hydrogen bonding and stabilization by aromatic C–H···π interactions.



Scheme 4 Structure elaboration of compound **5f**.



Scheme 5 Cu-mediated cyclization of compound **9**.

carried out in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in DMSO to give the desired product **8** in 50% yield.

Mechanistically, the reaction seems to proceed *via* Pd/C–Cu mediated *in situ* generation of an internal alkyne **E** (Scheme 1) which undergoes intramolecular cyclization in the presence of CuI present in the reaction mixture. To gain further evidence on intermediacy of alkyne **E** a representative alkyne *i.e.* 4-(3-(phenylethynyl)quinoxalin-2-yl)benzene-1,3-diol (**9**) prepared *via* the reaction of **3a** and **4a** was treated with CuI in toluene in the presence of Et_3N at 80 °C for 6 h when the cyclized product **5a** was isolated in 67% yield (Scheme 5).

The present $AlCl_3$-induced C–C bond formation followed by Pd/C–Cu mediated coupling-cyclization strategy provided a

Table 3 The % inhibition of growth of cancer cell lines by compound **5**[a]

	K-562 (leukemia)			MD-AMB-231 (breast)		
Compound (**5**)	100 μM	10 μM	1 μM	100 μM	10 μM	1 μM
5b	72.3	55.9	50.1	90.4	58.1	45.0
5c	38.4	31.5	25.1	91.1	74.9	63.6
5e	37.4	32.8	30.3	90.7	52.8	48.0
5g	31.0	34.2	22.8	90.5	75.6	40.4
5i	76.0	53.3	45.8	85.9	42.3	41.7

[a] Data presented are average of three experiments.

number of chromeno[4,3-*b*]quinoxaline derivatives in good yields. In compared to other Pd-catalysts the Pd/C catalyst used here can be easily separated from the product by simple filtration thereby decreasing the possibility of metal contamination in the products isolated. Moreover, due to the well known uses of Pd/C for hydrogenation reaction in industry the present strategy has potential for scale up synthesis.

Some of the compounds[10] (**5**) synthesized were tested *in vitro* against leukemia (K-562) and breast (MD-AMB-231) cancer cell lines in a MTT assay. Harmine, a member of beta-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines.[11] While **5b** and **5i** showed good activity against leukemia cells (Table 3), compounds **5b**, **5c**, **5e**, **5g** and **5i** were found to be effective against breast cancer and **5c** was best among them (Table 3, entry 2). Notably, IC_{50} value of Harmine was found to be 45 and 54 μM when tested against K562 and MDA-MB 231 cell lines in our MTT assay. Overall, this research has led to the identification of small molecule-based agents that could be useful for the potential treatment of leukemia or breast cancer. The compounds presented here therefore may have medicinal value.

Conclusions

In conclusion, we have developed a new strategy that allows regioselective construction of fused 2-ylidene chromene ring and thereby rapid access to a library of small molecules based on a novel structural motif. This is the first example of combining the $AlCl_3$-induced C–C bond formation with a Pd/C–Cu mediated coupling-cyclization strategy leading to various chromeno[4,3-*b*]-quinoxaline derivatives. Single crystal X-ray diffraction study of a representative compound confirmed the presence of an exocyclic C–C double bond with Z-geometry. The crystal structure analysis and hydrogen bonding patterns of the same compound along with its structure elaboration *via* propargylation followed by Sonogashira coupling of the resulting terminal alkyne is presented. A probable mechanism for the formation of 2-ylidene chromene ring is discussed. Some of the compounds synthesized showed anticancer properties when tested *in vitro*. Our study therefore suggests that the 6-ylidene chromeno quinoxalin framework could be an attractive template for the identification of novel anticancer agents.

Experimental

Chemistry

General methods. Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100–200 and 230–400 mesh) using hexene, ethyl acetate, dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6, solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

General procedure for the preparation of 4-(3-chloroquinoxalin-2-yl)benzene-1,3-diol (3). A mixture of 2,3-dichloroquinoxaline (**1**, 1.0 equiv.), an appropriate arene (**2**, 1.0 equiv.) and $AlCl_3$ (1.1 equiv.) in dichloroethane (5 mL) was stirred at 80 °C for 30 min under a nitrogen atmosphere. After completion of the reaction, the mixture was cooled to room temperature, poured into ice-cold water (15 mL), stirred for 10 min and then extracted with ethylacetate (3 × 20 mL). The organic layers were collected, combined, washed with cold water (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue obtained was purified by column chromatography on silica gel (230–400 mesh) using ethylacetate–hexene to give the desired product.

4-(3-Chloroquinoxalin-2-yl)benzene-1,3-diol (3a). Yellow solid; mp 176–178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (bs, 1H), 9.64 (bs, 1H), 8.10–8.08 (m, 1H), 8.05–8.02 (m, 1H), 7.89–7.85 (m, 2H), 7.15 (d, J = 8.4, 1H), 6.40–6.34 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 156.9, 153.3, 148.5, 140.7, 140.5, 131.7, 131.2, 130.9, 129.1, 128.1, 116.3, 107.0, 102.9; HPLC: 97.8%, column: Zorbax XDB C-18 150 × 4.6 mm 5μ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/20, 2/20, 9/95, 12/95, 15/20, 18/20; flow rate: 1.0 mL min^{-1}; UV 240 nm, retention time 7.8 min; m/z (CI) 273 (M + 1, 100); IR (KBr) ν_{max} 3289, 1623, 1598 cm^{-1}.

4-(3-Chloroquinoxalin-2-yl)-2-methylbenzene-1,3-diol (3b). Yellow solid; mp 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (bs, 1H), 9.03 (bs, 1H), 8.10–8.03 (m, 2H), 7.88–7.84 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 154.7, 153.4, 148.1, 140.54, 140.51, 131.1, 130.9, 129.0, 128.10, 128.08, 116.2, 111.6, 107.0, 9.3; IR (KBr) ν_{max} 3379, 1637, 1688 cm^{-1}; m/z (CI) 287 (M + 1, 100%).

General procedure for the preparation of chromeno[4,3-*b*]quinoxalin-3-ol (5). A mixture of 4-(3-chloroquinoxalin-2-yl)-benzene-1,3-diol (**3**) (1.0 mmol), 10% Pd/C (0.035 mmol), PPh_3 (0.35 mmol), CuI (0.06 mmol), and triethylamine (3.0 mmol) in toluene (5 mL) was stirred at 25–30 °C for 30 min under

nitrogen. A terminal alkyne (**4**) (1.5 mmol) slowly was added to this mixture. The mixture was then stirred at room temperature for 1.0 h and then at 75–80 °C for 6–7 h. After completion of the reaction the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The organic layers were collected, washed with water (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel (230–400 mesh) using hexane–ethyl acetate to afford the desired product.

6-Benzylidene-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5a). Light red solid; mp 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (bs, 1H), 8.25–8.23 (m, 1H), 8.04–7.99 (m, 4H), 7.83–7.78 (m, 2H), 7.53–7.49 (m, 2H), 7.40–7.36 (m, 1H), 7.30–7.28 (m, 1H), 6.79–6.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 154.9, 146.8, 142.6, 141.6, 141.5, 134.6 (2C), 131.0, 130.0 (3C), 129.2, 129.1, 128.6, 128.0, 127.8, 126.8, 112.9, 110.8, 108.8, 102.8; HPLC: 97.1%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.1% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/80, 2/80, 9/98, 13/98, 15/80, 18/80; flow rate: 1.0 mL min^{-1}; UV 229 nm, retention time 6.1 min; IR (KBr) ν_{max} 3439, 2923, 1614 cm^{-1}; *m*/*z* (CI) 337 (M − 1, 100%).

4-Methyl-6-(4-methylbenzylidene)-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5b). Light red solid; mp 231–233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (bs, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.95–7.92 (m, 2H), 7.82–7.70 (m, 2H), 7.74–7.67 (m, 2H), 7.63–7.58 (m, 1H), 7.25–7.23 (m, 2H), 7.19 (s, 1H), 6.71–6.68 (m, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 155.0, 146.2, 142.7, 142.6, 141.70, 141.68, 137.7, 131.9, 131.8, 130.8, 130.0, 129.9, 129.7, 129.2, 129.1, 128.6, 126.8, 112.8, 110.8, 109.0, 102.8, 21.4; HPLC: 97.9%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/80, 2/80, 9/98, 13/98, 15/80, 18/80; flow rate: 1.0 mL min^{-1}; UV 229 nm, retention time 7.5 min; IR (KBr) ν_{max} 2923, 1511, 1331 cm^{-1}; *m*/*z* (CI) 353 (M + 1, 100%).

5-(3-Hydroxy-6*H*-chromeno[4,3-*b*]quinoxalin-6-ylidene)pentanenitrile (5c). Light red solid; mp 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (bs, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.94–7.90 (m, 2H), 7.75–7.69 (m, 2H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.50 (s, 1H), 6.28 (t, *J* = 7.2 Hz, 1H), 2.59–2.52 (m, 4H), 1.82–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 155.6, 147.4, 142.7, 142.6, 141.5, 141.3, 130.9, 129.8, 129.0, 128.7, 126.8, 121.0, 120.4, 112.4, 110.6, 102.7, 24.1, 18.0, 15.9; HPLC: 96.6%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.01% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/60, 2/60, 9/98, 12/98, 15/60, 18/60; flow rate: 0.8 mL min^{-1}; UV 230 nm, retention time 6.2 min; IR (KBr) ν_{max} 3140, 3140, 1331 cm^{-1}; *m*/*z* (CI) 328 (M − 1, 100%).

4-Methyl-6-(4-methylbenzylidene)-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5d). Light red solid; mp 270–272 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (bs, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.96–7.91 (m, 2H), 7.83–7.81 (m, 2H), 7.75–7.69 (m, 2H), 7.52–7.45 (m, 2H), 7.25 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 155.0, 146.1, 142.7, 142.5, 141.7, 137.7, 132.0, 131.9, 131.8, 130.8, 129.9 (2C), 129.7 (2C), 129.1, 128.6, 126.8, 112.8, 110.8, 109.0, 102.8, 21.4, 9.3; HPLC: 98.4%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.1% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/80, 2/80, 9/98, 13/98, 15/80, 18/80; flow rate: 1.0 mL min^{-1}; UV 264 nm, retention time 9.6 min; IR (KBr) ν_{max} 2923, 1598, 1344 cm^{-1}; *m*/*z* (CI) 367 (M + 1, 100%).

5-(3-Hydroxy-4-methyl-6*H*-chromeno[4,3-*b*]quinoxalin-6-ylidene)pentanenitrile (5e). Light red solid; mp 146–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (bs, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.95–7.91 (m, 2H), 7.76–7.68 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.32 (t, *J* = 7.6 Hz, 1H), 2.62–2.58 (m, 2H), 2.57–2.53 (m, 2H), 2.16 (s, 3H), 1.87–1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 153.3, 147.5, 143.0, 142.7, 141.5, 141.1, 130.8, 129.7, 129.0, 128.6, 123.3, 121.0, 111.3, 111.1, 110.5, 110.2, 24.7, 24.1, 16.5, 8.4; HPLC: 97.8%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.01% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/80, 2/80, 9/98, 12/98, 15/80, 18/80; flow rate: 0.8 mL min^{-1}; UV 255 nm, retention time 4.9 min; IR (KBr) ν_{max} 3101, 1603, 1343 cm^{-1}; *m*/*z* (CI) 344 (M + 1, 100%).

6-(2,2-Dimethylpropylidene)-4-methyl-6*H*-chromeno[4,3-*b*]-quinoxalin-3-ol (5f). Yellow solid; mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 8.4 Hz, 1H), 7.95–7.91 (m, 2H), 7.63–7.59 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 5.34 (bs, 1H), 2.32 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 153.5, 145.8, 142.8, 142.6, 141.55, 141.52, 130.7, 129.7, 129.0, 128.6, 123.4, 121.3, 111.4, 110.8, 110.5, 31.9, 30.1 (3C), 9.2; HPLC: 96.3%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.1% formic acid in water, mobile phase B: CH_3CN (Isocratic); A : B (10 : 90); flow rate: 1.0 mL min^{-1}; UV 230 nm, retention time 6.0 min; IR (KBr) ν_{max} 3143, 1603, 1351 cm^{-1}; *m*/*z* (CI) 333 (M + 1, 100%).

4-Methyl-6-((trimethylsilyl)methylene)-6*H*-chromeno[4,3-*b*]-quinoxalin-3-ol (5g). Yellow solid; mp 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (bs, 1H), 8.00–7.98 (m, 1H), 7.92–7.89 (m, 2H), 7.72–7.66 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 2.17 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 157.9, 153.5, 143.2, 143.1, 141.9, 140.1, 131.4, 130.0, 129.5, 128.8, 123.6, 111.6, 110.9, 110.7, 106.4, 9.1, 0.001 (3C); IR (KBr) ν_{max} 2943, 1628, 1441 cm^{-1}; *m*/*z* (CI) 350 (M + 1, 100%).

6-(2-Hydroxy-2-methylpropylidene)-4-methyl-6*H*-chromeno-[4,3-*b*]quinoxalin-3-ol (5h). Light red solid; mp 176–178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (bs, 1H), 8.04–8.00 (m, 1H), 7.96–7.91 (m, 2H), 7.77–7.68 (m, 2H), 6.74–6.71 (m, 1H), 6.55 (s, 1H), 5.00 (bs, 1H), 2.16 (s, 3H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 153.4, 144.0, 142.9, 142.7, 141.5, 141.4, 130.9, 129.8, 129.0, 128.6, 123.4, 121.9, 111.4, 111.0, 110.4, 64.1, 31.5 (2C), 9.0; HPLC: 97.5%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/40, 2/40, 9/98, 12/98, 15/40, 18/40; flow rate: 0.8 mL min^{-1};

UV 230 nm, retention time 8.0 min; IR (KBr) ν_{max} 3230, 1605, 1102 cm^{-1}; *m/z* (CI) 333 (M − 1, 100%).

4-Methyl-6-pentylidene-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5i). Yellow solid; mp 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (bs, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.95–7.91 (m, 2H), 7.63–7.59 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.31 (t, J = 8.0 Hz, 1H), 2.13 (s, 3H), 2.01–2.03 (m, 2H), 1.54–1.50 (m, 2H), 1.42–1.38 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 151.1, 150.1, 143.3, 142.7, 141.6, 129.7, 129.3, 129.2, 128.8, 123.0, 112.8, 112.3, 111.2, 110.7, 110.0, 31.2, 25.1, 22.3, 14.0, 8.1; HPLC: 96.9%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/80, 2/80, 9/98, 13/98, 15/80, 18/80; flow rate: 1.0 mL min^{-1}; UV 255 nm, retention time 9.6 min; IR (KBr) ν_{max} 2925, 1605, 1434 cm^{-1}; *m/z* (CI) 333 (M + 1, 100%).

6-Hexylidene-4-methyl-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5j). Yellow solid; mp 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (bs, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.90–7.87 (m, 2H), 7.72–7.65 (m, 2H), 6.70–6.68 (m, 1H), 6.32 (t, J = 8.0 Hz, 1H), 2.43–2.39 (m, 2H), 2.12 (s, 3H), 1.54–1.51 (m, 2H), 1.37–1.33 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 153.6, 146.7, 143.3, 142.7, 141.6, 129.7, 129.2, 128.7, 123.0, 121.0, 112.8, 112.3, 111.2, 110.9, 110.7, 31.6, 28.7, 25.1, 22.4, 14.1, 8.1; HPLC: 97.8%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/90, 2/90, 9/98, 13/98, 15/90, 18/90; flow rate: 1.0 mL min^{-1}; UV 230 nm, retention time 8.6 min; IR (KBr) ν_{max} 2927, 1603, 1433 cm^{-1}; *m/z* (CI) 347 (M + 1, 100%).

6-Heptylidene-4-methyl-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5k). Yellow solid; mp 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.91–7.88 (m, 2H), 7.72–7.68 (m, 2H), 6.70 (d, J = 8.8 Hz, 1H), 6.30 (t, J = 8.0 Hz, 1H), 2.40 (q, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.54–1.48 (m, 2H), 1.37–1.33 (m, 2H), 1.28–1.27 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 153.5, 146.7, 143.1, 142.6, 141.5, 141.4, 130.6, 129.6, 129.0, 128.6, 123.4, 112.7, 111.2, 111.0, 110.5, 31.5, 29.0, 28.9, 25.0, 22.5, 14.4, 8.3; HPLC: 97.1%, column: Zorbax XDB C-18 150 × 4.6 mm 5µ, mobile phase A: 0.05% formic acid in water, mobile phase B: CH_3CN (gradient) T/%B: 0/90, 2/90, 9/98, 13/98, 15/90, 18/90; flow rate: 1.0 mL min^{-1}; UV 230 nm, retention time 10.6 min; IR (KBr) ν_{max} 2924, 1601, 1326 cm^{-1}; *m/z* (CI) 361 (M + 1, 100%).

4-Methyl-6-nonylidene-6*H*-chromeno[4,3-*b*]quinoxalin-3-ol (5l). Brick red solid; mp 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.93–7.90 (m, 2H), 7.73–7.68 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.31 (t, J = 8.0 Hz, 1H), 2.45–2.41 (m, 2H), 2.14 (s, 3H), 1.54–1.53 (m, 2H), 1.39–1.25 (m, 14H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.0, 159.8, 159.5, 150.9, 150.0, 140.7, 140.4, 130.1, 129.5, 129.0, 128.6, 128.5, 120.8, 116.3, 112.9, 112.8, 35.4, 31.7, 29.4, 29.3, 29.14, 29.12, 28.8, 26.6, 22.5, 14.3, 9.6; IR (KBr) ν_{max} 2854, 1592, 1338 cm^{-1}; *m/z* (CI) 417 (M + 1, 100%).

6-hexyl-4-methylbenzo[*b*]quinoxalinoxepin-3-ol (5kk). This compound was isolated in 10% yield along with **5k** when the reaction of **3b** and the alkyne **4k** was conducted in the presence of $PdCl_2(PPh_3)_2$, CuI in toluene at 80 °C for 8 h; yellow solid; mp 201–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 1H), 7.97–7.94 (m, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.67–7.64 (m, 2H), 6.78 (d, J = 8.8 Hz, 1H), 6.25 (s, 1H), 5.67 (bs, 1H), 2.48 (t, J = 7.6 Hz, 2H), 2.30 (s, 3H), 1.76–1.72 (m, 2H), 1.43–1.41 (m, 2H), 1.33–1.32 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.2, 151.0 (2C), 140.7, 129.74, 129.69, 129.4 (3C), 129.0 (2C), 128.0, 127.9, 116.3, 112.8, 31.6, 29.7, 28.9, 29.7, 22.5, 14.0, 9.1; *m/z* (CI) 361 (M + 1, 100%).

Preparation of 6-(2,2-dimethylpropylidene)-4-methyl-3-(prop-2-ynyloxy)-6*H*-chromeno[4,3*b*]quinoxaline (6). To a mixture of (*Z*)-6-(2,2-dimethylpropylidene)-4-methyl-6*H*-chromeno[4,3-*b*]-quinoxalin-3-ol (**5f**) (0.60 mmol), and K_2CO_3 (0.90 mmol) in anhydrous DMF (5 mL) was added propargyl bromide (0.72 mmol) at room temperature. The resulting mixture was then stirred at room temperature for 14 h. Upon completion of the reaction, the reaction mixture was diluted with ice-cold water. The solid obtained was filtered and washed with water to afford the desired compound **6** as yellow solid (yield 80%); mp 146–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 1H), 7.97–7.91 (m, 2H), 7.66–7.59 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 6.49 (s, 1H), 4.81 (d, J = 2.4 Hz, 2H), 2.55 (t, J = 2.8 Hz, 1H), 2.32 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.4, 145.8, 142.7, 142.6, 142.2, 142.0, 129.7, 129.0, 128.9, 128.6, 123.3, 122.0,114.0, 113.2, 107.1, 78.3, 75.8, 56.3, 31.9, 29.9 (3C), 9.0; IR (KBr) ν_{max} 3231, 2958, 2111, 1608, 1115; *m/z* (CI) 371 (M + 1, 100%).

Preparation of 6-(2,2-dimethylpropylidene)-4-methyl-3-(3-phenylprop-2-ynyloxy)-6*H*-chromeno[4,3-*b*]quinoxaline (8). A mixture of iodo benzene (**7**) (0.26 mmol) in DMSO (5 mL), $Pd(PPh_3)_2Cl_2$ (0.006 mmol), CuI (0.01 mmol), and Et_3N (0.39 mmol) were created under a nitrogen atmosphere. The acetylenic compound **6** (0.26 mmol) was added slowly to the mixture with stirring. The reaction mixture was allowed to stir at room temperature for 12 h. Then the reaction mixture was diluted with water (15 mL) and the product was extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography to afford the desired product as yellow solid (yield 50%); mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.8 Hz, 1H), 7.97–7.91 (m, 2H), 7.65–7.59 (m, 2H), 7.44 (dd, J = 6.8, 1.6 Hz, 2H), 7.33–7.29 (m, 3H), 6.93 (d, J = 8.8 Hz, 1H), 6.49 (s, 1H), 5.03 (s, 2H), 2.34 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.5, 145.8, 142.57 (2C), 142.3, 142.0, 131.8, 129.7, 129.04, 129.01, 128.9, 128.8, 128.7, 128.4, 128.3, 123.4, 122.15, 122.11, 114.0, 112.9, 107.4, 87.5, 83.6, 57.2, 31.9, 29.9 (3C), 9.1; IR (KBr) ν_{max} 2924, 2854, 2151, 1600, 1115; *m/z* (CI) 447 (M + 1, 100%).

Preparation of 5a from 9. A mixture of 4-(3-(phenylethynyl)-quinoxalin-2-yl)benzene-1,3-diol (**9**) (1.0 mmol) (obtained *via* the reaction of **3a** and **4a** in low yield at 45–50 °C),

CuI (0.06 mmol), and Et_3N (3.0 mmol) in toluene (5 mL) was stirred at 80 °C for 6 h. After completion of the reaction the mixture was cooled to room temperature, diluted with EtOAc (30 mL), and filtered through Celite. The organic layer was collected, washed with water (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (230–400 mesh) using hexane/ethyl acetate to afford the desired product **5a**.

Single crystal X-ray data for compound 5f. Single crystals suitable for X-ray diffraction of **5f** was grown from dimethyl formamide. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Bruker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[12] The crystal structure was solved by direct methods using SHELXS-97 and the data was refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[13]

Crystal data of **5f**: Molecular formula = $C_{21}H_{20}N_2O_2$, Formula weight = 332.15, crystal system = monoclinic, space group = $P2(1)/C$, a = 19.497(2) Å, b = 5.589(7) Å, c = 16.139(2) Å, V = 1687.6(4) Å^3, T = 296(2) K, Z = 4, Dc = 1.316 Mg m^{-3}, μ(Mo-Kα) = 0.09 mm^{-1}, 17 443 reflections measured, 4075 independent reflections, 2670 observed reflections [$I > 2.0\sigma(I)$], $R1\_obs$ = 0.040, goodness of fit = 1.042.

Biological assay

Cell lines and culture conditions. Human metastatic breast cancer cells, MDA-MB 231 and human chronic myeloid leukemia cells, K562, were procured from National Center for Cell Sciences, Pune, India. All cells were grown in RPMI-1640 supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 IU mL^{-1} penicillin, 100 mg mL^{-1} streptomycin and 2 mM-glutamine. Cultures were maintained in a humidified atmosphere with 5% CO_2 at 37 °C. The cells were subcultured twice each week, seeding at a density of about 2 × 10^3 cells per mL.

MTT assay. Cell viability was determined by (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells (5 × 10^3 cells per well) were seeded to 96-well culture plate and cultured with or without compounds at 1, 10 and 100 μM concentration for 24 h in a final volume of 200 μL. After treatment, the medium was removed and 20 μL of MTT (5 mg mL^{-1} in PBS) was added to the fresh medium. After 2 h incubation at 37 °C, 100 μL of DMSO was added to each well and plates were agitated for 1 min. Absorbance was read at 570 nm on a multi-well plate reader (Synergy Mx, Biotek Inc., USA). Percent inhibition of proliferation was calculated as a fraction of control (without compound).

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