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Ultrasound mediated catalyst free synthesis of 6*H*-1-benzopyrano [4,3-*b*]quinolin-6-ones leading to novel quinoline derivatives: Their evaluation as potential anti-cancer agents

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ABSTRACT

A facile and catalyst free synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones has been accomplished via the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde with various aromatic amines in the presence of ultrasound. Some of these compounds were converted to the corresponding 2-(3-(hydroxymethyl)quinolin-2-yl)phenols and further structure elaboration of a representative quinoline derivative is presented. Molecular structure of two representative compounds was confirmed by single crystal X-ray diffraction study. Many of these compounds were evaluated for their anti-proliferative properties in vitro against four cancer cell lines and several compounds were found to be active. Further in vitro studies indicated that inhibition of sirtuins could be the possible mechanism of action of these molecules.

1. Introduction

Coumarins are well known aromatic lactones isolated from a variety of plant sources[1] and possess diverse pharmacological activities. For example, the coumarin framework is present in a number of promising drug candidates such as nonpeptidic HIV protease inhibitors,[2] topoisomerase II[3] and tyrosine kinase inhibitors.[4] Quinoline derivatives on the other hand are known to have wide applications as drugs and pharmaceuticals.[5] A combination of chromen or benzopyran with a quinoline moiety in a single molecule, for example, 6*H*-chromeno[4,3-*b*]quinoline[6] or 1-benzopyrano[3,4-*f*]quinoline[7] have also been explored for the identification of promising bioactive molecules. While combination of coumarin and quinoline in a single molecule, for example, 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-one[8] is known as a separate class of heterocycle its use as a template for the identification of bioactive molecules is not common. In view of known cytotoxicities of coumarins and chromeno[4,3-*b*]quinoline derivatives[9] we hypothesized that design of small molecules based on 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-one (**A**, Fig. 1) or converting them into the corresponding quinoline derivatives (**B**, Fig. 1) might show anticancer properties. Herein we report synthesis and further transformation of a number of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-one derivatives along with the in vitro anticancer properties of some of the compounds synthesized.

2. Results and discussion

2.1. Chemistry

The 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones were synthesized previously from 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde using $AlCl_3$ as a catalyst[10] or via other methods.[8]

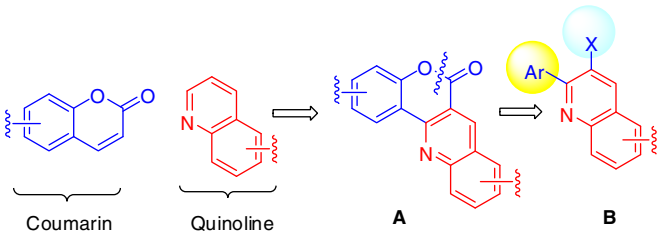

Figure 1. Design of benzopyranoquinolinone (**A**) and quinoline derivatives (**B**) as potential anticancer agents.

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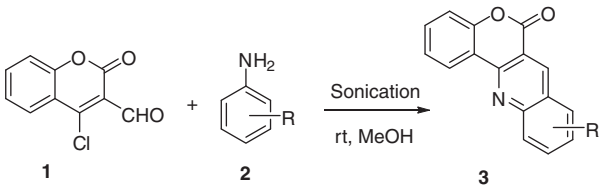


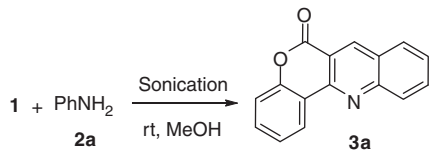
Scheme 1. Synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones from 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde.

However, we were particularly interested in developing a catalyst free method for the synthesis of this class of compounds. This prompted us to develop an ultrasound-promoted catalyst free synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones (**3**) from 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**1**) and anilines (**2**) under ambient conditions. In general the ultrasound-promoted chemical reactions offer several advantages over conventional process especially with respect to the reaction time and product yields.[11] The required starting material **1** was prepared from 4-hydroxy coumarin under Vilsmeier–Haack reaction conditions[12] and then reacted with aromatic amines in methanol under ultrasonication at room temperature to give **3** in good yields (Scheme 1). Initially the reaction of **1** with aniline (**2a**) was examined in a range of solvents to identify the best solvent for this process (Table 1). The use of MeOH was found to be effective as the reaction was completed within 5 min providing the product **3a** in 94% yield (entry 1, Table 1). The use of water increased the reaction time with significant decrease in product yield (entry 2, Table 1). The use of dichloromethane and toluene was found to be ineffective (entries 3 and 4, Table 1) and the reaction did not proceed in DMF (entry 5, Table 1). Thus MeOH was identified as the solvent for the present condensation reaction.

Having the optimized reaction condition for the preparation of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones in hand we then examined the generality and scope of this methodology. Thus a variety of aromatic amines (**2**) were reacted with chloro aldehyde (**1**) in MeOH at room temperature under ultrasonication and results are presented in Table 2. The reaction proceeded well in all these cases and the substituents like F, Cl, Br, OMe and Me present in the aromatic amines (**2**) were well tolerated. The reaction appeared to be clean as no formation of side product was observed and the desired product **3** was isolated in good to excellent yield in each case. All the compounds synthesized were well characterized by spectral (NMR, MS and IR) data. Additionally, the molecular structure of a representative compound **3a** was established unambiguously by single crystal X-ray diffraction (Fig. 2).[13]

We have developed a mild and catalyst free direct synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones in good yields. To demonstrate the potential of this methodology a number of compounds prepared were converted to quinoline derivatives (**4**, Table 3). Thus treatment of compound **3** with $NaBH_4$ in THF at room temperature gave 2-(3-(hydroxymethyl)quinolin-2-yl)phenols in good yields. All these compounds (**4a–d**) were characterized by spectral (NMR, MS and IR) data and the molecular structure of a representative compound **4d** was confirmed by X-ray analysis (Fig. 3).[14] Further structure elaboration of a quinoline derivative **4a** was carried out by converting it into an azide derivative **5a** (Scheme 2). Treating the azide **5a** with a terminal alkyne in the presence of CuI provided the corresponding triazole derivative **5b** (Scheme 2). Further, on reduction the azide **5a** provided the primary amine **5c** which on reaction with 4-chloro-3-nitro-5-sulfamoylbenzoic acid afforded a novel sulfonamide based compound **5d** (Scheme 2).

Table 1
Effect of solvents on the reaction of chloroaldehyde (**1**) and aniline (**2a**) under ultrasonication[a]



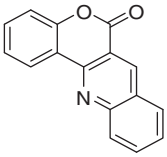
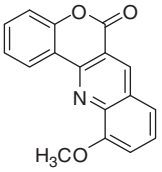
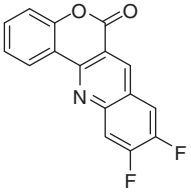
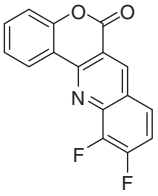
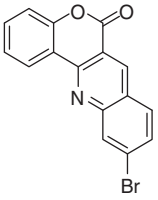
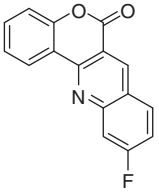
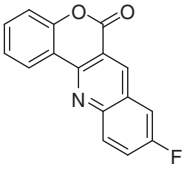
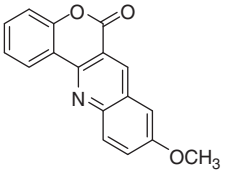
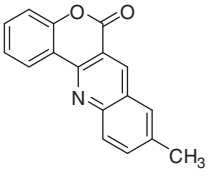
Entry	Solvent	Time (min)	Yield[b] (%)
1	MeOH	5	94
2	H_2O	15	65
3	DCM	20	46
4	Toluene	30	35
5	DMF	45	No reaction

[a] All the reactions were carried out using **1** (1.0 mmol) and **2a** (1.5 mmol) at room temperature.
[b] Isolated yield.

2.2. Pharmacology

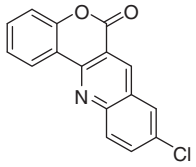
Many of the compounds synthesized, for example, **3**, **4** and **5** were tested for their anticancer properties in vitro. Cancer is the second leading cause of death[15] worldwide after cardiovascular diseases, according to WHO. We evaluated our compounds for their anti-proliferative properties in vitro against a number of cancer cell lines, for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), breast cancer cells (MDA-MB 231), and human neuroblastoma cells (IMR32). The test compounds were examined at various concentrations in a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and the IC_{50} values obtained for each compounds are summarized in Table 4. Harmine, a member of beta-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines[16] was used as a reference compound. While most of the compounds showed inhibition of leukemia cell growth as reflected by their IC_{50} values the best results however were obtained using compounds **4b**, **4c**, **4d**, **5a**, **5b** and **5d** (IC_{50} ~10–13 μM, Table 4). All these compounds are derivatives of 2-aryl substituted quinoline indicating that the 2-arylquinoline framework played a key role in the inhibition of leukemia cell growth. Compounds **3a, 3c, 3g, 3j, 5a, 5b** and **5d** (IC_{50} ~11–18 μM, Table 4) were found to be active against colon carcinoma cells whereas **3a, 3b, 3c, 3g, 3h, 3i, 3j, 5a, 5b** and **5d** (IC_{50} ~8–16 μM, Table 4) showed promising activities against breast cancer cells. While many of these compounds were found to be active against human neuroblastoma cells none of them however showed IC_{50} <20 μM except compound **5d** (IC_{50} ~18 μM, Table 4). In order to understand the mechanism of action some of the compounds were tested for their inhibitory potential against sirtuins. Being considered as important targets for cancer therapeutics sirtuins (class III NAD-dependent deacetylases) are shown to up-regulated in various types of cancer.[17] Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. The activity of test compounds was determined using Sirt1 fluorescence activity assay[18] using suramin, a known inhibitor of Sirt1 as a reference compound. At the concentration of 10 μM compounds **3d**, **4c**, **5a**, **5b**, **5c** and **5d** showed 48%, 48%, 53%, 62%, 59% and 61% inhibition, respectively, in compared to suramin's 79% inhibition indicating that the anticancer properties of these molecules are possibly due to their sirtuin inhibiting properties. To understand the nature of interactions between these compounds and the Sir1 protein a molecular docking simulation study was carried out using a representative compound **5b** (Fig. 4). The three dimensional model of hSirt1 (NCBI gi no: 7555471, 200–500 amino acid residues) was developed by

Table 2
Catalyst free synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones (**3**) from **1** (Scheme 1)[a]

Entry	**2**; R=	Product (**3**)	Time (min)	Yield[b] (%)
1	**2a**; H	 **3a**	5	95[8]
2	**2b**; 2-OCH_3	 **3b**	7	92[8]
3	**2c**; 3,4-F	 **3c**	8	90
4	**2d**; 2,3-F	 **3d**	9	92
5	**2e**; 3-Br	 **3e**	7	89
6	**2f**; 3-F	 **3f**	8	94
7	**2g**; 4-F	 **3g**	6	93
8	**2h**; 4-OCH_3	 **3h**	7	91[8]
9	**2i**; 4-CH_3	 **3i**	5	89[8]

(*continued on next page*)

Table 2 (*continued*)

Entry	2; R=	Product (3)	Time (min)	Yield[b] (%)
10	**2j**; 4-Cl	 **3j**	6	93[8]

[a] All the reactions were carried out using **1** (1.0 mmol) and **2** (1.5 mmol) under ultrasonication at room temperature.
[b] Isolated yield.

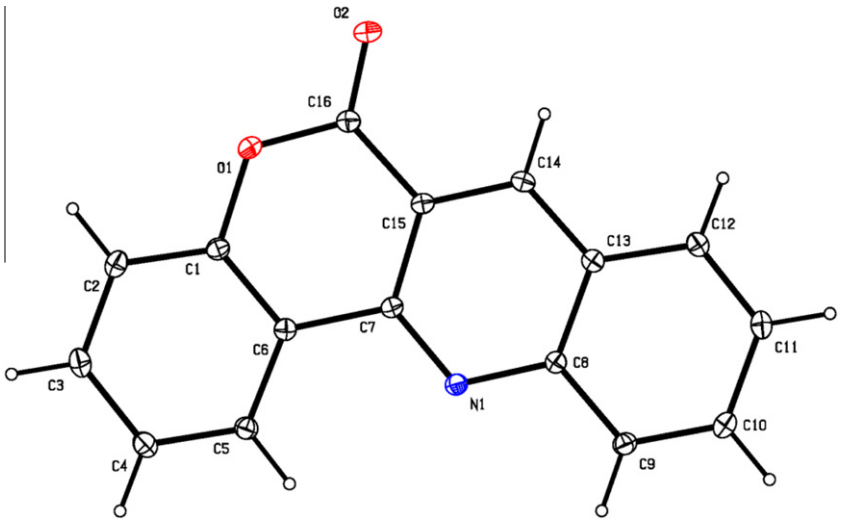


Figure 2. X-ray crystal structure of **3a** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

homology modeling using the templates PDB: 2HJH and PDB: 1J8F in the Modeller9v6. Four amino acid residues, for example, Arg274, Asn348, Cys362 and Pro293 were found to play key roles in this interaction with the overall binding energy of −10.6 Kcal/mol indicating that molecule **5b** interacts well with this protein.

3. Conclusions

In conclusion, 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones and various functionalized quinoline derivatives have been explored as new and potential anti cancer agents. Synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolin-6-ones were carried out by reacting 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde with various aromatic amines via a catalyst free method in the presence of ultrasound. To the best of our knowledge ultrasound mediated synthesis of this class of compounds was not known in the literature. Some of these compounds were converted to the corresponding 2-(3-(hydroxymethyl)quinolin-2-yl)phenols and further structure elaboration of a representative quinoline derivative was carried out. The single crystal X-ray diffraction study was used to confirm the molecular structure of two representative compounds unambiguously. Many of these compounds were evaluated for their anti-proliferative properties in vitro against four cancer cell lines, for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), breast cancer cells (MDA-MB 231), and human neuroblastoma cells (IMR32). A number of compounds showed promising anticancer properties. Further in vitro studies indicated that inhibition of sirtuins could be the possible mechanism of action of these molecules and was supported by a docking study. Overall, our study suggests that both benzopyranoquinolinones and quinolines presented here have medicinal importance and the basic framework of both these classes of heterocycles could be an attractive template for the identification of novel and potential anticancer agents.

4. Experimental section

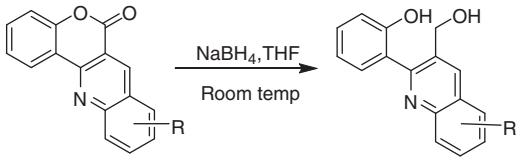
4.1. Chemistry—general methods

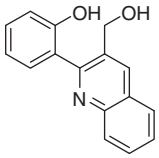
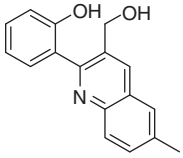
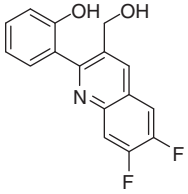
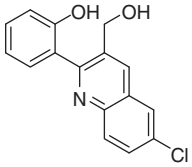
Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO solutions using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as internal standard and expressed in parts per million. 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 FTIR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were obtained on a mass spectrometer. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus.

4.2. General procedure for the preparation of 6*H*-chromeno[4,3-*b*]quinolin-6-one (3a–j)

A solution of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (1 mmol) and aromatic amine (1.5 mmol) in methanol (5 ml) was taken in a 10 mL reaction vial. After being capped, the vial containing the reaction mixture was kept under continuous ultrasound

Table 3
Synthesis of 2-(3-(hydroxymethyl)quinolin-2-yl)phenols (**4**)[a]



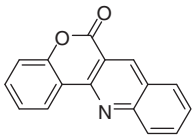
Entry	**3**; R =	Product (**4**)	Time (h)	Yield[b] (%)
1	H	 **4a**	2	85
2	4-CH_3	 **4b**	2.5	88
3	3,4-F	 **4c**	1.5	82
4	4-Cl	 **4d**	2	84

[a] All the reactions were carried out using compound **3** (4.05 mmol) and $NaBH_4$ (8.1 mmol) in dry THF (5 mL).
[b] Isolated yield.

irradiation. After completion of the reaction (confirmed by TLC), the reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography (*n*-hexane/ethylacetate 3:1) to afford the desired product.

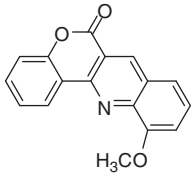
4.3. Spectral data of 6*H*-chromeno[4,3-*b*]quinolin-6-one (3a–j)

4.3.1. 6*H*-Chromeno[4,3-*b*]quinolin-6-one (3a)



white solid; yield (95%); R_f = 0.60 (30% EtOAc-*n*-Hexane); mp 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.67 (dd, J = 7.6 and 1.6 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.02–8.03 (m, 1H), 7.66–7.76 (m, 2H), 7.46–7.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 152.9, 150.5, 149.6, 141.4, 134.2, 133.1, 130.4, 129.2, 128.0, 127.6, 125.4, 125.1, 119.8, 117.7, 116.5; IR (cm^{-1}): 3070, 2928, 1740, 1599, 1465, 1190; MS (ES mass): m/z 248 (M+1, 100%); HRMS: calcd for $C_{16}H_{10}NO_2$: 248.0712, found 248.0710.

4.3.2. 11-Methoxy-6*H*-chromeno[4,3-*b*]quinolin-6-one (3b)



white solid; yield (95%); R_f = 0.35 (10% EtOAc-*n*-Hexane); mp 236–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.2 (s, 1H), 8.86 (dd, J = 7.6 and 1.2 Hz, 1H), 7.57–7.63 (m, 3H), 7.39–7.46 (m, 2H), 7.26 (d, J = 5.6 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 153.3, 152.4, 150.1, 136.0, 129.8, 129.7, 127.8, 127.0, 126.6, 125.9, 124.4, 122.1, 110.0, 114.9, 112.3, 56.2; IR (cm^{-1}): 3063, 2836, 1735, 1604, 1380, 1177, 751; MS (ES mass): m/z 278 (M+1, 10%); HRMS: calcd for $C_{17}H_{12}NO_3$: 278.0817, found 278.0819.

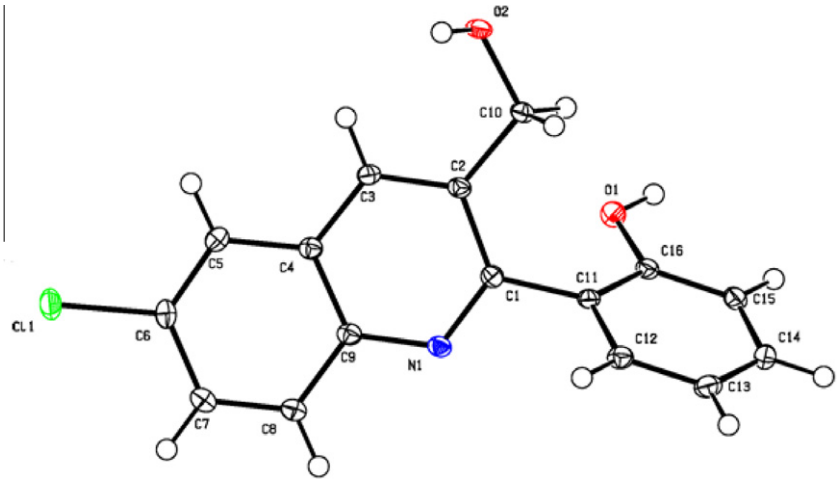
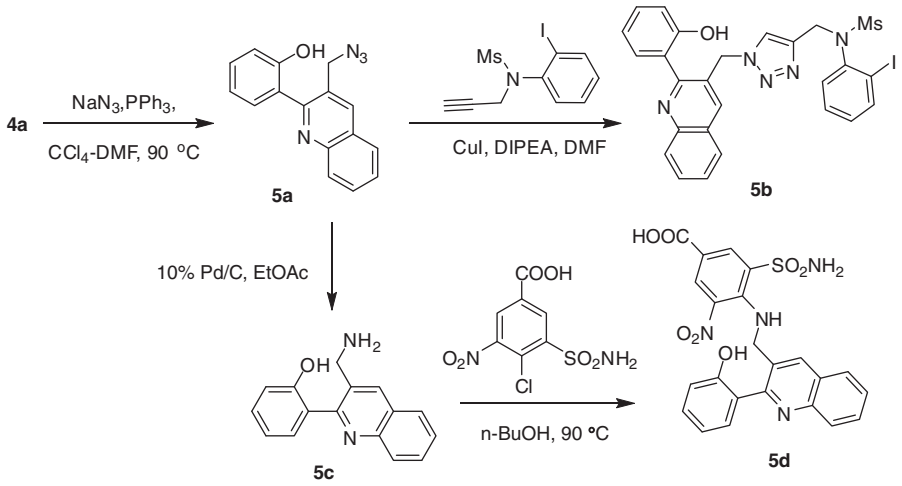


Figure 3. X-ray crystal structure of **4d** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.



Scheme 2. Structure elaboration of quinoline derivative **4a**.

Table 4
Cytotoxic properties of compounds **3**, **4** and **5** against various cancer cell lines

Compound	IC_{50} (μM)[a,b]			
	K562	Colo-205	MDA-MB 231	IMR32
3a	43	18	12	28
3b	35	24	16	46
3c	41	11	08	25
3d	28	29	23	36
3e	23	38	19	23
3f	35	21	29	41
3g	37	17	11	43
3h	39	41	09	36
3i	23	29	12	33
3j	32	16	14	46
4a	74	40	>100	>100
4b	12	>100	>100	>100
4c	12	>100	>100	63
4d	11	24	>100	65
5a	11	19	12	24
5b	13	12	08	38
5c	23	32	19	46
5d	10	19	08	18
Harmine	45	46	54	68

[a] IC_{50} represent the concentration of compound that causes a 50% growth inhibition to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.

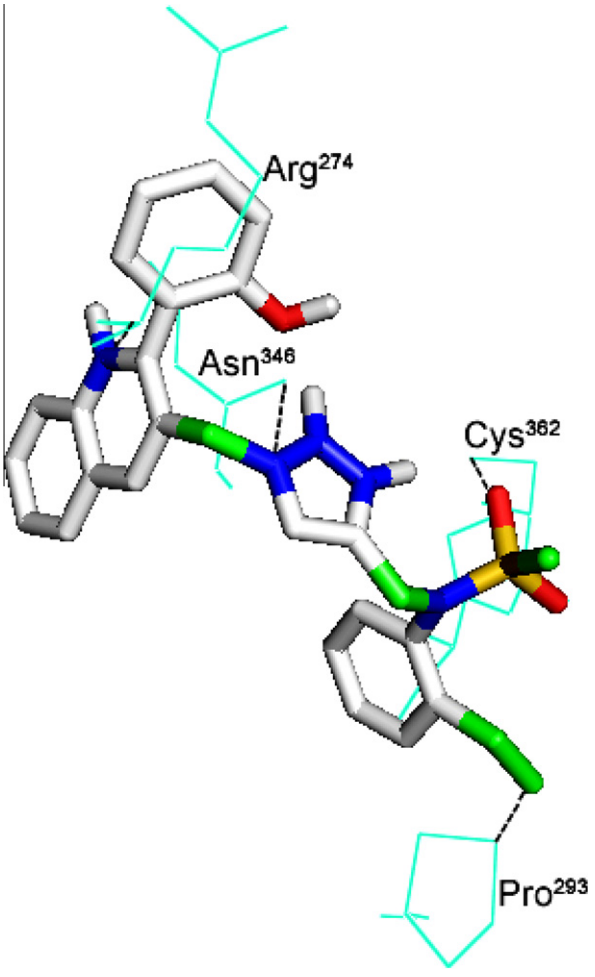
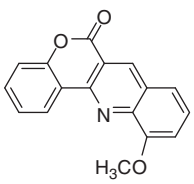


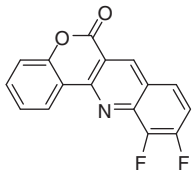
Figure 4. Docking of compound **5b** into the active site of hSirt1.

4.3.3. 9,10-Difluoro-6*H*-chromeno[4,3-*b*]quinolin-6-one (3c)



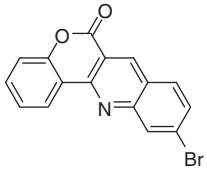
white solid; yield (90%); R_f = 0.4 (10% EtOAc-*n*-Hexane); mp 225–254 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.85 (dd, *J* = 8.0 and 1.6 Hz, 1H), 7.82–7.86 (m, 1H), 7.62–7.66 (m, 1H), 7.40–7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.7, 150.0, 140.1, 140.0, 132.7, 125.2, 125.1, 119.1, 117.4, 115.8, 115.6, 114.4, 114.3, 114.2, 114.1; IR (cm^{-1}): 3070, 2930, 1740, 1610, 1470, 1185; MS (ES mass): *m*/*z* 284 (M+1, 100%). HRMS: calcd for $C_{16}H_8F_2NO_2$: 284.0467, found: 284.0465.

4.3.4. 10,11-Difluoro-6*H*-chromeno[4,3-*b*]quinolin-6-one (3d)



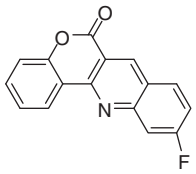
white solid; yield (92%); R_f = 0.42 (20% EtOAc-*n*-Hexane); mp 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.63 (dd, J = 7.6 and 1.2 Hz, 1H), 8.25–8.29 (m, 1H), 7.85–7.92 (m, 1H), 7.76–7.71 (m, 1H), 7.42–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 152.9, 150.6, 141.1, 133.2, 125.7, 125.5, 125.4 (2C), 125.3, 125.2, 124.9, 119.1, 118.8, 118.6, 117.4; IR (cm^{-1}): 3065, 2836, 1735, 1604, 1380, 1177; MS (ES mass): m/z 284 (M+1, 100%); HRMS: calcd for $C_{16}H_7F_2NO_2$: 284.0488, found 284.0476.

4.3.5. 10-Bromo-6*H*-chromeno[4,3-*b*]quinolin-6-one (3e)



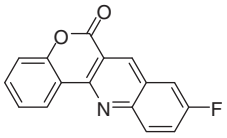
White solid; yield (89%); mp 246–248 °C; R_f = 0.47 (10% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 9.20 (s, 1H), 8.75 (dd, J = 8 and 1.6 Hz, 1H), 8.45 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 8.8 and 1.6 Hz, 1H), 7.60–7.64 (m, 1H),7.39–7.46 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 152.8, 150.4, 141.1, 132.9, 132.8, 131.8, 131.7, 131.2, 130.3, 125.8, 125.4, 125.1, 117.4, 115.9, 110; IR (cm^{-1}): 3070, 2840, 1740, 1604, 1370, 1185; MS (ES mass): m/z 327.1 (M+2, 100%); HRMS: calcd for $C_{16}H_9BrNO_2$: 327.2546, found 327.2462.

4.3.6. 10-Fluoro-6*H*-chromeno[4,3-*b*]quinolin-6-one (3f)



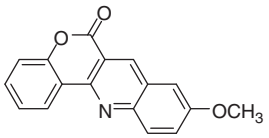
white solid; yield (94%); R_f = 0.45 (20% EtOAc-*n*-Hexane); mp 233–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.77 (dd, J = 8.0 and 1.6 Hz, 1H), 8.02–8.06 (m, 1H), 7.86 (dd, J = 10 and 2.4 Hz, 1H), 7.59–7.64 (m, 1H), 7.39–7.47 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.7, 153.0, 151.6, 150.5, 141.5, 133.4, 125.4, 125.1, 124.9, 119.4, 118.8, 118.5, 117.7, 116.0, 112.7, 112.5; IR (cm^{-1}): 3065, 2836, 1735, 1599, 1380, 1170; MS (ES mass): m/z 266.2 (M+1, 10%); HRMS: calcd for $C_{16}H_9FNO_2$: 266.2022, found 266.2016.

4.3.7. 9-Fluoro-6*H*-chromeno[4,3-*b*]quinolin-6-one (3g)



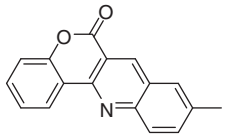
white solid; yield (93%); R_f = 0.55 (20% EtOAc-*n*-Hexane); mp 225–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.77 (dd, J = 8.0 and 1.6 Hz, 1H), 8.25–8.28 (m, 1H), 7.59–7.74 (m, 3H), 7.40–7.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 152.8, 150.4, 149.5, 141.4, 134.2, 133.1, 130.3, 129.2, 127.9, 127.5, 125.3, 125.0, 119.7, 117.7, 116.4; IR (cm^{-1}): 3100, 2990, 2836, 1737, 1601, 1496, 1237, 835; MS (ES mass): m/z 266.3 (M+1, 100%); HRMS: calcd for $C_{16}H_9FNO_2$: 266.3042, found 266.3028.

4.3.8. 9-Methoxy-6*H*-chromeno[4,3-*b*]quinolin-6-one (3h)



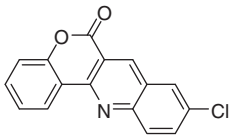
white solid; yield (96%); R_f = 0.71 (20% EtOAc-*n*-Hexane); mp 228–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.1 (s, 1H), 8.76 (dd, J = 10 and 1.6 Hz, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.55–7.60 (m, 2H), 7.39–7.45 (m, 2H), 7.23 (d, J = 2.8 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, TFA): δ 159.6, 153.8, 151.6, 147.6, 142.2, 138.9, 134.7, 134.6, 127.2, 124.8, 124.0, 122.1, 121.8, 118.9, 105.9, 105.6, 58.8; IR (cm^{-1}): 3090, 2980, 2845, 1745, 1601, 1490, 1245, 840; MS (ES mass): m/z 278 (M+1, 10%); HRMS: calcd for $C_{17}H_{12}NO_3$: 278.0819, found 278.0817.

4.3.9. 9-Methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one (3i)



white solid; yield (89%); R_f = 0.60 (30% EtOAc-n-Hexane); mp 233–235 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (s, 1H), 8.77 (dd, J = 8 and 1.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.74–7.76 (m, 2H), 7.56–7.58 (m, 1H), 7.38–7.45 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 152.8, 150.8, 149.6, 145.1, 140.9, 132.9, 130.3, 129.9, 128.0, 125.8, 125.3, 124.9, 119.8, 117.7, 115.6, 22.3; IR (cm^{-1}): 3125, 2995, 2840, 1740, 1595, 1480, 1250; MS (ES mass): m/z 262 (M+1, 100%); HRMS: calcd, for $C_{17}H_{12}NO_2$: 262.0879, found 262.0868.

4.3.10. 9-Chloro-6*H*-chromeno[4,3-*b*]quinolin-6-one (3j)



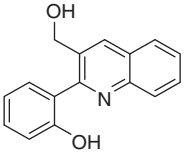
white solid; yield (93%); R_f = 0.4 (20% EtOAc-*n*-Hexane); mp 243–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.1 (s, 1H), 8.77 (dd, J = 7.6 and 1.6 Hz, 1H), 8.18–8.20 (d, J = 9.2 Hz 1H), 8.0 (s, 1H), 7.85 (dd, J = 9.2 and 2.4 Hz, 1H), 7.59–7.62 (m, 1H), 7.39–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 152.6, 149.7, 149.3, 139.9, 134.2, 133.3, 132.6, 131.0, 127.7, 127.6, 125.2, 125.0, 119.2, 117.4, 116.4; IR(cm^{-1}): 3063, 2836, 1735, 1604, 1380, 1177; MS (ES mass): m/z 282 (M+1, 100%); HRMS: calcd for $C_{16}H_9ClNO_2$, 282.0246, found 282.0242.

4.4. General procedure for the Preparation of 2-(3-(hydroxymethyl)quinolin-2-yl)phenol derivatives (4a–d)

A suspension of $NaBH_4$ (0.3 g, 8.1 mmol) in dry THF (5 mL) was stirred at 0 °C. To this was added a solution of 6*H*-chromeno[4,3-*b*]quinolin-6-one (1 g, 4.05 mmol) in THF (5 mL) and mixture was stirred at room temperature for 3–4 h. After completion of the reaction (monitored by TLC) the mixture was cooled to 0 °C and quenched by adding saturated NH_4Cl solution (5 mL). The mixture was then poured in ethyl acetate (50 mL) and stirred for 10 min. The organic layer was collected, washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue isolated was purified by flash chromatography on silica gel using EtOAc-*n*-hexane (2:8) as eluent. The desired product was isolated as a white solid (80%, 0.81 g).

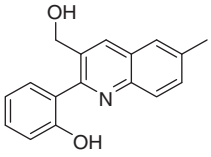
4.5. Spectral data of 2-(3-(hydroxymethyl)quinolin-2-yl)phenol derivatives (4a–d)

4.5.1. 2-(3-(Hydroxymethyl)quinolin-2-yl)phenol (4a)



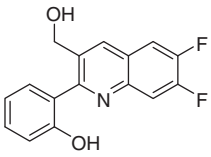
White solid; yield (85%); mp 155–157 °C; R_f = 0.65 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89(s, 1H), 8.51 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 8.2 Hz, 1H), 7.55 (dd, J = 7.4 and 1.6 Hz, 1H), 7.26 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 5.58 (t, J = 5.6 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 157.9, 157.2, 144.7, 138.3, 132.5, 131.2, 130.4, 129.8, 127.6, 127.5, 127.1, 126.7, 121.3, 119.1, 118.2, 62.9; IR (cm^{-1}): 3130, 3067, 2954; MS (ES mass): m/z 251.9 (M+1, 100%).

4.5.2. 2-(3-(Hydroxymethyl)-6-methylquinolin-2-yl)phenol (4b)



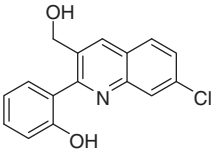
Brown solid; yield (88%); mp 145–146 °C; R_f = 0.65 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H), 8.34 (s, 1H), 7.84–7.87 (m, 2H), 7.74 (dd, J = 8.8 and 1.6 Hz, 1H), 7.20–7.32 (m, 2H), 6.91–6.97 (m, 2H), 5.37 (t, J = 5.6 Hz, 1H), 4.50 (d, J = 5.2 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.8, 144.4, 135.8, 135.2, 131.9, 131.1, 130.3, 129.6(2C), 128.1, 127.1, 126.7, 126.2, 119.0, 115.6, 60.0, 21.2; IR(cm^{-1}): 3090, 3041, 2957; MS(ES mass): m/z 266.2 (M+1, 10%).

4.5.3. 2-(6,7-Difluoro-3-(hydroxymethyl)quinolin-2-yl)phenol (4c)



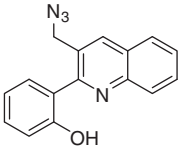
white solid; yield (82%); mp: 232–233 °C; R_f = 0.3 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (s, 1H), 8.40 (s, 1H), 8.02–8.05 (m, 1H), 7.84–7.87 (m, 1H), 7.20–7.31 (m, 2H), 6.90–6.96 (m, 2H), 5.38 (t, J = 5.6 Hz,1H), 4.52 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.4, 154.5(2C), 143.2, 135.8, 131.9, 130.1, 129.8, 126.4, 124.2, 119.0, 115.5, 114.9, 114.6, 113.4, 59.6; IR (cm^{-1}): 3143, 3074, 2924; MS (ES mass): m/z 288.1(M+1)$^+$, 100%).

4.5.4. 2-(6-Chloro-3-(hydroxymethyl)quinolin-2-yl)phenol (4d)



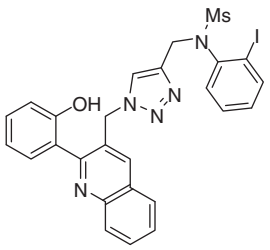
white solid; yield (84%); mp: 213–214 °C; R_f = 0.6 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.19–7.29 (m, 2H), 6.88–6.95 (m, 2H), 5.38 (t, J = 5.6 Hz, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.9, 155.1, 144.9, 137.0, 131.9, 131.1, 131.0, 130.6, 130.2, 129.7, 128.4, 127.0, 126.7, 119.4, 116.0, 60.2; IR (KBr, cm^{-1}) 2930, 2210, 1718, 1274; MS (ES mass): m/z 285.9 (M+1, 100%).

4.6. Preparation of 2-(3-(Azidomethyl)quinolin-2-yl)phenol (5a)



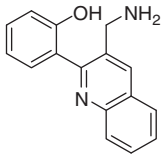
To a mixture of 2-(3-(hydroxyl methyl)quinolin-2-yl)phenol (0.8 g, 3.2 mmol), sodium azide (0.25 g, 3.84 mmol) and PPh_3 (1.0 g, 3.84 mmol) in 1:4 CCl_4–DMF (5 mL) was stirred at 90 °C for 2–3 h. After disappearance of starting material (monitored by TLC), the reaction mixture was cooled to room temperature and quenched with water (5 mL). After stirring the mixture for 5 min it was diluted with ethylacetate (50 mL). The organic layer was collected, washed thoroughly with water (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane (1:9) as eluant. The desired product was isolated as a white solid (90%, 0.79 g); mp: 124–126 °C; R_f = 0.4 (30% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.2 (s, 1H), 8.39 (s, 1H), 8.05 (d J = 8.8 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.60–7.64 (m, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 4.7 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 145.0, 139.4, 131.8, 131.4, 130.9, 129.7, 127.8, 127.5, 127.3, 125.5, 122.5, 119.2, 118.2, 117.3, 52.9; IR (KBr, cm^{-1}) 3041, 1667, 1487, 1345; MS (ES mass): m/z 276.9 (M+1, 100%); HRMS: calcd for $C_{16}H_{13}N_4O$: 277.2692, found 277.2688.

4.7. Preparation of *N*-((1-((2-(2-hydroxyphenyl)quinolin-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(2-iodophenyl) methanesulfonamide (5b)



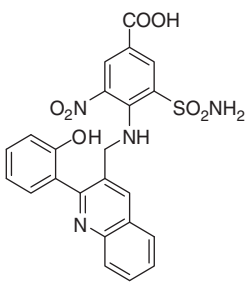
To a stirred solution of the *N*-(2-iodophenyl)-*N*-(prop-2-ynyl)methanesulfonamide (0.12 g, 0.33 mmol) in DMF (5 mL) was added copper iodide (30 mol %), 2-(3-(azidomethyl)quinolin-2-yl)phenol (0.092 mg) and DIPEA (3 equiv) under a nitrogen atmosphere. The mixture was stirred at 70 °C for 6 h. The progress of the reaction was monitored by TLC. After consumption of the reaction the mixture was cooled to room temperature and diluted with ethylacetate (50 mL). The mixture was filtered through celite pad. The filtrate was collected and concentrated under reduced pressure. The residue was purified with silica gel column chromatography using 4:6 EtOAc–hexane as eluant. The desired product was isolated as a white solid (0.12 g, 60%); mp: 198–199 °C; R_f = 0.4 (30% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 10.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.32–7.39 (m, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.07–7.13 (m, 2H), 6.97–7.00 (m, 2H), 5.87 (s, 2H), 5.08 (d, *J* = 1.6, 1H), 4.64 (d, *J* = 1.6, 1H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 156.4, 145.5, 143.8, 140.6, 140.3, 138.1, 132.2, 131.5, 131.1, 130.4, 129.6, 129.1, 128.0, 127.6, 127.5, 127.1, 126.5, 124.1, 121.8, 119.7, 118.4, 101.5, 53.4, 46.2, 41.4; IR (KBr, cm^{-1}) 3365, 2956, 1654; EI-MS: *m*/*z* 611.8 (M+1, 100%); HRMS: calcd for $C_{26}H_{23}IN_5O_3S$: 612.0522, found 612.0499.

4.8. Preparation of 2-(3-(aminomethyl)quinolin-2-yl)phenol (5c)



To a solution of 2-(3-(azidomethyl)quinolin-2-yl)phenol (0.7 g, 2.53 mmol) in EtOAc (5 mL) was added 10% Pd/C (0.026 g, 0.25 mmol) carefully. The reaction mixture was stirred under hydrogen atmosphere (filled in a balloon) at room temperature for 4 h. The progress of the reaction was monitored by TLC (9:1 EtOAc–MeOH, UV). After completion of the reaction the mixture was filtered through celite. The filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using 6:4 EtOAc–Hexane as eluant to give the desired product as a white solid (0.6 g, 95%). mp: 171–174 °C; R_f = 0.2 (40% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.69–7.74 (m, 2H), 7.51–7.61 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.12–6.97 (m, 3H), 4.2 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.5, 155.6, 146.7, 134.5, 133.9, 131.1, 130.1, 129.6, 128.9, 128.2, 127.8, 127.4, 126.9, 119.3, 116.7, 42.3; IR (KBr, cm^{-1}) 3041, 1667, 1487, 1345; EI-MS: *m*/*z* 251.2 (M+1, 100%).

4.9. Preparation of 4-((2-(2-hydroxyphenyl)quinolin-3-yl)methylamino)-3-nitro-5-sulfamoylbenzoic acid (5d)



A mixture of 2-(3-(aminomethyl)quinolin-2-yl)phenol (0.5 g, 2 mmol) and 4-chloro-3-nitro-5-sulfamyl benzoic acid (0.56 g, 2 mmol) in *n*-butanol (5 mL) was stirred at 80–90 °C for 3–4 h. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel using 6:4 EtOAc–hexane as eluant. The desired product was isolated as a yellow solid (400 mg, 41%); mp: 292–294 °C; R_f = 0.4 (30% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, DMSO-d_6 + acetone-d_6): δ 8.61 (d, *J* = 7.6 Hz, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.51 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.8 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 4.4 Hz, 1H), 7.38 (t, *J* = 6.4 Hz, 1H), 7.32 (bs, 1H), 7.2 (t, *J* = 8.4 Hz, 1H), 7.14 (bs, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 4.52 (s, 2H); ^{13}C NMR (100 MHz, Acetone-d_6): δ 164.4, 158.0, 155.0, 146.7, 136.6, 134.0, 133.8, 132.3, 131.7, 130.6, 130.0, 128.5(2C), 128.2(2C), 127.7, 127.1, 126.9, 125.2, 119.4, 116.1, 110.0, 48.9; IR (KBr, cm^{-1}) 2927, 1671, 1484, 1362; EI-MS: *m*/*z* 494.8 (M+1, 100%); HRMS: calcd for $C_{23}H_{19}N_4O_7S$: 495.0942, found 495.0940.

4.10. Single crystal X-ray data for compound 3a, 4d

Single crystals suitable for X-ray diffraction of **3a, 4d** were grown from methanol. 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 Broker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[19] 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.[20]

Crystal data of **3a:** Molecular formula = $C_{16}H_9NO_2$, Formula weight = 247.24, Crystal system = Monoclinic, space group = *P*2(1)/*n*, *a* = 16.772 (11) Å, *b* = 3.832 (3) Å, *c* = 18.299 (11) Å, *V* = 1117.72 (13) Å^3, *T* = 296 K, *Z* = 4, D_c = 1.389 Mg m^{-3}, μ(Mo-Kα) = 0.71073 mm^{-1}, 7702 reflections measured, 1251 independent reflections, 1123 observed reflections [I >2.0 σ (I)], R_1_obs = 0.042, Goodness of fit = 1.003. Crystallographic data (excluding structure factors) for **3a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 840017.

Crystal data of **4d**: Molecular formula = $C_{16}H_{12}ClNO_2$, Formula weight = 285.72, Crystal system = Orthorhombic, space group = *Pca*2$_1$, *a* = 10.568 (4) Å, *b* = 7.241 (3) Å, *c* = 17.2358 (6) Å, *V* = 1319.02 (9) Å^3, *T* = 296 K, *Z* = 4, D_c = 1.434 Mg m^{-3}, μ(Mo-Kα) = 0.71073 mm^{-1}, 7596 reflections measured, 2665 independent reflections, 2651 observed reflections [I >2.0 σ (I)], R_1_obs = 0.039, Goodness of fit = 0.876, Crystallographic data (excluding structure factors) for **4d** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 840016.

4.11. Pharmacology

Cell lines and culture conditions: Human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), breast cancer cells (MDA-MB 231), and human neuroblastoma cells (IMR32) 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 penicillin, 100 mg/ml 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/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/well) were seeded to 96-well culture plate and cultured with or without compounds at 1 and 10 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 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 (Victor3, Perkin Emler). In all of these experiments, three replicate wells were used to determine each point.

In Vitro assay for Sirt1 inhibition[18]: The activity of the small molecules on Sirt1 was determined using SIRT1 fluorescence activity assay kit from Cyclex Inc. according to manufacturer's protocol. Briefly, bacterially purified hSirt1 enzyme was incubated with the fluorophore labeled substrate peptide (25 μM) and cofactor, NAD^+ (25 μM) in presence or absence of 10 μM compounds (suramin, an inhibitor of Sirt 1 and compound **4b**) for 15 min at 37 °C. Then 50 μl of stop solution was added and incubated for 45 min at room temperature. Fluorescence was read at Ex: 360 nm and Em: 450 nm. Blank consists of all components of the reaction mixture except enzyme. The difference between the blank and control reading gives the enzyme activity. Blank value is subtracted from all the sample readings. The auto fluorescence of compound control contains all the components of reaction mixture including the compound but no enzyme. Finally a graph is plotted against the samples on X-axis and fluorescence value after subtracting blank and autofluorescence values from the sample. Absorbance/Fluorescence is directly proportional to the enzyme activity.

4.12. Docking study

The three dimensional model of hSirt1 (NCBI gi no: 7555471, 200–500 amino acid residues) was developed by homology modeling using the templates PDB: 2HJH and PDB: 1J8F in the Modeller9v6. To the developed model hydrogens were added and subjected to restrained minimization using the OPLS-AA force field in GROMACS 3.0 package to RMSD of 0.4 Å.

Molecular docking: The compound **5b** was sketched by using Chemdraw and converted them to their 3D representation using Dundee Prodrg server. The compound **4B** and protein (homology model of hSIRT1) were prepared for docking (i.e., adding hydrogens, gasteiger charges, Kollman charges) by using AutoDock Tools (ADT). AutoDOck 4.0 program was used for docking. The best model of hSirt1 was predicted and validated. The receptor hSirt1 with gird coordinates X: 60; Y:60; Z:60 was used for docking with the compound **5b**. The best 5 poses and corresponding scores have been evaluated by AutoDock 4.0 program.[21]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.12.001.

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