Bioorganic & Medicinal Chemistry Letters 23 (2013) 4195–4205

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Construction and functionalization of pyranone ring fused with pyran moiety: Design and synthesis of novel pyrano[4,3-*b*]pyran-5(4*H*)-ones as potential inhibitors of sirtuins

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ARTICLE INFO

Article history:
Received 21 March 2013
Revised 24 April 2013
Accepted 7 May 2013
Available online 15 May 2013

Keywords:
Pyranochromendione
Pyranopyranone
Iodocyclization
Sirtuins

ABSTRACT

Novel pyrano[4,3-*b*]pyran-5(4*H*)-one based small molecules were designed as potential inhibitors of sirtuins (i.e., yeast sir2, a homolog of human SIRT1). Elegant synthesis of these compounds was performed via a multi-step sequence consisting of MCR, Sandmeyer type iodination, Sonogashira type coupling followed by iodocyclization and then Pd-mediated various C–C bond forming reactions. The overall strategy involved the construction of a pyran ring followed by the fused pyranone moiety and subsequent functionalization at C-8 position of the resultant core pyrano[4,3-*b*]pyran-5(4*H*)-one framework. The crystal structure analysis of a representative iodolactonized product (**6d**) is presented. Some of the synthesized compounds showed promising inhibitory activities when tested against yeast sir2 in vitro. The compound **6g** showed dose dependent inhibition (IC_{50} = 78.05 μM) of yeast sir2 and good interactions with this protein in silico.

Naturally occurring α-pyrone and isocoumarin derivatives have attracted particular attention especially in drug discovery and pharmaceutical research because of their broad range of biological activities.[1] An impressive number of reports are now available in the literature that discloses a wide range of isocoumarin based small molecules of pharmacological importance including the clinical candidate NM-3.[2] Recently, we have reported 1,8-dioxo-octahydroxanthenes[3] (**A**, Fig. 1) and thieno[3,2-*c*]pyran-4-one based small molecules[4] (**B**, Fig. 1) as potential anticancer agents. While some of them showed promising growth inhibition when tested against a number of cancer cells their mechanism of action was not clearly understood. As part of our ongoing efforts on the identification of novel inhibitors of sirtuins we became interested in evaluating the sirtuin inhibitory properties of small molecules based on pyrano[4,3-*b*]pyran-5(4*H*)-one (**C**, Fig. 1). The design of **C** was performed by combining some of the structural features of both **A** and **B** in a single molecular entity. We anticipated that compounds based on **C** would show anticancer properties via inhibition of sirtuins.

The sirtuins are class III NAD-dependent deacetylases that catalyze NAD+ dependent removal of acetyl group to generate deacetylated proteins, nicotinamide, and *O*-acetyl-ADP-ribose. They play important role in diverse biological processes such as transcriptional silencing, regulation of apoptosis by deacetylation of p53, fatty acid metabolism, cell cycle regulation, and aging.[5] Among the seven human sirtuins for example SIRT1–7, the SIRT1 has been studied well which has several substrates such as p53, Ku70, NF-κB, forkhead proteins etc.[6] Studies have shown that sirtuins are up-regulated in many cancers and inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. Thus, inhibition of sirtuins is being

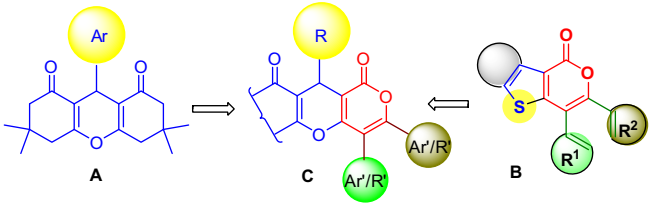

Figure 1. Design of novel pyrano[4,3-*b*]pyran-5(4*H*)-one based inhibitors (C) of sirtuins from the known cytotoxic agents A and B.

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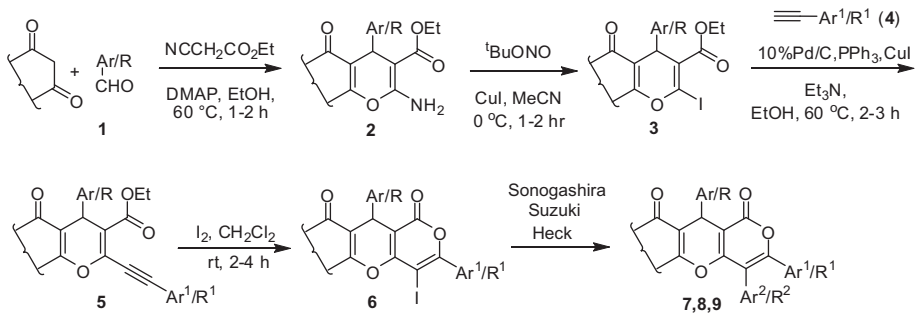
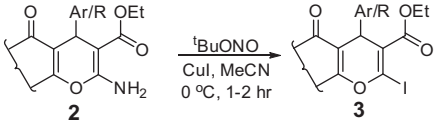
http://dx.doi.org/10.1016/j.bmcl.2013.05.014



Scheme 1. Synthesis of novel pyrano[4,3-*b*]chromendione and pyrano[4,3-*b*]pyran based novel small molecules.

Table 1
Preparation of 2-iodo substituted 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate ester derivatives (**3**)[a]



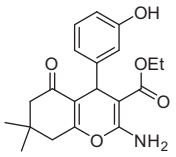
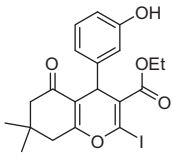
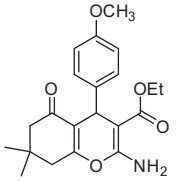
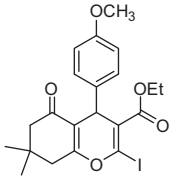
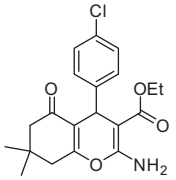
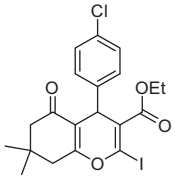
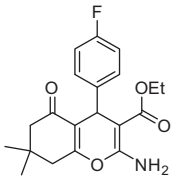
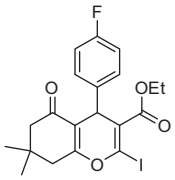
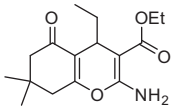
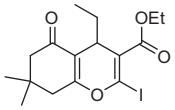
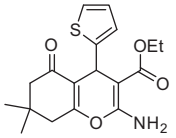
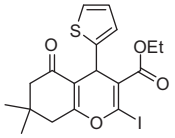
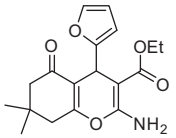
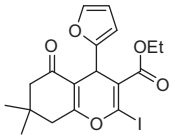
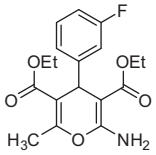
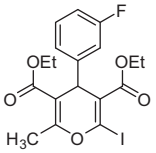
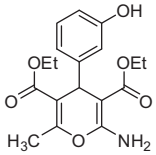
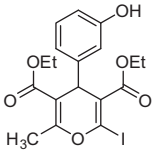
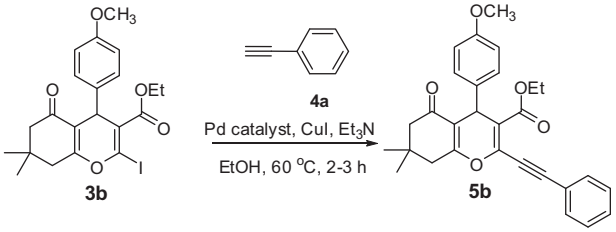
Entry	2-Aminochromene derivatives (**2**)		Time (h)	Product (**3**)		Yield (%)
1		**2a**	1		**3a**	82
2		**2b**	1		**3b**	88
3		**2c**	2		**3c**	86
4		**2d**	2		**3d**	85
5		**2e**	1		**3e**	82
6		**2f**	1		**3f**	75
7		**2g**	1		**3g**	73

Table 1 (*continued*)

Entry	2-Aminochromene derivatives (**2**)		Time (h)	Product (**3**)		Yield (%)
8		**2h**	2		**3h**	68
9		**2i**	2		**3i**	70

[a] All the reactions were carried out using the amine **2**, ^{t}BuONO and CuI in MeCN at 0 °C.

Table 2
Effect of reaction conditions on Sonogashira coupling of **3a** with phenylacetylene **4a**[a]



Entry	Pd-catalysts	Base	Time (h)	Yield[b] (%)
1	10% Pd/C–PPh_3	Et_3N	2	85
2	$Pd(PPh_3)_2Cl_2$	Et_3N	5	73

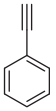
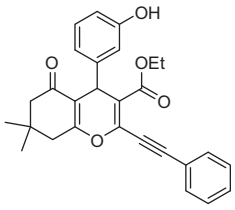
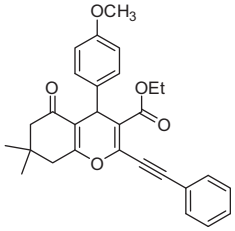
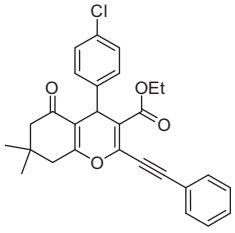
[a] All the reactions were carried out using compound **3b** (0.1 g, 0.2074 mmol), phenyl acetylene **4a** (0.02 mL, 0.2074 mmol), CuI (0.002 g, 0.0082 mmol), and Et_3N (0.85 mL, 0.6222 mmol), either 10% Pd/C (0.0020 mmol) & PPh_3 (0.001 g, 0.0040 mmol), or $Pd(PPh_3)_2Cl_2$, (0.0020 mmol) in ethanol (3 mL) under nitrogen.
[b] Isolated yield.

considered as a new approach for the discovery of novel anticancer drugs. While a number of inhibitors, for example nicotinamide, sirtinol, splitomicin, cambinol, tenovins, and EX527[7] have been reported none except EX527 (which is presently undergoing Phase 1a clinical trial for the treatment of Huntington's disease) have progressed into clinical trials as anticancer agents. This prompted us to explore pyrano[4,3-*b*]pyran-5(4*H*)-one (**C**) as potential and novel inhibitors of sirtuins. The design and selection of this class of compounds was further supported by the docking studies (see later for a discussion).

The synthesis of our target compounds **6**–**9** (or **C**, Fig. 1) involved a multi-step sequence consisting of a multi-component reaction (MCR), Sandmeyer type iodination, Sonogashira type coupling followed by iodocyclization and then Pd-mediated various C–C bond forming reactions (Scheme 1).

The starting material **2** was obtained through the MCR[8] of 1,3-diketones or β-keto esters, aldehydes and ethyl cyanoacetate in the presence of catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine

Table 3
Pd/C-mediated preparation of 2-alkynyl substituted 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate ester derivatives (**5**)[a]

Entry	2-Iodochromenone derivative (**3**)	Terminal alkyne (**4**)	Time (h)	Alkynyl ester (**5**)		Yield[c] (%)
1	**3a**	 **4a**	2		**5a**	81
2	**3b**	**4a**	1		**5b**	85
3	**3c**	**4a**	1		**5c**	70

(*continued on next page*)

Table 3 (*continued*)

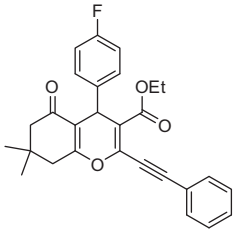
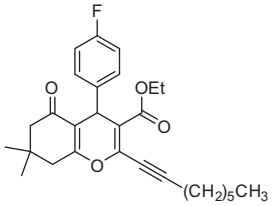
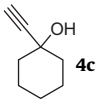
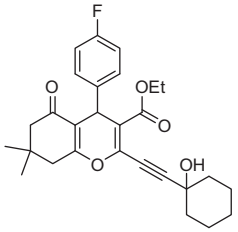
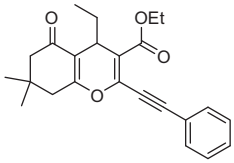
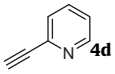
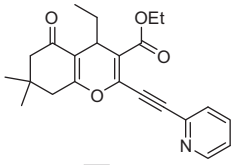
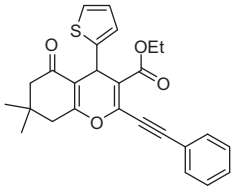
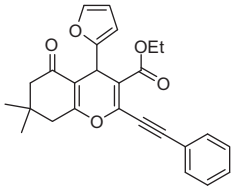
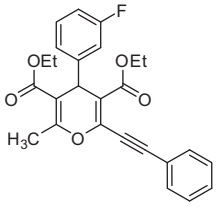
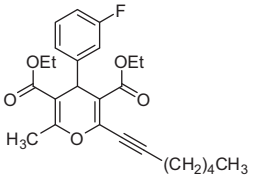
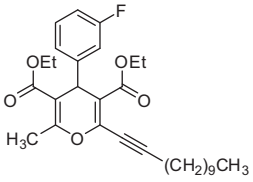
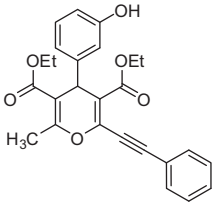
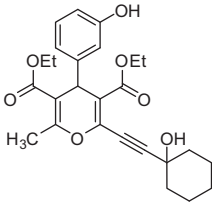
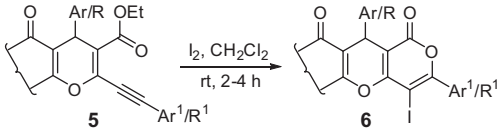
Entry	2-Iodochromenone derivative (**3**)	Terminal alkyne (**4**)	Time (h)	Alkynyl ester (**5**)		Yield[c] (%)
4	**3d**	**4a**	1		**5d**	73
5	**3d**	 **4b**	2		**5e**	68[b]
6	**3d**	 **4c**	1		**5f**	70
7	**3e**	**4a**	2		**5g**	77
8	**3e**	 **4d**	2		**5h**	63[b]
9	**3f**	**4a**	1		**5i**	82
10	**3g**	**4a**	2		**5j**	85
11	**3h**	**4a**	2		**5k**	74

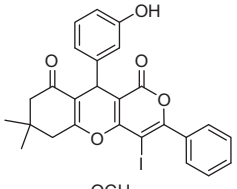
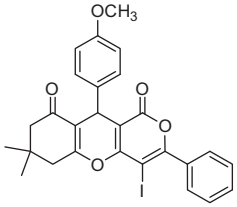
Table 3 (*continued*)

Entry	2-Iodochromenone derivative (**3**)	Terminal alkyne (**4**)	Time (h)	Alkynyl ester (**5**)		Yield[c] (%)
12	**3h**	 **4e**	2		**5l**	66
13	**3h**	 **4f**	2		**5m**	65[b]
14	**3i**	**4a**	1		**5n**	85
15	**3i**	**4c**	2		**5o**	80

[a] Reactions were carried out compound **3** (0.2074 mmol), terminal alkyne (**4**) (0.2074 mmol), 10% Pd/C (0.0020 mmol), PPh_3 (0.0040 mmol), CuI (0.0082 mmol), and Et_3N (0.6222 mmol) in EtOH (5.0 mL) at 60 °C.
[b] $Pd(PPh_3)_2Cl_2$ was used instead of 10% Pd/C–PPh_3.
[c] Isolated yield.

Table 4
I_2 mediated synthesis of 4-iodo-7,8-dihydropyrano[4,3-*b*]chromenedione and 8-iodo-4,5-dihydropyrano[4,3-*b*]pyran (**6**)[a]



Entry	Alkynyl ester (**5**)	Time (h)	Product (**6**)		Yield[b] (%)
1	**5a**	2		**6a**	93
2	**5b**	2		**6b**	97

(*continued on next page*)

Table 4 (*continued*)

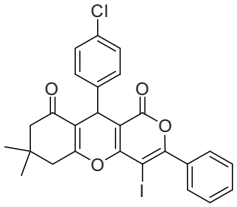
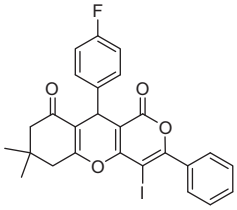
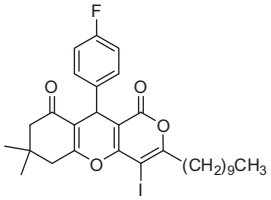
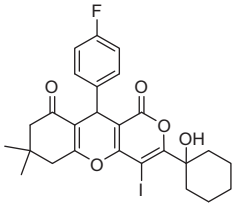
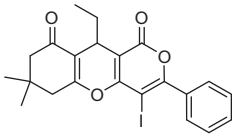
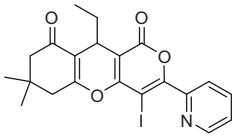
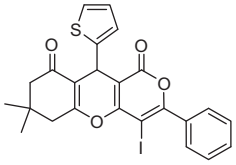
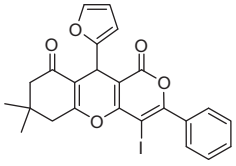
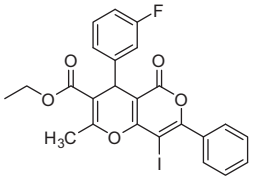
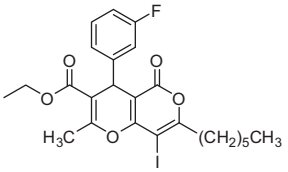
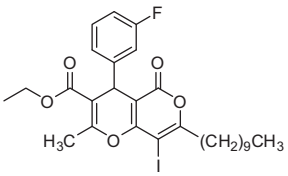
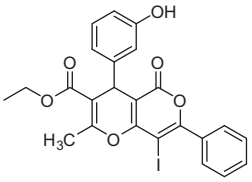
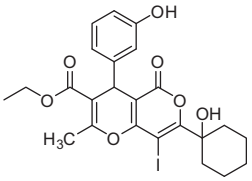
Entry	Alkynyl ester (**5**)	Time (h)	Product (**6**)		Yield[b] (%)
3	**5c**	2		**6c**	80
4	**5d**	2		**6d**	88
5	**5e**	4		**6e**	58
6	**5f**	4		**6f**	54
7	**5g**	2		**6g**	85
8	**5h**	4		**6h**	53
9	**5i**	2		**6i**	85
10	**5j**	2		**6j**	85
11	**5k**	4		**6k**	74

Table 4 (*continued*)

Entry	Alkynyl ester (**5**)	Time (h)	Product (**6**)		Yield[b] (%)
12	**5l**	4		**6l**	60
13	**5m**	4		**6m**	65
14	**5n**	4		**6n**	75
15	**5o**	4		**6o**	70

[a] All reactions were carried out by using alkynes **5** (0.9677 mmol) and I_2 (0.9677 mmol) in CH_2Cl_2 (3 mL).
[b] Isolated yields.

(DMAP) in ethanol. Compound **2** was then converted to the corresponding 2-iodo derivative **3** under a modified Sandmeyer conditions the results of which are summarized in Table 1.

The compound **3** was then coupled with various terminal alkynes **4** under Pd–Cu catalysis to give the desired internal alkyne **5**. Initially, we examined the coupling of **3b** with a terminal alkyne **4a** under two reaction conditions (Table 2). Since the use of Pd/C has been explored as an inexpensive, easily separable and recyclable catalyst for the alkynylation of aryl and heteroaryl halides[9] hence the initial coupling reaction of **3b** with **4a** was carried out in the presence of 10% Pd/C, PPh_3, CuI and Et_3N in ethanol. To our satisfaction, the desired product **5b** was isolated in 85% yield (entry 1, Table 2). Similarly, the use of $Pd(PPh_3)_2Cl_2$ in the presence of CuI was also found to be effective though the product yield was marginally low (entry 2, Table 2). Thus, a series of internal alkyne **5** were prepared in good to acceptable yields (Table 3) using either 10% Pd/C–PPh_3–CuI or $Pd(PPh_3)_2Cl_2$–CuI (e.g., entries 5, 8 and 13, Table 3) as catalyst system.

In recent years, I_2 or ICl-mediated intramolecular electrophilic cyclization of the alkynes in an *exo-dig* or *endo-dig* fashion has become convenient and economical method for the straightforward access of various iodo heterocycles.[10] The 2-alkynyl substituted 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate ester derivatives (**5**) thus prepared were then subjected to I_2-mediated electrophilic cyclization which provided the pyrano[4,3-*b*]pyran-5(4*H*)-one core that is 4-iodo-7,8-dihydropyrano[4,3-*b*]chromenedione or 8-iodo-4,5-dihydropyrano[4,3-*b*]pyran (**6**) exclusively via a regioselective 6-*endo-dig* ring closure (Table 4).

All the iodo compounds (**6**) prepared were characterized by spectral data and the molecular structure of a representative compound **6d** was determined unambiguously by X-ray crystallographic analysis (Fig. 2).[11]

Having prepared the iodo derivatives **6** we then focused on further structural elaboration of these compounds by using various Pd-catalyzed C–C bond forming reactions such as Sonogashira, Suzuki, and Heck coupling reactions. Thus, the compound **6a** and **6d** was reacted with a terminal alkyne in the presence of 10% Pd/C–PPh_3–CuI as catalysts and Et_3N as a base in EtOH to afford the corresponding 4-alkynyl substituted 7,8-dihydropyrano[4,3-*b*]chromene-1,9-(6*H*,10*H*)-dione derivative **7a** and **7b** (Table 5). Similarly, Suzuki coupling of compound **6a** and **6k** with an appropriate arylboronic acid provided **8a** and **8b** in good yield (Table 5).

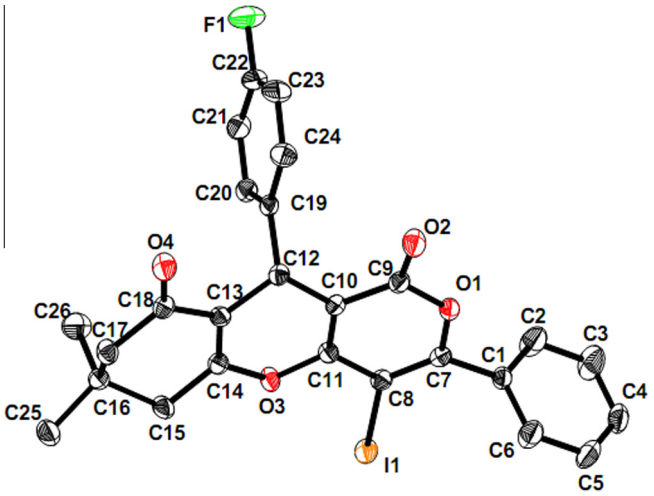
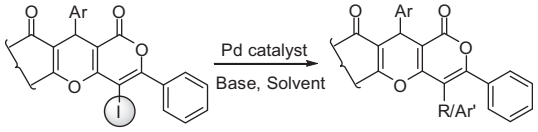
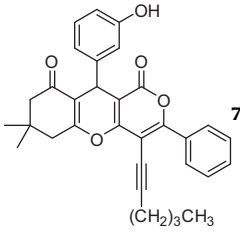
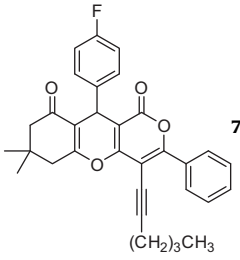
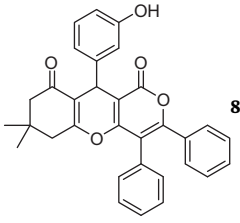
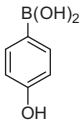
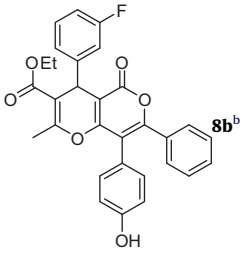
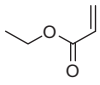
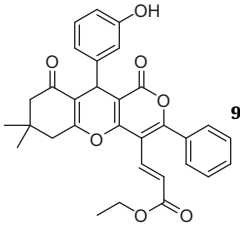


Figure 2. X-ray crystal structure of **6d** (ORTEP diagram). Thermal ellipsoidal diagram is drawn at 30% probability (hydrogen atoms are omitted for clarity).

Table 5
Functionalization of compounds (**6**) via Pd mediated C–C bond forming Sonogashira[a], Suzuki[b] and Heck[c] reactions



6 **7-9**

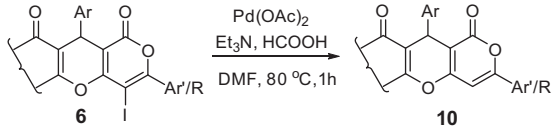
Entry	Iodo compound (**6**)	R = alkyne/acrylate Ar[1] = aryl boronic acid	Time (h)	Product (**7–9**)	Yield[d] (%)
1	**6a**	 **4g**	2	 **7a**[a]	73
2	**6d**	**4g**	2	 **7b**[a]	64
3	**6a**		1	 **8a**[b]	70
4	**6k**		1	 **8b**[b]	67
5	**6a**		1	 **9a**[c]	71

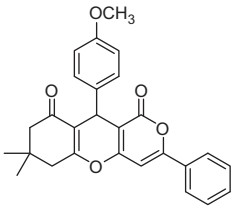
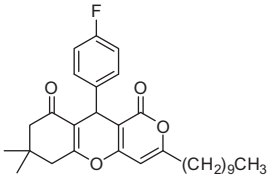
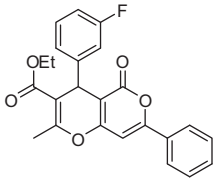
[a] Reaction were carried out using 10% Pd/C (0.0041 mmol), PPh_3 (0.0165 mmol), CuI (0.0041 mmol), Et_3N (0.82 mmol), and a terminal alkyne (0.7348 mmol) in EtOH (3 mL) at 60 °C.
[b] Reactions were carried out by using $Pd(OAc)_2$ (0.0041 mmol, 5 mol %), K_2CO_3 (0.82 mmol) an appropriate boronic acid (0.61 mmol) in DMF (3 mL) at 80 °C.
[c] Reaction was carried out by using $Pd(OAc)_2$ (0.0049 mmol, 5 mol %), K_2CO_3 (0.82 mmol), ethyl acrylate (0.82 mmol) in DMF (3 mL) at 80 °C.
[d] Isolated yields.

The compound **6a** afforded the corresponding alkene **9a** when coupled with ethyl acrylate under Heck conditions (Table 5). A Pd-mediated reductive deiodination of compound **6b**, **6d**, and **6k** afforded **10a**–**10c** in good yields (Table 6).

The identification of novel inhibitors of sirtuin being the goal of the present work and due to our continuing interest in this area[12] we tested some of the synthesized compounds (**6**–**8**) in vitro by using yeast cell based reporter silencing assay. Compounds were tested without separating their individual steroisomers at the concentration of 50 μM for their ability to inhibit yeast sirtuin family NAD-dependent histone deacetylase (HDAC) sir2 protein (a yeast homologue of mammalian SIRT1). Splitomicin,[13] a known inhibitor

Table 6
Pd-mediated reductive deiodination of compound **6b**, **6d**, and **6k**.[a]



Entry	Compound (**6**)	Product (**10**)		Yield[b] (%)
1	**6b**		**10a**	83
2	**6d**		**10b**	72
3	**6k**		**10c**	80

[a] All reactions were carried out by using compound **6** (0.3616), formic acid (0.0361 mmol), $Pd(OAc)_2$ (0.0036 mmol) and Et_3N (0.3616 mmol) in DMF (3 ml) at 80 °C for 1 h.
[b] Isolated yields.

Table 7
Yeast based in vitro assay for sir2 inhibition by compounds **6**–**8**[a]

Entry	Compound	% of inhibition
1	**6b**	32.38
2	**6d**	49.53
3	**6f**	25.30
4	**6g**	43.90
5	**6i**	43.20
6	**6j**	15.30
7	**6k**	0.50
8	**7a**	1.01
9	**8a**	3.30
10	**8b**	1.51

Splitomicin was used as a reference compound.
[a] Data represent the mean values of three independent determinations.

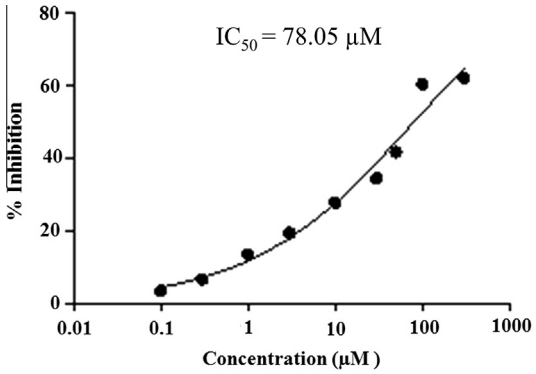
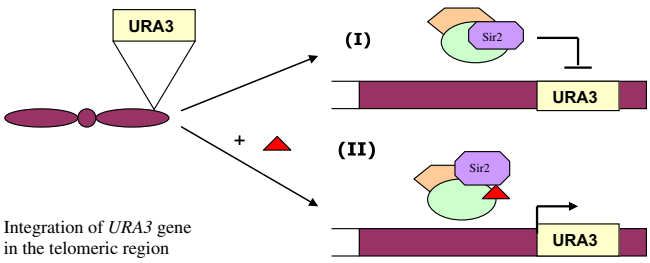


Figure 3. Dose dependent % inhibition of sir2 by the compound **6g**.

of sirtuin, was used as a reference compound. In this assay a yeast strain (TEL::URA3 strain (MATα ura3-52 lys2-801 ade2-101 trpΔ63 his3Δ200 leu3Δ200 leu2-Δ1 TEL adh4::URA) was used in which, a reporter gene URA3 was inserted in the silenced telomeric region where it is silenced by yeast sir2 protein (Scheme 2). Inhibition of sir2 protein by an inhibitor would allow the URA3 gene to be expressed thereby resulting in death of the yeast cell in presence of 5-FOA through the formation of toxic 5-fluorouracil. The results of our in vitro assay are summarized in Table 7. Among the compounds tested, **6b**, **6d**, **6g** and **6i** (entries 1, 2, 4, and 5, Table 7) showed inhibitory activities against yeast sir2 at 50 µM whereas **6k**, **7a**, **8a** and **8b** were inactive. In a dose response study the compound **6g** showed dose dependent inhibition of sir2 with an IC_{50} = 78.05 µM (Fig. 3).



Scheme 2. Cell based sir2 mediated reporter silencing assay in yeast. (I) Growth in presence of 5-fluoroorotic acid (5-FOA): sir2 mediated silencing of URA3 gene permits growth in FOA; (II) no growth in presence of FOA: inhibition of sir2 results in expression of URA3 gene and cell death in presence of FOA.

To understand the binding mode of the compound **6g** with yeast sir2 protein in silico docking was performed by using the crystal structure coordinating with NAD-dependent protein deacetylase (PDB ID: 2HJH).[14] Since two enantiomers are possible for compound **6g** hence the docking studies was performed by using both *R*- and *S*-isomer individually. The phenyl group at C-3 position of *S*-isomer was accommodated well into the hydrophobic pocket of the active site consisting of Arg 497, Gly 264, and Asp 273 residues and the dimethyl group at C-7 interacted with Lys 475 and Ser 473 (Figs. 4 and 5). While similar interactions were also observed in case of *R*-isomer (Fig. 4) the *S*-isomer however showed better score than the *R*-antipode. The dock score of individual isomer along with the contributing factors are listed in Table 8. It is evident from the dock score that the (*S*)-isomer showed better interactions with sir2 protein than its (*R*)-antipode indicating that further SAR studies need to be performed around the (*S*)-isomer. Overall, the compound **6g** is of further interest as a novel small molecule based inhibitor of sirtuins.

In conclusion, a series of novel pyrano[4,3-*b*]pyran-5(4*H*)-one based small molecules were designed as potential inhibitors of sir2. These compounds were obtained in good yields via an elegant multi-step method consisting of MCR (involving aldehydes, ethyl cyanoacetate and 1,3-diketone/β-keto ester), Sandmeyer type iodination, Sonogashira type coupling followed by iodocyclization and then Pd-mediated various C–C bond forming reactions. The crystal structure analysis of a representative iodolactonized product (**6d**) is presented. Some of the compounds synthesized showed encouraging inhibition of sir2 protein (a yeast homologue of mammalian SIRT1) when tested using yeast based assay. A representative compound **6g** showed dose dependent inhibition

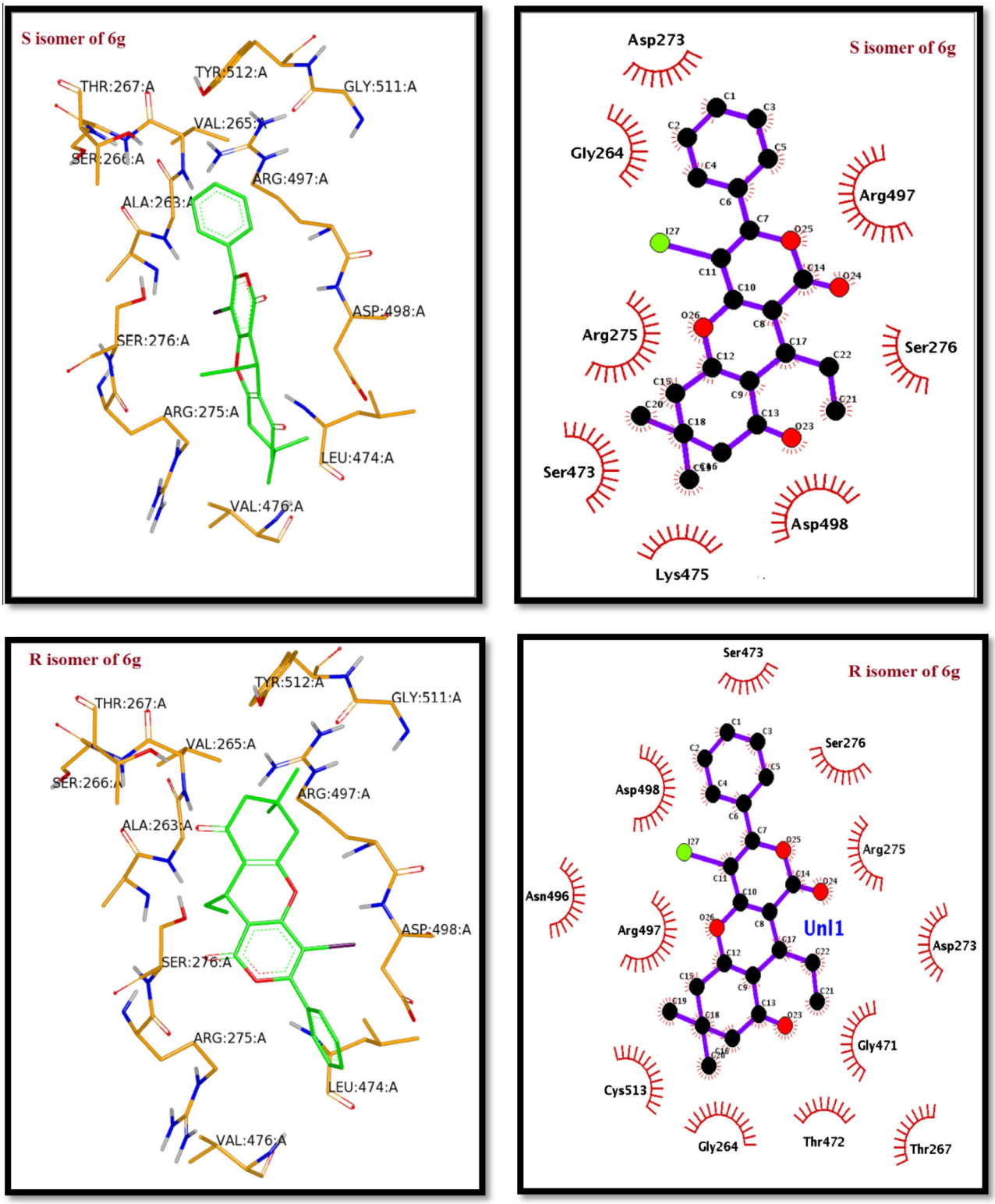


Figure 4. The binding mode of (*S*)- and (*R*)-isomers of compound **6g** and their 2D interaction plot.

(IC_{50} = 78.05 μM) of yeast sir2 and good interactions in silico (dock score −6.7) when docked into this protein. Overall, the pyrano[4,3-*b*]pyran-5(4*H*)-one framework presented here could be an attractive template for the identification of novel sir2 inhibitors and the corresponding synthetic strategy described could be useful for generating diversity based library of small molecules related to this scaffold.

Acknowledgments

The authors thank Professor Javed Iqbal for his encouragement. D.H. and M.P. thank DBT, New Delhi, India for financial support (Grant No. BT/PR13997/Med/30/310/2010). A.N. thanks CSIR—New Delhi, India for awarding a Senior Research Fellowship.

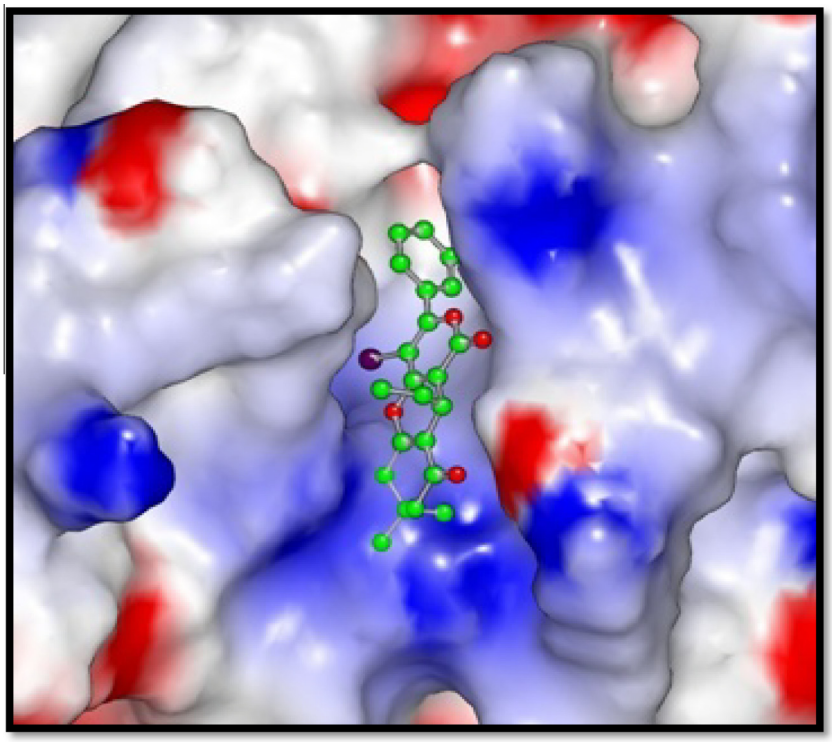


Figure 5. Binding mode of **6g** docked into the catalytic domain of Yeast sir2 (PDB ID: 2HJH).

Table 8
Factors contributing docking score of (*S*)- and (*R*)-isomers of compound **6g** with sir2 protein

Molecule	Dock score[a]	Steric	Protein desolvation	Ligand desolvation H-bond	Clash	Ligand desolvation	Hydrogen bond
Splitomicin	−8.5	−14.4	6.5	−0.5	0.1	0.5	−0.7
6g (*S*-isomer)	−6.7	−14.4	3.9	−0.01	0.3	1.3	0
6g (*R*-isomer)	−6.0	−17.9	4.8	−0.6	0.6	2.1	−0.6

[a] FRED Chemgauss4 score.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.014.

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