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Synthesis of benzofuran scaffold-based potential PTP-1B inhibitors☆

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Abstract—Protein tyrosine phosphatase 1B (PTP-1B) is an enzyme that plays a critical role in down-regulating insulin signaling through dephosphorylation of the insulin receptor. Studies have shown that PTP-1B knockout mice showed increased insulin sensitivity in muscle and liver as well as resistance to obesity. A series of hydroxy benzofuran methyl ketones and their naturally mimicking dimers and linear and angular furanochalcones and flavones have been evaluated as PTP-1B inhibitors. Screened compounds displayed good inhibitory activity.

1. Introduction

The complex metabolic syndrome, diabetes mellitus, is a major human health concern the world over and is estimated to affect 300 million people by the year 2025. India alone may have about 1/5 of the global diabetic population by 2025, a 3-fold increase over that in 1995—posing enormous economic and public health concerns to the country. Although our understanding of the disease progressed considerably in recent years, very few viable alternative therapeutic agents were developed since the chance discovery of sulfonylurea class of drugs during World War II followed later, by the biguanides.[1–5] Although treatment with highly active thiazolidinedione (TZD)[6] class of drugs has significantly improved the clinical situation, but suffers with adverse side effects of hepatotoxicity, weight gain, and edema. The alarming situation emphasized the need to explore the new molecular targets and strategies to develop novel antihyperglycemic agents. One such strategy is to design and synthesize inhibitors for protein tyrosine phosphatase-1B (PTP-1B), which is a legitimate target for the treatment of Type 2 diabetes by attenuating insulin resistance. PTP-1B, a cytosolic PTP, is thought to function as a negative regulator of insulin signal transduction and directly interacts with activated insulin receptor or insulin receptor substrate-1 (IRS-1) to dephosphorylate phosphotyrosine residue, resulting in down-regulation of insulin action.[7]

The two different reports suggest that PTP-1B knockout mice showed improved insulin sensitivity and resistance to weight gain.[8] Thus, PTP-1B inhibitors could potentially ameliorate insulin resistance and normalizes plasma glucose and insulin without inducing hypoglycemia and could be potential pharmacological agents for the treatment of obesity and T2DM.

In recent years, interest in the development of small molecule PTP-1B inhibitors has dramatically intensified.[9] Some of the potent and selective PTP-1B inhibitors that have emerged recently are shown in Figure 1. Recently, Pei et al.[10] have reported several α-haloacetophenone derivatives **I** as potent neutral protein tyrosine phosphatase inhibitors, which covalently alkylate the conserved catalytic cysteine residue in the PTP active site. Malamas et al.[11] reported two novel series of benzofuran/benzothiophene-biphenyl oxo-acetic acids and sulfonyl-salicylic acid as potent inhibitors of PTP-1B with good antihyperglycemic activity. They found that

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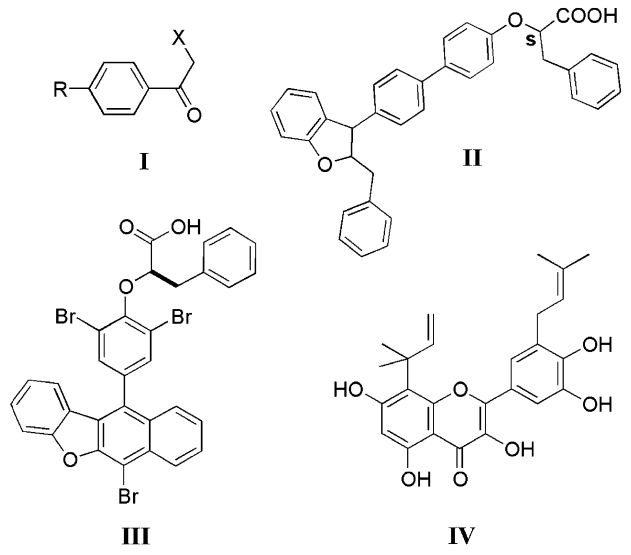


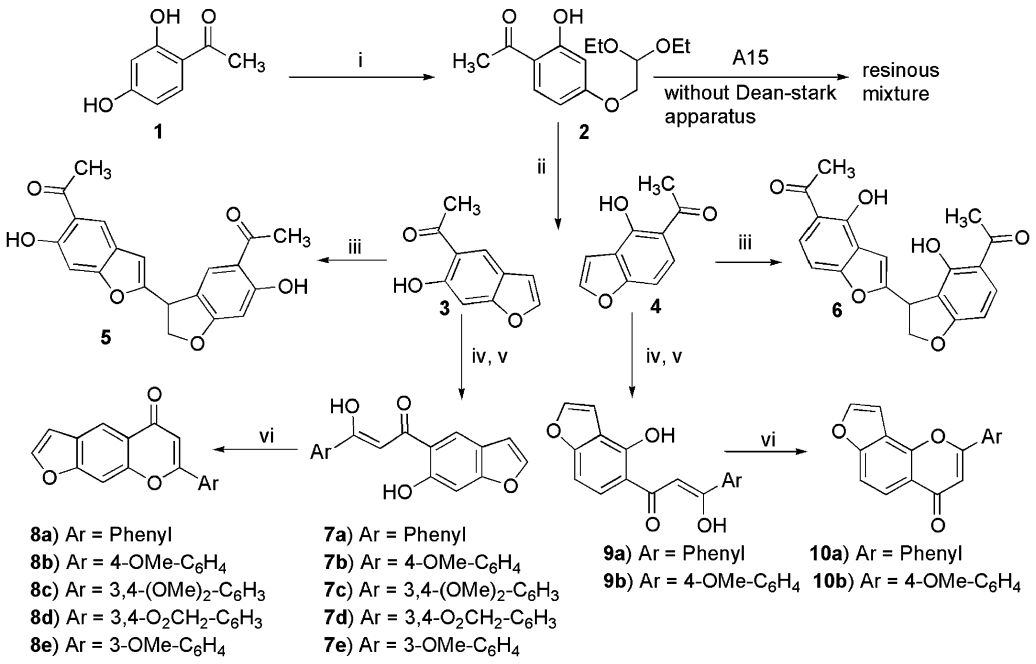
Figure 1. Structures of potent PTP-1B inhibitors.

compound **II** normalizes plasma glucose level at the 25 mg/kg dose (po) and 1 mg/kg dose (ip). Wrobel and co-workers[12] reported a series of 11-arylbenzo[*b*]naphtho[2,3-*d*]furan/thiophene derivatives **III**, which selectively inhibit PTP-1B over other PTPs and lowered the blood glucose level in *ob*/*ob* mice. Recently, Hu et al.[13] reported several flavonoids including a flavonol **IV**, which showed potent inhibitory activity against PTP-1B enzyme. Recently, we identified natural and unnatural benzofuran derivatives as protein tyrosine phosphatase inhibitors, which showed good inhibition at 100 μM concentration.[14] Based on known PTP-1B inhibitors and our medicinal chemistry efforts directed toward optimization of the substituents on the benzofuran core, it was envisaged that simulation of acetophenone moiety with fused furan skeleton might increase insulin sensitivity by inhibiting PTP-1B enzyme. In this paper, we report synthesis and PTP-1B inhibitory activity of nature-mimicking benzofurans, bibenzofurans, and furanoflavonoids.

The benzofuran ring system particularly functionalized with hydroxy and acetyl groups is of great interest because of their wide distribution in nature and useful biological activities associated with this skeleton.[15,16] In addition, these benzofurans with an adjacent hydroxy and acetyl functionality are key precursors for the synthesis of several naturally occurring angular and linear furanoflavonoids.[17] Numerous synthetic methodologies are available in the literature for the synthesis of functionalized benzofurans but access to benzofurans with adjacent hydroxy and acetyl functionalities shows paucity of references. We recently developed a novel route for the synthesis of vicinal hydroxy acetylbenzofurans by Amberlyst 15 (A15)-catalyzed cyclization of phenoxyacetal in two steps.[18]

2. Results and discussion

Our strategy for the synthesis of 5-acetyl-4-hydroxybenzofuran (**3**) and 5-acetyl-6-hydroxybenzofuran (**4**) includes a reaction of resacetophenone (**1**) and bromoacetaldehyde diethylacetal in the presence of anhydrous potassium carbonate in dry DMF, which afforded 1-[4-(2,2-diethoxyethoxy)-2-hydroxy-phenyl] ethanone (**2**) in 90% yield. The cyclization of phenoxyacetal (**2**) in refluxing toluene using A 15 as a catalyst using Dean–Stark apparatus with concomitant removal of azeotropes afforded 5-acetyl-4-hydroxybenzofuran (**3**) and 5-acetyl-6-hydroxybenzofuran (**4**) in 38% and 54% yield, respectively (Scheme 1). In the absence of Dean–Stark apparatus, the cyclization of **2** resulted in extensive polymerization leading to a resinous substance containing

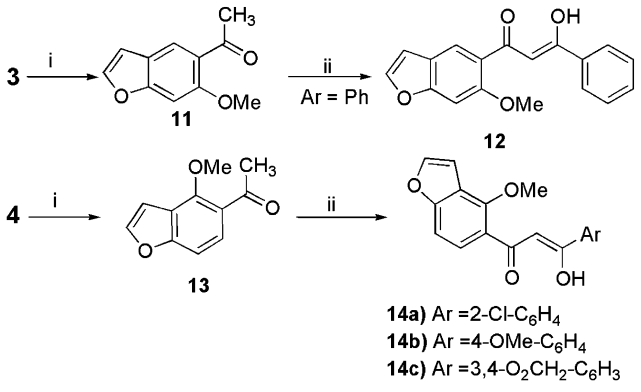


Scheme 1. Reagents and conditions: (i) $BrCH_2CH(OEt)_2$, DMF, K_2CO_3, 160 °C; (ii) A 15, toluene, reflux, Dean–Stark apparatus; (iii) A 15, toluene, reflux; (iv) ArCOCl, pyridine; (v) pyridine, *t*-BuOK; (vi) H_2SO_4/AcOH (1:3), 100 °C.

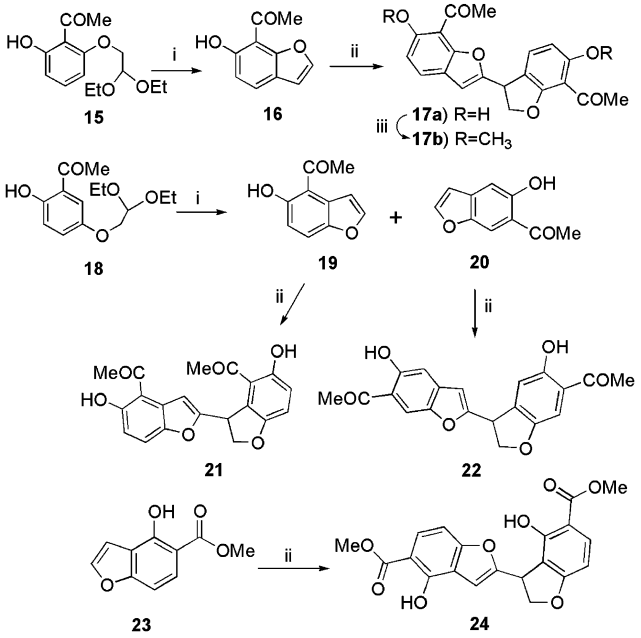
mixture of compounds as a major product (Scheme 1). During the isolation of compounds from resinous mixture, we isolated dimerized products (**5**, **6**) of **3** and **4**, which were possibly formed by self-dimerization in aqueous acidic medium. We therefore prepared bibenzofuran **5** and **6** separately by refluxing a solution of **3** or **4** in toluene in presence of A 15 without removal of azeotropic mixture in 89% and 81%, respectively.[18c] Interestingly, these benzofuran dimers are structurally similar to the natural dimers of dehydrotremetone and ageratone isolated from aerial parts of *Ophryosporus charua* and from the roots of *Ageratum houstonianum*, respectively.[16c,d] The isolation of dimers suggests a possible route for the formation of natural dimers isolated from plant sources. Further, 5-acetyl-4-hydroxybenzofuran (**3**) and 5-acetyl-6-hydroxybenzofuran (**4**) were used as precursor for the synthesis of the linear and the angular furanoflavonoid and their corresponding furanoflavones. Among the various literature procedures known for the synthesis of flavone ring, the Baker–Venkataraman rearrangement[19] followed by acid-catalyzed cyclization is the most common. The benzofurans **3** and **4** were separately treated with various aroyl chlorides in pyridine to form the corresponding benzoates followed by base-catalyzed rearrangement to yield corresponding β-hydroxyfuranochalcones **7a**–**e** and **9a**, **b** in good yields. The synthesis of the linear and angular furanoflavonoid **8a**–**e** and **10a**, **b** was achieved by acid-catalyzed cyclization of **7a**–**e** or **9a**, **b** to their corresponding furanoflavones in good yields.

We further synthesized the naturally mimicking furanochalcones as shown in Scheme 2. The hydroxy group of benzofuran **3** or **4** was converted to methoxy group by direct methylation with methyl iodide to yield **11** or **13**, respectively, in good yields. The compound **11** or **13** was condensed with aromatic acid esters in the presence of a strong base to yield furanochalcones (**12**, **14a**–**c**).

In order to explore the applicability of dimerization to prepare other derivatives, compound 7-acetyl-6-hydroxybenzofuran (**16**) was prepared by the reaction of 2,6-dihydroxyacetophenone and bromoacetaldehyde diethyl acetal to form an intermediate **15** followed by A 15-catalyzed cyclization (Scheme 3). The bibenzofuran (**17a**)



Scheme 2. Reagents and conditions: (i) CH_3I, K_2CO_3, acetone, reflux; (ii) ArCOOEt, dry benzene, KH, reflux.



Scheme 3. Reagents and conditions: (i) A 15, toluene, reflux, Deanstark apparatus; (ii) A 15, toluene, reflux; (iii) methyl iodide, acetone, K_2CO_3, reflux.

was converted to its methoxy derivative **17b** using methyl iodide in the presence of K_2CO_3 in acetone in 95% yield. Similarly, 4-acetyl-5-hydroxybenzofuran (**19**) and 6-acetyl-5-hydroxybenzofuran (**20**) were prepared in good yield by the cyclization of phenoxyacetal (**18**) using A 15 in toluene with concomitant removal of water. The benzofurans **19** and**20** on refluxing in toluene separately with A 15 afforded 2′,3′-dihydro-[2,3′]bibenzofuran **21** and **22**, respectively, in excellent yield. We also synthesized the dimer **24** of 4-hydroxy-benzofuran-5-carboxylic acid methyl ester[17d] (**23**) under similar reaction conditions. All the synthesized compounds were characterized by spectroscopic analysis.

Vanadate is a non-selective inhibitor of PTPs, and studies have shown that treatment with vanadate can normalize blood glucose level in diabetics.[7b,20] The effect of synthesized compounds on protein tyrosine phosphatase was studied by pre-incubating 100 μM of the compounds in the reaction system for 10 min and the residual PTPase activity determined according to the method of Goldstein et al.[21] Taking sodium vanadate as a control, we evaluated PTP-1B inhibitory activity of nature-mimicking benzofurans (**3** and **4**), bibenzofurans (**5**, **6**, **17a**, **b**, **22**, **24**), furanoflavonoids (**7a**–**e**, **8a**–**e**, **9a**, **b**, **10a**, **b**), and furanochalcones (**12** and **14a-c**) at 100 μM concentration and their results are summarized in Table 1.

Various hydroxy benzofuran methyl ketones and their nature-mimicking dimers have been evaluated as PTP1B inhibitors. The structure–activity relationship of the screened benzofuran derivatives revealed that dimers (**5**, **6**, **17a**, **b**, **22**, and **24**) of hydroxy-acetylbenzofurans (**3**, **4**, **16**, **20**, and **23**) showed good PTP-1B inhibitory activity (54.6–74.9%) except, **22** compared to their

Table 1. In vitro PTP-1B enzyme inhibitory activity for the compounds (**3**–**6**, **7a**–**e**, **8a**–**e**, **9a**, **b**, **10a**, **b**, **12**, **14a**–**c**, **17a**, **b**, **22**, **24**)

Compound	Inhibition[a] (%)	PTP-1B inhibitory activity			
		−Triton[b] X-100		+Triton[c] X-100	
		IC_{50} (μM)	K_i (μM)	IC_{50} (μM)	K_i (μM)
3	19.0	—	—	—	—
4	21.6	—	—	—	—
5	**74.9**	80.0	37.0	91.3	61.0
6	**67.4**	87.0	35.0	58.8	27.5
7a	24.3	—	—	—	—
7b	40.5	—	—	—	—
7c	32.4	—	—	—	—
7d	56.7	—	—	—	—
7e	NI	—	—	—	—
8a	**67.5**	94.0	57.0	61.3	45.0
8b	**75.6**	72.5	30.0	68.8	36.0
8c	24.3	—	—	—	—
8d	8.1	—	—	—	—
8e	NI	—	—	—	—
9a	40.5	—	—	—	—
9b	24.3	—	—	—	—
10a	21.0	—	—	—	—
10b	22.0	—	—	—	—
12	41.5	—	—	—	—
14a	27.0	—	—	—	—
14b	NI	—	—	—	—
14c	42.8	—	—	—	—
17a	**72.0**	75.0	64.0	56.3	54.0
17b	54.6	—	—	—	—
22	36.2	—	—	—	—
24	55.5	—	—	—	—
Na_2VO_3	56.0				

NI means no inhibition.

[a] Values are mean from three independent sets of experiments tested at 100 μM concentration.

[b] Compounds were examined without Triton X-100.

[c] Compounds were examined in the presence of 0.01% Triton X-100.

monomers (19–21.6%). It is evident from the activity profile of linear (**8a**, **b**) and angular (**10a**, **b**) furanoflavonoid that linear furanoflavonoids showed better inhibition (67.5%, 75.6%) against PTP-1B compared to their angular isomers (21%, 22%). None of the intermediate benzofuran chalcones (**7a**–**e** and **9a**, **b**) showed good inhibition.

Recent studies have demonstrated that the formation of aggregates of nonspecific inhibitors (promiscuous inhibitors) sometimes plays a major role in displaying enzyme inhibitory activity rather than a single 1:1 ligand–protein interaction.[22] These aggregates of ~30 to 400 nm in diameter have shown inhibition by interacting with protein through adsorption or absorption mechanism. It has also been demonstrated that promiscuous inhibition can be prevented and reversed using an appropriate concentration of nonionic detergents such as Triton X-100, saponin, or digitonin without compromising the enzyme assay performance.[23] In order to ruled out the possibility of promiscuous inhibition in our screening results, we re-examined the selected compounds **5**, **6**, **8a**, **8b**, and **17a** at 10, 25, 50, 75, and 100 μM concentration in the absence or in the presence of a detergent 0.01% Triton X-100. The IC_{50} and the dissociation constant K_i of the compounds are shown in Table 1, which suggests that the inhibitory activity of these compounds did not significantly change by the addition of an appropriate concentration of Triton X-100, as expected for promiscuous inhibitors. In contrast, these compounds **6**, **8a**, **8b**, **17a** showed increased catalytic enzyme activity (reduced IC_{50} values) in the presence of Triton X-100 probably due to the detergent causing a reduction in nonspecific protein binding onto the experimental plates. A decrease in enzyme inhibitory activity (or increased IC_{50} value) was observed for the compound **5** in the presence of Triton X-100, which suggests that the inhibitory activity may be due to the partial formation of aggregates of **5**. Among all the screened compounds, the benzofuran dimers **6**, **17a** and linear furanoflavonoids **8a**, **b** showed IC_{50} in the range of 56–69 μM with K_i of 27–54 μM.

In conclusion, we have synthesized various nature-mimicking hydroxybenzofuran methyl ketones and their dimer as well as linear and angular furanochalcones and flavones and evaluated their protein tyrosine phosphatase-1B inhibitory activity. In general, nature-mimicking benzofuran dimers **6**, **17a** showed good inhibitory activity (IC_{50}: 58.8 and 56.3 μM) against PTP-1B compared to their monomers. The linear furanoflavonoids **8a**, **b** showed better inhibition (67.5%, 75.6%) against PTP-1B compared to their angular isomers **10a**, **b** (21%, 22%).

3. Experimental

3.1. Chemistry

All the chemicals and reagents used were of analytical grade and were purchased from Sigma–Aldrich Chemical Co. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker WM-200, Bruker WM-300, at 200 and 300 MHz, respectively. $CDCl_3$ was taken as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for 1H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constant (J) are given in hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm^{-1}). Fast-atomic bombardment (FAB) spectrometer was used for mass spectra analysis. Melting points were measured with Buchi-530 melting point apparatus. All the reactions were carried out under anhydrous conditions and were monitored by TLC; visualization was done with UV-light (254 nm).

3.1.1. General procedure for synthesis of 2′,3′-dihydro-[2,3′]bibenzofuran (5, 6, 17a, 21, 22, and 24). The benzofuran (**3**, **4**, **16**, **19**, **20**, or **23**) was refluxed in toluene (35 mL) with A 15 (0.22 g) at 120 °C for 6–10 h. The resulting reaction mixture was filtered and the resin was washed with excess of toluene. The filtrate thus obtained was concentrated to dryness and a pure compound was isolated by silica gel column chromatography using 7% EtOAc in hexane as eluent.

3.1.1.1. 1-(5-Acetyl-4,4′-dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-5′-yl)-ethanone (5). Yellow solid; yield: 81%; mp: 189–190 °C; MS (FAB): m/z 353 (M^++1); IR (KBr): 1641 (CO), 3427 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.75–4.80 (m, 2H, CH_2), 4.92–4.96 (m, 1H, CH), 6.43 (s, 1H, ArH), 6.46 (s, 1H, CH), 6.99 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.91 (s, 1H, ArH), 12.46 (s, 1H, OH), 13.02 (s, 1H, OH); HRMS calcd for $C_{20}H_{16}O_6$ 352.0947, found 352.0918.

3.1.1.2. 1-(5-Acetyl-6,6′-dihydroxy-2′,3′-dihydro-[2,3′]-bibenzofuranyl-5′-yl)-ethanone (6). Yellow solid; yield: 89%; mp: 149–150 °C; MS (FAB): m/z 353 (M^++1); IR (KBr): 1638 (CO), 3433 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.57 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.81–4.88 (m, 1H, CH), 4.89–4.94 (m, 2H, CH_2), 6.48 (d, 1H, J = 8.6 Hz, ArH), 6.68 (s, 1H, CH), 6.96 (d, 1H, J = 8.8 Hz, ArH), 7.60 (d, 1H, J = 8.8 Hz, ArH), 7.70 (d, 1H, J = 8.6 Hz, ArH), 12.83 (s, 1H, OH), 13.15 (s, 1H, OH); HRMS calcd for $C_{20}H_{16}O_6$ 352.0947, found 352.0946.

3.1.1.3. 1-(7′-Acetyl-6,6′-dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-7-yl)-ethanone (17a). Yellow solid; yield: 92%; mp: 110–111 °C; MS (FAB): m/z 353 (M^++1); IR (KBr): 1637 (CO), 3449 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.69 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.80–4.88 (m, 2H, CH_2), 4.97–5.02 (m, 1H, CH), 6.44 (s, 1H, CH), 6.52 (d, 1H, J = 8.4 Hz, ArH), 6.88 (d, 1H, J = 8.6 Hz, ArH), 7.30 (d, 1H, J = 8.4 Hz, ArH), 7.56 (d, 1H, J = 8.6 Hz, ArH), 12.74 (s, 1H, OH), 12.81 (s, 1H, OH); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 31.6 (CH_3), 32.0 (CH_3), 41.1 (CH), 77.2 (CH_2), 103.5 (=CH), 107.3, 107.5, 110.3, 114.5, 117.2, 120.5, 128.5, 131.9, 154.2, 156.5, 161.8, 161.9, 164.0, 202.3, 203.5; HRMS calcd for $C_{20}H_{16}O_6$ 352.0947, found 352.0941.

3.1.1.4. 1-(4-Acetyl-5,5′-dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-4′-yl)-ethanone (21). Yellow semi-solid; yield: 83%; MS (FAB): m/z = 353 (M^++1); IR (KBr): 1645 (CO), 3437 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.73–4.88 (m, 3H, CH and CH_2), 6.41 (d, 1H, J = 8.6 Hz, ArH), 6.61 (s, 1H, CH), 6.95 (d, 1H, J = 8.6 Hz, ArH), 7.50–7.66 (m, 2H, ArH), 12.76 (s, 1H, OH), 13.08 (s, 1H, OH).

3.1.1.5. 1-(6′-Acetyl-5,5′-dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-6-yl)-ethanone (22). Yellow solid; yield: 75%; mp: 192–193 °C; MS (FAB): m/z = 353 (M^++1); IR (KBr): 1648 (CO), 3422 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.75–4.80 (m, 2H, CH_2), 4.82–4.99 (m, 1H, CH), 6.43 (s, 1H, ArH), 6.46 (s, 1H, CH), 6.99 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.91 (s, 1H, ArH), 12.47 (s, 1H, OH), 13.03 (s, 1H, OH); HRMS calcd for $C_{20}H_{16}O_6$ 352.0947, found 352.0987.

3.1.1.6. 4,4′-Dihydroxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-5,5′-dicarboxylic acid dimethyl ester (24). Yellow solid; yield: 86%; mp: 184–185 °C; MS (FAB): m/z = 385 (M^++1); IR (KBr): 1678 (CO), 3426 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.78–4.95 (m, 3H, CH and CH_2), 6.65 (s, 1H, CH), 6.47 (d, 1H, J = 8.6 Hz, ArH), 6.96 (d, 1H, J = 8.8 Hz, ArH), 7.72 (d, 1H, J = 8.8 Hz, ArH), 7.81 (d, 1H, J = 8.6 Hz, ArH), 12.42 (s, 1H, OH), 13.01 (s, 1H, OH); HRMS calcd for $C_{20}H_{16}O_8$ 384.0845, found 384.0870.

3.1.2. Procedure for the synthesis of compound 1-(5-acetyl-6,6′-dimethoxy-2′,3′-dihydro-[2,3′]bibenzofuranyl-5′-yl)-ethanone (17b). The mixture of **17a** with methyl iodide in the presence of K_2CO_3 in acetone was refluxed for 5 h and after completion of reaction; reaction mixture was filtered and evaporated under vacuum to yield the compound **17b** as colorless oil in good yield.

Yield: 95%; colorless oil; MS (FAB): m/z 381 (M^++1); IR (KBr): 1637 (CO) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.57 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.73–4.86 (m, 2H, CH_2), 4.93–4.97 (m, 1H, CH), 6.34 (s, 1H, CH), 6.48 (d, 1H, J = 8.4 Hz, ArH), 6.90 (d, 1H, J = 8.6 Hz, ArH), 7.29 (d, 1H, J = 8.4 Hz, ArH), 7.48 (d, 1H, J = 8.6 Hz, ArH); HRMS calcd for $C_{22}H_{20}O_6$ 380.1260, found 380.1274.

3.1.3. General procedure for the synthesis of compounds (7a–e and 9a–c). The mixture of **3** or **4** (6 mmol) and aroyl chloride (6 mmol) in dry pyridine (5 mL) was stirred at room temperature for an hour before heating at 100 °C for 10 min under anhydrous condition. The resulting solution was poured into 1 M HCl containing crushed ice, which yielded a solid benzoate in about 85% yield. The potassium tertiary butoxide was slowly added to magnetically stirred solution of the benzoate for about 5 h in dry pyridine. The resulting solution mixture was added to 10% acetic acid solution. The yellow solid of **7a–e** or **9a–b** thus obtained was filtered, dried, and crystallized in hexane–ethyl acetate to give yellow needle like crystals in good yield.

3.1.3.1. 3-Hydroxy-1-(6-hydroxy-benzofuran-5-yl)-3-phenyl-propenone (7a). Yellow solid; yield: 85%; mp: 125–126 °C; MS (FAB): *m/z* 281 (M^++1); IR (KBr): 1606 (CO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.73 (d, 1H, J = 2.2 Hz, CH), 6.89 (s, 1H, CH), 7.07 (s, 1H, ArH), 7.45–7.61 (m, 4H, CH & ArH), 7.95–7.99 (m, 2H, ArH), 8.05 (s, 1H, ArH), 12.24 (s, 1H, OH), 15.43 (s, 1H, OH); HRMS calcd for $C_{17}H_{12}O_4$ 280.0736, found 280.0694.

3.1.3.2. 3-Hydroxy-1-(6-hydroxy-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone (7b). Yield: 88%; mp: 155–156 °C; MS (FAB): *m/z* 311 (M^++1); IR (KBr): 1606 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 6.74 (d, 1H, J = 2.2 Hz, CH), 6.82 (s, 1H, CH), 7.01 (d, 2H, J = 9.2 Hz, ArH), 7.07 (s, 1H, ArH), 7.55 (d, 1H, J = 2.2 Hz, CH), 7.94 (d, 2H, J = 9.2 Hz, ArH), 8.04 (s, 1H, ArH), 12.30 (s, 1H, OH), 15.64 (s, 1H, OH); HRMS calcd for $C_{18}H_{14}O_5$ 310.0841, found 310.0827.

3.1.3.3. 3-(3,4-Dimethoxy-phenyl)-3-hydroxy-1-(6-hydroxy-benzofuran-5-yl)-propenone (7c). Yellow solid; yield: 91%; mp: 138–140 °C, MS (FAB): *m/z* 341 (M^++1); IR (KBr): 1611 (CO), 3418 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.74 (d, 1H, J = 2.2 Hz, CH), 6.81 (s, 1H, CH), 6.95 (d, 2H, J = 8.4 Hz, ArH), 7.08 (s, 1H, ArH), 7.46–7.64 (m, 3H, CH and ArH), 8.03 (s, 1H, ArH), 12.30 (s, 1H, OH), 15.64 (s, 1H, OH).

3.1.3.4. 3-Benzo[1,3]dioxol-5-yl-3-hydroxy-1-(6-hydroxy-benzofuran-5-yl)-propenone (7d). Yellow solid; yield: 88%; mp: 140–142 °C; MS (FAB): *m/z* 325 (M^++1); IR (KBr) 1626 (CO), 3424 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.10 (s, 2H, CH_2), 6.76 (d, 1H, J = 2.2 Hz, CH), 6.79 (s, 1H, CH), 6.93 (d, J = 8.1 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.54–7.62 (m, 2H, CH and ArH), 8.05 (s, 1H, ArH), 12.28 (s, 1H, OH), 15.65 (s, 1H, OH).

3.1.3.5. 3-Hydroxy-1-(6-hydroxy-benzofuran-5-yl)-3-(3-methoxy-phenyl)-propenone (7e). Yellow solid; yield: 92%; mp: 108–109 °C; MS (FAB): *m/z* 311 (M^++1); IR (KBr): 1608 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 6.74 (d, 1H, J = 2.2 Hz, CH), 6.87 (s, 1H, CH), 7.08–7.12 (m, 2H, ArH), 7.36–7.52 (m, 3H, ArH), 7.56 (d, 1H, J = 2.2 Hz, CH), 8.05 (s, 1H, ArH), 12.24 (s, 1H, OH), 15.43 (s, 1H, OH).

3.1.3.6. 3-Hydroxy-1-(4-hydroxy-benzofuran-5-yl)-3-phenyl-propenone (9a). Yellow solid; yield: 88%; mp: 150–151 °C (lit.[17f] 146 °C); MS (FAB): *m/z* 281 (M^++1); IR (KBr): 1606 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 6.83 (s, 1H, CH), 7.01 (d, 1H, J = 2.2 Hz, CH), 7.07 (d, 1H, J = 8.8 Hz, ArH), 7.49–7.54 (m, 3H, ArH), 7.58 (d, 1H, J = 2.2 Hz, CH), 7.73 (d, 1H, J = 8.8 Hz, ArH), 7.95 (d, 2H, J = 8.1 Hz, ArH), 13.05 (s, 1H, OH), 15.45 (s, 1H, OH); HRMS calcd for $C_{17}H_{12}O_4$ 280.0736, found 280.0766.

3.1.3.7. 3-Hydroxy-1-(4-hydroxy-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone (9b). Yield: 90%; mp: 129–130 °C; MS (FAB): *m/z* 311 (M^++1); IR (KBr) 1616 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 6.76 (s, 1H, CH), 6.94–7.02 (m, 3H, ArH), 7.08 (d, 1H, J = 8.8 Hz, ArH), 7.58 (d, 1H, J = 2.2 Hz, CH), 7.71 (d, 1H, J = 8.8 Hz, ArH), 7.93 (d, 2H, J = 9.0 Hz, ArH), 13.01 (s, 1H, OH), 15.66 (s, 1H, OH); HRMS calcd for $C_{18}H_{14}O_5$ 310.0841, found 310.0825.

3.1.4. General procedure for the synthesis of compounds 8a–e and 10a–b. A solution of **7** or **9** (6 mmol) in H_2SO_4/CH_3COOH (1:3) was refluxed on water bath for 1 h and after that it was poured on crushed ice to afford the precipitate. The precipitate thus obtained was purified by silica-gel column using hexane–ethylacetate as eluent to get compounds **8a–e** or **10a–b**.

3.1.4.1. 7-Phenyl-furo[3,2-*g*]chromen-5-one (8a). White solid; yield 90%; mp: 127–128 °C; MS (FAB): *m/z* = 263 (M^++1); IR (KBr): 1628 (CO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.83 (s, 1H, ArH), 6.93 (d, 1H, J = 2.2 Hz, CH), 7.52–7.58 (m, 3H, ArH), 7.69 (s, 1H, ArH), 7.75 (d, 1H, J = 2.2 Hz, CH), 7.94–8.00 (m, 2H, ArH), 8.50 (s, 1H, ArH); HRMS calcd for $C_{17}H_{10}O_3$ 262.0630, found 262.0629.

3.1.4.2. 7-(4-Methoxy-phenyl)-furo[3,2-*g*]chromen-5-one (8b). White solid; yield: 94%; mp: 238–239 °C; MS (FAB): *m/z* 293 (M^++1); IR (KBr): 1630 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.91 (s, 3H, OCH_3), 6.76 (s, 1H, ArH), 6.93 (d, 1H, J = 2.2 Hz, CH), 7.05 (d, 2H, J = 8.8 Hz, ArH), 7.44 (s, 1H, ArH), 7.67 (d, 1H, J = 2.2 Hz, CH), 7.92 (d, 2H, J = 8.8 Hz, ArH), 8.49 (s, 1H, ArH).

3.1.4.3. 7-(3,4-Dimethoxy-phenyl)-furo[3,2-*g*]chromen-5-one (8c). White solid; yield 94%; mp: 174–175 °C; MS (FAB): *m/z* = 323 (M^++1); IR (KBr): 1628 (CO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.98 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.77 (s, 1H, ArH), 6.93 (d, 1H, J = 2.2 Hz, ArH), 7.01 (d, 1H, J = 8.4 Hz, ArH), 7.43 (s, 1H, ArH), 7.60 (d, 1H, J = 8.4 Hz, ArH), 7.69 (s, 1H, ArH), 7.75 (d, 1H, J = 2.2 Hz, CH), 8.49 (s, 1H, ArH).

3.1.4.4. 7-Benzo[1,3]dioxol-5-yl-furo[3,2-*g*]chromen-5-one (8d). White solid; yield: 93%; mp: 255–256 °C; MS (FAB): *m*/*z* 307 (M^++1); IR (KBr): 1625 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 6.09 (s, 2H, CH_2), 6.71 (s, 1H, ArH), 6.90–6.99 (m, 2H, CH and ArH), 7.41 (s, 1H, ArH), 7.54 (d, 2H, J = 8.10 Hz, ArH), 7.66 (s, 1H, ArH), 7.74 (d, 1H, J = 2.2 Hz, CH), 8.48 (s, 1H, ArH).

3.1.4.5. 7-(3-Methoxy-phenyl)-furo[3,2-*g*]chromen-5-one (8e). White solid; yield: 91%; mp: 188–189 °C (lit.[17g] 187–188 °C); MS (FAB): *m*/*z* 293 (M^++1); IR (KBr): 1635 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.91 (s, 3H, OCH_3), 6.82 (s, 1H, ArH), 6.92 (d, 1H, J = 2.2 Hz, CH), 7.09 (d, 1H, J = 8.2 Hz, ArH), 7.41–7.57 (m, 3H, ArH), 7.69 (s, 1H, ArH), 7.75 (d, 1H, J = 2.2 Hz, ArH), 8.49 (s, 1H, ArH).

3.1.4.6. 2-Phenyl-furo[2,3-*h*]chromen-4-one (10a). White solid; yield: 92%; mp: 127–128 °C (lit.[17h] 127 °C); MS (FAB): *m*/*z* 263 (M^++1); IR (KBr) 1646 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (s, 1H, ArH), 7.23 (d, 1H, J = 2.2 Hz, CH), 7.56–7.60 (m, 4H, ArH), 7.78 (d, 1H, J = 2.2 Hz, CH), 7.96–8.00 (m, 2H, ArH), 8.18 (d, 1H, J = 8.8 Hz, ArH).

3.1.4.7. 2-(4-Methoxy-phenyl)-furo[2,3-*h*]chromen-4-one (10b). White solid; yield: 94%; mp: 218–219 °C (lit.[17i] 218-219 °C); MS (FAB): *m*/*z* 293 (M^++1); IR (KBr) 1655 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.81 (s, 1H, ArH), 7.06 (d, 2H, J = 8.8 Hz, ArH), 7.21 (d, 1H, J = 2.2 Hz, ArH), 7.58 (d, 1H, J = 8.8 Hz, ArH), 7.78 (d, 1H, J = 2.2 Hz, CH), 7.94 (d, 2H, J = 8.8 Hz, ArH), 8.17 (d, 1H, J = 8.8 Hz, ArH).

3.1.5. General procedure for the synthesis of compounds 12 and 14a–c. The mixture of benzofuran **3** or **4**, K_2CO_3, and methyl iodide in acetone was refluxed for 7–8 h and reaction mixture was filtered to get crude, which was subjected to column chromatography to get the compound **11** or **13** in good yield. The compound **11** or **13** was condensed with aryl ester using potassium hydride as base and dry benzene as solvent for 4–5 h, the reaction mixture was neutralized with 10% HCl and crude thus obtained was purified by column chromatography using silica gel having 3% ethyl acetate in hexane to get the compound **12** or **14** in good isolated yield.

3.1.5.1. 3-Hydroxy-1-(6-methoxy-benzofuran-5-yl)-3-phenyl-propenone (12). Yellow solid; yield 85%, mp: 116–118 °C; MS (FAB): *m*/*z* 295 (M^++1); IR (KBr) 1593 cm^{-1} (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 4.0 (s, 3H, OCH_3), 6.77 (d, 1H, J = 2.2 Hz, CH), 7.12 (s, 1H, CH), 7.15 (s, 1H, ArH), 7.45–7.53 (m, 3H, ArH), 7.58 (d, 1H, J = 2.2 Hz, CH), 7.92–8.01 (m, 2H, ArH), 8.19 (s, 1H, ArH).

3.1.5.2. 3-Hydroxy-1-(4-methoxy-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone (14a). Yellow solid; yield 81%, mp: 84–86 °C; MS (FAB): *m*/*z* 325 (M^++1); IR (KBr) 1597 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 6.95–7.02 (m, 3H, CH and ArH), 7.10 (s, 1H, ArH), 7.31 (d, 1H, J = 8.7 Hz, ArH), 7.62 (d, 1H, J = 2.2 Hz, CH), 7.86 (d, 1H, J = 8.7 Hz, ArH), 7.96 (d, 2H, J = 8.8 Hz, ArH); HRMS calcd for $C_{19}H_{16}O_5$ 324.0998, found 324.0950.

3.1.5.3. 3-(2-Chloro-phenyl)-3-hydroxy-1-(4-methoxy-benzofuran-5-yl)-propenone (14b). Yellow solid; yield 71%, mp: 98–99 °C; MS (FAB): *m*/*z* 331, 329 (M^++1); IR (KBr) 1599 cm^{-1} (CO); ^1H NMR (300 MHz, $CDCl_3$): δ 4.14 (s, 3H, OCH_3), 6.99 (d, 1H, J = 2.2 Hz, CH), 7.06 (s, 1H, ArH), 7.30 (d, 1H, J = 8.7 Hz, ArH), 7.36–7.42 (m, 2H, ArH), 7.45–7.50 (m, 1H, ArH), 7.62 (d, 1H, J = 2.2 Hz, CH), 7.68–7.72 (m, 1H, ArH), 7.90 (d, 1H, J = 8.7 Hz, ArH).

3.1.5.4. 3-Benzo[1,3]dioxol-5-yl-3-hydroxy-1-(4-methoxy-benzofuran-5-yl)-propenone (14c). Yellow solid; yield 87%; mp: 118–119 °C; MS (FAB): *m*/*z* 339 (M^++1); IR (KBr) 1655 cm^{-1} (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 3H, OCH_3), 6.05 (s, 2H, CH_2), 6.89 (d, 1H, J = 8.1 Hz, ArH), 6.99 (d, 1H, J = 2.2 Hz, ArH), 7.06 (s, 1H, CH), 7.30 (d, 1H, J = 8.8 Hz, ArH), 7.46 (s, 1H, ArH), 7.58 (d, 1H, J = 8.1 Hz, ArH), 7.62 (d, 1H, J = 2.2 Hz, CH), 7.86 (d, 1H, J = 8.8 Hz, CH), 16.98 (s, 1H, OH).

3.2. PTP-1B inhibitory assay

Protein tyrosine phosphatase inhibitory activity of compounds was determined by modified method of Goldstein et al.[21] The test compounds were preincubated for 10 min with the enzyme in the absence and presence of 0.01% Triton X-100. Assay was performed in a final volume of 1.0 ml in reaction mixture containing 10 mM pNPP in 50 mM HEPES buffer (pH 7.0) with 1 mM DTT and 2 mM EDTA. The reaction was stopped after 30 min of incubation at 37 °C by the addition of 500 μl of 0.1 N NaOH and the absorbance was determined at 410 nm. A molar extinction coefficient of 1.78×10^4 $M^{-1}cm^{-1}$ was utilized to calculate the concentration of the *p*-nitrophenolate ion produced in the reaction mixture. Sodium orthovanadate was included as standard in the enzyme assay.

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References and notes

1. Turner, N. C.; Clapham, J. C. *Prog. Drug Res.* **1998**, *51*, 35.
2. (a) Astrup, A.; Breum, L.; Toubo, S. *Obesity* **1995**, *3*(Suppl. 4), 537S; (b) Kelley, D. E. *Diabetes Rev.* **1995**, *3*, 366.
3. (a) Babenko, A. P.; Aguilar-Bryan, L.; Bryan, J. *Annu. Rev. Physiol.* **1998**, *60*, 667; (b) Aguilar-Bryan, L.;

Clement, J. P.; Gonzalez, G.; Kunjilwar, K.; Babenko, A.; Bryan *J. Physiol. Rev.* **1998**, *78*, 227.
4. (a) Bailey, C. J.; Turner, R. C. *N. Engl. J. Med.* **1996**, *334*, 574; (b) Dunn, C. J.; Peters, D. H. *Drugs* **1995**, *49*, 721; (c) Cusi, K.; DeFronzo, R. A. *Diabetes Rev.* **1998**, *6*, 89.
5. Coniff, R.; Krol, A. *Clin. Ther.* **1997**, *19*, 16.
6. (a) Ram, V. J. *Prog. Drug Res.* **2003**, *60*, 93; (b) Diamant, M.; Heine, R. J. *Drugs* **2003**, *63*, 1373.
7. (a) Elchelby, M.; Payette, P.; Michaliszyn, E.; Cromlish, W.; Collins, S.; Lee Loy, A.; Normandin, D.; Cheng, A.; Himms-Hagen, J.; Chan, C.; Ramanchandran, C.; Gresser, M. J.; Tremblay, M. L.; Kennedy, B. P. *Science* **1999**, *283*, 1544; (b) Kennedy, B. P. *Biomed. Pharmacother.* **1999**, *53*, 466.
8. (a) Kenner, K. A.; Anyanwu, E.; Olefsky, J. M.; Kusari, J. *J. Biol. Chem.* **1996**, *271*, 19810; (b) Chen, H.; Wertheimer, S. J.; Lin, C. H.; Katz, S. L.; Amrein, K. E.; Burn, P.; Quon, M. J. *J. Biol. Chem.* **1997**, *272*, 8026; (c) Walchli, S.; Curchod, M. L.; Gobert, R. P.; Arkinstall, S.; Hooft van Huijsduijnen, R. *J. Biol. Chem.* **2000**, *275*, 9792.
9. Reviews: (a) Taylor, S. D.; Hill, B. *Expert Opin. Investig. Drugs* **2004**, *13*, 199; (b) Zhang, Z.-Y.; Lee, S.-Y. *Expert Opin. Investig. Drugs* **2003**, *12*, 223; (c) Ukkola, O.; Santaniemi, M. *J. Intern. Med.* **2002**, *251*, 467.
10. Arabaci, G.; Guo, X.-C.; Beebe, K. D.; Coggeshall, K. M.; Pei, D. *J. Am. Chem. Soc.* **1999**, *121*, 5085.
11. Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W. X.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293.
12. Wrobel, J.; Sredy, J.; Moxhan, C.; Dietrich, A.; Li, Z.; Sawicki, D. R.; Seestaller, L.; Wu, L.; Katz, A.; Sullivan, Donald.; Tio, C.; Zhong-Yin, Z. *J. Med. Chem.* **1999**, *42*, 3199.
13. Chen, R. M.; Hu, L. H.; An, T. Y.; Li, J.; Shen, Q. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3387.
14. Maurya, R.; Goel. A.; Narender, T.; Srivastava, A. K.; Rastogi, A. K.; Agarwal, S. C.; Rajendran, S. M.; Nath, C.; Gupta, C. M.; Yadav, P. R.; Shweta, Dixit, M.; Tiwari, P.; Tripathi, B. K. Isolation and synthesis of novel furano- and pyranoflavonoids as antidiabetic agents: Ind. Pat. Appl. No. 0528/DEL/2006, dt. 28/02/2006.
15. (a) Elsohly, M. A.; Doorenbos, N. J.; Quimby, M. W.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L., Jr. *J. Pharm. Sci.* **1974**, *63*, 1623; (b) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 145; (c) Ferracini, V. L.; Roewer, I.; Gao, F.; Mabry, T. J. *Phytochemistry* **1989**, *28*, 1463; (d) Le-Van, N.; Pham, T. V. C. *Phytochemistry* **1981**, *20*, 485.
16. (a) Garcia de Quesada, T.; Rodriguez, B.; Valverde, S. *Phytochemistry* **1972**, *11*, 446; (b) Zalkow, L. H.; Keinan, E.; Steindel, S.; Kalyanaraman, A. R.; Bertrand, J. A. *Tetrahedron Lett.* **1972**, 2873; (c) Breuer, M.; Budzikiewicz, H.; Siebertz, R.; Proksch, P. *Phytochemistry* **1987**, *26*, 3055; (d) de Lampasona, M. E. P.; Catalan, C. A. N.; Gedris, T. E.; Herz, W. *Phytochemistry* **1997**, *46*, 1077; (e) Bohlmann, F.; Tsankova, E.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1983**, *22*, 557.
17. (a) Wagner, H.; Farkas, L. In *The Flavonoids*; Harborne, J. B., Mabry, T. J., Mabry, H., Eds.; Academic Press: New York, 1975; p 127; (b) Gripenberg, J. In *The Chemistry of Flavonoids Compounds*; Geissman, T. A., Ed.; MacMillan: New York, 1962; p 409; (c) Hossain, M. A. *J. Bangla. Acad. Sci.* **1999**, *23*, 9; (d) Lee, Y. K.; Morehead, A. T. *Tetrahedron* **1995**, *51*, 4909; (e) Shaikh, Y. A.; Trivedi, K. N. *J. Indian Chem. Soc.* **1971**, *48*, 1041; (f) Narayanaswami, S.; Rangaswami, S.; Seshadri, T. R. *J. Chem. Soc.* **1954**, 1871; (g) Ganguly, A.; Bhattacharyya, A.; Adityachoudhury, N. *Planta Med.* **1988**, *54*, 90; (h) Rangaswami, S.; Sastry, B. V. *Curr. Sci. India* **1955**, *24*, 13; (i) Lyra, E. A.; De Mello, J. F. *Gazz. Chim. Ital.* **1979**, *109*, 93.
18. (a) Goel. A.; Dixit, M. A process for the synthesis of 4/6-hydroxy-5-acetylcoumarones and uses thereof: Ind. Pat. Appl. No. 1730/DEL/2004, dt. 14/09/2004; (b) Goel, A.; Dixit, M. *Synlett* **2004**, 1990; (c) Dixit, M.; Sharon, A.; Maulik, P. R.; Goel, A. *Synlett* **2006**, 1497.
19. (a) Baker, W. *J. Chem. Res.* **1933**, 1381; (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767.
20. Sekar, N.; Li, J.; Shechter, Y. *Crit. Rev. Biochem. Mol. Biol.* **1996**, *31*, 339.
21. Goldstein, B. J.; Bittner-Kowalezyk, A.; White, M. F.; Harbeck, M. *J. Biol. Chem.* **2000**, *275*, 4283.
22. McGovern, S. L.; Caselli, E.; Grigorieff, N.; Shoichet, B. K. *J. Med. Chem.* **2002**, *45*, 1712.
23. (a) Ryan, A. J.; Gray, N. M.; Lowe, P. N.; Chung, C. *J. Med. Chem.* **2003**, *46*, 3448; (b) McGovern, S. L.; Helfand, B. T.; Feng, B.; Shoichet, B. K. *J. Med. Chem.* **2003**, *46*, 4265.