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Biaryls and heterobiaryls as α-glucosidase and protein tyrosine phosphatase inhibitors

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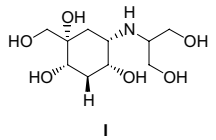
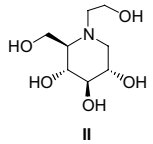
Abstract—Various 6-aryl-4-substituted-2*H*-pyran-2-one-3-carbonitriles (**1a–d**) have been synthesized as precursor for the synthesis of 3,4-dihydro-1*H*-isothiochroman (**2a**) and benzocycloalkanes (**2b–e**). Highly functionalized 9-thiaphenanthrene (**3b**) and phenanthrene (**3a**) have also been obtained from the reaction of **1c** with thiochroman-4-one and 1-tetralone separately. Similarly **4** has been obtained by the ring transformation of **1d** by 4-trifluoromethylacetophenone. Most of the synthesized compounds were evaluated for α-glucosidase and protein tyrosine phosphatase inhibitory activities. Some of the compounds, **2a**, **3a** and **b** and **4** displayed better α-glucosidase inhibitory activity compared to standard drug acarbose.

1. Introduction

α-Glucosidase inhibitors are a class of compounds that inhibit the breakdown of oligo and disaccharides from dietary complex carbohydrates and slowdown the absorption of absorbable monosaccharides available[1] and reduce the postprandial insulin and glucose peak. Delay in glucose absorption reduces postprandial hyperglycemia, which is associated with cardiovascular mortality.[2] Acarbose was the first member of α-glucosidase inhibitors, approved for the treatment of type 2 diabetes.[3] Recently, voglibose[4] **I** and miglitol[5] **II** have been also approved for clinical use for the management of type 2 diabetes. The major advantage of this class of compounds is that they are not associated with hypoglycemia and weight gain, which are the side effects of other class of antihyperglycemic agents.



I



II

The least side effects and various advantages of α-glucosidase inhibitors prompted us to design and synthesize new class of compounds, which could not only reduce the blood glucose level but also be least toxic.

Here, we report the α-glucosidase inhibitory activity of highly functionalized heterobiaryls and some 1,3 teraryls.

2. Chemistry

6-Aryl-4-substituted-2*H*-pyran-2-one-3-carbonitriles (**1a–d**) used as precursors for the synthesis of **2**, **3** and **4** were prepared by the reaction of aryl methyl ketone and methyl 2-cyano-3,3-methylthioacrylate in presence of powdered KOH in DMF and isolated as reported earlier[6] by us.

Compounds **2a–e** were obtained[7] by the ring transformation of 6-aryl-4-substituted-2*H*-pyran-2-ones-3-carbonitriles (**1a** and **b**) by appropriate alicyclic or heterocyclic ketones by stirring a mixture of **1**, a desired ketone and powdered KOH in DMF. The ring transformed products were isolated as reported[8] earlier. Similarly ring transformation of **1c** by 1-tetralone and

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thiochroman-4-one separately led to yield **3a** and **b**. Analogously 4-(1-pyrenyl)-2-(pyrrolidin-1-yl)-6-(4-trifluoromethylphenyl)benzonitrile **4** was prepared by the ring transformation of 6-(pyrene-1-yl)-4-(pyrrolidin-1-yl)-2*H*-pyran-2-one-3-carbonitrile (**1d**) by 4-trifluoromethylphenylacetophenone as shown in Scheme 1.

All the synthesized compounds were characterized by spectroscopic data and elemental analysis.[9]

3. Result and discussion

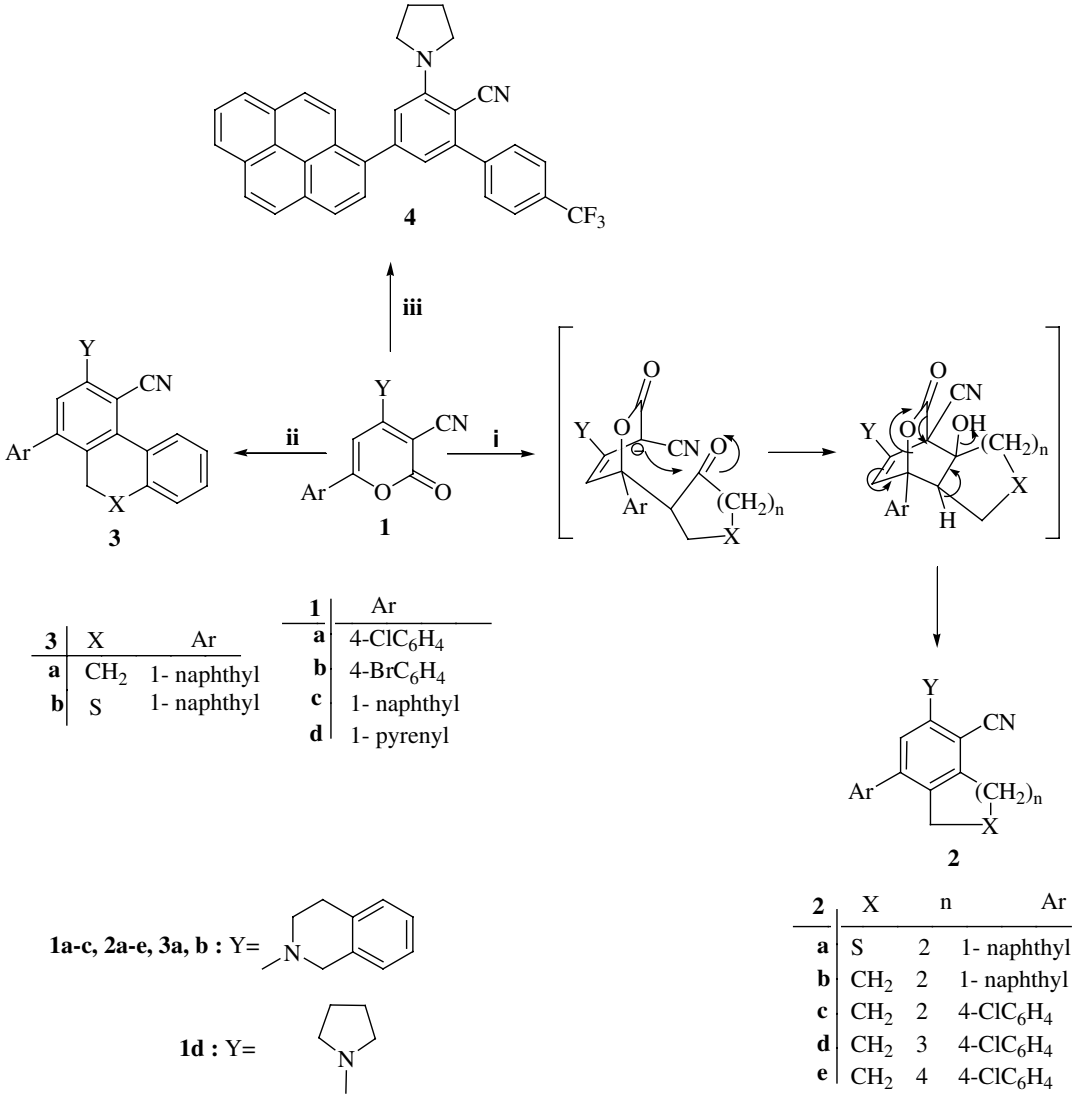
Most of the synthesized compounds were evaluated as α-glucosidase and protein tyrosine phosphatase (PTP) inhibitors. Some of the screened compounds demonstrated potent α-glucosidase inhibitory activity even better than standard drug acarbose. These compounds also display only moderate to marginal activity as PTP inhibitors. Only **3a** and **b** demonstrated 51.8% and 41.9% inhibition, respectively.

3.1. α-Glucosidase inhibitory activity[1]

Hundred microlitres of purified α-glucosidase (0.1 mg/mL) and 25 μL of glutathione (1.0 mg/mL) were made up to 1 mL by adding 0.67 μM phosphate buffer (pH 6.8). The reaction mixture was incubated at room temperature for 10 min with test chemical (10 μM) dissolved in DMSO. Reaction was started by addition of 50 μL 4-nitrophenyl-α-D-glucopyranoside (3 mg/mL) and increase in absorbance at 400 nm was recorded for 5 min at the interval of 30 s.

3.2. Protein tyrosine phosphatase inhibitory activity[10]

The effect of test compounds on protein tyrosine phosphatase was studied by pre-incubating 100 μM of the test chemicals in the reaction system for 10 min and the residual protein tyrosine phosphatase activity determined according to the method of Goldstein et al.[10] Activity of PTPase (LAR) was evaluated using *p*-nitrophenylphosphate (PNPP) as substrate. Assay mixture



3	X	Ar
a	CH_2	1- naphthyl
b	S	1- naphthyl

1	Ar
a	4-ClC_6H_4
b	4-BrC_6H_4
c	1- naphthyl
d	1- pyrenyl

2	X	n	Ar
a	S	2	1- naphthyl
b	CH_2	2	1- naphthyl
c	CH_2	2	4-ClC_6H_4
d	CH_2	3	4-ClC_6H_4
e	CH_2	4	4-ClC_6H_4

Scheme 1. Reagents and conditions: (i) alicyclic ketone/DMF/KOH/rt; (ii) tetralone/thiochroman-4-one/DMF/KOH; (iii) 4-trifluoromethylacetophenone/DMF/KOH/rt.

Table 1. α-Glucosidase and protein tyrosine phosphatase inhibitory activities of compounds **1a** and **b**, **2a**–**e**, **3a** and **b** and **4**

S.No.	% Inhibition at 100 μM concentration	
	α-Glucosidase	Protein tyrosine phosphatase
1a	51.9	18.2
1b	59.7	25.1
2a	96.1	26.7
2b	72.2	14.8
2c	20.7	23.2
2d	47.4	42.8
2e	28.8	24.2
3a	94.8	51.8
3b	98.7	41.9
4	93.8	12.5
Acarbose	90.0	—
Sod. orthovanadate	—	77.6

was made up to 1 mL containing 10 mM PNPP in 50 mM HEPES buffer (pH 7), with 1 mM EDTA and DTT. The reaction was stopped by the addition of 500 μL of 0.1 N NaOH and absorbance was determined at 410 nm. A molar extinction coefficient of $1.78 \times 10^4\ M^{-1}\ cm^{-1}$ was used to calculate the concentration of *p*-nitrophenolate ions produced in the reaction mixture.

Among the 10 screened compounds for α-glucosidase inhibitory activity only **2a** (96.1%), **3a** (94.8%), **3b** (98.7%) and **4** (93.8%) demonstrated more than 90% inhibition and were found even better than standard drug acarbose (90%). Out of four active compounds, **2a**, **3a** and **b** possess α-naphthyl substituent while **4** has 1-pyrenyl group. These results suggest that the presence of bulky aryl substituent is essential to display inhibitory activity. Another compound **2b** with α-naphthyl substituent also demonstrated inhibition to 72.2%. Other compounds with halophenyl substituent **1a** and **b** displayed only moderate activity. Rest of the compounds **2c** and **e** were not significantly active.

All the compounds screened for α-glucosidase inhibitory activity were also assayed for protein tyrosine phosphatase inhibitory property. Only **3a** (51.8%) and **3b** (41.9%) demonstrated moderate PTPase inhibitory activity.

The screening results are shown in Table 1.

Acknowledgements

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References and notes

1. (a) Lebovitz, H. E. *Endocrinol. Metab. Clin. North Am.* **1997**, *26*, 539–551; (b) Clissold, S. P.; Edward, C. *Drugs* **1988**, *35*, 214.
2. Donahue, R. P.; Abbott, R. D.; Reed, D. M.; Yano, K. *Diabetes* **1967**, *36*, 689.
3. Yee, H. S.; Fong, N. T. *Pharmacotherapy* **1996**, *26*, 539.
4. Yoshioka, K.; Azukari, K.; Ashida, K.; Kasamatsu, Y.; Yokoo, S.; Yoshida, T.; Kondo, M. *Horm. Metab. Res.* **1996**, *29*, 407.
5. Pogano, G.; Marena, S.; Corgiat-Mansin, L.; Cravero, F.; Giorda, C.; Bozza, M.; Rossi, C. M. *Diabetes Metab.* **1995**, *21*, 162.
6. (a) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *Liebigs Ann. Chem.* **1991**, 1229–1231; (b) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res., Synop.* **1991**, 98–99.
7. Ram, V. J.; Goel, A. *Synthesis* **1999**, 467–470.
8. (a) Farahanullah; Tripathi, B. K.; Srivastava, A. K.; Ram, V. J. *Bioorg. Med. Chem.* **2004**, *12*, 1543–1549; (b) Ram, V. J.; Agarwal, N.; Saxena, A.; Farhanullah; Sharon, A.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1426–1437.
9. *Characterization data*; *compound* (**2a**): yield 32%; mp 210–215 ° C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.26–2.37 (m, 4H, $2CH_2$), 3.16–3.21 (t, J = 5.7 Hz, 2H, NCH_2, isoquinolinyl), 3.43 (s, 2H, CH_2), 3.64–3.70 (t, J = 5.8 Hz, 2H, CH_2, isoquinolinyl), 4.35 (s, 2H, CH_2), 7.06 (s, 1H, ArH), 7.11–7.45 (m, 8H, ArH), 7.50–7.59 (m, 2H, ArH), 7.92–7.96 (d, J = 7.5 Hz, 1H, ArH); FAB-MS: 433 (M^++1); $C_{29}H_{24}N_2S$: calcd C, 80.52; H, 5.59; N, 6.48; found: C, 80.68; H, 5.68; N, 6.53. Compound (**2b**): yield 60%; mp 152–153 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60–1.63 (m, 2H, CH_2), 1.80–1.86 (m, 2H, CH_2), 2.11–2.28 (m, 2H, CH_2), 3.03–3.14 (m, 4H, $2CH_2$), 3.54–3.65 (m, 2H, NCH_2), 4.31 (s, 2H, NCH_2), 6.86 (s, 1H, ArH), 7.01–7.57 (m, 9H, ArH), 7.87–7.93 (m, 2H, ArH); IR (KBr): ν = 3427, 2360, 2212.5, 1590.7, 1450, 1355 cm^{-1}; FAB-MS: 414 (M^+); $C_{30}H_{26}N_2$: calcd C, 86.92; H, 6.32; N, 6.76; found: C, 86.86; H, 6.21; N, 6.82. Compound (**2c**): yield 55%; mp 176–178 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65–1.90 (m, 4H, $2CH_2$), 2.43–2.53 (m, 2H, CH_2), 2.98–3.14 (m, 4H, $2CH_2$), 3.56–3.61 (t, J = 5.7 Hz, 2H, NCH_2), 4.33 (s, 2H, NCH_2), 6.77 (s, 1H, ArH), 7.07–7.42 (m, 8H, ArH); IR (KBr): ν = 3425, 2365, 2210.5, 1590, 1453, 1384, 1273 cm^{-1}; FAB-MS: 399 (M^++1); $C_{26}H_{23}ClN_2$: calcd C, 78.28; H, 5.81; N, 7.02; found: C, 78.33; H, 5.92; N, 7.13. Compound (**2d**): yield 58%; mp 165–166 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55–1.79 (m, 6H, $3CH_2$), 2.62–2.67 (m, 2H, CH_2), 3.10–3.16 (m, 4H, $2CH_2$), 3.53–3.59 (t, J = 5.7 Hz, 2H, NCH_2), 4.30 (s, 2H, NCH_2), 6.75 (s, 1H, ArH), 7.06–7.43 (m, 8H, ArH); IR (KBr): ν = 3428, 2365, 2210.5, 1589.5, 1456, 1380, 1272.5 cm^{-1}; FAB-MS: 413 (M^+); $C_{27}H_{25}ClN_2$: calcd C, 78.53; H, 6.10; N, 6.78; found: C, 78.51; H, 6.21; N, 6.85. Compound (**2e**): yield 51%; mp 159–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38–1.87 (m, 8H, $4CH_2$), 2.63 (br s, 2H, CH_2), 3.06–3.16 (m,4H, $2CH_2$), 3.55–3.61 (t, J = 5.7 Hz, 2H, NCH_2), 4.31 (s, 2H, NCH_2), 6.76 (s, 1H, ArH), 7.06–7.42 (m, 8H, ArH); IR (KBr): ν = 3427, 2360, 2212.5, 1590.7, 1450, 1355 cm^{-1}; FAB-MS: 427 (M^+); $C_{28}H_{27}ClN_2$: calcd C, 78.76; H, 6.37; N, 6.56; found: C, 78.85; H, 6.42; N, 6.63. Compound (**3a**): yield 42%; mp 225–228 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.29–2.36 (m, 2H, CH_2), 2.58–2.65 (m, 2H, CH_2), 3.18–3.23 (t, J = 5.7 Hz, 2H, NCH_2, isoquinolinyl), 3.69–3.74 (t, J = 5.8 Hz, 2H, CH_2, isoquinolinyl), 4.39 (m, 2H, NCH_2, isoquinolinyl), 7.03–7.57 (m, 13H, ArH), 7.92–7.96 (m, 2H, ArH), 8.35–8.39 (d, J = 7.5 Hz, 1H, ArH); IR (KBr): ν = 3408, 3058, 2926, 2836, 2211, 1592, 1213 cm^{-1}; FAB-MS: 463 (M^++1); $C_{34}H_{26}N_2$: calcd C, 88.28; H, 5.67; N, 6.06; found: C, 88.32; H, 5.74; N, 6.14. Compound (**3b**): yield 35%; mp 208–210 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.20 (m, 2H, CH_2), 3.75 (m, 2H, CH_2), 4.42 (s, 2H, CH_2), 5.31 (s, 2H, NCH_2), 7.08–7.58 (m, 12H, ArH), 7.94–7.98 (m, 2H, ArH), 8.32–8.36 (d, J = 7.6 Hz, 1H, ArH); IR

(KBr): $v = 3400$, 3018, 2926, 2859, 2360, 2216.6, 1558, 1217 cm^{-1}; FAB-MS: 480 (M^+); $C_{33}H_{24}N_2S$: calcd C, 82.47; H, 5.03; N, 5.83; found: C, 82.55; H, 5.12; N, 5.87. Compound (**4**): yield 30%; mp 181–182 °C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.03$–2.09 (m, 4H, $2CH_2$), 3.46–3.55 (t, 4H, $2CH_2$), 6.97 (s, 1H, ArH), 7.27 (s, 1H, ArH), 7.97 (br s, 4H, ArH), 8.00–8.25 (m, 9H, ArH); IR (KBr): $v = 2205$ (s) cm^{-1}; FAB-MS: 516 (M^+); $C_{34}H_{23}F_3N_2$: calcd C, 79.06; H, 4.49; N, 5.42; found: C, 79.16; H, 4.63; N, 5.54.

10. Goldstein, B. J.; Bittner-Kowalezyk, A.; White, M. F.; Harbeck, M. *J. Biol. Chem.* **2000**, *275*, 4283–4289.