Design, synthesis and evaluation of 2,4-diarylpyrano[3,2-c]chromen-5(4H)-one as a new class of non-purine xanthine oxidase inhibitors

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Abstract

Keeping in view the recent success of molecular hybridization technique in drug design, 2,4-diarylpyrano[3,2-c]chromen-5(4H)-ones as conjugates of coumarins and chalcones have been designed and synthesized in the present study. The catalytic efficiency of various Lewis acids for the synthesis of designed conjugates under neat conditions was investigated, and SiO₂ (200–400 mesh)-ZnCl₂ was optimized as the best catalyst among the tested ones. The conjugates were evaluated for in-vitro xanthine oxidase activity. The results of the in-vitro assay were quite promising as some conjugates were endowed with remarkable inhibitory potential against the enzyme. HV-8, 11 and 12 were found to be highly potent inhibitors with HV-11 (the most potent inhibitor) possessing an IC₅₀ value of 2.21 μM. The most active conjugate HV-11 was evaluated for the type of inhibition and was found to be a mixed type inhibitor. The compliance of some selected conjugates to the Lipinski rule was also calculated.

Keywords

Conjugates, inhibition, lipinski rule, mixed, silica, xanthine oxidase

Introduction

Oxidative hydroxylation of hypoxanthine and xanthine catalyzed by xanthine oxidase to produce uric acid and reactive oxygen species leads to many diseases like gout and at least symptoms of diseases like oxidative damage to the tissue. Therefore, the selective inhibition of XO may result in broad spectrum chemotherapeutic for gout, cancer, inflammation and oxidative damage. Allpurinol, 2-alkyl hypoxanthines, pterin and 6-formylpterin represents the class of purine-based xanthine oxidase inhibitors. All these inhibitors have been successfully utilized and have proved their inhibitory potential towards the enzyme. However, these purine-based inhibitors have been successfully reported to be associated with Steven Johnson syndrome and worsening of renal function induced in some of the patients. Keeping in view these side effects, we have recently designed some non-purine xanthine oxidase inhibitors such as azaflavones, n-acetyl pyrazolines, naphthopyrans and 4,6-diaryl/heteroarylpyrimidin-2(1H)-ones. Keeping in view the promising xanthine oxidase inhibitory potential of these non-purine chemical architectures, the present study explores xanthine oxidase inhibitory evaluation of the designed 2,4-diarylpyrano[3,2-c]chromen-5(4H)-one as coumarin-chalcone conjugates (Figure 1).

Coumarins form an important class of compounds, which occupy a special role in nature. The presence of coumarin architecture in naturally occurring phytoconstituents with anticancer, anti-HIV, antituberculosis, anti-influenza, anti-alzheimer, anti-inflammatory, antiviral, antimicrobial and xanthine oxidase inhibitory activities makes it a privileged structure. Among the diverse array of biological activities possessed by coumarins, we are particularly interested towards their xanthine oxidase inhibitory potential which has also been extensively explored. Esculetin represents the most potent xanthine oxidase inhibitor of this class.

Chalcones (1,3-diaryl-2-propen-1-ones) with an enone system between two aromatic rings constitute an important class of natural products which serve as precursors for the preparation of various flavonoids and exhibit interesting pharmacological activities. Chalcones are also known as open chain flavonoid derivatives which are extensively reported as xanthine oxidase inhibitors. Recently, 3,5,2,4-tetrahydroxychalcone was found to be potent competitive inhibitor of the enzyme as indicated by the kinetic study. In vivo, intragastric administration of the chalcone was able to significantly reduce serum uric acid levels and inhibited hepatic xanthine oxidase activities of hyperuricemic mice in a dose-dependent manner.

Thus, the proved potential of coumarin and chalcones as xanthine oxidase inhibitors and recent success of molecular hybridization technique in drug design tempted us to design such conjugates. Pyran was selected as a linker for tethering coumarin with chalcones. The presence of pyran as a structural motif in various non-purine xanthine oxidase inhibitors supports the suitability of its selection as a linker.

Results and discussion

Chemistry

The usual strategy for the synthesis of 2,4-diarylpyrano[3,2-c]coumarins is to react 4-hydroxy coumarin with α,β-unsaturated compounds. There are some methodologies utilizing various
catalysts reported for the synthesis of 2,4-diaryl pyrano[3,2-c]coumarins, but each one suffers from some drawbacks such as environmentally hazardous (POCl₃), expensive catalysts (AuCl₃/3AgOTf) and some unavailable Brönsted acids. Recently, Bagdi et al. reported an efficient regioselective methodology for the synthesis of 2,4-diaryl pyrano[3,2-c]coumarins via copper (II) triflate. However, in view of limited efficient and environmentally friendly synthetic schemes and in continuation of our efforts to develop cost effective, highly yielding and environmentally friendly methodologies for non-purine xanthine oxidase inhibitors, we investigated the effects of some inexpensive and easily available Lewis acids under neat conditions for the synthesis of desired compounds.

In an attempt to investigate the catalytic efficiency of various Lewis acids (Table 1), a model reaction was performed with different catalyst for the synthesis of target compound (Scheme 1). All reactions were carried out using 1 mmol of hydroxy coumarin and chalcone.

Table 1 presents the yield of the model reaction under neat conditions for the synthesis of desired compounds. Further increase in temperature and time resulted in slight decrease in the yields with all the catalyst. Among the various Lewis acids tested, ZnCl₂ was found to be the best catalyzing model reaction in 50% yield. Thus, the catalytic efficiency of ZnCl₂ was further investigated by adsorbing it over different grades of silica. The yields of the model reaction were higher with ZnCl₂ adsorbed on SiO₂ (200–400 mesh) than the other grades of silica. The results clearly demonstrated the effect of increased effective surface area on the catalytic efficiency of silica-supported zinc chloride as the yield of the model reaction with SiO₂ (200–400 mesh)-ZnCl₂ was around 1.5-folds higher than silica (60–120 mesh). Thus, the optimum reaction conditions involve the use of SiO₂ (200–400 mesh)-ZnCl₂ at 100°C for 4 h. In order to examine the substrate scope of this reaction, variety of chalcone derivatives was used. Table 2 indicates that all the reactions with electronically and sterically diverse chalcone derivatives proceeded smoothly to afford the target compounds in moderate to good yields.

In the in-vitro xanthine oxidase assay, the conjugates were screened using bovine milk xanthine oxidase (grade 1, ammonium sulfate suspension) enzymatic assay as described in the literature. Allopurinol was employed as reference inhibitor. The results of the in-vitro assay (Table 2) indicated that HV-8, HV-11 and HV-12 were endowed with significant inhibitory potential against the enzyme. HV-11 with an unsubstituted phenyl ring (Ring A) and thiophenyl ring (Ring B) was the most potent among the series with an IC₅₀ value of 2.21 μM followed by HV-12 (unsubstituted phenyl ring – Ring A and 1-naphthyl – Ring B, IC₅₀ value 4.31 μM) and HV-8.
Table 2. Isolated yields, IC$_{50}$ values and type of inhibition.

| Code | Structure | Yield (%) | IC$_{50}$ (µM) |
|------|-----------|-----------|----------------|
| HV-1 | ![Structure](image1) | 82 | 25.42 |
| HV-2 | ![Structure](image2) | 84 | 78.31 |
| HV-3 | ![Structure](image3) | 83 | 80.21 |
| HV-4 | ![Structure](image4) | 85 | 65.32 |
| HV-5 | ![Structure](image5) | 83 | 72.1 |
| HV-6 | ![Structure](image6) | 68 | 16.71 |
| HV-7 | ![Structure](image7) | 72 | 21.31 |
| HV-8 | ![Structure](image8) | 75 | 8.21 |
| HV-9 | ![Structure](image9) | 84 | 75.21 |
| HV-10 | ![Structure](image10) | 69 | 56.21 |
| HV-11 | ![Structure](image11) | 75 | 2.21 |
| HV-12 | ![Structure](image12) | 81 | 4.31 |
Conjugates HV-11 and HV-12 were found to be more active than allopurinol (IC$_{50}$ = 8.79 μM), whereas HV-8 displayed a similar inhibitory profile to allopurinol. Enzyme kinetics study was performed for HV-11 (most active inhibitor). The Lineweaver–Burk plot (Figure 2) revealed that compound HV-11 was a mixed-type XO inhibitor. The pattern of graph shows that it is a form of mixed inhibition scenario. The $K_m$, $V_{max}$ and slope are all affected by the inhibitor. The inhibitor has increased the $K_m$ and slope ($K_m/V_{max}$) while decreasing the $V_{max}$. Moreover, carefully observing Figure 2, it was found that intersecting lines on the graph converge to the left of the y-axis and above the x-axis which indicates that the value of $z$ (a constant which defines the degree to which inhibitor binding affects the affinity of the enzyme for substrate) is greater than 1. This confirms that the inhibitor preferentially binds to the free enzyme and not the enzyme substrate complex. Table 2 also revealed some interesting generalizations about the structure–activity relationship (SAR). SAR study revealed (i) placement of any substituent on Ring A irrespective of its electronic effects resulted in decreased activity profile (compare HV-1 with HV-13, (unsubstituted phenyl – Ring A and 2-naphthyl – Ring B, IC$_{50}$ value 8.21 μM). Conjugates HV-11 and HV-12 were found to be more active than allopurinol (IC$_{50}$ = 8.79 μM), whereas HV-8 displayed a similar inhibitory profile to allopurinol. Enzyme kinetics study was performed for HV-11 (most active inhibitor). The Lineweaver–Burk plot (Figure 2) revealed that compound HV-11 was a mixed-type XO inhibitor. The pattern of graph shows that it is a form of mixed inhibition scenario. The $K_m$, $V_{max}$ and slope are all affected by the inhibitor. The inhibitor has increased the $K_m$ and slope ($K_m/V_{max}$) while decreasing the $V_{max}$. Moreover, carefully observing Figure 2, it was found that intersecting lines on the graph converge to the left of the y-axis and above the x-axis which indicates that the value of $z$ (a constant which defines the degree to which inhibitor binding affects the affinity of the enzyme for substrate) is greater than 1. This confirms that the inhibitor preferentially binds to the free enzyme and not the enzyme substrate complex. Table 2 also revealed some interesting generalizations about the structure–activity relationship (SAR). SAR study revealed (i) placement of any substituent on Ring A irrespective of its electronic effects resulted in decreased activity profile (compare HV-1 with HV-13, (unsubstituted phenyl – Ring A and 2-naphthyl – Ring B, IC$_{50}$ value 8.21 μM). Conjugates HV-11 and HV-12 were found to be more active than allopurinol (IC$_{50}$ = 8.79 μM), whereas HV-8 displayed a similar inhibitory profile to allopurinol. Enzyme kinetics study was performed for HV-11 (most active inhibitor). The Lineweaver–Burk plot (Figure 2) revealed that compound HV-11 was a mixed-type XO inhibitor. The pattern of graph shows that it is a form of mixed inhibition scenario. The $K_m$, $V_{max}$ and slope are all affected by the inhibitor. The inhibitor has increased the $K_m$ and slope ($K_m/V_{max}$) while decreasing the $V_{max}$. Moreover, carefully observing Figure 2, it was found that intersecting lines on the graph converge to the left of the y-axis and above the x-axis which indicates that the value of $z$ (a constant which defines the degree to which inhibitor binding affects the affinity of the enzyme for substrate) is greater than 1. This confirms that the inhibitor preferentially binds to the free enzyme and not the enzyme substrate complex. Table 2 also revealed some interesting generalizations about the structure–activity relationship (SAR). SAR study revealed (i) placement of any substituent on Ring A irrespective of its electronic effects resulted in decreased activity profile (compare HV-1 with HV-13,
20 and HV-10 with HV-11. (ii) Conjugates with phenyl rings possessing electron donating substituents (Ring B) were more active than the conjugates with unsubstituted phenyl rings and phenyl rings possessing electron withdrawing substituents (Ring B) (compare HV-6, HV-7, HV-14 and HV-17 with HV-2, 3, 4, 5, 9, 16, 19). Over all the preference order of substituents for Ring B is as follows: OCH3 > CH3 > H > halo and nitro. (iii) Placement of a heteroaryl ring as Ring B significantly enhanced the inhibitory profile (compare HV-1 with HV-11). (iv) Placement of a bicyclic ring as Ring B also led to enhancement of activity (HV-1 with HV-8 and HV-12). (v) 1-Naphthyl was favored over 2-naphthyl as ring as Ring B also led to enhancement of activity (HV-1 with HV-11). Overall HV-11 and -12 seems to be good hits among the series. Further detailed investigation on HV-11 and -12 is under progress.

**Experimental**

The reagents were purchased from Sigma Aldrich, Merck, CDH, Loba chem., Spectro chem., India, and used without further purification. All yields refer to isolated products after purification. Biotage Microwave Synthesizer (Model: Initiator) operating at 150°C with the microwave power maximum level of 400 W was used for the f ries rearrangement. Products were characterized by spectral data. 1H NMR and 13C NMR spectra were recorded on Bruker Advance II 400 NMR Spectrometer and JEOL AL 300 NMR Spectrometer. The spectra were measured in CDCl3 relative to TMS (0.00 ppm). Melting points were determined in open capillaries and were uncorrected.

**Procedure for the synthesis of 2,4-diaryl pyranol[3,2-c]coumarins**

The mixture of 4-hydroxy coumarin (1 mmol), differently substituted chalcones (1 mmol) and SiO2 (200–400 mesh)-ZnCl2 (10 mol%), was heated on an oil bath for 4 h. The reaction mixture was extracted with water and ethyl acetate. The ethyl acetate fraction was concentrated and subjected to column chromatography. The product was eluted with increasing % age of ethyl acetate in hexane. The remaining reactions were carried out following these general procedures. In each occasion, the spectral data (1H NMR, 13C NMR and MASS) of known compounds are 2,4-diphenylpyranol[3,2-c]chromen-5(4H)-one37, 4-(3-nitrophenyl)-2-phenylpyranol[3,2-c]chromen-5(4H)-one37, 2-phenyl-4-p-tolylpyranol[3,2-c]chromen-5(4H)-one37, 2-(4-chlorocyclohexa-2,4-dienyl)-4-(4-methoxyphenyl)pyranol[3,2-c]chromen-5(4H)-one37, 2-(4-chloro-46-dienyl)pyranol[3,2-c]chromen-5(4H)-one37, 2-(4-methylcyclohexa-2,4-dienyl)pyranol[3,2-c]chromen-5(4H)-one37, and 2-(4-methylcyclohexa-2,4-dienyl)pyranol[3,2-c]chromen-5(4H)-one37.

The physical data of the 14 new compounds are provided below.

**Characterization data**

The characterization data for the 14 newly synthesized compounds are given below.

4-(4-Chlorophenyl)-2-phenylpyranol[3,2-c]chromen-5(4H)-one (HV-2): m.p.: 87–88°C; 1H NMR (CDCl3, 300 MHz, δ,
4. (4-Bromomethyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-3): m.p.: 168–169°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.02 (1H, d, J = 6.6 Hz), 7.73 (2H, d, J = 6.3 Hz), 7.57 (1H, m), 7.39–7.45 (5H, m), 7.26–7.36 (4H, m), 5.80 (1H, d, J = 4.8 Hz), 4.68 (1H, d, J = 4.8 Hz). 13C NMR (CDCl3, 75 MHz, δ, TMS = 0): 31.172, 102.923, 103.480, 114.560, 116.862, 122.761, 124.237, 129.943, 130.242, 131.720, 132.204, 134.499, 147.255, 152.798. Anal. Calc. for C24H15NO5: C, 72.54; H, 4.74; Found: C, 72.68; H, 4.07.

4-(4-Fluorophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-4): m.p.: 142–143°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.03 (1H, d, J = 7.5 Hz), 7.75 (2H, d, J = 7.8 Hz), 7.59 (1H, m), 7.34–7.49 (7H, m), 7.00 (2H, m), 5.83 (1H, d, J = 4.8 Hz), 4.72 (1H, d, J = 4.8 Hz). Anal. Calc. for C28H22FNO5: C, 77.83; H, 4.08; Found: C, 78.11; H, 3.95.

4-(Nitrophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-5): m.p.: 190–191°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.18 (2H, d, J = 9.00 Hz), 8.04 (1H, d, J = 7.5 Hz), 7.73–7.81 (2H, m), 7.58–7.61 (3H, m), 7.35–7.48 (5H, m), 7.58 (1H, d, J = 4.8 Hz), 4.85 (1H, d, J = 4.8 Hz). 13C NMR (CDCl3, 75 MHz, δ, TMS = 0): 36.721, 102.141, 102.425, 114.200, 116.986, 117.586, 122.807, 123.013, 123.251, 123.489, 123.929, 124.070, 124.220, 124.466, 124.795, 125.041, 125.062, 125.586, 128.536, 128.939, 129.427, 129.740, 130.283, 130.356, 131.566, 131.129, 132.560, 133.077, 147.101, 147.834, 150.613, 152.867, 156.315, 161.289. Anal. Calc. for C28H19NO5: C, 72.54; H, 3.80; N, 3.52; Found: C, 72.48; H, 4.02; N, 3.76.

4-(3-Dimethoxyphenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-6): m.p.: 85–86°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.02 (1H, d, J = 7.8 Hz), 7.74 (2H, d, J = 6.3 Hz), 7.57 (1H, m), 7.36–7.46 (5H, m), 6.89 (1H, s), 6.93 (1H, d, J = 8.7 Hz), 6.80 (1H, d, J = 8.1 Hz), 5.85 (1H, d, J = 5.1 Hz), 4.66 (1H, d, J = 4.8 Hz), 3.86 (6H, s), 5.85 (1H, d, J = 5.1 Hz), 4.66 (1H, d, J = 4.8 Hz). Anal. Calc. for C28H27O5: C, 75.72; H, 4.89; Found: C, 75.84; H, 5.05.

4-(3-Methoxyphenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-7): m.p.: 132–133°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.00 (1H, d, J = 7.5 Hz), 7.72 (2H, d, J = 7.8 Hz), 7.42 (1H, m), 7.41 (2H, d, J = 7.5 Hz), 7.15–7.35 (5H, m), 6.84 (2H, d, J = 8.4 Hz), 5.81 (1H, d, J = 5.1 Hz), 4.66 (1H, d, J = 5.1 Hz), 3.84 (3H, s). 13C NMR (CDCl3, 75 MHz, δ, TMS = 0): 35.745, 55.299, 103.873, 114.005, 114.613, 116.816, 122.685, 124.182, 124.650, 126.130, 128.475, 128.697, 129.230, 129.587, 131.964, 132.685, 135.832, 146.770, 152.715, 155.510, 158.754, 161.568. Anal. Calc. for C28H26O5: C, 78.52; H, 4.74; Found: C, 78.69; H, 4.99.

4-(Naphthalen-2-yl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-8): m.p.: 178–179°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 7.74–8.14 (4H, m), 7.43–7.58 (5H, m), 7.28–7.36 (7H, m), 5.90 (1H, d, J = 3.9 Hz), 4.89 (1H, d, J = 3.9 Hz). 13C NMR (CDCl3, 75 MHz, δ, TMS = 0): 18.405, 36.823, 58.455, 103.706, 116.882, 122.743, 124.220, 124.735, 125.810, 126.103, 126.511, 127.199, 127.616, 127.940, 128.428, 128.706, 129.304, 132.068, 132.710. Anal. Calc. for C28H19O5: C, 83.57; H, 4.51; Found: C, 83.33; H, 4.77.

4-(Chlorophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one (HV-9): m.p.: 132–133°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 8.02 (1H, d, J = 8.1 Hz), 7.72 (2H, d, J = 7.8 Hz), 7.59 (1H, m), 7.19–7.31 (5H, m), 7.31–7.46 (4H, m), 5.80 (1H, d, J = 3.0 Hz), 4.69 (1H, d, J = 3.0 Hz). Anal. Calc. for C28H19ClO5: C, 76.55; H, 4.08; Found: C, 76.57; H, 4.06.

4-(2-Methoxyphenyl)-2-(3,4-dimethylphenyl)pyrano[3,2-c]chromen-5(4H)-one (HV-15): m.p.: 122–123°C; 1H NMR (CDCl3, 300 MHz, δ, TMS = 0): 7.98 (1H, bs), 7.36–7.56 (6H, m), 6.75–7.00 (4H, m), 6.06 (1H, d, J = 4.5 Hz), 4.76 (1H, d, J = 4.5 Hz), 3.95 (3H, s), 3.93 (3H, s), 3.87 (3H, s). Anal. Calc. for C27H27O5: C, 70.73; H, 4.84; Found: C, 71.01; H, 5.06.
Xanthine oxidase assay

Bovine xanthine oxidase (grade 1, ammonium sulfate suspension, Sigma–Aldrich) activity was assayed spectrophotometrically by measuring the uric acid formation at 293 nm using a Hitachi U-3010 UV–visible spectrophotometer at 25 °C. The reaction mixture contained 50 mM potassium phosphate buffer (pH 7.6), 75 μM xanthine and 0.08 units of xanthine oxidase. Inhibition of xanthine oxidase activity by various inhibitors was measured by following the decrease in the uric acid formation at 293 nm at 25 °C. The enzyme was pre-incubated for 5 min, with test compound, dissolved in DMSO (1% v/v), and the reaction was started by the addition of xanthine. Final concentration of DMSO (1% v/v) did not interfere with the enzyme activity. All the experiments were performed in triplicate, and values were expressed as means of three experiments.

Declaration of interest

The authors declare no conflict of interest.

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