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Original article

Synthesis and biological evaluation of 3-amino-2-pyrones as selective cyclooxygenase-1 (COX-1) inhibitors

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ABSTRACT

A group of 3-amino-2-pyrones were synthesized and their biological activities were evaluated for inhibiting cyclooxygenase (COX) activity. This study has led to the identification of COX-1-selective inhibitors. Among the tested compounds, the compound **5j** exhibited the most potent COX-1 inhibitory activity (IC_{50} = 19.32 μg/mL) and COX-1 selectivity index (SI = 41.98).

1. Introduction

Prostaglandin and thromboxane biosynthesis involves the transformation of arachidonic acid to prostaglandin H_2 (PGH_2), a reaction catalyzed by the sequential actions of COX and prostaglandin endoperoxidase synthase (PGHS) [1]. Two isoforms of COX (COX-1, COX-2) have been isolated [2]. COX-2 is reported to be inducible with various stimuli, while COX-1 is constitutively expressed in many organs or tissues. However, recent studies have shown many exceptions for this paradigm. For example, recent research implied that COX-1 can play an important role in early pathogenesis of Alzheimer disease, even as a potential target for early intervention of Alzheimer disease [3]. Moreover some experimental results have indicated possible involvement of COX-1 in pain and cancer development [4], thus providing the rationale for the development of selective COX-1 inhibitors. Although many selective COX-2 inhibitors [5] have been found, research on COX-1 selective inhibitors is less-advanced [6] due to the dogma that COX-1 inhibitors inevitably cause gastrointestinal toxicity [7]. So, the development of COX-1 selective inhibitors is important for the development of novel drugs to treat COX-associated diseases, such as inflammatory diseases and cancer.

2-Pyrones are found in numerous natural products [8] and exhibit a wide range of biological activities, such as anti-HIV [9], telomerase inhibition [10], antimicrobial [11], antifungal [12], cardiotonic [13], pheromonal [14], androgen-like [15] and phytotoxic [16] properties. Simple changes in the substitution pattern on the 2-pyrone ring often lead incredible diverse biological activity. For example, the 2-pyrone PD 107067 (**1**) (Fig. 1) has been shown to be an effective inhibitor of HIV protease [17], and Fairlamb et al. found that 4-substituted-6-methyl-2-pyrone (**2**) demonstrated remarkable antimicrobial activity, human ovarium carcinoma (A2780) and human chronic myelogenous leukemia (K562) inhibitory properties [18]. Recent studies have shown that 3,4,6-triphenylpyran-2-one (**3**) and 3,4-diphenylpyran-2-one (**4**) were selective COX-2 inhibitors with good anti-inflammatory and analgesic activity profiles [19]. Herein we want to report on synthetic details and novel selective COX-1 inhibitors of 3-amino-2-pyrones (**5**).

2. Experimental

The synthetic methods used to prepare the target 3-amino-2-pyrones are outlined in Scheme 1 [20]. The initial strategy was to synthesis the prop-2-yn-1-ols (**9**), which was achieved by the condensation of phenylacetylene or pent-1-yne with a substituted benzaldehyde in the presence of ethylmagnesium bromide. Subsequent oxidation of **9** using Jones reagent afforded the corresponding prop-2-yn-1-one (**10**). The 3-amino-2-pyrones **5** were obtained by hydrolysis of 3-amino-2-pyrone derivatives **11**, which are obtained by condensation of ethyl 2-(diphenylmethyleneamino)acetate **7** with prop-2-yn-1-one **10** in the presence of NaOH at 25 °C as shown in Scheme 1.

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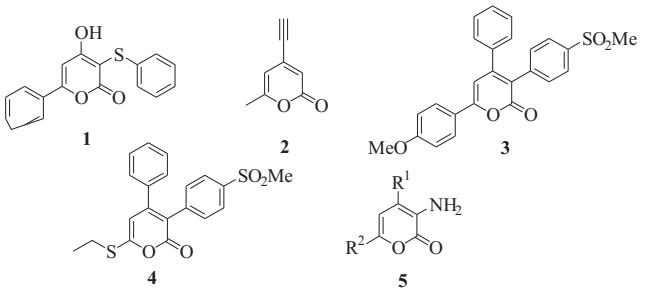
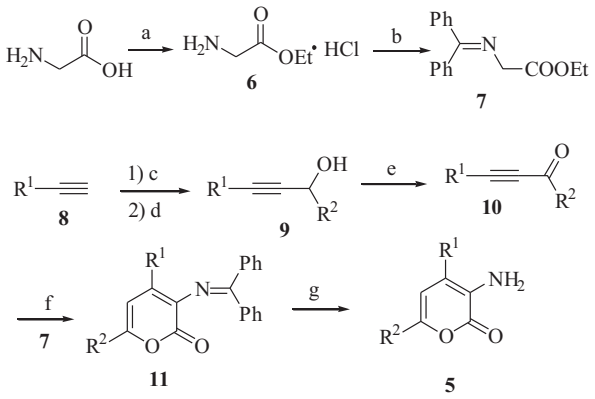
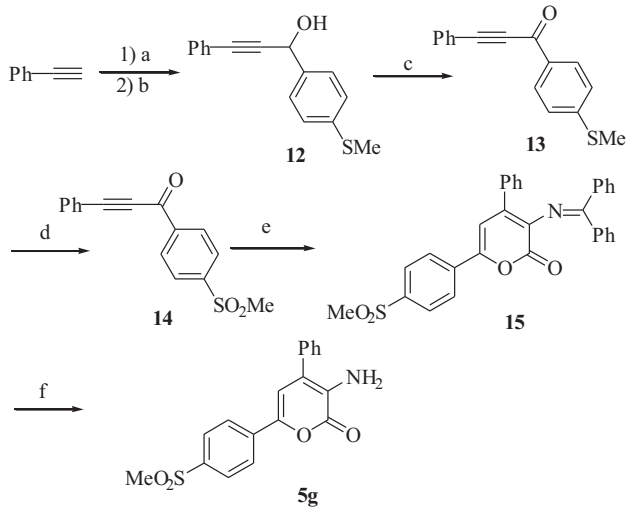


Fig. 1. The structures of compounds **1**–**5**.



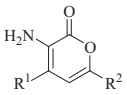
Scheme 1. Reagents and conditions: (a) EtOH, $SOCl_2$, reflux, 2.5 h; (b) CH_2Cl_2, Et_3N, diphenylmethanimine, 12 h; (c) THF, ethylmagnesium bromide, 0 °C, 4 h; (d) aldehyde, 0 °C ~r.t., 12 h; (e) propan-2-one, Jones reagent, 2–4 h; (f) CH_2Cl_2, NaOH, 4–12 h; (g) propan-2-one, 10% HCl, 2 h.

The 3-amino-2-pyrone with a C-4 4-methanesulfonylphenyl substituent **5g** was prepared using the reaction sequence shown in Scheme 2. Thus, the prop-2-yn-1-one derivative **13** was synthesized by condensation of 4-methylthiobenzaldehyde with ethynylbenzene in the presence of ethylmagnesium bromide to afford the prop-2-yn-1-ol **12** which was subsequently oxidized to the corresponding ketone **13** using MnO_2. Subsequent oxidation of **13** using aqueous oxone afforded the methanesulfonyl derivative **14** in good yield. The final cyclization reaction was carried out by



Scheme 2. Reagents and conditions: (a) THF, ethylmagnesium bromide, 0 °C, 4 h; (b) 4-(methylthio)benzaldehyde, 0 °C ~r.t., 12 h; (c) propan-2-one, MnO_2, 2 h; (d) propan-2-one, aqueous oxone, 2 h; (e) ethyl 2-(diphenylmethylene-amino)acetate, CH_2Cl_2, NaOH, 4 h; (f) propan-2-one, 10% HCl, 2 h.

Table 1
COX-inhibitory activity of the target compounds .



Compound	R^1	R^2	IC_{50} (μg/mL)		SI
			COX-1	COX-2	
5a	Ph	Ph	23.94	631.2	26.37
5b	Ph	4-F-Ph	26.33	105.7	4.01
5c	Ph	4-Cl-Ph	28.72	219.6	7.65
5d	Ph	4-MeO-Ph	43.79	75.70	1.73
5e	Ph	3,4-MeO-Ph	80.2	148.72	1.85
5f	Ph	3,4,5-MeO-Ph	48.84	581.37	11.90
5g	Ph	4-$MeSO_2$-Ph	89.65	<50%	–
5h	Pr	4-F-Ph	37.17	97.93	2.63
5i	Pr	3-CF_3-Ph	24.48	262.03	10.70
5j	Pr	4-Br-Ph	19.32	811.04	41.98

condensation of **14** with ethyl 2-(diphenyl-methyleneamino)acetate with prop-2-yn-1-one in the presence of NaOH as shown in Scheme 2.

3. Results and discussion

A group of 3-amino-2-pyrones were prepared to investigate the effect of different substituents on COX-1 selectivity and potency. The ability of the 3-amino-2-pyrones to inhibit the COX-1 and COX-2 isozymes was determined according to the reported method [21]. *In vitro* COX-1/COX-2 inhibition studies showed that all compounds **5** were selective inhibitors of the COX-1 isozyme with IC_{50} values with potency of 19.32–89.65 μg/mL range, and COX-1 selectivity indexes (SI) in the 3–40 μg/mL range (Table 1). These data also showed that the nature of the substituent attached to C-4 of 3-amino-2-pyrone ring influenced both selectivity and potency for COX-1 inhibitory activity. Our results indicated that the introduction of suitable substituents such as -F (**5b**) and -OMe (**5d**) at the *para*-position of C-4 phenyl ring increased potency for COX-2 inhibitory activity. According to these results, 3-fluorophenyl-2-(4-methylsulfonyl phenyl)-1,3-benzthiazinan-4-one **5j** was the most potent (IC_{50} = 19.32 μg/mL) and selective (SI = 41.98) COX-1 inhibitor among the synthesized compounds.

4. Conclusion

In summary, we have found that 3-amino-2-pyrones possess COX-1/2-inhibiting activity and show potent COX inhibiting activity preferentially to COX-1 subtype. Further structural development aimed at improvement of the COX-1/COX-2 selectivity and pharmacological application studies are in progress in our lab.

Acknowledgments

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