The synthesis of isotopic fluorine and iodine–labeled COX-II inhibitor and *in vitro* validation

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1. Introduction

In these day, NASIDs (non-steroidal anti-inflammatory drugs) such as aspirin, diclofenac and ibuprofen are the most common medications used to reduce pain and inflammation.

However, they act by inhibiting both COX-I and COX-II which can cause serious gastrointestinal side effects such as ulcers, stomach perforations and bleeds. COX-I produces prostaglandins believed to be responsible for the protection of the stomach lining. However, COX-II produces prostaglandins believed to be responsible for pain and inflammation.

Recently, the most widely studied selective COX-II inhibitor such as celecoxib and rofecoxib' one work by inhibiting the effect of COX-II on pain and inflammation without inhibiting COX-I which protects gastrointestinal lining(Fig 1).

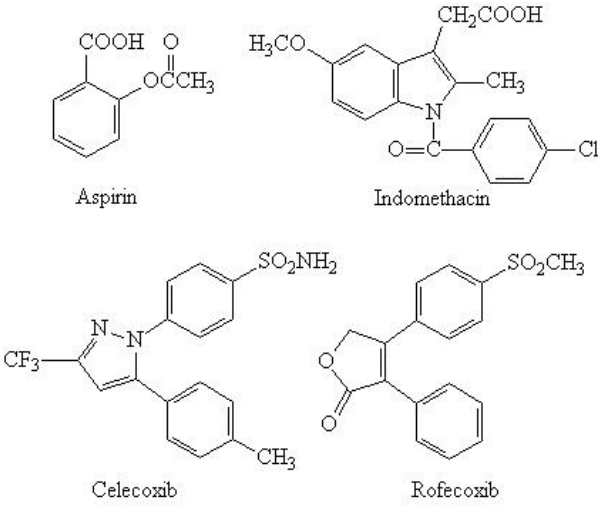


Fig 1. Other selective cyclooxygenase-2 (COX-II) inhibitors[1]

Especially, the isoxazolyl compounds have little side effects and the effects of them are known already.

Based on the general structure, three important sites are suggested : sites A (methylsulfonyl moiety), sites B (central phenyl ring), and sites C (terminal phenyl ring containing different substituents) (Fig 2).

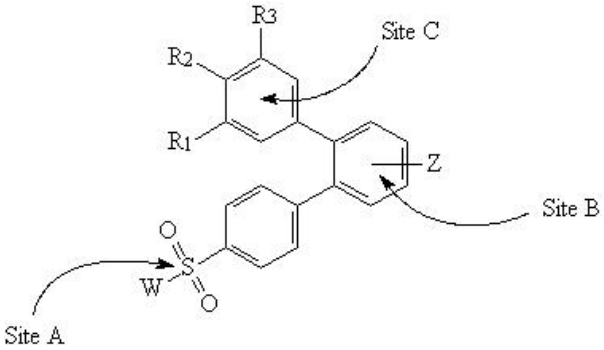
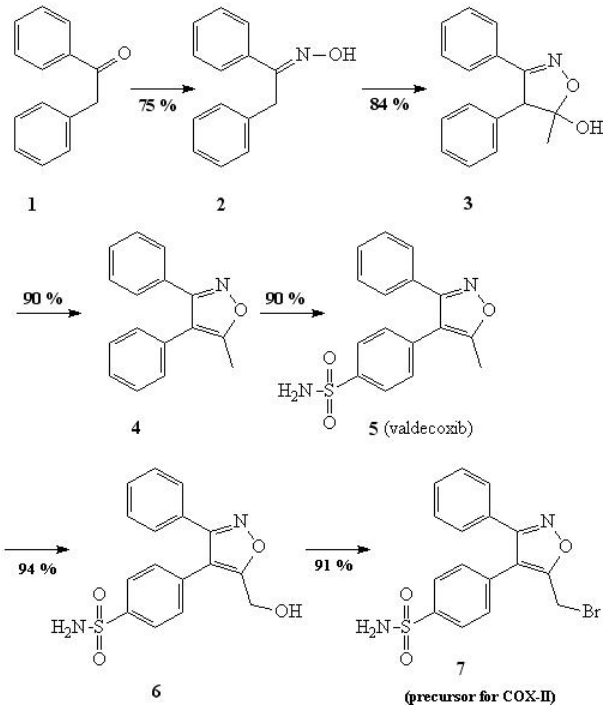


Fig 2. General structure of terphenyl methyl sulfones and sulfonamides : important imnteraction sites for COX-I/COX-II binding are indicated with arrows.

All three sites are important for COX-II binding while sites B and C are important for COX-I binding. For COX-II selectivity, only site C plays an important role.

2. Methods and Results

We prepared COX-II inhibitor which has isoxazolyl ring. The synthetic route for precursor (compound **7**) employed deoxybenzoin(**1**) as a starting material and proceeded in 44 % overall yield through 6 steps which contain formation of isoxazolyl ring as a key reaction (Sch. 1).



Scheme 1. The preparation of precursor for COX-II inhibitor (compound **7**)

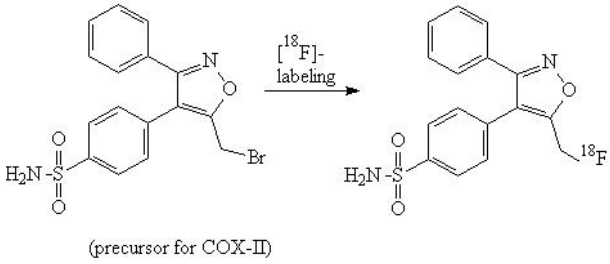
The selective COX-II inhibitor was labeled with ^{18}F *via* nucleophilic substitution reaction on the corresponding bromo precursor (compound 7) in high yield (table 1 & sch 2).

Table 1. Labeling with [^{18}F]F- for the preparation of COX-II inhibitor *

Entry	Temp	Time	Yield(TLC yield)
1	80 ℃	5 min	No reaction
2	80 ℃	15 min	2 %
3	80 ℃	30 min	20 %
4	95 ℃	5 min	2 %
5	95 ℃	15 min	5 %
6	95 ℃	30 min	45 %
7	110 ℃	5 min	15 %
8	110 ℃	15 min	30 %
9	110 ℃	30 min	55 %
10	125 ℃	5 min	over 95 %
11	125 ℃	15 min	over 95 %
12	125 ℃	30 min	over 95 %

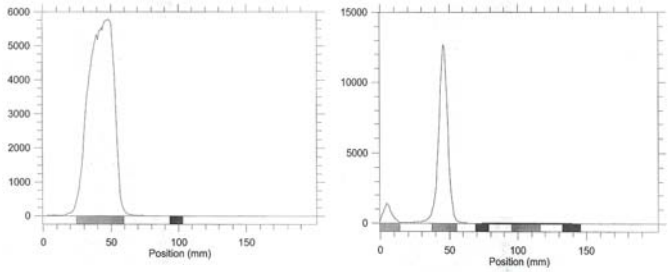
* Precedure for [18F] labeling

- A solution of 4 mg K_2CO_3 in 0.4 mL water was added to 10 mg Kryptofix 2.2.2 in 0.4 mL CH_3CN. To the dried K_2CO_3 / Kryptofix mixture, a solution of 2~3 mg precursor in 0.7 mL CH_3CN was added.



Scheme 2. Labeling with [^{18}F]F- for the preparation of COX-II inhibitor

In addition, we got a good result for stability test of labeled compound in serum (Fig. 3).



1 min 2.5 h

Fig 3. The stability test of labeled compound in serum at 37 ℃

3. Conclusion

The selective COX-II inhibitor was labeled with ^{18}F in high yield. [^{18}F]COX-II inhibitor was obtained with 47 % decay corrected radiochemical yield and the radiochemical purity was over 95 %. Our selective COX-II inhibitor has a good stability in serum and the lipophilicity was around 1.55

We expect that these results are sufficient for animal and human studies. In this study, we will also prepare other COX-II inhibitors which are labeled with iodine. And the results for biological studies will be discussed.

REFERENCES

1. Jashim Uddin et al; *Bioorganic & medicinal chem. Lett.*, **2004**, *14*, 4911-4914
2. Santanu Chakraborty et al; *Bioorganic & medicinal chem. Lett.*, **2004**, *14*, 4665-4670