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Triaryl (*Z*)-olefins suitable for radiolabeling with carbon-11 or fluorine-18 radionuclides for positron emission tomography imaging of cyclooxygenase-2 expression in pathological disease

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ABSTRACT

A group of (*Z*)-1,1-diphenyl-2-(4-methylsulfonylphenyl)alk-1-enes were synthesized using methodologies that will allow incorporation of a [^{11}C]OCH_3 substituent at the *para*-position of the C-1 phenyl ring, a [^{11}C]SO_2CH_3 substituent at the *para*-position of the C-2 phenyl ring, a [^{18}F]OCH_2CH_2F substituent at the *para*-position of the C-1 phenyl ring, and a [^{18}F]CH_2CH_2F substituent at the C-2 position of the olefinic bond. The [^{11}C] and [^{18}F] radiotracers are designed as potential radiopharmaceuticals to image cyclooxygenase-2 (COX-2) expression in any organ where COX-2 is upregulated. The COX-1/COX-2 inhibition data acquired suggest that compounds having a [^{11}C]OMe or [^{18}F]OCH_2CH_2F substituent at the *para*-position of the C-1 phenyl ring may be more suitable for imaging COX-2 expression in view of their ability to exclusively inhibit the COX-2 isozyme.

Positron emission tomography (PET) is a valuable medical imaging technique employing compounds labeled with a short-lived positron emitting radioisotope (radiotracer) for quantitative investigations of molecular and cellular transport processes in vivo. In this regard, PET offers exceptional possibilities to study physiology, metabolism, pharmacokinetics and modes of action of novel and established drugs. The most common positron emitters for this purpose include ^{11}C ($t_{1/2}$ = 20.4 min) and ^{18}F ($t_{1/2}$ = 109.6 min). Being bioisosteric with hydrogen, albeit with high electronegativity, ^{18}F is often used to replace hydrogen of otherwise non-fluorinated molecules with minimum effects on biomolecular interactions.[1] The inducible isozyme cyclooxygenase-2 (COX-2) is a relevant target for molecular imaging since low levels of COX-2 are produced during normal cell function in only a few tissues relative to COX-2 over expression that is associated with pathological conditions in a much larger number of organs.[2] COX-2 expression causes a number of undesirable pathophysiological effects that include pain, inflammation, fever, CNS ischemia, and COX-2 upregulation occurs in a variety of malignant tumors.[3–6] Accordingly, selective COX-2 inhibitors have, or may offer, potential for the chemoprevention of various types of cancer such as colon, breast, prostrate, stomach and pancreatic, wherein the over-expression of COX-2 produces COX-2–derived prostaglandins (PGs) that stimulate tumor growth.

A number of radiolabeled compounds have been prepared for use as PET, or SPECT (single photon emission computed tomography), radiotracers to image COX-2 and measure COX-2 over expression. Although [^{11}C]rofecoxib (**1**, see structure in Fig. 1) showed a correlation between [^{11}C]rofecoxib uptake and COX-2 distribution in healthy rats, it's inability to unambiguously detect COX-2 expression in rat inflammation models may have been due to low affinity for the COX-2 isozyme.[7] A [^{18}F] derivative of rofecoxib (**2**) has been synthesized as a potential PET radiotracer.[8] The [^{18}F] derivative of celecoxib (**3**) was synthesized as a potential marker for COX-2 activity.[9] Toyokuni et al. synthesized a [^{18}F]oxazole compound (**4**) as a potential radiotracer to image COX-2.[10] The CH_2F moiety in **4** is metabolically labile. Synthesis of the radioiodinated COX-2 inhibitory potential SPECT radiotracers **5**[11] and **6**[12] have also been reported. Despite recognition of the potential value of COX-2-targeted imaging agents such as **1**–**6**, there is a requirement for continued in vivo investigation using superior agents to establish the clinical utility of this strategy.

A number of general structure–activity relationships (SARs) have emerged for the tricyclic class of selective COX-2 inhibitors, viz: (i) many selective COX-2 inhibitors have two vicinal (adjacent) aryl substituents attached to a five- or six-membered central ring that acts as a scaffold such as benzene, pyridine, thiophene, pyrrole, imidazole, thiazole, cyclopentene, or pyrazole,[13,14] (ii) *para*-substituents on the adjacent aryl rings that provide optimal COX-2 selectivity, potency and oral activity are usually a COX-2 pharmacophore on one ring ($-SO_2Me$, $-SO_2NH_2$) and a F, Me or H substituent on the other aryl ring,[15] (iii) the *para*-position of the COX-2 pharmacophore is critical for COX-2 selectivity since placement at the *meta*-position of the aryl ring may abolish COX-2 activity,[13] (iv) reversing the position, or changing their position on the central ring (regioisomers) of the two aryl moieties (Ar and 4-MeO_2S(or H_2NO_2S)–C_6H_4–) can

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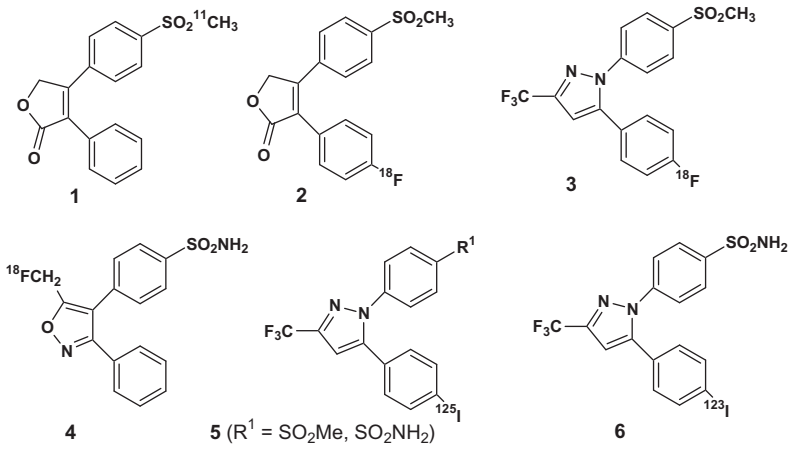


Figure 1. Some examples of selective COX-2 inhibitory compounds designed as PET (**1**–**4**), or SPECT (**5**–**6**), radiotracers.

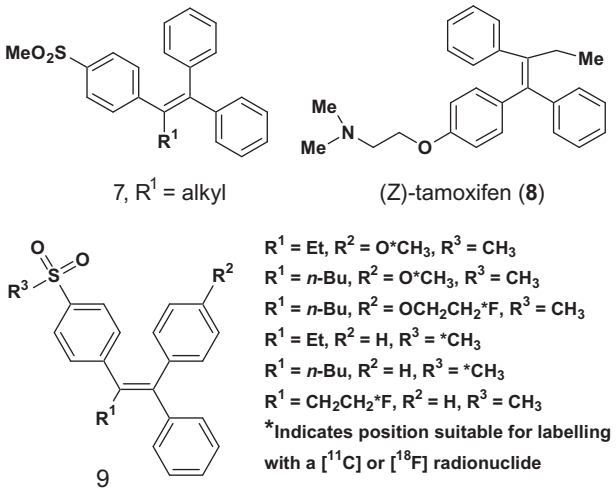
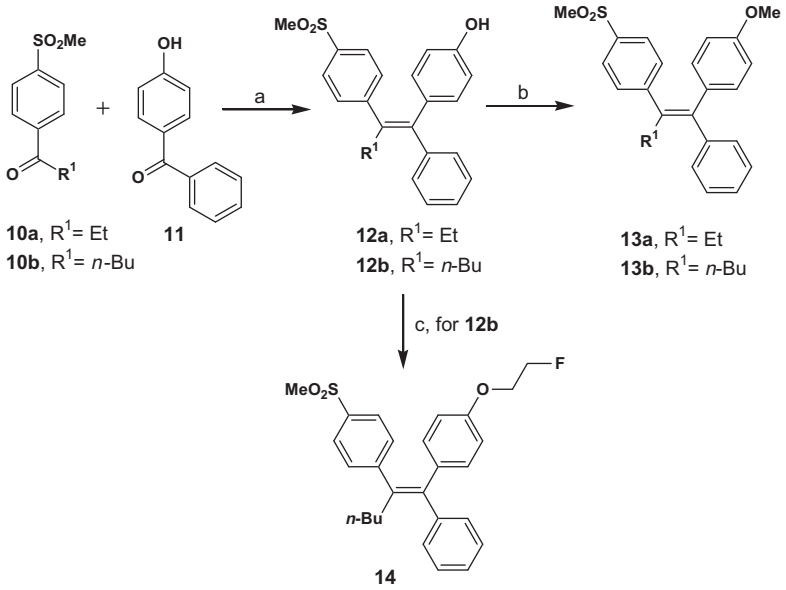


Figure 2. Some examples of tricyclic (*Z*)-olefins that exhibit selective COX-2 inhibitory and anti-inflammatory activities (**7**) and selective estrogen receptor antagonist activity against hormone-responsive breast cancers (**8**), and the putative positions (*) where a [^{11}C]- or [^{18}F]-radionuclide may be incorporated for assessment as imaging agents to target COX-2 expression or estrogen-responsive breast tumors (**9**).

either abolish or enhance COX-2 inhibitory activity,[14] (v) a lipophilic substituent (F, Me) at the *para*-position of one of the aryl rings usually enhances COX-2 inhibitory activity,[15] and a SO_2Me or SO_2NH_2 substituent at the *para*-position of one aryl ring usually provides optimal COX-2 inhibitory potency,[16] (vi) replacement of $-SO_2Me$ by $-SO_2CF_3$, –COMe, $-PO(OH)Me$, $-CO_2H$, $-PO(OH)_2$ or $-SO(=NH)Me$ generally abolishes COX-2 inhibitory activity,[17] (vii) an *ortho*-substituent on an aryl ring, which may distort the active orientation of the two aryl rings, such as 2-MeO–C_6H_4–, may abolish COX-2 inhibitory activity,[16] (viii) potency, selectivity and in vivo efficacy are affected by the substitution pattern on the aryl rings and the position of the COX-2 pharmacophore (SO_2Me, SO_2NH_2) moiety on an aryl ring may be important in preventing oxidative metabolism,[13] and (ix) the lower log *P* for SO_2NH_2 versus SO_2Me might improve absorption and provide a more rapid onset of action.[16]

In an earlier study, we reported a novel group of acyclic triaryl (*Z*)-olefins (**7**, see Fig. 2) that exhibit selective COX-2 inhibitory and anti-inflammatory activities.[18] Furthermore, this group of olefins **7** have a structural relationship to the selective estrogen receptor antagonist (*Z*)-tamoxifen (**8**) that is used to treat hormone-responsive breast cancers.[19] The SARs described in the preceding paragraph were used a guide to select putative positions (*) in the



Scheme 1. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 4.5 h; (b) 5 N NaOH, CH_3I, DMF, 60 °C, 3 min; (c) (i) K_2CO_3, Kryptofix 222, CH_3CN, 50 °C, 15 min; (ii) $TsOCH_2CH_2F$, reflux 10 min.