SYNTHESIS AND INHIBITORY ACTIVITY OF ISOINDOLINONE DERIVATIVES ON THROMBOXANE A_2 ANALOG (U-46619)-INDUCED VASOCONTRACTION

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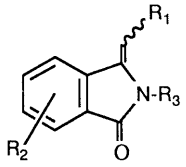
Newly synthesized isoindolinone derivatives inhibited the contraction of pig coronary artery induced by U-46619, a thromboxane A_2 analog.

KEYWORDS isoindolinone derivative; vasorelaxant; thromboxane A_2 analog (U-46619)

Thromboxane A_2 (TXA_2),[1] a potent platelet aggregater, vasocontracter, and bronchoconstricter, causes problems in circulatory disorders and asthmatic conditions. Thus, inhibitors of TXA_2 biosynthesis and TXA_2 receptor antagonists can be effective therapeutic agents for these diseases.[2] Recently, we have found that some isoindolinone derivatives inhibit TXA_2 analog (U-46619)[3]-induced vasocontraction.

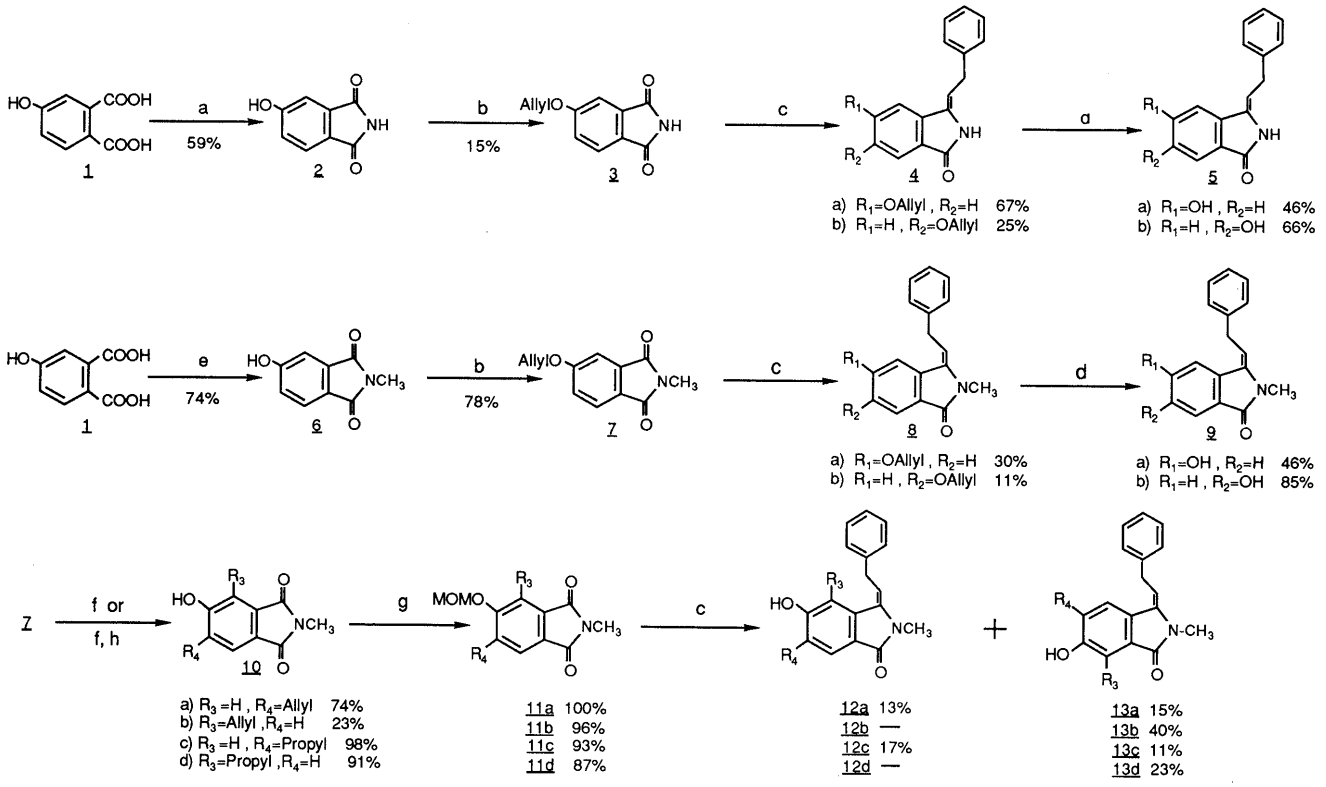


R_1 : (Z) or (E) Benzyl.
R_2 : OH, Alkyl.
R_3 : H, Alkyl, Alkylamine, Benzyl, Phenylethyl.

A variety of 5- or 6-hydroxy-3-(2-phenylethylidene)isoindolinones and N-substituted-3-(2-phenylethylidene)isoindolinones were synthesized from 4-hydroxyphthalic acid or potassium phthalimide in several steps and their inhibitory activities were tested.

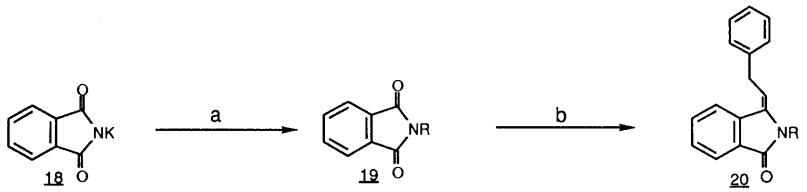
Synthesis routes are shown in Charts 1 and 2. Cyclization of 4-hydroxyphthalic acid 1 with 25% ammonia or 40% methylamine followed by treatment with allyl bromide gave 5-allyloxyphthalimide 3 or N-methyl-5-allyloxyphthalimide 7. Treatment of 3 and 7 with Grignard reagent followed by dehydration gave (Z)-4a and 4b or (E)-8a and 8b,[4] and successive removal of the protecting group of 4 or 8 afforded 5 and 9 respectively. On the other hand, Claisen rearrangements of 7 gave N-methyl-4-allyl-5-hydroxyphthalimide 10a and N-methyl-6-allyl-5-hydroxyphthalimide 10b. Similar treatment of 10 afforded the related compounds 12, and 13.

Then N-alkylation of potassium phthalimide 18 with various of alkyl, aminoalkyl, benzyl, and phenylethyl halides followed by treatment with Grignard reagent afforded (E)-N-substituted-3-(2-phenylethylidene)isoindolinones 20.



a) 25% NH_3, 190°C 4 h b) Allylbromide, K_2CO_3/acetone, reflux 48 h c) ß-Bromoethlybenzene, Mg/THF, 3% NH_3 NH_4Cl, aq HCl/THF
d) BCl_3/Chlorobenzene, -30°C 2 h e) 40% CH_3NH_2, 190°C 1 h f) 180°C 3 h g) Chloromethylmethylether, i-Pr_2NEt, r.t.
h) 5% Pd-C/H_2, Ethanol, r.t., 1 h

Chart 1



R= alkyl , alkyl alcohol , alkyl amine , benzyl , phenylethyl

a) R-X/DMF, 120°C 2 h b) ß-Bromoethylbenzene, Mg/THF, 3%NH_3 NH_4Cl, aq HCl/THF

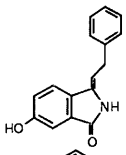
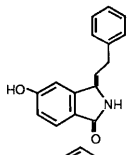
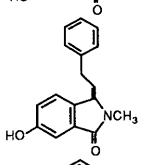
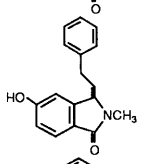
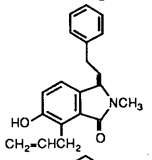
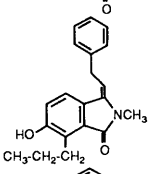
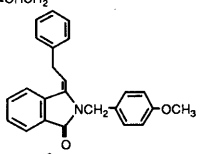
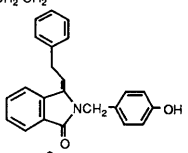
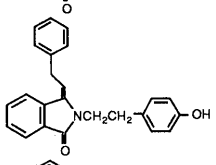
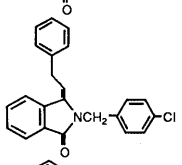
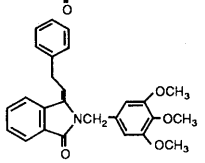
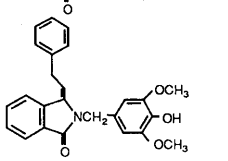
Chart 2

Typical compounds that inhibit U-46619-induced contraction of pig coronary artery are shown in Table I. The activity is expressed as the concentration which causes 50% inhibition (IC_{50}) of vasocontraction. 5- or 6-Allyloxy derivatives 4 and 8 showed no activity, but 5- or 6-hydroxy derivatives AKS-253, AKS-254, AKS-213, and AKS-210 were inhibitory.

The effect of the substituents at the 2-position on the inhibitory activity was approximately in the following order: benzyl ≥ phenylethyl > aminoalkyl > alkyl. It is noteworthy that the activities of p-hydroxybenzyl-type and p-hydroxyphenylethyl-type compounds AKS-186, AKS-198, and AKS-256 were inhibitory.

The inhibitory activity of these isoindolinone derivatives is reported for the first time in this paper.

Table I. Relaxing Activities of Isoindolinone Derivatives on Pig Coronary Artery Precontracted with 0.1μM U-46619

Compd. No.	Compound	IC_{50} (10^{-6}M)	Compd. No.	Compound	IC_{50} (10^{-6}M)
AKS-253		3.2	AKS-254		1.2
AKS-213		1.0	AKS-210 (9a)		0.8
AKS-226		1.8	AKS-232		1.1
AKS-182		2.4	AKS-186 (20)		0.6
AKS-198 (20)		0.7	AKS-239		No effect
AKS-255		0.9	AKS-256		1.0

Pig coronary artery was carefully isolated from fresh adult pig heart, and muscle strips approximately 2 mm wide or 10 mm long were prepared. Each strip was mounted in an organ bath filled with 10 ml of Tyrode's solution (158.3 mM NaCl, 4.0 mM KCl, 2.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 10.0 mM $NaHCO_3$, 0.4 mM NaH_2PO_4 and 5.6 mM glucose), maintained under a tension of 1.5 g at 37°C and bubbled with a 95% O_2-5% CO_2 gas mixture. Isometric tension was measured with a force displacement transducer and pen-writing recorder (TB-612T, WI-641G, Nihon Kohden).

The activity is expressed as the concentration that caused 50% inhibition (IC_{50}) of U-46619-induced vasocontraction.

REFERENCES AND NOTES

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