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5-Lipoxygenase inhibitors: convenient synthesis of 4-[3-(4-heterocyclylphenylthio)phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide analogues

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Abstract—A convenient synthetic route to 4-[3-(4-heterocyclylphenylthio)phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide analogues as 5-LO inhibitors is described. This methodology enabled rapid development of structure–activity relationships (SARs) leading to improvement of pharmacological properties. Thus, new compounds with higher 5-LO inhibitory potency were discovered. The stereo-chemistry requirements of the tetrahydropyran ring are also discussed.

1. Introduction

In our previous publications, **1** was disclosed to be a potent and orally active inhibitor of 5-lipoxygenase (5-LO).[1–3] With the aim of improving pharmacological properties of this novel series of 5-LO inhibitors, (i) modification of the tetrahydorpyran (THP) ring, (ii) replacement of 2-methylimidazole moiety with other heterocycles, and (iii) replacement of the carboxamide moiety with other functional groups were systematically investigated (Fig. 1). In the course of this study, a novel nickel(0) catalyzed aryl halide cross-coupling reaction was developed and is reported on herein.

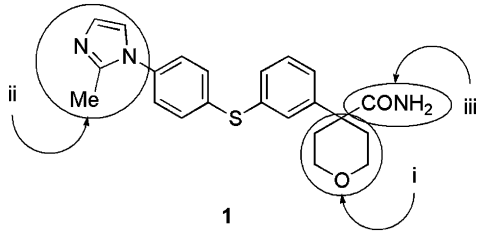
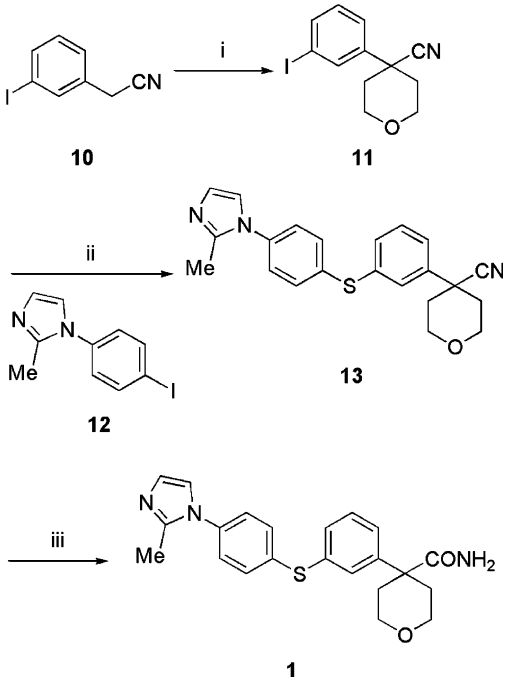


Figure 1. Strategy of structural modification of **1**.



Scheme 1. New synthesis of **1**. Reagents and conditions: (i) NaH, DMSO, rt, 30 min, then $(ClCH_2CH_2)_2O$, rt, 1 h (75%); (ii) $Ni(PEt_3)_2Cl_2$; $NaBH_3CN$, thiourea, 60 °C, 4 h; CaO, DMF, rt for 1.5 h; $Ni(PEt_3)_2Cl_2$; $NaBH_3CN$, **12**, 60 °C, 4 h; (iii) powdered KOH, *t*-BuOH, 80 °C, 4 h (63% from **11**).

Keywords: Leukotriene; Lipoxygenase; Inhibitor; Structure–activity relationship; Unsymmetric thioether.
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2. Chemistry

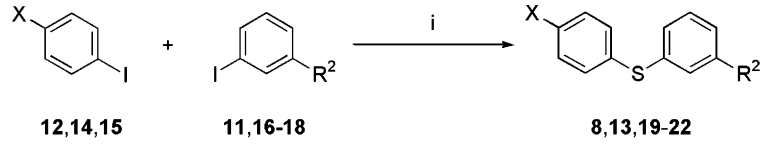
2.1. Nickel(0) catalyzed cross-coupling

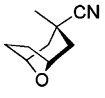
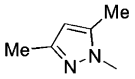
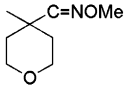
It has been reported that nickel(0) catalyzed coupling can produce an unsymmetric thioether from the corresponding aryl halide in the presence of thiourea.[4,5] Under similar reaction conditions the unsymmetric thioether **13** was synthesized from the known iodides **11** and **12** as shown as step ii in Scheme 1. Subsequent hydrolysis by standard methodology as developed in our laboratory afforded **1** in 63% total yield from **11**.[3,6]

2.2. Synthesis of analogues of 1

The novel nickel(0) catalyzed cross-coupling methodology described above was applied to the syntheses of **2**–**5** and **8**, and results are shown in Scheme 2. Key intermediates were prepared as shown in Schemes 3–5. Thus, triazole **14** was constructed in 39% yield from *p*-iodoaniline and *N*,*N*-dimethylformamide azine dihydrochloride, according to the literature procedure.[7] Pyrazole **15** was conveniently prepared by aromatic nucleophilic substitution of 4-fluoro-1-iodobenzene with 3,5-dimethylpyrazole. Bicyclic iodides **16** and **17** were synthesized as shown in Scheme 4. Diiodide **25** was prepared from the known ditosylate,[8] and the [3.2.1] bicyclic ring was formed by reacting **25** and 3-iodophenylacetonitrile (**10**) with sodium hydride as a base in DMSO. The resulting mixture of stereo-isomers was separated by column chromatography to afford **16** and **17**. The stereochemistry of **16** and **17** was elucidated by NOE as shown in Figure 2.

Scheme 5 shows the preparation of the *O*-methylated oxime **18**. The nitrile **11** was reduced to the corresponding carbaldehyde **26**, which was reacted with *O*-methyl hydroxylamine hydrochloride to give the desired iodide.



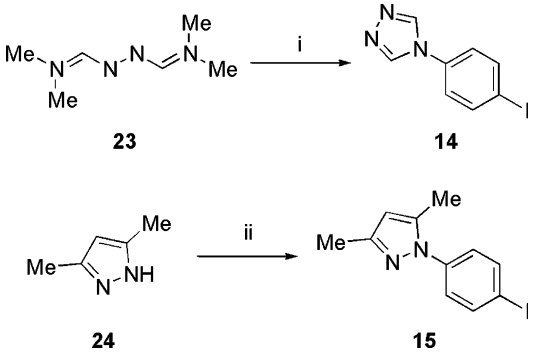
4-X-Phenyliodide		3-R^2-phenyliodide		step i		step ii	
	X-		-$R^{2\,a}$	product	yield (%)	product	yield (%)
12		**11**		**13**	ND[b]	**1**	75[c]
12		**16**		**19**	48	**2**	70
12		**17**		**20**	36	**3**	40
14		**11**		**21**	ND[b]	**4**	11[c]
15		**11**		**22**	43	**5**	86
12		**18**		**8**	78	–	–

[a] For **11**, **16** and **17**, "-R^2" is shown as "-Y-CN" in step ii.

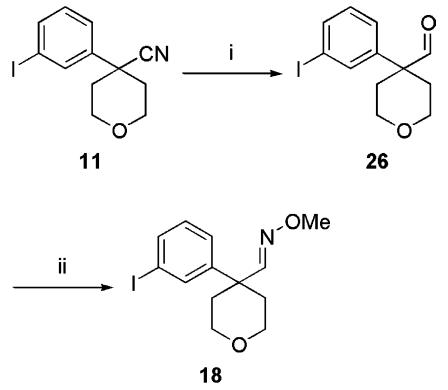
[b] ND: Not determined.

[c] Yield from two steps.

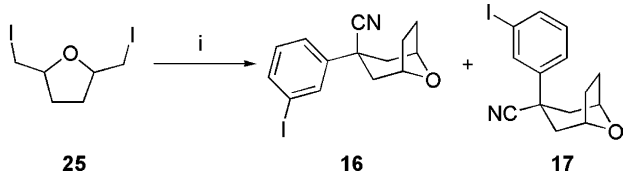
Scheme 2. Convenient synthesis of unsymmetric thioether 5-LO inhibitors. Reagents and conditions: (i) 4-X-phenyliodide, $Ni(PEt_3)_2Cl_2$; $NaBH_3CN$, thiourea, 60 °C, 4 h; CaO, DMF, rt for 1.5 h $Ni(PEt_3)_2Cl_2$; $NaBH_3CN$, 3-R^2–phenyliodide, 60 °C, 4 h; (ii) powdered KOH, *t*-BuOH, 80 °C, 4 h.



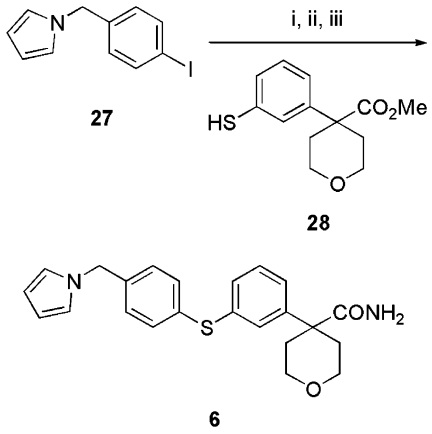
Scheme 3. Syntheses of **14** and **15**. Reagents and conditions: (i) *p*-iodoaniline, toluene, reflux, 3.5 h (39%); (ii) NaH, DMF, 4-fluoro-1-iodobenzene, 100 °C, 3 h (61%).



Scheme 5. Synthesis of **18**. Reagents and conditions: (i) DIBAL, −78 °C, 3 h, then 1 N HCl, rt, 30 min (79%); (ii) $MeONH_2$·HCl, rt, overnight (83%).



Scheme 4. Synthesis of bicyclic iodides, **16** and **17**. Reagents and conditions: (i) **10**, NaH, DMSO, rt, 15 min, then **25**, rt, overnight (**16**, 43%; **17**, 17%).



Scheme 6. Synthesis of **6**. Reagents and conditions: (i) $Pd(PPh_3)_4$, *t*-BuONa, EtOH, reflux, overnight (54%); (ii) LiOH, H_2O, MeOH, THF, reflux, 5 h (quant.); (iii) 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, $(NH_4)HCO_3$, rt, overnight (54%).

Pyrrol-1-ylmethyl analogue **6** was prepared from aryl iodide **27**[9,10] in a stepwise manner similar to that for the original preparation of **1**[3] with the exception that amidation was performed with ammonium bicarbonate and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, as shown in Scheme 6.[2] Amidation of the carboxylic acid via acid chloride failed most likely due to pyrrole ring decomposition. The imidazol-1-ylmethyl analogue **7** was prepared from iodide **30** in a similar manner (Scheme 7).

Scheme 8 depicts the synthesis of **9**. Although the direct reduction of nitrile **13** to carbaldehyde was tried, the desired compound was not obtained. However, two-step conversion of methyl ester **32**,[3] prepared from the carboxamide **1**, afforded the desired carbaldehyde, which was then converted to oxime **9** in the usual manner.

3. Biological testing

SAR studies were routinely conducted based on inhibition of LTB_4 (leukotriene B_4) synthesis in A-23187 simulated human whole blood (HWB) for 5-LO, and oral activity was assessed by platelet activating factor (PAF) induced thrombosis in male mice.[1]

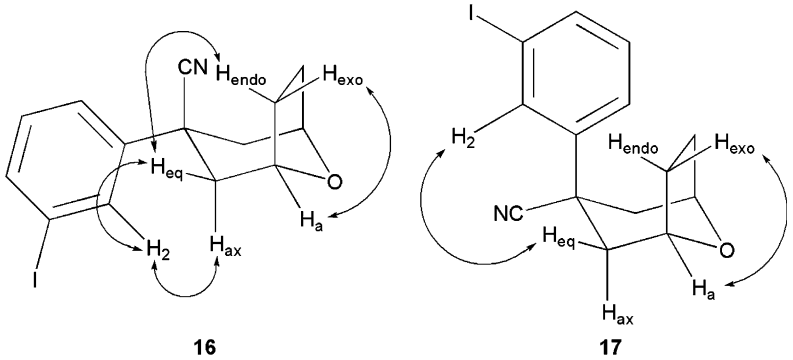
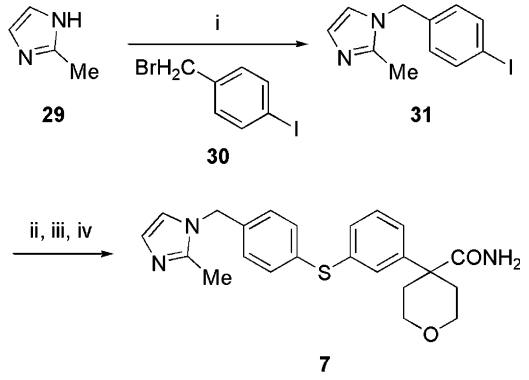
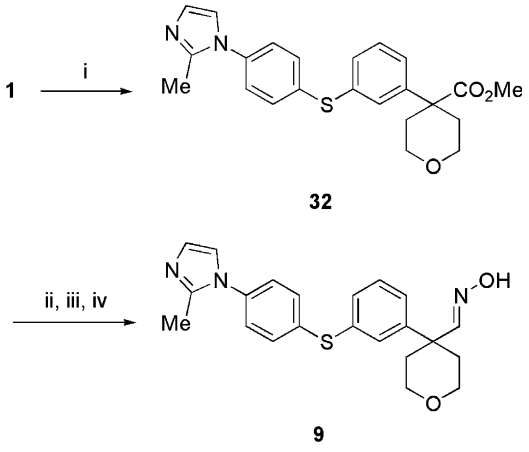


Figure 2. NOE experiment of **16** and **17** possessing [3.2.1] ring system.



Scheme 7. Synthesis of **7**. Reagents and conditions: (i) K_2CO_3, MeCN, reflux, 15 h, (44%); (ii) **28**, $Pd(PPh_3)_4$, *t*-BuONa, EtOH, reflux, overnight; (iii) LiOH, H_2O, MeOH, THF, reflux, 5 h; (iv) 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, $(NH_4)HCO_3$, rt, overnight (28% from **31**).



Scheme 8. Synthesis of **9**. Reagents and conditions: (i) HCl–MeOH, reflux, overnight (35%); (ii) $LiAlH_4$, THF, 0 °C then rt, 30 min, 69%; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then −20 °C, 2 h (77%); (iv) $MeONH_2$·HCl, MeOH, pyridine, rt, 5 h (70%).

4. Results and discussion

4.1. Modification of tetrahydropyran ring

In order to elucidate stereo-chemistry requirements on the THP ring of **1**, bicyclic compounds **2** and **3** were designed and synthesized. As shown in Table 1, compound **2** was found to be active in vitro and in vivo (IC_{50} = 0.83 ± 0.16 μM (n = 3) in HWB and ED_{50} = 7 mg/kg in PAF thrombosis, respectively), whereas **3** was essentially inactive. From the NOE experiments carried out on intermediates **16** and **17** (Fig. 2), the biologically active form has the phenyl ring at the 4-position on THP ring of **2** oriented equatorially, as depicted in Figure 3. Zeneca has reported that 5-LO inhibitory activities of a similar THP series were dependent upon the proportion of the equatorial phenyl ring orientation at the 4-position, and that the potent intrinsic inhibitory activity resides in equatorial-oriented phenyl ring analogues.[11] Our finding appears to be consistent with their report. However, it was also reported that the binding mode of **1** to 5-LO is different from that for the representative Zeneca's

Table 1. 5-LO Inhibitory activities of **1** and analogues

Compd	HWB IC_{50} (μM)	PAF thrombosis ED_{50} (mg/kg)
1 HCl[a]	0.23 ± 0.05 (15)[b]	3.7 ± 0.3 (3)[b]
2	0.83 ± 0.16 (3)[b]	7
3	>1 (−7% Inh)[c]	N.D.[d]
4	>1 (1% Inh)[c]	N.D.[d]
5	>1 (−1% Inh)[c]	N.D.[d]
6	0.27 ± 0.09 (3)[b]	3
7	0.14	>20
8	0.15 ± 0.03 (6)[b]	2
9	2.0 ± 0.1 (3)[b]	N.D.[d]

[a] Ref. 3.
[b] Shown with ±SD (number of determinations).
[c] % Inhibition at 1 μM.
[d] Not determined.

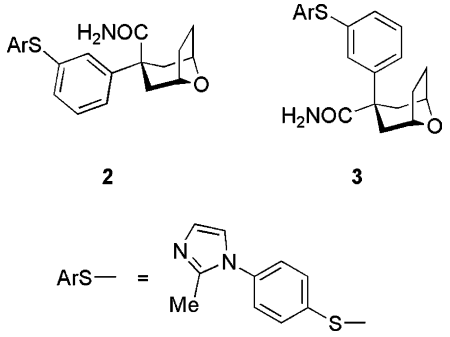


Figure 3. Stereochemistry of **2** and **3**.

5-LO inhibitor ZM230487.[12] Therefore, our finding on the stereo-requirements on the THP ring may be unique to the imidazole 5-LO inhibitor analogues, such as **1**, **2**, and **3**.

4.2. Replacement of 2-methylimidazole moiety

Replacement of the imidazole ring with other heterocycles such as triazole (**4**) or pyrazole (**5**) resulted in loss of intrinsic in vitro potency. On the other hand, pyrrol-1-ylmethyl analogue **6** retained the in vitro and in vivo potency of **1**. While 2-methylimidazol-1-ylmethyl analogue **7** exhibited comparable in vitro potency to **1**, in vivo activity (oral dosing) was not observed. Thus, the effect of methylene insertion between the heterocyclic moiety and the neighboring phenyl ring seems to be dependent upon the remaining part of the molecules and the details are not unclear at the moment.

4.3. Replacement of carboxamide moiety

Replacement of the carboxamide with hydroxyimine was also investigated. *O*-Methyl hydroxyimine (**8**) was more potent in vitro and in vivo than **1**. On the other hand, hydroxyimine (**9**) was approximately 10-fold less active in vitro.

5. Conclusion

A convenient synthesis of analogues of **1** was developed using a nickel(0) catalyzed aryl halide cross-coupling

reaction, which accelerated the SAR around **1**. Stereochemistry requirements on THP ring were elucidated, and finally, the *O*-methyl hydroxyimine (**8**) was found to be the more potent inhibitor of 5-LO than **1**. In order to determine the therapeutic potential of **8** and its analogues and investigate their mechanistic feature of 5-LO inhibition, further work is required.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2005.03.041.

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