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Synthesis of useful fragments in drug discovery: 2-Amino-5-*tert*-butylpyridine and its oxidised analogues

Christopher G. Thomson *, John Reilly, David A. Sandham

Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, United Kingdom

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ABSTRACT

A novel and robust synthesis of the fragment, 2-amino-5-*tert*-butylpyridine, has been described, which has been shown to have improved physicochemical properties over 4-*tert*-butylaniline, when considering drug-like properties. The synthesis also yields fragments containing more highly oxidised precursors to the *tert*-butyl group as intermediates. These fragments can be incorporated into final target molecules, yielding pharmaceutical compounds and their putative CYP-mediated oxidative metabolites, which can aid in elucidation of metabolic clearance processes.

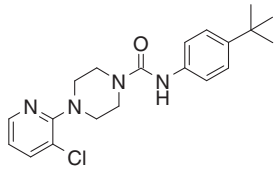
A number of biologically active compounds contain the *tert*-butyl phenyl moiety, such as BCTC[1] and terfenadine[2] (Fig. 1).

Whilst the inclusion of this lipophilic group often results in compounds of higher affinity, especially when compared to its parent phenyl derivative, it seldom leads to compounds which improve the 'drug-like' or 'lead-like' properties[3] across the chemical series.

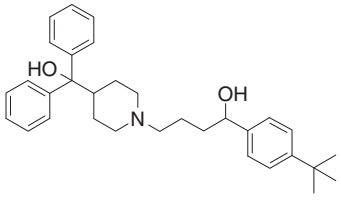
Within the context of a recent drug discovery program, a lead series contained the 4-*tert*-butylaniline (**1**) moiety, akin to BCTC. In an attempt to improve drug-like properties, 2-amino-5-*tert*-butylpyridine (**2**) was identified as a possible replacement fragment (Fig. 2), the key observation being that the 2-pyridyl nitrogen was tolerated by the target pharmacophore. Insertion of the nitrogen leads to a modest reduction in calculated log *P* of the fragment (Fig. 2). 2-Amino-5-*tert*-butylpyridine is known in the literature,[4] but a new route was sought that not only supplied the target compound, but also yielded fragments **3** and **4**, which could be used to synthesize putative oxidative metabolites of the lead molecules.

The *tert*-butyl group is often oxidised quickly via CYP450 enzymes when exposed to metabolic processes in vivo, as in the well documented case of the H1 antagonist, terfenadine. Terfenadine can cause cardiac side-effects,[5] such as QTc prolongation and Torsades de Pointes,[6] attributed to blockade of the hERG channel. Terfenadine acts as a pro-drug—the *tert*-butyl group undergoing initial in vivo metabolic oxidation, to the phenylisobutanol compound, then further oxidation to the carboxylic acid (Fig. 3). The acid containing compound shows reduced binding to the hERG channel and hence avoids cardiac side-effects. This acid metabolite of terfenadine is the active anti-histamine, fexofenadine, and is now marketed as such.

Our approach to the synthesis of **2** centred on the enolate coupling chemistry of Hartwig et al.[7] 2-Amino-5-bromopyridine (**5**) was di-*p*-methoxy benzyl protected,[8] as reductive cleavage of



BCTC
TRPV1 antagonist



Terfenadine
H1 Antagonist

Figure 1. Pharmaceutically active compounds containing the *tert*-butylphenyl group.

* Corresponding author.
E-mail address: christopher.thomson@novartis.com (C.G. Thomson).

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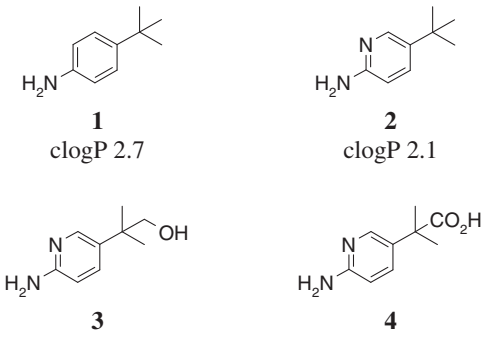


Figure 2. 2-Amino-5-*tert*-butylpyridine as a replacement for 4-*tert*-butylaniline, and its putative oxidation products via CYP mediated metabolism of the *tert*-butyl group.

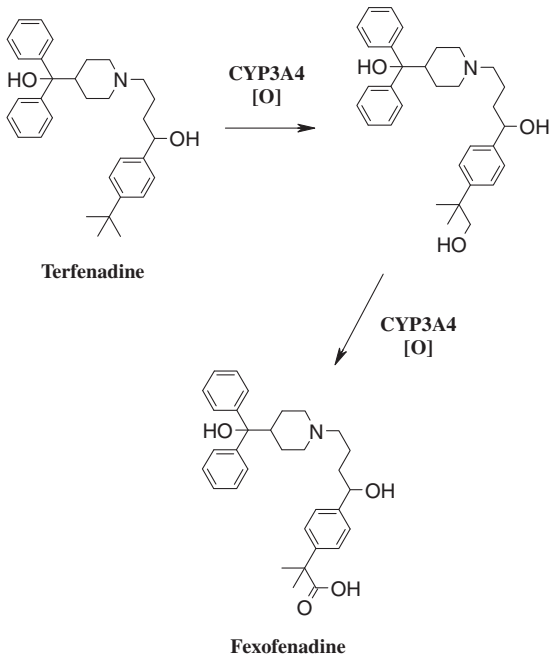
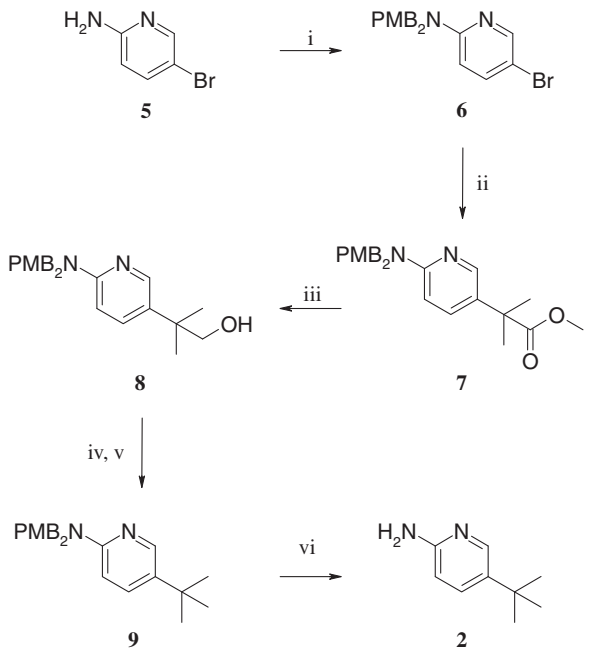


Figure 3. The metabolic fate of terfenadine.

benzyl groups could not be carried out at the end of the synthesis without reduction of the pyridine core. The enolate coupling of **6** (Scheme 1) with methyl isobutyrate resulted in a good yield of ester (**7**), and this was easily reduced to the alcohol (**8**).

With **8** in hand, transformation to the desired *tert*-butyl compound was attempted via conversion of the hydroxyl moiety to a leaving group and subsequent reduction. Iodination or mesylation reactions of **8** were poor yielding, and all attempts to reductively remove the subsequent iodine or mesylate leaving groups resulted in polymerisation. The successful approach to formation of **9** was oxidation of the alcohol to the aldehyde, which was converted to the *tert*-butyl group using Wolff–Kishner reduction.

The ester (**7**), alcohol (**8**) and tert-butyl intermediate (**9**) could be deprotected using TFA,[9] and fragments **2**, **3** and the methyl ester of **4** incorporated into the final molecules via standard amine derivatization. This gave the target molecule, along with putative CYP-mediated oxidation products (following base hydrolysis of the ester to acid in the case of **4**). The synthesis is amenable to scale, with 60 g of compound **2** being produced within Novartis laboratories.



Scheme 1. Reagents and conditions: (i) PMBnBr, 60% NaH/mineral oil, DMA, 0 °C, 1 h, 76% yield[8]; (ii) methyl isobutyrate, $LiNCy_2$, $Pd(dba)_2$, $P(t\text{-}Bu)_3$, toluene, overnight at ambient temperature, 78% yield; (iii) $LiBH_4$, THF, 2 days at ambient temperature, quantitative; (iv) Dess-Martin Periodinane, DCM, 10 min at ambient temperature, 87% yield; (v), Hydrazine hydrate, KOH, diethylene glycol, heated at reflux, 72 h, 71% yield; (vi) TFA, 5 h at ambient temperature, 91% yield.

Compound		1	2
HPLC %HSA*		78.5	38.9
HPLC CHI IAM¥		35.5	33.0
HPLC $LogD_{7.4}$†		2.83	1.53
PSA / Å^2		26.0	38.9
Calculated pK_a		5.2	8.0
HT-sol.Ω /mM	pH 6.8	<0.005	0.059
	FASSIF	<0.005	0.072

* HPLC estimation of binding to human serum albumin.[10]
¥ HPLC estimation of partitioning into artificial membranes.[11,12]
† HPLC estimation of logD.[13]
Ω Internal high throughput solubility assay, in pH6.8 buffer, or simulated fasted intestinal fluid (FASSIF).[14]

Figure 4. Comparison of the physicochemical properties for fragments **1** and **2**.

Finally, in order to gauge the success of the approach in improving physicochemical properties over **1**, HPLC methods[10–13] were used to estimate the lipophilicity, membrane affinity and protein binding of fragments **1** and **2**. This showed estimated log *D* to be reduced by approximately 1 unit (Fig. 4), and binding to human serum albumin (HSA) to be significantly reduced. Membrane affinity (CHI IAM) remained largely unchanged. Polar surface area (PSA) of fragment **2** is increased by around 13 Å^2 compared with **1**. High

throughput equilibrium solubility measurement showed a significant improvement for **2** over **1**, in both pH 6.8 buffer, and simulated fasted intestinal fluid,[14] due to **2** being partially ionized (see Fig. 4 for pK_a estimation).

The physicochemical properties of the 2-amino-5-*tert*-butylpyridine fragment have been shown to be superior to 4-*tert*-butylaniline when considering drug-like properties: as well as reducing the estimated log *D* and increasing PSA, this fragment also shows an estimated reduction in binding to human serum albumin and improved solubility. In conclusion, a novel, robust and scalable synthesis of 2-amino-5-*tert*-butylpyridine has been described; a useful fragment for incorporation into final target molecules, potentially leading to molecules with improved drug-like properties. The synthesis also yields intermediates containing the putative CYP-mediated oxidation products of the *tert*-butyl group, so aiding the identification of metabolic and clearance processes of parent molecules.

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