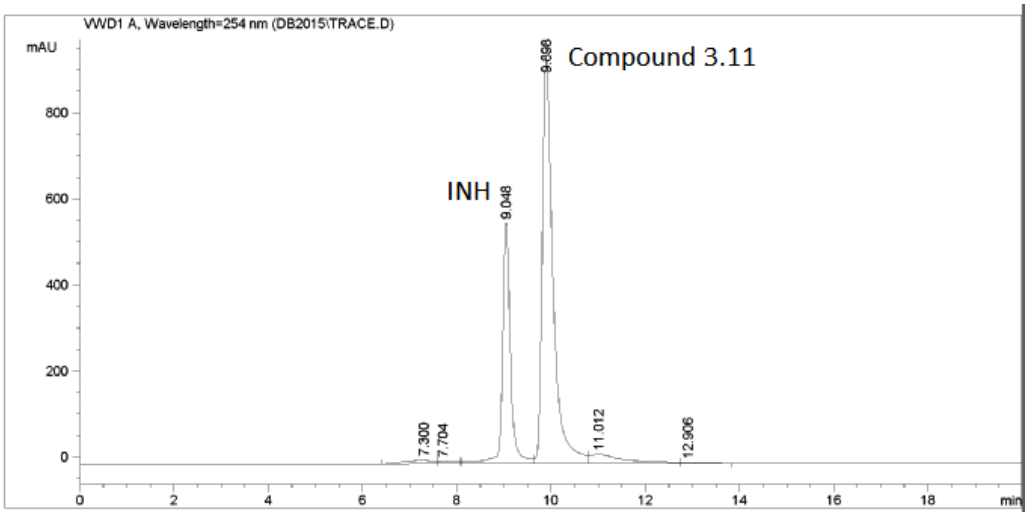
RESPONSES TO COMMENTS

Comment: *My only substantial concern is the remarkable high activity of the INH conjugate, compd* ***3.11.*** *Its anti-mycobacterial activity is stated (p. 150) is to be 15 µg/mL vs. 10 µg/mL of INH itself (a front-rank drug against TB for 50 years). In contrast the in vitro data for compound* ***3.11*** *set out in Chapter 3 and is not particularly different from that for the compds in Chapts 1 and 2 (Kcat, Km, ITC data). One worries that in vivo INH is being released from* ***3.11*** *to give the excellent MIC. There is some brief discussion about this inconsistency (pp. 150-151) discounting the likelihood of hydrolysis to release free INH. I am not sure how to test for the potential release (radiochemistry?), but perhaps for the next student this question could be answered. The other possibility is that some other key enzyme (s) may very well be inhibited by* ***3.11*** *as, for example, the INH primary targets.*

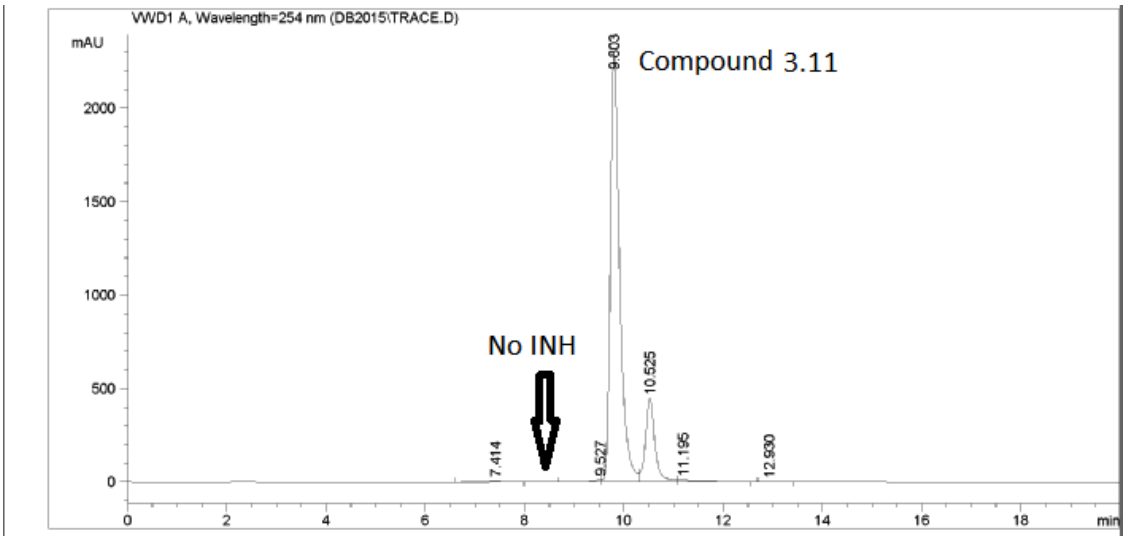
Response: In response to aforesaid possibility of liberation of free INH, we have included (pp 151) the following experiment to discount the likelihood of hydrolysis to release free INH:

To crosscheck the possibility of release of INH during *in vivo* experiment, we separately incubated the dual inhibitor **3.11** in culture media in presence of *M. smegmatis* for 24 h. The culture was then lyophilized, dissolved in solvent and subjected to HPLC (**Trace 2)** which was compared with an HPLC trace (**Trace 1**) of a solution containing a mixture of compound **3.11** and Isoniazid (**Trace 1**). From the comparison of these two traces, it could be clearly seen that there was no trace of Isoniazid in culture media. Above data supports that anti-mycobacterial activity of synthesized dual inhibitors is due to the activity of intact compound and not due to any release of isoniazid during incubation. However, in order to detect free INH beyond the HPLC detection limit, one may think of radiolabelled assay which may be done in future.

(**Trace 1 and 2 are now inserted in p. 176 in experimental section**)



Trace 1: HPLC trace of compound **3.11**+ INHmixture**;** Eluent: 100 % methanol;Flow rate: 1.2 ml /min; Ret. Time for compound **3.11**: 9.8 min; Ret. Time for INH: 9.0 min.



Trace 2: HPLC trace of compound **3.11**after 24 h incubation in culture;Eluent: 100 % methanol; Flow rate: 1.2 ml /min; Ret. Time for compound **3.11**: 9.8 min; No trace of INH.

Minor points/corrections:

1. *p. 4, line 8: "harvesting" should be "harbouring"?*

   Response: Corrected

2. *p. 21, line 11: "converts";*

   Response: Corrected

3. *p. 35, line 1: "exclusive" should be "extensive";*

   Response: Corrected

4. *p. 76, lines 14 and 15: exponents missing??*

   Response: Corrected

5. *All exptal sections, there are many 1H-NMR where dd = a good coupling constant J = NN.N Hz and a second with only one significant figure, J = N (see p. 52 ff, and p. 102 ff. Other entries are correct as J = N.N = Hz;*

   Response: Corrected as per suggestion