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ANTHELMINTIC β–HYDROXYKETOAMIDES (BKAS)

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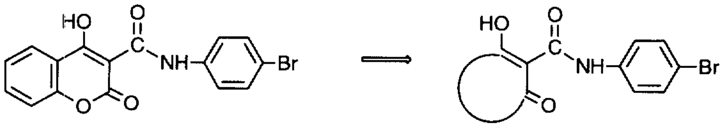
Abstract: We have prepared several anthelmintic coumarins based on the β-hydroxyketoamide (BKA) template and have shown that this template remains valid over a wide range of changes to the coumarin moiety allowing for the inclusion of carbocyclic, bicyclic, and heterocyclic rings.

Helminths, especially parasitic nematodes, cause substantial health problems in humans and domestic animals. Currently, three distinct chemical classes are used for broad spectrum control of gastrointestinal nematodes: benzimidazoles, imidazothiazoles, and macrocyclic lactones.[1] None of these drugs is ideally suited for all therapeutic situations, and each class has been challenged by the development of drug-resistant nematode strains.[2] Expansion of the anthelmintic arsenal is thus an urgent goal.

Recently, several natural products such as parherquamides,[3] marcfortines,[4] and PF-1022A[5] have shown promising biological activity, but undesired side effects or difficulty of production prohibit development of these compounds. In addition to their antibacterial[6] and insecticidal[7] activity, 4-hydroxycoumarins have been found active against helminths.[8] Following our discovery of the anthelmintic activity of compound **1**, we set about unmasking the template within this structure that could account for its activity. Core structure **2**, a β-hydroxyketoamide (BKA), represents our current understanding of this template as revealed by the anthelmintic activity of the compounds of Table 1 against the economically important helminth, *Haemonchus contortus*.



1 **2**

To prepare the BKAs, the corresponding diketo compounds **3**, **6**, **8**, and **10** (Scheme 1) were treated with 4-bromphenylisocyanate (**4**) in the presence of triethylamine. This produced BKAs **5**,[9,10] **7**, **9**, and **11**, respectively, in 40–80% yields. Alternatively, the corresponding esters **12**, **14**,[11] and **18** were treated with 4-

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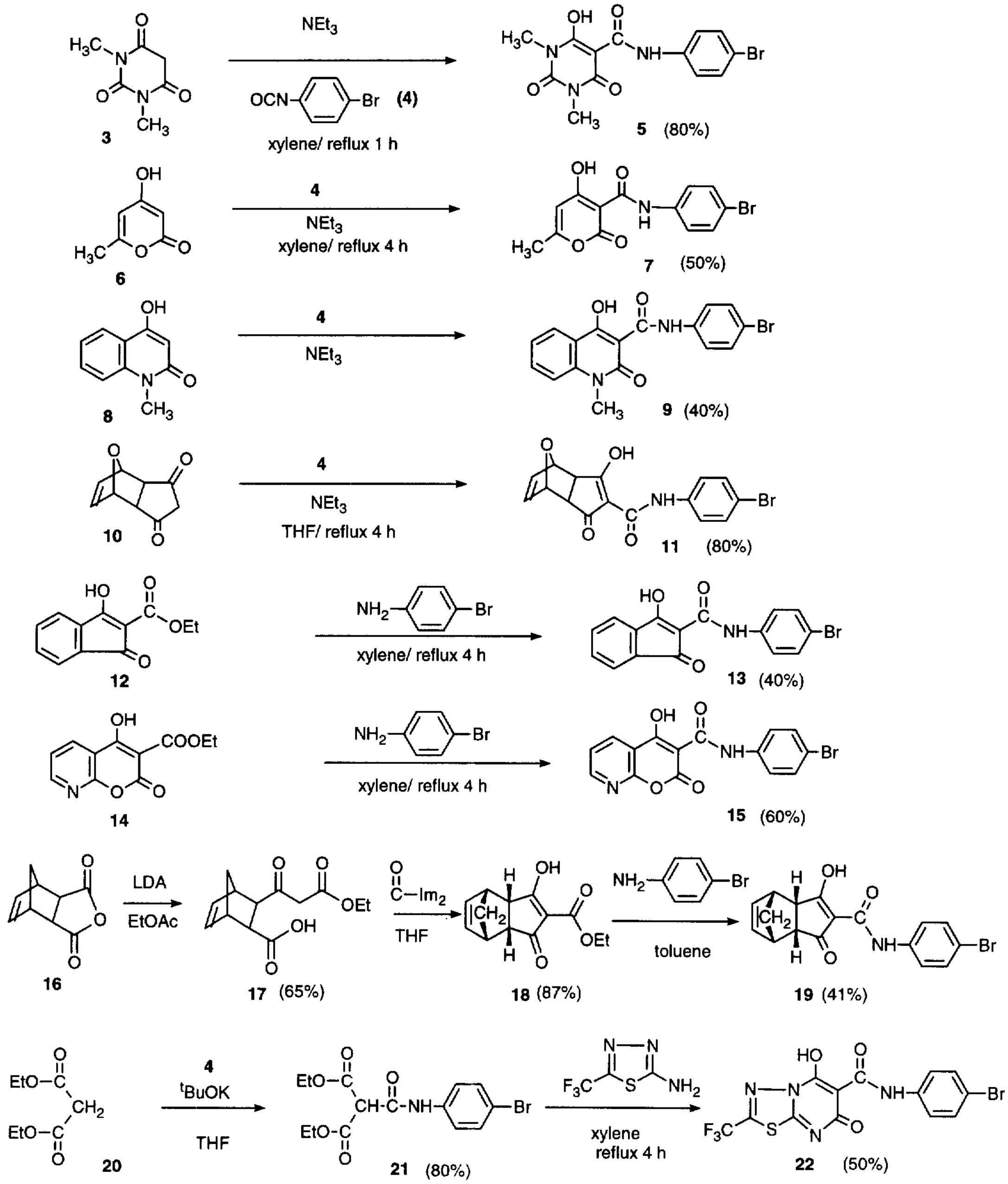
bromoaniline under refluxing xylene or THF to give BKAs **13**,[12] **15**, and **19**, respectively, in 40–60% yields. Compound **17** was prepared in 65% yield by treating **16** with LDA followed by ethyl acetate (−78 °C to 25 °C for 1 h). Upon treatment with carbonyl diimidazole in THF, compound **17** gave ester **18** in 87% yield. Diethyl



malonate **20** when treated with potassium *t*-butoxide in THF reacted with **4** to give **21** in 80% yield. BKA **22**[13] was prepared in 50% yield by treating compound **21** with 4-bromoaniline under refluxing xylene.

These BKAs were evaluated against *Haemonchus contortus* in our jird model.[14] Several of the compounds exhibited better activity than our original lead as shown in Table 1.

Table 1. Percentage clearance of *Haemonchus contortus* from jirds per os with 1,000 exsheathed infected larvae of a levamisole-susceptible strain of parasite, treated on day 10 postinoculation (PI) with BKA analogs, and examined on day 13 PI.

Compound	Dose (mg/ kg)	Percentage clearance
1	68	89
5	68	100
5	25	81
7	68	76
9	68	81
11	68	92
13	68	100
15	68	100
19	68	98
22	68	82

In conclusion, we prepared several BKAs based on the template depicted in structure **2**. All of these have exhibited anthelmintic activity. The validity of this template is demonstrated by its ability to transcend significant changes in the coumarin portion of the molecule to allow for the inclusion of carbocyclic, bicyclic, and heterocyclic rings without loss of anthelmintic activity. Further SAR studies to determine the extent to which the p-bromophenyl moiety can be replaced with other groups are in progress.

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References and Notes.

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1. Lynn, R. C. *Georgia's Parasitology for Veterinarians*, W. B. Saunders, Philadelphia, 1995, 247.
2. Prichard, R. *Veterinary Parasitology* **1994**, *54*, 259.
3. (a) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiotics* **1990**, *43*, 1375; (b) Liesch, J.; Wichmann, C. *J. Antibiotics* **1990**, *43*, 1380; (c) Shoop, W. L.; Egerton, J. R.; Eary, C. H.; Suhayda, D. *J. Parasitology* **1990**, *76*, 349; (d) Ostlind, D. A.; Mickle, W. G.; Ewanciw, D. V.;

Andriuli, F. J.; Campbell, W. C.; Hernandez, S.; Mochale, S.; Munguira, E. *Research in Veterinary Science* **1990**, *48*, 260; (e) Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiotics* **1991**, *44*, 492; (f) Blizzard, T. A.; Marino, G.; Sinclair, P. J.; Mrozik, H. European Pat. Appl. EP 0 354 615 A1, 1990; (g) Schaeffer, J. M.; Blizzard, T. A.; Ondeyka, J.; Goegelman, R.; Sinclair, P. J.; Mrozik, H. *Biochemical Pharmacology* **1992**, *43*, 679; (h) Mrozik, H. U.S. Pat. Appl. US 4,866,060, 1989; (i) Blizzard, T. A.; Mrozik, H. U.S. Pat. Appl. US 4,923,867, 1990; (j) Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135.

4. Polonsky, J; Merrien, M. A.; Prange, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun.* **1980**, 601.
5. Saski, T.; Takag, M.; Takasi, Y.; Miyadoh, S.; Okada, T.; Koyama M. *J. Antibiotics* **1994**, *37*, 1233.
6. Dutton, C. J.; Sutcliffe, J.; Yang, B. PCT int. Appl., WO 9405649, 1994; *Chem. Abstr.* **1994**, *121*, 57334h.
7. Beriger, E. U.S. Pat. Appl. US 4,078,075. 1978; *Chem. Abstr.* **1978**, *89*, 43114v.
8. Pankavich, J. A. U.S. Pat. Appl. US 587,786. 1976; *Chem. Abstr.* **1976**, *84*, 164616r.
9. This compound showed 100% clearance in our in-house sheep trial against *Haemonchus contortus* at a dose of 4 mg/kg.
10. Compound **3** (0.78 g, 5 mmol) and 4-bromophenylisocyanate (0.99 g, 5 mmol) were suspended in xylene (100 mL), triethylamine (0.28 mL, 2 mmol) added and the mixture heated under reflux for 1 h. The reaction mixture was cooled to room temperature and the precipitate collected, washed with xylene and ether, and finally dried to give a BKA **5** as a white solid (1.4 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.41 (s, 3H), 7.42 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 11.91 (s, 1H, NH), 13.89 (s, 1H, enolic OH). MS (ES+): *m/z* 354, 356 (M + H).
11. McCombie, S. W.; Lin, S.-I.; Tagat, J. R. *Heterocycles* **1993**, *35*, 93.
12. Compound **12** (1.02 g, 5 mmol) and 4-bromoaniline (0.86 g, 5 mmol) were suspended in xylene (100 mL) and heated to reflux for 4 h. The reaction mixture was cooled to room temperature and the precipitate collected, washed with xylene and ether, and dried to give BKA **13** as a white solid (0.7 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$ + Net_3) δ 7.4-7.7 (m, 9H), 10.97 (s, 1H, NH). MS (ES+); *m/z* 344, 346(M + H).
13. Compound **21** (1.74 g, 5 mmol) and 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (0.85 g, 5 mmol) were suspended in xylene (100 mL) and heated to reflux for 4 h. The reaction mixture was cooled to room temperature and the precipitate collected, washed with xylene and ether, and dried to give BKA **22** as a white solid (1.08 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$ + NEt_3) δ 7.33 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 12.59 (s, 1H, NH). MS (ES+); *m/z* 435, 437 (M + H).
14. Conder, G. A.; Jen, L.-W.; Marbury, K. S.; Johnson, S. S.; Guimond, P. M.; Thomas, E. M.; Lee, B. L. *J. Parasitology* **1990**, *76*, 168.