

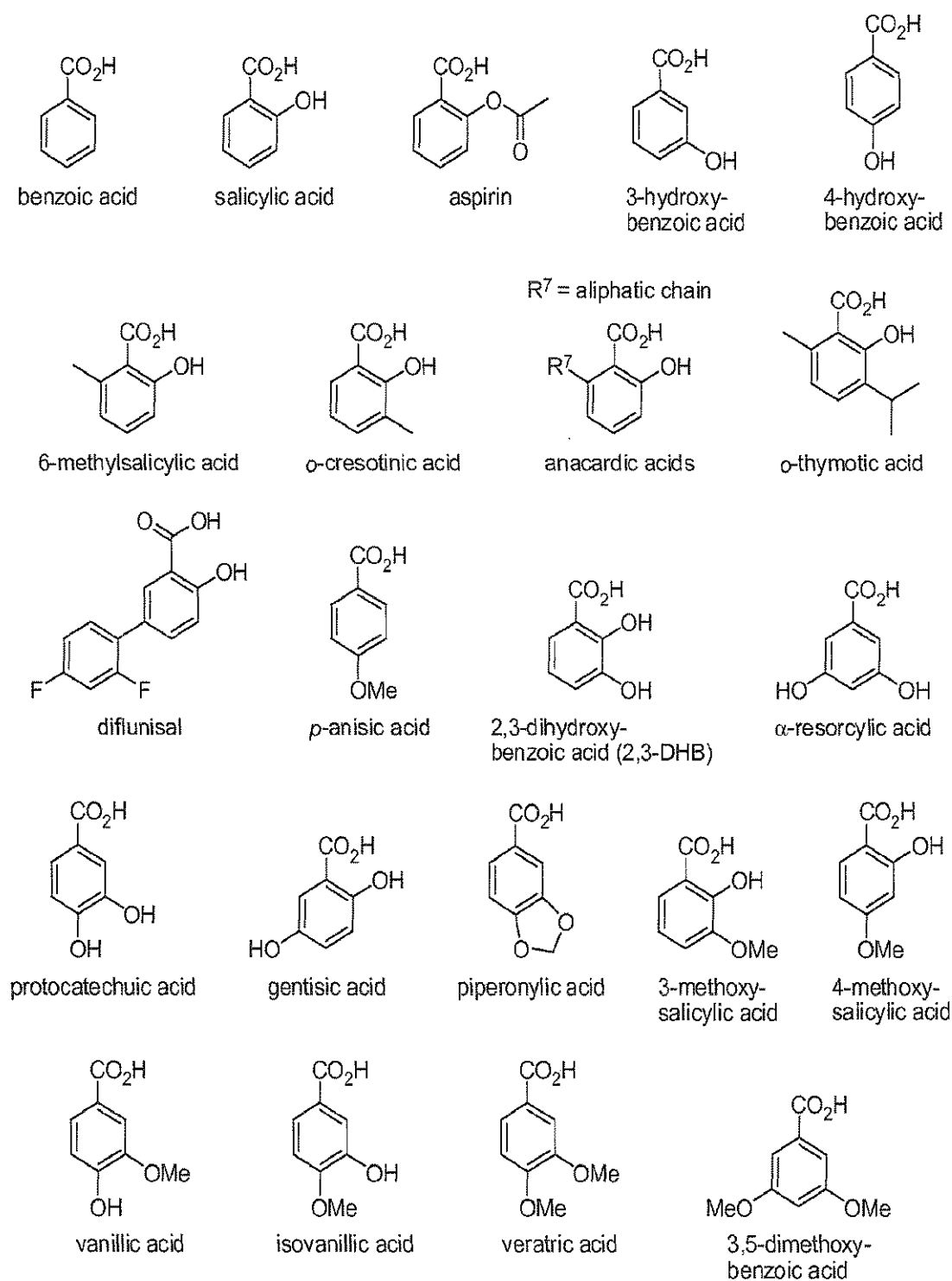
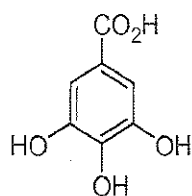
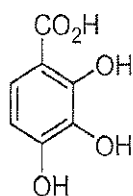
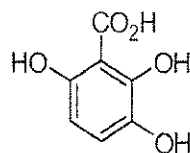
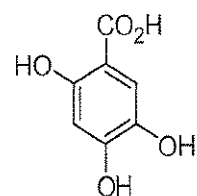
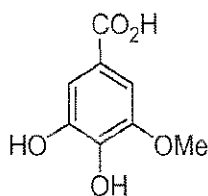
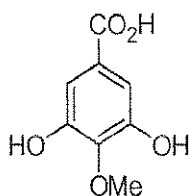
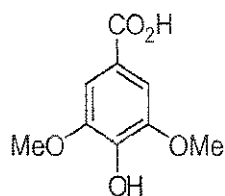
FIGURE 1Structures of some hydroxybenzoates

FIGURE 1 (cont'd.)

gallic acid

2,3,4-trihydroxy-
benzoic acid2,3,6-trihydroxy-
benzoic acid2,4,5-trihydroxy-
benzoic acid3-O-methylgallic acid
(3-OMGA)4-O-methylgallic acid
(4-OMGA)

syringic acid

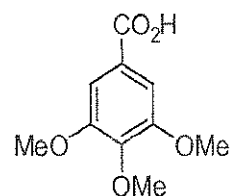
3,4,5-trimethoxy-
benzoic acid

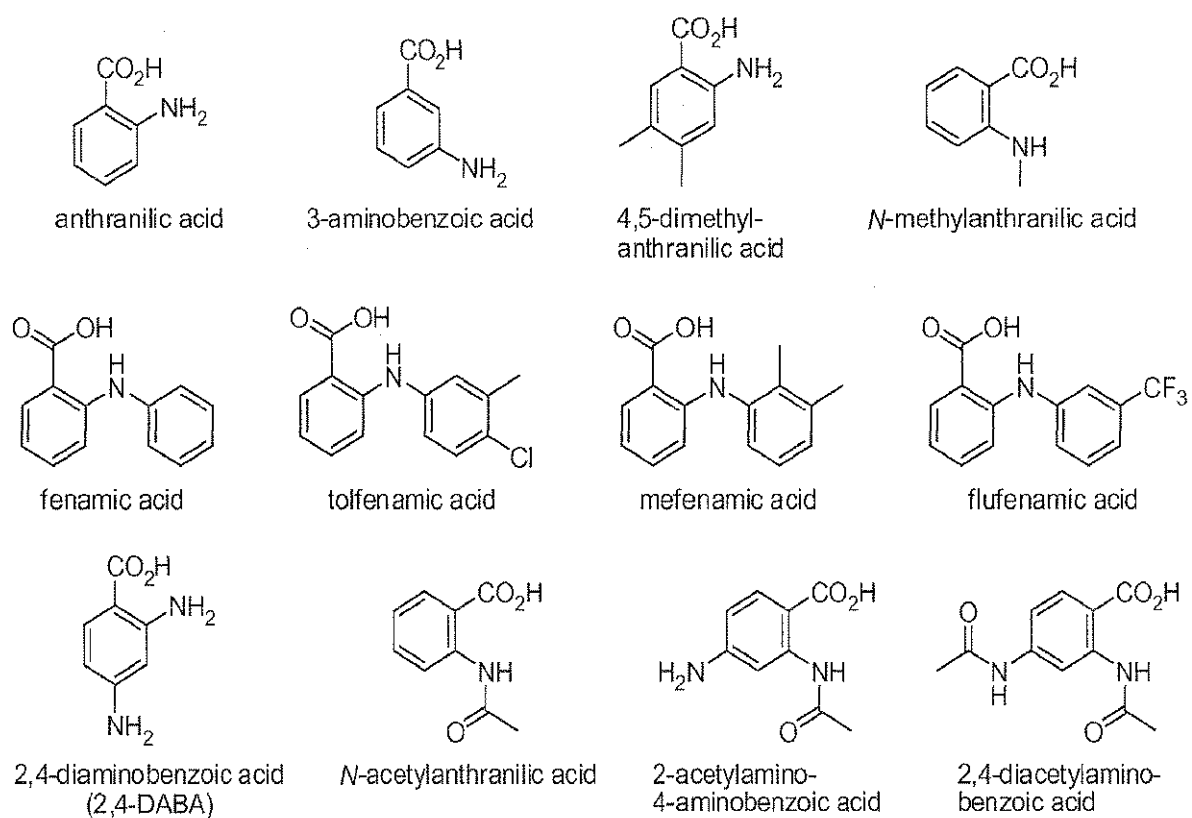
FIGURE 2Structures of some aminobenzoates

FIGURE 3

Structures of some aminohydroxybenzoates

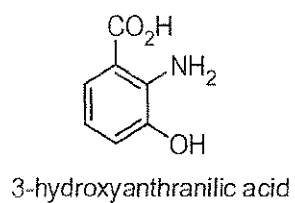
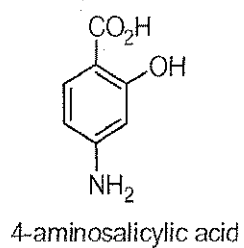
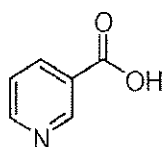
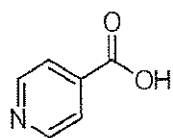
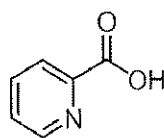


FIGURE 4Structures of some heteroaryl carboxylic acids

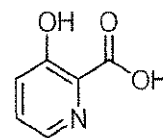
nicotinic acid



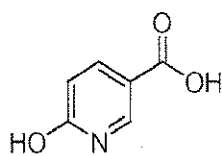
isonicotinic acid



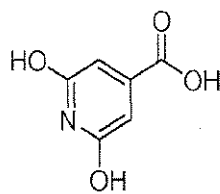
picolinic acid



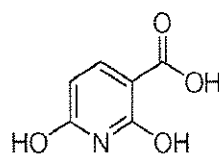
3-hydroxypicolinic acid



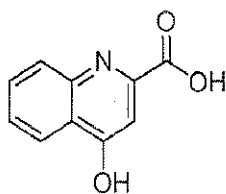
6-hydroxynicotinic acid



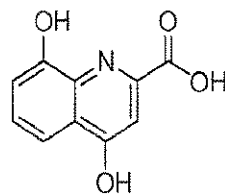
citrazinic acid



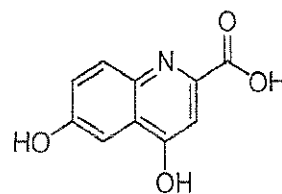
2,6-dihydroxynicotinic acid



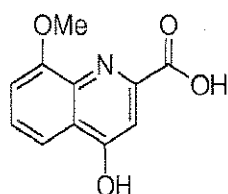
kynurenic acid



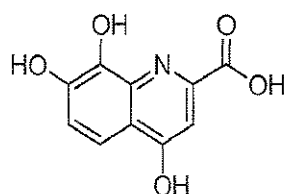
xanthurenic acid



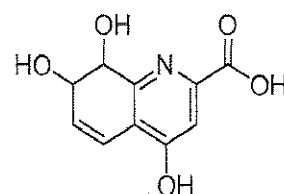
6-hydroxy-kynurenic acid



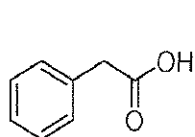
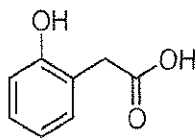
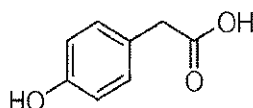
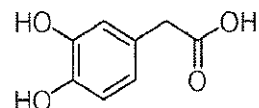
8-methoxykynurenic acid



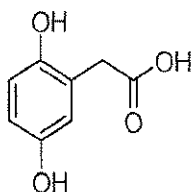
7,8-dihydroxykynurenic acid



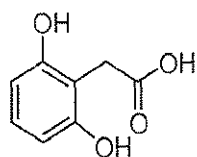
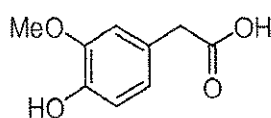
7,8-dihydro-7,8-dihydroxykynurenic acid

FIGURE 5Structures of some phenylacetatesphenylacetic acid
(hydratropic acid)2-hydroxyphenyl-
acetic acid4-hydroxyphenyl-
acetic acid

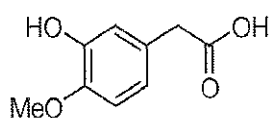
homoprotocatechuic acid



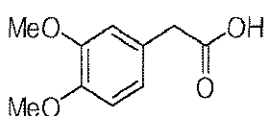
homogentisic acid

2,6-dihydroxy-
phenylacetic acid

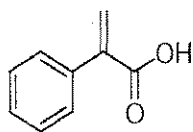
homovanillic acid



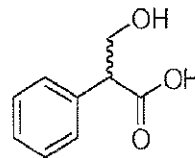
homoisovanillic acid



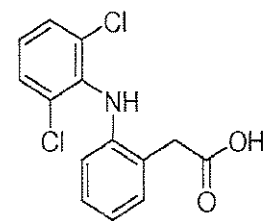
homoveratric acid



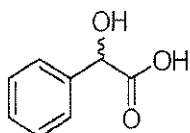
atropic acid



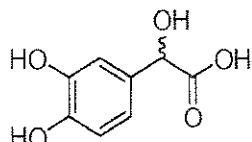
tropic acid



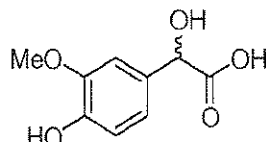
diclofenac



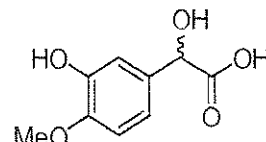
mandelic acid



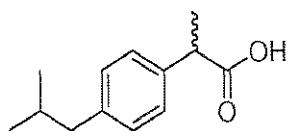
3,4-dihydroxymandelic acid



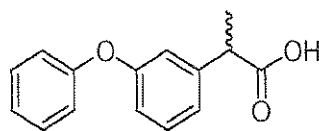
vanillylmandelic acid



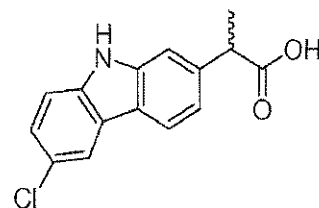
isovanillylmandelic acid



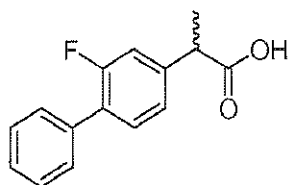
ibuprofen



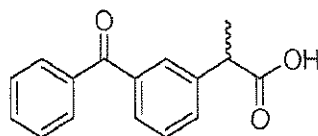
fenoprofen



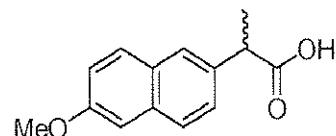
carprofen



flurbiprofen



ketoprofen



naproxen

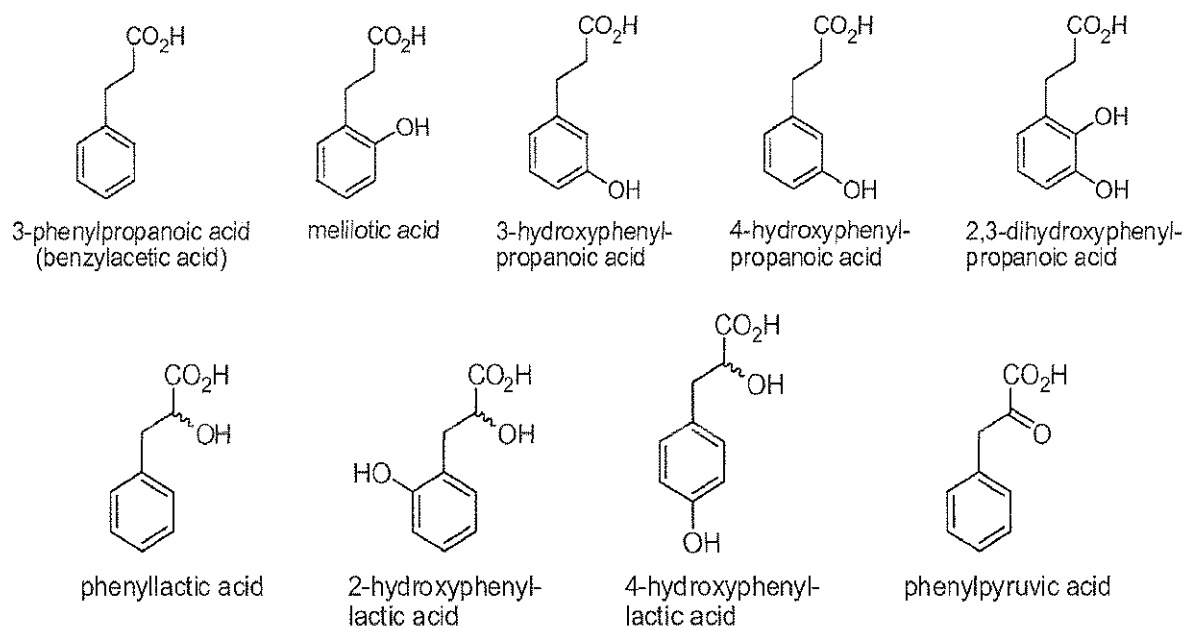
FIGURE 6Structures of some benzylacetates

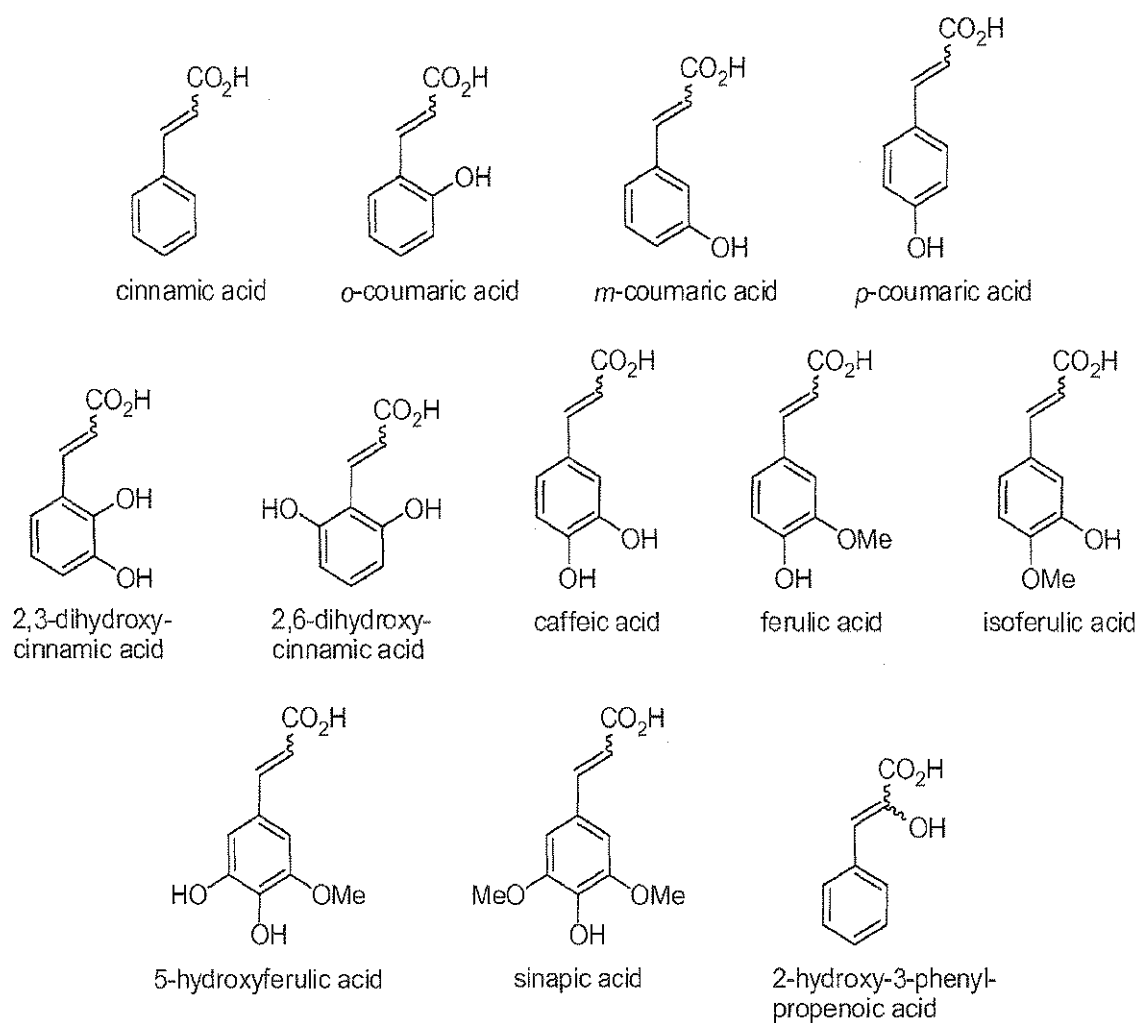
FIGURE 7Structures of some cinnamates

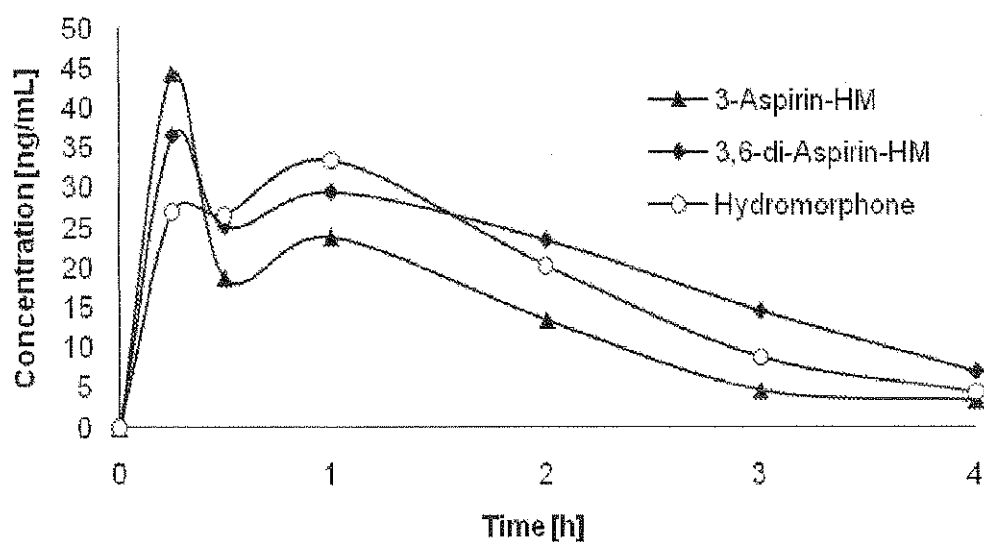
FIGURE 8**Oral PK Curves**

Figure 8. Oral rat study comparing hydromorphone, 3-aspirin-HM and 3,6-di-aspirin-HM.

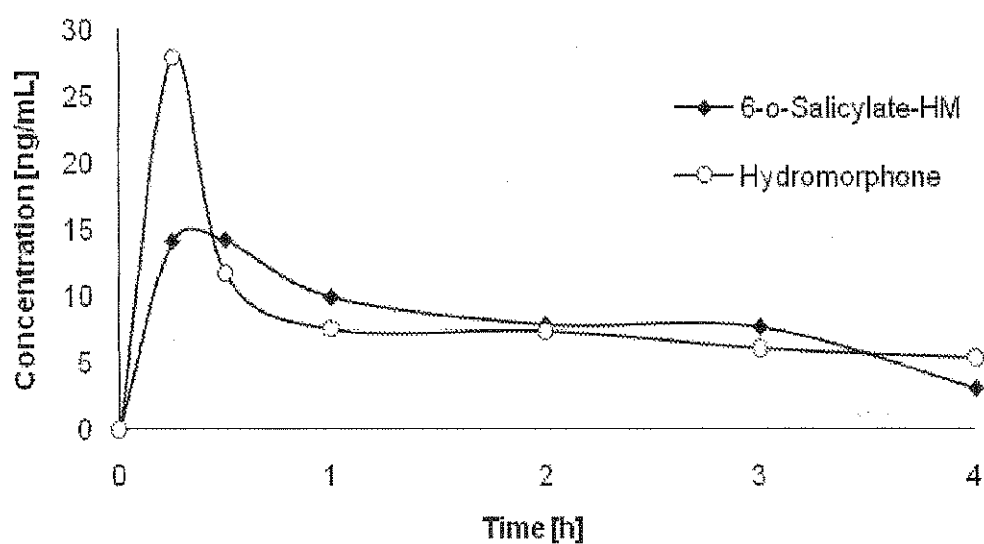
FIGURE 9**Oral PK Curves**

Figure 9. Oral rat study comparing hydromorphone and 6-o-salicylate-HM.

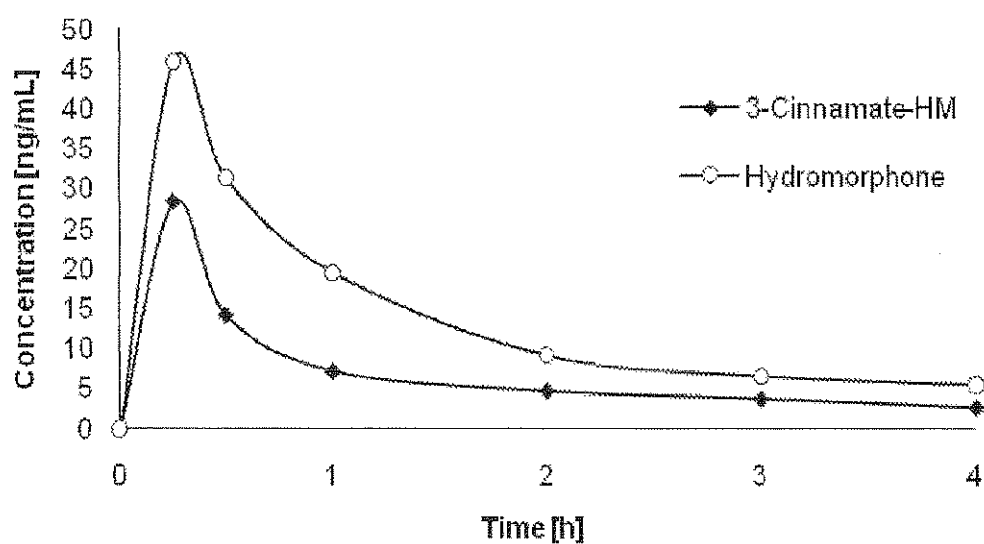
FIGURE 10**Oral PK Curves****Figure 10. Oral rat study comparing hydromorphone and 3-cinnamate-HM.**

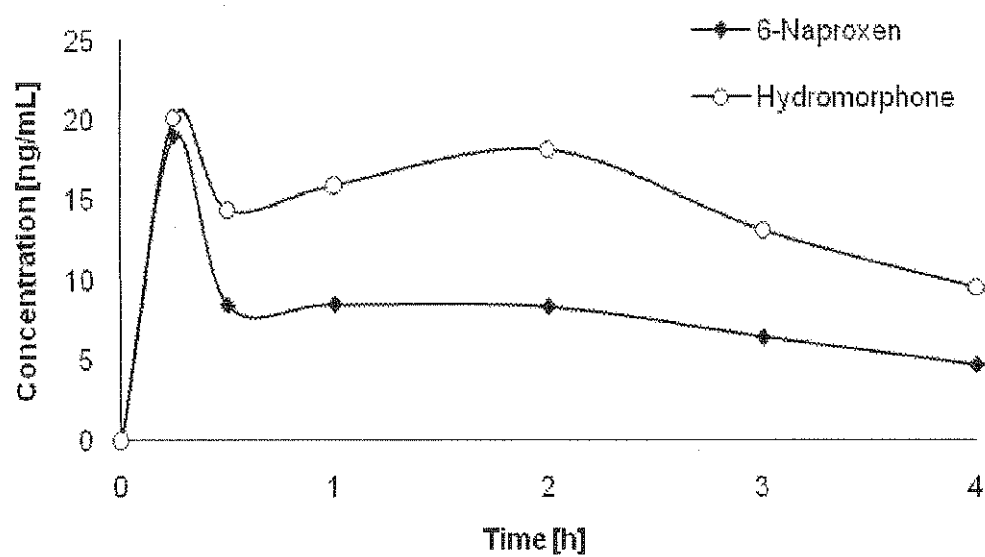
FIGURE 11**Oral PK Curves****Figure 11. Oral rat study comparing hydromorphone 6-naproxen-HM.**

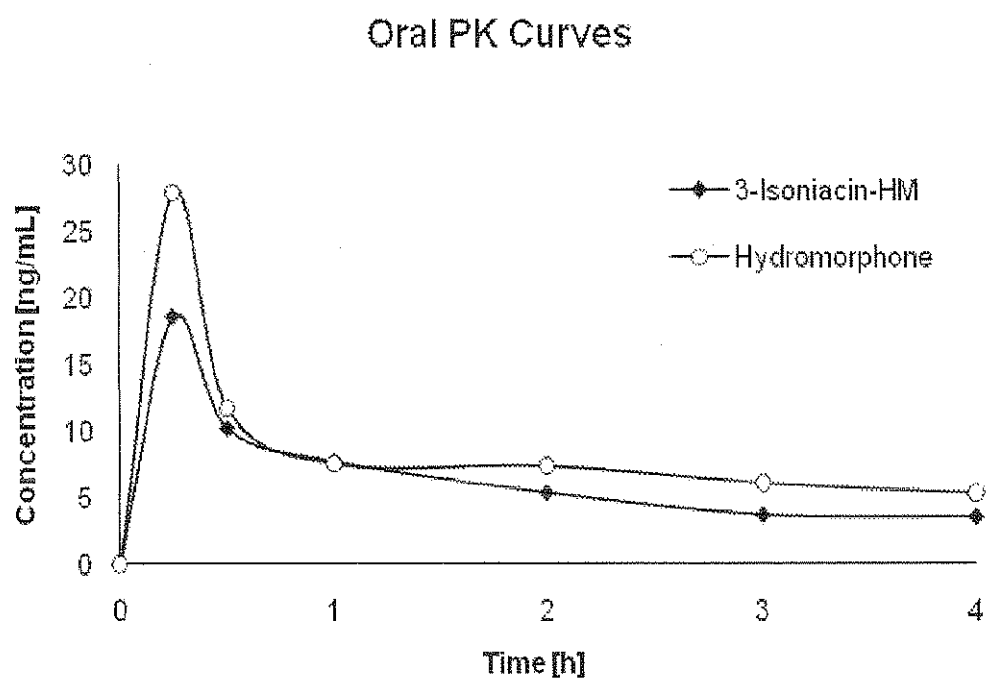
FIGURE 12

Figure 12. Oral rat study comparing hydromorphone 3-isoniacin-HM.

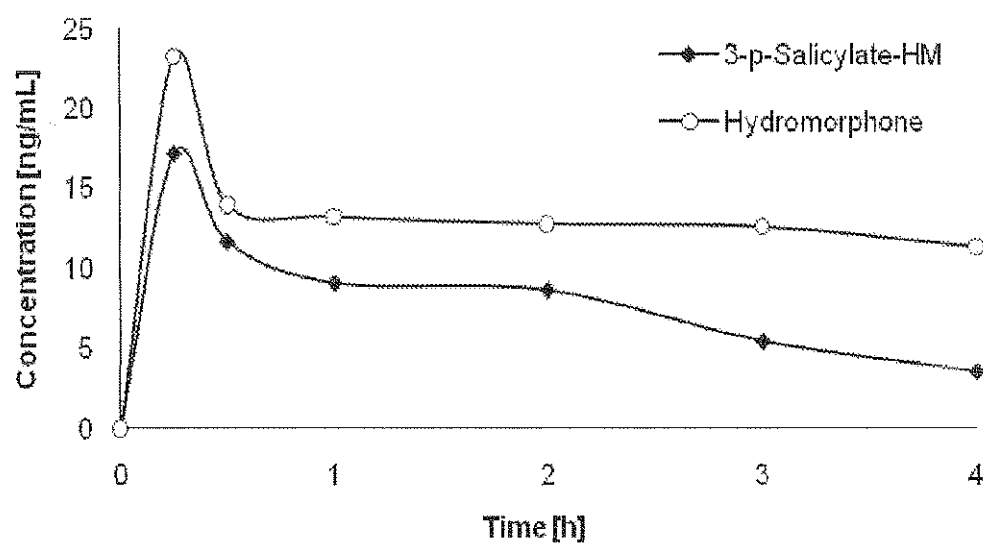
FIGURE 13**Oral PK Curves****Figure 13. Oral rat study comparing hydromorphone and 3-p-salicylate-HM.**

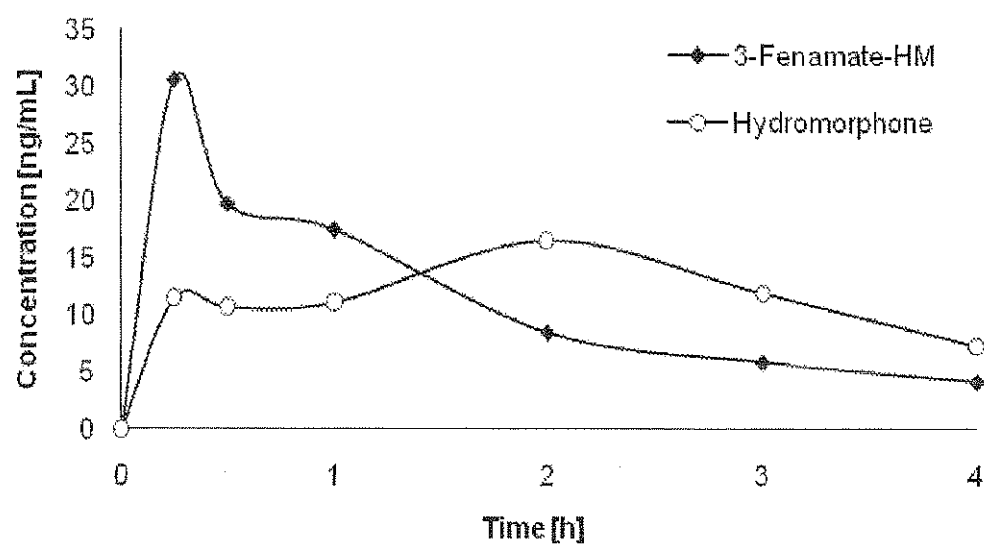
FIGURE 14**Oral PK Curves****Figure 14. Oral rat study comparing hydromorphone and 3-fenamate-HM.**

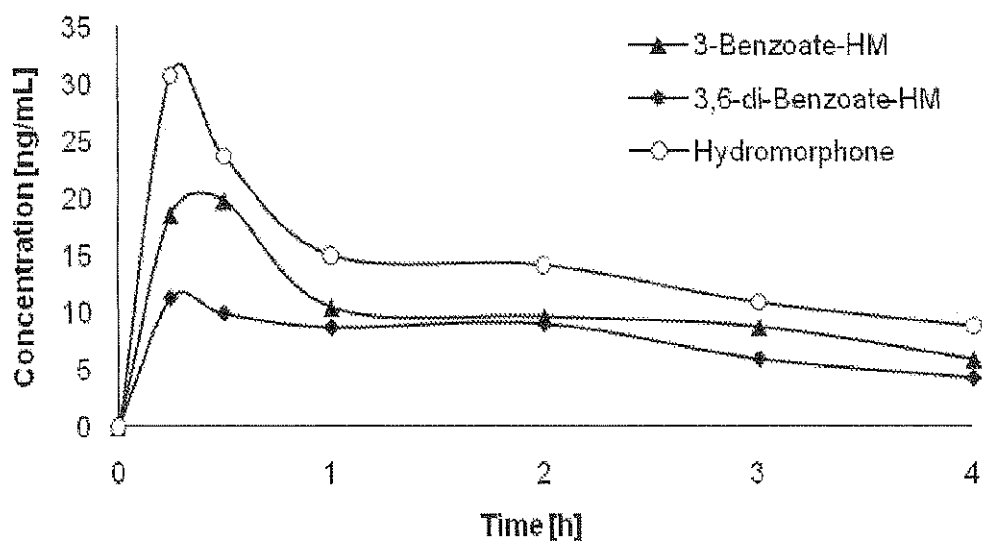
FIGURE 15**Oral PK Curves**

Figure 15. Oral rat study comparing hydromorphone, 3-benzoate-HM and 3,6-di-benzoate-HM.

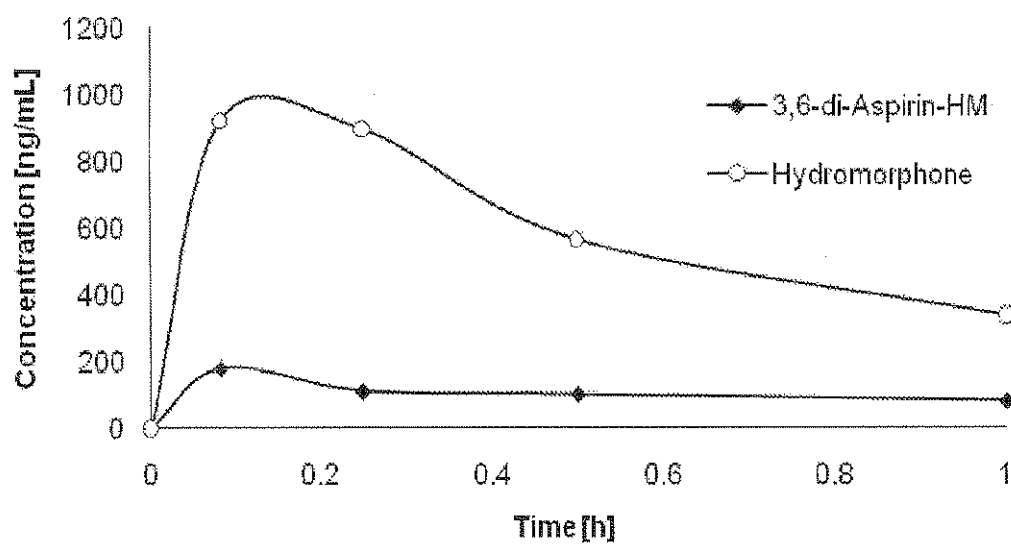
FIGURE 16**Intranasal PK Curves****Figure 16. Intranasal rat study comparing hydromorphone and 3,6-di-aspirin-HM.**

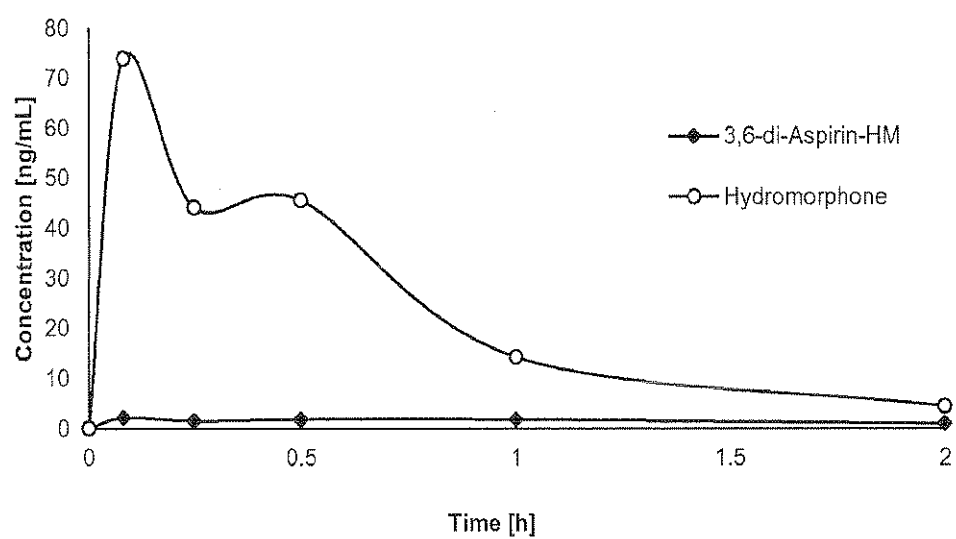
FIGURE 17**Intravenous PK Curves**

Figure 17. Intravenous rat study comparing hydromorphone and 3,6-di-aspirin-HM.

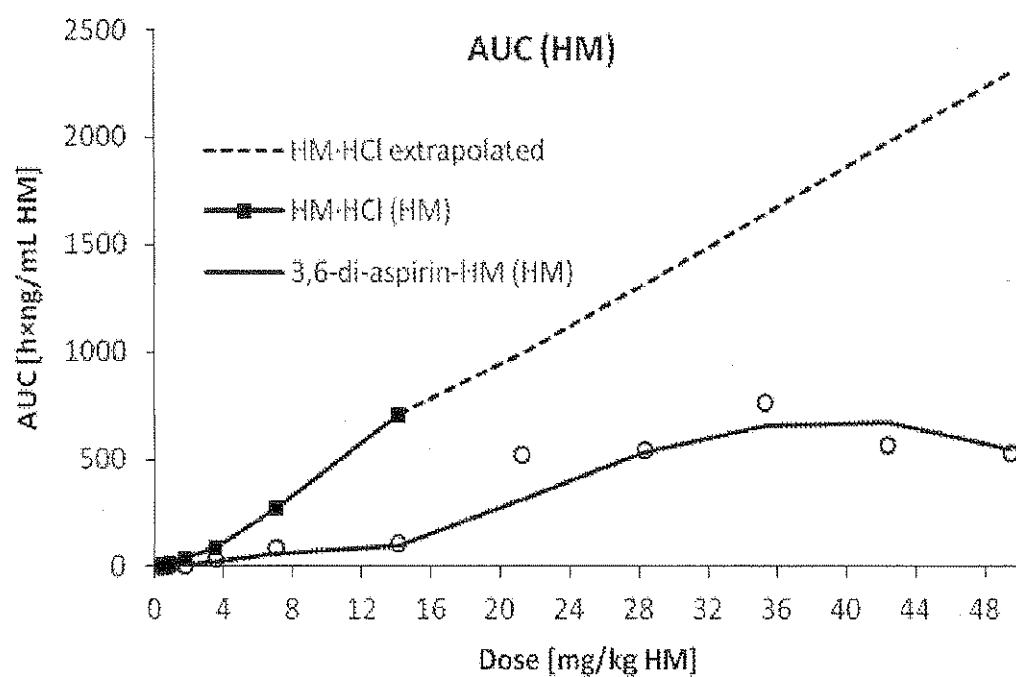
FIGURE 18**Figure 18. Dose escalation in rats**

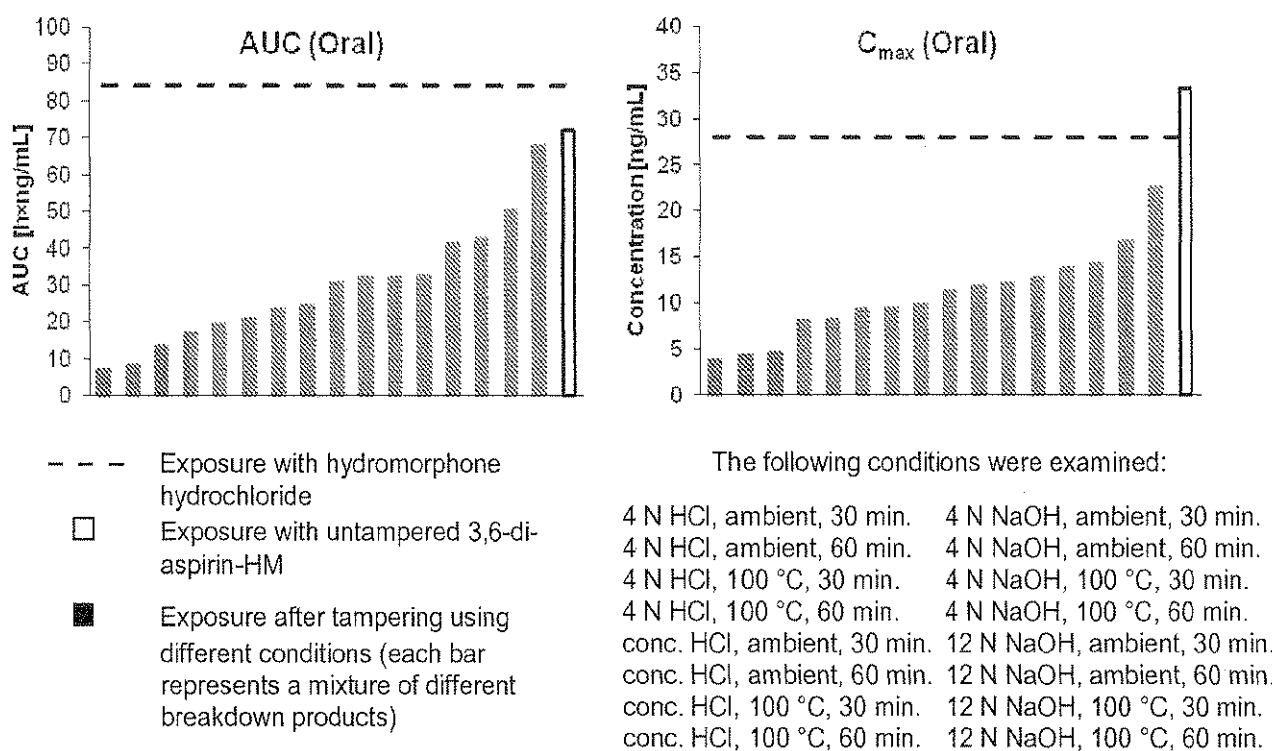
FIGURE 19**Figure 19. Reduced potency of breakdown products**

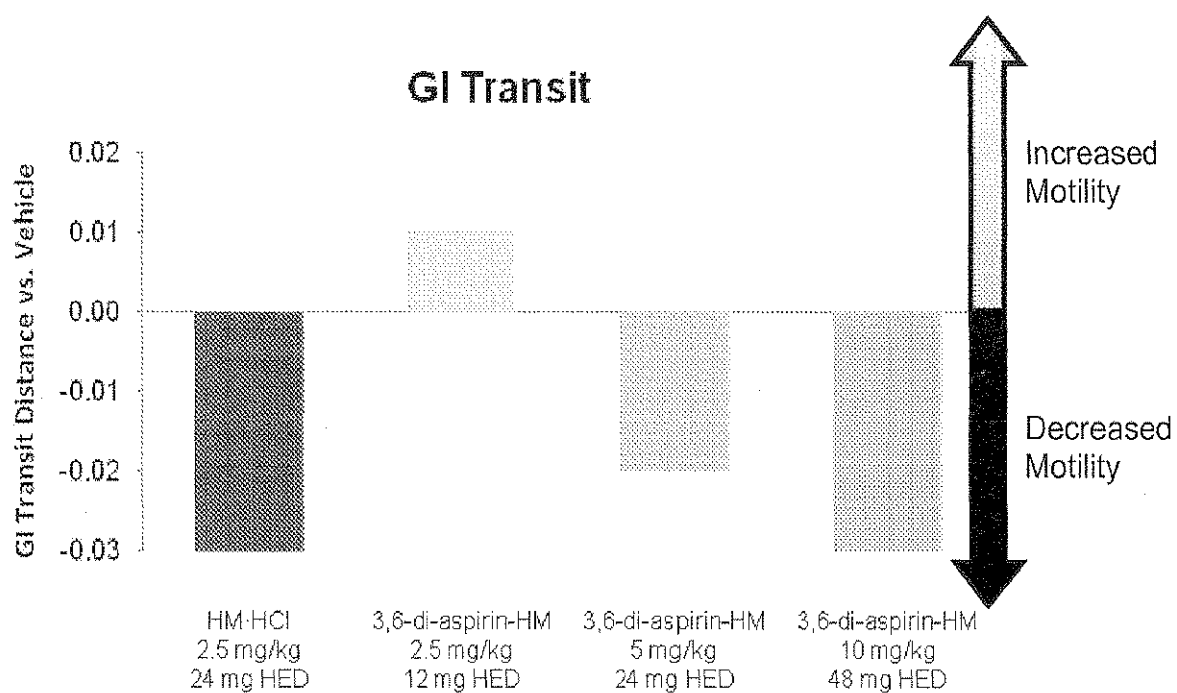
FIGURE 20

Figure 20. Motility with 3,6-di-aspirin-HM compared to hydromorphone hydrochloride

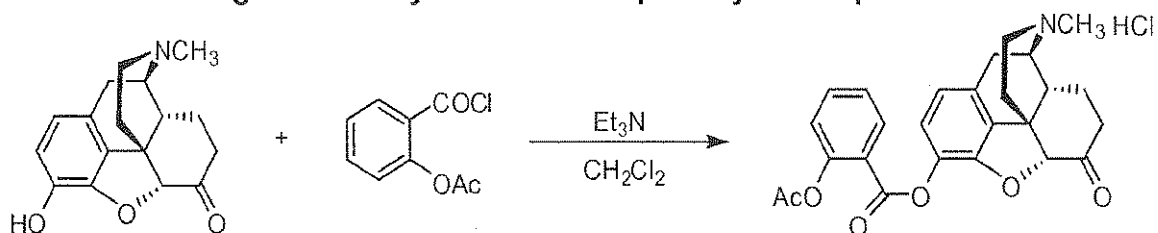
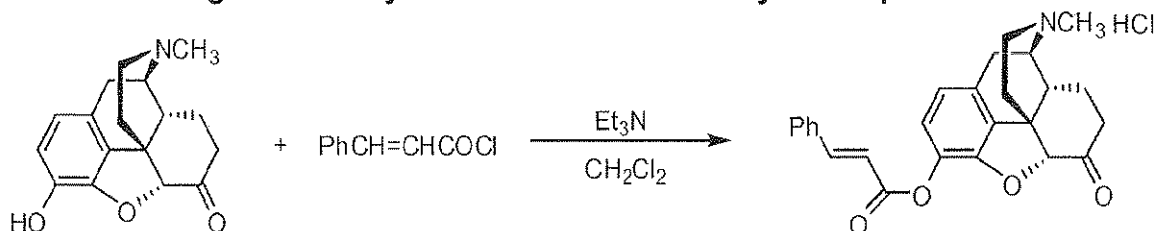
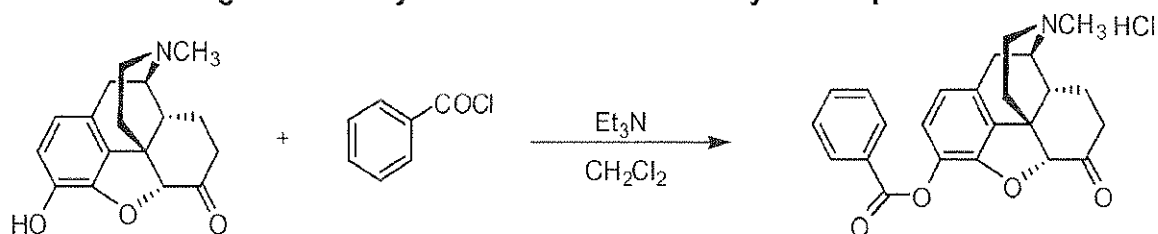
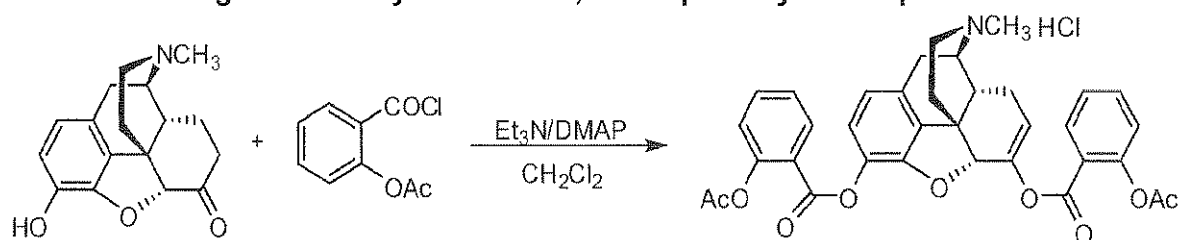
FIGURE 21**Figure 21A: Synthesis of 3-aspirin-hydromorphone:****Figure 21B: Synthesis of 3-cinnamate-hydromorphone:****Figure 21C: Synthesis of 3-benzoate-hydromorphone:****Figure 21D: Synthesis of 3,6-di-aspirin-hydromorphone:**

FIGURE 21 (cont'd.)**Figure 21E: Synthesis of 6-salicylate-hydromorphone:**