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Praziquantel analogs with activity against juvenile *Schistosoma mansoni*

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ABSTRACT

Six amide and four urea derivatives of praziquantel were synthesized and tested for antischistosomal activity against juvenile and adults stages of *Schistosoma mansoni* in infected mice. Only one of these had significant activity against adult worms, but, unlike praziquantel, six of these had low to modest activity against juvenile worms. A praziquantel ketone derivative had the best combination of activity against juveniles and adults, but it had no effect on the motility of adult *S. mansoni* in ex vivo culture. Cytochrome P450 metabolic stability data support the hypothesis that the major *trans*-cyclohexanol metabolite of praziquantel plays an important role in the antischistosomal activity of this drug.

Schistosomiasis is a widespread tropical disease[1] caused by infection with parasitic trematodes (flukes). Five blood fluke species infect humans—*Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*; the first three of these are the most widely distributed and cause the highest disease burden.[2] Praziquantel (PZ) is the drug of choice for schistosomiasis[3,4] and is very effective for this purpose.[1,4] The mechanism of action of PZ is uncertain, although most evidence points towards a perturbation of calcium homeostasis.[1,4,5] Even though no clinically significant resistance to PZ has developed,[6] schistosome isolates with diminished sensitivity to PZ continue to be identified.[7] Since the last review of PZ SAR in 1983,[8] very few new PZ analogs have been synthesized. Nonetheless, a continued interest in PZ SAR is illustrated by the recent report of Ronketti et al.[9] in which the authors describe the activity of aromatic-ring substituted PZ analogs. As one of the few liabilities of PZ is its low efficacy against juvenile forms of schistosomes,[1] we envisioned an investigation of PZ analogs with potential broad-spectrum antischistosomal activity against both juvenile and adult forms, and secondarily, with potentially better metabolic stability. PZ undergoes rapid first-pass drug metabolism[3] to form a major *trans*-cyclohexanol metabolite[5,10] (Fig. 1) that is reported to be equal to[11] or 4- to 10-fold less effective[3,9] than the parent drug against *S. mansoni*.

As most data show[5] that PZ metabolites, including the major *trans*-cyclohexanol metabolite, are less active than the parent, part of our design strategy (Fig. 2) was to increase metabolic stability.

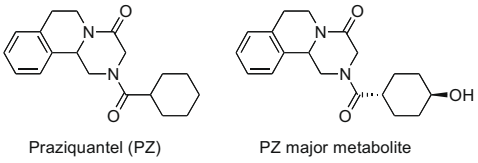

Figure 1. Praziquantel (PZ) and its major metabolite.

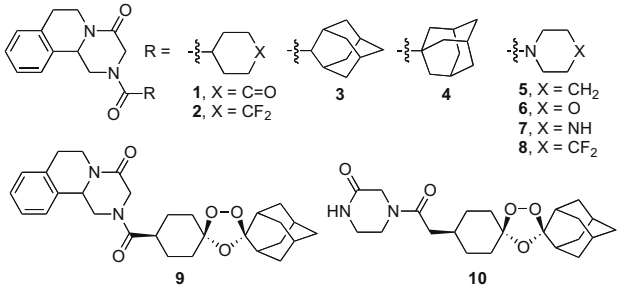

Figure 2. Target PZ analogs **1**–**10**.

PZ derivative **1** is the ketone oxidation product of the *trans*-cyclohexanol metabolite. The geminal difluoro substituent in **2** would be expected to block the formation of this or similar cyclohexanol metabolites. Adamantyl analogs **3** and **4** are conformationally constrained analogs of the cyclohexane substructure of PZ. Ureas **5**–**8** are PZ analogs in which the cyclohexyl is replaced with a piperidine (**5**), morpholine (**6**), piperazine (**7**), and difluoropiperidine

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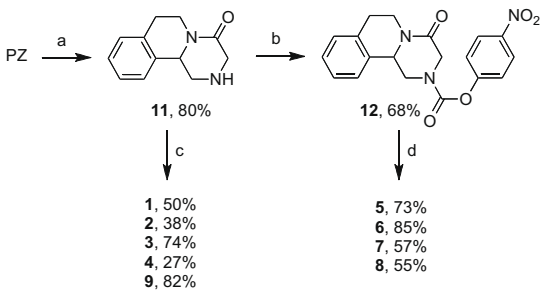
(**8**). These more polar PZ ureas would be predicted to be more metabolically stable than PZ, and if metabolized, avoid the complicating stereochemistry that arises with formation of the cyclohexanol metabolites of PZ. Based on the observation that antimalarial semisynthetic artemisinins and synthetic ozonides, unlike PZ, show higher in vivo activity against juvenile schistosomes than adult worms,[2,12] we designed **9**, a PZ-ozonide hybrid designed to create a potential broad-spectrum molecule. Ozonide **10** is a control for **9** without the tetrahydroisoquinoline substructure of PZ. Even though most of the antischistosomal properties of PZ are derived from its more active R enantiomer,[8,11,13] target PZ analogs **1**-**9**[14] were synthesized as racemates.

Although a three-step synthesis of piperazinone **11** has been described,[15] we elected to obtain **11** directly by selective amide bond hydrolysis of the readily available and inexpensive PZ (Scheme 1). In this respect, the acetamide derivative of PZ was reported[16] to undergo hydrolysis with refluxing HCl for 3 h to give **11** in 65–80% yields, but the concentration of HCl was not specified. Using similar, but more precisely defined reaction conditions (refluxing 1 N HCl, 3 h), Mitsui and Arizono[17] hydrolyzed PZ to afford, after neutralization with sodium bicarbonate, **11** in 27% yield. We found that refluxing PZ in 2 N HCl for 20 h afforded, after neutralization, **11** in 80% yield. Reaction of **11**[15] and the corresponding carboxylic acids[18] with EDCI/HOBt/Et_3N in acetonitrile afforded amides **1**–**4** and **9** in moderate to good yields. Intermediate **12**, the 4-nitrophenylcarbamate derivative of **11**, provided a convenient means to obtain ureas **5**–**8** in good to high yields by treatment with piperazine or the requisite piperidine derivatives. Ozonide **10** was obtained as previously described.[19]

In vitro (Table 1) and in vivo (Table 2) antischistosomal activities against *S. mansoni* were assessed following previously described methods.[12,20,21] Briefly, for the in vitro screen, adult *S. mansoni* worms are obtained from infected mice by portal perfusion using warm perfusion medium (Dulbecco's Modified Eagle's Medium [DMEM], 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, 20 mM Hepes, 10 U/mL heparin [Sigma, UK]). Host red blood cells were removed, and the medium was replaced with complete medium (DMEM plus 10% fetal calf serum, 2 mM L-glutamine, and 100 μg/mL each of penicillin and streptomycin). Test compounds were then added from 10 mg/mL DMSO stock solutions to achieve concentrations of 10 μg/mL. At 120 h, compound activity was assessed by motility disturbances and morphological changes. For the in vivo screen, mice were infected with ca. 80 *S. mansoni* cercariae on day 0 followed by administration of single 400 mg/kg oral doses of test compounds dissolved or suspended in a solubilizing 3% ethanol and 7% Tween 80 vehicle to groups of three mice on day 21 post-infection (juvenile stage) and groups of five mice on day 49 post-infection (adult stage). At 28 days post-treatment, animals were sacrificed by the CO_2 method and dissected to assess total and female worm reduction as described in detail by Xiao et al.[12]



Scheme 1. Reagents and conditions: (a) 2 N HCl, reflux, 24 h, then 20% NaOH; (b) 4-nitrophenyl chloroformate, pyridine/CH_2Cl_2, 4 h; (c) carboxylic acid derivative, EDCI, HOBt, Et_3N, CH_3CN, rt, 24 h; (d) piperazine/piperidine derivative, CH_3CN, 80 °C, 24 h.

Table 1
Effects of 10 μg/mL concentrations of **1**–**10** on adult *S. mansoni* in ex vivo culture

Compd	Motility reduction (%)	Qualitative assessment
Vehicle	0	No effect, many eggs
1	0	Males and females shrunken, granular, opaque, normal motility, no eggs
2	25	Females—slender, normal movement, males—dark, granular, opaque, shrunken, occasional movement of anterior ends dark, no eggs
3	0	No effect, no eggs
4	0	No effects, many eggs
5	38	All worms dark, granular, opaque, females—slender and slow, males—shrunken with occasional movement of anterior ends, no eggs
6	0	No effect, no eggs
7	0	No effect, many eggs
8	0	No effect, very few eggs
9	0	No effect, many eggs
10	0	No effect, no eggs
PZ	100	All worms dark, granular, opaque, with tegument damage, males—curled-up, no eggs

Table 2
Effects of single 400 mg/kg oral doses of **1**–**10** administered to mice harboring 21-day-old juvenile and 49-day-old adult *S. mansoni* infections

Compd	Juvenile		Adult	
	TWR[a] (%)	FWR[b] (%)	TWR (%)	FWR (%)
Vehicle[c]	0	0	0	0
1	25	41[d]	79[d]	81[d]
2	38[d]	44[d]	40	39[e]
3	9	9	4	2
4	42[d]	56[d]	0	0
5	27[d]	34[d]	1	9
6	14	22	0	0
7	25	23	0	0
8	38[d]	38[d]	12	0
9	0	0	0	0
10	85[d,f]	85[d,f]	1	13
PZ	7	18	96[d]	98[d]

[a] TWR = total worm reduction rate.
[b] FWR = female worm reduction rate.
[c] 3% ethanol and 7% Tween 80 solubilizing vehicle.
[d] p <0.05 from the Kruskal–Wallis test comparing the medians of the responses between the treatment and control groups.
[e] p = 0.053 from the Kruskal–Wallis test comparing the medians of the responses between the treatment and control groups.
[f] Data from a single 200 mg/kg oral dose.

For the target compounds tested against adult *S. mansoni* in vitro (Table 1), only **2** and **5** reduced worm motility (by 25 and 38%, respectively). For comparison, PZ killed 100% of adults and had an IC_{50} of 0.37 μg/mL in this experiment. Similarly, a qualitative assessment showed that **2** and **5** had the most significant effect on worm function, although **1** also produced significant morphological abnormalities. From the in vivo adult worm reduction data (Table 2), a somewhat different activity profile for these three compounds was evident. These data revealed that **1** was the only compound with significant activity, whereas **2** had marginal activity and **5** was inactive. With the exception of **1**, the much lower to no activity of PZ analogs **2**–**10** against adult worms parallels earlier SAR trends where most alterations[22] of the cyclohexane substructure (e.g., cyclopentane, cycloheptane, tetrahydropyran) of PZ[8,22] lowered in vivo activity by an order of magnitude or greater.

Like PZ, **3**, **6**, and **7** had no significant activity against juvenile worms (Table 2). However, PZ derivatives **1**, **2**, **4**, **5**, and **8** had modest activity against juvenile worms (female worm burden reductions of 34–56%). Like other structurally related ozonides,[12] ozonide **10** had high activity against the juvenile worms, whereas

PZ-ozonide hybrid **9** was completely inactive, similar to what was recently reported[23] for six 1,2,4-trioxane-PZ hybrids. In sum, although we identified new PZ derivatives with activity against juvenile *S. mansoni*, none of these had activity against adult *S. mansoni* equal to that of PZ. Of these PZ derivatives, ketone **2** had the best combination of activity against juveniles and adults.

To assess whether the two geminal difluoro-substituted **2** and **8** were more metabolically stable than their methylene counterparts PZ and **5**, in vitro metabolic stability of these compounds were determined using human liver microsomes. Briefly, compounds (1 μM) were incubated with 0.5 mg/mL microsomes at 37 °C and the reactions were initiated by the addition of a NADPH regenerating system and were terminated by the addition of ice-cold MeOH. Loss of parent compound over a 120 min incubation period was monitored using LC–MS/MS. Similar to a previous CYP450 study of PZ,[24] dehydrogenation and monohydroxylation were the major metabolic pathways for PZ and its analogs. Predicted human hepatic extraction ratios (ER) were calculated using appropriate scaling factors as previously described by Obach.[25] ER values of 0.44 and 0.59 for **2** and PZ and 0.36 and 0.43 for **8** and **5** revealed that geminal difluoro substitution produced only small increases in metabolic stability. Similarly, these data also reveal that metabolic stability increased only marginally when the exocyclic amide in PZ was replaced with a urea in **5**. In sum, these data suggest that other metabolic pathways besides CYP450-mediated oxidation of the cyclohexyl distal methylene carbon are predominant in **2** and **8**, and support the hypothesis[3] that the major *trans*-cyclohexanol metabolite[26] of PZ plays an important role in the antischistosomal activity of this drug. Indeed, it is possible that the relatively high activity of ketone **2** against adult *S. mansoni* may derive from its in vivo reduction to this *trans*-cyclohexanol metabolite. Experiments to test this hypothesis and probe other metabolic ambiguities of PZ are in progress.

Acknowledgments

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14. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer in $CDCl_3$ solvent. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^{1}H, and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Combustion analysis confirmed that all target compounds possessed purities ⩾95%. Melting points are uncorrected. *2-[(4-Oxocyclohexyl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**1**) (3:1-mixture of two rotamers): mp 130–132 °C; For the major rotamer: ^{1}H NMR δ 1.97–2.23 (m, 4H), 2.29–2.68 (m, 4H), 2.72–3.12 (m, 5H), 4.17 (d, J = 17.0 Hz, 1H), 4.52 (d, J = 17.1 Hz, 1H), 4.69–4.89 (m, 2H), 5.14 (d, J = 13.2 Hz, 1H), 7.09–7.39 (m, 4H); ^{13}C NMR δ 28.44, 28.52, 28.64, 38.09, 39.02, 39.69, 45.18, 48.97, 54.68, 54.75, 125.27, 126.90, 127.44, 129.23, 132.34, 134.56, 163.79, 172.65, 209.43. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.10; H, 6.94; N, 8.80. *2-[(4,4-Difluorocyclohexyl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**2**) (4:1-mixture of two rotamers): mp 183–185 °C; For the major rotamer: ^{1}H NMR δ 1.65–2.09 (m, 6H), 2.13–2.34 (m, 2H), 2.51–2.63 (m, 1H), 2.75–3.03 (m, 4H), 4.11 (d, J = 17.6 Hz, 1H), 4.43 (d, J = 17.1 Hz, 1H), 4.69–4.88 (m, 2H), 5.14 (dd, J = 13.6, 2.9 Hz, 1H), 7.09–7.38 (m, 4H); ^{13}C NMR δ 25.32 (t, J = 9.2 Hz), 25.43 (t, J = 9.2 Hz), 28.61, 32.74 (t, J = 25 Hz), 32.75 (t, J = 25 Hz), 38.23, 39.09, 45.22, 49.02, 54.81, 122.34 (t, J = 241 Hz), 125.37, 126.98, 127.51, 129.30, 132.45, 134.64, 163.91, 172.79. Anal. Calcd for $C_{19}H_{22}F_2N_2O_2$: C, 65.50; H, 6.36; N, 8.04. Found: C, 65.75; H, 6.24; N, 8.26. *2-[(1-Adamantyl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**3**) (4:1 mixture of two rotamers): mp 119–121 °C; For the major rotamer: ^{1}H NMR δ 1.57–2.43 (m, 14H), 2.72–3.07 (m, 5H), 4.06 (d, J = 17.1 Hz, 1H), 4.37 (d, J = 17.6 Hz, 1H), 4.69–4.93 (m, 2H), 5.19 (d, J = 11.7 Hz, 1H), 7.05–7.39 (m, 4H); ^{13}C NMR δ 27.14, 27.82, 28.72, 30.11, 30.18, 32.66, 32.68, 37.47, 38.79, 38.93, 39.05, 45.24, 46.52, 49.78, 54.90, 125.40, 126.93, 127.37, 129.29, 132.87, 134.69, 164.48, 174.10. Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.63; H, 7.58; N, 7.90. *2-[(2-Adamantyl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**4**): mp 165–167 °C; ^{1}H NMR δ 1.69–1.85 (m, 6H), 1.98–2.17 (m, 9H), 2.72–3.07 (m, 4H), 4.00 (d, J = 18.0 Hz, 1H), 4.79–4.89 (m, 2H), 4.92 (dd, J = 17.8, 1.2 Hz, 1H), 5.14 (ddd, J = 13.7, 4.0, 2.0 Hz, 1H), 7.15–7.35 (m, 4H); ^{13}C NMR δ 28.10, 28.20, 28.28, 28.67, 36.40, 38.78, 41.73, 48.44, 50.13, 54.88, 54.92, 125.11, 126.85, 127.31, 129.35, 132.71, 134.85, 164.63, 175.79. Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 76.00; H, 7.54; N, 8.00. *2-(1-Piperidinylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**5**): mp 137–139 °C; ^{1}H NMR δ 1.49–1.71 (m, 6H), 2.73–3.05 (m, 4H), 3.19–3.35 (m, 4H), 3.95 (d, J = 17.0 Hz, 1H), 4.12 (dd, J = 17.0, 1.2 Hz, 1H), 4.41 (ddd, J = 13.7, 3.9, 2.0 Hz, 1H), 4.84 (ddd, J = 12.7, 4.9, 2.4 Hz, 1H), 5.07 (dd, J = 10.2, 3.4 Hz, 1H), 7.17–7.33 (m, 4H); ^{13}C NMR δ 24.54, 25.65, 28.82, 38.80, 47.60, 49.29, 51.47, 54.40, 125.37, 126.79, 127.14, 129.29, 133.29, 134.84, 163.03, 165.17. Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.34; H, 7.34; N, 13.94. *2-(4-Morpholinylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**6**): mp 138–140 °C; ^{1}H NMR δ 2.73–3.05 (m, 4H), 3.19–3.44 (m, 4H), 3.65–3.82 (m, 4H), 3.97 (d, J = 17.1 Hz, 1H), 4.16 (d, J = 17.5 Hz, 1H), 4.41–4.47 (m, 1H), 4.81–4.87 (m, 1H), 5.06 (dd, J = 10.2, 3.0 Hz, 1H), 7.17–7.33 (m, 4H); ^{13}C NMR δ 28.75, 38.83, 46.99, 49.02, 51.23, 54.25, 66.48, 125.32, 126.83, 127.24, 129.32, 132.98, 134.78, 162.65, 164.68. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.80; H, 6.54; N, 13.50. *2-(1-Piperazinylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**7**): mp 116–118 °C; ^{1}H NMR δ 2.73–3.05 (m, 8H), 3.21–3.43 (m, 4H), 3.96 (d, J = 17.1 Hz, 1H), 4.15 (dd, J = 17.5, 1.4 Hz, 1H), 4.43 (ddd, J = 13.2, 3.9, 2.0 Hz, 1H), 4.83 (ddd, J = 12.2, 4.4, 2.4 Hz, 1H), 5.06 (dd, J = 10.2, 3.9 Hz, 1H), 7.17–7.33 (m, 4H); ^{13}C NMR δ 28.76, 38.83, 45.73, 47.66, 49.14, 51.33, 54.31, 125.34, 126.81, 127.19, 129.30, 133.10, 134.79, 162.82, 164.93. Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.86; H, 7.02; N, 17.62. *2-[(4,4-Difluoropiperidinyl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**8**). mp 121–123 °C; ^{1}H NMR δ 1.93–2.17 (m, 4H), 2.73–3.06 (m, 4H), 3.28–3.53 (m, 4H), 3.99 (d, J = 17.1 Hz, 1H), 4.14 (dd, J = 17.1, 1.3 Hz, 1H), 4.43 (ddd, J = 13.7, 3.9, 1.9 Hz, 1H), 4.83 (ddd, J = 12.7, 4.8, 2.4 Hz, 1H), 5.06 (dd, J = 10.7, 3.9 Hz, 1H), 7.16–7.33 (m, 4H); ^{13}C NMR δ 28.73, 33.77 (t, J = 23 Hz), 38.83, 43.52 (t, J = 5.3 Hz), 49.10, 51.33, 54.19, 121.53 (t, J = 242 Hz), 125.29, 126.83, 127.27, 129.33, 132.90, 134.78, 162.29, 164.56. Anal. Calcd for $C_{18}H_{21}F_2N_3O_2$: C, 61.88; H, 6.06; N, 12.03. Found: C, 61.61; H, 6.06; N, 12.16. *2-[(Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decane-8′-yl)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**9**) (4:1-mixture of two rotamers): mp 168–170 °C; For the major rotamer: ^{1}H NMR δ 1.59–2.21 (m, 22H), 2.41–2.53 (m, 1H), 2.72–3.05 (m, 4H), 4.09 (d, J = 17.6 Hz, 1H), 4.44 (d, J = 17.1 Hz, 1H), 4.69–4.88 (m, 2H), 5.15 (d, J = 10.7 Hz, 1H), 7.09–7.38 (m, 4H); ^{13}C NMR δ 26.38, 26.44, 26.55, 26.84, 28.67, 33.51, 33.55, 34.75, 34.77, 36.35, 36.75, 39.03, 39.11, 45.18, 49.03, 54.89, 107.64, 111.52, 125.42, 126.98, 127.47, 129.28, 132.62, 134.66, 164.15, 173.43. Anal. Calcd for $C_{29}H_{36}N_2O_5$: C, 70.71; H, 7.37; N, 5.69. Found: C, 70.58; H, 7.21; N, 5.64. *2-[(4-Nitrophenoxy)carbonyl]-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one* (**12**) (7:3-mixture of two rotamers): mp 133–135 °C; ^{1}H NMR δ 2.74–3.41 (m, 4H), 4.07 (d, J = 18.0 Hz, 0.3H), 4.18 (d, J = 17.5 Hz, 0.7H), 4.53–5.09 (m, 4H), 7.17–7.34 (m, 4H), 7.35 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 28.67, 38.93, 47.35, 47.61, 47.89, 48.33, 54.90, 55.18, 122.15, 122.33, 125.19, 125.23, 125.31, 125.35, 126.93, 127.03, 127.67, 127.76, 129.44, 129.60, 131.83, 131.97, 134.88, 135.22, 145.10, 151.36, 151.65, 155.52, 163.93, 164.37. Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 61.76; H, 4.47; N, 11.75.
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