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Graphical Abstract

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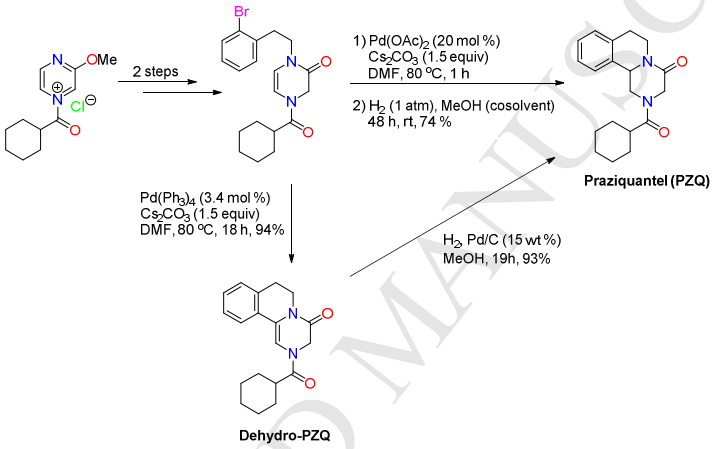
Alfred L. Williams [a, b, *] and Valentine R. St. Hilaire [b, †]

[a] *Department of Pharmaceutical Sciences, North Carolina Central University, Durham, NC, 27707 United States*
[b] *Biomanufacturing Research Institute and Technology Enterprise (BRITE), North Carolina Central University, Durham, NC 27707 United States*



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[a]Department of Pharmaceutical Sciences, North Carolina Central University, Durham, NC, 27707 United States
[b]Biomanufacturing Research Institute and Technology Enterprise (BRITE), North Carolina Central University, Durham, NC 27707 United States

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ABSTRACT

Starting from 3-methoxy *N*-acylpyrazinium salts, a new approach towards the synthesis of the antischistosomal drug praziquantel (PZQ) has been developed. Utilization of a palladium-catalyzed intramolecular Heck reaction to form dehydro-PZQ followed by a Hydrogenation step, in a stepwise or one-pot manner, allowed for the gram scale synthesis of PZQ in 4 or 5 steps and in good overall yields. This methodology proved to be well suited for generating the pyrazino[1,2-a] isoindole and pyrazino[1,2-a] benzazepine analogues of PZQ.

1. Introduction

Over the years, praziquantel (PZQ) has been the drug mainly used for the treatment of the parasitic disease Schistosomiasis (bilharziasis).[1] Recognized as one of many neglected tropical diseases by the World Health Organization (WHO), Schistosomiasis is caused by a trematode flatworm called a *Schistosoma*.[1,2] It has been estimated that more than 200 million people are infected and calculated that 700 million people are at risk of infection.[3]

The synthesis of PZQ has been reported by several groups.[4] Starting from isoquinoline, the initial synthesis of this drug by researchers at Merck used a Reissert reaction to generate a key cyano dihydroisoquinoline intermediate which was then transformed into PZQ in 4 steps.[4i] Kim and coworkers used a Pictet-Spengler reaction towards the synthesis of PZQ. Under acidic conditions, an amido acetal intermediate was cyclized to generate the piperazine and isoquinoline ring system of PZQ in a single step.[4g] A multicomponent approach developed by Cao et al used an Ugi reaction followed by a Pictet-Spengler reaction to give PZQ in 3 steps with an overall yield of 45%.[4b] Another method that has received some attention involved using acidic or radical conditions to generate PZQ from a phenethyl substituted Δ^5-2-oxopiperazine cyclic precursor.[4f-g]

PZQ is highly effective against all schistosome species that are known to infect humans and is used in mass treatment campaigns.[5] Because of its widespread use, drug resistance is a major concern so some researchers have been investigating new ways into synthesizing analogues of PZQ.[6] During our recent investigation into the regioselective reduction of 3-subsituted *N*-acylpyrazinium salts, we showed that the Δ^5-2-oxopiperazine ring system could be easily synthesized in one step and in very good yield.[7] We envisioned that this reaction could be very useful towards making PZQ and its potential analogues by providing a rapid entry into the synthesis of the substituted cyclic precursor mentioned above.

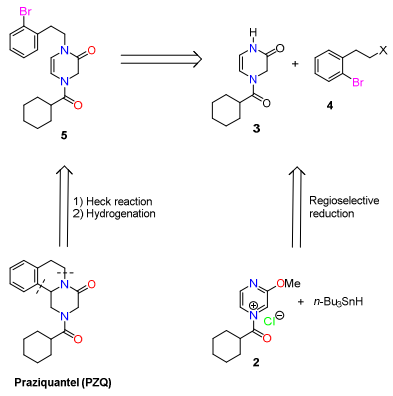


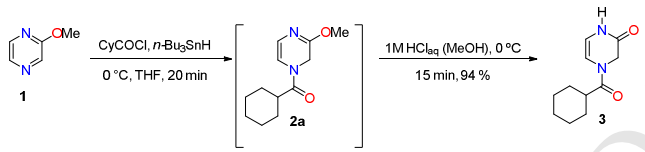
Figure 1. Retrosynthetic Analysis of PZQ.

* Corresponding author. Email: awilliams@nccu.edu (A.Williams)
†Current Address: Department of Chemistry, University of Miami, 1301 Memorial Drive, Coral Gables, FL 33146-0431

Our strategy towards synthesizing PZQ is depicted in Figure 1. Instead of using *N*-2-bromophenethyl substituted Δ^5-2-oxopiperazine **5** to form PZQ via a radical reaction, as mentioned by Todd and coworkers,[4f] we propose that PZQ can be obtained from **5** by first using a Pd-catalyzed intramolecular Heck reaction to generate dehydro-PZQ **6** followed by the reduction of its double bond.[8] Intramolecular Heck reactions can tolerate a variety of functionality and have been used to synthesize biologically active small molecules.[9] *N*-alkylation of Δ^5-2-oxopiperazine **3** with 2-bromophenethyl **4** should give us **5**. As we previously reported, **3** can be synthesized from the regioselective reduction of 3-methoxy *N*-acylpyrazinium salt **2**.[7] In our ongoing efforts exploring the synthetic utility of pyrazinium salts, herein we describe a new approach towards the synthesis of the antischistosomal drug PZQ and its ring contracted and expanded analogues.

2. Results/Discussion

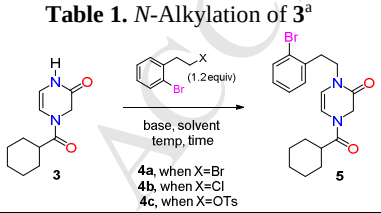
Our journey into the synthesis of PZQ began by first synthesizing Δ^5-2-oxopiperazine **3** on a five gram scale (Scheme 1). To accomplish this, cyclohexanecarbonyl chloride was added, over 10 min, to a solution of the commercially available food additive 2-methoxypyrazine **1** and *n*-Bu_3SnH in THF at 0 °C. Formation of dihydropyrazine **2a** was monitored by TLC. When the reaction was completed after 20 min, the in situ generated **2a** was hydrolyzed to **3** by adding 1M HCl_{aq} in MeOH and stirring the reaction mixture at 0 °C for 15 min. After the crude material was isolated, purification by silica gel flash chromatography gave **3** in an excellent yield of 94% (Scheme 1).



Scheme 1. Synthesis of Δ^5-2-oxopiperazine **3**

With **3** now in hand, exploration of the reaction conditions for its *N*-alkylation to generate **5** was started. An initial attempt at using **3** and 2-bromophenethyl alcohol in a Mitsunobu reaction resulted in no product **5**. Based on a report describing the *N*-alkylations of 2-piperazinones,[10] **3** was reacted with 2-bromophenethyl bromide **4a** or chloride **4b** in the presence of NaH, K_2CO_3, and Cs_2CO_3 in DMF at 80 °C for 36 h. (Table 1, entry 1-6).[11]

Table 1. *N*-Alkylation of **3**[a]



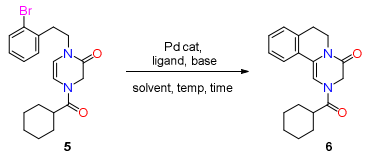
entry	phenethyl	base (equiv)	solvent	yield(%)[b,c]
1	4a	NaH (1.2)	DMF	–
2	4a	K_2CO_3 (3.0)	DMF	21
3	4a	Cs_2CO_3 (1.2)	DMF	14
4	4b	NaH (1.2)	DMF	7
5	4b	K_2CO_3 (3.0)	DMF	14
6	4b	Cs_2CO_3 (1.2)	DMF	18
7	4a	K_2CO_3 (3.0)	Dioxane	13
8	4b	K_2CO_3 (3.0)	Dioxane	3
9[d]	4a	Cs_2CO_3 (1.2)	THF	25
10	4a	Cs_2CO_3 (1.2)	Dioxane	46
11	4b	Cs_2CO_3 (1.2)	Dioxane	40
12[d]	4c	NaH (1.2)	DMF	46
13[d]	4c	NaH (3.0)	Toluene	57
14	4c	Cs_2CO_3 (1.1)	Dioxane	85
15[e]	4c	Cs_2CO_3 (1.5)	THF	88

[a]Unless otherwise specified, all reactions were heated at 80 °C for 36 h. [b]Isolated yield. [c]2-Bromostyrene was produced when phenethyl halides **4a-b** were used. [d]Reaction was heated for 48 h. [e]Reaction with THF was heated to reflux.

Under these conditions, the reaction resulted in low yields of **5** along with **4a** and **4b** undergoing an elimination reaction to give 2-bromostyrene which was detected by crude NMR. Using Dioxane as the solvent gave a slight increase in yield (40-46%) but only when Cs_2CO_3 was used as the base (Table 1, entry 7-11). With the alkyl halides not giving us desirable yields, our attention was directed towards using 2-bromophenethyl tosylate **4c**.[12] Reacting **4c** with NaH gave us **5** in yields of 46% and 57% (Table 1, entry 12-13). When **4c** was reacted in the presence of Cs_2CO_3 using Dioxane or THF as the solvent, we were pleased to see that **5** was generated in 85% and 88% respectively after 36 h (Table 1, entry 14-15).

Having now established our *N*-alkylating conditions, our attention turned toward the formation of PZQ's pyrazino[2,1-a]isoquinoline ring system using an intramolecular Heck process. (Table 2).

Table 2. Optimization of Intramolecular Heck Reaction to form Dehydro-PZQ 6[a]



entry	Pd cat. (mol %)	ligand (mol%)	solvent	time (h)	yield (%)[b]
1[c]	$Pd(PPh_3)_4$ (1)	–	DMF	48	–
2	$Pd(PPh_3)_4$ (3)	–	DMF	15	91
3	$Pd(PPh_3)_4$ (5)	–	DMF	3	85
4	$Pd(PPh_3)_4$ (10)	–	DMF	1	85
5[d]	$Pd(PPh_3)_4$ (20)	–	THF	44	88
6[e]	$Pd(PPh_3)_4$ (10)	–	2-MeTHF	41	75
7[e]	$Pd(PPh_3)_4$ (20)	–	2-MeTHF	22	80
8	$Pd(PPh_3)_4$ (20)	–	Toluene	21	90
9	$Pd(PPh_3)_4$ (20)	–	Dioxane	21	93
10[c]	$Pd(OAc)_2$ (1)	PPh_3 (2)	DMF	48	–
11	$Pd(OAc)_2$ (3)	PPh_3 (6)	DMF	48	20
12	$Pd(OAc)_2$ (5)	PPh_3 (10)	DMF	1	88
13	$Pd(OAc)_2$ (10)	PPh_3 (20)	DMF	1	95
14	$Pd(OAc)_2$ (10)	–	DMF	3	88
15	$Pd(OAc)_2$ (20)	–	DMF	1	88

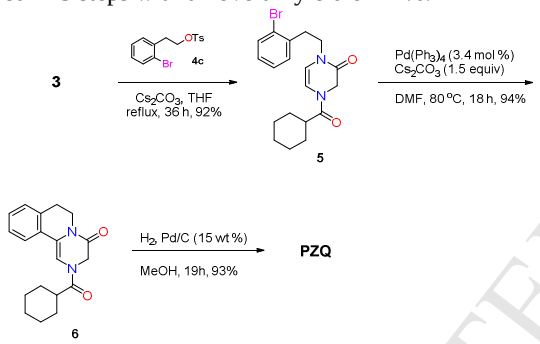
[a]Unless otherwise specified, all reactions were carried out using 1.5 equiv of Cs_2CO_3 as the base and heated at 80 °C. [b]Isolated yields. [c]Product **6** was not observed by LC/MS. [d]Reactions performed in THF were heated to reflux. [e]When 2-MeTHF was used as the solvent, debrominated **5** was observed by crude NMR.

Reaction conditions that were reported in our synthesis of imidazoisoindol-3-ones from 2-haloaryl imidazolinones were first examined.[13] Under these conditions, we were delighted to see that using 3 mole % of $Pd(PPh_3)_4$ in DMF gave a 91% yield of dehydro-PZQ **6** after 15 h (Table 2, entry 2). Reducing the amount of this catalyst to 1 mole % resulted in no product being

formed while increasing it to 5-10 mol % shortened the reaction times but lowered the yield (Table 2, entry 1,3-4). An examination of the effects that different solvents such as THF, 2-MeTHF, Toluene and Dioxane have on this reaction revealed that 10-20 mol % of $Pd(PPh_3)_4$ was required to give **6** in yields of 75-93% (Table 2, entry 5-9).

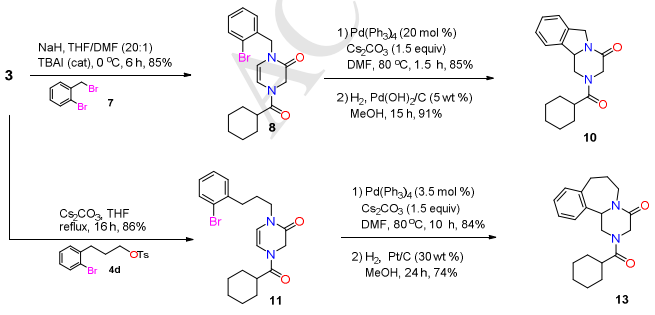
Next, our catalyst system was switched to $Pd(OAc)_2$ and PPh_3 in DMF (Table 2, entry 10-13). When 1 mol % $Pd(OAc)_2$ was used, no reaction was observed. An increase to 3 mol % produced only a 20% yield of **6** after 48 h (Table 2, entry 10-11). Increasing $Pd(OAc)_2$ to 5 and 10 mol % resulted in the reaction going to completion in 1 h and giving yields of **6** in 88% and 95% respectively (Table 2, entry 12 and 13). When the reaction was repeated without the PPh_3 ligand, **6** was obtained in a yield of 88% when using 10 and 20 mol % of $Pd(OAc)_2$ (Table 2, entry 14-15).

With the optimization of our *N*-alkylation and intramolecular Heck reactions completed, demonstration of their use towards the gram scale synthesis of PZQ (Scheme 2) was performed. Starting with 3.0 g of **3**, *N*-alkylation with 3.4g of tosylate **4c** gave 5.2 g of the cyclic precursor **5** in an excellent yield of 92%. Next, using $Pd(PPh_3)_4$ as our catalyst and 2.5 g of **5**, the intramolecular Heck reaction proceeded smoothly to completion in 18 h to generate 1.9 g of dehydro-PZQ **6** in 94% yield. Hydrogenation of 1.5 g of **6** in MeOH using H_2 (balloon pressure) and Pd/C gave 1.4 g of PZQ in a yield of 93%. The ^1H and ^{13}C NMR analysis of our PZQ was consistent with those reported in the literature.[4f] By this new approach, PZQ was provided in 5 steps with an overall yield of 72%.



Scheme 2. Gram Scale Synthesis of PZQ

Due to the success of using this methodology to synthesize PZQ, its use towards the generation of pyrazino[1,2-a] isoindole (ring contracted) **10** and pyrazino[1,2-a] benzazepine (ring expanded) **13** analogues of PZQ was conducted (Scheme 3). Currently, there is only one report describing the synthesis of **10**.[14]

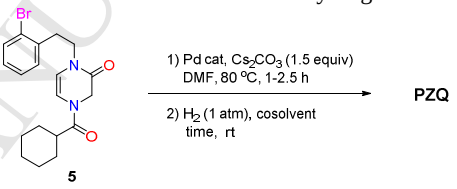


Scheme 3. Synthesis of PZQ Analogues

Ring expanded **13** was shown to be made by cyclizing a α-hydroxy lactam under acidic condition.[15] Both compounds **10** and **13** were found to have anthelmintic activity.[14,15] To synthesize these analogs, **3** was first reacted with commercially available 2-bromobenzyl bromide in the presence of NaH and TBAI using THF/DMF (20:1) as the solvent to give the cyclic precursor **8** in 85% yield. Bromopropyl tosylate **4d**[12] was used to generate **11** in 86% yield using the optimized alkylating conditions described above (Scheme 3). Next, our intramolecular Heck reaction was used to generate the ring contracted and expanded dehydro-PZQ analogs **9** and **12** in good yields of 85% and 84% respectively.[16] Hydrogenation of **9** using $Pd(OH)_2/C$ proceeded smoothly to produce the desired ring contracted PZQ **10** in 91 % yield (Scheme 3). When Pd/C was used on **12**, the reaction did not go to completion after 72 h. Switching to a Pt/C catalyst gave ring expanded PZQ **13** in a yield of 74% after 24 h (Scheme 3).

Although this new method proved to be very efficient at providing PZQ and its analogues, streamlining our synthetic process to reduce the number of steps was explored. Since both our intramolecular Heck and Hydrogenation steps required the use of a palladium catalyst, it became apparent to us that these two steps could potentially be combined to perform a one-pot intramolecular Heck/Hydrogenation reaction. A search of the literature showed that $Pd(OAc)_2$ and PPh_3 in DMF used to convert a variety of alkenes and aryl halides to their corresponding Heck products followed by Hydrogenation (1 atm) to give the desired alkanes.[17]

Table 3. One-Pot Intramolecular Heck/Hydrogenation Reaction



entry	Pd cat. (mol %)	cosolvent (ratio)	time (h)[a]	yield (%)[b]
1	$Pd(OAc)_2$ (20)	–	120	48
2	$Pd(OAc)_2$ (20)	MeOH (1:1)	72	9
3[c]	$Pd(OAc)_2$ (20)	MeOH (1:5)	48	74
4	$Pd(OAc)_2$ (20)	EtOH (1:5)	72	5
5	$Pd(OAc)_2$ (20)	THF (1:5)	48	–

[a]Hydrogenation times at balloon pressure. [b]Isolated yields. [c]Reaction was performed on a 1 gram scale.

Encouraged by this work, an effort for incorporating this one-pot methodology into our PZQ synthesis was launched (Table 3). Since our Heck reaction works well in the absence of the PPh_3 ligand (Table 2) we commenced by first generating dehydro-PZQ **6** by reacting **5** with 20 mol % of $Pd(OAc)_2$ in DMF. By using this procedure, we avoid the need to remove PPh_3 during purification. The reaction was monitored by LC/MS and went to completion in 1 h. Next, the reaction mixture was allowed to stir under a hydrogen atmosphere (balloon pressure) at room temperature. After 48 h, no PZQ was detected as determined by TLC. The reaction was allowed to continue and after 120 h, PZQ was isolated in 48% yield (Table 3, entry 1).

Due to the long reaction time and low yield in DMF, it was surmised that a new solvent system needed to be identified for the Hydrogenation step. It was noted that an excellent yield of PZQ during the Hydrogenation of Heck product **6** using MeOH as the solvent (Scheme 2) was obtained. From this result, it seemed reasonable for us to look at its use as a cosolvent during the Hydrogenation step of our one-pot process. After running our Heck reaction again to completion, degassed MeOH was added to the reaction mixture to give a 1:1 ratio of DMF/MeOH. As mentioned above, the reaction was stirred under a hydrogen atmosphere and after 72 h, PZQ was isolated in a disappointing 9% yield (Table 3, entry 2). Not to be dismayed, we decided to

increase the amount of the MeOH cosolvent to give a 1:5 DMF/MeOH. To our excitement, a 74% yield of PZQ was generated after allowing the hydrogenation to run for 48 h (Table 3, entry 3). When EtOH and THF were looked at to determine their usefulness as cosolvents, low yields or no PZQ product (Table 3, entry 4 and 5) were observed. The success of our one-pot reaction allows us to now generate PZQ in 4 steps with an overall yield of 61%.

3. Conclusion

In conclusion, we have successfully demonstrated the use of 3-methoxy *N*-acylpyrazinium salts towards the synthesis of the antischistosomal drug praziquantel (PZQ). By this method, Δ^5-2-oxopiperazine **3** can be easily made in one step. *N*-Alkylation of **3** followed by an intramolecular Heck and Hydrogenation reactions allowed us to obtain PZQ in 5 steps and in good overall yield. Taking advantage of the versatility of the Pd catalyst, we developed a one-pot intramolecular Heck/Hydrogenation reaction which reduced the number of steps in our PZQ synthesis. This synthetic approach was shown to be well suited for preparing ring contracted and expanded analogues of PZQ. The ability to use 3-methoxy *N*-acylpyrazinium salts towards the generation of other biologically active small molecules and natural products is currently underway in our laboratory.

4. Experimental section

4.1. General information

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated Toluene and THF were dried using a solid-cartridge solvent purification system. All reactions were performed in oven-dried glassware (either in round-bottom flasks or 25 ml vials fitted with rubber septa) under an atmosphere of nitrogen and the reaction progress was monitored by thin-layer chromatography, GC/MS (EI) and/or LC/MS (ESI-APCI). Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates and precoated 170−220 μm layer thickness neutral aluminum oxide Si 60 F_{254} plates. Visualization was by ultraviolet light and/or by staining with phosphomolybdic acid (PMA). Purifications were carried out on flash silica gel columns with EtOAc/hexanes mixtures as eluent. Melting points were measured on a capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 500 MHz spectrometer. Chemical shifts (δ) for proton are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to it (TMS 0.0 ppm). Coupling constants (*J*) are reported in Hertz. Multiplicities are reported using the following abbreviations: br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Chemical shifts (δ) for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual solvent peaks: ($CDCl_3$ 77.0 ppm). Rotameric ratios of all compounds were determined by ^{1}H NMR. HRMS data was recorded on an LC-TOF.

4.1.1. Preparation of 4-Cyclohexylcarbonyl-1,2-dihydro-2-pyrazinone **(3)**

To a solution of 2-methoxypyrazine (5.0 g, 45.4 mmol), in 40 ml of anhydrous THF was added tributyltin hydride (15.0 mL, 54.9 mmol) and the resulting solution stirred under nitrogen at 0 °C. Cyclohexylcarbonyl chloride (8.0 mL, 59.8 mmol) was added over 10 min and stirring continued until reaction completion in 20 min as determined by TLC (neutral alumina, EtOAc/hexanes (1/19, v/v)). A 1M solution of HCl in methanol (20.0 mL) was then added to the reaction mixture that was stirred under nitrogen at 0 °C until reaction completion in 30 min as determined by TLC (SiO_2, EtOAc/hexanes (2/3, v/v). The reaction mixture was quenched with 50 mL of water, extracted with ethyl acetate (3 × 50 mL), washed with saturated sodium bicarbonate (10 mL), and then dried over anhydrous Na_2SO_4. Purification by silica gel flash column chromatography (100% hexanes: to remove tin by-products, followed by methanol/dichloromethane 2−5%) afforded 4-cyclohexanecarbonyl-1,2-dihydro-2-pyrazinone **3** (8.9 g, 94%) as a pale yellow solid (mp 160−163 °C dec). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.71 and 8.38 (2 brs due to rotamers, 1H), 6.70 and 6.23 (2d due to rotamers, *J* = 5.5 Hz, *J* = 6.0 Hz, 1H), 5.75 and 5.70 (2t due to rotamers, *J* = 5.0, *J* = 6.0 Hz, 1H), 4.32 (s, 2H), 2.53 and 2.43 (2t due to rotamers, *J* = 11.5 Hz, *J* = 12.0 Hz, 1H) 1.87−1.66 (m, 4H), 1.58−1.46 (m, 2H), 1.35−1.20 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 173.9, 166.6, 164.95, 109.5, 109.2, 109.1, 108.9, 108.7, 48.3, 45.42, 41.0, 40.8, 28.9, 25.7, 25.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{16}NaN_2O_2$ $[M + Na]^+$ 231.1104, found 231.1106.

4.1.2. General Procedure for the Tosylation of Phenethyl Alcohols. Representative Procedure for the Preparation of 2-Bromophenethyl 4-toluenesulfonate **(4c)**.[18]

To a solution of *p*-toluenesulfonyl chloride (2.84 g, 14.9 mmol) and triethylamine (6.3 mL, 45.2 mmol) in 15 ml of anhydrous dichloromethane at 0 °C, was added over 10 min, 2-bromophenethyl alcohol (2.0 g, 9.9 mmol) then stirred under nitrogen at room temperature for 16 h. The reaction mixture was quenched into water (15 mL) extracted into dichloromethane (2 × 30 mL), washed with saturated $NaHCO_3$ (15 mL) and then purified by silica gel column flash chromatography (EtOAc/hexanes 0−30%) to afford 2-bromophenethyl 4-toluenesulfonate **4c** (3.4 g, 96%) as a white crystalline solid. mp 38−39 °C (lit: mp 39−39.5 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.24−7.13 (m 2H), 7.08 (td, *J* = 2.0 Hz, *J* = 2.5 Hz, *J* = 7.0 Hz, *J* = 7.5 Hz, *J* = 8.0 Hz, 1H), 4.24 (t, *J* = 7.0 Hz, 2H), 3.08 (t, *J* = 7.0 Hz, *J* = 6.5 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 135.4, 132.8, 132.7, 131.4, 129.7, 128.6, 127.7, 127.5, 124.3, 68.7, 35.6, 21.5.

3-(2-Bromophenyl)propyl 4-toluenesulfonate **(4d)**:[18]: 88% yield; white crystalline solid; mp: 40−42 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.0, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 6.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.97 (quintet, *J* = 6.0, *J* = 6.5, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.8, 139.7, 133.9, 130.5, 129.9, 128.0, 127.9, 127.5, 124.3, 69.6, 32.0, 28.8, 21.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NaBrO_3S$ $[M+Na]^+$ 390.9980, found 390.9962.

4.1.3. General Procedure for the Alkylation of 4-Cyclohexyl-carbonyl-1,2-dihydro-2-pyrazinone ***(3)****: Representative Procedure for the Preparation of 4-Cyclohexylcarbonyl-1-(2-bromophenethyl)-1,2-dihydro-2-*pyrazinone **(5)***

4-Cyclohexanecarbonyl-2-pyrazinone (3.0 g, 14.4 mmol), cesium carbonate (7.13 g, 21.9 mmol) and 2-(2-bromophenyl)ethyl 4-toluenesulfonate (5.63 g, 15.9 mmol) in 75 mL of anhydrous THF was flushed with nitrogen and then heated at reflux for 36 h. The reaction mixture was quenched with 15 mL of water, extracted with ethyl acetate (3 × 40 mL), dried over Na_2SO_4 then purified by silica gel flash column chromatography (EtOAc/hexanes 5−75%) to afford 4-cyclohexylcarbonyl-1-(2-

bromophenethyl)-1,2-dihydro-2-pyrazinone **5** (5.2 g, 92%) as an off-white to yellow amorphous solid (71:39 mixture of rotamers). mp: 109−110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, J = 8.0 Hz, 1H), 7.25−7.20 (m, 2H), 7.13−7.09 (m, 1H), 6.63 and 6.10 (2d due to rotamers, J = 6.0 Hz, 1H), 5.52 and 5.40 (2d due to rotamers, J = 6.0 Hz, 1H), 4.32 and 4.31 (2s due to rotamers, 2H), 3.77 (t, J = 7.0 Hz, 2H), 3.05 (t, J = 7.0 Hz, J = 8.0 Hz, 2H), 2.53−2.38 (m, 1H), 1.89−1.66 (m, 5H), 1.58−1.46 (m, 2H), 1.36−1.19 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 173.6, 163.7, 162.3, 137.5, 137.3, 132.9, 131.3, 131.1, 128.6, 127.7, 124.5, 114.0, 113.8, 109.5, 108.9, 48.7, 46.1, 46.0, 45.9, 40.9, 34.7, 28.9, 25.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{24}BrN_2O_2$[M + H]$^+$ 391.1016, found 391.1009.

4-(Cyclohexanecarbonyl)-[3-(2-bromophenyl)propyl]-1,2-dihydro-2-pyrazinone **(11)**: 86% yield; white crystalline solid (78:22 mixture of rotamers); mp: 92−93°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, J = 7.5 Hz, 1H), 6.72 and 6.23 (2d due to rotamers, J = 6.5 Hz, 1H), 5.65 and 5.58 (2d due to rotamers, J = 6.5 Hz, J = 6.0 Hz, 1H), 4.34 (s, 2H), 3.61 (t, J = 7.0 Hz, J = 7.5 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), (m, 1H), (m, 2H, (m, 5H), (m, 2H), (m, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ:173.7, 173.6, 163.6, 162.3, 140.3, 132.9, 130.2, 127.9, 127.6, 124.3, 113.6, 113.3, 109.7, 109.3, 48.7, 45.9, 45.6, 45.4, 40.8, 33.3, 28.9, 28.8, 28.4, 28.2, 25.7, 25.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}BrN_2NaO_2$ [M + Na]$^+$ 427.0992, found 427.0993.

4.1.4. Preparation of 4-[(2-Bromophenyl)methyl]-1-(cyclohexylcarbonyl)-2H-pyrazin-3-one **(8)**

To a stirring mixture of 4-cyclohexanecarbonyl-2-pyrazinone (1.5 g, 7.2 mmol), sodium hydride (0.33 g, 8.25 mmol) and tetrabutylammonium iodide (0.030 g, 0.081 mmol) in 23 mL of THF/DMF (20/1, v/v) under nitrogen at 0 °C was added a solution of 2-bromobenzyl bromide (2.1 g, 8.4 mmol) in 4 mL of THF/DMF (20/1, v/v) over 10 min. After stirring for 6 h, the reaction went to completion as determined by TLC (SiO_2, EtOAc/hexanes (2/3, v/v)). The reaction mixture was quenched with 6.0 mL of water, extracted with dichloromethane (2 × 50 mL), dried over anhydrous Na_2SO_4 then purified by silica gel flash column chromatography (0−30% EtOAc/hexanes) to afford 4-[(2-bromophenyl)methyl]-1-(cyclohexylcarbonyl)-2*H*-pyrazin-3-one **8** (2.3 g, 85%) as a yellow oil (79:21 mixture of rotamers). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 7.0 Hz, 1H) 7.38−7.12 (m, 3H), 6.73 and 6.24 (2d due to rotamers, J = 6.0 Hz, J = 6.5 Hz, 1H), 5.66 and 5.60 (2d due to rotamers, J = 6.0 Hz, J = 6.0 Hz, 1H), 4.85 and 4.83 (2s due to rotamers, 2H), 4.43 (s, 2H), 2.50 (t, J = 11.05 Hz, 1H), 1.94−1.74 (m, 4H), 1.62−1.41 (m, 2H), 1.26 (brs, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 163.9, 162.6, 135.1, 134.8, 133.1, 129.7, 129.5, 129.4, 127.9, 123.5, 113.2, 112.8, 110.0, 109.6, 48.8, 48.7, 48.5, 45.9, 40.9, 28.9, 28.8, 25.7, 25.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}BrN_2NaO_2$ [M + Na]$^+$ 399.0679, found 399.0684.

4.1.5. General Experimental Procedure for the intramolecular Heck reaction: Representative Procedure for the Preparation of 2-(Cyclohexanecarbonyl)-6,7-dihydro-3H-pyrazino[2,1-a]isoquinolin-4-one **(6)**

A mixture of 4-cyclohexylcarbonyl-1-(2-bromophenethyl)-1,2-dihydro-2-pyrazinone (2.5 g, 6.4 mmol), cesium carbonate (3.13 g, 9.61 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.25 g, 0.22 mmol) in 40 mL of anhydrous DMF was degassed and then heated at 80 °C for 18 h under nitrogen. The volatiles were stripped under vacuum then the solid residue purified by silica gel flash column chromatography (EtOAc/hexanes 5−75%) to afford 2-(cyclohexanecarbonyl)-6,7-dihydro-3*H*-pyrazino[2,1-*a*]isoquinolin-4-one **6** (1.9 g, 94%) as a tan crystalline solid (68 : 32 mixture of rotamers). mp: 144−145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 and 7.47 (2d due rotamers, J = 8.0 Hz, J = 8.5 Hz) 1H), 7.31−7.15 (m, 3H), 7.33 and 6.77 (2s due to rotamers, 1H), 4.43 (s, 2H), 3.91 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 5.5 Hz, J = 6.0 Hz, 2H), 2.65 and 2.50 (2t due to rotamers, J = 11.5 Hz, J = 12.0 Hz, 1H), 1.92−1.68 (m, 5H), 1.63−1.49 (m, 2H), 1.50−1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 173.9, 163.9, 162.5, 134.1, 133.4, 128.6, 128.4, 128.2, 128.0, 127.8, 127.3, 123.2, 122.7, 121.6, 121.4, 106.2, 105.6, 48.3, 45.5, 41.1, 41.0, 38.6, 38.4, 29.0, 28.9, 28.8, 28.7, 25.7, 25.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_2O_2$ [M+H]$^+$ 311.1754, found 311.1745.

2-(Cyclohexanecarbonyl)-3,6,6a,10a-tetrahydropyrazino[2,1-a]isoindol-4-one **(9)**: 85% yield; white crystalline solid (70:30 mixture of rotamers); mp[19] 166−168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.44 (m, 1H), 7.41−7.29 (m, 3H), 6.75 (s, 1H), 4.92 and 4.91 (2s due to rotamers, 2H), 4.47 and 4.45 (2s due to rotamers, 2H), 2.66 and 2.49 (2t due to rotamers, J = 11.5 Hz, 1H), 1.93−1.69 (m, 5H), 1.64−150 (m, 2H), 1.41−1.23 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 173.8, 163.3, 161.7, 136.2, 135.5, 132.5, 132.2, 129.0, 128.8, 128.4, 128.3, 126.6, 123.5, 123.3, 120.0, 119.5, 101.5, 100.9, 50.6, 50.5, 48.6, 46.3, 41.4, 41.1, 29.1, 29.0, 25.8, 25.7, 25.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}N_2O_2$ [M+H]$^+$ 297.1598, found 297.1589.

2-(Cyclohexanecarbonyl)-3,6,7,8-tetrahydropyrazino[2,1-a][2]benzazepin-4-one **(12)**: 84% yield; white crystalline solid (76:24 mixture of rotamers); mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ [7.46 (d, J = 6.0 Hz) and 7.40−7.13 (m, 4H)], 6.87 and 6.31 (2s due to rotamers, 1H), 4.44 (brs, 2H), 3.67 (brs, 2H), 2.78 (t, J = 6.5 Hz, J = 7.0 Hz, 2H), 2.61 and 2.50 (2t due to rotamers, J = 6.5 Hz, J = 7.0 Hz, 1H), 2.04−1.67 (m, 6H), 1.62−1.49 (m, 3H), 1.36−1.21 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 173.8, 164.2, 162.9, 138.3, 137.7, 132.7, 129.5, 129.2, 129.1, 128.9, 128.2, 128.0, 127.3, 127.2, 126.8, 108.5, 107.7, 48.5, 45.6, 41.0, 39.8, 39.6, 30.2, 29.0, 28.9, 26.0, 25.9, 25.7, 25.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ [M+H]$^+$ 325.1911, found 325.1917.

4.1.6. General experimental procedure for the Hydrogenation of compounds 6, 9 and 12: Representative Procedure for the Preparation of 2-(Cyclohexanecarbonyl)-5,6,10b,4a-tetrahydropyrazino[2,1-a]isoquinolin-4-one **(Praziquantel) (PZQ)**

A mixture of 2-(cyclohexanecarbonyl)-6,7-dihydro-3*H*-pyrazino[2,1-*a*]isoquinolin-4-one **6** (1.50 g, 4.83 mmol), and Pd/C (0.23 g, 15 wt %) in 100 mL of methanol was degassed and then stirred at room temperature for 19 h under hydrogen at balloon pressure. The reaction mixture was filtered through a bed of diatomaceous earth and volatiles stripped under vacuum to afford 1.51 g of the crude PZQ. The crude material was purified by flash silica gel column chromatography (5−75% EtOAc/hexanes) to afford Praziquantel (**PZQ)** (1.40 g, 93%) as a white crystalline solid (77:23 mixture of rotamers). mp: 137−138 °C (lit[20] mp: 137−138 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.11 (m, 4H), 5.16 (dd, J = 13.5. Hz, J = 2.5. Hz, 1H), 4.94−4.74 (m, 2H), 4.47 and 4.37 (2d due to rotamers, J = 17.5 Hz, J = 13 Hz, 1H), 4.08 and 3.86 (2d due to rotamers, J = 18.0 Hz, J = 18.5 Hz, 1H), [3.26 (t, J = 10.5 Hz, J = 12.5 Hz,) and 3.04−2.75 (m, total 4H)], 2.61−2.41 (m, 1H), 1.97−1.65 (m, 4H), 1.65−1.45 (m, 2H), 1.45−1.19 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 174.3, 165.6, 164.4, 135.5, 134.8, 132.8, 132.1, 129.7, 129.3, 127.7, 127.4, 127.1, 127.0, 125.5, 125.2, 55.8, 55.0, 49.6, 49.0, 46.3, 45.2, 40.8, 40.7, 39.1, 38.6, 29.5, 29.3, 29.0, 28.9, 28.7, 25.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}N_2O_2$ [M+H]$^+$ 313.1911, found 313.1915.

2-(Cyclohexanecarbonyl)-1,3,6,10b-tetrahydropyrazino[2,1-a]isoindol-4-one (**10**)[21]: 91% yield; white crystalline solid (73:27 mixture of rotamers); mp: 180−181 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.44−7.32 (m, 3H), 7.30 (d, *J* = 6.5 Hz, 1H), 5.21 (dd, *J* = 3.5 Hz, *J* = 13.0 Hz, 1H), 5.17 (d, *J* = 15 Hz, 1H), 5.03 and 4.93 (2d due to rotamers, *J* = 9.0 Hz, *J* = 9.5 Hz, 1H), 4.68−4.56 (m, 1H), 4.47 and 4.52 (2d due to rotamers, *J* = 17.5 Hz, *J* = 12.5 Hz, 1H), 4.11 and 3.82 (2d due to rotamers, *J* = 17.0 Hz, *J* = 18.5 Hz, 1H), 3.20 and 2.71 (2t due to rotamers, *J* = 12.0 Hz, 1H), 2.57 and 2.47 (2m due to rotamers *J* = 3.0 Hz, 3.5 Hz, 11.0 Hz, 11.5 Hz, 12.0 Hz, 1H), 1.94−1.67 (m, 5H), 1.67−1.48 (m, 2H), 1.48−1.21 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ175.1, 174.6, 165.3, 164.1, 137.0, 136.7, 136.4, 136.1, 129.2, 128.9, 128.1, 127.94123.5, 123.2, 122.4, 122.1, 61.8, 61.3, 51.1, 50.9, 48.6, 47.64, 46.7, 43.8, 41.2, 29.3, 29.1, 29.0, 25.7. HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_2NaO_2$ $[M+Na]^+$ 321.1579, found 321.1570.

2-(Cyclohexanecarbonyl)-1,3,6,7,8,12b hexahydropyrazino[2,1-a][2]benzazepin-4-one (**13**)[22]: 74% yield; white crystalline solid (70:30 mixture of rotamers); mp 187−189 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ7.36−7.10 (m, 4H), 4.94−4.70 (m, 1H), 4.50−4.25 (m, 2H), [4.11 (d, *J* = 17.0 Hz), 3.97 (d, *J* = 13.5 Hz), 3.85 (d, *J* = 19.0 Hz), 1H], 3.70−3.53 (m, 2H), 3.04−2.98 (m, 2H), 2.79−2.62 (m, 1H), 2.45 (t, *J* = 11.0 Hz, *J* = 11.5 Hz, 1H), 2.33−2.08 (m, 1H), 1.97−1.45 (m, 7H), 1.39−1.19 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ174.9, 174.4, 162.7, 164.5, 138.6, 138.5, 135.6, 135.0, 130.9, 130.6, 128.9, 128.5, 127.3, 127.1, 63.2, 61.4, 48.5, 48.4, 46.3, 44.3, 44.0, 42.6, 40.9, 40.8, 31.6, 30.5, 29.5, 29.1, 29.0, 25.7, 25.3, 25.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}N_2O_2$ $[M+H]^+$ 327.2067, found 327.2071.

4.1.7. Procedure for the one-pot Heck/Hydrogenation reaction: Preparation of 2-(Cyclohexanecarbonyl)-5,6,10b,4a-tetrahydropyrazino[2,1-a]isoquinolin-4-one **(Praziquantel) (PZQ)**:[20]

4-Cyclohexylcarbonyl-1-(2-bromophenethyl)-1,2-dihydro-2-pyrazinone **5** (1.0 g, 2.56 mmol), cesium carbonate (1.25 g, 3.84 mmol) and palladium acetate (115 mg, 0.512 mmol) in 20 mL of anhydrous DMF was degassed, stirred at 80 °C for 2.5 h under nitrogen then cooled to ambient temperature. Next, anhydrous methanol (100 mL) was added to the reaction mixture that was again degassed, and then stirred under balloon pressure hydrogen at ambient temperature for 48 h. The reaction mixture was filtered through a bed of diatomaceous earth, volatiles stripped under vacuum then the solid residue purified by silica gel flash column chromatography (EtOAc/hexanes 5−75%) to afford Praziquantel (**PZQ)** (0.59 g, 74%) as a white crystalline solid.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at

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20. (a) Kim, J. H.; Lee, V. S.; Park, H.; Kim, C. S. *Tetrahedron* **1998**, *54*, 7395−7400. (b) Todd, M. H.; Ndubaku, C.; Bartlett, P. A. *J. Org. Chem* **2002**, *67*, 3985-3988.
21. Used $Pd(OH)_2/C$ as the catalyst.
22. Used Pt/C as the catalyst.