JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

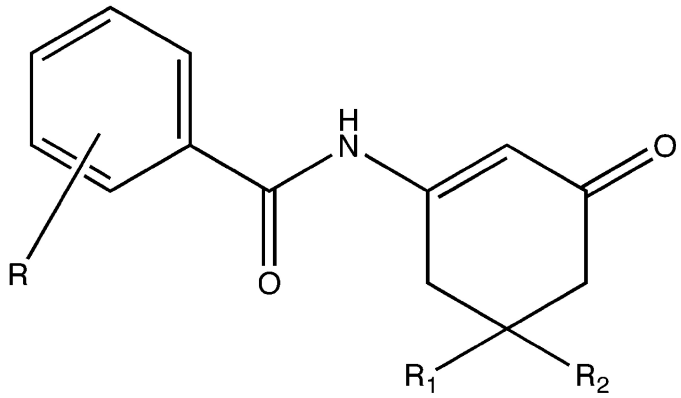
Article

A Base-Catalyzed Solution-Phase Parallel Synthesis of Substituted Vinylic Benzamides from 3-Amino-2-cyclohexanones

Alan J. Anderson, Jesse M. Nicholson, Oladapo Bakare, Ray J. Butcher, and K. R. Scott

J. Comb. Chem., **2004**, 6 (6), 950-954• DOI: 10.1021/cc0498837 • Publication Date (Web): 22 September 2004

Downloaded from http://pubs.acs.org on March 20, 2009



R = H; 3-Cl; 3,4-di OCH_3; 3-$O(CH_2)_3CH_3$,4-OCH_3; 3-*O*-cyclopentyl, 4-OCH_3
R_1 = H or CH_3
R_2 = H or CH_3

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

A Base-Catalyzed Solution-Phase Parallel Synthesis of Substituted Vinylic Benzamides from 3-Amino-2-cyclohexanones

Alan J. Anderson,[†,‡] Jesse M. Nicholson,[†] Oladapo Bakare,[†] Ray J. Butcher,[†] and K. R. Scott*[,§]

Department of Chemistry, Graduate School, Howard University, Washington, D.C. 20059, and Department of Pharmaceutical Sciences, School of Pharmacy, Howard University, Washington, D.C. 20059

Received July 14, 2004

An improved method for the synthesis of benzamides from 3-amino-2-cyclohexenones is presented. Using sodium hydride, a base-catalyzed *N*-benzoylation provided significantly higher yields (71−79%) for the reported compounds. This novel protocol was applied in the solution-phase parallel synthesis of a 12-member library of vinylic benzamide derivatives of 3-amino-2-cyclohexenones in 63−90% yield, using a Radley's Carousel Reaction Station.

Introduction

In our extensive study of enaminones,[1−17] we have found several analogues that possess excellent anticonvulsant activity. In addition, Carson et al.[18] indicated in their report on their highly active aroyl(aminoacyl)pyrroles (**1**; see Figure 1) that there existed a structural similarity to the *N*-benzyl enaminones (**2**) synthesized in our laboratories.[1] Furthermore, Carson indicated that the extensive charge delocalization that involved the N atom and the carbonyl oxygen was similar in both the acyl pyrroles[19] and the enaminones.[20] Recently, we have noted that, in addition to charge delocalization, the distances between the carbonyl group to the vinyl hydrogen and the carbonyl group to the amino hydrogen are requirements for modulation of the P-glycoprotein (P-gp) efflux transport in multidrug resistance.[21] Several enaminones possess this property.[22,23]

Subsequently, we synthesized a series of benzamide derivatives (**3**) and compared the activity of these analogues to the reported benzylamines.[9] This study was hampered by poor yields. The procedure (Scheme 1) involved amination of the respective β-diketones,[24] forming enaminones (**4**) followed by acylation with the respective benzoyl chlorides with triethylamine as the acid scavenger. Careful monitoring of this reaction minimized the possible β-acylation to **5**.

In our design of the synthesis of additional analogues of the benzamide derivatives for structure−activity relationship studies, we considered the simultaneous synthesis of several analogues; however, the reactions in Scheme 1 did not appeal to us for parallel synthesis, because of the low yields afforded by this reaction path. Hence, we exploited a more-efficient and better-yielding reaction that could be amenable to solution-phase parallel synthesis of several of the benzamide analogues. We herein report a novel base-catalyzed coupling of enaminones with substituted benzoyl chlorides and its use in the solution-phase parallel synthesis of a small library of vinylic benzamides.

Results and Discussion

The direct *N*-acylation of enaminone **4** to produce the benzamide derivative **3** (Scheme 1) has been used by several laboratories.[9,25,26] However, these methods were limited in several areas: (i) the reported yields were moderately low, in the range of 6−32%; (ii) the reaction conditions varied, with no single procedure being ideal; and (iii) extensive purification techniques were needed to obtain the desired product. The factors contributing to the above include (i) poor nucleophilicity of the cyclic enaminone system; (ii) competing side reactions; i.e., O, Cα, and *N*-acylation, in theory, can occur; and (iii) the rapacious HCl byproduct, which, in theory, can consume an equivalent amount of unreacted enaminone **4**, thus cutting the theoretical yield by 50%. These obstacles limited this method as an attractive candidate for parallel synthesis or other high-throughput synthetic methods. Our current methodology (Scheme 2) involves the *N*-deprotonation of the enaminone system, **6**, with two equivalents of sodium hydride (NaH) in tetrahydrofuran (THF) under a nitrogen atmosphere, generating the dianion **8** (see Scheme 3). The subsequent reaction involved the addition of 1 equiv of the appropriate benzoyl chloride **7** to dianion **8**, producing the amide salt intermediate. The reaction mixture was quenched with water and neutralized with HCl, which liberated the amide from its salt and destroyed the excess NaH to yield the crude benzamide derivatives **9** (see Scheme 2). The addition of water to the reaction transformed any unreacted acid chloride to its corresponding acid for the typical aqueous extraction. The complete hydrolysis of the aromatic acid chloride to the subsequent carboxylic acid was detected via thin-layer

* Author to whom correspondence should be addressed. Telephone: +1-202-806-7288. Fax: + 1-202-806-7805. E-mail address: kscott@howard.edu.
† Department of Chemistry, Graduate School.
‡ Current address: Department of Chemistry, Harvard University, Cambridge, MA 02138.
§ Department of Pharmaceutical Sciences.

10.1021/cc0498837 CCC: $27.50 © 2004 American Chemical Society
Published on Web 09/22/2004

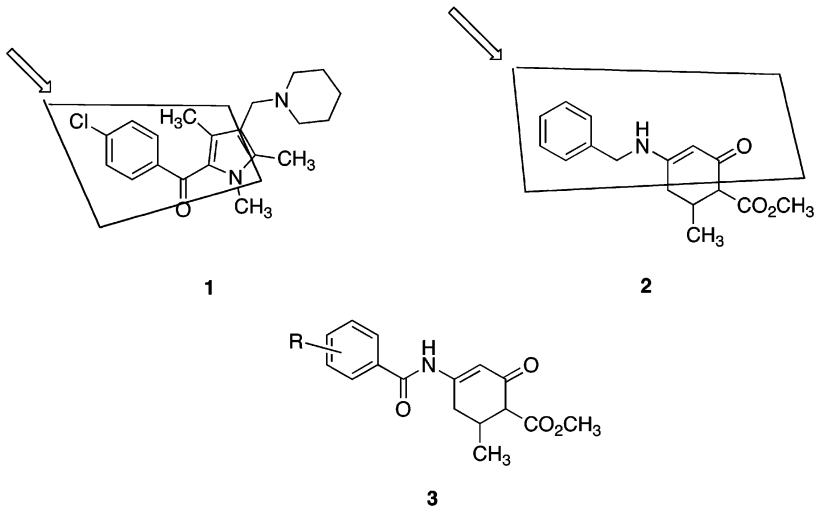
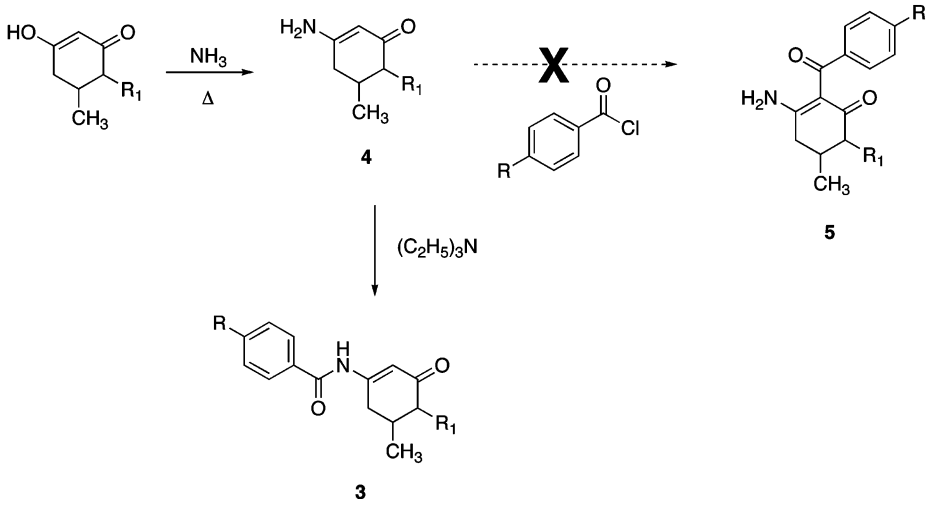
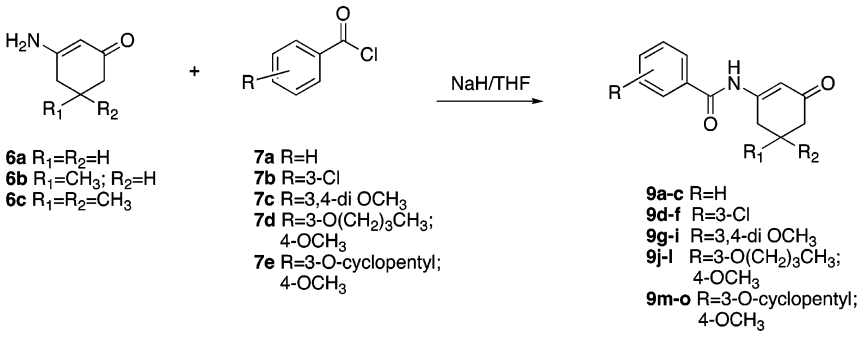


Figure 1. Structural interrelationship of the aroyl(aminoacyl)pyrroles (**1**, from Carson et al.[18]) and methyl 4-*N*-(benzylamino)-6-methyl-2-oxocyclohex-3-ene-1-carboxylate.

Scheme 1



Scheme 2



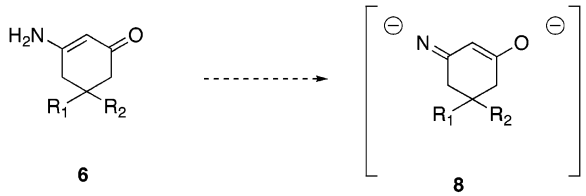
6a $R_1=R_2=H$
6b $R_1=CH_3$; $R_2=H$
6c $R_1=R_2=CH_3$

7a R=H
7b R=3-Cl
7c R=3,4-di OCH_3
7d R=3-$O(CH_2)_3CH_3$; 4-OCH_3
7e R=3-O-cyclopentyl; 4-OCH_3

9a-c R=H
9d-f R=3-Cl
9g-i R=3,4-di OCH_3
9j-l R=3-$O(CH_2)_3CH_3$; 4-OCH_3
9m-o R=3-O-cyclopentyl; 4-OCH_3

chromatography (TLC) and its removal by liquid−liquid extraction with aqueous $NaHCO_3$ was very satisfactory. As shown in Table 1, this reaction furnished the benzamide derivatives **9a**−**9c**, with an average yield of 75%, which is a considerable improvement over yields previously reported in the literature (average yield of 23%).[9,25,26] Although the dianion **8** has been advanced as the purported intermediate, another explanation could be that a monoanion was produced with 1 equiv of NaH, while the second equivalent consumes the HCl that is generated in the reaction. Note that compound **6b** is chiral and was formed by the amination of 5-methyl-

Scheme 3



cyclohexane-1,3-dione; the latter compound exists as a single enantiomer, as verified by Friary et al.[27] The products, **9b**,

Table 1. Yields of Benzamides **9a**−**c**, Compared to Reported Values

				Melting Point Data			Yield Data		
compound	R_1	R_2	reaction time (min)	mp, observed (°C)	mp, from literature (°C)	reference	yield, observed (%)	yield, from literature (%)	reference
9a	H	H	40	177−178	178−179	25	79	14.9	24
9b	CH_3	H	40	135−137	136.5−138	9	71	29.4	25
9c	CH_3	CH_3	40	144−146	146−148	24	76	25.0	9

Table 2. Parallel Solution-Phase Synthesis of Benzamides **9d**−**o**

compound	R_1	R_2	melting point, mp (°C)	yield (%)
9d	H	H	138−139	79
9e	CH_3	H	128−129	84
9f	CH_3	CH_3	138.5−140	90
9g	H	H	187.5−189	63
9h	CH_3	H	152−154	71
9i	CH_3	CH_3	163−165	69
9j	H	H	120−121	80
9k	CH_3	H	160−161	82
9l	CH_3	CH_3	119−121	81
9m	H	H	171−172	85
9n	CH_3	H	128−129	84
9o	CH_3	CH_3	149−150	85

9e, **9h**, **9k**, and **9n** are also chiral; however, their enantiomeric purity was not determined.

Upon establishing the novel protocol with the unsubstituted *N*-benzoyl vinylogous amides **9a**−**c**, we extended this methodology to the solution-phase parallel synthesis of a diverse 12-member library of benzamide derivatives **9d**−**o** (Table 2), using a Radley's Carousel Reaction Station. The library contained three different cyclic enaminones **6a**−**c**, which were *N*-deprotonated with NaH, and then reacted, in sequence, with four different substituted aroyl chlorides (**7b**−**e**). The acid chlorides were in slight excess (1.05 equiv) to ensure the complete conversion of the enaminones to the corresponding benzamide derivatives. After the reaction was complete (10 min), the mixture was quenched with water. As noted in Table 2, the yields were in the range of 63−90%, with the yields of the dimethoxy catechol ethers (**9g**−**i**) being the lowest of the series.

The amido and enaminone C═O stretching frequencies of all of the benzamides, as well as the N−H stretching frequency of each compound, were identified in the infrared (IR) spectra (see Experimental Section). The presence of the amido proton at 8.10−9.81 ppm in the ^{1}H NMR spectra of the products confirmed the fact that the reaction occurred as predicted. The presence of the catechol ether moieties was also confirmed from the ^{1}H NMR studies.

In conclusion, we have shown a rapid, versatile method for the preparation of vinylic benzamides that is readily adaptable to combinatorial synthesis. This method also provides higher yields than those previously reported for this type of compound. The results of biological evaluations will be published shortly.

Experimental Section

Melting points (denoted as mp) were determined on a Thomas-Hoover capillary melting point apparatus. The IR spectra were obtained on a Nicolet Magna-IR 560 spectrometer. The samples were recorded as KBr pellets. The ^{1}H and ^{13}C NMR spectra were determined either on a Bruker 1 Ultra Shield-400 MHz NMR spectrometer or a General Electric model QE 300 MHz NMR spectrometer. The samples were dissolved either in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) that contained 0.03% tetramethylsilane (TMS) as an internal reference. Elemental analyses (C, H, N, and Cl) were determined by Schwarzkopf Microanalytical Laboratory, in Woodside, NY. The analytical results for the elements were within ±0.4% of the theoretical values. 3-Aminocyclohex-2-enone (**6a**),[28] 3-amino-5-methylcyclohex-2-enone (**6b**),[9] and 3-amino-5,5-dimethylcyclohex-2-enone (**6c**)[28,29] were prepared using literature methods. All reagents were obtained from Aldrich Chemical Co., in Milwaukee, WI. Compounds **7d** and **7e** were prepared using literature methods.[30]

General Synthetic Procedure. Using a Radley's Carousel Reaction Station with 12 reaction bottles (24 mm × 150 mm), the appropriate enaminone from **6a**−**c** (0.75 g) in anhydrous THF (35 mL) was added to each reaction bottle, under a nitrogen atmosphere. Each reaction tube was then cautiously treated with NaH (2.4 equiv, 60% dispersion in oil, previously washed with petroleum ether) while being stirred vigorously. THF (<6 mL) was used to rinse the residual NaH into each reaction vessel. The reaction tubes were capped and stirred at 55−60 °C for 25 min. After cooling to room temperature, the appropriate benzoyl chloride from **7b**−**e** (1.05 equiv) in dry THF (10 mL) was carefully added to each tube. Each reaction vessel was capped and stirred for an additional 10 min, after which point 10 mL of water was added to each reaction tube to quench the reaction. The mixtures of the individual reaction tubes were transferred to 250-mL Erlenmeyer flasks, neutralized with concentrated HCl (∼5 mL), and transferred to a 250-mL separatory funnel that contained dichloromethane (25 mL). After separation, the organic phase was washed successively with water (25 mL), 10% $NaHCO_3$ (25 mL), and again with water (25 mL). The organic phase was subsequently dried over anhydrous sodium sulfate and evaporated in vacuo, and the resulting residue was triturated twice with anhydrous ether (25 mL). The residue obtained was recrystallized from ethyl acetate or a methanol/ethyl acetate mixture to obtain the benzamide derivatives **9d**−**9o**.

3-Chloro-*N*-(3-oxocyclohex-1-enyl)benzamide (9d). Yield: 79%, pale yellow crystals from ethyl acetate (EtOAc), mp = 138−139 °C. ν_{max}: 3339.41, 1685.35, 1618.78 cm^{-1}. δ ^{1}H ($CDCl_3$): 2.10 (2H, quint, J = 6.54 Hz, CH_2); 2.41 (2H, t, J = 6.78 Hz, CH_2); 2.74 (2H, t, J = 5.73 Hz, CH_2); 6.72 (1H, s, ═CH); 7.28−7.81 (4H, m, aromatic ring); 8.10 (1H, s, NH). ^{13}C ($CDCl_3$): δ 21.7; 28.6; 36.7; 112.8; 125.6; 127.7; 130.2; 135.0; 134.4; 135.6; 156.17; 165.1; 200.3. Anal.

Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53%; H, 4.84%; Cl, 14.20%; N, 5.61%. Found: C, 62.52%; H, 4.67%; Cl, 14.27%; N, 5.59%.

3-Chloro-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (9e). Yield: 84%, white solid from EtOAc/MeOH, mp = 168−169 °C. ν_{max}: 3350.34, 1688.51, 1617.51 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.13 (3H, d, J = 6.52 Hz, CH_3); 2.07−2.79 (5H, cyclohexene ring); 6.71 (1H, s, =CH); 7.28−7.34 (4H, m, aromatic ring); 8.18 (1H, s, NH). ^{13}C (DMSO-d_6): δ 21.0; 29.3; 36.8; 44.9; 112.4; 125.6; 127.7; 130.2; 132.6; 135.1; 135.6; 155.4; 165.0; 168.6; 200.3. Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76%; H, 5.35%; Cl, 13.44%; N, 5.31%. Found: C, 63.74%; H, 5.25%; Cl, 13.55%; N, 5.30%.

3-Chloro-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (9f). Yield: 90%, white solid from EtOAc, mp = 138.5−140 °C. ν_{max}: 3288.19, 1690.47, 1639.26, 1618.78 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.08 (6H, s, gem 2 × CH_3); 2.19 (2H, s, CH_2); 2.56 (2H, s, CH_2); 6.82 (1H, s, =CH); 7.35−7.80 (4H, m, aromatic ring); 8.88 (1H, s, NH). ^{13}C (DMSO-d_6): δ 28.2 (gem CH_3); 32.9; 42.3; 50.5; 111.5; 125.8; 127.9; 130.0; 132.4; 134.8; 135.6; 154.7; 165.6; 200.8. Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.87%; H, 5.81%; Cl, 12.76%; N, 5.04%. Found: C, 64.82%; H, 5.60%; Cl, 12.70%; N, 4.87%.

3,4-Dimethoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (9g). Yield: 63%, yellow solid from EtOAc/MeOH, mp = 187.5−189 °C. ν_{max}: 3267.71, 1680.23, 1634.40 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.94 (2H, quint, J = 7.21 Hz, CH_2); 2.26 (2H, t, J = 6.87 Hz, CH_2); 2.63 (2H, t, J = 5.62 Hz, CH_2); 3.83 (6H, s, 2 × OCH_3); 6.76 (1H, s, =CH); 7.07 (1H, d, J = 8.52 Hz, aromatic H); 7.44 (1H, d, J = 2.08 Hz, aromatic H); 7.56 (1H, dd, J = 6.35 Hz, aromatic H); 9.32 (1H, s, NH). ^{13}C (DMSO-d_6): δ 21.8; 28.2; 37.0; 56.1 (gem CH_3); 111.3; 111.5; 111.6; 122.1; 126.5; 148.8; 152.7; 166.5; 166.6; 199.2. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44%; H, 6.22%; N, 5.09%. Found: C, 65.15%; H, 6.05%; N, 4.99%.

3,4-Dimethoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)-benzamide (9h). Yield: 84%, white solid from EtOAc/MeOH, mp = 168.5−169 °C. ν_{max}: 3283.07, 1680.23, 1623.90 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.03 (3H, d, J = 6.23 Hz, CH_3); 2.03−2.73 (5H, m, cyclohexene ring); 3.84 (6H, s, 2 × OCH_3); 6.76 (1H, s, =CH); 7.07 (1H, d, J = 8.44 Hz, aromatic H); 7.45 (1H, s, aromatic H); 7.57 (1H, d, J = 8.38 Hz, aromatic H); 9.32 (1H, s, NH). ^{13}C (DMSO-d_6): δ 21.2; 29.2; 36.3; 45.1; 56.1; 56.2; 111.2; 111.3; 112.1; 122.1; 148.8; 152.7; 156.9; 166.5; 167.3; 199.3. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42%; H, 6.62%; N, 4.84%. Found: C, 66.43%; H, 6.68%; N, 4.66%.

3,4-Dimethoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)-benzamide (9i). Yield: 83%, light-yellow solid from EtOAc/MeOH, mp = 163−165 °C. ν_{max}: 3359.89, 1690.47, 1613.66, 1608.31 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.04 (6H, s, gem CH_3); 2.16 (2H, s, CH_2); 2.57 (2H, s, CH_2); 3.84 (6H, s, 2 × OCH_3); 6.79 (1H, s, =CH); 7.08 (1H, d, J = 8.44 Hz, aromatic H); 7.46 (1H, s, aromatic H); 7.58 (1H, d, J = 8.34 Hz, aromatic H); 9.77 (1H, s, NH). ^{13}C (DMSO-d_6): δ 28.3; 32.8; 41.8; 50.6; 56.1; 56.2; 110.4; 111.3; 111.6; 122.2; 126.4; 148.8; 152.7; 155.4; 166.6; 167.3; 199.2. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31%; H, 6.98%; N, 4.62%. Found: C, 67.05%; H, 6.84%; N, 4.63%.

3-*n*-Butoxy-4-methoxy-*N*-(3-oxocyclohex-1-enyl)benzamide (9j). Yield: 80%, pale-white solid from EtOAc, mp = 120−121 °C. ν_{max}: 3283.07, 1675.11, 1623.90 cm^{-1}. δ ^{1}H (DMSO-d_6): 0.94 (3H, t, J = 7.44 Hz, CH_3); 1.45 (2H, quint, J = 7.35 Hz, CH_2); 1.72 (2H, t, J = 6.87 Hz, CH_2); 1.92 (2H, t, J = 5.98 Hz, CH_2); 2.25 (2H, t, J = 6.09 Hz, CH_2); 2.33 (2H, t, J = 5.54 Hz, CH_2); 3.84 (3H, s, OCH_3); 4.02 (2H, t, J = 6.44 Hz, OCH_2); 6.75 (1H, s, =CH); 7.07 (1H, d, J = 8.43 Hz, aromatic H); 7.43 (1H, s, aromatic H); 7.55 (1H, d, J = 8.95 Hz, aromatic H); 9.82 (1H, s, NH). ^{13}C (DMSO-d_6): δ 14.2; 19.2; 21.8; 28.2; 31.3; 37.0; 56.2; 68.5; 111.4; 111.6; 112.8; 122.1; 126.6; 148.2; 152.9; 157.7; 166.6; 199.3. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12%; H, 7.30%; N, 4.41%. Found: C, 67.85%; H, 7.32%; N, 4.35%.

3-*n*-Butoxy-4-methoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (9k). Yield: 82%, white solid from EtOAc/MeOH, mp = 160−161 °C. ν_{max}: 3316.93, 1675.11, 1629.02, 1603.41 cm^{-1}. δ ^{1}H (DMSO-d_6): 0.94 (3H, t, J = 7.34 Hz, CH_3); 1.03 (3H, d, J = 6.18 Hz, CH_3); 1.43−1.56 (2H, quint, J = 6.95 Hz, CH_2); 1.69−1.76 (2H, m, CH_2); 2.01−2.72 (5H, m, cyclohexene ring); 3.84 (3H, s, OCH_3); 4.02 (2H, t, J = 6.36 Hz, OCH_2); 6.75 (1H, s, =CH); 7.07 (1H, d, J = 8.45 Hz, aromatic H); 7.43 (1H, s, aromatic H); 7.55 (1H, d, J = 8.42 Hz, aromatic H); 9.73 (1H, s, NH). ^{13}C (DMSO-d_6): δ 14.2; 19.2; 21.2; 29.2; 31.3; 36.3; 45.1; 56.2; 68.4; 111.2; 111.5; 112.7; 122.1; 126.5; 148.2; 152.9; 156.9; 166.6; 199.4. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86%; H, 7.60%; N, 4.23%. Found: C, 68.88%; H, 7.60%; N, 4.03%.

3-*n*-Butoxy-4-methoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (9l). Yield: 81%, light-tan solid from EtOAc/MeOH, mp = 119−121°C. ν_{max}: 3334.28, 1685.35, 1603.41, 1598.29 cm^{-1}. δ ^{1}H (DMSO-d_6): 0.94 (3H, t, J = 7.34 Hz, CH_3); 1.03 (6H, s, 2 × CH_3); 1.40−1.50 (2H, m, CH_2); 1.67−1.76 (2H, quint, J = 7.56 Hz, CH_2); 2.15 (2H, s, CH_2); 2.56 (2H, s, CH_2); 3.84 (3H, s, OCH_3); 4.02 (2H, t, J = 6.36 Hz, OCH_2); 6.76 (1H, s, =CH); 7.06 (1H, d, J = 8.50 Hz, aromatic H); 7.45 (1H, s, aromatic H); 7.55 (1H, d, J = 8.35 Hz, aromatic H); 9.75 (1H, s, NH). ^{13}C (DMSO-d_6): δ 14.2; 19.2; 28.3 (gem CH_3); 31.3; 32.8; 41.8; 50.6; 53.1; 56.2; 68.5; 110.4; 111.4; 112.2; 126.4; 148.2; 152.9; 155.5; 166.6; 199.2. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54%; H, 7.88%; N, 4.05%. Found: C, 69.61%; H, 7.97%; N, 4.05%.

3-Cyclopentyloxy-4-methoxy-*N*-(3-oxocyclohex-1-enyl)-benzamide (9m). Yield: 81%, pale-white solid from EtOAc, mp = 171−172 °C. ν_{max}: 3271.00, 1675.98, 1621.70 cm^{-1}. δ ^{1}H (DMSO-d_6): 1.58−1.93 (10H, m, cyclopentyl H and CH_2); 2.22−2.38 (2H, m, CH_3); 2.63−2.69 (2H, m, CH_2); 3.35 (3H, s, OCH_3); 4.87 (1H, m, OCH); 6.50 (1H, s, =CH); 7.08 (1H, d, J = 8.63 Hz, aromatic H); 7.40 (1H, s, aromatic H); 7.53 (1H, d, J = 8.41 Hz, aromatic H); 9.81 (1H, s, NH). ^{13}C (DMSO-d_6): δ 21.8; 24.0 (2 × CH_2); 28.2 (gem CH_3); 37.0 (2 × CH_2); 56.2; 80.3; 111.6; 111.7; 114.7; 122.1; 126.6; 147.0; 153.6; 157.7; 166.6; 199.2. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28%; H, 7.04%; N, 4.25%. Found: C, 69.39%; H, 7.02%; N, 4.21%.

3-Cyclopentyloxy-4-methoxy-*N*-(5-methyl-3-oxocyclohex-1-enyl)benzamide (9n). Yield: 84%, pale-yellow solid

from EtOAc, mp = 128−129 °C. ν_{max}: 3310.18, 1678.17, 1613.17, 1603.41 cm^{-1}. δ ^1H (DMSO-d_6): 1.03 (3H, d, J = 6.10 Hz, CH_3); 1.58−1.89 (8H, m, cyclopentyl); 2.25−2.86 (5H, m, cyclohexene); 3.83 (3H, s, OCH_3); 4.88 (1H, m, OCH−); 6.75 (1H, s, =CH); 7.06 (1H, d, J = 8.47 Hz, aromatic H); 7.42 (1H, s, aromatic H); 7.55 (1H, d, J = 8.42 Hz, aromatic H); 9.85 (1H, s, NH). ^{13}C (DMSO-d_6): δ 21.2; 24.1 (2 × CH_2); 29.2; 32.7; 36.3 (2 × CH_2); 45.1; 56.2; 80.3; 111.2; 111.7; 114.6; 122.1; 126.5; 147.0; 153.6; 157.0; 166.6; 199.3. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95%; H, 7.34%; N, 4.08%. Found: C, 69.78%; H, 7.18%; N, 4.00%.

3-Cyclopentyloxy-4-methoxy-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)benzamide (9o). Yield: 85%, pale-yellow solid from EtOAc, mp = 149−150 °C. ν_{max}: 3359.89, 1685.35, 1608.31, 1598.29 cm^{-1}. δ ^1H (DMSO-d_6): 1.03 (6H, s, 2 × CH_3); 1.59−1.90 (8H, m, cyclopentyl); 2.15 (2H, s, CH_2); 2.56 (2H, s, CH_2); 3.83 (3H, s, OCH_3); 4.87 (1H, m, OCH−); 6.76 (1H, s, =CH); 7.07 (1H, d, J = 8.47 Hz, aromatic H); 7.42 (1H, s, aromatic H); 7.55 (1H, d, J = 7.91 Hz, aromatic H); 9.85 (1H, s, NH). ^{13}C (DMSO-d_6): δ 24.1 (2 × CH_2); 28.3 (gem CH_3); 32.7 (2 × CH_2); 42.8; 50.6; 56.2; 80.3; 104.0; 110.4; 111.7; 114.6; 122.1; 126.5; 147.0; 153.6; 155.6; 166.6; 199.2. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56%; H, 7.61%; N, 3.92%. Found: C, 70.35%; H, 7.64%; N, 3.93%.

Acknowledgment. This was taken, in part, from the dissertation of A.J.A. submitted in partial fulfillment of the Ph.D. Degree at Howard University, 2003. This research was supported by the following grants from the National Institutes of Health: No. 1 R21 GM634940-02 (for which K.R.S. is the principal investigator) and No. 2 G12 RR003048 (from the RCMI Program, Division of Research Infrastructure, National Center for Research Resources).

References and Notes

(1) Edafiogho, I. O.; Hinko, C. N.; Chang, H.; Moore, J. A.; Mulzac, D.; Nicholson, J. M.; Scott, K. R. *J. Med. Chem.* **1992**, *35*, 2798−2805.
(2) Mulzac, D.; Scott, K. R. *Epilepsia* **1993**, *34*, 1141−1146.
(3) Nicholson, J. M.; Edafiogho, I. O.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 76−78.
(4) Edafiogho, I. O.; Moore, J. A.; Farrar, V. A.; Nicholson, J. M.; Scott, K. R. J. *Pharm. Sci.* **1994**, *83*, 79−84.
(5) Edafiogho, I. O.; Moore, J. A.; Alexander, M. S.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 1155−1170.
(6) Scott, K. R.; Edafiogho, I. O.; Richardson, E. L.; Farrar, V. A.; Moore, J. A.; Tietz, E. I.; Hinko, C. N.; Chang, E.; El-Assadi, A.; Nicholson, J. M. *J. Med. Chem.* **1993**, *36*, 1947−1955.
(7) Scott, K. R.; Rankin, G. O.; Stables, J. P.; Alexander, M. S.; Edafiogho, I. O.; Farrar, V. A.; Kolen, K. R.; Moore, J. A.; Sims, L. D.; Tonnu, A. D.; Scott, K. R. *J. Med. Chem.* **1995**, *38*, 4033−4043.
(8) Laws, M. L.; Roberts, R. R.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Goodwin, A. M.; Smith, C.; Scott, K. R. *Bioorg. Med. Chem*. **1998**, *6*, 2289−2299.
(9) Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415−2425.
(10) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417−436.
(11) Cox, D. S.; Du, J.; Scott, K. R.; Gao, H.; Eddington, N. D. *J. Chromatogr. B* **2000**, *749*, 191−196.
(12) Cox, D. S.; Scott, K. R.; Gao, H.; Raje, S.; Eddington, N. D. *J. Pharm. Sci.* **2001**, *90*, 1540−1552.
(13) Cox, D. S.; Gao, H.; Raje, S.; Scott, K. R.; Eddington, N. D. *Eur. J. Pharm. Biopharm*. **2001**, *52*, 145−150.
(14) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. *Eur. J. Med. Chem.* **2002**, *37*, 635−648.
(15) Cox, D. S.; Scott, K. R.; Gao, H.; Eddington, N. D. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1096−1104.
(16) Eddington, N. D.; Cox, D. S.; Khurana, M.; Salama, N. N.; Stables, J. P.; Harrison, S. J.; Negussie, A.; Taylor, R. S.; Tran, U. Q.; Moore, J. A.; Barrow, J. C.; Scott, K. R. *Eur. J. Med. Chem.* **2003**, *38*, 49−64.
(17) Khurana, K.; Salama, N. N.; Scott, K. R.; Nemieboka, N. N.; Bauer, K.; Eddington, N. D. *Biopharm. Drug Dispos*. **2003**, *24*, 397−407.
(18) Carson, J. R.; Carmosin, R. J.; Pitis, P. M.; Vaught, J. L.; Almond, H. R.; Stables, J. P.; Wolf, H. H.; Swinyard, E. A.; White, H. S. *J. Med. Chem* **1997**, *40*, 1578−1584.
(19) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977; pp 284−289.
(20) Cook, A. G. *Enaminones: Synthesis and Reactions*, 2nd Edition; Marcel Dekker: New York, 1988; pp 284−289.
(21) Seelig, A.; Li Blatter, X.; Wohnsland, F. *Int. J. Clin. Pharmacol. Ther*. **2000**, *38*, 111−121.
(22) Salama, N. N.; Eddington, N. D.; Payne, D.; Wilson, T. L.; Scott, K. R. *Curr. Med. Chem.* **2004**, *11*, 763−771.
(23) Salama, N. N.; Scott, K. R.; Eddington, N. D. *Int. J. Pharm.* **2004**, *273*, 135−147.
(24) Zymalkowski, F.; Rimek, H. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1961**, *294*, 759−764.
(25) Ostercamp, D. L. *J. Org. Chem.* **1970**, *35*, 1633−1641.
(26) Ninomiya, I.; Naito, T.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, *20*, 2257−2261.
(27) Friary, R. J.; Gilligan, J. M.; Szajewski, R. P.; Falci, K. J.; Franck, R. W. *J. Org. Chem.* **1973**, *38*, 3487−3491.
(28) Benary, E. *J. Am. Chem. Soc.* **1927**, *60*, 1826−1836.
(29) Baraldi, P.; Manfredini, S.; Simoni, D. *Synthesis* **1983**, 902−903.
(30) Ashton, M.; Cook, D.; Fenton, G.; Karlsson, J.; Palfreyman, M.; Taeburn, D.; Ratcliffe, A.; Souness, J.; Thurairatnam, S.; Vicker, N. *J. Med. Chem.* **1994**, *37*, 1696−1703.

CC0498837