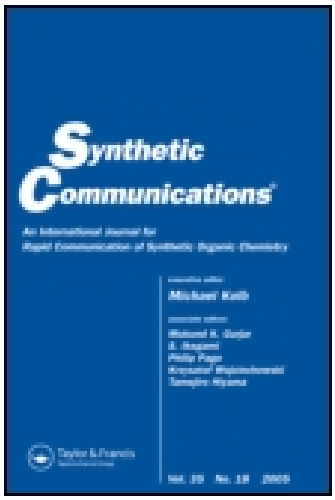


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Syntheses of 4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2 Z -enoic Acid Arylamides as Candidate Cytotoxic Agents

Amitabh Jha [a b] & Jonathan R. Dimmock [a]

[a] College of Pharmacy and Nutrition , University of Saskatchewan , Saskatoon, Canada

[b] ALviva Biopharmaceuticals Inc. , Saskatoon, S7N, Canada

Published online: 21 Aug 2006.

To cite this article: Amitabh Jha & Jonathan R. Dimmock (2003) Syntheses of 4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2 Z -enoic Acid Arylamides as Candidate Cytotoxic Agents, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:7, 1211-1223, DOI: 10.1081/SCC-120017198

To link to this article: http://dx.doi.org/10.1081/SCC-120017198

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 7, pp. 1211–1223, 2003

Syntheses of 4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic Acid Arylamides as Candidate Cytotoxic Agents

Amitabh Jha[#] and Jonathan R. Dimmock*

College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada

ABSTRACT

The title compounds were designed and synthesized as candidate cytotoxic agents. They were synthesized by reacting 3,5-bisphenylmethylene-piperidin-4-one with the appropriate 3-arylcarbamoylacrylic acids. These reactions follow an unusual mechanism and deviate from the previously reported reactions on similar substrates.

*Current address: ALviva Biopharmaceuticals Inc., Saskatoon, S7N, Canada.
[†]Correspondence: Jonathan R. Dimmock, College of Pharmacy and Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon, SK S7N 5C9, Canada; E-mail: dimmock@skyway.usask.ca.

DOI: 10.1081/SCC-120017198 0039-7911 (Print); 1532-2432 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Key Words: Arylmaleamic acids; *N*-Acyl-3,5-bisphenylmethylene-4-piperidones; Stereochemistry; Molecular modeling.

A number of 3,5-bisarylidene-piperidin-4-ones including 3,5-bisphenylmethylene-piperidin-4-one (**1**) possess significant cytotoxic properties.[1–3] Conversion of some of these molecules into the corresponding *N*-acryloyl analogs in general led to significant increases in cytotoxicity[4] which was considered to be due, inter alia, to the presence of an additional site for electrophilic attack with cellular constituents.[3–8] In the present investigation, replacement of one of the methylene protons of the *N*-acryloyl group by an arylcarbamoyl substituent was planned for the following reasons. First, the arylcarbamoyl group will increase the electrophilicity of the double bond; for example, the Taft σ^* value of the phenylcarbamoyl group is 1.56.[9] Second, an aryl group was incorporated into the design of the *N*-acyl function in order that the polarity of the olefinic double bond would vary being dependent on the electronic nature of the aryl substituents. A correlation between cytotoxicity and the Hammett σ values of the aryl substituents may emerge which would guide amplification of the series. The aryl ring was positioned so that

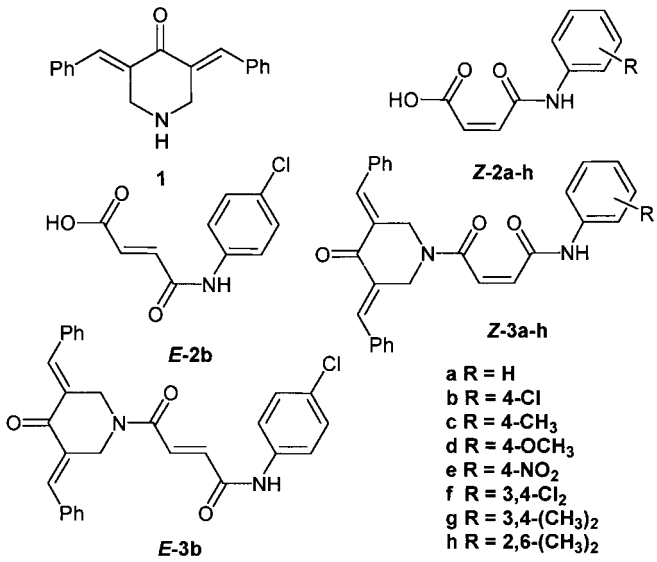


Figure 1. Structures of compounds **1**–**3**.

steric impedance to attack by cellular nucleophiles would be unlikely to occur.

We wish to report herein the unusual chemistry involved in the syntheses of these compounds and to offer the most plausible justification for the deviation from the expected route which is supported by calculations and experiments.

Eight arylmaleamic acids (***Z*-2a–h**) were synthesized by a literature procedure.[10] The structures are portrayed in Figure 1 and the physical data are summarized in Table 1.

Initially, the conventional condensation conditions of acyl halide with amine were considered for the condensation of 3,5-diphenylmethylene-piperidin-4-one (**1**) with the acid chlorides of the aryl maleamic acids (***Z*-2a–h**). Various attempts to prepare the acid chlorides were undertaken including the use of thionyl chloride, oxalyl chloride and phosphorus pentachloride. However the desired compounds were not obtained which was probably due to decomposition of one of the starting materials (acids), a phenomenon noted earlier from our laboratory.[11] The high electrophilicity of the maleamic acid double bond[12] is perhaps responsible for the decomposition of the aryl maleamic acids under these conditions.

Subsequently we discovered a literature report[12] for the synthesis of compounds similar to our desired products via reactions that involved the use of ethyl chloroformate under cold, inert and aprotic conditions. The reported mechanism involved the formation of an active isoimide **B** rather than a mixed anhydride from arylmaleamic acids **A** (Sch. 1). Some of these isoimides have been isolated and characterized.[16] These isoimides react like mixed anhydrides with primary or secondary amines to yield the amides **C**.[12,16,17]

The geometry of the added double bond of the product isolated was found to be temperature dependent.[12] Reactions carried out at -60°C resulted in products with mainly the *Z* configuration of the *N*-acyl group double bond while those carried out at -12°C resulted in products with exclusively the *E* configuration of the same double bond. Isomerization of ***Z*-C** noted at -12°C was attributed to a Michael-type addition of the excess of amine to the double bond.[12] Subsequent elimination of the amine led to the formation of thermodynamically more stable products ***E*-C** (Sch. 2).

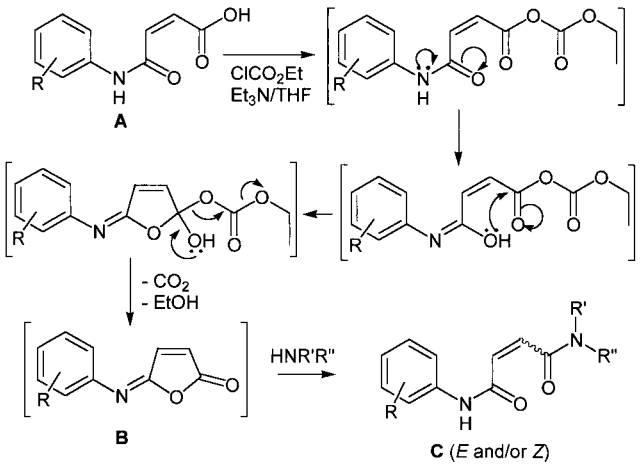
In the present investigation, a modification of the method was employed in which the temperatures used were between 0°C and room temperature (see Experimental). Condensation between the aryl maleamic acids ***Z*-2a–h** and **1** took place leading to ***Z*-3a–h**. Unlike the earlier report,[12] we consistently isolated the products with the *Z* configuration

Table 1. Physical data for compounds ***Z*-2a–h**. All of these compounds have been described previously.[13–15]

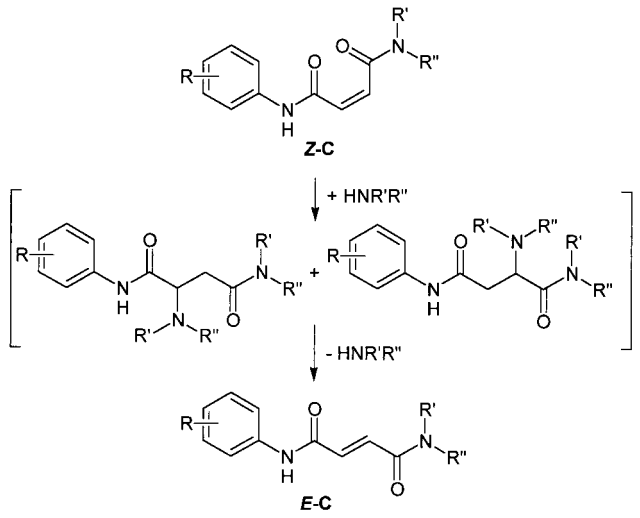
Compound	Molecular formula	Yield (%)	M.p. (°C)	Lit. M.p. (°C)	Elemental analysis					
					Calculated			Found		
					C	H	N	C	H	N
***Z*-2a**	$C_{10}H_9NO_3$	93	208–210	206–208[13]	62.82	4.74	7.33	62.52	4.82	7.25
***Z*-2b**	$C_{10}H_8ClNO_3$	94	196–197	196–198[13]	53.23	3.57	6.21	53.08	3.55	6.19
***Z*-2c**	$C_{11}H_{11}NO_3$	97	197–199	192–193[13]	64.38	5.40	6.83	64.18	5.25	6.77
***Z*-2d**	$C_{11}H_{11}NO_4$	98	187	184–188[14]	59.73	5.01	6.33	59.60	4.87	6.28
***Z*-2e**	$C_{10}H_8N_2O_5$	99	194–196	190–193[13]	50.85	3.41	11.86	50.68	3.24	11.75
***Z*-2f**	$C_{10}H_7Cl_2NO_3$	97	211–214	210–213[14]	46.18	2.17	5.39	45.97	2.51	5.39
***Z*-2g**	$C_{12}H_{13}NO_3$	94	173	NR[15]	65.74	5.98	6.39	65.57	5.84	6.31
***Z*-2h**	$C_{12}H_{13}N_2O_3$	76	170	166–168[14]	65.74	5.98	6.39	65.65	6.02	6.39

NR = Not reported.

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016



Scheme 1.



Scheme 2.

of the double bond of the *N*-acyl group under the reaction conditions used. The ^{1}H NMR spectra revealed coupling constants of the olefinic protons to be 11.7 Hz, which is characteristic of the *Z* geometry.[18] To ascertain the geometry unequivocally we decided to synthesize one

geometrical isomer with the *E* configuration and examine its physical and spectral properties.

Encouraged with the literature report[12] of reversible addition/elimination of dimethylamine across the double bond leading to the *E* geometry at −12°C or higher temperatures, we thought that it should be easy to isomerize compounds ***Z*-3a–h** to the *E* isomers by treating them with dimethylamine in a suitable solvent. Also, we performed energy minimization studies using CS Chem3D Pro® software[19] on the *E* and *Z* forms of compounds **3a–h** and as expected we found that the *E* isomers are consistently more stable than the *Z* forms by 1.38–7.11 kCal/mol (Table 2). So the isomerization reaction should, in principle, be favored.

All attempts of isomerizing compounds ***Z*-3a–h** to the *E* geometry by treating them with dimethylamine at temperatures between 0 and 50°C in chloroform failed to give the desired product. Instead a mixture of products were formed with very similar tlc behavior ($CHCl_3$:MeOH; 19:1). The ^{1}H NMR of the crude products indicated the presence of a complex mixture of dimethylamine adducts. No attempts were made to purify them. In fact, an irreversible addition of dimethylamine can indeed lead to a very complex mixture, as there are at least three sites of addition in every molecule subjected to the isomerization reactions.

We then chose to synthesize compound ***E*-3b** by reacting 4-chlorophenyl-fumaramic acid (***E*-2b**) with **1**. ***E*-2b** was synthesized by a literature procedure[20] and was condensed with **1** using the same procedure that was used for the synthesis of compounds ***Z*-3a–h** (*c,f*. Experimental). The coupling constant of the olefinic protons of ***E*-3b** was found to be 15.0 Hz, which is distinctly characteristic of the *E* geometry. This proved that the

Table 2. Minimized energy of compounds **3a–h** with the *E* and *Z* stereochemistry.

	E	*Z*	ΔE_{min}
Compound	$E_{min(E)}$	$E_{min(Z)}$	$E_{min(Z)} - E_{min(E)}$
3a	40.81	44.47	3.66
3b	33.74	37.51	3.77
3c	33.17	36.82	3.65
3d	3.35	6.99	3.64
3e	43.62	50.73	7.11
3f	28.67	32.21	3.54
3g	27.06	30.46	3.40
3h	29.23	30.61	1.38

compounds resulting from the reaction of ***Z*-2a–h** with **1** have the *Z* configuration.

The question arises as to why isomerization occurs when the reacting amine is dimethylamine[12] but not when it is **1**. It is likely that a low molecular weight amine (dimethylamine) may react with the olefinic double bond as indicated in Sch. 2. On the other hand, the size of the secondary amine **1** may be excessive for reaction with the olefinic group present in the *N*-acyl function of ***Z*-3a–h**. In addition, compound **1** is a 3-aminoketone and the pKa values of various 3-aminoketones are in the region of 7.0–7.3 approximately[21,22] in contrast to dimethylamine for example, which possesses a pKa of 10.73.[23] Hence the nucleophilicity of **1** will be substantially lower than the smaller amines employed in the previously reported study.[12]

CONCLUSION

Though the reaction between an isoimide (formed in situ by the reaction between an aryl maleamic acid and ethyl chloroformate and triethylamine in THF) and secondary amine leads to the formation of amides, the geometry of the maleamic acid amide double bond likely depends on the steric bulk and basicity of the amine. Greater bulk and/or weak basicity leads to the kinetically controlled reaction giving rise to the relatively less stable *Z* geometry. The *E* geometry on the double bond of the *N*-acyl group of title compounds can be conveniently obtained from aryl fumaramic acids. The cytotoxicity of many of these compounds described in this study will be reported subsequently.

EXPERIMENTAL

General

All the chemicals used in the synthetic methods were purchased from the Aldrich Chemical Company. Compound **1** was made by a literature procedure.[1] Melting points were recorded on an electrothermal apparatus and are uncorrected. Precoated fluorescent silica gel tlc plates purchased from EM Science were used to monitor the progress of reactions. ^{1}H NMR spectra were recorded on an AC Bruker 500 MHz NMR spectrometer. Elemental analyses were undertaken by Mr. Ken Thoms, Department of Chemistry, University of Saskatchewan.

General Procedure for the Syntheses of the Aryl Maleamic Acids (*Z*-2a–h)

Maleic anhydride (0.02 mole) and the appropriate aryl amine (0.02 mole) were dissolved in chloroform (100 mL) and stirred for 7 h under anhydrous conditions. The resultant precipitate was removed by filtration, washed with chloroform and dried. The aryl maleamic acids were obtained as powders in high yields (76–99%) and were quite pure as evident by their melting points and elemental analysis data. The percentage yield, melting points, literature melting points (whenever known), and elemental analysis data are reported in Table 1.

Synthesis of 3-(4-chlorophenylcarbamoyl)-*E*-acrylic acid (E-2b). Thionyl chloride (150 mmol) was added dropwise to suspension of fumaric acid (60 mmol) in dry chloroform (50 mL) followed by the addition of DMF (4 drops) as a catalyst. The solution was heated under reflux at 90°C for 16 h. The excess of $SOCl_2$ and chloroform were removed in vacuo. The residue was dissolved in chloroform (100 mL) and a solution of 4-chloroaniline (30 mmol) in chloroform (50 mL) was added dropwise over 5 min and the mixture was stirred for 10 min at room temperature. The mixture was then extracted with 1N aqueous NaOH. The NaOH soluble aqueous fraction was acidified with concentrated HCl to pH ~ 1. The precipitate was collected at suction and was boiled in water for 20 min. The insoluble solid was filtered quickly when hot to yield the product as light yellow solid.

3-(4-Chlorophenylcarbamoyl)-*E*-acrylic acid (E-2b). Light yellow solid (16%), rf 0.22 (7:3 $CHCl_3$:CH_3OH); M.p. 268–269°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 6.65 & 7.11 (1H each, d, $J = 15.4$ Hz; *E*-vinylic-H), 7.38 & 7.69 (2H each, d, $J = 8.9$ Hz, Ar-H), 10.61 (1H, s, NHCO) and 13.00 (1H, bs, COOH).

General Procedure for the Synthesis of 4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2-enoic Acid Arylamides (*Z*-3a–h) and *E*-3b

The appropriate arylcarbamoyl acrylic acid (0.003 mole) and triethylamine (0.003 mole) were dissolved in dry tetrahydrofuran (60 mL) and cooled to 0°C using an ice bath. Under anhydrous conditions, ethyl chloroformate (0.003 mole) in dry tetrahydrofuran (40 mL) was added dropwise over a 10 min period. The mixture was stirred for 12 h at room temperature, cooled to 0°C and 3,5-bisphenylmethylene-piperidin-4-one hydrochloride (0.003 mole) was added. Subsequently

triethylamine (0.003 mole) in dry tetrahydrofuran (40 mL) was added dropwise over 10 min. The reaction was then stirred for 16 h during which time the temperature slowly rose to room temperature. The solvents were then evaporated under vacuum. Water (30 mL) was added to the residue and the product was triturated and filtered. The solid product thus obtained was digested in methanol (30 mL) to remove unwanted side products and unreacted starting materials. It was then filtered, washed with cold methanol (30 mL) and dried.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid phenylamide (*Z*-3a). Yellow solid (36%), rf 0.70 (19:1 $CHCl_3$:CH_3OH); M.p. 197°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 4.75 & 4.91 (2H each, bs, $2 \times N$-CH_a, $2 \times N$-CH_b), 6.03 & 6.42 (1H each, d, $J = 11.7$ Hz, $2 \times Z$-vinylic-H), 7.05–7.11 (1H, m), 7.24–7.46 (7H, m), 7.49–7.59 (8H, m), 7.76 (1H, s) and 10.05 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{29}H_{24}N_2O_3$: C 77.66, H 5.39, N 6.25, Found: C 77.57, H 5.44, N 6.27.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (4-chlorophenyl)amide (*Z*-3b). Yellow solid (57%), rf 0.64 (19:1 $CHCl_3$:CH_3OH); M.p. 208–209°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 4.75 & 4.91 (2H each, bs, $2 \times N$-CH_a, $2 \times N$-CH_b), 6.00 & 6.45 (1H each, d, $J = 11.7$ Hz, $2 \times Z$-vinylic-H), 7.26–7.27 (2H, m), 7.36–7.39 (5H, m), 7.45–7.61 (8H, m), 7.75 (1H, s) and 10.17 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{29}H_{23}ClN_2O_3$: C 72.12, H 4.80, N 5.80, Found: C 71.99, H 4.59, N 6.03.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (4-methylphenyl)amide (*Z*-3c). Yellow solid (56%), rf 0.70 (19:1 $CHCl_3$:CH_3OH); M.p. 196°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 2.26 (3H, s, $ArCH_3$), 4.75 & 4.91 (2H each, bs, $2 \times N$-CH_a, $2 \times N$-CH_b), 6.01 & 6.39 (1H each, d, $J = 11.7$ Hz, $2 \times Z$-vinylic-H), 7.12 (2H, d, $J = 8.2$) 7.26–7.28 (2H, m), 7.37–7.54 (9H, m), 7.58–7.60 (2H, m), 7.75 (1H, s) and 9.96 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{30}H_{26}N_2O_3$: C 77.90, H 5.67, N 6.06, Found: C 77.72, H 5.81, N 5.93.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (4-methoxyphenyl)amide (*Z*-3d). Yellow solid (53%), rf 0.66 (19:1 $CHCl_3$:CH_3OH); M.p. 204°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 3.74 (3H, s, OCH_3), 4.75 & 4.91 (2H each, bs, $2 \times N$-CH_a, $2 \times N$-CH_b), 5.99 & 6.38 (1H each, d, $J = 11.7$ Hz, $2 \times Z$-vinylic-H), 6.89 (2H, d, $J = 8.97$ Hz), 7.27–7.29 (2H, m), 7.37–7.39 (3H, m), 7.45–7.49 (3H, m), 7.51–7.54 (3H, m), 7.58–7.60 (2H, m), 7.75 (1H, s) and 9.92 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{30}H_{26}N_2O_4$: C 75.30, H 5.48, N 5.85, Found: C 75.29, H 5.38, N 5.87.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (4-nitrophenyl)amide (*Z*-3e). Yellow solid (45%), rf 0.49 (19:1 $CHCl_3$:CH_3OH); M.p. 220°C (decomposition); ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 4.76 & 4.93 (2H each, bs, 2 × *N*-CH_a, 2 × *N*-CH_b), 6.05 & 6.56 (1H each, d, $J = 11.7$ Hz, 2 × *Z*-vinylic-H), 7.24–7.27 (2H, m), 7.37–7.39 (3H, m), 7.45–7.61 (6H, m), 7.75–7.77 (3H, m), 8.23 (2H, d, $J = 9.2$ Hz) and 10.62 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{29}H_{23}N_3O_5$: C 70.58, H 4.70, N 8.51. Found: C 70.57, H 4.58, N 8.47.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (3,4-dichlorophenyl)amide (*Z*-3f). Yellow solid (41%), rf 0.55 (19:1 $CHCl_3$:CH_3OH); M.p. 195°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 4.75 & 4.92 (2H each, bs, 2 × *N*-CH_a, 2 × *N*-CH_b), 5.99 & 6.50 (1H each, d, $J = 11.7$ Hz, 2 × *Z*-vinylic-H), 7.26–7.27 (2H, m), 7.38–7.40 (4H, m), 7.45–7.60 (7H, m), 7.76 (1H, s), 7.93 (1H, d, $J = 2.3$ Hz) and 10.32 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{29}H_{22}Cl_2N_2O_3$: C 67.32, H 4.29, N 5.41, Found: C 67.15, H 4.25, N 5.37.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (3,4-dimethylphenyl)amide (*Z*-3g). Yellow solid (43%), rf 0.59 (19:1 $CHCl_3$:CH_3OH); M.p. 196°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 2.18 & 2.22 (3H each, s, 2 × $ArCH_3$), 4.75 & 4.91 (2H each, bs, 2 × *N*-CH_a, 2 × *N*-CH_b), 6.01 & 6.38 (1H each, d, $J = 11.7$ Hz, 2 × *Z*-vinylic-H), 7.05–7.07 (2H, d, $J = 8.2$ Hz) 7.23–7.28 (3H, m), 7.34–7.40 (4H, m), 7.45–7.51 (1H, m), 7.52–7.54 (3H, m), 7.58–7.61 (2H, m) and 9.89 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{31}H_{28}N_2O_3$: C 78.13, H 5.92, N 5.88, Found: C 78.23, H 6.18, N 5.85.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*Z*-enoic acid (2,6-dimethylphenyl)amide (*Z*-3h). Yellow solid (37%), rf 0.64 (19:1 $CHCl_3$:CH_3OH); M.p. 200°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 2.06 (6H, s, 2 × $ArCH_3$), 4.77 & 4.84 (2H each, bs, 2 × *N*-CH_a, 2 × *N*-CH_b), 6.15 & 6.46 (1H each, d, $J = 11.7$ Hz, 2 × *Z*-vinylic-H), 7.02–7.09 (3H, m), 7.43–7.62 (10H, m), 7.63 & 7.69 (1H each, s) and 9.46 (1H, bs, NHCO). Elemental analysis: Calcd. for $C_{31}H_{28}N_2O_3$-0.25H_2O: C 77.39, H 5.97, N 5.82, Found: C 77.18, H 5.56, N 5.52.

4-(3,5-Bisphenylmethylene-4-oxo-piperidin-1-yl)-4-oxo-but-2*E*-enoic acid (4-chlorophenyl)amide (*E*-3b). Light yellow solid (67%), rf 0.63 (19:1 $CHCl_3$:CH_3OH); M.p. 231–235°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 4.95 & 4.98 (2H each, bs, 2 × *N*-CH_a and 2 × *N*-CH_b), 6.88 & 7.20 (1H each, d, $J = 15.0$ Hz, 2 × *E*-vinylic-H), 7.35 & 7.61 (4H, d, $J = 8.9$ Hz), 7.47–7.57 (10H, m), 7.70 and 7.74 (1H each, s) and 10.46 (1H, bs, NHCO).

ACKNOWLEDGMENTS

We thank Purdue Neuroscience Company, USA for financial support.

REFERENCES

1. Dimmock, J.R.; Arora, V.K.; Quail, J.W.; Pugazhenthi, U.; Allen, T.M.; Kao, G.Y.; De Clercq, E. Cytotoxic evaluation of some 3,5-diarylidene-4-piperidones and various related quaternary ammonium compounds and analogs. J. Pharm. Sci. **1994**, *83* (8), 1124–1130.
2. Dimmock, J.R.; Arora, V.K.; Chen, M.; Allen, T.M.; Kao, G.Y. Cytotoxic evaluation of some *N*-acyl and *N*-acyloxy analogues of 3,5-bis(arylidene)-4-piperidones. Drug Des. Discovery **1994**, *12* (1), 19–28.
3. Dimmock, J.R.; Padmanilayam, M.P.; Puthucode, R.N.; Nazarali, A.J.; Motaganhalli, N.L.; Zello, G.A.; Quail, J.W.; Oloo, E.O.; Kraatz, H.B.; Prisciak, J.S.; Allen, T.M.; Santos, C.L.; Balzarini, J.; De Clercq, E.; Manavathu, E.K. A conformational and structure-activity relationship study of cytotoxic 3,5-bis(arylidene)-4-piperidones and related N-acryloyl analogues. J. Med. Chem. **2001**, *44* (4), 586–593.
4. Dimmock, J.R.; Arora, V.K.; Duffy, M.J.; Reid, R.S.; Allen, T.M.; Kao, G.Y. Evaluation of some *N*-acyl analogues of 3,5-bis(arylidene)-4-piperidones for cytotoxic activity. Drug Des. Discovery **1992**, *8* (4), 291–299.
5. Baluja, G.; Municio, A.M.; Vega, S. Reactivity of some α,β-unsaturated ketones towards sulfhydryl compounds and their antifungal activity. Chem. Ind. (London) **1964**, (50), 2053–2054.
6. Dimmock, J.R.; Erciyas, E.; Raghavan, S.K.; Kirkpatrick, D.L. Evaluation of the cytotoxicity of some Mannich bases of acetophenone against the EMT6 tumor. Pharmazie **1990**, *45* (10), 755–757.
7. Dimmock, J.R.; Raghavan, S.K.; Logan, B.M.; Bigam, G.E. Antileukemic evaluation of some Mannich bases derived from 2-arylidene-1,3-diketones. Eur. J. Med. Chem. **1983**, *18* (3), 248–254.
8. Mutus, B.; Wagner, J.D.; Talpas, C.J.; Dimmock, J.R.; Phillips, O.A.; Reid, R.S. 1-*p*-Chlorophenyl-4,4-dimethyl-5-diethylamino-1-penten-3-one hydrobromide, a sulfhydryl-specific compound which

reacts irreversibly with protein thiols but reversibly with small molecular weight thiols. Anal. Biochem. **1989**, *177* (2), 237–243.
9. Perrin, D.D.; Dempsey, B.; Serjeant, E.P. In *pKa Prediction of Organic Acids and Bases*; Chapman and Hall: London, 1981, p. 123.
10. Barakat, M.Z.; Shehab, S.K.; El-Sadr, M.M. Some maleimides, maleamic acids and phthalimides. J. Chem. Soc. **1957,** 4133–4135.
11. Arora, V.K. PhD Thesis. Synthesis of thiol-depleting agents with selective toxicity to malignant cells. University of Saskatchewan, Saskatoon, 1991.
12. Canoira, L.; Rodriguez, J.G. Synthesis and isomerization of the *N*,*N*-dimethylamides of the 2′-chloromaleanilic acids. J. Chem. Res. Miniprint **1988**, (11), 2836–2855.
13. Machida, M.; Machida, M.I.; Kanaoka, Y. Hydrolysis of N-substituted maleamides: Stability of fluorescence thiol reagents in aqueous media. Chem. Pharm. Bull. **1977**, *25* (10), 2739–2743.
14. Roth, M. Spiro-β-lactams from [2+2] cycloaddition of ketenes to iminolactones. Helv. Chim. Acta **1979**, *62* (6), 1966–1977.
15. Capraro, H.G.; Winkler, T.; Martin, P. [2+2] Cycloaddition of maleic isoimides with ketenes and reaction of spiro-β-lactams to muconic and tetramic acids. Helv. Chim. Acta. **1983**, *66* (1), 362–378.
16. Roderick, W.R.; Bhatia, P.L. Action of trifluoroacetic anhydride on *N*-substituted amic acids. J. Org. Chem. **1963**, *28* (8), 2018–2024.
17. Canoira, L.; Rodriguez, J.G. Synthesis of oxindole derivatives from *N*-alkenyl-*o*-chloroamines with zero-valent Nickel complex. J. Heterocyclic Chem. **1985**, *22* (6), 1511–1518.
18. Silverstein, R.M.; Bassler, G.C.; Morrill, T.C. Proton spin-coupling constants. In *Spectrometric Identification of Organic Compounds*; 5th Edition, John Wiley & Sons, Inc.: New York, 1991, p. 221.
19. CS Chem3D Pro® Computational Chemistry Software, CambridgeSoft Corporation, 100 Cambridge Park Drive, Cambridge, MA 02140–2317, USA.
20. Siegel, M.; Pressman, D. The reactions of antiserum homologous to the *p*-azomaleanilate and *p*-azofumaranilate ion groups. J. Am. Chem. Soc. **1954**, *76*, 2863–2866.
21. Casy, A.F.; Harper, N.J.; Dimmock, J.R. Tertiary alcohols and related compounds from 2-dimethylaminomethylcyclohexanone. J. Chem. Soc. **1964**, (Oct), 3635–3638.
22. Dimmock, J.R.; Phillips, O.A.; Wonko, S.L.; Hickie, R.A.; Tuer, T.G.; Ambrose, S.J.; Reid, R.S.; Mutus, B.; Talpas, C.J.

Evaluation of some Mannich bases of conjugated styryl ketones and related compounds versus the WiDr colon cancer *in vitro*. Eur. J. Med. Chem. **1989**, *24* (3), 217–226.

23. Albert, A.; Serjeant, E.P. In *The Determination of Ionization Constants*, *A Laboratory Manual*. 3rd Ed.; Chapman and Hall: London, 1984; p. 151.

Received in the USA May 15, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016