Asian Journal of Chemistry Vol. 16, No. 1 (2004), 357–364

Synthesis, Structure Elucidation and Antimicrobial Activity of N-substituted α-Benzamido-β-[3-Methoxy-4-(*p*-Toluene Sulfonyloxy)]-Cinnamamides

ANAND K. JAIN*, S.C. MEHTA AND N.M. SHRIVASTAVA†
Department of Pharmacology
G.R. Medical College, Gwalior-474 009, India

3-Methoxy-4-(*p*-toluene sulfonyloxy)-benzaldehyde was condensed with acylglycine in presence of sodium acetate and catalytic amount of acetic anhydride yielded 2-phenyl-4-[3-methoxy-4-(*p*-toluenesulfonyloxy)-benzylidene]-5-oxazolone. This compound on reaction with hydrazine hydrate, ammonia and different primary amines yielded N-substituted α-benzamido-β-[3-methoxy-4-(*p*-toluenesulfonyloxy)] cinnamohydrazide/cinnamamides. The newly synthesised azalactone derivatives were characterized by their physical properties, elemental and spectral analysis. All these compounds were screened for their antimicrobial activity against *E. coli, Klebsiella, Staphylococci* and *Diplococci.*

Key Words: 2-Phenyl-4-[3-methoxy-4-(*p*-toluene sulfonyloxy)-benzylidene-5-oxazolone], N-substituted cinnamohydrazide/cinnamamides, Antimicrobial activity.

INTRODUCTION

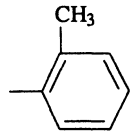
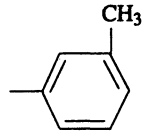
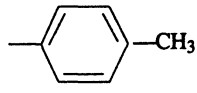
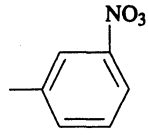
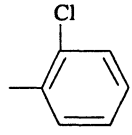
Using aldehyde as starting material, substances of potential interest of chemotherapy have been synthesised. Beside this, reactions of azalactone have been widely investigated since they were useful as intermediate in the synthesis of α-amino acids and quinolines. During the Second world war chemistry of oxazolone made considerable advance because it was linked with the chemistry of penicillins for which a structure having an oxazolone moiety was proposed. Beside this the compounds bearing sulfonyl group (—SO_2) showed immense biological activity, *e.g.*, sulfonamides, antileprotic drugs sulfones, etc. But the actions and properties of compounds bearing sulfonyloxy (—SO_2·O) group have not been encountered in literature, which led to the synthesis of compounds containing sulfonyloxy group (—SO_2·O), using oxazolone as intermediate. The present workers have synthesized eight compounds, *i.e.*, N-substituted α-benzamido-β-[3-methoxy-4-(*p*-toluenesulfonyloxy)]-cinnamohydrazide/cinnamamides using oxazolone as intermediate. Their structures were elucidated by physical properties, elemental and spectral analysis. Their antimicrobial studies were also done.

†Department of Pharmacology, Gandhi Medical College, Bhopal (M.P.)

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr discs with a Perkin-Elmer spectrum Bx FT-IR system spectrophotometer. ^1H NMR were obtained in $CDCl_3$ on a Bruker 400 MHz Advance FT NMR using TMS as internal standard and mass spectra were determined on a Finnigan MAT TSQ 7000 mass spectrophotometer.

TABLE-1
PHYSICAL PROPERTIES OF N-SUBSTITUTED α-BENZAMIDO-β-[3-METHOXY-4-(*p*-TOLUENE SULFONYLOXY) CINNAMOHYDRAZIDE/CINNAMAMIDES

Compound/Primary amine	R	m.w.	Abbreviation	Colour (m.p. °C)	m.f. (yield %)
Hydrazine hydrate	—NH_2	481	HHDA	Light yellow (205)	$C_{24}H_{23}N_3O_6S$ (51.44)
Ammonia	—H	466	AMDA	Yellow (132)	$C_{24}H_{22}N_2O_6S$ (53.94)
Aniline	—C_6H_5	542	ANDA	Orange yellow (137)	$C_{30}H_{26}N_2O_6S$ (68.95)
o-Toluidine		556	OTDA	Dark yellow (144)	$C_{31}H_{28}N_2O_6S$ (54.06)
m-Toluidine		556	MTDA	Dark yellow (turmeric) (122)	$C_{31}H_{28}N_2O_6S$ (67.92)
p-Toluidine		556	PTDA	Light yellow (105)	$C_{31}H_{28}N_2O_6S$ (59.02)
m-Nitroaniline		587	MNADA	Shining yellow (82)	$C_{30}H_{25}N_3O_8S$ (58.16)
o-Chloroaniline		576	OCADA	Yellowish green (169)	$C_{30}H_{25}N_2O_6S{\cdot}Cl$ (38.95)

Preparation of 3-methoxy-4-(*p*-toluene sulfonyloxy benzaldehyde)

p-Toluene sulfonyl chloride was condensed with vanillin (3-methoxy-4-hydroxy benzaldehyde) in presence of pyridine. The mixture was heated on a

water bath for 15–20 min; then it was poured in distilled water with continuous stirring. It was filtered, washed with cold dil. NaOH and cold dil. HCl, dried and finally crystallized with acetone.

IR (cm^{-1}): 1790 (—CO—OC), 3060 and 2900–2800 ν(C—H stretching) 1600 ν(C=N cyclic); 1370 ν(SO_2·O)

Preparation of 2-phenyl-4-[3-methoxy-4-(*p*-toluene sulfonyloxy)-benzylidene]-5-oxazolone

A mixture of 3-methoxy-4-(*p*-toluene sulfonyloxy)-benzaldehyde and benzoylglycine (1 mol each) was taken in a round-bottom flask and sodium acetate and acetic anhydride were added to it. It was heated on a water bath for 2 h. Then the contents were cooled, filtered, dried and crystallized with acetone.

IR (cm^{-1}): 1650 ν(—CHO), 1290 ν(O—CH_2), 1320 ν(—CH_3) 1370 ν(—SO_2·O), 1600 ν(C=N cyclic), 1370 ν(SO_2·O)

Perparation of N-substituted α-benzamido-β-[3-methoxy-4-(*p*-toluene sulfonyloxy)]-cinnamohydrazide/cinnamamides

N-Substituted α-benzamido-β-[3-methoxy-4-(*p*-toluene sulfonyloxy)]-cinnamohydrazide/cinnamamides were prepared according to the literature methods[1–6].

Chemical Reaction:

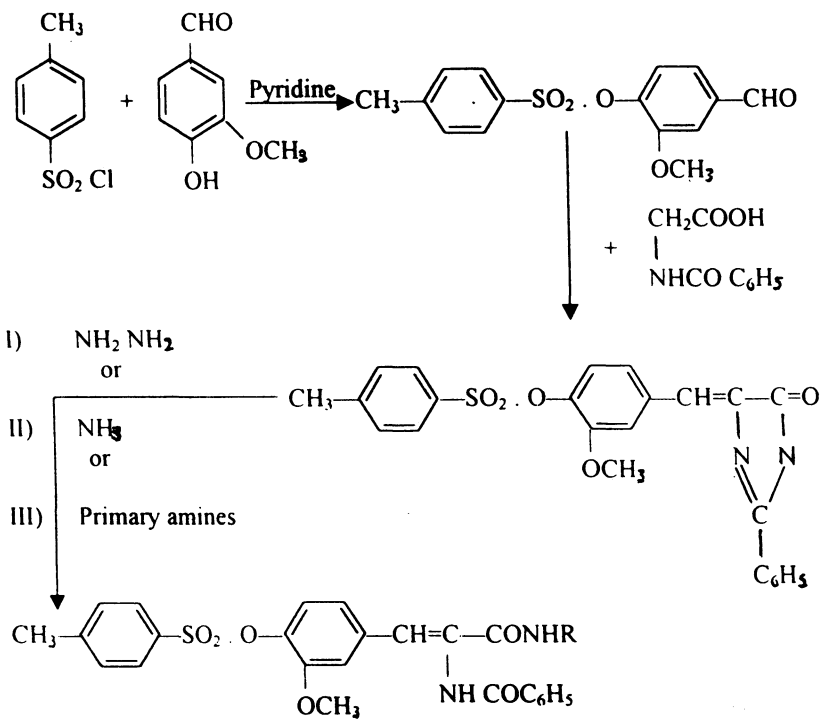


TABLE-2

ELEMENTAL AND SPECTRAL DATA OF N-SUBSTITUTED α-BENZAMIDO-β-[3-METHOXY-4-(*p*-TOLUENE SULFONYLOXY)]-CINNAMOHYDRAZIDE/CINNAMAMIDES

S. No.	Name of derivative	Elemental analysis: found (calcd.) (%)					IR (cm^{-1})	^1H NMR ($CDCl_3$)	Mass m/e (RA %)
		C	H	N	S	Cl			
1.	Hydrazine hydrate derivative (HHDA)	58.11 (59.87)	4.52 (4.78)	8.81 (8.73)	6.62 (6.65)	— —	3433 ν(NH_2), 3080 ν(ArCH), 2611, 1610 ν(C═O), 1518, 1057, 1025, 965 ν(CH═CH)	2.75 (3H, CH_3) 3.85 (2H, NH_2) 7.25–7.60 (H) merged with aromatic peaks	481 M^+ (4.8), 383 (4.0), 343 (13.6), 278 (14.4), 246 (2.4), 213 (2.4), 192 (2.4), 167 (1.2), 166 (25.6), 156 (6.4), 139 (25.8), 123 (18.4), 105 (33.6), 92 (14.0), 91 (32.8), 77 (32.8), 64 (100)
2.	Ammonia derivative (AMDA)	63.31 (61.80)	4.65 (4.72)	6.17 (6.00)	6.92 (6.86)	— —	3373 ν(NH_2), 2918 ν(CH or OCH_3), 1643 ν(C═C), 1595 ν(C═O), 1503 ν(CH_3), 1464, 1372, 1202, 1176 ν(C—S) 1118, 1090, 1030, 855 ν(CH═C) or phenyl or aryl, 815, 749, 713, 662, 545	2.25–2.50 (3H, CH_3), 3.25–3.40 (OCH_3), 3.60–3.75 (2H, NH_2), 6.8–8.20 (NH merged with aromatic peak)	466 M^+ (1.6), 449 (6.4), 387 (2.4), 308 (5.7), 306 (74.4), 294 (10), 278 (6.0), 341 (1.2), 232 (5.6), 206 (2.8), 167 (1.2), 162 (5.4), 157 (14.0), 155 (100), 151 (44.8), 139 (14.4), 121 (17.6), 106 (60.9), 91 (96.8), 77 (3.6), 65 (3.6)

S. No.	Name of derivative	Elemental analysis: found (calcd.) (%)					IR (cm^{-1})	^1H NMR ($CDCl_3$)	Mass m/e (RA %)
		C	H	N	S	Cl			
3.	Aniline derivative (ANDA)	67.35 (66.42)	4.92 (4.80)	5.32 (5.16)	5.69 (5.90)	— —	3386 ν(NH), 2928 ν(CH or OCH_3), 1598 ν(C═O), 1500 ν(—CH_3), 1371 ν(C—O), 1293, 1176, 1032, 856 ν(C═O), 751, 712, 547	2.25–2.50 (3H, CH_3), 3.35 (OCH_3), 6.40–7.75, (NH merged with aromatic ring)	542 M^+ (7.2), 525 (1.6), 383 (1.6), 381 (6.4), 369 (36.0), 359 (6.4), 308 (0.8), 307 (6.7), 204 (2.0), 227 (6.4), 226 (14.4), 208 (2.4), 197 (21.6), 180 (44.0), 163 (9.6), 156 (17.6), 139 (12.8), 107 (9.2), 105 (63.2), 93 (100), 77 (70.4), 65 (52.2).
4.	*o*-Toluidine derivative (OTDA)	67.25 (66.90)	4.92 (4.80)	5.32 (5.03)	5.65 (5.75)	— —	3422 ν(—NH), 2925 ν(CH or OCH_3), 1719 ν(C═O), 1638 ν(C═C), 1596 ν(C═O amide), 1497, 1459, 1369, 1296, 1176 ν(C—S), 1119, 1090, 1029, 943, 859 ν(Ar or Ph or H═C), 748, 696, 664, 547	2.1 (3H, CH_3), 2.25 (OCH_3), 3.35, 6.6–7.7 (NH merged with aromatic peaks)	556 M^+ (4.8), 540 (6.4), 538 (14.4), 408 (4.8), 395 (36.0), 383 (73.6), 355 (6), 340 (6), 321 (6), 278 (6), 240 (36.4), 225 (6.4), 212 (9.6), 194 (59.2), 180 (14.4), 167 (17.6), 155 (17.6), 139 (8.8), 118 (17.6), 65 (36.0)

S. No.	Name of derivative	Elemental analysis: found (calcd.) (%)					IR (cm^{-1})	^1H NMR ($CDCl_3$)	Mass m/e (RA %)
		C	H	N	S	Cl			
5.	*m*-Toluidine derivative (MTDA)	66.31 (66.90)	5.17 (5.03)	5.80 (5.03)	5.96 (45.75)	— —	3385 ν(NH), 2918.66 ν(OCH_3), 1597.92 ν(C═O amide), 1504, 1462, 1371, 1293, 1176 ν(C—S), 1118, 1090, 1032, 854 ν(Ph or Ar or CH═C), 751, 713, 662, 546	1.9 (3H, CH_3), 2.2–2.4 (OCH_3), 2.65, 2.95–3.55, 6.2–6.5, 6.6–7.5, (NH merged with aromatic peak)	556 M^+ (5.6), 538 (6.0), 397, 383 (31.2), 321 (6.4), 293 (6.4), 278 (3.2), 246 (2.4), 240 (6.0), 212 (1.6), 211 (12.0), 194 (36.4), 180 (2.4), 163 (6.0), 155 (16.8), 137 (14.4), 123 (10.8), 106 (63.2), 91 (100), 77 (93.6), 65 (44.8), 51 (58.4).
6.	*p*-Toluidine derivative (PTDA)	65.39 (66.90)	4.95 (5.03)	5.45 (5.03)	5.93 (5.75)	— —	3393 ν(NH), 2918 ν(OCH_3), 1654 ν(C═C), 1598 ν(C═O, amide), 1508, 1371, 1288, 1177 ν(C—S), 1118, 1091, 1032, 852 ν(Ph or Aryl or CH═C), 713, 546	0.71, 1.1, 1.2, 1.8–2.35 (CH, CH_3), 2.68, 3.2 (OCH_3), 3.2–3.25, 6.6–7.7 (NH merged with aromatic peak)	556 N^+ (9.6), 536 (14.4), 395 (3.6), 385 (8.0), 321 (13.6), 290 (9.6), 261 (2.4), 246 (1.2), 231 (6.4), 193 (2.4), 187 (10.0), 172 (96.8), 178 (12.8), 157 (6.0), 128 (4.8), 121 (10.0), 106 (100), 86 (6.0), 77 (20.8), 59 (6.0), 511 (11.2).

S. No.	Name of derivative	Elemental analysis: found (calcd.) (%)					IR (cm^{-1})	^1H NMR ($CDCl_3$)	Mass m/e (RA %)
		C	H	N	S	Cl			
7.	*m*-Nitro-aniline derivative (MNADA)	62.37 (61.32)	3.99 (4.25)	6.93 (7.15)	5.39 (5.45)	— —	3441 ν(NH), 2918 ν(OCH_3), 1626 ν(C═C), 1526 (—NO_2), 1349 ν(C═O), 1176 ν(C—S), 1118, 1090, 1029, 857 ν(Ph or aryl or CH═C), 815, 737, 712, 690, 545	2.0, 2.2–2.35 (3H, CH_3), 2.94, 3.22, 3.39 (OCH_3), 3.5, 3.54, 6.48, 6.58, 6.6–8.25 (NH merged with aromatic peaks)	587 M^+ (8.0), 426 (20.0), 308 (0.8), 306 (12.8), 273 (5.6), 271 (100), 256 (3.4), 224 (6.0), 208 (14.0), 193 (6.4), 182 (10.0), 162 (10.0), 155 (36.0), 149 (10.4), 127 (10.0), 123 (4.4), 105 (10.0), 95 (4.4), 91 (60.8), 77 (13.6), 69 (3.2), 51 (4.8).
8.	*o*-Chloro amiline derivative (OCADA)	63.01 (62.44)	4.07 (4.33)	4.93 (4.86)	5.69 (5.55)	6.27 (6.16)	3448 ν(NH), 2918 ν(OCH_3), 1786 ν(C═O), 1649 ν(C═C), 1599 ν(C═O, amide), 1500, 1421, 1382, 1289, 1153 ν(C—S), 1091, 857 ν(Ph or aryl or CH═C), 747, 702, 546	1.65, 2.05, 2.30 (3H, CH_3), 3.25 (OCH_3), 370, 7.1–8.1 (NH merged with aromatic ring).	576 M^+ (2.4), 449 (17.42), 408 (18.18), 349 (1.51), 306 (85.6), 294 (20.45), 253 (6.06), 241 (3.03), 211 (3.03), 183 (14.39), 169 (2.27), 155 (100), 151 (66.66), 141 (13.63), 109 (6.43), 95 (21.6), 91 (82.57), 77 (14.0), 65 (18.18).

The physical properties of N-substituted α-benzamido-β-[3-methoxy-4-(*p*-toluenesulfonyloxy)]-cinnamohydrazide/cinnamamides are described in Table-1 and elemental and spectral data are described in Table-2.

Antimicrobial Activity[7-10]

All eight compounds namely HHDA, AMDA, ANDA, OTDA, MTDA, PTDA, MNADA and OCADA were tested for their antimicrobial activity against *E. coli, Klebsiella, Staphylococci* and *Diplococci* by disc method at the concentration of 25 μg and 50 μg in agar media.

Amongst the compounds tested, compounds AMDA, OTDA and MTDA exhibited very good activity against *E. coli* and *Staphylococci* at the concentration of 50 μg, while compound ANDA exhibited moderate activity against *Staphylococci* at the same concentration. Remaining compounds were found inactive.

ACKNOWLEDGEMENTS

The authors are thankful to Dr. T.N. Pradhan, Dean and Head of the Department of Pharmacology, G.R. Medical College, Gwalior for providing chemicals and laboratory facilities and Dr. (Mrs.) Savita Bharat, Assistant Professor, Department of Microbiology, G.R. Medical College, Gwalior for helping in antimicrobial studies.

REFERENCES

1. Harington and Berger, *Bid. Chem. J.*, **21**, 169 (1927).
2. S.P. Rastogi and (Miss) Arora, *J. Indian Chem. Soc.*, **43**, 651 (1966).
3. A.H. Harhash, Kassab and Elbanani, *Indian J. Chem.*, **9**, 789 (1971).
4. A.R. Tiwari and V.S. Jolly (Private Communication).
5. Granacher and Gulbas, *Helv. Chim. Acta*, 10819 (1927).
6. B.P. Asthana and P.I. Ittyerah, *J. Indian Chem. Soc.*, **46**, 137 (1969).
7. Machie and McCartley, Handbook of Practical Bacteriology (1953).
8. Pharmacopoeia of India (The Indian Pharmacopoeia)-2, 3rd Edn. (1985).
9. Biology Assay and Tests, British Pharmacopoeia, Appendix XIV, A164–A-172 (1996).
10. P.K. Martindale, The Complete Drugs Reference, 32nd Edn. (Ph. D.), London, p. 91123 (1999).

(*Received*: 17 May 2003; *Accepted*: 18 October 2003) AJC–3193