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Synthesis, characterization and biological evaluation of N-aryl amino-4-acetamido-2-ethoxy benzamides

Jayesh V.Padaliya[1]*, M.V.Parsania[2]

H.& H.B.Kotak institution of science, Rajkot Gujarat, (INDIA)

M.M.Science college, Morbi, Gujarat, (INDIA)

E-mail: Jayesh Patel 123@Yahoo.com

ABSTRACT

4-acetamido-2-ethoxy benzoyl hydrazine **(2)** obtains by reacting hydrazine with methyl-4-acetamido-2-ethoxy benzoate. Further, compound **(2)** was condensed with different aromatic acid chloride in the presence of pyridine to afforded new N-arylamino-4-acetamido-2-ethoxy benzamides in good yields (65 to 80 %). The structure of newly synthesized compounds was confirmed by IR, ^{1}H NMR, Mass spectral studies and elemental analysis. All the synthesized compounds have been screener for antimicrobial activity.

KEYWORDS

4-Aceteimido-2-ethoxy benzoyl hydrazine;
Different aromatic acid chloride;
Pyridine;
N-aryl amino-4-acetamido-2-ethoxy benzamides;
Antimicrobial activity.

INTRODUCTION

The arylacetamide derivatives exhibit broad spectrum of therapeutic activity. The several biological activity associated with arylacetamide have been described as antiulcer[1], antiallergy[2], antimicrobial[3], tranquilizer[4], analgesic[5], anticonvalsant[6], cardiofonic[7], flerbicidal[8], etc.

Dumot and Delerck[9] have studied the hypnotic and sedative effect of urides, carbamides, acetamides and sulphones. Iodo-acetamide and N-ethyl malemide inhibit a number of viruses including the pleuropheumonia and entro group[10].

Yaan etal[11] and Lida etal[12] have synthesized arylacetamide derivatives as anticancer agent. Babizhayer etal[13] have prepared arylacetamides as anti-inflammatory agents. N. C. Desai[14] has described anticancer anti-HIV and antibacterial activity of aryl acetamides.

In view of therapeutic activities of arylacetamide derivatives and p-amino salicylic acid moiety, it was contemplated to synthesise some new arylacetamide derivatives, in seanch of agents possessing higher biological activity with least side effect.

In presence work we have first prepared 4-acetamido-2-ethoxy benzoyl hydrazine and condensed with different aromatic acid chloride which obtains due to the reaction different aromatic acid with Thionyl chloride. To produce higher functionalized N-arylamino-4-acetamido-2-ethoxy benzamide derivative in good yields for biological interest.

RESULTS AND DISCUSSION

The starting material 4-acetamido-2-ethoxy benzoyl hydrazine (2) was prepared by reacting me-

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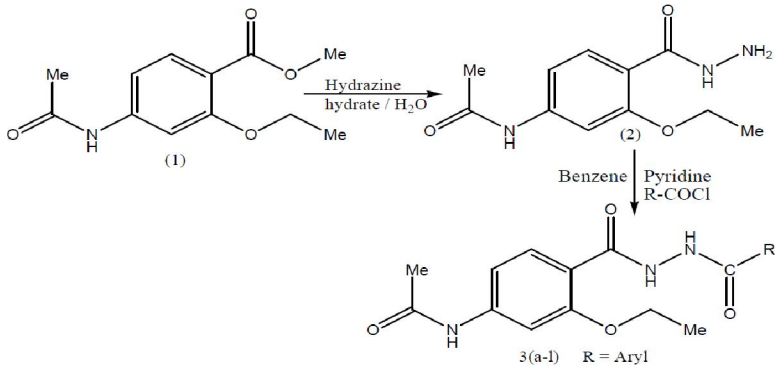
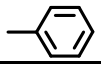
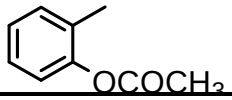
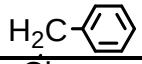
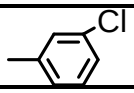
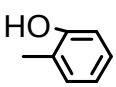
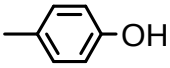
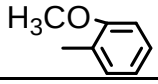
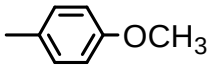
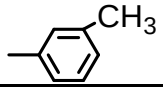
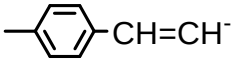


Scheme 1 : Synthesis of some newN-arylamino-4-acetamido-2-ethoxybenzamides

TABLE 1 : Synthesis of some new N-arylamino-4-acetamido-2-ethoxy benzamides

Entry	R	Product	Temp in ^oC	Time in hrs.	Yield
1		3a	70	10	66
2		3b	72	15	68
3		3c	70	12	63
4		3d	74	13	72
5		3e	74	15	79
6		3f	74	12	85
7		3g	80	18	71
8		3h	78	19	74
9		3i	76	15	78
10		3j	78	20	77
11		3k	81	24	72
12		3l	80	17	76

thyl-4-acetamido-2-ethoxy phenyl benzoate (1) with hydrazine hydrate at ambient temperature. The yield of compounds is good (65 to 80%). The different aromatic acid chlorides are reactive with 4-acetamido-2-ethoxy benzoyl hydrazine (2). The different aromatic acid chloride was prepared by re-

TABLE 2 : Antimicrobial activity of the compounds (3a-l)

Compound	Antimicrobial activity zone of inhibition in mm				Antifungal activity zone of inhibition in mm
	P.Valganis	E.Coli	B.Mega	S.aureus	
3a	24	11	18	21	13
3b	13	23	14	22	19
3c	15	15	20	12	18
3d	25	12	20	19	23
3e	17	12	15	12	17
3f	14	24	25	22	15
3g	20	15	23	11	19
3h	12	14	12	14	18
3i	13	15	11	11	22
3j	23	18	20	22	25
3k	17	20	14	19	16
3l	12	16	20	15	11

ported procedure[15,16] by reaction of different aromatic acid with Thionyl chloride. The different aromatic acid chloride was not isolated but direct condensed with 4-acetamido-2-ethoxy benzoyl hydrazine (2) in the presence of pyridine at 70-80º C. Benzene is used as solvent and content was stirred for several hours at 70-80º C. Then cool at room temperature. After work up afforded new N-arylamino-4-acetamido-2-ethoxy benzamides (3) (a-l) in good moderate yields.

The IR spectrum of 3a exhibited an absorption band at 1654 cm^{-1} due to the >C=O stretching for –CONHNH- and >C=O of $–NHCOCH_3$ at 1647 cm^{-1}, >C=O str. (amide) at 1685 cm^{-1}. C-N str. Vibration at 1115 cm^{-1}, N-H stretching at 3271 cm^{-1} and N-H deformation at 1590 cm^{-1}.

In the ^{1}H NMR spectrum of 3a, singlet at δ 2.33 for three protons of $–NHCOCH_3$, singlet at 8.60 for NH-NH consist two protons. Triplet for three protons at 1.5 and quartet for two protons at 4.28 indicate the presence of $–OCH_2CH_3$ group, multiplate at 6.83-8.36 consist six protons indicate aromatic character.

The structure of (3a) was farther confirmed by Mass spectral analysis. It exhibited a molecular ion peak at M/Z 341 corresponding to its molecular weight.

Similarly, IR, NMR, Mass spectroscopy and elemental analysis, characterized all the compounds.

EVALUATION OF ANTIMICROBIAL ACTIVITE

The newly synthesized N-aryl sulphonamido-4-acetamido-2-ethoxy benzamides compounds(4a-p) have been screened for antimicrobial activity against staphylococtus aureus, Escherichia coli, B. mega, P.valgaris using amoxicillin, ampicillin, ciprofloxacin erythromycin as standard and antifungal activity against aspergillus niger using griseofulvin as standard by the cup-plate method[24,25]. The results are cited in TABLE-2.

S_1= amoxicillin, S_2= Ampicillin, S_3= ciprofloxacin, S_4= erythromyclin, S_5 = griseofulvin among the compounds tested for antibacterial activity, the compounds (3a),(3d). (3g), (3k) exhibit good activity against P.valgaris, B.mega. While compounds (3b), (3f), (3j) exhibit promising activity against E- coil and S.aureas. compounds. (3d),(3f), (3j), exhibit good bacterial as well as antifungal activity against E-coli, P. vulgarius, B. Mega respectively.

EXPERIMENTAL

General procedures, melting points were estimated in open capillaries and may be uncorrected. IR spectra were recorded on KBr discs, using RTIR-8400 spectrometer. ^{1}H NMR spectra were taken on

a BRUKER AVANCE IT 400 spectrometer in $CDCl_3$ /DMSO. Chemical shift and are given in ppm relative to TMS. Mass spectra were determined using direct inlet probe on a SCMS-QP2010 mass spectrometer (shimadzu). Elemental analyses were preformed on a Carlo Erba EA1108 elemental analyzer at SAIF, CDRI Lucknow. Reactions were monitored on Merk alumina thin layer chromatography (TLC, UV 254nm) plates. Visualization was accomplished either on UV chamber or in iodine paper.

General procedure for the synthesis of N-arylamino-4-acetamido-2-ethoxy benzamides

A mixture of methyl-4-acetamido-2-ethoxy benzoate (2.21 gm, 0.01M) (1) and hydrazine hydrate (2.0 ml, 0.04M) in methanol was refluxes for 7 hrs. The solution was then poured on to crushed ice, filtered and the resulting solid was crystallized from ethanol to afforded 4-acetamido-2-ethoxy benzoyl hydrazine (2).

A mixture of aromatic acid (0.01 M) and Thionyl chloride (10 ml) was refluxed for 6 hrs. Excess of Thionyl chloride was removed by distillation under vaccum and the resulting aromatic acid chloride was not isolated but directly reacts with 4-acetamido-2-ethoxy benzoyl hydrazine (1) at 70-80º C for 10-24bhrs in the presence of benzene as solvent. TLC monitored reaction. The solvent was removed in vaccume and resulting reaction mixture was poured on to crush ice and ice water. The separated product was filtered and crystallizes from ethanol to give pure compounds (3a-l). The reaction temp. time and yields are depicted in TABLE-1.

N-Benzoylamino-4-acetamido-2-ethoxy benzamide (3a)

Off white solid, M. P. 160º C, IR (KBr) ν_{max} = 3271 cm^{-1} (N-H str), 1654 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1647 cm^{-1} (>C=O str. of –CONHNH), 1685 cm^{-1} (>C=O str. of –NHCOR), 3030 cm^{-1} (C-H str. of aromatic), 2940, 2860, 1575, 1250, 1145, 1025, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.55 (T, 3H, -OCH_2CH_3), 2.33 (S, 3H, -$NHCOCH_3$), 4.28 (Q, 2H, -OCH_2CH_3), 8.60 (S, 2H, -NHNH), 6.83-8.36 (M, 8H, Ar-H). MS (EI): 341 M/Z. Anal. Calculated for $C_{18}H_{19}N_3O_4$; C, 63.34; H, 5.57; N, 12.32; Found: C, 63.90; H, 5.50; N, 12.80%.

N-(O-Acetoxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3b)

White solid, M. P. 172º C, IR (KBr) ν_{max} = 3300 cm^{-1} (N-H str), 1660 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1650 cm^{-1} (>C=O str. of –CONHNH), 1685 cm^{-1} (>C=O str. of –NHCOR), 1700 cm^{-1} (>C=O str. of –$OCOCH_3$), 3040 cm^{-1} (C-H str. of aromatic), 2930, 2880, 1580, 1265, 1145, 1030, 730, 770, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.4 (S, 3H, -$NHCOCH_3$), 4.4 (Q, 2H, -OCH_2CH_3), 1.9 (S, 3H, -$OCOCH_3$), 6.9-9.6 (M, 7H, Ar-H). MS (EI): 399 M/Z. Anal. Calculated for $C_{20}H_{21}N_3O_6$; C, 60.15; H, 5.26; N, 10.53; Found: C, 60.50; H, 5.20; N, 10.60%.

N-(Methylene benzoylamino)-4-acetamido-2-ethoxy benzamide (3c)

White solid, M. P. 85º C, IR (KBr) ν_{max} = 3280 cm^{-1} (N-H str), 1650 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1640 cm^{-1} (>C=O str. of –CONHNH), 1680 cm^{-1} (>C=O str. of –$COCH_2R$), 3030 cm^{-1} (C-H str. of aromatic), 2940, 2870, 1575, 1260, 1140, 1030, 690, 720, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.5 (S, 3H, -$NHCOCH_3$), 4.3 (Q, 2H, -OCH_2CH_3), 3.9 (S, 2H, -CH_2), 6.8-9.2 (M, 8H, Ar-H). MS (EI): 355 M/Z. Anal. Calculated for $C_{19}H_{21}N_3O_4$; C, 64.22; H, 5.92; N, 11.83; Found: C, 64.00; H, 6.04; N, 12.10%.

N-(O-Chloro benzoylamino)-4-acetamido-2-ethoxy benzamide (3d)

White solid, M. P. 125º C, IR (KBr) ν_{max} = 3290 cm^{-1} (N-H str), 1645 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1660 cm^{-1} (>C=O str. of –CONHNH), 1675 cm^{-1} (>C=O str. of –COR), 3040 cm^{-1} (C-H str. of aromatic), 2950, 2830, 1560, 1240, 1160, 1025, 740, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.5 (S, 3H, -$NHCOCH_3$), 4.5 (Q, 2H, -OCH_2CH_3), 6.9-9.4 (M, 7H, Ar-H). MS (EI): 375 M/Z. Anal. Calculated for $C_{18}H_{18}N_3O_4Cl$; C, 57.6; H, 4.8; N, 11.2; Found: C, 57.75; H, 4.3; N, 11.3%.

N-(m-chloro benzoylamino)-4-acetamido-2-ethoxy benzamide (3e)

Off white solid, M. P. 130º C, IR (KBr) ν_{max} = 3370 cm^{-1} (N-H str), 1630 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1650 cm^{-1} (>C=O str. of –CONHNH), 1675 cm^{-1} (>C=O str. of –COR), 3030 cm^{-1} (C-H str. of aromatic), 2970, 2840, 1550, 1230, 1150, 1030, 750, 810, 840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.6 (T, 3H, -OCH_2CH_3), 2.4 (S, 3H, -$NHCOCH_3$), 4.4 (Q, 2H, -OCH_2CH_3), 6.9-9.3 (M, 7H, Ar-H). MS (EI): 375 M/Z. Anal. Calculated for $C_{18}H_{18}N_3O_4Cl$; C, 57.6; H, 4.8; N, 11.2; Found: C, 57.65; H, 4.84; N, 11.26%.

N-(p-chloro benzoylamino)-4-acetamido-2-ethoxy benzamide (3f)

White solid, M. P. 215º C, IR (KBr) ν_{max} = 3270 cm^{-1} (N-H str), 1645 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1655 cm^{-1} (>C=O str. of –CONHNH), 1670 cm^{-1} (>C=O str. of –NHCOR), 3035 cm^{-1} (C-H str. of aromatic), 2920, 2840, 1550, 1225, 1150, 1030, 840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.3 (S, 3H, -$NHCOCH_3$), 4.4 (Q, 2H, -OCH_2CH_3), 6.9-9.2 (M, 7H, Ar-H). MS (EI): 375 M/Z. Anal. Calculated for $C_{18}H_{18}N_3O_4Cl$; C, 57.6; H, 4.8; N, 11.2; Found: C, 57.67; H, 4.9; N, 11.3%.

N-(o-Hydroxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3g)

Buff colour solid, M. P. 210º C, IR (KBr) ν_{max} = 3310 cm^{-1} (N-H str), 3450 cm^{-1} (O-H str), 1655 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1645 cm^{-1} (>C=O str. of –CONHNH), 1670 cm^{-1} (>C=O str. of –NHCOR), 3030 cm^{-1} (C-H str. of aromatic), 2940, 2860, 1565, 1240, 1150, 1025, 690, 710, 830 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.3 (S, 3H, -$NHCOCH_3$), 4.4 (Q, 2H, -OCH_2CH_3), 6.1 (S, 1H, -OH), 6.9-9.2 (M, 7H, Ar-H). MS (EI): 341 M/Z. Anal. Calculated for $C_{18}H_{19}N_3O_4$; C, 63.35; H, 5.57; N, 12.32; Found: C, 63.50; H, 5.38; N, 12.10%.

N-(p-Hydroxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3h)

Off white solid, M. P. 230º C, IR (KBr) ν_{max} = 3280 cm^{-1} (N-H str), 3440 cm^{-1} (O-H str), 1650 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1635 cm^{-1} (>C=O str. of –CONHNH), 1675 cm^{-1} (>C=O str. of –NHCOR), 3030 cm^{-1} (C-H str. of aromatic), 3050, 1650, 1560, 1240, 1150, 1040, 840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.3 (S, 3H, -$NHCOCH_3$), 4.3 (Q, 2H, -OCH_2CH_3), 6.3 (S, 1H, -OH), 6.7-9.7 (M, 7H, Ar-H). MS (EI): 341 M/Z. Anal. Calculated for $C_{18}H_{19}N_3O_4$; C, 63.35; H, 5.57; N, 12.32; Found: C, 63.20; H, 5.40; N, 12.40%.

N-(O-Methoxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3i)

White solid, M. P. 150º C, IR (KBr) ν_{max} = 3250 cm^{-1} (N-H str), 1650 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1635 cm^{-1} (>C=O str. of –CONHNH), 1670 cm^{-1} (>C=O str. of –NHCOR), 3030, 1565, 1225, 1150, 1020, 830 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.6 (T, 3H, -OCH_2CH_3), 2.4 (S, 3H, -$NHCOCH_3$), 4.5 (Q, 2H, -OCH_2CH_3), 4.0 (S, 3H, -OCH_3), 6.8-9.2 (M, 7H, Ar-H). MS (EI): 371 M/Z. Anal. Calculated for $C_{19}H_{21}N_3O_5$; C, 61.45; H, 5.66; N, 33.96; Found: C, 61.40; H, 5.60; N, 33.98%.

N-(m-Methyl benzoylamino)-4-acetamido-2-ethoxy benzamide (3k)

White solid, M. P. 125º C, IR (KBr) ν_{max} =1665 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1650 cm^{-1} (>C=O str. of –CONHNH), 1685 cm^{-1} (>C=O str. of –NHCOR), 3030 cm^{-1} (C-H str. of aromatic), 2930, 2850, 1570, 1255, 1150, 1030, 810,840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.7 (T, 3H, -OCH_2CH_3), 2.4 (S, 3H, -$NHCOCH_3$), 4.5 (Q, 2H, -OCH_2CH_3), 2.3 (S, 3H, -CH_3), 7.7-9.2 (M, 7H, Ar-H). MS (EI): 355 M/Z. Anal. Calculated for $C_{19}H_{21}N_3O_4$; C, 64.22; H, 5.92; N, 11.83; Found: C, 64.30; H, 5.90; N, 11.85%.

N-(α-Ethylene benzoylamino)-4-acetamido-2-ethoxy benzamide (3l)

Pale yellow solid, M. P. 115º C, IR (KBr) ν_{max} = 1655 cm^{-1} (>C=O str. of –$NHCOCH_3$), 1640 cm^{-1} (>C=O str. of –CONHNH), 1665 cm^{-1} (>C=O str. of –NHCOR), 3285 cm^{-1} (N-H str.), 3030, 3100, 1570, 1250, 1145, 1040, 690, 720, 840 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 1.8 (T, 3H, -OCH_2CH_3), 2.5 (S, 3H, -$NHCOCH_3$), 4.4 (Q, 2H, -OCH_2CH_3), 6.7-9.3 (M, 10H, Ar-H + CH=CH). MS (EI): 367 M/Z. Anal. Calculated for $C_{20}H_{21}N_3O_4$; C, 65.40; H, 5.7; N, 34.33; Found: C, 65.35; H, 5.65; N, 34.39%.

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CONCLUSION

In conclusion, in this article we have been reported some novel highly functionalized N-arylamino-4-acetamido-2-ethoxy benzamide in good yield and evaluated for antimicrobial activity. Some of the newly synthesized compounds exhibited good to excellent activity against both gram positive and gram negative bacteria and fungi.

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REFERENCES

[1] Ikuo Veda, Katsayaki Ishi, Katsue Shinogaki; Maso Seiki and Hieha Chieo Akai, Chem.Pharm.Bull., **38**, 3035 **(1990)**; Chem.Abstr., **114**, 135867 **(1991)**.

[2] D.T.Connor, M.D.Mullican; U.S.US, **4**, 764, 525, **(1988)**; Chem.Abstr., **109**, 211063c **(1988)**.

[3] Y.D.Kulkarni, Alis.Mohd, S.Rowhani; Indian Drugs, **25(12)**, 505-7 **(1988)**; Chem.Abstr., **110**, 114786f **(1989)**.

[4] Goesta Floravall et al.; Ear.Pat.Appl.Ep., **60**, 235 **(1982)**; Chem.Abstr., **98**, 98, 53687 **(1983)**.

[5] E.F.Lioma, C.Dacampu, M.Capo; J.Pharmacol., **43(9)**, 68 **(1991)**; Chem.Abstr., **114**, 1778 **(1991)**.

[6] E.E.Beedle, D.W.Robertson; Ear.Pat.Appl.Ep., **279**, 633 **(1988)**; Chem.Abstr., **110**, 7875n **(1989)**.

[7] K.Sakakibara, N.Yoneshima, T.Osava; Jpn.Kokai Tokyo Koho Jp., **62**, 158, 252 **(1987)**; Chem.Abstr., **108**, 112238p **(1988)**.

[8] Y.Itami, T.Harada et al.; Jpn.Kokai Tokyo Koho Jp., **62**, 252, 755 **(1987)**; Chem.Abstr., **109**, 12859m **(1988)**.

[9] P.Dumont, A.Delerek; J.Pharma.Beig., **14**, 157-63, 177-81, 193-7, 211-15, 249-53 **(1932)**; Chem.Abstr., **26**, 3331**(1932)**.

[10] K.Philipson, P.W.Choppin; J.Exp.Med., **112**, 455 **(1960)**; Chem.Abstr., **54**, 22828c **(1960)**.

[11] Z.L.Yaan, S.P.Xu; Yaoxuze Xuebao, **29(6)**, 468 **(1994)**; Chem.Abstr., **122**, 105374r **(1995)**.

[12] T.Lida, T.Kaminuma, N.Koge, M.Tajima, M.Yonagi, H.Okamato; Jpn.Kokai Tokyo Koho Jp., **06**, 316, 531 **(1994)**; Chem.Abstr., **122**, 151388w **(1995)**.

[13] M.Babizhyer, M.C.Segain; PCT In Appl.Wo, **9**, 419, 325 **(1994)**; Chem.Abstr., **122**, 133186z **(1995)**.

[14] B.R.Shah, N.C.Desai et al; Indian J.Chem., **34B**, 201-8 **(1995)**.

[15] W.E.Burge; A.M.J.Physiol., **48**, 133 **(1919)**; Chem.Abstr., **13**, 1869 **(1920)**.

[16] B.Radziszeziski; Ber., **18**, 355 **(1985)**.

[17] A.R.Sundane, K.Rudresh, N.D.Satyanarayan, S.P.Filre Math; Indian J.Pharm.Sci., **60**, 379 **(1989)**.

[18] K.N.Siand, R.N.Dar, B.M.Chopara, R.N.Kaul; Indian J.Pharma.Sci., **27**, 141 **(1965)**.