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Synthesis of some new benzo[a]phenothiazines and their ribofuranosides as possible medicinal values

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ABSTRACT

Synthesis of 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo[a] phenothiazine-5-ols, 5-acetyle12H-benzo[a]phenothiazines and 5-methoxy-12H-benzo[a]phenothiazines have been carried out from 9-chloro-6-(3-chloro-4-Fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo[a]phenothiazine-5-ones, which have been synthesized by condensing zinc mercaptide of 2-amino-5-chloro-benzenethiol and 2-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-3-chloro-1,4-methyl/2-trifluoromethylanilino)-3-chloro-1,4-naphthoquinones. The ribofuranosides *viz.* N-(2′, 3′, 5′-tri-O-benzoyl-β- D-ribofuranosyl) -5-acetoxy-9-chloro-6- (3-chloro-4-fluoro/3-chloro-)-4-methyl/2-trifluromethylanilino)-12H-benzo[a] phenothiazines have been synthesized by condensing heterocyclic base with (+)-β-D-ribofuranose-1-acetate-2,3,5-tribenzoate, in toluene in presence of $SnCl_4$ at 155-160°C. The structures of all the synthesized compounds have been established by elemental analysis, I R and ^{1}H NMR spectral data. The entire synthesized heterocyclic base and their ribofuranosides have been screened for their antifungal and antibacterial activities.

INTRODUCTION

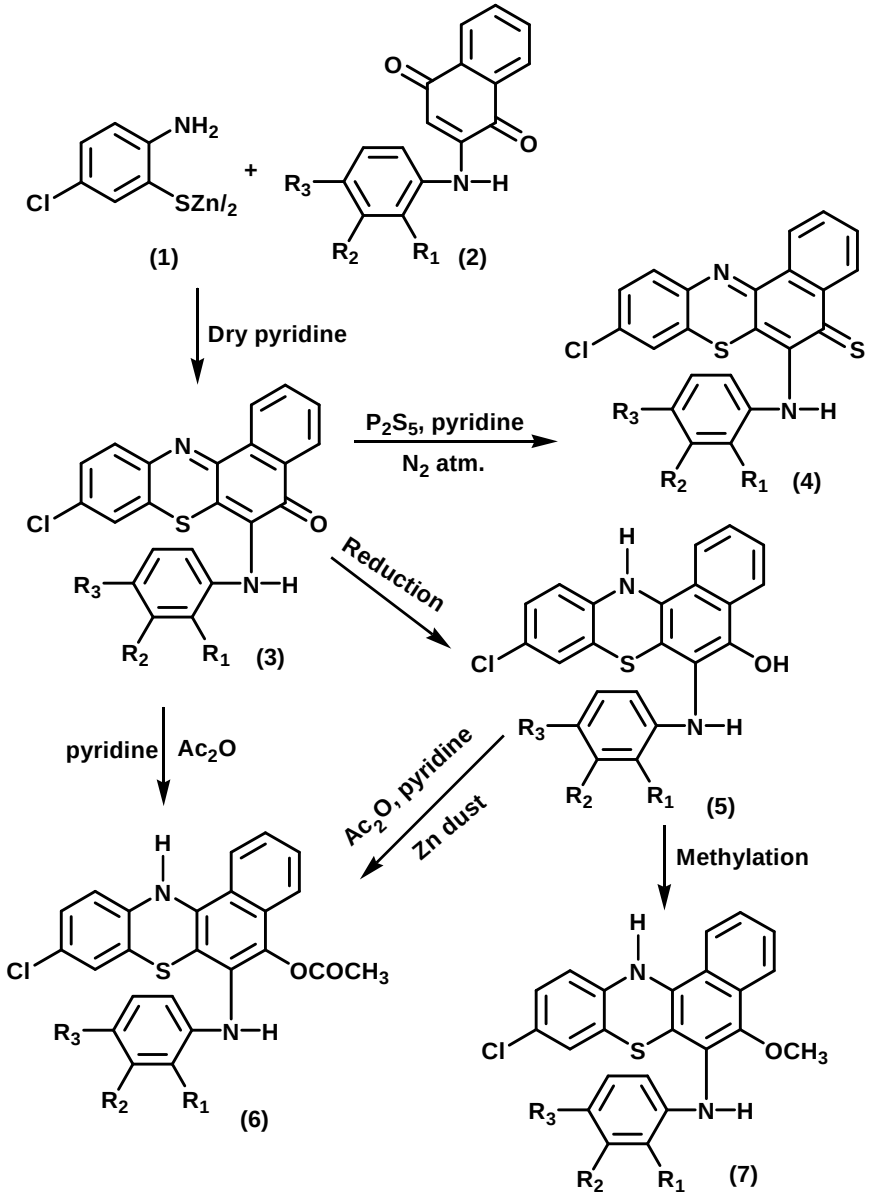
Perusal of the literature on pharmacological studies reported for 5H – benzo[a]phenothiazines class of compounds are well known chemotherapeutic agent to possess various biological activities such as antiallergic[1] antiflammatory[2] antibacterial[3] and antifungal[4,5], anticarinogenic[6,7], cytotoxic[8], antileukemic[9], antimutagenisity[10,11], antiumor[12] and antiplasmid[13] etc.

Beside theses are also useful as light sensitive copying material[14], antioxidants[15], stabilizers[16], Co-catalysts[17], indicators[18], dyes[19], lubricants[20] and coating agents[21] etc. On account of variety of therapeutic applications, significant amount of work has been reported on the synthesis of 5H-benzo[a]phenothiazine.

In view of the above results, an effort has been made to further investigate some new derivatives of benzo[a]phenothiazines and their ribofuranosides as potential chemotherapeutic agents.

RESULTS AND DISCUSSIONS

2,3-dichloro-1,4-naphthoquinone (0.01 mole) was refluxed with 3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylaniline in presence of 2-picoline and ethanol to gave of 2-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-3-chloro-1,4-naphthoquinones **(2)**. Compound **(2)** on treatment with zinc mercaptide of 2-amino-5-chlorobenzenethiol I in dry pyridine afforded 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo[a]phenothiazine-5-ones **(3)**. Compound **(1)** was prepared by the reported method[22] starting from substituted anilines. Compound **(3)** on refluxing with P2S5 in dry pyridine gave 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo [a] phenothiazine-5-thiones **(4)**. The compound 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluorome- thylanilino)-12H-benzo [a] phenothiazine-5-ols **(5)** was synthesized



Scheme 1

by on reduction of compounds **(3)** by treatment with sodium dithionite. Reductive acetylation of compound **(3)** with zinc dust Ac_2O and alternatively acetylation of compound **(5)** with Ac_2O in pyridine afforded 5-acetoxy-9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12-H-benzene [a] phenothiazine **(6)**. Compound **(5)** on treatment with dimethylsulphate and alkali in presence of sodium dithionate yielded 9-chloro-5-methoxy-6-(3-chloro-4-fluoro/3-chloro-4-metyl/2-trifluoromethyl- anilino)-12H-benzo [a] phenothiazine **(7)** (Scheme 1).

Compounds **(6)** & **(7)**, in toluene in presence of $SnCl_4$ at 0°C and 155-160°C with sugar viz (+)-β-D-ribofuranose-1-acetate-2,3,5-tribenzoate gave N-(2′, 3′, 5′-tri-O-benzoyl-β-D-ribofuranosyl)-5-acetoxy-9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo[a]phenothiazines **(8)** and N-(2′, 3′, 5′-tri-O-benzoyl-β-D-ribofuranosyl)-9-chloro-5-methoxy-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo[a]phenothiazines **(9)** (Scheme 2).

Spectral studies

IR

The IR spectra of compound **(3)** showed >NH stretching vibration in the region 3165-3135cm^{-1}, as a

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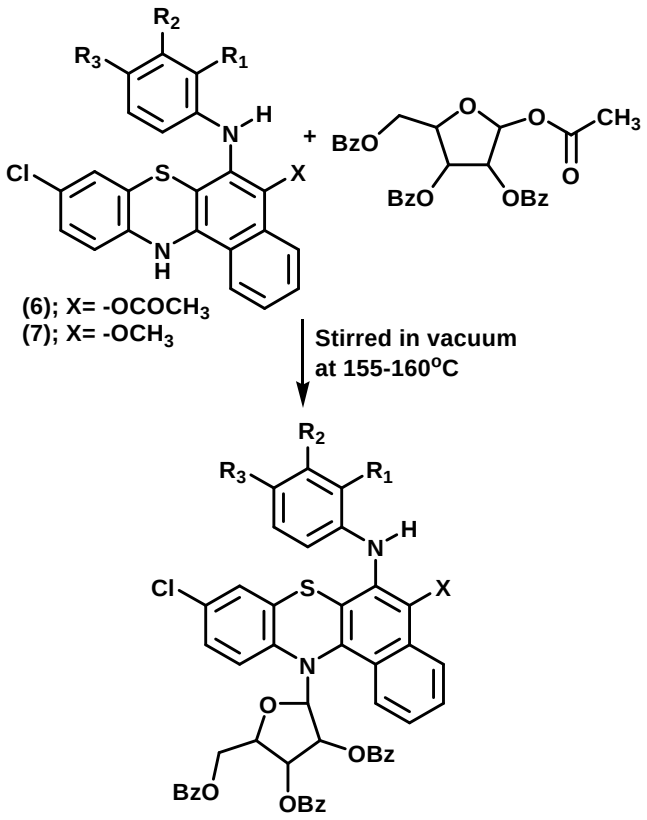

Scheme 2

weak band and the > C = O group appeared as strong band at 1690-1675cm^{-1}. Band between 1540-1510cm^{-1} and 1340 – 1335cm^{-1} were assigned to C = N and C-N starching vibration, in compounds **(3)** and **(4)** respectively. The disappearance of band due to >C = O group and appearance of new band due to >C = S in compounds **(4)** in the region 1145-1125cm^{-1} indicated the formation of compounds **(4)** from compound **(3)**. Reduction of compound **(3)** to compound **(5)** was confirmed from the absence of >C = O group band and appearance of band due to –OH group in the region 2825-2875cm^{-1}. >NH stretching vibration was observed in the region 3350 –3295cm^{-1} in compounds **(5)**, **(6)** & **(7)**. The >C = O group and C–O–C linkage in compounds **(7)** & **(9)** showed absorption bands in the 1735-1720cm^{-1} and 1185-1030cm^{-1}, respectively. Band for C–Cl group was observed between 790-765cm^{-1}. IR spectral data are shown in TABLE 1 & 3.

^{1}H NMR

In the ^{1}H NMR spectra of compounds **(3)-(9)**, the multiplet for aromatic protons appeared in the region δ 6.57-8.34. The >NH protons signal of aniline group in all there compounds was found to be merged with aromatic proton signals, whereas, the >NH proton signal of phenothiazine ring in compounds **(5)-(7)** appeared between δ 8.71-9.05.

The – OCH_3 protons and –CH_3 proton in these compounds showed a singlet in the region δ 3.87-3.95 and δ 2.31-2.45, respectively. A peak due to >NH protons of the phenothaizine ring in compounds **(7)** and **(9)** was found to be absent, indicating the site of attachment of the sugar and C – 4' H and >CH_2 protons (C-5') of the sugar moiety gave a multiplet in the region δ 4.35-4.75 and protons of C-2'H and C-3'H appeared in the region δ 5.57-5.90. C-1'H proton gave a singlet at δ 6.55, confirming the β–configuration of the sugar. Spectral data of ^{1}H NMR are shown in TABLE 2 & 3.

Antimicrobial activity

Antimicrobial evaluation of all the synthesized compounds were carried out against Escherichia coli (gram negative bacteria), Staphylococcus aureus (gram positive bacteria), and fungi e.g. Aspergillus niger, Aspergillus flatus and Rusarium oxysporium. These compounds were tested at the concentration of 100μg/disc in agar-gar media following the method due to Bauer et al.[22]. These results have been tabulated in the form of inhibition zones (mm) and activity indices (inhibition area of sample/inhibition area of the standard). STREPTOMYCIN and MYCOSTAIN were used, as reference compounds, for antimicrobial and antifungal activities, respectively. All the compounds were found to be moderately active against Escherichia coli, Staphylococcus aurous, Aspergillus niger, Aspergillus flavus and Fusarium oxysporium. A close look at the activity indices reveals that the ribofuranosides are better antimicrobial agents than their parent bases.

EXPERIMENTAL

Melting points were determined is open capillary tubes and are uncorrected. IR spectra were recorded in KBr disks on a Shimadzu FT – IR spectrometer and ^{1}H NMR spectra on Jeol AL-300 NMR spectrometer in $CDCl_3$/DMSO –d_6 using TMS as an internal standard. The homogeneity of all the synthesized compounds were checked by TLC using silica gel as absorbent and

TABLE 1 : IR (KBr : ν_{max} cm^{-1}) spectral data of the synthesized benzo[*a*]phenothiazines

Compd. No.	>NH	>C = S	>C = O	>C = C<	>C = N	C–S–C	C–O–C	OH	C–Cl
3a	3135	–	1690	1605	1530	675	1245-1030	–	765
3b	3155	–	1685	1610	1510	645	1240-1060	–	775
3c	3165	–	1675	1620	1520	650	1260-1050	–	780
4a	3320	1125	–	1605	1525	645	1220-1045	–	745
4b	3325	1145	–	1610	1535	655	1255-1035	–	740
4c	3320	1135	–	1605	1540	670	1265-1055	–	760
5a	3345	–	–	1620	–	645	1230-1035	2875	755
5b	3325	–	–	1600	–	670	1270-1060	2885	745
5c	3295	–	–	1625	–	665	1250-1065	2925	765
6a	3320	–	1725	1620	–	655	1245-1065	–	755
6b	3335	–	1755	1605	–	685	1240-1050	–	765
6c	3345	–	1735	1595	–	660	1235-1045	–	780
7a	3350	–	–	1610	–	645	1245-1020	–	770
7b	3345	–	–	1625	–	675	1225-1065	–	755
7c	3325	–	–	1605	–	650	1235-1070	–	760

TABLE 2 : ^{1}H NMR spectral data of the synthesized benzo[*a*]phenothiazines

Compd. No.	Ar-H & N-H anilino	>NH ring	$–OCH_3$	CH_3	–OH
3a	6.70-8.23	–	–	–	–
3b	6.57-7.95	–	–	2.31	–
3c	6.72-8.22	–	–	–	–
4a	6.63-8.09	–	–	–	–
4b	6.85-8.34	–	–	2.34	–
4c	6.97-8.32	–	–	–	–
5a	6.75-7.89	8.85	–	–	9.80
5b	6.79-8.33	8.80	–	2.39	9.72
5c	6.82-8.07	8.71	–	–	9.69
6a	6.57-8.25	8.95	–	–	–
6b	6.90-8.12	8.75	–	2.45	–
6c	6.95-8.25	8.87	–	–	–
7a	6.75-7.98	9.05	3.95	–	–
7b	6.83-8.29	8.90	3.87	2.35	–
7c	7.04-8.27	8.85	3.95	–	–

visualization was accomplished by UV light or iodine vapour in a chamber.

Synthesis of 2-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-3-chloro-1,4-naphthoquinones (2)

These compounds were mixture of 2,3-dichloro-1,4-naphthoquinone (0.01 mole), 3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylaniline (0.016 mole) 2-picoline (0.01 mole) in ethanol (10ml) was refluxed for 4 hrs. On cooling, a shining red crystalline was filtered, washed thoroughly with methanol, dried and recrystallized from benzene.

Synthesis of benzo[a]phenothiazines (Scheme 1.3) synthesis of 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo[a]phenothiazine-5-ones (3)

A mixture of 2-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-3-chloro-1, 4-naphthaquinone **(2)** (0.01 mole) and zinc mercaptide of substituted-2-aminobenzenethiol **(1)** (0.005 mole), in dry pyridine (50ml) was refluxed for 3 hrs. The reaction contents were cooled and equal volume of methanol was added followed by crushed ice. The solid, thus obtained was filtered, washed with ethanol, 5% hydrochloric acid and recrystallized from benzene-petroleum ether (60-80°C).

Synthesis of 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo[a]phenothiazine-5-thiones (4)

A mixture of substituted-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-5H-benzo[a]phenthiazine-5one **(3)** (0.01 mole) and P_2S_5 (0.01 mole) in 25ml dry pyridine was stirred at 130°C under nitrogen atmosphere for 12 hrs. After completion of the reaction, the contents of the flask was cooled and poured into a cold solution of NaCl (15 g min 60 ml water).

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TABLE 3 : IR and ^{1}H NMR spectral data of the synthesized ribofuranosides of benzo[*a*]phenothiazines

Compd. No.	IR (KBr : ν_{max} cm^{-1})					^{1}H NMR (δ ppm from TMS)			
	>NH anilino	>C = O	C-O-C	C-S-C	C-Cl	Ar–H and >NH anilino	–OCH_3	–CH_3	-$OCOCH_3$
8a	3275	1730	1185-1055	650	780	6.60-8.25	–	–	2.33
8b	3320	1735	1180-1165	655	765	6.63-8.09	–	2.04	2.28
8c	3285	1725	1175-1075	645	785	6.60-8.22	–	–	2.25
9a	3295	1720	1160-1030	640	770	6.63-8.27	3.82	–	–
9b	3310	1730	1185-1045	650	790	6.59-8.07	3.71	2.07	–
9c	3290	1725	1160-1065	635	775	6.66-8.28	3.79	–	–

Synthesis of 9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo[a]phenothiazine-5-ols (5)

A mixture of compound **(3)** (0.005 mole) and sodium dithionite (0.01 mole) in water (5ml) and acetone (50ml) were refluxed for 2 hrs. The colorless solution, thus obtained, was allowed to cool and poured into a very dilute solution of sodium dithionite (0.5gm) in ice cold water (1 liter). The precipitate so obtained was extracted by ether.

Synthesis of 5-acetoxy-9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12-H-benzene[a]phenothiazine (6)

Method A: By reductive acetylation of (3)

A mixture of substituted 5H-benzo[a]phenothiazine-5-one **(3)** (0.001 mole) and zinc dust (0.001 mole) in acetic anhydride (1.5ml) and pyridine (0.2ml) was stirred for 15 minutes at room temperature. The excess of zinc dust was removed by filtration and the filtrate was poured into the crushed ice which gave brown precipitate. It was then extracted from chloroform. The chloroform layer was washed with saturated aqueous solution of sodium bicarbonate and then dried over anhydrous sodium sulphate. It was filtered and the solvent was distilled off. The crude product, thus obtained was recrystallized from benzene petroleum ether (60-80°C).

Method B: By acetylation of (5)

Acetic anhydride (1.5ml) was added to substituted 12H-benzo[a]phenothiazine-5-ol **(5)** (0.001 mole) in pyridine (0.2ml). The reaction mixture was refluxed for 6 hrs. Over a steam bath. The reaction mixture of the flask was cooled, filtered and dried. These compounds were recrystallized from petroleum-ether (60-80°C).

Synthesis of 9-chloro-5-methoxy-6-(3-chloro-4-fluoro/3-chloro-4-metyl/2-trifluoromethylanilino)-12H-benzo[a]phenothiazine (7)

A mixture of compound V (0.001 mole), sodium dithionite (0.002 mole) in 10% ethanol potassium hydroxide solution (12ml) was refluxed for 15 minutes. Dimethylsulphate (0.001 mole) was then added to the above reaction mixture and it was again refluxed for 6 hrs. The reaction contents was cooled and then poured into crushed ice. A brown precipitate 50 obtained was filtered, washed with ethanol, dried and recrystallized from benzene.

Synthesis of N-(2′, 3′, 5′-tri-O-benzoyl-β-D-ribofuranosyl)-5-acetoxy-9-chloro-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo [a] phenothiazi-nes (8) and N-(2′, 3′, 5′-tri-O-benzoyl-β-D-ribofuranosyl)-9-chloro-5-methoxy-6-(3-chloro-4-fluoro/3-chloro-4-methyl/2-trifluoromethylanilino)-12H-benzo [a] phenothiazines (9)

A concentrated solution of compound **(1)**/**(2)** (0.002 mole) in toluene, (+)-β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (0.002 mole) was added and stirred, in vacuum, on an oil bath, at 155-160°C, for 15 minutes. The vacuous was broken and the reaction was protected from moisture, by using a guard tube. Stirring was, further, continued for 10 hrs. with application of vacuum for 15 minutes at every hour. The melt was dissolved in methanol, boiled for 10 minutes and cooled to room temperature. The precipitate was filtered and the filtrate was evaporated to dryness. The viscous residue, thus obtained, was dissolved in ether, filtered, concentrated and kept in a refrigerator overnight, to get crystalline ribofuranoside.

REFERENCES

[1] Y.Guindon, Y.Girard, C.K.Lau, R.Fortin, J.Rokach, C.Yoakim; (Merck Frosst Canada Inc.) U.S. US 4, 611, 056 (Cl. 544-31; CO7D265/38), 09 Sep., US Appl. 539, 215, 05 Oct. (1983) 25 **(1986)**; Chem., Abstr., **106**, 33082 **(1987)**.

[2] R.Sharma, R.D.Goyal, L.Prakash; Phosphorus, Sulfur and Silicon, **80**, 23 **(1993)**.

[3] G.Singh, Swati, A.K.Sharma, L.Prakash; Indian J.Heterocycl.Chem., **6(1)**, 9 **(1996)**; Chem.Abstr., **125**, 3288638 **(1996)**.

[4] D.A.Shirley, J.C.Gilmer, W.D.Waters; J.Chem. Socc.Part 4, 5260 **(1964)**.

[5] N.Motohashi, S.R.Gollapudi, R.Emrani, K.R.Bhattiprolu; Canc.Invest., **9(3)**, 305 **(1991)**.

[6] R.R.Gupta, M.Jain, R.S.Rathore, A.Gupta; J.Fluor.Chem., **62**, 191 **(1993)**.

[7] N.Motohashi, H.Sakagami, K.Kanata, Y.Yamamoto; Anticancer Res., **11(5)**, 1933 **(1991)**; Chem.Abstr., **116**, 165862 **(1992)**.

[8] K.Sakagami, H.Takahashi, H.Yoshida, M.Yamamura; Anticancer Res.B, **15(6)**, 2533 **(1955)**.

[9] M.Tanaka, K.Wayda, J.Molnar, C.Parkanyi, J.J.Aaron, N.Motohashi; Anticancer Res.A, **17(2)**, 839 **(1997)**; Chem.Abstr., **126**, 338484 **(1997)**.

[10] M.Tanaka, K.Wayda, J.Molnar, N.Motohashi; Anticancer Res.B, **16(6)**, 3625 **(1996)**; Chem.Abstr., **126**, 233220 **(1997)**.

[11] N.Motohashi, T.Kurihara, W.Yamanaka, K.Satoh, H.Sakagami, J.Molnar; Anticancer Res.A, **17(SA)**, 3431 **(1997)**; Chem.Abstr., **133**, 175801 **(2000)**.

[12] N.Motohashi, T.Kurihara, K.Satoh, H.Sakagami, I.Mucsi, R.Purztai, M.Szabo, J.Molnar; Anticancer Res.A, **19(3)**, 1837 **(1999)**; Chem.Abstr., **132**, 116953 **(2000)**.

[13] M.Noburu, S.Hirashi, K.Teruo, C.Klara, N.Joseph; Anticancer Res., **12(1)**, 135 **(1992)**.

[14] N.V.Gevaert-Afga; Neth.Appl., **6**, 605, 085 **(1966)**; Chem.Abstr., **66**, 7121 **(1967)**.

[15] J.C.Mollica, A.Singh; S.African Pat., **6801**, 996 **(1967)**; Chem.Abstr., **70**, 69169 **(1969)**.

[16] B.L.Burford, O.S.Kauder; Belz., **665**, 496 **(1964)**; Chem.Abstr., **64**, 19902 **(1966)**.

[17] F.J.Mais, H.Fiege, A.G.Bayer; Eur.Pat.Appl.Ep., **505**, 874 (Cl. CO7C17/12) 30 Sept., DE Appl. **4**, 110, 051, 27 Mar., (1991) 7 **(1992)**; Chem.Abstr., **118**, 22009 **(1993)**.

[18] N.V.De Bataafsche; Brit Pat., **789**, 947 **(1958)**; Chem.Abstr., **52**, 9585 **(1958)**.

[19] M.Gerhard, H.Siegfried, W.Horst, L.Toachim, N.Manfred; Ger.Pat., **139**, 268 **(1979)**; Chem. Abstr., **93**, 151668 **(1980)**.

[20] M.Gerhard, H.Siegfried, W.Horst, L.Toachim, N.Manfred; Ger.Pat., **139**, 269 **(1979)**; Chem. Abstr., **93**, 115943 **(1980)**.

[21] T.Shimizu, I.Kaneko, Y.Shimakura; Eur.Pat.Ep., **126**, 991 (Cl.CO8F21/00), 05 Dec., **(1984)**, J.P.Appl., 83/75, 557, 28 Apr. **(1983)**; 39 pp.

[22] R.L.Mital, S.K.Jain; J.Chem.Soc.C, 2148 **(1969)**.

[23] A.W.Bauer, W.M.M.Kibby, J.C.Sherris, M.Turck; Am.J.Clin.Path., **45**, 493 **(1966)**.