SYNTHESIS OF AMINOMETHYL ANGELICINS AND PSORALENS AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

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Abstract

Several hydrophilic aminomethyl angelicins and psoralens have been synthesized condensing corresponding bromomethyl derivatives with different cyclic and acyclic amines for possible photochemotherapeutic activity.

Introduction

Among psoralens, 8-methoxypsoralen (8-MOP), a naturally occuring furocoumarin is currently being used in the clinical treatment for skin diseases characterized by hyperproliferation of the cutaneous cells in combination with UV-A irradiation (1,2). The pharmacological mechanism of these compounds are although not completely established but their action of curing is widely considered due to the intercalation with DNA strands of the cells (3,4). However these type of compounds are reported to produce some unwarranted side effects on the skin such as skin toxicity (5-7) etc.. Therefore compounds like angelicins or which form only mono adducts with DNA (8) during the application are of present importance. Several researchers have reported the synthesis of angelicins such as 4,4'-dimethylangelicin, 4,5'-dimethylangelicin and 6,4'-dimethylangelicin, using different methods in the literature (9). The efficiency of the drug could be enhanced further by increasing the affinity and photoreactivity of the drug towards DNA. Thus aminomethyl psoralens and angelicins were synthesized to increase hydrophilicity of the drug, which ultimately improve therapy's efficiency.

Experimental

Melting points were determined by open capillary method and are uncorrected. Purity of the compounds was checked by TLC on silica gel G plates using iodine vapour as visualizing agent. Elemental analysis was carried out on Colemen instrument or Perkin-Elmer C,H,N,S analyzer (Model-2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (Spectrum RX 1) as KBr disks. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brucker 200MHz or Perkin-Elmer 90MHz spectrophotometer. Chemical shifts are relative to tetramethylsilane. Starting compounds 1a,b and 4a,b were synthesized according to the procedure described by Kaufman (9).

General procedure for synthesis of 2a,b and 5a,b

Angelicins/psoralens 1a,b,4a,b (0.01mol), freshly prepared NBS (0.01mol) and a pinch of benzoyl peroxide were refluxed in CCl_4 (80ml) under 200W-tungsten lamp for 16h. When the reaction got over, solution was filtered hot, excess of CCl_4 was distilled out and remaining left for evaporation. Obtained products 2a,b,5a,b were purified by column chromatography using benzene as eluent and recrystallized from benzene or ethanol. Melting points, yields, molecular formula and elemental analysis of the products are recorded in Table-1.

Table-1: Characterization data of compounds prepared 2a,b, 5a,b, 3a-k and 6a-i

Compd	M. P. (°C)	Yield (%)	Mol Formula	Analysis Found (Calcd) % C	H	N
2a	235-236	72	$C_{12}H_7O_3Br$	51.42(51.61)	2.61(2.51)	-
2b	208-210	67	$C_{13}H_9O_3Br$	52.95(53.24)	3.29(3.07)	-
5a	160-162	68	$C_{12}H_7O_3Br$	51.53(51.61)	2.32(2.51)	-
5b	168-170	65	$C_{13}H_9O_3Br$	52.95(53.24)	3.25(3.07)	-
3a	145-146	73	$C_{17}H_{17}O_3N$	71.91(72.08)	6.12(6.01)	4.71(4.95)
3b	161-162	66	$C_{16}H_{15}O_4N$	67.21(67.37)	5.50(5.26)	4.82(4.91)
3c	154-156	66	$C_{22}H_{20}O_3N_2$	73.15(73.33)	5.22(5.55)	7.95(7.78)
3d	109-110	78	$C_{16}H_{17}O_3N$	70.68(70.85)	6.35(6.27)	5.04(5.17)
3e	130-132	76	$C_{16}H_{17}O_5N$	63.18(63.37)	5.47(5.61)	4.71(4.62)
3f	144-145	69	$C_{18}H_{19}O_3N$	72.35(72.72)	6.44(6.36)	4.43(4.71)
3g	179-180	68	$C_{17}H_{17}O_4N$	67.90(68.22)	6.06(5.68)	4.51(4.68)
3h	207-209	70	$C_{23}H_{22}O_3N_2$	73.17(73.52)	6.14(5.85)	7.19(7.48)
3i	93-95	69	$C_{17}H_{19}O_3N$	71.31(71.57)	6.97(6.66)	4.65(4.91)
3j	127-128	71	$C_{17}H_{19}O_5N$	64.65(64.35)	6.29(5.99)	4.15(4.41)
3k	198-200	62	$C_{18}H_{20}O_3N_2$	69.53(69.23)	6.72(6.41)	8.75(8.97)
6a	119-120	70	$C_{17}H_{17}O_3N$	72.21(72.08)	5.82(6.01)	4.87(4.95)
6b	162-164	70	$C_{16}H_{15}O_4N$	67.12(67.37)	5.01(5.26)	4.78(4.91)
6c	180-182	75	$C_{22}H_{20}O_3N_2$	73.45(73.33)	5.68(5.55)	7.52(7.78)
6d	116-118	76	$C_{16}H_{17}O_3N$	70.61(70.85)	6.45(6.27)	5.21(5.17)
6e	139-140	80	$C_{16}H_{17}O_5N$	63.22(63.37)	5.49(5.61)	4.78(4.62)
6f	149-150	65	$C_{18}H_{19}O_3N$	72.40(72.72)	6.06(6.36)	4.36(4.71)
6g	180-182	69	$C_{17}H_{17}O_4N$	68.32(68.22)	5.55(5.68)	5.02(4.68)
6h	191-193	79	$C_{23}H_{22}O_3N_2$	73.29(73.52)	5.72(5.85)	7.57(7.48)
6i	159-160	65	$C_{18}H_{20}O_3N_2$	69.59(69.23)	6.07(6.41)	9.28(8.97)

8-Bromomethylangelicin 2a

IR (KBr) ν_{max} (cm^{-1}): 3080, 2989, 2952, 1732, 1616, 1114

^{1}H-NMR ($CDCl_3$): δ 4.70 (s, 2H, CH_2Br, C-8); 6.40 (d, J=9Hz, 1H, C-3); 7.20 (s, 1H, C-9); 7.40 (d, J=8.5Hz, 1H, C-6); 7.55 (d, J=8.5Hz, 1H, C-5); 7.80 (d, J=9Hz, 1H, C-4).

8-Bromomethyl-4-methylangelicin 2b

IR (KBr) ν_{max} (cm^{-1}): 3082, 2986, 2949, 1731, 1620, 1125

^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3, C-4); 4.55 (s, 2H, CH_2Br, C-8); 6.20 (s, 1H, C-3); 7.00 (s, 1H, C-9); 7.30 (d, J=9Hz, 1H, C-6); 7.45 (d, J=9Hz, 1H, C-5).

^{13}C-NMR ($CDCl_3$): δ 121.31, 113.00, 108.31, 103.60, 78.40, 77.00, 75.59, 22.61, 19.36

7-Bromomethylpsoralen 5a

IR (KBr) ν_{max} (cm^{-1}): 3073, 2991, 2942, 1734, 1627, 1118

^{1}H-NMR ($CDCl_3$): δ 4.65 (s, 2H, CH_2Br, C-7); 6.30 (d, J=9Hz, 1H, C-3); 6.85 (s, 1H, C-6); 7.40 (s, 1H, C-5); 7.70 (s, 1H, C-9); 7.85 (d, J=9Hz, 1H, C-4).

7-Bromomethyl-4-methylpsoralen 5b

IR (KBr) ν_{max} (cm^{-1}): 3068, 2995, 2946, 1733, 1632, 1130

^{1}H-NMR ($CDCl_3$): δ 2 55 (s, 3H, CH_3, C-4); 4.60 (s, 2H, CH_2Br, C-7); 6.25 (s, 1H, C-3); 6.90 (s, 1H, C-6); 7.45 (s, 1H, C-5); 7.75 (s, 1H, C-9).

^{13}C-NMR ($CDCl_3$): δ 116.75, 113.71, 105.86, 99.90, 78.44, 77.04, 75.63, 22.70, 19.18

General procedure for synthesis of 3(a-k) and 6(a-i)

To a solution of 2a,b,5a,b (0.001mol) in N,N-dimethylformamide (7ml), secondary amine (0.004mol) was added and refluxed for 50-55min.. After the reaction, mixture was cooled and poured over the crushed ice. The solid separated was purified by column chromatography using chloroform or mixture of chloroform and methanol in varying proportions to get aminomethyl product 3(a-k) and 6(a-i), which were recrystallized from benzene or ethanol.

8-Piperidinomethylangelicin 3a

IR (KBr) ν_{max} (cm^{-1}): 3075, 2985, 2957, 1725, 1615, 1118

^{1}H-NMR ($CDCl_3$): δ 1.70 (m, 6H, 3xCH_2 away from N in piperidine ring, C-8); 2.60 (m, 4H, 2xCH_2 adjacent to N in piperidine ring, C-8); 3.65 (s, 2H, CH_2, C-8); 6.35 (d, J=9Hz, 1H, C-3); 6.85 (s, 1H, C-9); 7.25 (m, 2H, C-6 and C-5); 7.75 (d, J=9Hz, 1H, C-4).

8-Morpholinomethylangelicin 3b

IR (KBr) ν_{max} (cm^{-1}): 3082, 2984, 2948, 1720, 1613, 1601, 1114

^{1}H-NMR ($CDCl_3$): δ 2.65 (m, 4H, 2xCH_2 adjacent to N in morpholine ring, C-8); 3.80 (m, 6H, 2xCH_2 adjacent to O in morpholine ring overlapped with CH_2, C-8); 6.40 (d, J=9Hz, 1H, C-3); 6.95 (s, 1H, C-9); 7.25-7.45 (m, 2H, C-6 and C-5); 7.80 (d, J=9Hz, 1H, C-4).

8-N,N-Diethanolaminomethylangelicin 3e

IR (KBr) ν_{max} (cm^{-1}): 3412, 3074, 2981, 2955, 1724, 1617, 1117

^{1}H-NMR ($CDCl_3$): δ 2.80 (t, 4H, 2xCH_2 adjacent to N, C-8); 3.70 (t, 4H, 2xCH_2 attached to OH, C-8); 3.95 (s, 2H, CH_2, C-8); 6.40 (d, J=9.5Hz, 1H, C-3); 6.95 (s, 1H, C-9); 7.35 (d, J=9Hz, 1H, C-6); 7.40 (d, J=9Hz, 1H, C-5); 7.85 (d, J=9.5Hz, 1H, C-4).

8-N-Phenylpiperazinomethyl-4-methylangelicin 3h

IR (KBr) ν_{max} (cm^{-1}): 3081, 2985, 2949, 1721, 1618, 1600, 1152

^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3, C-4); 2.70 (m, 4H, 2xCH_2 adjacent to N in piperazine ring, C-8); 3.20 (m, 4H, 2xCH_2 adjacent to N-C_6H_5 in piperazine ring, C-8); 3.75 (s, 2H, CH_2, C-8); 6.20 (s, 1H, C-3); 6.80 (s, 1H, C-9); 6.90-7.15 (m, 5H, N-C_6H_5); 7.30 (d, J=9Hz, 1H, C-6); 7.40 (d, J=9Hz, 1H, C-5).

8-N-Methylpiperazinomethyl-4-methylangelicin 3k

IR (KBr) ν_{max} (cm^{-1}): 3085, 2984, 2936, 1719, 1617, 1597, 1161

^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, N-CH_3, C-8); 2.45 (s, 3H, CH_3, C-4); 2.55 (m, 8H, 4xCH_2 of piperazine ring, C-8); 3.70 (s, 2H, CH_2, C-8); 6.20 (s, 1H, C-3); 6.90 (s, 1H, C-9); 7.30 (d, J=9Hz, 1H, C-6); 7.40 (d, J=9Hz, 1H, C-5).

7-Morpholinomethylpsoralen 6b

IR (KBr) ν_{max} (cm^{-1}): 3069, 2981, 2940, 1716, 1629, 1116

^{1}H-NMR ($CDCl_3$): δ 2.50 (bs, 4H, 2xCH_2 adjacent to N in morpholine ring, C-7); 3.75 (bs, 6H, 2xCH_2 adjacent to O in morpholine ring overlapped with CH_2, C-7); 6.25 (d, J=9Hz, 1H, C-3); 6.60 (s, 1H, C-6); 7.35 (s, 1H, C-5); 7.55 (s, 1H, C-9); 7.75 (d, J=9Hz, 1H, C-4).

7-N-Phenylpiperazinomethylpsoralen 6c

IR (KBr) ν_{max} (cm^{-1}): 3071, 2985, 2934, 1730, 1630, 1597, 1125

^{1}H-NMR ($CDCl_3$): δ 2.70 (m, 4H, 2xCH_2 adjacent to N in piperazine ring, C-7); 3.25 (m, 4H, 2xCH_2 adjacent to N-C_6H_5 in piperazine ring, C-7); 3.75 (s, 2H, CH_2, C-7); 6.35 (d, J=9.2Hz, 1H, C-3); 6.70 (s, 1H, C-6); 6.85-7.30 (m, 5H, N-C_6H_5); 7.45 (s, 1H, C-5); 7.60 (s, 1H, C-9); 7.80 (d, J=9.2Hz, 1H, C-4).

7-N,N-Diethanolaminomethylpsoralen 6e

IR (KBr) ν_{max} (cm^{-1}): 3374, 3071, 2985, 2935, 1729, 1631, 1137

^{1}H-NMR ($CDCl_3$): δ 2.70 (bs, 4H, 2xCH_2 adjacent to N, C-7); 3.60 (bs, 4H, 2xCH_2 attached to OH, C-7); 3.90 (s, 2H, CH_2, C-7); 6.25 (d, J=9.5Hz, 1H, C-3); 6.65 (s, 1H, C-6); 7.25 (s, 1H, C-5); 7.55 (s, 1H, C-9); 7.85 (d, J=9.5Hz, 1H, C-4).

7-Piperidinomethyl-4-methylpsoralen 6f

IR (KBr) ν_{max} (cm^{-1}): 3067, 2980, 2934, 1727, 1630, 1576, 1136

^{1}H-NMR ($CDCl_3$): δ 1.60 (m, 6H, 3xCH_2 away from N in piperidine ring, C-7); 2.50 (s, 3H, CH_3, C-4); 2.55 (m, 4H, 2xCH_2 adjacent to N in piperidine ring, C-7); 3.70 (s, 2H, CH_2, C-7); 6.25 (s, 1H, C-3); 6.65 (s, 1H, C-6); 7.40 (s, 1H, C-5); 7.70 (s, 1H, C-9).

7-N-Methylpiperazinomethyl-4-methylpsoralen 6i

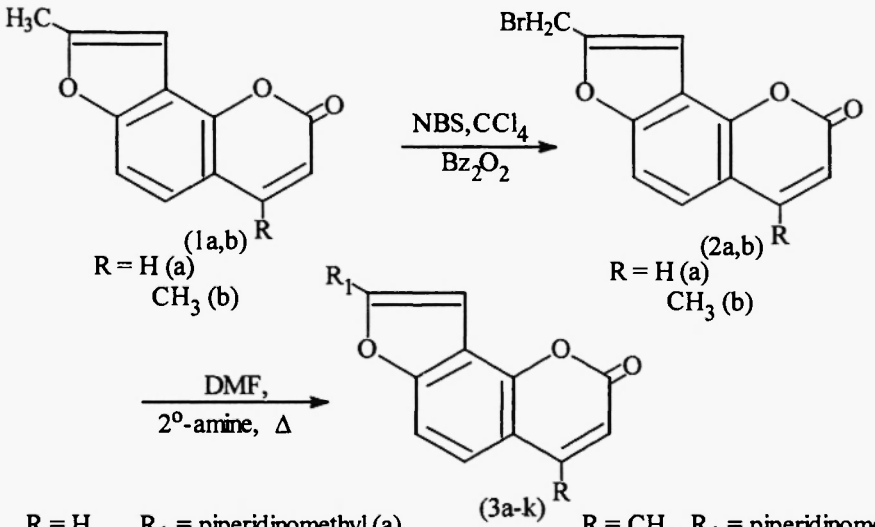
IR (KBr) ν_{max} (cm^{-1}): 3069, 2981, 2934, 1723, 1629, 1580, 1137

^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, N-CH_3, C-7); 2.50 (s, 3H, CH_3, C-4); 2.60 (m, 8H, 4xCH_2 of piperazine ring, C-7); 3.75 (s, 2H, CH_2, C-7); 6.25 (s, 1H, C-3); 6.65 (s, 1H, C-6); 7.40 (s, 1H, C-5); 7.65 (s, 1H, C-9).

Results and Discussion

The synthesis of aminomethyl furocoumarins was achieved by many workers (10-12), which includes a three-step procedure involving chloromethylation, displacement of chlorine by potassium phthalimide and subsequent hydrazinolysis. In order to obtain higher yields of aminomethyl derivatives, a new methodology is developed for their synthesis. In this procedure the angelicin and psoralen derivatives will be first brominated to convert into bromomethyl derivatives and are then subsequently treated with secondary amine to furnish the corresponding aminomethyl furocoumarins.

Thus 8-methyl/4,8-dimethyl angelicin 1a,b and 7-methyl/4,7-dimethyl psoralen 5a,b were subjected to bromination with N-bromosuccinimide (NBS) in CCl_4 using benzoyl peroxide as reaction initiator. (Schemes-1 and 2).



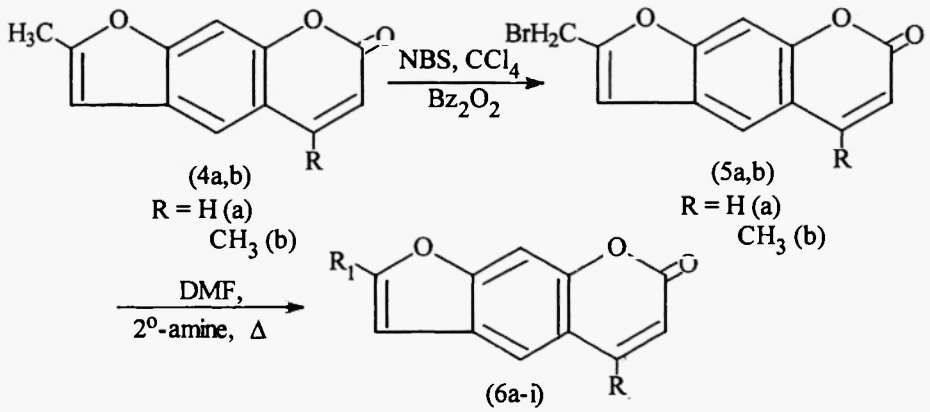
(1a,b) R = H (a), CH_3 (b)

(2a,b) R = H (a), CH_3 (b)

(3a-k)

R = H, R_1 = piperidinomethyl (a)
R = H, R_1 = morpholinomethyl (b)
R = H, R_1 = N-phenylpiperizinomethyl (c)
R = H, R_1 = N,N-diethylaminomethyl (d)
R = H, R_1 = N,N-diethanolaminomethyl (e)
R = CH_3, R_1 = piperidinomethyl (f)
R = CH_3, R_1 = morpholinomethyl (g)
R = CH_3, R_1 = N-phenylpiperizinomethyl (h)
R = CH_3, R_1 = N,N-diethylaminomethyl (i)
R = CH_3, R_1 = N,N-diethanolaminomethyl (j)
R = CH_3, R_1 = N-methylpiperazinomethyl (k)

SCHEME-1



(4a,b) R = H (a), CH_3 (b)

(5a,b) R = H (a), CH_3 (b)

(6a-i)

R = H, R_1 = piperidinomethyl (a)
R = H, R_1 = morpholinomethyl (b)
R = H, R_1 = N-phenylpiperizinomethyl (c)
R = H, R_1 = N,N-diethylaminomethyl (d)
R = H, R_1 = N,N-diethanolaminomethyl (e)
R = CH_3, R_1 = piperidinomethyl (f)
R = CH_3, R_1 = morpholinomethyl (g)
R = CH_3, R_1 = N-phenylpiperizinomethyl (h)
R = CH_3, R_1 = N-methylpiperazinomethyl (i)

SCHEME-2

The formation of bromomethyl derivatives 2a,5a was confirmed from their elemental analysis, IR and PMR spectra, whereas in 2b,5b both the methyl groups at 4,8 and 4,7 have identical chemical shifts. It was difficult to understand which methyl group had undergone bromination. ^{13}C-NMR gave the distinct chemical shifts of two methyl groups. Chemical shift of furan ring methyl group at C-8/C-7 in 2b,5b moved down field from δ 14 to 22 after bromination. Besides a down field chemical shift of furan ring proton at C-9/C-6 is also noticed from δ 6.60 to 7.00 after bromination, which clearly establishes the bromination at C-8/C-7 methyl group of furan ring.

Bromomethyl derivatives 2a,b,5a,b obtained were then condensed with different secondary amines resulted in the formation of corresponding aminomethyl angelicins/psoralens 3(a-k),6(a-i). Structures of the products were characterized on the basis of their elemental analysis, IR and/or PMR spectra.

In conclusion we have shown the synthesis of several potential chemotherapeutic agents in a convenient manner and their activity study is also being carried out which is in good progress.

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References

1. J. A. Parrish, T. B. Fitzpatrick, L. N. Tanenbaum, New Engl. J. Med. **291**, 1207 (1974).
2. R. Edelson, C. Berger, F. Gasparro, B. Jegasoth, P. Heald, B. Wintroub, E. Vonderhe, R. Knobler, K. Wolff, G. Plewig, New Engl. J. Med. **316**, 297 (1987).
3. D. Kanne, K. Straub, E. Hearst, H. Rapoport, J. Am. Chem. Soc. **104**, 6754 (1982).
4. F. Dall'Acqua, M. Terbojevich, S. Marciani, D. Vadaldi, M. Recher, Chem. Biol. Inter. **21**, 103 (1987).
5. T. F. Anderson and J. J. Vosruhees, Ann. Rev. Pharmacol. Toxicol. **20**, 135 (1980).
6. G. Ronto, K. Toth, S. Gaspar, G. Csik, J. Photochem. Photobiol.,B: Biol. **12**, 9 (1992).
7. R. Stern, S. Zielen, J. A. Parrish, J. Invest. Dermatol. **78**, 147 (1982).
8. F. Dall'Acqua, D. Vedaldi, S. Caffieri, A. Guitto, F. Bordin, P. Rodighiero, Natl. Cancer Inst. Monogr. **66**, 55 (1984).
9. K. D. Kaufman, J. Org. Chem. **26**, 117 (1961).
10. K. D. Kaufman, US 4 294 822 (1081), Chem. Abstr. 96 (1982), 35244k.
11. S. T. Issacs, C. J. Shen, J. E. Hearst, H. Rapoport, Biochemistry **16**, 1058 (1977).
12. K. D. Kaufman, D. J. Erb, T. M. Blok, R. W. Carlson, D. J. Knoechel, L. McBride, T. J. Zeitlow, J. Heterocycl. Chem. **19**, 1051 (1982).

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