Synthesis and biological activities of some quinoxaline derivatives bearing aromatic halogen nucleus

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Manuscript received 4 April 2002, revised 1 January 2003, accepted 21 March 2003

1-Aryl-3-(3'-chlorophenyl)-2-propen-1-ones (**1a-j**) on reaction with bromine in acetic acid yielded 1-aryl-3-(3'-chlorophenyl)-2,3-dibromopropan-1-ones (**2a-j**). Reaction of **2a-j** with *o*-phenylenediamine afforded the corresponding 2-(3'-chlorophenyl)-3-substituted-benzylquinoxaline (**3a-j**). The synthesized compounds were evaluated for their anticancer, antitubercular and antimicrobial activities.

Various interesting pharmacological properties have been associated with quinoxaline and its derivatives¹. Our interest in the synthesis of pharmacological active compounds prompted us to synthesize some quinoxaline derivatives bearing *m*-chlorobenzaldehyde nucleus.

All the compounds have been synthesized by literature methods². The starting compound 3-chlorobenzaldehyde on reaction with different acetophenones gave 1-aryl-3-(3'-chlorophenyl)-2-propen-1-ones (**1a-j**). Bromination of **1a-j** gave the corresponding 1-aryl-3-(3'-chlorophenyl)-2,3-dibromopropan-1-ones (**2a-j**), which on condensation with *o*-phenylenediamine in presence of concentrated H₂SO₄ afforded 2-(3'-chlorophenyl)-3-substituted-benzylquinoxalines (**3a-j**).

The anticancer screening of some selected compounds was carried out at National Cancer Institute, Department of Health & Human Service, Bethesda, U.S.A. The study was related with *in vitro* anticancer screening of 60 human cell lines derived from human solid tumors against which compounds were tested at a minimum of five concentrations at 10-fold dilution. At its primary anticancer assay, a 3-cell panel consisting of NCI-H 460 (lung), NCF-7 (breast) and SF-268 (CNS) was used. A 48 h continuous drug exposure protocol was used, and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth³. The optical densities were read on an automated spectrophotometric plate reader at a single wavelength of 515 nm. Regarding the molecular manipulations, compounds **3c** and **3g** were found active anticancer agents at primary anticancer screening. Compounds **3c** and **3g** at a 1.00E-04 molar concentration gave % growth of cells (colourimetry method) of (lung) NCI-H-460(-61), (breast) NCF-7(-65), (CNS)

1, 2, 3a	R = C ₆ H ₅ -
b	R = 4-Br-C ₆ H ₄ -
c	R = 4-Cl-C ₆ H ₄ -
d	R = 2,4-(Cl) ₂ -C ₆ H ₃ -
e	R = 2-OH-C ₆ H ₄ -
f	R = 4-OH-C ₆ H ₄ -
g	R = 2-OH-5-CH ₃ -C ₆ H ₃ -
h	R = 4-OCH ₃ -C ₆ H ₄ -
i	R = 4-CH ₃ -C ₆ H ₄ -
j	R = 4-NO ₂ -C ₆ H ₄ -

SF-268(-78) and (lung) NCI-H460(43), (breast) NCF-7(16), (CNS) SF-268(34), respectively.

Antitubercular activity was evaluated at 6.25 $\mu\text{g/ml}$ concentration against *Mycobacterium tuberculosis* H₃₇Rv in Bactec 12B medium using the Alamar radiometric system. The antimycobacterial activity data were compared with standard drug rifampin at 0.25 $\mu\text{g/ml}$ concentration which showed 98% inhibition. The compounds having 4-bromo, 4-chloro, 2,4-dichloro, 4-methyl and 4-methoxy showed significant activity, while others showed good activity. The zone of inhibition is shown in mm. Compounds **1a**, **i**, **2a-c**, **e**, **f**, **h**, **j**, **3b**, **d** (zone of inhibition 56–74 mm) showed good activity, while **3j** (89) showed significant activity. Other compounds were moderately active or inactive.

Antimicrobial activity was assayed by using the cup-plate agar diffusion method⁴ against bacteria *Escherichia coli*, *Proteus vulgaris*, *Bacillus megaterium*, *Staphylococcus aureus* and fungus *Aspergillus niger* at 40 $\mu\text{g/ml}$ concentration using amoxycillin (zone of inhibition 20–26 mm), ampicillin (16–28), ciprofloxacin (10–26), erythromycin (20–26) and griseofulvin (25) as standards. By visualizing the antimicrobial activity data, it could be observed that compounds **1c** (20 mm) and **1f** (19) were active against *E. coli*, **1c**, **e**, **3a**, **g**, **h** (19–22) were active against *P. vulgaris*, **1c** (19) was active against *B. megaterium*, and **2e**, **g**, **3d**, **b**, **e**, **g** (18–21) exhibited significant activity against *S. aureus*. compounds **2j**, **3a**, **b**, **g**, **i** (21–24 mm) displayed maximum activity against *A. niger*.

Experimental

M.ps. were determined in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu FTIR-8400 instrument, ¹H NMR spectra on a Bruker AC-300 MHz FT NMR spectrometer using TMS as an internal standard and mass spectra on a Jeol D-300 spectrometer. All the compounds gave satisfactory elemental analyses.

1-(4-Methoxyphenyl)-3-(3'-chlorophenyl)-2-propen-1-ones (1a-j): An ethanolic solution of 3-chlorobenzaldehyde (0.01 mol) and 4-methoxyacetophenone (0.01 mol) in presence of catalytic amount of 30% KOH was stirred for 24 h at room temperature. The resulting solution was then poured over crushed ice and then crystallized from ethanol: **1h** (72%), m.p. 95° (Found: C, 63.75; H, 4.28. C₁₆H₁₃OCl requires: C, 63.68; H, 4.31%; ν_{max} 3044 (CH=CH, vinyl), 1676 (C=O), 1606 (C=C, aromatic), 743 cm⁻¹ (C-C δ 2.43 (3H, s, CH₃), 7.26 (1H, d, CH-CH vinyl), 7.73 (1H, d, CH=CH vinyl), 6.94–8.04 (8H, m, ArH); m/z 272.

Similarly, other compounds were prepared (yields

70–89%): **1a**, m.p. 70°; **b**, 72°; **c**, 100°; **d**, 108°; **e**, 132°; **f**, 158°; **g**, 124°; **h**, 95°; **i**, 80°; **j**, 130°.

1-(4-Methoxyphenyl)-3-(3'-chlorophenyl)-2,3-dibromopropan-1-ones (2a-j): To a solution of 1-(4-methoxyphenyl)-3-(3'-chlorophenyl)-2-propen-1-one (0.01 mol) in acetic acid (20 ml), bromine in acetic acid (1 ml; 10%) was added slowly. The reaction mixture was stirred for 1h, then poured over crushed ice. The resulting white solid was washed with distilled water, dried and crystallized from chloroform: methanol (1:1) mixture: **2h** (80%), m.p. 180° (Found: C, 44.36; H, 2.88. C₁₆H₁₃O₂Br₂Cl requires: C, 44.39; H, 3.00%; ν_{max} 1678 (C=O), 756 (C-Cl) 586 cm⁻¹ (C-Br); δ 3.91 (3H, s, OCH₃), 5.57 (1H, d, CH-CH), 5.72 (1H, d, CH-CH), 7.00–8.10 (8H, m, ArH); m/z 432.

Similarly, other compounds were prepared (yields 68–88%): **2a**, m.p. 138°; **b**, 130°; **c**, 141°; **d**, 158°; **e**, 140°; **f**, 184°; **g**, 165°; **h**, 180°; **i**, 136°; **j**, 152°.

2-(3'-Chlorophenyl)-3-(4-methoxybenzyl)quinoxaline (3a-j): A mixture of 1-(4-methoxyphenyl)-3-(3'-chlorophenyl)-2,3-dibromopropan-1-one (0.01 mol) and benzene-1,2-diamine (0.01 mol) was taken in methanol (25 ml). A few drops of concentrated sulfuric acid were added to it and the reaction mixture was heated at 80° for 30 min on a water-bath. It was then diluted with water and the crude mass was extracted with solvent ether to remove insoluble benzene-1,2-diamine. Ether was distilled off and solid obtained was crystallized from ethanol: **3h** (67%), m.p. 156° (Found: C, 73.18; H, 4.69; N, 7.73. C₂₂H₁₇N₂OCl requires: C, 73.23; H, 4.71; N, 7.76%; ν_{max} 1564 cm⁻¹ (C=N).

Similarly, other compounds were prepared (yields 65–76%): **3a**, m.p. 138°; **b**, 140°; **d**, 155°; **e**, 145°; **f**, 125°; **g**, 140°; **h**, 156°; **i**, 118°; **j**, 126°.

Acknowledgement

The authors are thankful to Prof. and Head A. R. Parikh, Department of Chemistry, Saurashtra University, for cooperation and also thankful to R.S.I.C., Chandigarh, C.D.R.I., Lucknow, for spectral, analytical data and to TAACF, U.S.A. for providing antitubercular screening data.

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