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# Synthesis of Some New Fluorine Containing 2-(*N*-Arylamino)/2-methyl-4-aryl Thiazoles and Their Bactericidal Activity†

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Sixteen fluorine containing 2-(*N*-arylamino)/2-methyl-4-aryl thiazoles have been synthesised and characterized by spectral (IR and NMR) studies. Some representative compounds have also been screened for their bactericidal activity.

The thiazoles are used as bacteriostatics,[1] antiinflammatory and antiviral agents,[2] fungistatics,[3] antivirus drugs,[4] analgesics and as tranquilizers.[5] 2-Acetamido-5-chloromercuric and 2-acetamido-5-bromomercuric thiazoles are active against *E. coli* and *Staphylococcus aureus in vitro*.[6] 2-Amino-5-alkyl thiazoles have been formulated as active analgesics, antipyretics, tranquilizers and as antiinflammatory agents.[7] Antitumour activity has also been reported in some thiazole derivatives.[8] In connection with our comprehensive studies on new fluorine containing biologically active compounds,[9] we have now synthesized and characterized a series of new thiazoles (Table I). The bactericidal activity of some compounds has also been evaluated and encouraging results obtained.

## EXPERIMENTAL

*Preparation of fluorinated aryl thioureas*

4-Fluorophenyl-, 3-(trifluoromethyl)phenyl-, 4-chlorophenyl- and cyclohexyl thioureas have been synthesised from corresponding amines.[10]

*Preparation of fluorinated aryl hydrocarbons*

4-Fluoro-, 4-fluoro-3-methyl-, 4-trifluoromethyl benzenes and 4-fluoronaphthalene have been synthesised by Balz-Schiemann reaction.[11]

*Preparation of fluorinated aryl ketones*

4-Fluoro-, 4-fluoro-3-methyl-, 4-trifluoromethyl acetophenones and 4-fluoro acetonaphthone were synthesised by the method of Buu Hoi *et al.*[12~14]

*Preparation of fluorinated phenacyl bromides*

4-Fluoro-, 4-fluoro-3-methyl-, 4-trifluoromethyl phenacyl bromides and 4-fluoro-1-($\omega$-bromoacetyl) naphthalene have been prepared from appropriate fluorinated arylketones (0.01 M) on treatment with calculated quantities of bromine (0.01 M) dissolved in glacial acetic acid.

*Synthesis of 2-(N-arylamino)/2-methyl-4-arylthiazoles*

A mixture consisting of appropriate phenacyl bromide (0.01 M), substituted aryl thiourea (0.01 M) or thioacetamide and absolute ethanol or dry benzene (30 ml) was heated under reflux for 7 hr. The solvent was distilled off and the corresponding hydrobromide was recrystallized from a suitable solvent and tested on TLC for purity. The sixteen fluorine containing thiazoles prepared are reported in Table I, along with their analytical data and Mps.

Free base was obtained by treating the corresponding hydrobromide salt with ammonia solution until it was alkaline. The precipitated mass was filtered off, washed several times with water and recrystallized from a suitable solvent. 2-N-Pyridyl-4-fluoro phenylthiazole was, however, obtained from corresponding hydrobromide by treating it with 10% sodium hydroxide solution and the free base was recrystallised from ethanol.

*Disk diffusion test for bactericidal sensitivity*[15]

The disk diffusion method consists in impregnating a small disk of standard filter paper with varying amounts of a compound. The compound is placed in plates of culture medium to which, earlier, has been spread uniformly an inoculum of the bacterial isolate to be tested. After incubation, the sensitivity is determined by measuring the easily visible areas of inhibition of growth produced by the diffusion of the compound from the disk into the surrounding medium by viewing the plate against a ruler. The inhibition

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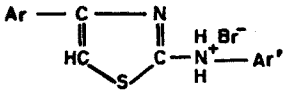
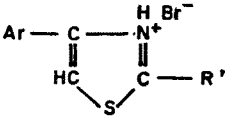
TABLE I. ANALYTICAL DATA OF FLUORINE CONTAINING 2-(*N*-ARYLAMINO)/2-METHYL-4-ARYL THIAZOLES



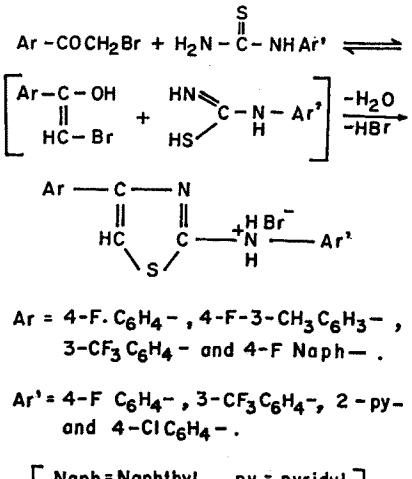
| S.N. | Substituents in Ar | Ar′/R′ | Molecular formula[b] | Yield % | Mp°C | Calcd. N% | Found |
|---|---|---|---|---|---|---|---|
| 1 | 4–F | 4–$FC_6H_4$– | $C_{15}H_{11}BrF_2N_2S$ | 67.7 | 200~204 | 7.66 | 7.86 |
| 2 | 4–F | –$C_6H_{11}$ | $C_{15}H_{18}BrFN_2S$ | 48.5 | 155 | 7.84 | 7.50 |
| 3 | 4–F | 3–$CF_3C_6H_4$– | $C_{16}H_{11}BrF_4N_2S$ | 63.6 | 182~185 | 6.91 | 7.10 |
| 4 | 4–F, 3–$CH_3$ | 3–$CF_3C_6H_4$– | $C_{17}H_{13}BrF_4N_2S$ | 80.8 | 162 | 6.68 | 6.54 |
| 5 | 4–F, 3–$CH_3$ | –$C_6H_{11}$ | $C_{16}H_{20}BrFN_2S$ | 46.9 | 155 | 7.81 | 7.34 |
| 6 | 4–F, 3–$CH_3$ | 2–pyridyl | $C_{15}H_{13}BrFN_3S$ | 86.6 | 251 | 11.47 | 11.00 |
| 7 | 4–F | 2–pyridyl | $C_{14}H_{11}BrFN_3S$ | 30.6 | 270 | 11.96 | 11.60 |
| 8 | 4–$CF_3$ | 3–$CF_3C_6H_4$– | $C_{17}H_{11}BrF_6N_2S$ | 24.2 | 110 | 5.58 | 5.50 |
| 9 | 4–$CF_3$ | 4–$ClC_6H_4$– | $C_{16}H_{11}BrClF_3N_2S$ | 32.2 | 137 | 6.43 | 6.25 |
| 10 | 4–F, 3–$CH_3$ | 4–$FC_6H_4$– | $C_{16}H_{13}BrF_2N_2S$ | 63.1 | 169 | 7.50 | 7.32 |
| 11[a] | 4–F | 4–$FC_6H_4$– | $C_{19}H_{13}BrF_2N_2S$ | 56.6 | 203 | 6.68 | 6.69 |
| 12[a] | 4–F | –$C_6H_{11}$ | $C_{19}H_{20}BrFN_2S$ | 63.0 | 196 | 6.87 | 6.70 |
| 13 | 4–F | –$CH_2$·CH=$CH_2$ | $C_{12}H_{12}BrFN_2S$ | 52.9 | 113 | 8.88 | 8.62 |
| 14 | 4–F, 3–$CH_3$ | –$CH_2$·CH=$CH_2$ | $C_{13}H_{14}BrFN_2S$ | 70.9 | 61 | 8.51 | 8.24 |



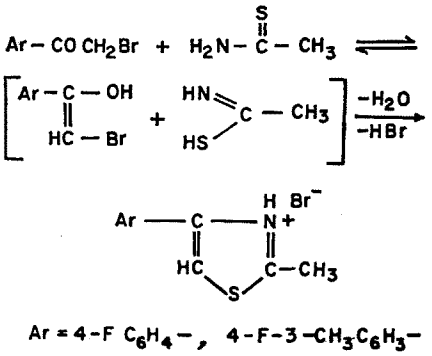
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 15 | 4–F | –$CH_3$ | $C_{10}H_9BrFNS$ | 46.3 | 185 | 5.10 | 5.28 |
| 16 | 4–F, 3–$CH_3$ | –$CH_3$ | $C_{11}H_{11}BrFNS$ | 49.9 | 102 | 4.87 | 4.68 |

[a] In case of compound Nos. 11 & 12 Ar=Naphthyl.

[b] Satisfactory C and H analyses results were obtained.




SCHEME 1.




SCHEME 2.

displayed by test bacteria was compared with that produced on the standard bacterium (*Staph. aureus* strain NCTC 6571). 3-Replicates were used for each drug on concentrations of 5, 8, 10 and 15 μg/disc. Sensitivity of some representative compounds are given in the Table II.

*Spectral studies*

The compounds have been characterized by IR and NMR spectral studies.

TABLE II. BACTERICIDAL ACTIVITY OF 2-(*N*-ARYLAMINO)/2-METHYL-4-ARYL THIAZOLES

| S. No. | Observed result with the test species[a] | M.I.C. ($\mu$g/disk) |
|---|---|---|
| 1 | Moderately sensitive | 4 |
| 2 | Moderately sensitive | 4 |
| 3 | Resistance | 6 |
| 4 | Moderately sensitive | 4 |
| 5 | Sensitive | 3 |
| 6 | Moderately sensitive | 5 |
| 9 | Resistance | 7 |
| 11 | Sensitive | 2 |
| 12 | Sensitive | 2 |
| 14 | Sensitive | 3 |
| 15 | Sensitive | 2 |
| 16 | Sensitive | 2 |

[a] Three replicates have been taken for each compound.
Sensitive=Zone of inhibition between 10~14 mm.
Moderately sensitive=Zone of inhibition between 8~10 mm.
Resistance=Zone of inhibition between 4~7 mm.

*IR spectra*: Characteristic absorption bands have been observed in the region of 3090~3550 $cm^{-1}$ (N–H), 1500~1680 $cm^{-1}$ (C=N–), 1000~1200 $cm^{-1}$ (C–F).

*$^1$HNMR spectra*: In $^1$HNMR spectra, TMS was taken as internal standard. A methine (=CH–) resonance signal at $\delta$ 6.42~7.0 ppm is in harmony with proposed structure of 2-(*N*-arylamino)/2-methyl-4-aryl thiazoles.

*Mass spectra*: Mass spectrum of 2-cyclohexylamino-4-(4′-fluoro-3′-methylphenyl) thiazole exhibited $M^+$ value at *m/e* 290. Loss of HCN from ion $M^+$ and sulfur containing species are general characteristic of the mass spectrum.

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