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# Novel 1, 2, 3, 5, 6-Thiatetraazepine; their Synthesis, Antibacterial, Antifungal Studies and their Isomerisation into 1, 2, 3, 5, 6-Pentaazepine

**P. S. Ingole[1*], V. R. Tembhare[2], C. S. Bhaskar[2], B. N. Berad[3]**
*1.P.G. Department of Chemistry, Shri Shivaji Science College, Amravati – 444 603*
*2.Department of Chemistry, Art's, Commerce & Science College, Koradi – 441111*
*3.Department of Chemistry, RTM, Nagpur University,Nagpur – 440033*

## ABSTRACT

2 (H/substituted)-4-aryl-5H,6H, 7-arylimino-1,2,3,5,6-thiatetraazepines (6) have been obtained by basification of 2-(H/substituted)-4-aryl-5H,6H-7-arylmino-1,2,3,5,6-thiatetraazepine monohydrochloride (5). The latter were synthesized by the interaction of N-aryl-S-chloro isothiocarbamoyl chloride (4) and 1-(H / substituted)-3-aryl-dihydroformazan (3), which were prepared initially by the condensation of aryl acid hydrazide (1) and hydrazine hydrate or substituted hydrazine (2). Compound (6) on benzoylation with benzoyl chloride and excess 10 % sodium hydroxide solution afforded benzoyl derivatives (7) and on boiling with aqueous ethanolic sodium hydroxide solution isomerizes into corresponding 1, 2, 3, 5, 6-pentaazepines (8). The structures of all the synthesized compounds were established on the basis of elemental analysis, equivalent weight determination, spectral analysis like IR, $^{1}$H-NMR and Mass. These newly synthesized compounds (6) were screened for their antifungal and antibacterial activity.

**Keywords:** Synthesis, 1, 2, 3, 5, 6-thiatetraazepine, antibacterial antifungal activity, isomerisation into 1, 2, 3, 5, 6-pentaazepine.

*Corresponding Author Email: preetiingole@gmail.com
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## INTRODUCTION

Recently, one method is reported for the synthesis of 1, 2, 3, 5, 6-thiatetrazepine in the literature[1] from thiocarbohydrazide. However, the synthesis of 1,3,4,6-thiatriazepine, benzo—1,2,5-thiadiazepines, 1,3,4-thiadiazepines and tricyclic 1,3,6-thiadiazepines have been reported[2-8]. Pyrollo-benzothiadiazepines have shown to possess anti HIV-1 and anti-HIV –1RT inhibitory activity comparable to nevirapine[9-11]. In an attempt to synthesize new heterocyclic systems and also to have simple and alternative method for new heterocyclic systems, we are reporting the synthesis of novel thiatetraazepines in this present communication.

## MATERIALS AND METHODS

All the reagents used in this synthesis were of analytical grade and used without further purification. The melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer spectrophotometer in nujol mull and as KBr pellets. $^1$H NMR spectra was recorded in DMSO/$CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed in ppm. Completion of all the reactions was monitored under TLC.

The parent compound 3-(pyrid-4yl) - dihydroformazan (3a) was prepared by known method[12], by refluxing the mixture of isoniazide (1a) (0.01 mol) and hydrzine hydrate (2a) (0.01 mole) in ethanoilc medium for 1 hour. After completion of reaction, the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure and the crude product was obtained. It was crystallized from ethanol and identified as 3-(pyrid-4yl)-dihydroformazan (3a), m.p. 184$^0$C.

**Synthesis of 2H/aryl-4-(pyrid-4yl)-5H, 6H, 7-p-tolylimino-1, 2, 3, 5, 6-thiatetraazepine (6a):**

3-(Pyrid-4yl)-dihydroformazan (3a) (0.01 mole) was refluxed with N-p-tolyl-S-chloroisothiocarbamoyl chloride (4a) (0.01 mole) in boiling chloroform medium for 4 hours. Evolution of hydrogen chloride gas was clearly noticed. After completion of reaction, chloroform was distilled off, when a solid sticky mass was obtained. It was repeatedly washed with petroleum ether (60-80$^0$C) and was crystallized from ethanol. It was acidic to litmus and on determination of equivalent weight, found to be a monohydrochloride of 2H –4- (pyrid-4yl)-5H, 6H – 7- p-tolylimino-1,2,3,5,6-thiatetraazepine (5a). The compound (5a) on basification with dilute ammonium hydroxide solution afforded a free base crystallized from ethanol and identified as 2H-4-(pyrid –4yl)-5H, 6H-7-p-tolylimino-1,2,3,5,6-thiatetraazepine (6a).

**Synthesis of 2-benzoyl-4-(pyrid-4yl)-5H,6H-7-p-tolylimino-1,2,3,5,6-thiatetraazepine (7a) :**

The compound 2H-4-(pyrid-4yl)-5H,6H-7-p-tolylimino-1,2,3,5,6-thiatetrazepine (6a)(0.01 mole)

was placed in excess 10 % sodium hydroxide solution. To this the drop-wise addition of benzoyl chloride was made with a constant stirring. The compound was slowly benzolyated and a solid product was observed. After completion of the reaction the product was filtered, washed with water and dried. It was crystallized from ethanol and identified as 2-benzoyl-4-(pyrid-4yl)-5H, 6H-7-p-tolylimino-1, 2, 3, 5, 6-thiatetraazepine (7a),

**Synthesis of 1-p-tolyl-2H-4-(pyrid-4yl)-5H, 6H-7-thio-1, 2, 3, 5, 6-pentaazepine (8a):**

2H-4-(pyrid-4yl)-5H,6H-7-p-tolylimino-1,2,3,5,6-thiatetraazepine (6a) (0.01 mole) was refluxed for 1.5 hours with 5 % aqueous ethanolic sodium hydroxide solution (25 ml) on water bath. After completion of the reaction, the reaction mixture was cooled and solid obtained (8a). It was filtered, washed and crystallized from ethanol,

**Antibacterial Activity**

The title compounds (6a-f) were screened for their antibacterial activity using cup-plate diffusion method. The bacterial organisms used included both gram positive and gram negative strains like E.Coli, S. Aureus, B. Subtilis, A. Aerogenes, P. Vulgaris. Sensitivity plates were seeded with a bacterial inoculum of 1 x $10^6$ CIU / ml in each well diameter (10 mm) so that concentration of each test compounds was 100 μg/ml. The zones of inhibition were recorded after incubation for 24 hrs using vernier calliper.

**Antifungal Activity**

Synthesized compounds (6a-f) were also screened for their antifungal activity using cup-plate diffusion method. The fungi used were C. albicans, A. niger and A.flavus. The method is similar to the antibacterial activity. The zones of inhibition were recorded after incubation for 37 hrs using vernier caliper. Inhibition zones record of the compounds clearly indicated that 6e was highly active against A. niger.

## RESULTS AND DISCUSSION

The compound, 1 (H/substituted)-3-aryl-dihydroformazans, were prepared by refluxing the mixture of aryl acid hydrazide (1) and hydrazine hydrate or substituted hydrazine (2) for 1 hour in ethanolic medium. On completion of reaction the solids appeared which were crystallized from ethanol and were identified as 1 (H/substituted)-3-aryl-dihydroformazans (3a-f).

Initially, 1 (H substituted) –3-aryl-dihydroformazan (3) (0.01 mole) was refluxed with N-p-tolyl-S-chloroisothiocarbamoyl chloride (4a) (0.01 mole) in boiling chloroform medium for 4 hrs. Evolution of hydrogen chloride gas was noticed. After completion of reaction, chloroform was distilled off, when a solid sticky masses were obtained. They were washed repeatedly with

petroleum ether (60-80$^0$C) to afford the granular solids. They were crystallized from ethanol and on determination of equivalent weight, identified as monoydrochlorides of 2 (H/substituted)-3-aryl-5H, 6H-7-arylimino-1,2,3,5,6- thiatetraazepines (5). These salts on basification with dilute ammonium hydroxide afforded the free bases (6). The results are presented in table 1.

These compounds were boiled for 1.5 hr with 5 % aqueous ethanolic 1:1 sodium hydroxide solution (25.0 ml) on water bath. The reaction mixture was cooled and solids obtained were filtered, washed and crystallized from ethanol, The obtained compounds (8) were found to be desulphurizable with hot alkaline plumbite solution indicating presence of >C = S linkage. The results are presented in table 2.

On the other hand, the compounds (6) were placed in excess 10 % sodium hydroxide solution. To this, the drop wise addition of benzoyl chloride (0.01 mole) was made with a constant stirring. The compound got slowly benzoylated and solids were separated out which on crystallization with ethanol afforded benzoyl derivatives (7) the results are presented in table 3. The formation of products 3-8 have been shown in scheme1.

**Synthesis of 2H/aryl-4-(pyrid-4yl)-5H, 6H, 7-p-tolylimino-1, 2, 3, 5, 6-thiatetraazepine (6a):**

Yield 79 %, m.p. 210$^0$C. (Found : C, 56.30, H, 4.91; N, 27.77; S, 10.36; Calcd. For $C_{14}H_{14}N_6S_1$; C, 56.36; H, 4.73; N, 28.17; S, 10.75 % ). The spectral analysis results are given below[13-14]: The main absorption bands observed in Infrared spectrum□ □$_{max}$[6] 3484, 3306, 3218 (NH), 1608 (C=N), 1528 (Ar -C = C) 1359 (C-N), 1206 (N – N), 691 (C-S) cm$^{-1}$.

The PMR spectrum of the product also clearly indicated the presence of □ ($CDCl_3$ + DMSO-d6) 9.00 – 8.10, (4H, dd, pyridyl protons), 7.42 (1H, S, NH), 7.39 (1H, S, NH), 7.26 (1H, S, NH), 7.23 – 7.10 (4H, m, Ar – H), 2.34 (3H, S, Ar – $CH_3$).

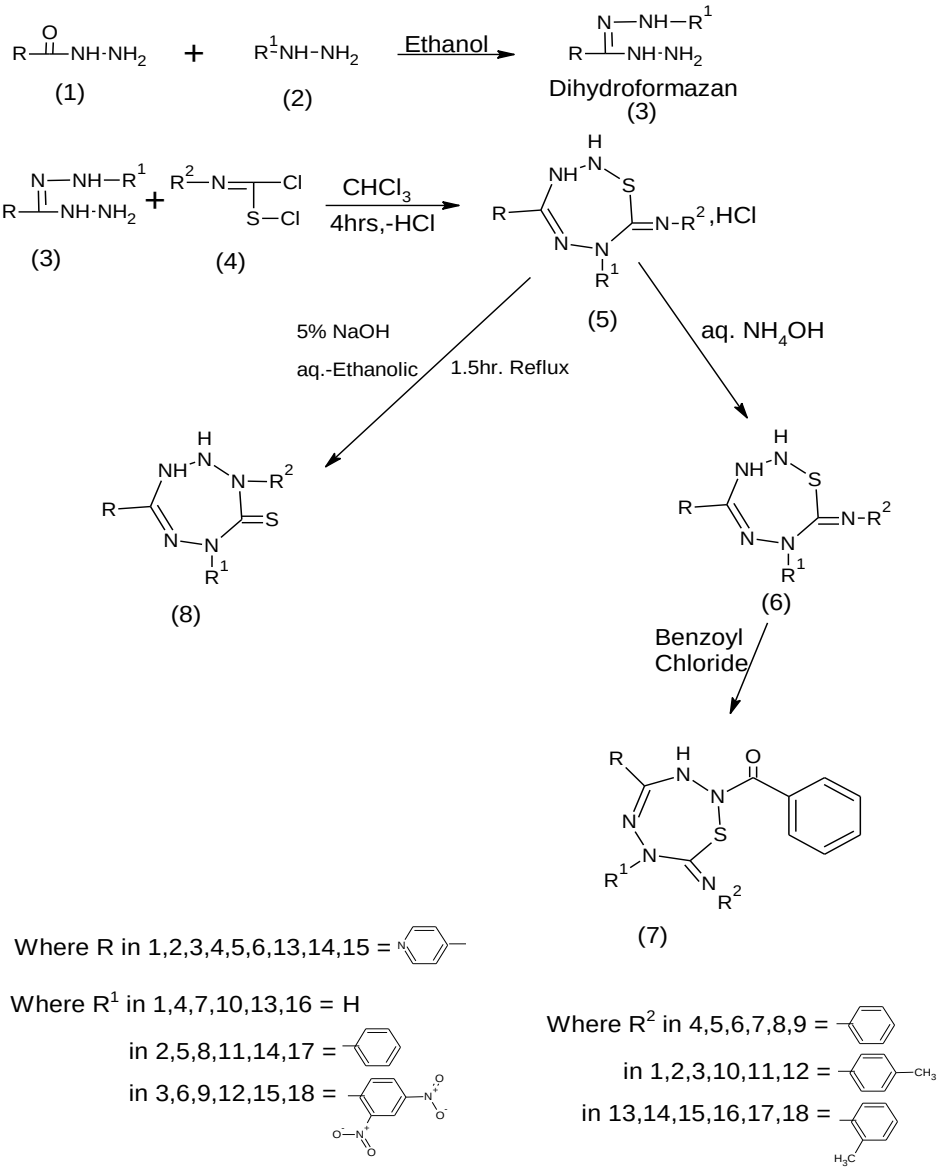
Mass Spectrum indicates ; M/Z (relative intensity) 298 ($M^+$, 26.5), 297 ($M^+$ +1, 41.1), 150 (25), 106 (28.3).

**Synthesis of 2-benzoyl-4-(pyrid-4yl)-5H,6H-7-p-tolylimino-1,2,3,5,6-thiatetraazepine (7a) :**

Yield 69%, m. p. 180$^0$C. (Found : C, 62.32; H, 4.63; N, 20.43; S, 7.52; Calcd. For $C_{21}H_{18}N_6O_1S_1$ : C, 62.67; H, 4.51; N, 20.88; S, 7.97 % )

The main absorption bands observed in Infrared spectrum□ □$_{max}$ 3280 (NH), 3170 (NH), 1671 (C = N), 1542 (Ar C = C), 1311 (C - N), 1206 (N – N), 689 (C – S).

The PMR spectrum of the product also clearly indicated the presence of δ($CDCl_3$ + DMSO –d6) 9.05 and 8.15 (4H, dd, pyridyl protons), 7.35 (1H, S, NH), 7.26 (1H, S, NH), 7.26 (1H, S, NH), 7.7 to 7.96 (9H, m, Ar-H), 2.34 (3H, S, Ar – CH3).




Where R,$R^1$ and $R^2$ are applicable to all entries in Table 1,2,3

## Reaction Scheme

**Synthesis of 1-p-tolyl-2H-4-(pyrid-4yl)-5H, 6H-7-thio-1, 2, 3, 5, 6-pentaazepine (8a):**

Yield 68%, m. p. 311$^0$C. (Found ; C, 57.73; H, 4.28; N, 26.68 ; S, 10.03; Calcd. For $C_{14}H_{14}N_6S_1$; C, 58.05; H, 4.55; N, 27.08; S, 10.33 %).

The absorption bands in the Infrared Region are □ □$_{max}$ 3450, 3167, 3095 (NH), 1636 (C = N), 1510 (C = C), 1335 (C – N), 1246 (C = S), 1223 (N – N).

The PMR spectra gives the following signals δ ($CDCl_3$ + DMSO – d6), 8.76 and 7.81 (4H, dd, pyridyl protons), 7.34 (1H, S, NH), 7.25 (1H, S, NH), 7.06 (1H, S, NH), 7.13 to 7.52 (4H, m, Ar – H), 2.32 (3H, S, Ar – $CH_3$).

**Antibacterial activity & Antifungal activity**[15-16]

Inhibition zones record of the compounds clearly indicated that 6a and 6e were highly active whereas 6b, 6c and 6f were moderately active against E.coli compound 6b highly active against A. aerogenes. Majority of the compounds were found to be slightly active. The results are presented in the table 4.

Whereas compounds 6a, 6b, 6d were moderately active. All the compounds showed satisfactory antifungal activity. The results are presented in the table 5.

**Table -1: 2H (substituted)-4(pyrid-4yl)-5H, 6H – 7-arylimino-1, 2, 3, 5, 6-Thiatetraazepines (6)**

| Entry | Compd. | R | R' | R'' | Yield (%) | m. p. ($^{O}$C) | Elemental Analysis*: Found (Calculated) % | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | N | S |
| 1 | 6a |  | H |  | 79 | 210 | 27.77(28.17) | 10.36(10.75) |
| 2 | 6b |  |  |  | 75 | 186 | 21.99(22.44) | 8.18(8.56) |
| 3 | 6c |  |  |  | 68 | 153 | 23.72(24.13) | 6.53(6.90) |
| 4 | 6d |  | H |  | 78 | 192 | 29.11(29.56) | 10.92(11.28) |
| 5 | 6e |  |  |  | 72 | 177 | 22.92(23.32) | 8.48(8.90) |
| 6 | 6f |  |  |  | 70 | 164 | 24.53(24.88) | 6.73(7.12) |
| 7 | 6g |  | H |  | 69 | 187 | 24.33(24.72) | 10.98(11.32) |
| 8 | 6h |  |  |  | 77 | 160 | 19.12(19.48) | 8.47(8.92) |
| 9 | 6i |  |  |  | 73 | 190 | 21.44(21.81) | 6.69(7.13) |
| 10 | 6j |  | H |  | 70 | 134 | 23.17(23.55) | 10.38(10.78) |
| 11 | 6k |  |  |  | 65 | 180 | 18.39(18.75) | 8.18(8.59) |
| 12 | 6l |  |  |  | 78 | 146 | 20.74(21.15) | 6.54(6.92) |
| 13 | 6m |  | H |  | 73 | 112 | 27.78(28.17) | 10.36(10.75) |
| 14 | 6n |  |  |  | 63 | 175 | 22.06(22.44) | 8.14(8.56) |
| 15 | 6o |  |  |  | 75 | 183 | 23.74(24.13) | 6.52(6.90) |
| 16 | 6p |  | H |  | 75 | 205 | 23.14(23.55) | 10.39(10.78) |
| 17 | 6q |  |  |  | 71 | 132 | 18.33(18.75) | 8.19(8.59) |
| 18 | 6r |  |  |  | 70 | 148 | 20.70(21.15) | 6.52(6.92) |

**Table 2: Synthesis of 2(H/Substituted)-4-aryl-5H,6-benzoyl-7-arylimino-1,2,3,5,6-Thiatetraazepines (7)**

| Entry | Compd. | R | R' | R'' | Yield (%) | m. p. ($^{O}$C) | Elemental Analysis*: Found (Calculated)% | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | N | S |
| 1 | 7a |  | H |  | 67 | 180 | 20.43(20.88) | 7.52(7.97) |
| 2 | 7b |  |  |  | 69 | 191 | 17.14(17.56) | 6.28(6.70) |
| 3 | 7c |  |  |  | 80 | 184 | 19.26(19.71) | 5.25(5.64) |
| 4 | 7d |  | H |  | 69 | 157 | 17.67(18.08) | 7.87(8.28) |
| 5 | 7e |  |  |  | 73 | 193 | 14.72(15.11) | 6.47(6.92) |
| 6 | 7f |  |  |  | 82 | 202 | 17.33(17.71) | 5.35(5.79) |
| 7 | 7g |  | H |  | 73 | 196 | 21.23(21.63) | 7.83(8.25) |
| 8 | 7h |  |  |  | 81 | 210 | 17.70(18.09) | 6.45(6.90) |
| 9 | 7i |  |  |  | 70 | 183 | 19.80(20.21) | 5.34(5.78) |
| 10 | 7j |  | H |  | 79 | 175 | 17.03(17.44) | 7.6(7.99) |
| 11 | 7k |  |  |  | 68 | 215 | 14.26(14.66) | 6.30(6.71) |
| 12 | 7l |  |  |  | 74 | 167 | 16.85(17.27) | 5.23(5.65) |
| 13 | 7m |  | H |  | 84 | 153 | 20.46(20.88) | 7.56(7.97) |
| 14 | 7n |  |  |  | 78 | 198 | 17.11(17.56) | 6.28(6.70) |
| 15 | 7o |  |  |  | 93 | 189 | 19.26(19.71) | 5.25(5.64) |
| 16 | 7p |  | H |  | 84 | 220 | 17.00(17.44) | 7.60(7.99) |
| 17 | 7q |  |  |  | 80 | 149 | 14.21(14.66) | 6.29(6.71) |
| 18 | 7r |  |  |  | 79 | 165 | 16.88(17.27) | 5.23(5.65) |

**Table -3: Synthesis of 1-aryl-2(H/substituted)-4-aryl-5H,6H-7-Thio-1,2,3,5,6-Pentaazepines (8)**

| Entry | Compd. | R | R' | R'' | Yield (%) | m. p. ($^{O}$C) | Elemental Analysis*: Found (Calculated)% | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | N | S |
| 1 | 8a |  | H |  | 68 | 311 | 26.68(27.08) | 10.03(10.33) |
| 2 | 8b |  |  |  | 80 | 282 | 21.35(21.75) | 8.01(8.30) |
| 3 | 8c |  |  |  | 84 | 243 | 23.11(23.52) | 6.49(6.73) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4 | 8d |  | H |  | 82 | 199 | 27.94(28.36) | 10.57(10.82) |
| 5 | 8e |  |  |  | 68 | 303 | 22.21(22.56) | 8.2(8.61) |
| 6 | 8f |  |  |  | 70 | 273 | 23.82(24.23) | 6.57(6.93) |
| 7 | 8g |  | H |  | 69 | 320 | 23.32(23.71) | 10.49(10.86) |
| 8 | 8h |  |  |  | 72 | 230 | 18.54(18.85) | 8.25(8.63) |
| 9 | 8i |  |  |  | 70 | 265 | 20.87(21.25) | 6.59(6.95) |
| 10 | 8j |  | H |  | 73 | 257 | 22.25(22.64) | 9.97(10.36) |
| 11 | 8k |  |  |  | 69 | 213 | 17.92(18.17) | 8.07(8.32) |
| 12 | 8l |  |  |  | 65 | 245 | 20.22(20.62) | 6.34(6.74) |
| 13 | 8m |  | H |  | 77 | 263 | 26.69(27.08) | 9.93(10.33) |
| 14 | 8n |  |  |  | 85 | 197 | 21.35(21.75) | 7.89(8.30) |
| 15 | 8o |  |  |  | 72 | 187 | 23.17(23.52) | 6.40(6.73) |
| 16 | 8p |  | H |  | 69 | 179 | 22.25(22.64) | 10.01(10.36) |
| 17 | 8q |  |  |  | 88 | 202 | 17.83(18.17) | 7.93(8.32) |
| 18 | 8r |  |  |  | 81 | 183 | 20.24(20.62) | 6.37(6.74) |

**Table 4: Antibacterial activity of 2(H/substituted)-4-aryl-5H, 6H-7arylimino-1,2,3,5,6-thiatetrazepine(6)**

| Organism | 6a | 6b | 6c | 6d | 6e | 6f |
|---|---|---|---|---|---|---|
| E. coli | +++ | ++ | ++ | + | +++ | ++ |
| S. aureus | ++ | ++ | +++ | + | + | - |
| B. subtilis | + | - | ++ | ++ | - | ++ |
| A. aerogenes | - | +++ | + | - | + | + |
| P. vulgaris | - | + | + | + | + | +++ |

(Diameter of inhibition zone in mm) (Concentration 100 □ g/ml)Standard drug - Streptomycin
(-) Resistant < 12.0 mm (+) Slightly Sensitive > 12.0 mm to 15.0 mm
(++) Moderately Sensitive > 15.0 mm to 25.0 mm (+++) Highly Sensitive > 25.0 mm

**Table 5 : Antifungal activity of Antibacterial activity of 2(H/substituted)-4-aryl-5H,6H-7-arylimino-1,2,3,5,6-thiatetrazepine(6)**

| Organism | 6a | 6b | 6c | 6d | 6e | 6f |
|---|---|---|---|---|---|---|
| C. albicans | ++ | + | + | - | - | - |
| A. Niger | ++ | ++ | + | ++ | +++ | + |
| A. flavus | - | - | + | - | - | ++ |

(Diameter of inhibition zone in mm) (Concentration 100 mg/ml) Standard drug - Clotrimazole
(-) Resistant < 10.0 mm (+) Slightly Sensitive > 10.0 mm to 14.0 mm
(++) Moderately Sensitive > 14 mm to 20 mm (+++) Highly Sensitive > 20.0 mm

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