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Synthesis and Studies of Antibacterial Agents

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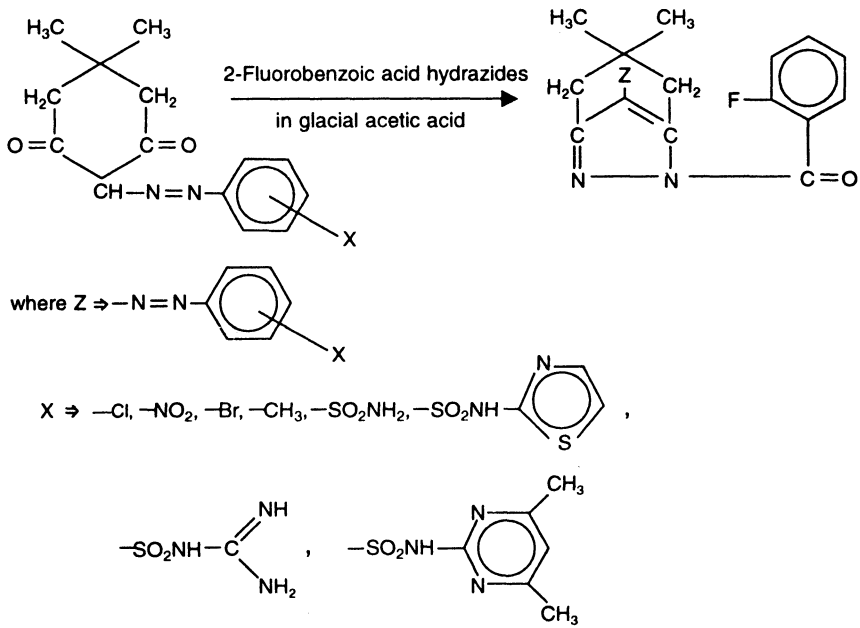
A new series of heterocyclic compounds namely N^1-(2-fluorobenzoyl)-5,5′-dimethyl cyclohexane 4-(sulpha/substituted pheyl azo)-1,2-diazoles have been synthesised and screened for their biological activity.

INTRODUCTION

Heterocyclic compounds specially diazole derivatives possess varied biological activity and have found application as potential pharmaceutical agents, such as potential anti-inflammatory[1, 2], tranquillizing, muscle relaxant, hypnotic, anticonvulsant[3–7], antituberculous[8], antineoplastic[9], antidiabetic[10], antifertility[11], antiepileptic[12], proteolytic[13], antiobesity, anticholinergic[14] antitumour[15, 16] activity.

In view of the importance of sulpha/substituted hydrazono derivatives of 5,5′-dimethyl cyclohexane-1,3-diones[17] as precursors for the synthesis of potential biological active diazole derivatives. It was though worthwhile to synthesise different sulpha/substituted hydrazono derivatives of 5,5′-dimethyl cyclohexane-1,3-diones, and their cyclised products with 2-fluorobenzoic acid hydrazides with the hope that it would show promising biological activity.



EXPERIMENTAL

All the chemicals used are either BDH or E. Merck and AR grade.

Synthesis of Bicyclic-N^1-(2-Fluorobenzoyl)-5,5'-Dimethyl Cyclohexane-4-(x) Azo-1,2-Diazoles

A mixture of sulpha/substituted hydrazono 5,5'-dimethyl cyclohexane-1-3-diones (0.05 moles) and 2-fluoro benzoic acid hydrazides (0.05 mole) was refluxed in glacial acetic acid (30 mL) for 4 h and the contents were left overnight. The coloured solid mass was filtered, washed with water, dried and crystallized from glacial acetic acid to furnish shining coloured crystals of N^1-(2-fluorobenzoyl)-5,5'-dimethyl cyclohexane-4-(x) azo-1,2-diazoles.

Their characteristics are recorded in Table-1. The yields vary from 75 to 85%.

TABLE-1

CHARACTERISTICS OF N^1-(2-FLOURO BENZOYL)-5,5'-DIMETHYL CYCLOHEXANE-4-(X) AZO-1,2-DIAZOLES

S.No.	Substituted Groups (X) (Colour)	m.p. (°C)	Molecular formula	N %, Found (Calcd.)	R_f Value
1.	2-Chloro phenyl (Pale yellow)	163	$C_{21}H_{18}N_4OClF$	14.01 (14.12)	0.7194
2.	4-Nitro phenyl (Yellow)	175	$C_{21}H_{18}N_5O_3F$	16.89 (17.19)	0.8391
3.	4-Methyl phenyl (Dark yellow)	183	$C_{22}H_{21}N_4OF$	18.14 (18.49)	0.8333
4.	4-Bromo phenyl (Orange)	162	$C_{21}H_{18}N_4OBrF$	12.35 (12.69)	0.6106
5.	2,4,6,-Tribromo phenyl (Light yellow)	179	$C_{21}H_{16}N_4OBr_3F$	9.12 (9.35)	0.7251
6.	2,3-Dimethyl-1-Phenyl pyrazolone (Shinning brown)	180	$C_{26}H_{25}N_6O_2F$	17.52 (17.79)	0.7338
7.	2-Sulphonamidobenzene (Pale yellow)	153	$C_{21}H_{20}N_5O_3SF$	15.43 (15.87)	0.7045
8.	N^1-2-Acetyl Sulphonamido benzene (Pale yellow)	189	$C_{23}H_{22}N_5O_4SF$	13.99 (14.49)	0.8531
9.	N^1-2-Thiazolyl sulphonamido benzene (Shining yellow)	171	$C_{24}H_{21}N_6O_3SF$	16.82 (17.07)	0.7935
10.	N^1-2-Guanyl sulphonamido benzene (Orange)	165	$C_{22}H_{22}N_7O_3SF$	20.17 (20.28)	0.8521
11.	N^1-2-(4,6-Dimethyl) pyrimidyl sulphonamido benzene (Yellow)	193	$C_{27}H_{26}N_7O_3SF$	16.94 (17.91)	0.6818

*The R_f values for all the compounds: on silica Gel plates (thickness 0.5 mm.), developing solvent acetone/DMF (3 : 1), on saturated chambers at room temperature (20 ± 1°C)

The homogeneity and purity of the compounds were checked through TLC and structure were established by elemental analysis, IR, NMR spectroscopic studies. R_f values are determined using acetone/DMF solvents.

IR spectra in KBr were recorded on a Perkin-Elmer grating IR spectro-

photometer. The spectra had characteristic peaks at 750 cm^{-1} ν(C—Cl), 1120 cm^{-1} ν(C—F), 1220 cm^{-1} ν(—$C(CH_3)_2$)), 2950 cm^{-1} ν(—CH_2), 1680 cm^{-1} ν(C=N), 1440 cm^{-1} ν(C—N), 1670 cm^{-1} ν(>C=O) which help in establishing the structure.

The structures of substituted bicyclic hetero compounds were also confirmed by ^{1}H-NMR spectral studies. NMR ($CDCl_3$): (δ) 2.21 (2S, 6, C_1 ), 3.12 (S, 4, —$\underline{CH_2}$), 4.25 (dd, 4, ArH-F, *ortho* to X, J = 20 and 2 Hz), 7.43 (bS, 4, ArH, C_1—Cl).

TABLE-2
NAME OF THE COMPOUNDS (DILUTION 1000 PPM)

S. No.	Name of bacteria	N^1-(2-Fluoro benzoyl) 5,5′-dimethyl cyclohexane-4-N^1-2-acetyl sulphonamido benzene azo-1,2-diazole	N^1-(2-Fluoro benzoyl) 5,5′-dimethyl cyclohexane-4-N^1-2-sulphonamido benzene azo-1,2-diazole	N^1-(2-Fluoro benzoyl) 5,5′-dimethyl cyclohexane-4-N^1-2-guanyl sulpho-namido benzene azo-1,2-diazole	N^1-(2-Fluoro-benzoyl) 5,5′-dimethyl cyclohexane-4-N^1-2-thia-zolyl sulpho-namido benzene azo-1,2-diazole	N^1-(2-Fluoro-benzoyl) 5,5′-dimethyl cyclohexane-4-N^1-2-(4,6-dimethyl) pyrimidyl sulphonamido benzene azo-1,2-diazoles
1.	*Bacillus subtilis*	+	++	–	++	–
2.	*Clostridium sporogenes*	–	+++	–	–	+
3.	*Micrococcus luteus*	++	–	+	–	–
4.	*Staphylococcus epidermis*	+	–	++	++	++
5.	*Staphylococcus aureus*	–	++	–	+	+

– = inhibition, + = zone size 2.0 to 4.0 mm, ++ = zone size 4.0 to 6.0 mm, +++ = zone size greater than 6.0 mm.

Biological Activity

The newly synthesised compounds were screened against pathogenic organism such as *Bacillus subtilis* (ATCC 6633), *Clostridium sporogenes* (ATCC 11437), *Micrococcus luteus* (ATCC 9341), *Staphylococcus epidermis* (ATCC 12228), Staphylococcus aureus (NCTT 7447) (ATCC = American type culture collection, NTCC = National type culture collection).

The microbiolical reagents used in the present studies are:

(1) Acetonitrile, and

(2) Buffer Solution: dipotassium hydrogen phosphate 16.73 g + potassium

dihydrogen phosphate 0.593 g, dissolve in 1000 mL (sterile) water for inj. IP and adjust pH to 8.0 with 18 N phosphoric acid or 10 N potassium hydroxide.

(3) Nutrient-agar media IP Hi-Media Labs. (Pvt) Ltd.):

Composition	*g/L*
Beef extract	10.00
Peptone	10.00
Sodium chloride	5.00
Agar	12.00

Suspend 37.00 g in 1000 mL distilled water, boil to dissolve the medium completely sterilized by autoclaving at 15 lbs pressure (121°C) for 15 min, apply further procedure as per IP cylinder plate/cup plate method. The compounds namely, N^1-(2-fluorobenzoyl)-5,5-dimethyl cyclohexane-4-(2-sulphonamidobenzene, N^1-2-guanyl sulphonamidobenzene, N^1-2-thiazolyl sulphonamidobenzene, N^1-2-(4,6-dimethyl) pyrimidyl sulphonamidobenzene, N^1-2-(acetyl sulphonamidobenzene) azo-1,2-diazoles showed significant activity. Their results are recorded in Table-2.

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