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Research Article

Synthesis, Antimicrobial Activity of Substituted Fluoro- *N*-((1, 3-diphenyl-1*H*-pyrazol-4-yl) methylene) benzenamines and Fluoro-3-phenyl-2-(1,3-diphenyl-1*H*-pyrazol-4-yl) thiazolidin-4-ones.

Sunil S. Bhagat[1*], Balaji D. Rupnar[1], Amol J. Shirsat[1], Ajit K. Dhas[2], Charansingh H. Gill[3]

[1]Department of Chemistry, R. B. Attal Arts, Science & Commerce College, Georai, Beed, Maharashtra, India.

[2]Department of Chemistry, Deogiri College, Aurangabad, Maharashtra, India.

[3]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India.

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***Corresponding author E-mail address:** *sunilbhagat2010@gmail.com*

ABSTRACT
Nitrogen- and sulfur-containing heterocycles play an important role, not only for life science, but also in many other industrial fields related to special and fine chemistry. The chemistry of thiazolidin-4-one ring systems is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities. In addition to this pyrazole also shows unique pharmaceutical activity. Herein we report synthesis of thiazolidin-4-one from various substituted formyl pyrazole and substituted fluoroaniline.

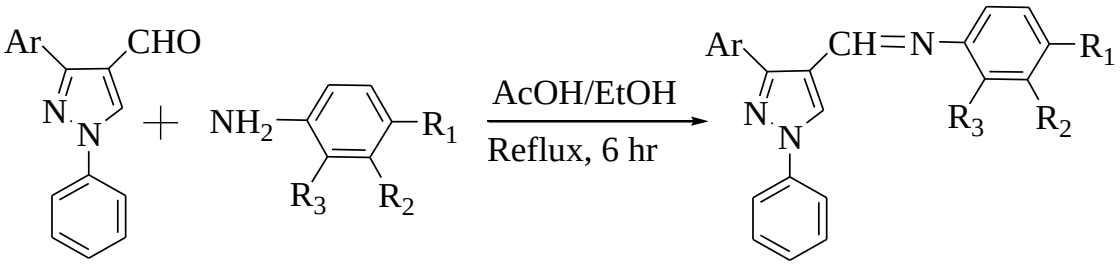
KEYWORDS
Schiff bases, Pyrazole imines, 4-thiazolidinone, antimicrobial, Gram+ve and Gram–ve microorganisms.

1. INTRODUCTION

A primary amine and an aldehyde by typically condensation formed Schiff bases. Preparation of different biologically active compounds is possible through Schiff bases as versatile intermediates. Furthermore, Schiff bases are reported to have variety of antimicrobial activities including antifungal, antibacterial, anti cancer and herbicidal activities [1-5]. Five-membered ring system containing with two adjacent nitrogen are pyrazoles. These are one of the significant members of heterocyclic compounds in organic chemistry. They have attracted scientist due to wide application in material and pharmaceutical industry [6-9].Schiff bases are used as very useful chelating drugs. Substitution of the pyrazole ring was mainly aimed to prepare derivatives of Schiff bases to which show various biological activities such as evaluate for their biological applications. [10-13]. Microorganisms are showing Increasing resistance to currently available drugs such antimicrobial agents are the major concern about morbidity and mortality all over the world. Hence novel antimicrobial drug development is still required. Azomethine functional group carrying –C,N– compounds which are called as Schiff bases have great significance in medicinal and pharmaceutical fields because of their most versatility as synthetic intermediates in organic chemistry and also showing a good range of antimicrobial activities, such as antituberculosis [14], anticancer [15], analgesic and anti-inflammatory [16], anticonvulsant [17] These Schiff bases are good intermediates for the synthesis of many heterocyclic ring systems like thiazolidinones [18], azetidinones [19]

Chemist over the years attracted by numerous bioactive molecules which were made up of various heteroatoms such as nitrogen, sulphur and oxygen. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. 1,3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position [20] The 4- thiazolidinone is very important and has been used in a number of clinically used drugs. They have been useful as antitubercular, anti-inflammatory, as antiviral agents, antimicrobial and especially as anti-HIV agents. Presence of arylazo, [21] sulfamoylphenylazo [22] or phenylhydrazono [23] moieties at different positions of the thiazolidone ring enhanced anti-microbial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan [24] Numerous reports have appeared in the literature which highlight their chemistry and pharmacological uses [25 -26]

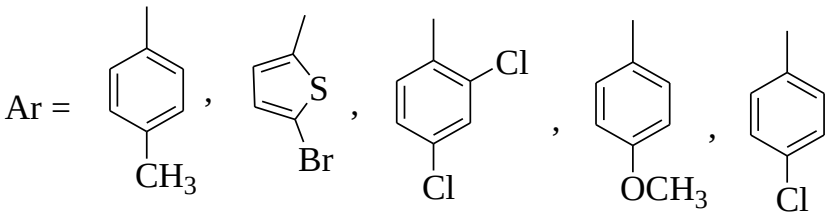
2. MATERIALS AND METHODS



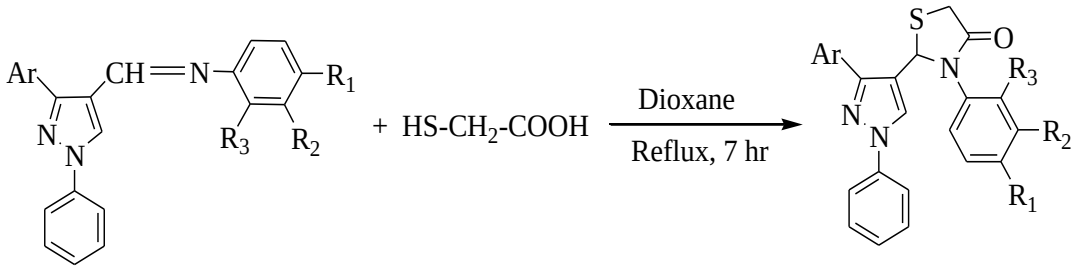
1(a-j) **2** **3(a-j)**

R_1=F,R_2=R_3=H

R_1=R_3=F,R_2=H



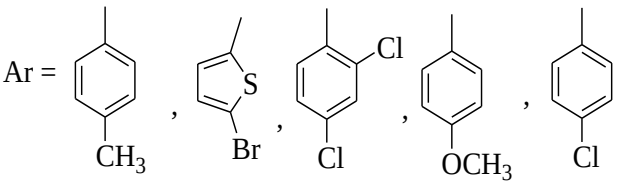
Scheme 1



3(a-j) **4** **5(a-j)**

R_1=F,R_2=R_3=H

R_1=R_3=F,R_2=H



Scheme 2

General procedure for the synthesis of (E)-N-((3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-4-fluorobenzenamine (3d)

A mixture of 4-formyl pyrazole **1**(1.0gm, 0.0030mol) and aniline **2** (0.39ml, 0.0036mol) in 10ml ethanol containing few drops of glacial acetic acid was refluxed for 3-5hr. After completion of

reaction (checked by TLC), the excess of solvent removed on rotary evaporator to yield solid which was washed with petroleum ether followed by crystallization from ethanol. The compounds 3(a-j) were prepared by following the general procedure. Physical data are recorded in Table 1. Their structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

General procedure for the synthesis of 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-(4-fluorophenyl)thiazolidin-4-one(5d)

To a solution of imine 3d (0.2 gm, 0.00046mol) in dry dioxane was added thioglycollic acid 4 (0.08 gm, 0.00093mol).The contents were refluxed for 6h until completion of reaction. Excess solvent was removed under reduced pressure and the residue treated with saturated solution of $NaHCO_3$, extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and solvent distilled off. The residue on recrystallization from ethanol gave 4-thiazolidinone. The compounds 5(a-j) were prepared by following the general procedure. Physical data are recorded in Table 2. Their structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

Table 1. Physical data of compounds 3(a-j)

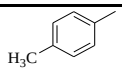
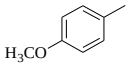
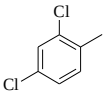
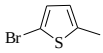
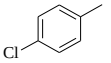
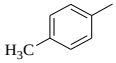
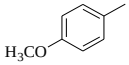
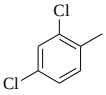
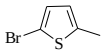
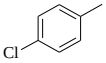
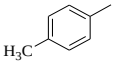
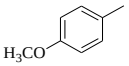
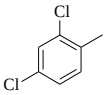
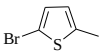
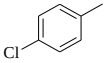
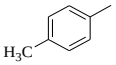
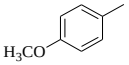
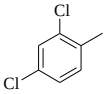
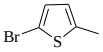
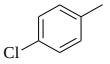
Comp.	Ar	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
3a		H	H	F	140-142	65
3b		H	H	F	144-146	87
3c		H	H	F	148-150	75
3d		H	H	F	138-140	63
3e		H	H	F	156-158	72
3f		F	H	F	154-156	64
3g		F	H	F	132-134	90
3h		F	H	F	162-164	73
3i		F	H	F	110-112	84
3j		F	H	F	144-146	74

Table 2. Physical data of compounds 5(a-j)

Comp.	Ar	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
5a		H	H	F	172-174	68

5b		H	H	F	164-166	74
5c		H	H	F	156-158	72
5d		H	H	F	240-242	68
5e		H	H	F	232-234	58
5f		F	H	F	244-246	60
5g		F	H	F	208-210	68
5h		F	H	F	224-226	70
5i		F	H	F	212-214	62
5j		F	H	F	242-244	64

Selected spectral data of some representative compounds (3d)

IR (cm^{-1}): 1091 (Ar-Br), 1595 (C=N), 1616(C=C). **^{1}H NMR (**DMSO) δ ppm: 7.219-7.412 (m, 6H, Ar-H), 7.532-7.571 (m, 2H, Ar-H), 7.921-7.996 (m, 3H, Ar-H), 8.642(s, 1H, -CH=N-), 9.142(s, 1H, Pyrazole-H). **ES-MS (**m/z): 426 (M+1), 428 (M+3).

Selected spectral data of some representative compounds (5d)

IR (cm^{-1}): 1062(Ar-Br), 1217(C-F), 1597(C=N), 1688 (C=O).**^{1}H NMR** ($CDCl_3$) δ ppm: 3.8551-3.8943 (d, 1H, -CH_2- Thiazolidinone ring, *J*=15.68 Hz), 3.9674-4.0047 (d, 1H, -CH_2- Thiazolidinone ring, *J*=14.92Hz), 6.5488 (s,1H, -CH-Thiazolidinone ring) , 6.9808-7.0026(d, 1H, Ar-H, *J*=8.72 Hz) ,7.0026-7.0239(d, 1H, Ar-H, *J*=8.52 Hz), 7.1051-7.1381(m, 2H, Ar-H), 7.2458-7.3222(m, 2H, Ar-H), 7.3880-7.4712(m, 3H, Ar-H), 7.7238-7.7595 (m, 2H, Ar-H), 8.4709(s, 1H, Pyrazole-H).**ES-MS (**m/z): 500.1 (M+1), 502(M+3).

3. RESULTS AND DISCUSSION

The pyrazole derivatives were synthesized successfully in moderate to good yields. The newly synthesized compounds were identified on the basis of melting point range, IR, 1H NMR, Mass spectral analysis. All the newly synthesized derivatives were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity

Compounds 3(a-j) and 5(a-j) were screened for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 25923), Staphylococcus albus, Klebsiella pnuemoniae* using Ciprofloxacin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Fluconazole as standard drug. All the tests were evaluated at 100 µg/ml concentration. The culture media was Muller Hinton agar. The zone of inhibition was

measured in mm after 24 hr of incubation at 37oC. DMSO is used as control. Microbial data for corresponding compounds is summarized in Table 3.

Table 3 In-*vitro* antimicrobial activity of various substituted Fluoro- *N*-((1, 3-diphenyl-1*H*-pyrazol-4-yl) methylene) benzenamines Fluoro-3-phenyl-2-(1, 3-diphenyl-1*H*-pyrazol-4-yl) thiazolidin-4-ones.

Disc Diffusion Method

Sr. No.	**Compound No.**	Inhibition Zone Diameter (mm)					
		Candida sp.	*S. aureus*	*S.albus*	*Klebsiella pnuemoniae*	*E. coli*	***Pseudomonas sp.***
1.	3a	----	2	3	5	2	**4**
2.	3b	----	6	4	2	2	**1**
3.	3c	----	9	14	9	6	**6**
4.	3d	----	2	3	7	8	**4**
5.	3e	----	2	4	6	7	**3**
6.	3f	1	12	15	11	14	**19**
7.	3g	2	1	1	7	10	**6**
8.	3h	----	3	4	9	15	**11**
9.	3i	----	5	3	2	1	**1**
10.	3j	----	2	5	4	2	**7**
11.	5a	----	3	7	2	4	**6**
12.	5b	----	5	12	6	4	**5**
13.	5c	----	7	4	9	8	**5**
14.	5d	----	8	5	4	5	**3**
15.	5e	----	7	5	6	4	**6**
16.	5f	1	10	15	12	10	**17**
17.	5g	2	3	1	7	10	**8**
18.	5h	----	4	4	9	11	**11**
19.	5i	----	6	3	5	3	**1**
20.	5j	----	4	4	8	4	**3**
21.	Control	8	3	3	4	6	**10**
22.	Ciprofloxacin	---	20	22	22	21	**23**
23.	**Fluconazole**	**23**	**---**	**---**	**---**	**---**	**---**

4. ACKNOWLEGDEMENTS

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