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Original article

Antimicrobial studies of 2,4-dichloro-5-fluorophenyl containing oxadiazoles

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Abstract

A series of 2,4-dichloro-5-fluorophenyl containing 1,3,4-oxadiazoles (**10** and **11**) were synthesized by $POCl_3$ cyclization of 2,4-dichloro-5-fluorobenzoyl hydrazide (**4**) and 2-(2,4-dichloro-5-fluorophenyl)cinchoninyl hydrazide (**8**) with aryloxyacetic acids (**9**). The structures of newly synthesized compounds were characterized by spectral and elemental analyses. All the compounds were screened for their antibacterial and antifungal activities. Compounds **10a**, **10d** and **11g** showed very good antimicrobial activity. Compound **10d** showed good bactericidal and fungicidal activities.

Keywords: 2,4,-Dichloro-5-fluorobenzoyl hydrazide; Cinchoninyl hydrazide; $POCl_3$ cyclization; 1,3,4-Oxadiazoles; Antimicrobial activity

1. Introduction

In recent days active research has been initiated on halogen containing heterocycles, particularly fluorine containing heterocycles. 2,4-Dichloro-5-fluoroacetophenone is used in the synthesis of drugs like ciprofloxacin and their analogues [1]. Moreover, incorporation of fluorine could alter the course of reaction as well as biological activities [2–4]. Furthermore, the introduction of fluorine atom or CF_3 group into an organic molecule largely enhances the pharmacological properties as compared with the non-fluorinated analogues.

Incorporation of fluorine may also lead to increased lipid solubility thereby enhancing the rates of absorption and transport of drugs in vivo. The replacement of hydrogen or a hydroxyl group by fluorine is a strategy widely used in drug development to alter biological function. Despite the fact that fluorine has greater size than hydrogen, several studies have demonstrated that fluorine is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites [5].

Quinoline ring structure is found in plant alkaloids such as Cinchonin and Quinine, which are used in the treatment of malaria [6]. Cinchophen (2-phenylquinoline-4-carboxylic acid) is used as an analgesic and its hydrochloride salt finds application as antipyretic and uricosuric drug [7]. Some cinchophen derivatives display anti-inflammatory, analgesic [8], immunosuppressive [9], antifebrile anodyne, antirheumatic and glucosuria metabolic activities [10] etc.

1,3,4-Oxadiazoles are thermally stable and neutral heteroaromatic molecules. 1,3,4-Oxadiazole derivatives display quite a broad spectrum of biological activities such as antimicrobial [11], antimycobacterial [12], antiviral [13], anticonvulsant [14], antiproliferative [15], anti-inflammatory [16] and insecticidal properties [17]. Certain 1,3,4-oxadiazoles also find application as photosensitisers, liquid crystals and organic light emitting diodes [18]. Polyhalogen substituted oxadiazoles showed various activities [17].

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Prompted by the biological activities of fluorine containing heterocycles, cinchophen and 1,3,4-oxadiazoles, it was contemplated to synthesize 2,4-dichloro-5-fluorophenyl containing 1,3,4-oxadiazoles and to pursue in vitro antibacterial and antifungal screening. The results of the antibacterial and antifungal activities are discussed in this paper.

2. Chemistry

2,4-Dichloro-5-fluorobenzoic acid was obtained by haloform reaction of 2,4-dichloro-5-fluoroacetophenone [11]. 2,4-Dichloro-5-fluorobenzoyl hydrazide (**4**) was prepared from the corresponding acid according to the literature method [17]. 2-(2,4-Dichloro-5-fluorophenyl)cinchoninic acid (**6**) was prepared by reaction of isatin (**5**) with 2,4-dichloro-5-fluoroacetophenone under Pfitzinger conditions [19]. 2-(2,4-Dichloro-5-fluorophenyl)cinchoninyl hydrazide (**8**) was obtained from corresponding acid by esterification and further treatment with hydrazine hydrate. Aryloxyacetic acids (**9**) were prepared from the corresponding phenols [20]. Aryloxyacetic acids when treated with **4** and **8** in presence of $POCl_3$ produced 2,5-disubstituted-1,3,4-oxadiazoles (**10** and **11**) in good yields. The reaction sequences are outlined in Schemes 1–3.

3. Results and discussion

The IR spectrum of compound **10a**, showed an absorption band at 3075 cm^{-1} due to aromatic stretch. Another absorption band at 2924 cm^{-1} was due to aliphatic stretch. The absorption band for C=N group was observed at 1616 cm^{-1}. The other prominent absorption bands observed in the IR spectrum are at 1267 (C–O–C), 1083 (C–F), 821 and 758 (C–Cl) cm^{-1}.

The ^1H NMR spectrum of **10a**, showed a singlet at δ 2.25 attributable to CH_3 protons. The OCH_2 protons resonated as a singlet at δ 4.62. The aromatic protons of *p*-cresyloxy moiety appeared as two doublets at δ 6.90 and δ 7.14 ($J = 8.5$ Hz) each integrating for two protons, respectively. A doublet at δ 7.97 ($J_{H-F\ meta} = 6.4$ Hz) integrating for one proton was attributable to the C_3 proton of dichlorofluorophenyl moiety. The C_6 proton of dichlorofluorophenyl moiety resonated as doublet at δ 8.07 ($J_{H-F\ ortho} = 9.4$ Hz).

Further evidence for the formation of oxadiazole (**10a**) was obtained by recording its mass spectrum. The mass spectrum of the compound (**10a**) showed molecular ion peak at *m*/*z* 352, in conformity with the molecular formula $C_{16}H_{11}Cl_2FN_2O_2$. The other fragmentation peaks observed are at *m*/*z* 191 (10%) and 107 (22%). The characterization data of oxadiazoles (**10** and **11**) are given in Table 1.

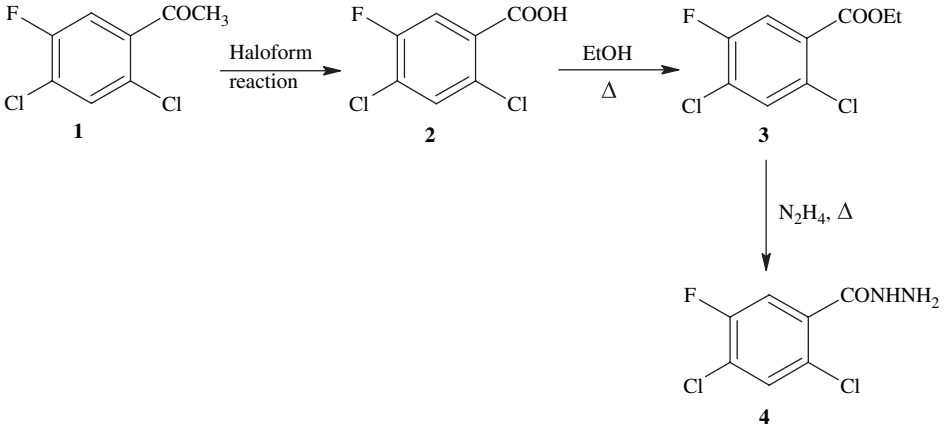
4. Pharmacology

4.1. Antibacterial studies

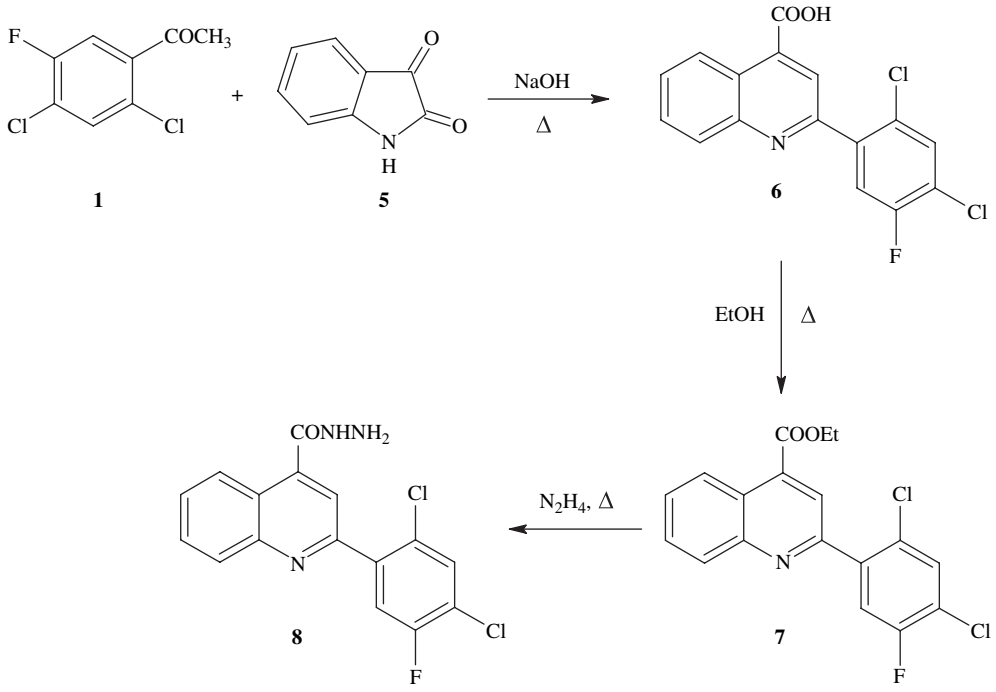
The newly prepared compounds were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphylococcus aureus* (ATCC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method [21,22]. A standard inoculum ($1-2 \times 10^7$ c.f.u./ml 0.5 McFarland standards) was introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.25 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. The plates were inverted and incubated for 24 h at 37 °C. Ciprofloxacin was used as a standard drug. Inhibition zones were measured and compared with the controls. The bacterial zones of inhibition values are given in Table 2.

Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 5×10^5 c.f.u. of actively dividing bacteria cells. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC).

To obtain the minimum bacterial concentration (MBC), 0.1 ml volume was taken from each tube and spread on agar plates. The number of c.f.u. was counted after 18–24 h of



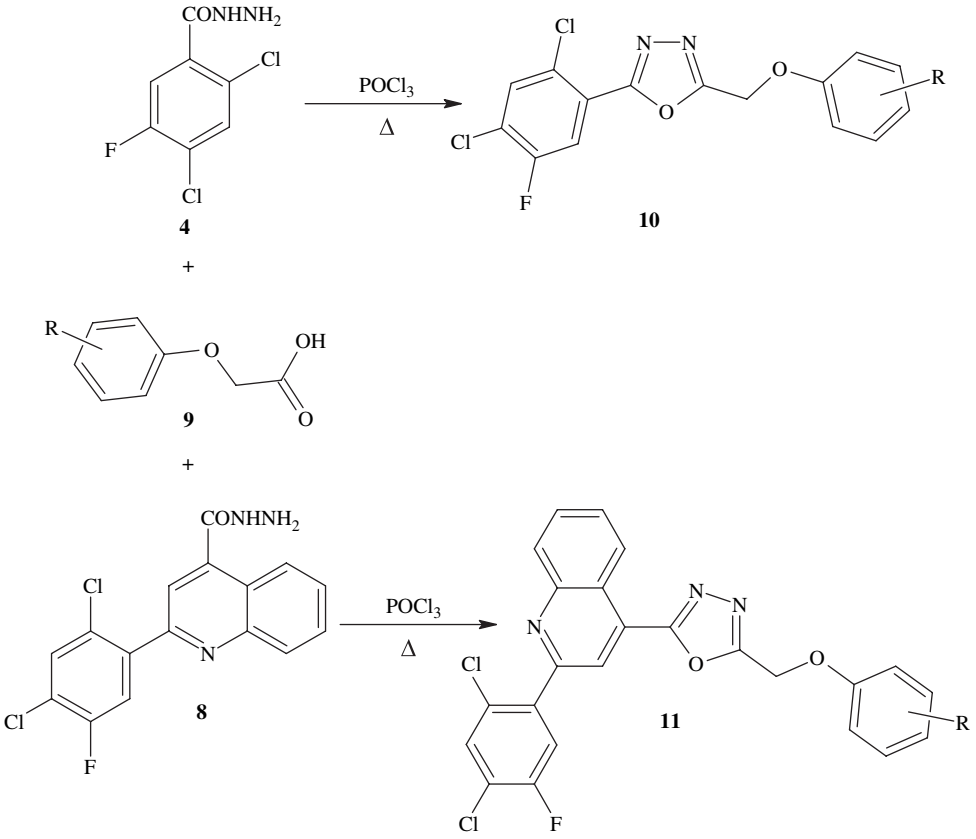
Scheme 1.



Scheme 2.

incubation at 35 °C. MBC was defined as the lowest drug concentration at which 99.9% of the inoculum was killed. The minimum inhibitory concentration and minimum bactericidal concentration are given in Table 3.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Compounds **10a**, **10b**, **10d**, **11d**, **11c** and **11g** showed good inhibition against *S. aureus* and *E. coli* species



Scheme 3. Synthesis of 2,5-disubstituted-1,3,4-oxadiazole (**10** and **11**).

Table 1
Characterization data of oxadiazoles (**10** and **11**)

Compd.		R	Mol. formula	M.p. [°C]	Yield [%]	Analysis (%) found (calculated)		
						C	H	N
10a	Dichlorofluorophenyl	4-CH_3	$C_{16}H_{11}Cl_2FN_2O_2$	110–112	78	53.95 (54.39)	3.00 (3.12)	7.05 (7.19)
10b	Dichlorofluorphenyl	2-CH_3	$C_{16}H_{11}Cl_2FN_2O_2$	169–172	65	54.09 (54.39)	3.05 (3.12)	7.10 (7.19)
10c	Dichlorofluorophenyl	2-Cl	$C_{15}H_8Cl_3FN_2O_2$	104–106	72	47.85 (48.19)	2.08 (2.14)	7.42 (7.50)
10d	Dichlorofluorophenyl	4-Cl-2-CH_3	$C_{16}H_{10}Cl_3FN_2O_2$	126–128	81	49.31 (49.55)	2.22 (2.58)	7.15 (7.23)
10e	Dichlorofluorophenyl	4-Cl-3-CH_3	$C_{16}H_{10}Cl_3FN_2O_2$	136–138	70	49.40 (49.55)	2.29 (2.58)	7.10 (7.23)
11a	Cinchoninyl	4-CH_3	$C_{25}H_{16}Cl_2FN_3O_2$	162–164	75	62.21 (62.50)	3.20 (3.33)	8.63 (8.75)
11b	Cinchoninyl	2-CH_3	$C_{25}H_{16}Cl_2FN_3O_2$	174–177	68	62.25 (62.50)	3.25 (3.33)	8.60 (8.75)
11c	Cinchoninyl	4-Cl	$C_{24}H_{13}Cl_3FN_3O_2$	159–161	72	57.22 (57.54)	2.47 (2.60)	8.21 (8.39)
11d	Cinchoninyl	2-Cl	$C_{24}H_{13}Cl_3FN_3O_2$	215–217	77	57.31 (57.54)	2.40 (2.60)	8.15 (8.39)
11e	Cinchoninyl	4-Cl-2-CH_3	$C_{25}H_{15}Cl_3FN_3O_2$	186–189	80	57.95 (58.31)	2.80 (2.85)	8.09 (8.04)
11f	Cinchoninyl	4-Cl-3-CH_3	$C_{25}H_{15}Cl_3FN_3O_2$	194–197	85	58.03 (58.31)	2.75 (2.85)	8.04 (8.04)
11g	Cinchoninyl	2.4-Cl_2	$C_{24}H_{12}Cl_4FN_3O_2$	200–02	71	53.48 (53.83)	2.12 (2.24)	7.49 (7.85)

at 6.25 μg/ml concentrations. Compounds **10a**, **10b**, **10d**, **11c** and **11g** exhibited good antibacterial activity almost equivalent to that of standard. The MBC of few compounds was found to be the same as MIC but in most of the compounds it was two or three or four folds higher than their corresponding MIC result. Compound **10d** showed good bactericidal activity against *S. aureus*, *P. aeruginosa* and *K. pneumoniae* bacterial strains.

4.2. Antifungal studies

The newly prepared compounds were screened for their antifungal activity against *Candida albicans*, *Aspergillus fumigatus*, *Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured) in DMSO by agar diffusion method [23,24]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty millilitres of agar media was poured into each petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The fungal activity of each compound was compared with Greseofulvin as standard drug. Inhibition zones were measured and compared with the controls. The fungal zones of inhibition values are given in Table 4.

The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls was inoculated with approximately 1.6×10^4–6×10^4 c.f.u./ml. The cultures were incubated for 48 h at 35 °C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentration (MIC). To obtain the minimum fungicidal concentration (MFC), 0.1 ml volume was taken from each tube and spread on agar plates. The number of c.f.u. was counted after 48 h of incubation at 35 °C. MFC was defined as the lowest drug concentration at which 99.9% of the inoculum was killed. The minimum inhibitory concentration and minimum fungicidal concentration are given in Table 5.

Table 2
Zone of inhibition (mm) of oxadiazoles (**10** and **11**)

Compd.	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
10a	22	25	32	18
10b	19	27	28	16
10c	15	18	15	12
10d	20	24	29	19
10e	10	15	–	12
11a	15	10	8	15
11b	12	12	–	–
11c	19	25	32	18
11d	–	20	22	–
11e	17	–	12	–
11f	–	17	26	–
11g	20	26	30	17
Standard	22	27	32	19

– Indicates bacteria are resistant to the compounds >100 μg/ml. Ciprofloxacin is used as the standard.

Table 3
MIC and MBC results of oxadiazoles (**10** and **11**)

Compd.	*Staphylococcus aureus*		*Escherichia coli*		*Pseudomonas aeruginosa*		*Klebsiella pneumoniae*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
10a	6.25	12.5	6.25	6.25	6.25	12.5	12.5	25
10b	6.25	25	6.25	25	6.25	6.25	12.5	50
10c	12.5	50	6.25	12.5	12.5	25	25	50
10d	6.25	6.25	6.25	12.5	6.25	6.25	6.25	6.25
10e	25	50	12.5	100	–	–	–	–
11a	12.5	100	25	50	25	50	12.5	25
11b	12.5	25	12.5	25	–	–	–	–
11c	6.25	12.5	6.25	6.25	6.25	25	12.5	25
11d	–	–	6.25	50	25	50	25	100
11e	6.25	25	–	–	12.5	50	–	–
11f	–	–	12.5	25	6.25	25	–	–
11g	6.25	6.25	6.25	12.5	6.25	12.5	12.5	12.5
Standard	6.25	12.5	6.25	12.5	6.25	12.5	12.5	12.5

– Indicates bacteria are resistant to the compounds >100 μg/ml; MIC (μg/ml) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit bacterial growth; MBC (μg/ml) = minimum bactericidal concentration, i.e., the lowest concentration to completely kill bacteria.

Table 4
Zone of inhibition (mm) of oxadiazoles (**10** and **11**)

Compd.	*Candida albicans*	*Aspergillus fumigatus*	*Trichophyton mentagrophytes*	*Penicillium marneffei*
10a	27	26	24	18
10b	15	10	–	8
10c	10	19	12	–
10d	28	25	22	19
10e	–	8	–	10
11a	–	–	17	15
11b	25	–	18	–
11c	12	16	15	20
11d	20	–	–	12
11e	–	12	19	–
11f	–	15	–	12
11g	29	27	21	19
Standard	30	27	24	20

– Indicates fungus are resistant to the compounds >100 μg/ml; greseofulvin is used as the standard drug.

The antifungal screening data showed only moderate activity. Among the screened compounds, **10a**, **10d** and **11g** showed good inhibition against all the fungal strains. The MBC of few compounds was found to be the same as MIC but in most of the compounds it was two or three or four folds higher than the corresponding MIC result. Compound **10d** showed good fungicidal activity against *C. albicans*, *A. fumigatus* and *P. marneffei* fungal strains.

5. Conclusion

We have synthesized series of 2,4-dichloro-5-fluorophenyl bearing 1,3,4-oxadiazoles. Among the synthesized oxadiazoles, compounds with methyl, chloromethyl and dichloro substituents in the phenyl ring at 5th position of oxadiazoles were found to increase the antimicrobial activity. Compound with chloromethylphenyl moiety showed good bactericidal and fungicidal activities.

Table 5
MIC and MFC results of oxadiazoles (**10** and **11**)

Compd.	*Candida albicans*		*Aspergillus fumigatus*		*Trichophyton mentagrophytes*		*Penicillium marneffei*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
10a	6.25	6.25	6.25	12.5	6.25	6.25	6.25	12.5
10b	12.5	25	25	100	–	–	25	100
10c	25	50	6.25	12.5	12.5	50	–	–
10d	6.25	6.25	6.25	6.25	6.25	25	6.25	6.25
10e	–	–	25	50	–	–	25	50
11a	–	–	–	–	6.25	6.25	12.5	25
11b	6.25	25	–	–	6.25	12.5	–	–
11c	12.5	50	6.25	25	6.25	12.5	6.25	12.5
11d	6.25	12.5	–	–	–	–	12.5	25
11e	–	–	12.5	50	6.25	12.5	–	–
11f	–	–	12.5	25	–	–	12.5	50
11g	6.25	6.25	6.25	12.5	6.25	25	6.25	6.25
Standard	6.25	12.5	6.25	12.5	6.25	12.5	6.25	12.5

– Indicates bacteria are resistant to the compounds >100 μg/ml; MIC (μg/ml) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit fungal growth; MFC (μg/ml) = minimum fungicidal concentration, i.e., the lowest concentration to completely kill fungus.

6. Experimental protocols

6.1. Chemistry

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker or AMX 400 MHz NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a FAB mass spectrometer operating at 70 eV. The purity of compounds was checked by thin layer chromatography (TLC) on silica gel plate using a mixture of petroleum ether and ethyl acetate.

6.2. Procedure for the preparation of 2,4-dichloro-5-fluorobenzoyl hydrazide (*4*)

2,4-Dichloro-5-fluorobenzoic acid was obtained by haloform reaction of 2,4-dichloro-5-fluoroacetophenone [11]. 2,4-Dichloro-5-fluorobenzoyl hydrazide (**4**) was prepared according to the literature method [17].

6.3. General procedure for the preparation 2-(2,4-dichloro-5-fluorophenyl)-cinchoninyl hydrazide (*8*)

2-(2,4-Dichloro-5-fluorophenyl)cinchoninic acid (**6**) was prepared by reaction of isatin and 2,4-dichloro-5-fluoroacetophenone under Pfitzinger conditions [19] and converted to hydrazide by usual methods.

6.4. General procedure for the preparation of aryloxyacetic acids (*9*)

Aryloxyacetic acids (**9**) were prepared from the corresponding phenols according to the literature procedure [20].

6.5. Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (*10* and *11*)

A mixture of hydrazide (**4** and **8**) (0.01 mol), aryloxyacetic acid (**9**) (0.01 mol) and phosphorus oxychloride (10 ml) was refluxed on a water bath for ~9 h. Excess of phosphorus oxychloride was removed under reduced pressure. The reaction mixture was cooled and poured onto crushed ice and neutralized with aqueous ammonia. The resulting solid product was filtered, dried and recrystallized from a mixture of ethanol and dimethylformamide.

6.5.1. Compound *10c*

IR (KBr, υ cm^{-1}): 3097 (Ar-H), 2965 (C–H), 1585 (C=N), 1105 (C–F), 827 and 731 (C–Cl); ^{1}H NMR (δ, $CDCl_3$): 5.63 (s, 2H, OCH_2), 7.02–7.07 (m, 1H, *o*-chlorophenoxy protons), 7.32–7.40 (m, 2H, *o*-chlorophenoxy protons), 7.46 (d, 1H, *o*-chlorophenoxy protons $J = 7.8$ Hz), 8.05 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 9.3$ Hz), 8.13 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.6$ Hz).

*6.5.2. Compound **10d***

IR (KBr, υ cm^{-1}): 3080 (Ar-H), 2915 (C–H), 1600 (C=N), 1089 (C–F), 833 and 736 (C–Cl); ^{1}H NMR (δ, $CDCl_3$): 2.22 (s, 3H, CH_3), 5.34 (s, 2H, OCH_2), 6.91 (dd, 1H, *p*-chloro-*o*-cresyloxy proton, $J = 8.2$ Hz), 7.12 (d, 1H, *p*-chloro-*o*-cresyloxy proton, $J = 2.2$ Hz), 7.15 (s, 1H, *p*-chloro-*o*-cresyloxy proton), 7.63 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.4$ Hz), 7.85 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 8.9$ Hz); mass (%): M^+ 387 (25), 191 (10), 155 (22).

*6.5.3. Compound **10e***

IR (KBr, υ cm^{-1}): 3089 (Ar-H), 2915 (C–H), 1604 (C=N), 1101 (C–F), 831 and 736 (C–Cl); ^{1}H NMR (δ, DMSO-d_6): 2.35 (s, 3H, CH_3), 5.34 (s, 2H, OCH_2), 6.81 (dd, 1H, *p*-chloro-*m*-cresyloxy proton, $J = 2.9$ Hz), 6.91 (d, 1H, *p*-chloro-*m*-cresyloxy proton, $J = 2.8$ Hz), 6.96 (d, 1H, *p*-chloro-*m*-cresyloxy proton, $J = 8.2$ Hz), 7.63 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.5$ Hz), 7.84 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 8.9$ Hz); mass (%): M^+ 387 (11), 191 (55), 141 (14), 128 (10), 64 (30).

*6.5.4. Compound **11a***

IR (KBr, υ cm^{-1}): 3095 (Ar-H), 2986 (C–H), 1602 (C=N), 1105 (C–F), 854 and 740 (C–Cl); ^{1}H NMR (δ, DMSO-d_6): 2.31 (s, 3H, CH_3), 4.66 (s, 2H, OCH_2), 6.93 (d, 2H, *p*-cresyloxy proton, $J = 8.5$ Hz), 7.12 (d, 2H, *p*-cresyloxy proton, $J = 8.5$ Hz), 7.75–7.93 (m, 3H, cinchoninyl protons), 8.04 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.7$ Hz), 8.14–819 (m, 2H, cinchoninyl protons), 9.04 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 7.9$ Hz).

*6.5.5. Compound **11d***

IR (KBr, υ cm^{-1}): 3081 (Ar-H), 1557 (C=N), 1102 (C–F), 835 and 727 (C–Cl); ^{1}H NMR (δ, DMSO-d_6): 4.85 (s, 2H, OCH_2), 6.95–7.46 (m, 4H, *o*-chlorophenoxy and cinchoninyl protons), 7.75–7.93 (m, 4H, *o*-chlorophenoxy and cinchoninyl protons), 8.04 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} =$ 6.7 Hz), 8.15 (d, 1H, cinchoninyl proton, $J = 8.1$ Hz), 8.38 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 8.2$ Hz).

*6.5.6. Compound **11e***

IR (KBr, υ cm^{-1}): 3089 (Ar-H), 2895 (C–H), 1602 (C=N), 1098 (C–F), 821 and 740 (C–Cl); mass (%): M^+ 514 (90), 387 (25), 290 (43), 191(10), 155 (25), 125 (10).

*6.5.7. Compound **11f***

IR (KBr, υ cm^{-1}): 3099 (Ar-H), 2955 (C–H), 1610 (C=N), 1108 (C–F), 832 and 721 (C–Cl); ^{1}H NMR (δ, DMSO-d_6): 2.19 (s, 3H, CH_3), 5.62 (s, 2H, OCH_2), 7.25–7.29 (m, 3H, *p*-chloro-*m*-cresyloxy and cinchoninyl protons), 7.89–8.02 (m, 3H, *p*-chloro-*m*-cresyloxy and cinchoninyl protons), 8.06 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} =$ 6.7 Hz), 8.24 (d, 1H, cinchoninyl proton, $J = 8.1$ Hz), 8.34 (s, 1H, cinchoninyl proton), 9.04 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 8.4$ Hz); mass (%): 514 (M^+, 25), 389 (5), (65), 289 (12), 155 (22).

*6.5.8. Compound **11g***

IR (KBr, υ cm^{-1}): 3091 (Ar-H), 1578 (C=N), 1110 (C–F), 838 and 727 (C–Cl); ^{1}H NMR (δ, DMSO-d_6): 5.73 (s, 2H, OCH_2), 7.42–7.49 (m, 2H, dichlorophenyl protons), 7.63 (d, 1H, dichlorophenyl protons, $J = 2.2$ Hz), 7.86–8.01 (m, 3H, cinchoninyl protons), 8.05 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ meta} = 6.7$ Hz), 8.24 (d, 1H, cinchoninyl protons, $J = 8.2$ Hz), 8.34 (s, 1H, cinchoninyl proton), 9.04 (d, 1H, dichlorofluorophenyl proton, $J_{H-F\ ortho} = 8.2$ Hz); mass (%): M^+ 534 (65), 373 (8), 289 (12).

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