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Synthesis, characterization and antibacterial activity studies on some fluorine containing quinoline-4-carboxylic acids and their derivatives

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A series of 3-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl-2-(2,4-dichloro-5-fluorophenyl)quinolines **5** have been synthesized by the condensation of hitherto unreported quinoline-4-carboxylic acids **3** with various 3-substituted-4-amino-5-mercapto-1,2,4-triazoles **4**. The structures of newly synthesized compounds have been confirmed on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. The newly synthesized compounds are evaluated for their antibacterial activities.

Keywords: Quinoline-4-carboxylic acids; Fluoroheterocycles; 1,2,4-triazoles; 1,3,4-thiadiazoles; antibacterial activity

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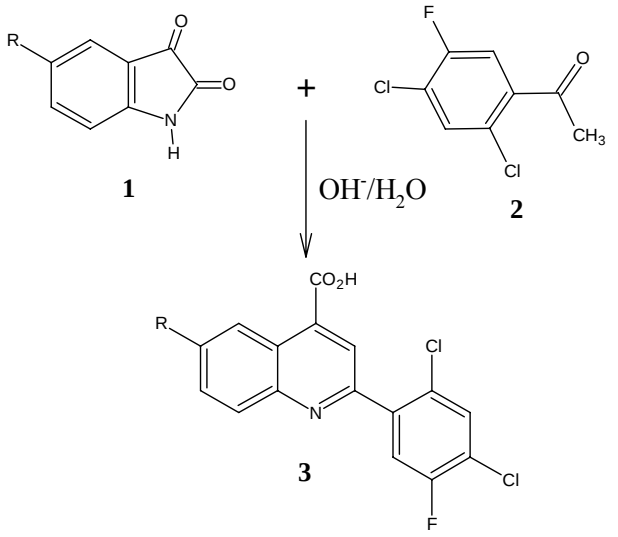
Quinoline and its derivatives are known for their anti-malarial and therapeutic properties[1]. A number of quinoline derivatives are known to possess anti-tumor, anti-bacterial, anti-fungal, hypotensive, anti-leishmanial, anti-HIV, analgesic and anti-inflammatory activities[2-7]. Applications of quinoline derivatives are fast spreading from antimalarial drugs to almost every branch of medicinal chemistry[8,9]. A fluorine atom located at a suitable position of a bio-active molecule is found to exert a profound pharmacological effect[10,11].

Prompted by recent literature observations[12a] and as a part of our search for bio-active quinoline derivatives[12b], we undertook the synthesis of fluorine containing quinoline-4-carboxylic acids and their heterocyclic derivatives. The results of these studies along with the antibacterial activities of these compounds are reported in this paper. 2-(2,4-Dichloro-5-fluorophenyl)quinoline-4-carboxylic acid **3** (R=H) was prepared by heating isatin **1** with 2,4-dichloro-5-fluoroacetophenone **2** in the presence of sodium hydroxide followed by acidification. Similarly, 6-bromo-2-(2,4-dichloro-5-fluorophenyl)-quinoline-4-carboxylic acid **3** (R=Br) was prepared from 5-bromoisatin (**Scheme I**). The condensation of quinoline-4-carboxylic acids **3** with various 3-substituted-4-amino-5-mercapto-1,2,4-triazoles in the presence of phosphorus oxychloride afforded 3-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl-2-(2,4-dichloro-5-fluorophenyl)quinolines **5 (Table I, Scheme II)**. The quinoline-4-carboxylic acids **3** and their triazolothiadiazole derivatives **5** were characterized by elemental analysis and spectral (IR, ^{1}H NMR and mass) data.

In the ^{1}H NMR spectrum of quinoline-4-carboxylic acids **3a**, the signals due to two protons of 2,4-dichloro-5-fluorophenyl ring appeared as two doublets at δ 8.79 (J = 9 Hz) and 8.69 (J = 6 Hz), respectively. The remaining aromatic protons appeared as multiplet in the region δ 6.7-8.2. The mass spectrum of this compound showed an intense molecular ion peak at m/z 334 consistent with its molecular formula, $C_{16}H_7Cl_2FNO_2$ with its isotopic peaks at m/z 336 and 338. The loss of chlorine radical from the molecular ion resulted in the formation of a peak at m/z 299. The loss of CO_2 from the molecular



R = H, Br

Scheme I

Mechanism for Scheme I

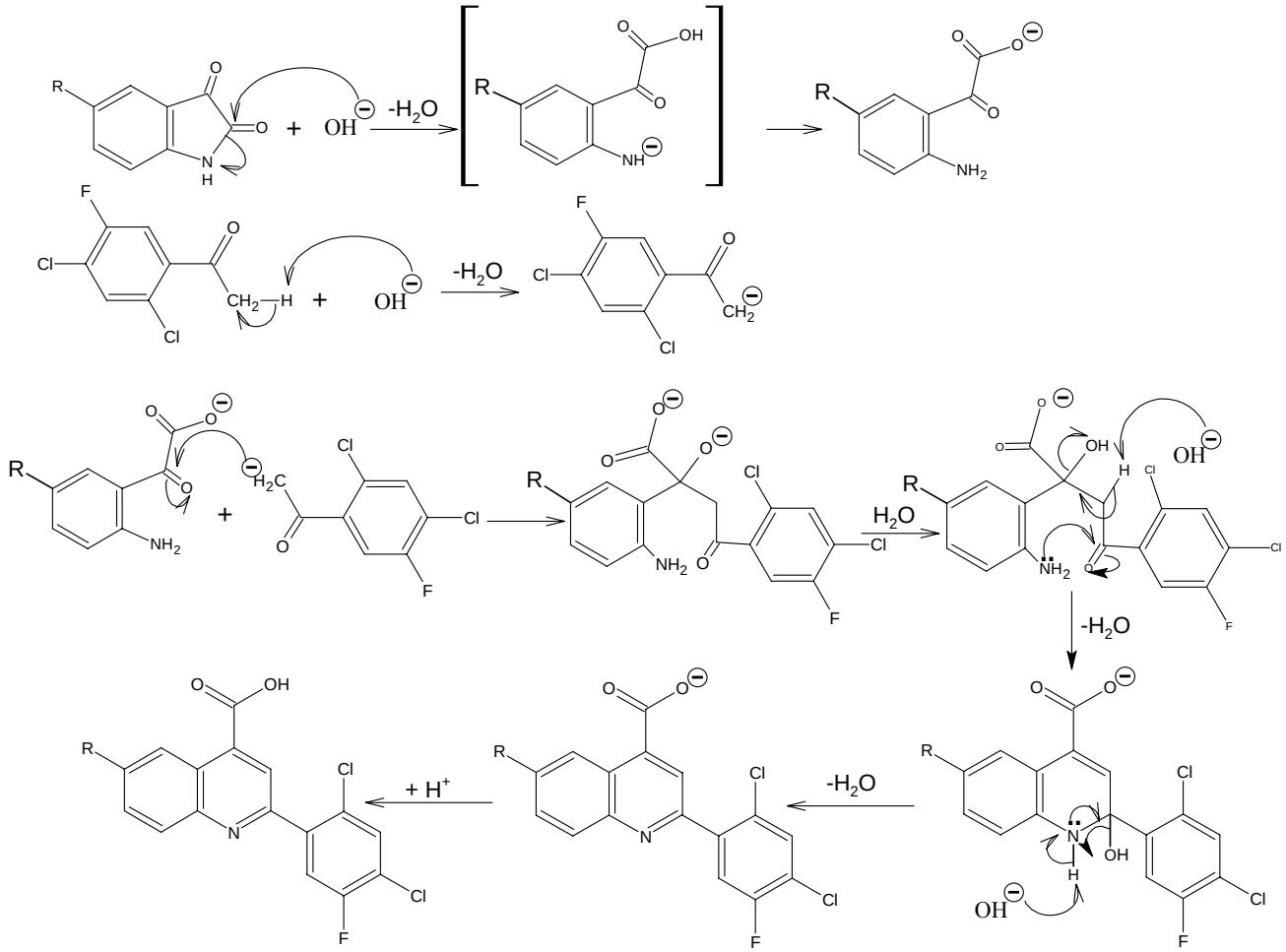


Table I — Physicochemical data of triazolothiadiazole derivatives **5a-t**

Compd	R	R_1	Mol. formula	m.p. (°C)	Yield (%)
5a	H	H	$C_{18}H_8Cl_2FN_5S$	248-50	82
5b	H	CH_3	$C_{19}H_{10}Cl_2FN_5S$	185-86	74
5c	H	$CH_3CH_2CH_2$	$C_{21}H_{14}Cl_2FN_5S$	204-06	70
5d	H	$C_6H_5CH_2$	$C_{25}H_{14}Cl_2FN_5S$	86-88	75
5e	H	$C_6H_5NHCH_2$	$C_{25}H_{15}Cl_2FN_6S$	128-30	68
5f	H	2-$ClC_6H_4OCH_2$	$C_{25}H_{13}Cl_3FN_5OS$	168-69	73
5g	H	4-$ClC_6H_4OCH_2$	$C_{25}H_{13}Cl_3FN_5OS$	178-80	72
5h	H	2,4-$Cl_2C_6H_3OCH_2$	$C_{25}H_{12}Cl_4FN_5OS$	195-97	69
5i	H	3,4-$(CH_3)_2C_6H_3OCH_2$	$C_{27}H_{18}Cl_2FN_5OS$	138-40	72
5j	H	4-Cl-3-$CH_3C_6H_3OCH_2$	$C_{26}H_{15}Cl_3FN_5OS$	230-32	78
5k	Br	H	$C_{18}H_7BrCl_2FN_5S$	164-66	70
5l	Br	CH_3	$C_{19}H_9BrCl_2FN_5S$	192-93	68
5m	Br	$CH_3CH_2CH_2$	$C_{21}H_{13}BrCl_2FN_5S$	160-62	82
5n	Br	$C_6H_5CH_2$	$C_{25}H_{13}BrCl_2FN_5S$	158-60	71
5o	Br	$C_6H_5NHCH_2$	$C_{25}H_{14}BrCl_2FN_6S$	128-30	70
5p	Br	2-$ClC_6H_4OCH_2$	$C_{25}H_{12}BrCl_3FN_5OS$	148-50	73
5q	Br	4-$ClC_6H_4OCH_2$	$C_{25}H_{12}BrCl_3FN_5OS$	208-10	69
5r	Br	2,4-$Cl_2C_6H_3OCH_2$	$C_{25}H_{11}BrCl_4FN_5OS$	225-26	74
5s	Br	3,4-$(CH_3)_2C_6H_3OCH_2$	$C_{27}H_{17}BrCl_2FN_5OS$	160-62	69
5t	Br	4-Cl-3-$CH_3C_6H_3OCH_2$	$C_{26}H_{14}BrCl_3FN_5OS$	118-20	75

All the compounds analyzed satisfactorily for their N content. They agree to the theoretical values within ± 0.4%. Solvent of crystallization: Ethanol + DMF mixture.

IR (KBr, cm^{-1}): **3a**: 3400(O-H), 3090(Ar-H), 1700(C=O), 1630(C=N), 1580(C=C), 1088(C-F), 908(C-H), 729(C-Cl), 720(C-Cl); **3b**: 3421(O-H), 3099(Ar-H), 1705(C=O), 1630(C=N), 1578(C=C), 1090(C-F), 910(C-H), 750(C-Cl), 725(C-Cl), 653(C-Br); **5e**: 3402(N-H), 3060(Ar-H), 2931(C-H), 1625(C=N), 1593(C=C), 1087(C-F), 732(C-Cl); **5m**: 3015(Ar-H), 2992(C-H), 2900(C-H), 1643(C=N), 1603(C=C), 1490(C-H), 1090(C-F), 900(C-H), 740(C-Cl); **5p**: 3097(Ar-H), 2997(C-H), 1630(C=N), 1093(C-F), 900(C-H), 731(C-Cl).

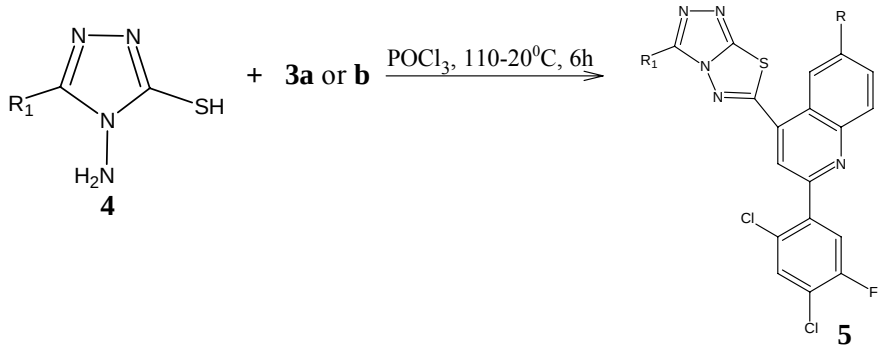
^{1}H NMR(DMSO-d_6, δ): **3a**: 6.7-8.2(2H, m, ArH), 8.69(1H, d, *J*=6.0Hz, ArH); 8.79(1H, d, *J*=9.0Hz, ArH); **5b**: 2.5(s, 3H, CH_3), 7.3-8.3(m, 7H, ArH); **5d**: 2.9(s, 2H, CH_2), 6.63-8.32(m,12H, ArH); **5e**: 4.92(s, 1H, NH), 5.30(s, 2H, NCH_2), 8.69(d, 1H, Ar-H, *J*=6.02Hz), 8.79(d, 1H, Ar-H, *J*=9.04Hz), 6.65-8.26(m, 10H, Ar-H); **5m**: 0.9-1.1(t, 3H, *J*=3.0Hz, CH_3), 1.7-1.85(sextet, 2H, *J*=4.5Hz, CH_2), 2.65-2.90(t, 2H, *J*=6.0Hz, CH_2), 6.92-8.26(m, 6H, ArH); **5o**: 4.85(s, 1H, NH), 5.27(s, 2H, NCH_2), 6.68-8.30(m, 9H, Ar-H), 8.65(d, 1H, Ar-H, *J*=6.1Hz), 8.80(d, 1H, Ar-H, *J*=9.1Hz).

MS (m/z, % abundance): **3a**: 334(M^+, 52), 336(M+2, 32), 38(M+4, 5), 299(M-Cl, 27), 290(M-CO_2, 25), 189(M^+ of 2,4-dichloro-5-flourobenzonitrile cation, 100)**,** 191(M+2 of 2,4-dichloro-5-flourobenzonitrile cation, 69), 193(M+4 of 2,4-dichloro-5-flourobenzonitrile cation, 10), 163(2,4-dichloro-5-flourophenyl cation, 32), 165(2,4-dichloro-5-flourophenyl cation, 22), 167(2,4-dichloro-5-flourophenyl cation, 7); **5i**: 549 (M^+, 5.9), 428(12.5), 163(4.5), 84(100); **5p**: 507(M - *p*-chlorophenoxy radical), 127(55.4), 84(100).

ion gave a peak at m/z 290. The base peak observed at m/z 189 was due to the formation of the 2,4-dichloro-5-fluorobenzonitrile cation. This further underwent fragmentation to give 2,4-dichloro-5-fluorophenyl cation with m/z value of 163.

The absence of absorption band due to NH stretching frequency in the IR spectra of compounds **3a** and **3b** clearly indicated the formation of quinoline-4-carboxylic acids. IR spectrum of compound **3a** showed the characteristic absorption bands at stretching frequencies - 3400 (O-H), 1700 (C=O), 1630 (C=N), 1586 (C=C), 1088 (C-F) and 729 cm^{-1} (C-Cl).

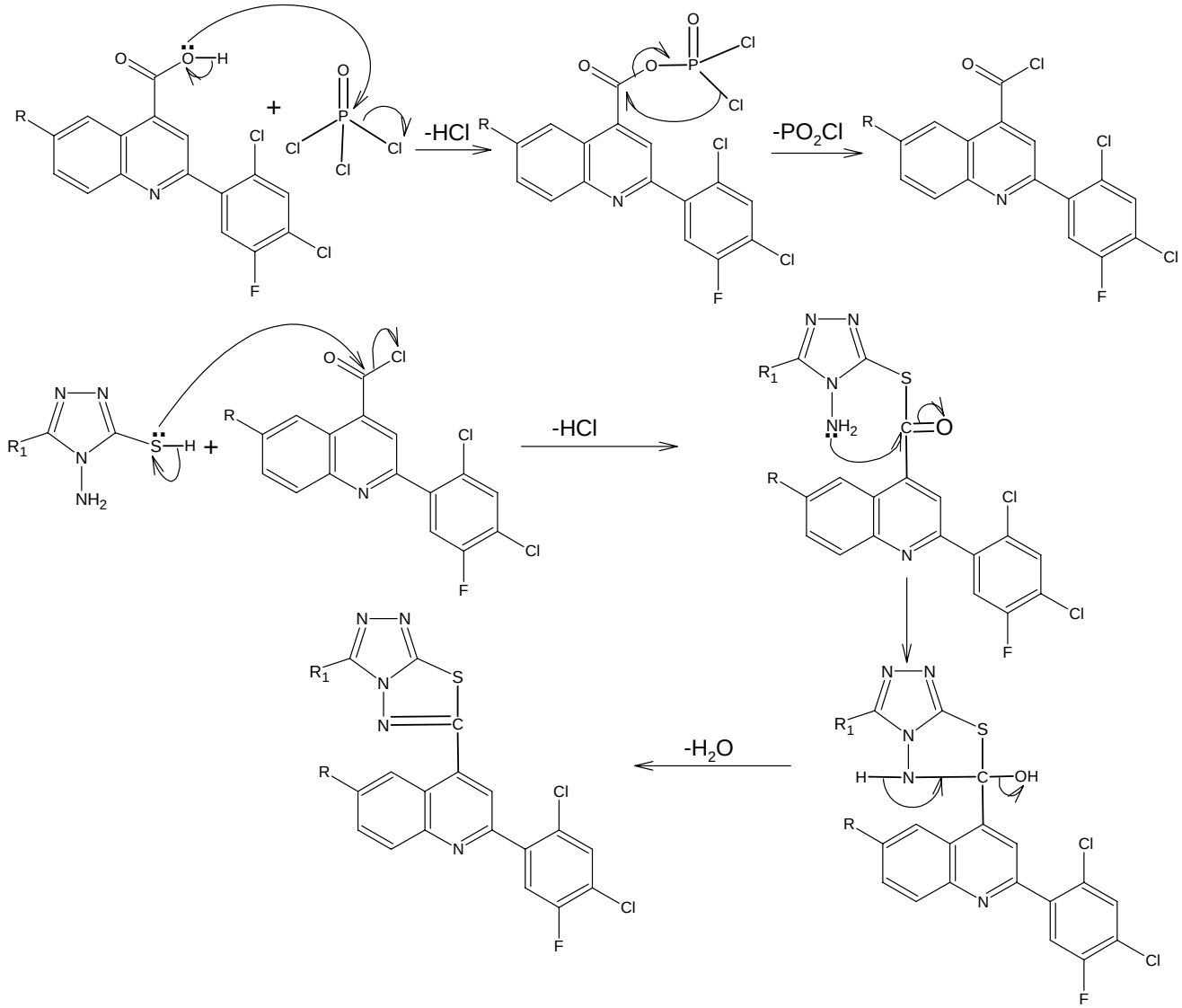
In the ^{1}H NMR spectrum of triazolothiadiazolyl quinoline **5e**, the NH protons appeared as a singlet at δ 4.92. The anilinomethyl protons appeared as a singlet at δ 5.83. The signals due to the protons of 2,4-dichloro-5-fluorophenyl moiety was seen as two



R_1 = H , CH_3 , $CH_3CH_2CH_2$, $C_6H_5CH_2$, $C_6H_5NHCH_2$, 2-$ClC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$, 3,4-$(CH_3)_2C_6H_3OCH_2$, 4-Cl-3-$CH_3C_6H_3OCH_2$.

Scheme II

Mechanism for Scheme II



doublets at δ 8.79 (J = 9Hz) and 8.69 (J = 6 Hz) respectively. The remaining aromatic protons appeared as complex multiplet in the region δ 6.65-8.26 integrating for ten protons.

The mass spectrum of triazolothiadiazolyl quinoline **5i** showed the molecular ion peak at m/z 549 consistent with the molecular formula, $C_{27}H_{18}Cl_2FN_5OS$. The peak at m/z 163 could be assigned to the formation of 2,4-dichloro-5-fluorophenyl cation during fragmentation. A peak seen at m/z 84 confirmed the formation of CH_2=C=N--C^+=S ion during fragmentation.

In the IR spectra of triazolothiadiazolylquinolines, the absorption bands corresponding to the NH stretching frequency of the starting triazole and the carboxyl group of quinoline-4-carboxylic acid were absent. This confirmed the involvement of these groups in the ring formation. The IR spectrum of compound **5e** showed the prominent absorption bands at stretching frequencies-3402 (NH), 3060 (Ar-H), 2939 (C-H), 1625 (C=N), 1593 (C=C), 1087 (C-F) and 737 cm^{-1} (C-Cl).

Biological activity

Anti-bacterial activity

The quinoline-4-carboxylic acids and their triazolothiadiazole derivatives were screened for their *in vitro* anti-bacterial activity against *S. aureus*, *E. coli* and *B. subtilis* by serial dilution method[13]. Solutions of the test compounds were kept in dimethyl formamide. Nitrofurazone (furacin) was used as a standard drug for comparison and solvent control was kept. The minimum inhibitory concentrations (MIC values) of the above compounds are given in **Table II**. It is interesting to note that the compounds **5f**, **5h**, **5p**, **5r** and **5t** showed very good anti-bacterial activity.

Table II — Anti-bacterial activities of quinoline-4-carboxylic acids **3** and their triazolothiadiazole derivatives **5**

Compd	Minimum inhibitory concentration in μg/mL		
	S. aureus	*E. coli*	*B. subtilis*
3a	12.5	12.5	12.5
3b	6.0	6.0	12.5
5a	12.5	6.0	12.5
5b	12.5	6.0	6.0
5c	6.0	6.0	6.0
5d	6.0	12.5	12.5
5e	12.5	12.5	25.0
5f	6.0	3.0	6.0
5g	25.0	12.5	12.5
5h	3.0	3.0	6.0
5i	25.0	12.5	6.0
5j	25.0	6.0	12.5
5k	12.5	6.0	12.5
5l	6.0	6.0	12.5
5m	12.5	12.5	6.0
5n	6.0	6.0	12.5
5o	12.5	12.5	12.5
5p	6.0	3.0	6.0
5q	12.5	6.0	12.5
5r	3.0	6.0	6.0
5s	6.0	12.5	12.5
5t	6.0	6.0	3.0
Furacin	12.5	6.0	12.5

Experimental Section

Melting points were determined by capillary method and are uncorrected. IR spectra in KBr pellets were recorded on a Shimadzu FTIR 8700 spectrophotometer; ^{1}H NMR spectra in $CDCl_3$/$CDCl_3$-DMSO-d_6 mixture on a Bruker AC 300F 300 MHz NMR spectrometer using TMS as an internal standard; and mass spectra on a JEOL JMS 300 mass spectrometer operating at 70 eV. The required aminomercaptotriazoles and 5-bromoisatin were prepared according to the literature methods[14-16].

Preparation of 2-(2,4-dichloro-5-fluorophenyl)quinoline-4-carboxylic acids 3a, b. A solution of sodium hydroxide (2 g, 0.05 mole) and isatin/5-bromoisatin **1** (0.01 mole) in water (25 mL) was heated till a clear solution was obtained. 2,4-Dichlor-5-fluorophenyl-acetophenone **2** (0.05 mole) was added to it in small portions with occasional shaking and heating was continued for 2 hr. The reaction mixture was chilled in an ice-bath. The solid mass formed was collected by filtering through a sintered glass crucible (G-4). The sodium salt of quinoline-4-carboxylic acid obtained was dissolved in water (100 mL). Quinoline-4-carboxylic acid was precipitated by neutralizing this solution with glacial acetic acid. It was collected by filtration, washed with water, dried and re-crystallized from dimethyl formamide. **3a** (R=H): yield 78%, m.p. 224-26°C; **3b** (R=Br): yield 76%, m.p. 245-47°C.

Preparation of 4-(3-substituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazol-6-yl)-2-(2,4-dichloro-5-fluorophenyl)quinolines 5a-t. A mixture of 3-substituted-4-amino-5-mercapto-1,2,4-triazole **4** (0.01 mole), quinoline-4-carboxylic acid **3** (0.01 mole) and phosphorus oxychloride (10 mL) was heated under

reflux for 6 hr. The reaction mixture was cooled and allowed to stand at room temperature for 2 hr. It was then poured onto crushed ice. The solid mass formed was collected by filtration, washed with sodium bicarbonate solution (5%), then with water and dried. Recrystallized from a mixture of ethanol and dimethyl formamide (2:1) to get compounds **5** in 68-82% yields.

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