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SYNTHESIS OF BIOLOGICALLY ACTIVE NOVEL SERIES OF FLUORINATED ISOXAZOLE AND THIOPYRIMIDINES

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Abstract

We report here, a series of novel and unreported yet the construction of the novel fluorinated indole ring system, which then converted into a new series of fluorinated indole i.e. Isoxazole, (3a-g) and Thiopyrimidine(4 a-g) via chalcone synthesis (1a-g). Some of the synthesized derivatives are assayed for their *in-vitro* antibacterial activity against a panel of pathogenic as well as standard bacterial strains such as *Klebsiella pneumoniae, Salmonella typhimurium, P. aeroginosa, Bacillus subtilis Escherichia coli* and *Staphylococcus aureus.*

Keywords: Indole,2-(chlromethyl)-3methyl-4-(2,2,2-trifluroethoxy) pyridine, Isoxazole, Thiopyrimidine, Synthesis. Antibacterial.

1. Introduction

Indole, a potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties viz., anti-inflammatory [1–3], anticonvulsant [4], cardiovascular [5], antibacterial [6]. Furthermore, fluoro substituted indole derivatives has received wide attention from either synthetic or pharmaceutical view for a long time due to their wide potential bioactivities [7-10].Besides Isoxazole represent a class of compounds of great biological importance. For instance, Isoxazole posses a broad spectrum of biological activity [11] (insecticidal, antibacterial, antibiotic, antitumour, antifungal, etc). Isoxazoline also serves as an important building block for the synthesis of biologically active molecules [12], and a prodrug for an antiarthritic agent. [13] Drugs such as Isocarboxazide, Oxacillin, Leflunomide, and

Micafungin are the examples to substantiate the pharmaceutical acceptance of such heterocyclic systems. In fact, Valdecoxib is an isoxazoline derivatives now widely used in the market as an anti-inflammatory drug. [14]

Pyrimidine is widely found as a core structure in variety of compounds that exhibit important biological activity,[15] particularly being calcium channel blockers ,[16] Girardet found that 4-amino-5-oxopyrido-[2,3,d]-pyrimidine ribosides were potent inhibitor of cancer cell profilation.[17] Recently Kidwai M. and co-workers have studied the antimalarial properties of 2,4-di-amino-5-p-chlorophenyl-6-ethyl pyrimidines ,[18]Pyrimidines and their derivatives are studied by Wichman J. and Tsuji K. for their biological activities. [19-20] Pyrimidine forms an integral part of a large number of therapeutically important compounds like thiamine, riboflavin, purine bases, sulfadiazine etc. Most of the pyrimidine derivatives has been found to possess pharmacological activity and are used as drugs.

Among the wide range of heterocycles explored to develop pharmaceutically important molecules, the development of new and simple approach to synthesize the fluoro substituted Indole derivatives from commercially or rapidly available materials still remains a challenge. Encouraged by these observations we have synthesized newer heterocyclic indole derivatives in the hope of obtaining better antimicrobial activity. To the best of our knowledge, no report has been cited in the literature on the reaction of Insole and 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluroethoxy) pyridine hydrochloride, Hence, with a view to assess the pharmacological profile of this class of compounds, we plan here to synthesize some new congeners of Indole, Isoxazole and Thiopyrimidine heterocycles by incorporating the 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluroethoxy) pyridine moieties in a single molecular framework. The motto of using fluorinating compound 2-(chloromethyl)-3methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride due to its biological activity in the drug like lanzoprazole. It is a proton pump inhibitor (PPI) that reduces gastric acid secretion and has successfully been used to heal and relieve symptoms of gastric or duodenal ulcers and gastro-esophagal reflux.[21] The present work, therefore, deals with the synthesis of the title compounds starting from indole and 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluroethoxy) pyridine hydrochloride.

2. Experimental

Melting points were taken on a precision melting point apparatus (DBK) instrument and were uncorrected. IR spectra were obtained in potassium bromide (KBr)disks on a Bruker IR spectrometer ,and ^{1}H NMR spectra were obtained on deuteriochlroform (CDCL3) and or DMSO-d6 solution on a Varian 400 MHz spectrometer. Mass spectra were recorded on a MicroMass spectrometer by Waters. The yields unless otherwise mentioned are for pure product. All the raw materials, reagents and solvents were used of commercial grade only.

4.1. *Synthesis of 1-((3-methyl-4-(2,2,2-triflureothoxy)pyridine-2-yl) methyl)-1H-indole (1.I)*

Indole (5 gm, 0.042 mole) was dissolved in N,N-dimethylformamide (50 ml) under nitrogen atm. The reaction mixture was cooled to 0-5ºC and added sodium hydride (60 % in mineral oil, 2.05 gm, and 0.085 mole) portion wise. The reaction mixture was stirred for 30 ºC at same temperature. To the above stirred solution added solution of 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluoroethoxy) pyridine hydrochloride (12.9 gm, 0.047 mole) in N,N-dimethylformamide (25 ml) dropwise over 30 minutes. The resulting reaction mixture was stirred for 4-6 hrs. at 30-35ºC. After completion of reaction (checked by TLC) reaction mass poured into ice cold (500ml) a white solid was precipited out, which was then separated by filtration, washed with water to get 4.5gm titled compound.

IR (KBr, cm^{-1}): 3055 and 2960(Ar-CH stretching & bending),1578 (C=N)1258(C-F), **^{1}H NMR in (DMSO-d$_6$):** δ 2.14 (s, 3H,-C<u>H</u>$_3$ protons),δ 4.8-4.9 (m,2H,-O-C<u>H</u>$_2$-CF$_3$ protons, multiplates due to fluorine coupling),δ 5.49 (s,2H,-N-C<u>H</u>$_2$- protons), δ 6.4-6.45 (d,1H,indole-CH=C<u>H</u> proton),δ7.50-7.59 (d,1H, indole N-C<u>H</u>=CH proton), δ 6.90-8.26 (6H, aromatic and pyridine ring protons).Mass (m/z): 321 M+1).

4.2. Synthesis of 1-((3-methyl-4-(2,2,2-triflureothoxy)pyridine-2-yl) methyl)-1H-indole-3-carballdehyd(1.II)

Under nitrogen atm. phosphourus oxychloride (3.58 gm, 0.0235 mole) was added dropwise to N,N-dimethylformamide (15 ml) under stirring at 0^{0}C. The reaction mixture stirred for 1hrs. at same temperature. To the reaction mixture added solution of 1-((3-methyl-4-(2,2,2-

triflureothoxy) pyridine-2-yl)methyl)-1H-indole(1I) (5gm,0.015mole) in N,N-dimethyl formamide at 0-5ºC. The reaction mixture was stirred at 35ºC for 1hrs. and poured into ice cold water (90 ml) a clear red colored solution was obtained. Which on basify with 10% sodium hydroxide solution solid precipitate out. Then these crystals were separated by filtration, washed withwater to get titled compound 3.4 gm. **IR (KBr, cm^{-1}):** 2996 and 2922(Ar-CH stretching & bending), 1655(C=O), 1579(C=N), 1267 (C-F). **^{1}H NMR in (DMSO-d_6):** δ 2.25 (s,3H,-CH_3 protons),δ 4.80-4.9 (m,2H,-O-CH_2-CF_3 protons multiplates due to fluorine coupling), δ 5.65 (s,2H,- N-CH_2- protons), δ 8.12(s, 1H, indole N-CH=CH proton), δ7.0-8.0 (6H aromatic and pyridine protons),δ 9.80 (s,1H, aldehyde proton) Mass (m/z): 349 M+1).

4.3. Synthesis of 1-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1H-indole -3-yl)-3-phenylprop-2-en-1-one.(chalcone)(1a)

To the stirred solution of of 1-((3-methyl-4-(2,2,2-triflureothoxy)pyridine-2-yl)methyl)-1H-indole-3-carbaldehyde(1.II) (1.0 gm, 0.0028 mole) and aceto phenone (0.34 gm 0.0028 mole.) in 15 ml ethanol. Aqueous solution of pottassium hydroxide (KOH) (0.48 gm, 0.0086 mole) was added dropwise over 30 min. The resulting mixture was stirred at reflux temperature for 8-10 hrs. After completion of reaction (Checked by TLC) the reaction mixture was poured into ice water and neutralized with hydrochloric acid. The solid was precipited out which was filtered, washed with water and crystallized from absolute ethanol.

Similarly the other compounds of this series were prepared. Their percentage yield and melting points data of the compounds are recorded in Table-1.3. Their structures have been confirmed by Mass, IR and H1NMR spectra.

IR (KBr, cm^{-1}): 2990 and 3054 (Ar-CH stretching & bending),1646(-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1566 (C=N), 1288(C-F).**^{1}H NMR in (DMSO-d_6)**: δ 2.25(s,3H,-CH_3),δ4.80-4.90 (m,2H,-O-CH_2-CF_3 protons multi plates due to fluorine coupling), δ 5.60 (s,2H,- N-CH_2- protons),δ 7.0-7.1 (d, 1H, vinylic proton) δ 7.2-8.1

(12H, aromatic, indole and pyridine protons), δ8.21-8.25 (d,1H, vinylic proton). **Mass (m/z)**: 451 M+1).

4.4. ***1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1H-indole-3-yl)-1-(4-nitrophenyl)prop-2-en-1-one. (1.b)***

IR (KBr, cm^{-1}): 2996 and 3058(Ar-CH stretching & bending),1649(-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1568 (C=N), 1269(C-F).**^{1}H NMR in (DMSO-d_6)**: δ2.23(s,3H,-$\underline{CH_3}$), δ4.82-4.93 (m,2H,-O-$\underline{CH_2}$-CF_3 protons multiplates due to fluorine coupling), δ 5.57 (s,2H,- N-$\underline{CH_2}$- protons), δ 7.03-7.13 (d, 1H, vinylic proton), δ 7.23-8.13 (11H, aromatic indole and pyridine protons), δ 8.22-8.28 (d, 1H, vinylic proton). **Mass (m/z)**: 496 M^+1).

4.5.*1-(4-fluorophenyl)-3-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1H-indole-3-yl)prop-2-en-1-one. (1.c)*

IR (KBr, cm^{-1}): 2987 and 3043(Ar-CH stretching & bending),1654(-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1572 (C=N), 1281(C-F). **^{1}H NMR in (DMSO-d_6)**: δ 2.21 (s,3H,-$\underline{CH_3}$), δ 4.82-4.93 (m,2H,-O-$\underline{CH_2}$-CF_3 protons, multiplates due to fluorine coupling), δ 5.62 (s,2H,- N-$\underline{CH2}$- protons),δ 7.03-7.12 (d, 1H, vinylic proton), δ 7.0-8.13 (11H, aromatic, indole and pyridine protons), δ 8.22-8.28 (d, 1H, vinylic proton). **Mass (m/z)**: 469 M^+1).

4.6.*1-(4-fluorophenyl)-3-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1H-indole-3-yl)prop-2-en-1-one.(1.d)*

IR (KBr, cm^{-1}): 2989 and 3056 (Ar-CH stretching & bending),1643 (-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1565 (C=N).**^{1}H NMR in (DMSO-d_6)**: δ 2.29 (s,3H,-$\underline{CH_3}$), δ 4.89-4.98 (m,2H,-O-$\underline{CH_2}$-CF_3 protons, multiplates due to fluorine coupling), δ 5.69 (s,2H,-N-$\underline{CH_2}$- protons), δ 7.13-7.20 (d, 1H, vinylic proton) δ7.22-8.17 (11H, aromatic, indole and pyridine protons.), δ 8.28-8.31 (d, 1H, vinylic proton). **Mass (m/z)**: 485M^+1).

4.7.*1-(4-iodophenyl)-3-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)1H-indole-3-yl)prop-2-en-1-on* ***(1.e)***

IR (KBr, cm^{-1}): 2979 and 3043 (Ar-CH stretching & bending),1647 (-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1567 (C=N).**^{1}H NMR in (DMSO-d_6)**: δ 2.22 (s,3H,-C$\underline{H_3}$), δ 4.81-4.92 (m,2H,-O-$\underline{CH_2}$-CF_3 protons, multiplates due to fluorine coupling), δ 5.54 (s,2H,-N-C$\underline{H_2}$- protons),δ 7.03-7.12 (d, 1H, vinylic proton), δ 7.12-8.10 (11H, aromatic, indole and pyridine protons.), δ 8.20-8.26 (d, 1H, vinylic proton). **Mass (m/z)**: 576 M^+1).

4.8.*1-(2-hydroxyphenyl)-3-(1-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-1H-indol-3-yl)prop-2-en-1-one. (1.f)*

IR (KBr, cm^{-1}): 3519(-OH), 2975 and 3041(Ar-CH stretching & bending), 1640 (-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1562 (C=N). **^{1}H NMR in (DMSO-d_6)**: δ2.28(s,3H,-CH_3),δ 4.87-4.96 (m,2H,-O-CH_2-CF_3 protons, multiplates due to fluorine coupling), δ 5.68 (s,2H,-N-CH_2- protons),δ 7.13-7.19 (d, 1H, vinylic proton), δ 7.22-8.16 (11H, aromatic, indole and pyridine protons.), δ 8.25-8.29 (d,1H,vinylic proton),δ11.28(s,1H, -OH proton, exchanges with D_2O). **Mass (m/z)**: 467 M^+1).

4.9.1-*(2-hydroxy-3-methylphenyl)-3-(1-((3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-yl)methyl)-1H-indol-3-yl)prop-2-en-1-one. (1g)*

IR (KBr, cm^{-1}): 3534(-OH),2988 & 3063 (Ar-CH stretching & bending), 1648 (-C=O stretching lowering in carbonyl frequency is attributed to extended conjugation), 1569 (C=N).**^{1}H NMR in (DMSO-d_6)**: δ 2.19 (s,3H,-CH_3), δ 2.27(s,3H,-CH_3) δ 4.77-4.86 (m,2H,-O-CH_2-CF_3 protons, multiplates due to fluorine coupling), δ 5.45 (s,2H,- N-CH_2- protons),δ 7.13-7.19 (d, 1H, vinylic proton), δ 7.17-8.10 (10H, aromatic, indole and pyridine protons.), δ 8.17-8.26 (d, 1H, vinylic proton) ,δ 11.13 (s , 1H, -OH proton, exchanges with D_2O). **Mass (m/z)**: 481 M^+1).

4.10. *Synthesis of 2-(5-(4-(1H-1,2,4-triazol-1-yl)phenyl)-4,5-dihydroisoxazol-3-yl)phenol (3a)*

To a suspension 1-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1*H*-indole-3-yl)-3-

phenylprop-2-en-1-one. (1a) (1.0 gm, 0.0022 mole) in 20 ml of ethanol were added hydroxylamine hydrochloride (0.018 gm, 0.0026 mole.) and potasium hydroxide. (0.025gm, 0.0044mole)The reaction mass was heated to reflux for 8-12 h. After completion of reaction (checked by TLC), reaction mixture was cooled to room temperature and added 50 ml chilled water slowly. The reaction mass was neutralized with dilute hydrochloric acid, the separated product was filtered, washed with cold water (10 ml) and crystallized from ethanol. Similarly the other compounds of this series were prepared. Their percentage yield and melting points data of the compounds are recorded in Table-1.4 Their structures have been confirmed by Mass, IR and H1NMR spectra

IR (KBr) cm^{-1}3058 & 2952(Ar-CH stretching & bending), 1579(C=N). **^{1}H NMR (DMSO) -d_6** δ 2.14 (s,3H,-C$\underline{H}_3$ protons),δ 2.30-2.51(d,2H, Isoxazole -C$\underline{H}_2$ protons), δ 4.8-4.9 (m,2H,-O-C$\underline{H}_2$-CF_3), δ 5.62 (s,2H N-C$\underline{H}_2$-protons), δ 5.90-6.02 (dd, 1H, -CH,chiral Isoxazole proton), δ 6.90-8.31(12H aromatic, indole & pyridine protons).**Mass (m/z)** 466 (M+1)

4.11. *3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl)methyl)- 1H-indole 3-yl)-5-(4-nitrophenyl)-4,5-dihydroisoxazole(3b)*

IR (KBr) cm^{-} 3058 and 2952(Ar-CH stretching & bending), 1579(C=N).**^{1}H NMR (DMSO) -d_6** δ2.11(s,3H,-C$\underline{H}_3$protons), δ 2.33-2.43(d, 2H, Isoxazole-C$\underline{H}_2$protons),δ4.78-4.89(m,2H,-O-C$\underline{H}_2$-CF_3),δ5.65 (s,2H,-N-C$\underline{H}_2$-protons), δ5.89-6.03 (dd, 1H,-C$\underline{H}$,chiral Isoxazole proton), δ 6.86-8.23(11H aromatic, indole & pyridine protons).**Mass (m/z)** 511 (M+1)

4.12. *5-(4-fluorophenyl)-3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl) methyl)-1H-indole3-yl)-4,5-dihydroisoxazole(3c)*

IR (KBr) cm^{-} 3052 and 2941(Ar-CH stretching & bending), 1585(C=N).**^{1}H NMR (DMSO) -d_6** δ2.20(s,3H,-C$\underline{H}_3$protons), δ2.23-2.41(d,2H, Isoxazole -C$\underline{H}_2$ protons), δ4.78-4.89(m,2H,-O-C$\underline{H}_2$-CF_3),δ5.67(s,2H, N-CH_2-protons), δ 5.89-6.03 (dd, 1H,-C$\underline{H}$,chiral Isoxazole proton), δ 6.86-8.23(11H aromatic, indole & pyridine protons).

Mass (m/z) 484 (M+1)

4.13. ***5-(4-chlorophenyl)-3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl) methyl)- 1H-indole 3-yl)-4,5-dihydroisoxazole (3d)***

IR (KBr) cm^{-} 3033 and 2934(Ar-CH stretching & bending), 1576(C=N).**^{1}H NMR (DMSO) -d$_6$** δ 2.12(s,3H,-C$\underline{H}_3$ protons),δ 2.13-2.33(d,2H, Isoxazole -C$\underline{H}_2$ protons), δ 4.70-4.82 (m,2H,-O-C$\underline{H}_2$-CF_3),δ 5.41-5.49(s,2H,N-C$\underline{H}_2$-protons), δ 5.82-6.0(dd, 1H,-C$\underline{H}$,chiral Isoxazole proton), δ 6.81-8.12(11H aromatic, indole & pyridine protons).**Mass (m/z)** 500 (M+1)

4.14. ***5-(4-iodophenyl)-3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl) methyl)- 1H-indole 3-yl)-4,5-dihydroisoxazole (3e)***

IR (KBr) cm^{-} 3023 & 2930(Ar-CH stretching & bending),1579(C=N). **^{1}H NMR (DMSO) -d$_6$** δ2.08(s,3H,-C$\underline{H}_3$ protons),δ 2.10-2.25(d,2H, Isoxazole -C$\underline{H}_2$protons),δ4.67-4.77(m,2H,-O-C$\underline{H}_2$-CF_3),δ5.40 (s,2H,N-C$\underline{H}_2$-protons), δ5.73-5.96 (dd,1H,-C$\underline{H}$,chiral Isoxazole proton), δ 6.81-8.12(11H aromatic, indole & pyridine protons)..**Mass (m/z)** 592 (M+1)

4.15. ***2-(3-(1-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-1H-indol-3-yl)-4,5-dihydroisoxazol-5-yl)phenolxazole (3f)***

IR (KBr) cm^{-} 3478(OH), 3033 & 2946(Ar-CH stretching & bending), 1586(C=N).
^{1}HNMR(DMSO)-d$_6$ δ2.12(s,3H,-C$\underline{H}_3$protons),δ 2.15-2.29 (d,2H, Isoxazole -C$\underline{H}_2$protons),δ4.63-4.81(m,2H,-O-C$\underline{H}_2$-CF_3),δ5.47 (s,2H,N-C$\underline{H}_2$-protons), δ 5.78-5.98 (dd,1H,-C$\underline{H}$,chiral Isoxazole proton), δ 6.76-8.17(11H aromatic, indole & pyridine protons). δ10.78 (s,1H,-OH proton, exchanges with D_2O).**Mass (m/z)** 482 (M+1)

4.16. ***2-methyl-6-(3-(1-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl) methyl) -1H-indol-3-yl)-4,5-dihydroisoxazol-5-yl)phenol (3g)***

IR (KBr) cm^{-} 34783485(OH), 3030 and 2952(Ar-CH stretching & bending),1589(C=N). **^{1}H NMR (DMSO) -d$_6$** δ2.07(s,3H,-C$\underline{H}_3$protons), δ 2.19(s,3H,-C$\underline{H}_3$ protons), δ 2.22-2.31 (d,2H, Isoxazole-C$\underline{H}_2$protons), δ 4.68-4.86(m,2H,-O-C$\underline{H}_2$-CF_3),δ5.51 (s,2H,N-C$\underline{H}_2$-protons), δ 5.83-6.03 (dd, 1H,-C$\underline{H}$,chiral Isoxazole proton), δ6.79-8.23(10H aromatic, indole & pyridine protons). δ 10.86 (s,1H, -OH proton, exchanges with D_2O). **Mass (m/z)** 496 (M+1)

4.17. ***Synthesis of 6-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1Hindole3yl)-4-phenyl-3,4dihydropyrimidine-2(1H)-thione (Thiopyrimidines) (4a)***

To the stirred suspension of 1-(1-((3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl)-1*H*-indole-3-yl)-3-phenylprop-2-en-1-one.(1a) (1.0 gm, 0.0022 mole) in 15 ml of absolute ethanol, added thiourea (0.34 gm 0.0044 mole) and sodium ethoxide (0.32 gm, 0.0047 mole) at room temp. The reaction mixture was then refluxed for 8 hrs. After completion of the reaction confirmed by TLC, the reaction mass was concentrated on rotavapour. To the residue 45 ml ice water added and P^H of the reaction mass was acidify using concentrated hydrochloric acid. The solid obtained was filter, washed with water, and crystallized from aqueous ethanol.

Similarly the other compounds of this series were prepared. Their percentage yield and melting points data of the compounds are recorded in Table-1.5. Their structures have been confirmed by Mass, IR and H^1NMR spectra.

IR (KBr) cm^{-1}3178 (NH), 2954 (Ar-CH stretching & bending), 1580 (C=C),1260 (C=S). **^{1}H NMR (DMSO) -d_6** δ2.22(s,3H,-C$\underline{H}_3$),δ4.85-4.93(m,2H,-O-C$\underline{H}_2$-CF_3 protons, multiplates due to fluorine coupling), δ5.65(s,2H,N-C$\underline{H}_2$-protons),δ5.7-5.8(d,1H,NH-C$\underline{H}$- thiopyrimidine methane proton), δ6.0-6,3(d,1H, CH=C$\underline{H}$- thiopyrimidine methine proton), δ 7.3 (s,1H, N$\underline{H}$ thiopyrimidine proton),δ6.9-8.2(12H, aromatic,indole & pyridine ring protons), (d,1H-NH proton, was not seen up to 8.4 ppm) **Mass (m/z)** 509 (M+1)

4.18.*4-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1H-indole3-)-6-(nitrophenyl-3,4dihydropyrimidine-2(1H)-thione (4b)*

IR (KBr) cm$^-$3170(NH), 2951 (Ar-CH stretching & bending), 1576 (C=C), 1255 (C=S).**^{1}H NMR (DMSO) -d_6** δ 2.12 (s,3H,-C$\underline{H}_3$), δ 4.77-4.82 (m,2H,-O-C$\underline{H}_2$-CF_3 protons, multiplates due to fluorine coupling), δ 5.56 (s,2H,-N-C$\underline{H}_2$-protons),δ5.67-5.73(d,1H,NH-C$\underline{H}$- thiopyrimidine methine proton), δ 5.94-6.04(d,1H, CH=C$\underline{H}$- thiopyrimidine methine proton), δ 7.13 (s,1H, N$\underline{H}$ thiopyrimidine proton), δ6.8-8.01 (11H, aromatic,indole & pyridine ring protons) (s,1H-N$\underline{H}$ proton, was not seen up to 8.4 ppm).**Mass (m/z)** 534(M+1)

4.19.*6-(4-fluoro-phenyl)-4(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1H-indole 3-yl)-3,4dihydropyrimidine-2(1H)-thione (4C)*

IR (KBr) cm^{-}3187(NH), 2965 (Ar-CH stretching & bending), 1585 (C=C), 1268 (C=S).^{1}**H NMR (DMSO) -d$_6$** δ 2.25 (s,3H,-C$\underline{H}_3$), δ 4.84-4.89 (m,2H,-O-C$\underline{H}_2$-CF_3 protons multiplates due to fluorine coupling), δ 5.63 (s,2H,-N-C$\underline{H}_2$- protons), δ 5.69-5.79 (d,1H,NH-C$\underline{H}$- thiopyrimidine methine proton), δ 6.03-6.17 (d,1H, CH=C$\underline{H}$- thiopyrimidine methine proton), δ7.25 (s,1H, N$\underline{H}$ thiopyrimidine proton), δ 6.89-8.21 (11H, aromatic,indole & pyridine ring protons) (s,1H-NH proton, was not seen up to 8.4 ppm).**Mass (m/z)** 527(M+1)

4.20.*6-(4-chloro-phenyl)-4(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1H-indole 3-yl)-3,4dihydropyrimidine-2(1H)-thione (4d)*

IR (KBr) cm^{-}3181(NH), 2962 (Ar-CH stretching & bending), 1578 (C=C), 1261 (C=S).^{1}**H NMR (DMSO) -d$_6$** δ 2.17 (s,3H,-C$\underline{H}_3$), δ 4.78-4.81 (m,2H,-O-C$\underline{H}_2$-CF_3 protons, multiplates due to fluorine coupling), δ 5.54 (s,2H,N-C$\underline{H}_2$ protons), δ 5.61-5.72 (d,1H,NH-C$\underline{H}$- thiopyrimidine methine proton), δ 5.96.-6.11(d,1H, CH=C$\underline{H}$- thiopyrimidine methine proton) δ 7.21 (s,1H, N$\underline{H}$ thiopyrimidine proton), δ 6.81-8.19 (11H, aromatic,indole & pyridine ring protons), (s,1H-NH proton, was not seen up to 8.4 ppm) **Mass (m/z)** 543(M+1)

4.21.*6-(4-chloro-phenyl)-4(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1H-indole 3-yl)-3,4dihydropyrimidine-2(1H)-thione (4e)*

IR (KBr) cm^{-}3170(NH), 2952 (Ar-CH stretching & bending), 1569 (C=C), 1253 (C=S).^{1}**H NMR (DMSO) -d$_6$** δ 2.14 (s,3H,-C$\underline{H}_3$), δ 4.72-4.79 (m,2H,-O-C$\underline{H}_2$-CF_3 protons, multiplates due to fluorine coupling), δ 5.38-5.50 (s,2H,-N-C$\underline{H}_2$- protons), δ5.54-5.67(d,1H,NH-C$\underline{H}$- thiopyrimidine methine proton), δ 5.91-6.01(d,1H, CH=C$\underline{H}$- thiopyrimidine methine proton), δ 7.12 (s,1H, N$\underline{H}$ thiopyrimidine proton), δ 6.4-8.12 (11H, aromatic,indole & pyridine ring protons), (s, 1H-NH proton, was not seen up to 8.4 ppm) **Mass (m/z)** 635(M+1)

4.22. *6-(2-hydroxyphenyl)-4-(1-((3-methyl-4-(2,2,2trifluoroethoxy)pyridin-2-yl)methyl)-1H-indol-3-yl)-3,4-dihydropyrimidine-2(1H)-thione(4f)*

IR (KBr) cm^{-}3474 (OH), 3165(NH), 2943 (Ar-CH stretching & bending), 1563 (C=C), 1246 (C=S).^{1}**H NMR (DMSO) -d$_6$** δ2.18 (s,3H,-C$\underline{H}_3$), δ 4.77-4.84 (m,2H,-O-C$\underline{H}_2$-CF_3 protons,

multiplates due to fluorine coupling), δ 5.59 (s,2H,-N-C<u>H</u>$_2$- protons), δ 5.59-5.74(d,1H,NH-C<u>H</u>-thiopyrimidine methine proton), δ 5.96-6.07(d,1H, CH=C<u>H</u>- thiopyrimidine methine proton), δ 7.18 (s,1H, N<u>H</u> thiopyrimidine proton), δ 6.56-8.24 (11H, aromatic,indole & pyridine ring protons), (s, 1H-NH proton, was not seen up to 8.4 ppm), δ 11.12 (s , 1H, -OH proton, exchanges withD_2O).**Mass (m/z)** 525(M+1)

4.23. ***6-(2-hydroxy-3-methylphenyl)-4-(1-((3-methyl-4(2,2,2trifluoroethoxypyridin-2-yl)methyl)-1H-indol-3-yl)-3,4-dihydropyrimidine-2(1H)-thione (4g)***

IR (KBr) cm^{-}3498 (OH), 3179(NH), 2951 (Ar-CH stretching & bending), 1568 (C=C), 1257 (C=S).**^{1}H NMR (DMSO) -d$_6$** δ 1.98 (s,3H,-C<u>H</u>$_3$), δ 2.10 (s,3H,-C<u>H</u>$_3$), δ 4.73-4.80 (m,2H,-O-C<u>H</u>$_2$-CF_3 protons multiplates due to fluorinecoupling),δ5.54(s,2H,-N-C<u>H</u>$_2$-protons), δ5.56-5.70(d,1H,NH-C<u>H</u>-thiopyrimidine methine proton), δ 5.93-6.13(d,1H, CH=C<u>H</u>- thiopyrimidine methine proton), δ 7.24 (s,1H, N<u>H</u> thiopyrimidine proton), δ 6.63-8.29 (11H, aromatic,indole & pyridine ring protons) (s, 1H-NH proton, was not seen up to 8.4 ppm), 11.19 (s , 1H, -OH proton, exchanges with D_2 O). **Mass (m/z)** 539(M+1)

Antimicrobial activity

All the synthesized derivatives are then assayed for their *in-vitro* antibacterial activity against a panel of pathogenic as well as standard bacterial strains such as *Staphylococcus aureus, Salmonella typhimurium, , Bacillus megaterium,* and *Escherichia coli*. Based on previous literature and scope of the bacterial species are selected. Gentamycin and Kanamycin were procured from commercial sources. The purities and potencies of the agents recovered from commercial preparations are documented by showing that the MICs of antibacterials within acceptable limits against the known strains.

2.2. Determination of MIC in terms of Zone of Inhibition:

The antibacterial activity was tested by agar disc diffusion method. The killing or growth inhibition properties of the agents also scored as clear zone of inhibition surrounding the disc and were measured in mm scale.

3. Materials & Method:

- The bacterial strains were inoculated into fresh sterile MHB (Muller Hinton Broth) media tube (4.5 ml) and were incubated for 18-24 hrs at 37 ^{0}C in a B. O. D. incubator
- Standard antibiotic Gentamycin and Kanamycin were prepared clear solutions with final (1mg/ml).
- The above antibiotic solutions were poured on sterile disc at a final concentration of 40 mcg/disc for Gentamycin and Kanamycin.
- All discs were dried completely by incubating into hot air oven in sterile petri dishes.
- On MHA (Muller Hinton Agar) plates, the bacterial suspension was poured and spread evenly with the help of glass spreader.
- After drying the plates completely, the antibiotic loaded discs were kept on the plates.
- All plates were incubated at 37 ^{0}C in a B. O. D. (Biological Oxygen Demand) incubator for 24 hours.
- Results were recorded and antibiotic activity was quantified by measuring the zone of inhibition surrounded to the disc and it were meseared in ‘mm’ scale and presented in the following Table 1.1 & 1.2.

1. Result and Discussion:

The important role of fluorine in medicinal and pharmaceutical chemistry has been indisputable and well reflected by a large number of recent publications, including some excellent reviews. [22-25] Introduction of fluorine into a biologically active molecule often enhances the metabolic stability and modulates physicochemical properties such as basicity or lipophilicity. Moreover the presence of fluorine can enhance the binding affinity of drug molecules to the target protein. Due to the growing importance of fluorinated organic compounds in biochemical systems there has been an existing and increasing demand for organic compounds containing fluorine atoms.[26] The importance of Indole derivatives as the active therapeutic agents, in particular, as antibacterial while considering these facts an attempt have been made to

synthesize new fluoronitated series of 1-(1-((3-methyl-4-(2,2,2-trifluro ethoxy) pyridine-2-yl)methyl)-1*H*-indole-3-yl)-3-phenylprop-2-en-1-one.(Chalcone) which are then converted into Isoxazole and thiopyrimidine series .

The synthetic strategy is outlined in Scheme I, II and in Scheme III. In the present work, we had synthesized N-protected indole using 2-(chloromethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride to give novel 1-((3-methyl-4-(2,2,2-triflureothoxy)pyridine-2-yl)methyl)-1*H*-indole.(1.I) Which was converted to 3 formyl indole (1.II) using Vilsmeier-Haack reaction condition. Finally the titled chalcones has been synthesized by carrying condensation of 1-((3-methyl-4-(2,2,2-triflureothoxy)pyridine-2-yl)methyl)-1*H*-indole-3-carbaldehyde and substituted acetophenone in presence of aqueous potassium hydroxide (KOH) as a base in absolute ethanol using Claisen-Schmidth condensation. Then Chalcone converted into Isoxazole and thiopyrimidine derivatives of fluorinated indole using Hydroxyamine Hydrochloride and urea resp. All the new compounds are synthesized in good yield; the physical data of all new synthesized compounds are recorded in the Table 1.3, 1.4&1.5.

In the conclusion, we have developed a biologically interested new series of fluorinated indole i.e. Chalcones (1a-g) and their corresponding products; Isoxazole (3a-g) and thiopyrimidine (4a-g) possessing the Indole and 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluroethoxy) pyridine hydrochloride according to a known method and proceeds from readily available commercial reagent. We believe that the simplicity with which the substituted new series of fluorinated indole are prepared in this work could trigger a new area of research among synthetic and medicinal chemists to unravel the biological properties of this series of indole and 2-(chloromethyl)-3 methyl-4-(2,2,2-trifluroethoxy) pyridine analogs which may lead to the discovery of new and valuable biologically active molecules.

***Conclusion**:*

The selected compounds which have been tested for their antibacterial activity by using agar disc method as shown in above table. The antibacterial activity of 3a and 3c has

improved against *K. pneumonia*, but inferior to the positive control. Activity against *B. subtilis* of 3c is superior amongst the synthesized derivatives. The overall activity of all the compounds is inferior as compared to Gentamicin and Kanamycin. Therefore the synthesized derivatives don't show any promising activity against Gentamicin, Kanamycin.

The antibacterial activity with series of 4 was performed by agar disc method by measuring the zone of inhibition in mm. In this series there has been marked antibacterial activity and was seen in 4c against *B. subtilis* and *E.coli.* The other derivatives tested were almost inactive or mild active against the above bacterial species. The overall activity of all the compounds is inferior as compared to Gentamicin and Kanamycin. Therefore the synthesized derivatives don't show any promising activity against Gentamicin, Kanamycin

Caption for Scheme:-

Scheme-I: Synthesis of chalcones(1a-g).

Scheme-II: Synthesis of fluorinated Isoxazole, via chalcone synthesis (3a-g) .

Scheme-III: Synthesis of fluorinated Thiopyrimidine, via chalcone synthesis (4 a-g) .

Caption for Table:-

Table 1.1. Antibacterial data of some 3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2yl)methyl)- 1H-indole 3-yl)-5-phenyl-4,5-dihydroisoxazole (Isoxazole) (3a-d).

Table 1.2. Antibacterial data of new substituted 6-(1-((3-methyl-4-(2,2,2- trifluroethoxy pyridine-2-yl)methyl)-1Hindole3yl)-4-phenyl-3,4dihydropyrimidine-2(1H)thione (Thiopyrimidines) (4a-d).

Table 1.3. Physical data of novel synthesized substituted of 1-(1-((3- methyl-4(2,2,2trifluro ethoxy)pyridine-2-yl)-1H-indole-3-yl)-3-phenylprop-2-en-1- one(chalcone)(1a-g).

Table 1.4. Physical data of novel synthesized 3-(1-3-methyl-4-(2,2,2-trifluroethoxy). pyridine-2-yl)methyl)- 1H-indole 3-yl)-5-phenyl-4,5-dihydroisoxazole (Isoxazole) (3a-g).

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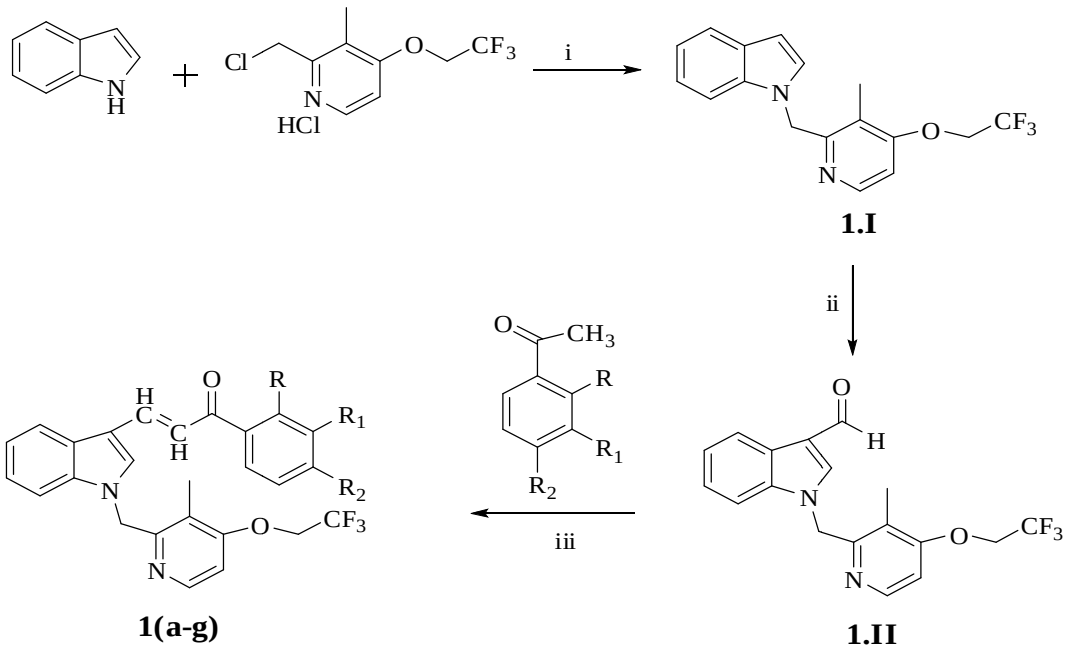
Scheme-I

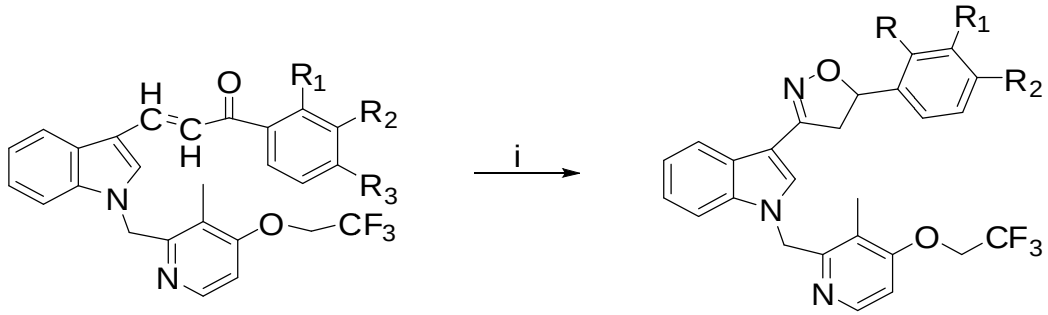
Synthesis of chalcones (1a-g).



Reagents and conditions: i) NaH/DMF/H_2O, 0-5^{0}C, ii) DMF/$POCl_3$,0-35^{0}C, iii) KOH/ Ethanol.

Scheme-II

Synthesis of fluorinated Isoxazole, via chalcone synthesis (3a-g) .

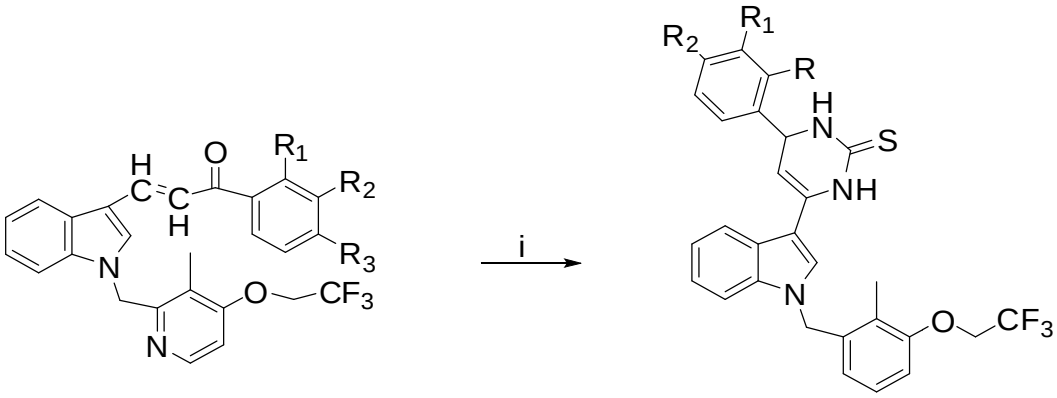


1(a-g) 3 (a-g)

Reagents and conditions: i) $NH_2OH.HCl/KOH$/ Ethanol / Reflux.

Scheme-III

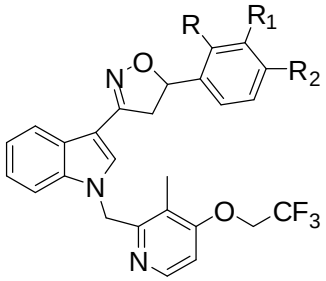
Synthesis of fluorinated Thiopyrimidine via chalcone synthesis (4 a-g).



1(a-g) 4 (a-g)

Reagents and conditions: i) Thiourea,/sodium ethoxide/ Ethanol / Reflux.

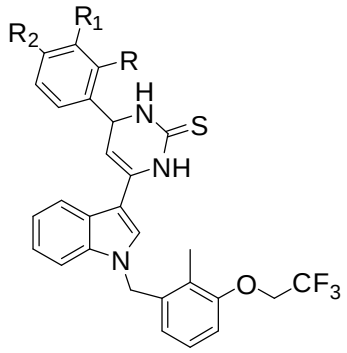
Table 1.1. Antibacterial data of some 3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl)methyl)- 1*H*-indole 3-yl)-5-phenyl-4,5-dihydroisoxazole (Isoxazole) (3a-d)



Antibacterial activity in terms of Zone of Inhibition (mm) when tested at 40 mcg/disc)

Entry	R	R_1	R_2	*K. pneumonia*	*S.typhy*	*P. aurogenosa*	*B.Subtilis*	*E.coli*	*S.auerues*
3a	H	H	H	11	5	2	4	3	3
3b	H	H	NO_2	2	0	1	3	4	2
3c	H	H	F	7	5	1	10	3	2
3d	H	H	Cl	3	4	2	1	2	4
Gentamicin(40 mcg/disc)				17	12	19	18	14	9
Kanamycin(40 mcg/disc)				21	16	24	16	19	11

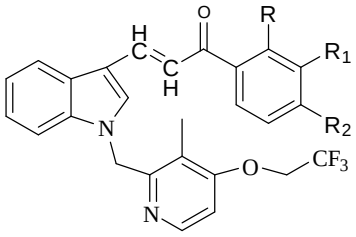
Table 1.2 Antibacterial data of new substituted 6-(1-((3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl)methyl)-1Hindole3yl)-4-phenyl-3,4dihydropyrimidine-2(1H)-thione (Thiopyrimidines) (4a-d)



Antibacterial activity in terms of Zone of Inhibition (mm) when tested at 40 mcg/disc)

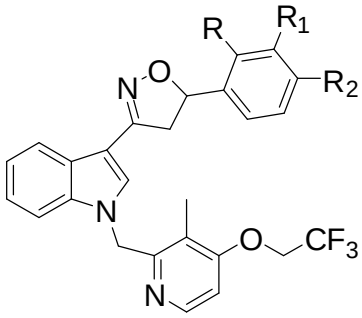
Entry	R	R_1	R_2	*K.pneumonia*	*S.typhy*	*P. auroginosa*	*B.Subtilis*	*E.coli*	*S.auerues*
4a	H	H	H	2	4	0	1	0	2
4b	H	H	NO_2	1	5	0	5	0	0
4c	H	H	F	1	1	0	3	3	2
4d	H	H	Cl	1	3	1	2	1	1
Gentamicin(40 mcg/disc)				19	14	13	19	17	11
Kanamycin(40 mcg/disc)				24	17	20	18	16	13

Table 1.3 Physical data of novel synthesized substituted of 1-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)-1H-indole-3-yl)-3-phenylprop-2-en-1-one.(chalcone)(1a-g).



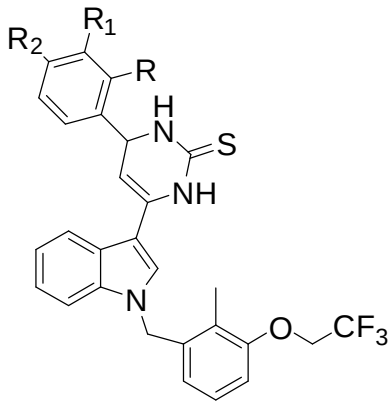
Sr. No	Entry	R	R_1	R_2	Molecular formula	Yield %	M.P(^{0}c)
1.	1a	H	H	H	$C_{26}H_{21}F_3N_2O_2$	78	182-84
2.	1b	H	H	NO_2	$C_{26}H_{20}F_3N_3O_4$	72	230-32
3.	1c	H	H	F	$C_{26}H_{20}F_4N_2O_2$	81	186-87
4.	1d	H	H	Cl	$C_{26}H_{20}ClF_3N_2O_2$	74	201-03
5.	1e	H	H	I	$C_{26}H_{20}F_{3I}N_2O_2$	71	214-16
6.	1f	OH	H	H	$C_{26}H_{21}F_3N_2O_3$	76	189-91
7.	1g	OH	CH_3	H	$C_{27}H_{23}F_3N_2O_3$	69	195-96

Table 1.4 Physical data of novel synthesized 3-(1-3-methyl-4-(2,2,2-trifluroethoxy) pyridine-2-yl)methyl)- 1*H*-indole 3-yl)-5-phenyl-4,5-dihydroisoxazole (Isoxazole) (3a-g)



Sr. No	Entry	R	R_1	R_2	Molecular formula	Yield %	M.P(^{0}c)
1.	3a	H	H	H	$C_{26}H_{22}F_3N_3O_2$	65	149-51
2.	3b	H	H	NO_2	$C_{26}H_{21}F_3N_4O_4$	68	167-71
3.	3c	H	H	F	$C_{26}H_{21}F_4N_3O_2$	70	137-39
4.	3d	H	H	Cl	$C_{26}H_{21}ClF_3N_3O_2$	67	174-76
5.	3e	H	H	I	$C_{26}H_{21}F_3IN_3O_2$	64	196-98
6.	3f	OH	H	H	$C_{26}H_{22}F_3N_3O_3$	56	187-89
7.	3g	OH	CH_3	H	$C_{27}H_{24}F_3N_3O_3$	59	179-81

Table 1.5 Physical data of newly synthesized 6-(1-((3-methyl-4-(2,2,2-trifluroethoxy)pyridine-2-yl)methyl)-1Hindole3yl)-4-phenyl-3,4dihydropyrimidine-2(1H)-thione (Thiopyrimidine) (4a-g).



Sr. No	Entry	R	R_1	R_2	Molecular formula	Yield %	M.P(^{0}c)
1.	4a	H	H	H	$C_{27}H_{23}F_3N_4OS$	69	119-21
2.	4b	H	H	NO_2	$C_{27}H_{22}F_3N_5O_3S$	65	103-05
3.	4c	H	H	F	$C_{27}H_{22}F_4N_4OS$	70	97-99
4.	4d	H	H	Cl	$C_{27}H_{22}ClF_3N_4OS$	68	112-14
5.	4e	H	H	I	$C_{27}H_{22}F_3IN_4OS$	73	137-39
6.	4f	OH	H	H	$C_{27}H_{23}F_3N_4O_2S$	65	154-56
7.	4g	OH	CH_3	H	$C_{28}H_{25}F_3N_4O_2S$	67	163-65

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