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Synthesis, Characterization and Biological Evaluation of Some Novel Thiophene Anchored Fluorinated Heterocycles

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ABSTRACT

A new series of thiophene anchored 1,3,4-thiadiazole, 1,2,4-triazole, 2-heteryl chromone, 1,5-benzothiazepine, pyrazoline, 2-styryl chromone derivatives containing fluorine are synthesized, characterized by spectral methods and screened them for various biological activities.

Key words: 1,3,4-Thiadiazole, 1,2,4-Triazole, 2-Heteryl chromone, 1,5-Benzothiazepine, Pyrazoline, 2-Styryl chromone.

INTRODUCTION

Thiophene is sulfur containing five membered heterocyclic compound widely used as building block in agrochemicals[1]. Thiophene containing compounds exhibit antimicrobial[2], antiparasitic[3], anticancer[4] and anticonvulsant [5] activities.

2-Styryl chromones are associated with various pharmacological activities such as antiallergic[6], cytotoxic[7], antioxidant[8], anti-inflammatory[9] and antibacterial[10]. 2-Styryl chromones are also acts as [2]-amyloid imaging agents[11]. Pyrazole derivatives are known for various potent biological activities such as antibacterial[12], antioxidant[12], anticancer[13], ACE inhibitor[14].

Thiadiazole derivatives possess antitumor[15], antiinflammatory[16], SIRT1 inhibitor[17], antihypertensive[18], antimicrobial[19] activities. 1,2,4-Triazole anchored compounds are associated with antimicrobial[19], antioxidant[20], anti-inflammatory[20], CYP enzyme inhibitor[21], anxiolytic[22] activities.

Compounds containing chromone scaffold are acts as breast cancer resistance protein ABCG2 inhibitor[23], monoamine oxidase inhibitor[24], adenosine A_{2A} receptor antagonists[25]. Some 1,5-benzothiazepines are antifungal[26],

anticonvulsant[27], anti breast cancer[28], antithrombotic[29], antidepressant[30] agents. Compounds having pyrazoline moity are known to possess anti-inflammatory[31], antimalarial[32], antitubercular[33], antidepressant[34] activities.

The activities associated with these various heterocycles prompted us to synthesize some novel thiophene anchored fluorinated heterocycles.

Biological activities

Antimicrobial activity

Synthesized compounds were screened for their antifungal and antibacterial activities. The *in vitro* antimicrobial activities of the synthesized compounds were assessed against fungi and bacteria. The fungi used were *C. albicans*, *A. Fumigatus and A. Niger*. The bacterias used were *S. aureus, E. coli, S. Epidermidis and P. Vulgaris.*

Fluconazole and Amikacin were used as standards for comparison for antifungal and antibacterial activities respectively. The activities were determined by measuring the diameter of the inhibition zone in mm.

None of the compounds is a suitable candidate for antifungal and antibacterial indication as shown in Table 2.

EXPERIMENTAL

Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc.^{1}H NMR spectra were recorded on Bruker 400 MHz NMR spectrometer in DMSO as a solvent and TMS as an internal standard. Peak values are shown in ´ (ppm). Mass spectra were recorded on Finnigan mass spectrometer.

2-{[4-Bromo-5-(methylsulfanyl)thiophen-2-yl]carbonyl}-*N*-phenylhydrazinecarbothioamide 2

Equimolar amounts (0.01 mole) of compound **1** and aryl isothiocyanate were dissolved in 15 mL of ethanol. The reaction mixture was heated under reflux for 55 minutes. The progress of reaction was monitored by TLC. After completion of reaction the contents were cooled and the solid obtained was filtered and crystallized from ethanol to get compound **2**.

2a

IR (KBr, cm^{-1}): 3327, 3228, 3113, 1643, 1257; ^{1}H NMR (DMSO): δ 2.22 (s, 3H), 3.3 (s, 3H), 7.00-7.20 (m, 4H), 7.8 (s, 1H), 9.5 (s, 2H), 10.6 (s, 1H); MS: m/z 430 (M^+); Elemental Anal. Calcd.: C, 38.89; H, 3.26; N, 9.72; found: C, 38.91; H, 3.29; N, 9.74 %.

2b

IR (KBr, cm^{-1}): 3324, 3220, 3117, 1640, 1262; ^{1}H NMR (DMSO): δ 2.21 (s, 3H), 7.04-7.21 (m, 4H), 7.87 (s, 1H), 9.54 (s, 2H), 10.64 (s, 1H); MS: m/z 418 (M^+); Elemental Anal. Calcd.: C, 37.15; H, 2.64; N, 10.00; found: C, 37.18; H, 2.67; N, 10.04 %.

2c

IR (KBr, cm^{-1}): 3330, 3224, 3109, 1647, 1255; ^{1}H NMR (DMSO): δ 2.21 (s, 3H), 7.03-7.20 (m, 4H), 7.86 (s, 1H), 9.53 (s, 2H), 10.62 (s, 1H); MS: m/z 434 (M^+); Elemental Anal. Calcd.: C, 35.75; H, 2.54; N, 9.62; found: C, 35.78; H, 2.57; N, 9.65 %.

2d

IR (KBr, cm^{-1}): 3328, 3225, 3111, 1641, 1257; ^{1}H NMR (DMSO): δ 2.22 (s, 3H), 7.00-7.25 (m, 5H), 7.83 (s, 1H), 9.52 (s, 2H), 10.65 (s, 1H); MS: m/z 400 (M^+); Elemental Anal. Calcd.: C, 38.81; H, 3.01; N, 10.44; found: C, 38.84; H, 3.05; N, 10.48 %.

2e

IR (KBr, cm^{-1}): 3330, 3224, 3119, 1651, 1264; ^{1}H NMR (DMSO): δ 2.20 (s, 3H), 3.34 (s, 3H), 7.05-7.24 (m, 4H), 7.81 (s, 1H), 9.53 (s, 2H), 11.01 (s, 1H); MS: m/z 430 (M^+); Elemental Anal. Calcd.: C, 38.89; H, 3.26; N, 9.72; found: C, 38.92; H, 3.29; N, 9.74 %.

5-(4-Bromo-5-(methylthio)thiophen-2-yl)-*N*-phenyl-1,3,4-thiadiazol-2-amine 3

Thiosemicarbazide 2 (0.001 mole) was dissolved in 3 mL of conc. H_2SO_4 in 50 mL beaker. The reaction mixture was stirred at room temperature for 3 hr. After completion of reaction 10 g of crushed ice was added in it. The solid obtained was separated by filtration and crystallized from 1:1 mixture of DMF and water to afford thiadiazole 3.

3a

IR (KBr, cm^{-1}): 3161, 1633, 1591; ^1H NMR (DMSO): δ 2.3 (s, 3H), 3.5 (s, 3H), 6.9-7.4 (m, 4H), 7.8 (s, 1H), 10.9 (s, 1H); MS: m/z 412 (M^+); Anal. Calcd.: C, 40.58; H, 2.92; N, 10.14; found: C, 40.60; H, 2.94; N, 10.17 %.

3b

IR (KBr, cm^{-1}): 3166, 1630, 1587; ^1H NMR (DMSO): δ 2.31 (s, 3H), 6.95-7.82 (m, 5H), 10.94 (s, 1H); MS: m/z 400 (M^+); Anal. Calcd.: C, 38.81; H, 2.25; N, 10.44; found: C, 38.84; H, 2.28; N, 10.47 %.

3c

IR (KBr, cm^{-1}): 3156, 1638, 1598; ^1H NMR (DMSO): δ 2.30 (s, 3H), 6.91-7.83 (m, 5H), 10.91 (s, 1H); MS: m/z 416 (M^+); Anal. Calcd.: C, 37.28; H, 2.17; N, 10.03; found: C, 37.31; H, 2.20; N, 10.06 %.

3d

IR (KBr, cm^{-1}): 3167, 1632, 1588; ^1H NMR (DMSO): δ 2.31 (s, 3H), 6.92-7.89 (m, 6H), 10.93 (s, 1H); MS: m/z 382 (M^+); Anal. Calcd.: C, 40.63; H, 2.62; N, 10.93; found: C, 40.66; H, 2.65; N, 10.96 %.

3e

IR (KBr, cm^{-1}: 3164, 1629, 1592; ^1H NMR (DMSO): δ 2.3 (s, 3H), 3.52 (s, 3H), 6.91-7.86 (m, 4H), 10.9 (s, 1H); MS: m/z 412 (M^+); Anal. Calcd.: C, 40.58; H, 2.92; N, 10.14; found: C, 40.61; H, 2.95; N, 10.17 %.

5-(4-Bromo-5-(methylthio)thiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol 4

A mixture of thiosemicarbazide 2 and 10 mL of 1N NaOH was heated under mild reflux for 1.5 hr. The progress of reaction was monitored by TLC. After completion of reaction the contents were cooled and poured into crushed ice. Then it was acidified with glacial acetic acid. The product was separated by filtration and crystallized from the mixture (1:1) of DMF and water to get corresponding triazole 4.

4a

IR (KBr, cm^{-1}): 3070, 2997, 1583, 1517; ^1H NMR (DMSO): δ 2.0 (s, 3H), 3.5 (s, 3H), 6.4-7.5 (m, 5H), 14.11 (s, 1H); MS: m/z 412 (M^+); Anal. Calcd.: C, 40.58; H, 2.92; N, 10.14; found: C, 40.61; H, 2.95; N, 10.17 %.

4b

IR (KBr, cm^{-1}): 3077, 2990, 1578, 1514; ^1H NMR (DMSO): δ 2.01 (s, 3H), 6.49-7.56 (m, 5H), 14.12 (s, 1H); MS: m/z 400 (M^+); Anal. Calcd.: C, 38.81; H, 2.25; N, 10.44; found: C, 38.84; H, 2.28; N, 10.47 %.

4c

IR (KBr, cm^{-1}): 3081, 2983, 1588, 1521; ^1H NMR (DMSO): δ 2.01 (s, 3H), 6.48-7.58 (m, 5H), 14.11 (s, 1H); MS: m/z 416 (M^+); Anal. Calcd.: C, 37.28; H, 2.17; N, 10.03; found: C, 37.32; H, 2.20; N, 10.07; %.

4d

IR (KBr, cm^{-1}): 3085, 2990, 1580, 1517; ^1H NMR (DMSO): δ 2.01 (s, 3H), 6.4-7.57 (m, 6H), 14.1 (s, 1H); MS: m/z 382 (M^+); Anal. Calcd.: C, 40.63; H, 2.62; N, 10.93; found: C, 40.67; H, 2.65; N, 10.96 %.

4e

IR (KBr, cm^{-1}): 3074, 2991, 1589, 1510; ^1H NMR (DMSO): δ 2.02 (s, 3H), 3.55 (s, 3H), 6.46-7.59 (m, 5H), 14.10 (s, 1H); MS: m/z 412 (M^+); Anal. Calcd.: C, 40.58; H, 2.92; N, 10.14; found: C, 40.62; H, 2.95; N, 10.18;%.

(*E*)-3-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one 10.

Equimolar amount of compound **8** (0.02 mole) and substituted o-hydroxy acetophenone (0.02 mole) were dissolved in 25 mL of alcohol in conical flask. To this reaction mixture 40% KOH (10mL) was added. The reaction mixture was stirred at room temperature for 48 hrs. The contents were then poured into crushed ice and neutralized with acetic acid. The yellow solid thus obtained was filtered and crystallized from alcohol to afford compound **10**.

10a

IR (KBr, cm^{-1}): 3134 (O-H), 1637 (C=O), 1568 (C=N), 1556 (-C=C-), 1508 (-C=C-, aromatic), 1155 (Ar-F); ^1H NMR (DMSO- d_6): d 7.26- 8.22 (m, 11H, Ar-H and =CH), 9.44 (s, 1H), 13.2 (s, 1H, -O-H); MS: m/z 458 (M^+);; Anal. Calcd.: C, 57.53; H, 2.85; N, 6.10; found: C, 57.56; H, 2.88; N, 6.13 %.

10b

IR (KBr, cm^{-1}): 3132 (O-H), 1633 (C=O), 1566 (C=N), 1549 (-C=C-), 1511 (-C=C-, aromatic), 1158 (Ar-F); ^{1}H NMR (DMSO- d_6): d 7.25- 8.34 (m, 12H, Ar-H and =CH), 9.47 (s, 1H), 13.21 (s, 1H, -O-H); MS: m/z 424 (M^+); Anal. Calcd.: C, 62.19; H, 3.32; N, 6.59; found: C, 62.21; H, 3.35; N, 6.62%.

10c

IR (KBr, cm^{-1}): 3129 (O-H), 1631 (C=O), 1569 (C=N), 1556 (-C=C-), 1510 (-C=C-, aromatic), 1157 (Ar-F); ^{1}H NMR (DMSO- d_6): d 7.27- 8.24 (m, 12H, Ar-H and =CH), 9.45 (s, 1H), 13.22 (s, 1H, -O-H); MS: m/z 468 (M^+); Anal. Calcd.: C, 56.30; H, 3.01; N, 5.97; found: C, 56.34; H, 3.05; N, 6.01 %.

10d

IR (KBr, cm^{-1}): 3130 (O-H), 1637 (C=O), 1571 (C=N), 1551 (-C=C-), 1501 (-C=C-, aromatic), 1149 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.2 (s, 3H), 7.25-8.22 (m, 11H, Ar-H and =CH), 9.46 (s, 1H), 13.20 (s, 1H, -O-H); MS: m/z 438 (M^+); Anal. Calcd.: C, 62.94; H, 3.67; N, 6.38; found: C, 62.98; H, 3.70; N, 6.41 %.

10e

IR (KBr, cm^{-1}): 3134 (O-H), 1641 (C=O), 1561 (C=N), 1555 (-C=C-), 1509 (-C=C-, aromatic), 1155 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.24 (s, 3H), 2.29 (s, 3H), 7.27- 8.23 (m, 11H, Ar-H and =CH), 9.44 (s, 1H), 13.2 (s, 1H, -O-H); MS: m/z 418 (M^+); Anal. Calcd.: C, 68.88; H, 4.58; N, 6.69; found: C, 68.92; H, 4.62; N, 6.73 %.

10f

IR (KBr, cm^{-1}): 3140 (O-H), 1635 (C=O), 1567 (C=N), 1547 (-C=C-), 1499 (-C=C-, aromatic), 1146 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.24 (s, 3H), 7.21- 8.26 (m, 12H, Ar-H and =CH), 9.45 (s, 1H), 13.20 (s, 1H, -O-H); MS: m/z 404 (M^+); Anal. Calcd.: C, 68.30; H, 4.24; N, 6.93; found: C, 68.34; H, 4.28; N, 6.97%.

2-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one 11

Compound 10 (0.001 mole) was dissolved in 15 ml DMSO. To this reaction mixture catalytic amount of iodine (0.01 gm) was added. The reaction mixture was heated to 100 to 110^{0}C for 1.5 hrs and left overnight. Then 100 ml ice cold water was added in it. The solid thus obtained was filtered and washed with dil. sodium thiosulphate followed by water. The product was crystallized from alcohol to afford compounds 11.

11a

IR (KBr, cm^{-1}): 1655 (C=O), 1567 (C=N), 1513 (C=C), 1158 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 6.77 (s, 1H, Ar-H), 7.14-8.16 (m, 9H, Ar-H), 9.22 (s, 1H); MS: m/z 456 (M^+); Anal. Calcd.: C, 57.78; H, 2.42; N, 6.13; found: C, 57.82; H, 2.46; N, 6.17 %.

11b

IR (KBr, cm^{-1}): 1649 (C=O), 1561 (C=N), 1508 (C=C), 1156 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 6.71 (s, 1H, Ar-H), 7.13-8.18 (m, 10H, Ar-H), 9.24 (s, 1H); MS: m/z 422 (M^+); Anal. Calcd.: C, 62.49; H, 2.86; N, 6.62; found: C, 62.53; H, 2.89; N, 6.65%.

11c

IR (KBr, cm^{-1}): 1651 (C=O), 1562 (C=N), 1516 (C=C), 1149 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 6.73 (s, 1H, Ar-H), 7.15-8.13 (m, 10H, Ar-H), 9.23 (s, 1H); MS: m/z 466 (M^+); Anal. Calcd.: C, 56.54; H, 2.59; N, 5.99; found: C, 56.57; H, 2.62; N, 6.02 %.

11d

IR (KBr, cm^{-1}): 1659 (C=O), 1571 (C=N), 1510 (C=C), 1148 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 6.77 (s, 1H, Ar-H), 7.15-8.19 (m, 9H, Ar-H), 9.23 (s, 1H); MS: m/z 436 (M^+); Anal. Calcd.: C, 63.23; H, 3.23; N, 6.41; found: C, 63.27; H, 3.27; N, 6.45%.

11e

IR (KBr, cm^{-1}): 1645 (C=O), 1569 (C=N), 1513 (C=C), 1155 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 2.23 (s, 3H), 2.29 (s, 3H), 6.79 (s, 1H, Ar-H), 7.13-8.15 (m, 9H, Ar-H), 9.21 (s, 1H); MS: m/z 416 (M^+); Anal. Calcd.: C, 69.21; H, 4.11; N, 6.73; found: C, 69.25; H, 4.14; N, 6.76 %.

11f

IR (KBr, cm^{-1}): 1650 (C=O), 1562 (C=N), 1507 (C=C), 1146 (Ar-F), ^{1}H NMR (DMSO- d_6): δ 2.23 (s, 3H), 6.78 (s, 1H, Ar-H), 7.14-8.17 (m, 10H, Ar-H), 9.23 (s, 1H); MS: m/z 402 (M^+); Anal. Calcd.: C, 68.64; H, 3.76; N, 6.96; found: C, 68.68; H, 3.79; N, 6.99 %.

Table 1: Characterization data of synthesized compounds

Compd	R_1	R_2	R_3	m.p. (°C)	Yield (%)
2a	H	OCH_3	H	186	65
2b	H	H	F	180	74
2c	H	H	Cl	184	71
2d	H	H	H	179	73
2e	OCH_3	H	H	155	61
3a	H	OCH_3	H	180	60
3b	H	H	F	199	65
3c	H	H	Cl	172	73
3d	H	H	H	177	60
3e	OCH_3	H	H	190	62
4a	H	OCH_3	H	235	68
4b	H	H	F	209	72
4c	H	H	Cl	222	56
4d	H	H	H	240	60
4e	OCH_3	H	H	200	66
10a	Cl	H	Cl	218	72
10b	H	H	Cl	186	69
10c	H	H	Br	178	66
10d	H	CH_3	Cl	158	69
10e	CH_3	H	CH_3	160	68
10f	H	CH_3	H	160	63
11a	Cl	H	Cl	258	62
11b	H	H	Cl	264	68
11c	H	H	Br	254	67
11d	H	CH_3	Cl	258	69
11e	CH_3	H	CH_3	238	65
11f	H	CH_3	H	196	61
12a	Cl	H	Cl	190	67
12b	H	H	Cl	171	63
12c	H	H	Br	194	70
12d	H	CH_3	Cl	178	69
12e	CH_3	H	CH_3	156	62
12f	H	CH3	H	130	59
13a	Cl	H	Cl	230	73
13b	H	H	Cl	188	78
13c	H	H	Br	200	74
13d	H	CH_3	Cl	208	71
13e	CH_3	H	CH_3	232	69
13f	H	CH_3	H	164	64
15a	Cl	H	Cl	178	62
15b	H	H	Cl	154	67
15c	H	H	Br	168	66
15d	H	CH_3	Cl	160	61
15e	H	H	CH_3	142	58
16a	Cl	H	Cl	250	69
16b	H	H	Cl	270	63
16c	H	H	Br	274	68
16d	H	CH_3	Cl	234	60
16e	H	H	CH_3	165	52
17a	Cl	H	Cl	275	62
17b	H	H	Cl	295	65
17c	H	H	Br	284	60
17d	H	CH_3	Cl	298	63
17e	H	H	CH_3	272	61

2-(5-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenol 12.

Compound 10 (0.003 mol) was taken in 100 mL RBF with 15 mL dioxane. To this reaction mixture 1 mL hydrazine hydrate was added and the contents were heated under refluxed for 4 hours. Then to the reaction mixture 2 mL gl. acetic acid was and heating was continued for further 3 hours. After complete heating contents were cooled to room temperature and poured over crushed ice. The solid thus obtained was separated by filtration and crystallized with alcohol to get compounds 12. Products obtained were identified with help of spectral data. Their characterization data is given in the Table-1.

12a

IR (KBr, cm^{-1}): 3405 (-O-H), 3320 (-N-H), 3071 (Ar-H), 1587 (C=N); ^{1}H NMR (DMSO): δ 3.20 (dd, 1H), 3.74 (dd, 1H), 5.1 (t, 1H), 7.17-8.13 (m, 10H, aromatic and N-H protons), 8.58 (s, 1H, pyrazole proton), 12.00 (s, 1H, -O-H proton); MS: m/z 472 (M^+); Anal. Calcd.: C, 55.82; H, 3.19; N, 11.84; found: C, 55.86; H, 3.23; N, 11.88 %.

12b

IR (KBr, cm^{-1}): 3409 (-O-H), 3325 (-N-H), 3074 (Ar-H), 1580 (C=N); ^{1}H NMR (DMSO): δ 3.21 (dd, 1H), 3.74 (dd, 1H), 5.11 (t, 1H), 7.16-8.14 (m, 11H, aromatic and N-H protons), 8.57 (s, 1H, pyrazole proton), 12.01 (s, 1H, -O-H proton); MS: m/z 438 (M^+); Anal. Calcd.: C, 60.20; H, 3.67; N, 12.77; found: C, 60.24; H, 3.71; N, 12.80 %.

12c

IR (KBr, cm^{-1}): 3402 (-O-H), 3322 (-N-H), 3070 (Ar-H), 1581 (C=N); ^{1}H NMR (DMSO): δ 3.22 (dd, 1H), 3.74 (dd, 1H), 5.12 (t, 1H), 7.11-8.12 (m, 11H, aromatic and N-H protons), 8.59 (s, 1H, pyrazole proton), 12.04 (s, 1H, -O-H proton); MS: m/z 482 (M^+); Anal. Calcd.: C, 54.67; H, 3.34; N, 11.59; found: C, 54.71; H, 3.38; N, 11.63 %.

12d

IR (KBr, cm^{-1}): 3410 (-O-H), 3320 (-N-H), 3072 (Ar-H), 1577 (C=N); ^{1}H NMR (DMSO): δ 2.23 (s, 3H), 3.21 (dd, 1H), 3.72 (dd, 1H), 5.11 (t, 1H), 7.16-8.16 (m, 10H, aromatic and N-H protons), 8.57 (s, 1H, pyrazole proton), 12.02 (s, 1H, -O-H proton); MS: m/z 452 (M^+); Anal. Calcd.: C, 60.99; H, 4.01; N, 12.37; found: C, 61.03; H, 4.05; N, 12.41 %.

12e

IR (KBr, cm^{-1}): 3407 (-O-H), 3324 (-N-H), 3065 (Ar-H), 1579 (C=N); ^{1}H NMR (DMSO): δ 2.23 (s, 3H), 2.25 (s, 3H), 3.23 (dd, 1H), 3.73 (dd, 1H), 5.12 (t, 1H), 7.16-8.14 (m, 10H, aromatic and N-H protons), 8.56 (s, 1H, pyrazole proton), 12.01 (s, 1H, -O-H proton); MS: m/z 432 (M^+); Anal. Calcd.: C, 66.65; H, 4.89; N, 12.95; found: C, 66.69; H, 4.93; N, 12.99 %.

12f

IR (KBr, cm^{-1}): 3401 (-O-H), 3325 (-N-H), 3066 (Ar-H), 1591 (C=N); ^{1}H NMR (DMSO): δ 2.24 (s, 3H), 3.21 (dd, 1H), 3.72 (dd, 1H), 5.13 (t, 1H), 7.15-8.13 (m, 11H, aromatic and N-H protons), 8.55 (s, 1H, pyrazole proton), 12.00 (s, 1H, -O-H proton); MS: m/z 418 (M^+); Anal. Calcd.: C, 66.01; H, 4.58; N, 13.39; found: C, 66.05; H, 4.62; N, 13.43 %.

2-((*E*)-2-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4-yl)phenol 13.

Compound 10 (0.001 mol) and *o*-amino thiophenol (0.001 mol) was suspended in 10 ml ethanol. Reaction mass was heated to reflux at 90^{0}C for 4-5h. To the reaction mixture 2 ml glacial acetic acid was added and heating continued for further 3h. Contents were cooled and poured into crushed ice. The product obtained was separated by filtration and crystallized from ethanol. Products obtained were identified with help of spectral data. Their characterization data is given in the Table-1.

13a

IR (KBr): 3413 (-O-H), 3066 (Ar-H), 1590 & 1566 (C=N), 612 (C-S) cm^{-1}; ^{1}H NMR (DMSO): δ 3.12 (t, 1H), 3.76 (dd, 1H), 5.57 (dd, 1H), 7.18-8.05 (m, 13H, Ar-H), 8.51 (s, 1H, pyrazole proton), 15.9 (s, 1H, -O-H proton); MS: m/z 565 (M^+); Anal. Calcd.: C, 59.36; H, 3.20; N, 7.42; found: C, 59.40; H, 3.23; N, 7.46;%.

13b

IR (KBr): 3411 (-O-H), 3070 (Ar-H), 1594 & 1570 (C=N), 611 (C-S) cm^{-1}; ^{1}H NMR (DMSO): δ 3.11 (t, 1H), 3.75 (dd, 1H), 5.57 (dd, 1H), 7.17-8.04 (m, 14H, Ar-H), 8.50 (s, 1H, pyrazole proton), 15.95

Table 2: Antimicrobial activity results for concentration 1000µg/ml

Compd	Antifungal test models			Antibacterial test models			
	C. albicans	*A. fumigatus*	*A. Niger*	*S. aureus*	*E. coli*	*S. epidermidis*	*P. Vulgaris*
2a	12	8	10	12	11	12	-
2b	10	-	12	10	8	10	8
2c	-	-	10	-	10	-	-
2d	10	8	8	12	6	12	8
2e	10	6	8	11	10	10	8
3a	8	6	8	10	11	8	-
3b	10	-	6	12	10	8	12
3c	6	8	6	8	12	6	-
3d	11	6	8	8	10	8	6
3e	8	-	6	11	8	6	-
4a	10	8	8	12	10	8	6
4b	10	6	4	10	10	6	-
4c	12	6	6	11	10	8	4
4d	10	8	-	10	6	6	8
4e	8	4	6	12	10	8	4
10a	8	4	10	8	8	6	8
10b	4	6	8	6	4	4	-
10c	8	6	-	4	6	8	6
10d	6	4	-	10	8	-	-
10e	10	6	4	6	8	9	8
10f	4	6	4	8	6	6	4
11a	8	6	-	6h	8h	6	-
11b	6	8	6	12	10	11	12
11c	11	6	8	10	6	8	-
11d	10	6	4	6	8	11	-
11e	8	4	6	8	6	6	-
11f	4	8	6	6	7	4	-
12a	11	10	8	6	4	6	8
12b	10	5	6	4	6	6	4
12c	10	6	6	12	10	6	6
12d	8	6	6	10	8	10	8
12e	10	6	6	12	8	6	12
12f	8	4	6	10	6	8	4
13a	10	6	8	10	8	6	6
13b	6	8	6	8	6	8	4
13c	8	10	10	6	8	10	6
13d	8	4	-	8	10	8	-
13e	6	8	-	8	10	6	-
13f	6	7	-	8	6	10	6
15a	8	8	6	10	8	6	-
15b	6	6	4	9	6	8	-
15c	8	6	-	10	6	4	-
15d	8	8	8	4	6	10	-
15e	8	4	-	4	7	8	-
16a	12	8	4	6	8	10	4

16b	12	10	8	6	4	6	-
16c	8	6	6	12	10	13	-
16d	10	8	6	12	10	10	-
16e	10	8	6	10	8	6	6
17a	10h	8	6	6h	8h	8	4
17b	12	8h	-	10	12h	10	8
17c	12	6	-	8	12	6	-
17d	6	4	6	7	9	6	-
17e	12	6	8	11	14	16	-
Fluconazole 10µg/disc	24	14	20	NA	NA	NA	NA
Amikacin20µg/ml	NA	NA	NA	28	20	23	18

NT: Not tested, h: hazy.

(s, 1H, -O-H proton); MS: m/z 531 (M^+); Anal. Calcd.: C, 63.21; H, 3.60; N, 7.90; found: C, 63.25; H, 3.64; N, 7.94 %.

13c

IR (KBr): 3409 (-O-H), 3062 (Ar-H), 1597 & 1562 (C=N), 616 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 3.12 (t, 1H), 3.77 (dd, 1H), 5.54 (dd, 1H), 7.16-8.07 (m, 14H, Ar-H), 8.52 (s, 1H, pyrazole proton), 15.93 (s, 1H, -O-H proton); MS: m/z 575 (M^+); Anal. Calcd.: C, 58.33; H, 3.32; N, 7.29; found: C, 58.37; H, 3.36; N, 7.33 %.

13d

IR (KBr): 3407 (-O-H), 3068 (Ar-H), 1590 & 1568 (C=N), 611 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 2.24 (s, 3H), 3.10 (t, 1H), 3.73 (dd, 1H), 5.57 (dd, 1H), 7.17-8.07 (m, 13H, Ar-H), 8.50 (s, 1H, pyrazole proton), 15.92 (s, 1H, -O-H proton); MS: m/z 545 (M^+); Anal. Calcd.: C, 63.78; H, 3.88; N, 7.69; found: C, 63.82; H, 3.92; N, 7.73 %.

13e

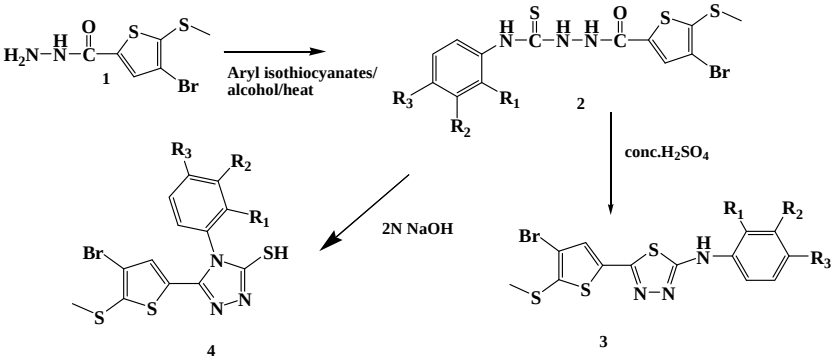
IR (KBr): 3410 (-O-H), 3066 (Ar-H), 1594 & 1565 (C=N), 610 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 2.24 (s, 3H), 2.26 (s, 3H), 3.13 (t, 1H), 3.74 (dd, 1H), 5.56 (dd, 1H), 7.16-8.01 (m, 13H, Ar-H), 8.53 (s, 1H, pyrazole proton), 15.91 (s, 1H, -O-H proton); MS: m/z 525 (M^+); Anal. Calcd.: C, 68.55; H, 4.60; N, 7.99; found: C, 68.59; H, 4.64; N, 8.03 %.

13f

IR (KBr): 3404 (-O-H), 3062 (Ar-H), 1584 & 1559 (C=N), 610 (C-S) cm^{-1}; ^1H NMR (DMSO): δ 2.21 (s, 3H), 3.12 (t, 1H), 3.74 (dd, 1H), 5.57 (dd, 1H), 7.14-8.03 (m, 14H, Ar-H), 8.54 (s, 1H, pyrazole proton), 15.90 (s, 1H, -O-H proton); MS: m/z 511 (M^+); Anal. Calcd.: C, 68.08; H, 4.33; N, 8.21; found: C, 68.11; H, 4.37; N, 8.24 %.

(*E*)-2-Acetylphenyl 3-(1-(4-fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)acrylate 15

Equimolar amount (0.05 moles) of the compounds **14** and substituted 2-hydroxy



Scheme 1:

acetophenone were taken in dry beaker. To this mixture was dissolved in 15 ml dry pyridine. The reaction mixture was then cooled to 0^0C. To this reaction mixture $POCl_3$ (0.06 moles) was added drop wise maintaining temperature below 10^0C. Then reaction mixture was kept overnight at room temperature. It was then poured over crushed ice with vigorous stirring. Product was separated by filtration, washed with ice-cold water and then with 2% ice-cold solution of NaOH followed by ice-cold water again. Purification by crystallization after drying with alcohol afforded **15**.

15a

IR (KBr, cm^{-1}): 3120 (O-H), 1736 (C=O), 1549 (C=N), 1545 (-C=C-), 1499 (-C=C-, aromatic), 1147 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.21 (s, 3H), 7.05- 8.30 (m, 11H, Ar-H and =CH), 8.44 (s, 1H, pyrazole proton); MS: m/z 500 (M^+); Anal. Calcd.: C, 57.50; H, 3.02; N, 5.59; found: C, 57.54; H, 3.06; N, 5.63 %.

15b

IR (KBr, cm^{-1}): 3129 (O-H), 1734 (C=O), 1554 (C=N), 1544 (-C=C-), 1494 (-C=C-, aromatic), 1143 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.20 (s, 3H), 7.08- 8.35 (m, 12H, Ar-H and =CH), 8.48 (s, 1H, pyrazole proton); MS: m/z 466 (M^+); Anal. Calcd.: C, 61.74; H, 3.45; N, 6.00; found: C, 61.78; H, 3.48; N, 6.03 %.

15c

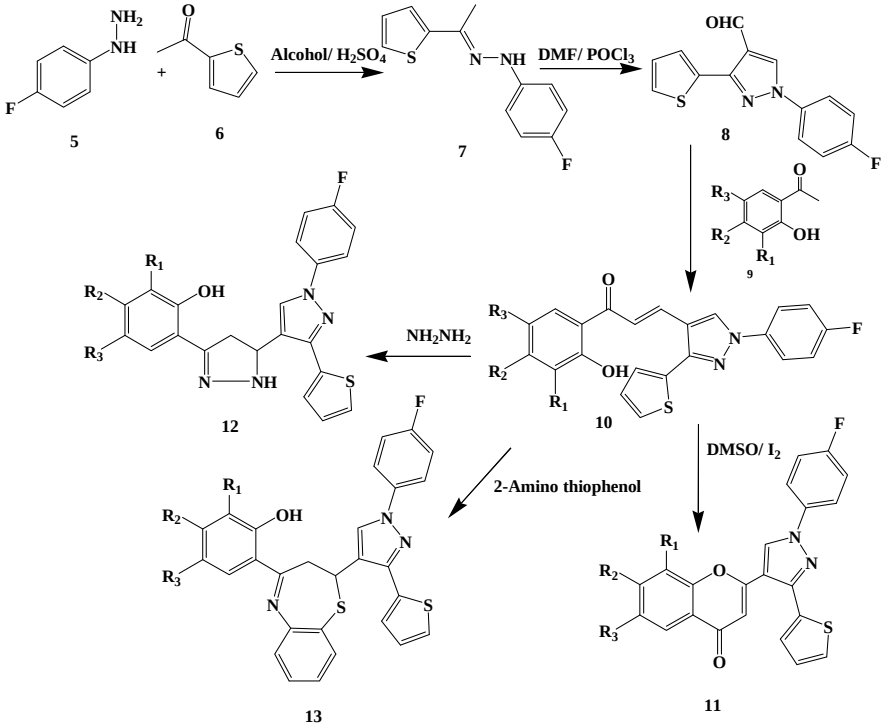
IR (KBr, cm^{-1}): 3124 (O-H), 1739 (C=O), 1558 (C=N), 1558 (-C=C-), 1506 (-C=C-, aromatic), 1142 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.21 (s, 3H), 7.03- 8.31 (m, 12H, Ar-H and =CH), 8.47 (s, 1H, pyrazole proton); MS: m/z 510 (M^+); Anal. Calcd.: C, 56.37; H, 3.15; N, 5.48; found: C, 56.40; H, 3.18; N, 5.52 %.

15d

IR (KBr, cm^{-1}): 3130 (O-H), 1732 (C=O), 1551 (C=N), 1549 (-C=C-), 1495 (-C=C-, aromatic), 1141 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.20 (s, 3H), 7.03- 8.37 (m, 11H, Ar-H and =CH), 8.49 (s, 1H, pyrazole proton); MS: m/z 480 (M^+); Anal. Calcd.: C, 62.43; H, 3.77; N, 5.82; found: C, 62.47; H, 3.80; N, 5.85 %.

15e

IR (KBr, cm^{-1}): 3135 (O-H), 1739 (C=O), 1559 (C=N), 1535 (-C=C-), 1503 (-C=C-, aromatic), 1151 (Ar-F); ^{1}H NMR (DMSO- d_6): d 2.20 (s, 3H),



Scheme 2:

2.31 (s, 3H), 7.00- 8.27 (m, 12H, Ar-H and =CH), 8.42 (s, 1H, pyrazole proton); MS: m/z 446 (M^+); Anal. Calcd.: C, 67.25; H, 4.29; N, 6.27; found: C, 67.28; H, 4.33; N, 6.30 %.

(*E*)-5-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione 16

Compound 15 (0.03 moles) was dissolved in 15 ml of dry pyridine. To this mixture powdered KOH (1 gm) was added and the reaction mixture was stirred on the magnetic stirrer for 3 hours. Then it was poured over crushed ice and acidified with acetic acid. The product was then separated by filtration, washed with water, dried and crystallized with acetic acid to afford 16.

16a

IR (KBr): 3094 (O-H), 1643 (C=O), 1623 (-C=C-), 1133 (Ar-F) cm^{-1}; ^1H NMR (DMSO- d_6): δ 6.17-8.03 (m, 11H, Aromatic and olefinic protons), 11.54 (s, 1H, phenolic proton), 15.21 (1H, enolic proton); MS: m/z 500 (M^+); Anal. Calcd.: C, 57.50; H, 3.02; N, 5.59; found: C, 57.54; H, 3.06; N, 5.63 %.

16b

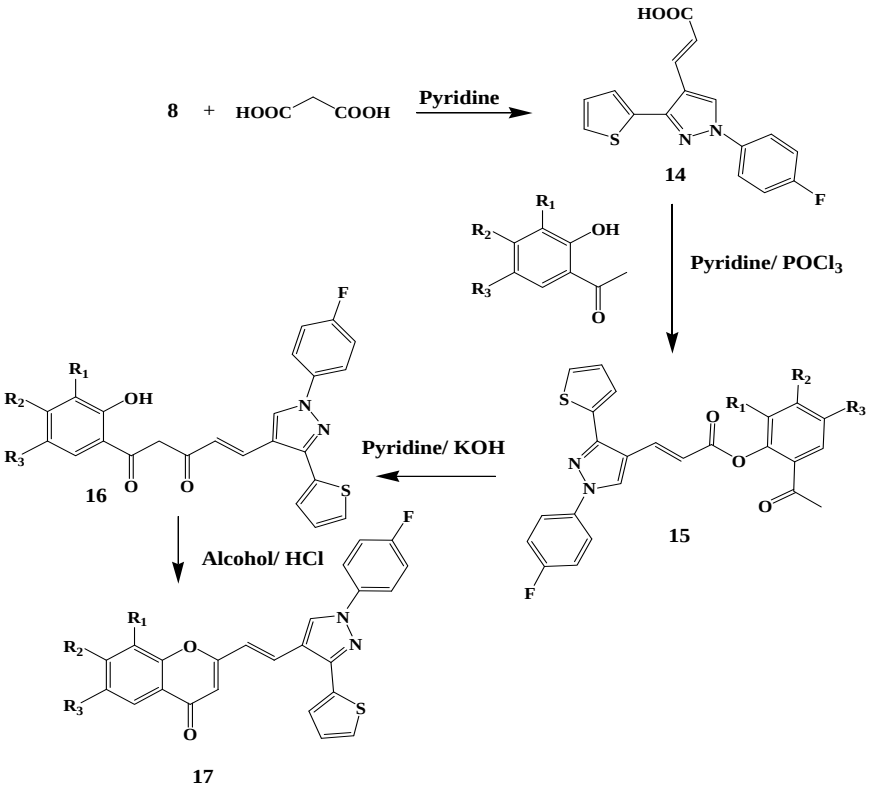
IR (KBr): 3105 (O-H), 1649 (C=O), 1620 (-C=C-), 1140 (Ar-F) cm^{-1}; ^1H NMR (DMSO- d_6): δ 6.11-8.10 (m, 12H, Aromatic and olefinic protons), 11.58 (s, 1H, phenolic proton), 15.20 (1H, enolic proton); MS: m/z 466 (M^+); Anal. Calcd.: C, 61.74; H, 3.45; N, 6.00; found: C, 61.78; H, 3.49; N, 6.04 %.

16c

IR (KBr): 3087 (O-H), 1635 (C=O), 1620 (-C=C-), 1123 (Ar-F) cm^{-1}; ^1H NMR (DMSO- d_6): δ 6.12-8.06 (m, 12H, Aromatic and olefinic protons), 11.55 (s, 1H, phenolic proton), 15.19 (1H, enolic proton); MS: m/z 510 (M^+); Anal. Calcd.: C, 56.37; H, 3.15; N, 5.48; found: C, 56.40; H, 3.18; N, 5.51 %.

16d

IR (KBr): 3101 (O-H), 1652 (C=O), 1626 (-C=C-), 1142 (Ar-F) cm^{-1}; ^1H NMR (DMSO- d_6): δ 2.31 (s, 3H), 6.20 -8.12 (m, 11H, Aromatic and olefinic protons), 11.49 (s, 1H, phenolic proton), 15.25 (1H, enolic proton); MS: m/z 480 (M^+); Anal. Calcd.: C, 62.43; H, 3.77; N, 5.82; found: C, 62.47; H, 3.81; N, 5.86 %.



Scheme 3:

16e

IR (KBr): 3087 (O-H), 1633 (C=O), 1627 (-C=C-), 1147 (Ar-F) cm^{-1}; ^1H NMR (DMSO- d_6): δ 2.20 (s, 3H), 6.23-8.01 (m, 12H, Aromatic and olefinic protons), 11.48 (s, 1H, phenolic proton), 15.21 (1H, enolic proton); MS: m/z 446 (M^+); Anal. Calcd.: C, 67.25; H, 4.29; N, 6.27; found: C, 67.28; H, 4.32; N, 6.30 %.

2-((*E*)-2-(1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)vinyl)-4*H*-chromen-4-one 17

Compound **16** (0.01 moles) was dissolved in 15 ml glacial acetic acid in RBF. To this reaction mixture 1 ml conc. HCl was added and contents were refluxed for 2 hours. Then it was cooled and poured over crushed ice. The product was then separated by filtration, washed with water, dried and crystallized with acetic acid to afford **17**.

17a

IR (KBr, cm^{-1}): 1651 (C=O), 1559 (C=N), 1505 (C=C), 1149 (Ar-F); ^1H NMR (DMSO- d_6): 6.64 (s, 1H, Ar-H), 7.01-8.52 (m, 11H, Ar-H), 9.12 (s, 1H); MS: m/z 482 (M^+); Anal. Calcd.: C, 59.64; H, 2.71; N, 5.80; found: C, 57.82; H, 2.46; N, 6.17 %.

17b

IR (KBr, cm^{-1}): 1654 (C=O), 1548 (C=N), 1509 (C=C), 1156 (Ar-F); ^1H NMR (DMSO- d_6): d 6.65 (s, 1H, Ar-H), 7.07-8.40 (m, 12H, Ar-H), 9.16 (s, 1H); MS: m/z 448 (M^+); Anal. Calcd.: C, 64.21; H, 3.14; N, 6.24; found: C, 64.24; H, 3.17; N, 6.27 %.

17c

IR (KBr, cm^{-1}): 1659 (C=O), 1557 (C=N), 1501 (C=C), 1152 (Ar-F); ^1H NMR (DMSO- d_6): d 6.63 (s, 1H, Ar-H), 7.05-8.50 (m, 12H, Ar-H), 9.13 (s, 1H); MS: m/z 500 (M^+); Anal. Calcd.: C, 58.43; H, 2.86; N, 5.68; found: C, 58.46; H, 2.89; N, 5.71 %.

17d

IR (KBr, cm^{-1}): 1653 (C=O), 1549 (C=N), 1498 (C=C), 1141 (Ar-F); ^1H NMR (DMSO- d_6): d 2.31 (s, 3H), 6.65 (s, 1H, Ar-H), 7.01-8.42 (m, 11H, Ar-H), 9.15 (s, 1H); MS: m/z 462 (M^+); Anal. Calcd.: C, 64.86; H, 3.48; N, 6.05; found: C, 64.90; H, 3.52; N, 6.09 %.

17e

IR (KBr, cm^{-1}): 1658 (C=O), 1560 (C=N), 1514 (C=C), 1145 (Ar-F); ^1H NMR (DMSO- d_6): d 2.28 (s, 3H), 6.61 (s, 1H, Ar-H), 7.04-8.39 (m, 12H, Ar-H), 9.14 (s, 1H); MS: m/z 428 (M^+); Anal. Calcd.: C, 70.08; H, 4.00; N, 6.54; found: C, 70.12; H, 4.03; N, 6.58 %.

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