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Synthesis, Characterization and Biological Activities of Pyrazole Based Heterocycles

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In this work, a unique pyrazolyl compounds comprising flourine and thiophene were synthesized. In brief, esters **3a-f** were synthesized by reacting thiophene and pyrazolyl acid (**1**) with various 2-hydroxyacetophenones (**2a-f**). The 1,3-diketones **4a-f** were formed by Baker-Venkataraman rearrangement of esters **3a-f**. Compounds **4a-f** were cyclized to form chromene derivatives **5a-f**, which further converted into pyrazolyl derivatives **6a-f**. The majority of the compounds in series **3a-f, 4a-f, 5a-f** and **6a-f** showed promising antibacterial activity against *S. typhii, S. aureus, B. subtilis* and *E. coli*. Compounds **4e** and **4f** exhibited considerable antifungal activity against *A. niger*, while the majority of the compounds had promising activity against *T. viride*. At 1 mg/mL concentration, some of the synthesized compounds shown potential α-amylase inhibitory action.

Keywords: Baker-Venkataraman rearrangement, Chromone, Pyrazole, Antimicrobial activity.

INTRODUCTION

Carbonyl compounds such as 1,3-diketones are one of the most important classes of compounds in organic synthesis. The large number of heterocyclic drug moieties such as pyrazole, isoxazole, imidazole, carbazole and thiazole are synthesized *via* diketone intermediate [1]. Some of the well-known drugs with heterocyclic moieties synthesized through β-diketone intermediates include crizotinib an anticancer agent, tepoxalin, lonazolac and celecoxib as an non-steroidal anti-inflammatory (pyrazole), sunitinib for treatment of both renal cell carcinoma and gastrointestinal stromal tumors, atorvastatin as statin, (containing pyrazole), ondansetron for serotonin 5-HT_3 receptor antagonism (containing imidazole), cefdinir as an antibacterial (containing thiazole).

Substituted chromones like 2-styrylchromone derivatives are oxygenated heterocyclic compounds, which play an important function in nature, due to their respective pharmaceutical, biological and biocidal activities [2]. They are distinguished by an adhesion of a styryl group to a two-position of structure. 2-Styrylchromones are therapeutically active in different areas such as anti-inflamatory [3,4], antimicrobial [5,6], anticancer [7,8], antioxidant [9,10], antiviral [11,12] and neuroprotective activities [13]. In focus of these various 2-heterosubstituted chromone have been investigated for their medicinal properties [14]. In many chemical reactions, the chromone ring system is useful starting material for the preparation of a broad range of synthetic derivatives.

Thiophene is an essential pharmacophore because of its diverse biological and pharmacological spectrum [15,16]. Thiophene corresponds to a class of heterocyclic compounds with a five-membered ring and sulphur as a heteroatom. The biologically active thiophene moiety exhibits a wide range of activities such as antiparasitic [17,18], anticancer [19,20], antiviral [21], anti-inflammatory [22], enzyme inhibitors [23] and antimicrobial activity [24,25]. Due to these vast variety of biological activities, thiophene-containing heterocyclic compounds have piqued the attention of researchers. Some widely viable drugs, which comprise thiophene as an active ingredient are antianxiety drug etizolam, Anticonvulsant agents such as tigabine, anticancer agents rolaxifene and OSI-930. Antihypertensive agent tienilic acid, anti-inflammatory drug suprophen and tiaprofenic acid, methapyrilene as an antihistamine, ticlopidine an antiplatelet agent and olanzapine an antisychotic agent.

Due to its innumerable chemical, agrochemical and pharmacological [26,27] properties, pyrazole is the most studied heterocycle in the azole family. The existence of pyrazole nucleus in various structures results in diversified applications in several fields including electronics, medicine and agriculture. Compound containing pyrazole shows a huge variety of bioactivities, which include antioxidant [28,29], anti-inflammatory [30,31], anticancer [32,33], antiviral [34,35], FAAH (fatty acid amide hydrolase) [36], antibacterial and antifungal [31,37,38], insecticidal [39], analgesic [40], 5α-reductase inhibitor [41], anti-enzymatic (anti-SIRT 1 and SIRT 2) [42], *etc*.

EXPERIMENTAL

The melting points of the synthesized compounds were determined using an open capillary process and are not corrected. Spectral characterization was carried out on an IR Affinity-I Fourier transform infrared spectrophotometer of Shimadzu (IR), Bruker Avance Neo 500 MHz spectrophotometer (^{1}H NMR) and Waters SYNAPT G2 HDMS (HRMS).

2-Acetylphenyl(2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3a): In 12 mL of dry pyridine, a mixture of compounds (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-prop-2-enoic acid (**1**) (0.001 mol) and 2-hydroxyacetophenone (**2a**) (0.01 mol) was dissolved and cooled to 0 ºC. $POCl_3$ (0.01 mol) was slowly added to this reaction mixture at 0-5 ºC with stirring, left the reaction mixture overnight and sprayed over crushed ice. The final product **3a** was purified and washed in a cold 1% NaOH solution before being washed with water. Using ethanol, the product was recrystallized. The same process was used to produce compounds **3b-f**.

2-Acetylphenyl (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3a): Yield: 73.15%, m.p.: 218-220 ºC. IR (KBr, ν_{max}, cm^{-1}): 3126, 3082, 1739, 1681, 1114, 839, 765; HRMS: *m/z* 466.9120 (M+); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H), 6.79 (d, 1H, *J* = 15.72 Hz), 7.07 (ddd, 1H, *J* = 8.16, 8.51, 2.49 Hz), 7.19 (s, 1H), 7.28 (dd, 1H, *J* = 8.16, 8.29 Hz), 7.39 (t, 2H, *J* = 8.22 Hz), 7.49 (dd, 1H, *J* = 8.29, 2.49 Hz), 7.82-7.92 (m, 4H), 8.01 (d, 1H, *J* = 8.51 Hz), 9.33 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{16}ClFN_2O_3S$: C, 61.72 (61.75); H, 3.48 (3.50); Cl, 7.58 (7.56); F, 4.08 (4.10); N, 6.01 (6.05); O, 10.27 (10.30); S, 6.87 (6.90).

2-Acetyl-4-methylphenyl (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3b): Yield: 72.25%, m.p.: 190-192 ºC. IR (KBr, ν_{max}, cm^{-1}): 3130, 1720, 1680, 1192, 835, 783; HRMS: *m/z* 480.9386 (M+); ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H), 2.60 (s, 3H), 6.89 (d, 1H, *J* = 15.48 Hz), 7.30 (s, 1H), 7.38 (d, 1H, *J* = 8.01 Hz), 7.49 (t, 2H, *J* = 7.98 Hz), 7.61 (d, 1H, *J* = 8.01 Hz), 7.92-8.02 (m, 4H), 8.11 (s, 1H), 9.43 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_2O_3S$: C, 62.42 (62.40); H, 3.79 (3.83); Cl, 7.36 (7.40); F, 3.96 (3.98); N, 5.83 (5.85); O, 9.96 (9.98); S, 6.68 (6.70).

2-Acetyl-6-methylphenyl (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3c): Yield: 71.27%, m.p.: 178-180 ºC. IR (KBr, ν_{max}, cm^{-1}): 3128, 3084, 1720, 1691, 1153, 829, 783; HRMS: *m/z* 480.9362 (M+); ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H), 2.52 (s, 3H), 6.81 (d, 1H, *J* = 15.74 Hz), 7.13 (dd, 1H, *J* = 8.37, 8.16 Hz), 7.22 (s, 1H), 7.30 (d, 1H, *J* = 8.37 Hz), 7.41 (t, 2H, *J* = 8.24 Hz), 7.84-7.94 (m, 4H), 8.03 (d, 1H, *J* = 8.16 Hz), 9.35 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_2O_3S$: C, 62.41 (62.43); H, 3.80 (3.82); Cl, 7.35 (7.36); F, 3.97 (3.98); N, 5.85 (5.87); O, 9.95 (9.98); S, 6.67 (6.69).

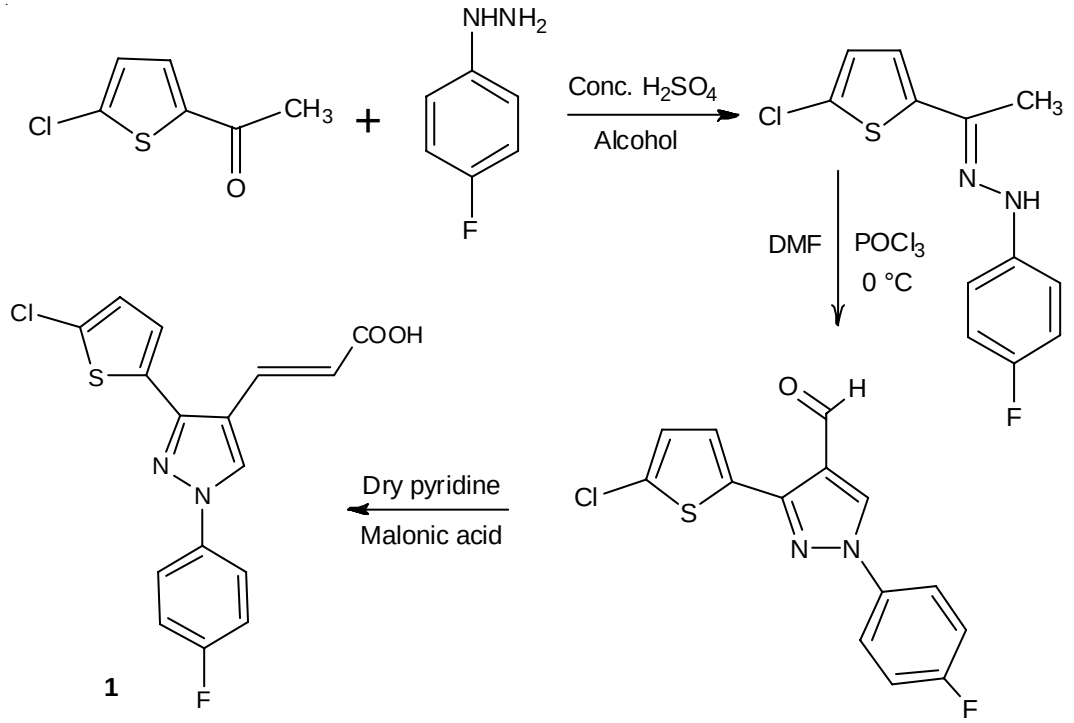
2-Acetyl-4-chlorophenyl (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3d): Yield: 74.13%, m.p.: 212-214 ºC. IR (KBr, ν_{max}, cm^{-1}): 3128, 3074, 1732, 1674, 1126, 835, 796; HRMS: *m/z* 501.3482 (M+); ^{1}H NMR (DMSO-d_6): δ 2.64 (s, 3H), 6.93 (d, 1H, *J* = 15.46 Hz), 7.34 (s, 1H), 7.42 (d, 1H, *J* = 8.05 Hz), 7.53 (t, 2H, *J* = 7.96 Hz), 7.59 (d, 1H, *J* = 8.05 Hz), 7.96-8.06 (m, 4H), 8.15 (s, 1H), 9.47 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{15}Cl_2FN_2O_3S$: C, 57.51 (57.53); H, 3.01 (3.03); Cl, 14.16 (14.18); F, 3.78 (3.80); N, 5.58 (5.60); O, 9.55 (9.51); S, 6.42 (6.45).

2-Acetyl-4,6-dichlorophenyl(2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3e): Yield: 74.45%, m.p.: 258-260 ºC. IR (KBr, ν_{max}, cm^{-1}): 3126, 3082, 1739, 1681, 1114, 835, 781; HRMS: *m/z* 536.9821 (M+); ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H), 6.85 (d, 1H, *J* = 15.6 Hz), 7.26 (s, 1H), 7.34 (s, 1H), 7.45 (t, 2H, *J* = 8.1 Hz), 7.88-7.98 (m, 4H), 8.07 (s, 1H), 9.39 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{14}Cl_3FN_2O_3S$: C, 53.82 (53.84); H, 2.61 (2.60); Cl, 19.87 (19.90); F, 3.53 (3.55); N, 5.24 (5.25); O, 8.95 (8.98); S, 5.98 (5.99).

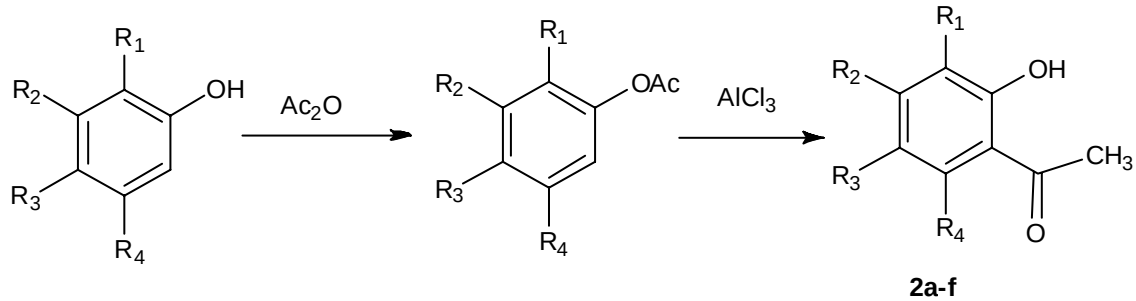
2-Acetyl-4-chloro-3,5-dimethylphenyl (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (3f): Yield: 71.15%, m.p.: 182-184 ºC, IR (KBr, ν_{max}, cm^{-1}): 3074, 1729, 1697, 1155, 835, 802; HRMS: *m/z* 529.4098 (M+); ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H), 2.62 (s, 3H), 2.78 (s, 3H), 6.91 (d, 1H, *J* = 15.66 Hz), 7.32 (s, 1H), 7.51 (t, 2H, *J* = 8.16 Hz), 7.58 (s, 1H) 7.94-8.04 (m, 4H), 9.45 (s, 1H); Anal. calcd. (found) % for $C_{26}H_{19}Cl_2FN_2O_3S$: C, 58.97 (58.99); H, 3.64 (3.66); Cl, 13.37 (13.40); F, 3.61 (3.65); N, 5.31 (5.35); O, 9.06 (9.16); S, 6.05 (6.10).

(4*E*)-5-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione (4a): (2*E*)-3-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]prop-2-enoate (**3a**) (0.05 mol) was dissolved in 12 mL dry pyridine in a 100 mL RB flask and 1.5 g powdered KOH was added while stirring constantly. The reaction mixture was stirred for 5 to 6 h at room temperature before being poured over crushed ice and acidified with HCl to produce the product **4a**. Filtration was used to isolate the product, which was then crystallized from the ethanol. Compounds **4b-f** were prepared using the same process.

(4*E*)-5-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione (4a): Yield: 78.25%, m.p.: 166-168 ºC. IR (KBr, ν_{max}, cm^{-1}): 3072, 1689, 1631, 1178, 831, 746; HRMS: *m/z* 466.9120 (M+); ^{1}H NMR (DMSO-d_6): δ 3.24 (s, 2H), 6.39 (d, 1H, *J* = 13.92 Hz), 7.02 (dd, 1H, *J* = 8.33, 2.73 Hz), 7.09 (dd, 1H, *J* = 8.45, 2.73 Hz), 7.15-7.18 (m, 3H), 7.31-7.38 (m, 4H), 7.84 (broad



Scheme-I



Scheme-II

signal, 2H), 8.95 (s, 1H), 11.21 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{16}ClFN_2O_3S$: C, 61.76 (61.78); H, 3.44 (3.46); Cl, 7.58 (7.60); F, 4.09 (4.10); N, 6.01 (6.05); O, 10.26 (10.30); S, 6.86 (6.88).

(4*E*)-5-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(2-hydroxy-5-methylphenyl)pent-4-ene-1,3-dione (4b): Yield: 77.42%, m.p.: 198-200 ºC. IR (KBr, ν_{max}, cm^{-1}): 3066, 1701, 1629, 1174, 831, 715; HRMS: *m/z* 480.9388 (M+); ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 2H), 3.34 (s, 2H), 6.49 (d, 1H, *J* = 13.68 Hz), 7.22 (d, 1H, *J* = 8.35 Hz), 7.25-7.28 (m, 3H), 7.41-7.48 (m, 4H), 7.94 (broad signal, 2H), 9.05 (s, 1H), 12.13 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_2O_3S$: C, 62.41 (62.40); H, 3.79 (3.81); Cl, 7.35 (7.40); F, 3.97 (3.98); N, 5.86 (5.88); O, 9.97 (9.99); S, 6.66 (6.63).

(4*E*)-5-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(2-hydroxy-3-methylphenyl)pent-4-ene-1,3-dione (4c): Yield: 81.10%, m.p.: 142-144 ºC. IR (KBr, ν_{max}, cm^{-1}): 3059, 1697, 1631, 1155, 831, 758; HRMS: *m/z* 480.9358 (M+); ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H), 3.26 (s, 2H), 6.41 (d, 1H, *J* = 13.94 Hz), 7.16-7.20 (m, 4H), 7.33-7.40 (m, 4H), 7.86 (broad signal, 2H), 8.97 (s, 1H), 13.10 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_2O_3S$: C, 62.45 (62.44); H, 3.75 (3.77); Cl, 7.39 (7.40); F, 3.93 (3.92); N, 5.82 (5.80); O, 9.99 (9.98); S, 6.65 (6.64).

(4*E*)-1-(5-Chloro-2-hydroxyphenyl)-5-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)pent-4-ene-1,3-dione (4d): Yield: 74.26%, m.p.: 272-274 ºC. IR (KBr, ν_{max}, cm^{-1}): 3082, 2922, 1697, 1629, 1174, 831, 729; HRMS: *m/z* 501.3567 (M+); ^{1}H NMR (DMSO-d_6): δ 3.38 (s, 2H), 6.53 (d, 1H, *J* = 13.66 Hz), 7.23 (d, 1H, *J* = 8.65 Hz), 7.29-7.32 (m, 3H), 7.45-7.52 (m, 4H), 7.98 (broad signal, 2H), 9.09 (s, 1H), 11.45 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{15}Cl_2FN_2O_3S$: C, 57.52 (57.50); H, 3.01 (3.05); Cl, 14.13 (14.15); F, 3.81 (3.80); N, 5.58 (5.60); O, 9.58 (9.60); S, 6.38 (6.40).

(4*E*)-5-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(3,5-dichloro-2-hydroxyphenyl)pent-4-ene-1,3-dione (4e): Yield: 76.15%, m.p.: > 290 ºC. IR (KBr, ν_{max}, cm^{-1}): 3082, 1685, 1647, 1180, 867, 738; HRMS: *m/z* 537.1790 (M+); ^{1}H NMR (DMSO-d_6): δ 3.3 (s, 2H), 6.45 (d, 1H, *J* = 13.8 Hz), 7.21-7.24 (m, 3H), 7.37-7.44 (m, 4H), 7.90 (broad signal, 2H), 9.01 (s, 1H), >10 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{14}Cl_3FN_2O_3S$: C, 53.82 (53.84); H, 2.61 (2.59); Cl,

19.87 (19.88); F, 3.53 (3.55); N, 5.25 (5.27); O, 8.95 (8.98); S, 5.97 (5.96).

(4*E*)-1-(3-Chloro-6-hydroxy-2,4-dimethylphenyl)-5-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)pent-4-ene-1,3-dione (4f): Yield: 79.17%, m.p.: 172-174 ºC. IR (KBr, ν_{max}, cm^{-1}): 3074, 1687, 1631, 1155, 842, 738; HRMS: *m/z* 529.4102 (M+); ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H), 2.70 (s, 3H), 3.36 (s, 2H), 6.51 (d, 1H, *J* = 13.86 Hz), 7.22 (s, 1H), 7.27 (d, 1H), 7.43-7.50 (m, 4H), 7.96 (broad signal, 2H), 9.07 (s, 1H), 10.96 (s, 1H); Anal. calcd. (found) % for $C_{26}H_{19}Cl_2FN_2O_3S$: C, 59.01 (59.03); H, 3.60 (3.62); Cl, 13.41 (13.42); F, 3.55 (3.58); N, 5.31 (5.30); O, 9.08 (9.10); S, 6.03 (6.05).

2-{(*Z*)-2-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]ethenyl}-4*H*-chromen-4-one (5a): (4*E*)-5-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione (**4a**) (0.001 mol) was added in RB flask attached with refluxed condenser containing a solution of 12 mL ethanol and 2-3 mL HCl and then reflux for 1-2 h. TLC was used to track the reaction's progression. After heating, once the reaction mixture had reached room temperature, it was gently sprayed over crushed ice. Filtration was used to isolate the product **5a**, which was then crystallized from the ethanol. The same procedure was used to produce compounds **5b-5f**.

(*E*)-2-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-4*H*-chromen-4-one (5a): Yield: 62%, m.p.: 222-224 ºC. IR (KBr, ν_{max}, cm^{-1}): 3124, 1695, 1651, 1159, 827, 748; HRMS: *m/z* 448.8961 (M+); ^{1}H NMR (DMSO-d_6): δ 6.91 (s, 2H), 7.06 (ddd, 1H, *J* = 8.38, 8.55, 2.93 Hz), 7.13-7.19 (m, 2H), 7.25-7.37 (m, 4H), 7.46 (dd, 1H, *J* = 8.43, 2.93 Hz), 7.54 (d, 1H, *J* = 5.92 Hz), 7.78-7.79 (broad signal, 2H), 8.35 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{14}ClFN_2O_2S$: C, 64.19 (64.20); H, 3.16 (3.20); Cl, 7.92 (7.98); F, 4.21 (4.25); N, 6.26 (6.25); O, 7.14 (7.16); S, 7.11 (7.10).

(*E*)-2-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-6-methyl-4*H*-chromen-4-one (5b): Yield: 61%, m.p.: 218-220 ºC. IR (KBr, ν_{max}, cm^{-1}): 3122, 1693, 1651, 1161, 827, 794; HRMS: *m/z* 462.9229 (M+); ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H), 7.01 (s, 2H), 7.23-7.29 (m, 2H), 7.35-7.47 (m, 4H), 7.52 (d, 1H, *J* = 8.15 Hz), 7.64 (d, 1H, *J* = 5.68 Hz), 7.88-7.89 (broad signal, 2H), 8.45 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{16}ClFN_2O_2S$: C, 64.84 (64.85); H, 3.50 (3.48); Cl, 7.68 (7.66); F, 4.08 (4.06); N, 6.08 (6.10); O, 6.90 (6.89); S, 6.91 (6.93).

(*E*)-2-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-8-methyl-4*H*-chromen-4-one (5c): Yield: 67%, m.p.: 286-288 ºC. IR (KBr, ν_{max}, cm^{-1}): 3122, 1697, 1647, 1159, 833, 746; HRMS: *m/z* 462.9233 (M+); ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H), 6.94 (s, 2H), 7.10 (dd, 1H, *J* = 8.66, 8.35 Hz), 7.15-7.21 (m, 2H), 7.27-7.39 (m, 4H), 7.56 (d, 1H, *J* = 5.94 Hz), 7.80-7.81 (broad signal, 2H), 8.37 (s, 1H); Anal. calcd. (found) % for $C_{25}H_{16}Cl$-FN_2O_2S: C, 64.88 (64.90); H, 3.46 (3.48); Cl, 7.64 (7.65); F, 4.12 (4.10); N, 6.02 (6.04); O, 6.92 (6.93); S, 6.95 (6.97).

(*E*)-6-Chloro-2-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-4*H*-chromen-4-one (5d): Yield: 64%, m.p.: 278-280 ºC. IR (KBr, ν_{max}, cm^{-1}): 3122, 1689, 1651, 1157, 829, 785; HRMS: *m/z* 483.3412 (M+); ^{1}H NMR (DMSO-d_6): δ 7.05 (s, 2H), 7.27-7.33 (m, 2H), 7.39-7.51 (m, 4H), 7.59 (d, 1H, *J* = 8.29 Hz), 7.68 (d, 1H, *J* = 5.66 Hz), 7.92-7.93 (broad signal, 2H), 8.49 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{13}Cl_2FN_2O_2S$: C, 59.66 (59.63); H, 2.69 (2.68); Cl, 14.69 (14.70); F, 3.91 (3.93); N, 5.84 (5.86); O, 6.60 (6.62); S, 6.61 (6.62).

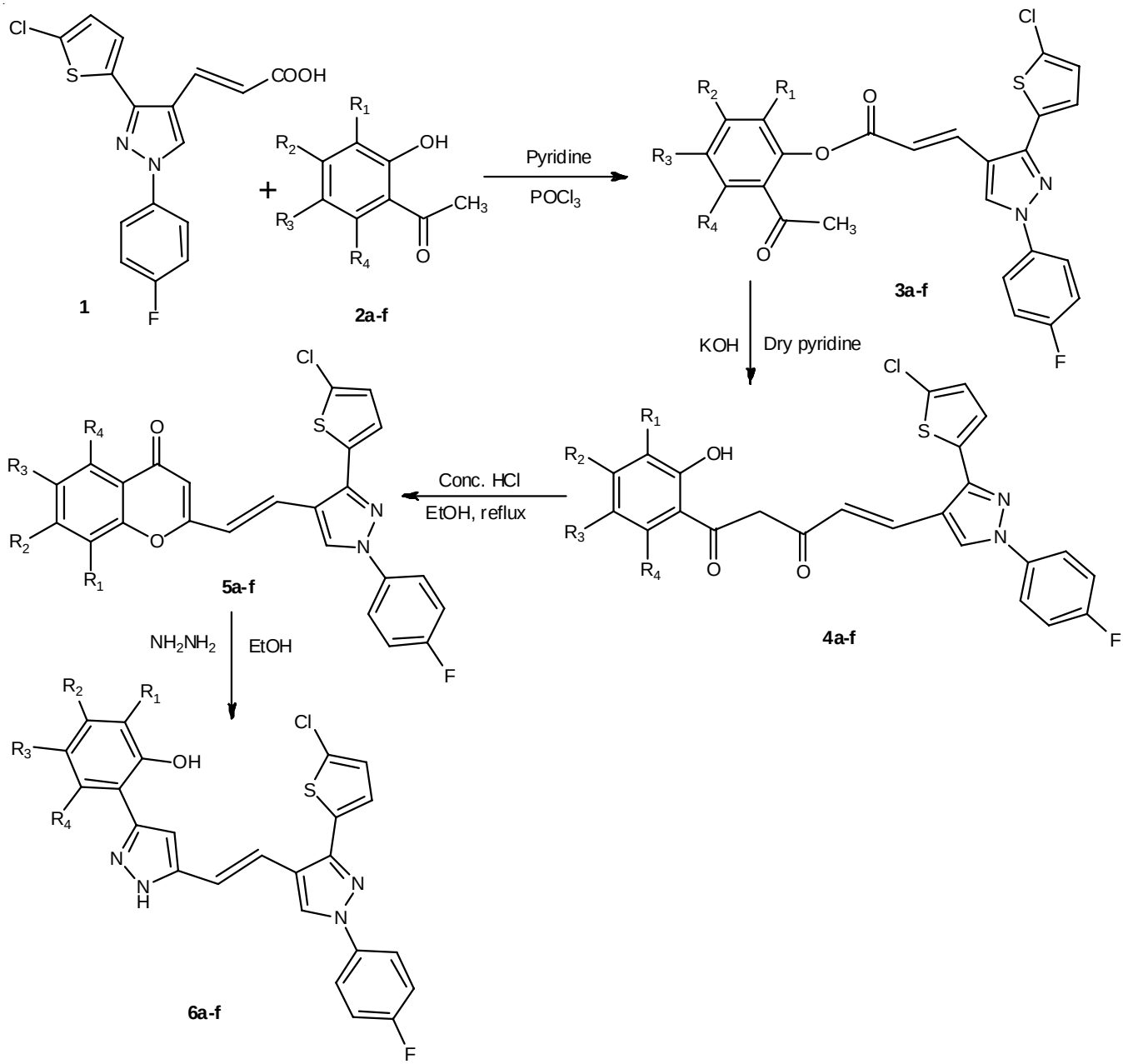
(*E*)-6,8-Dichloro-2-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-4*H*-chromen-4-one (5e): Yield: 63%, m.p.: 218-220 ºC. IR (KBr, ν_{max}, cm^{-1}): 3138, 1693, 1649, 1178, 831, 738; HRMS: *m/z* 519.1416 (M+); ^{1}H NMR (DMSO-d_6): δ 6.97 (s, 2H), 7.19-7.25 (m, 2H), 7.31-7.43 (m, 4H), 7.60 (d, 1H, *J* = 5.8 Hz), 7.84-7.85 (broad signal, 2H), 8.41 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{12}Cl_3FN_2O_2S$: C, 55.65 (55.66); H, 2.36 (2.37); Cl, 20.52 (20.51); F, 3.69 (3.68); N, 5.45 (5.47); O, 6.16 (6.20); S, 6.17 (6.20).

(*E*)-6-Chloro-2-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-5,7-dimethyl-4*H*-chromen-4-one (5f): Yield: 65%, m.p.: 284-286 ºC. IR (KBr, ν_{max}, cm^{-1}): 3134, 1697, 1637, 1157, 831, 798; HRMS: *m/z* 511.3945 (M+); ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 2.79 (s, 3H), 7.03 (s, 2H), 7.31 (d, 1H, *J* = 15.29 Hz), 7.37-7.49 (m, 4H), 7.66 (d, 1H, *J* = 5.86 Hz), 7.59 (s, 1H), 7.91 (d, 1H, *J* = 15.29 Hz), 8.47 (s, 1H); Anal. calcd. (found) % for $C_{26}H_{17}Cl_2FN_2O_2S$: C, 61.04 (61.06); H, 3.37 (3.40); Cl, 13.85 (13.83); F, 3.74 (3.75); N, 5.52 (5.55); O, 6.24 (6.25); S, 6.25 (6.26).

2-(5-{(Z)-2-[3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]ethenyl}-1*H*-pyrazol-3-yl)phenol (6a): In 100 mL RB flask containing 30 mL ethanol, 2-{(Z)-2-[3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl]ethenyl}-4*H*-chromen-4-one (**5a**) and hydrazine hydrate (0.005 mol) were dissolved and reaction mixture was refluxed for 4 h. Reaction progress track by TLC and after the reaction was completed, the reaction mixture was cooled and poured over crushed ice before being neutralized with glacial acetic acid. Filtration was used to isolate the final product **6a** from the ethanol, which was then crystallized. Compounds **6b-f** were made using the same procedure (**Scheme-III**).

(*E*)-2-(5-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)phenol (6a): Yield: 59%, m.p.: 230-232 ºC. IR (KBr, ν_{max}, cm^{-1}): 3234, 3072, 1514, 1155, 835, 758; HRMS: *m/z* 462.9258 (M+); ^{1}H NMR (DMSO-d_6): δ 6.51 (d, 1H, *J* = 15.82 Hz), 7.05 (ddd, 1H, *J* = 8.29, 8.66, 2.85 Hz), 7.19-7.21 (m, 3H), 7.36 (m, 3H), 7.43 (dd, 1H, *J* = 8.43, 2.85 Hz), 7.52-7.59 (t, 2H), 7.84 (m, 3H), 9.14 (s, 1H) 12.34 (s,1H); Anal. calcd. (found) % for $C_{24}H_{16}ClFN_4OS$: C, 62.25 (62.30); H, 3.50 (3.55); Cl, 7.64 (7.65); F, 4.12 (4.11); N, 12.14 (12.15); O, 3.44 (3.45); S, 6.91 (6.90).

(*E*)-2-(5-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)-4-methylphenol (6b): Yield: 58.15%, m.p.: 192-194 ºC. IR (KBr, ν_{max}, cm^{-1}): 3122, 2920, 1514, 1161, 831, 711; HRMS: *m/z* 476.9524 (M+); ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 3H), 6.61 (d, 1H, *J* = 15.58 Hz), 7.29-7.31 (m, 3H), 7.46 (m, 3H), 7.55 (d, 1H, *J* = 8.07 Hz), 7.62-7.69 (t, 2H), 7.94 (m, 3H), 9.24 (s, 1H) 12.44 (s,1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_4OS$: C, 62.92



Scheme-III

(62.95); H, 3.82 (3.82); Cl, 7.45 (7.46); F, 3.96 (3.98); N, 11.77 (11.80); O, 3.37 (3.40); S, 6.70 (6.71).

(*E*)-2-(5-(2-(3-(5-Chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)-6-methylphenol (6c): Yield: 61.10%, m.p.: 196-198 ºC. IR (KBr, ν_{max}, cm^{-1}): 3255, 2951, 1514, 1168, 833, 742; HRMS: *m/z* 476.9534 (M+); ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H), 6.53 (d, 1H, *J* = 15.84 Hz), 7.09 (dd, 1H, *J* = 8.97, 8.21 Hz), 7.21-7.23 (m, 3H), 7.38 (m, 3H), 7.54-7.61 (t, 2H), 7.86 (m, 3H), 9.16 (s, 1H) 12.36 (s,1H); Anal. calcd. (found) % for $C_{25}H_{18}ClFN_4OS$: C, 62.98 (62.99); H, 3.78 (3.80); Cl, 7.41 (7.40); F, 4.00 (4.01); N, 11.71 (11.70); O, 3.37 (3.38); S, 6.74 (6.75).

(*E*)-4-Chloro-2-(5-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)-phenol (6d): Yield: 57.56%, m.p.: 270-272 ºC. IR (KBr, ν_{max}, cm^{-1}): 3122, 2920, 1529, 1159, 831, 713; HRMS: *m/z* 497.3711 (M+); ^{1}H NMR (DMSO-d_6): δ 6.65 (d, 1H, *J* = 15.56 Hz), 7.33-7.35 (m, 3H), 7.50 (m, 3H), 7.61 (d, 1H, *J* = 7.97 Hz), 7.66-7.78 (t, 2H), 7.98 (m, 3H), 9.28 (s, 1H) 12.48 (s,1H); Anal. calcd. (found) % for $C_{24}H_{15}Cl_2FN_4OS$: C, 57.92 (57.91); H, 3.06 (3.08); Cl, 14.28 (14.30); F, 3.84 (3.85); N, 11.24 (11.30); O, 3.24 (3.26); S, 6.43 (6.45).

(*E*)-2,4-Dichloro-6-(5-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)phenol (6e): Yield: 59.40%, m.p.: 258-260 ºC. IR (KBr, ν_{max}, cm^{-1}): 3377, 3078, 1514, 1155, 856, 742; HRMS: *m/z* 533.0173 (M+); ^{1}H NMR (DMSO-d_6): δ 6.57 (d, 1H, *J* = 15.7 Hz), 7.25-7.27 (m, 3H), 7.42 (m, 3H), 7.58-7.65 (t, 2H), 7.90 (m, 3H), 9.20 (s, 1H) 12.40 (s, 1H); Anal. calcd. (found) % for $C_{24}H_{14}Cl_3FN_4OS$: C, 54.16 (54.20); H, 2.67 (2.69); Cl, 20.02

(20.10); F, 3.59 (3.61); N, 10.51 (10.50); O, 3.03 (3.05); S, 6.01 (6.10).

(*E*)-4-Chloro-2-(5-(2-(3-(5-chlorothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)vinyl)-1*H*-pyrazol-3-yl)-3,5-dimethylphenol (6f): Yield: 62.15%, m.p.: 278-280 ºC. IR (KBr, ν_{max}, cm^{-1}): 3253, 2920, 1514, 1155, 835, 717; HRMS: *m/z* 525.4243 (M+); ^{1}H NMR (DMSO-d_6): δ 6.63 (d, 1H, *J* = 15.76 Hz), 7.31-7.33 (m, 2H), 7.48 (m, 3H), 7.54 (s, 1H), 7.64-7.71 (t, 2H), 7.96 (m, 2H), 9.26 (s, 1H) 12.46 (s,1H); Anal. calcd. (found) % for $C_{26}H_{19}Cl_2FN_4OS$: C, 59.47 (59.50); H, 3.62 (3.65); Cl, 13.47 (13.49); F, 3.64 (3.65); N, 10.64 (10.65); O, 3.07 (3.10); S, 6.08 (6.10).

RESULTS AND DISCUSSION

As shown in **Schemes I** and **II**, a well-known literature strategy was applied to synthesize different acetophenones **2a-f** and pyrazolyl acid (**1**). The esters, **3a-f** were synthesized using condensation of **1** and **2a-f**. The formation of **3a-f** has been confirmed using several spectral techniques. Compound **3e** shows IR bands of ester carbonyl at 1739 cm^{-1} and ketone carbonyl at 1681 cm^{-1} also band at 3126 cm^{-1}. In HRMS molecular ion peak at 536.9821 support **3e** formation. ^{1}H NMR signal at 6.85 indicates an olefinic proton, while the signal at δ 9.39 ppm indicates a pyrazole ring proton. In pyridine, the molecules **3a-f** undergo Baker-Venkataraman rearrangement to produce 1,3-diketones **4a-f**. Spectral analysis verified the formation of diketones, **4a-f**. Compound **4e** shows bands at 3082, 1685 cm^{-1} in its IR spectrum and the M+2 ion peak at 537.1790 in HRMS. The most important confirmation of **4e** formation is in ^{1}H NMR spectra, which shows signal at δ 3.30 of methylene of 1-3 dicarbonyl. Refluxing these compound **4a-f** in ethanol with conc. HCl yielded 2-substituted styryl chromones **5a-f**. The IR band at 3068, 1693 cm^{-1} and the M+2 ion peak at 519.1461 are in support to the formation of **5e**. ^{1}H NMR spectra validate chromone formation as there is absence of downfield signal above δ 10.0 implies absence of O-H and also appearance of singlet at δ 6.97 is due to 3-position proton of chromone. The chromone rings open when **5a-f** are refluxed in ethanol and hydrazine hydrate and the pyrazoles **6a-f** are formed. In the IR spectrum, the absence of carbonyl peak and presence of peak at 3377 cm^{-1} and in the HRMS M+2 ion peak at 533.0173 supports the compound **6d** formation. The appearance of a singlet at 12.40 in ^{1}H NMR spectra of O-H proton is the most important confirmation.

Amylase inhibitory activity: All the synthesized compounds were investigated for α-amylase inhibitory activity using protocol reported previously [43]. In comparison to the reference drug acarbose, compounds **5c** and **5d** have promising α-amylase inhibitory activity (Table-1).

Microbial analysis: *In vitro* tests were performed against two fungal and four bacterial strains of the compounds **1**, **3a-f**, **4a-f**, **5a-f** and **6a-j** (Table-2). This experiment was conducted using the agar well diffusion method. The antibacterial and antifungal reference medicines were ciprofloxacin and fluconazole, respectively, with DMSO serving as a negative control. Compounds **1**, **3c**, **3e**, **3f**, **4b**, **4e**, **4f**, **5d**, **5f** and **6a** have showed very good activity against gram positive bacteria *B. subtilis* while other compounds are moderately active. Compounds **1**, **3e**, **3f**, **4b**, **4c**, **4e** and **4f** showed promising activity against *Staphylococcus aureus* while some of the other compounds are moderately active. Compounds **1**, **3d**, **3e**, **3f**, **4a-f** and **6e** have showed very good activity against *Salmonella typhi* while some compounds are moderately active. Compounds **1**, **3e**, **3f**, **4e** and **4f** gave promising activity against *E. coli*, while some of the other compounds are moderately active. Compounds **4e** and **4f** have shown promising action against *Aspergillus niger*, while compounds **1**, **3b**, **3e**, **3f**, **4a**, **4e**, **4f**, **5a**, **5e** and **5f** had good activity.

TABLE-1
AMYLASE INHIBITORY ACTIVITY
(CONCENTRATION 1 mg/mL)

Compound	Inhibition (%)
4e	3.21
5c	5.35
5d	6.79
5e	2.14
6c	4.28
Acarbose	45.00

Conclusion

In this study, unique pyrazolyl compounds comprising flourine and thiophene were synthesized and spectroscopic proof unambiguously supports the proposed compounds. In comparison to the reference drug acarbose, compounds **5c** and **5d** have promising α-amylase inhibitory activity. As far as diabetic experts are concerned, these combinations can be classified as lead compounds. The antimicrobial results revealed that each of the included compounds further fundamentally altered to improve their antimicrobial character.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-2
ANTIMICROBIAL ACTIVITY (ZONE OF INHIBITION AT 1 mg/mL IN mm)

Compound	R_1	R_2	R_3	R_4	Antibacterial activity				Antifungal activity	
					Bacillus subtilis	*Staphylococcus aureus*	*Salmonella typhii*	*Escherichia coli*	*Aspergillus niger*	*Trichoderma viride*
1	–	–	–	–	22	15	21	15	–	27
3a	H	H	H	H	12	12	11	12	–	–
3b	H	H	CH_3	H	13	12	11	12	–	22
3c	CH_3	H	H	H	16	12	11	11	–	–
3d	H	H	Cl	H	12	13	14	11	–	18
3e	Cl	H	Cl	H	22	19	18	16	–	27
3f	H	CH_3	Cl	CH_3	16	16	19	13	–	25
4a	H	H	H	H	12	13	16	11	–	23
4b	H	H	CH_3	H	14	14	14	11	–	20
4c	CH_3	H	H	H	11	16	18	11	–	20
4d	H	H	Cl	H	–	–	–	–	–	–
4e	Cl	H	Cl	H	15	15	19	13	14	23
4f	H	CH_3	Cl	CH_3	16	14	20	15	20	21
5a	H	H	H	H	12	–	13	11	–	21
5b	H	H	CH_3	H	–	–	12	11	–	–
5c	CH_3	H	H	H	11	–	13	11	–	–
5d	H	H	Cl	H	14	–	–	11	–	–
5e	Cl	H	Cl	H	–	12	13	11	–	22
5f	H	CH_3	Cl	CH_3	17	12	13	12	–	22
6a	H	H	H	H	16	–	11	12	–	12
6b	H	H	CH_3	H	12	–	12	11	–	–
6c	CH_3	H	H	H	12	–	13	11	–	–
6d	H	H	Cl	H	–	–	–	–	–	–
6e	Cl	H	Cl	H	–	–	14	–	–	–
6f	H	CH_3	Cl	CH_3	–	–	–	–	–	–
Ciprofloxacin					28	23	–	26	–	–
Fluconazole					–	–	–	–	28	29

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