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Design, synthesis and characterization of novel fluorinated styryl chromones

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(E)-3-(3-(Trifluoromethyl)-5-nitrophenyl)acrylic acid **1** when treated with substituted 2-hydroxyacetophenones **2** in dry pyridine and $POCl_3$ affords compound **3** which when reacted with pyridine/KOH by B. V. transformation gives **4**. Compound **4** on refluxing with acetic acid in HCl gives **5**. The structures of all synthesized compounds have been confirmed by spectroscopic techniques.

Keywords: Fluorine, diketone, styryl chromones

Substitution of hydrogen atom by fluorine into potentially active drug molecule alters lipophilic, electronic, steric parameters as well as pharmacokinetic and pharmacodynamic properties of drugs. Fluorine containing molecule is considered as an important tool in the design of new drugs[1]. Fluorine incorporated drugs are endowed with wide spectrum of biological activities such as insecticidal[2], anticoagulant[3], antimicrobial[4], antitumor[5] and anticancer[6].

β-Diketones are important intermediates in many drug syntheses[7]. The diketone derivatives are associated with broad spectrum of biological activities like corrosion inhibitor[8], antimicrobial[9], inhibition of amyloid α aggregation[10], antiinflammatory[11], *etc*.

Chromone moiety is a core fragment of different flavonoids like flavones, isoflavones and flavonols[12]. Large number of chromone derivatives are known for their pharmacological properties like such as anti-picornavirus capsid-binders[13], antitumor[14], anticancer[15]. Styryl chromones is one of the small family of chromone compounds exhibiting different biological activities like cytotoxicity[16], antiproliferative[17], monoamine oxidase inhibitors[18] and anti-noroviral agents[19].

Based on this valuable literature observations associated with fluorine, diketone and chromones the present work describes an attempt towards synthesis of fluorine containing different diketones and chromones (Scheme I).

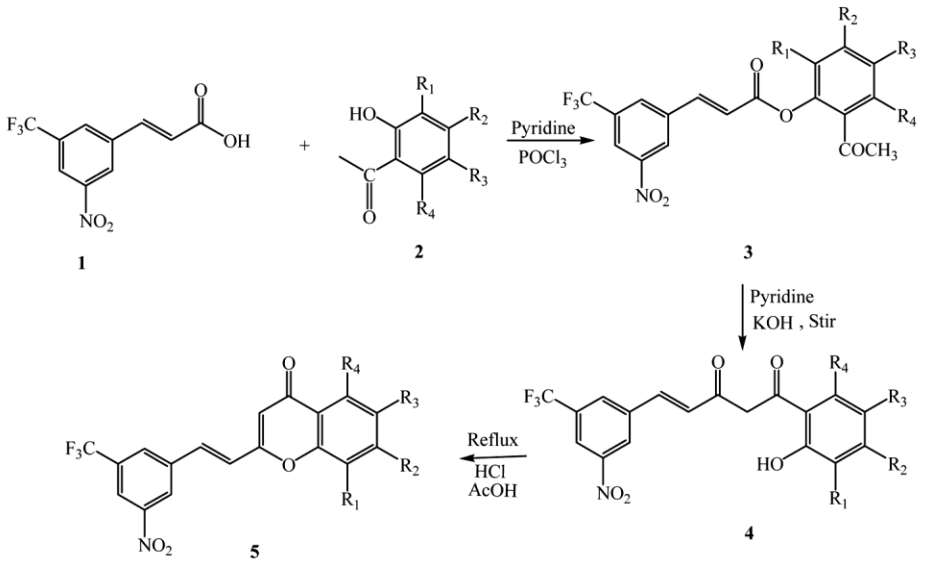
Experimental Section

Melting points were determined in open capillaries in liquid paraffin bath and are uncorrected. Mass spectra were recorded on Waters Acquity TQD mass spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance II 500 MHz NMR spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). IR spectra were recorded on Shimadzu IR Affinity-1S spectrophotometer.

(E)-2-Acetylphenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3a-e

Equimolar quantities of 2-(4-fluorophenyl)-5-phenylbenzofuran-3-carboxylic acid **1** (0.004M) and substituted 2-hydroxyacetophenone **2** (0.004M) was dissolved in pyridine (20 mL) maintained at about 0°C then $POCl_3$ (0.004 M) was slowly added maintaining the temperature below 4°C. After complete addition the reaction mixture was kept overnight. Resulting reaction mixture was poured over crushed ice, solid thus obtained was separated by filtration and crystallized from ethanol to afford **3**.

(E)-2-Acetylphenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)
acrylate, 3a: m.p. 68°C. Yield 90%. IR: 2929, 1690, 1521, 1351, 1154, 678 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.56 (s, 3H), 6.75 (d, *J* = 16 Hz, 1H), 7.19 (dd, *J* = 4.6 Hz, 1H), 7.29 (dd, *J* = 3 and 4.6 Hz, 1H), 7.54 (dd, *J* = 3 Hz, 1H), 7.58-7.79 (m, 4H), 7.93 (d, *J* = 16 Hz, 1H); MS:



Scheme I

m/z (M+1), 380. Anal. Calcd: C, 57.00; H, 3.19. Found: C, 57.02; H, 3.22%.

(E)-2-Acetyl-4-fluorophenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3b: m.p. 83°C. Yield 73%. IR: 2923, 1688, 1519, 1348, 1150, 675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.56 (s, 3H), 6.73 (d, *J* = 16 Hz, 1H), 7.17 (dd, *J* = 4.6 Hz, 1H), 7.26 (dd, *J* = 3 and 4.6 Hz, 1H), 7.52 (dd, *J* = 3 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 16 Hz, 1H); MS: *m/z* (M+1), 398. Anal. Calcd: C, 54.42; H, 2.79. Found: C, 54.43; H, 2.81%.

(E)-2-Acetyl-4-chlorophenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3c: m.p. 96°C. Yield 84%. IR: 2926, 1691, 1516, 1350, 1154, 1035, 678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.54 (s, 3H), 6.70 (d, *J* = 16 Hz, 1H), 7.08 (dd, *J* = 4.6 Hz, 1H), 7.20 (dd, *J* = 3 and 4.6 Hz, 1H), 7.50 (dd, *J* = 3 Hz, 1H), 7.53 (d, *J* = 3 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.73 (dd, *J* = 7.4 and 3 Hz, 1H), 7.91 (d, *J* = 16 Hz, 1H); MS: *m/z* (M+1), 415. Anal. Calcd: C, 52.25; H, 2.68. Found: C, 52.29; H, 2.71%.

(E)-2-Acetyl-4-methylphenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3d: m.p. 76°C. Yield 74%. IR: 2920, 1682, 1515, 1351, 1152, 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.50 (s, 3H), 6.68 (d, *J* = 16 Hz, 1H), 7.04 (dd, *J* = 4.6 Hz, 1H), 7.16 (dd, *J* = 3 and 4.6 Hz, 1H), 7.49 (dd, *J* = 3 Hz, 1H), 7.52 (d, *J* = 3 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.70 (dd, *J* = 7.4 and 3 Hz, 1H), 7.88 (d, *J* = 16 Hz, 1H); MS: *m/z* (M+1), 394. Anal. Calcd: C, 58.02; H, 3.59. Found: C, 58.04; H, 3.62%.

(E)-2-Acetyl-4,6-dimethylphenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3e: m.p. 76°C. Yield 80%. IR: 2921, 1684, 1516, 1350, 1150, 670 cm^{-1}; ^1H NMR: δ 2.36 (s, 3H), 2.39 (s, 3H), 2.49 (s, 3H), 6.66 (d, *J* = 16 Hz, 1H), 7.02 (dd, *J* = 4.6 Hz, 1H), 7.19 (dd, *J* = 3 and 4.6 Hz, 1H), 7.49 (dd, *J* = 3 Hz, 1H), 7.50 (d, *J* = 3 Hz, 1H), 7.64 (d, *J* = 3 Hz, 1H), 7.80 (d, *J* = 16 Hz, 1H); MS: *m/z* (M+1), 408. Anal. Calcd: C, 58.97; H, 3.96. Found: C, 58.99; H, 3.99.

(E)-2-Acetyl-4-chloro-5-methylphenyl 3-(3-(trifluoromethyl)-5-nitrophenyl)acrylate, 3f: m.p. 84°C. Yield 78%. IR: 2920, 1686, 1514, 1347, 1151, 1030, 670 cm^{-1}; ^1H NMR: δ 2.32 (s, 3H), 2.52 (s, 3H), 6.71 (d, *J* = 16 Hz, 1H), 7.06 (dd, *J* = 4.6 Hz, 1H), 7.23 (dd, *J* = 3 and 4.6 Hz, 1H), 7.46 (dd, *J* = 3 Hz, 1H), 7.55 (s, 1H), 7.62 (s, 1H), 7.90 (d, *J* = 16 Hz, 1H); MS: *m/z* (M+1), 428. Anal. Calcd: C, 53.35; H, 3.06. Found: C, 53.39; H, 3.08.

(E)-5-(3-(Trifluoromethyl)-5-nitrophenyl)-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione, 4a-e

Ester **3** (0.002 M) was dissolved in 10 mL pyridine and powdered KOH (2 gm) was added. Reaction mixture was stirred at RT for 3 h. After completion of the reaction (monitored by TLC) contents were poured over crushed ice and acidified with conc. HCl. The solid thus obtained was filtered, dried and crystallized from ethanol to afford **4**.

(E)-5-(3-(Trifluoromethyl)-5-nitrophenyl)-1-(2-hydroxyphenyl)pent-4-ene-1,3-dione, 4a: m.p. 102°C. Yield 78%. IR: 3315, 2986, 1699, 1517, 1162 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (s, 1H), 6.68 (d, *J* = 16 Hz, 1H), 6.98 (dd, *J* = 4.6 Hz, 1H), 7.34 (dd, *J* = 3 Hz, 1H), 7.56-7.62 (m, 3H), 7.74-7.80 (m, 2H), 7.67 (d, *J* = 16 Hz, 1H), 11.18 (s, 1H), 14.46 (s, 1H); MS: *m/z* (M+1), 380. Anal. Calcd: C, 57.00; H, 3.19. Found: C, 57.03; H, 3.21.

(E)-1-(5-Fluoro-2-hydroxyphenyl)-5-(3-(trifluoromethyl)-5-nitrophenyl)pent-4-ene-1,3-dione, 4b: m.p. 128°C. Yield 70%. IR: 3310, 2980, 1695, 1519, 1160 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.27 (s, 1H), 6.67 (d, *J* = 16 Hz, 1H), 6.97 (dd, *J* = 4.6 Hz, 1H), 7.36 (dd, *J* = 3 Hz, 1H), 7.54-7.64 (m, 2H), 7.72-7.81 (m, 2H), 7.68 (d, *J* = 16 Hz, 1H), 11.19 (s, 1H), 14.49 (s, 1H); MS: *m/z* (M+1), 398. Anal. Calcd: C, 54.42; H, 2.79. Found: C, 54.45; H, 2.81.

(E)-1-(5-chloro-2-hydroxyphenyl)-5-(3-(trifluoromethyl)-5-nitrophenyl)pent-4-ene-1,3-dione, 4c: m.p. 132°C. Yield 72%. IR: 3312, 2982, 1696, 1514, 1158 cm^{-1}; ^1H NMR: δ 6.24 (s, 1H), 6.63 (d, *J* = 16 Hz, 1H), 6.95 (dd, *J* = 4 Hz, 1H), 7.37 (dd, *J* = 3 Hz, 1H), 7.52-7.63 (m, 2H), 7.70-7.80 (m, 2H), 7.65 (d, *J* = 16 Hz, 1H), 11.16 (s, 1H), 14.45 (s, 1H); MS: *m/z* (M+1), 415. Anal. Calcd: C, 52.25; H, 2.68. Found: C, 52.27; H, 2.69.

(E)-1-(5-methyl-2-hydroxyphenyl)-5-(3-(trifluoromethyl)-5-nitrophenyl)pent-4-ene-1,3-dione, 4d: m.p. 118°C. Yield 66%. IR: 3314, 2981, 1692, 1516, 1157 cm^{-1}; ^1H NMR: δ 2.10 (s, 3H), 6.22 (s, 1H), 6.62 (d, *J* = 16 Hz, 1H), 6.93 (dd, *J* = 4.6 Hz, 1H), 7.34 (dd, *J* = 3 Hz, 1H), 7.50-7.60 (m, 2H), 7.70-7.80 (m, 2H), 7.64 (d, *J* = 16 Hz, 1H), 11.17 (s, 1H), 14.47 (s, 1H); MS: *m/z* (M+1), 394. Anal. Calcd: C, 58.02; H, 3.59. Found: C, 58.05; H, 3.62.

(E)-5-(3-(Trifluoromethyl)-5-nitrophenyl)-1-(2-hydroxy-3,5-dimethylphenyl)pent-4-ene-1,3-dione, 4e: m.p. 158°C. Yield 62%. IR: 3315, 2984, 1693, 1517, 1156 cm^{-1}; ^1H NMR: δ 2.10 (s, 3H), 2.12 (s, 3H), 6.24 (s, 1H), 6.60 (d, *J* = 16 Hz, 1H), 6.90 (dd, *J* = 4.6 Hz, 1H), 7.32 (dd, *J* = 3 Hz, 1H), 7.50-7.62 (m, 2H), 7.70 (d, 1H), 7.64 (d, *J* = 16 Hz, 1H), 11.16 (s, 1H), 14.44 (s, 1H); MS: *m/z* (M+1), 408. Anal. Calcd: C, 58.97; H, 3.96. Found: C, 58.98; H, 3.98.

(E)-1-(5-Chloro-2-hydroxy-4-methylphenyl)-5-(3-(trifluoromethyl)-5-nitrophenyl)pent-4-ene-1,3-dione, 4f: m.p. 108°C. Yield 64%. IR: 3312, 2983, 1694, 1515, 1162 cm^{-1}; ^1H NMR: δ 2.11 (s, 3H), 6.25 (s, 1H), 6.62 (d, *J* = 16 Hz, 1H), 6.92 (dd, *J* = 4.6 Hz, 1H), 7.30 (dd, *J* = 3 Hz, 1H), 7.60 (dd, 1H), 7.68 (s, 1H), 7.70 (s, 1H), 7.64 (d, *J* = 16 Hz, 1H), 11.15 (s, 1H), 14.46 (s, 1H); MS: *m/z* (M+1), 428. Anal. Calcd: C, 53.35; H, 3.06. Found: C, 53.37; H, 3.09.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-4*H*-chromen-4-one, 5a-e

Compound **4** (0.002M) was dissolved in acetic acid (15 mL) and minimum quantity of conc. HCl (1.5 mL) was added into it. The reaction mixture was heated under reflux for 2 h. After completion of reaction, it was poured over crushed ice. The product obtained was separated by filtration and crystallized from ethanol to afford the title compound **5**.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-4*H*-chromen-4-one, 5a: m.p. 134°C. Yield 60%. IR: 3057, 1696, 1644, 1527, 1331, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.40 (s, 1H), 6.86 (d, *J* = 16 Hz, 1H), 7.43 (dd, *J* = 3 Hz, 1H), 7.56-7.64 (m, 4H), 7.65 (dd, *J* = 3 Hz, 1H), 7.68 (d, *J* = 16 Hz, 1H), 7.85 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 362. Anal. Calcd: C, 59.84; H, 2.79. Found: C, 59.87; H, 2.81.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-6-fluoro-4*H*-chromen-4-one, 5b: m.p. 148°C. Yield 65%. IR: 3054, 1698, 1642, 1524, 1329, 1113 cm^{-1}; ^1H NMR: δ 6.37 (s, 1H), 6.86 (d, *J* = 16 Hz, 1H), 7.42 (dd, *J* = 3 Hz, 1H), 7.54-7.58 (m, 2H), 7.61 (dd, *J* = 3 Hz, 1H), 7.64 (d, *J* = 16 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.83 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 380. Anal. Calcd: C, 57.00; H, 2.39. Found: C, 57.03; H, 2.41.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-6-chloro-4*H*-chromen-4-one, 5c: m.p. 172°C. Yield 64%. IR: 3058, 1695, 1640, 1523, 1325, 1112 cm^{-1}; ^1H NMR: δ 6.36 (s, 1H), 6.82 (d, *J* = 16 Hz, 1H), 7.41 (dd, *J* = 3 Hz, 1H), 7.52-7.57 (m, 2H), 7.60 (dd, *J* = 3 Hz, 1H), 7.62 (d, *J* = 16 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.81 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 396. Anal. Calcd: C, 54.63; H, 2.29. Found: C, 54.64; H, 2.31.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-6-methyl-4*H*-chromen-4-one, 5d: m.p. 168°C. Yield 48%. IR: 3056, 1694, 1641, 1522, 1326, 1115 cm^{-1}; ^1H NMR: δ 2.38 (s, 3H), 6.35 (s, 1H), 6.80 (d, *J* = 16 Hz, 1H), 7.38 (dd, *J* = 3 Hz, 1H), 7.51-7.54 (m, 2H), 7.61 (dd, *J* = 3 Hz, 1H), 7.60 (d, *J* = 16 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.80 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 376. Anal. Calcd: C, 60.81; H, 3.22. Found: C, 60.85; H, 3.24.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-6,8-dimethyl-4*H*-chromen-4-one, 5e: m.p. 182°C. Yield 54%. IR: 3053, 1694, 1640, 1522, 1323, 1110 cm^{-1}; ^{1}H NMR: δ 2.35 (s, 3H), 2.40 (s, 3H), 6.32 (s, 1H), 6.78 (d, *J* = 16 Hz, 1H), 7.41 (dd, *J* = 3 Hz, 1H), 7.50 (d, *J* = 2 Hz, 1H), 7.54 (dd, *J* = 3 Hz, 1H), 7.62 (d, *J* = 16 Hz, 1H), 7.76 (d, *J* = 2 Hz, 1H), 7.81 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 390. Anal. Calcd: C, 61.70; H, 3.62. Found: C, 61.73; H, 3.64.

2-(3-(Trifluoromethyl)-5-nitrostyryl)-6-chloro-7-methyl-4*H*-chromen-4-one, 5f: m.p. 172°C. Yield 58%. IR: 3052, 1693, 1642, 1523, 1320, 1112 cm^{-1}; ^{1}H NMR: δ 2.37 (s, 3H), 6.34 (s, 1H), 6.74 (d, *J* = 16 Hz, 1H), 7.40 (dd, *J* = 3 Hz, 1H), 7.54 (s, 1H), 7.58 (dd, *J* = 3 Hz, 1H), 7.64 (d, *J* = 16 Hz, 1H), 7.71 (s, 1H), 7.83 (dd, *J* = 3 Hz, 1H); MS: *m/z* (M+1), 410. Anal. Calcd: C, 55.69; H, 2.71. Found: C, 55.71; H, 2.74.

Results and Discussion

In current study we have synthesized novel fluorine containing different styryl esters, diketones and chromones. The structures of all the synthesized compounds were confirmed by spectral techniques.

Conclusions

Results showed that compounds bearing halogen like fluorine, chlorine have greater yield than compounds bearing alkyl substituent like methyl and dimethyl in dikeone and chromone derivatives.

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References

1 Purser S, Moore P R, Swallow S & Gouverneur V, *Chem Soc Rev*, 37 (2008) 320.
2 Wang B, Wang H, Liu H, Xiong L, Yang N, Zhang Y & Li Z, *Chinese Chem Lett*, 31 (2020) 739.
3 Wang F, Ren Y-J & Dong M-H, *Bioorg Med Chem*, 24 (2016) 2739.
4 Meng H & Kumar K, *J Am Chem Soc*, 129 (2007) 15615.
5 Xia Y, Yang Z-Y, Xia P, Hackl T, Hamel E, Mauger A, Wu J-H & Lee K-H, *J Med Chem*, 44 (2001) 3932.
6 Isanbor C & O'Hagan D, *J Fluorine Chem*, 127 (2006) 303.
7 Pradhan J & Goyal A, *Int J Pharma Res Allied Sci*, 4 (2015) 1.
8 Fragoza-Mar L, Olivares-Xometl O, Dominguez-Aguilar M A, Flores E A, Arellanes-Lozada P & Jimenez-Cruz F, *Corros Sci*, 61 (2012) 171.
9 Viswanathan A, Sala A, Yli-Harja O & Kandhavelu M, *Eur J Pharm Sci*, 66 (2015) 83.
10 Das S & Smid S D, *Toxicology Lett*, 300 (2019) 67.
11 Bhise N A, Al-Horaibi S A, Gaikwad S T & Rajbhoj A S, *Rasayan J Chem*, 12 (2019) 101.
12 Rackova L, Firakova S, Kostalova D, Stefek M, Sturdik E & Majekova M, *Bioorg Med Chem*, 13 (2005) 6477.
13 Conti C & Desideri N, *Bioorg Med Chem*, 18 (2010) 6480.
14 Duan Y-D, Jiang Y-Y, Guo F-X, Chen L-X, Xu L-L, Zhang W & Liu B, *Fitoterapia*, 135 (2019) 114.
15 Middleton E, Kandaswami C & Theoharides T C, *Pharnacol Rev*, 52 (2000) 673.
16 Bhatnagar S, Sahi S, Kackar P, Kaushik S, Dave M K, Shukla A & Goel A, *Bioorg Med Chem Lett*, 20 (2010) 4945.
17 Shaw A Y, Chang C-Y, Liau H-H, Lu P-J, Chen H-L, Yang C-N & Li H-Y, *Eur J Med Chem*, 44 (2009) 2552.
18 Takao K, Yahagi H, Uesawa Y & Sugita Y, *Bioorg Chem*, 77 (2018) 436.
19 Rocha-Pereira J, Cunha R, Pinto D C G A, Silva A M S & Nascimento M S J, *Bioorg Med Chem*, 18 (2010), 4195.