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Multi-component one pot assisted synthesis,anti-bacterial capabilities and scanning electron microscopy of novel corticosteroid thiopyran

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Abstact:
Corticosteroids as an influential class of multi-cyclic molecules particularly performing pivotal roles in governing regular physiological processes as well asspotting the biological sites which are related to diseases. There is manifest that a statistic of biologically most important steroids are modified forthwith in clinic for thesuccour of diseases. Ring system[1] as well as side chain[2] chemical modification of the steroid impart procedures of the functional groups alteration[3]. These compoundscould be used for performing physiological measures and addressing biologically disease-related sites[4–8] particularly steroid hormones such as corticosteroids that are amalgamated and exonerate in the adrenal gland play an indispensable portrayal in governing stress.
Keywods: diseases, biological, steroid, corticosteroids, hormones.

Introduction

Corticosteroids enforce every tissue type, synchronizing an array of processes of the cardiovascular, immune, metabolism, reproduction, behaviour, cell survival, musculoskeletal systems etc.[9–11]. Their potent anti-inflammatory and immunosuppressive capabilities made them the physician's preferred choice for the treatment of several dermatological, autoimmune, and ocular diseases[12]. However, these drugs also have the potential to cause sometimes severe adverse effects, particularly if high doses are used for prolonged periods[13]. Side effects of corticosteroids include cushing syndrome, acne, susceptibility to infections, high blood pressure, stomach ulcer, glaucoma and water/electrolyte retention, would ultimately decrease the effectiveness of the drug to constrain the discontinuance of the drug[14]. We have tried to synthesize corticosteroids heterocycles. At present, due to their intriguing biological activity and structure, steroidal heterocycles, have drawn wide attention[15–18]. Thiopyran, sulphur atom containing heterocycles, have heightened consideration of steroidal heterocycles. Distinctive biological activities[19,20] have been recognized by these compounds. In medicinal chemistry, thiopyrans are used but receives less contemplation[21], often in the compounds of natural products with variousactivities such as anti-bacterial[22], anti-hyperplasia[23], anti-psychiatric[24] , and anticanceractivities against tumor cell lines[25,26]. Inhibition of deoxyribonucleic acid-proteinkinases[27] is also attributed by substituted thiopyrans. However, tedious synthetic routes, long reaction time, harsh reaction conditions, and narrow application scope of substrates requires for the synthesis of thiopyrans.

With the application of previous studies[28], we have planned to present an efficient multi component synthesis of corticosteroids thiopyran as potential anti-bacterial
agent. Adding feather to our awareness, about the synthesis of corticosteroids thiopyran, the reaction of corticosteroids with malononitrile, triethylamine and carbondisulphide has been portrayed.

Experimental section

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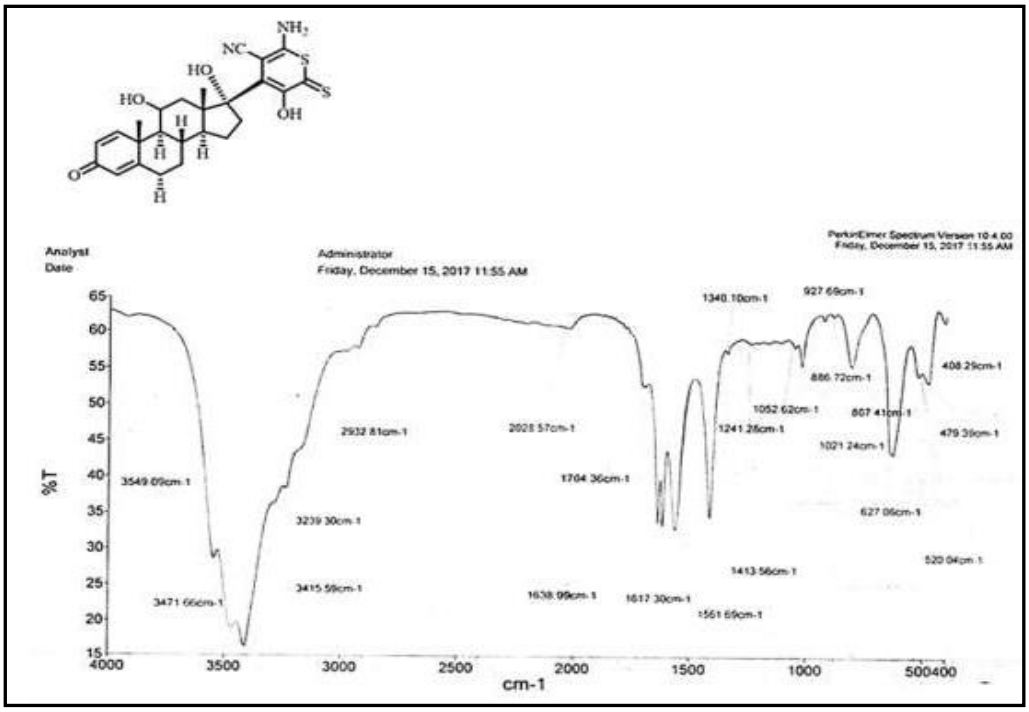
Materials and methods

Materials were procured from previous literature[28,29].

General methods for the synthesis of corticosteroid thiopyran (6-10) Corticosteroids **(1-5)** (1 mmol) was disolved in ethanol (5 mL) and malononitrile (1.5mmol) was added portion wise followed by drop wise addition of triethylamine. Thencarbon disulphide (4 mL) was added in one potion. The resulting reaction mixture washeated at 60°C with constant stirring for about 6- 10 h. The monitoring of the reaction progress by TLC analysis using 10% acetone-benzene as a mobile phase was carriedout. Cooling of the reaction mixture at room temperature and formation of solidproduct was collected by filteration while keeping the reaction mixture overnight. Thedesired product obtained as precipitate/ solid compound was purified by recrystallization from ethanol.

Spectral data of *6'-amino-3'-hydroxy-2'thioxo-2'H-thiopyran-5'-carbinotrile-4'(17)-prednisolone* (6) Yield (80%), **M.P.**: 175-177 °C; **IR (KBr, ν, cm^{-1})**: 3549-3414, 2210, 1638, 1241, 627. **^{1}H NMR (400 MHz, $CDCl_3$, ppm)**: δ 7.36 (s, 2H, NH_2 exchangeable with D_2O),4.48 (s, 1H, C_{11}-OH), 5.09 (s, 1H, C_{17}-OH), 3.04 (m, 1H, C_{11}-αH), 1.42 (C_{10}-CH_3) and 0.89 (C_{13}-CH_3). **^{13}C NMR (100 MHz, $CDCl_3$, ppm)**: δ207.26, 186.99, 186.85, 170.48, 157.34, 156.87, 127.77, 127.61, 122.24, 108.1, 90.51, 85.69, 70.18, 61.62, 50.45, 47.62, 44.34, 39.31, 32.70, 32.20, 31.49, 30.98, 24.16, 18.18, 17.68. Anal. Calc. for $C_{25}H_{28}N_2O_3S_2$; C, 64.08; H, 6.02; N, 5.98. Found; C, 64.02; H, 6.00; N, 5.93. **MS (EI)**: m/z calculated 484.15, found 484.10. All the values are shown belowin the given spectra.

FT-IR spectrum



^{1}H NMR spectrum

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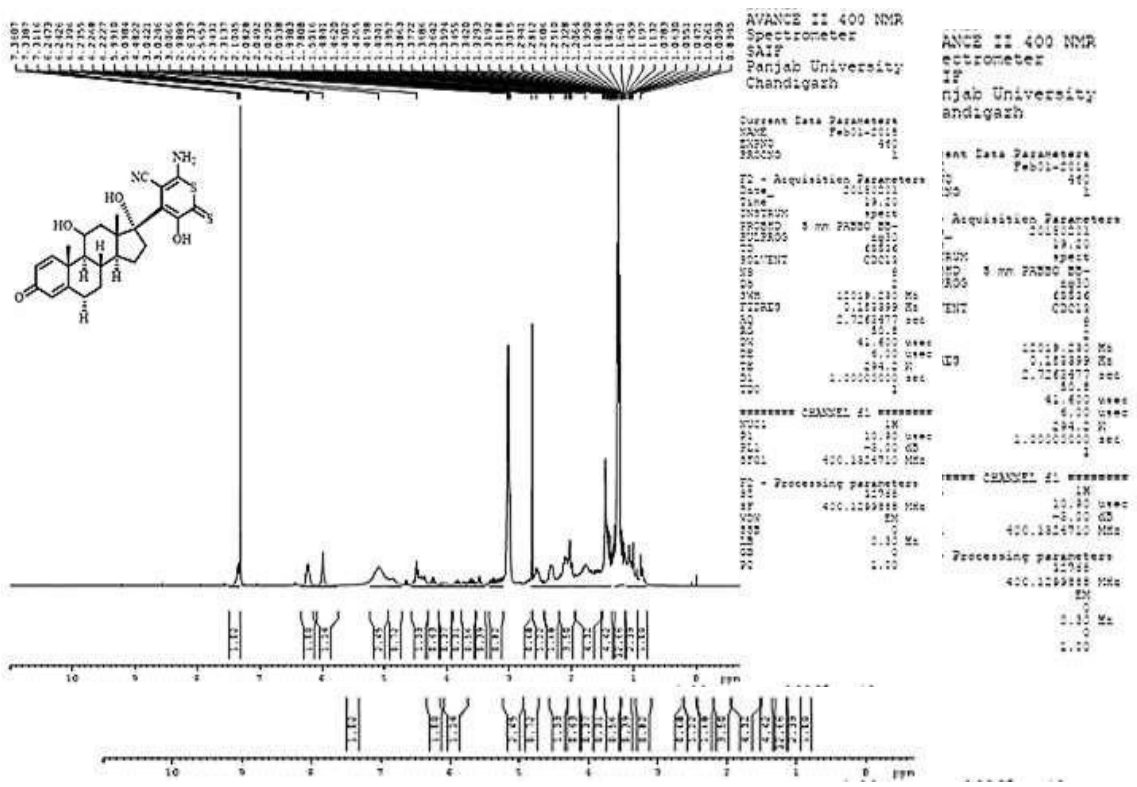
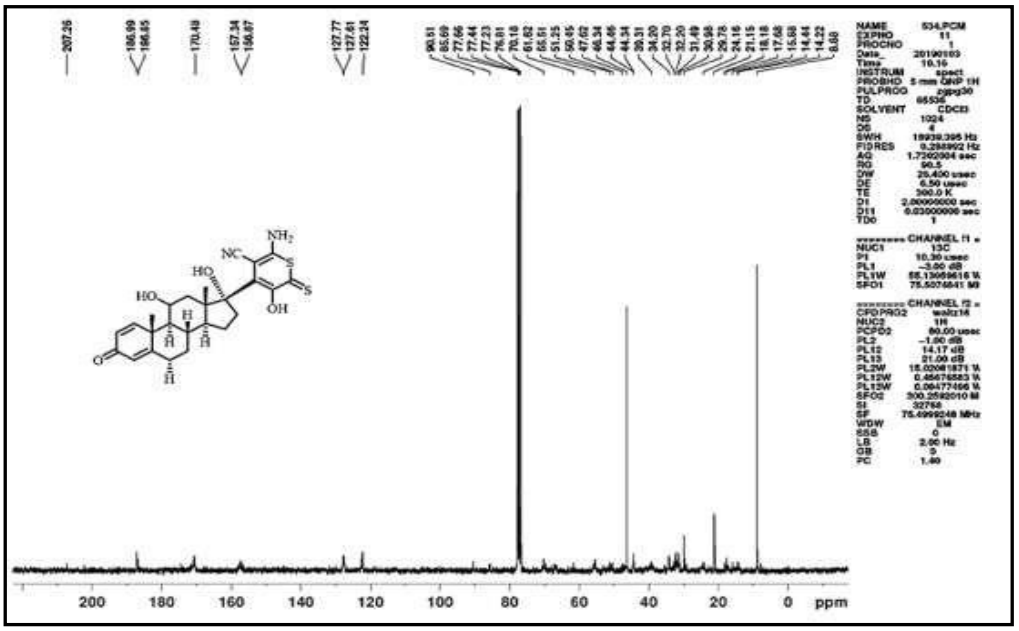


^{13}C NMR spectrum



ESI-MS spectrum

Spectral data of *6'-amino-3'-hydroxy-2'thioxo-2'H-thiopyran-5'- carbonitrile-4'(17)-6α-methyl-prednisolone* (7)

Yield (82%), **M.P.**: 180-182ºC; **IR (KBr, ν, cm^{-1})**: 3550-3336, 2207, 1649, 1242,

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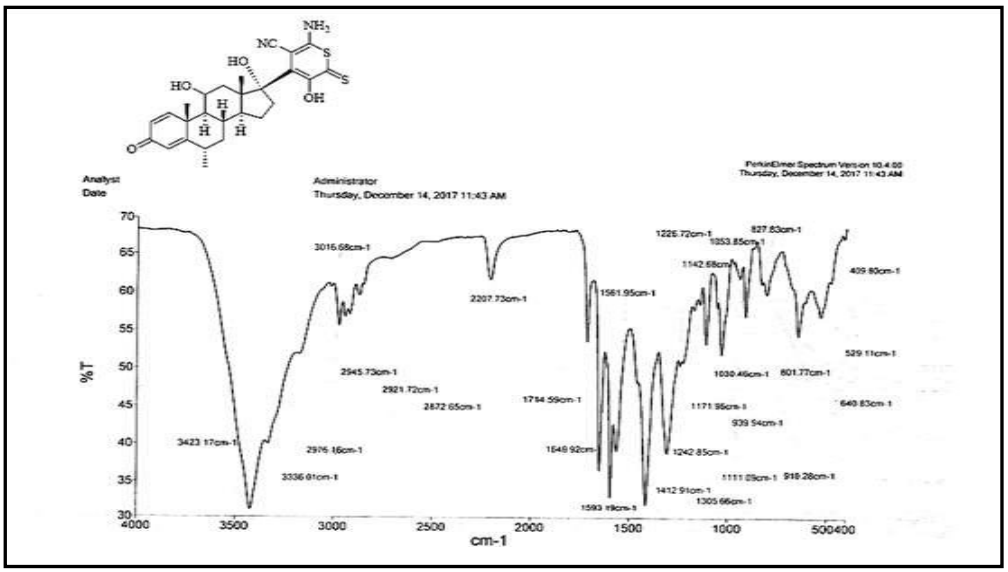
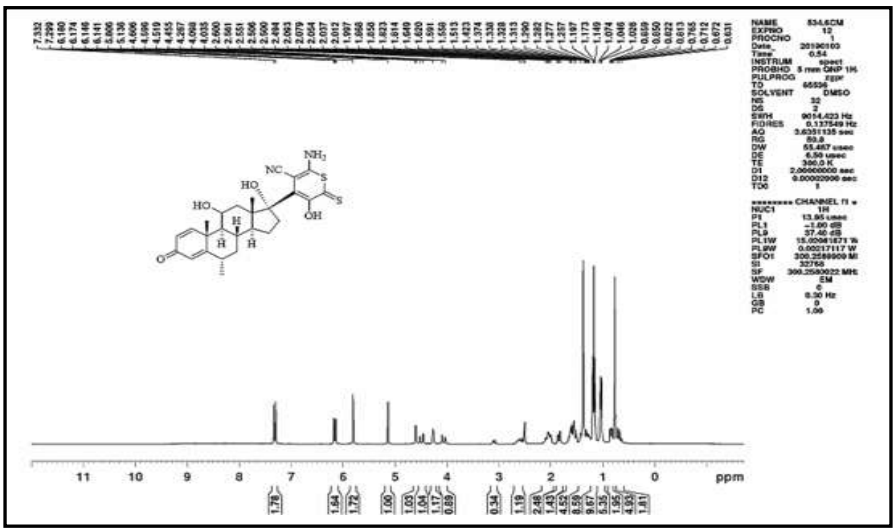
640. **^{1}H NMR (400 MHz, $CDCl_3$, ppm)**: δ 7.33 (s, 2H, NH_2 exchangeable with D_2O),4.26 (s, 1H, C_{11}-OH), 4.45 (s, 1H, C_{17}-OH), 4.03 (m, 1H, C_{11}-αH), 1.07 (C_6-CH_3), 1.42 (C_{10}-CH_3) and 0.85 (C_{13}-CH_3). **^{13}C NMR (100 MHz, $CDCl_3$, ppm)**: δ 211.51, 185.09, 173.40, 157.22, 151.1, 146.23, 126.62, 124.24, 118.70, 108.1, 94.0, 88.37, 68.38, 55.90, 50.89, 46.51, 45.82, 43.97, 36.9, 32.92, 32.43, 30.80, 23.47, 21.25, 17.56, 16.87. Anal. Calc. for $C_{26}H_{30}N_2O_3S_2$; C, 64.70; H, 6.27; N, 5.80. Found; C, 64.65; H, 6.21; N, 5.76**. MS (EI)**: m/z calculated 498.66, found 498.35. All the valuesare shown below in the given spectra.

FT-IR spectrum



^{1}H NMR spectrum



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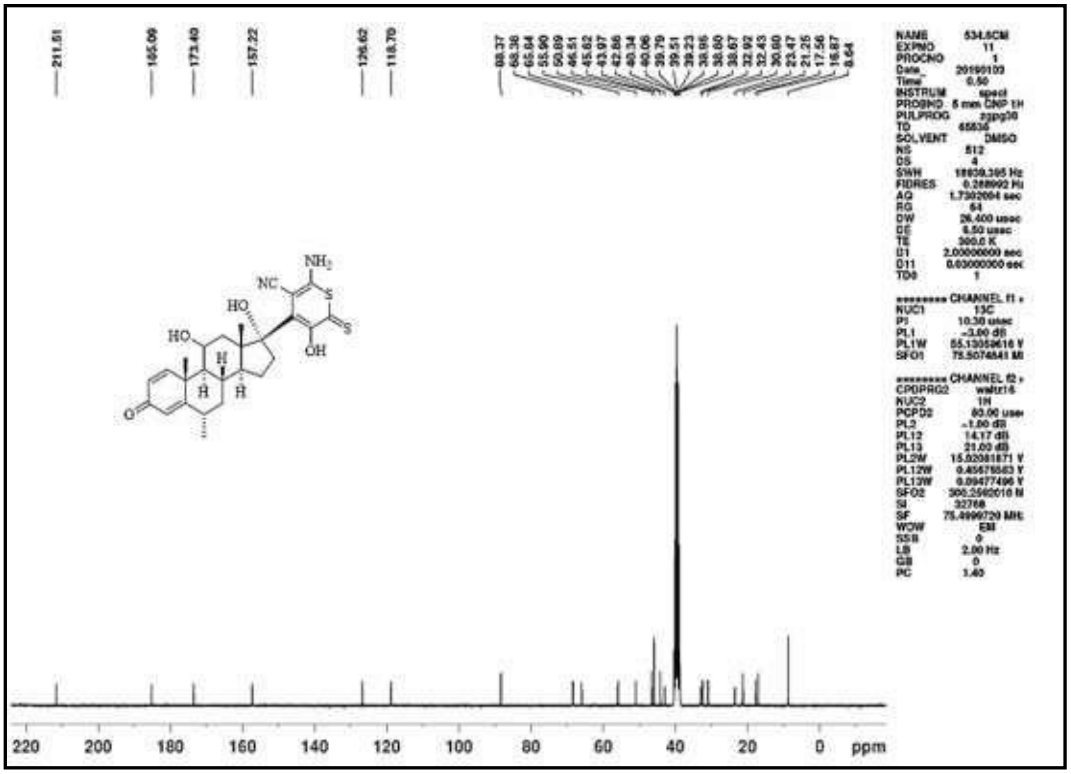
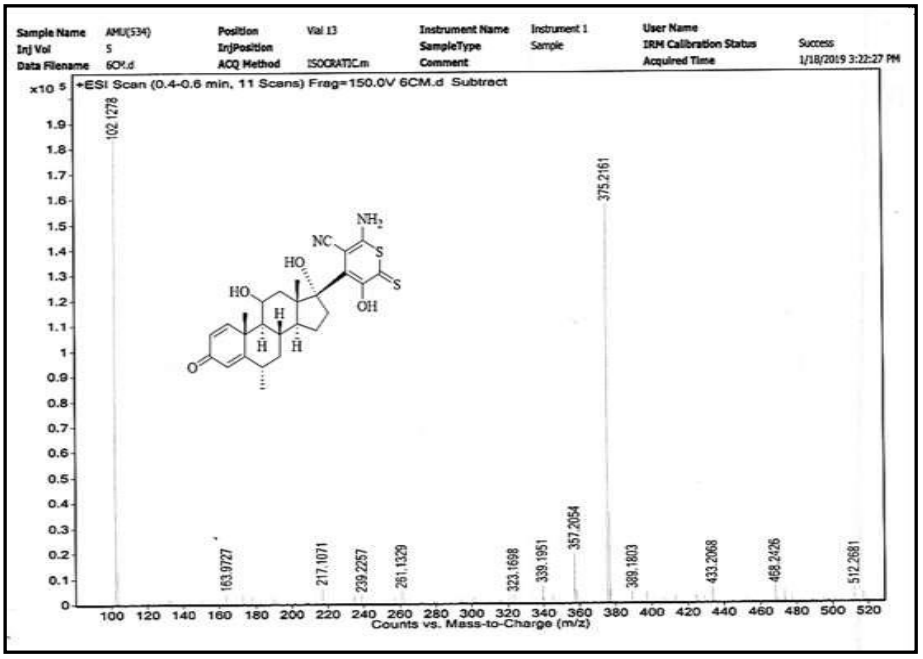


ESI-MS spectrum



Spectral data of *6'-amino-3'-hydroxy-2'thioxo-2'H-thiopyran-5'- carbonitrile-4'(17)-*

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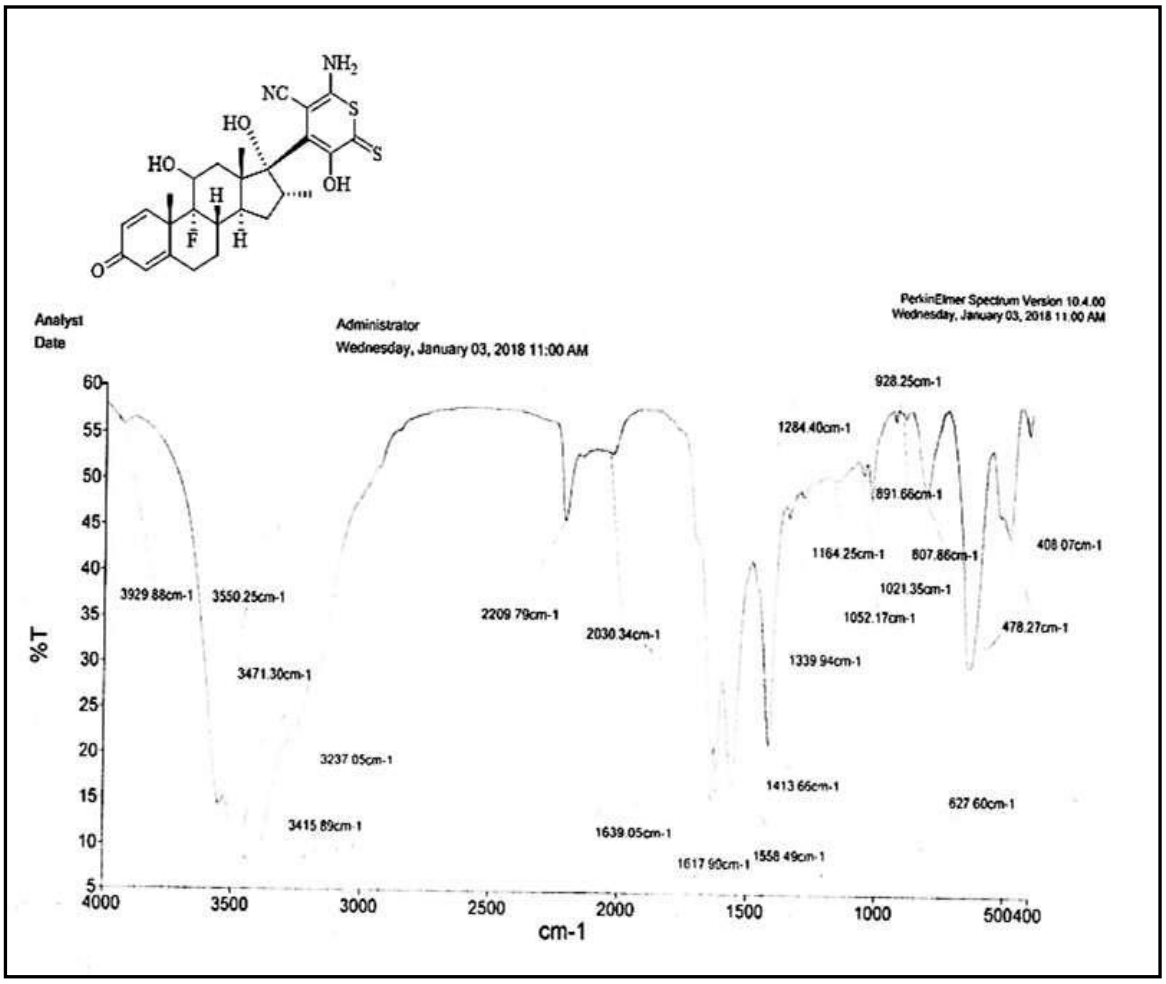
***dexamethasone* (8)**

Yield (84%), **M.P.**: 133-135°C; **IR (KBr, ν, cm^{-1})**: 3550-3415, 2209, 1639, 1284, 627. **^{1}H NMR (400 MHz, $CDCl_3$, ppm)**: δ 8.85 (s, 2H, NH_2 exchangeable with D_2O), 4.47 (s, 1H, C_{11}-OH), 4.66 (s, 1H, C_{17}-OH), 4.10 (m, 1H, C_{11}-αH), 1.51 (C_{10}- CH_3), 0.86 (C_{13}-CH_3) and 0.84 (C_{16}-CH_3). **^{13}C NMR (100 MHz, $CDCl_3$, ppm)**: δ 211.15, 185.35, 167.17, 155.68, 154.55, 142.22, 128.98, 124.11, 115.53, 112.70, 98.63, 97.38, 95.14, 71.16, 47.49, 45.75, 40.34, 39.79, 35.85, 34.94, 33.82, 30.37, 27.4, 22.88, 16.64, 15.30. Anal. Calc. for $C_{26}H_{29}FN_2O_3S_2$; C, 62.38; H, 5.84; N, 5.60. Found; C, 62.35; H, 5.81; N, 5.56. **MS (EI)**: m/z calculated 516.65, found 516.32. Allthe values are shown below in the given spectra.

FT-IR spectrum



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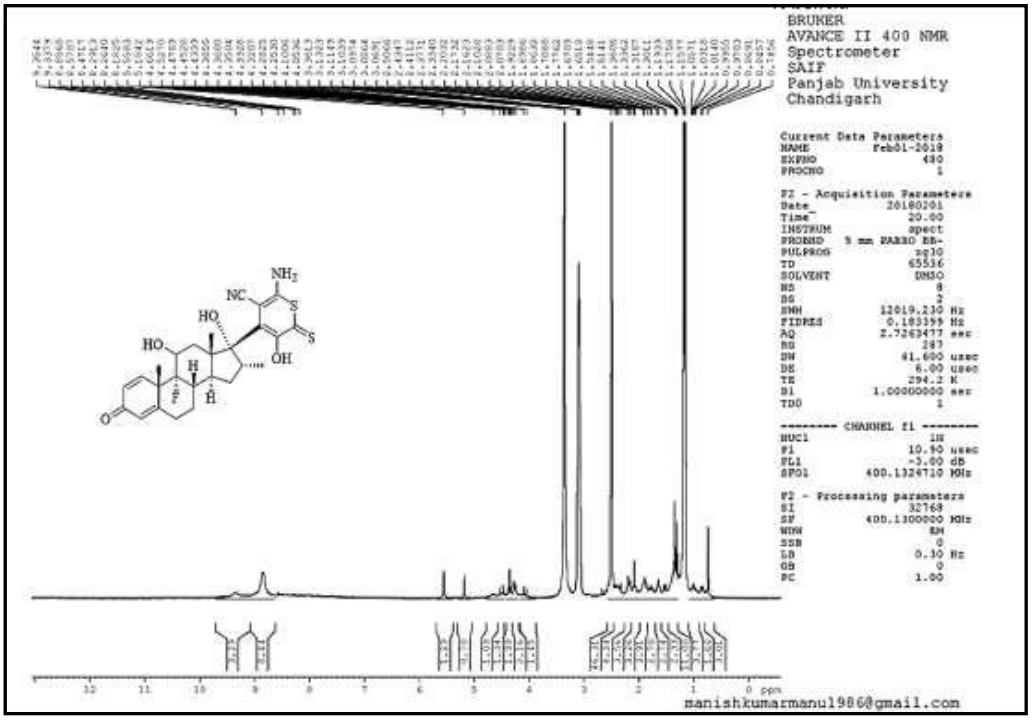
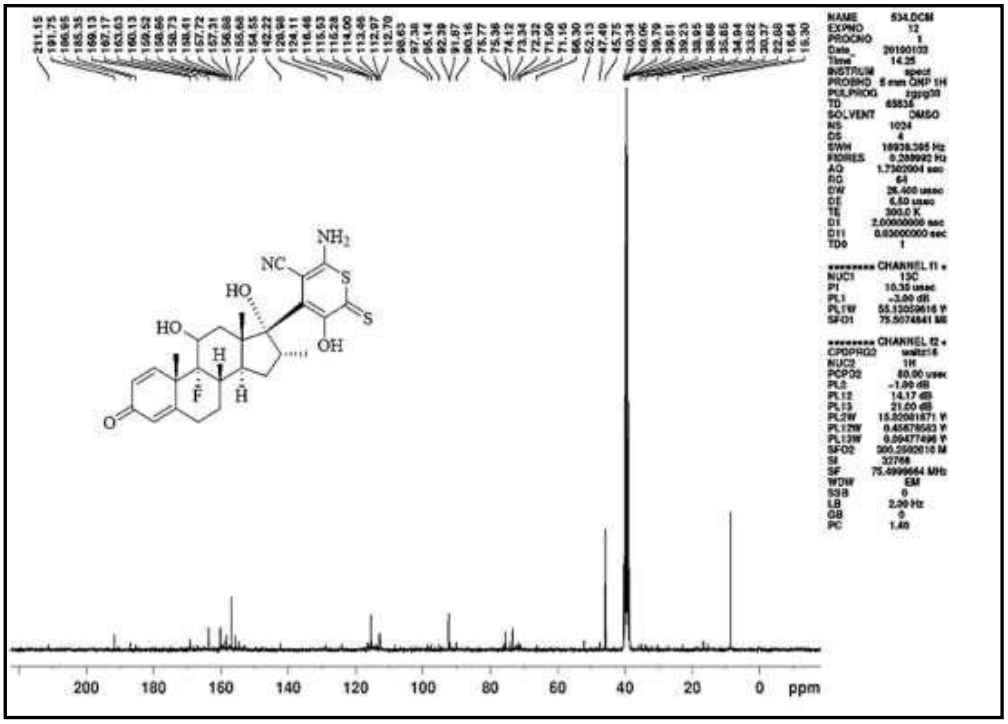
^{1}H NMR spectrum



^{13}C NMR spectrum



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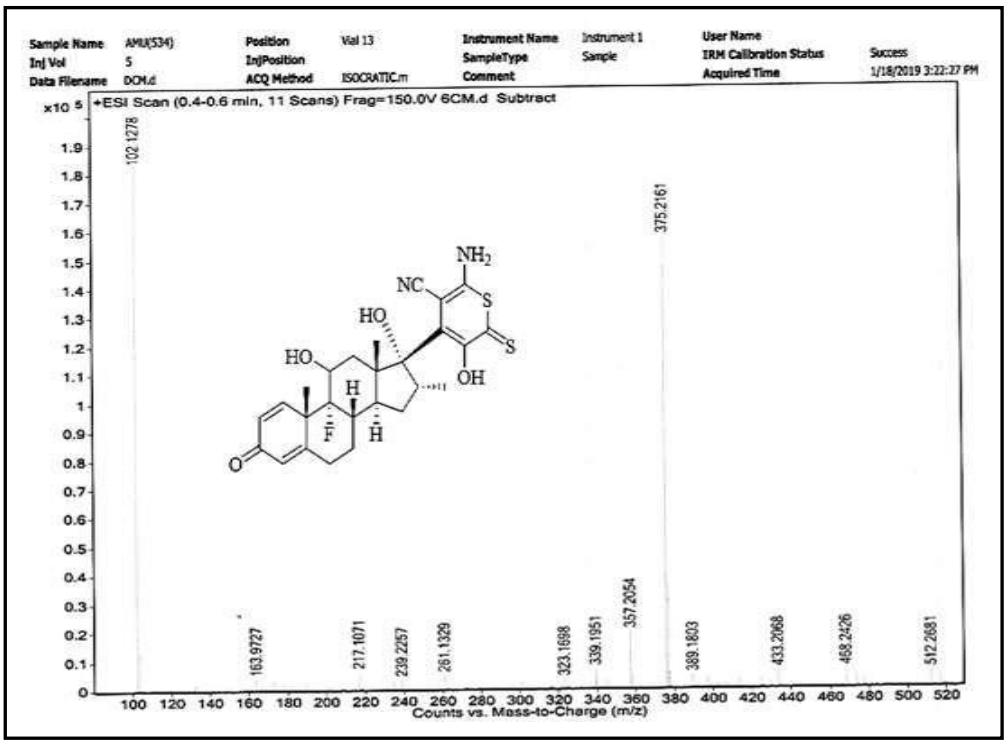
ESI-MS spectrum



Spectral data of *6'-amino-3'-hydroxy-2'thioxo-2'H-thiopyran-5'-carbonitrile-4'(17)-triamcinolone* (9)

Yield (80%), **M.P.**: 138-140ºC; **IR (KBr, ν, cm^{-1})**: 3547-3418, 2209, 1638, 1242, 622. **^{1}H NMR (400 MHz, CDCl$_3$, ppm)**: δ 6.51 (s, 2H, NH_2 exchangeable with D_2O),4.77 (s, 1H, C_{11}-OH),5.26 (s, 1H, C_{16}-OH), 5.99 (s, 1H, C_{17}-OH), 4.14 (m, 1H, C_{11}-αH), 4.50 (m,1H,C_{11}-αH), 1.45 (C_{10}-CH_3) and 0.83 (C_{13}-CH_3). **^{13}C NMR (100 MHz, CDCl$_3$, ppm)**: δ 211.64, 185.30, 166.98, 156.82, 154.53, 152.74, 129.01, 124.17, 115.50, 102.25, 99.93, 98.56, 92.41, 87.53, 71.33, 48.09, 43.16, 40.34, 38.68, 35.82, 30.27, 27.34, 22.95, 22.88, 16.70. Anal. Calc. for $C_{25}H_{27}FN_2O_4S_2$; C, 59.74; H, 5.41; N, 5.57. Found; C, 59.71; H, 5.39; N, 5.53. **MS (EI)**: m/z calculated 502.62, found 502.41. All the values are shown below in the given spectra.

Results and discussion

Chemistry

Inspired by the potential of sulfur containing heterocyclic compound and fascinating biological properties of corticosteroids we devised a manageable and productive one- pot multi component synthesis of corticosteroids thiopyran derivatives. The synthetic route employed for the preparation of corticosteroids thiopyran derivatives **(6-10)** is depicted in **Scheme 3.1**. Synthesis of the desired products (**6-10)** have been successfully achieved by the reaction of corticosteroids **(1-5)** with malononitrile in presence of triethyl amine as a base catalyst. This is followed by the reaction with carbon disulfide to afford respective products **(6-10)**. Five different corticosteroids have been used as starting substrate namely prednisolone **(1)**, 6α-methyl-prednisolone**(2)**, dexamethasone **(3)**, triamcinolone **(4)**, and hydrocortisone **(5).**

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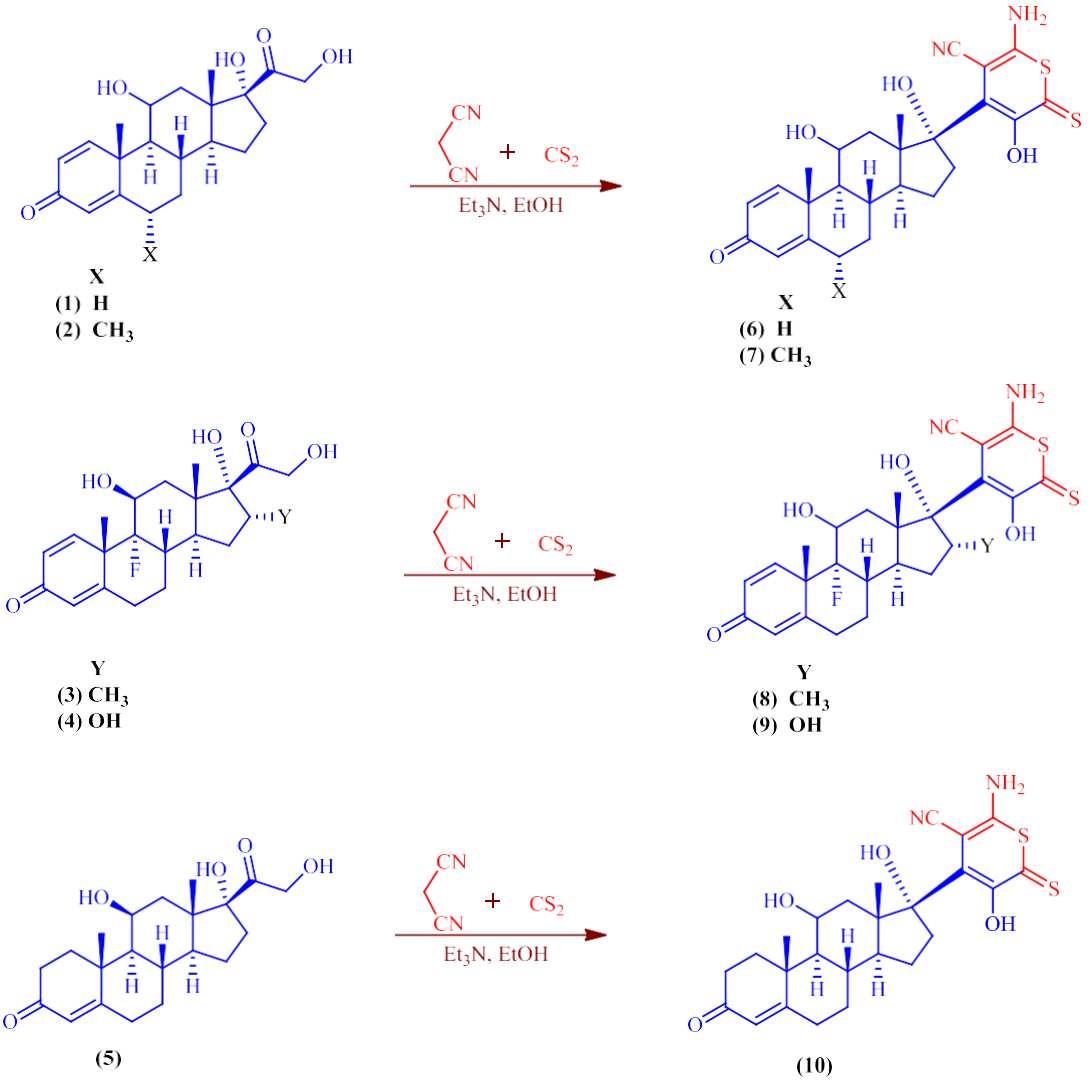

Conclusion

Heterocyclization reaction suggested by the structure activity relationship of corticosteroids derivative into thiopyran derivatives **(6-10)** showed high antibacterial activity. We describe a facile one-pot multicomponent synthesis of corticosteroid thiopyran derivatives. Excellent yields of the products, simple work-up,easily available starting materials and non-chromatographic purification are some main advantages of this protocol. Exploration of potent moieties, like thiopyran ring system as elucidated in this work, would be exhilarated by inspecting new molecules. Our prediction about these compounds having new ring systems with modificationand derivatization may show even enhance antibacterial activity. The scanning electron microscope of corticosteroid thiopyran **(6-10)** flourish with brick-shapedagglomerates with dull edges and a rugged exterior.

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