



Synthesis of New Class Furochromenethylthiourea Compounds derived from Formylfurochromone Compound

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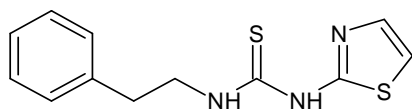
Abstract

Treatment of formylfurochromone 1 with nitro methane to form nitro-furochromenethyl derivative 2 followed by reduction to give amino-furochromone derivative 3 which used as key intermediates for the synthesis of furochromenethylthiourea derivatives 10a,b and 13a-d at reaction aminofurochromone derivative 3 with each of imidazole-carbothioamide 4a,b derivatives, isothiocyanates derivatives 7, thiocarbonyl reagent 8, isocyanate/ isothiocyanates 12a-d. Thiourea compounds 11a-c was formed at the reaction of the isothiocyanates 5 with different amines. In addition, the condensation of furochromenethyl isothiocyanates 5 with amino pyridine 6a, b was afforded the compounds 10a, b. Also reaction of compound 3 with potassium cyanate 14 lead to semicarbazide derivative 15.

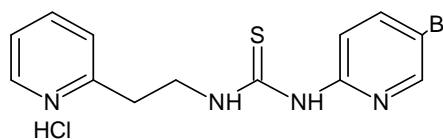
Keywords: Furochromenethylthiourea, Aminofurochromone, Isothiocyanates, Semicarbazide

Introduction

Trovirdine is currently in phase one clinical trials for potential use in the treatment of AIDS [1-5]. Structure- activity relationship studies of Phenethylthiazolylthiourea (PETT) derivatives have been identified as a new series of non-nucleoside inhibitors of HIV -1 resulted in the identification of *N*- [2-(2-pyridyl)ethyl]-*N*-[2-(5-bromopyridyl)]-thiourea hydrochloride (trovirdine, LY300046.HCl) as a highly potent anti-HIV-1 agent. Extension of these structure- activity relationship studies to identify additional compounds in the series which improved properties is ongoing. A part of this work is described in this study [6,7]. Replacement of one aromatic moiety of the FETT compounds by various substituted heteroaromatic rings was studied



LY 73497

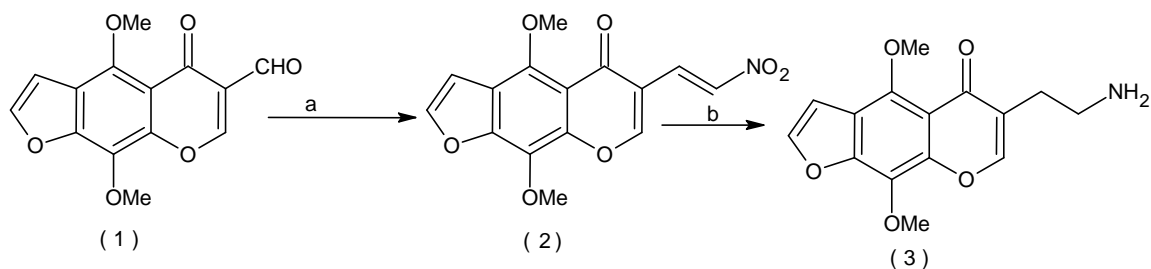


LY 300046 HCl

Trovirdine

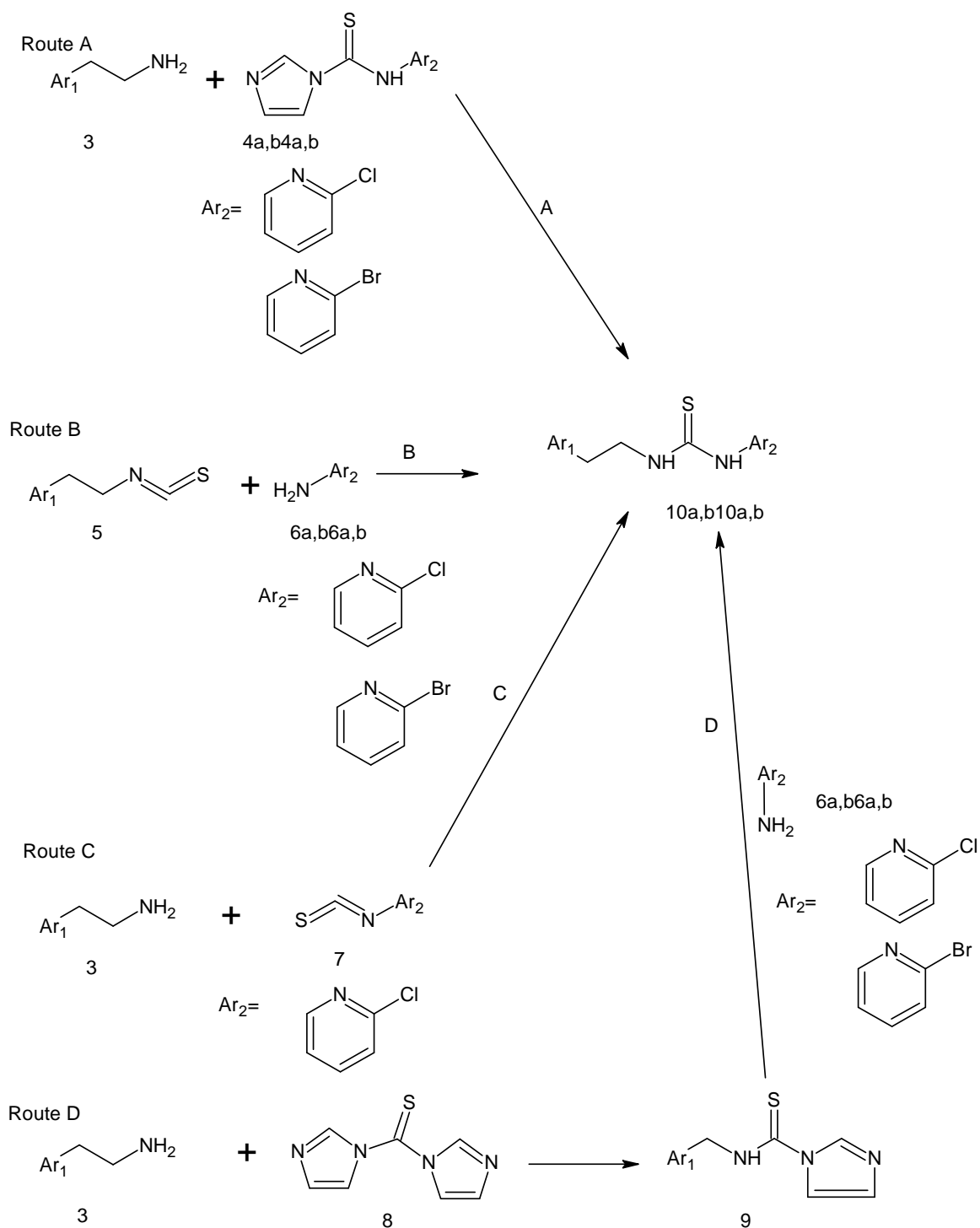
Results and Discussion

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1-6. The intermediate 3 was prepared by condensation of aldehyde [8] 1 with nitromethane [9-12] to afford compound 2 followed by reduction with LiAlH₄ (Scheme 1) [9,10] Compound 3 was characterized by the presence of a strong peak at 3422 cm⁻¹ in the IR spectrum. The appearance of a br. signal, equivalent to two protons in the ¹HNMR spectrum at 2.02 ppm which represents the NH₂ protons.



Scheme 1

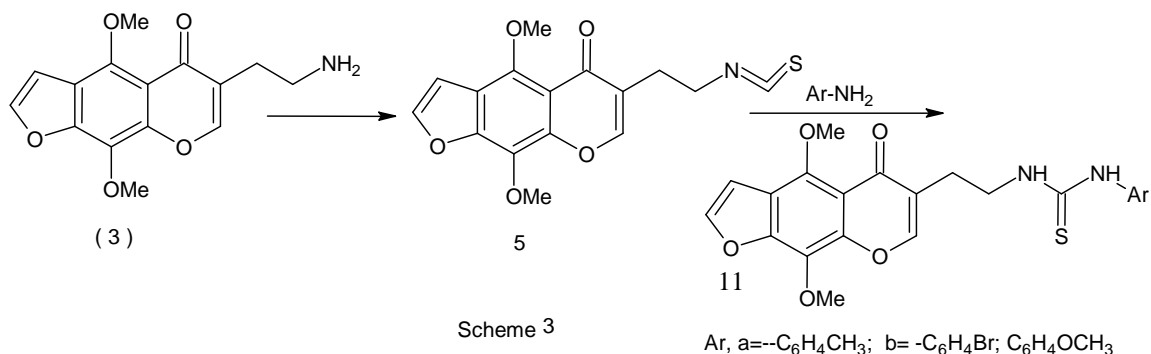
The compounds described in the present study were synthesized according to the general routes A-D depicted in Scheme 2. In (route A), thiocarbonyl reagents 4a, b derived from appropriate amino pyridines 6a, b and 1, 1-thiocarbonyldiimidazole 8 were condensed with furochromenethylamine 3, according to Scheme 1. Furochromenethyl Isothiocyanates 5 (route B) were condensed with amino pyridine 6a, b (prepared by the reaction of 2-amino-5-chloro or bromopyridine with sodium cyanide). Isothiocyanates 7 derived from 2-amino-5-chloro or bromopyridine 6a, b and 1, 1-thiocarbonyldiimidazole 8 were reacted with furochromenethylamine 3 (route C). A thiocarbonyl reagent 9 (route D) which was prepared from a furochromenethylamine 3 and 1, 1-thiocarbonyldiimidazole 8 was condensed with the appropriate amino pyridines 6a, b, the new compounds 10a, b were obtained in good yields. Compound 10a, b was characterized by the presence of a two band at 3245, 3189 cm⁻¹ (NH) in the IR spectrum, the appearance of a two singlet signal, equivalent to two protons in the ¹HNMR spectrum 4.00, 2.11 ppm which represents the 2NH protons. The compounds were synthesized as per Scheme 2.



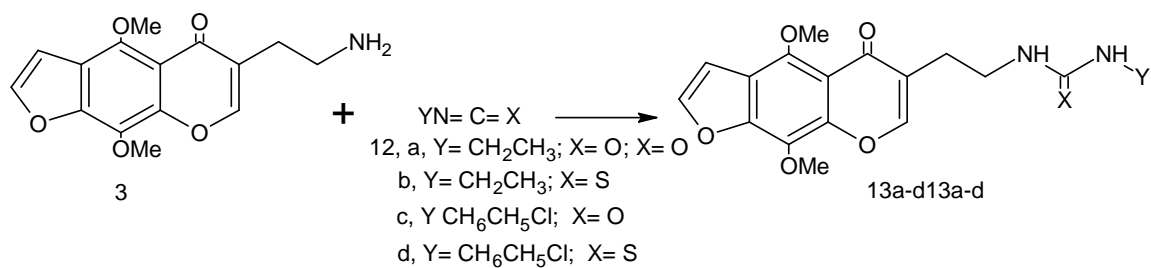
Scheme 2

However, in one of our previous studies [9,14] formation of desired compound 11a-c. At reaction of the Isothiocyanates 5 with different amines (p-toluidine, p- bromoaniline and p- anisidine) to afford the desired thiourea 11a-c. Most of the thiourea was isolated

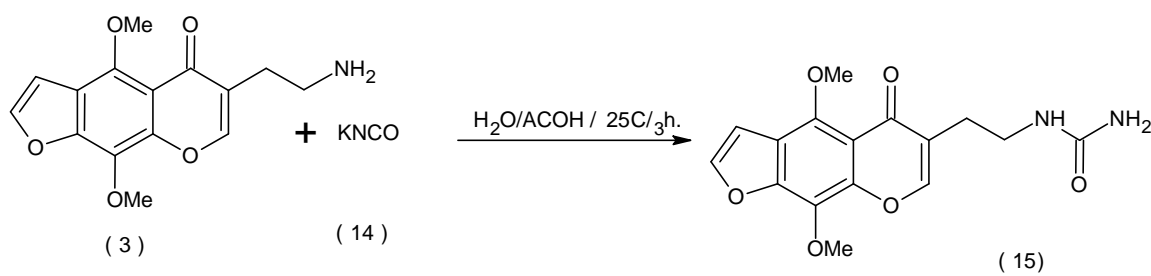
as solid foams which could not be crystallized; however, in most cases analytically pure samples could be obtained by column chromatography. These compounds prepared according to (Schemes 3) [9,14]. Structures of these compounds were characterized using ^1H NMR and IR.



Thiourea is conveniently prepared by coupling amines with an isocyanate/ Isothiocyanates under mild reaction condition [9,14-16]. So, treatment of compound 3 with certain alkyl or aryl isocyanate/ Isothiocyanates 12a-d in dioxane yielded the corresponding 13a-d Scheme 4.



The reaction of 3 with potassium cyanate 14 in aqueous acetic acid at room temperature, leads to 1-substituted semicarbazide [17-19] 15 with excellent yields.



The newly synthesized compounds were characterized by IR, ¹H NMR and mass spectral studies. Representative compounds of the synthesized products were tested and evaluated as antimicrobial agents.

Materials and Methods

All melting points were determined on a Gallenkamp apparatus were uncorrected. The IR spectra were recorded in KBr disks, on a Jasco Fourier Transform Infrared Spectrophotometer Model FT/IR3000E. The ¹H NMR were recorded (DMSO-*d*₆), on JOEL JNM-EX 270 FTNMR system (NRC) and chemical shifts (δ) are expressed in ppm using TMS as an internal standard Splitting patterns are indicated as s, singlet; d, doublet; m, multiple, b, broad signal. The MS were performed at 70 e V on a Finnegan MAT SSQ 7000 spectrometer. Elemental analysis were carried out at the Micro analytical Laboratory of the National Research Centre, Cairo, Egypt and their elemental analysis were generally found to be within ± 0.04% of the theoretical values, The purity of the synthesized compounds was evidenced by TLC, all solvents which were used for recrystallization and column chromatography were of analytical grade. Nevirapine was synthesized according to published methods [2].

4,9-dimethoxy-6-[2-nitrovinyl]-5H-furo[3,2-g]chromen-5-one (2):

A solution of 1 (0.47g, 171 mmol) and ammonium acetate (0.06g) in nitro methane (2.4ml) was heated at reflux for 1.5 h. under nitrogen. After the mixture cooled to room temperature, ethyl acetate was added, and the organic phase was washed twice with water and dried (Na₂SO₄). The solvent was evaporated in vacuo to give a residue which was purified by column chromatography (silica gel, from dichloromethane as eluent) followed by crystallized from Mol. Formula = C₁₅H₁₃NO₇, Mol. weight= 319.27, yield % =90.54, Solvent= acetone/ n-hexane. mp= 238- 240°C. IR(cm⁻¹), 1640(C=O) ¹H NMR (*d*, ppm) (DMSO-*d*₆) 7.70, 7.12 (2H, 2d, olefin), 7.58, 6.66 (2H, 2d, H₃, H₂, J = 2.00 Hz), 7.22 (1H, s, H₇), 4.16, 4.09 (6H, 2s, 2OCH₃). Mass (*m/z*), *m/e* = 319.06 (27%), 318.06 (16.06%), 317.05 (100%).

6-(2-aminoethyl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (3):

Compound 2 (0.29g, 1mmol) was added portion wise to a stirred ice- cooled suspension of LiAlH₄ (0.23g, 6mmol) in dry THF (15ml) under nitrogen and the mixture was stirred at room temperature for 5h. The reaction mixture was cooled to 0° C, and then water was added drop wise to destroy the excess hydride, the resulting mixture was filtered off, and the filtrate was concentrated in vacuo and then partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (Na₂SO₄), and then concentrated under reduced pressure to give a crude oily amine which was used without further purification. Mol. Formula = C₁₅H₁₅NO₅, Mol. weight= 289.27, yield % =71.06, mp= 180- 182°C. IR (cm⁻¹), 3422 (brs, NH₂), 1644 (C=O). ¹H NMR (*d*, ppm) (DMSO-*d*₆) 7.57, 6.62 (2H, 2d, H₃, H₂, J = 2.50 Hz), 7.45 (1H, s, H₇), 4.16, 4.09 (6H, 2s, 2OCH₃),

3.23, 2.01 (2H, 2t, ethane), 2.02 (2H, br., 2NH₂). Mass (*m/z*), *m/e*= 291.09 (20%), 290.08 (17.08%), 289.10 (100%).

1-(6-chloro or bromopyridin-2-yl)-3-[2-(4, 9-dimethoxy-5-oxo-5H-furo [3, 2-g] chromen-6-yl) ethyl] thiourea (10a, b):

Route A. General Procedure.

To a suspension of compounds 4a, b (1.1 equiv) in acetonitrile or DMF, (2ml/ mmol) was added furochromenethylamine 3 (1 equiv). The reaction mixture was heated to 80- 110⁰C for 12-15 h and cooled to room temperature. The reaction mixture was worked up, and the crude material was purified by recrystallization.

N-(5-chloro or-bromopyridin-2-yl)-2,3-dihydro-1H-imidazole-1-carbothioamide 4a,b:

A solution of 1,1'-thiocarbonyldiimidazole 8 (4.95g, 25mmol) and 2-amino-5-chloropyridine or 2-amino-5-bromopyridine 6a,b (3.55,4.46g, 25mmol) in acetonitrile (75mL) was stirred at room temperature for 23h. the resulting precipitate was collected by filtration to provide 5.63, 5.42 g (77%, 76%) of the title product: ¹H-NMR (300MHz, DMSO-d₆) δ 8.57(m, 1H), 8.30(m, 1H), 8.15 (m, 1H), 8.03 (br s, 1H), 7.75 (m, 1H), 7.15 (d, 1H), 6.80 (s, 1H)

Route B. General Procedure:

Method A:

A solution of 1, 1'-thiocarbonyldiimidazole 8 (1 equiv) and furochromenethylamine 3 (1 equiv) in acetonitrile (4 ml/ mmol) was stirred at room temperature for 1h. The solution was evaporated and the residue dissolved in DMF (4ml/mmol). Amino pyridine derivatives (1 equiv) was added as a solid and the solution was stirred at 95⁰C for 24h. The reaction mixture was cooled to room temperature, poured into ethyl acetate, and washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated and the residue purified by triturating in dichloromethane.

Method B:

A solution of furochromenethylamine derivative 3 (1 equiv) in acetonitrile (2 ml/mmol) was added to a stirred solution of 1, 1'-thiocarbonyldiimidazole 8 (1.03 equiv) in acetonitrile (3 ml/mmol) at room temperature. The solution was stirred at room temperature for 1 h, and the solvent was evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/ hexanes, 1:1) to provide pure furochromenethyl Isothiocyanate 5. Sodium hydride (1 equiv) was added to a solution of amino pyridine 6a, b (1 equiv) in THF at 0 °C under N₂. The reaction mixture was stirred at 0°C for 30 min. furochromenethyl Isothiocyanate 5 (1 equiv) in THF was added, and the reaction mixture was allowed to reach room temperature and then stirred overnight. Saturated ammonium chloride and diethyl ether was added, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by recrystallization.

Route C. General Procedure:

Furochromenethylamine 3 (1 equiv) and compound 7 (1 equiv) in acetonitrile (2 ml/mmol) were stirred at room temperature for 0.5 h. The mixture was filtered. The precipitate was dried and recrystallized from acetonitrile.

2-(5-Chloropyridyl) Isothiocyanate 7:

2-Amino-5- chloropyridine 6a (10.28 g) was added in portions, with stirring, over a period of 25 min to a solution of 1,1- thiocarbonyldiimidazole 8 (14.26 g) in acetonitrile (100 ml) at room temperature, stirring was continued, and the solution/suspension was left for a few hours. The precipitate was filtered and washed with acetonitrile (3- 25 ml). The solid residue was dissolved in hot acetone and filtered. The acetone solution was evaporated in vacuo, and the residue was dissolved in hot ethyl acetate and filtered through a pad of silica (diameter 7 cm. 3cm). The silica was washed with another portion of hot ethyl acetate. The combined solutions were evaporated in vacuo to yield a crude product (5 g) of the title product: ¹H NMR (250 M Hz, DMSO-*d*₆) 7.54 (1H, d), 8.17 (1H, 2d), 8.63 (1H, d).

Route D. General Procedure:

Furochromenethylamine 3 (1 equiv) in acetonitrile was added drop wise to a solution of 1, 1- thiocarbonyldiimidazole 8 in acetonitrile at 0°C during 20 min. The reaction mixture was allowed to reach room temperature. The solvent was evaporated. Amino pyridine (1.2 equiv) in DMF was added, and the mixture was stirred at 100°C for 15 h. The reaction mixture was cooled to room temperature the organic layer was washed with dilute HCl, water, and chromatography on silica gel. brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by Compound 10a, Mol. Formula = C₂₁H₁₈ClN₃O₅S, Mol. weight= 459.90, yield % =61.50, Solvent= dichloromethane, mp= -171- 180°C · IR(cm⁻¹), 3297, 3220 (NH),1644 (C=O),1250 (C=S). ¹H NMR (*d*, ppm) (DMSO-*d*₆), 7.62, 6.64 (2H, 2d, H₃, H₂, J = 2.50 Hz), 7.75 (1H, t, pyridine₄), 6.92-6.09 (2d, 2H, pyridine H_{3,5}), 7.08 (1H, s, H₇), 4.01, 3.98 (6H, 2s, 2OCH₃), 3.49, 2.22 (4H, tt, ethane) 4.00, 2.11 (2H, 2s, 2NH exchangeable D₂O), 3.83, 3.66 (2H, t, J = 2.4 Hz, CH₂), 2.22, 2.18 (2H, t, J = 2.4 Hz, CH₂). Mass (*m/z*), *m/e* = 459.07 (33%), 460.07 (20.0%), 461.06 (22. 4%), 312 (44), 205 (100).

Compound 10b, Mol. Formula = C₂₁H₁₈ BrN₃ O₅S, Mol. weight=504.35, yield % =39.98, solvent= acetonitrile, mp= 174- 177°C. IR (cm⁻¹), 3250, 3174 (NH), 1646 (C=O), 1268 (C=S). ¹H NMR (*d*, ppm) (DMSO-*d*₆), 7.62, 6.64 (2H, 2d, H₃, H₂, J = 2.50 Hz), 7.65 (1H, t, pyridine₄), 7.09-6.81 (2H, 2d, pyridine H_{3,5}), 7.08 (1H, s, H₇), 4.01, 3.98 (6H, 2s, 2OCH₃), 3.49, 2.22 (4H, 2t, ethane), 4.00, 2.11 (2H, 2s, 2NH exchangeable D₂O), 3.83, 3.66 (2H, t, J = 2.4 Hz, CH₂), 2.22, 2.18 (2H, t, J = 2.4 Hz, CH₂), Mass (*m/z*), *m/e* = 505.01 (33%), 504.02 (22.3%), 503.02 (41.5%), 312 (62), 205 (100).

1-(4-methyl, bromo or methoxyphenyl)-3-[2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)ethyl]thiourea 11a-c :

A solution of furochromenethyl amine derivative 3 (1 equiv) in acetonitrile (2 ml/mmol) was added to a stirred solution of 1, 1-thiocarbonyldiimidazole 8 (1.03 equiv) in acetonitrile (3 ml/mmol) at room temperature. The solution was stirred at room temperature for 1 h, and the solvent was evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/ hexanes, 1:1) to provide pure furochromenethyl Isothiocyanates 5. Sodium hydride (1 equiv) was added to a different amines (p-toludine- p- Bromoaniline and p- anisidine) (1 equiv) in THF at 0 °C under N₂. The reaction mixture was stirred at 0°C for 30 min. furochromenethyl Isothiocyanates 5 (1 equiv) in THF was added, and the reaction mixture was allowed to reach room temperature and then stirred overnight. Saturated ammonium chloride and diethyl ether was added, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by recrystallizations.

furochromenethyl Isothiocyanates 5

2-Amino- furochromenethyl 3 (10.28 g) was added in portions, with stirring, over a period of 25 min to a solution of thiocarbonyldiimidazole (14.26 g) in acetonitrile (100 ml) at room temperature. The stirring was continued, and the solution/suspension was left at room temperature for a few hours. The precipitate was filtered and washed with acetonitrile (3 - 25 ml). The solid residue was dissolved in hot acetone and filtered. The acetone solution was evaporated in vacuo, and the residue was dissolved in hot ethyl acetate and filtered through a pad of silica (diameter 7 cm - 3 cm). The silica was washed with another portion of hot ethyl acetate. The combined solutions were evaporated in vacuo to yield a crude product (5 g), poured into ice. The organic layer was washed with dilute HCl, water, and brine, dried over anhydrous sodium sulfate, and concentrated. The product was purified by chromatography on silica gel.

1-(2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6yl)ethyl)-3-p-tolylthiourea 11a

Mol. Formula = C₂₃H₂₂N₂O₅S, Mol. weight= 438. 5, yield % =56.50, mp= 214- 216°C, IR (cm⁻¹), 3234, 3200 (NH), 1642 (C=O), 1287 (C=S). ¹H NMR (*d*, ppm) (DMSO-*d*₆), 7.52, 6.64 (2H, 2d, H₃, H₂, J = 2.50 Hz), 7.12 (1H, s, H₇), 6.85-6.33 (4H, 2d, Ar.), 4.00, 3.99 (6H, 2s, 2OCH₃), 4.00, 2.10 (2H, 2s, 2NH exchangeable D₂O), 3.64, 2.00 (4H, 2t, ethane), 2.35(3H, s, CH₃), mass (*m/z*), *m/e* = (438.12): *m/z*: (%) = 440.12 (6.5), 439.13(22.7), 438.02 (40), 312 (50), 205 (100).

1-(4-bromophenyl)-3-(2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)ethyl)thiourea 11b

Mol. Formula = C₂₂H₁₉ BrN₂O₅S, Mol. weight= 503.37, yield % =44.00, mp= 208- 211 °C. IR(cm⁻¹), 3222, 3219 (NH), 1640 (C=O), 1276 (C=S). ¹H NMR (*d*, ppm) (DMSO-*d*₆), 7.52, 6.64 (2H, 2d, H₃, H₂, J = 2.50 Hz), 6.98 (1H, s, H₇), 7.18-6.35 (4H, 2d, Ar.), 4.02, 3.99 (6H, 2s, 2OCH₃), 4.00, 2.00 (2H, 2s, 2NH exchangeable D₂O), 3.49, 2.22 (4H,

2t, ethane), mass (m/z), $m/e = (502.02): m/z: (%) = 504.02 (60), 502.02(46.9), 503.02 (24), 312 (35), 205 (100).$

1-(2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)ethyl)-3-(4-methoxy phenyl) thiourea 11c

Mol. Formula = $C_{23}H_{22}N_2O_6S$, Mol. weight= 454.50, yield % =50.05, mp= 198- 201 °C, IR(cm^{-1}), 3229, 3215 (NH), 1633 (C=O), 1288 (C=S). 1H NMR (d , ppm) (DMSO- d_6), 7.52, 6.60 (2H, 2d, $H_2, H_3, J = 2.50$ Hz), 7.08 (1H, s, H_7), 6.52-6.35 (4H, 2d, Ar.), 3.99, 3.98 (6H, 2s, $2OCH_3$), 4.00, 2.00 (2H, ss, 2NH exchangeable D_2O), 3.48, 2.12 (4H, tt, ethane), (3H, s, OMe). Mass (m/z), $m/e = 454.12 (70), 455.12 (26.3), 456.02 (33), 312 (65), 205 (90).$

1-(4- ethyl or chlorophenyl)-3- (2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl) ethyl)urea/ thiourea (13a-d)

To a suspension of compound 3 (0.01 mol) are treated with an equimolar amount of the appropriate isocyanate/ Isothiocyanates, namely (ethyl-, and p- chlorophenyl isocyanate/ isothiocyanates) 12a-d (0.01 mol) in dioxane (50ml) under reflux at 80°C for 1h (after few minutes crystals began to separated) and then at 25°C for 1h. After a few hours the separated crystals were filtrated off, and washed with dioxane and ethanol.

Compound 13a: Mol. Formula = $C_{18}H_{20}N_2O_6$, Mol. weight= 360.36, yield % =66.33, mp= 176- 178 °C IR(cm^{-1}), 3353, 3251 (NH), 1620 (C=O). 1H NMR (d , ppm) (DMSO- d_6), 7.50, 6.87 (2H, 2d, $H_3, H_2, J = 2.50$ Hz), 6.99 (1H, s, H_7), 4.00, 3.98 (6H, 2s, $2OCH_3$), 3.23, 2.10 (2H, 2s, 2NH exchangeable D_2O), 3.20, 2.00 (4H, 2t, ethane), 3.00, 1.27 (5H, qt, ethane). Mass (m/z), $m/e = m/z: (%) = 362.14 (3.1), 361.14(16.9), 360.13 (44), 312 (65), 205 (100).$

Compound 13b: Mol. Formula = $C_{18}H_{20}N_2O_5S$, Mol. weight= 376.43, yield % =43.65, mp= 142- 145 °C IR(cm^{-1}), 3247, 3276 (NH), 1632 (C=O), 1265 (C=S). 1H NMR (d , ppm) (DMSO- d_6), 7.55, 6.69 (2H, 2d, $H_3, H_2, J = 2.50$ Hz), 7.00 (1H, s, H_7), 4.00, 3.98 (6H, 2s, $2OCH_3$), 3.99, 2.11 (2H, 2s, 2NH exchangeable D_2O), 3.20, 2.22 (4H, 2t, ethane), 3.32, 1.33 (5H, qt, ethane). Mass (m/z), $m/e = 378.11 (6.9), 377.11(20.9), 376.02 (33), 312 (30), 205 (100)$

Compound 13c: Mol. Formula = $C_{22}H_{19}ClN_2O_6$, Mol. weight= 442.09, yield % =73.21, mp= 238- 240 °C IR(cm^{-1}), 3305, 3242 (NH), 1640 (C=O). 1H NMR (d , ppm) (DMSO- d_6), 7.55, 6.69 (2H, 2d, $H_3, H_2, J = 2.50$ Hz), 7.28 (1H, s, H_7), 7.15-6.33 (4H, 2d, Ar.), 4.01, 3.99 (6H, 2s, $2OCH_3$), 4.00, 2.00 (2H, 2s, 2NH exchangeable D_2O), 3.44, 2.10 (4H, 2t, ethane). Mass (m/z), $m/e = 444.09 (33), 443.10(22.10), 442.09 (20), 312 (25), 205 (100)$

Compound 13d: Mol. Formula = $C_{22}H_{19}ClN_2O_5S$, Mol. weight=458.91, yield % =57.41, mp= 248- 250 °C, IR(cm^{-1}), 3324, 3245 (NH), 1623 (C=O), 1253 (C=S). 1H NMR (d , ppm) (DMSO- d_6), 7.57, 6.99 (2H, 2d, $H_3, H_2, J = 2.50$ Hz), 7.08 (1H, s, H_7), 7.08-6.34 (4H, 2d, Ar.), 4.05, 3.98 (6H, 2s, $2OCH_3$), 4.01, 2.11 (2H, 2s, 2NH exchangeable D_2O),

3.45, 2.20 (4H, 2t, ethane). Mass (m/z), m/e = 460.07(3.4), 459.07 (35), 458.02(43.3), 503.02 (30), 312 (76), 205 (94).

1-[2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)ethyl]urea 15

A solution of potassium cyanate 14 (0.022mol) in water (10ml) was added drop wise within 15 minutes, under stirring, at 0°C to a compound 3 (0.02 mol) in a mixture of acetic acid (40 ml) and water (40 ml). After about 10 minutes, white crystals began to separate from the solution. The reaction mixture was stirred at 20- 25°C for 3hrs. The precipitate was filtered off, and washed with water and ethanol for the physical data and analytical results of the semicarbazide 15. Mol. Formula = C₁₆H₁₆N₂O₆, Mol. weight= 332.31, yield % =62.15, Solvent= Ethanol/ water, mp= 194- 195, , IR(cm^{-1}), 3300, 3221 (NH), 1623 (C=O),. ¹H NMR (*d*, ppm) (DMSO-*d*₆), 7.34, 6.99 (2H, 2d, H₃, H₂, J = 2.50 Hz), 7.00 (1H, s, H₇), 4.00, 3.98 (6H, 2s, 2OCH₃), 3.20, 2.22 (4H, tt, ethane), 6.00 (3H, s, br, NH, NH₂ exchangeable D₂O),. Mass (m/z), m/e = 334.11 (2.7), 333.10 (18.00), 332.10 (100), 312 (60), 205 (100).

References

- [1] O. D'Cruz, Uckun F. M, *Current HIV Research* , **2006**, 4, 3, 329-45.
- [2] K.D. Hargrave, J.R. Proudfoot, K.G. Grozinger, E. Cullen, S.R. Kapadia, U.R. Patel, V.U. Fuchs, S.C. Mauldin, J. Vitous, M.L. Behnke, J.M. Klunder, K. Pal, J.W. Skiles, D.W. McNeil, J. J.M. Rose, G.C. Chow, M.T. Skoog, J.C. Wu, G. Schmidt, W.W. Engel, W.G. Eberlein, T.D. Saboe, S.J. Campbell, A.S. Rosenthal, J. Adams, *J. Med. Chem.*, **1991**, 34, 2231-2241.
- [3] E. Sandström, B Öberg, Antiviral Therapy in Human Immunodeficiency Virus Infections, Part 1. Drugs, **1993**, 45, 4, 488- 508.
- [4] *Antiviral agents Bull*, **1994**, 7, 6, 161.
- [5] Staduvine approved in the US. Scrip, **1994**, 1937, 23.
- [6] C. Ahgren, K. Backro, F.W. Bbll, A.S. Cantrell, M. Clemens, J.M. Colacino, J.B. Deeter, J.A. Engelhardt, M. Hogberg, S.R. Jaskunas, N.G. Johansson, C.L. Jordan, J.S. Kasher, M.D. Kinnick, P. Lind, C. Lopez, J.M. Morin, J.R. Muesing, R. Noreen, B. Oberg, C.J. Paget, J.A. Palkowitz, C.A. Parrish, P. Pranc, M.K. Rippy, C. Rydergard, C. Sahlberg, S. Swanson, R.J. Ternansky, T. Unge, R.T. Vasileff, L. Vrang, S.J. West, H. Zhang And X. Zhou, *Antibacterial Agents and Chemotherapy*, **1995**, 39, 6, 1329–1335.

- [7] O. D'Cruz, T.K. Venkatachalam, Mao Ch., S. Qazi and F.M. Uckun, *Biology of reproduction*, **2002**, 67, 1959–1974 .
- [8] N.M. Fawzy, *J. Heterocyclic. Communication*, **2008**, 169-182.
- [9] A.S. Cantrell, P. Engelhardt, H. Marita, *Journal of Medicinal Chemistry*, **1996**, 39, 21, 4261- 4274.
- [10] G. Spadoni, C. Balsamini, A. Bedini, G. Diamantini, B. Di Giacomo, A. Tontini and G. Tarzia G, *J. Med. Chem.* **1998**, 41, 19, 3624- 3634.
- [11] J.M. Nulty, J.A. Steere and S. Wolf, *Tetrahedron Letters*, **1998** , 39, 8013- 8016.
- [12] Vogel's Textbook of Practical Organic Chemistry, 4th ed.; Longman: London and New York, **1978**, 796.
- [13] J.C. Jochims, A. Seeliger, *Angew. Chem.*, **1967**, 79.
- [14] L. Shenquan, T. Cheng, H. Bin, A. Micheal, E.S. Carsten and C.A. Micheal , *J. Med. Chem.* **1998**, 41, 4693- 4705.
- [15] S. Bondock, W. Khalifa, A.A. Fadda, *European Journal of Medicinal Chemistry*, **2007**, 42, 948- 954.
- [16] A.A. Kadi, N.R. El-Brollosy, O. Al-Deeb, E.E. Habib, T.M. Ibrahim, A.A. El-Emam, *European Journal of Medicinal Chemistry*, **2007**, 42 , 235-242.
- [17] C. Neochoritis, C.A. Tsoleridis and S.J. Stephanidou, *Tetrahedron*, **2008**, 64, 16, 3527-3533.
- [18] M. Balogh, I. Hermech, Z. Mészáros and L. Pusztay, *J. Heterocyclic Chem.*, **1980**, 17, 175-179.
- [19] A.A. El- Emam and J. Lehmann, *Monatshefte für Chemie*, **1994**, 125, 587- 591.