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Synthesis, reactions of 1,2,3,4-tetrahydropyrimidin-2(1*H*)-thione derivatives and *in-vitro* screening for antibacterial and anticancer

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ABSTRACT

The bi-functional 2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **2a-d** were prepared by the reaction of ethyl acetoacetate and thiourea or urea with aldehydes using NH_4Cl as a catalyst. Reaction of compounds **2a,c** with mono and bi-halogenated compounds depends on the reaction conditions and the strength of the base used. While **2a,c** and **7** were allowed to react with p-fluorobenzaldehyde, yielded the corresponding products **10a,b and 11** respectively. Oxidation of **2a-c** gave compounds **2b**, **13-16** dependent on the oxidizing agent used. Chlorination of **2a,c** gave the chlorinated derivative **18a,b** which reacted with thiourea to give thioureidopyrimidine **19a,b**. Reactions of **2a,c** with hydrazine monohydrated, semicarbazide hydrochloride, sodium hydroxide and $POCl_3$/DMF were also investigated. Microbiological and pharmacological results indicated that the synthesized compounds possess a broad spectrum of activity. The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Introduction

Tetrahydropyrimidinone and tetrahydropyrimidinethione derivatives have broad biologically activities. Many synthetic samples have been studied as antibacterial, antiviral, antihypertensive, and anticancer agents [1], and the natural products containing these heterocyclic moieties have been studied as new leads for AIDS therapies [2]. The Biginelli reaction of a β-keto ester, an aldehyde, and urea or thiourea is considered as one of the most efficient ways to synthesize tetrahydropyrimidinones and tetrahydropyrimidinthiones [3-5]. So it was planned to synthesize 1,2,3,4-tetrahydropyrimidin-2(1*H*)-ones and 1,2,3,4-tetrahydropyrimidinethione derivatives and to check their activities as antimicrobial activity, antioxidant and anticancer agents.

Materials and Methods

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3-300 infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were run at 300, 75 MHz, on a Varian Mercury VX-300 NMR spectrometer respectively, using TMS as internal standard in deuterated chloroform or deuterated dimethylsulphoxide. Chemical shifts are quoted δ in ppm and J in Hz. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70e.V. All the spectral measurements as well as elemental analyses were carried out at the Micro analytical Center of Cairo University, Egypt. The antimicrobial activities were carried out at AL-Azhar University, Faculty of Science, Fermentation Biotechnology and Applied Microbiology (Ferm-BAM) Center, Egypt. The pharmacological activities were carried out at, pharmacology Department, Faculty of Pharmacy, Mansoura University, Egypt. All the chemical reactions are monitored by TLC. All the newly synthesized compounds gave satisfactory elemental analyses (± 0.2%).

Ethyl4-aryl-6-methyl-2-thioxo/oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a-d)

A mixture of aromatic aldehyde such as piperonal and / or 3,4-dimethoxybenzaldehyde (40 mmol), thiourea and / or urea (60 mmol), ethyl acetoacetate (150 mmol, 2 ml) and ammonium chloride (1.87 mmol, 1g) was heated with stirring at 100 ºC for 4 h. After cooling and poured

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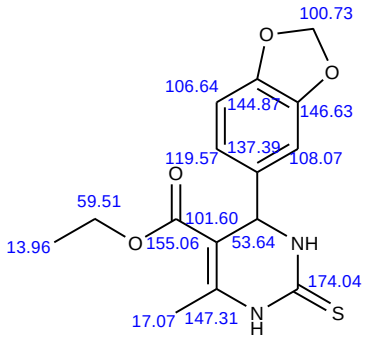
onto ice, the solid product that formed was filtrated out and washed with water, dried and recrystallized from proper solvent to give compounds **2a-d** respectively.

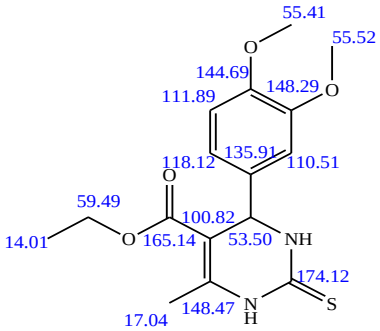
Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate 2a recrystallized from ethanol to afford **2a** as yellow crystals, mp 174-175ºC, yield 98%. FT-IR (KBr, cm^{-1}): 3315, 3180ν_{NH}, 1664$\nu_{C=O}$ (ester), 1334$\nu_{C=S}$.^{1}H NMR (300 MHz, DMSO): δ 1.09-1.19 (t, 3H,-OCH$_2$CH$_3$, J= 6.6Hz), 2.28 (s, 3H, CH$_3$), 3.98-4.05 (q, 2H,-OCH$_2$CH$_3$, J=6.6Hz), 5.08 (s, 1H, benzilic), 5.99 (s, 2H, O-CH$_2$-O), 6.66-6.87 (m, 3H, Ar-H) and 9.57, 10.28 (2s, 2H, exchangeable with D$_2$O, 2NH); MS (EI, m/z(%)): 320 (M+, 100.0), 319 (46.5), 318 (8.6), 292 (14.6), 291 (74.3), 276 (3.3), 275(12.6), 248(14.2), 247(79.9), 232(18.6), 200 (12.2), 199 (73.9),189 (4.6), 188 (15.3), 175 (13.5), 173 (11.5), 172(10.6), 171(29.0),124 (3.1), 123(4.0), 94 (16.6), 93 (10.0), 78 (6.6), 77 (12.4), 51 (14.6), 50 (9.3); Anal. Calc.; $C_{15}H_{16}N_2O_4S$, (320): C, 56.24; H, 5.03; N, 8.74; S, 10.01. Found: C, 56.14; H, 4.99; N, 8.69; S, 10.05; ^{13}C-NMR (75 MHz, DMSO-d_6) is given below.



2a

Ethyl4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 2b recrystallized from ethanol to afford **2b** as yellow crystals, mp 191-192°C, yield 73%. FT-IR (KBr, cm^{-1}): 3245ν_{NH}, 1707$\nu_{C=O}$ (ester), 1646$\nu_{C=O}$ (pyrimidinone). ^{1}H NMR (300 MHz, DMSO): 1.08-1.12 (t, 3H,-OCH$_2$CH$_3$, J=6.9Hz), 2.24(s, 3H, CH$_3$), 3.90-4.00 (q, 2H,-OCH$_2$CH$_3$, J=6.9Hz), 5.07 (s, 1H, benzilic), 5.97 (s, 2H, O-CH$_2$-O), 6.67-7.60(m, 3H, Ar-H), and 7.64, 9.13 (2s, 2H, exchangeable with D$_2$O, 2NH); MS (EI, m/z(%)): 304 (M+, 43.5), 303 (24.9), 302 (4.1), 276 (14.4), 275 (86.0), 258 (22.7), 232 (15.1), 231 (68.6), 230 (26.3),184 (12.1),183 (100.0),182 (55.6), 156 (8.2), 155 (51.7), 138 (6.2), 137 (17.6), 122 (24.7), 121 (24.3), 110 (28.8), 93 (15.3), 94 (11.2); Anal. Calc.; $C_{15}H_{16}N_2O_5$, (304): C, 59.21; H, 5.30; N, 9.21; Found: C, 59.02; H, 5.15; N, 9.05.

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylateand 2c recrystallized from benzene to afforded **2c** as yellow crystals, mp 171-173°C, (lit.[6] mp: 172-174 °C) yield 92%. FT-IR (KBr, cm^{-1}): 3309, 3170ν_{NH}, 1663$\nu_{C=O}$ (ester), 1333$\nu_{C=S}$.^{1}H NMR (300 MHz, DMSO): δ 1.09-1.14 (t, 3H,-OCH$_2$CH$_3$, J=6.6Hz), 2.27 (s, 3H, CH$_3$), 3.71 (s, 6H, 2-OCH$_3$), 3.98-4.05 (q, 2H,-OCH$_2$CH$_3$, J=6.9Hz), 5.12 (s, 1H, benzilic), 6.69-7.35 (m, 3H, Ar-H), and 9.54, 10.24 (2s, 2H, exchangeable with D$_2$O, 2NH); MS (EI, m/z(%)): 336 (M+, 100.0), 308 (13.8), 307 (83.8), 306 (8.9), 290 (14.3), 289 (19.7), 264 (13.4), 263 (91.8), 200 (9.2), 199 (86.1),172 (5.0),171 (31.4),153 (16.2), 154 (3.8), 138 (7.2), 126 (21.2), 78 (45.0), 60 (12.0),53 (9.6), 51(22.7); Anal. Calc.; $C_{16}H_{20}N_2O_4S$, (336): C, 57.12; H, 5.99; N, 8.33; S, 9.53; Found: C, 57.01; H, 5.89; N, 8.19; S, 9.47; ^{13}C-NMR (75 MHz, DMSO-d_6) is given below.



2c

Ethyl4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 2d recrystallized from ethanol to afforded **2d** as white crystals, mp180-182 °C,(lit. [6] mp: 176-177 °C), yield 83%. FT-IR (KBr, cm^{-1}): 3340, 3238ν_{NH}, 1706$\nu_{C=O}$ (ester), 1651$\nu_{C=O}$ (pyrimidinone) .^{1}H NMR (300 MHz, DMSO): δ 1.09-1.13 (t, 3H,-OCH$_2$CH$_3$, J=7.5Hz), 2.24 (s, 3H, CH$_3$), 3.30,3.71 (s, 6H, 2-OCH$_3$), 3.96-4.03 (q, 2H,-OCH$_2$CH$_3$, J=7.5Hz), 5.10 (s, 1H, benzilic), 6.70-7.80 (m, 3H, Ar-H), and 7.64, 9.11 (2s, 2H, exchangeable with D$_2$O, 2NH); MS (EI, m/z(%)): 320 (M+, 52.1), 292 (18.0), 248 (15.0), 247 (71.2), 232 (14.4), 231 (15.0), 218 (2.8), 184 (9.8), 183 (92.1), 138 (41.0),112 (4.7), 96 (17.1), 82 (11.2), 78 (13.3), 77 (48.0), 74 (3.5), 71 (10.5), 70 (10.8), 69 (20.1), 55(23.1); Anal. Calc.; $C_{16}H_{20}N_2O_5$, (320): C, 59.99; H, 6.29; N, 8.74; Found: C, 59.87; H, 6.15; N, 8.65.

Ethyl 6-aryl-2-(ethylthio)-4-methyl-1,6-dihydropyrimidine-5-carboxylate (3a,b)

To a stirred solution of **2a,c** (6.25 mmol) in dry ethanol (25 ml) ethyl iodide (6.22 mmol, 0.47 ml) was added. The reaction mixture was heated under reflux for 6h in the presence of ethanolic potassium hydroxide (5 g/ 25ethanol). The solid product that separated out was left to cool and then acidified with cold hydrochloric acid (2N, 30ml), washed with water (4x30ml), filtered off, dried and then recrystallized to give **3a,b** respectively.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-2-(ethylthio)-4-methyl-1,6-dihydropyrimid-ine-5-carboxylate 3a recrystallized from ethanol /dioxane as brown crystals, mp 270-272°C, yield 71%. FT-IR (KBr, cm^{-1}): 3418 ν_{NH}, 1705 $\nu_{C=O}$ (ester); MS (EI, m/z (%)): 349 (M+1, 27.8), 322 (22.2), 246 (38.2), 200 (33.3), 121 (66.7), 91 (27.8), 85 (38.9), 80 (50.0), 78 (38.9), 76 (38.9),

62 (66.7), 57 (100.0), 55 (100.0), 53 (55.6); Anal. Calc.; $C_{17}H_{20}N_2O_4S$, (348): C, 58.60; H, 5.79; N, 8.04; S, 9.20; Found: C, 58.57; H, 5.65; N, 7.98; S, 9.11.

Ethyl 6-(3,4-dimeth-oxyphenyl)-2-(ethylthio)-4-methyl-1,6-dihydropyrimidine-5-carboxylate 3b recrystallized from ethanol as brown crystals, mp 236-241 °C, yield 60 %. FT-IR (KBr, cm^{-1}): 3536 ν_{NH}, 1708 $\nu_{C=O}$ (ester), 1651 $\nu_{C=N}$; MS (EI, m/z (%)): 364 (M, 00.0), 370 (18.5), 327 (40.7), 324 (18.5), 284 (59.3), 282 (48.1), 236 (29.6), 190 (22.2), 82 (25.9), 78 (33.3), 77 (100.0), 76 (70.4), 74 (25.9); Anal. Calc.; $C_{18}H_{24}N_2O_4S$, (364): C, 59.32; H, 6.64; N, 7.69; S, 8.80; Found: C, 59.19; H, 6.49; N, 7.58; S, 8.72.

Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-2-imino-7-methyl-3,5-dihydro-2*H*-thiazolo [3,2-a]pyrimidine-6-carboxylate 4

A mixture of **2a** (2 mmol, 0.64g) and chloroacetonitrile (3 mmol, 0.2 ml) in dry DMF (30 ml) was heated under reflux for 12h. Most of solvent was evaporated and the reaction mixture was then poured onto ice, the solid product that formed was filtrated off, dried and recrystallized from benzene/ethanol (2:1) to give compound **4** as brown crystals, mp > 300 °C, yield 72**%.** FT-IR (KBr, cm^{-1}): 3428, 3352$\nu_{NH,NH2}$, 1698 $\nu_{C=O}$ (ester), 1650 $\nu_{C=N}$,1600 $\nu_{C=C}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87-0.88 (t, 3H, $OCH_2\underline{CH_3}$), 1.21 (s, 3H, CH_3), 1.96 (s, 1H, NH, exchangeable with D_2O), 2.37-2.74 (dd, 2H, CH_2CN), 4.08-4.21 (q, 2H, $CH_3\underline{CH_2}O$), 5.90 (s, 1H, benzilic), 6.06 (s, 2H, O-CH_2-O), 6.55-6.92(m, 3H, ArH) ; MS (EI, m/z (%)): 359 (M^+, 12.1), 287 (60.6), 286 (22.7), 260 (12.71), 122 (19.7), 82 (19.7), 78 (21.2), 74 (9.1), 73 (27.3), 62 (31.8), 60 (19.7), 59 (21.2), 57 (90.9), 55 (100);Anal. Calc.; $C_{17}H_{17}N_3O_4S$, (359): C, 56.81; H, 4.77; N, 11.69; S, 8.92; Found: C, 56.75; H, 4.71; N, 11.65; S, 8.87.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-1-(3-chloro-2-hydroxypropyl)-2-mercapto-4-methyl-1,6-dihydropyrimidine-5-carboxylate 5

A mixture of **2a** (1 mmol, 0.32g) epichlorohydrin (1.2 mmol, 0.11ml) and potassium carbonate (2 mmol, 0.2g) in dry methanol (20 ml) was stirred at room temperature for 14h, Most of solvent was evaporated and the reaction mixture was then poured onto ice/water, the solid product that formed was filtrated off, dried and recrystallized from benzene to give compounds **5** as white crystals, mp 188-189 °C, yield 45**%.** FT-IR (KBr, cm^{-1}): 3400 ν_{OH}, 3228ν_{NH}, 1705 $\nu_{C=O}$ (ester), 1646 $\nu_{C=N}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17-1.26 (t, 3H, $OCH_2\underline{CH_3}$, J = 6Hz), 1.62 (s, 1H, SH, exchangeable with D_2O), 2.35 (s,3H, CH_3), 2.45-2.61 (m, 2H, NCH_2), 3.41-3.49 (m, 3H, CH_2Cl, $\underline{CH}OH$), 4.05-4.12 (q, 2H, $CH_3\underline{CH_2}O$, J=6Hz), 5.34 (s, 1H, benzilic), 5.56 (s ,1H, OH, exchangeable with D_2O), 5.94 (s, 2H, O-CH_2-O), 6.72-6.81 (m, 3H, ArH), 7.68 (s, 1H, NH, exchangeable with D_2O); MS (EI, m/z (%)): 410 (M-2H, 7.8), 304 (42.2), 275 (100), 232 (20.3), 231 (62.5), 184 (17.2), 183 (84.4), 156 (14.1), 155 (50.0), 122 (28.1), 121 (31.3), 110 (26.6), 94 (12.5), 80 (10.9), 78 (21.9), 77 (34.4), 59 (10.9), 57 (32.8); Anal. Calc.; $C_{18}H_{21}N_2O_5S$ (412.89): C, 52.36; H, 5.13; N, 6.78; S, 7.77; Found: C, 52.30; H, 5.01; N, 6.71; S, 7.70.

Ethyl 1-acetyl-6-(benzo[d][1,3]dioxol-5-yl)-4-methyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylate 6

Method A:

A mixture of **2a** (1 mmol) acetyl chloride and/or acetic anhydride (10 ml) was heated on water bath for 3h, the reaction mixture was cooled, then poured onto ice/water, the solid product that formed was filtrated off, dried and recrystallized from ethanol to give compounds **6** as white crystals, mp 131-133 °C, yield 44**%.** FT-IR (KBr, cm^{-1}): 3244ν_{NH}, 2611ν_{SH}, 1707 $\nu_{C=O}$ (ester), 1659 $\nu_{C=O}$ (amide), 1225 $\nu_{C=S}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27-1.29 (t, 3H, $OCH_2\underline{CH_3}$, J = 6Hz), 1.72 (s, 1H, SH, exchangeable with D_2O), 2.42 (s, 3H, CH_3), 2.54 (s, 3H, CH_3CO), 4.14-4.26 (q, 2H, $CH_3\underline{CH_2}O$, J=6Hz), 5.88 (s, 1H, benzilic), 5.95 (s, 2H, O-CH_2-O), 6.55-6.84 (m, 3H, ArH), 8.46 (s, 1H, NH, exchangeable with D_2O); MS (EI, m/z (%)): 362 (M^+, 5.7), 319 (100), 320 (30.5), 318 (49.2), 246 (24.4), 153 (12.6), 94 (10.2), 77 (12.6),57 (8.5); Anal. Calc.; $C_{17}H_{18}N_2O_5S$ (362.4): C, 56.34; H, 5.01; N, 7.73; S, 8.85; Found: C, 56.29; H, 5.11; N, 7.76; S, 8.80**.**

Ethyl5-aryl-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo [3,2-a]pyrimidine-6-carbo-xylate (7a,b)

Method A:

A mixture of **2a,c** (3 mmol), chloroacetyl chloride (1.2 mmol, 0.95ml) and triethyl amine (1 ml) in dry benzene (30 ml) was heated under reflux for 6h. Most of solvent was evaporated and the reaction mixture was then poured onto ice, the solid product that formed was filtrated off, dried and recrystallized from the proper solvent to give compounds **7a,b** respectively.

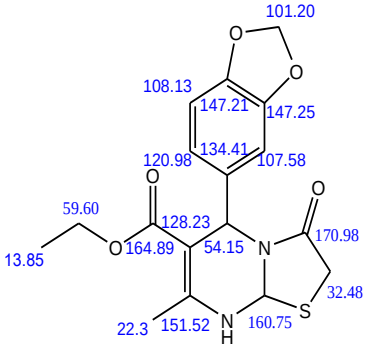
Method B:

A mixture of **2a,c** (10 mmol) in dry acetone and ethyl bromoacetate (10 mmol) was heated on water bath at 80°C for 23 h in the presence of anhydrous potassium carbonate (2.76 g). The most of solvent was evaporated and the reaction mixture was then poured onto ice, the solid product that precipitated out was filtered off, washed with water (3x30ml), dried and then recrystallized from the suitable solvent to give **7a,b**.

Method C:

A mixture of **2a,c** (6.25 mmol) and chloroacetic acid (10 mmol, 0.59 g) in dry DMF (30 ml) was heated at reflux for 2 h. most of solvent was evaporated and the reaction mixture was then poured onto ice, the solid product that formed was filtered off and washed with water (4x30ml), dried and recrystallized from the proper solvent to afford **7a,b**.

Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate 7a recrystallized from light petroleum ether 80-100 / benzene (3:1) as brown crystals, mp 205-206°C, yield79%. FT-IR (KBr, cm^{-1}): 1728, 1694 $\nu_{C=O}$,1652 $\nu_{C=N}$; ^{1}H NMR (300 MHz, DMSO): δ 1.09-1.23 (t, 3H,-$OCH_2\underline{CH_3}$, J=6.0Hz), 2.41 (s, 3H, CH_3), 4.11 (s, 2H, -SCH_2), 4.04-4.07 (q, 2H,-$O\underline{CH_2}CH_3$, J=6.0Hz), 5.80 (s, 1H, benzilic), 6.00 (s, 2H, O-CH_2-O), 6.70-7.36 (m, 3H, Ar-H); MS (EI, m/z(%)): 360 (M+, 46.1), 316 (7.2), 315 (13.9), 288 (21.7), 287 (100.0), 260 (10.6), 259 (26.1), 239 (51.7), 211 (28.9), 165 (12.8), 92 (6.7),78 (31.1),75 (8.9); Anal. Calc.; $C_{17}H_{16}N_2O_5S$, (360): C, 56.66; H, 4.47; N, 7.77; S, 8.90; Found: C, 56.52; H, 4.35; N, 7.65; S, 8.83. ^{13}C-NMR (75 MHz, DMSO) is given below.



Ethyl 5-(3,4-dimethoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate 7b recrystallized from toluene /ethanol (1:1) as dark brown crystals, mp177-178ºC, yield63%. FT-IR (KBr, cm^{-1}): 1737, 1703 $\nu_{C=O}$,1612 $\nu_{C=N}$.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16-1.21 (t, 3H,-$OCH_2\underline{CH_3}$, J=7.2Hz), 2.48 (s, 3H, CH_3), 3.71 (s, 2H, -SCH_2), 3.88 (s, 6H, 2-OCH_3), 4.08-4.13 (q, 2H,-$O\underline{CH_2}CH_3$, J=6.3Hz), 6.03 (s, 1H, benzilic), 6.77-6.91 (m, 3H, Ar-H); MS (EI, m/z(%)): 376 (M+, 35.3), 331 (11.8), 304 (25.5), 303 (100.0), 302 (49.0), 274 (15.7), 238 (27.5), 239 (49.0), 94 (13.7), 90 (19.6), 73 (17.6); Anal. Calc.; $C_{18}H_{20}N_2O_5S$, (376): C, 57.43; H, 5.36; N, 7.44; S, 8.52; Found: C, 57.35; H, 5.28; N, 7.32; S, 8.61.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-2-(2-chloroacetylthio)-4-methyl-1,6-dihydro-pyrimidine-5-carboxylate 8

A mixture of **2a** (1mmol, 0.32g) in ethanol and chloroacetyl chloride (1mmol, 0.79 ml) was refluxed for 3 h in the presence of potassium hydroxide (1mmol, 0.5 g). The solid that precipitated out was filtered off, washed with water (3x30ml), dried and then recrystallized from benzene as brown crystals, mp184-185 ºC, yield 40%. FT-IR (KBr, cm^{-1}): 3229ν_{NH}, 1704, 1646 $\nu_{C=O}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16-1.25 (t, 3H,-$OCH_2\underline{CH_3}$), 2.33 (s, 3H, CH_3), 4.05-4.12 (q, 2H,-$O\underline{CH_2}CH_3$), 5.31 (s, 1H, benzilic), 5.85 (s, 2H, CH_2Cl), 5.93 (s, 2H, -O-CH_2-O), 6.70-6.78 (m, 3H, Ar-H), 8.16 (s, 1H, NH, exchangeable with D_2O); MS (EI, m/z(%)): 396 (M+, 00.0), 362 (1.0), 276 (14.9), 275 (100), 232 (58.6), 231 (58.6), 230 (31.0), 154 (13.0), 78 (42.9), 58 (77); Anal. Calc.; $C_{17}H_{17}ClN_2O_5S$ (396.85): C, 51.45; H, 4.32; Cl, 8.93; N, 7.06; S, 8.08; Found: C, 51.40; H, 4.28; Cl, 8.88; N, 7.00; S, 8.10.

Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-)-7-methyl-2-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate 9

A mixture of **2a** (1mmol, 0.32g) in ethanol and chloroacetyl chloride (1 mmol, 0.79 ml) was refluxed for 15 h in the presence of sodium ethoxide (0.32g/25ml ethanol) The solid that precipitated out was poured on ice/HCl, filtered off, washed with water (3x30ml), dried and then recrystallized from ethanol as brown crystals, mp144-147 ºC, yield 30%. FT-IR (KBr, cm^{-1}): 1720, 1708 $\nu_{C=O,}$ 1617 $\nu_{C=N}$; MS (EI, m/z(%)): 360 (M+, 27.3), 362 (M+2, 9.1), 288 (25.8), 287 (60.6), 122 (19.7), 121 (18.2), 84 (24.2), 73 (27.3), 71 (50.0), 69 (40.9), 57 (90.91), 56 (74.2), 55 (100), 54 (31.8); Anal. Calc.; $C_{17}H_{16}N_2O_5S$, (360): C, 56.66; H, 4.47; N, 7.77; S, 8.90; Found: C, 56.60; H, 4.50; N, 7.72; S, 8.85**.**

3,3'-[(4-Fluorophenyl)methylene]bis-[ethyl4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahy-dropyrimidine-5-carboxylate](10a,b)

A mixture of **2a,c** (6 mmol) and p-fluorobenzaldehyed (3 mmol, 0.34 ml) in acetic acid (15 ml), acetic anhydride (15 ml) in the presence of fused sodium acetate (3 mmol, 2. 50g) was refluxed for 7-9 h, and left to cool. The solid product that formed was filtered off and washed with water (3x30 ml), dried and recrystallised to afford **10a,b** respectively.

3,3'-[(4-Fluorophenyl)methylene]bis-[ethyl4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate] 10a

recrystallised from light petroleum 80-100 / benzene (3:1) as grey crystals, mp 189-190 °C, yield. FT-IR (KBr, cm^{-1}): 3233 ν_{NH}, 1700 $\nu_{C=O}$ (ester),1646 $\nu_{C=N}$.^{1}H NMR (300 MHz, DMSO): δ 1.15-1.21 (t, 6H,2-$OCH_2\underline{CH_3}$, J=6.6Hz), 2.30 (s, 6H, $2CH_3$), 4.07-4.14 (q, 4H, 2-$O\underline{CH_2}CH_3$, J=7.2Hz), 5.98(s, 3H, benzilic), 5.99 (s, 4H, 2-O-CH_2-O), 6.37-6.86 (m, 10H, Ar-H), 10.10 (s, 2H, exchangeable with D_2O, 2NH); MS (EI, m/z(%)): 746 (M+, 00.0), 670 (0.3), 594 (0.7), 346 (17.8), 303 (100.0), 304 (19.3), 302 (15.6), 276 (4.5), 275 (28.0), 274 (13.0), 258 (9.2), 257 (17.0), 227 (15.4), 226 (6.4), 160 (2.0), 135 (1.9), 131 (2.2), 107 (1.2), 103 (6.4), 92 (2.6), 78 (4.5), 63 (12.6), 61 (2.9), 59 (4.2); Anal. Calc.; $C_{37}H_{35}$ $FN_4O_8S_2$, (746): C, 59.50; H, 4.72; F, 2.54; N, 7.50; S, 8.59; Found: C, 59.42; H, 4.68; F, 2.48; N, 7.39; S, 8.45.

3,3'-[(4-Fluorophenyl)methylene]bis-[ethyl4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate] 10b

recrystallized from ethanol as white crystals, mp over 300°C, yield 99%. FT-IR (KBr, cm^{-1}): 3433 ν_{NH}, 1714 $\nu_{C=O}$ (ester), 1640 $\nu_{C=N}$. ^{1}H NMR (300 MHz, DMSO): δ 1.10-1.16 (t, 6H, 2-$OCH_2\underline{CH_3}$, J=7.2Hz), 1.73 (s, 6H,

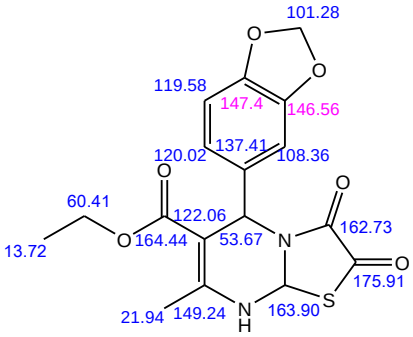
$2CH_3$), 3.73 (s, 12H, $4OCH_3$), 3.99-4.25 (q, 4H,2-$O\underline{CH_2}CH_3$, J=6.9Hz), 4.37, 5.40 (2s, 3H, benzilic), 6.69-7.50 (m, 6H, Ar-H), 9.90, 10.22 (2s, 2H, exchangeable with D_2O, 2NH); MS (EI, m/z(%)): 778 (M+, 00.0), 378 (12.2), 336 (49.0), 335 (100.0), 319 (24.5), 291 (24.5), 290 (8.2), 273 (34.7), 263 (67.3), 261 (20.4), 246 (20.4), 247 (12.2), 230 (22.4), 215(12.2), 153 (10.2), 78 (22.4), 77 (38.8), 60 (40.8), 59 (32.7), 57 (26.5); Anal. Calc.; $C_{39}H_{43}FN_4O_8S_2$, (778): C, 60.14; H, 5.56; F, 2.44; N, 7.19; S, 8.23; Found: C, 60.00; H, 5.45; F, 2.32; N, 6.99; S, 8.12.

3,3'-[(4-Fluorophenyl)methylene]bis-[Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl -3-oxo-3,5-dihydro-2H-thiazolo[3,2-a] pyrimidine-6-carboxylate] 11.

A mixture of **7a** (5.55 mmol, 2 g) in glacial acetic acid (1 ml) acetic acid anhydride (1 ml) and p-fluorobenzaldehyde (5.55mmol , 0.6 ml), in the presence anhydrous zinc chloride (2 g) was heated on oil bath at 110-120 °C for 9 h. The reaction mixture poured on ice, the solid product that separated out was filtered, dried and then recrystallized from ethanol to afford **11** as green crystals, mp 248-250 °C, yield. FT-IR (KBr, cm^{-1}): 3426 ν_{OH}, 1714 $\nu_{C=O}$ (ester),1600 $\nu_{C=N}$.^{1}H NMR (300 MHz, DMSO): δ 1.13-1.34 (t, 6H, 2-$OCH_2\underline{CH_3}$, J=6.6Hz), 2.20 (s, 6H, $2CH_3$), 4.05-4.08 (q, 4H,2-$O\underline{CH_2}CH_3$, J=6.9Hz), 5.90 (s, 3H, benzilic), 6.64 (s, 4H, 2-O-CH_2-O), 6.55-7.81 (m, 10H, Ar-H), 8.97 (br. s, 2H, exchangeable with D_2O, 2OH); MS (EI, m/z(%)):827 (M+1, 37.3), 826 (M+, 43.6), 774 (75.4), 702 (62.7), 701 (13.4), 698 (66.6), 344 (57.9), 330 (52.3), 285 (51.5), 257 (50.7), 140 (83.3), 113 (15.0), 103 (40.4), 93 (100.0), 71 (29.3), 50 (31.75); Anal. Calc.; $C_{41}H_{35}FN_4O_{10}S_2$, (826): C, 59.55; H, 4.27; F, 2.30; N, 6.78; S, 7.76; Found: C, 59.46; H, 4.14; F, 2.21; N, 6.63; S, 7.68.

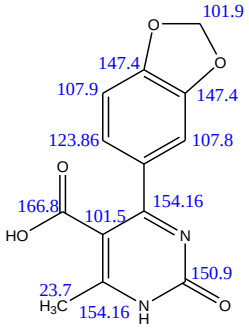
Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-7-methyl-2,3-dioxo-3,5-dihydro-2*H*-thiazolo [3,2-a]pyrimidine-6-carboxylate 12.

A solution of **2a** (1 mmol, 0.32g) in dry benzene (15ml) was stirred at room temperature for 10 minutes in the presence of triethyl amine then the solution of oxalyl chloride (1 mmol, 0.09g) in dry benzene (15ml) was added dropwise during 30 minutes stirring. After this the mixture was refluxed for 14 h and then left over night. The solid product that precipitated down was collected and recrystallized from petroleum ether 40-60 to afford **12** as Yellow crystals, mp 129-130 ^oC, yield 52 %. FT-IR (KBr, cm^{-1}): 1710, 1754 $\nu_{C=O}$, 1619 $\nu_{C=N}$.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16-1.29 (t, 3H,$OCH_2\underline{CH_3}$,J=6Hz), 2.54 (s, 3H,CH_3), 4.07-4.22 (q, 2H,$O\underline{CH_2}CH_3$,J=6Hz), 5.95 (s,1H, benzilic), 6.07 (s, 2H, O-CH_2-O), 6.70-7.30 (m, 3H, ArH); MS (EI, m/z (%)): 376 (M+2, 6.44), 374 (M^+, 79.07), 330 (2.08), 320 (61.81), 319 (13.82), 318 (34.20), 317 (40.36), 316 (1.01), 291 (41.05), 274 (22.66), 214 (12.77), 213 (39.46), 200 (5.90), 173 (11.38), 172 (9.41), 171 (12.52), 122 (10.20), 121 (11.69), 116 (5.60), 115 (16.58); Anal. Calc.; $C_{17}H_{14}N_2O_6S$ (374): C, 54.54, H, 3.77, N, 7.48, S, 8.57; Found C, 54.49, H, 3.69, N, 7.38, S, 8.62. ^{13}C-NMR (75 MHz, $CDCl_3$) is given below.



4-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid 13.

A mixture of **2b** (7.23 mmol, 2.20 g) in acetone (10 ml) potassium permanganate (12.6 mmol, 2 g) in water (70 ml) was heated under reflux for 4 h, then a brown suspension was produced. The brown MnO_2 was filtered off; and the filtrate was collected, neutralized by using 2N hydrochloric acid (20ml). The solid product that formed was filtered off, dried and recrystallized from ethanol to afford **13** as brown crystals, mp 233-232°C, yield %. FT-IR (KBr, cm^{-1}): 3379, 3335 ν_{OH} & ν_{NH}, 1711$\nu_{C=O}$ (acid),1674$\nu_{C=O}$.^{1}H NMR (300 MHz, DMSO): δ 2.08 (s, 3H, CH_3), 6.12 (s, 2H, O-CH_2-O), 6.99-7.02 (d,1H, Ar-H), 7.31 (s,1H, exchangeable with D_2O, OH enol), 7.52 (s, 1H, Ar-H), 7.59-7.62 (d, 1H, Ar-H), 8.04 (s,1H, exchangeable with D_2O,NH), 10.32 (s,1H, exchangeable with D_2O, COOH); MS (EI, m/z(%)): 274 (M, 0.00), 260 (11.05), 229 (13.79), 176 (10.47), 173 (12.21), 150 (22.87), 149 (100), 142 (10.47), 121 (41.47), 121 (41.47), 120 (12.02), 98 (10.66), 94 (11.63), 74 (13.76), 70 (16.67), 59 (15.12); Anal.Calc.;$C_{13}H_{10}N_2O_5$, (274): C, 56.94; H, 3.68; N, 10.22; Found: C, 56.89; H, 3.63; N, 10.17.^{13}C-NMR (75 MHz, DMSO-d_6) is given below.



Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-2-(4-(benzo[d][1,3]dioxol-5-yl)-5-(ethoxycarb-onyl)-6-methyl-3,4-dihydropyrimdin-2-yloxy)-6-methyl-3,4-dihydropyrimidine-5-carboxylate 14.

A mixture of **2a** (5 mmol, 1.6 g) in 1,4 dioxan (7.5 ml), 30% hydrogen peroxide (10 mmol, 1.1 ml) and selenium dioxide (0.25 mmol, 0.28 g) were stirred under reflux

of 6 h. The most of solvent was evaporated and the reaction mixture was then poured onto ice, the solid product that formed was filtered off and washed with water (4x20 ml), recrystallized from petroleum ether 40-60/benzene to afford **14** as brown crystals, mp 155-158°C, yield 18%. FT-IR (KBr, cm^{-1}): 3222ν_{NH}, 1708$\nu_{C=O}$, 1642 $\nu_{C=N}$; ^{1}H NMR (300 MHz, DMSO): δ 1.08-1.22 (t, 6H, 2-OCH$_2$CH$_3$, J=6.3Hz), 2.30 (s, 6H, 2CH$_3$), 3.99-4.27 (q, 4H, 2-OCH$_2$CH$_3$, J=6.8Hz), 5.48 (s, 2H, benzilic), 5.97 (s, 4H, 2-O-CH$_2$-O), 6.69-6.99 (m, 6H,Ar-H), 9.10 (s, 2H, exchangeable with D_2O, 2NH); MS (EI, m/z (%)): 590 (M, 0.00), 588 (4.3), 288 (38.3), 260 (25.5), 259 (100.0), 215 (51.1), 122 (34.0), 121 (44.7), 110 (14.9), 96 (29.8), 95 (48.91), 94 (40.40), 87 (21.3), 78 (17.0), 77 (44.7), 59 (17.0) ; Anal. Calc.; $C_{30}H_{30}N_4O_9$, (590): C, 61.01; H, 5.12, N, 9.49; Found: C, 61.15; H, 5.01, N, 9.30.

Ethyl 4-aryl-2-(4-aryl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimdin-2-yldi-thio)-6-methyl-3,4-dihydropyrimidine-5-carboxylate 15a,b

A mixture of **2a,c** (10 mmol) and sodium nitrite (50 mmol, 1g) in acetic acid (20 ml) was stirred at room temperature for 2 h. The reaction mixture was then poured onto ice, the solid product that formed was filtered off, washed with water (4x30ml), dried and then recrystallised to give **15a,b** respectively.

Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-2-(4-(benzo[d][1,3]dioxol-5-yl)-5-(ethoxycarb-onyl)-6-methyl-3,4-dihydropyrimdin-2-yldithio)-6-methyl-3,4-dihydropyrimidine-5-carboxylate 15a recrystallised from light petroleum ether 80-100/benzene (1:1) as yellow crystals, mp 129-130 °C, yield 35%. FT-IR (KBr, cm^{-1}): 1707 $\nu_{C=O}$ (ester), 1644 $\nu_{C=N}$.^{1}H NMR (300 MHz, DMSO): δ 1.10-1.13 (t, 6H, 2-OCH$_2$CH$_3$), 2.04 & 2.07 (2s, 6H, 2CH$_3$), 3.51-4.00 (q, 4H, 2-OCH$_2$CH$_3$), 5.97 (s, 4H, 2-O-CH$_2$-O), 6.73-6.83 (m, 6H, Ar-H); MS (EI, m/z(%)):638 (M, 0.0), 590 (25.0), 589 (20.8), 304 (29.2), 276 (16.7), 275 (33.3), 230 (16.7), 229 (29.2), 214 (33.3), 170 (41.7), 103 (29.2), 77 (62.5), 74 (33.3), 71 (41.7), 60 (83.3), 57 (100.0); Anal. Calc.; $C_{30}H_{30}N_4O_8S_2$, (638.15): C, 56.41; H, 4.73; N, 8.77; S, 10.04; Found: C, 56.33; H, 4.59; N, 8.68; S, 9.97.

Ethyl 4-(3,4-dimethoxyphenyl)-2-(4-(3,4-dimethoxyphenyl)-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimdin-2-yldithio)-6-methyl-3,4-dihydropyrimidine-5-carboxylate 15b recrystallized from petroleum ether 40-60°C as yellow crystals, mp 133-135°C, yield 42%. FT-IR (KBr, cm^{-1}): 1706 $\nu_{C=O}$ (ester), 1632 $\nu_{C=N}$.^{1}H NMR (300 MHz, DMSO): δ 1.14-1.20 (t, 6H, 2-OCH$_2$CH$_3$), 1.99 (s, 6H, 2CH$_3$), 3.70 (s, 12H, 4-OCH$_3$), 4.02-4.23 (q, 4H, 2-OCH$_2$CH$_3$), 6.41-7.19 (m, 6H, Ar-H); MS (EI, m/z(%)): 670 (M, 00.0), 612 (7.0), 580 (5.6), 398 (7.0), 224 (18.3), 147 (19.7), 105 (100.0), 90 (21.1), 78 (9.9), 74 (4.2), 64 (14.1), 63 (5.6); Anal. Calc.; $C_{32}H_{38}N_4O_8S_2$, (670): C, 57.30; H, 5.71; N, 8.35; S, 9.56; Found: C, 57.21; H, 5.67; N, 8.24; S, 9.45.

Reaction of ethyl 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetra-hydropyrimidine-5-carboxylate 2a with potassium dichromate; Formation of 16

A mixture of **2a** (3.12 mmol), potassium dichromate (3.06 mmol, 0.91 g) and acetic acid (15 ml) in the presence of concentrated sulphuric acid (97%, 1ml) was heated at 70-80°C, on water bath with stirring, then reaction mixture was poured onto ice, the solid product that formed was filtered off and washed with water (3x40ml), dried and recrystallized from methanol to afford **16** as brown crystals, mp over 300°C, yield. FT-IR (KBr, cm^{-1}): 3239 ν_{NH}, 1701$\nu_{C=O}$ (ester),1036 $\nu_{S=O}$.^{1}H NMR (300 MHz, DMSO): δ 1.10 (t, 6H, 2-OCH$_2$CH$_3$), 2.24 (s, 6H, 2CH$_3$), 3.95-4.23 (q, 4H, 2-OCH$_2$CH$_3$), 5.20 (s, 2H, benzilic), 5.90 (s, 4H, 2-O-CH$_2$-O), 6.62-6.92 (m, 6H, Ar-H), 9.25 (s, 2H, exchangeable with D_2O, 2NH); MS (EI, m/z(%)): 670 (M, 00.0), 272 (23.1), 162 (19.2), 135 (19.2), 105 (100), 106 (19.2), 92 (19.2), 77 (84.6), 64 (100.0), 51 (80.8); Anal. Calc.; $C_{30}H_{30}N_4O_{10}S_2$, (670): C, 53.72; H, 4.51; N, 8.35; S, 9.56; Found: C, 53.65; H, 4.43; N, 8.22; S, 9.42.

6-Aryl-1-formyl-4-(2-oxoethylidene)-2-thioxo-hexahydropyrimidine-5-carboxylic acid 17a,b

$POCl_3$ (4mmol, 0.69gm) was added to cooled DMF (1.603mmole, 0.117gm,) at 0°C, a solution of **2c** in DMF (10ml) was added dropwise, the reaction was heated on water bath at 65-70°C for 4 hrs; the reaction was cooled and then poured on cold water; the precipitated that formed was filtered off and recrystallized from the suitable solvent to give **17a,b** respectively.

6-(Benzo[d][1,3]dioxol-5-yl)-1-formyl-4-(2-oxoethylidene)-2-thioxo-hexahydro-pyrimidine-5-carboxylic acid 17a recrystallized from ethanol as brown crystals mp 248-250 °C, yield 47 %. FT-IR (KBr, cm^{-1}): 3445 ν_{OH}, 3223 ν_{NH}, 1706, 1670, $\nu_{C=O}$.^{1}H NMR (300 MHz, DMSO): δ 3.51 (s, 1H, methine), 5.54 (d, 1H, benzilic), 5.99 (s, 2H, O-CH$_2$-O), 6.76-6.92 (m, 3H, ArH), 7.36 (s, 1H, ethylene), 8.61 (s, 1H, NCHO), 9.45 (s, 1H, C=C-CHO), 10.41 (s, 1H, NH, exchangeable with D_2O), 11.45 (s, 1H, OH, exchangeable with D_2O); MS (EI, m/z(%)): 350 (M+2, 0.11), 348 (M^+, 0.24), 330 (56.06), 298 (14.84), 297 (82.78), 269 (26.7), 121 (31.87), 80 (100), 77 (14.75); Anal. Calc.; $C_{15}H_{12}N_2O_6S$, (348.33): C, 51.72; H, 3.47; N, 8.04; S, 9.21; Found: C, 51.68; H, 3.40; N, 7.99; S, 9.13.

6-(3,4-Dimethoxyphenyl)-1-formyl-4-(2-oxoethylidene)-2-thioxo-hexahydro-pyrimidine-5-carboxylic acid 17b recrystallized from benzene as brown crystals mp 133-135 °C, yield 46 %. FT-IR (KBr, cm^{-1}): 3438 broad $\nu_{OH,NH}$, 1709, 1660 $\nu_{C=O}$.^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85-3.93 (m, 7H,6OCH$_3$,1H methine), 5.51-5.52 (d, 1H, benzilic), 6.78-6.82 (m,4H, 3ArH, 1H ethylene), 8.03 (s, 1H, NCHO), 8.40 (s,1H, NH, exchangeable with D_2O), 9.44 (s, 1H, =CCHO), 10.63 (s, 1H, OH, exchangeable with D_2O); MS (EI, m/z (%)):364 (M^+, 00.0), 348 (13.3), 318 (11.1), 313 (100), 314 (27.8), 286 (31.1), 256 (15.6), 200 (28.9), 82 (17.3),

71 (15.6); Anal. Calc.; $C_{16}H_{16}N_2O_6S$, (364.37): C, 52.74; H, 4.43; N, 7.69; S, 8.80; Found: C, 52.70; H, 4.38; N, 7.64; S, 8.75.

Ethyl 6-aryl-2-chloro-4-methyl-1,6-dihydropyrimidine-5-carboxylate (18a,b)

A mixture of **2b,d** (6.58 mmol) and phosphorus pentachloride (0.16 mmol, 0.5 g) in phosphorus oxychloride (10 ml) was heated on water bath at 100 ^oC for 10 h. The reaction mixture was poured into cold water (40 ml) and the precipitated solid was filtered off, washed with water, dried and recrystallized from the suitable solvent to give **18a,b** respectively.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-2-chloro-4-methyl-1,6-dihydropyrimidine-5-carboxylate 18a recrystallized from ethanol as brown crystals, mp over 300°C, yield 65.72%. FT-IR (KBr, cm^{-1}): 3337 ν_{NH}, 1695 $\nu_{C=O}$ (ester).^{1}H NMR (300 MHz, DMSO): δ 1.08-1.28 (t, 3H, -$OCH_2\underline{CH_3}$, J=6.6Hz), 2.13 (s, 3H, CH_3), 3.97-4.02 (q, 2H, -$O\underline{CH_2}CH_3$, J=6.6Hz), 5.97 (s,1H, benzilic), 6.11 (s, 2H, -O-CH_2-O), 6.73-6.82 (m, 3H, Ar-H), 7.62 (s, 1H, exchangeable with D_2O, NH); MS (EI, m/z (%)): 326 (M+2, 13.6), 324 (M, 15.8), 292 (14.6), 264 (14.6), 144 (13.6), 141 (13.1), 126 (17.6), 110 (17.1), 98 (25.9), 95 (28.7), 94 (99.7), 80 (100.0), 69 (18.3), 59 (14.6), 57 (16.3), 55(18.6); Anal. Calc.; $C_{15}H_{15}ClN_2O_4$, (324): C, 55.82; H, 4.68; Cl, 10.98; N, 8.68; Found: C, 55.77; H, 4.59; Cl, 10.85; N, 8.59.

Ethyl 2-chloro-6-(3,4-di-methoxyphenyl)-4-methyl-1,6-dihydropyrimidine-5-carboxylate 18b recrystallized from ethanol as brown crystals, mp 244-248°C, yield 66 %. FT-IR (KBr, cm^{-1}): 3545 ν_{NH}, 1692 $\nu_{C=O}$ (ester), 1604 $\nu_{C=N}$.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26-1.42(t, 3H, -$OCH_2\underline{CH_3}$, J=6.0Hz), 1.78 (s, 1H, exchangeable with D_2O, NH), 2.50 (s, 3H, CH_3), 3.96 (s,3H,OCH_3), 4.20-4.40 (q, 2H, -$O\underline{CH_2}CH_3$, J=6.0Hz), 5.46 (s,1H, benzilic), 6.95-7.27 (m, 3H, Ar-H); MS (EI, m/z (%)): 338 (M, 00.0), 327 (26.8), 326 (20.4), 324 (24.6), 310 (28.7), 291 (28.0), 266 (25.7), 251 (31.8), 238 (4.1), 138 (2.6), 130 (28.7), 110 (12.1), 96 (21.5), 86 (26.5), 84 (44.3), 83 (57.5); Anal. Calc.; $C_{16}H_{19}ClN_2O_4$, (338): C, 56.72; H, 5.65; Cl, 10.46; N, 8.27; Found: C, 56.68; H, 5.52; Cl, 10.38; N, 8.19.

Ethyl 6-aryl-4-methyl-2-thioureido-1,6-dihydropyrimidine-5-carboxylate (19a,b).

A mixture of **18a,b** (6.11 mmol) and thiourea (6.11 mmol, 0.49 g) in glacial acetic acid (13 ml) and ethanol (10 ml) was refluxed for 6 h. the solvent was distilled off and viscous mass poured onto ice, filtered off and washed with water (3x30ml), dried and recrystallized to afford **19a,b** respectively.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-4-methyl-2-thioureido-1,6-dihydropyrimidine-5-carboxylate 19a: recrystallized from ethanol dioxin (1:1) as brown crystals, mp >300°C, yield 65.72%. FT-IR (KBr, cm^{-1}): 3321 & 3199 $\nu_{NH2,NH}$, 1692 $\nu_{C=O}$ (ester), 1237 $\nu_{C=S}$. MS (EI, m/z (%)):364 (M+2, 32.1), 333 (22.2), 322 (28.3), 278 (23.7), 277 (31.0), 204 (14.1), 124 (39.4), 122 (4.2), 110 (22.6), 84 (100.0), 82 (24.9), 63 (57.8); Anal. Calc.; $C_{16}H_{18}N_4O_4S$, (362): C, 53.03; H, 5.01; N, 15.46; S, 8.85; Found: C, 52.98; H, 4.95; N, 15.32; S, 8.69.

Ethyl 6-(3,4-dimethoxyphenyl)-4-methyl-2-thioureido-1,6-di-hydropyrimidine-5-carboxylate19b: recrystallized from ethanol dioxin (1:1) as brown crystals, mp >300°C, yield 62.78 %. FT-IR (KBr, cm^{-1}): 3304 & 3154 $\nu_{NH2,NH}$, 1682 $\nu_{C=O}$ (ester), 1278 $\nu_{C=S}$. MS (EI, m/z (%)): 380 (M, 23.4), 369 (39.6), 325 (27.9), 323 (23.4), 322 (23.4), 306 (4.8), 295 (27.2), 276 (20.3), 262 (21.3), 248 (18.9), 234 (25.1), 220 (14.8), 190 (21.3), 188 (22.4), 179 (7.9), 173 (27.7), 165 (8.2), 150 (2.0), 131 (20.6), 120 (26.5), 104 (19.3); Anal. Calc.; $C_{17}H_{22}N_4O_4S$, (380): C, 53.95; H, 5.86; N, 14.80; S, 8.47; Found: C, 53.85; H, 5.72; N, 14.68; S, 8.36.

Reaction of Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetra-hydropyrimidine-5-carboxylate 2a with hydrazine hydrate; Formation of 20

A mixture of **2a** (1 mmol, 0.32g) and hydrazine hydrate (1 mmol, 0.05ml) was fused at 100-105 ^oC for 4h. The reaction mixture was poured onto ice/HCl to give the solid product **20** which was filtered off, washed with water (3x30ml) and recrystallized from ethanol as yellow crystals, mp 235-236 ^{o} C, yield 27 %. FT-IR (KBr, cm^{-1}): 3606ν_{NH}, 1634 $\nu_{C=O,}$ 1600 $\nu_{C=N}$. ^{1}H NMR (300 MHz, DMSO): δ 2.52 (s, 6H, $2CH_3$), 6.00 (s, 2H, exchangeable with D_2O, 2NH), 6.12 (s, 4H, 2-O-CH_2-O), 6.92-8.56 (m, 6H,Ar-H), 10.46 (s, 2H, exchangeable with D_2O, 2NHCO); MS (EI, m/z (%)):M (576,0.00), 486 (0.5), 354 (3.5), 353 (12.2), 351 (15.9), 204 (23.9), 149 (52.1), 148 (100.00), 146 (85.3), 121 (22.7), 118 (12.2), 77 (17.0), 60 (16.7), 59 (30.1); Anal. Calc.; $C_{27}H_{20}N_6O_6S_2$, (576): C, 54.16; H, 3.50; N, 14.58; S, 11.12; Found: C, 54.02; H, 3.45; N, 14.50; S, 11.01.

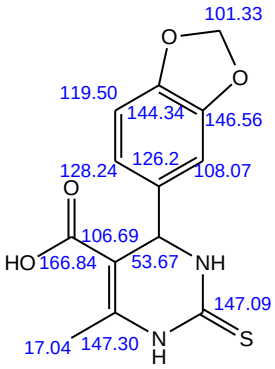
1-(6-(Benzo[d][1,3]dioxol-5-yl)-4-methyl-1,6-dihydropyrimidine-5-carbonyl) semicarbazide (21).

A mixture of **2a** (1 mmol, 0.32g) and semicarbazide hydrochloride (1 mmol, 1.11 g) in ethanol (60 ml) was heated under reflux in the presence of sodium hydroxide (4g) for 10 h. The excess ethanol was distilled off and viscous mass poured onto crushed ice, filtered off and washed with water (4x40ml) and finally recrystallized from methanol to afford **21** as yellow crystals, mp 255-256 ^oC, yield %. FT-IR (KBr, cm^{-1}): 3461, 3278$\nu_{NH2,NH}$, 1709, 1670 $\nu_{C=O,}$ 1611$\nu_{C=N}$. ^{1}H NMR (300 MHz, DMSO): δ 1.98 (s, 3H, CH_3), 6.02 (s,1H, benzilic), 6.11 (s, 2H, O-CH_2-O), 6.40 (s,1H, exchangeable with D_2O, NH), 6.80-7.70 (m, 3H, ArH), 8.50 (s,1H, N=CH), 10.05 (s, 4H, exchangeable with D_2O, 2NH, $1NH_2$); MS (EI, m/z (%)): 317 (M+,0.00), 303 (8.42), 294(63.16), 277 (73.68), 249 (13.68), 232 (83.16), 223 (57.89), 203 (61.05), 137 (100.00), 122 (61.05), 88 (77.89), 84 (56.84); Anal. Calc.; $C_{14}H_{15}N_5O_4$, (317): C, 52.99, H, 4.76; N, 22.07; Found C, 52.87, H, 4.70; N, 22.00.

4-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid 22

A mixture of **2a** (1mmol, 0.32g) and ethanolic NaOH

(5g/25ml ethanol) was heated under reflux for 3h the reaction mixture was then cooled and poured onto ice HCl, the solid product that formed was filtered off and washed with water(3x30ml), dried, and recrystallized from ethanol to give **22** as white crystals, mp 229-230 ^{o}C, yield 38 %. FT-IR (KBr, cm^{-1}): 3344ν_{NH}, 1687$\nu_{C=O,}$ 1655$\nu_{C=C}$. ^{1}H NMR (300 MHz, DMSO): δ 2.28 (s, 3H, CH_3), 5.08 (s,1H, benzilic), 5.98 (s, 2H, O-CH_2-O), 6.67-6.87 (m, 3H, ArH), 9.46,10.16 (2s,2H, exchangeable with D_2O, 2NH), 12.12 (s, 1H, exchangeable with D_2O, OH); MS (EI, m/z (%)): 292 (M+, 18.21), 247 (17.34), 206 (21.10), 191 (15.61), 176 (20.52), 122 (20.23), 108 (15.90), 78 (18.21), 77 (20.52), 56 (37.28), 55 (100.00) ; Anal. Calc.; $C_{13}H_{12}N_2O_4S$ (292); C, 53.42, H, 4.14, N, 9.58, S, 10.97; Found C, 53.37, H, 4.01, N, 9.49, S, 10.88. ^{13}C-NMR (75 MHz, DMSO-d_6) is given below.

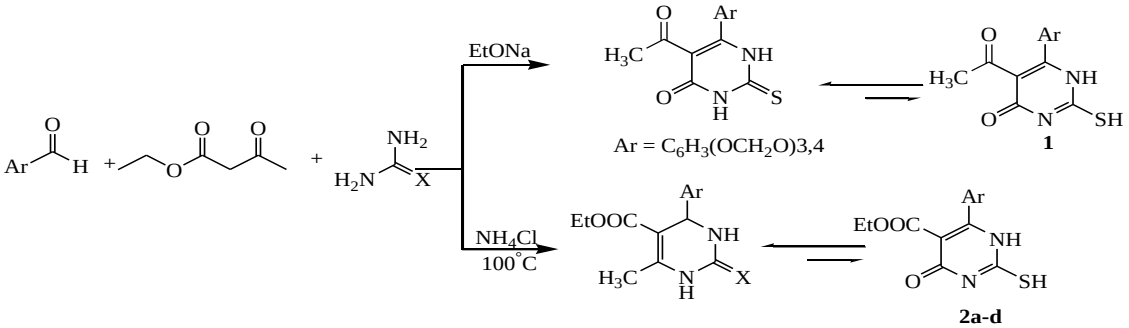


Results and discussion:

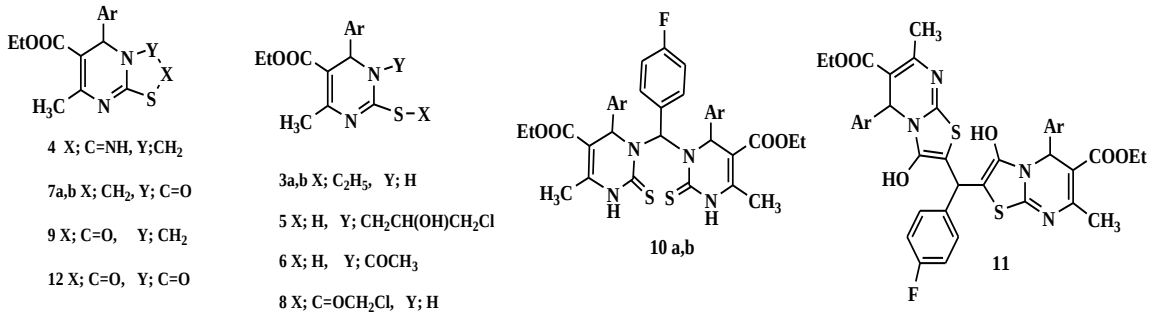
In continuous of our previous work [5] on the synthesis of acetyl thioxo-tetrahydropyrimidine derivative **1** using sodium ethoxide as a catalyst, we extend to the synthesis of 1,2,3,4-tetrahydropyrimidine derivatives **2a-d** [6] in good yields by one-pot cyclic condensation of aldehydes, ethyl acetoacetate and thiourea or urea using NH_4Cl as a catalyst under solvent-free condition [7] at 100°C (**Scheme 1**). We conclude that this reaction depends on the reaction conditions and the catalyst used.

The reactivity of the nucleophilic centres of the tetrahydropyrimidine **2a,c** when reacted with mono and di-halogenated compounds was altered depending on the reaction conditions and the base that used. When the reaction was carried out in weak base such as $KHCO_3$, K_2CO_3 or DMF the nucleophilicity of the nitrogen atom is predominated, while, using strong base such as NaOH, NaOEt, and KOH it predominates the sulfur nucleophilicity, this is due to the presence of the sulfur atom between the two nitrogen atoms which decrease its nucleophilicity, so it needs a strong base to carry out the reactions (**Scheme 2**).

Reaction of **2a,c** with ethyl iodide [8] in the presence of aqueous ethanolic sodium hydroxide gave ethylthiopyrimidine derivatives **3a,b** respectively. While treatment of **2a** with chloroacetonitrile in DMF and epichlorohydrin in $KHCO_3$ afforded 2-iminothiazolo-pyrimidine **4** and 1-(3-chloro-2-hydroxypropyl)-2-mercaptopyrimidine respectively **5.**



Scheme 1: Synthesis of 1,2-dihydropyrimidinthione and 1,2,3,4-tetrahydropyrimidin-2(1*H*)-ones and thiones.



Scheme 2: Compounds **3-11.**

Acetylation of compound **2a** using acetyl chloride afforded the acetyl pyrimidine derivative **6.** The structure of this compound was confirmed by the reaction of **2a** with acetic anhydride which gave the same product **6** and also by spectroscopic data.

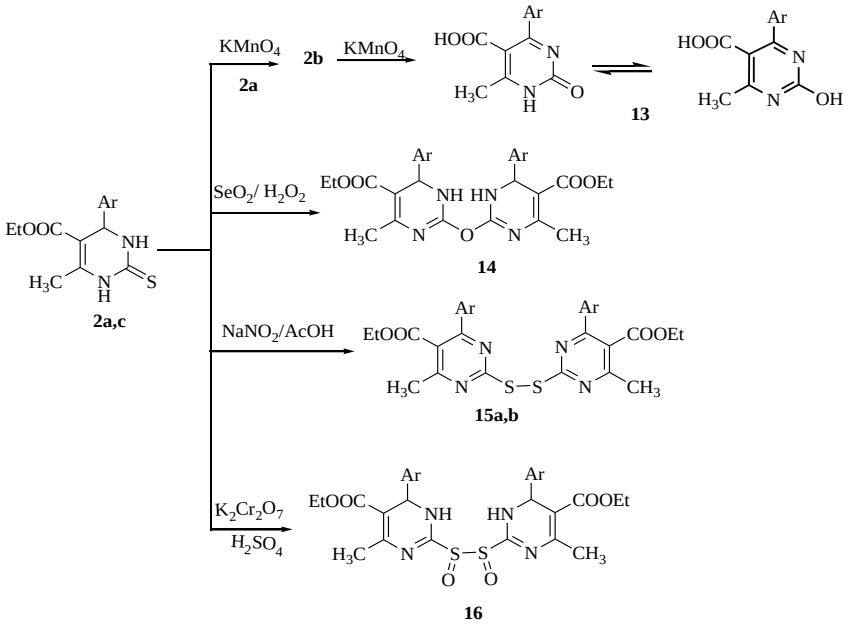
Reaction of the pyrimidinethiones **2a,c** with various electrophilic species, such as ethyl bromoacetate, chloroacetyl chloride and chloroacetic acid [8] in K_2CO_3 or DMF afforded the same cyclic products thiazolo[3,2-α]pyrimidine **7a,b** *via* nucleophilic attack of the nitrogen atom upon the methylene carbon of ethyl bromoacetate, and chloroacetic acid, and upon the carbonyl group of chloroacetyl chloride followed by exo-trig ring closure. The reaction of pyrimidinethione **2a** with chloroacetyl chloride in KOH or NaOEt as strong bases afforded 2-chloroacetylthiopyrimidine **8** and thiazolo[3,2-a]pyrimidine **9** respectively. The structures of these compounds were confirmed by ^{1}H-NMR and ^{13}C-NMR.

The condensation of the NH of the thiopyrimidines **2a,c** and the active methylene group of the thiazolo pyrimidine **7a** with p-fluorobenzaldehyde [9] gave the bis compounds **10a,b** and the diol-dimer product **11** respectively. Structure of **11** is established on the basis of both spectral data and elemental analysis. The IR spectrum showed absorption band at 3420, 1714 cm^{-1} attributed to ν OH group, and ν C=O of ester with the absence of ν C=O thiazolo; and its ^{1}H-NMR spectrum displayed a singlet signal equivalent to3CH benzilic at δ 5.90, and also a singlet signal equivalent to two protons at δ 8.97 (2OH).

The reaction of **2a** with oxalyl chloride [5] as a bi-functional reagent in dry benzene afforded the thiazolopyrimidine **12** *via* two consecutive tetrahedral mechanisms.

The oxidation of **2a,c** depending on the strength of the oxidizing agent and also on the reaction conditions (**Scheme 3**). The removal of the sulfur atom from the tetra-hydropyrimidinethione **2a** proceeds under various oxidative conditions [10-12]. Oxidation of **2a,b** using potassium permanganate solution gave the pyrimidinone **2b** and 4-(benzo[d][1,3]dioxol-5-yl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid **13** respectively. $KMnO_4$ gives potassium sulfonate which undergoes rapid hydrolysis upon exposure to acid solution (2N, HCl) to give the pyrimidinone **2b**.The employment of selenic derivatives represents a mild method which compares favorably with other literature processes [13]. Selenium dioxide oxidizes **2a** to pyrimdin-2-yloxy-pyrimidine derivative **14**. Mild oxidizing agent such as sodium nitrite [14] in the presence of acetic acid converts the thiols **2a,c** to the disulfide derivatives **15a,b.** It has been claimed that mild oxidation converts thiols to disulfides [15]. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide. Oxidation of thiols to the corresponding disulfides [16] is a characteristic functional group transformation, in which further oxidation(s) of the products to give disulfide S-oxides (thiolsulfinates), disulfide S-dioxides (thiolsulfonates), and sulfonic acids are possible. Thus oxidation of **2a** using potassium dichromate in the presence of acetic acid and sulfuric acid gave the bis-pyrimidine sulfoxide derivative **16**.

VilsmeiereHaack formylation is an efficient, economical, and mild reaction for formylation of a wide variety of reactive compounds [17, 18]. Reaction of **2a,c** with $POCl_3$/DMF afforded the 6-aryl-1-formyl-4-(2-oxoethylidene)-2-thioxohexahydro-pyrimidine-5-carboxylic acid derivatives **17a,b**.



Scheme 3: Oxidation of compounds **2a,c.**

Chlorination of the dihydropyrimidinone **2b,d** with $PCl_5/POCl_3$ [19] mixture afforded the corresponding chloropyrimidine derivatives **18a,b** (**Scheme 4**).

When the chloropyrimidine derivatives **18a,b** were allowed to react with thiourea [19] in boiling ethanol and acetic acid, they afforded thioureido-pyrimidine **19a**,**b** respectively.

The pyrimidinethiones **2a** underwent nucleophilic displacement upon treatment with hydrazine hydrate to afford the corresponding bis compound **20**.

The reactions of **2a** with the active amino group of the semicarbazide hydrochloride afforded 1,6-dihydropyrimidine-5-carbonylsemicarbazide **21**. The active amino group acts as a nucleophile which attacks the carbonyl group of the ester group of **2a** followed by desulfurization *via* hydrolysis of the thiol group to give the desired product **21.**

The action of alkali such as sodium hydroxide [20] on **2a** hydrolyzed the ester group to give the acid **22.**

1. Biological activities:

Antimicrobial, anticancer and antioxidant activities of some compounds were investigated using the standard method against different bacterial, fungal strains, anticancer and antioxidant in comparison with standard drugs.

1.1. Antimicrobial activity

The organisms were tested against the activity of 10 mg/ml of the samples; results are depicted in table 1:

2. Pharmacological activity

2.1. Antitumor

Compounds **2a, 20** showed the highest activity against HePG2; and compounds **16, 20** showed the highest activity against MCF-7.

2.2. Antioxidant

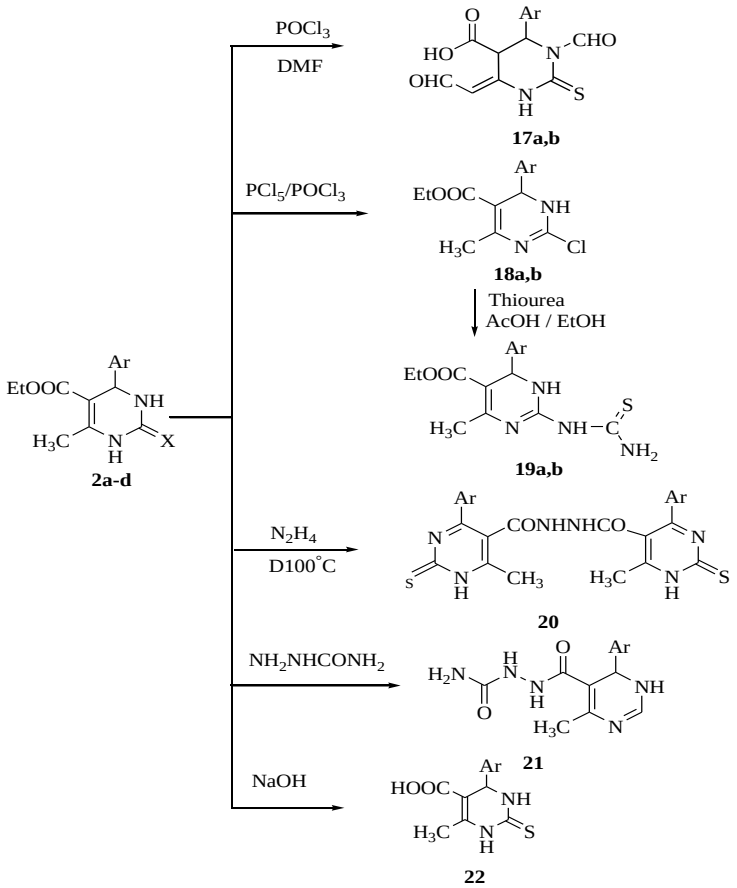
Compounds **16, 20** exhibited the highest activity; compounds **2a,c, 3**, **11** showed moderate activity; compounds **2b,d; 7a,b; 10a,b; 15a,b** showed lower activity as antioxidant.

2.3. Bleomycin-dependent DNA damage

Compound **15** exhibited higher activity as antioxidant agents than the standard (ascorbic acid), and Compound **20** exhibited moderate activity. The pharmacological activities are shown in Table 2.

Conclusion:

Reaction of the pyrimidinethiones with various electrophilic species depends on the reaction conditions and the base that used, and also the oxidation of pyrimidinethiones depending on the strength of the oxidizing agent and on the reaction conditions. Some compounds showed antimicrobial, anticancer and antioxidant activities.



Scheme 4: Synthesis of compounds **17-22.**

Table 1.

Test organism / Sample №	*Bacillus subtillus*	*E. coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Candida albicans*	*A. niger*
2a	19	11	—	—	—	—
2b	—	—	—	—	—	—
2c	14	15	14	11	13	—
2d	—	—	—	—	—	—
7a	—	—	—	—	—	—
7b	—	—	—	—	—	—
10a	12	16.5	—	13.5	—	—
10b	—	—	—	—	—	—
11	13.5	14	—	15	—	—
15a	—	12	—	12.5	13	—
15b	—	—	—	—	—	—
16	12.5	13.5	—	12	—	—
20	14	11	—	12	14	—
St.	31.5	30	35	32	25.0	23

-Well diameter 8mm (100µl of each one was tested).
-St. = standard which is Miphinicol at conc.1mg/ml for gram positive bacteria, while Ciprofloxacin was used as standard for gram negative bacteria at concentration 1mg/ml. Flucoral was used as standard for fungi. Amikacin was tested as standard at concentration 1mg/ml for Candida albicans.

Table 2.

Compound	*In vitro* cytotoxic activity against human tumor cell IC50 (µmol/L)		Bleomycin dependent-DNA damage	Antioxidant activity (ABTS method)	
	HepG2	MCF-7	Absorbance	Inhibition (%)	Absorbance
2a	49.8	63.9	—	38.51	0.332
2b	76.3	67.4	—	10.55	0.483
2c	59.1	51.6	—	49.25	0.274
2d	66.6	76.7	—	10.92	0.481
7a	54.5	74.9	—	12.3	0.475
7b	70.3	86.4	—	14.44	0.462
10a	90.7	79.0	—	20.74	0.428
10b	64.0	91.7	—	13.70	0.466
11	56.5	62.6	—	38.70	0.331
15a	77.6	62.1	—	17.77	0.444
15b	79.6	89.3	—	18.51	0.440
16	38.4	42.5	0.051	88.51	0.062
20	43.2	42.7	0.080	82.03	0.097
St[a]	9.30	13.1	—	—	—
ABTS	—	—	—	0	0.540
Asc. Acid[b]	—	—	0.064	88.88	0.093

[a] 5-Flurouracil is used as standard for antitumor. [b] ascorbic acid is used as standard for antioxidant.

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