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# SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL PYRAZOLES AND OXADIAZOLES DERIVATIVES

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The Thiocarbonic acid S-(7,7-dimethyl-5-oxo-4-substitured phenyl-1,2,3,4,5,6,7,8-octahydroquinazolin-2-yl)ester-O-ethyl ester (**2a-c**) was synthesized by reacting compounds (**1a-c**) with ethyl chloroformate in dry acetone at refluxed temperature. Compounds (**2a-c**) on reaction with hydrazine hydrate in refluxing ethanol afforded respective carbohydrazide **(3a-c).** The hydrazide (**3a-c**) was subjected to cyclocondensation with acetyl acetone in dry methanol containing catalytic amount of conc. hydrochloric acid to yield 3-Methyl-5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid S-(7,7-dimethyl-5-oxo-4-substituted phenyl-1,2,3,4,5,6,7,8-octahydro-quinazolin-2yl) ester (**4a-c)**. The compound (**3a-c**) on reaction with carbon disulphide and potassium hydroxide in dry methanol under reflux conditions afforded 7,7-dimethyl-4-substituted phenyl-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylsulfanyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one.(**5a-c).** The structures of the compounds were elucidated on the basis of their spectral techniques and also their antimicrobial activity was evaluated against gram positive and gram negative bacteria.

**Keywords:** Pyrimidines, pyrazoles and oxadiazoles etc

## Introduction:

A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of hetero atoms or groupings imparts preferential specificities in their biological response. The chemistry and biological study of heterocyclic compounds has been interesting field for a long time due to medicinal and agricultural applications. Pyrimidines and their derivatives are well known for their potential biological activity such as fungicide[1-2], algaecide[3] and as antibiotic[4].

Some of pyrozole derivatives are the most active classes of compounds possessing wide spectrum of biological importance such as anti-inflammatory, anti-pyretic and analgesic properties[5-7] also some of 3, 5-dimethyl pyrazoles and 3-methyl pyrazol-5-ones compounds showed anti-inflammatory, analgesic, ulcerogenic and lipid per oxidation activities[8]. On the same line, 1, 3, 4-oxdiazoles compounds exhibited anti-cancer[9], anticonvulsant[10] and antidiabetic[11] activities. In view of these findings and in continuation of our ongoing search for new heterocyclic systems of biological importance, we have synthesized the title compounds and screened them for their antimicrobial activities.

**Result and Discussion:**

The title compounds were synthesized as outlined in **Scheme-1**. The starting material 7,7-Dimethyl-4-substituted phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (**1a-c**) were synthesized using reported procedure[12]. The precursor Thiocarbonic acid S-(7,7-dimethyl-5-oxo-4-substitured phenyl-1,2,3,4,5,6,7,8-octahydroquinazolin-2-yl)ester-O-ethyl ester (**2a-c**) were synthesized by reacting compounds (**1a-c**) with ethyl chloroformate in dry acetone at refluxed temperature. Compounds (**2a-c**) on reaction with hydrazine hydrate in refluxing ethanol afforded respective carbohydrazide (**3a-c).**

The hydrazide (**3a-c**) was subjected to cyclocondensation with acetyl acetone in dry methanol containing catalytic amount of conc. hydrochloric acid to yield 3-Methyl-5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid S-(7,7-dimethyl-5-oxo-4-substituted phenyl-1,2,3,4,5,6,7,8-octahydro-quinazolin-2yl) ester (**4a-c)**.

The compound (**3a-c**) on reaction with carbon disulphide and potassium hydroxide in dry methanol under reflux conditions afforded 7,7-dimethyl-4-substituted phenyl-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylsulfanyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one.(**5a-c).**

Similarly other derivatives in the series were prepared and structures of these compounds were confirmed by their spectral studies and elemental analysis.

**3-Methyl-5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid S-(7,7-dimethyl-5-oxo-4-(4'-methoxy phenyl-1,2,3,4,5,6,7,8-octahydro-quinazolin-2yl) ester (4a).**

Yield: 66 %, mp >300°C; IR (KBr) $cm^{-1}$: 3290 (NH); 2215 (C=N), 1700 (C=O); 1660 (C=O); $^1H$ NMR (DMSO-d6, δ, ppm): 0.9 (s, 3H, $CH_3$); 1.12 (s, 6H, 2x $CH_3$); 1.88 (s,2H, $CH_2$), 2.26 (s, 2H, $CH_2$), 2.86 (s, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 4.59 (s, 1H, CH), 7.01-7.58 (m, 4H, Ar-H); 8.24 (s, 1H, NH). 13C NMR (DMSO-d6, δ , ppm): 19.7 ($CH_3$), 26.8 (2x $CH_3$), 35.2 ($CH_2$), 46.6 (CH), 47.8 ($CH_2$), 51.2 ($CH_2$), 56.0 ($OCH_3$), 70.5 (CH), 120.6-130.8 (C=C & Ar-C), 168.8 (C=O), 172 (C=O), 175 (C=O). Anal. % $C_{22}H_{26}N_4O_4S$: C, 59.71; H, 5.92; N, 12.66. Found: C, 59.41; H, 5.72; N, 12.73.

**3-Methyl-5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid S-(7,7-dimethyl-5-oxo-4(2'-hydroxy phenyl)-1,2,3,4,5,6,7,8-octahydro-quinazolin-2yl) ester (4b).**

Yield: 54 %, mp 280°C; IR (KBr) $cm^{-1}$: 3364 (NH); 3120 (OH); 2213 (C=N); 1712 (C=O); 1684 (C=O); $^1H$ NMR (DMSO-d6, δ, ppm): 0.94 (s, 3H, $CH_3$); 1.23 (s, 6H, 2x $CH_3$); 1.94 (s,2H, $CH_2$), 2.18 (s, 2H, $CH_2$), 2.74 (s, 2H, $CH_2$), 4.41 (s, 1H, CH), 5.10 (s, 1H, OH), 7.21-8.14 (m, 4H, Ar-H); 8.44 (s, 1H, NH). 13C NMR (DMSO-d6, δ , ppm): 19.84 ($CH_3$), 26.14 (2x $CH_3$), 34.10 ($CH_2$), 45.14 (CH), 47.87 ($CH_2$), 51.48 ($CH_2$), 68.75 (CH), 116.46-128.81 (C=C & Ar-C), 166.48 (C=O), 173.48 (C=O), 176.84 (C=O). Anal. % $C_{21}H_{24}N_4O_4S$: C, 58.86; H, 5.65; N, 13.07. Found: C, 58.78; H, 5.58; N, 12.95.

**3-Methyl-5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid S-(7,7-dimethyl-5-oxo-4(4'-chloro phenyl)-1,2,3,4,5,6,7,8-octahydro-quinazolin-2yl) ester (4c).**

Yield: 71 %, mp > 300°C; IR (KBr) $cm^{-1}$: 3310 (NH); 2225 (C=N); 1725 (C=O); 1674 (C=O); $^1H$ NMR (DMSO-d6, δ, ppm): 0.92 (s, 3H, $CH_3$); 1.21 (s, 6H, 2x $CH_3$); 1.89 (s, 2H, $CH_2$), 2.21 (s, 2H, $CH_2$), 2.84 (s, 2H, $CH_2$), 4.65 (s, 1H, CH), 7.18-7.68 (m, 4H, Ar-H); 8.65 (s, 1H, NH). 13C NMR (DMSO-d6, δ, ppm): 19.78 ($CH_3$), 26.11 (2x $CH_3$), 34.24 ($CH_2$), 45.38 (CH), 47.74

($CH_2$), 51.39 ($CH_2$), 68.61 (CH), 119.34-127.47 (C=C & Ar-C), 169.21 (C=O), 174.54 (C=O), 179.21 (C=O). Anal. % $C_{21}H_{23}N_4O_3SCl$: C, 56.43; H, 5.19; N, 12.54. Found: C, 56.21; H, 5.08; N, 12.45.

**4-(4-methoxy-phenyl)-7,7'-dimethyl-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2ylsulfanyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one, (5a)**

Yield: 71 %, mp >280°C; IR (KBr) $cm^{-1}$: 3284 (NH); 2210 (C=N); 1700 (C=O); $^1H$ NMR (DMSO-d6, δ, ppm): 1.14 (s, 6H, 2x $CH_3$); 1.79 (s,2H, $CH_2$), 2.76 (s, 2H, $CH_2$), 3.84 (s, 3H, $OCH_3$), 4.49 (s, 1H, CH), 7.12-7.68 (m, 4H, Ar-H); 8.19 (s, 1H, NH), 9.14 (s,1H,NH). 13C NMR (DMSO-d6, δ, ppm): 25.87 (2x $CH_3$), 47.26 (CH), 47.96 ($CH_2$), 53.42 ($CH_2$), 56.18 ($OCH_3$), 115.46-129.58 (Tetra-C, C=C & Ar-C), 154.24 (C=N), 156.54 (C=N), 179.68 (C=O), 185.21 (C=S), Anal. % $C_{19}H_{22}N_4O_3S_2$: C, 54.52; H, 5.30; N, 13.39. Found: C, 54.48; H, 5.22; N, 13.26.

**4-(4-hydroxy-phenyl)-7,7'-dimethyl-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2ylsulfanyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one, (5b)**

Yield: 62 %, mp = 264°C; IR (KBr) $cm^{-1}$: 3315 (NH); 3125 (OH); 2195 (C=N); 1765 (C=O); $^1H$ NMR (DMSO-d6, δ, ppm): 1.12 (s, 6H, 2x $CH_3$); 1.84 (s,2H, $CH_2$), 2.64 (s, 2H, $CH_2$), 4.65 (s, 1H, CH), 5.14 (s, 1H, OH), 7.25-8.14 (m, 4H, Ar-H); 8.24 (s, 1H, NH), 9.28 (s,1H,NH). 13C NMR (DMSO-d6, δ, ppm): 25.67 (2x $CH_3$), 47.19 (CH), 47.86 ($CH_2$), 53.38 ($CH_2$), 118.24-131.37 (Tetra-C, C=C & Ar-C), 154.65 (C=N), 156.24 (C=N), 179.98 (C=O), 185.76 (C=S), Anal. % $C_{18}H_{20}N_4O_3S_2$: C, 53.45; H, 4.98; N, 13.85. Found: C, 53.28; H, 4.84; N, 13.76.

**4-(4-Chloro-phenyl)-7,7'-dimethyl-2-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2ylsulfanyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one, (5c)**

Yield: 74 %, mp = 251°C; IR (KBr) cm-1: 3324 (NH); 2205 (C=N); 1734 (C=O); 1H NMR (DMSO-d6, δ, ppm): 1.16 (s, 6H, 2x CH3); 1.76 (s,2H, CH2), 2.41 (s, 2H, CH2), 4.36 (s, 1H, CH), 7.14-8.04 (m, 4H, Ar-H); 8.36 (s, 1H, NH), 9.14 (s,1H,NH). 13C NMR (DMSO-d6, δ, ppm): 25.14 (2x CH3), 47.26 (CH), 47.56 (CH2), 53.14 (CH2), 116.16-129.65 (Tetra-C, C=C & Ar-C), 154.21 (C=N), 156.36 (C=N), 178.21 (C=O), 184.96 (C=S), Anal. % C18H19ClN4O2S2: C, 51.12; H, 4.53; N, 8.38. Found: C, 51.08; H, 4.39; N, 8.28.

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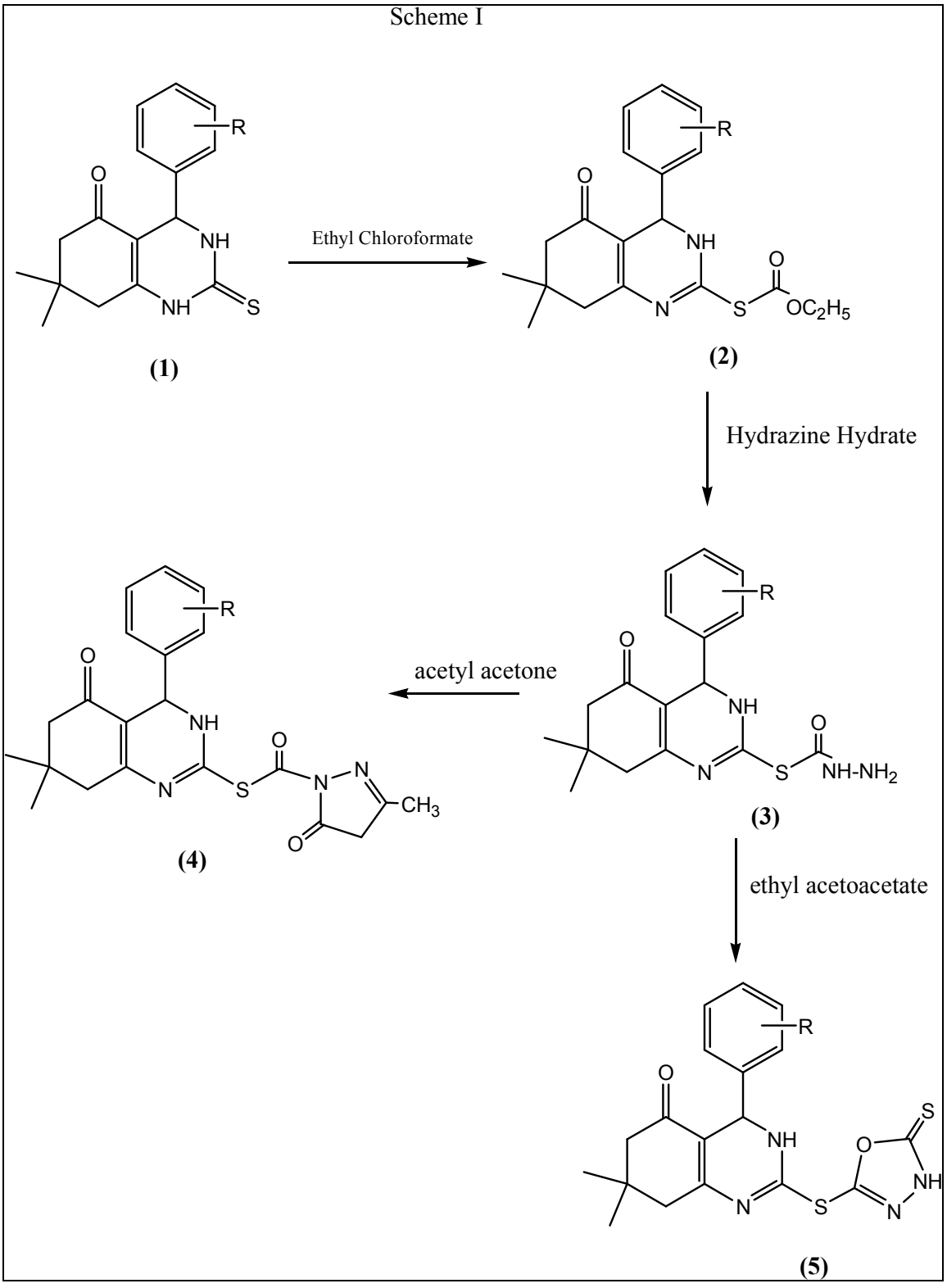
Scheme I


R
O
NH
NH
S
Ethyl Chloroformate
(1)
(2)
Hydrazine Hydrate
(3)
acetyl acetone
(4)
ethyl acetoacetate
(5)
NH-NH2
CH3
OC2H5

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