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A facial and convenient protocol for the synthesis of new thiazole, thiazolidinone and pyrazothiazole derivatives

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Abstract: We have developed a facile method for the synthesis of a new series of thiazole, thiazolidinone and pyrazothiazole derivatives via the reaction 1,2- and 1,3-dicarbonyl compounds with ethyl bromoacetate, ethyl bromopyruvate or phenacyl bromide in ethanol as a solvent at ambient temperature or under reflux conditions. Major advantages of the present protocol include user friendly process, simple work-up, and inexpensive catalyst. Treatment of 1,3-dicarbonyl compounds (2, 6), isatin (9), or ninhydrine (12) and (15a-b) with thiosemicarbazide (1) in the presence of sodium acetate and HCl as a catalyst under heating or ambient temperature in ethanol as a solvent produced thiosemcarbazone derivatives (3, 7, 10, 13, 16a-b). These derivatives were utilized as key intermediates for synthesis of new thiazole, thiazolidinone and pyrazothiazole derivatives via the reaction with ethyl bromoacetate, ethyl bromopyruvate or phenacyl bromide in ethanol as a solvent at ambient temperature or under reflux conditions. The chemical structures of the newly synthesized compounds were characterized by FT-IR, 1H-NMR, 13C-NMR spectral and elemental analysis.

Keywords: Monothiosemicarbazone, 1,2- and 1,3-dicarbonyl compounds, Thiazole, thiazolidinone, Pyrazothiazole.

Introduction

Thiazoles and their derivatives have attracted continuingly interest over the years, because of their varied biological activities [1,2]. They have been recently used in drug development for the treating allergies [3], hypertension, inflammation, schizophrenia [4], bacterial, HIV infections [5], hypnotics [6], and more recently for the treating of pain [7], as fibrinogen receptor antagonists with antithrombotic activity [8], and as new inhibitors of bacterial DNA gyrase B [9]. The thiazolium ring presents in vitamin B1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids. In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds.

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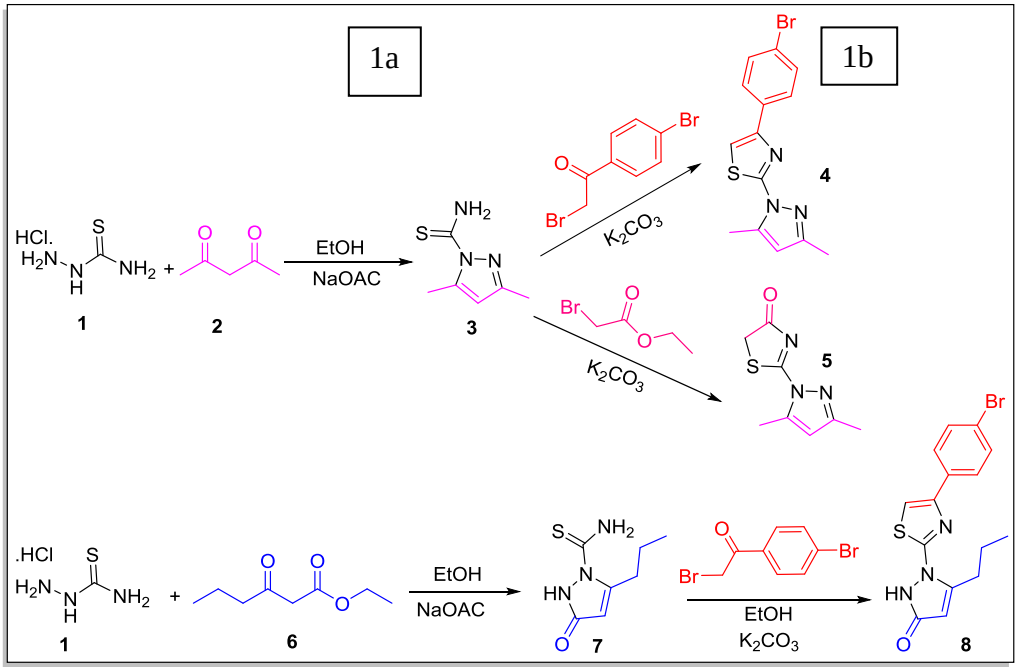
Thus the thiazole nucleus has been studied in the field of organic and medicinal chemistry [10]. In view of the above-mentioned findings to identify new candidates that may be valuable in designing new, potent, selective and less toxic antimicrobial agents, in the present work, we report the synthesis of monothiosemicarbazone of 1, 3-bicarbonyl derivatives and some new thiazole and thiazolidinone derivatives starting from monothiosemicarbazone of 1, 3-bicarbonyl derivatives in order to investigate their antimicrobial activity.

Result and Discussion

The synthetic strategies adopted to obtain the target compounds, are depicted in schemes **1-4**. All new compounds described below were characterized by elemental analysis and their spectral data, some of which are cited in the text to support a structural assignment. Known compounds are referenced. The 1,3-diketone, acetylacetone **2** reacted with

thiosemicarbazide**1** in aqueous ethanolic HCl at room temperature to give pyrazole **3**, which was reacted with 4-bromophenacyl bromide to give the 2-pyrazolylthiazole **4** and with ethyl bromoacetate to give the 2-pyrazolylthiazolidine **5**. In a similar way, the *β*-keto ester, ethyl 3-oxohexanoate **6** gave the pyrazolone**7** and thence reaction with 4-bromophenacyl bromide gave the 2-thiazolyl-4-aryl-pyrazolone **8** (Scheme **1**).

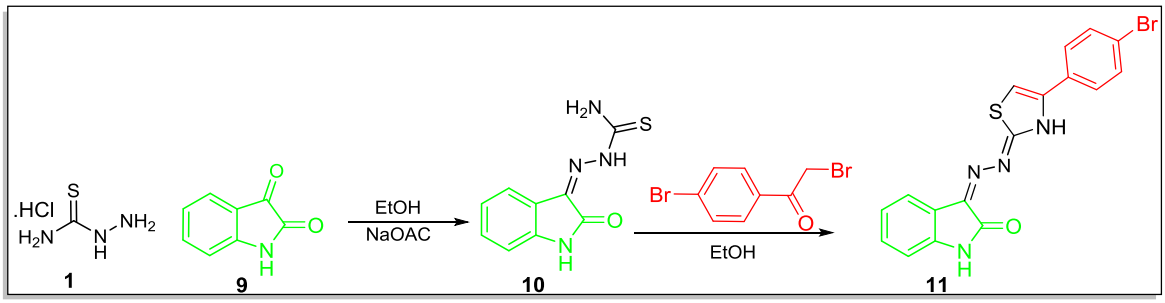


Scheme 1: Synthesis of new thiazole, thiazolidinone and pyrazothiazole derivatives.

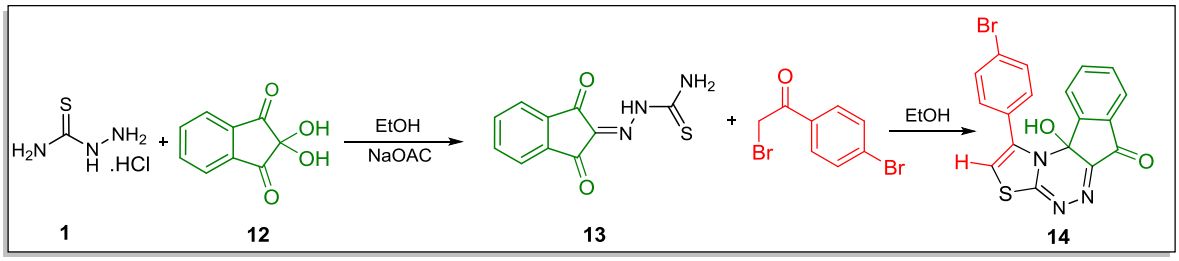
Spectroscopic data [IR, ^{1}H-NMR, ^{13}C-NMR] and element analysis showed that, the cyclization reaction occurred at these conditions. Thus refluxing of **3** with phenacyl bromide or ethyl bromoacetate and 3-oxo-5-propyl-2,3-dihydro-1H-pyrazole-1-carbothioamide **7** with phenacyl bromide in EtOH revealed the formation of **4**, **5** and **8** respectively.

The IR spectrum of 4-(4-bromophenyl)-2-(3, 5-dimethyl-1H-pyrazol-1-yl) thiazole **4** showed an absorption band at 1536-1620 cm^{-1} corresponding to C=C and C=N stretching and at 3079 cm^{-1} corresponding to CH-Ar. The ^{1}H-NMR spectrum of **4** exhibited two singlets at δ = 7.92 and 6.22 ppm due to the HC= thiazole and CH-pyrazole rings respectively, and two signals at δ = 2.21 and 2.71 assigned to the methyl groups (CH_3) which confirmed the structure of **4**. Two doublets at δ 7.65 and 7.90 ppm corresponded to the aromatic protons present in the molecule. The ^{13}C-NMR spectrum of **4** displayed a downfield signal at δ 162.41 ppm for the thiazole ring. The above spectral data and elemental analysis results supported the formation of compound **4**. The spectral data of compounds **5** and **8** also supported their structures. Treatment of thiosemicarbazide with isatin**9**in aqueous ethanolic HCl at room temperature by reaction at the 3-position to give corresponding thiosemicarbazone**10** which, when reacted with 4-bromophenacyl bromide, gave the thiazolylindolinone **11**(Scheme **2**).

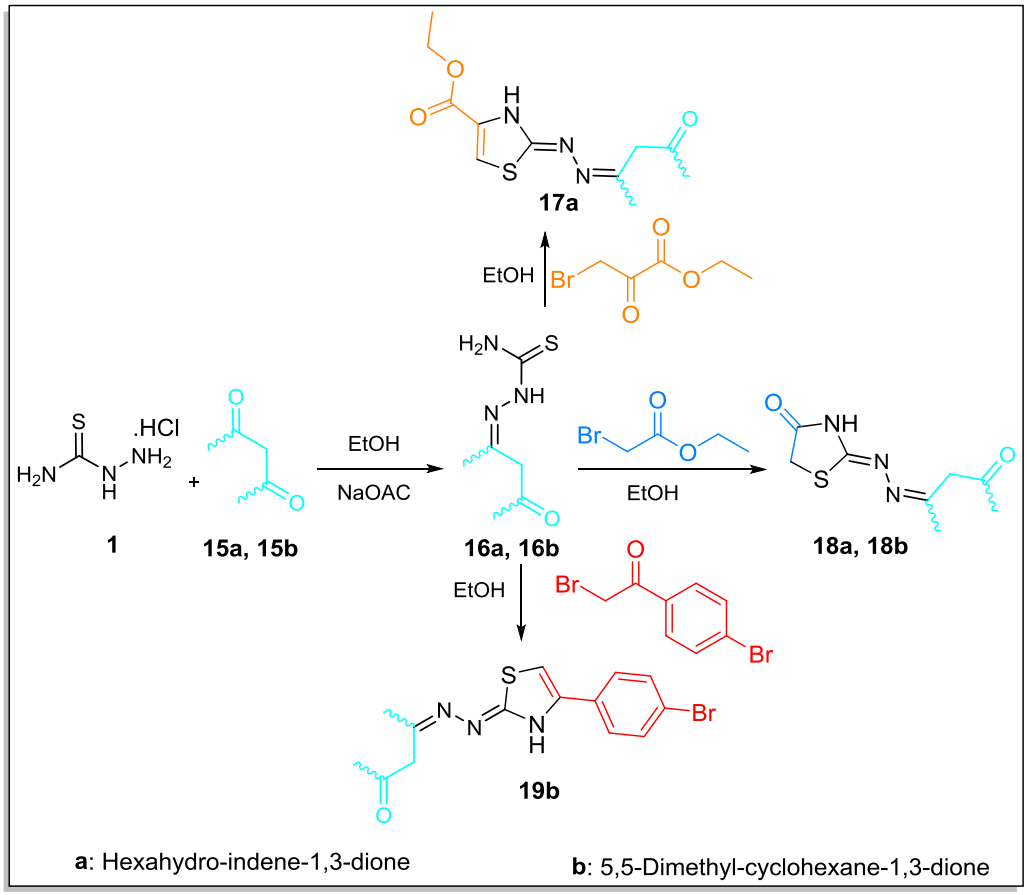
A more complex pentacyclic product was obtained when ninhydrin12was subjected to a similar sequence of reactions (Scheme **3**). Two cyclic 1,3-diketones (Scheme **4**) were also reacted with thiosemicarbazide to give condensation products 16 which, when reacted with 4-bromophenacyl bromide gave, respectively, compound 17, 18, 19. Comment on the fact that neither of the initial condensation products can be cyclized to pyrazoles (C=O groups too far apart).



Scheme 2: Synthesis of (Z)-3-(2-(4-(4-bromophenyl) thiazol-2-yl)hydrazono)indolin-2-one (**11**).



Scheme 3. Synthesis of 2-(2-(4-(4-bromophenyl) thiazol-2-yl) hydrazono)-1H-indene-1, 3(2H)-dione (**14**).



Scheme 4: Synthesis of thiazol and thiazolidinone derivatives **17a**, **18a**, **18b** and **19b.**

The FT-IR spectra of Schiff bases of **10**, **13**, and **16a-b** indicated adsorption bands at 3130-3338 cm^{-1} for –NH and $–NH_2$ groups. The ^{1}H-NMR spectra of hydrazones showed peaks of hydrazide (NH), amine (NH_2), and imine (-N=CH) protons. These were all singlets, and each one indicated the intensity of proton in 500 MHz ^{1}H-NMR. The results also indicated the formation of hydrogen bonding (H---S) in the thioamide part of the molecule leading to a broad singlet. These findings all strongly confirmed the foarmation of hydrazone. Therefore, to improve structure-activity relationship with respect to antimicrobial properties, we cyclized the thiosemicarbazone functionality into thiazolidinone or thiazole. Thus, refluxing **10**, **13** and **16** with phenacylbromide in ethanol revealed the formation of, **11**, **14** and **19b** respectively.

Compounds **11**, **14** and **19b** were characterized by the presence of strong bands at 1689, 1692, and 1715 cm^{-1} in the IR spectrum which related to carbonyl groups respectively. Another piece of evidence for cyclization was appearance of two single signals, equivalent to two protons in the ^{1}H-NMR spectrum at 7.69, 11.24 ppm for **11** which represented H-C=C and NH protons of the thiazol nucleus and 5.08, 7.51 ppm for **14** relating to the presence of OH and thiazolin ring protons and 7.37, 7.79 ppm for **19b**.

Conclusion

In conclusion, we have developed a facile method for the synthesis of new series of thiazole, thiazolidinone and pyrazothiazole derivatives via the reaction 1,2- and 1,3-dicarbonyl compounds with ethyl bromoacetate, ethyl bromopyruvate or phenacyl bromide in ethanol as a solvent at ambient temperature or under reflux conditions.

Experimental

All of the chemicals and solvents such as ethyl acetate, ethanol, DMF, and methanol obtained from Merck Chemical. Co. and were used without further purification. Schiff bases-thiosemicarbazone derivatives were prepared was according to a known procedure [9-13]. Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were obtained on a Matson-1000 FT-IR spectrometer. Peaks are reported in wave numbers (cm^{-1}). All NMR spectra were recorded on a Bruker model DRX-500 AVANCE (^{1}H: 500 MHz,^{13}C: 125 MHz) NMR spectrometer. Chemical shift are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d_6 as a solvent. Element analyses (C, H, and N) were performed with a Heracus CHN-O-Rapid analyzer. Purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F_{254} percolated sheets in n-Hexane/ethyl acetate mixture and spots were developed using iodine vapors'/ultraviolet light as visualizing agent.

General procedure for synthesis of compounds 4, 5, 8, 11, 14, 17a, 18a-b and 19b.

A mixture of thiosemicarbazone derivative (0.001mol) and phenacyl bromide/ethyl bromoacetate or ethyl bromopyruvate (0.001mol) in ethanol (15 ml) in the presence of K_2CO_3 (0.001mol) as a base was refluxed on oil bath for 3-5 h. The progress of reaction was monitored by TLC at appropriate time interval. The excess of solvent was distilled off and the solid that separated was collected by filtration, and dried to get the desired product. The product was recrystallized from ethanol.

4-(4-bromophenyl)-2-(3, 5-dimethyl-1H-pyrazol-1-yl)thiazole (4).

Brown light powder (78%); M.p. 136-139^{0}C. FT-IR (KBr) υ_{max} = 1572, 1620 (C=N), 3079 (CH, Ar) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 2.21 (3H, s, CH_3), 2.71 (3H, s, CH_3), 6.22 (1H, s, CH-pyrazol), 7.65 (2H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 7.90 (2H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 7.92 (1H, s, HC= thiazol) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ =14.08 (CH_3), 14.27 (CH3), 110.77 (CH= thiazole), 112.01, 142.07, 150.91 (3C, pyrazol), 122.12, 128.58, 132.61, 133.90 (6C, aromatic), 152.01, 162.41 (2C, thiazole) ppm. Anal. Calcd. For ($C_{14}H_{12}BrN_3S$): C, 50.31; H, 3.62; N, 12.57 %. Found: C, 50.45; H, 3.53; N, 12.62 %.

2-(3, 5-dimethyl-1H-pyrazol-1-yl) thiazol-4(5H)-one (5).

Yellow light powder (75%); M.p. 143 ^{0}C,FT-IR (KBr) υ_{max} =1598 (C=N), 1670 (C=O) 3059 (CH,Ar) Cm^{-1}.^{1}H-NMR (500 MH_Z, DMSO): δ = 2.21 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.75 (2H, s, CH_2-thiazolone), 6.23 (1H, s, CH-pyrazol) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ =14.10 (CH_3), 14.32 (CH_3), 47.14 (CH_2-thiazolone), 113.37, 143.60,152.11 (3C, pyrazol), 163.17, 180.11 (N=C-S, C=O) ppm. Anal. Calcd. For ($C_8H_9N_3OS$): C, 49.21; H, 4.65; N, 21.52 %. Found: C, 49.56; H, 4.70; N, 21.42 %.

1-(4-(4-bromophenyl)thiazol-2-yl)-5-propyl-1H-pyrazol-3(2H)-one (8).

Brown lightpowder (73%); M.p. 155-160 ^{0}C, FT-IR (KBr) υ_{max}= 1578 (C=N), 1630 (C=O), 3100 (CH, Ar), 3390 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 0.96

(3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.66 (2H, sex, $^3J_{HH}$ = 7 H_Z, CH_2), 2.53 (2H, t, $^3J_{HH}$ = 7 H_Z, CH_2), 5.31 (1H, s, HC= pyrazolone), 7.65 (2H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 7.84 (1H, s, H-thiazol), 7.97 (2H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 12.39 (1H, s, NH-pyrazolone) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ = 14.42 (CH_3), 21.18 (CH_2), 39.19 (CH_2), 98.72, 165.19 (2C, pyrazolone), 168.12 (C=O), 124.17, 130.09, 132, 53, 133.8 (6C, aromatic), 108.12, 153.90, 178.11 (3C, thiazol) ppm. Anal. Calcd. For ($C_{15}H_{14}BrN_3OS$): C, 49.46; H, 3.87; N, 11.54 %. Found: C, 49.38; H, 3.91; N, 11.34 %.

3-(2-(4-(4-bromophenyl) thiazol-2-yl)hydrazono)indolin-2-one (11).

Yellow light powder (78%); M.p. 298 ^{0}C, FT-IR (KBr) υmax = 1670, 1640 (C=N), 1692 (C=O),3040 (CH, Ar), 3174-3257 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 7.96 (1H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 7.09 (1H, t, $^3J_{HH}$ = 7 H_Z, aromatic), 7.34 (1H, t, $^2J_{HH}$ = 10 H_Z, aromatic), 7.53 (1H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 7.60 (2H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 7.69 (1H, s, HC= thiazol), 7.85 (2H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 11.24 (1H, s, NH), 13.34 (1H, s, NH) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ = 108.48 (1C, S-C=C thiazole), 11.93, 120.57, 120.74, 121.89, 123.27, 128.59, 131.39, 132.47, 133.09, 134.04, 142.21, (12C, aromatic, C=N indolin, C=N thiazole), 150.72 (1C, C=C-N thiazole), 164.05 (1C, C=O), 167.08 (1C, C=N thiazole) ppm. Anal. Calcd. For ($C_{17}H_{11}BrN_4OS$): C, 51.14; H, 2.78; N, 14.03%. Found: C, 51.02; H, 2.83, N, 14.24%.

1-(4-bromophenyl)-10b-hydroxyindeno[1,2-e]thiazolo[2,3-c][1,2,4]triazin-6(10bH)-one (14).

Yellow powder (67%); M.p. 246-247 ^{0}C, FT-IR (KBr) υ_{max} = 1579 (C=N), 1715 (C=O), 3016 (CH, Ar), 3438 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 5.08 (1H, s, OH), 7.51 (1H, s, H-thiazol), 7.59-7.64 (2H, m, aromatic), 7.71-7.75 (2H, m, aromatic), 7.80-7.79 (3H, m, aromatic), 7.93 (1H, d, $^2J_{HH}$ = 8 H_Z, aromatic), 8.08 (1H, d, $^2J_{HH}$ = 8 H_Z, aromatic) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ = 108.90 (S-C=C thiazole), 119.93, 121.07, 121.74, 122.00, 123.68, 128.89, 132.48, 133.02, 134.49, 136.04,137.19,143.23, (12C, aromatic, C=N indene, C=N thiazole), 150.88(C=C-N thiazole) , 167.78, 168.68 (2C, 2C=N thiazole), 170.01 (1C, C=O).

ethyl-2-(2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazole-4-carboxylate (17a).

Yellow light powder (70%); M.p. 150-155 ^{0}C, FT-IR (KBr) υ_{max} = 1627 (C=N), 1679, 1715 (C=O), 3056 (CH, Ar), 3320 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ =1.28 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 4.25 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 3.46 (2H, s, CH_2-inden), 7.59-8.29 (6H, m, NH, H-thiazole, aromatic) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ =14.23 (CH_3), 37.40 (CH_2 indene ring), 60.31 (CH_2), 114.56 (1C, S-C=C thiazole), 127.87, 132.90, 133.37, 133.40,135,20, 143.63, 146.20, (7C, 6C aromatic, N-C=C thiazole), 158.18, 162.01, 173.63 (3C, C=N indene, C=O, NH-C=N), 198.04 (1C, C=O) ppm. Anal. Calcd. For ($C_{15}H_{13}N_3O_3S$): C, 57.13; H, 4.16; N, 13.33 %. Found: C; 57.06; H, 4.20; N, 13.47%.

(3-oxo-2, 3-dihydro-1H-inden-1-ylidene)hydrazono)thiazolidin-4-one (18a).

Yellow light powder (70%); M.p. 267-270 ^{O}C, FT-IR (KBr) υ_{max} = 1623 (C=N), 1687, 1735 (C=O), 3086 (CH, Ar), 3485 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 3.45 (2H, s, CH_2), 3.92 (2H, s, CH_2), 7.68 (1H, t, $^3J_{HH}$ = 7 H_Z, aromatic), 7.78 (1H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 7.83 (1H, t, $^3J_{HH}$ = 7 H_Z, aromatic), 7.98 (1H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 12.11 (1H, s, NH) ppm. ^{13}C-NMR (125 MH_Z, DMSO): δ = 33.77 (CH_2thiazolidinone ring), 36.43 (CH_2indenone), 122.92, 123.77, 132.73, 136.27, 139.94, 146, 67 (6C, aromatic), 160.25, 161.00 (2C=N), 174.70 (C=O, thiazolidinone),199.92 (C=O indenone ring) ppm. Anal. Calcd. For ($C_{12}H_9N_3O_2S$): C, 55.59; H, 3.50; N, 16.21 %. Found: C, 55.68; H, 3.39, N, 16.32 %.

(3, 3-dimethyl-5-oxocyclohexylidene)hydrazono) thiazolidin-4-one (18b).

Yellow lightpowder (67%); M.p. 267-270 ^{O}C, FT-IR (KBr) υ_{max} = 1629 (C=N), 1726 (C=O), 3006 (CH, Ar), 3482 (NH) Cm^{-1}.^{1}H-NMR (500 MH_Z, DMSO): δ = 1.06 (6H, s, $2CH_3$), 1.90 (2H, s, CH_2), 2.53 (2H, s, CH_2), 2.53 (2H, s, CH_2), 4.09 (2H, s, CH_2) ppm.^{13}C-NMR (125 MH_Z, DMSO): δ = 28.60 (2C, CH_3), 33.27 (CH_2thiazolidine), 45.00, 40.36, 47.40, 55.20 (3C, $3CH_2$), 160.31, 165.90, 175.25 (3C, 2C=N, C=O thiazolidine), 212.00 (C=O) ppm. Anal. Calcd. For ($C_{11}H_{15}N_3O_2S$) C, 52.15; H, 5.97; N, 16.59 %. Found: C, 52.28; H, 5.89, N, 16.61 %.

5-(2-(4-(4-bromophenyl)thiazol-2-yl)hydrazono)-3,3-dimethylcyclohexanone (19b).

Brown lightpowder (67%); M.p. 248-251^{0}C, FT-IR (KBr) υ_{max} = 1689 (C=O), 3067 (CH, Ar), 3433 (NH) Cm^{-1}. ^{1}H-NMR (500 MH_Z, DMSO): δ = 1.14 (6H, s, CH_3), 2.02, 2.36 (2H, m, CH_2), 2.62 (4H, m, CH_2), 7.37 (1H, s, HC=C), 7.55-7.57 (4H, m, Ar), 7.79 (1H, s, NH) ppm. Anal. Calcd. For ($C_{17}H_{18}BrN_3OS$): C, 52.05; H, 4.62; N, 10.71%. Found: C, 52.13; H, 4.57, N, 10.76%.

Acknowledgment

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