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Using of some novel derivatives of thiourea for Synthesis of pharmaceutical compounds of 5-Arylidine-2-imino-4-thiazolidinones and their medicinal properties study as anti-inflammatory agents

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Abstract**—** *Thiazolidinone belongs to important groups of heterocyclic compounds. Recently this compounds displays activities such as antioxidants, anti-inflammatory, anti-virus and tuberculostatic. In this project we reported an effective reaction to synthesis of novel thiazolidinone-4-one in the presence of deep Eutectic Solvent as catalyst by Aldol condensation, derivatives of thiourea asymmetric and aldehydes.The primary deivatives phenyl thiourea were obtained by the reaction of derivatives Aniline with Ammonium thiocyanate and HCl in refluxing free solvent and Next reaction between deivatives phenyl thiourea and chloro acetyl chloride in refluxing ethanol. Subsequent synthesis of 5-Arylidene-2-imino-4-thiazolidinones was performed by condensation of amino thiazolidinone with aldehydes in the presence of catalysts Deep Eutectic Solvent.*

This method have several advantage such as synthesis free solvent, short duration of action, the use of catalysts deep eutectic solvent, being environmentally friendly and simple procedure.The structure of synthesized compounds (3f-h) characterized by infra-red spectroscopy (FTIR), ^{1}H *Nuclear magnetic resonances, and* ^{13}C *Nuclear magnetic resonances.*

Keywords—5-Arylidene-2-imino-4-thiazolidinones, thiourea asymmetric, Aniline derivatives, Ammonium thiocyanate, Deep Eutectic Solvent.

I. INTRODUCTION

Ionic liquids (ILs) are a new chemical compounds that have revolution in the chemical industry in recent years. These compounds, which are "green chemicals", as solvents, play a very important role in reducing the use of harmful, toxic and harmful compounds to the environment. Ionic liquids can replace many common solvents in the pharmaceutical industry. One of the reasons that has intensified research on ionic liquids today is that scientists are looking for a suitable alternative to volatile organic solvents in the industry. Volatile organic solvents are the most important source of environmental pollution in the chemical and pharmaceutical industries. This new compound are non-toxic towards the environment, inexpensive and biodegradable[1,2].

Thiourea derivatives is an organosulfor compound [3]. It is structurally similar to urea, except that the oxygen atom is replaced by a sulfur atom, but the properties of urea and thiourea differ significantly.

Thiourea occurs in two tautomeric forms. In aqueous solutions the thione form predominates.The thiol form which is also known as an isothiourea, can be encountered in substituted compounds such as isothiouronium salts [4,5]. The thiazolidinones are hetrocyclic compounds with a broad spectrum.

Thiazolidinones and their derivatives display a large variety of pharmacological activities includingantihistaminic [6], analgesic [7], iinflammatory[8], anti-microbial[9],anti-HIV[10] and anti-cancer[11].

The most common synthetic pathway is the coupling reaction between a phenyl thiourea with ammonium thiocyanat in the presence of strong mineral acid afforded.

The strong mineral acid afforded the phenyl imino thizolidinone derivatives[12,13].

II. EXPERIMENTAL

General

All chemicals or solvents used were purchased from standard commercial suppliers (Sigma Aldrich and Merck) and used as received without further purification**.** All reactions were monitored by TLC (Thin-Layer

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Chromatography) , silica gel F254, made by Merck, Germany. The melting points were measured with a Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded using KBr disks in a Shimadzu FTIR 300 spectrophotometer, in units of cm^{-1}**.** The ^{1}H and ^{13}C NMR spectra in 1d were recorded on a Bruker 300 MHz spectrometer in DMSO as a solvent chemical shifts were given in ppm in DMSO-d6 using TMS as an internal standard.

Preparation of product (1) and (2):

1.1 2-Methoxy phenyl thiourea (1)

In a vessel 1mmol anisidine, 1mmol ammonium thiocyanat and few ml. of concentration Hydrochloric acid were charged with stirring & then the mixture was heated on water bath to 100˚C for 1 hours. The reaction mixture was separated by filtration, it was dried and the precipitate re-crystallized from ethanol.

Yield 94%, m.p: 155-157˚C; FT-IR (KBr, cm^{-1}); 3330 (NH), 3167 (CH), 2049 (C=S), 1600 (C=C), 1266 (C-O). ^{1}HNMR (DMSO-300MHz) δ ppm: 12.06 (s, 1H, NH_{BRS}), 9.08 (s, 2H, NH2 BRS), 7.01-7.50 (m, 4H, Haromatic), 3.60 (s, 3H, OCH3).

1.2 2-Methoxy phenyl imino thiazolidin-4-one (2)

The white solid of (0.182 g, 1mmol) of 2-methoxy phenyl thiourea (1) obtained from the previous step with 1mmol of chloro acetyl chloride was put at reflux in ethanol (10ml) for 4 hours while stirring. The resulting solid was filtered and then dried. The precipitate re-crystallized from ethanol [14]

Yield 97%, m.p: 150-152˚C; FT-IR (KBr, cm^{-1}); 3437(NH), 2839(CH), 1682(C=O lactam), 1629(C=N), 1498(C=C). ^{1}HNMR (DMSO-300MHz) δ ppm: 12.18 (s, 1H, NH_{BRS}), 6.84-7.39 (m, 4H, H aromatic), 3.88 (s, 3H, OCH3), 3.51 (s, 2H, CH2).

1.3 5-(Orto chloro benzylidene)-2-methoxy phenyl imino thiazolidin-4-one (3f)

0.222 gr (1mmol) of 2-methoxy phenyl imino thiazolidin-4-one (2) obtained from the previous step and 1mmol of 2-chloro benzaldehyde was put at refluxing ethanol(10ml) for 4hours while stirring.then 7 drops of catalysts deep Eutectic was added. The reaction mixture was filtered and then dried. The precipitate re-crystallized from ethanol.

Yield 88%, m.p: 193-196˚C; FT-IR (KBr, cm^{-1}); 3418(NH lactam), 3191(CH), 1679(C=O lactam), 1613(C=N), 1544(C=C), 744(C-Cl). ^{1}HNMR (DMSO, 300MHz) δ ppm: 12.18(s, 1H, NH_{BRS}), 6.57-8.05 (m, 9H, Haromatic), 3.73 (s, 3H, OCH3).

1.4 5-(Orto nitro benzylidene)-2-methoxy phenyl imino thiazolidin-4-one (3g)

1mmol (0.222gr) of 2-methoxy phenyl imino thiazolidin-4-one (II) obtained from the previous step and 1mmol o f 2-nitro benzaldehyde was put at refluxing ethanol(10ml) for 5 hours while stirring.then 7 drops of catalysts deep Eutectic was added. The reaction mixture was filtered and then dried. The precipitate re-crystallized from ethanol.

Yield 91%, m.p: 212-215˚C; FT-IR (KBr, cm-1); 3329 (N-H lactam), 3214 (C-H), 1680 (C=O lactam), 1605 (C=N); 1524 (C=C); 1339 (N=O); 1242 (C-N). ^{1}HNMR (D_2O, 300MHz) δ ppm: 12.18(s, 1H, NH_{BRS}), 7.82-8.16 (m, 4H, Haromatic), 7.69 (s, 1H, C=CH), 6.51-7.39 (m, 4H, Haromatic), 3.71(s, 3H, OCH3).

^{13}CNMR(DMSO, δ ppm): 190.9, 164.0, 150.3, 147.2, 146.8, 130.8, 128.4, 122.7, 122.1, 118.9, 117.9, 115.1, 55.6, 39.4.

1.5 5-(Meta nitro benzylidene)-2-methoxy phenyl imino thiazolidin-4-one (3h)

1mmol (0.222gr) of 2-methoxy phenyl imino thiazolidin-4-one (II) obtained from the previous step and 1mmol of 3-nitro benzaldehyde was put at refluxing ethanol(10ml) for 6 hours while stirring.then 7 drops of catalysts deep Eutectic was added. The reaction mixture was filtered and then dried. The precipitate re-crystallized from ethanol.

Yield 93%, m.p: 212-215˚C; FT-IR (KBr, cm^{-1}); 3287(NH lactam), 3079(CH), 1694(C=O lactam), 1605(C=N), 1527(C=C), 1353(N=O), 1244(C-N). ^{1}HNMR (DMSO, 300MHz) δ ppm: 12.18 (s, 1H, NH_{BRS}), 6.57-8.31 (m, 9H, H aromatic), 3.70(s, 1H, OCH3).

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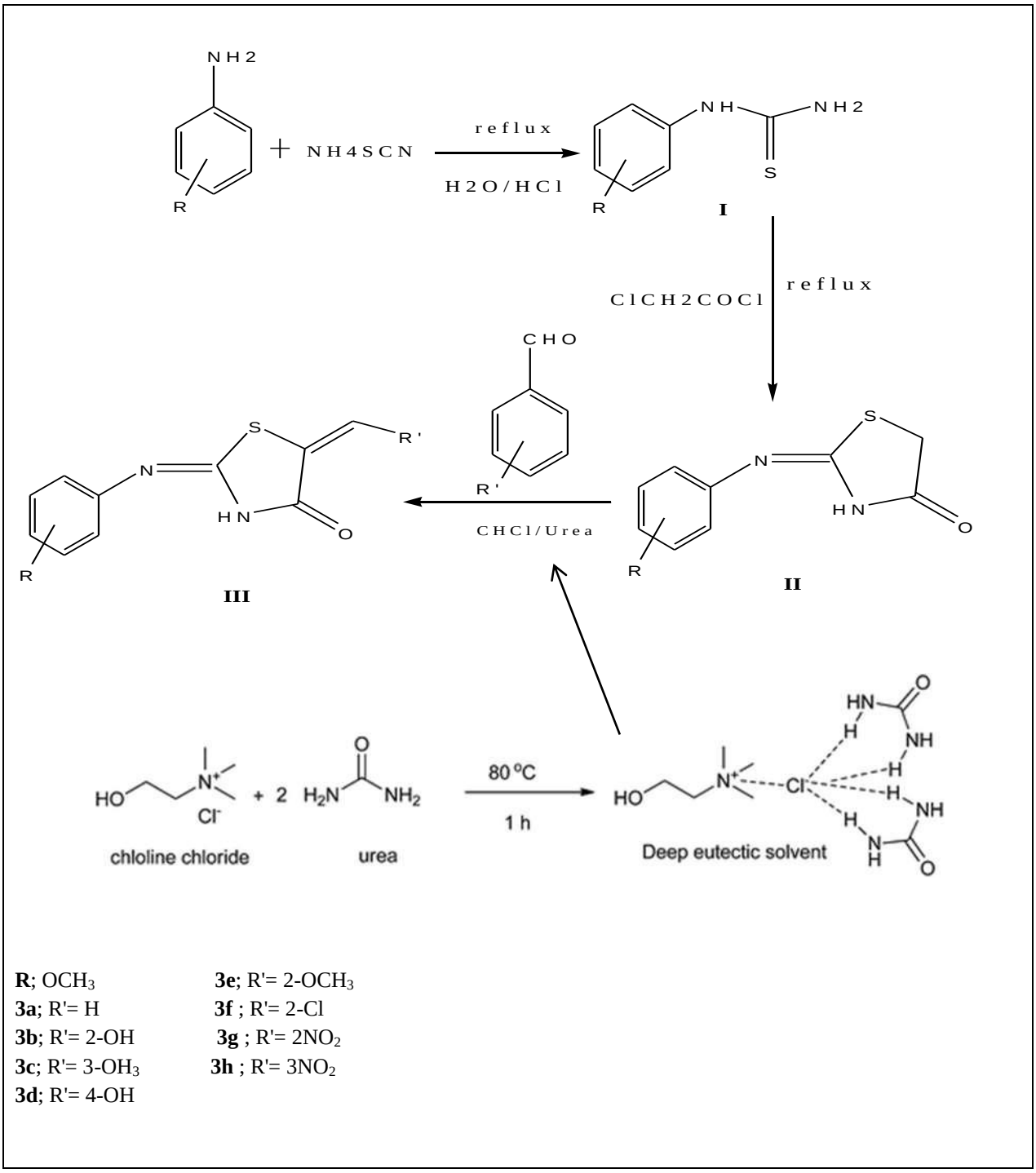
III. FIGURES AND TABLES



R; OCH_3 **3e**; R'= 2-OCH_3
3a; R'= H **3f** ; R'= 2-Cl
3b; R'= 2-OH **3g** ; R'= $2NO_2$
3c; R'= 3-OH_3 **3h** ; R'= $3NO_2$
3d; R'= 4-OH

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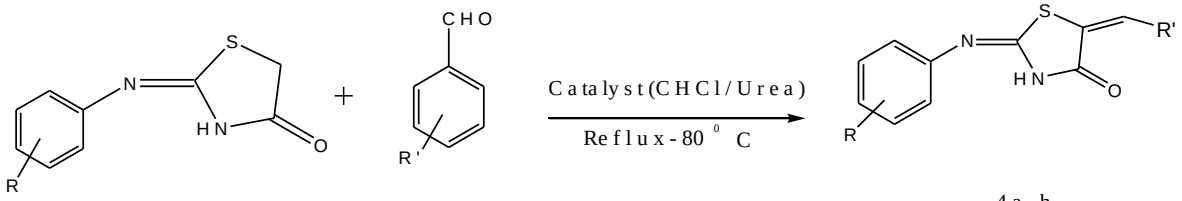
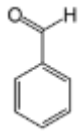
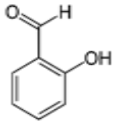
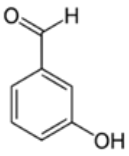
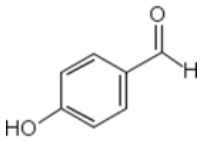
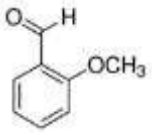
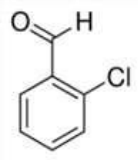
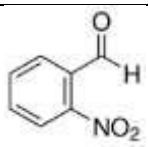
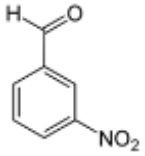


II Aldehyde **4a-h**

Entry	Aldehyde	Product	Time (hr)	Yield %	m.p (°C)
1		3a	4	80	185-189
2		3b	6	78	213-216
3		3c	3	78	213-216
4		3d	5	78	213-216
5		3e	4	82	215-218
6		3f	4	88	193-196
7		3g	5	91	212-215
8		3h	6	93	212-215

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Antibacterial Activity

All four compounds (3f-h) were screened against two bacteria for their antibacterial activity. Antibacterial activity was carried out against Gram negative bacteria, Escherichia Coli (ATCC, 6538) and Gram positive bacteria, Staphylococcus aureus (ATCC, 25922) by disk diffusion method using Mueller–Hinton Agar against.

The agar diffusion method was used for determination of the inhibition zone. Gentamicin we used as standard drug for antibacterial activities. Their turbidities matched that of a McFarland no. 0.5 turbidity standard. The stock solution of four compounds was prepared in dimethyl sulfoxide (DMSO). A loop of the standardised inoculums of the bacteria was issue over the surface of agar plates by using swabs. All the inoculated plates were incubated at 37 ºC and results were evaluated after 24 hr of incubation for bacteria. The concentration of these compound (3f-h) were placed on Muller Hinton agar. Finally, after 24 hr area of growth inhibition were measured. Loops containing 10 µg of 5 DMSO were used as the negative control. The tests are repeated 4 times and the average results are shown in table 2. All of the compounds showed good antibacterial activities (Table 2).

Table.2: Bacteria inhibition zone around disks containing samples.

Compound	S. aureus(mm)	E. Coli(mm)
3a	95	120
3d	45	90
3f	20	110
3g	60	115
3h	52	50
Gentamicine	**50**	**50**

IV. CONCLUSION

In this study described the green chemistry and we employed a choline chloride/urea as catalyst to synthesize thiazolidine-4-one derivatives (3a-h) (scheme1). The reaction with deep eutectic solvent as environmentally friendly catalyst. This reaction was more efficient in good yield in short time duration. Finally, after complete the reaction, that's possible to separate the catalyst. The results led to the synthesis of 5 – arylidene– 2- imino thiazolidine-4- ones substances with possibly particular biological and medicinal properties.The structure of synthesis compounds (f-g) were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic methods. All the physical, chemical properties, IR, NMR of the compounds are reported in experimental parts. All the compounds 3a–h display antibacterial effect against Gram positive bacterias, S. aureus, and E. coli Gram negative bacteria. Specifically, the synthesized compounds screened for their biological study which displayed moderate to good activity.

REFERENCES

[1] Mobinikhaledi, A,; Foroughifar, N,; BodaghiFard, (2010) .M. A. Eco-friendly and Efficient Synthesis of Pyrano[2,3-d] pyrimidinone and Tetrahydrobenzo pyran Derivatives in Water. Metal-Organic and Nano-Metal Chemistry.,40, 179-185.

[2] Ruß, C,; König, B, (2012). Low melting mixtures in organic synthesis – an alternative to ionic liquids?, Green Chem., , 14, 2969-2982.

[3] "Thiourea" (2016, Jan 21). Oxford Dictionaries. Oxford University Press. Retrieved.

[4] "Thiourea". (2016 Jan 21).Merriam-Webster Dictionary. Retrieved.

[5] Bernd Mertschenk, Ferdinand Beck, Wolfgang Bauer, (2002). "Thiourea and Thiourea Derivatives" in Ullmann's Encyclopedia of Industrial Chemistry by Wiley-VCH Verlag GmbH & Co. KGaA. All rights reserved. doi:10.1002/14356007.a26_803

[6] Agrawal, V.K.; Sachan, S.; Khadikar,(2000). P.V. QSAR studies on antihistaminic activity of some thiazolidine-4-ones. Acta Pharm., , 50, 281–290. (b) Diurno, M.V.; Mazzoni, O.; Correale, G.; Monterrey, I.G.; Calignano, A.; La Rana, G.; Bolognese, A(1999)Synthesis and structure–activity relationships of 2-(substituted phenyl)-3-[3-(N,Ndimethylamino)-propyl]-1,3-thiazolidin-4-ones acting as H1-histamine antagonists. II Farmaco. 54, 579–583.

[7] Bhati, S. K.; Kumar, A. Bhati, S. K.; Kumar,(2008). A. Synthesis of new substituted azetidinoyl and thiazolidinoyl-1,3,4-thiadiazino (6,5-b) indoles as promising anti-inflammatory agents. Eur. J. Med. Chem., , 43, 2323-2338.

[8] Vigorita, M.G.; Ottanà, R.; Monforte, F.; Maccari, R.; Monforte, M.T.; Trovato, A.; Taviano, M.F.; Miceli, N.; De Luca, G.; Alcaro, S.(2003). Ortuso, F. Chiral 3,3'- (1,2-ethanediyl)-bis[2-(3,4-dimethoxyphenyl)-4-thiazolidinones] with anti-inflammatory activity. Part 11: Evaluation of COX-2 selectivity and modeling. Bioorg. Med. Chem. 11, 999–1006.

[9] Chawla, P,; Singh, R,; Saraf SK, (2011). Effect of chloro and fluoro groups on the antimicrobial activity of 2,5-disubstituted 4-thiazolidinones: a comparative study. Med Chem Res, 21, 3263–3271

[10] Rawal, R. K.; Srivastava, T.; Haq, W.; Katti, (2004).S. B. J. An expeditious synthesis of thiazolidinones and tetathiazanones Chem. Res., , 5, 368. (b) Rawal, R. K.; Tripathi, R. K.; Katti, S. B.; Pannecouque, C.; De Clercq, E. (2007).Synthesis

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and Biological Evaluation of 2, 3-Diaryl substituted-1, 3-thiazolidin-4-ones as Anti-HIV Agents. Med. Chem. 3, 355-367.

[11] Havrylyuk, D,; Mosula, L,; Zimenkovsky, B,; Vasylenko, O,; Gzella, A,; Lesyk R. (2010). Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. Eur J Med Chem. 45, 5012–5021.

[12] Öcal, N,; Aydoğan, F,; Yolaçan, C,; Turgut, Z. (2003).Synthesis of some furo-thiazolidine derivatives starting from aldimines . J. Heterocyclic Chem., 40, 721-724.

[13] Mobinikhaledi, A,; Foroughifar, N,; Kalhor, M,; Mirabolfathy, M, (2010). Synthesis and antifungal activity of novel 2-benzimidazolylimino-5-arylidene-4-thiazolidinones. J. Heterocyclic Chem. 47, 77-80.

[14] Nahri-Niknafs, B,; Ahmadi, A, (2014). An Improved Process for the Production of 5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole as a Fungicide. J .Org. Chem. 8, 2, 77-81.