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Chemistry of novel piprazine-thiazole derivatives- their synthesis and microbial evaluation

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ABSTRACT

Compound 1 was converted into its Acid derivative using aq sodium hydroxide solution ***(2)****, which on further treatment with thionyl chloride to yield the respective acid chloride (3) which was further treated with the ammonium isothiocynate & aromatic amine to give the respective phenyl thioureas derivative (4) ,which further react with 2-bromo-acetophenone to give Thiazolo (5) derivatives. The structures of the synthesized compounds were confirmed by Physico-chemical test and spectral techniques. Representative samples were screened for their antimicrobial activity against gram positive and gram negative bacteria.*

Keywords: Thiazole, pyrazole, pyrazine.

INTRODUCTION

Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), and Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug). It has been noticed continuously over the years that Interesting biological activities [1-2] were associated with thiazole derivatives. Recently the applications of thiazoles were found in drug development for the treatment of allergies [3], hypertension [4], and inflammation [5], schizophrenia [6] bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain [10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B. [12] The chemistry of 1,2,3-triazoles has also received much attention because of their wide range of applications as they have been used as fungicides, herbicides, light stabilizers, fluorescent whiteners, optical brightening agents, and corrosion retardants [14-16]. N, N-Phthalyl-L-glutamic anhydride is a crucial reagent for y-glutamylations. A useful Synthetic route to glutamylaminoacids and glutamylamino peptides has been successfully established by the utilization of compounds protected by the phthalyl group.

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of 6[ethyl-3-methyl-butanoate-2-yl]-5,7-dioxo pyrolo [3,4b] pyrazine (1):
To mixture of N, N phathalic anhydride (1mol) & L- valin methyl ester (1mol) was directly heated to 140 ºC. For 2 hr. reaction progress was monitor by TLC. Upon completion hexane was added to reaction mass, solid mass separate out, filters it and washed with hexane to yield the white product.
M.P.- 145-150 °C, yield - 90 %

Synthesis of 6[3-methyl-butanoic-2-yl]-5,7-dioxo pyrolo [3,4b] pyrazine (2)
A suspension of **(1)** (0.01 mol) and aq NaOH solution (3 Mole) was heated for 2 hr at 50 ºC. Reaction was monitor by TLC, upon completion mixture was cooled to RT. The solid product was separate out by adjusting the pH 2. Filter the product, washed with water and pet ether to yield the white product.
M.P - 180 °C, yield - 80%

Synthesis of 6[3-methyl-carbonyl chloride-2-yl]-5,7-dioxo pyrolo[3,4b] pyrazine (3)
Compound 2 (1 mole) was dissolve in dichloro methane and cooled to 0 to 5 ºC. Thionyl chloride (1.1 mole) was slowly added drop wise at below 5 ºC. After addition, heat the reaction mass up to reflux for1 hr. Reaction monitored by TLC. Upon completion, reaction mixture was quenched into the water & dichloromethane. Separate the dichloromethane wash the organic layer with water & saturated NaCl solution, distilled out MDC completely to yield product (3)
M.P. - 140-142 °C, yield - 76 %

Synthesis of 5 by one pot reaction
Ammonium thiocyanate (1.5 mmole) & TBAB (0.1mmole), water (3 ml), acyl chloride (1.0 mmole) & aryl amine (1 mmole) were mixed and the suspension was stirred at room temp for 45 min until the product was separated out fully **(4)** (a-d) **6[1-oxo-1-(4'-methoxy phenyl)thiourea-3-methyl-butane-2-yl]-5,7-dioxo pyrolo[2,3b] pyrazine.**
α-bromoacetone / α-Bromoacetophenoe (1mmole) was then added to the suspension of thiouera & mixture was reflux for 30 mins (50 min for α-Bromoacetopheone) after the reaction was completed (monitor by TLC) crude product was obtained by filtration & recrystallization offered pure product (5).
M.P =192.195 °C, yield = 71%

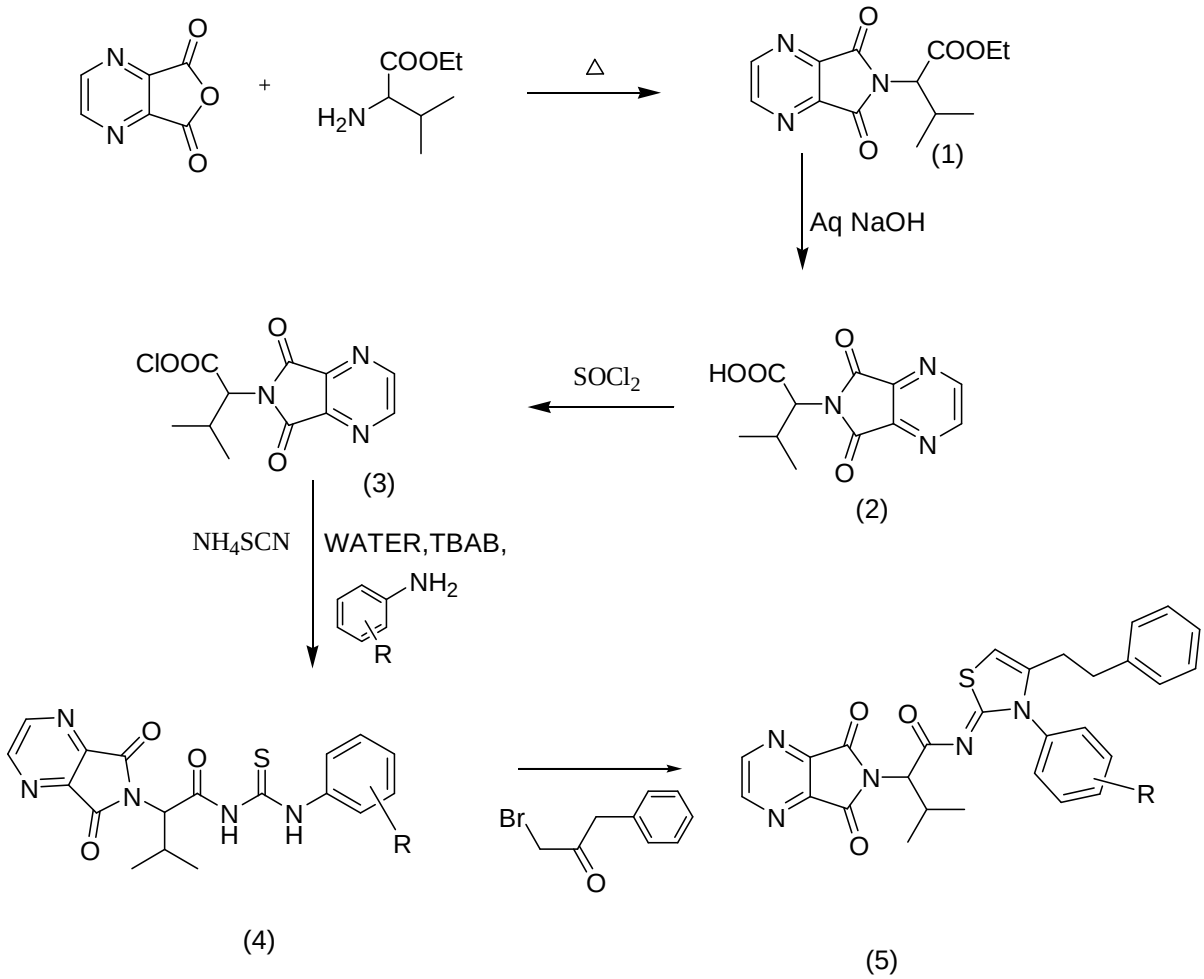
Spectral Interpretation: 6[ethyl-3-methyl-butanoate-2-yl]-5,7-dioxo pyrolo[3,4b] pyrazine
Yield: 90%; m.p. =145-150°C: IR (cm-1): 1735 (C=O), 1685(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.11 (d, 3H, 2×CH_3), 1.30 (t, 3H, CH_3), 2.91 (m, 1H, CH), 4.11(q, 2H, OCH_2),4.30 (d,1H,N-CH), 9.10-9.20 (d, 2H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 14.24 (CH_3), 17.45; (2×CH_3), 27.23(CH), 57.14 (N-CH), 62.21 (O-CH_2), 140-145 (Ar-C), 165.42 (C=O), 179.29 (C=O). LCMS; m/z: 277; Anal.Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15% Found: C, 56.52; H, 5.18, N, 15.35 %

(2) 6[3-methyl-butanoic-2-yl]-5, 7-dioxo pyrolo [3,4b] pyrazine
Yield: 80%; m.p. =180-185°C: IR (cm-1): 3240 (COOH), 1685(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.16 (d, 3H, 2×CH_3), 2.81 (m, 1H, CH), 4.23 (d,1H,N-CH), 9.20-9.25 (d, 2H, Ar -H),10.2 (s,1H ,OH) ^{13}C NMR (DMSO-d6, δ/ ppm): 17.55 (2×CH_3), 28.23(CH), 58.14 (N-CH), 142-146 (Ar-C), 168.42 (C=O), 176.29 (C=O). LCMS; m/z: 249; Anal.Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 6.85% Found: C, 52.92; H, 4.38, N, 6.35 %

(3) 6[3-methyl-carbonyl chloride-2-yl]-5,7-dioxo pyrolo[3,4b] pyrazine
Yield: 76%; m.p. =130-132°C: IR (cm-1): 1685(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.16 (d, 3H, 2×CH_3), 2.81 (m, 1H, CH), 4.40 (d,1H,N-CH), 9.10-9.25 (d, 2H, Ar -H), ^{3}C NMR (DMSO-d6, δ/ ppm): 17.55 (2×CH_3), 29.23(CH), 59.14 (N-CH), 141-148(Ar-C), 166.42 (C=O), 178.29 (C=O). LCMS; m/z: 249; Anal.Calcd for $C_{11}H_{10}N_3O_3Cl$: C, 49.36; H, 3.77; Cl, 13.25, N, 15.70% Found: C, 49.92; H, 3.38, Cl, 15.35, N, 14.98 %

(5) 6[1-oxo-1-(N-2-imino-3, 4 biphenyl thiazole)-3-methyl-butane-2-yl]-5,7-dioxo pyrolo[2,3b] pyrazine.
Yield: 71%; m.p. =192-195°C: IR (cm-1): 1685(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.06 (d, 3H, 2×CH_3), 2.71 (m, 1H, CH), 4.32 (d,1H,N-CH), 5.50(s,1H, CH),6.12-7.50 (d, 10H, Ar-H),9.06-9.15 (d, 2H, Ar -H), ^{3}C NMR (DMSO-d6, δ/ ppm): 18.55 (2×CH_3), 28.23(CH), 60.14 (N-CH),106 (CH),115-140(Ar-C) , 142-148(Ar-C), 156(C=N),165.42 (C=O), 180.29 (C=O). LCMS; m/z: 249; Anal.Calcd for $C_{26}H_{21}N_5O_3S$: C, 64.58; H, 4.38; N, 14.48% Found: C, 64.21; H, 4.29, N, 14.32 %

Genral reaction Scheme



6[1-oxo-1-(N-2-imino-3-p-bromo phenyl, 4-phenyl thiazole)-3-methyl-butane-2-yl]-5, 7-dioxo pyrolo[2,3b] pyrazine.

Yield: 77%; m.p. =182-185°C: IR (cm-1): 1685(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.16 (d, 3H, 2×CH_3), 2.81 (m, 1H, CH), 4.42 (d,1H,N-CH), 5.43(s,1H, CH),6.52-7.42 (d, 9H, Ar-H),9.16-9.25 (d, 2H, Ar -H), ^{3}C NMR (DMSO-d6, δ/ ppm): 17.56 (2×CH_3), 27.24(CH), 58.14 (N-CH),108 (CH),118-136 (Ar-C) , 144-149(Ar-C), 155(C=N),168.42 (C=O), 179.29 (C=O). LCMS; m/z: 562; Anal.Calcd for $C_{26}H_{20}N_5O_3SBr$: C, 55.52; H, 14.58; N, 13.45% Found: C, 55.40; H, 14.29, N, 13.32 %

6[1-oxo-1-(N-2-imino-3-p-methoxy phenyl, 4-phenyl thiazole)-3-methyl-butane-2-yl]-5,7-dioxo pyrolo[2,3b] pyrazine

Yield: 73%; m.p. =165-170°C: IR (cm-1): 1680(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.04 (d, 3H, 2×CH_3), 2.91 (m, 1H, CH), 4.36 (d,1H,N-CH), 3.68(s,3H, OCH_3) 5.46, (s,1H, CH),6.63-7.33(d, 9H, Ar-H),9.03-9.15 (d, 2H, Ar -H), ^{3}C NMR (DMSO-d6, δ/ ppm): 18.26 (2×CH_3), 29.34(CH),54.28 (OCH_3) 59.24 (N-CH),110 (CH),115-139 (Ar-C) , 142-148(Ar-C), 157(C=N),165.42 (C=O), 175.29 (C=O). LCMS; m/z: 514; Anal.Calcd for $C_{27}H_{23}N_5O_4S$: C, 63.14; H, 4.51; N, 13.64% Found: C, 63.40; H, 4.29, N, 13.32 %

6[1-oxo-1-(N-2-imino-3-p-methyl phenyl, 4-phenyl thiazole)-3-methyl-butane-2-yl]-5,7-dioxo pyrolo[2,3b] pyrazine

Yield: 80%; m.p. =155-160°C: IR (cm-1): 1680(C=O amide), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.12 (d, 3H, 2×CH_3), 2.85 (m, 1H, CH), 4.26 (d,1H,N-CH), 2.11(s,3H, CH_3) 5.52, (s,1H, CH),6.58-7.50(d, 9H, Ar-H),9.11-9.16 (d, 2H,

Ar -H), ^{3}C NMR (DMSO-d6, δ/ ppm): 19.23 (2×CH_3), 21.28 (CH_3) ,28.44(CH),) 60.24 (N-CH),108 (CH),112-138 (Ar-C) , 140-145(Ar-C), 158(C=N),164.42 (C=O), 178.29 (C=O). LCMS; m/z: 498; Anal.Calcd for $C_{27}H_{23}N_5O_3S$: C, 65.17; H, 4.66; N, 14.14% Found: C, 65.46; H, 4.31, N, 14.38 %

Antimicrobial and antifungal activities

All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [15, 16]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in **TABLE I**.

Table I. Antimicrobial activities of some newly synthesized compounds

Compds	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
3	17	15	18	21	17	10	8
4	16	16	17	21	19	10	9
5	15	14	18	19	18	11	9
6	18	19	19	20	18	12	10
DMSO	0	0	0	0	0	0	0
Amphicilin®	24	20	19	22	24	14	14

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcus lactis; A. niger = Aspergillus niger; P. Sp. = Penicillium Sp; C. Albicans = candida Albicans.
The sensitivity of microorganisms to the tested compounds is identified in the following manner;*
Highly Sensitive = Inhibition zone: 15-20 mm
Moderately Sensitive = Inhibition zone: 10-15 mm
Slightly Sensitive = Inhibition zone: 5-10 mm
Not Sensitive = Inhibition zone: 0 mm
** Each result represents the average of triplicate readings.*

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