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Synthesis and antimicrobial studies of novel heterocyclic compounds containing piperazine ring

Hitendra D. Raj[1] and Yogesh S. Patel[2*]

[1]*Chemistry Department, M. B. Patel Science College, Sardar Patel University, Anand, Gujarat, India*
[2]*Chemistry Department, Government Science College, Gariyadhar, Gujarat, India*

ABSTRACT

*1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(1)** undergoes facile condensation with aromatic aldehydes to afford the corresponding 1-(4-(arylideneamino)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(2a-h)** in good yields. Cyclocondensation of compounds **(2a-h)** with thioglycolic acid yields 2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one **(3a-h)**. The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.*

Keywords: 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone, Schiff base, thiazolidine, antibacterial and antifungal activities.

INTRODUCTION

The heterocyclic compounds such as 4-thiazolidinones [1,2], fused thiazolidinones [3,4], 2-pyrrole and 2-pyrrolidinones [4,5], 1,3,5-oxadiazine and tetrazole [6] have prominent role in pharmaceutical. Schiff bases and amides derived from various heterocyclic compounds displayed broad range of biological activity. Literature assessment reveals that heterocyclic compounds indicate that they have coordinating behaviors with the transition metal ions [7,8]. Heterocyclic compounds also display biochemical and physiochemical effects [9-12]. If both these moiety clubbed into one molecule, it will be afford as good bioactive compound. 4-thiazolidinones are also known to exhibit antitubercular [13], antibacterial [14], antifungal [15] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone and 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone moieties which may enhance the drug activity of compounds to some extent or they might possess some of the above mentioned biological activities. Hence the present communication comprises the synthesis of 2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one **(3a-h)**. The synthetic approach is shown in **scheme-1**.

MATERIALS AND METHODS

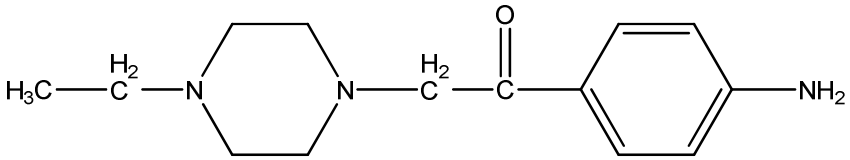
Materials

All chemicals used were of laboratory grade. 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone was prepared by reported method [16].

Measurement

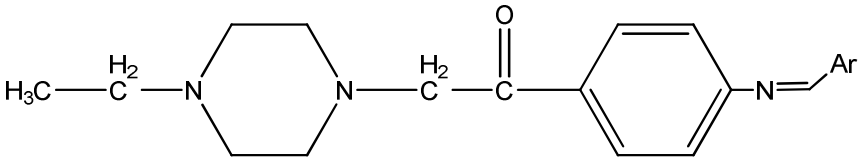
Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz.

***Preparation of* 1-(4-(arylideneamino)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone (2a-h):**
A mixture of 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(1)**, (0.01mole) and the aromatic aldehydes **(a-h)** in ethanol (15ML) was refluxed on a water bath for 3-4 hrs. The solid separated was collected by filtration, dried and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in **Table-1**.



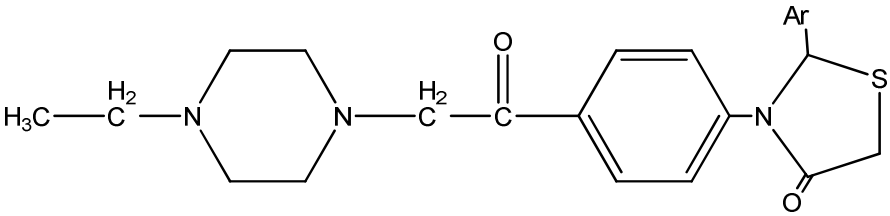
1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone
(1)

ArCHO(a-h) /Methanol



1-(4-(arylideneamino)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone
(2a-h)

$SHCH_2COOH$
$ZnCl_2/DMF$



2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one
(3a-h)

Scheme-1

Where Ar= (a) C_6H_5 (b) $2\text{-}CH_3\text{-}C_6H_4$
(c) $4\text{-}CH_3\text{-}C_6H_4$ (d) $2\text{-}OH\text{-}C_6H_4$
(e) $4\text{-}OH\text{-}C_6H_4$ (f) $2\text{-}OCH_3\text{-}C_6H_4$
(g) $4\text{-}OCH_3\text{-}C_6H_4$ (h) $2\text{-}ClC_6H_4$

Synthesis of 2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one (3a-h):
A mixture 1-(4-(arylideneamino)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(2a-h)** (0.01 mole) in THF (30ML) and thioglycolic acid (0.01 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed for 13-14hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: chloroform (6.5:3.5; v/v) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one **(3a-h)**, which were obtained in good yield. The yields, melting points and other characterization data of these compounds are given in **Table-2**.

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/Ml by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline

as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 3h and 3f were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline **Table-3**.

Table:-1 Analytical Data and Elemental Analysis of Compounds (2a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	$C_{21}H_{25}N_3O$ (335)	82	230-231	75.19	75.1	7.51	7.4	12.53	12.5
2b	$C_{22}H_{27}N_3O$ (349)	79	218-220	75.61	75.5	7.79	7.7	12.02	11.9
2c	$C_{22}H_{27}N_3O$ (349)	78	215-217	75.61	75.5	7.79	7.7	12.02	12.0
2d	$C_{21}H_{25}N_3O_2$ (351)	75	214-216	71.77	71.7	7.17	7.1	11.96	11.9
2e	$C_{21}H_{25}N_3O_2$ (351)	76	214-216	71.77	71.7	7.17	7.1	11.96	11.9
2f	$C_{22}H_{27}N_3O_2$ (365)	78	208-210	72.30	72.2	7.45	7.4	11.50	11.4
2g	$C_{22}H_{27}N_3O_2$ (365)	75	211-213	72.30	72.3	7.45	7.4	11.50	11.4
2h	$C_{21}H_{24}ClN_3O$ (369)	74	217-219	68.19	68.1	6.54	6.5	11.36	11.3

***** *Uncorrected*

Table:-2 Analytical Data and Elemental Analysis of Compounds (3a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{23}H_{27}N_3O_2S$ (409)	72	220-225	67.45	67.4	6.65	6.6	10.26	10.2	7.83	7.8
3b	$C_{24}H_{29}N_3O_2S$ (423)	69	218-219	68.05	68.0	6.90	6.8	9.92	9.8	7.57	7.5
3c	$C_{24}H_{29}N_3O_2S$ (423)	67	214-216	68.05	68.0	6.90	6.9	9.92	9.9	7.57	7.5
3d	$C_{23}H_{27}N_3O_3S$ (425)	68	213-214	64.92	64.8	6.40	6.4	9.87	9.8	7.54	7.5
3e	$C_{23}H_{27}N_3O_3S$ (425)	67	219-221	64.92	64.9	6.40	6.3	9.87	9.8	7.54	7.5
3f	$C_{24}H_{29}N_3O_3S$ (439)	65	206-208	65.58	65.5	6.65	6.6	9.56	9.5	7.29	7.29
3g	$C_{24}H_{29}N_3O_3S$ (439)	67	222-224	65.58	65.5	6.65	6.6	9.56	9.5	7.29	7.29
3h	$C_{23}H_{26}ClN_3O_2S$ (443)	68	214-216	62.22	62.1	5.90	5.8	9.46	9.4	7.22	7.1

***** *Uncorrected*

Table:-3 Antibacterial Activity of Compounds (3a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3a	44	61	60	67
3b	45	65	61	68
3c	45	67	64	69
3d	46	62	62	68
3e	49	67	63	70
3f	51	74	71	74
3g	48	69	66	70
3h	53	73	68	75
Tetracycline	55	79	74	84

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum*. The antifungal activities of all the compounds **(3a-h)** were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1ml. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA

medium and autoclaved at 120°C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate
Y = Area of colony in test plate

The fungicidal activity displayed by various compounds **(3a-h)** is shown in Tables-4.

Table-4 Antifungal Activity of Compounds (3a-h)

Compounds	*Nigrospora Sp.*	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*
3a	56	49	59	52
3b	58	51	59	56
3c	64	63	60	54
3d	58	51	59	56
3e	58	51	59	56
3f	70	66	70	60
3g	56	49	59	52
3h	58	51	59	56

RESULTS AND DISCUSSION

It was observed that 1-(4-aminophenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(1)** undergoes facile condensation with aromatic aldehydes to afford the corresponding 1-(4-(arylideneamino)phenyl)-2-(4-ethylpiperazin-1-yl)ethanone **(2a-h)**. The structures of **(2a-h)** were confirmed by elemental analysis and IR spectra showing an absorption bands at around, 1630-1670 cm^{-1}(C=N), 3420 (NH), 2980 (CH_2), 1725 (CO), 3030-3080 cm^{-1} (C-H, of Ar.), 3450 (OH), 2815-2850 cm^{-1} (-OCH_3). **^{1}H NMR :** 7.48-8.15 (9H,m,Ar- H), 8.43-8.80 (1H,s,-N=CH), ~3.74 (s,2H,N-CH_2), 2.40-2.68 (t,8H,CH_2), ~2.70 (s,2H,N-CH_2-CH_3), ~1.80 (s,3H,CH_3), 2b; 2.28 (3H,s,-CH_3), 2c; 2.30 (3H,s,CH_3), 2d; 5.12 (1H,s,-OH), 2e; 5.19 (1H,s,-OH), 2f; 3.82 (3H,s,-OCH_3), 2g; 3.87 (3H,s,-OCH_3). The C, H, N analysis data of all compounds are presented in **Table-1**.

The structures assigned to 2-aryl-3-(4-(2-(4-ethylpiperazin-1-yl)acetyl)phenyl)thiazolidin-4-one **(3a-h)** were supported by the elemental analysis and IR spectra showing an absorption bands at 1690 cm^{-1} (C=O of thiazolidinone ring), 718 cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095 cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H of Ar.). **^{1}H NMR:** 8.89-7.24 (9H, m,Ar - H), ~6.50 (1H, s, CH), 4.2-3.8 (2H,s,thiazole ring -CH), ~3.74 (s,2H,N-CH_2), 2.40-2.68 (t,8H,CH_2), ~2.70 (s,2H,N-CH_2-CH_3), ~1.80 (s,3H,CH_3), 3b; 2.28 (3H,s,-CH_3), 3c; 2.30 (3H,s,CH_3), 3d; 5.12 (1H,s,-OH), 3e; 5.19 (1H,s,-OH), 3f; 3.82 (3H,s,-OCH_3), 3g; 3.87 (3H,s,- OCH_3). The C, H, N, S analysis data of all compounds are presented in **Table-2**.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in **Scheme-1**. The IR data also equivalent for assignment of the predicted structure.

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