Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(4):180-184
(http://derpharmachemica.com/archive.html)

Synthesis and biological evaluation of 2, 4-thiazolidinedione incorporated imidazo[1, 2-a] pyridines

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ABSTRACT

Codensation of different phenacyl bromides with 2-amino pyridine afforded 2–aryl imidazo(1,2-a) pyridines ***1(a-e)*** *. Vilsmeier-Haack reaction of* ***1(a-e)*** *gave 2–aryl imidazo (1,2-a) pyridine -3-carbaldehydes* ***2(a-e).*** *Further, the condensation of these carbaldehydes with thiazolidinedione in glacial acetic acid gave (5-{[2-aryl imidazo [1,2-a]pyridine-3-yl]methylidene}-1,3-thiazolidine-2,4-diones* ***3(a-e)*** *in good yields. The structures of the synthesized compounds were confirmed on the basis of spectral data and the compounds were screened for in vitro anti cancer activity and in vivo anti-inflammatory activity. Compound 4d exhibited superior activity against MCF-7 and HCT-116 cell lines at IC_{50} values of 14.02 and 18.12 µM. However, compound 4b showed slightly less activity against MCF-7 and HCT-116 cell lines with IC_{50} values of 22.8 and 24.0 µM. In antiinflammatory screening, compound 4c exhibited maximum activity and the results are comparable with the standarad drug, ibuprofen.*

Key words: Imidazo [1,2-a] pyridine-3- carbaldehydes, Thiazolidinedione, Vilsmeier-Haack reaction, MTT assay, Antiinflammatory activity.

INTRODUCTION

Imidazo [1,2-a] pyridines are bridge - head nitrogen heterocycles and compounds containing this heterocycle have been reported for various biological activities **(1-5).** Several drug formulations containing this heterocycle are currently available in the market as anxiolytics, sedative and hypnotics, anti-ulcer and PDE3 inhibitors. In recent years, the scaffold, thiazolidendione [TZD] has generated a lot of interest being a main moiety in PPARγ inhibitors. Diverse biological activites like anti-microbial**(6-8),** anti-cancer**(9),** anti-inflammatory**(10),** anti-obesity**(11),** anti-diabetic**(12-15**) etc., have been reported for derivatives containing this moiety in the past few years. Stimulated by this information and in continuation of our efforts to design new biologically active molecules, in the present study, we synthesized five new hybrid molecules by linking the above two pharmacophores into a single molecule with an intention to have efficacy and synergistic activity. In this context, we synthesized new derivatives by condensing 2–aryl imidazo pyridine carbaldehydes with thiazolidinedione in acetic acid medium in presence of piperdine to give 5-{[2-aryl imidazo [1,2-a]pyridine-3-yl]methylidene}-1,3-thiazolidine-2,4-diones **3(a-e).** The structures of the synthesized compounds have been confirmed on the basis of physical and spectral data. Finally, this new class of hybrids have been evaluated for cytotoxic activity against 2-cell lines (MCF-7 and HCT- 116) by MTT assay method. Further, anti inflammatory study of the compounds was also performed using carrageenan induced rat paw edema method.

MATERIALS AND METHODS

All the solvents and chemicals used were of synthetic grade from SD fine chemicals Ltd., E.Merck, NR chemicals Ltd. and Aldrich chemicals. Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E- Merck 0.25 mm silica gel plates. Visualization was accomplished with UV light (256 nm) and iodine chamber. Purification of synthesized compounds was done by re-crystallization process. The purity of the

compounds was checked by a single spot in TLC. Melting points were determined in open capillary tubes using ANALAB melting point apparatus and are uncorrected. All the ^{1}H NMR spectra were recorded on AVANCE 300 MHz spectrometer using DMSO-d_6 as solvent and tetra methyl silane (TMS) as an internal standard. Chemical shift values are listed in δ scale. The IR spectra were recorded on Schimadzu FTIR spectrophotometer by using 1% potassium bromide discs. Mass spectra of the compounds were recorded on Agilent 6430 triple quadruple LC-MS system and were given in mass units (m/z).

EXPERIMENTAL PROCEDURES

General procedure for Synthesis of 2-aryl imidazo [1, 2-*a*] pyridines 1(a-e)

A mixture of 0.01 mol of phenacyl bromide and 0.01 mol of 2-amino pyridine was taken in 20-25 ml of acetone and kept for stirring at room temperature for nearly 1-2 hrs and the precipitate obtained was filtered. The filtrate on concentration in Rota evaporator gave the product which was washed thoroughly with acetone to remove traces of amino pyridine. The compound was purified by recrystallization from acetone. The percentage yield was 88%.

General procedure for Synthesis of 2-aryl imidazo [1, 2-*a*] pyridine-3-carbaldehydes 2(a-e)

To an ice cold solution of DMF (0.3 mol), was added $POCl_3$ (0.036 mol) drop-wise and the temperature was maintained below 10°C since an exothermic reaction takes place. To the reaction mixture, an ice-cold solution of 2-aryl imidazo [1,2-*a*] pyridine (0.1 mol) dissolved in $CHCl_3$ was added slowly. After completion of addition, the reaction mixture was refluxed for about 12 hrs and the reaction was monitored by TLC. The reaction mixture was neutralised by using $NaHCO_3$ in cold condition and then washed with water and extracted with $CHCl_3$ and dried over anhyd.Na_2SO_4. The product obtained was purified by recrystallization from ethanol. The percentage yield was 70%.

General procedure for Synthesis of 2-aryl imidazo[1,2-a]pyridine-3-yl]methylidene}-1,3-thiazolidine-2,4-diones 3(a-e)

To a mixture of 2-aryl imidazo [1, 2-*a*] pyridine-3-carbaldehyde (0.02 mol) and 1, 3-thiazolidine-2, 4-dione (0.02 mol) in glacial acetic acid (10-15 ml), was added 2-3 drops of piperidine and refluxed for 18-20 hrs. The reaction mixture was cooled and added to ice cold water to obtain precipitate, which was filtered and washed thoroughly with water to give the product. The product was purified by recrystallization from ethanol.

BIOLOGICAL ACTIVITY

CYTOTOXIC ACTIVITY

All the synthesized compounds were screened for MTT assay against MCF-7, HCT-116 and Vero(normal) cell lines and the test was performed at Natco Laboratories, Hyderabad. $1x10^4$ cells/well were seeded in 100 µl DMEM supplemented with 10% FBS in each well of 96 well microculture plates and incubated for 24 hr at 37^0C in a CO_2 incubator. After incubation, cells were treated with test compounds **3(a-e)** at 100,50,25,12.5,6.25 µg/ml concentrations for 48hr. After 48 hr of incubation, media was removed and to each well 10 µl of MTT(5 mg/ml) was added and the plates were further incubated for 4 hrs. Supernatant liquid from each well was carefully removed and formazon crystals were dissolved in 100µl of DMSO and absorbance was measured at 540 nm wavelength.

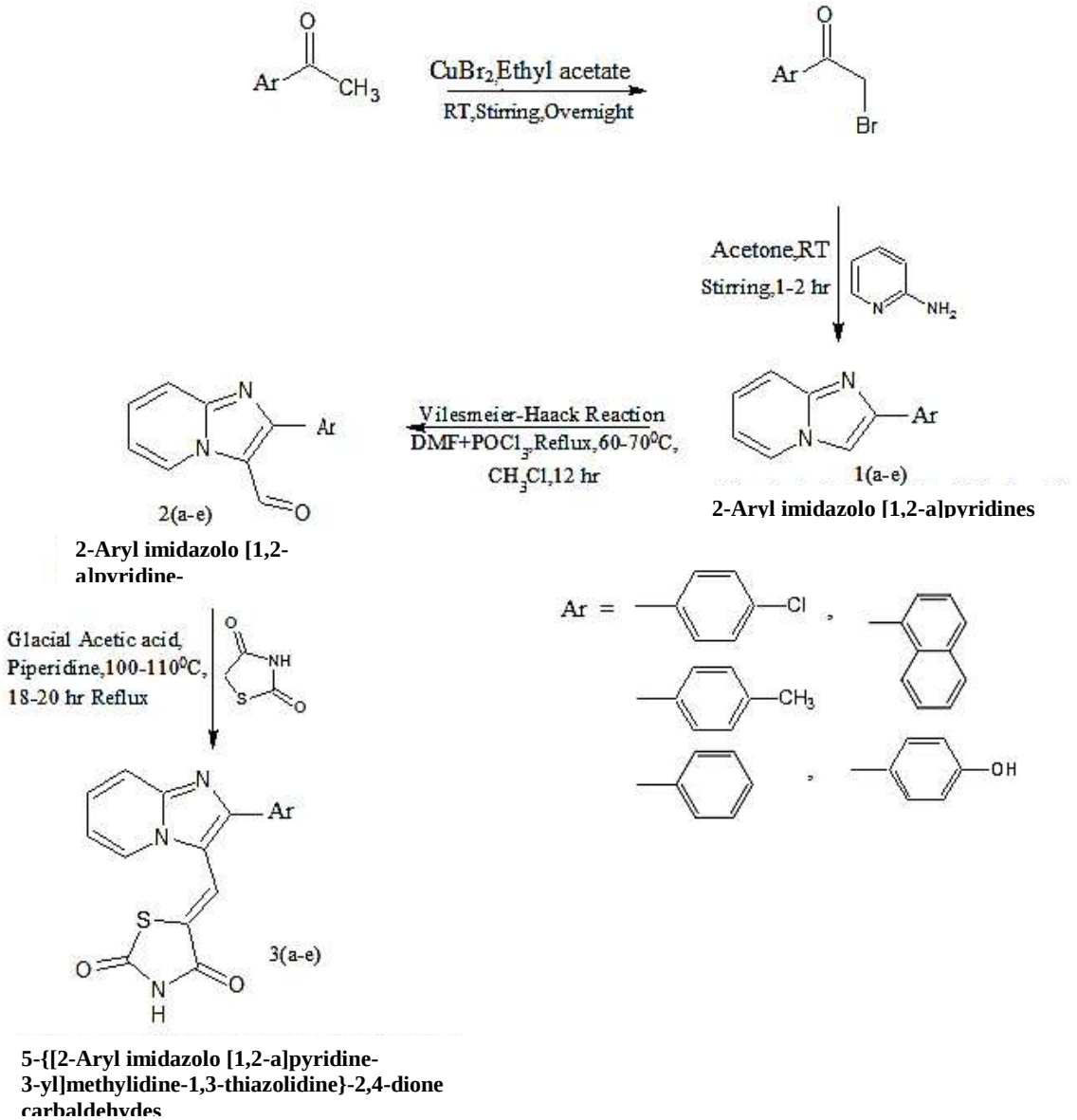
ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory activity of five derivatives was tested by Carrageenan induced rat paw edema method as per the procedure described in our earlier work **(2)** using ibuprofen as standard drug.

RESULTS AND DISCUSSION

The plan of the synthesis is given under scheme 1. Different acetophenoes were converted into phenacyl bromides using cupric bromide as brominating agent in ethyl acetate by stirring over night at room temperature. Reaction of phenacyl bromides with 2- amino pyridine in dry acetone gave 2–aryl imidazo (1,2-a) pyridines **1(a-e**). Vilsmeier-Haack reaction of **1(a-e)** gave 2–aryl imidazo (1,2 -a) pyridine carbaldehydes **2(a-e**) in good yields. The structures of imidazo pyridine carbaldehydes were confirmed by FTIR and mass spectral data. The compounds showed absorption peaks around 1640 cm^{-1} due to carbonyl absorption of aldehyde. Further, the mass ion peaks of 100% intensity in mass spectra corresponding to their molecular weights confirmed the structures. Thiazolidinedione was synthesized seperately by standarad procedure and was condensed with carbaldehydes in acetic acid to obtain 5-{[2-aryl imidazo [1,2-a]pyridine-3-yl]methylidene}-1,3-thiazolidine-2,4-diones **3(a-e).**The structures were confirmed on the basis of FTIR, mass and ^{1}HNMR spectral data. In ^{1}HNMRspectra, the NH proton appeared as singlet around δ 10.0, a singlet around δ9.5 was due to methine proton and the aromatic protons appeared in the range of δ7.0-8.0. I.R spectra of the compounds showed absorption peaks around 1735,1700and 1630 cm^{-1}due to two C=O absorptions and C=C absorption. Further, confirmation was obtained from mass spectral data.

Scheme for synthesis of compounds



Scheme -1

Physical and Spectral data of synthesized compounds:

(3a) 5-{[2-(4-chlorophenyl) imidazo [1,2-*a*] pyridin-3-yl] methylidene}-1,3-thiazolidine-2,4-dione: Light yellow coloured solid ; Yield:71%; M.p: 147-149^{0}C; IR:(KBr)cm^{-1}: 1735,1701,1631and 750 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) :δ10.1(s,1H,NH),9.7(s,1H,=CH),7.1-7.8(s,8H,Ar); Mass (m/z):354 (M-H); Anal.calcd.for $C_{17}H_{10}N_3O_2SCl$ calculated C,57.39; H, 2.83; Cl,9.96; N,11.81; O,8.99; S,9.01% Found: C,57.65; H,2.76; Cl,10.00; N,11.89; O,8.69; S,9.05%

(3b)5-{[2-(4-methyl phenyl) imidazo [1,2-*a*] pyridin-3-yl]methylidene}-1,3-thiazolidine-2,4-dione:Yellow coloured solid; Yield:73%; M.p: 147-148^{0}C; IR:(KBr)cm^{-1}: 1705,1633and1494cm^{-1} ;^{1}HNMR (400 MHz, $CDCl_3$) : δ10.1(s,1H,NH),9.7(s,1H,=CH); Mass (m/z) : 334 (M-H); Anal.calcd.for $C_{18}H_{13}N_3O_2S$ calculated C,64.46; H, 3.91; N,12.53; O,9.54; S,9.56 Found :C,65.35; H, 3.80; N,12.58; O,9.23; S,9.48%

(3c)5-[(2-phenyl imidazo [1,2-*a*]pyridin-3-yl) methylidene] -1,3-thiazolidine-2,4-dione:Yellow coloured solid; Yield:75%; M.p: 145-150^{0}C; IR:(KBr)cm^{-1}: 1739,1699and1635cm^{-1} ;^{1}HNMR (400 MHz, $CDCl_3$) :δ10.1(s,1H,NH), 9.7(s,1H,=CH) 7.1-7.8(s,8H,Ar); Mass (m/z) :320(M-H); Anal.calcd.for $C_{17}H_{11}N_3O_2S$ calculated C,63.54; H, 3.45;N,13.08; O,9.96; S,9.98% Found :C, 63.35; H, 3.35; N,12.89; O,9.82; S,9.85%

(3d)5-{[2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-3-yl] methylidene}-1,3-thiazolidine2,4-dione:Light brown coloured solid; Yield:70%; M.p: 145-150^{0}C ; IR:(KBr)cm^{-1}: 1737,1697and1635cm^{-1} ; ^{1}HNMR (400 MHz, $CDCl_3$) : δ10.1(s,1H,NH),9.7(s,1H,=CH) 7.1-7.8(s,11H,Ar); Mass (m/z) :370 (M-H);Anal.calcd.for $C_{21}H_{13}N_3O_2S$ calculated C,67.91; H, 3.53;N,11.31; O,8.62; S,8.63% Found :C, 67.35; H, 3.45; N,11.20; O,8.5; S,8.50%

(3e) 5-{[2-(4-hydroxyphenyl) imidazo[1,2-*a*] pyridin-3-yl]methylidene}-1,3-thiazolidine-2,4-dione:Brown coloured solid; Yield:70%; M.p: 145-150^{0}c ; IR:(KBr)cm^{-1}: 1739,1695and1604cm^{-1} ; Mass : m/z :336 (M-H);Anal.calcd.for $C_{17}H_{11}N_3O_3S$ calculated C,60.52; H, 3.29;N,12.46; O,14.23; S,9.50% Found: C, 58.35; H, 2.91; N,11.89; O,13.5; S,8.50%

BIOLOGICAL ACTIVITY

ANTICANCER ACTIVITY

In the present investigation, the synthesized compounds were screened against Vero, MCF-7 and HCT-116 cell lines using MTT assay and the IC_{50} values of the compounds were recorded in table 1. Among the five compounds, compound **3d** exhibited maximum activity against MCF-7 and HCT-116 cell lines at IC_{50} values of 14.02 and 18.12 µM, while the compound **3b** showed slightly less activity against MCF-7 and HCT-116 cell lines with IC_{50} values of 22.8 and 24.0 µM. Other compounds have shown moderate activity.

IC_{50} values[a] (µM) of compounds from 3(a-e)

Table-1

Compound	Cytotoxicity expressed as IC_{50}(µM) in cell lines		
	Vero[b]	MCF-7[c]	HCT-116[d]
3a	173.4	54.1	60.8
3b	>400	82.0	66.0
3c	145.8	14.02	18.12
3d	132.0	33.8	42.0
3e	160.8	28.8	32.0
Doxorubcin	3.1	1.544	1.964

[a]50%Inhibitory concentration after 48 hrs of drug treatment and the values are average of three individual experiments.
[b] Kidney epithelial cells isolated from monkey
[c] Breast cancer cell line
[d]Human colon cancer cell line

Anti-inflammatory activity of synthesized compounds 3(a-e)

The mean edema volume and percentage inhibition were recorded and presented in Table 2. The results obtained in this investigation indicated that the percentage protection against edema formation with compound **3c** was significant, while the other compounds showed moderate protection. The test was done by using standard procedure against inflammation induced by Carrageenan at 0.5, 1, 2, 3 and 4 hr intervals.

Table-2

Compound	**Paw edema(ml)(Mean±S.E)**					**% Inhibition After 3h**
	30 min	1 h	2h	3h	4h	
Control	0.27±0.013	0.34±.020	0.61±.019	0.72±0.028	0.80±.0011	-
Standard	0.17±0.011	0.18±0.009	0.20±0.008	0.23±0.007	0.24±0.007	68
4a	0.18±.008	0.21±0.011	0.32±0.014	0.39±0.017	0.42±0.019	45
4b	0.19±0.007	0.22±0.010	0.35±0.012	0.38±0.010	0.41±0.009	47
4c	0.20±0.005	0.23±0.007	0.25±0.008	0.29±0.013	0.32±0.015	**59**
4d	0.21±0.005	0.24±0.009	0.35±0.009	0.40±0.011	0.55±0.015	44
4e	0.22±0.004	0.25±0.008	0.37±0.014	0.44±0.016	0.57±0.017	38
*Standard and test compounds were administered orally at a dose of 100 mg/kg Each value represents mean ±SE of six animals; *P < 0.05 was considered significant when compared to control*						

Acknowledgements

The authors are thankful to the Management of G. Pulla Reddy College of Pharmacy, Hyderabad for providing facilities. The authors also extend their sincere thanks to Natco Laboratories, Sanath nagar, Hyderabad for providing cytotoxic reports. Thanks to University of Hyderabad (HCU) for providing Mass and NMR spectral data.

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