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Synthesis, Characterisation and Biological Activity of 2-2-(5-(4-Methoxyphenyl)-3phenyl-4,5-Dihydro-1H-Pyrazol-1-Yl)-2-Methyl-4-Oxo-3-Substituted Phenyl Thiazolidin-5-Yl) Acetic Acid

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Abstract

This article includes the synthesis of thiazolidinone based heterocyclic derivatives has been presented. 2-2-(5-(4-methoxyphenyl)-3phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-substituted phenyl thiazolidin-5-yl) acetic acid were synthesised by condensation of (E)-3-(4-(methoxy) phenyl)-1-phenylprop-2-en-1-one with acetic acid and hydrazine followed by cyclization of Schiff's bases with 2-mercaptosucicinic acid to give corresponding derivatives of 2-(2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-phenylthiazolidin-5-yl)acetic acid. Thiazolidinones play an important role in medicinal chemistry, because many of its derivatives have demonstrated significant biological activity. These compounds have shown biological activity as antibacterial and anti-inflammatory activities this structure of synthesized compounds was confirmed by spectral studies (IR and ^{1}H-NMR) and elemental analysis. The antibacterial activity of the compounds has also been screened against *Staphylococcus aureus* and *Escherichia coli*.

Keywords: Chalcones; Thiazolidinones; Antibacterial activity; biological activities

Introduction

Heterocyclic compounds are important to medicinal chemists because of their unique chemical properties and wide-ranging biological activities. Many heterocyclic compounds such as imidazole, thiazole, oxadiazole and pyrazole possess biological activities. Thiazole is a very important heterocyclic compound which shows many pharmacological activities like anticancer [1], antibacterial [2], antifungal [3], antidiabetic [4], antimicrobial [5] etc. These diversity in biological activity of thiazolidine has attracted many researchers to explore its structural activity. Thiazolidine derivatives have been reported as anticancer, anti-inflammatory and many other biological activities [6-8]. The present work reports the synthesis of certain 4-oxothiazolidinyl derivatives containing pyrazole moiety using Schiff Base.

Experimental

Melting points were determined on an ANALAB Automatic Melting point apparatus open capillary tubes and are therefore uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer Frantier (FTIR) spectrometer and ^{1}H NMR spectra of compounds were recorded in DMSO by Bruker 400 MHz FT-NMR Spectrometer. Reactions were monitored by TLC performed on silica gel plates, the spots were located by UV.

Synthesis of 1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1yl) ethanone(I)

This compound is prepared by reported method [9]. To a mixture of (E)-3-(4-(methoxy) phenyl)-1-phenylprop-2-en-1-one (2.94 g, 10 mmol) and hydrazine hydrate (1.0 g, 20 mmol) in acetic acid (25 ml), were added two drops of concentrated hydrochloric acid. The mixture was refluxed for 5 hours. The precipitated solids were filtered, dried and recrystallized from ethanol. The crystals, suitable for X-ray diffraction analysis, were obtained from a mixture of ethyl acetate and dichloromethane (v:v/1:1) by slow evaporation. Reported melting point: 172°C Literature melting point: 174.36°C.

IR (KBr, cm^{-1}): 3445 (NH), 2925, 2842 (C-H), 1672 (C=O, cyclic), 1615 (C=N), 1310 (C-N), 785 (C-Cl); 1H NMR (CDCl3, δ, ppm): 3.70 (s, 2H, -CH_2-), 6.25-7.63 (m, 10H, Ar-H) 9.45 (s, 1H, -NH-).

General preparation for the synthesis of N-(1-(5-(4-substituted phenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl) ethylidene)aniline) [Schiff Bases] (II a-e)

A mixture of 1-(5-(4-methoxyphenyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-1-yl) ethanone (2.94 gm, 0.01 M) in 30 ml ethanol and substituted aniline (0.01 mol) was taken in round bottom flask and swirled thoroughly. The reacting mixture was then refluxed for required 3 hours. Completion of the reaction mixture was monitored by TLC using hexane: ethyl acetate (7:3) the reaction was allowed to cool to room temperature and kept for 4 hour. The solid separated was filtered by suction, washed with ethanol and dried. The crude product was purified by crystallised form ethanol.

Spectral studies

II(a). N-(1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethylidene)aniline

White Solid, Yield: 67%, m.p: 143°C, m/z: 369

IR (KBr) cm^{-1}: 3390 (-NH) cm^{-1}, 1215 (-C-O) cm^{-1}, 2920 (-CH), 1578 (C=N) cm^{-1}

^{1}H-NMR (DMSO-d6): 2.17(s, 3H, CH_3), 3.32(s, 3H, OCH_3), 6.94-7.18(m, 13H, Ar-H), 10.16(s, 1H, NH).

II(b). 4-methoxy-N-(1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethylidene) aniline: Cream white Solid, Yield: 63%, m.p: 148°C, m/z: 399

IR (KBr) cm^{-1}: 3390 (-NH) cm^{-1}, 1150 (-C-O) cm^{-1}, 2920 (-CH), 1569 (C=N) cm^{-1}

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^{1}H-NMR (DMSO-d6): 2.35(s, 3H, CH_3), 2.99 -3.82(s, 6H, OCH_3), 2.17 (s, 3H, CH_3), 7.03-8.34(m, 12H, Ar-H).

II(c). 2,4-dichloro-N-(1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethylidene) aniline: Off white Solid, Yield: 69%, m.p: 144°C, m/z : 437.11

IR (KBr) cm^{-1}: 3430 (-NH) cm^{-1}, 762 (C-Cl), 1292 (-C-O) cm^{-1}, 2824 (-CH), 1614 (C=N) cm^{-1}

^{1}H-NMR (DMSO-d6): 2.35(s, 3H, CH_3), 2.99-3.82(s, 6H, OCH_3), 2.17(s, 3H, CH_3), 7.08-7.13(d, 12H, Ar-H).

II(d). N-(1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethylidene)-3-nitroaniline

Yellowish white Solid, Yield: 60%, m.p: 147°C, m/z: 414.17

IR (KBr) cm^{-1}: 3435 (-NH) cm^{-1}, 1295 (-C-O) cm^{-1}, 2843 (-CH) cm^{-1}, 1362 (N=O) cm^{-1}, 1315 (C-N) cm^{-1}, 1602 (C=N) cm^{-1}

^{1}H-NMR (DMSO-d6): 2.35 (s, 3H, CH_3), 2.99 -3.82 (s, 6H, OCH_3), 2.17 (s, 3H, CH_3), 7.99-8.10 (m, 12H, Ar-H).

II(e). N-(1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)ethylidene)-4-methylaniline: White Solid, Yield: 65 %, m.p: 138°C, m/z: 383

IR (KBr) cm^{-1}: 3390 (-NH) cm^{-1}, 1215 (-C-O) cm^{-1}, 2920 (-CH), 1578 (C=N) cm^{-1}

^{1}H-NMR (DMSO-d6): δ 2.34 (d, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.94-7.18 (m, 8H, Ar-H), 7.20 (d, 4H, Ar-H).

General method for the synthesis of 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-substituted phenyl thiazolidin-5-yl)acetic acid(III a-e)

A mixture of Schiff Base (II a-e) (0.01 mol) and 2-mercaptosuccinic acid (1.50 g, 0.01 mol) dissolved in DMF (25 ml). A pinch of anhydrous $ZnCl_2$ is then added and refluxed for 8-10 hrs in oil bath. Completion of mixture was confirmed by TLC using benzene: chloroform (8:2). The reaction mixture was then poured into crushed ice, filtered and washed with water. After drying the crude product was recrystallised using absolute ethanol. General method has been shown in Scheme 1.

Spectral studies

III(a). 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-phenylthiazolidin-5-yl)acetic acid

IR (KBr) cm^{-1}: 3061, 2936(Ar-CH), 1742, 1682 (C=O), 1601(C=N), 1704 (C=O, thiazol ring), 1511 (C=C).

^{1}H-NMR (DMSO-d6): 3.39-3.43 (dd, 1H, C4-H of Pyrazole), 3.91-3.96(dd, 1H, C4-H of thiazole), 6.92-7.18(m, 13H, ArH), 11.0 (s, -OH), 3.06(d, 2H, -CH_2COOH).

III(b). 2-(3-(4-methoxyphenyl)-2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxothiazolidin-5-yl)acetic acid

IR(KBr) cm^{-1}: 2850(Ar-CH), 1742, 1672(C=O), 1607(C=N), 1704(C=O, thiazol ring), 1511(C=C), 1108 (C-O-C), 1637 (N=CH).

^{1}H-NMR (DMSO-d6): 3.39-3.43 (dd, 1H, C4-H of Pyrazole), 3.91-3.96 (dd, 1H, C4-H of thiazole), 7.04-7.38 (m, 13H, ArH), 11.0 (s, -OH), 3.06(d, 2H, -CH_2COOH), 3.83 (s, 3H, -OCH_3).

III(c). 2-(3-(2,4-dichlorophenyl)-2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxothiazolidin-5-yl)acetic acid

IR (KBr) cm^{-1}: 749 (C-Cl), 1736 (C=O of thiazolone), 3076 (Ar-CH), 1742, 1600 (C=N) cm^{-1}, 1511 (C=C), 1108 (C-O-C), 1637 (N=CH).

^{1}H-NMR (DMSO-d6): 3.39-3.43 (dd, 1H, C4-H of Pyrazole), 3.91-3.96 (dd, 1H, C4-H of thiazole), 7.18-7.86 (m, 12H, ArH), 10.9 (s, -OH), 2.**89** (d, 2H, -CH_2COOH), 3.92 (s, 3H, -OCH_3).

III(d). 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-3-(3-nitrophenyl)-4-oxothiazolidin-5-yl) acetic acid

IR (KBr) cm^{-1}: 1764 (C=O of thiazolone), 3076(Ar-CH), 1742, 1680 (C=N) cm^{-1}, 1511 (C=C), 1312 (C-N), 1637 (N=CH), 1554, 1362 (N=O).

^{1}H-NMR (DMSO-d6): 3.39-3.43 (dd, 1H, C4-H of Pyrazole), 3.91-3.96 (dd, 1H, C4-H of thiazole),7.99 (s, 4H, ArH), 7.08-7.79 (m, 9H, ArH), 2.62 (s, 3H, CH_3), 10.9 (s, -OH), 2.89(d, 2H, -CH_2COOH), 3.92 (s, 3H, -OCH_3).

III(e). 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-(p-tolyl)thiazolidin-5-yl)acetic acid:

IR (KBr) cm^{-1}: 2967(CH, aliphatic), 1736(C=O of thiazolone), 3049(Ar-CH), 1742, 1598(C=N) cm^{-1}, 1511 (C=C), 1637 (N=CH).

^{1}H-NMR (DMSO-d6): 2.42 (s, 3H, CH_3), 3.39-3.43 (dd, 1H, C4-H of Pyrazole), 10.9 (s, -OH), 3.78-3.84 (dd, 1H, C4-H of thiazole), 7.18-7.86 (m, 12H, ArH), 2.89 (d, 2H, -CH_2COOH) (Table 1).

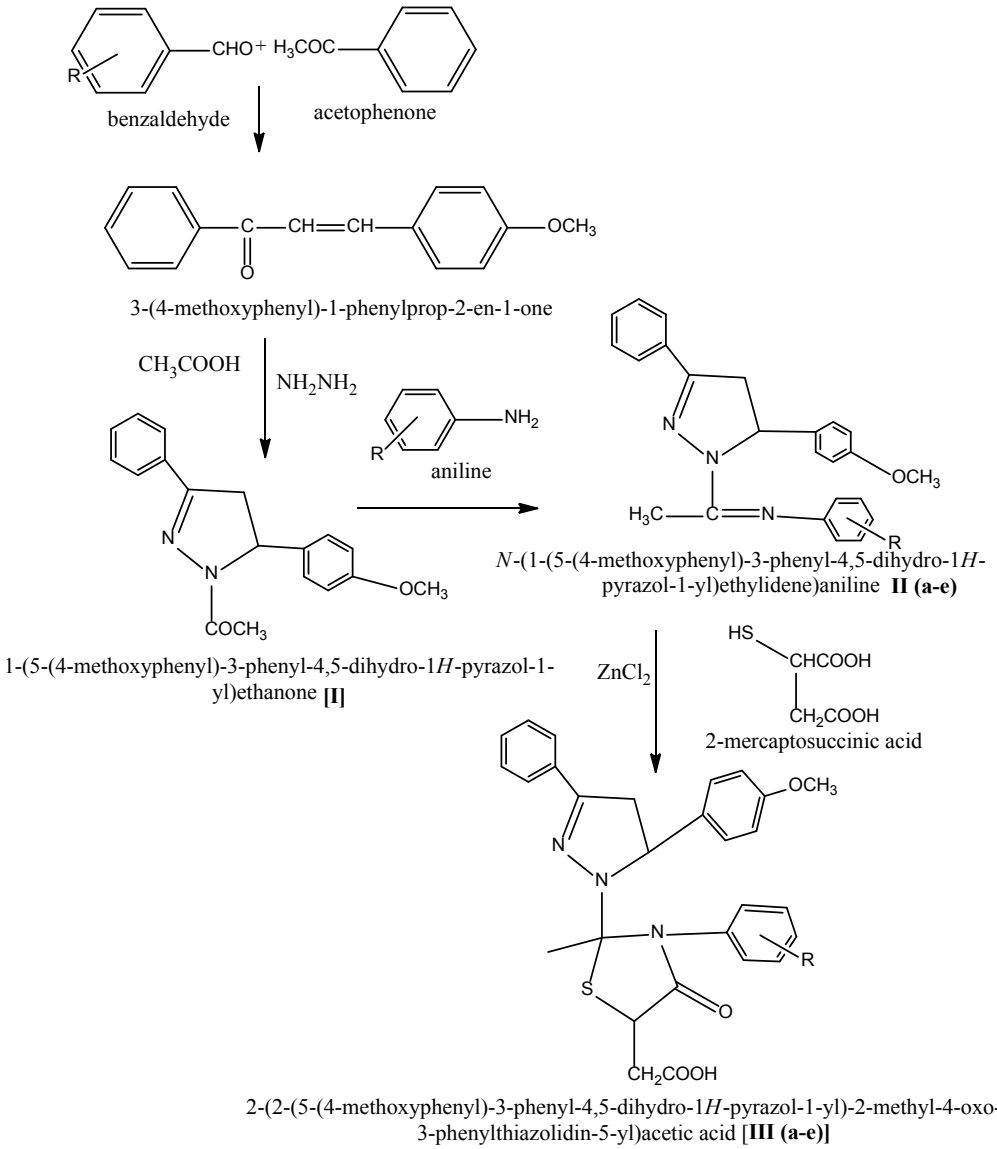
Antimicrobial activity

The antibacterial activity of all the synthesized compounds [III (a-e)] were examined against different Gram-positive bacteria (ATCC 25923 and ATCC 6051) and Gram negative bacteria (*Escherichia coli* ATCC 25922) by measuring zone of inhibition. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water were done as per the standard procedure [10]. Discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. Stock solutions of synthesized compounds diluted in DMF. The antibacterial activity was performed by Paper disc method. Test compounds were dissolved in 10% DMF, to produce the concentration level 50 mcg/ml solution. Ciprofloxacin was used as standard drug at a concentration of 50 mcg/ml. The test samples and standard drugs were placed in a bore made in petridishes which contained different organisms and incubated at 370°C for 24 h. The result of the antibacterial activity was determined by measuring the zone inhibition and the result are given in Table 2.

Result and Discussion

The Scheme of synthesised Schiff Base and thiazolidinone derivatives is shown above. All the derivatives are characterised by FTIR and ^{1}H-NMR. The ^{1}HNMR spectra (DMSO) of the Schiff bases (IIa-e) exhibited signals at 2.17 ppm due to the azomethine protons which indicated the formation of Schiff base.

Thiazolidine-4-one derivatives (III a-e) prepared by adding 2-mercaptosuccinic acid to Schiff base derivatives with anhydrous zinc chloride, FTIR spectrum of these derivatives show disappearance (-N=CH-) group and the absorption bands at (1750-1743) cm^{-1} appear due to carbonyl group, ^{1}H-NMR used to characterization for some of the derivatives show appear signals due to methylene and carbonyl



Scheme 1: Synthesis of 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-phenylthiazolidin-5-yl)acetic acid [III a-e].

Compound	R	Molecular Formula	% Yield	Melting point	m/z
IIIa	-H	$C_{28}H_{27}N_3O_4S$	62	165˚C	501.17
IIIb	4– OCH_3	$C_{29}H_{29}N_3O_5S$	69	171˚C	531.18
IIIc	2,4 - Cl	$C_{28}H_{25}C_{l2}N_3O_4S$	67	180˚C	569.09
IIId	3-NO_2	$C_{28}H_{26}N_4O_6S$	71	175˚C	546.16
IIIe	4-CH_3	$C_{29}H_{29}N_3O_4S$	73	168˚C	515.19

Table 1: Details of different compounds.

Antimicrobial activity: zone of inhibition (50 mcg/ml) (mm)			
	Gram positive bacteria		Gram negative bacteria
Compound no.	*S. aureus*	*B. sutilis*	*E. coli*
III -a	15	18	12
III -b	20	22	23
III-c	14	17	6
III-d	10	14	15
III-e	18	20	18
Ciprofloxacin	25	24	30

Table 2: Antimicrobial activity of 2-(2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-methyl-4-oxo-3-phenylthiazolidin-5-yl)acetic acid.[III a-e].

groups in thiazolidinone ring. A singlet due to the -OH proton of $-CH_2COOH$ group appeared at 2.89 for the thiazolidinone derivatives (III a-e), which is absent in Schiff base (II a-e). All the synthesised Thiazolidinones were screened for the antimicrobial activity.

Conclusion

Compounds III(c) and III(d) which contain electron with drawing chloro and Nitro functional group respectively did not promote much activity against *E. coli* whereas compounds III(b) and III(e) which contain electron donating methoxy and methyl functional group show promising activity against *S. aureus, B. subtilis* and *E. coli*.

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References

1. Gras M, Therrien B, Süss-Fink G, Casini A, Edafe F, et al. (2010) Anticancer activity of new organo-ruthenium, rhodium and iridium complexes containing the 2-(pyridine-2-yl) thiazole N, N-chelating ligand. J Organomet Chem 695: 1119-1125.
2. Kaspady M., Narayanaswamy VK, Raju M, and Rao GK (2009) Synthesis, antibacterial activity of 2, 4-disubstituted oxazoles and thiazoles as bioisosteres. Lett Drug Des Discov 6: 21-28.
3. Çapan G, Ulusoy N, Ergenç N, and Kiraz M (1999) New 6-phenylimidazo [2, 1-b] thiazole derivatives: Synthesis and antifungal activity. Monatsh Chem 130:1399-1407.
4. Sohda T, Momose Y, Meguro K, Kawamatsu Y, Sugiyama Y, et al. (1990) Studies on antidiabetic agents. Synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy) benzyl]-2, 4-thiazolidinediones. Arzneimittelforschung 40: 37-42.
5. Güzeldemirci NU, Küçükbasmacı O (2010) Synthesis and antimicrobial activity evaluation of new 1, 2, 4-triazoles and 1, 3, 4-thiadiazoles bearing imidazo [2, 1-b] thiazole moiety. Eur J Med Chem 45: 63-68.
6. Pandeya SN, Smitha S, Jyoti M, Sridhar SK (2005) Biological activities of isatin and its derivatives. Acta Pharm 55: 27-46.
7. Siddiqui N, Arshad MF, Ahsan W, Alam MS (2009) Thiazoles: a valuable insight into the recent advances and biological activities. Int J Pharm Sci Drug Res 1: 136-143.
8. Jain AK, Vaidya A, Ravichandran V, Kashaw SK, Agrawal RK (2012) Recent developments and biological activities of thiazolidinone derivatives: A review. Bioorg Med Chem 20: 3378-3395.
9. Abbas A, Hussain S, Hafeez N, Lo KM, and Hasan A (2010) 1-[5-(4-Methoxyphenyl)-3-phenyl-4, 5-dihydro-1H-pyrazol-1-yl] ethanone. Acta Crystallogr Sect E Struct Rep Online 66: 03174-03174.
10. Cruickshank R, Duguid JP, Marion BP, Swain RHA (1975) Medicinal Microbiology, 12th edn.; Churchill Livingstone: London, UK 2: 196-202.