Research Article

Synthesis and Antimicrobial Evaluation of Some Novel Sulfonamide Derivative Containing Pyrazoline Moiety

Shaikh Sharif *, Dr. Yogen H. Talia
Department of Chemistry, Pacific University, Udaipur, Rajasthan, India.
***Corresponding author's E-mail:** Sharif_s@rediffmail.com

Received: 08-03-2018; **Revised:** 02-04-2018; **Accepted:** 13-04-2018.

ABSTRACT

In the present study, synthesis of some novel Pyrazoline contains Sulfonamide analog [7a-l] have been carried out by condensing various chalcones with hydrazine hydrate by using ethanol as a solvent in presence of sodium acetate under reflux condition. Structures of synthesized compounds have been confirmed by spectral data (IR, 1H NMR) and elemental analysis. These compounds have also been evaluated for their antibacterial activities.

Keywords: Sulfonamide, Pyrazoline, Chalcone, Reflux, Spectral data, Antimicrobial activity.

INTRODUCTION

Sulfonamide compounds, known as chemotherapeutic agents are known for various biological activities such as antibacterial[1], anticancer[2], anti-inflammatory[3], anti-diabetic[4], anti - epileptic[5], antifungal etc.[6] N-Aryl and N-alkyl cyclic imides have been attracted more attention of organic and medicinal chemists due to the different applications in biological, synthetic, and polymer chemistry[7,8].

Pyrazolines are important nitrogen-containing five membered heterocyclic compounds. Several Pyrazoline derivatives possess important pharmacological activities and therefore they are useful materials for drug research. Pyrazolines are used as antitumer[9], immunosuppressive[10], antibacterial[11] and antitubercular agents. Some of the Pyrazoline derivatives are reported to possess anti-inflammatory[12], anticancer[13], antidibatic[14], antidepressant[15] properties. It also finds applications as dyestuffs, analytical reagent and agrochemicals[16]. All these activities developed our interest to synthesize a new series of Pyrazoline derivatives having sulfonamide moiety.

Condensation of 3-ethyl-4-methyl-2-oxo-N-(2-phenylethyl)-2,5-dihydro-1H-pyrrole-1-carboxamide with 4-amino acetophenone gave N-(2-{4-[(4-acetylanilino) sulfonyl] phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide [1] in a very good yield. This product [1] further on condensation with various aldehydes to give different 3-ethyl-4-methyl-N-{2-[4-({4-[2E)-3-(N-substitutedphenyl)-2-propenoyl] anilino} sulfonyl) phenyl]ethyl}-2-oxo-2,5-dihydro-1H-pyrrole-1-carboamides [2], which, on reaction with hydrazine hydrate, gives N-{2-[4-({4-[5-(substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl]anilino}sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro -1 H-pyrrol-1-carboxamides [7a-l]. The structures of synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR data. All these compounds were also evaluated for their in vitro antibacterial activities.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. All the products have been characterized by elemental analysis, IR and ^{1}H NMR studies. IR spectra were recorded on Perkin Elmer 100 spectrophotometer by using KBr disc. ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) using TMS as an internal standard. Chemical shift in δ ppm.

Procedure for the synthesis of N-(2-{4-[(4-acetylanilino) sulfonyl] phenyl} ethyl)-3-ethyl-4-methyl-2-oxo-2, 5-dihydro-1H-pyrrole-1-carboxamide [1]

Chlorosulfonic acid (45.0 gm, 0.378 mol) was charged in 500 ml 3-nacked round bottom flask. 3-Ethyl-4-methyl-2-oxo-N-(2-phenylethyl)-2, 5-dihydro-1H-pyrrole- 1-carboxamide (15.0 gm, 0.055 mol) was added slowly lot wise by maintaining temperature below 15°C during 2 hours. The mixture was then heated to 42-45°C for 3 hours. After completion of reaction (monitored by TLC , System - n-Hexane: Ethyl acetate, 6:4), the mass quenched to ice water (500 ml) which filtered to give wet sulfonyl chloride compound. It was added to Acetone (80 ml) followed by addition of 4-aminoacetophenone (8.0 gm, 0.059 mole) and pyridine (4.26 gm, 0.053mol) below 15°C. This mixture was refluxed for 3-4 hrs. After completion of reaction (monitored by TLC, System - n-Hexane: Ethyl acetate, 6:4), solvent was removed and water added to the mass. The solid thus obtained was isolated by filtration and dried. Finally, it was crystallized from n-Hexane to give N-(2-{4-[4-acetylanilino sulfonyl] phenyl} ethyl-4-methyl-2-oxo-2, 5-dihydro-1H-pyrrole-1-carboxamide [1] as a pale yellow crystalline powder. Yield 81 %, M.P. 152°C.

Procedures for the synthesis of 3-Ethyl-4-methyl-N-{2-[4-({4-[2E)-3-phenyl-2-propenoyl] anilino} sulfonyl) phenyl] ethyl}-2-oxo-2, 5-dihydro-1H-pyrrole-1- carboxamide. [2]

N-(2-{4-[(4-Acetylanilino) sulfonyl] phenyl} ethyl)-3-ethyl-4-methyl-2-oxo-2, 5-dihydro-1H-pyrrole-1-carboxamide [1] (10 gm, 0.213 mol) was dissolved in 10 ml of 95% ethanol. To this, sodium hydroxide (1.02 gm, 0.0256mol) in 10 ml of water was added slowly followed by drop wise addition of Benzaldehyde (2.59 gm, 0.023mol). The mixture was stirred for 6-8 hours. After the completion of reaction, (monitored by TLC System-Chloroform: Methanol, 8:2) water added, acidified with dilute hydrochloric acid and filtered. Finally, product was recrystalised from alcohol to give 3-Ethyl-4-methyl-N-{2-[4-({4-[2E)-3-phenyl-2-propenoyl] anilino} sulfonyl) phenyl] ethyl}-2-oxo-2, 5-dihydro-1H-pyrrole-1-carboxamide [2] as yellow colored powder. Yield: 70%, M.P. 124-126°C

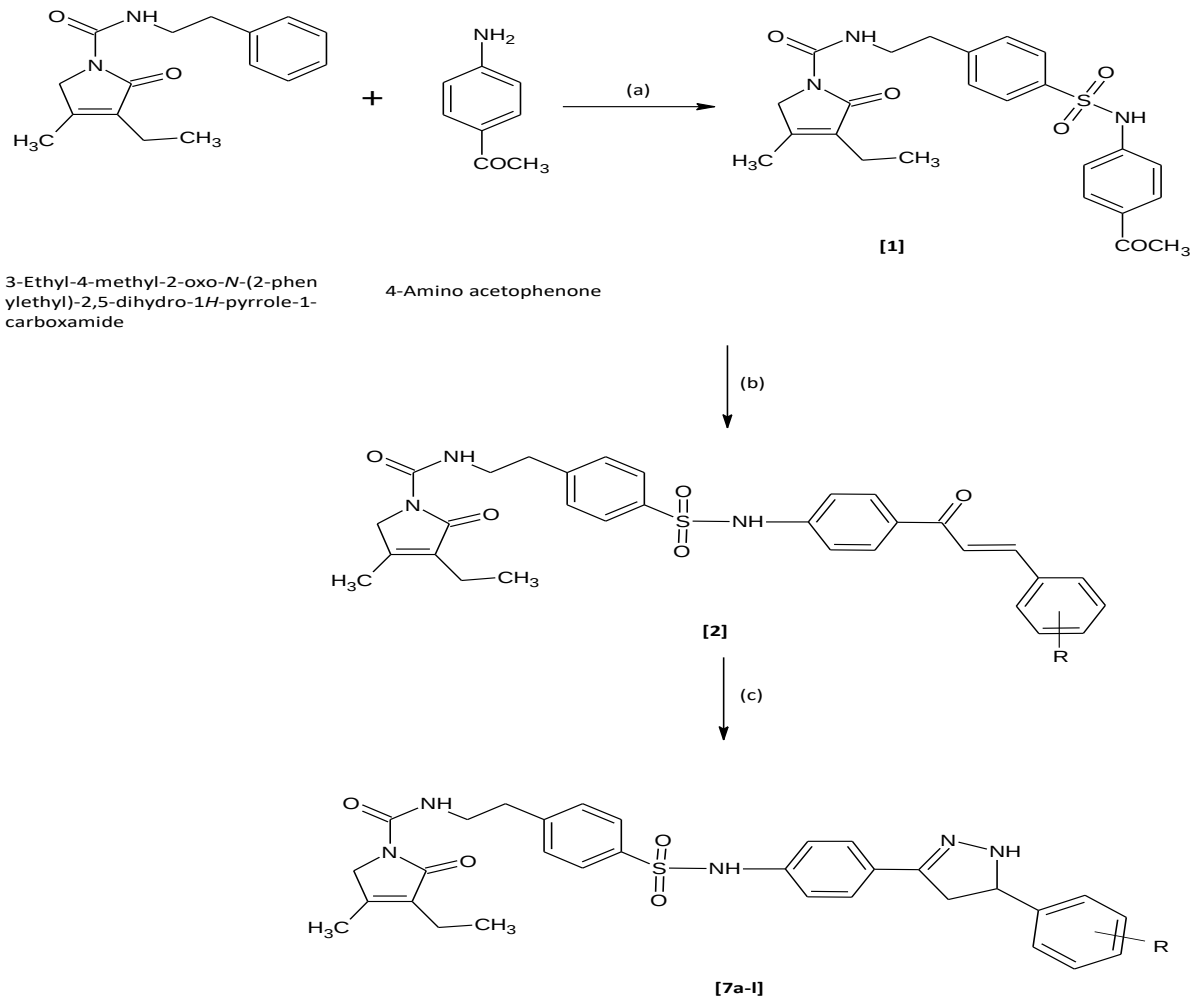
Similarly, carboxamide (1) reacted with various aldehydes to give related chalcones.

Procedure for the synthesis of **N-{2-[4-({4-[5-Phenyl)-4, 5-dihydro-1H-pyrazol-3-yl] anilino} sulfonyl) phenyl] ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-carboxamide [7a]**:

3-Ethyl-4-methyl-N-{2-[4-({4-[2E)-3-phenyl-2-propenoyl] anilino} sulfonyl) phenyl] ethyl}-2-oxo-2, 5-dihydro-1H-pyrrole-1-carboamide [2] (5 gm. 0.009 mol) dissolved in 30 ml ethanol. To this, Hydrazine hydrate (0.449 gm, 0.009 mol) and Sodium acetate (1.47 gm, 0.0177 mol) was added slowly. The mixture was refluxed for 8 hours. After completion of reaction (monitored by, TLC System-Chloroform: Methanol: 9:1), it was poured in ice cold water. The resulting precipitate was filtered and recrystalised from alcohol to give [7a] as a yellow coloured powder. Yield: 63%., M.P. 145-149°C.

NMR δ ppm in (DMSO-d_6) 5.82 (1H, q, NH), 5.32 (1H, d, NH), 8.10 (1H, t, HN), 6.5-7.65 (10H, m, Ar-H).

Similarly, reaction of various Chalcones carried out with Hydrazine hydrate to give related Pyrazoline derivative [7a-l]. Their data are shown in table-1.



Scheme - 1

Reagent & Condition: (a) Chlorosulfonic acid, Pyridine, Acetone 3-4 hrs Reflux; (b) Benzaldehyde, NaOH, EtOH, Dil. HCl (c) Hydrazine Hydrate, Sodium acetate , EtOH, 10 hrs Reflux.

Table 1: Physical characterization

Code No	R	Mole. Wt	M.P. (°C)	Yield (%)	Elemental analysis (%) Found / Calc		
					C	H	N
7-a	-H	571.68	145-149	63	65.10/65.12	6.21/6.23	12.27/12.25
7-b	4-F	589.68	146-152	72	63.16/63.14	5.87/5.85	11.90/11.87
7-c	4-Cl	606.13	159-164	69	61.40/61.42	5.72/5.69	11.52/11.55
7-d	4-NO_2	616.68	138-143	81	60.39/60.37	5.63/5.60	13.60/13.62
7-e	4-OH, 3-OCH_3	617.71	159-165	77	62.20/62.22	6.13/6.11	11.40/11.38
7-f	3-OH, 4-OCH_3	617.71	155-162	72	62.24/62.22	6.09/6.11	11.37/11.38
7-g	4-OH, 3-OCH_3, 5-NO_2	662.71	134-141	81	58.02/57.99	5.55/5.53	12.70/12.68
7-h	3,4-CH_3	599.74	137-142	75	66.10/66.08	6.67/6.65	11.65/11.67
7-i	2,3,4-OCH_3	661.76	157-162	65	59.87/59.89	6.05/6.03	10.60/10.58
7-j	3,4-OH, 5-NO_2	548.68	149-153	69	67.88/67.86	6.27/6.29	15.33/15.31
7-k	3,4-CH_3,-5-Cl	634.18	142-147	63	62.47/62.49	6.14/6.12	11.06/11.04
7-l	2-OH	578.86	142-150	68	64.35/64.37	6.17/6.15	12.12/12.09

Table 2: In vitro antimicrobial activity of newly synthesized compound [7a-l].

Antibacterial Activity - Zone of Inhibition (mm)		
	Gram negative	Gram positive
Code. No.	*Escherichia coli*	*Staphylococcus aureus*
7-a	200	500
7-b	500	500
7-c	200	500
7-d	125	500
7-e	200	250
7-f	250	250
7-g	250	62.5
7-h	500	100
7-i	500	62.5
7-j	250	125
7-k	200	100
7-l	125	250
Ref-1	100	250
Ref-2	25	50

Where Ref-1=Ampicillin, Ref-2= Ciprofloxacin.

N-{2-[4-{5-(4-chlorophenyl)-4, 5-dihydro-1H-pyrazol-3-yl} sulfonyl) phenyl] ethyl} - 3- ethyl - 4-metyl-2-oxo-4, 5-dihydro-1H-pyrrole-1-carboxamide [7c]

IR (cm^{-1}) 1700(–COHN str), 1667 (C=O), 3286 (-NH), 1357 (-C-H), 1606 (C=C), 2971 (-CH_3), 1331(S=O), 1158 (SO_2NH), 651(C-Cl) , 1513(C=N), 1229 (C-N), 709 (C-S).

N-{2-[4-{5-(3,4-dimethylphenyl)-4, 5-dihydro-1H-pyrazol-3-yl} sulfonyl) phenyl] ethyl} - 3- ethyl - 4-metyl-2-oxo-4, 5-dihydro-1H-pyrrole-1-carboxamide [7h]

IR (cm^{-1}) 1701(–COHN str), 1660 (C=O), 3286 (-NH), 1356 (-C-H), 1610 (C=C), 2970 (-CH_3), 1329(S=O), 1155 (SO_2NH), 1513(C=N), 1228 (C-N), 682 (C-S).

Antimicrobial activity

The antimicrobial assay method has been determined by using Kirby-Bauer disc diffusion method, in this method, reference drug and the compound to be tested were dissolved in dimethyl sulfoxide (DMSO) and disc was prepared with whatman filter paper. Plates were prepared with maeller-Hinton agar medium for rapidly growing organism. Inoculum was prepared with sterile saline and turbidity was adjusted to 10^8 Cfu [colony forming unit] per milliliter. Common standard strain was used for screening of antibacterial activities. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic is immediately sub cultured by spreading a loopful evenly over a quarter of plate medium for the growth of the test organisms and put for incubation at 37°C overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of organism is recorded as the MIC. The amount of growth from the controlled tube before incubation is compared and the results of antimicrobial activities are given.

RESULTS AND DISCUSSIONS

All the synthesized compounds of scheme (7a-l) have been successfully carried out and tested for their antibacterial in vitro against gram negative (Escherichia coli) and gram positive (Staphylococcus aureus) bacteria strains by measuring the inhibition zone in mm as recommended by National Committee for Clinical Laboratory Standard (NCCLS).The summary of antimicrobial activity shown in table-2. It reveals comparable activity with standard drug. Most of the

compound showed moderate to good antibacterial activity against the strain used.

CONCLUSION

The substituted Pyrazoline derivative having sulfonamide moieties are already known for different biological activities. As per the result of the screening described in table-2, it is clearly indicated that the compound of the scheme [7a-l] are having good antibacterial activity equipotent with the standard drugs. From the above results; one can establish that the synthesized Pyrazoline derivative can be rich source for the exploitation. Therefore in search of new generation of the active compound, it may be useful to explore the possibility in this area by making or introducing different functional group as substitution. This may result into better pharmacological agents.

REFERENCES

1. Nassir, N.; Yatimah , A.; Zanariah, A.; Raied, M. S.; Ekhlass, M. T.; Aidil, A. H. Synthesis and Antibacterial Evaluation of Some Novel Imidazole and Benzimidazole Sulfonamides, Molecules, 18, 2013, 11978-11995.
2. Oana M. D.; Florentina, L.; Cornelia, V.; Mihai, M.; Valentin, N.; Romona, F.; Dragos, P.; Lenuta, P. Synthesis and Biological Evaluation of New 2-Azetidinones with Sulfonamide Structures, Molecules, 18, 2013, 4140-4157.
3. Bano, S.; Javed, K.; Ahmad, S.; Rathish, I.G.; Singh, S.; Alam, M.S. Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents, Eur. J. Med. Chem. 46, 2011, 5763-5764.
4. Muhammad, A.; Saima , N.; Aziz, u.; Rehman, S. R.; Khalid ,M. K.; Muhammad, A.; Rumana, N.; Umber, A.T. Evaluation of Sulfonamide Derivatives of Dagenan Chloride as Lipoxygenase and α Glucosidase Inhibitors, J. Pharm. Res, 14(1), 2015, 47-54.
5. Ajeet, A. K.; Mishra, A. K. Recent Advances in Development of Sulfonamide Derivatives and Their Pharmacological Effects, Am. J. Pharm. Sci. 2015, 3(1), 2015, 18-24.
6. Muzammi, T. P.; Khetani, D.B. Synthesis and Characterization of Schiff base m-nitro aniline and their complexes, Res. J. Chem. Sci, 5(5), 2015, 52-55.
7. Thierry, V.; Alain, P.; Andre, L.; Richard, N. G. Re-examination of Microwave-Induced Synthesis of Phthalamide Tetrahedron, 56, 2000, 5473–5478.
8. Jayakumar R.; Balaj, R.; Nanjundan, S. Studies on copolymers of 2-(N-phthalimido) ethyl methacrylate with methyl methacrylate, Eur. Polym. J. 36 (8), 2000, 1659 -1666.
9. Taylor E.C., Patel H., Kumar H., synthesis of pyrazolo[3,4-d]pyrimidine analogs of the potent antitumer agent n-(4-[2-(2-amino-4(3H)-oxo-7h-pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl)-l-glutamic acid (LY231514),Tetrahedron, 48, 1992, 8089-8100.
10. Lombardino J. G., Otterness I.G., Novel immunosuppressive agents. Potent immunological activity of some benzothiopyrano [4, 3-c] pyrazol-3-ones, J Med. Chem., 20, 1977, 830-834.
11. Holla B.S., Akberali P.M, and Shivananda M.K., Studies on aryl furan derivatives: Part X. Synthesis and antibacterial properties of arylfuryl-D2-pyrazolines II Farmaco, 55, 2000, 26-263.
12. Bansal E., Srivastava V.K., Kumar A., Eur. Synthesis and anti-inflammatory activity of 1-acetyl-5-substitute daryl-3-(β-aminonaphthyl)-2-pyrazolines and β-(substitute diaminoethyl)amido naphthalene. J. Med. Chem., 36, 2001, 81-92.
13. Manna F., Chimenti F., Floravanti R., Bolasco A., Seecci D., Chimenti P., Ferlini C., Scambia G., Synthesis and in vitro anticancer activity of natural product analogs on the based on the acridine skeleton 1,2,4-oxadiazoline and Pyrazoline derivatives against Cdc25b, Bioorg. Med. Chem. Lett., 15, 2005, 4632-4635.
14. Ahn J.H., Kim., Jung S.H., Kang S.K., Kim K. R., Rhee S.D., Yang S.D., Cheon H.G., Kim S.S., Synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent anti-diabetic agents, Bioorg. Med. Chem. Let., 14, 2004, 4461-4465.
15. Prasad Y.R., Rao A.L. Prasoona L., Murli K. Kumar P.R. Synthesis and antidepressant activity of some 1, 3, 5-triphenyl-2-pyrazolines and 3-(2H-hydroxynaphthalen-1-yl)-1, 5-diphneyl-. 2-pyrazolines, Med. Bioorg Chem. Lett., 15, 2005, 5030-5034.
16. Mulder R., Wellinga K., Van Daalen J.J., Naturwissenschaften, 62, 1957, 531-532.

Source of Support: Nil, **Conflict of Interest:** None.