Research Article

Synthesis, Spectrochemical and Antimicrobial Activity of 2-Acylamino–7,9-diaryl6-methyl-8-(2'acylamino-1'3'4',-thiadiazolyl)methy-l–thia-3,4,8,triazaspiro[4,5]dec-2-ene

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Abstract

New heterocyclic ketoesters dithiosemi-carbazone and corresponding spiro-1, 3, 4-thiadiazolines are prepared using 2,6-diaryl piperidones as substrates.The synthesized compounds are charactersised by elemental analysis, spectral and analytical data.They are also screened for their antibacterial and antifungal activity against gram negative between *E.Coli* and fungi *A.Niger*.

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Keywords: Piperidones, dithiosemicarbazones, spiro-1, 3, 4-thiadiazolines, Heterocyclization, Antimicrobial activity

Introduction

The name 'spirocyclane ' was first introduced by Baeyer in 1900[1,2] .Spirocyclane structure was found in wide range of natural compounds isolated from various sources.A large number of spiro heterocycles are synthesized and their applicability in various fields are tested.1,3,4-thiadiazole are associated with diverse biocidal activities by virtue of the toxophonic N=C-S grouping. A large number of thiadiazolines have been reported to be antifungal[3], antibacterial[4] , antilukemia agents[5], optically active liquid crystals[6],photographic materials,diuretic[7] and CNS depressants[8]. One of the methods to prepare 1,3,4-thiadiazoline involve cyclization of thiosemicarbazones. 2,6-diaryl-4-piperidones are reported as substrates for preparing spiro heterocycles. The introduction of an inbuilt spiro system in an heterocyclic ring may cause an increase in the potency of the system. These observations led us to prepare the title compounds and study their antimicrobial acvtivity.

In the present work, the title compounds are synhthesised from dithiosemicarbazones of 2, 6-diaryl-4-piperidones as substartes[9 - 11]. N-substitution of the piperidin-4-ones is done by reaction with ethylbromoacetate in acetone medium using anhydrous K_2CO_3 as base. N-substituted ester formed is converted into thiosemicarbazone on condensation with thiosemicarbazide in ethanol medium. Dithiosemicarbazones obtained are cyclised using Ac_2O as cyclising agents and neutralized with ammonia.

Experimental work

Melting points of the compounds are determined using an open capillary in a Tempo apparatus and are uncorrected. IR spectra is recorded on Perkin Elmer FT-IR 1600 series spectrometer and varian 300 instrument.1H NMR and C13 NMR are recorded on VARIAN 300 MHZ spectrometer. All chemical shifts are reported in δ ppm using TMS as internal standard. Mass spectra on varian Eric, 410 Proster Binary LC with 500 Ms IT DDA Detector.Elemental analysis was done on CHNS (O) analyser.Model FLASH EA 1112 series.

General procedure for preparation of ethyl-2-(3-methyl-4-oxo-2, 6-diarylpiperidin-1-yl) acetate (2a-c)

To a solution of 2,6-diaryl-3-methylpiperidin-4-one(0.01m) in acetone, ethylbromoacetate (2ml) was added and anhydrous K_2CO_3(2g) was added to act as a base.The mixture was refluxed for about 15 hrs on a steam bath and

filtered hot.Excess solvent was removed and then poured into ice, filtered, washed with water and recrystallised repeatedly from methanol gave compounds(2a-c).

Ethyl -2-(3-methyl-4-oxo-2,6-diphenylpiperidine-1-yl) acetate (2a):m.f.C_{22} $H_{25}NO_3$; m.p. 59◦C; N (3.98%, calc.)IR (KBr. √max,cm^{-1}) 1700-1750 (C=O of COOEt), 1697 (C=O) of ring) ; 3100-3000 (aromatic –C-H), 1600 (aromatic C=C str); 1450 (N=CH_2); ^{1}H NMR (δppm)-0.81 (d, 3H-CH_3) 0.99 -1.21 (t-3H, >N- $CH_2COOCH_2CH_3$), 2.13-2.4 (m , 3H C_3H,C_5H) 3.3-3.6 (m, 2H, C_2(H) & C_6(H), 3.78 (S, 2H , > N-CH_2-COOEt) 4.11(t, 3H-CH_2 of ester), 7.3-7.7 (m- 8H aryl H's).

^{13}C NMR (δppm) 12.3, 13.9, 32.8, 36.8, 50.4 to 52.3, 43.8 to 44.7, 61, 64, 126.9, 129.6, 174.2, 200.7.
Mass (m/e) 351 (M^+) 295, (21.9%) 223 (100%) 146 (59)

Ethyl -2- (3-methyl- 4-oxo- 2,6-di (p-anisyl) – piperidin-1-yl acetate (2b) m.f.C_{24} $H_{29}NO_5$; m.p. 110◦C; N (7.06%, calc.) IR KBr (√cm^{-1}) 3020 – 2929 (C-H aryl) 2841 (C-H ali) 1744 (C=O ester) ; 1685 (C=O ring) 1604 (C=C aryl); 1425 (N-CH_2) ; 1263 (C=O of aryl ether)

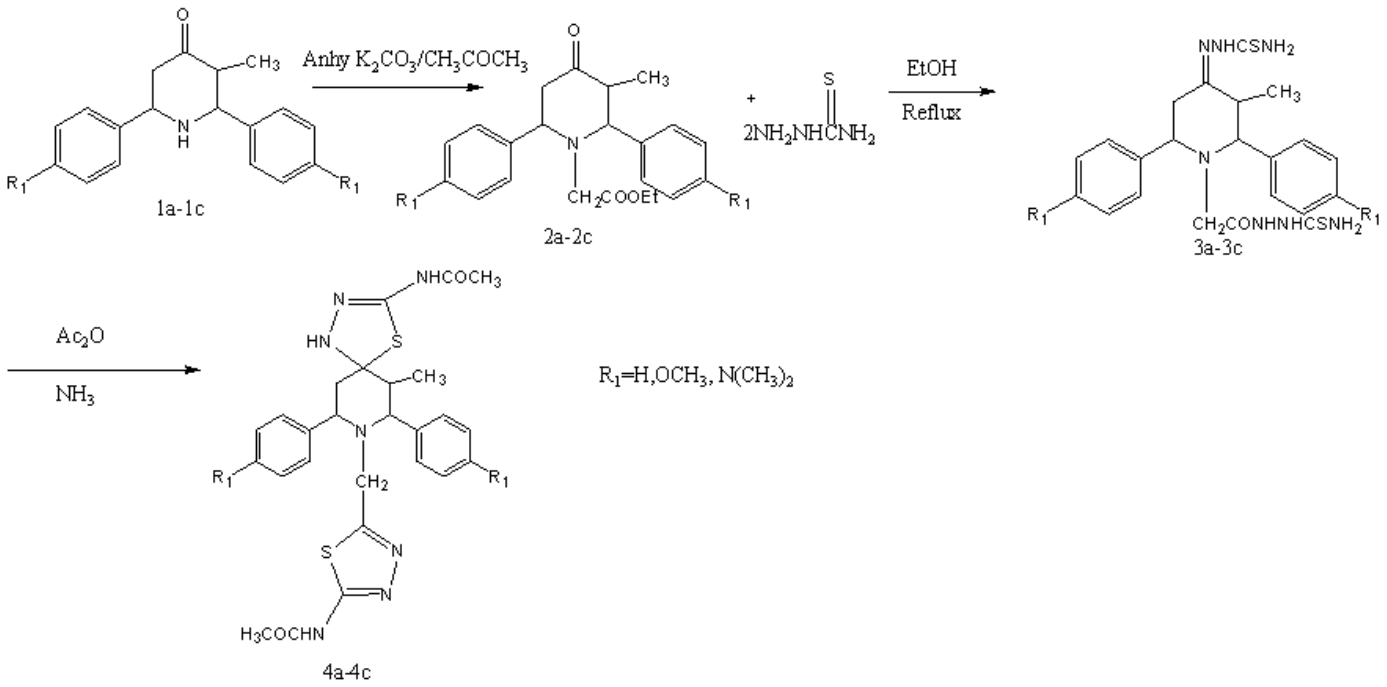
^{1}H NMR . (1.2 to 1.3, 6H of 2CH_3) , 3.01 (2H, C_3-H,C_5-H) 3.23 (2H, C_6-H) 3.1 (S, 3H, -OCH_3) 4.2 to 4.3 (9.1, CH_2 of ester & N-CH_2) 6.7 to 7.7 (m Ar-H)

^{13}C NMR 11.0, 13.9, 20.6, 20.7, 49.7 to 50.1, 59.4, 63.9, 70.5, 127.2 to 138.8 (Ar-C) 169.9 (<C=O of ester 208.2 (C=O of ring)

Ethyl-2(3-methyl-4-oxo-2,6-di(p-N,N-dimethylaminophenyl)piperidin-1-ylacetate (2C) m.f.C_{26} $H_{35}N_3O_3$; m.p. 93-95◦C; N (3.98%, calc.)

IR KBr pellets (√ cm-1) 2914.4 (C-H aryl) 2822 (C-H ali) 1710 (C=O ester) 1661 (C=O ring) 1600 (C=C aryl) 1432 (N-NH_2)

^{1}H NMR 0.8 (3H, CH_3) 1.8 (t,3H, CH_3 of ester) 3.9 (2H, NCH_2) 5.0 to 5.6 (q,2H, CH_2 of ester) 6.8 to 8 (Ar-H).



Scheme 1 Synthesis

General Procedure for preparation of Aceto-2-(3-methyl-2,6-diaryl-4-thiosemicarbazo-piperidin-5-yl)thiosemisemicarbazide(3a - c)

Michael condensation of between >C=O group and thiosemicarbazide led to the formation of the dithiosemicarbazones(3a - c). A mixture of ester (0.01m) and thiosemicarbazide (0.02m) in ethanol (30ml) were refluxed for 6hrs in a steam bath. It was concentrated, cooled and poured into crushed ice. The solid separated was filtered, washed and recrystallised repeatedly from methanol to get half-white crystals of(3a-c).

Aceto-2-(3-methyl-2,6-diphenyl-4-thiosemicarbazo-piperidin-1-yl)thiosemicarbazide.(3a)[12,13]
m.f.$C_{22}H_{27}N_7OS_2$; m.p. 170◦C; N (20.89%, calc.), S (13.64%, calc.)
IR[12](KBr Pellets cm^{-1}) 3422 (NH_2), 3252 (2°NH),3090 (C-H aryl) ,2971 (C-H ali), 1709 (C=O),1588 (C=C aryl), 1493 (C=N), 1453($N=CH_2$),1258(C=S).
^{1}H NMR[13] (δ ppm),1.2 (d,3H,CH_3),2.49(C3-H),C5-H),3.32-3.81(C_2-H,C_6-H) 3.79(2H,N-CH_2),6.99-7.69(Ar-H),8.32(NH of $NHCSNH_2$).
^{13}C NMR (δ ppm) 10.47(CH_3),21.0,23.7(C_3,C_5)38.9,45.8(C_2,C_6),62.9(N-CH_2)122.5to 133.9(Aryl C's) 157.1(C=N)166.8(-C=S)174.6(>C=O)
Mass 469 (M+), 438(100%), 421 (70%),304(65%),275(55%).

Aceto-2-(3-methyl-2,6-di-p-anisyl-1,4-thiosemicarbazide-piperidin-1-yl)thiosemicarbazide.(3b)
m.f.$C_{24}H_{31}N_7O_3S_2$; m.p. 226◦C; N (18.52%, calc.), S (12.1%, calc.)
IR[12](KBr Pellets √cm^{-1})3450-3250 (NH_2,NH),3049(C-H aryl) 2925(C-H ali),1726(C=O),1493(C=N),1243(C=S).
^{1}H NMR[13] (δ ppm),0.69-0.79 (d,3H,CH_3),3.03-3.12(6H,OCH_3),2.49-2.26(C_3-H),2.66-2.80(C_5-H) 3.30(2H,N-CH_2),3.71-3.86(C_2-H,C_6-H),7.16-8.08(Ar-H),9.8-10.4(NH),10.53(NH_2).
^{13}C NMR (δ ppm) 12(CH_3),56 (OCH_3)30.6-40.1(C_3,C_5),59.3(C_2,C_6),69 (N-CH_2) 126.9-129.2(Aryl C's) 145(C=N)162(-C=S)180(>C=O)

Aceto-2-(3-methyl-2,6-di-p-N,N-dimethylaminophenyl)-4-thiosemicarbazo-piperidin-1-yl)thiosemicarbazide.(3c)
m.f.$C_{29}H_{47}N_9OS_2$; m.p. 182◦C; N (20.97%, calc.), S (10.64%, calc.)
IR[12](KBr Pellets √cm^{-1})3374.4 (NH_2),3332.1(N-H) ,3155.7(C-H aryl)1644.3(C=O),1600.7(C=C aryl),1464(C=N),1227.9(C=S)
^{1}H NMR (δ ppm),0.9 (3H,CH_3),3.9(2H,NCH_2),6.8-8.0(Ar-H)8.3-8.7(NH),9.7-9.8(NH_2).
^{13}C NMR (δ ppm) 14(CH_3),40.2 (N-$(CH_3)_2$),54 (N-CH_2),111.4-132.6(Aryl C's) 151.14(C=N),157.92(-C=S),168.4(C=O)

General procedure for the preparation of 2-acylamino-6-methyl-7,9-diaryl-8(2'acylamino-1',3',4',thiadiazolyl)methyl-1-thia3,4,8-triaza-spiro[4,5]dec-2-ene(4a-4c)

The title compounds (4a-4c) were obtained from their corresponding dithiosemicarbazones(3a-3c)using acetic anhydride as cyclising agent,neutralized with ammonia and poured into crushed ice. The precipitates formed were filtered and recrystallised repeatedly from methanol to get pure samples.

2-Acylamino- -7,9-diphenyl-6-methyl -8(2'acylamino-1',3',4',thiadiazolyl)methyl-1-thia-3,4,8-triaza-spiro[4,5]dec-2-ene(4a)
m.f.$C_{26}H_{29}N_7O_2S_2$; m.p. 96◦C; N (18.31%, calc.), S (11.96%, calc.)
IR[12](KBr Pellets √cm^{-1})3500(N-H) ,2976(C-H aryl)2900 (C-H ali) 1716.2(C=O of $NHCOCH_3$)),1601.7(C=C aryl),1492.3(C=N),1454.2(N-CH_2),1028(N=N),754.3(C-S-C),1601.79,1155.72,1028.11,754.3(thiadiazole ring[14,15]
^{1}H NMR[13] (δ ppm),0.98 (d,3H,CH_3),2.35-3(C_6-H,C_{10}H),3.34-4.39(m, C_7H,C_9H),3.78,3.93(N-CH_2,$NHCOCH_3$),7.31-7.25(Ar-H),10.54(NH).
13C NMR (δ ppm) 13(CH_3),21,22(C_6,C_{10}),52,52(C_7,C_9),60($NHCOCH_3$)62 (N-CH_2),82,84(C_5),121-130(ArylC's),140-148(C=N),170(-C=O of $NHCOCH_3$)
Mass
561(M+),530(9%),444(20%),360(12.25%),338.7(15%),326(35%),254(100%),161(27.5%,136(22.5%).

2-acylamino- -7,9-di-(p-anisyl)-6-methyl -8(2'-amino-1',3',4',thiadiazolyl)methyl-1-thia-3,4,8-triaza-spiro[4,5]dec-2-ene(4b)
m.f.$C_{28}H_{33}N_7O_2S_2$; m.p. 103◦C; N (17.34%, calc.), S (10.75%, calc.)
IR[12](KBr Pellets √cm^{-1})3300-3100(N-H) ,2978(C-H aryl),2836.09 (C-H ali) 1720.34(C=O of $NHCOCH_3$)),1604.32(C=C aryl),1496.99(C=N),1439.42(N-CH_2),1256.39(C-OCH_3), 1110.60,1053.62,1018.86,814.9,616.84(thiadiazole ring.

^{1}H NMR[13] (δ ppm),1.2 (3H,CH_3),1.8-2.4(bm,5H,C_6-H,C_{10}H,NHCOCH_3),2.8-3.0 (C_7-H,C_9-H),3.4-48H,OCH_3&NCH_2),6.8-7.0(m,aryl H's), 8.7-9.9-N-H.
^{13}C NMR (δ ppm) 12(CH_3),36,37(C_6,C_{10}),45(C_7,C_9),56(OCH_3)61 (N-CH_2),70(C_5),127-130(ArylC's),142(C=N),180(-C=O), 156(C=O).

2-acylamino- -7,9-di-(p-N,N-dimethyl aminophenyl)-6-methyl -8(2'-acylamino-1',3',4',thiadiazolyl)methyl-1-thia-3,4,8-triaza-spiro[4,5]dec-2-ene(4c).
m.f.$C_{30}H_{39}N_9S_2$; m.p. 130◦C; N (21.39%, calc.), S (10.86%, calc.)
IR[12](KBr Pellets √cm^{-1})3422(N-H) ,2922(C-H aryl), 1708(C=O),1622(C=C aryl),1548(C=N),1384(N-CH_2),1246,1125,1020,813,744,619,519(thiadiazole ring).
^{1}H NMR[13] (δ ppm),1.32 (3H,CH_3),1.678-2.4(C_6-H,C_{10}H),3.10-3.19(N-(CH_3)$_2$),3.80(N-CH_2),6.28 (C_7-H,C_9-H),732-7.76.0(aryl H's), 9.16-N-H.
13C NMR (δ ppm) 11.02(CH_3),13.9(NHCOCH_3),30.6(-N-(CH3)$_2$),20.6,20.7(C_6,C_{10}),50.1-50.7(C_7,C_9),59.4(N-CH_2),70.5(C_5),127.2-129-(ArylC's),137.1(C=N),208(C=O).

Results and Discussion

The present work describes the synthesis, characterization and antimicrobial activity of novel spiroheterocycles 2-acylamino-6-methyl-7,9-diaryl-8(2'amino-1',3',4',thiadiazolyl)-1-thia--3,4,8-triazaspiro[4,5]dec-2-ene(4a-4c) using 3-methyl 2,6-diarylpiperidin-4-one(1a-c) following literature procedure [18]. Compound (1a-c) were converted into keto esters (2a-c) on reaction with ethylbromoacetate in presence of anhydrous K_2CO_3&acetone as solvent. These ketoesters were condensed with thiosemi-carbazide to form dithiosemicarbazones (3a-c) which in turn were heterocycled to form spirothiadiazolines(4a-c) using acetic anhydride as the cyclising agent followed by neutralization with NH_3.

All the synthesized compounds were characterized by elemental analysis and spectral data. The structures of the keto-esters were assigned on the basis of IR, ^{1}HNMR, ^{13}CNMR & Mass spectral data. Keto-esters showed the presence of two carbonyl groups in the region 1650-1750cm-1 in IR spectra. Also they showed frequencies corresponding to –N-CH_2 in the region 1450-1400cm-1. ^{13}C NMR signals were obtained for both carbonyl carbons in the range above 160 δ ppm.

Dithiosemicarbazone (3a-c) showed the absence of carbonyl group and presence of N&S as characteristic elements on elemental analysis. IR spectra of dithiosemicarbazones showed absorption corresponding to-C=N,NH&NH_2 of –NNHCSNH_2 moiety. In ^{1}H NMR, NH &NH_2 proton signals were obtained between 8-104 δ ppm for all the compounds. ^{13} CNMR spectra showed absorption corresponding due to C=S in the region 160-175 δ.
Spiro-1,3,4-thiadiazolines were characterized by IR, ^{1}HNMR, ^{13}CNMR & Mass spectral data.IR spectra showed the presence of carbonyl stretch ohf NHCOCH_3 group in the region 1600-1700cm-1 and –NH stretch in the region 3100-3300cm-1. ^{1}H NMR showed signals at 8.0-9.0 for 2°NH of NHCOCH_3. ^{13}C NMR signals was observed for carbonyl of NHCOCH_3 in the region ~180-200 δ at 70-80 δ for spiro carbon.

Compounds (3a-c) and spiro-thiazolins (4a-c) were tested for microbial activity against against the gram negative bacteria , E.coli and fungus Aspergillus Niger by the parer disc diffusion method. The screening was done at two different concentrations 50ppm and 100 ppm in DMSO[19] in table 1. All the compounds showed positive inhibition activity against both bacteria and fungus at both concentrations as the activity was found to be higher in higher concentrations.

Table 1. Antimicrobial activity against E-coli and A-Niger

Compound	E-Coli		A.Niger	
	50 ppm	100 ppm	50 ppm	100 ppm
3a	19	20	15	17
3b	19	20	16	18
3c	21	22	15	16
4a	22	24	17	18
4b	20	25	15	17
4c	18	22	14	16

Conclusion

Synthesis, spectro-chemical and antimicrobial activity of ketoesters, dithiosemicarbazones and 2-acylamino-7,9-di-(p-diaryl)-6-methyl -8(2'-acylamino-1',3',4',thiadiazolyl)methyl-1-thia-3,4,8-triaza-spiro[4,5]dec-2-ene are reported in this paper.

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Publication History
Received 19th Sep 2013
Revised 15th Dec 2013
Accepted 20th Dec 2013
Online 05th Jan 2014