June 2009 Volume 5 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(2), 2009 [190-194]

Synthesis and pharmacological activities of some new pyrimidines and thiadiazoles bearing mefenamic acid

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Received: 29th April, 2009 ; Accepted: 4th May, 2009

ABSTRACT

The thiosemicarbohydrazides **(3a-e)** prepared from the reaction of 2-[2,3-dimethylphenyl) amino] benzocarbohydrazide **(2)** and aryl isothiocyanate. Which upon condensation with malonic acid in presence of acetyl chloride and sulphuric acid afforded 2-(2,3-dimethyl phenyl amino)-N-(4,6-dioxo-3-(aryl substituted)l-2-mercaptotetra- hydro pyrimidine-1-(2H)-yl) benzamide **(4a-e)** and 5-[2-(2, 3-dimethylphenyl amino) phenyl]-N—(aryl substituted)-1,3,4-thiadiazole-2-amine **(5a-e)**, respectively. The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, mass spectral data and elemental analysis.

KEYWORDS

Mefanamic acid;
Pyrimidines;
Thiadiazoles;
Antimicrobial;
Analgesic;
Anti-inflammatory;
Hypnotic.

INTRODUCTION

Pyrimidines and thiadiazoles derivatives from a component in number of useful drugs and are associated with many biological, pharmaceuitical and therapeutically activities[1-4]. Therefore, pyrimidines and thiadia zoles derivatives are important synthons to synthesis organic chemist. Literature Survey revealed different synthetic approaches for developing pyrimidines [5-8] and thiadiazoles[9-11] ring systems are reported. In view of above this and in continuation of our research on the synthesis of biologically active heterocycles[12,13].

The present work describes the synthesis of some unexplored novel condensed heterocyclic compounds. These compounds are expected to be associated with interesting biological activities. In the present investigation 2-[(2, 3-dimethylphenyl) amino] benzocarbo hydrazide **2** upon condensation with aryl isocyanate in presence of methanol were refluxed for 4hrs to afford thiosemicarbohydrazide **(3a-e)**. Which upon condensation with malonic acid in acetyle chloride were refluxed for 2hrs at 40^{0}C furnished the compounds 2-(2,3-dimethyl phenyl amino)-N-(4,6-dioxo-3-aryl-2-mercaptotetrahydro pyrimidine-1-(2H)-yl) benzamide **(4a-e)**, the compound **(3a-e)** treated with concentrated sulphuric acid undergo cyclisation give compounds 5-[2-(2,3-dimethylphenyl amino) phenyl]-N-aryl-1,3,4-thiadiazole-2-amine **(5a-e)**. The purity of the compounds was checked by TLC. All newly synthesized compounds were characterized on the basis of IR, ^{1}HNMR, Mass spectral data and elemental analysis. The synthesized compounds were studied for antimicrobial, anti-inflammatory and selected compounds were screened for hypnotics activity.

EXPERIMENTAL

The reagents and solvents used for the synthesis were

obtained commercially and further purified. The melting points were determined by open capillaries and are uncorrected.

Infra red spectra were recorded on an FTIR-8400 Shimadzu Spectrophotometer Department of Pharmaceutical Chemistry, Karnataka College of pharmacy, Bidar. The ^{1}HNMR spectra were recorded ACF 200 Supercon-Switzerland NMR Spectraphotometer. The chemical shifts were expressed in ppm (delta scale). Mass spectra were taken by using LC-MS 2010 (SHIMADZU) and the purity of the compounds was checked by TLC.

2-[(2,3-dimethylphenyl)amino]benzocarbohydrazide (2)

To a solution of 2-[(2,3-dimethylphenyl) amino] ethyl benzoate (1) (0.01mol) anhydrous alcohol (50ml), hydrazine hydrate 99% (0.3mol) and Conc. Sulphuric acid (6-8drops) were added. The reaction mixture was refluxed for 24h. The excess of solvent was distilled under reduced pressure and the mixture was poured on crushed ice with constant stirring. The solid separated was filtered, washed, dried and recrystallized from ethanol. Yield 79%, m.p 170^{0}C, (Found C, 70.50, H, 6.67, N, 16.57 $C_{15}H_{17}N_3O$ requires C, 70.56, H, 6.71, N, 16.46 %).

2-[2-(2, 3-dimethyl phenylamino)benzoyl]-N-(aryl substituted) hydrazine carbothioamide (3a-e)

To a solution of 2-(2, 3-dimethylphenyl amino) benzohydrazide (2) (0.01mol) in ethanol (40ml), aryl isothiocynate (0.01mol) was added. The reaction mixture was heated under reflux. After about 2.5h the solid started separating and heating was continue further for 2.5h. The solid afford 2-[2-(2, 3-dimethyl phenylamino) benzoyl]-N-aryl hydrazine carbothioamide **(3a-e)** was collected and crystallized from suitable solvents.

The solvents of crystallization, m.p, percentage yield and elemental analysis were summarized in TABLE 1.

2-(2,3-dimethyl phenyl amino)-N-(4,6-dioxo-3—(aryl substituted)l-2-mercaptotetra- hydro pyrimidine-1-(2H)-yl) benzamide (4a-e)

To a solution of (0.01mol) of 2-{2-[(2, 3-dimethyl phenyl) amino] benzoyl}-N-aryl hydrazine carbothio amide **(3a-e)** in acetyl chloride (10ml), malonic acid (0.02mol) was added. The reaction mixture was heated for 6h at 40^{0}C. The reaction mixture was cooled and poured into crushed ice; the solid 2-(2, 3-dimethyl phenyl amino)-N-(4,6-dioxo-3-aryl-2-mercaptotetrahydro pyrimidine-1-(2H)-yl) benzamide **(4a-e)**, separated was collected and crystallized from suitable solvents.

5-[2-(2, 3-dimethylphenyl amino) phenyl]-N-(aryl substituted)-1,3,4-thiadiazole-2-amine (5a-e)

2-{2-[(2,3-dimethyl phenyl)amino] benzoyl}-N-aryl hydrazine carbothioamide **(3a-e)** (0.01mol) was added slowly to concentrated sulphuric acid with stirring at the temperature below 0^{0}C the temperature was maintained at 0^{0}C for another 1h. The reaction mixture was then allowed to stand at room temperature overnight. The contents were warmed to 50^{0}C, cooled and

TABLE 1: Physical data of the synthesized compounds

Comp. no	R	M P (^{0}C)	Yield (%)	Molecular formula	Solvent for Cryst…	Rf value	Found (%) (calc)		
							C	H	N
(3a)	C_6H_5	208-209	72.23	$C_{22}H_{22}ON_4S$	Benzene	0.36	67.67(67.60)	5.68(5.64)	14.35(14.41)
(3b)	C_6H_4Cl(p)	230-231	85.45	$C_{22}H_{21}ON_4ClS$	Ethanol	0.41	62.18(62.21)	4.98(4.89)	13.18(13.27)
(3c)	$C_6H_4OCH_3$(p)	195-197	70.63	$C_{23}H_{24}O_2N_4S$	Ethanol	0.45	65.69(65.71)	5.75(5.80)	13.32(13.41)
(3d)	$C_6H_4CH_3$(o)	248-250	68.72	$C_{23}H_{24}ON_4S$	Benzene	0.38	68.29(68.28)	5.98(5.94)	13.85(13.87)
(3e)	$C_6H_4NO_2$(p)	201-204	75.27	$C_{22}H_{21}O_3N_5S$	Ethanol	0.43	60.67(60.71)	4.86(4.90)	16.08(16.11)
(4a)	C_6H_5	186-189	80.54	$C_{25}H_{22}O_3N_4S$	Ethanol	0.47	65.48(65.50)	4.84(4.88)	12.22(12.24)
(4b)	C_6H_4Cl(p)	150-152	78.45	$C_{25}H_{21}O_3N_4ClS$	Ethanol	0.61	60.91(60.94)	4.29(4.19)	11.36(11.39)
(4c)	$C_6H_4OCH_3$(p)	175-177	82.21	$C_{26}H_{24}O_4N_4S$	Ethanol	0.53	63.92(63.97)	4.95(5.00)	11.47(11.51)
(4d)	$C_6H_4CH_3$(o)	210-211	75.33	$C_{26}H_{24}O_3N_4S$	Benzene	0.55	66.08(66.11)	5.12(5.19)	11.86(11.89)
(4e)	$C_6H_4NO_2$(p)	180-182	69.75	$C_{25}H_{21}O_5N_5S$	Benzene	0.31	59.63(59.67)	4.20(4.26)	13.91(13.99)
(5a)	C_6H_5	152-154	70.09	$C_{22}H_{20}N_4S$	Ethanol	0.61	77.40(77.50)	5.61(5.64)	12.31(12.64)
(5b)	C_6H_4Cl(p)	208-210	80.36	$C_{22}H_{19}N_4ClS$	Ethanol	0.44	70.30(71.01)	4.83(4.89)	11.18(11.31)
(5c)	$C_6H_4OCH_3$(p)	165-166	70.38	$C_{23}H_{22}ON_4S$	Benzene	0.31	73.67(73.91)	5.30(5.00)	16.36(16.91)
(5d)	$C_6H_4CH_3$(o)	130-134	78.71	$C_{23}H_{22}N_4S$	Benzene	0.56	74.14(74.88)	5.66(5.82)	15.72(15.77)
(5e)	$C_6H_4NO_2$(p)	175-178	80.19	$C_{22}H_{19}O_2N_3S$	Ethanol	0.63	77.72(77.97)	5.96(6.00)	11.82(11.99)

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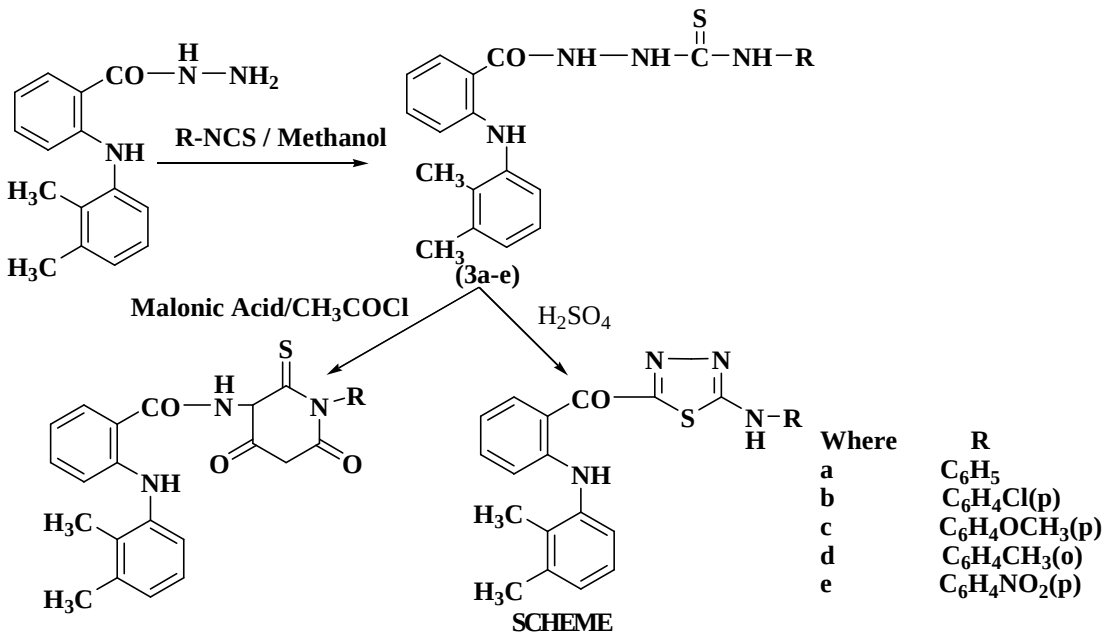

SCHEME

poured into crushed ice. The resulting solution was neutralized with dilute ammonia solution. The solid 5-[2-(2, 3-dimethylphenyl amino) phenyl]-N-aryl-1, 3, 4-thiadiazole-2-amine **(3a-e)**, separated was collected dried and crystallization with suitable solvents.

RESULT AND DISUSSION

The synthesis of compounds **(3b)** as followed by condensation of compound **(2)** with phenyl isothio cyanates in methanol for about 2h. Furnished compounds 3b in good yield. The IR spectrum of compound **(3b)** showed bands at 3301, 3224 cm^{-1} due to CONHCS / NHCS, 1662 cm^{-1} due to C=O, 1587 cm^{-1} due to C=N and 1255 cm^{-1} due to C=S functional groups respectively. The ^{1}HNMR spectrum of the compound **(3b)** displayed two singlet peaks at δ 2.1 and δ 2.3 due to six protons of two methyl groups of aromatic ring, another two singlet at δ 8.0 and δ 9.1 due to three protons of each CONHNH and NHCS functional groups respectively, 11 aromatic protons have resonated as a multiplet in the region δ 6.6-7.8. Further the structure of compound **(3b)** is supported by mass spectrum exhibited a molecular ion peak at m/z 424 which aggress with its molecular weight. The other prominent peaks are obtained at m/z 241, 194, 153, 127, 90, and 45. The spectral data were in agreement with it structure.

The remaining structures of compound **(3a,c,d,e)** were prepared same as **(3b)** and agree with the spectra data.

The compound **(4a)** was prepared by the reaction of **(3a)** with malonic acid in acetyl chloride were refluxed for 2h at 40^0C furnished the compound **(4a)** in good yield.

The IR spectrum of compound 4a showed characteristic absorption band at 3313 cm^{-1} due to CONH/NH, 2923, 2856 cm^{-1} due to CH stretching of methyl groups (asymmetric and symmetric), 1722 cm^{-1} due to C=O. The ^{1}HNMR spectrum of the compound 4a showed singal due to 12 aromatic protons have resonated in the region δ 6.6-7.4 as multiplet. A singlet peak absorbed at δ 8.1 due to one proton of CONH, another two singlets peak absorbed at δ 4.6 and δ 4.0 due to two proton of cyclic methylene function of pyrimidinedione and one proton of Ph-NH-Ph, two singlet at δ 2.1 and δ 2.3 due to two methyl groups of aromatic ring. Further the structure of compound 4a is supported by mass spectrum exhibited a molecular ion peak at m/z 458 which aggress with its molecular weight. Probably it has undergone into fragmentation after loosing -CH_2CO to generate a cat ion at m/z 416 $(C_{17}H_{16}N_4O_2S)^+$ one side another side loosing pyrimidine thio with phenyl moiety to generate a radical at m/z 241 $(C_{15}H_{15}N_2O)^+$-1H. Further undergoes fragmentation by eliminating –NH and –CO to get a radical at

m/z 227 $(C_{15}H_{14}NO)^+$ and m/z 199 $(C_{14}H_{14}N)^+$ respectively. Finally eliminating the phenyl moiety to get a radical at m/z 123 $(C_8H_{10}N)^+$. The fragmentation pattern supports the proposed structure of compound **(4a)**. The spectral data were in agreement with it structure.

The remaining structures of compound **(4b,c,d,e)** were prepared same as **(4a)** and agree with the spectra data.

When compound **(3a)** was treated with concentrated sulphuric acid undergo cyclisation give compound **(5a)** in good yield. The IR spectrum of compound **(5a)** showed bands at 3388cm^{-1} due to NH stretching ,2921, 2854 cm^{-1} due to CH stretching of methyl groups (asymmetric and symmetric), 1740 cm^{-1}due to C=O, 1751 cm^{-1} due to C=C, 1456 cm^{-1} due to CH bending of methyl groups and 1038 cm^{-1} due to C-O-C functional groups. Its ^{1}HNMR spectrum of the compound 5a displayed two singlet at δ 2.1 and δ 2.3 due to six protons of two methyl groups of aromatic ring, another singlet at δ 4.1 due to one proton of Ph-NH-Ph, δ 8.1 due to one proton of NH between thiadiazole and phenyl as singlet and multiplet at δ 6.8-7.4 due to 12 protons of aromatic hydrogen. The mass spectrum of the compound **(5a)** exhibited a molecular ion peak at m/z 372 which aggress with its molecular weight. The other prominent peaks are obtained at m/z 268, 223, 167, 150, 111, 77 and 48. The spectral data were is agreement with its structure. The remaining structures of compound **(5b,c,d,e)** were prepared same as **(5a)** and agree with the spectra data.

TABLE 2: Antimicrobial activity of synthesized compounds

Comp no.	Zone of inhibition in mm*			
	Antibacterial activity		Antifungal activity	
	E.coli	*B.subtilis*	*A.niger*	C.albicans
(3a)	15	14	15	14
(3b)	17	15	17	18
(3c)	17	18	16	17
(3d)	13	14	13	14
(3e)	11	13	11	13
(4a)	10	11	10	11
(4b)	21	19	18	16
(4c)	19	18	17	17
(4d)	12	15	12	10
(4e)	13	12	09	12
(5a)	12	10	12	10
(5b)	21	20	18	17
(5c)	17	19	17	18
(5d)	12	11	15	11
(5e)	11	10	11	10
Control(DMF)	6	6	6	6
Ciprofloxacin	24	25	--	--
Flucanazole	--	--	20	20

***Bore of the diameter 6mm, standard: Ciprofloxacin and Flucanazole**

Evaluation of antimicrobial, anti-inflammatory and hypnotic activity

Antibacterial and antifungal activity

The newly synthesized compounds were subjected to *invitro* antimicrobial activity against by Cup-Plate diffusion method[14] using organisms *E.coli*, *B.subtilis* for antibacterial activity where as *A.niger* and *C.albican* for antifungal activity. All the test compounds were prepared at the concentration of 100μg/ml in distilled DMF. The solution of ciprofloxacine and flucanazole were prepared at the concentration of 100μg/ml in sterile water as standard solution for compression of antibacterial and antifungal activities and DMF was used as

TABLE 3 : Anti-inflammatory activity of compounds (4a-e) and (5a-e)

Comp no.	R	Dose (mg/kg body weight)	Mean value(± SE) of oedema volume at different intervals		Percentage of anti inflammation at different intervals	
			2h	4h	2h	4h
Control (2% gum acacia)	-	100	0.252(±0.009)	0.205(±0.007)	-	-
Standard(Phenyl butazone)	-	100	0.126(±0.018)	0.036(±0.003)	50.00	82.43
(4a)	C_6H_5	100	0.136(±0.002)	0.101(±0.002)	46.03	50.73
(4b)	C_6H_4Cl(p)	100	0.123(±0.004)	0.099(±0.005)	51.19	51.70
(4c)	C_5H_4N	100	0.112(±0.011)	0.092(±0.001)	55.55	55.12
(4d)	$C_6H_4NH_2$(m)	100	0.120(±0.009)	0.100(±0.006)	52.38	51.21
(4e)	$C_6H_5CH_2$	100	0.143(±0.001)	0.113(±0.006)	43.25	44.87
(5a)	C_6H_5	100	0.153(±0.002)	0.121(±0.003)	39.28	40.97
(5b)	C_6H_4Cl(p)	100	0.143(±0.003)	0.109(±0.004)	43.25	46.82
(5c)	C_5H_4N	100	0.162(±0.002)	0.129(±0.001)	35.71	37.07
(5d)	$C_6H_4NH_2$(m)	100	0.144(±0.003)	0.111(±0.002)	42.85	45.85
(5e)	$C_6H_5CH_2$	100	0.161(±0.005)	0.126(±0.009)	36.11	38.53

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TABLE 4: Hypnotic activity results of compounds (4a-e) and (5a-e)

Comp no.	No. of animals used for each comp	Body weight(g)	Dose(mg/kg) body(wt)	Average onset of action (min)	Average duration of action(min)	Route of administration
Standard (pentobarbital)	4	20-25	45	0.4	34	Ip
Control (2% gum acacia)	4	20-25	--	No onset of action	No duration of action	Per oral
Test compounds (4a-e and 5a-e)	4	20-25	50	No onset of action	No duration of action	Per oral
Test compounds (4a-e and 5a-e)	4	20-25	100	No onset of action	No duration of action	Per oral
Test compounds (4a-e and 5a-e)	4	20-25	200	No onset of action	No duration of action	Per oral

control for both activity, the results were presented in TABLE 2.

The compounds **(3b, 4b, 4c, 5b)** and **(5c)** shown good antibacterial activity against *E.coli, B.subtilis* and remaining compounds are exhibited moderate activity against the *E.coli, B.subtilis.* In fungicidal activity the compounds **(3b,c)**, **(4b,c)**, **(5b)** and **(5c)** exhibited significant antifungal activity against *A.niger* and *C.albican* where as remaining compounds are exhibited moderate to weak activity against the *A.niger* and *C.albican,* The results were presented in TABLE 2.

Anti-inflammatory activity (3a-e) and (4a-e)

Carrageenan induced rat paw oedema method was adopted to evaluate anti-inflammatory activity of some synthesized compounds. Phenylbutazone was used as standard drug. Compounds **(4a)**, **(5a)** and **(5e)** have shown moderate anti-inflammatory activity and compound have not shown any significant anti-inflammatory Activity against the standard drug phenylbutazone.

Hypnotic activity

The hypnotic activity was evaluated for some selected compounds at dose of 50mg/kg, 100mg/kg and 200mg/kg body weight of an animal. Pentobarbital was used as standard drug. None of the compounds showed promising hypnotic activity.

ACKNOWLEDGMENTS

The authors also thank to President, KRE' Societys Karnataka College of Pharmacy Sri Channabasappa Halhalli and Principal, Krantikumar M.Sirse, K.C.P.Bidar for providing research facilities to carryout this work. The authors wish to thank Mr. M. Mugali, Asst. Prof. Dept of Microbiology and Mr. Sunil Gandhe Asst. Prof. Dept of Pharmacology K.C.P.Bidar, for the help rendered for carrying out the antibacterial, antifungal, anti-inflammatory and hypnotic activity.

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