ISSN: 0975-8232

IJPSR (2010), Vol. 1, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received 05 March, 2010; received in revised form 20 April, 2010; accepted 20 May, 2010

SYNTHESIS OF 3- (1 – BENZYL - 1H - BENZO [D] IMIDAZOL – 2 - L AMINO) – 2 - (3 – ARYL - 1- PHENYL - 1H - PYRAZOL - 4 - YL) THIAZOLIDIN - 4- ONES AND THEIR ANTIMICROBIAL ACTIVITIES

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Keywords:

1- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl) hydrazine,
Pyrazoles,
Schiff base,
Thiazolidinones,
Antimicrobial activity

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ABSTRACT

Reaction of 1- (1- benzyl- 1H- benzo [d] imidazol- 2- yl) hydrazine (1) with 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (2a-f) in ethanol yielded the corresponding Schiff bases (3a-f). Further, cyclization of compounds 3a- f with thioglycollic acid in benzene in presence of anhydrous $ZnCl_2$ furnished desired novel compounds 3- (1 – Benzyl - 1h - Benzo [D] Imidazol – 2 - L Amino) – 2 - (3 – Aryl - 1- Phenyl - 1h - Pyrazol - 4 - Yl) Thiazolidin - 4- Ones (4a- f) in 41-65% yield. All the synthesized compounds were screened for antibacterial and antifungal activities. Among the synthesized compounds 3b, 3d, 4a and 4f have shown good activity against bacteria *P. aeruginosa, S. aureus and P. vulgaris,* where as other compounds have shown moderate to poor activity against all the organisms. The compounds 3a and 3c exhibited good activity against fungal strains *A. niger and A. flavus.* All remaining synthesized compounds exhibited moderate to poor activity against all the organisms. The structures of synthesized compounds have been established by spectral studies and elemental analysis.

INTRODUCTION: Benzimidazoles constitute an important group of heterocyclic compounds and have been shown to exhibit wide range of pharmacological activities such as antifungal, antibacterial, antiparasitic and anthelmintic [1-3]. Some of the benzimidazole analogs like thiabendazole, mebendazloe and albebdazole are widely used as anthelmintic drugs [4]. In addition, N_1 and C_2- subtituted benzimidazoles and their derivatives have been found to be potent biologically active compounds as well. Further, N_1-subtituted benzimidazoles have exhibited anti-microbial [5] and also antiviral activity [6] against human cytomegalovirus and herpes simplex virus type-1. The biological activities of these compounds depend upon the substitution on the benzimidazole at the N-1 or C-2 position. In addition, pyrazole and thiazolidinone derivatives are also known to exhibit a wide range of biological activities such as anti-hyperglycaemic, analgesics, anti-inflammatory, antipyretic, antibacterial and sedative-hypnotics [7-11]. In continuation of our research work on benzimidazoles [12-14] and pyrazoles [15], we report here the synthesis and antimicrobial activity of some novel 3 (1-benzyl- 1H- benzo [d] imidazole- 2-yl amino)- 2- (3- aryl- 1- phenyl- 1H- pyrazole- 4-yl) thiazolidine- 4- ones.

EXPERIMENTAL:

Chemistry: Melting points were recorded by using Thomas-Hoover melting point apparatus and were uncorrected. IR spectra in KBr disc were recorded on Perkin- Elmer- Spectrum-one FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR in DMSO-d_6 on amx 400 MHz spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on a JEOL SX 102 Mass spectrometer using Argon/Xenon (6kv, 10 mA) as the FAB gas. Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator. 3- aryl- 1- phenyl- 1H-pyrazole- 4-carbaldehydes were prepared by known literature method [16].

General procedure for the synthesis of Schiff bases (3a- f): A mixture 1- (1- benzyl- 1H-benzo [d] imidazol- 2- yl) hydrazine **(1)** (0.01 mol) and 3- aryl- 1- phenyl- 1H- pyrazole- 4-carbaldehydes **(2a-f)** (0.01 mol) in ethanol (20 ml) containing 3-4 drops of conc. HCl was refluxed on a water bath for 8 hours. Concentrated and the residue was recrystalized from methanol yielded desired compounds **3a-f**.

1- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl)- 2- ((1, 3- diphenyl- 1H- pyrazol- 4-yl) methylene) hydrazine (3a): Yield 1.5 g (60%). IR (KBr): 3253, 3182 (NH). ^1H NMR: 10.0 (s, 1H, N_1H), 7.9-7.6 (2H 1 N=CH, C_5H of pyrazole), 7.5-7.0 (m, 19H, ArH), 5.2 (s, 2H, methylene proton). Mass (m/z) = 468 (M^+, 10%). Anal. Calcd for $C_{30}H_{24}N_6$: C, 76.90; H, 5.16; N, 17.94. Found: C, 75.90; H, 5.15; N, 16.94.

1- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl)- 2- ((3- (4- nitrophenyl)- 1- phenyl- 1H- pyrazol- 4-yl) methylene) hydrazine (3b): Yield 1.2 g (55%). IR (KBr): 3139, 3121 (NH). ^1H NMR: 10.2 (s, 1H, N_1H), 7.8-7.6 (2H 1 N=CH, C_5H of pyrazole), 7.5-7.0 (m, 18H, ArH), 5.2 (s, 2H, methylene proton). Mass (m/z) = 513 (M^+, 10%). Anal. Calcd for $C_{30}H_{23}N_7O_2$: C, 70.16; H, 4.51; N, 19.09. Found: C, 69.16; H, 4.50; N, 19.08.

1- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl)- 2- ((1-phenyl- 3- *p*- tolyl- 1H- pyrazol- 4-yl) methylene) hydrazine (3c): Yield 1.2 g (65%). IR (KBr): 3413, 3123 (NH). ^1H NMR: 10.1 (s, 1H, N_1H), 7.8-7.6 (2H, 1 N=CH, C_5H of pyrazole), 7.5-7.0 (m, 18H, ArH), 5.2 (s, 2H, methylene

proton), 2.2(s, 3H, CH_3). Mass (m/z) = 482 (M^+, 10%). Anal. Calcd for $C_{31}H_{26}N_6$: C, 77.15; H, 5.43; N, 17.41. Found: C, 77.14; H, 5.42; N, 17.40.

1- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl)- 2- ((3-(2, 4- dimethoxyphenyl)- 1- phenyl- 1H- pyrazol- 4-yl) methylene)hydrazine (3d): Yield 1.4 g (45%). IR (KBr): 3123, 3113 (NH). ^{1}H NMR: 9.9 (s, 1H, N_1H), 8.0-7.6(2H, 1 N=CH, C_5H of pyrazole), 7.5-7.2 (m, 17H, ArH), 5.3 (s, 2H, methylene proton), 3.8 (s, 6H, OCH_3). Mass (m/z) = 528 (M^+, 15%). Anal. Calcd for $C_{32}H_{28}N_6O_2$: C, 72.71; H, 5.34; N, 15.90. Found: C, 72.70; H, 5.32; N, 15.89.

1- (1- Benzyl- 1H- Benzo [d] imidazol- 2- yl)- 2- ((3-(2, 5- dimethoxyphenyl)- 1- phenyl- 1H- pyrazol- 4-yl) methylene) hydrazine (3e): Yield 1.5 g (50%). IR (KBr): 3213, 3113 (NH). ^{1}H NMR: 10.0 (s, 1H, N_1H), 8.0-7.6 (2H, 1 N=CH, C_5H of pyrazole), 7.5-7.2 (m, 17H, ArH), 5.2 (s, 2H, methylene proton), 3.8 (s, 6H, OCH_3). Mass (m/z) = 528 (M^+, 10%). Anal. Calcd for $C_{32}H_{28}N_6O_2$: C, 72.71; H, 5.34; N, 15.90. Found: C, 72.69; H, 5.31; N, 15.88.

3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (3- (2- hydroxyphenyl)- 1- phenyl- 1H-pyrazol- 4- yl) methylene) hydrazine (3f): Yield 1.2 g (55%). IR (KBr): 3135, 3123 (NH). ^{1}H NMR: 10.8 (s, 1H, N_1H), 8.0 (s, 1H, OH), 7.8-7.6 (2H, 1 N=CH, C_5H of pyrazole), 7.0-7.5 (m, 18H, ArH). Mass (m/z) = 484 (M^+, 20%). Anal. Calcd for $C_{30}H_{24}N_6O$: C, 74.36; H, 4.99; N, 17.34. Found: C, 74.35; H, 4.97; N, 17.32;

General procedure for the synthesis of 3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (3-aryl-1-phenyl- 1H- pyrazol- 4- yl) thiazolidine- 4- one (4a- f): A mixture of Schiff base (0.001 mol), thioglycollic acid (0.001 mol) and a pinch of $ZnCl_2$ in 10 ml of benzene were refluxed for 24 hours. Concentrated the reaction product under reduced pressure yielded semisolid. It was then neutralized with $NaHCO_3$ (10%). Separated solid was filtered, dried and recrystallized from ethanol gave targeted compounds **4a-f**.

3- (1 -Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (1, 3- diphenyl- 1H- pyrazol- 4- yl) thiazolidin- 4- one (4a): Yield 0.4 g (45%). IR (KBr): 3172, 3123 (NH). 1676 C=O. ^{1}H NMR: 10.0 (s, 1H, N_1H), 7.8-7.2 (m, 20H, 19ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Mass (m/z) = 542 (M^+, 10%). Anal. Calcd for $C_{32}H_{26}N_6OS$ C, 70.83; H, 4.83; N, 15.49. Found: C, 70.82; H, 4.82; N, 15.48.

3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)-2- (3- (4- nitrophenyl)- 1-phenyl- 1H- pyrazol- 4- yl) thiazolidin- 4- one (4b): Yield 0.24 g (55%). IR (KBr): 3235, 3123 (NH). ^{1}H NMR: 10.0 (s, 1H, N_1H), 8.2-7.2 (m, 19H, 18ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Mass (m/z) = 587 (M^+, 15%). Anal. Calcd for $C_{32}H_{25}N_7O_3S$: C, 65.40; H, 4.29; N, 16.68. Found: C, 65.39; H, 4.28; N, 16.66.

3- (1- Benzyl - 1H - benzo [d] imidazol- 2- ylamino) - 2 - (1- phenyl- 3- p- tolyl- 1H- pyrazol- 4- yl) thiazolidin- 4- one (4f): Yield 0.16 g (50%). IR (KBr): 3245, 3211 (NH). ^{1}H NMR: 9.9 (s, 1H, N_1H), 7.8-7.2 (m, 19H, 18ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone), 2.2 (s, 3H, CH_3). Mass (m/z) = 556 (M^+, 15%). Anal. Calcd for $C_{33}H_{28}N_6OS$: C, 71.20; H, 5.07; N, 15.10. Found: C, 71.19; H, 5.08; N, 15.08.

3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (3- (2, 4- dimethoxyphenyl)- 1- phenyl- 1H-pyrazol- 4- yl) thiazolidin- 4- one

(4c): Yield 0.15 g (65%). IR (KBr): 3245, 3111 (NH). ^{1}H NMR: 10.0 (s, 1H, N_1H), 7.9-7.2 (m, 17H, 16ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Anal. Calcd for $C_{34}H_{30}N_6O_3S$: C, 67.76; H, 5.02; N, 13.94. Found: C, 67.75; H, 5.01; N, 13.92.

3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (3- (2, 5- dimethoxyphenyl)- 1- phenyl- 1H-pyrazol- 4- yl) thiazolidin- 4- one (4d): Yield 0.25 g (41%). IR (KBr): 3268, 3112 (NH). ^{1}H NMR: 10.2 (s, 1H, N_1H), 7.8-7.2 (m, 17H, 16ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Anal. Calcd for $C_{34}H_{30}N_6O_3S$: C, 67.76; H, 5.02; N, 13.94. Found: C, 67.72; H, 5.02; N, 13.93.

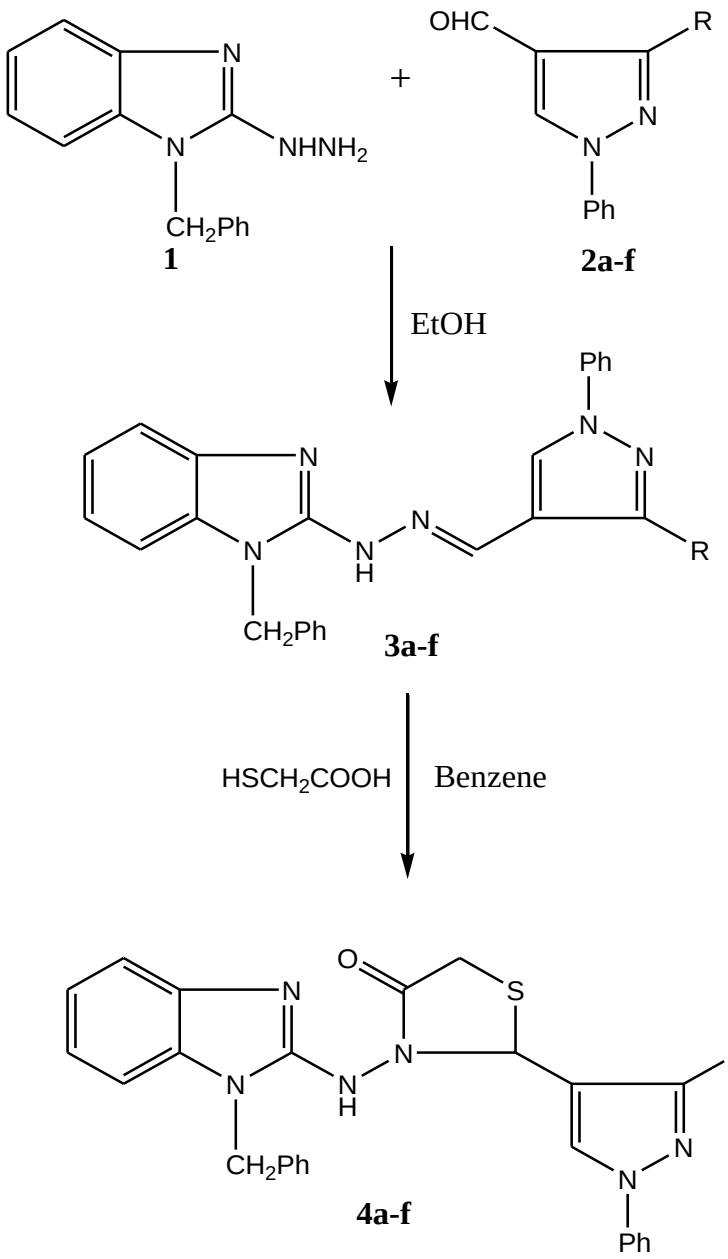
3- (1- Benzyl- 1H- benzo [d] imidazol- 2- yl amino)- 2- (3- (2- hydroxyphenyl)- 1- phenyl- 1H- pyrazol-4- yl) thiazolidin- 4- one (4e): Yield 0.18 g (60%). IR (KBr): 3345, 3211 (NH). ^{1}H NMR: 10.2 (s, 1H, N_1H), 7.8-7.2 (m, 19H, 18ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Mass (m/z) = 558 (M^+, 10%). Anal. Calcd for $C_{32}H_{26}N_6O_2S$: C, 68.80; H, 4.69; N, 15.04. Found: C, 68.79; H, 4.68; N, 15.02.

RESULTS AND DISCUSSION: The desired novel compounds **4a-f** were synthesized in two steps starting from 2- hydrazinobenzimidazole **(1)** (Scheme- 1)**.** Reaction of **1** with 3- aryl- 1- phenyl- 1H- pyrazole- 4-carbaldehydes **(2a-f)** in ethanol in the presence of 2-3-drops of conc. HCl under reflux for 8 hours gave the corresponding Schiff bases **(3a-f)** in 41-65% yield (Table-1). The IR spectrum of compound **3a** shows absorptions at 3253 and 3182 cm^{-1} due to NH and formation of compound **3a** was further confirmed by its ^{1}H NMR spectrum shows signals at δ 10.0 (s, 1H, N_1H), 7.9-7.6(2H 1 N=CH, C_5H of pyrazole), 7.5-7.0 (m, 19H, ArH), 5.2 (s, 2H, methylene proton). Mass spectrum of compound **3a** shows molecular ion peak at m/z = 468 (M^+, 10%).

Cyclization of Schiff bases **3a-f** with thioglycollic acid in refluxing benzene in the presence of $ZnCl_2$ for 24 hours furnished 3- (benzo [d] imidazol- 2- yl amino)- 2- (3- aryl- 1- phenyl- 1H- pyrazol- 4-yl) thiazolidin- 4- ones (**4a-f)**. Formation of compound **4a** was confirmed by the IR spectra shows absorptions at 3172, 3123 and 1676 cm^{-1} due to NH and C=O group. ^{1}H NMR spectrum of compound **4a** shows signals at δ10.0 (s, 1H, N_1H), 7.8-7.2 (m, 20H, 19ArH, C_5H of pyrazole), 5.6 (s, CH of thiazolidinone), 5.2 (s, 2H, methylene proton), 3.2 (d, CH_2 of thiazolidinone). Further formation of compound **4a** was confirmed by mass spectra shows molecular ion peak at m/z = 542 (M^+, 10%). Physical constants of all the synthesized compounds are tabulated in Table 1.

TABLE 1: PHYSICAL CONSTANT OF THE SYNTHESIZED COMPOUNDS

COMPOUND	R	YIELD (%)	M. PT. ^oC
3a	C_6H_5	60	180-182
3b	4-NO_2 C_6H_4	55	214-216
3c	4-CH_3 C_6H_4	65	172-174
3d	2,4-$(OCH_3)_2$ C_6H_3	45	186-188
3e	2,5- $(OCH_3)_2$ C_6H_3	50	160-162
3f	2-OH C_6H_4	60	222-224
4a	C_6H_5	45	250-252
4b	4-NO_2 C_6H_4	55	Semisolid
4c	4-CH_3 C_6H_4	50	Semisolid
4d	2,4-$(OCH_3)_2$ C_6H_3	65	Semisolid
4e	2,5- $(OCH_3)_2$ C_6H_3	41	Semisolid
4f	2-OH C_6H_4	60	Semisolid



	a	b	c	d	e	f
R=	C_6H_5	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	2,4-$(OCH_3)_2C_6H_3$	2,5-$(OCH_3)_2C_6H_3$	2-OHC_6H_4

Scheme 1

Antimicrobial Activity: The antimicrobial activities were performed by cup plate method. The sample was dissolved in DMF at the concentration of 1000 µg/ml. Antibacterial activity screened against *P. aeruginosa, S. aureus and P. vulgaris.* Antifungal activity was carried out against A*. niger* and *A. flavus* under aseptic conditions. Gentamycin and fluconazole were used as standard drug for antibacterial and antifungal activities respectively. The zone of inhibition was compared with standard drug after 24 hours of incubation at 25^{o}C for antibacterial activity and 48 hours at 30^{o}C for antifungal activity. Results are tabulated in Table 2.

CONCLUSION: A simple and convenient method has been developed to synthesize novel 3 - (benzo [d] imidazole – 2 - yl amino) - 2- (3 - aryl- 1 – phenyl - 1H - pyrazole - 4 - yl) thiazolidin- 4- one (**4a- f).** Further, it reveals that the presence of pyrazole moiety attached to benzimidazole ring enhances the antibacterial activity.

TABLE 2: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

COMPOUND	DOSE (µG/ML)	ANTIBACTERIAL ACTIVITY			ANTIFUNGAL ACTIVITY	
		ZONE OF INHIBITION (MM)			ZONE OF INHIBITION (MM)	
		S. AUREUS	*P. VULGARIS*	*P. AERUGINOSA*	*A. NIGER*	*A. FLAVUS*
3a	1000	08	10	16	20	18
3b	1000	12	12	18	16	16
3c	1000	10	14	10	18	20
3d	1000	14	08	16	20	06
3e	1000	06	16	14	18	14
3f	1000	06	08	10	14	16
4a	1000	14	11	12	20	12
4b	1000	12	10	06	18	14
4c	1000	06	14	06	14	10
4d	1000	12	14	14	08	10
4e	1000	10	16	06	12	18
4f	1000	14	18	16	12	16
Control (DMF)	-	0	0	0	0	0
Standard (Gentamycin & Fluconazole)	1000	16	22	20	22	18

** Zone of inhibition excluding well size 6mm

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