JSR Publications

Available Online

J. Sci. Res. **3** (1), 121-128 (2011)

JOURNAL OF SCIENTIFIC RESEARCH

www.banglajol.info/index.php/JSR

Synthesis and Pharmacological Evaluation of 7-chloro-6-fluoro-2-(5-aminooxazol/thiazol-2-aryldenylamino)-benzo(1,3)thiazoles

B. M. Gurupadayya*, Ch. Sambireddy, M. N. Purohit, and G. V. Pujar

Department of Pharmaceutical Chemistry, J.S.S. College of Pharmacy, J.S.S. University, Mysore-570 015, India

Received 25 September, accepted in revised form 24 November 2010

Abstract

New series of 7-chloro-6-fluoro-2-(5-aminooxazol/thiazol-2-aryldenylamino)-benzo (1,3)thiazoles (Schiff's base)(5a-g, 6a-g) were synthesized from 7-chloro-6-fluoro-2-(5-amino-oxazol/thiazol-2-amino)-benzothiazole (4a-b). Structures of the compounds were verified by ^{1}H-NMR spectra. The synthesized compounds were screened for *in vivo* analgesic and antiinflammatory activities. Some of the compounds showed moderate activities.

Keywords: Benzothiazole; Schiff's base; Analgesic activity; Antiinflammatory activity.

doi:10.3329/jsr.v3i1.6166 J. Sci. Res. **3** (1), 121-128 (2011)

1. Introduction

Many of the benzothiazole derivatives have been extensively used as lead drugs since many years. The chemical modification on these drugs has been carried out to enhance their biological profile. The chemistry of benzothiazole has received attention in recent years as it possesses wide spectrum of pharmacological activities. Wide ranges of substituted benzothiazole and related heterocycles have potential biological activities. Heterocycles bearing a benzothiazole ring residues are reported to show antitumour [1], anti-inflammatory [2-3], analgesic [4] , sedative [5], antitubercular [6], oxidase inhibitors [7], antimicrobial [8], antidiabetic [9] and anticonvulsant [10] activities. In the present work we synthesized some novel 7-chloro-6-fluoro-2-(5-aminooxazol/thiazol-2-aryldenylamino)-benzo (1,3) thiazole analogs and evaluated for *in vivo* analgesic and antiinflammatory activities.

2. Materials and Methods

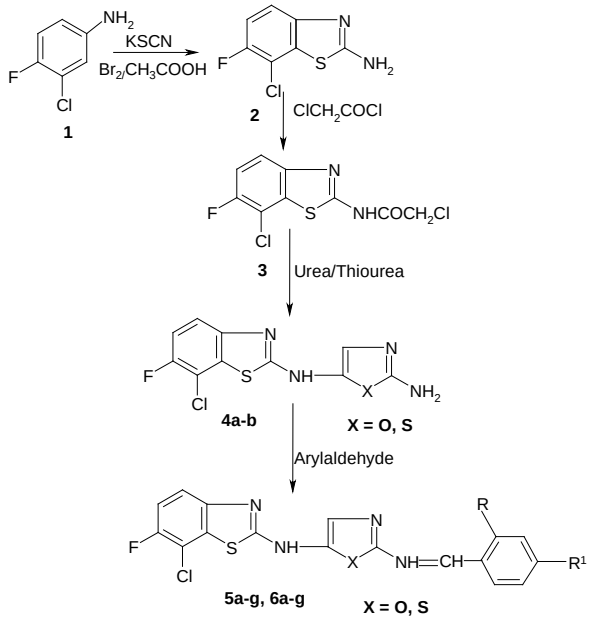
The purity of all the synthesized compounds was confirmed by using thin layer chromatography (TLC) and melting point. TLC of the compounds was run by using silica

* *Corresponding author*: bm_guru2004@yahoo.co.in

gel G as stationary phase and by using suitable solvent mixture. Different analytical techniques such as IR and NMR were used to characterize the synthesized compounds. The IR spectra were recorded on Shimadzu FT-IR 8400-S spectrophotometer by KBr pellet technique. The ^{1}H-NMR spectra were recorded on AMX-400 NMR spectrophotometer at 400 MHz using DMSO/$CDCl_3$ as the solvent and TMS as internal standard. Chemical shifts are expressed in ppm.

Methods

The title compounds were prepared in following steps (scheme is also shown):



Preparation of 7-chloro-6-fluoro-2-chloro-acetamidebenzothiazole (3)

To a cooled solution of 7-chloro 6-fluoro 2-amino benzothiazole (**2**) [11] in ethanol (10.15 g, 0.05 mol), chloroacetylchloride (5.8 ml, 0.05 mol) was added drop wise for 1 h while stirring. Further the mixture was stirred for 2 h and refluxed for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled and poured onto crushed ice. The separated solid was filtered, washed with water and recrystallized from methanol.

Preparation of 7-chloro-6-fluoro-2-(5-aminooxazol-2-amino) benzothiazole (4a)

A solution of compound **3** (5.56 g, 0.02 mol) and urea (1.5 g, 0.025 mol) in dry methanol (50 ml) was refluxed for 12 h. After completion of the reaction (monitored by TLC), it was cooled and poured onto crushed ice. The separated solid was filtered, washed with sodium bicarbonate (2%) solution and recrystallized from ethanol.

Preparation of 7-chloro-6-fluoro-2-(5-aminothiazolyl)-2-aminobenzothiazole (4b)

To a solution of **3** (5.56 g 0.02 mol) in absolute ethanol (50 ml) thiourea (1.9 g, 0.025 mol) was added and the reaction mixture was refluxed for 12 h. After completion of the reaction (monitored by TLC), it was cooled and poured onto crushed ice. The separated solid was filtered, washed with sodium bicarbonate (2%) solution and recrystallized from ethanol**.**

General method for preparation of 7-chloro-6-fluoro-2-(5-aminooxazol/thiazol-2-aryldenylamino-benzo (1,3) thiazoles (Schiff's bases) (5a-g and 6a-g)

To solution of **4a** or **4b** (0.005 mol) and appropriate aryl aldehyde (0.01 mol) in absolute ethanol (25 ml) few drops of concentrated sulphuric acid were added. The mixture was refluxed on a water bath for 3-4 h, till the completion of the reaction (monitored by TLC). The reaction mixture was cooled and poured onto crushed ice to obtain the solid, which was dried and crystallized by DMSO. Physical and analytical data of synthesized compounds is summarized in Table 1 and characterization data in Table 2.

Table 1. Physical and analytical data of synthesized compounds.

Comp. No.	R	R^1	M.P. (^{0}C)	Yield (%)	Molec. formula	Molec. weight	Rf value
2	--		168	66.48	$C_7H_4ClFN_2S$	202	0.62
3	--		218	64.24	$C_9H_5C_{l2}FN_2OS$	279	0.64
4a	--		214	61.38	$C_{10}H_6ClFN_4OS$	284	0.61
4b	--		220	60.58	$C_{10}H_6ClFN_4S_2$	299	0.62
5a	H	H	214	59.12	$C_{17}H_{10}ClFN_4OS$	372	0.52
5b	OH	OCH_3	163	64.34	$C_{18}H_{12}ClFN_4O_3S$	418	0.53
5c	OH	H	200	57.48	$C_{17}H_{10}ClFN_4O_2S$	388	0.54
5d	H	OCH_3	209	58.32	$C_{18}H_{12}ClFN_4O_2S$	402	0.59
5e	H	$N(CH_3)_2$	195	63.58	$C_{19}H_{15}ClFN_5OS$	415	0.52
5f	H	Cl	206	65.28	$C_{17}H_9Cl_2FN_4OS$	406	0.64
5g	H	NO_2	190	68.34	$C_{17}H_9ClFN_5O_3S$	417	0.53
6a	H	H	110	67.34	$C_{17}H_{10}ClFN_4S_2$	388	0.75
6b	OH	OCH_3	240	63.48	$C_{18}H_{12}ClFN_4O_2S_2$	434	0.62
6c	OH	H	192	59.58	$C_{17}H_{10}ClFN_4OS_2$	404	0.65
6d	H	OCH_3	66	64.48	$C_{18}H_{12}ClFN_4OS_2$	418	0.59
6e	H	$N(CH_3)_2$	220	59.01	$C_{19}H_{15}ClFN_5S_2$	431	0.54
6f	H	Cl	228	62.25	$C_{17}H_9C_{l2}FN_4S_2$	423	0.48
6g	H	NO_2	235	68.50	$C_{17}H_9ClFN_5O_2S_2$	433	0.50

Table 2. Characterization data of the synthesized compounds.

Comp. No.	IR (KBr) cm^{-1}	^1H NMR (δ ppm, $CDCl_3$/TMS)
2	3470 (NH); 3090,(Aromatic C-H); 1641(C=N); 1329(C-N); 1197 (C-F); 758 (C-Cl).	7.5-8.0 (d, 2H, ArH); 4.1(s, 2H, NH_2).
3	3454 (NH); 3060 (C-H-Ar); 1637(C=O);1622 (C=N); 1325 (C-N);1103 (C-F); 759(C-Cl).	8.4 (s, 1H, NH); 7.3-8.0 (d, 2H, ArH) 4.8 (s, 2H, CH_2).
4a	3473(NH); 3018(C-H-Ar);1647 (C=N);1340(C-N); 1190(C-F); 710 (C-Cl).	9.2 (s, 1H, NH); 7.3-7.9 (m, 3H, ArH) 5.2 (s, 2H, NH_2).
4b	3475 (NH); 3095 (C-H-Ar); 1651(C=N); 1340 (C-N);1193 (C-F); 715 (C-Cl).	9.2 (s, 1H, NH); 7.3-7.9 (m, 3H, ArH); 5.1(s, 1H, NH_2).
5a	3308(NH); 3010(CH-Ar); 1647(N=CH); 2366 (C-S);119 (C-F); 719 (C-Cl).	8.5 (s, 1H, NH); 7.1-8.1 (m, 8H, ArH); 3.8(s,1H, N=CH).
5b	3306 (NH); 3010(C-H-Ar); 2362 (C-S); 1195(C-F); 719(C-Cl).	8.4 (s, 1H, NH); 7.1-8.2 (m, 6H, ArH); 4.9(s, 1H, OH); 3.8 (s, 1H, NH); 4.3 (s, 1H, OCH_3).
5c	3306 (NH); 3041(C-H-Ar); 2343 (C-S); 1649 (N=CH); 119 (C-F); 719(C-Cl).	
5d	3410 (NH); 3010(C-H-Ar); 2340 (C-S); 1649 (N=CH); 1195 (C-F); 719(C-Cl).	
5e	3309 (NH); 3009(C-H-Ar); 2370 (C-S); 1654 (N=CH); 1195 (C-F); 719(C-Cl).	8.2 (s, 1H, NH); 7.0-8.0 (m, 6H, ArH); 5.6 (s,1H, OH); 3.2 (s, 1H, N=CH); 3.4 (s, 1H, OCH_3).
5f	3308 (NH); 3009(C-H-Ar); 2362 (C-S); 1662(N=CH); 1197 (C-F); 719(C-Cl).	
5g	3458 (NH); 3010(C-H-Ar); 2362 (C-S); 1664 (N=CH); 119 (C-F); 719(C-Cl).	
6a	3306 (NH); 3037(C-H-Ar); 2366 (C-S); 1656(N=CH); 116 (C-F); 721(C-Cl).	
6b	3308 (NH); 3010(C-H-Ar); 2082 (C-S); 1647 (N=CH); 119 (C-F); 717(C-Cl).	8.5 (s, 1H, NH); 7.2-8.0 (m, 8H, ArH); 3.8 (s, 1H, N=CH).
6c	3402 (NH); 3009(C-H-Ar); 2366 (C-S); 1651(N=CH); 1195 (C-F); 719(C-Cl).	
6d	3304 (NH); 3009(C-H-Ar); 2364 (C-S); 1656(N=CH); 1197 (C-F); 732(C-Cl).	
6e	3489(NH); 3020(C-H-Ar); 2085 (C-S); 1662(N=CH); 1199 (C-F); 717(C-Cl).	8.5 (s, 1H, NH); 7.3-8.0 (m, 6H, ArH); 5.2 (s, 1H, OH); 3.4 (s, 1H, N=CH); 3.8 (s, 1H, OCH_3).
6f	3308 (NH); 3009(C-H-Ar); 2362 (C-S); 1662(N=CH); 119 (C-F); 719(C-Cl).	
6g	3458 (NH); 3010(C-H-Ar); 2362 (C-S); 1664(N=CH); 119 (C-F); 719(C-Cl).	

Pharmacological screening

In vivo anti inflammatory activity

In vivo Anti-inflammatory activity of synthesized compounds was evaluated using carrageenan induced rat hind paw oedema [12]. The animals were divided into control, standard and test groups, each consisting of six animals. The first group was treated with Tween-80 (1%) suspension which served as control, second group was administered with a dose of 20 mg/kg suspension of diclofenac sodium intraperitoneally which served as standard and other groups were treated with 30 mg/kg of suspension of test compounds in

Tween-80. After 30 min, the rats were injected with 0.1 ml of carrageenan (1% w/v) to the sub plantar region of left paw of the rats. The volume of paw was measured using mercury displacement technique with the help of plethysmograph both in control and animals treated with standard and test compounds at 0, 1, 2 and 3 h after injection of carrageenan. The percentage inhibition of oedema was calculated by using formula, percentage inhibition = (1–*Vt*/*Vc*) 100, where *Vt* is the mean paw volume of the test drug, *Vc* is the mean paw volume of the control. The results are recorded in Table 3.

Table 3. Results of Antiinflammatory activity of the synthesized compounds.

Comp.	Paw volumes (ml) ± SEM and % reduction					
	1 Hour		2 Hour		3 Hour	
	Mean± SEM	% RPOV	Mean± SEM	% RPOV	Mean± SEM	% RPOV
5a	1.50± 0.07*	14.60	1.74± 0.07†	17.14	1.87± 0.06‡	22.08
5b	1.43± 0.03†	19.66	1.53± 0.05†	27.14	1.70± 0.04‡	29.16
5c	1.40± 0.05†	21.34	1.45± 0.05‡	30.95	1.63± 0.04‡	32.08
5d	1.42± 0.03†	20.22	1.57± 0.11†	25.23	1.63± 0.10‡	32.08
5e	1.50± 0.04*	15.73	1.78± 0.05†	15.23	1.90± 0.02†	20.83
5f	1.32± 0.07†	25.84	1.35± 0.05†	35.71	1.35± 0.04‡	43.75
5g	1.38± 0.05†	22.47	1.40± 0.06†	33.33	1.43± 0.05‡	40.41
6a	1.38± 0.05	22.47	1.70± 0.05†	14.04	1.80± 0.05‡	25.00
6b	1.30± 0.03†	26.96	1.65± 0.03†	21.42	1.75± 0.06‡	27.08
6c	1.48± 0.04†	22.00	1.57± 0.05‡	25.23	1.65± 0.06‡	31.25
6d	1.45± 0.04†	18.50	1.53± 0.04‡	27.14	1.63± 0.06‡	32.08
6e	1.28± 0.03†	28.08	1.42± 0.06‡	32.38	1.48± 0.04‡	38.30
6f	1.78± 0.05	43.24	2.10± 0.05	33.33	1.43± 0.05‡	40.41
6g	0.90± 0.05†	28.08	2.15± 0.03‡	35.20	1.52± 0.05‡	42.00
Control	1.78± 0.05	--	2.10± 0.05	--	2.4± 0.03	--
Diclofenac	0.99± 0.05†	43.24	1.11± 0.03‡	46.00	1.11± 0.05‡	54.00

RPEV = Reduction in Paw Edema volume.
$^{*}p<0.05$, $^{\dagger}p<0.01$, $^{\ddagger}p<0.001$, when compared with control.

In vivo analgesic activity

The animals were divided into four groups of six animals each. The animals, which showed reaction time of 2-3 s, were selected for experiment and analgesic activity of synthesized compounds was studied by tail flick method [13]. The tail received radiant heat from a wire, which is heated by passing a current of 6 mA. The time taken for the withdrawal of tail was recorded before the administration of the compounds and for 30, 60, 90 and 120 min after administration of compounds. The cut off time for determination of latent period was taken as 40 s to avoid the injury to the skin and based on our pilot studies. One group served as a

standard (pentazocine hydrochloride) with dose of 10 mg/kg body weight and another group served as control (1% Tween-80) and rest of the groups used for the test drugs. The test compounds and pentazocine hydrochloride were suspended in 1% Tween-80 which was used as vehicle for the control group. The tested compounds were administered at the dose of 30 mg/kg body weight in the form of suspension and administered intraperitoneally. The results of analgesic activity are shown in Table 4. The animal experimental protocols were approved by Institutional Animal Ethical Committee (IAEC).

Table 4. Results of analgesic activity of the synthesized compounds.

Comp.	ABRT in sec Pre treatment 'O' min	ABRT in seconds after treatment			
		15 min	30 min	45 min	60 min
5a	3.60 ± 0.08	4.5± 0.06‡	5.53± 0.04‡	6.03± 0.13‡	7.20 ±0.2‡
5b	3.80± 0.02	4.5± 0.06‡	5.05± 0.08‡	7.40±0.2‡	7.40 ±0.2‡
5c	3.60± 0.02	4.62± 0.10‡	4.67± 0.06‡	5.50± 0.14‡	5.30± 0.03‡
5d	3.20± 0.04	5.5± 0.22‡	5.5± 0.22‡	4.4± 0.20‡	3.40± 0.37
5e	3.40± 0.10	3.83± 0.31	6.83± 0.48‡	6.00± 0.37‡	6.50±0.22‡
5f	2.62± 0.04	2.67± 0.21	3.33± 0.21	6.67± 0.21	8.00± 0.37
5g	3.60 ± 0.10	4.17± 0.31	5.17± 0.31†	8.00±0.26‡	9.83±0.31‡
6a	3.20± 0.15	4.00± 0.26	5.5± 0.34†	6.17± 0.31‡	6.67± 0.21‡
6b	3.50± 0.02	5.33± 0.33‡	6.83± 0.78‡	5.20± 0.21‡	5.33± 0.21‡
6c	3.10± 0.06	3.17± 0.48†	4.17± 0.40‡	6.67±0.5‡	7.67±0.21‡
6d	3.60± 0.06	4.33± 0.80†	5.76± 0.04‡	6.33± 0.12†	5.25± 0.08‡
6e	3.60± 0.20	3.67± 0.21	3.83± 0.31	4.33± 0.22	4.33± 0.42
6f	3.50± 0.02	5.33‡± 0.33	8.83± 0.78‡	5.67± 0.21‡	8.33± 0.21‡
6g	3.60± 0.10	4.17 ± 0.31	5.17± 0.31†	8.00±0.26‡	9.83±0.31‡
Control	3.60± 0.06	3.60 ± 0.10	3.50± 0.15	3.60±0.15	3.40±0.06
Pentazocine HCl	3.60± 0.08	4.93 ± 0.18‡	8.90± 0.15‡	10.10±0.2‡	12.50± 0.1‡

ABRT: Average basal reaction time.
$^{*}p<0.05$, $^{†}p<0.01$, $^{‡}p<0.001$, when compared with control.

3. Results and Discussion

The required starting material 7-chloro-6-fluoro-2-aminobenzothiazole (compound **2**) was prepared from reported method using 3-chloro-4-fluoro aniline (compound **1**). It was then refluxed with chloroacetyl chloride in ethanol to get an intermediate compound, 7-chloro-6-fluoro-2-chloroacetamidobenzothiazole (compound **3**). The IR spectrum of **3** exhibited absorbance bands at 3454 cm^{-1} and 1637 cm^{-1} due to NH and C=O stretching. Its ^{1}H-NMR spectrum was recorded in $CDCl_3$ exhibited a singlet at 8.4 ppm due to –NH integrating for

one proton, aromatic protons resonated as multiplet at 7.3-8.0 ppm and $–CH_2$ protons appear as singlet at 4.8 ppm. The compound **3** was refluxed with urea and thiourea separately to produce 7-chloro-6-fluoro-2-(5-aminooxazol-2-amino) benzothiazole (compound **4a**) and 7-chloro-6-fluoro-2-(5-aminothiazol-2-amino) benzothiazole (compound **4b**) respectively. The IR spectrum of **4a** exhibited absorbance band at 3473 cm^{-1} due to $–NH_2$ group. Its ^{1}H-NMR spectrum was recorded in $CDCl_3$ exhibited, a singlet integrating at 9.2 ppm due to NH, a broad singlet at 5.2 ppm for two protons of NH_2 and aromatic protons resonated at 7.3 ppm and 7.9 ppm. Similarly, the IR spectrum of compound **4b** exhibited $–NH_2$ absorbance band at 3475 cm^{-1}. Its ^{1}H-NMR spectrum was recorded in $CDCl_3$ exhibited a singlet integrating at 9.2 ppm due to NH, a broad singlet at 5.1 ppm for two protons of NH_2. The aromatic protons resonate between 7.3-7.9 ppm. Schiff bases were prepared from **4a** and **4b** by reacting with appropriate aromatic aldehydes in absolute alcohol in the presence of concentrated sulfuric acid. IR spectrum of benzylidene-(7-chloro-6-fluorobenzothiazol-2-yl) oxazole-2,5-diamine (compound **5a**) exhibited –NH absorbance band, C-H stretching, C-S band and N=CH band at 3308, 3010, 2366 and 1647 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **5a** was recorded in DMSO exhibited singlet at 8.5 ppm due to NH integrating for one proton. The aromatic protons resonate between 7.1-8.2 ppm. Whereas N=CH proton appeared at 3.8 ppm. In the similar way, remaining Schiff bases were identified. The spectral data of the synthesized compounds are given in Table 2.

The compounds **5f**, **5g**, **6f** and **6g** were found to possess moderate anti-inflammatory activity having percentage of inhibition to the extent of 38.30%, 40.41%, 42.38% and 43.75% as compared with diclofenac sodium, which showed percentage inhibition of 54.20%. The compounds **5f, 5g**, **6f** and **6g** were found to show considerable analgesic activity while the remaining compounds were found to be exhibit less active when compared to standard. Hence electron donating group at position 4 of benzylidene-(7-chloro-6-fluorobenzothiazol-2-yl)oxazol/thiazol-2,5-diamine is necessary for anti-inflammatory and analgesic activity.

Acknowledgement

The authors are thankful to the Principal, JSS College of Pharmacy, Mysore for providing necessary facilities. They are also thankful to the Director NMR Research Centre, Indian Institute of Science, Bangalore for spectral data.

References

1. E. Kashiyama, I. Hutchinson, M. S. Chua, S. F. Stinson, L. R. Phillipse, and G. Kaur, J. Med. Chem., **42** (20) 4172 (1997). doi:10.1021/jm990104o
2. M. Santagati, M. Modica, A. Santagati, F. Russo, V. Cutili, F. Di Pietro, and M. Amico-Roxas, Pharmazie **49** (12) 880 (1994). PMid:7838878
3. B. M. Gurupadayya, M. Gopal, B. Padmashali, and Y. N. Manohara, Indian J. Pharm. Sci., **70** (5), 572 (2008). doi:10.4103/0250-474X.45393
4. S. Yous, J. H. Poupaert, P. Chavatte, J. G. Esplard, D. H. Calgnard, and D. Lesicur, Drug Des. Discov. **17** (4), 331 (2001). PMid:11765136

5. A. Liozzo and V. G. Longo, Physiology and behavior **3** (1), 91 (1968). doi:10.1016/0031-9384(68)90037-1
6. R. Gasparov, M. Lavoca, I. M. Shabeer, and Z. Oldlerova, Farmaco **52** (4), 251 (1997).
7. C. Michael, Z. Van, L. J. Michael, E. G. David, and S. G. Leo, J. Med. Chem. **48** (9), 3141 (2005). doi:10.1021/jm0492094
8. M. A. Mahran, S. M. El-Nassry, S. R. Allam, and L. A. El-Zawawy, Pharmazie **58** (8), 527 (2003). PMid:12967026
9. M. Michael, L. Ernest, and C. F. Geoffrey, Biochemical Pharmacology **35** (12), 1971 (1986). doi:10.1016/0006-2952(86)90729-X
10. R. S. Chopade, R. H. Bahekar, P. B. Khodekar, and K. P. Bhusari, Arch Pharma (Weinheim), **335** (8), 381 (2002). doi:10.1002/1521-4184(200211)335:8<381::AID-ARDP381>3.0.CO;2-S
11. B. M. Gurupadaiah, E. Jayachandran, B. Shivakumar, A. N. Nagappa, and L. V. G. Nargund, Indian J. Heterocyclic Chem. **7**, 213 (1998).
12. S. G. Kaskhediker, P. Trivedi, G. T. Abolare, R. S. Goud, and S. C. Chaturvedi, Indian Drugs **28**, 232 (1991).
13. S. B. Kasture, S. V. Kasture, R. P. Phate, and S. C. Pal, Indian Drugs **36**, 588 (1999).