Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(5):348-353

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis, Characterisation and Antimicrobial Activity Studies of Some New N-Substituted Piperidine Derivatives of 2-(4-chloro-4-(4 chlorophenyl)) Piperidine

AA Kaneria*, NM Thumar, KD Ladva and MS Vadodaria

Chemical Research Laboratory, Shree M&N Virani Science College, Rajkot, Gujarat, India

---

ABSTRACT

An efficient and convenient procedure has been developed for the synthesis of some new N-substituted piperidine derivatives like 2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-aryl-1,3,4-oxadiazoles 5a-j and N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)- 4-hydroxypiperidin-1-yl) acetohydrazides 6a-j. The structures of the new compounds have been evaluated on the basis of FT-IR, ^{1}H NMR and mass spectroscopy data. They have also been screened for their antimicrobial activities against various strains of bacteria and fungi.

Keywords: Piperidine; Oxadiazole; Acetohydrazide; Antimicrobial activity

---

INTRODUCTION

In recent years research is concern on nitrogen containing heterocyclic compounds and their pharmaceutical importance [1,2]. Piperidine is a six membered heterocyclic compound containing five carbon and one nitrogen atom. The chemical nature of Piperidine is basic. The piperidine ring exhibits excellent structural attribute of many alkaloid, natural products and drug product [3]. Watson et al. reported that there were thousands of piperidine compounds mentioned in clinical and preclinical studies during a recent 10 year period [4]. Many of drugs having piperidine nucleus used as different therapeutic agents in recent scenario. Peroxitine (1) as antidepressant [5,6], methylphenidate (2), ethylphenidate (3) [7], pipradrol (4), desoxypipradrol (5) [8] as analeptics/nootropics (Stimulants) raloxifene (6) as SERM (selective estrogen receptor modulators) [9], minoxidil (7) as vasodilators [10], risperidone (8), thioridazine (9), mesoridazine (10), haloperidol (11), pimozide (12), droperidol (13), and melperone (14) as Neuroleptics (antipsychotics) [5], pethidine (meperidine) (15), loperamide (16) as anti-opioids [11,12], tiagabine (17) as anticonvulsant [13], solifenacin (18) used in the treatment of an overactive bladder [14], carmegliptine (19) used as an anti-diabetes drug [15], aplaviroc (20) as anti-HIV drug [16]. Piperidine derivatives are also active as local anesthetics, such as mepivacaine (21), ropivacaine (22), and bupivacaine (23) [17]. Piperidine derivatives are also potent as antimicrobial agents [18,19], anesthetic agents [20] and Aryl hydrocarbon receptor [21] (Figure 1).

We have synthesized some new piperidine derivatives like 2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-aryl-1,3,4-oxadiazoles 5a-j and N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)- 4-hydroxypiperidin-1-yl)acetohydrazides 6a-j as shown in Scheme 1. The newly synthesized compounds were characterized by IR, Mass and 1H NMR spectroscopy. All the synthesized compounds were evaluated for their antimicrobial activity (Table 1).

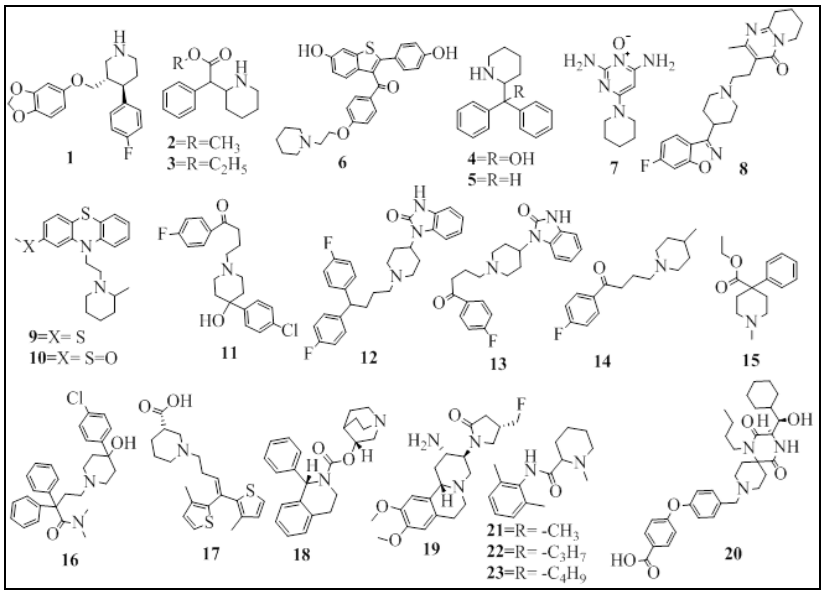


Figure 1: Piperidine derivatives as therapeutic agents

EXPERIMENTAL SECTION

All chemicals were purchased from commercial suppliers and used without further purification. The progress of the reaction was monitored by analytical TLC on precoated plates (silica gel 60, F_{254}) and visualized with UV light. Melting points were determined using open capillary tube and are uncorrected. Flash column chromatography was performed with silica gel (60-120 mesh). ^{1}H NMR spectra were recorded using DMSO-d_6 as a solvent on a Bruker 400 MHZ and chemical shifts are expressed in parts per million (ppm) related to internal standard TMS. Infrared spectra were determined on a Shimadzu IR Affinity-1S. Mass spectrums were determined on LC/MS (Waters) and Shimadzu, GCMS-QP-2010 (Direct inlet probe).

Table 1: Physical data for the product 5a-j and 6a-j

Comp. No.	R	M.P. (°C)	Yield (%)	Color
5a	2-chloro phenyl	145	57	White
5b	4-bromo benzyl	194	55	Light yellow
5c	4-fluoro phenyl	201	60	Off white
5d	Thiophene	185	63	White
5e	4-methyl phenyl	195	70	Light yellow
5f	3,4-dimethoxy phenyl	245	66	White
5g	Phenyl	188	58	Light yellow
5h	4-nitro phenyl	135	71	Yellow
5i	4-methoxy phenyl	156	61	Off white
5j	Benzyl	172	66	White
6a	Phenyl	88	85	Light yellow
6b	4-fluoro phenyl	89	78	Light yellow
6c	2-bromo phenyl	80	83	Light yellow
6d	4-bromo phenyl	112	88	Off white
6e	4-chloro phenyl	130	92	Off white
6f	3,4-difluoro phenyl	106	90	Off white
6g	4-methoxy phenyl	97	78	Light yellow
6h	4-hydroxy, 3-methoxy phenyl	110	86	Off white
6i	Pyridine	95	90	Light yellow
6j	2,4,5-trifluoro phenyl	116	88	Off white

Preparation of methyl-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetate (3)

To a stirred solution of 4-(4-chlorophenyl) piperidin-4-ol 1 (50.0 g, 195.87 mmol) and methyl 2-bromo-2-(2-chlorophenyl)acetate 2 in N,N-dimethylformamide (100 ml, 1T), potassium carbonate (9.6 g, 39.1 mmol) was

added. The resultant solution was stirred for five hours at 60-70°C. The progress of reaction was monitored by TLC. After completion of reaction, cool the reaction mass and dump into chilled water (500 ml). The product was extracted with dichloromethane (100 ml × 2). The combine organic layer was wash with water (250 ml × 2) followed by 10% sodium chloride solution (250 ml). The organic layer dry over sodium sulfate and distill under vacuum to give title compound 3, Yield: 91%.

Preparation of 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetohydrazide (4)

To a stirred solution of 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetate 3 (48.0 g, 178.23 mmol) in isopropyl alcohol (480 ml, 10T), hydrazine hydride (17.84 g, 356.4 mmol) was added drop wise. The resulting solution was stirred at 50-60°C for eight hours. The progress of reaction was monitored by TLC. After completion of reaction, cool the reaction mass and dump into chilled water (500 ml). The solid product was fallout which was stir for two hours at 10-15°C. The product was isolated by filtration and wash with isopropyl alcohol (50 ml X 2). The crude product was purified in ethanol to give pure product 4 as white solid (42.0 g), Yield: 87.5%, m/z=395.2.

General procedure for preparation 2-((4-chloro-4-(4-chlorophenyl) piperidin-1-yl)(2-chlorophenyl) methyl)-5-aryl-1,3,4-oxadiazole (5a-j)

To a stirred solution of 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetohydrazide 4 (1.0 g, 2.53 mmol) and aromatic carboxylic acid (2.78 mmol) in toluene (10 ml), phosphorus oxychloride (3.8 mmol) was added drop wise. This mixture was stirred for two hours at 50-60°C. The progress of reaction was monitored by TLC. After completion of reaction cool the reaction mass and filter it. The solid product was wash with toluene (5 ml X 2). The solid product was then dissolved into ethyl acetate (25 ml) and wash with water (10 ml), followed by the wash of sodium bicarbonate solution (25 ml) and brine solution (10 ml). The ethyl acetate layer dry over sodium sulfate and distill solvent under vacuum. The crude product was purified by column chromatography in ethyl acetate and cyclohexane to give title compound (5a-j), Yield 55-72%.

General procedure of preparation N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chloro phenyl) -4-hydroxypiperidin-1-yl) acetohydrazide (6a-j)

To a stirred solution of 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetohydrazide 4 (1.0 g, 2.53 mmol) and aromatic aldehyde (2.78 mmol) in ethanol (10 ml), catalytic amount of conc.sulphuric acid was added. This mixture was stirred for four hours at 25-35°C. The progress of reaction was monitored by TLC. After completion of reaction, cool the reaction mass and distill under vacuum. The crude product was wash crystallize in isopropyl alcohol (20 ml) to give pure product (6a-j), Yield 78-92%.

2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-(4-chloro-phenyl)-1,3,4-oxadiazole (5c)

Off white solid, **Yield:** 60%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ=1.514-1.638 (m, 2H), 1.863-2.067 (m, 2H), 2.458-2.509 (m, 2H), 2.708-2.806 (m, 2H), 4.981 (s, 1H), 6.996-7.017 (d, 2H), 7.283-7.412 (m, 4H), 7.440-7.537 (m, 3H), 7.626-7.647 (d, 2H), 7.841-7.899 (m, 1H) ppm; **Mass:** m/z=534.1(^{35}Cl)(M+H)$^+$, 536.1(^{37}Cl)(M+H)$^+$; **IR (cm^{-1}):** 3012.81, 2929.87, 2850.79, 1734.01, 1716.65, 1506.41, 1489.05, 1228.66, 1217.08, 756.10.

2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (5d)

White solid, **Yield:** 63%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ=1.470-1.614 (m, 2H), 1.927-1.992 (m, 1H), 2.057-2.130 (m, 1H), 2.360-2.505 (m, 2H), 2.662-2.715 (t, 1H), 3.071-3.098 (d, 1H), 4.963 (s, 1H), 7.171-7.193 (t, 1H), 7.310-7.404 (m, 4H), 7.459-7.537 (m, 3H), 7.814-7.844 (q, 3H) ppm; **Mass: m/z**=504.1(^{35}Cl)(M+H)$^+$, 506.1(^{37}Cl)(M+H)$^+$; **IR cm^{-1}:** 3078.39, 3030.17, 2839.22, 1734.01, 1716.65, 1699.29, 1506.41, 1489.05, 1228.66, 1217.08, 754.10, 719.45.

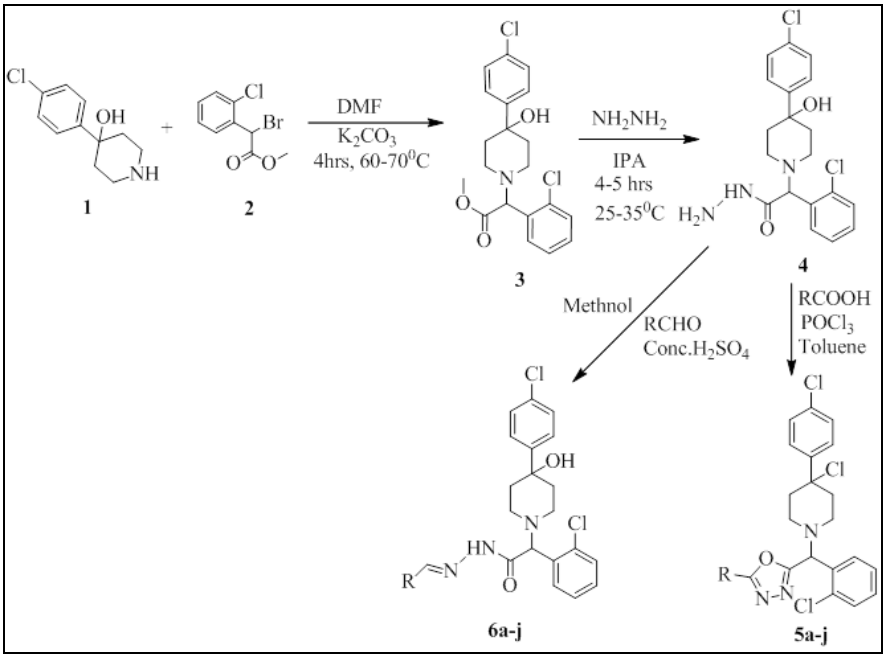
2-benzyl-5-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-1,3,4-oxadiazole (5j)

White solid, **Yield:** 85%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ= 1.517-1.639 (m, 2H), 1.866-2.018 (m, 2H), 2.458-2.510 (m, 2H), 2.685-2.810 (m, 2H), 3.874 (s, 2H), 4.983 (s, 1H), 7.227-7.248 (d, 1H), 7.285-7.411 (m, 4H), 7.439-7.547 (m, 3H), 7.628-7.646 (d, 2H), 7.738-7.752 (d, 1H), 7.851-7.897 (m, 2H) ppm; **Mass:** m/z= 513.2 (^{35}Cl)(M+H)$^+$, 515.2 (^{37}Cl)(M+H)$^+$; **IR cm^{-1}:** 3030.17, 2970.38, 2837.29, 1734.01, 1716.65, 1506.41, 1489.05, 1228.66, 775.4.

N'-benzylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetohydrazide (6a)
Light yellow solid, **Yield:** 83%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ=1.389-1.618 (m, 2H), 1.953-1.984 (m, 2H), 2.517-2.617 (m, 2H), 4.608 (s, 1H), 4.945-4.998 (d, 1H), 7.312-7.547 (m, 8H), 7.619-7.771 (m, 2H), 7.859-7.980 (m, 2H), 78.429 (s, 1H), 11.740 (s, 1H) ppm; **Mass:** m/z= 482 $(M)^+$; **IR cm^{-1}:** 3064.89, 3030.17, 2949.16, 2833.43, 1683.86, 1670.35, 1653.00, 1373.32, 1093.64, 754.17, 688.59.

2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-N'-(3,4-difluorobenzylidene)acetohydrazide (6f)
Off white solid, **Yield:** 90%. **Yield:** 90%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ=1.519-1.635 (m, 2H), 1.852-2.073 (m, 2H), 2.486-2.509 (m, 2H), 2.603-2.805 (m, 2H), 4.589 (s, 1H), 4.922-4.984 (d, 1H), 7.362-7.397 (m, 4H), 7.458-7.560 (m, 5H), 7.708-7.732 (m, 1H), 7.827-7.918 (m, 1H), 8.389 (s, 1H), 11.837 (s, 1H) ppm; **Mass:** m/z= 518 $(M)^+$; **IR cm^{-1}:** 3213.41, 3064.89, 3012.81, 2947.23, 2837.29, 1683.86, 1670.35,1653.00,1373.32, 1251.80, 1093.64, 754.17, 669.30.

2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)-N'-(4-methoxybenzylidene)acetohydrazide (6g)
Light yellow, **Yield:** 78%. **^{1}H NMR (400 MHz, DMSO-d^6):** δ=1.514-1.638 (m, 2H), 1.863-2.067 (m, 2H), 2.458-2.509 (m, 2H), 2.681-2.806 (m, 2H), 3.798 (s, 3H), 4.561 (s, 1H), 4.922-4.981 (d, 1H), 6.996-7.017 (d, 2H), 7.301-7.455 (m, 4H), 7.474-7.537 (m, 3H), 7.626-7.647 (d, 2H), 7.841-7.899 (m, 1H), 8.341 (s, 1H), 11.589 (s, 1H) ppm; **Mass:** m/z=512 $(M)^+$; **IR cm^{-1}:** 3213.34, 3072.60, 2947.23, 2837.29, 1683.86, 1670.35, 1653.00,1373.32, 1249.87, 1230.58, 1093.64, 1037.70, 754.17, 669.30.



Scheme 1: Synthesis of 2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-aryl-1,3,4-oxadiazoles 5a-j and N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)- 4-hydroxypiperidin-1-yl)acetohydrazides

RESULTS AND DISCUSSION

Synthesis of new 2-((4-chloro-4-(4-chlorophenyl)piperidin-1-yl)(2-chlorophenyl)methyl)-5-aryl-1,3,4-oxadiazoles and N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl) acetohydrazides is outlined in scheme 1. 4-(4-chlorophenyl) piperidin-4-ol **1** was reacted with methyl 2-bromo-2-(2-chlorophenyl)acetate **2** in the presence of base like potassium carbonate in dimethylformamide to give methyl 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxy piperidin-1-yl)acetate **3** which was then converted in to 2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)acetohydrazide **4** scaffold by reaction with hydrazine hydride in isopropyl alcohol at 50-60°C. The scaffold react with different aromatic carboxalic acid in the presence of phosphorus oxychloride in toluene at 50-60°C to give crude 2-((4-chloro-4-(4-chlorophenyl) piperidin-1-yl)(2-chlorophenyl)

methyl)-5-aryl-1,3,4-oxadiazole derivatives. This crude product was purified by column chromatography to give analytical grade pure new 2-((4-chloro-4-(4-chlorophenyl) piperidin-1-yl)(2-chlorophenyl) methyl)-5-aryl-1,3,4-oxadiazole derivatives (5a-j). All the reactions were smooth, and provided the products in the range of 55-71% yield. The scaffold 4 was made to react with different aromatic aldehyde in the presence catalytically conc. sulfuric acid in ethanol at 25-35°C to give crude N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl) acetohydrazide. This crude product was purified in ethanol to give analytical pure N'-arylidene-2-(2-chlorophenyl)-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl) acetohydrazide derivatives (6a-j) All the reactions were smooth, and provided the products in the range of 78-90% yield.Similarly, all these compounds were characterized on the basis of spectral studies. All the compounds were screened for their antibacterial and antifungal activities using ampicillin, streptomycin and nystatin as standard drugs.

Antimicrobial Activity

The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method. The strains employed for the activity were procured from [MTCC – Micro Type Culture Collection] Institute of Microbial Technology, Chandigarh. The compounds 5a-j and 6a-j were screened for their antibacterial activity against *Escherichia coli (E.coli)* (MTCC1687), *Pseudomonas aeruginosa (P.aeruginosa)* (MTCC3541), *Staphylococcus aureus (S.aureus)* (MTCC737), *Bacillus megaterium* (MTCC2444) as well as antifungal activity against *Aspergillus niger* (MTCC282) and *Aspergillus flavus* (MTCC418). DMSO was used as vehicle to get desired concentration of compounds to test upon microbial strains. The standard antibiotics used for comparison in the present study were ampicillin, streptomycin for evaluating antibacterial activity as well as nystatin for antifungal activity. 1000 µg/mL, 500 µg/mL, 250 µg/mL, 125 µg/mL and 62.5 µg/mL, concentrations of the synthesized drugs were taken. The protocols are summarized in (Table 2).

An examination of the data (Table 2) reveals that amongst all the synthesized compounds 5c, 5h, 5i, 6a, 6h, 6i and 6j exhibited excellent activity against Gram positive bacteria, gram negative bacteria and fungi.

Table 2: Antimicrobial activity of compounds 5a-j and 6a-j

Compounds	*Bacillus megaterium*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Aspergillus flavus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
5a	1000	1000	1000	1000	1000	1000
5b	1000	1000	1000	1000	1000	1000
5c	500	500	500	500	500	500
5d	1000	1000	1000	1000	1000	1000
5e	1000	1000	1000	1000	500	250
5f	1000	250	250	250	250	1000
5g	1000	1000	500	500	500	1000
5h	500	500	500	500	500	1000
5i	250	250	500	250	250	250
5j	1000	1000	1000	1000	1000	1000
6a	500	500	125	125	125	125
6b	500	1000	500	1000	500	500
6c	1000	1000	1000	1000	1000	1000
6d	1000	1000	500	500	1000	1000
6e	1000	500	500	1000	500	1000
6f	500	500	500	500	500	500
6g	500	500	500	1000	500	1000
6h	250	500	250	500	500	500
6i	500	500	500	500	500	500
5j	500	500	250	250	250	500

CONCLUSION

A series of some new derivatives 5a-j and 6a-j has been synthesized and characterized. The structure of all newly synthesized compound 5a-j and 6a-o was established on the basis of spectral analysis like IR, ^{1}H NMR and mass data. The physical characterization data are listed in Table 1. It can be concluded from Table 2 that compounds 5c, 5h, 5i, 6a, 6h, 6i and 6j exhibited excellent activity against Gram positive bacteria, gram negative bacteria and fungi.

ACKNOWLEDGEMENT

The authors are thankful to UGC for financial support under the scheme of innovative PG Program and also to Atmiya *in vitro* Testing Laboratory, Yogidham, Rajkot for antimicrobial activity studies.

REFERENCES

[1] A Kaneria; N Thumar; K Ladva; M Vadodaria. *Chem Biol Interface.* **2016**, 6, 109-117.
[2] N Thumar; A Kaneria; M Vadodaria; K Ladva. *J Chem Pharm Res.* **2016**, 8, 662-667.
[3] D O'Hagan. *Nat Prod Rep.* **2000**, 17, 435-446.
[4] PS Watson; B Jiang; B Scott. *Org Lett.* **2000**, 2, 3679-3681.
[5] A Ahmed; KI Molvi; S Nazim; I Baig; T Memon; M Rahil. *J Chem Pharm Res.* **2012**, 4, 872-880.
[6] ET Mellerup; P Plenge. *Psychopharmacol.* **1986**, 89, 436-439.
[7] RM Nevels; NH Weiss; AE Killebrew; ST Gontkovsky. *Ger J Psychiatry.* **2013**, 16, 29-42.
[8] LD Simmler; A Rickli; Y Schramm; MC Hoener; ME Liechti. *Biochem Pharmacol.* **2014**, 88, 237-244.
[9] E Barrett-Connor. *Ann NY Acad Sci.* **2001**, 949, 295-303.
[10] DA Sica. *J Clin Hypertens.* **2004**, 6, 283-287.
[11] KS Latta; B Ginsberg; RL Barkin. *Am J Ther.* **2002**, 9, 53-68.
[12] T Mellstrand. *Scand J Gastroenterol Suppl.* **1987**, 130, 65-66.
[13] WJ Giardina. *J Epilepsy.* **1994**, 7, 161-166.
[14] M Maniscalco; D Singh-Franco; WR Wolowich; R Torres-Colón. *Clin Ther.* **2006**, 28, 1247-1272.
[15] P Mattei; M Boehringer; P Di Giorgio; H Fischer; M Hennig; J Huwyler; B Koçer; B Kuhn; BM Loeffler; A Macdonald; R Narquizian; E Rauber; E Sebokova; U Sprecher. *Bioorg Med Chem Lett.* **2010**, 20, 1109-1113.
[16] M Baumann; IR Baxendale. *Beilstein J Org Chem.* **2013**, 9, 2265-2319.
[17] ME Bräu, P Branitzki; A Olschewski; W Vogel; G Hempelmann. *Anesth Analg.* **2000**, 91, 1499-1505.
[18] N Bhasker; BV Suba Reddy. *J Chem Pharm Res.* **2016**, 8, 1035-1040.
[19] M Mittal; SM Sarode; RM Shingare; G Vidyasagar; B Shrivastava. *J Chem Pharm Res.* **2011**, 3, 766-774.
[20] N Elbaridi; AD Kaye; S Choi; RD Urman. *Pain Physician* **2017**, 20, SE23-SE31.
[21] M Yar; L Shahzadi; A Farooq; S Jalil Imran; JP Cerón-Carrasco; H Den-Haan; S Kumar; J Peña-García; H Pérez-Sánchez; A Grycova; Z Dvorak; R Vrzal. *Bioorg Chem.* **2017**, 71, 285-293.