Med Chem Res (2007) 16:179–187
DOI 10.1007/s00044-007-9022-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of 1-benzhydryl-sulfonyl-piperazine derivatives as inhibitors of MDA-MB-231 human breast cancer cell proliferation

C. S. Ananda Kumar · S. Nanjunda Swamy · N. R. Thimmegowda · S. B. Benaka Prasad · George W. Yip · K. S. Rangappa

Received: 15 April 2007 / Accepted: 4 June 2007 / Published online: 1 August 2007

Abstract A series of novel 1-benzhydryl-sulfonyl-piperazine derivatives 7(a-e) were designed by a nucleophilic substitution reaction of 1-benzhydryl-piperazine with various sulfonyl chlorides and characterized by ^{1}H nuclear magnetic resonance (NMR), liquid chromatography mass spectrometry (LC/MS), Fourier-transform infrared (FTIR), and elemental analysis. Our research is focused on identifying synthetically occurring chemotherapeutic substances capable of inhibiting, retarding, or reversing the process of multistage carcinogenesis. The title compounds were evaluated for their efficacy in inhibiting MDA-MB-231 breast cancer cell proliferation. Compound 1-benzhydryl-4-(4-tert-butyl-benzenesulfonyl)-piperazine (7d) showed significant inhibitory activity.

Keywords 1-benzhydryl-piperazine derivatives · Sulfonyl chlorides · MDA-MB-231 · Cell proliferation

Introduction

Breast cancer is a malignant cell growth in the breast. Breast cancer is the most common type of cancer diagnosed in women, excluding skin cancer. Almost one third (32%) of all cancers diagnosed in women are breast cancer. However, the

C. S. Ananda Kumar · S. Nanjunda Swamy ·
N. R. Thimmegowda · S. B. Benaka Prasad · K. S. Rangappa
Department of Studies in Chemistry, University of Mysore, Mysore, India

G. W. Yip (✉)
Department of Anatomy, National University of Singapore, Singapore, Singapore
e-mail: georgeyip@nus.edu.sg

K. S. Rangappa (✉)
DOS in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, India
e-mail: rangappaks@gmail.com

incidence of breast cancer varies by race and ethnicity. American, Indian, and Native Alaskan women have the lowest incidence whereas Caucasian women have the highest incidence of breast cancer diagnoses. In recent years, there has been an explosion of life-saving treatment advances against breast cancer, bringing new hope and excitement. Instead of only one or two options, there are now many treatment choices that fight the complex mix of cells in each individual cancer. The decisions between surgery, then perhaps radiation, hormonal (anti-estrogen) therapy, and/or chemotherapy, can feel overwhelming.

Piperazines are currently the most important building blocks in drug discovery, with a high number of positive hits encountered in biological screens of this heterocycle and its congeners. The piperazine template forms the molecular backbone, possesses versatile binding properties with a frequently occurring binding motif, and provides potent and selective ligands for a range of different biological targets in medicinal chemistry. The piperazine scaffold and its analogues are important pharmacophores that can be found in biologically active compounds across a number of different therapeutic areas (Berkheij et al., 2005; Guo et al. 2004). These include anticancer (Gillet et al. 1998; Gabriel et al., 2000; Hulme et al., 1999), antifungal (Upadhayaya et al., 2004), antibacterial, antimalarial, antipsychotic agents (Choudhary et al., 2006), HIV protease inhibitors (Vacca et al., 1994; Askin et al., 1994; Rossel et al., 1995) and antidepressants (EGYT, 1975). MST-16[4,4-1,2-(ethanediyl) bis(1-isobutoxycarbonyloxy-methyl-2,6-piperazinedi-one)] was recently approved as an oral anticancer drug for clinical use in Japan (Yoshida, 1999). The piperazine analogues have been shown to have potent antiproliferative activity against colon, prostate, breast, lung, and leukemia tumors; additional studies have demonstrated the ability of the lead piperazines to suppress and eliminate experimental tumors in small-animal models performed by the National Cancer Institute (NCI). Mechanistic evaluations have shown that piperazines inhibit microtubule synthesis by a unique mechanism, inhibit cell cycle progression, and inhibit angiogenesis, which is critical to a tumor cell's ability to grow and metastasize. The piperazines kill tumor cells directly through the induction of apoptosis. The anti-tumor mode of action of the piperazines is quite distinct from that of Taxol and in addition they are significantly more potent, active against a variety of different tumor types, and are orally bioavailable, when compared to Taxol. In the literature, we also found that diaryl piperazine derivatives were identified as potent and selective dopamine D_4 receptor antagonists (Mark et al., 2004; Glase et al., 1997; Perrone et al., 2000), enterovirus inhibitors (Chern et al., 2004), and inhibitors of dopamine uptake in the central nervous system (Kimura et al., 2003a, b; Guo et al., 2004; Kimara et al. 2004). Piperazine sulfonamides exhibit diverse pharmacological activity such as MMP-3 enzyme inhibition and carbonic anhydrase inhibition (Chern et al., 2004; Amin and Welsh, 2003). In continuation of our research on the synthesis of bioactive heterocycles and their biological evaluation (Nanjunda Swamy et al., 2006; Narendra Sharath Chandra et al., 2006, 2007; Priya et al., 2005; Thimmegowda et al., 2007; Anil Kumar et al., 2007, 2007), we describe here the synthesis of 1-benzhydryl-sulfonyl-piperazine derivatives and their effect on inhibition of proliferation of MDA-MB-231 human breast cancer cells.

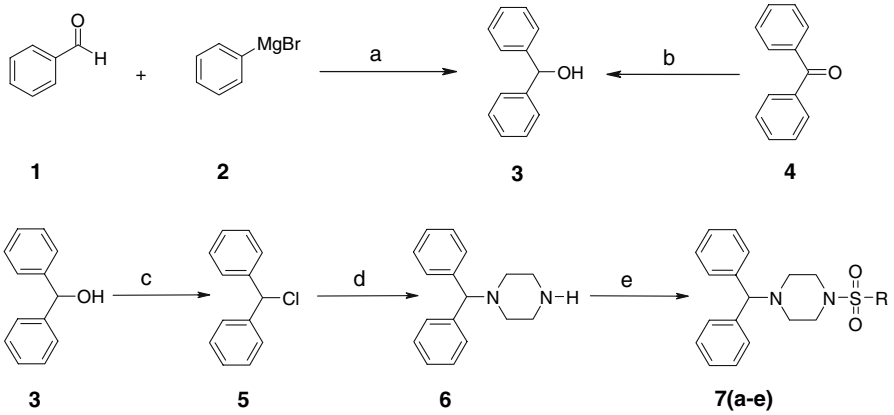
Chemistry

1-benzhydryl-piperazine derivatives 7(a-e) were prepared by the method summarized in Scheme 1. Initially compound 3, benzhydrol, was synthesized by a Grignard reaction under nitrogen with benzaldehyde (1) and phenyl magnesium bromide (2); the obtained yield was found to be 60%. Finally, we synthesized benzhydrol by reduction of benzophenone using sodium borohydride and achieved a 90% yield. Herein, we report the synthesis of 1-benzhydryl-piperazine from benzophenone for the first time. Compound 3 was subsequently treated with thionyl chloride to give the corresponding benzhydryl chloride (5), which was directly reacted with piperazine and anhydrous potassium carbonate using dimethyl formamide as a solvent at 80°C to give the target key intermediate 1-benzhydryl-piperazine (6). The nucleophilic substitution reactions of (6) with different sulfonyl chlorides (R-SO_2-Cl) were carried out in the presence of triethylamine and dichloromethane as the solvent with a good yield of 76–85% and good purity. Synthesized molecules **7**(a-e) were structurally characterized by ^{1}H NMR, LC/MS, IR and elemental analysis. The chemical structures, physical data and purity of all the synthesized compounds are given in Table 1.

Results and discussion

Chemistry

The N-substitution of 1-benzhydryl-piperazine with different sulfonyl chlorides was confirmed by the disappearance of the N-H group in IR and ^{1}H NMR data. Compounds **7**(a-e) were also confirmed by IR data, which showed asymmetric



Scheme 1. Reagents and conditions: (a) dry THF, room temperature, 4 hrs, under N_2; (b) $NaBH_4$, methanol, room temperature, 5 hrs; (c) thionyl chloride, methylene dichloride (MDC), 0–5°C, 4 hrs; (d) piperazine, K_2CO_3, DMF, 80°C, 8 hrs; (e) R-SO_2Cl, 6(a-e), MDC, triethylamine, room temperature, 5–6 hr, where R-SO_2Cl is:, 6a: Methanesulfonyl chloride, 6b: 4-methyl-benzenesulfonyl chloride, 6c: 4-chloro-benzenesulfonyl chloride, 6d: 4-tert-butyl-benzenesulfonyl chloride, 6e: 3,5-dimethyl-isoxazole-4-sulfonyl-chloride

Table 1 Chemical structures, physical data, and purities of synthesized compounds

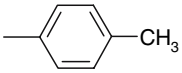
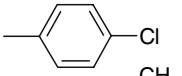
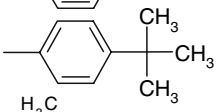
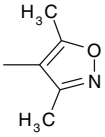
Compound	R	Yield (%)	m.p. (°C)	Purity
7a		85	192–194	99.21
7b		82	173–175	99.14
7c		80	153–155	98.65
7d		84	198–200	99.62
7e		76	179–181	98.90

Table 2 Percentage inhibition of MDA-MB-231 cell proliferation

Piperazine derivatives	% Inhibition ± SD	*P* value (Student's *t*-test)
7a	3.79 ± 0.2552	0.25520
7b	10 ± 0.0086	0.00860
7c	1 ± 0.8673	0.86730
7d	28.6 ± 0.0003	0.00030
7e	20.6 ± 0.001	0.001

stretching frequency of O=S=O at 1350 cm^{-1} and symmetric stretching frequency at 1280 cm^{-1}. Several new derivatives of 1-benzhydryl-piperazine **7**(a-e) were synthesized and evaluated for their anti-cancer activities. The obtained products were purified by column chromatography using hexane:ethyl acetate (8:2) as an eluent.

Biology: *in vitro* cell viability assay – MTS assay

To check the anticancer activity, we carried out the reactions of 1-benzhydryl-piperazine with different sulfonyl chlorides containing aliphatic, substituted aromatic, and heterocyclic groups. Our results reveal that the title compounds showed inhibition of proliferation of MDA-MB-231 human breast cancer cells (Table 2). Among the tested compounds, the inhibitory activity was observed in the following order 7d > 7e > 7b > 7a > 7c. Compounds 7d and 7e exhibited 28.6 ± 0.0003% (P = 0.00030) and 20.6 ± 0.001% (P = 0.001) inhibition of proliferation of MDA-MB-231 breast cancer cells, respectively. Similarly compounds 7a, 7b and 7c showed 3.79 ± 0.2552% (P = 0.2552), 10 ± 0.0086% (P = 0.0086), and 1 ± 0.8673% (P = 0.8673) inhibition, respectively. Compound 7d exhibited good inhibition compared to compound 7b; the inhibition of the

compound 7d may be due to the presence of a tertiary butyl group, a strong electron-donating group. Compound 7c showed less inhibition (1%), which might be due to the presence of an electronegative chloro group. Similarly compound 7e showed 20.6% inhibition, which might due to the isoxazole ring containing methyl groups. Compound 7a showed 3.79% inhibition with a methyl group only. From our results, it could be concluded that inhibition increases with the number of electron-donating groups, whereas in the presence of electron-withdrawing groups the observed inhibition is not significant. Thus, we conclude that the presence of electron-donating groups may be responsible for the observed inhibition. Further modification of the groups in the basic scaffold to increase efficacy and *in vivo* work is under progress.

Conclusion

Currently, a large variety of chemotherapeutic drugs are used to treat cancer. Unfortunately, many compounds have limited efficacy due to problems of delivery and penetration and a moderate degree of selectivity for cancer cells. From our studies, it is clear that compound 7d inhibits MDA-MB-231 human breast cancer cell proliferation. The 1-benzhydryl-sulfonyl-piperazine derivatives were obtained with good yield and purity. This study sheds light on the identification of this new series of agents for cancer therapy.

Experimental

Melting points were determined using a SELACO-650 hot-stage melting-point apparatus and were used uncorrected. Infrared (IR) spectra were recorded using a Jasco FTIR-4100 device. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Shimadzu AMX 400-Bruker, 400 MHz spectrometer using dimethyl sulfoxide (DMSO) as a solvent and trimethylsilyl (TMS) as an internal standard (chemical shift in δ ppm). Spin multiplets are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), and m (multiplet). Mass and purity were recorded on a LC-MSD-Trap-XCT. Elemental (CHNS) analyses were obtained on a Vario EL III Elementar device. Silica gel column chromatography was performed using Merck 7734 silica gel (60-120 mesh) and Merck thin-layer chromatography (TLC) plates.

General procedure for the synthesis of 1-benzhydryl-piperazine (6)

A solution of piperazine dihydrochloride (10.0 g, 62.86 mmol) in dimethyl formamide was taken, anhydrous potassium carbonate (43.44 g, 314.3 mmol) was added to the solution and stirred for 10 min, and then benzhydryl chloride (11.46 g, 56.58 mmol) was added. The reaction mixture was heated to 80°C for 8 hrs, and monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the residue was taken in water and extracted with ethyl acetate. Finally

a water wash was given to the organic layer, followed by drying with anhydrous sodium sulphate. The solvent was evaporated to obtain the crude product, which was purified by column chromatography over silica gel (60-120 mesh) using chloroform:methanol (9:1) as the eluent.

General procedure for the synthesis of 1-benzhydryl-sulfonyl-piperazine derivatives 7(a-e)

A solution of 1-benzhydryl-piperazine 6 (1.0 eq) in dry dichloromethane was taken and cooled to 0–5°C in an ice bath. Triethylamine (3.0 eq) was added to the cold reaction mixture and stirred for 10 min, and then different sulfonyl chlorides (1.0 eq) were added. The reaction mixture was stirred for 5–6 hrs at room temperature, and monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally a water wash was given to the organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to obtain the crude product, which was purified by column chromatography over silica gel (60-120 mesh) using hexane:ethyl acetate (8:2) as the eluent.

Synthesis of 1-benzhydryl-4-methanesulfonyl-piperazine (7a)

This was obtained from 1-benzhydryl-piperazine (6) (0.5 g, 1.98 mmol), methanesulfonyl chloride (0.226 g, 1.98 mmol), triethylamine (0.601 g, 5.94 mmol). The product obtained was a white crystalline solid (0.556 g, 85%). IR (KBr, cm^{-1}): 3029, 2959, 2850, 1346, 1285. ^{1}H NMR (DMSO, 400 MHz) δ: 7.38 (d, 4H, Ar-H), 7.27 (t, 4H, Ar-H), 7.15 (t, 2H, Ar-H), 4.25 (s, 1H, -CH-), 2.92 (br s, 4H, -CH_2-), 2.50 (br s, 4H, -CH_2-), 2.7 (s, 3H, -CH_3-). MS: 331.56. Anal. calcd. for $C_{18}H_{22}N_2O_2S$ (in %): C-65.43, H-6.71, N-8.48, S-9.70. Found C-65.40, H-6.68, N-8.45, S-9.66.

Synthesis of 1-benzhydryl-4-(toluene-4-sulfonyl)-piperazine (7b)

This was obtained from 1-benzhydryl-piperazine (6) (0.5 g, 1.98 mmol), 4-methylbenzenesulfonyl chloride (0.377 g, 1.98 mmol), triethylamine (0.601 g, 5.94 mmol). The product obtained was a white crystalline solid (0.644 g, 82%). IR (KBr, cm^{-1}): 3029, 2962, 1398, 1346, 1280. ^{1}H NMR (DMSO, 400 MHz) δ: 7.63-7.7 (m, 4H, Ar-H), 7.35 (d, 4H, Ar-H), 7.25 (t, 4H, Ar-H), 7.15 (t, 2H,Ar-H), 4.3 (s, 1H, -CH), 2.9 (br s, 4H, -CH_2-), 2.4 (br s, 4H, -CH_2-), 2.4 (s, 3H, -CH_3-). MS: 407.3. Anal. calcd. for $C_{24}H_{26}N_2O_2S$ (in %): C-70.91, H-6.45, N-6.89, S-7.89. Found C-70.87, H-6.41, N-6.86, S-7.87.

Synthesis of 1-benzhydryl-4-(4-chloro-benzenesulfonyl)-piperazine (7c)

This was obtained from 1-benzhydryl-piperazine (6) (0.5 g, 1.98 mmol), 4-chlorobenzene sulfonyl chloride (0.417 g, 1.98 mmol), triethylamine (0.601 g, 5.94

mmol). The product obtained was an off-white crystalline solid (0.676 g, 80%). IR (KBr, cm^{-1}): 2961, 2889, 1350, 1279, 707. ^1H NMR (DMSO, 400 MHz) δ: 7.7-7.8 (m, 4H, Ar-H), 7.4 (d, 4H, Ar-H), 7.28 (t, 4H, Ar-H), 7.16 (t, 2H, Ar-H), 4.3 (s, 1H, -CH), 3.0 (br s, 4H, $-CH_2-$), 2.41 (br s, 4H, $-CH_2-$). MS: 427.90. Anal. calcd. for $C_{23}H_{23}ClN_2O_2S$ (in %): C-64.70, H-5.43, N-6.56, S-7.51. Found C-64.66, H-5.40, N-6.54, S-7.50.

Synthesis of 1-benzhydryl-4-(4-tert-butyl-benzenesulfonyl)-piperazine (7d)

This was obtained from 1-benzhydryl-piperazine (6) (0.5 g, 1.98 mmol), 4-tert-butyl-benzenesulfonyl chloride (0.460 g, 1.98 mmol), triethylamine (0.601 g, 5.94 mmol). The product obtained was an off-white amorphous solid (0.746 g, 84%). IR (KBr, cm^{-1}): 3028, 2852, 1346, 1279, 1399. ^1H NMR (DMSO, 400 MHz) δ: 7.63-7.7 (m, 4H, Ar-H), 7.35 (d, 4H, Ar-H), 7.25 (t, 4H, Ar-H), 7.15 (t, 2H,Ar-H), 4.3 (s, 1H, -CH), 2.94 (br s, 4H, $-CH_2-$), 2.42 (br s, 4H, $-CH_2-$), 1.3 (s, 9H, $(-CH_3)_3-$). MS: 449.58. Anal. calcd. for $C_{27}H_{32}N_2O_2S$ (in %): C-72.29, H-7.19, N-6.24, S-7.15. Found C-72.25, H-7.15, N-6.20, S-7.12.

Synthesis of 1-benzhydryl-4-(3,5-dimethyl-isoxazole-4-sulfonyl)-piperazine (7e)

This was obtained from 1-benzhydryl-piperazine (6) (0.5 g, 1.98 mmol), 3,5-dimethyl-isoxazole-4-sulfonyl-chloride (0.387 g, 1.98 mmol), triethylamine (0.601 g, 5.94 mmol). The product obtained was a white crystalline solid (0.619 g, 76%). IR (KBr, cm^{-1}): 3055, 2956, 2831, 1345, 1296. ^1H NMR (DMSO, 400 MHz) δ: 7.38 (d, 4H, Ar-H), 7.27 (t, 4H, Ar-H), 7.17 (t, 2H, Ar-H), 4.25 (s, 1H, -CH-), 3.05 (br s, 4H, $-CH_2-$), 2.55 (br s, 4H, $-CH_2-$), 2.4 (s, 6H, $-CH_3$). MS: 412.1. Anal. calcd. for $C_{22}H_{25}N_3O_3S$ (in %): C-64.21, H-6.12, N-10.21, S-7.79. Found C-64.19, H-6.08, N-10.20, S-7.76.

Biology

Culturing mammalian cell lines

MDA-MB-231 human breast cancer cells were grown in Roswell Park Memorial Institute (RPMI) medium (Sigma), supplemented with 10% fetal bovine serum (FBS). The cells were maintained at 37°C in a 5% CO_2 incubator. They were subsequently dislodged from the substratum by 1X trypsin treatment for 5 min followed by inactivation using FBS.

Cell proliferation assay

The MTS assay was performed using the Promega CellTiter 96® aqueous nonradioactive cell proliferation assay as previously described (Zou et al., 2004). Briefly, MB-MB-231 cells were added to the wells of a 96-well plate at a density of

2000 cells/well. The test compounds at 2 mM concentration dissolved in 1% DMSO were added, and the cultures were continued for 72 hrs. Replenishment with fresh compounds was done after the first 48 hrs. At the end of 72 hrs of treatment, the cultured medium was removed and 20 µl/well of combined MTS/PMS solution was added and incubated for 4 hrs. The absorbance at 490 nm was recorded using an ELISA plate reader.

Acknowledgements The authors are grateful to the UGC, Govt. of India for financial support to K.S.R. under project UGC-SAP (phase I) DRS programme DV4/375/2004-05, and to the National Medical Research Council, Singapore for financial support from grants NMRC/0772/2003 and NMRC/1023/2005 (G.W.Y.). One of the authors, S.N.S, thanks the CSIR, Govt. of India for the award of a CSIR senior research fellowship.

References

Berkheij M, et al. (2005) Synthesis of 2-substituted piperazines via direct α-lithation. Tetrahedron Lett 15:2369–2371

Gillet R, Jeannesson P,Sefraoui H, Arnould-GueArin ML, Kirkiacharian S, Jardillier JC, Pieri F (1998) Piperazine derivatives of butyric acid as differentiating agents in human leukemic Cells. Cancer Chemother Pharmaco 41:252–255

Gabriel FE, Gu J, Slater LM, Hara K, Jacobs JW (2000) Tumor apoptosis induced by epoxide-containing piperazines: a new class of anti-cancer agents. Cancer Chemother Pharmacol 45:183–191

Hulme C, et al. (1999) Novel applications of ethylgyyoxalate with the Ugi MCR. Tetrahedron Lett 40:5295

Upadhayaya RS, Sinha N, Jain S, Kishore N, Chandra R, Arora SK (2004) Optically active antifungal azoles: synthesis and antifungal activity of (2R,3S)-2-(2,4-difluorophenyl)-3-(5-{2-[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl/1-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol. Bioorg Med Chem 12:2225

Choudhary P, Kumar R, Verma K (2006) Synthesis and antimicrobial activity of N-alkyl and N-aryl piperazine derivatives. Bioorg Med Chem 14:1819–1826

Vacca JP, et al. (1994) The design of a potent and orally bioavailable HIV protease inhibotor. J Med Chem 37:3443

Askin D, et al. (1994) Highly diastereoselective reaction of a chiral, non-racemic amide enolate with (S)-glycidyl tosylate. Synthesis of the orally active HIV-1 protease inhibitor L-735,524. Tetrahedron Lett 35:673

Rossen K, et al. (1995) Asymmetric hydrogenation of tetrahydropyrazines: Synthesis of (S)-piperazine-2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor indinavir. Tetrahedron Lett 36:6419

EGYT (1975) Pyridine derivatives having antidepressant activity. US-3865828

Yoshida M, Maehara Y,Sugimachi K (1999) MST-16, a Novel Bis- dioxopiperazine Anticancer Agent, Ameliorates Doxorubicin-induced Acute Toxicity While Maintaining Antitumor Efficacy. Clinical Cancer Research 5:4295–4300

Mark A, et al. (2004) Synthesis and functional activity of (2-aryl-1-piperizinyl)-*N*-(3- methylphenyl) acetamides: selective dopamine D_4 receptor agonists. Bioorg Med Chem 12:3471–3483

Glase SA, Akunne HC, Georgic LM, Heffner TG, Mackenzie RG, Manley PJ, Pugsley TA, Wise LD (1997) Substituted [(4-Phenylpiperazinyl)- methyl]benzamides: Selective Dopamine D_4 Agonists. J Med Chem 40:1771

Perrone R, Berardi F, Colabufo NA, Leopoldo M, Tortorella V (2000) A Structure-Affinity Relationship Study on Derivatives of *N*-[2-[4-(4- Chlorophenyl) piperazin-1-yl]ethyl]-3-methoxybenzamide, a High-Affinity and Selective D4 Receptor Ligand. J Med Chem 43:270

Chern JH, et al. (2004) Design, synthesis, and structure-activity relationships of pyrazolo[3,4-d]pyrimidines: a novel class of potent enterovirus inhibitors. Bioorg Med Chem Lett 14:2519–2525

Kimura M, et al. (2003a) Synthesis of novel diphenyl piperazine derivatives and their activities as inhibitors of dopamine uptake in the central nervous system. Bio Med Chem 11:1621–1630

Kimura M, et al. (2003b) Novel diphenylalkyl piperazine derivatives with high affinities for the dopamine Transporter. Bio Med Chem 11:3953–3963

Kimura M, et al. (2004) Efficient asymmetric syntheses, determination of absolute configurations and biological activities of 1-[4,4-bis(4-fluorophenyl)butyl]-4-[2-hydroxy-3- (phenylamino)propyl]-piperazine as a novel potent dopamine uptake inhibotor in the central nervous system. Bioorg Med Chem 12:3069–3078

Guo CC, Tong RB, Li KL (2004) Chloroalkyl piperazine and nitrogen mustard porphyrins: Synthesis and anticancer activity. Bioorg Med Chem 12:2469–2475

Kimara M, Masuda T, Yamada K (2004) Antioxidative activities of novel diphenylalkyl piperazine derivatives with high affinities for the dopamine transporter. Bioorg Med Chem Lett 14:4287–4290

Chern JH, et al. (2004) Design, synthesis, and structure–activity relationships of pyrazolo[3,4-d]pyrimidines: a novel class of potent enterovirus inhibitors. Bioorg Med Chem Lett 14(10):2519–2525

Amin EA, Welsh WJ (2003) Three-Dimensional Quantitative Structure-Activity Relationship (3D-QSAR) Models for a Novel Class of Piperazine-Based Stromelysin-1 (MMP-3) Inhibitors: Applying a "Divide and Conquer" Strategy. J Med Chem 44:3849–3855

Nanjunda Swamy S, et al. (2006) Microwave-assisted synthesis of *N*-alkylated benzotriazole derivatives: Antimicrobial Studies. Bioorg Med Chem Lett 16:999–1004

Narendra Sharath Chandra JN, Sadashiva CT, Kavitha CV, Rangappa KS (2006) Synthesis and in vitro antimicrobial studies of medicinally important novel N-alkyl and N-sulfonyl derivatives of -[bis(4-fluorophenyl)-methyl]piperazine. Bioorg Med Chem 14:6621–6627

Priya BS, Anil Kumar C, Nanjunda Swamy S, Basappa, Naveen S, Rangappa KS (2007) 2-(2-(2-Ethoxybenzoylamino)-4-chlorophenoxy)-*N*-(2-ethoxybenzoyl)benzamine inhibits EAT cell induced angiogenesis by down regulation of VEGF secretion. Bioorg Med Chem Lett 17:2775–2780

Thimmegowda NR, et al. (2007) Synthesis and Evaluation of Tricyclic Dipyrido Diazepinone Derivatives as Inhibitors of Secretory Phospholipase A2 with Anti-Inflammatory Activity. Curr Top Med Chem 7:811–820

Narendra Sharath Chandra JN, et al. (2007) Chemistry and Structural Evaluation of Different Phospholipase A2 Inhibitors in Arachidonic Acid Pathway Mediated Inflammation and Snake Venom Toxicity. Curr Top Med Chem 7:787–800

Anil Kumar C, et al. (2007) N- substituted-2-butyl-5-chloro-3H-imidazole-4-carbaldehyde derivatives as anti-tumor agents against Ehrlich ascites tumor cells *in vivo.* J Med Chem 3:269–276

Anil Kumar C, et al. (2007) Pro-apoptotic activity of imidazole derivatives mediated by up-regulation of Bax and activation of CAD in Ehrlich Ascites Tumor cells. Invest New Drugs (in press). doi:10.1007/s10367-006-9033-4

Zou XH, (2004) Chondroitin Sulfate in Palatal Wound Healing. J Dent Res 83(11):880–885