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Synthesis, Characterization And Antibacterial Studies For *N*-Alkyl And *N*-Aryl Of [1-(4-Chlorophenyl) Cyclopropyl] (Piperazin-1-Yl) Methanone Derivatives

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ABSTRACT

*A series of N-Alkyl and N-aryl substituted piperazine derivatives has been synthesized in presence in the presence of cesium carbonate with DMF solvent to yield piperzine derivatives **3a-j**. The structures of all the synthesized compounds have been characterised by elemental analysis and spectral studies. All compounds have been tested for antibacterial activity.*

Keywords: Piperazine, *N*-alkyl, Cyclopropane, *N*-Aryl, Antibacterial.

INTRODUCTION

Piperazine is an interesting heterocyclic moiety as constituent of several biologically active molecules. The polar nitrogen atoms in the piperazine ring confer bioactivity to molecules and enhance favourable interaction with macromolecules [1,2]. Piperazinyl-linked ciprofloxacin dimers are potent antibacterial agents against resistant strains, antimalarial agents and potential antipsychotic agents [3,5]. Piperazine derivatives containing tetrazole nucleus have been reported as antifungal agents [6] Substituted benzamide piperazine derivatives have shown strong agonistic activity while the substituted acetamide piperazine derivative have better dopamine D receptor agonist activity as compared to substituted benzamide piperazine derivatives [7,8] Diphenyl piperazine derivatives possess broad pharmacological action on central nervous broad pharmacological action on central nervous system (CNS), especially on dopaminergic neurotransmission.Thus, based on these observations in the literature, the present study was initiated with aim of identifying the structural requirements of piperazines in terms of Antibacterial activity.

MATERIALS AND METHODS

All the IR spectra were recorded on Bruker alpha FTIR spectrophotometer, ^{1}H NMR spectra were measured on Bruker AV 400MHZ using $CDCl_3$ and DMSO as solvent. Chemical shifts are expressed in δ ppm. All the reactions were followed and checked by TLC (silica coated on alumina) using ethylacetate-pet ether (3:7) and further purification was done by column chromatography using 60-120 mesh silica gel.

t-Butyl 4-(1-(4-Chlorophenyl)cyclopropanecarbonyl)piperazine-1-carboxylate (1) : 1-(4-Chloro phenyl) cyclopropanecarboxylic acid (2.00 g, 0.0102 mol, 1.0 eq) was dissolved in dry tetrahydrofuran (20 mL). The solution was stirred for 10 min at ambient temperature. 1-Ethyl-3-(3-dimethyl l aminopropyl) carbodiimide hydrochloride (2.15 g, 0.01122 mol, 1.1 eq) was added, followed by 1-hydroxybenzotriazole (1.718 g, 0.01122 mol, 1.1 eq) and *N*,*N*-diisopropylethylamine (3.955 g,0.0305 mol, 3.0 eq). The reaction mixture was stirred for 20 min at ambient temperature, then it was cooled to 0 °C. Boc-piperazine (*tert*-butyl piperazine-1-carboxylate) (1.894 g, 0.0102 mol, 1.0 eq) was added portion-wise to the mixture and stirring was continued for 6 h at ambient temperature. The completion of the reaction was monitored by TLC. The reaction mass was diluted with ethyl acetate (25 mL) and washed with sodium bicarbonate solution (10%, 25 mL) followed by water (15 mL) and brine (15 mL). It was finally dried over sodium sulphate (5.0 g) and concentrated under reduced pressure. The crude mass was purified by column chromatography using silica gel and 10% ethyl acetate in hexane to get 3.4 g of t-butyl 4-(1-(4-chlorophenyl)cyclopropanecarbonyl) piperazine-1-carboxylate (1).
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 365.2**;** ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.40 (d, *J* = 2.0 Hz, 2H), 7.17 (d, *J* = 3.0 Hz, 2H), 3.63 (m, 2H), 2.96 (m, 2H), 1.37 (q, 2H), 1.18 (q, 2H); 1.2 (s, 9H); Elemental analysis: Calculated (%) for $C_{14}H_{17}ClN_2O$: C 62.54, H 6.91, N 7.68; Found: C 62.55, H 6.94, N 7.62.

[1-(4-Chlorophenyl)cyclopropyl](piperazin-1-yl)methanone (2) : Compound **1** (3.4 g, 0.00934 mol, 1.0 eq) was dissolved in dry methylene dichloride (20.4 mL) and the mixture was cooled to o to 5^0C. Trifluoroacetic acid (3.19 g, 0.028 mol,3.0 eq) was added slowly to the cooled mixture and stirred for 6 h at ambient temperature. The completion of the reaction was confirmed by checking the TLC. The reaction mixture was concentrated under reduced pressure and it was dissolved in methylene dichloride (30 mL). It was washed with water (15 mL), brine (15 mL) and dried over sodium sulphate (6 g). The crude mass obtained was purified by column chromatography using silica gel and methanol (3%) in methylene dichloride to get 1.8 g of purified [1-(4-chlorophenyl)cyclopropyl] (piperazin-1-yl)methanone (**2**).
LC-MS (ESI, Positive): m/z: $[M+H]^+$: 265.2**;** ^{1}H NMR: (400 MHz, DMSO-d_6): δ 9.32 (s, 1H, NH), 7.40 (d, *J* = 2.0 Hz, 2H), 7.17 (d, *J* = 3.0 Hz, 2H), 3.63 (m, 2H), 2.96 (m, 2H), 1.37 (q, 2H), 1.18 (q, 2H); Elemental analysis: Calculated for $C_{14}H_{17}ClN_2O$: C 63.51,H 6.47 N, 10.58; Found: C, 63.53 H 6.46, N 10.57.

General procedure for 3a-j : Compound **2** (0.5 g, 0.00188 mol 1.0 eq) was dissolved in dry DMF solvent (10mL).The solution was stirred for 10 min at ambient temperature. Cesium carbonate (1.5 eq) was added, followed by Alkyl or aryl halides. The reaction mass was heated to 40-45 ^{0}C for 2-3 hr, the completion of reaction was monitored by TLC. After completion of the reaction, the reaction mass was diluted with ethyl acetate the organic layer was washed with water, brine solution dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuum and the crude was purified by column chromatography.

4- (4-allylpiperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3a) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 305.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37-7.33 (m, 2H), 7.18-7.14 (m, 2H), 5.78-5.72 (m, 1H), 5.16-5.08 (m, 2H), 3.42-3.37 (m, 4H), 2.89-2.87 (d, *J*=6.4 Hz, 2H), 2.26-2.13 (m, 4H), 1.29-1.27 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for $C_{17}H_{21}ClN_2O$:C 66.99, H 6.94, N 9.19; Found: C 66.85, H 6.82, N 9.10.

(4-benzylpiperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3b) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 355.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (m, 4H), 7.28-7.23 (m, 3H), 7.09-7.06 (m, 2H), 3.64-3.46 (m, 4H), 3.44 (s, 2H), 2.60-2.39 (m, 4H), 1.42-1.39 (m, 2H), 1.14-1.11 (m, 2H); Elemental analysis: Calculated (%) for $C_{21}H_{23}ClN_2O$: C 71.07, H 6.53, N 7.89; Found: C 69.92, H 6.43, N 7.56.
(4-(4-(benzyloxy)benzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3c) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 462.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44-7.36 (m, 4H) 7.33-7.29 (m, 3H), 7.23-7.14 (m, 3H) 6.90-6.82 (m, 3H), 5.08 (s, 2H), 3.45-3.38 (m, 4H), 3.33 (s, 2H), 2.50-2.27 (m,

4H), 1.30-1.27 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for $C_{28}H_{29}ClN_2O_2$: C 72.95, H 6.34, N 6.08; Found: C 72.62, H 6.23, N 5.96.

(1-(4-chlorophenyl)cyclopropyl)(4-propylpiperazin-1-yl)methanone (3d) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 307.9; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.09-7.07 (m, 2H), 3.64-3.42 (m, 4H), 2.37-2.13 (m, 6H) 1.47-1.40 (m, 4H), 1.15-1.12 (m, 2H), 0.91-0.87 (t, *J*=7.2 Hz, 3H); Elemental analysis: Calculated (%) for $C_{17}H_{23}ClN_2O$: C 66.55, H 7.56, N 9.13; Found: C 66.41, H 7.32, N 9.09.

(1-(4-chlorophenyl)cyclopropyl)(4-methylpiperazin-1-yl)methanone (3e) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 280.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.10-7.08 (m, 2H), 3.64-3.44 (m, 4H), 2.37-2.13 (m, 4H), 2.62 (s, 3H), 1.43-1.40 (m, 2H), 1.16-1.13 (m, 2H); Elemental analysis: Calculated (%) for $C_{15}H_{19}ClN_2O$: C 64.63, H 6.87, N 10.05; Found: C 64.52, H 6.75, N 9.98.

(1-(4-chlorophenyl)cyclopropyl)(4-(pent-4-enyl)piperazin-1-yl)methanone (3f) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 333.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.24 (m, 2H), 7.11-7.07 (m, 2H), 5.81-5.74 (m, 1H), 5.01-4.92 (m, 2H), 3.64-3.42 (m, 4H),2.29-2.25 (m,4H), 2.12-2.01(m, 4H), 1.56-1.50 (m, 2H), 1.43-1.40 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for $C_{19}H_{25}ClN_2O$: C 68.56, H 7.57, N 8.42; Found: C, 68.23, H 7.46, N 8.23.

(4-butylpiperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3g) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 321.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 7.12-7.06 (m, 2H), 3.64-3.43 (m, 4H), 2.29-2.25 (m, 6H), 1.59-1.30 (m, 4H) 1.27-1.12 (m, 4H), 0.94-0.89 (t, *J*=7.2 Hz, 2H); Elemental analysis: Calculated (%) for $C_{18}H_{25}ClN_2O$: C 67.38, H 7.85, N 8.73; Found: C 67.11, H 7.75, N 8.65.

(4-(but-3-enyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3h) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 319.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 7.10-7.07 (m, 2H), 5.77-5.73 (m, 1H), 5.06-5.00 (m, 2H), 3.64-3.42 (m, 4H), 2.38-2.34 (m, 4H), 2.22-2.17 (m, 4H), 1.68-1.66 (m, 2H) 1.43-1.40 (m, 2H), 1.16-1.14 (m, 2H); Elemental analysis: Calculated (%) for $C_{18}H_{23}ClN_2O$: C 67.81, H 7.27, N 8.79; Found: C 67.75, H 7.20, N 8.58.

(1-(4-chlorophenyl)cyclopropyl)(4-ethylpiperazin-1-yl)methanone (3i) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 293.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.10-7.08 (m, 2H), 3.64-3.44 (m, 4H), 2.37-2.32 (m, 4H), 2.16-2.14 (m, 2H), 1.43-1.40 (m, 2H), 1.16-1.13 (m, 2H), 1.05-1.02 (t, *J*=7.2 Hz, 3H); Elemental analysis: Calculated (%) for $C_{16}H_{21}ClN_2O$: C 65.63, H 7.23, N 9.57; Found: C 65.56, H 7.15, N 9.51.

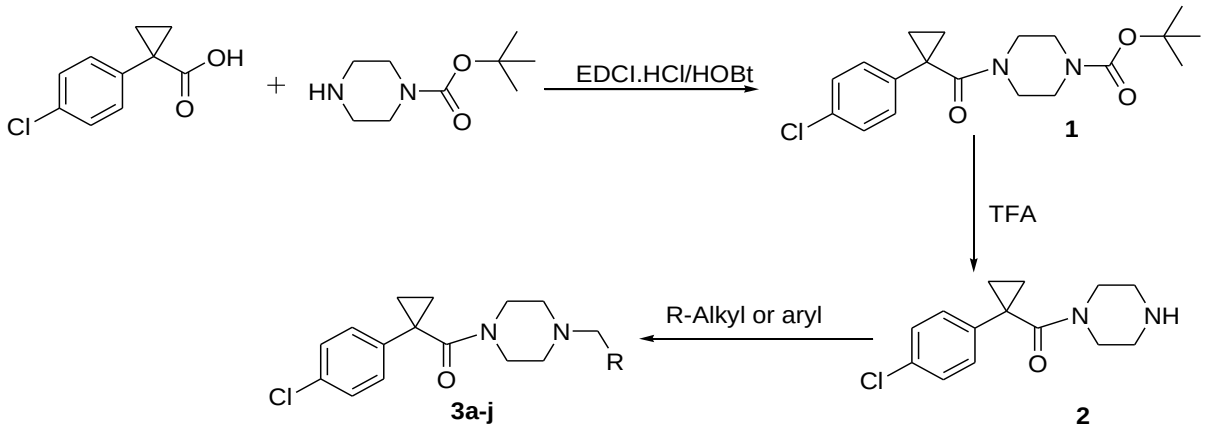
(4-(4-methoxybenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3j) : LC-MS (ESI, Positive): m/z: $[M+H]^+$: 386.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.10-7.06 (m, 2H), 6.99-6.96 (m, 2H), 6.61-6.58 (m, 2H) 3.65-3.46 (m, 4H), 3.87 (s, 3H) 3.46 (s, 2H), 2.60-2.39 (m, 4H), 1.42-1.39 (m, 2H), 1.14-1.11 (m, 2H); Elemental analysis: Calculated (%) for $C_{22}H_{25}ClN_2O_2$: C 68.65, H 6.55, N 7.28; Found: C 68.61, H 6.32, N 7.15.

RESULTS AND DISCUSSION

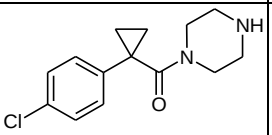
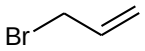
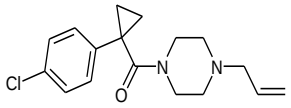
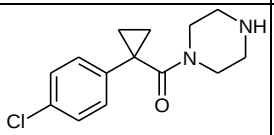
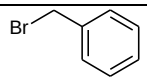
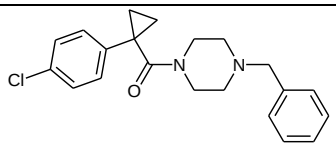
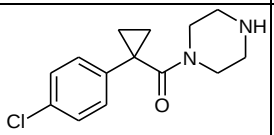
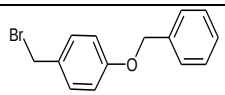
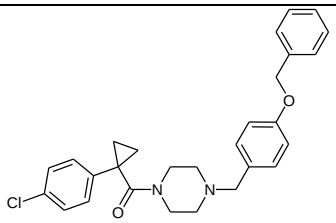
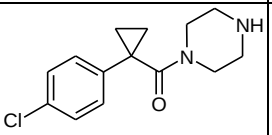
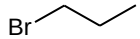
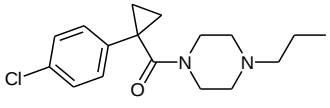
According to our aim, we planned to synthesize arylcyclopropyl piperazines with substituted alkyl and aryl halides. 1-(4-Chlorophenyl) cyclopropyl] (piperazin-1-yl) methanone (1.0 eq) was dissolved in dry DMF solvent (10 mL). The solution was stirred for 10 min at ambient temperature. Then cesium carbonate (1.5 eq) was added followed by alkyl or aryl halide (1.1 eq). The reaction mass was heated to 40-45^{0}C for 2-3 h, the completion of reaction was monitored by TLC. After completion, the reaction mass was diluted with ethyl acetate, the organic layer was washed water followed by brine solution and dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuum and the crude was purified by column

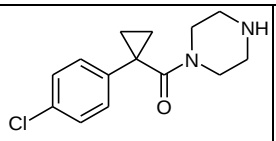
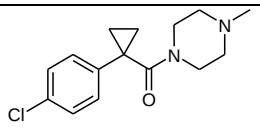
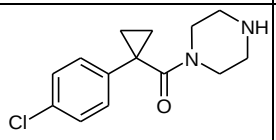
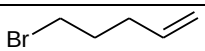
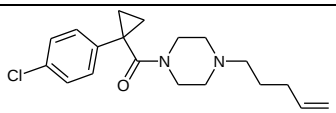
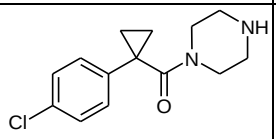
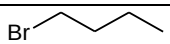
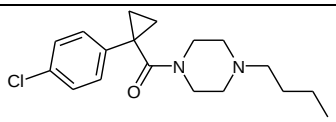
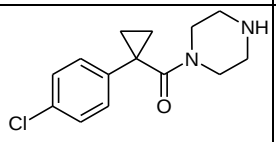
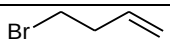
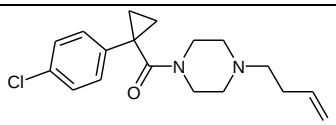
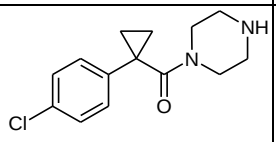
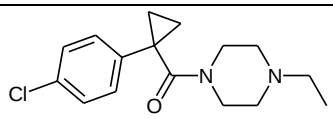
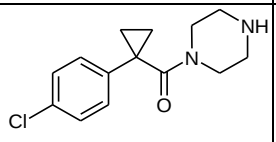
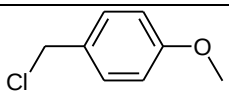
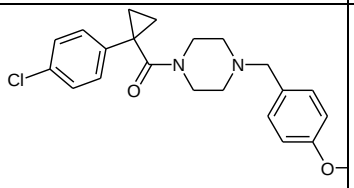
chromatography using 60-120 mesh silica gel. The series of reactions carried out have been depicted in **scheme 1**.

Scheme 1



Scheme 1: Synthesis of piperazine methanone derivatives 3a-j.

Compound No.	Cyclopropane methanone	Alkyl/Aryl halides	Piperazine derivative	% Yield
3a				85
3b				81
3c				80
3d				83

3e				78
3f				87
3g				80
3h				81
3i				82
3j				80

APPLICATIONS

Pharmacology

Preparation of discs: The test drug stock solution was prepared by dissolving 10mg of drug in DMSO with sonication and solubilized part was separated by centrifugation. Sufficient amount of stock solution was loaded on to the sterile discs to prepare 500 and 250µg ml^{-1}. The discs were allowed to drying under aseptic conditions.

Microorganisms: The microbial cultures *Escherichia coli* was procured from National Centre for Industrial Microorganisms (NCIM), Pune, India.

Preparation and Standardization of Stock cultures: Cultures on receipt were sub cultured in NA and SDA plates and further stored in slants as stock cultures. For the experiments, stock culture was prepared by inoculating each culture from slants to flask in sterile NB and SDB and incubated at 37^0C for 24hr and at room temperature for 48hrs. The stock culture was adjusted to 0.3 OD (Bacteria) at 650nm by using spectrophotometer.

Sterile NA and SDA plates were prepared and 0.1 ml of the inoculum from standardized culture of test organism was spread uniformly with L shaped rods. The prepared discs of the test substance, standard

antibiotic and solvent control were placed on to the plates carefully. The plates were placed at 4^0C for 1 h to allow the diffusion of test solution into the medium and plates were incubated at a temperature optimal for the test organism and for a period of time sufficient for the growth of at least 10 to15 generations (usually 24 hours at 37^0C) for bacteria. The zone of inhibition of microbial growth around the disc was measured in mm. Given samples shows inhibitory activity against bacteria strain. The results are tabulated in table.1

Table 1: Disc diffusion susceptibility of Test drugs (Bacteria)

RR No.	**Disc diffusion susceptibility in mm**	
	E.coli	
	500µg disc^{-1}	**250µg disc^{-1}**
3a	20.1	12.2
3b	20.3	14.5
3c	19.4	11.3
3d	21.2	10.1
3e	20.6	19.2
3f	19.8	11.0
3g	18.6	12.4
3h	19.5	11.3
3i	23.6	12.5
3j	22.1	11.0
Standard (Ciprofloxacin) 30µl	29.8	

All the synthesized compounds have been purified by column chromatography. The structures have been confirmed by elemental analysis and spectroscopic techniques like ^{1}H-NMR, LC-MS. All the compounds are tested for antibacterial activity.

CONCLUSIONS

The research work is focused on the efficient synthesis of cyclopropylpiperazine derivatives. The reactions performed are eco-friendly. In addition, some of the tested compounds have exhibited significant antibacterial activity. The publication of these facts would be of significant use for the scientific community. All synthesized cyclopropyl piperazine derivatives have been tested for antibacterial activity. And these compounds are showing activity.

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REFERENCES

[1] A.Todorovic, H.C.Luevano, *Peptides,* **2005**, 26, 2026.
[2] L.E.Donnelly, D.F.Roger, *Curr Opin Drug Discov Develop,* **2003**, 6, 815.

[3] R.J.Kerns, M.J.Rybak, G.W.Kaatz, F.Vaka , R.Cha, R.G.Grucz, V.U.Diwadkar, *Bioorg Med Chem Lett*, **2003**, 13, 2109.
[4] A.Ryckebusch, R.Poulain, L.Maes, M.A.Debreu-Fontaine, E.Mouray, P.Grellier, C.J.Sergheraert, *Med Chem*, **2003**, 46, 542.
[5] J.P.Yevich, J.S.New, D.W.Smith, W.G.Lobeck, J.D.Catt, J.L.Minielli, M.S.Eison, D.P.Taylor, L.A. Riblet, D.L.Temple D. L, *J Med Chem*, **1986**, 29, 359.
[6] R.S.Upadhayaya, N.Sinha, S.Jain, N.Kishore, R.Chandra, S.K.Arora, *Bioorg Med Chem*, **2004**, 12, 2225.
[7] S.A.Glase, H.C.Akunne, L.M.Georgia, T.G.Heffner, R.G.Mackengie, P.J.Manley, T.A.Pugsley, L.D.Wise, *J Med Chem*, **1997**, 40, 1771.
[8] M.A.Matulenko , A.A.Hakeem, T.Kolasa , M.Nakane , M.A.Terranova , M.E.Uchic , L.N.Miller, R. Chang, D.L.Donnelly-Roerts, M.T.Namovic, R.B.Moreland, J.D.Brioni, A.O.Stewart, M.Kimara, T.Masuda, K.Yamada, *Bioorg Med Chem*, **2004**, 12, 3471.