CHAPTER-II

Synthesis of [1-(4-chlorophenyl) cyclopropyl] (piperazin-1-yl) methanone derivatives
INTRODUCTION

Disubstituted piperazines exhibit wide range of biological properties as reported in the literature. In the last decade, a number of piperazine derivatives have been synthesized and evaluated for their cytotoxic activity [1-6]. Additional clinical drug development studies of the piperazine compounds in small-animal models by the US National Cancer Institute (NCI) demonstrated that these targets had the ability to suppress experimental tumours. As a result of the study for the lead compounds, it has been reported that inhibitory action was observed against colon, prostate, breast, lung and immune cell tumours in many indole carrying small anticancer molecules [7]. In addition, piperazines have been found to possess several biological activities [8-11] including Antituberculosis activity [12]. The polarity of nitrogen atoms of piperazine ring enhances favourable interaction with biomacromolecules and thus confers the biological activity [13-14]. 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 anticancer and Antituberculosis activity.

Treatment of microbial infections including bacterial, fungal, and tubercular is becoming difficult because of everlasting problem of microbial resistance towards antibiotics hence the need for new generations of anti-infective agents, and in particular new antimicrobial agents, is constant for effective treatment of microbial infections [15]. Medicinal chemists have been highly successful in the recent years in reshaping the scaffolds of earlier antibiotics, both natural and synthetic in which heterocyclic nucleus constitutes a part of pharmacophore which is essential for a particular pharmacological activity [16-17]. A heterocyclic compound is a cyclic compound that has hetero atoms such as N, O and S as members of its ring(s) having
medicinal importance [18], Piperazine is such a medicinally important heterocyclic nucleus which consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring. The piperazine nucleus has been classified as a privileged structure and is frequently found in biologically active compounds across a number of different therapeutic areas [19]. Some of these therapeutic areas include antimicrobial, anti-tubercular, antipsychotic, anticonvulsant, antidepressant, anti-inflammatory, cytotoxic, antimalarial, antiarrhythmic, antioxidant and antiviral activities etc. possessed by the compounds having piperazine nucleus [20-21].

Patil et al., synthesized a novel series of substituted phenyl acetamide piperazine derivatives (1). The antimicrobial activities for all the synthesized compounds were evaluated against Gram-positive bacteria (*Staphylococcus aureus, Streptococcus pyogenes*) and Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*). The antibacterial activity was evaluated using Ciprofloxacin as a standard drug. The antifungal activity was studied against *Candida albicans* and *Aspergillus niger*. One compound showed good antifungal activity against *Aspergillus niger* when compared with standard drug Greseofulvin [22].

![1]

A series of substituted piperazine derivatives (2) were synthesized by Chaudhary et al. and tested for antimicrobial activity. The antibacterial activity was tested against *Staphylococcus aureus, Pseudomonas aeruginosa, Streptomyces epidermidis* and *Escherichia coli* whereas antifungal activity against *Aspergillus*
fumigatus, Aspergillus flavus and Aspergillus niger. All synthesized compounds showed significant activity against bacterial strains by using Gentamycin as standard drug but were found to be less active against tested fungi [23].

Sharma et al., synthesized a series of N-nicotinoyl-1-ethyl-6-fluoro-1,4-dihydro-7-piperazin-1-yl-4-oxoquinoline-3-carboxylates (3). All the synthesized compounds were evaluated for antibacterial activity against four different stains of bacteria. Some compounds exhibited moderate to significant minimum inhibitory concentration (MIC) values when compared with standard drug [24].

A novel series of 2-(4-cyano-3-trifluoromethylphenyl amino)-4-(quinoline-4-yloxy)-6-(piperazinyl/piperidinyl)-Striazines (4) were synthesized by Patel et al. Preliminary screening of test compounds against eight bacteria (Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Proteus vulgaris, Shigella flexneria), four fungi (Aspergillus niger, Aspergillus fumigatus, Aspergillus clavatus, Candida albicans) and Mycobacterium tuberculosis indicated that among twenty one studied compounds, few were the most active. Ciprofloxacin and Pyrazinamide were used as standard drugs [25].
El-Din *et al.*, reported the synthesis of some novel N-4-piperazinyl derivatives of norfloxacin (5). The antibacterial activities of newly synthesized compounds were evaluated and correlated with their physicochemical properties. Results revealed that some of the tested compounds exhibited better inhibitory activities than standard drug Norfloxacin against *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia* and *Staphylococcus aureus* stains. Correlation results showed that there is no single physicochemical parameter that can determine the effect of N-4 piperazinyl group on the activity of these fluoroquinolones, where lipophilicity, molecular mass and electronic factors may influence the antibacterial activity [26].

The title compounds, 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichloro phenyl)piperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones (6) were synthesized by Patel *et al.* and tested for their antibacterial and antifungal activity in-vitro against microorganisms viz. *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*, *C. albicans*, *A. niger* and *A. clavatus* by taking...
Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Greseofulvin as their respective standard drugs [27].

![Chemical Structure](image)

The Piperazine chemistry has been developed extensively and is still developing. Presently there are a number of drugs are used clinically, which comprise Piperazine moiety in association with various heterocyclic rings.

In view of these, it was thought to synthesize a new series of piperazine moiety and to evaluate the new compounds for their pharmacological activity.

**PRESENT WORK**

In our present research work we are planned to synthesis of 1-(4-chlorophenyl)cyclopropyl[(piperazin-1-yl)methanone derivatives using reductive amination method with sodium triacetoxy borohydride as a reducing agent. Compound 2 (1.0 eq) was dissolved in dry THF solvent (10 mL). The solution was stirred for 10 min at ambient temperature. Then added aldehyde (1.1 eq) followed by sodium triacetoxyborohydride (1.4 eq) and glacial acetic acid (1.5 eq). The reaction mixture was heated to 70°C for 14 hr, the completion of reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate, the organic layer was washed with saturated sodium bicarbonate solution followed by water, brine solution and dried over anhydrous sodium sulphate. The organic layer was evaporate under reduced pressure and the crude was purified by column chromatography using 60-120 mesh silica gel. Pure compound obtained after column purification 3a-t was synthesized. All the synthesized compounds were characterized.
by elemental analysis, IR, $^1$H NMR and mass spectral data. The sequences of reactions carried out have been depicted in the Scheme-1. and derivatives are depicted in table-1.

**Scheme-I**

![Scheme-I diagram]

**Table 1: Synthesis of piperazine methanone derivatives 3a-t**

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EXPERIMENTAL

Preparation of t-Butyl 4-(1-(4-chlorophenyl)cyclopropanecarbonyl)piperazine-1-carboxylate (1).

The synthesis of compound 1 using acid amine coupling method with 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl) and 1-hydroxybenzotriazole (HOBT.H2O). 1-(4-Chlorophenyl) cyclopropane carboxylic acid (2.00 g, 10.2 mmol.) was dissolved in dry tetrahydrofuran (20 mL). The reaction mixture was stirred for 10 min at ambient temperature. To this added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.15 g, 11.22 mmol.) followed by 1-hydroxybenzotriazole (1.718 g, 11.22 mmol.) and N,N-diisopropylethylamine (3.955 g, 30.5 mmol.). The reaction mixture was stirred for 20 min at ambient temperature, and then it was cooled to 0°C. Boc-piperazine (tert-butyl piperazine-1-carboxylate) (1.894 g, 10.2 mol.) 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 mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution followed by water and brine. It was finally dried over sodium sulphate and evaporate under reduced pressure. The crude 3.4 g of t-butyl 4-(1-(4-chlorophenyl)cyclopropanecarbonyl) piperazine-1-carboxylate 1 was obtained. The compound 1 structure was confirmed by 1H-NMR, LCMS, IR and CHNS analysis.

![Structure of compound 1](image)

LC-MS (ESI, Positive): m/z: [M+H]⁺: 365.2; ¹H NMR: (400 MHz, DMSO-d₆): 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), IR (KBr) ν (cm⁻¹): 1646 (C=O); Elemental analysis:
Calculated (%) for C₁₄H₁₇ClN₂O: C 62.54, H 6.91, N 7.68; Found: C 62.55, H 6.94, N 7.62.

**Preparation of 4-(1-(4-Chlorophenyl)cyclopropanecarbonyl)piperazine-1-carboxylate (2).**

Compound 1 (3.4 g, 9.34 mmol.) was dissolved in dry dichloromethane and the mixture was cooled to 5⁰C. Trifluoroacetic acid (3.19 g, 28.0 mmol.) was added slowly to the cooled mixture and stirred for 6 h at ambient temperature. The completion of the reaction was monitored by TLC. The reaction mixture was evaporated under reduced pressure and it was dissolved in dichloromethane washed with water brine and dried over sodium sulphate. The crude product was 1.8 g of [1-(4-chlorophenyl)cyclopropyl] (piperazin-1-yl)methanone 2 was obtained.

![Image](attachment:image.png)

**2**

LC-MS (ESI, Positive): m/z: [M+H]⁺: 265.2; ¹H NMR: (400 MHz, DMSO-d₆): 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 C₁₄H₁₇ClN₂O: C 63.51, H 6.47, N 10.58; Found: C 63.53, H 6.46, N 10.57.

**General procedure for 3a-t**

1-(4-chlorophenyl) cyclopropyl][piperazin-1-yl)methanone derivatives was prepared by reductive amination method with sodium triacetoxy borohydride as a reducing agent. Compound 2 (1.0 eq) was dissolved in dry THF solvent (10 mL). The solution was stirred for 10 min at ambient temperature. Then added aldehyde (1.1 eq) followed by sodium triacetoxyborohydride (1.4 eq) and glacial acetic acid (1.5 eq). The reaction mass was heated to 70⁰C for 14 hr, the completion of reaction
was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate, the organic layer was washed with 10% sodium bicarbonate solution followed by water, brine solution and dried over anhydrous sodium sulphate. The organic layer was evaporate under reduced pressure and the crude reaction mixture was purified by column chromatography using 60-120 mesh silica gel. Pure compound obtained after column purification 3a-t was synthesized.

**SPECTRAL DATA**

4-((1H-Indol-3-yl)methyl)piperazin-1-yl)(1-4Chlorophenyl)cyclopropyl)methanone (3a)

![3a](image)

LC-MS (ESI, Positive): m/z: [M+H]+: 394.3; 1H NMR (400 MHz, DMSO-d6): δ 10.92 (bs, 1H, NH), 7.59-7.58 (d, J = 6.4 Hz, 1H), 7.35-7.33 (m, 3H), 7.19-7.13(m, 3H), 7.08-6.96(m, 1H), 3.60-3.33 (m, 6H), 2.31-1.91(m, 4H), 1.27-1.25 (m, 2H), 1.16-1.14 (m, 2H), 1.18 (q, J = 5.0 Hz, 2H); IR (KBr) ν(cm⁻¹): 3321 (N-H), 1671 (C=O); Elemental analysis: Calculated (%) for C_{23}H_{24}ClN_{3}O: C 70.13, H 6.14, N 10.64; Found: C 70.15, H 6.12, N 10.50.

1-(4-Chlorophenyl)cyclopropyl)(4-(pyridin-3-ylmethyl)piperazin-1-yl)methanone (3b)

![3b](image)

LC-MS (ESI, Positive): m/z: [M+H]+: 356.3; 1H NMR (400 MHz, DMSO-d6): δ 8.50-8.48 (dd, J = 4.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.30-7.28 (d, J = 6.0 Hz, 2H), 7.18-7.15 (m, 2H), 3.47 (s, 2H), 3.45-3.38 (m, 4H), 3.34-2.30 (m, 4H), 1.31-1.28 (m,
2H), 1.18-1.15 (m, 2H); Elemental analysis: Calculated (%) for C$_{20}$H$_{22}$Cl$_3$N$_5$O: C 67.50, H 6.23, N 11.81; Found: C 67.52, H 6.22, N 11.78.

1-(4-Chlorophenyl)cyclopropyl)(4-(quinolin-6-ylmethyl)piperazin-1-yl)methanone (3c)

![Chemical Structure 3c]

LC-MS (ESI, Positive): m/z: [M+H]$^+$: 406.0; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.95-8.93 (m, 1H), 8.86-8.85 (m, 1H), 8.49-8.47 (m, 1H), 7.77-7.4 (m, 2H), 7.35-7.30 (m, 2H), 7.29-7.27 (m, 1H), 7.21-7.15 (m, 2H), 3.62 (s, 2H), 3.45-3.38 (m, 4H), 3.34-2.30 (m, 4H), 1.30-1.27 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C$_{24}$H$_{24}$Cl$_3$N$_5$O: C 71.01, H 5.96, N 10.35; Found: C 71.10, H 6.01, N 10.41.

4-((1H-Imidazol-2-yl)methyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3d)

![Chemical Structure 3d]

LC-MS (ESI, Positive): m/z: [M+H]$^+$: 346.0; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 13.5 (bs, 1H), 7.55 (s, 1H), 7.38-7.31 (m, 2H), 7.19-7.15 (m, 2H), 6.92 (s, 1H), 3.46 (s, 2H), 3.45-3.38 (m, 4H), 2.40-2.24 (m, 4H), 1.31-1.28 (m, 2H), 1.18-1.15 (m, 2H); Elemental analysis: Calculated (%) for C$_{18}$H$_{21}$Cl$_3$N$_4$O: C 62.69, H 6.14, N 16.25; Found: C 62.71, H 6.16, N 16.31.
**1-(4-Chlorophenyl)cyclopropyl(4-((5-nitrothiazol-2-yl)methyl)piperazin-1-yl)methanone (3e)**

![Structure 3e]

LC-MS (ESI, Positive): m/z: [M+H]^+ 406.0; ^1^H NMR (400 MHz, DMSO-\textit{d}_6): δ 8.01-8.00 (d, \(J = 4.4\) Hz, 1H), 7.38-7.35 (d, \(J = 8.8\) Hz, 2H), 7.18-7.16 (d, \(J = 8.8\) Hz, 2H), 7.09-7.08 (d, \(J = 4.0\) Hz, 1H), 3.74 (s, 2H), 3.45-3.38 (m, 4H), 2.40-2.24 (m, 4H), 1.32-1.29 (m, 2H), 1.18-1.15 (m, 2H); ^13^C NMR (400 MHz,CDCl3): δ 169.30, 153.65, 147.72, 139.97, 130.75, 130.15, 128.64, 127.11, 125.68, 56.08, 51.99, 28.68, 15.8, Elemental analysis: Calculated (%) for C\textsubscript{19}H\textsubscript{20}ClN\textsubscript{3}O\textsubscript{3}S: C 53.13, H 4.71, N 13.77; Found: C 53.18, H 4.70, N 13.73.

**1-(4-Chlorophenyl)cyclopropyl(4-((6-methylpyridin-2-yl)methyl)piperazin-1-yl)methanone (3f)**

![Structure 3f]

LC-MS (ESI, Positive): m/z: [M+H]^+ 370.9; ^1^H NMR (400 MHz, DMSO-\textit{d}_6): δ 7.63-7.59 (m, 1H), 7.37-7.34 (d, \(J = 8.4\) Hz, 2H), 7.19-7.14 (m, 3H), 7.10-7.08 (m, 1H), 3.74 (s, 2H), 3.49-3.40 (m, 4H), 2.36 (s, 3H), 2.33-2.19 (m, 4H), 1.30-1.27 (m, 2H), 1.17-1.14 (m, 2H); ^13^C NMR (400 MHz,CDMSO-\textit{d}_6): δ 169.65, 157.52, 140.44, 137.18, 131.12, 129.03, 127.51, 212.84, 120.12, 63.94, 52.70, 29.10, 24.43, 15.75 IR (KBr) v/cm\(^{-1}\): 1698 (C=O),779 (C-Cl); Elemental analysis: Calculated (%) for C\textsubscript{21}H\textsubscript{24}ClN\textsubscript{3}O: C 68.19, H 6.54, N 11.36; Found: C, 68.21, H 6.50, N 11.31.
**1-(4-Chlorophenyl)cyclopropyl)(4-((1-methyl-1H-pyrrol-2-yl)methyl)piperazin-1-yl)methanone (3g)**

![Chemical Structure 3g]

LC-MS (ESI, Positive): m/z: [M+H]^+: 358.3; ^1^H NMR (400 MHz, DMSO-\(d_6\)): δ 7.38-7.35 (m, 2H), 7.20-7.14 (m, 2H), 6.64-6.63 (m, 1H), 5.84-5.83 (m, 2H), 3.54 (s, 2H), 3.46-3.39 (m, 4H), 3.34 (s, 3H), 2.23-2.11 (m, 4H), 1.29-1.26 (m, 2H), 1.18-1.14 (m, 2H); Elemental analysis: Calculated (%) for C\(_{20}\)H\(_{24}\)ClN\(_3\)O: C 67.12, H 6.76, N 11.74; Found: C 67.11, H 6.72, N 11.71.

**4-(4-Phenoxybenzyl)piperazin-1-yl)(1-(4-Chlorophenyl)cyclopropyl)methanone (3h)**

![Chemical Structure 3h]

LC-MS (ESI, Positive): m/z: [M+H]^+: 448.6; ^1^H NMR (400 MHz, DMSO-\(d_6\)): δ 8.50-8.48 (dd, \(J = 4.4\) Hz, 2H), 7.38-7.35 (m, 2H), 7.30-7.28 (d, \(J = 6.0\) Hz, 6H), 7.18-7.15 (m, 5H), 7.00-6.95 (2m, H), 3.49 (s, 2H), 3.47-3.40 (m, 4H), 3.36-3.32 (m, 4H), 1.32-1.29 (m, 2H), 1.19-1.16 (m, 2H); IR (KBr) \(\nu(\text{cm}^{-1})\): 1665 (C=O); Elemental analysis: Calculated (%) for C\(_{27}\)H\(_{25}\)ClN\(_2\)O\(_2\): C 72.55, H 6.09, N 6.27; Found: C 72.61, H 6.29, N 6.12.

**1-(4-Chlorophenyl)cyclopropyl)(4-((4,5-dimethylfuran-2-yl)methyl)piperazin-1-yl)methanone (3i)**

![Chemical Structure 3i]
LC-MS (ESI, Positive): m/z: [M+H]^+ 377.1; ^1H NMR (400 MHz, DMSO-d6): δ 7.39-7.34 (m, 2H), 7.19-7.14 (m, 2H), 5.59 (s, 1H), 3.6 (s, 2H), 3.46-3.39 (m, 4H), 2.23-2.11 (m, 4H), 2.10 (s, 3H), 1.92 (s, 3H), 1.19-1.15 (m, 2H); ^13C NMR (400 MHz, DMSO-d6): δ 169.62, 148.62, 146.59, 140.44, 131.13, 129.01, 127.54, 114.39, 112.51, 54.30, 52.06, 29.10, 15.68; Elemental analysis: Calculated (%) for C_{21}H_{25}ClN_{2}O_{2}: C 67.64, H 6.76, N 7.51; Found: C 67.68, H 6.72 N 7.52.

(4-(4-tert-Butylbenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3j)

LC-MS (ESI, Positive): m/z: [M+H]^+ 411.9; ^1H NMR (400 MHz, DMSO-d6): δ 7.25-7.22 (m, 2H), 7.07-7.02 (m, 4H), 6.80-6.77 (m, 2H), 3.58 (s, 2H), 3.46-3.39 (m, 4H), 3.35-2.31 (m, 4H), 1.41 (s, 9H), 1.31-1.28 (m, 2H), 1.18-1.15 (m, 2H); Elemental analysis: Calculated (%) for C_{20}H_{31}ClN_{2}O: C 73.06, H 7.60, N 6.82; Found: C 73.10, H 7.62, N 6.80.

(4-(4-Fluorobenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3k)

LC-MS (ESI, Positive): m/z: [M+H]^+ 373.8; ^1H NMR (400 MHz, DMSO-d6): δ 7.28-7.25 (m, 2H), 7.10-7.05 (m, 4H), 6.85-6.83 (m, 2H), 3.62 (s, 2H), 3.47-3.40 (m, 4H), 3.36-2.32 (m, 4H), 1.32-1.29 (m, 2H), 1.19-1.16 (m, 2H); Elemental analysis:
Calculated (%) for C_{21}H_{22}ClF_{2}N_{2}O: C 67.65, H 5.95, N 7.51; Found: C 67.48, H 5.90, N 7.58.

(4-(4-Bromobenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3l)

LC-MS (ESI, Positive): m/z: [M+H]^+: 434.7; ^1H NMR (400 MHz, DMSO-d$_6$): δ 7.26-7.24 (m, 2H), 7.10-7.08 (m, 2H), 7.04-7.01 (m, 2H), 6.83-6.80 (m, 2H), 3.59 (s, 2H), 3.45-3.38 (m, 4H), 3.35-2.30 (m, 4H), 1.31-1.28 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C_{21}H_{22}BrClN_{2}O: C 58.15, H 5.11, N 6.46; Found: C 58.26, H 5.21, N 6.54.

(4-(4-Hydroxybenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3k)

LC-MS (ESI, Positive): m/z: [M+H]^+: 371.8; ^1H NMR (400 MHz, DMSO-d$_6$): δ 7.30-7.28 (m, 2H), 7.15-7.12 (m, 2H), 7.10-7.08 (m, 2H), 6.86-6.82 (m, 2H), 6.10 (s, 1H), 3.59 (s, 2H), 3.45-3.38 (m, 4H), 3.35-2.25 (m, 4H), 1.33-1.27 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C_{21}H_{23}ClN_{2}O$_2$: C 68.01, H 6.25, N 7.55; Found: C 68.15, H 6.30, N 7.60.
(4-(4-Methoxybenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3n)

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\text{N} \\
\text{N} \\
\text{O} \\
\text{3n}
\end{array}
\]

LC-MS (ESI, Positive): m/z: [M+H]^+ : 385.9; \(^1\)H NMR (400 MHz, DMSO-\text{d}_6): \(\delta\)
7.40-7.37 (m, 2H), 7.25-7.22 (m, 2H), 7.20-7.18 (m, 2H), 6.96-6.92 (m, 2H), 3.81 (s, 3H), 3.65 (s, 2H), 3.50-3.42 (m, 4H), 3.40-2.45 (m, 4H), 1.38-1.30 (m, 2H), 1.18-1.15 (m, 2H); Elemental analysis: Calculated (%) for C\(_{21}\)H\(_{25}\)ClN\(_2\)O\(_2\): C 68.65, H 6.55, N 7.28; Found: C 68.75, H 6.65, N 7.38.

(4-(4-Chlorobenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3o)

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{N} \\
\text{N} \\
\text{3o}
\end{array}
\]

LC-MS (ESI, Positive): m/z: [M+H]^+ : 390.3; \(^1\)H NMR (400 MHz, DMSO-\text{d}_6): \(\delta\)
7.16-7.14 (m, 2H), 7.00-6.98 (m, 2H), 6.94-6.91 (m, 2H), 6.73-6.70 (m, 2H), 3.55 (s, 2H), 3.40-3.33 (m, 4H), 3.30-2.25 (m, 4H), 1.28-1.24 (m, 2H), 1.13-1.10 (m, 2H); Elemental analysis: Calculated (%) for C\(_{21}\)H\(_{23}\)Cl\(_2\)N\(_2\)O: C 64.79, H 5.70, N 7.20; Found: C 64.75, H 5.65, N 7.08.

(4-(3,4,5-Trimethoxybenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3p)

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{3p}
\end{array}
\]
LC-MS (ESI, Positive): m/z: [M+H]^+: 445.9; ^1H NMR (400 MHz, DMSO-d6): δ 7.40-7.37 (m, 2H), 7.20-7.18 (m, 2H), 6.12 (s, 2H), 3.84 (s, 9H), 3.69 (s, 2H), 3.50-3.42 (m, 4H), 3.40-2.45 (m, 4H), 1.38-1.30 (m, 2H), 1.18-1.16 (m, 2H); Elemental analysis: Calculated (%) for C_{21}H_{22}Cl_{2}N_{2}O: C 64.78, H 6.57, N 6.30; Found: C 64.88, H 6.40, N 6.40.

(4-(4-Methylbenzyl)piperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone (3q)

LC-MS (ESI, Positive): m/z: [M+H]^+: 369.9; ^1H NMR (400 MHz, DMSO-d6): δ 7.55-7.52 (m, 2H), 7.40-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.10-7.06 (m, 2H), 3.70 (s, 2H), 3.52-3.42 (m, 4H), 3.40-2.60 (m, 4H), 2.31 (s, 3H), 1.40-1.34 (m, 2H), 1.18-1.15 (m, 2H); Elemental analysis: Calculated (%) for C_{22}H_{25}ClN_{2}O: C 71.63, H 6.83, N 7.59; Found: C 71.58, H 6.80, N 7.55.

(1-(4-Chlorophenyl)cyclopropyl)(4-((naphthalen-1-yl)methyl)piperazin-1-yl)methanone (3r)

LC-MS (ESI, Positive): m/z: [M+H]^+: 405.9; ^1H NMR (400 MHz, DMSO-d6): δ 8.94-8.92 (m, 1H), 7.95-7.90 (m, 2H), 7.80-7.40 (m, 6H), 7.25-7.20 (m, 2H), 3.95 (s, 2H), 3.45-3.38 (m, 4H), 3.34-2.30 (m, 4H), 1.32-1.28 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C_{22}H_{25}ClN_{2}O: C 74.15, H 6.22, N 6.92; Found: C 74.28, H 6.33, N 6.99.
(4-Benzylpiperazin-1-yl)(1-(4-chlorophenyl)cyclopropyl)methanone(3s)

LC-MS (ESI, Positive): m/z: [M+H]^+: 355.8; ^1H NMR (400 MHz, DMSO-d6): \( \delta \) 7.95-7.90 (m, 2H), 7.75-7.35 (m, 5H), 7.25-7.20 (m, 2H), 3.65 (s, 2H), 3.45-3.38 (m, 4H), 3.34-2.30 (m, 4H), 1.32-1.28 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C\(_{22}\)H\(_{25}\)ClN\(_2\)O: C 71.01, H 6.53, N 7.89; Found: C 71.18, H 6.63, N 7.99.

(1-(4-Chlorophenyl)cyclopropyl)(4-((furan-2-yl)methyl)piperazin-1-yl)methanone(3t)

LC-MS (ESI, Positive): m/z: [M+H]^+: 345.8; ^1H NMR (400 MHz, DMSO-d6): \( \delta \) 7.55-7.52 (m, 1H), 7.40-7.38 (m, 2H), 7.10-7.06 (m, 2H), 6.95-6.90 (m, 2H), 3.58 (s, 2H), 3.45-3.38 (m, 4H), 3.34-2.30 (m, 4H), 1.32-1.28 (m, 2H), 1.17-1.14 (m, 2H); Elemental analysis: Calculated (%) for C\(_{22}\)H\(_{25}\)ClN\(_2\)O: C 66.18, H 6.14, N 8.12; Found: C 66.23, H 6.19, N 8.19.
REFERENCES


### Statistic report

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VarioMICRO V1.7.0 10/15/2009, CHNS Mode, Ser. No.: 15084052
Elementar Analysensysteme GmbH
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Peak ID | Time | Mass Found
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**Sample Set Name:** 267172013  
**Acq. Method Set:** uplc ms  
**Processing Method:** 2  
**Channel Name:** MS TIC  
**Proc. Date/Time:** SQ 1: MS Scan MS TIC  

**Match Plot**

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  - Retention Time: 1.82

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Run Time: 5.6 Minutes

Date Acquired: 12/26/2013 10:53:38 AM IST
Date Processed: 12/26/2013 12:23:05 PM IST

Acquired by: jay
Sample Solv Name: 26061201.3
AQC Method Set: upic_ms
Processing Method: 2
Channel Name: MS TIC
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Project Name: Doc2013
Date Printed: 12/26/2013
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