PART-A

STUDIES ON PYRAZINE DERIVATIVES
Pyrazine contains two nitrogen atoms in its aromatic ring. Pyrazine play an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. Especially, amides and sulfonamides of pyrazines have been used on various topics as anti-tuberculosis, dyes and pigments, oral anti diabetics, nutrition supplement, insecticides and fungicides.

In general pyrazine is prepared by the catalytic reaction of diamines with dioles in a vapour phase, dehydrogenation of piperazine or dealkylation of methyl pyrazine. Pyrazine and their derivatives form an important class of compounds present in several natural flavors and complex organic molecules, it is also responsible for flavor in foodstuffs, like cheese, tea coffee, cooked meats nice aroma etc.

SYNTHETIC ASPECT

Various methods for the preparation of pyrazine derivatives have been cited in literature, some of them are as under.

1. The pyrazine derivatives have synthesized by direct conversion of \( \alpha \)-hydroxy ketones and \( \alpha \)-keto oximes in the presence of a catalytic amount of ceric ammonium nitrate was reported by A. Shaabani et al.

\[
\text{NC-NH}_2 + \text{HO-OR} \xrightarrow{\text{CAN, Air, H}_2\text{O, rt., 45 min}} \text{NC-N}_2 \text{NC-OR}
\]

2. B. M. Latha et al. have synthesized pyrazine from ethylenediamine on copper oxide/copper chromite catalysts.
3. Microwave-assisted synthesis of pyrazine derivatives from α-halo ketone in 7% NH₃ solution was given by T. Utsukihara et al.⁸

4. Synthesis of 2-methyl pyrazine from zinc-modified ferrierite (FER) catalysts was documented by R. Anand et al.⁹

5. W. T. Reichle et al.¹⁰ have given the synthesis which involve the reaction of diketones with appropriate diamines, which gave the diazine which readily oxidized to the pyrazines.

**THERAPEUTIC IMPORTANCE**

Over recent years there has been an increasing interest in the chemistry of pyrazine derivatives because of their biological significance.

1. Analgesic¹¹
2. Antiallergic¹²
3. Antibacterial¹³
4. Anti-inflammatory¹⁴
5. Antiviral¹⁵
6. Diuretic¹⁶
7. Anticancer¹⁷
8. Anti HIV¹⁸
9. Anti hypertensive¹⁹
10. Cardiovascular²⁰
11. Antioxidant²¹
12. Antimycobacterial²²

L. E. Seitz et al.²³ have synthesized and evaluated antimycobacterial activity of pyrazine derivatives (1). H. Foks et al.²⁴ have synthesized and screened antibacterial activity of 1H-pyrazolo[3,4-b]pyrazine derivatives.
Studies on nitrogen containing heterocyclic…

Pyrazine derivative (2) with an allylsulfur moiety have hepatoprotective effects against toxicants. Effect of 2-AP on hepatic tumorigenesis in association with glutathione S-transferase (GST) induction was examined in rats exposed to aflatoxin B1 (AFB1) was given by T. G. Ha et al.25

H. Foks et al.26 have synthesized and checked tuberculostatic activity of 4-substituted 3,4,5,6-tetrahydro-2H-[1,2']-bis-pyrazine derivatives (3). F. Micheli et al.27 have synthesized pyrido [2,3-b] pyrazine-8-oxide derivatives as selective glycine antagonist with in vivo activity.

Synthesis and evaluation of substituted N-phenylpyrazine-2-carboxamides (4) as herbicides and abiotic elicitors was reported by M. Dolezal et al.28

K. Zurbonsen and coworkers29 have studied antiproliferative, differentiating and apoptotic effects elicited by imidazo[1,2-a]pyrazine derivatives (5). T. Yanai et al.30 have
synthesized novel pyrazine compounds produced from chitin by the activity of the enzyme from vibrio alginolyticus TK-24.

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1 = \text{H, Br} \\
\text{R}^2 = \text{Br, NH}_2, \text{NHCH}_3, \text{NHCH}_2\text{CH}_3 \\
\text{R}^3 = \text{CN, H} \\
\text{R}^4 = \text{H, Br, CH}_2\text{OH, CH}_2\text{OCH}_3
\end{array}
\end{array}
\]

Pyrazine derivatives (6) tested against human keratinocyte cells stressed UVB irradiation showed high anti oxidative properties was given by J. Cavalier et al.\textsuperscript{31}

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{OH, OCH}_3
\end{array}
\end{array}
\]

B. A. Ellsworth et al.\textsuperscript{32} have studied structure activity relationships for a series of pyrazine carboxamide (7) as CB1 antagonists. Pharmaceutical properties of the series (7) were improved via inclusion of hydroxyl containing side chains. This structural modification sufficiently improved ADME properties of an orally inactive series such that food intake reduction was achieved in rat feeding models.

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\]

J. W. Corbett et al.\textsuperscript{33} have synthesized indanylpyrazines (8) and reported corticotrophin releasing factor type-1 receptor antagonists.
N. Sinha et al.\textsuperscript{34} have synthesized and screened antimycobacterial activity of some pyrazine derivatives (9). K. Yoshiizumi et al.\textsuperscript{35} have synthesized and studied structure activity relationships of 5,6,7,8-tetrahydropyrido[3,4-\textit{b}]pyrazine based hydroxamic acids as HB-EGF shedding inhibitors.

![Chemical Structure](image)

Pyrazin-2-yl-formamide thiosemicarbazones (10) related to their tuberculostatic activity was reported by A. Olczak et al.\textsuperscript{36}

![Chemical Structure](image)

The novel structures 5,7-disubstituted 6-amino-5\textit{H}-pyrrolo[3,2-\textit{b}]pyrazine-2,3-dicarbonitriles (11) and their promising protein kinase inhibitors with antiproliferative activity was given by G. G. Dubinina et al.\textsuperscript{37}

![Chemical Structure](image)

Synthesis and tuberculostatic activity of pyrazinyl substituted derivatives (12) was reported by H. Foksi et al.\textsuperscript{38}

![Chemical Structure](image)
J. Bostrom et al.\textsuperscript{39} have studied scaffold hopping, synthesis and structure activity relationships of 5,6-diaryl-pyrazine-2-amide derivatives (13) of CB1 receptor antagonists.

![Diagram of compound 13]

Synthesis and biological activity of 5-arylcyanopyrazine-2-carboxylic acid derivatives (14) was given by M. Dolezal et al.\textsuperscript{40}

![Diagram of compound 14]

M. Dolezal et al.\textsuperscript{41} have synthesized and reported antimycobacterial evaluation of substituted pyrazine carboxamide derivatives (15).

![Diagram of compound 15]

J. Krinkova et al.\textsuperscript{42} have synthesized and evaluated biological activity of 5-alkyl-6-(arylsulfanyl)pyrazine-2-thioamides derivatives (16).

![Diagram of compound 16]

C. G. Bonde coworkers\textsuperscript{43} have synthesized and given preliminary evaluation of some pyrazine derivatives (17) as antimicrobial agents.
T. Asaki et al.\textsuperscript{44} have studied structure activity on diphenylpyrazine derivatives (18) of prostacyclin receptor agonists.

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{R}_1 \\
\text{O} \\
\text{R}_1 \text{ = ethyl, allyl, cyclopropyl}
\end{array}
\]

Synthesis and antiinflammatory activity of methyl substituted imidazo[1,2-\textit{a}]pyrazine derivatives (19) was reported by M. G. Rimoli et al.\textsuperscript{45}

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R}_1 \text{R}_2 \\
\text{R}_1 \text{ = CH}_3, \text{CH}_2\text{COOH, COOH} \\
\text{R}_2 \text{ = H, COOH}
\end{array}
\]

Synthesis of two new hybrid metal-organic polymers using flexible pyrazine crystal structures were given by C. Zhang et al.\textsuperscript{46} Synthesis and biological evaluation of pyrido[2,3-\textit{b}]pyrazine-\textit{N}-oxide as selective glycine antagonists was reported by A. Cugola et al.\textsuperscript{47} J. E. Dowling et al.\textsuperscript{48} have synthesized of [1,2,4]triazolo[1,5-\textit{a}]pyrazines as adenosine A\textsubscript{2A} receptor antagonists. C. A. Hargreaves and coworkers\textsuperscript{49} have studied tetrahydropyrido[2,3-\textit{b}]pyrazine scaffolds. H. Mukaiyama et al.\textsuperscript{50} have synthesized and given C-SRC inhibitory activity of imidazo[1,5-\textit{a}]pyrazine derivatives as an agent for treatment of acute ischemic stroke. D. R. Owen et al.\textsuperscript{51} have studied structure activity relationships of pyrazine derivatives as a novel non competitive mGluR1 antagonists. Synthesis and antimycobacterial activity of pyrazine derivatives documented by L. E. Seitz et al.\textsuperscript{52} Imidazo[1,2-\textit{a}]pyrazine shows the bronchodilatory and cyclic nucleotide phosphodiesterase inhibitory activities was given by T. O. Vitse et al.\textsuperscript{53}

Thus the important role displayed by pyrazine and its derivatives for various therapeutic and biological activities prompted us to synthesize some pyrazine derivatives.
in order to achieve compounds having better therapeutic activities, which summarized in this part as under.

STUDIES ON PYRAZINE DERIVATIVES

PART-I: STUDIES ON 2-(PIPERIDINE-4-YLMETHOXY)PYRAZINE DERIVATIVES
REFERENCES

PART-I

STUDIES ON 2-(PIPERIDIN-4-YLMETHOXY)PYRAZINE DERIVATIVES
INTRODUCTION

Pyrazine nucleus possesses remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products. In view of our ongoing interest in the synthesis of some new potentially bioactive pyrazine derivatives (1) have been described as under.

\[
\begin{align*}
N & N \\
O & NR_2 \\
R_1 & N-R^2
\end{align*}
\]

(1)

The synthesis of compound 2-(piperidin-4-ylmethoxy)pyrazine derivatives has been attracted widespread attention due to their diverse pharmacological properties like anti-inflammatory, antibiotic, antifungal, herbicidal, antitubercular, etc. To approach this goal synthesis of some new 2-(piperidin-4-ylmethoxy)pyrazine derivatives have been undertaken.

SYNTHETIC ASPECT

Various methods of bromination, diazotization, mitsunobu reaction, suzuki cross coupling and deprotection of pyrazine derivatives have been cited in literature, some of the methods are as under.

BROMINATION

1. Bromination of 2-amino pyrazine in presence of bromine and pyridine in CHCl₃ was given by S. Sevilla et al.¹

\[
\begin{align*}
\text{Br}_2, \text{pyridine} & \quad \rightarrow \\
\text{CHCl}_3 & \quad \text{Br}_{\text{N}} \text{NH}_2
\end{align*}
\]

2. F. D. Weal et al.² have synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine, N-bromosuccinamide in acetonitrile solution.

\[
\begin{align*}
\text{NBS, CH}_3\text{CN} & \quad \rightarrow \\
\text{overnight, rt} & \quad \text{Br}_{\text{N}} \text{NH}_2
\end{align*}
\]
3. 2-Amino pyrazine react with N-bromosuccinamide in DMSO solution to give 2-amino-3,5 dibromo pyrazine was reported by B. Jiang et al.³

![Chemical structure of 2-amino pyrazine reacting with N-bromosuccinamide in DMSO solution](image)

4. A. M. Stadler et al.⁴ have synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine, N-bromosuccinamide in CH₂Cl₂ solution.

![Chemical structure of 2-amino pyrazine reacting with N-bromosuccinamide in CH₂Cl₂ solution](image)

5. T. Itoh et al.⁵ have synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine with brominating agent.

![Chemical structure of 2-amino pyrazine reacting with brominating agent](image)

### DIAZOTIZATION

1. Preparation of 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, NaNO₂ and H₂SO₄ was reported by F. Jing et al.⁶

![Chemical structure of 2-amino-5-bromopyrazine reacting with NaNO₂ and H₂SO₄](image)

2. H. Mukaiyama et al.⁷ have prepared 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, NaNO₂ and CH₃COOH in dioxane solution.

![Chemical structure of 2-amino-5-bromopyrazine reacting with NaNO₂ and CH₃COOH in dioxane](image)

3. S. Nobuhiro et al.⁸ have studied diazotization of 2-amino-5-bromopyrazine in sulphuric acid and sodium nitrate.
4. H$_2$SO$_4$ and sodium nitrate react with 2-aminopyrazine to give 2-hydroxypyrazine which was given by Y. Jun et al.$^{9}$

5. A. E. Erickson et al.$^{10}$ have synthesized 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, NaNO$_2$ and H$_2$SO$_4$.

### MITSUNOBU REACTION

1. Use of sonication for the coupling of sterically hindered substrates in the phenolic mitsunobu reaction was reported by S. D. Lepore et al.$^{11}$

2. Organocatalytic mitsunobu reaction of phenol and acid in THF was documented by T. Y. S. But et al.$^{12}$

3. Di-p-chlorobenzyl azodicarboxylate (DCAD) was introduced as a novel, stable and solid variety of mitsunobu coupling in CH$_2$Cl$_2$ was given by B. H. Lipshutz et al.$^{13}$
4. Carbon nucleophiles in the Mitsunobu reaction, mono- and dialkylation of bis(2,2,2-trifluoroethyl) malonates was given by J. M. Takacs et al.\textsuperscript{14}

\[
\begin{align*}
\text{R}_1\text{OH} + \begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{COOCH}_2\text{CF}_3
\end{array}
\rightarrow \begin{array}{c}
\text{R}_1\text{COOCH}_2\text{CF}_3
\end{array}
\end{align*}
\]

5. Second-generation tags for fluorous chemistry exemplified with a new fluorous Mitsunobu reagent and fluorous triphenylphosphine in THF was reported by Q. Chu et al.\textsuperscript{15}

6. Multipolymer solution-phase organocatalytic Mitsunobu reaction of phenol and acid in THF was reported by A. M. Harned et al.\textsuperscript{16}

**SUZUKI CROSS COUPLING**

1. The well known Suzuki reaction\textsuperscript{17} is the organic reaction of an aryl or vinyl-boronic acid with an aryl or vinyl-halide catalyzed by a palladium (0) complex forming carbon-carbon bond. Some reported reactions are described as under.

2. In 1981, A.Suzuki and N.Miyaura et al.\textsuperscript{18} have made a breakthrough in the methodology for biaryl compounds using aryl boronic acids and aryl bromide under homogeneous palladium catalyzed conditions in the presence of base.
3. Z.Du et al.¹⁹ have reported an ultrafast and highly efficient ligand-free Suzuki-Miyaura cross-coupling reaction between aryl bromides/iodides and aryl boronic acids using palladium chloride as catalyst in PEG-400/H₂O in air at room temperature. TEM showed that palladium nanoparticles were generated in situ from PdCl₂/PEG-400/H₂O without use of other reductants. The catalyst system can be recycled to reuse three times with good yields.

\[
\begin{align*}
\text{Ar-X} + \text{Ar′-B(OH)₂} & \xrightarrow{\text{PdCl₂}} \text{Ar-Ar′} \\
\text{PEG-400/H₂O, K₂CO₃} & \text{rt}
\end{align*}
\]

4. Yu-L.Zhao et al.²⁰ have prepared a highly practical and reliable Nickel catalyst for Suzuki–Miyaura coupling of aryl halides with various aryl boronic acid.

\[
\begin{align*}
\text{Br} + \text{B(OH)₂} & \xrightarrow{\text{NiCl₂(dipp)} (1\%), K₂PO₄ (3.0 eq.)} \text{Dioxane, 100 °C} \\
\text{R}
\end{align*}
\]

5. S.Lou et al.²¹ have developed Palladium/Tris(tert-butyl)phosphine-Catalyzed Suzuki Cross-Couplings of aryl and heteroaryl halides with aryl and heteroaryl boronic acids in the Presence of Water.

\[
\begin{align*}
\text{R-X} & \xrightarrow{\text{R′-B(OH)₂}} \text{R-R′} \\
\text{X=Cl, Br, I} & \text{0.5% Pd₃(dba)₃} \\
& \text{1.2% [HP(t-Bu)₃]BF₄} \\
& \text{3.3 eq. KF-2H₂O} \\
& \text{THF, rt}
\end{align*}
\]

7. Y. Zhang et al.\textsuperscript{23} have been developed one-pot process for the synthesis of 8-arylquinolines via Pd-catalyzed borylation of quinoline-8-yl halides and subsequent Suzuki-Miyaura coupling with aryl halides using \( n\)-BuPAd\(_2\) as ligand.

\[
\begin{align*}
\text{FG} & \quad \text{Br} & \quad \text{Pd(\text{dba})\textsubscript{2}, n-BuPAd\textsubscript{2}, KOAc, DMAc, 90\degree C} & \quad \text{ArX, aq. K\textsubscript{2}CO\textsubscript{3}, 90\degree C} & \quad \text{FG} \\
\text{FG} & \quad \text{pyrazine} & \quad \text{B-O} & \quad \text{B-O} & \quad \text{FG} \\
\end{align*}
\]

8. J. Spencer et al.\textsuperscript{24} have reported synthesis of a (piperazin-1-ylmethyl)biaryl library via microwave-mediated Suzuki–Miyaura cross-couplings.

9. Q. Tang et al.\textsuperscript{25} have developed Suzuki–Miyaura coupling reactions of 5-chloro-1-phenyl-tetrazole with various functionalized aryl boronic acids in the presence of catalytic amounts of SPhos/Pd(OAc)\(_2\) or RuPhos/Pd(OAc)\(_2\).

10. J.-M. Begouin et al.\textsuperscript{26} have reported cobalt-catalyzed cross-coupling between aryl zinc halides and 2-chloropyrimidine/2-chloropyrazine prepared in situ.
11. T. Itoh et al.\textsuperscript{27} have discovered a direct synthesis of hetero-biaryl compounds containing an unprotected NH\textsubscript{2} group \textit{via} Suzuki–Miyaura reaction by using Pd(OAc)\textsubscript{2} and D-t-BPF ligand as a catalyst.

12. L.C.W. Chang et al.\textsuperscript{28} synthesized 2,6-disubstituted and 2,6,8-trisubstituted purines as adenosine receptor antagonists \textit{via} Suzuki–Miyaura reaction.

13. C. A.Fleckenstein et al.\textsuperscript{29} have reported an efficient Suzuki-Miyaura coupling of (hetero)aryl chlorides with Thiophene- and Furan boronicacids in aqueous \textit{n}-butanol.


15. Microwave-assisted efficient copper-promoted \textit{N} arylation of amines with arylboronic acids was given by S. Chen et al.\textsuperscript{31}
16. Stepwise cross-coupling reactions in pyrazine derivatives was reported by C. Yang et al.\textsuperscript{32}

17. A novel and versatile entry to asymmetrically substituted pyrazines was reported by V. P. Mehta et al.\textsuperscript{33}

18. Microwave-assisted synthesis C-C bond formation of pyrazine derivatives was documented by S. Sevilla et al.\textsuperscript{1}

19. Palladium imidazolium carbene catalyzed aryl, vinyl and alkyl suzuki-miyaura cross coupling synthesis was given by M. B. Andrus et al.\textsuperscript{34}

20. New coupling partners in room temperature suzuki reaction of alkyl bromides under remarkable mild conditions was reported by J. H. Kirchhoff et al.\textsuperscript{35}
21. S. Li et al.\textsuperscript{36} have synthesized Pd(OAc)$_2$-catalyzed room temperature suzuki cross-coupling reaction in aqueous media under aerobic conditions.

22. C. Baillie et al.\textsuperscript{37} have documented and given its applications in the suzuki-miyaura coupling of aryl chlorides in presence of ferrocenyl monophosphine ligand in dioxane.

23. Suzuki-miyaura cross-coupling reaction under ligand free conditions was given by W. J. Liu et al.\textsuperscript{38}

24. Phosphine free palladium acetate catalyzed suzuki reaction in water was given by L. Liu et al.\textsuperscript{39}

25. A highly active catalyst for suzuki-miyaura cross coupling reactions of heteroaryl compounds was reported by K. L. Billingsley et al.\textsuperscript{40}
26. Y. M. A. Yamada et al.\textsuperscript{41} have prepared highly active catalyst for the heterogeneous suzuki-miyaura reaction by assembled complex of palladium and non-cross-linked amphiphilic polymer.

\[
\text{Ar-X + HetAr'-B(OH)₂} \xrightarrow{\text{Pd(OAc)₂, K₃PO₄, n-butanol, 100 °C}} \text{Ar—Ar'}
\]

**DEPROTECTION**

1. B. Li et al.\textsuperscript{42} have used aqueous phosphoric acid is an effective, environmentally benign, selective and mild reagent for the deprotection of tert-buty carbamates.

\[
\text{R}^1\text{-X} + \text{R}^2\text{-B(OH)₂} \xrightarrow{(\text{ArPh₂P})₂\text{PdCl₂}} \text{Na₂CO₃, H₂O, 100 °C} \rightarrow \text{R}^1\text{-R}^2
\]

2. A stereo conservative deprotection method of amino groups was reported by D. M. Shendage et al.\textsuperscript{43}

\[
\text{O} \xrightarrow{\text{HCl-MeOH}} \text{rt, 1 h} \rightarrow \text{NH}
\]

3. Selective removal of the tert-butoxycarbonyl group from secondary amines using zinc bromide as the deprotecting reagent was given by S. C. Nigama et al.\textsuperscript{44}

\[
\text{O} \xrightarrow{\text{ZnBr₂, CH₂Cl₂}} \text{NH}
\]
4. N. B. Narasimhulu et al.\textsuperscript{45} have studied deprotection of piperidine derivatives from tert-butyl piperidine and TFA in chloroform solution.

\[
\begin{align*}
\text{H}_2\text{C} & \equiv \text{N} \quad \text{CF}_3\text{COOH} \\
& \text{CH}_2\text{Cl}_2, \text{rt} \\
\text{H}_2\text{C} & \equiv \text{NH}
\end{align*}
\]

5. Reaction of tert-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate in HCl in dioxane solution to gave 4-(prop-2-yn-1-yl)piperidine was carried out by N. D. Waal et al.\textsuperscript{46}

\[
\begin{align*}
\text{HC} \equiv \text{C} & \quad \text{HCl in dioxane} \\
& \text{HC} \equiv \text{NH}
\end{align*}
\]

6. F. Bois et al.\textsuperscript{47} have studied deprotection of (2S)-2-methylpiperidine from tert-butyl (2R)-2-methylpiperidine-1-carboxylate, CF\textsubscript{3}COOH and anisole in dichloromethane solution.

\[
\begin{align*}
\text{CF}_3\text{COOH} & \quad \text{PhOMe, CH}_2\text{Cl}_2 \\
& \text{NHCH}_3
\end{align*}
\]

**REACTION MECHANISM OF MITUSNOBU**
REACTION MECHANISM OF DEPROTECTION

\[
\begin{align*}
\text{O} & \text{N} \quad \text{H} \\
\text{O} \quad \text{C} & \text{N} \quad \text{H} \\
\text{H} & \text{N} \quad \text{H} \quad \text{CO}_2 \\
\text{R'} &
\end{align*}
\]

REACTION MECHANISM OF SUZUKI COUPLING

\[
\begin{align*}
\text{R}_1 - \text{R}_2 & \rightarrow \text{Pd}(0) \\
\text{R}_2 - \text{Pd}(II) - \text{R}_1 & \rightarrow \text{NaO}^+ \text{Bu} \\
\text{R}_2 - \text{Pd}(II) - \text{X} & \rightarrow \text{NaX} \\
\text{R}_1 - \text{B} - \text{O}^+ \text{Bu} & \rightarrow \text{R}_1 - \text{B} - \text{O}^+ \text{Bu} \\
\text{R}_1 - \text{B} & \rightarrow \text{NaO}^+ \text{Bu} \\
\text{R}_2 & \rightarrow \text{Pd}(II) - \text{R}_1 \\
\text{R}_2 - \text{Pd}(II) - \text{X} & \rightarrow \text{NaX}
\end{align*}
\]

THERAPEUTIC IMPORTANCE

2-(Piperidine-4-yl methoxy)pyrazine derivatives have been tested for various pharmacological activities, which have been summarized as under.

1. Analgesic\textsuperscript{48}
2. Antibacterial\textsuperscript{49}
3. Antifungal\textsuperscript{50}
4. Anti-inflammatory\textsuperscript{51}
5. Antiviral\textsuperscript{52}
6. Anticancer\textsuperscript{53}
7. Anti HIV\textsuperscript{54}

A. V. Shindikar et al.\textsuperscript{55} have designed, synthesized, and tested \textit{in vivo} activity in mice against \textit{mycobacterium tuberculosis} H37Rv of pyrazine derivatives (2). K. J. French et al.\textsuperscript{56} have studied cyclohexyl-octahydro-pyrrolo[1,2-\textit{a}]pyrazine based inhibitors of human \textit{N}-myristoyltransferase-1.
D. Sriram et al.\textsuperscript{57} have synthesized pyrazinamide derivatives (3) and reported antitubercular properties. D. C. Scopes et al.\textsuperscript{58} have synthesized new k-receptor agonists based upon a 2-[(alkylamino)methy]piperidine nucleus.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{image1}};
\end{tikzpicture}
\end{center}

Synthesis, anticancer, anti-inflammatory and analgesic activity evaluated of some pyrazine derivatives have been (4) reported by S. M. Sondhi et al.\textsuperscript{59} B. S. Huegi et al.\textsuperscript{60} have synthesized and reported pharmacological studies on 4,4-disubstituted piperidine derivatives as a potent analgesic properties.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{image2}};
\end{tikzpicture}
\end{center}

B. C. Gordon et al.\textsuperscript{61} have synthesized pharmaceutical composition containing piperidine derivatives (5) and documented their use as modulators of chemokine CCR5 receptors. Synthesis and analgesic activity of some spiro[dibenz[h,f]oxepin]-10,4’-piperidine] derivatives was reported by H. H. Ong et al.\textsuperscript{62}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{image3}};
\end{tikzpicture}
\end{center}
Antimycobacterial and H1-antihistaminic activity of 2-substituted piperidine derivatives (6) was given by R. Weis et al. A. Z. Kabdraisova et al. have reported synthesis and biological activity of N-(2-thoxyethyl)piperidine derivatives of anabasin. Some piperidine substituted with benzimidazoles was reported by V. Sundari et al. as bioactive substance. A. Seza et al. have studied antimicrobial activity of some piperidine substituted halogenobenzene derivatives.

S. J. Philippe et al. have prepared piperidine derivatives (7) and tested antibiotics activity. Effect of substituents on N-(1-piperidinobenzyl)acetamide and their antimicrobial activity was reported by N. Raman et al. M. Yoshifumi et al. have studied antimicrobial and anti-plaque activity of N'-alkyl-N-(2-aminoethyl)piperidine against dental plaque bacteria.

Synthesis and structure activity relationships of 2-phenyl-1-[(pyridinyland piperidinylmethyl)amino]-3-(1H-1,2,4-triazol-1-yl)propan-2-ols (8) as antifungal agents was given by F. Giraud et al. K. K. Goel et al. have synthesized and screened for antimicrobial activity of piperidin-4-one derivatives. K. Canan et al. have synthesized and tested antimicrobial activity of some novel 2-[4-(substituted piperidin-1-ylcarbonyl)phenyl]-1H-benzimidazole derivatives.
M. Ishikawa et al.\textsuperscript{73} have synthesized and given structure activity relationships of \textit{N}-aryl-piperidine derivatives (9) as potent (partial) agonists for human histamine H3 receptor. M. Tibor et al.\textsuperscript{74} have studied histamine H3 receptor antagonists of 1-(4-Phenoxyethyl) benzyl)piperidines derivatives.

G. D. Maynard et al.\textsuperscript{75} have synthesized and reported SAR of 4-(1H-benzimidazole-2-carbonyl)piperidines (10) with dual histamine H\textsubscript{1}/tachykinin NK\textsubscript{1} receptor antagonist activity. A. G. Magid et al.\textsuperscript{76} have synthesized substituted piperidine derivatives as novel H1-antagonists. V. Claudio et al.\textsuperscript{77} studied antinociceptive profile of 2,3,6-trisubstituted piperidine alkaloids.

C. E. Gutteridge et al.\textsuperscript{78} have studied \textit{N}-(3-phenylsulfonyl-3-piperidinoyl)-phenylalanine derivatives (11) as potent, selective VLA-4 antagonists. Study of piperidine carboxylic acid derivatives of 10\textit{H}-pyrazino[2,3-\textit{b}][1,4]benzothiazine as orally active adhesion molecule inhibitors investigated by K. Toshihiko et al.\textsuperscript{79}
C. G. Barber et al.\textsuperscript{80} have investigated 1-amino-1-phenyl-3-piperidinylbutanes (12) CCR5 antagonists for the treatment of HIV. Analgesic and anti-inflammatory activity screening of 6-acyl-3-piperidinomethyl-2(3\textit{H})-benzoxazolone derivatives was reported by E. D. Demir et al.\textsuperscript{81}

S. Imamura et al.\textsuperscript{82} synthesized and reported biological evaluation of piperidine-4-carboxamide derivatives (13) as CCR5 antagonists as anti-HIV-1 agents. Synthesis and biological activity of piperidinoaryl carbamides and their derivatives was reported by V. M. Gujrati et al.\textsuperscript{83} W. Tao et al.\textsuperscript{84} have synthesized diketopiperidine derivatives as HIV attachment inhibitors and reported, pharmaceutical compositions and use in the treatment of HIV infection and AIDS.

R. H. K. Foster and coworkers\textsuperscript{85} have studied piperidine derivatives with morpholine like analgesia activity. Study of (2S)-1-(arylacetyl)-2-(aminomethyl)piperidine derivatives and highly selective kappa opioid analgesics was
Studies on nitrogen containing heterocyclic...

given by V. Vecchietti et al. The M. Eiichi and coworkers have synthesized and reported antiallergic activity of novel pyrazine derivative. Synthesis and anti mycobacterial evaluation of some pyrazine-2-carboxylic acid hydrazide derivatives was documented by A. A. Mohamed et al. G. Katarzyna et al. have synthesized and screened antibacterial activity of novel pyrazine derivative obtained from amidoximes. Synthesis and antibacterial activity of 6-methoxypyrazine-2-carboxylic acid hydrazide derivatives was reported by G. Katarzyna et al. Synthesis and antimicrobial activity of 2,3-(substituted phenyl)pyrazine dicarboxamide was given by N. S. Rao et al. Pyrazine-2-substituted carboxamide derivatives synthesis, antimicrobial and leuconostoc mesenteroides growth inhibition activity study investigated by A. H. F. Wahab et al. N. B. Patel et al. have synthesized and reported antimicrobial activity of 2-[3-(ary lureido)carbonyl]pyrazine derivatives. A study of 2-piperidino-1-ethanol and its derivatives as antimicrobial additives to oils was reported by S. A. Gamzaeva et al.

Looking to the interesting properties of 2-(piperidine-4-ylmethoxy)pyrazine, we have synthesized some new 2-(piperidine-4-ylmethoxy)pyrazine, which have been describe as under.

PART-I: STUDIES ON 2-(PIPERIDINE-4-YL METHOXY) PYRAZINE DERIVATIVES

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-BROMOPHENYL)PYRAZIN-2-YL)OXY)METHYL) PIPERIDIN-1-YL)(ARYL)METHANONES

SECTION-II: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-METHOXY-3-METHYLPHENYL)PYRAZIN-2-YL)OXY) METHYL) PIPERIDIN-1-YL)(ARYL)METHANONES

SECTION-III: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-FLUOROPYRIDIN-3-YL)PYRAZIN-2-YL)OXY) METHYL) PIPERIDIN-1-YL)(ARYL)METHANONES

2-(Piperidin-4-ylmethoxy)pyrazine derivatives...
SECTION-IV: SYNTHESIS AND BIOLOGICAL EVALUATION OF ARYL(4-(((5-(m-TOLYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)METHANONES

SECTION-V: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-METHOXYPHENYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL)METHANONES
Part – A

[Part – I (Section-i)]

Synthesis and biological evaluation of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(aryl)methanones
SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-BROMOPHENYL)PYRAZIN-2-YL)OXY)METHYL) Piperidin-1-YL)(ARYL) METHANONES

Pyrazine nucleus possesses remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products. In view of these findings, it appeared of interest to synthesize 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA, as shown in reaction scheme.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, \(^1\)H NMR, \(^13\)C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of 5-Bromopyrazin-2-amine.

To a stirred cooled to 0°C solution of 2-aminopyrazine (10.0 g, 0.105 mol) in dry DCM (250 ml), N-bromosuccinamide (18.72 g, 0.105 mol) was added portion wise. The mixture was stirred at 0°C for 24 hours. The reaction was monitored on TLC. After completion of the reaction, saturated aqueous solution of sodium carbonate was added (200 ml) to quench the reaction. The organic layer was washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography on silica gel (eluent: 2 : 8 = E.A. : Hexane) to obtain pure product. Yield: 70 %, mp 133-135°C.

[B] Preparation of 5-Bromopyrazin-2-ol.

Sodium nitrite (8.9 g, 0.129 mol) was added portion wise with stirring to concentrated H$_2$SO$_4$ (49 ml) at 0°C and the mixture was warmed to dissolved the solid. The mixture was cooled to 5°C. To this a solution of 5-bromopyrazin-2-amine (15.0 g, 0.086 mol) in concentrated H$_2$SO$_4$ (71 ml) was added slowly. The reaction mixture was stirred below 5°C for 30 minute and warmed to 40°C for 2 hours. The reaction mixture was poured onto crushed ice. The aqueous solution was extracted with ethyl acetate (250 ml x 3) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo, and the solid product was obtained. Yield: 50 %, mp 80-82°C.
[C] **Preparation of 5-Bromopyrazin-2-yl methanesulfonate.**

To a stirred cooled (ice bath) solution of 5-bromopyrazin-2-ol (5.0 g, 0.028 mol) in dry DCM (25 ml), TEA (5.85 ml, 0.042 mol) and CH$_3$SO$_2$Cl (2.80 ml, 0.034 mol) was added drop wise in solution at 0°C. The reaction mixture was stirred for 2 hours at room temperature (monitored by TLC), and the solvent was removed *in vacuo*. The product was filtered, washed with water and dried to give analytical pure product. Yield: 80 %, mp 85-87°C.

[D] **Preparation of tert-butyl 4-((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.**

To a stirred suspension of K$_2$CO$_3$ (3.036 g, 0.022 mol) and 5-bromopyrazin-2-yl methanesulfonate (3.0 g, 0.011 mol) in dry DMF (30 ml), tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (2.54 g, 0.011 mol) was added. The solution was heated on a water bath for 2 hours at 75-80°C. (monitored by TLC). The reaction mixture was poured onto crushed ice, thus the precipitate obtained, was filtered and washed with water to give pure product. Yield: 68 %, mp 99-101°C.

[E] **Preparation of tert-butyl 4-((5-(4-bromophenyl)pyrazin-2-yl oxy) methyl)piperidine-1-carboxylate.**

A solution of tert-butyl 4-((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was further stirred for 5.0 minutes. To this solution (4-bromophenyl)boronic acid(0.880 g, 0.0044 mol), isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K$_2$CO$_3$ (10.0 ml, 0.02 mol) in water was added drop wise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 6 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.
[F] Preparation of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy)pyrazine.

A mixture of HCl\text{(g)} in dioxane (10 ml) and tert-butyl 4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed \textit{in vacuo}. Water and ethyl acetate was added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combined organic layers were washed with water followed by brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The solvent was evaporated under vacuum to give pure product. Yield: 63 %, mp 152-154\textdegree C.


To a cooled mixture of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy) pyrazine (0.2 g, 0.570 mmol) and aryl acid (0.570 mmol) in dry DMF (3 ml), HBTU[2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate](0.261 g, 0.690 mmol), DIPEA[di isopropyl ethyl amine] (0.089 g ≅ 0.117 ml,0.690 mmol) and TEA (0.1 ml, 0.850 mmol) was added to basify the content at 0\textdegree C. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in Table-1a.
Table-1a: Physical constants of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substitution</th>
<th>MF</th>
<th>MW</th>
<th>Yield (%)</th>
<th>R_t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R CH₃</td>
<td>C₂₄H₂₄BrN₃O₂</td>
<td>466.37</td>
<td>79</td>
<td>0.52</td>
</tr>
<tr>
<td>1b</td>
<td>H₂C</td>
<td>C₂₄H₂₄BrN₃O₂</td>
<td>466.37</td>
<td>67</td>
<td>0.51</td>
</tr>
<tr>
<td>1c</td>
<td>N</td>
<td>C₂₂H₂₁BrN₄O₂</td>
<td>453.33</td>
<td>76</td>
<td>0.43</td>
</tr>
<tr>
<td>1d</td>
<td></td>
<td>C₂₂H₂₁BrN₄O₂</td>
<td>453.33</td>
<td>66</td>
<td>0.40</td>
</tr>
<tr>
<td>1e</td>
<td>OCH₃</td>
<td>C₂₄H₂₄BrN₃O₃</td>
<td>482.36</td>
<td>75</td>
<td>0.46</td>
</tr>
<tr>
<td>1f</td>
<td></td>
<td>C₂₄H₂₃BrN₃O₂</td>
<td>452.34</td>
<td>84</td>
<td>0.47</td>
</tr>
<tr>
<td>1g</td>
<td>NH O CH₃</td>
<td>C₂₅H₂₅BrN₄O₃</td>
<td>509.39</td>
<td>69</td>
<td>0.32</td>
</tr>
<tr>
<td>1h</td>
<td>R Br</td>
<td>C₂₄H₂₃Br₂N₃O₂</td>
<td>545.26</td>
<td>71</td>
<td>0.39</td>
</tr>
<tr>
<td>1i</td>
<td>H₂N</td>
<td>C₂₃H₂₂BrN₄O₂</td>
<td>546.25</td>
<td>68</td>
<td>0.35</td>
</tr>
<tr>
<td>1j</td>
<td>Br</td>
<td>C₂₃H₂₁BrClN₃O₂</td>
<td>486.78</td>
<td>82</td>
<td>0.42</td>
</tr>
</tbody>
</table>

TLC solvent system: E.A. : Hexane = 6 : 4
ANALYTICAL DATA

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl)methanone (1a). mp 146-148°C; IR (DRS): 3072, 3031, 2975, 1645, 1563, 1523, 1440, 1352, 1299, 1170, 1054, 883, 835, 749, 695 cm⁻¹; MS: m/z = 466 [M⁺]; Anal. Calcd for C₂₄H₂₄BrN₃O₂: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.70; H, 5.07; N, 8.90%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone (1b). mp 176-178°C; IR (DRS): 3083, 3015, 2852, 1652, 1586, 1520, 1480, 1365, 1254, 1169, 1063, 878, 743, 699 cm⁻¹; MS: m/z = 467 [M⁺+1]; Anal. Calcd for C₂₄H₂₄BrN₃O₂: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.40; H, 5.09; N, 8.91%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridine-4-yl) methanone (1c). mp 234-236°C; IR (DRS): 3095, 3012, 2883, 1654, 1593, 1534, 1454, 1356, 1266, 1164,1052, 890, 822, 723, 705 cm⁻¹; MS: m/z = 454 [M+1⁺]; Anal. Calcd for C₂₂H₂₁BrN₄O₂: C, 58.29; H, 4.67; N, 12.36. Found: C, 58.01; H, 4.50; N, 12.25%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (1d). mp 167-169 °C; IR (DRS): 3066(Ar, C-H str.), 3001(Ar, C-H str.), 2935(C-H str.), 1626(amide, C=O str.), 1531(Ar, C=C str.), 1446(Ar, C=C str.), 1346(C-H ben), 1294(C-Br str.), 1172(C-N str.), 1049(C-N str.), 1008(C-O-C str.), 829(C-H o,p, ben), 750(C-H o,p, ben) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ppm, 1.45-1.56(m, 2H, CH), 1.81-1.85(d, J=12.72 Hz, 1H, CH), 1.97-2.01(d, J=12.4 Hz, 1H, CH),2.17(m, 1H, CH), 2.84-2.90(t, 1H, CH), 3.10-3.96 (t, 1H, CH), 3.98-4.01(d, J=12.16 Hz, 1H, CH), 4.25-4.26(d, J=6.48 Hz, 2H, 2CH), 4.80-4.83 (d, J=12.24 Hz, 1H, CH), 7.35(m, 1H, ArH), 7.57-7.63(m, 3H, ArH), 7.77-7.83(m, 3H, ArH), 7.82-8.27(d, J=1.24 Hz, 1H, ArH), 8.46-8.46(d, J=1.24 Hz, 1H, ArH), 8.60(m, 1H, ArH). ) ¹³C NMR (100 MHz, CDCl₃): δ ppm, 28.53, 35.93, 42.75, 46.42, 70.40, 114.61, 118.27, 123.07, 127.66, 132.08, 134.93, 135.47, 137.22, 142.38, 144.26, 152.55, 159.10; MS: m/z = 452 [M-1⁺]; Anal. Calcd for C₂₂H₂₁BrN₄O₂: C, 58.01; H, 4.50; N, 12.23%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl) methanone (1e). mp 201-203°C; IR (DRS): 3070, 2999, 2918, 2852, 1726, 1627, 1581, 1531, 1444, 1274, 1173, 1246, 1168, 1045, 987, 889, 831, 800, 752, 707 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ppm, 1.39-1.42(m, 2H, CH), 1.80-2.01(m, 2H, CH), 2.11-2.14(m,
1H, CH), 2.83(m, 1H, CH), 3.03(m, 1H, CH), 3.82-3.85(d, J=11.84 Hz, 4H, OCH3, CH), 4.17-4.19(d, J=6.36 Hz, 2H, 2CH), 4.75-4.78(d, J= 11.64 Hz, 1H, CH), 6.94-6.99(m, 1H, ArH), 7.29-7.36(m, 1H,ArH), 7.58-7.60(d, J=8.48 Hz, 3H, ArH), 7.77-7.80(d, J=8.52 Hz, 3H, ArH), 8.16-8.16(d, J=1.08 Hz ,1H, ArH). 13C NMR (100 MHz, CDCl3): δ ppm, 29.71, 35.87, 35.98, 42.35, 46.32, 55.38, 70.36, 112.30, 115.40, 118.91, 123.10, 126.21, 127.67, 128.88, 129.61, 132.09, 135.38, 137.23, 142.80, 144.42, 156.59, 159.65, 170.32; MS: m/z = 483 [M+1]+; Anal. Calcd for C24H24BrN3O3: C, 59.76; H, 5.01; N, 8.71. Found: C, 59.55; H, 4.89; N, 8.60%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone (1f). mp 154-156°C; IR (DRS): 3087, 2958, 2832, 1684, 1585, 1456, 1269, 1175, 1036, 838, 796, 742, 693 cm^-1; MS: m/z = 452 [M]+; Anal. Calcd for C23H22BrN3O2: C, 61.07; H, 4.90; N, 9.29. Found: C, 61.01; H, 4.70; N, 9.04%.

N-(4-(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl) acetamide (1g). mp 235-237°C; IR (DRS): 3445, 3015, 2918, 2823, 1648 1610, 1545, 1445, 1355, 1290, 1115, 1020, 825, 796, 743, 698 cm^-1; MS: m/z = 509 [M]+; Anal. Calcd for C25H25BrN4O3: C, 58.95; H, 4.95; N, 11.00. Found: C, 58.19; H, 4.88; N, 10.91%.

(4-(Bromomethyl)phenyl)(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (1h). mp 157-159°C; IR (DRS): 3053, 2968, 2843, 1556, 1503, 1453, 1354, 1258,1135, 1032, 840, 799, 735, 689 cm^-1; MS: m/z = 546 [M]+; Anal. Calcd for C24H23Br2N3O2: C, 52.87; H, 4.25; N, 7.71. Found: C, 52.78; H, 4.14; N, 7.49%.

(2-Amino-5-bromophenyl)(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (1i). mp 196-198°C; IR (DRS): 3442, 3403, 3085, 2998, 2854, 1636, 1558, 1428, 1322, 1237, 1141, 1052, 835, 769, 733, 680 cm^-1; MS: m/z = 547 [M+1]^+; Anal. Calcd for C23H22Br2N4O2: C, 50.57; H, 4.06; N, 10.26. Found: C, 50.38; H, 3.97; N, 10.20%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(4-chlorophenyl) methanone (1j). mp 127-129°C; IR (DRS): 3052, 3015, 2963, 2846, 1652, 1563, 1458, 1352, 1236, 1169, 1046, 885, 834, 756, 701 cm^-1; MS: m/z = 487 [M+1]^+; Anal. Calcd for C23H21BrClN3O2: C, 56.75; H, 4.35; N, 8.63. Found: C, 56.52; H, 4.25; N, 8.53%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (1d).

IR Spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone (1e).
Mass spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (1d).

Mass spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(1e).
$^1$H NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (1d).

Expanded spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (1d).
$^1$H NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(1e).

Expanded spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(1e).
Studies on nitrogen containing heterocyclic…

$^{13}$C NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone ($1d$).

$^{13}$C NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone($1e$).
ANTIMICROBIAL ACTIVITY

Biological evaluation of (4-(((5-(4-(bromo phenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

All of the synthesized compounds (1a-j) were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.

**Minimal Inhibition Concentration [MIC]**

The main advantage of the *Broth Dilution Method* for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary and secondary screening.
2. The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.
4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
5. The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.
Methods used for primary and secondary screening

Each synthesized compounds were diluted in DMSO to obtain 2000 μg mL⁻¹ concentration, as a stock solution. Inoculum size for test strain was adjusted to 10⁸ cfu (colony forming unit) per milliliter by comparing the turbidity.

Primary screen: In primary screening 1000 μg mL⁻¹, 500 μg mL⁻¹ and 250 μg mL⁻¹ concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The compounds found active in primary screening were similarly diluted to obtain 200 μg mL⁻¹, 100 μg mL⁻¹, 50 μg mL⁻¹, 25 μg mL⁻¹, 12.5 μg mL⁻¹, and 6.250 μg mL⁻¹ concentrations.

Reading Result: The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10⁸ organism/mL.

The results obtained from antimicrobial susceptibility testing are depicted in Table 1b.
Table-1b: Antimicrobial activity of(4-((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Antibacterial Activity</th>
<th>Antifungal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram +ve Bacteria</td>
<td>Gram −ve Bacteria</td>
</tr>
<tr>
<td></td>
<td>S.aureus</td>
<td>S.pyogenus</td>
</tr>
<tr>
<td>1a</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>1b</td>
<td>125</td>
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<tr>
<td>1c</td>
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<td>1i</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>1j</td>
<td>125</td>
<td>250</td>
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</table>

MINIMAL INHIBITION CONCENTRATION

<table>
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<tr>
<th>Standard Drugs</th>
<th>S.aureus (microgramme/ml)</th>
<th>S.pyogenus (microgramme/ml)</th>
<th>E.coli (microgramme/ml)</th>
<th>P.aeruginosa (microgramme/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamycin</td>
<td>0.25</td>
<td>0.5</td>
<td>0.05</td>
<td>1</td>
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<tr>
<td>Ampicillin</td>
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<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Chloramphenicol</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>50</td>
<td>50</td>
<td>25</td>
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<tr>
<td>Norfloxacin</td>
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MINIMAL FUNGICIDAL CONCENTRATION

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<tr>
<th>Standard Drugs</th>
<th>C.Albicans (microgramme/ml)</th>
<th>A.Niger (microgramme/ml)</th>
<th>A.Clavatus (microgramme/ml)</th>
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<tbody>
<tr>
<td>Nystatin</td>
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<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Greseofulvin</td>
<td>500</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Part – A

[Part – I (Section-ii)]

Synthesis and biological evaluation of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones
SECTION-II
SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-METHOXY-3-METHYLPHENYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Many pyrazine derivatives have displayed diverse pharmacological activities. In view of our on going interest in the synthesis of some new 2-(piperidin-4-yl methoxy) pyrazine derivatives have been synthesized by the condensation of 2-(4-methoxy-3-methyl phenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. \(^1\)H NMR and \(^{13}\)C NMR were determined in CDCl\(_3\) solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.
See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of tert-butyl 4-(((5-(4-methoxy-3-methylphenyl)pyrazine-2-yl)oxy)methyl) piperidine-1-carboxylate.

A solution of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (4-methoxy-3-methylphenyl)boronic acid (0.660 g, 0.004 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K\(_2\)CO\(_3\) (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minute. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 6 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na\(_2\)SO\(_4\). The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.
[C] **Preparation of 2-(4-methoxy-3-methylphenyl)-5-(piperidin-4-ylmethoxy) pyrazine.**

A mixture of HCl(g) in dioxane (10 ml) and tert-butyl 4-(((5-(4-methoxy-3-methyl phenyl)pyrazine-2-yl)oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate were added into the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combined organic layers were washed with water followed by brine and dried over anhydrous Na₂SO₄. The solvent was evaporated under vacuum to give pure product. Yield: 66 %, mp 136-138°C.

[D] **General procedure for the preparation of (4-(((5-(4-methoxy-3-methyl phenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.**

To a cooled mixture of 2-(4-methoxy-3-methylphenyl)-5-(piperidin-4-ylmethoxy)pyrazine (0.2 g, 0.640 mmol) and aryl acid (0.640 mmol) in dry DMF(3ml), HBTU[2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.288 g, 0.760 mmol), DIPEA[diisopropyl ethyl amine], (0.098 g ≅ 0.129 ml,0.760 mmol) and TEA (0.11 ml, 0.960 mmol) was added to basify the content at 0°C. The reaction mixture was stirred for 10 hour at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in Table-2a.

[E] **Biological evaluation of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.**

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-2b.
Table-2a: Physical constants of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substitution</th>
<th>R</th>
<th>MF</th>
<th>MW</th>
<th>Yield (%)</th>
<th>R&lt;sub&gt;f&lt;/sub&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>–CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;29&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>431.52</td>
<td>82</td>
<td>0.52</td>
</tr>
<tr>
<td>2b</td>
<td>–H&lt;sub&gt;3&lt;/sub&gt;C</td>
<td></td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;29&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>431.52</td>
<td>72</td>
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<tr>
<td>2c</td>
<td>–N</td>
<td></td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;</td>
<td>418.48</td>
<td>73</td>
<td>0.43</td>
</tr>
<tr>
<td>2d</td>
<td>–N</td>
<td></td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>0.44</td>
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<tr>
<td>2e</td>
<td>–CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;29&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>431.52</td>
<td>80</td>
<td>0.46</td>
</tr>
<tr>
<td>2f</td>
<td>–</td>
<td></td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>2g</td>
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<td>474.55</td>
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<tr>
<td>2h</td>
<td>–Br</td>
<td></td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;28&lt;/sub&gt;BrN&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>510.42</td>
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<td>0.36</td>
</tr>
<tr>
<td>2i</td>
<td>–H&lt;sub&gt;2&lt;/sub&gt;N</td>
<td></td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;BrN&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>2j</td>
<td>–Cl</td>
<td></td>
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<td>451.94</td>
<td>77</td>
<td>0.46</td>
</tr>
</tbody>
</table>

TLC solvent system:- MeOH : CHCl<sub>3</sub> = 2 : 8
ANALYTICAL DATA

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone (2a). mp 150-152°C; IR (DRS): 3056, 2985, 2864, 1683, 1625, 1552, 1463, 1352, 1170, 780, 696, cm⁻¹; MS: m/z = 431 [M⁺]; Anal. Calcd for C₂₈H₂₉N₃O₃: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.09; H, 6.70; N, 9.66%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone (2b). mp 134-138°C; IR (DRS): 2989, 2949, 2856, 1699, 1681, 1629, 1541, 1465, 1340, 1172, 1028, 775, 651 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 1.17-1.41(m, 2H, CH), 1.71-1.79(m, 1H, CH), 1.94-1.99(m, 1H, CH), 2.11(m, 1H, CH), 2.24(s, 3H, CH₃), 2.30(s, 3H, CH₃), 2.81(m, 1H, CH), 2.99-3.05(m, 1H, CH), 3.43(d, 1H, CH), 3.85(s, 3H, OCH₃), 4.21-4.23(d, J = 6.32 Hz, 2H, 2CH), 4.69-4.72(d, J = 12.8 Hz, 1H, CH), 6.93-6.96(d, J = 8.36 Hz, 1H, ArH), 7.08-7.29(m, 4H, ArH), 7.74-7.76(d, J = 9.68 Hz, 2H, ArH), 8.21(s, 1H, ArH), 8.53(s, 1H, ArH). ¹³C NMR (100 MHz, DMSO): δ ppm 16.10, 18.46, 28.23, 28.75, 29.34, 35.29, 45.78, 46.31, 55.06, 69.69, 109.93, 124.44, 125.11, 125.55, 126.05, 127.82, 127.93, 128.30, 128.89, 133.30, 133.66, 136.43, 144.47, 157.83, 158.23, 168.63. MS: m/z = 431 [M⁺]; Anal. Calcd for C₂₆H₂₉N₃O₃: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.19; H, 6.56; N, 9.68%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridine-4-yl) methanone (2c). mp 140-144°C; IR (DRS): 3046, 2985, 2846, 1678, 1635, 1546, 1452, 1368,1166, 1045, 880, 835, 780, 754, 703 cm⁻¹; MS: m/z = 418 [M⁺]; Anal. Calcd for C₂₅H₂₆N₄O₅: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.32; H, 6.21; N, 13.29%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridine-2-yl) methanone (2d). mp 104-106°C; IR (DRS): 3027, 2978, 1835, 1666, 1564, 1456, 1378, 1089, 890, 834, 754, 699 cm⁻¹; MS: m/z = 418 [M⁺]; Anal. Calcd for C₂₅H₂₆N₄O₅: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.82; H, 6.18; N, 13.26%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(m-tolyl) methanone (2e). mp 96-98°C; IR (DRS): 3003(Ar, C-H str.), 2941(C-H str.), 2929(C-H str.), 2883(C-H str.), 2860(C-H str.), 1633(amide, C=O str.), 1533(Ar, C=C str.), 1456(Ar, C=C str.), 1346(C-H ben), 1170(C-N str.), 1066(C-O-C str.), 1026(C-O-C str.), 883(C-H o,p, ben), 812(C-H o,p, ben), 754(C-H o,p, ben), cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 1.24-1.31(m, 2H, CH), 1.79(m, 1H, CH), 1.91(m, 1H, CH), 2.08-2.13(m,
1H, CH), 2.24(s, 3H, CH3), 2.36(s, 3H, CH3), 2.80(m, 1H, CH), 3.06(m, 1H, CH), 3.67-3.71(d, J= 19.2 Hz, 1H, CH), 3.85(s, 3H, OCH3), 4.21-4.23(d, J= 6.44 Hz, 2H, 2CH), 4.60-4.65(d, J= 19.04 Hz, 1H, CH), 6.94-6.96(d, J= 8.32 Hz, 1H, ArH), 7.13-7.17(t, 2H, ArH), 7.21-7.23(d, J= 7.56 Hz, 1H, ArH), 7.27-7.31(t, 1H, ArH), 7.75-7.77(d, J= 9.32 Hz, 2H, ArH), 8.23-8.23 (d, J=0.92 Hz, 1H, ArH), 8.54-8.55(d, J= 0.88 Hz, 1H, ArH).

13C NMR (100 MHz, DMSO): δ ppm, 15.60, 20.94, 28.23, 28.75, 29.34, 35.27, 45.78, 46.31, 55.08, 69.73, 109.97, 123.40, 124.46, 126.02, 126.94, 127.83, 127.94, 127.97, 129.72, 133.68, 136.13, 136.30, 137.60, 144.45, 157.83, 158.25, 169.22; MS: m/z = 431 [M]+; Anal. Calcd for C26H29N3O3: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.17; H, 6.70; N, 9.69%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl)methanone (2f). mp 101-102°C; IR (DRS): 3083, 3015, 2956, 2863, 1688, 1635, 1525, 1470, 1342, 1162, 1010, 883, 764, 693 cm−1; MS: m/z = 417 [M]+; Anal. Calcd for C25H27N3O3: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.85; H, 6.25; N, 9.90%.

N-(4-(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide (2g). mp 189-190°C; IR (DRS): 3460, 3028, 2976, 2846, 1647, 1532, 1465, 1323, 1032, 1045, 838, 756, 704 cm−1; MS: m/z = 475 [M]+; Anal. Calcd for C27H30N4O4: C, 68.34; H, 6.37; N, 11.81. Found: C, 68.23; H, 6.33; N, 11.41%.

(4-(Bromomethyl)phenyl)(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (2h). mp 137-139°C; IR (DRS): 3091, 3027, 2923, 2856, 1641, 1523, 1470, 1347, 1056, 830, 745 cm−1; MS: m/z = 510 [M]+; Anal. Calcd for C26H28BrN3O3: C, 61.18; H, 5.53; N, 8.23. Found: C, 61.11; H, 5.19; N, 8.02%.

(2-Amino-5-bromophenyl)(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (2i). mp 135-136°C; IR (DRS): 3443, 3383, 3056, 2947, 2856, 1544, 1426, 1330, 1041, 830, 741, 631 cm−1; MS: m/z = 513 [M+2]+; Anal. Calcd for C25H27BrN3O3: C, 58.71; H, 5.32; N, 10.96. Found: C, 58.69; H, 5.06; N, 10.43%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(m-tolyl)methanone(2e).

Mass spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(2b).
Mass spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(m-tolyl)methanone(2e).

\[ m/z = 431 \]

\(^1\)H NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(2b).
Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(2b).
$^1$H NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(m-tolyl)methanone(2e).

Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(m-tolyl)methanone(2e).
Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(m-tolyl)methanone(2e).

\[ \begin{align*}
\text{13C NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(2b).}
\end{align*} \]
$^{13}$C NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(m-tolyl)methanone(2e).
### Table-2b: Antimicrobial activity of (4-(((5 -(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

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### MINIMAL FUNGICIDAL CONCENTRATION

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Synthesis and biological evaluation of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl) methanones
SECTION-III

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-FLUORO PYRIDIN-3-YL)PYRAZIN-2-YL)OXY)METHYL) Piperidin-1-YL)(ARYL) METHANONES

Pyrazine derivatives have been attracted widespread attention due to their diverse pharmacological properties. Looking to this, the synthesis of 2-(piperidin-4-ylmethoxy) pyrazine derivatives have been undertaken by the condensation of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ solution on a Bruker AC 400 MHz spectrometer. Purity of the synthesized compounds was checked by HPLC Agilent 1100 series. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of $\text{tert}$-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of $\text{tert}$-butyl 4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carboxylate.

A solution of $\text{tert}$-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (2-fluoropyridin-3-yl)boronic acid (0.620 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K$_2$CO$_3$ (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 7 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.
[C] Preparation of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine.

A mixture of HCl(g) in dioxane (10 ml) and tert-butyl 4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed in vacuo. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3), and the combine organic layers were washed with water followed by brine and dried over anhydrous Na₂SO₄. The solvent was evaporated under vacuum to give pure product. Yield: 56 %, mp 94-96°C.

[D] General procedure for the preparation of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

To a cooled mixture of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine (0.2 g, 0.690 mmol) and aryl acid (0.690 mmol) in dry DMF (3 ml), HBTU[2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.314 g, 0.830 mmol), DIPEA[diisopropyl ethyl amine], (0.107 g ≈ 0.141 ml, 0.830 mmol) and TEA (0.19 ml, 1.03 mmol) was added to basify the content at 0°C. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in Table-3a.

[E] Biological evaluation of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-3b.
Table-3a: Physical constants of \([(4-((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.\]

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<td>3g</td>
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TLC solvent system: E.A.: Hexane = 6 : 4
ANALYTICAL DATA

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone (3a). mp 92-94°C; IR (DRS): 3070, 2948, 2863, 1636, 1521, 1453, 1339, 1158, 1012, 842, 801, 746, 695 cm$^{-1}$; MS: m/z = 407 [M+1]$^+$; Anal. Calcd for C$_{23}$H$_{23}$FN$_4$O$_2$: C, 67.97; H, 5.70; N, 13.78. Found: C, 67.91; H, 5.45; N, 13.58%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone (3b). mp 86-87°C; IR (DRS): 3098, 3048, 2940, 2853, 1628, 1525, 1450, 1329, 1175, 1017, 880, 831,740 cm$^{-1}$; MS: m/z = 406 [M]+; Anal. Calcd for C$_{23}$H$_{23}$FN$_4$O$_2$: C, 67.97; H, 5.70; N, 13.78. Found: C, 67.88; H, 5.44; N, 13.59%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-4-yl) methanone (3c). mp 164-168°C; IR (DRS): 3044, 2925, 2858, 1627, 1545, 1468, 1316, 1170, 1033, 820, 768,720 cm$^{-1}$; MS: m/z = 394 [M+1]$^+$; Anal. Calcd for C$_{21}$H$_{20}$FN$_5$O$_2$: C, 64.11; H, 5.12; N, 17.80. Found: C, 64.02; H, 4.96; N, 17.64%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (3d). mp 260-262°C; IR (DRS): 3087, 3051, 2948, 2891, 1620, 1542, 1478, 1298, 1150, 1031, 880, 804, 721 cm$^{-1}$; MS: m/z = 394 [M+1]$^+$; Anal. Calcd for C$_{21}$H$_{20}$FN$_5$O$_2$: C, 64.11; H, 5.12; N, 17.80. Found: C, 64.05; H, 5.01; N, 17.63%.


(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone (3f). mp 95-96°C; IR (DRS): 3078, 3042, 2935, 2860, 1610, 1564, 1488,1250, 1320, 1112, 1007, 810, 768, 737 cm$^{-1}$; MS: m/z = 392 [M]$^+$; Anal. Calcd for C$_{22}$H$_{21}$FN$_4$O$_2$: C, 67.33; H, 5.39; N, 14.28. Found: C, 67.18; H, 5.04; N, 14.27%.

N-(4-((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl) phenylacetamide (3g). mp 212-214°C; IR (DRS): 3329, 3248, 3024,2914, 2866, 1689, 1645, 1612, 1531, 1448, 1350, 1263, 1176,1010, 879, 765, 711 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): δ ppm, 1.24-1.36(m, 2H, CH), 1.86-1.92(m, 2H, CH), 2.08(s, 3H, OCH$_3$), 2.11-2.16(m, 1H, CH), 2.85-3.08(m, 2H,CH), 3.90-3.93(d, $J$= 13.64 Hz, 1H, CH), 4.24-
4.26(d, J=6.4 Hz, 2H, 2CH),4.55-4.58(d, J=13.6 Hz, 1H, CH), 7.30-7.32(d, J= 8.56 Hz, 2H, ArH), 7.40-7.43(d, J=2.0 Hz, J= 2.04 Hz, 1H, ArH), 7.63-7.65(d, J= 8.52 Hz, 2H, ArH),8.25-8.26(d, J= 1.28 Hz, 1H, ArH), 8.28-8.32( m, 1H, ArH), 8.89-8.90(d, J=1.36 Hz, 1H, ArH), 9.35-9.36(d, J= 1.36 Hz, 1H ,ArH), 10.04(s, 1H, NH). 13C NMR (100 MHz, DMSO): δ ppm,13.86, 22.11, 23.94, 28.52, 28.73, 28.88, 29.03, 31.31, 35.27, 69.84, 105.39, 114.16, 118.34, 122.27, 125.21, 127.43, 129.83, 130.27, 133.87, 135.39, 138.81, 139.83, 140.31, 141.14, 150.6, 168.38, 169.00.; MS: m/z = 449 [M]+; Anal. Calcd for C24H24FN5O3: C, 64.13; H, 5.38; N, 15.58. Found: C, 64.02; H, 5.19; N, 15.43%.

(4-(Bromomethyl)phenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-yl)methanone (3h). mp 79-81°C; IR (DRS): 3101, 3038, 2940, 2853, 1618, 1525, 1450, 1329, 1247,1175, 1017, 840, 768, 703, 635 cm⁻¹; MS: m/z = 486 [M+1]⁺; Anal. Calcd for C23H22BrFN4O2: C, 56.92; H, 4.57; N, 11.54. Found: C, 56.80; H, 4.48; N, 11.52%.

(2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (3i). mp 245-247°C; IR (DRS): 3236(-NH₂ str.), 3034(Ar,C-H str.), 2924(C-H str.), 2850(C-H str.),1707(amide, C=O str.),1624(amide, C=O str.),1575(Ar, C=C str.),1506(Ar, C=C str.),1450(Ar, C=C str.),1388(C-H ben),1246(C-Br str.),1174(C-F str.),1074(C-N str.),1003(C-O-C str.),893(C-H, o,p, ben), 852(C-H, o,p, ben), 802(C-H, o,p, ben),740(C-H o,p, ben),704(C-C o,p, ben)cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.23-1.40 (m, 2H, 2CH), 1.91-1.94 (m, 1H, CH), 2.11-2.14 (m, 1H, CH), 2.48-2.54 (m, 1H, CH), 2.94-2.99 (m, 1H, CH), 3.28-3.37 (m, 1H, CH), 3.68-3.71 (d, J=12.48 Hz, 1H, CH), 4.23-4.24 (d, J=6.52 Hz, 2H, 2CH), 4.54-4.57 (d, J=12.84 Hz, 1H, CH), 5.30 (s, 2H, NH₂), 6.67-6.69 (d, J=8.52 Hz, 1H, ArH), 7.20-7.21 (m, 2H, ArH), 7.41-7.43 (m, 1H, ArH), 7.57-7.58 (m, 1H, ArH), 7.79-7.80 (m, 1H, ArH), 8.01-8.02 (d, J=1.24 Hz, 1H, ArH), 8.16-8.17 (d, J=1.20 Hz, 1H, ArH);MS: m/z = 486 [M⁺]; Anal. Calcd for C22H21BrFN4O2: C, 54.33; H, 4.35; N, 14.40. Found: C, 54.06; H, 4.02; N, 14.33%.

(4-Chlorophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (3j). mp 170-171°C; IR (DRS): 3066, 3053, 2978, 2851, 1622, 1510, 1442, 1346,1245, 1165, 1037, 836, 796, 702 cm⁻¹; MS: m/z = 427 [M+1]⁺; Anal. Calcd for C22H20ClFN4O2: C, 61.90; H, 4.72; N, 13.12. Found: C, 61.37; H, 4.65; N, 12.91%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (3i).

IR Spectrum of N-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl)acetamide (3g).
Mass spectrum of \( N-(4-(4-(((5-(2\text{-}fluoropyridin-3\text{-}yl})pyrazin-2\text{-}yl)oxy)methyl)piperidine-1\text{-}carbonyl)phenyl)acetamide(3g). \)

\[
\text{m/z}=449
\]

\(^1\text{H} \) NMR spectrum of \( (2\text{-}Amino-5\text{-}bromophenyl)(4-(((5-(2\text{-}fluoropyridin-3\text{-}yl})pyrazin-2\text{-}yl)oxy)methyl)piperidin-1\text{-}yl)\)methanone(3i).
Studies on nitrogen containing heterocyclic…

Expanded spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (3i).

Expanded spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (3i).
$^1$H NMR spectrum of $N$-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl)acetamide(3g).

Expanded spectrum of $N$-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl)acetamide(3g).
$^{13}$C NMR spectrum of $N$-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl)acetamide (3g).
Table-3b: Antimicrobial activity of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

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<th>Antifungal Activity</th>
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**MINIMAL INHIBITION CONCENTRATION**

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**MINIMAL FUNGICIDAL CONCENTRATION**

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Part – A

[Part – I (Section-iv)]

Synthesis and biological evaluation of Aryl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidine-1-yl)methanones.
SECTION-IV

SYNTHESIS AND BIOLOGICAL EVALUATION OF ARYL(4-(((5-(m-TOLYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)METHANONES

Pyrazine play an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. In view of these reports, we have synthesized 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(piperidin-4-ylmethoxy)-5-(m-tolyl)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreement with the structures assigned.

[A] Preparation of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.
See, Part-A, Part-I, Section-I Experimental Section [D].

[B] Preparation of tert-butyl 4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.
A solution of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution 1-benzothiophen-3-yl-3-boronic acid (0.594 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K$_2$CO$_3$ (10 ml, 0.02 mol) in water was added drop wise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 5 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(piperidin-4-ylmethoxy)-5-(m-tolyl)pyrazine.
A mixture of HCl$_{10}$ in dioxane (10 ml) and tert-butyl 4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for over-night
(monitored by TLC), and the solvent was removed in vacuo. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combine organic layers were washed with water followed by brine and dried over anhydrous Na₂SO₄. The solvent was evaporated under vacuum to give pure product. Yield: 69 %, mp 87-88°C.

[D] General procedure for the preparation of Aryl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanones.

To a cooled mixture of 2-(piperidin-4-ylmethoxy)-5-(m-tolyl)pyrazine (0.2 g, 0.700 mmol) and aryl acid (0.700 mmol) in dry DMF (3 ml), HBTU [2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.318 g, 0.840 mmol), DIPEA[di isopropyl ethyl amine], (0.108 g ≈ 0.142 ml,0.840 mmol) and TEA (0.21 ml, 1.05 mmol) was added to basify the content at 0°C. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC). The reaction mixture was poured onto crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in Table-4a.

[E] Biological evaluation of Aryl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine -1-yl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-4b.
**Table-4a:** Physical constants of Aryl(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-yl)methanones.

![Chemical structure](image)

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<th>MW</th>
<th>Yield (%)</th>
<th>R	extsubscript{f} value</th>
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TLC solvent system:- E.A. : Hexane = 5 : 5
ANALYTICAL DATA

**P-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (4a).**
mp 124-126°C; IR (DRS): 3083, 3049, 2953, 2848, 1678, 1531, 1444, 1329, 1176, 1016, 854, 792, 748, 701 cm⁻¹; MS: m/z = 401 [M⁺]; Anal. Calcd for C$_{25}$H$_{27}$N$_3$O$_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.11; H, 6.72; N, 10.40%.

**O-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (4b).**
mp 118-120 °C; IR (DRS): 3049(Ar, C-H Str.), 2914 (C-H Str.), 2860 (C-H Str.), 1631 (amide, C=O Str.), 1599 (Ar, C=C Str.), 1535 (Ar, C=C Str.), 1444 (Ar, C=C Str.), 1340 (C-H ben), 1201 (C-N Str.), 1168 (C-N Str.), 1006 (C-O-C Str.), 900 (C-H o,p, ben), 767 (C-H o,p, ben); $^1$H NMR(400 MHz (DMSO): δ ppm 1.17-1.39(m, 2H, CH), 1.71-1.79(m, 1H, CH), 1.94-1.97(m, 1H, CH), 2.11-2.13(m, 1H, CH), 2.40(s, 3H, CH$_3$), 2.78-2.81(m, 1H, CH), 2.98-3.05(m, 1H, CH), 3.42-3.43(d, J = 6.4 Hz, 1H, CH), 4.23-4.24(d, J = 6.4 Hz, 2H, 2CH), 4.69-4.72(d, J = 13.04 Hz, 1H, CH), 7.08-7.10(d, J = 7.0 Hz, 1H, ArH), 7.16-7.29(m, 5H, ArH), 7.32-7.35(t, 1H, ArH), 7.72-7.77(t, 1H, ArH), 8.26(s, 1H, ArH), 8.60(s, 1H, ArH). $^{13}$C NMR (100 MHz, DMSO): δ ppm, 18.46, 18.65, 21.12, 28.22, 28.73, 29.34, 35.15, 35.27, 45.76, 46.30, 69.79, 122.80, 125.13, 125.24, 125.47, 125.56, 126.30, 128.30, 128.46, 129.02, 129.89, 130.03, 133.30, 133.54, 133.99, 135.86, 136.44, 137.09, 137.83, 144.40, 158.73, 168.62.; MS: m/z = 401 [M⁺]; Anal. Calcd for C$_{25}$H$_{27}$N$_3$O$_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.19; H, 6.64; N, 10.36%.

**Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (4c).**
mp 84-86 °C; IR (DRS): 3049 , 2912 , 2852, 1631, 1533, 1464, 1338, 1278, 1168, 1018 , 798, 727 cm⁻¹. $^1$H NMR (400 MHz CDCl$_3$): δ ppm 1.21-1.28(m, 1H, CH), 1.34-1.43(m, 1H, CH), 1.76-1.79(d, J = 12.64 Hz, 1H, CH), 2.0 2.09(m, 1H, CH), 2.35(s, 3H, CH$_3$), 2.74-2.80(t, 1H, CH), 2.98-3.04(t, 1H, CH), 3.59-3.62(d, J = 12.96 Hz, 1H, CH), 4.17-4.19(d, J = 6.0 Hz, 2H, 2CH), 4.69-4.72(d, J = 12.2 Hz, 1H, CH), 7.13-7.15(d, J = 7.44 Hz, 1H, ArH), 7.26-7.30(m, 1H, ArH), 7.59-7.70(m, 2H, ArH), 8.20(s, 1H, ArH), 8.40(s, 1H, ArH), 8.58-8.63(t, 2H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$): δ ppm, 21.56, 28.48, 29.58, 29.70, 35.87, 35.90, 41.92, 47.34, 70.01, 70.06, 121.09, 123.23, 123.52, 126.92, 128.44, 129.54, 132.00, 134.61, 134.94, 136.37, 137.45, 138.68, 143.84, 145.66, 147.80, 150.31, 150.70, 159.04, 167.71; MS: m/z = 388 [M⁺]; Anal. Calcd for C$_{23}$H$_{24}$N$_4$O$_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.09; H, 6.10; N, 14.13%.
Studies on nitrogen containing heterocyclic...

Pyridin-2-yl(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (4d). mp 100-102°C; Purity by HPLC: 88 %; IR (DRS): 3078, 3011, 2933, 2908, 1656, 1533, 1465, 1344, 1172, 1010, 888, 831, 748, 699 cm⁻¹; MS: m/z = 489 [M+1]⁺; Anal. Caled for C₂₃H₂₄N₄O₂: C, 71.11; H, 6.23; N, 14.42. Found: C, 70.86; H, 6.12; N, 14.36%.

(3-Methoxyphenyl)(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone (4e). mp 98-99°C; IR (DRS): 3098, 3054, 2879, 1677, 1556, 1527, 1440, 1327, 1166, 1014, 848, 799, 747, 699 cm⁻¹; MS: m/z = 417 [M⁺]; Anal. Caled for C₂₃H₂₇N₃O₃: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.66; H, 6.40; N, 10.04%.

Phenyl(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone (4f). mp 73-75°C; IR (DRS): 3061, 3025, 2958, 2871, 1668, 1548, 1421, 1314, 1151, 1038, 845, 799, 736 cm⁻¹; MS: m/z = 387 [M⁺]; Anal. Caled for C₂₄H₂₅N₃O₂: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.16; H, 6.28; N, 10.67%.

N-(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxy)phenyl acetamide (4g). mp 114-116°C; IR (DRS): 3457, 3042, 2946, 2821, 1688, 1556, 1443, 1331, 1224, 1157, 1032, 842, 805, 796, 748 cm⁻¹; MS: m/z = 445 [M⁺]; Anal. Caled for C₂₆H₂₈N₄O₃: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.15; H, 6.31; N, 12.44%.

(4-(Bromomethyl)phenyl)(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone (4h). mp 69-71°C; IR (DRS): 3105, 3048, 2951, 2820, 1676, 1530, 1455, 1323, 1112, 1041, 834, 769, 698, 621 cm⁻¹; MS: m/z = 481 [M+1]⁺; Anal. Caled for C₂₅H₂₆BrN₃O₂: C, 62.50; H, 5.46; N, 8.75. Found: C, 62.39; H, 5.19; N, 8.54%.

(2-Amino-5-bromophenyl)(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone (4i). mp 160-161°C; IR (DRS): 3483, 3450, 3020, 2940, 2843, 1696, 1542, 1450, 1320, 1330, 1116, 1018, 856, 788, 716, 631 cm⁻¹; MS: m/z = 482 [M⁺]; Anal. Caled for C₂₅H₂₆BrN₄O₂: C, 59.88; H, 5.23; N, 11.64. Found: C, 59.84; H, 5.20; N, 11.09%.

(4-Chlorophenyl)(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone (4j). mp 106-108°C; IR (DRS): 3125, 3083, 2910, 2830, 1629, 1515, 1443, 1334, 1241, 1118, 1019, 821, 788, 731, 670 cm⁻¹; MS: m/z = 422 [M⁺]; Anal. Caled for C₂₄H₂₄ClN₃O₂: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.10; H, 5.70; N, 9.59%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of O-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone(4b).

IR Spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone(4c).
Mass spectrum of $O$-tolyl(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone(4b).

Mass spectrum of Pyridin-4-yl(4-((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone(4c).
$^1$H NMR spectrum of $O$-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone(4b).

Expanded spectrum of $O$-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone(4b).
Studies on nitrogen containing heterocyclic...

Expanded spectrum of \( O\text{-tolyI}(4-((5\text{-}(m\text{-tolyI})\text{pyrazin-2-yl})\text{oxy})\text{methyl})\text{piperidin-1-yl}) \text{methanone} (4b). \)

\[\text{NMR spectrum of Pyridin-4-yl}(4-((5\text{-}(m\text{-tolyI})\text{pyrazin-2-yl})\text{oxy})\text{methyl})\text{piperidin-1-yl})\text{methanone} (4c).\]

\(^1\text{H NMR spectrum of Pyridin-4-yl}(4-((5\text{-}(m\text{-tolyI})\text{pyrazin-2-yl})\text{oxy})\text{methyl})\text{piperidin-1-yl})\text{methanone} (4c).\)
Expanded spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone (4c).

Expanded spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone (4c).
$^{13}\text{C}$ NMR spectrum of $O$-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone(4b).

$^{13}\text{C}$ NMR spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone(4c).
### Table-4b: Antimicrobial activity of Aryl((5-((5-(m-toly1)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanones.

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**MINIMAL INHIBITION CONCENTRATION**

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**MINIMAL FUNGICIDAL CONCENTRATION**

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Part – A

[Part – I (Section-v)]

Synthesis and biological evaluation of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones
SECTION-V
SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-METHOXY PHENYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Pyrazine plays an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. In view of these reports, we have synthesize 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(2-methoxy-phenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, $^1$H NMR, $^{13}$C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.
EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. $^1$H NMR and $^{13}$C NMR were determined in CDCl$_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of tert-butyl 4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

A solution of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (2-methoxyphenyl)boronic acid (0.664 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K$_2$CO$_3$ (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 5 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(2-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazine.

A mixture of HCl(g) in dioxane (10 ml) and tert-butyl 4-(((5-(2-methoxy phenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxilate was stirred at room temperature for
overnight (monitored by TLC), and the solvent was removed \textit{in vacuo}. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combine organic layers were washed with water followed by brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under vacuum to give pure product. Yield: 62 %, mp 71-72 °C.

[D] \textbf{General procedure for the preparation of (4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.}

To a cooled mixture of 2-(2-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazine (0.2 g, 0.700 mmol) and aryl acid (0.700 mmol) in dry DMF (3 ml), HBTU[2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate](0.318 g, 0.840 mmol), DIPEA[di isopropyl ethyl amine] (0.108 g ≅ 0.142 ml,0.840 mmol) and TEA (0.21 ml, 1.05 mmol) was added to basify the content at 0°C. The reaction mixture was stirred for 10 hour at room temperature (monitored by TLC). The reaction mixture was poured onto crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in Table-5a.

[E] \textbf{Biological evaluation of (4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.}

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in Table-5b.
Table-5a: Physical constants of (4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

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<th>MW</th>
<th>Yield (%)</th>
<th>R&lt;sub&gt;f&lt;/sub&gt; value</th>
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<td>0.53</td>
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<td>5b</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C</td>
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<td>417.50</td>
<td>70</td>
<td>0.51</td>
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<tr>
<td>5c</td>
<td>N</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;32&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>5d</td>
<td></td>
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TLC solvent system: E.A.: Hexane = 6 : 4
ANALYTICAL DATA

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone (5a). mp 102-104°C; IR (DRS): 3089, 3039, 2933, 2858, 1618, 1531, 1444, 1329, 1211,1176, 1016, 854, 788, 699 cm⁻¹; MS: m/z = 417 [M⁺]; Anal. Calcd for C_{25}H_{27}N_{3}O_{3}: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.11; H, 6.41; N, 10.01%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone (5b). mp 147-149°C; IR (DRS): 3078, 2958, 2858, 1634, 1525, 1478, 1278, 1054, 888, 841, 754, 703 cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 1.18-1.40(m, 2H, CH), 1.74-1.77(d, J=12.12 Hz, 1H, CH), 1.96-1.99(d, J=12.12 Hz, 1H, CH), 2.12-2.15(m, 1H, CH), 2.23(s, 3H, CH₃), 2.82(t, 1H, CH), 3.0-3.06(t, 1H, CH), 3.44-3.46(d, J=7.2 Hz, 1H, CH), 3.88(s, 3H, OCH₃), 4.24-4.25(d, J=5.92 Hz, 2H, 2CH ), 4.71-4.74(d, J=12.92 Hz, 1H ,CH), 7.03-7.10(m, 2H , ArH), 7.19-7.29(m, 4H, ArH), 7.34-7.38(t, 1H ,ArH), 7.74-7.76(d, J=7.32 Hz, 1H, ArH), 8.27 (s, 1H, ArH), 8. 65(s, 1H, ArH). ¹³C NMR (100 MHz, DMSO): δ ppm,18.46, 18.63, 28.22, 28.73, 29.33, 35.29, 45.77, 55.23, 69.67, 111.19, 120.55, 125.01, 125.53, 128.28, 129.60, 129.87, 130.02, 133.82, 136.34, 141.07, 142.80, 156.26, 158.03, 168.75.MS: m/z = 418 [M+1⁺]; Anal. Calcd for C_{25}H_{27}N_{3}O_{3}: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.90; H, 6.30; N, 9.88%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(piridin-4-yl) methanone (5c). mp 63-65°C; Purity by HPLC: 89 %; IR (DRS): 3078, 2958, 2858, 1634, 1525, 1478, 1278, 1054, 888, 841, 754, 703 cm⁻¹; MS: m/z = 404 [M⁺]; Anal. Calcd for C_{23}H_{24}N_{4}O_{3}: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.10; H, 5.90; N, 13.73%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone (5d). mp 111-112°C; Purity by HPLC: 88 %; IR (DRS): 3081, 3054, 2933, 2908, 1626, 1533, 1465, 1344, 1172, 1010, 878, 831, 748, 699 cm⁻¹; MS: m/z = 405 [M+1⁺]; Anal. Calcd for C_{23}H_{24}N_{4}O_{3}: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.27; H, 5.88; N, 13.72%.

(3-Methoxyphenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone (5e). mp 116-118°C IR (DRS): 3108, 3064, 3015, 2924, 2879, 1627, 1556, 1527, 1440, 1327, 1166, 1014, 831, 798, 727, 676 cm⁻¹; MS: m/z = 433 [M⁺]; Anal. Calcd for C_{25}H_{27}N_{3}O_{4}: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.20; H, 6.23; N, 9.50%.
Studies on nitrogen containing heterocyclic…

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxygeny)methyl)piperidin-1-yl)(phenyl)methanone (5f). mp 173-175°C; IR (DRS): 3085, 3047, 2938, 2871, 1636, 1548, 1421, 1314, 1151, 1018, 888, 834, 746, 703 cm⁻¹; MS: m/z = 403 [M]+; Anal. Calcd for C₂₄H₂₅N₃O₃: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.40; H, 6.18; N, 10.37%.

N-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxygeny)methyl)piperidin-1-carbonyl)phenyl)acetamide (5g). mp 129-131°C; IR (DRS): 3416(N-H str.), 3173(Ar, C-H str.), 3097(Ar, C-H str.), 3043(Ar, C-H str.), 2937(C-H str.), 2854(C-H str.), 1691(amide, C=O str.), 1599(Ar, C=C str.), 1531(Ar, C=C str.), 1496(Ar, C=C str.), 1338(C-H ben), 1257(C-H ben), 1172(C-N str.), 1020(C-O-C str.), 758(C-H o.p. ben) cm⁻¹; ¹H NMR (400 MHz, DMSO): δ ppm 1.24-1.36(m, 2H, CH), 1.86-1.92(m, 2H, CH), 2.08(s, 3H, OCH₃), 2.11-2.16(m, 1H, CH), 2.85-3.08(m, 2H, CH), 3.83-3.93(m, 4H, OCH₃, CH), 4.24-4.26(d, J=6.4 Hz, 2H, 2CH), 4.55-4.58(d, J=13.0 Hz, 1H, CH), 7.03-7.09(m, 2H, ArH), 7.30-7.39(m, 3H, ArH), 7.74-7.76(d, d J= 1.56 Hz, 1.48 Hz, 1H, ArH), 8.28-8.29(d, J=1.08 Hz, 1H, ArH), 8.65-8.66(d, J= 1.16 Hz, 1H, ArH), 10.0(s, 1H, NH). ¹³C NMR (100 MHz, DMSO): δ ppm, 22.17, 23.92, 35.29, 55.29, 69.75, 111.29, 118.37, 120.57, 125.03, 127.41, 129.64, 130.04, 130.26, 133.87, 140.30, 141.08, 142.79, 156.30, 158.09, 168.38, 169.06. MS: m/z = 460 [M]+; Anal. Calcd for C₂₆H₂₈N₄O₄: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.76; H, 6.02; N, 12.04%.

(4-(Bromomethyl)phenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxygeny)methyl)piperidin-1-yl)methanone (5h). mp 90-92°C; IR (DRS): 3048, 2951, 2820, 1636, 1530, 1455, 1323, 1112, 1041, 824, 621 cm⁻¹; MS: m/z = 497 [M+1]+; Anal. Calcd for C₂₅H₂₆BrN₃O₃: C, 60.49; H, 5.28; N, 8.47. Found: C, 60.39; H, 5.19; N, 8.42%.

(2-Amino-5-bromophenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxygeny)methyl)piperidin-1-yl)methanone (5i). mp 239-241°C; IR (DRS): 3483, 3410, 3083, 3043, 2940, 2843, 1616, 1542, 1450, 1320, 1330, 1116, 1018, 780, 703, 631 cm⁻¹; MS: m/z = 498 [M+1]+; Anal. Calcd for C₂₅H₂₇BrN₄O₂: C, 57.95; H, 5.07; N, 11.26. Found: C, 57.02; H, 5.02; N, 11.22%.

(4-Chlorophenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxygeny)methyl)piperidin-1-yl)methanone (5j). mp 167-169°C; IR (DRS): 3083, 3010, 2954, 2830, 1629, 1515, 1443, 1334, 1241, 1118, 1019, 841, 768, 690 cm⁻¹; MS: m/z = 464 [M+1]+; Anal. Calcd for C₂₅H₂₆ClN₃O₂: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.50; H, 5.46; N, 9.59%.
SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

IR Spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(5b).

IR Spectrum of N-(4-((4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide(5g).
Mass spectrum of (4-((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone (5b).

Mass spectrum of N-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl) phenyl)acetamide (5g).
$^1$H NMR spectrum of (4-((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone (5b).

Expanded spectrum of (4-((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone(5b).
Expanded spectrum of (4-((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone(5b).

$^1$H NMR spectrum of N-(4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide(5g).
Studies on nitrogen containing heterocyclic…

Expanded spectrum of $N$-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide (5g).

Expanded spectrum of $N$-(4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide (5g).
$^{13}$C NMR spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone (5b).

$^{13}$C NMR spectrum of $N$-(4-((4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl) phenyl)acetamide (5g).
Table-5b: Antimicrobial activity of (4-((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl) piperidin-1-yl)(aryl)methanones.

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**MINIMAL INHIBITION CONCENTRATION**

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**MINIMAL FUNGICIDAL CONCENTRATION**

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