JSR Publications

Available Online

J. Sci. Res. **18** (2), 339-353 (2026)

JOURNAL OF SCIENTIFIC RESEARCH

www.banglajol.info/index.php/JSR

An Efficient Multicomponent Reaction for the Synthesis of New Benzofuran-pyrazole Hybrids: In Situ Approach and Antioxidant Activity

H. B. Vasveliya[1,2], J. H. Pandya[2*], H. K. Tilavat[3], A. J. Jivani[3]

[1]Department of Chemistry, D K V Arts and Science College, Jamnagar 361 008, Gujarat, India

[2]Department of Chemistry, Kotak Institute of Science, Rajkot, 360001, Gujarat, India

[3]Department of Chemistry, Saurashtra University, Rajkot 360005, Gujarat, India

Received 24 April 2025, accepted in final revised form 11 November 2025

Abstract

A one-pot, base-assisted method was used to synthesise tetrahydrobenzofuran-pyrazole derivatives (4a-4j) in acetonitrile under reflux utilising 4-(1*H*-pyrazol-1-yl)benzaldehyde, 5,5-dimethylcyclohexane-1,3-dione, and phenacyl bromides. After rigorously optimising catalysts, solvents, and reaction conditions, Et_3N with pyridine in acetonitrile gave high yield in 6 h. After substrate scope analysis, 4-methoxy, 3,4-dimethoxy, and 3,4,5-trimethoxy derivatives failed to produce stable products due to steric and electronic effects while 4-thiomethyl phenacyl bromide decomposed and lacrimated due to its instability. Synthesised compounds' antioxidant potential was evaluated using the DPPH assay. The strongest radical-scavenging activity was found in 4-nitro (4a, IC_{50}= 12.90 µM) and 4-ethyl (4i, IC_{50}= 14.50 µM) derivatives, equivalent to ascorbic acid (IC_{50} = 12.10 µM. However, halogen-substituted derivatives showed moderate to weak action, with 4-fluoro (4d, IC_{50} = 56.01 µM) being the least effective.

Keywords: Multicomponent reactions (MCRs); Tetrahydrobenzofuran-pyrazole derivatives; Antioxidant activity; Heterocyclic frameworks.

doi: https://dx.doi.org/10.3329/jsr.v18i2.81246 J. Sci. Res. **18** (2), 339-353 (2026)

1. Introduction

Multicomponent reactions (MCRs) are chemical reactions that involve the simultaneous interaction of three or more reactants to form a single product or a set of products in one step [1]. These reactions are highly efficient, offering the advantage of building complexity in a single operation, reducing the number of steps required in traditional synthesis methods [2,3]. MCRs are widely used in organic chemistry, particularly in the synthesis of pharmaceuticals, agrochemicals, and complex natural products, as they allow for rapid diversification of molecular structures with minimal waste and high selectivity [4-6].

* *Corresponding author:* jhpandya@gmail.com

Nitrogen- and oxygen-bearing compounds are essential in organic chemistry due to their wide range of reactivity and biological significance [7]. Nitrogen-containing heterocycles, like pyrazole, play a crucial role in drug discovery, as they often exhibit diverse biological activities such as anti-inflammatory, antimicrobial, and anticancer effects [8-11]. Oxygen-containing heterocycles, such as tetrahydrobenzofuran, are similarly valuable, particularly [12-14] in the synthesis of natural products and pharmaceutical agents. The presence of these atoms within a ring structure can profoundly influence a compound's stability, reactivity, and overall chemical behaviour, making them key scaffolds in various chemical and medicinal applications [15,16]. Tetrahydrobenzofuran is a bicyclic compound consisting of a benzene ring fused with a tetrahydrofuran (THF) ring. The THF ring is an oxygen-containing heterocycle, and its inclusion imparts interesting chemical properties, such as solubility in organic solvents and the potential for further functionalization [17,18]. Tetrahydrobenzofuran derivatives are commonly explored in medicinal chemistry due to their potential for interaction with biological targets, including their use in neuroactive compounds and other therapeutic agents. These compounds are also found in natural products, contributing to their importance in synthetic chemistry [19]. Pyrazole is a five-membered, nitrogen-containing heterocycle known for its versatility and wide range of biological activities. The two nitrogen atoms within the pyrazole ring make it an important building block in the design of pharmaceuticals [20]. Pyrazole derivatives are recognized for their roles in the treatment of inflammatory diseases, cancer, and infections. Their ability to form stable complexes with metal ions and their reactivity with a variety of electrophiles make pyrazoles attractive candidates for drug development and synthetic chemistry [21-23].

The combination of various heterocycles into a single molecule creates a novel hybrid structure that holds promise for drug development [24]. The oxygen and nitrogen bearing adducts can provide solubility and structural rigidity and offer specific interactions with biological targets. This combination could result in compounds with enhanced pharmacological profiles, showing potential in various therapeutic areas such as anti-inflammatory, anticancer, or antimicrobial treatments [25,26]. Researchers are increasingly interested in such fused heterocyclic systems for their ability to offer new mechanisms of action and increased potency compared to single heterocyclic counterparts [27]. Fig. 1 illustrates representative examples of clinically used drugs containing heteroaryl scaffolds such as pyrazoles, and benzofurans which are widely recognized for their pharmacological versatility. Compounds like Celecoxib (a COX-2 inhibitor), Antipyrine (an analgesic and antipyretic), Edaravone (a neuroprotective agent), and Amiodarone (an antiarrhythmic drug) highlight the therapeutic significance of pyrazole and benzofuran derivatives. Similarly, heteroaryl frameworks such as those found in Benzbromarone (a uricosuric agent) and Ebselen (an organoselenium compound with antioxidant properties) emphasize the importance of fused heterocycles in medicinal chemistry. These scaffolds contribute to diverse biological activities including anti-inflammatory, antioxidant, cardiovascular, and neuroprotective effects. The structural diversity and clinical relevance of these marketed

drugs underline the rationale for designing and synthesizing new heteroaryl-based molecules [28-31].

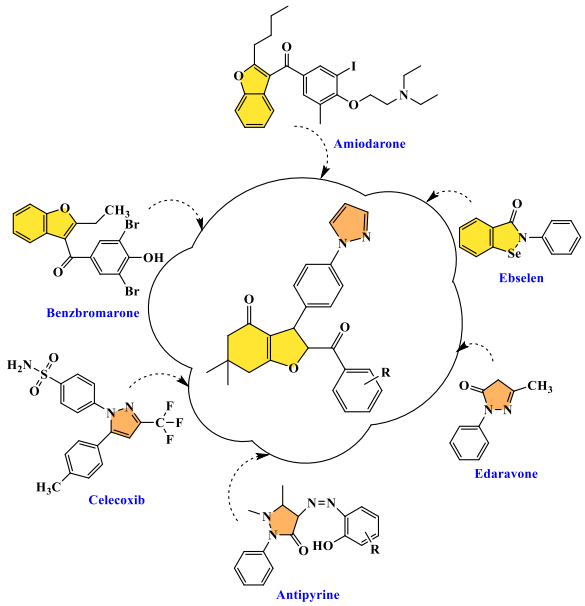


Fig. 1. Rational design strategy of novel drug candidates based on benzofuran and pyrazole scaffolds.

Incorporating the pyrazole moiety, our research has resulted in the synthesis of a new set of tetrahydrobenzofuran-4(2*H*)-one derivatives 4a-4j. The enormous therapeutic promise of benzofurans and pyrazole compounds makes this achievement all the more noteworthy. We utilized a synthetic technique that included dimedone, 4-(1*H*-pyrazol-1-yl)benzaldehyde, and diverse phenacyl bromides for the subtract scope to create these novel compounds. The tetrahydrobenzofuran-4(2*H*)-ones, 4a-4j that were recently synthesized were all characterized using a variety of spectroscopic methods, and their yields ranged from modest to good. The described technique has many advantages, such as the utilization of an efficient and cost-effective catalyst, a large substrate scope, a relatively fast reaction time, and a high reaction yield.

2. Experimental

2.1. *Materials and methods*

The reaction's chemicals were purchased in India from Sigma-Aldrich, TCI, and Sisco Research Laboratories Pvt. Ltd., and they were utilized without any additional purification. The reactions were monitored using thin-layer chromatography (TLC) on aluminum plates (F254 silica gel 60). We present the data unaltered from our use of the open capillary tube method to find the melting points of the compounds we made. Nuclear magnetic resonance (NMR) spectra were acquired using a standard 5 mm probe and a proton noise decoupling

mode-equipped 400 MHz JOEL JNM-ECX500II (delta) spectrometer. The solvent employed was deuterated DMSO, and TMS was utilized as a reference for NMR (^{1}H and ^{13}C) spectra. The ^{1}H NMR signals were abbreviated using a variety of symbols: "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "dd" for double doublet, and "m" for multiplet. Mass spectra were recorded in Agilent 7890B GC with 5977B MS using in house method.

2.2. *Synthetic procedure for the 3-(4-(1H-pyrazol-1-yl)phenyl)-6,6-dimethyl-2-(substituted phenyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4a-4j)*

4-(1*H*-pyrazol-1-yl)benzaldehyde, 3 (1 g, 5.81 mmol), 5,5-dimethylcyclohexane-1,3-dione, 1 (0.82 g, 5.81 mmol), substituted phenacyl bromide, 2 (5.81 mmol), and pyridine (1.01 g, 12.7 mmol) were charged and heated at reflux temperature for 3.0 h in a 100 mL RBF that contained acetonitrile solvent. After adding 1.29 g (12.8 mmol) of triethyl amine, the mixture was heated for the three hours to 70 °C. Following the completion of the reaction (which was monitored by TLC), the resultant mixture was allowed to cool to room temperature before being placed into ice-cold water and stirred for ten hours at room temperature. Crude products were obtained by filtering and washing the separated solid with water. In order to obtain analytically pure products, the product was purified using column chromatography (Silica Gel; 60-120 mesh; 60 % ethyl acetate: Hexane). The derivatives (4a-4j) were characterized by ^{1}H NMR, ^{13}C NMR, IR, and MS.

2.3. *Analytical data*

2.3.1. *3-(4-(1H-pyrazol-1-yl)phenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-3,5,6,7 tetrahydro-benzofuran-4(2H)-one (4a)*

This compound was obtained as a light yellow colored solid, mp 207-209 °C. IR (cm^{-1}): 2954 (C-H), 1705 (>C=O), 1627, 1519 (aromatic ring skeleton), 1342, 1219 (NO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δppm: 8.49 (s, 1H, Ar-H), 8.38-8.36 (d, 2H, Ar-H), 8.12-8.10 (d, 2H, Ar-H), 7.83-7.81 (d, 2H, Ar-H), 7.75 (s, 1H, Ar-H), 7.30-7.28 (d, 2H, Ar-H), 6.55 (s, 1H, Ar-H), 6.35-6.34 (d, 1H, -Chiral-H), 4.43 (s, 1H, -Chiral-H), 2.65-2.55 (m, 2H, CH_2), 2.20-2.14 (t, 2H, CH_2), 1.26 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 201.8 (>C=O), 193.0 (>C=O), 176.9. 163.4, 141.4, 139.8, 139.2, 132.0, 128.9, 128.1, 125.0, 124.7, 119.1, 118.9, 116.9, 116.0, 114.3, 108.2, 90.8 (-CH), 51.0 (-CH), 48.2 (-CH_2), 34.7 (-CH_2), 31.7 (-CH_3), 31.6 (-CH_3); MS (m/z): 457 [M^+]; Elemental analysis of Calculated = C, 68.26; H, 5.07; N, 9.19 for $C_{26}H_{23}N_3O_5$ and found = C, 68.25; H, 5.08; N, 9.20.

2.3.2. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(4-chlorobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-4(2H)-one (4b)*

This compound was obtained as a white colored solid, mp 201-203 °C. IR (cm^{-1}): 2962 (C-H), 1705 (>C=O), 1643, 1597 (aromatic ring skeleton), 756 (C-Cl). ^{1}H NMR (400 MHz,

DMSO-d_6) δppm: 8.50 (s, 1H, Ar-H), 8.39-8.37 (d, 2H, Ar-H), 8.11-8.09 (d, 2H, Ar-H), 7.82-7.80 (d, 2H, Ar-H), 7.77 (s, 1H, Ar-H), 7.31-7.29 (d, 2H, Ar-H), 6.56 (s, 1H, Ar-H), 6.36 (s, 1H, -Chiral-H), 4.44 (s, 1H, -Chiral-H), 2.66-2.56 (m, 2H, CH_2), 2.21-2.15 (t, 2H, CH_2), 1.27 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 201.7 (>C=O), 193.1 (>C=O), 176.8, 163.3, 141.3, 139.7, 139.1, 132.1, 128.8, 128.2, 125.1, 124.6, 119.2, 118.8, 116.8, 116.1, 114.2, 108.1, 90.7 (-CH), 51.1 (-CH), 48.3 (-CH_2), 34.8 (-CH_2), 31.6 (-CH_3), 31.8 (-CH_3); MS (m/z): 446 [M^+]; Elemental analysis of Calculated = C, 69.87; H, 5.19; N, 6.27 for $C_{26}H_{23}ClN_2O_3$ and found = C, 69.88; H, 5.18; N, 6.26.

2.3.3. *3-(4-(1H-pyrazol-1-yl)phenyl)-6,6-dimethyl-2-(4-methylbenzoyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4c)*

This compound was obtained as a cream colored solid, mp 191-193 °C. IR (cm^{-1}): 2952 (C-H), 1711 (>C=O), 1612, 1521 (aromatic ring skeleton). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.49 (s, 1H, Ar-H), 7.95 (s, 2H, Ar-H), 7.83-7.75 (s, 5H, Ar-H), 7.36-7.28 (s, 5H, Ar-H), 6.55 (s, 1H, Ar-H), 6.27 (s, 1H, -Chiral-H), 4.28 (s, 1H, -Chiral-H), 2.89 (s, 2H, CH_2), 2.73 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.10-1.08 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 203.5 (>C=O), 193.2 (>C=O), 176.9, 162.7, 145.3, 141.4, 139.7, 139.2, 131.1, 129.9, 129.4, 128.8, 128.1, 119.1, 114.3, 108.2, 91.0 (-CH), 51.0 (-CH), 48.0 (-CH_2), 37.1 (-CH_2), 31.2 (-CH_3), 28.6 (-CH_3), 21.1 (-CH_3); MS (m/z): 426 [M^+]; Elemental analysis of Calculated = C, 76.03; H, 6.14; N, 6.57 for $C_{27}H_{26}N_2O_3$ and found = C, 76.02; H, 6.15; N, 6.56.

2.3.4. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(4-fluorobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4d)*

This compound was obtained as a brown colored solid, mp 196-198 °C. IR (cm^{-1}): 2962 (C-H), 1715 (>C=O), 1626, 1532 (aromatic ring skeleton), 1019 (C-F). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.51 (s, 1H, Ar-H), 8.40 (s, 2H, Ar-H), 8.13 (s, 2H, Ar-H), 7.84-7.82 (d, 2H, Ar-H), 7.76 (s, 1H, Ar-H), 7.29-7.27 (d, 2H, Ar-H), 6.54 (s, 1H, Ar-H), 6.33 (s, 1H, -Chiral-H), 4.42 (s, 1H, -Chiral-H), 2.67 (s, 2H, CH_2), 2.19-2.13 (t, 2H, CH_2), 1.25 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 201.6 (>C=O), 193.8 (>C=O), 176.6, 163.5, 141.5, 139.5, 139.4, 132.4, 128.6, 128.4, 125.3, 124.5, 119.4, 118.6, 116.7, 116.4, 114.0, 108.0, 90.9 (-CH), 51.3 (-CH), 48.4 (-CH_2), 37.4 (-CH_2), 31.8 (-CH_3), 31.7 (-CH_3); MS (m/z): 430 [M^+]; Elemental analysis of Calculated= C, 72.54; H, 5.39; N, 6.51 for $C_{26}H_{23}FN_2O_3$ and found = C, 72.55; H, 5.38; N, 6.50.

2.3.5. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(3,4-dichlorobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4e)*

This compound was obtained as a white colored solid, mp 219-221 °C. IR (cm^{-1}): 2960 (C-H), 1708 (>C=O), 1622, 1529 (aromatic ring skeleton), 789 (C-Cl). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.52 (s, 1H, Ar-H), 7.96 (s, 2H, Ar-H), 7.82-7.74 (s, 5H, Ar-H), 7.35-7.27 (s, 5H, Ar-H), 6.54 (s, 1H, Ar-H), 6.28 (s, 1H, -Chiral-H), 4.27 (s, 1H, -Chiral-H), 2.90

(s, 2H, CH_2), 2.74 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.11-1.09 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 203.4 (>C=O), 193.1 (>C=O), 176.8, 162.8, 145.2, 141.3, 139.6, 139.1, 131.2, 129.8, 129.5, 128.7, 128.2, 119.2, 114.2, 108.3, 91.1 (-CH), 51.1 (-CH), 48.1 (-CH_2), 37.2 (-CH_2), 31.3 (-CH_3), 28.5 (-CH_3); MS (m/z): 480 [M^+]; Elemental analysis of Calculated = C, 64.87; H, 4.61; N, 5.82 for $C_{26}H_{22}Cl_2N_2O_3$ and found= C, 64.88; H, 4.60; N, 5.83.

2.3.6. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(4-bromobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-4(2H)-one (4f)*

This compound was obtained as a red colored solid, mp 230-232 °C. IR (cm^{-1}): 2972 (C-H), 1712 (>C=O), 1630, 1521 (aromatic ring skeleton), 687 (C-Br). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.48 (s, 1H, Ar-H), 8.37-8.35 (d, 2H, Ar-H), 8.10-8.08 (d, 2H, Ar-H), 7.81-7.78 (d, 2H, Ar-H), 7.74 (s, 1H, Ar-H), 7.32-7.30 (d, 2H, Ar-H), 6.53 (s, 1H, Ar-H), 6.34-6.32 (d, 1H, -Chiral-H), 4.45 (s, 1H, -Chiral-H), 2.64-2.54 (m, 2H, CH_2), 2.22-2.16 (t, 2H, CH_2), 1.28 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 203.3 (>C=O), 193.3 (>C=O), 176.7, 162.6, 145.1, 141.5, 139.4, 139.3, 131.3, 129.7, 129.3, 128.5, 128.3, 119.3, 114.4, 108.4, 91.3 (-CH), 51.3 (-CH), 48.3 (-CH_2), 37.3 (-CH_2), 31.1 (-CH_3), 28.7 (-CH_3); MS (m/z): 491 [M^+]; Elemental analysis of Calculated = C, 63.55; H, 4.72; N, 5.70 for $C_{26}H_{23}BrN_2O_3$ and found = C, 63.56; H, 4.71; N, 5.71.

2.3.7. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(4-azidobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-4(2H)-one (4g)*

This compound was obtained as a dark yellow colored solid, mp 211-213 °C. IR (cm^{-1}): 2961 (C-H), 1716 (>C=O), 2147 (N_3), 1631, 1525 (aromatic ring skeleton). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.53 (s, 1H, Ar-H), 8.41-8.39 (d, 2H, Ar-H), 8.14 (s, 2H, Ar-H), 7.85 (s, 2H, Ar-H), 7.78 (s, 1H, Ar-H), 7.28-7.26 (d, 2H, Ar-H), 6.57 (s, 1H, Ar-H), 6.37-6.35 (d, 1H, -Chiral-H), 4.41 (s, 1H, -Chiral-H), 2.68-2.58 (m, 2H, CH_2), 2.23-2.17 (t, 2H, CH_2), 1.24 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 201.5 (>C=O), 193.2 (>C=O), 176.7, 163.7, 141.2, 139.6, 139.3, 132.3, 128.7, 128.5, 125.5, 124.8, 119.3, 118.7, 116.4, 116.3, 114.1, 108.4, 90.6 (-CH), 51.2 (-CH), 48.6 (-CH_2), 37.5 (-CH_2), 31.5 (-CH_3), 31.4 (-CH_3); MS (m/z): 453 [M^+]; Elemental analysis of Calculated = C, 68.86; H, 5.11; N, 15.44 for $C_{26}H_{23}N_5O_3$ and found = C, 68.86; H, 5.11; N, 15.44.

2.3.8. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(2-chlorobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-4(2H)-one (4h)*

This compound was obtained as an off-white colored solid, mp 204-206 °C. IR (cm^{-1}): 2970 (C-H), 1720 (>C=O), 1645, 1505 (aromatic ring skeleton), 796 (C-Cl). ^{1}H NMR (400 MH_Z, DMSO-d_6) δppm: 8.54 (s, 1H, Ar-H), 7.97 (s, 2H, Ar-H), 7.84-7.76 (s, 5H, Ar-H), 7.34-7.26 (s, 5H, Ar-H), 6.57 (s, 1H, Ar-H), 6.29 (s, 1H, -Chiral-H), 4.25 (s, 1H, -Chiral-H), 2.87 (s, 2H, CH_2), 2.72 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.09-1.07 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 203.7 (>C=O), 193.5 (>C=O), 176.5, 162.5, 145.4, 141.2, 139.5,

139.4, 131.5, 129.5, 129.6, 128.4, 128.6, 119.7, 114.6, 108.6, 91.4 (-CH), 51.2 (-CH), 48.4 ($-CH_2$), 37.6 ($-CH_2$), 31.4 ($-CH_3$), 28.4 ($-CH_3$); MS (m/z): 446 [M^+]; Elemental analysis of Calculated = C, 69.58; H, 5.24; N, 7.40 for $C_{26}H_{23}ClN_2O_3$ and found = C, 69.59; H, 5.23; N, 7.41.

2.3.9. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(4-ethylbenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro-benzofuran-4(2H)-one (4i)*

This compound was obtained as a cream colored solid, mp 200-202 °C. IR (cm^{-1}): IR (cm^{-1}): 2962 (C-H), 1712 (>C=O), 1632, 1530 (aromatic ring skeleton). ^1H NMR (400 MH_Z, DMSO-d_6) δppm: 8.47 (s, 1H, Ar-H), 7.94 (s, 2H, Ar-H), 7.81-7.73 (s, 5H, Ar-H), 7.37-7.29 (s, 5H, Ar-H), 6.53 (s, 1H, Ar-H), 6.26 (s, 1H, -Chiral-H), 4.24 (s, 1H, -Chiral-H), 2.88 (s, 2H, CH_2), 2.70 (s, 2H, CH_2), 2.43 (s, 3H, CH_2), 2.41 (s, 3H, CH_3), 1.12-1.10 (s, 3H, CH_3), 1.05 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 203.8 (>C=O), 193.6 (>C=O), 176.4, 162.4, 145.5, 141.6, 139.8, 139.7, 131.6, 129.4, 129.7, 128.2, 128.7, 119.8, 114.7, 108.7, 91.6 (-CH), 51.5 (-CH), 48.6 ($-CH_2$), 37.7 ($-CH_2$), 31.5 ($-CH_3$), 28.1 ($-CH_3$), 28.3 ($-CH_2$), 21.0 ($-CH_3$); MS (m/z): 440 [M^+]; Elemental analysis of Calculated = C, 76.34; H, 6.41; N, 6.36 for $C_{28}H_{28}N_2O_3$ and found = C, 76.35; H, 6.40; N, 6.35.

2.3.10. *3-(4-(1H-pyrazol-1-yl)phenyl)-2-(3-chloro-4-fluorobenzoyl)-6,6-dimethyl-3,5,6,7-tetrahydro benzofuran-4(2H)-one (4j)*

This compound was obtained as a black colored solid, mp 215-217 °C. IR (cm^{-1}): 2941 (C-H), 1713 (>C=O), 1645, 1520 (aromatic ring skeleton), 1010 (C-F). ^1H NMR (400 MH_Z, DMSO-d_6) δppm: 8.5 (s, 1H, Ar-H), 7.91 (s, 2H, Ar-H), 7.80-7.72 (s, 5H, Ar-H), 7.33-7.25 (s, 5H, Ar-H), 6.58 (s, 1H, Ar-H), 6.25 (s, 1H, -Chiral-H), 4.29 (s, 1H, -Chiral-H), 2.91 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.08-1.06 (s, 3H, CH_3); ^{13}C NMR (100 MH_Z, DMSO-d_6) δppm: 201.4 (>C=O), 193.7 (>C=O), 176.5, 163.6, 141.1, 139.9, 139.5, 132.5, 128.5, 128.6, 125.6, 124.4, 119.6, 118.4, 116.1, 116.2, 114.4, 108.5, 90.0 (-CH), 51.4 (-CH), 48.7 ($-CH_2$), 37.6 ($-CH_2$), 31.4 ($-CH_3$), 31.3($-CH_3$); MS (m/z): 464 [M^+]; Elemental analysis of Calculated= C, 67.17; H, 4.77; N, 6.03 for $C_{26}H_{22}ClFN_2O_3$ and found= C, 67.16; H, 4.78; N, 6.02.

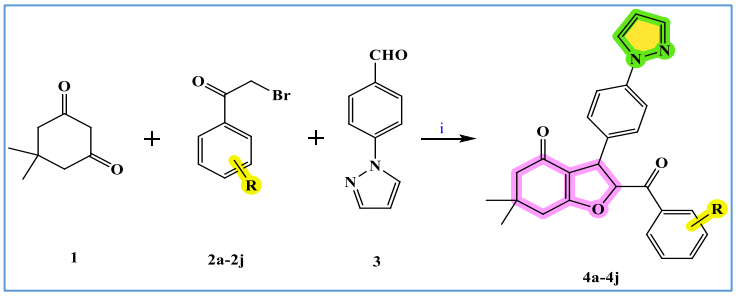
3. Results and Discussion

3.1. *Chemistry*

Multicomponent reactions (MCRs) have gained significant attention in organic synthesis due to their efficiency, atom economy, and ability to construct complex molecules in a single step. Several studies have reported the use of MCR strategies for synthesizing heterocyclic frameworks with biological significance. Inspired by these methodologies and based on previously reported procedures, we designed a one-pot, base-assisted approach for the synthesis of the target compounds [32].

The synthesis was carried out in a using acetonitrile as the reaction medium. To this, 4-(1*H*-pyrazol-1-yl)benzaldehyde (3), 5,5-dimethylcyclohexane-1,3-dione/dimedone (1), and phenacyl bromide (2) were added, followed by pyridine as a base. The reaction mixture was heated under reflux conditions for 3 h, enabling the formation of the intermediate product through a likely Knoevenagel condensation or Michael addition pathway.

After the initial stage, triethylamine was added to the reaction mixture, and the temperature was raised to 70 °C for an additional 3 h. The presence of triethylamine may have facilitated the enolate formation, promoting further cyclization or nucleophilic substitution steps in the reaction mechanism. The final product was characterized by using standard spectroscopic techniques to confirm its structure and purity (Scheme 1, Fig. 2).



Reaction and conditions: i) Pyridine, TEA, Acetonitrile, <70 °C

Scheme 1. *In situ* reaction pathway for the synthesis of Benzofuran-pyrazole hybrids (4a-4j).

3.2. *Reaction optimization*

To determine the optimal reaction conditions, various bases, solvents, and catalyst combinations were screened, and the results are summarized in Table 1. The reaction was evaluated by varying the catalyst type and concentration, as well as the solvent and reaction time, while maintaining reflux conditions.

In the initial screening, triethylamine (Et_3N, 10 mol%) in DMF (Entry 1) provided a 42 % yield after 10 h, whereas changing the solvent to acetonitrile (ACN) significantly improved the yield to 60 % (Entry 2). The combination of Et_3N with pyridine (Py) in ACN (Entry 3) further enhanced the reaction efficiency, delivering the highest yield of 81% in 12 h, suggesting a synergistic catalytic effect.

When K_2CO_3 (10 mol%) was employed as a base, the yields were considerably lower, with 30 % in DMF (Entry 4) and 36 % in ACN (Entry 5). The addition of pyridine (Entry 6) improved the yield to 62 %, though still lower than the Et_3N/Py combination. Similarly, the use of Cs_2CO_3 (10 mol%) with pyridine (Entry 7) required a longer reaction time (20 h) and provided a moderate 69 % yield, whereas Cs_2CO_3 alone in DMF (Entry 8) led to an even lower 50 % yield. Reducing the catalyst loading of Cs_2CO_3 to 5 mol% (Entry 9) in ACN still resulted in a decent 65 % yield, indicating the reaction efficiency was not significantly dependent on higher catalyst loading. Finally, using only pyridine (10 mol%)

(Entry 10) gave a relatively low yield of 44 %, highlighting the necessity of an additional base for better conversion.

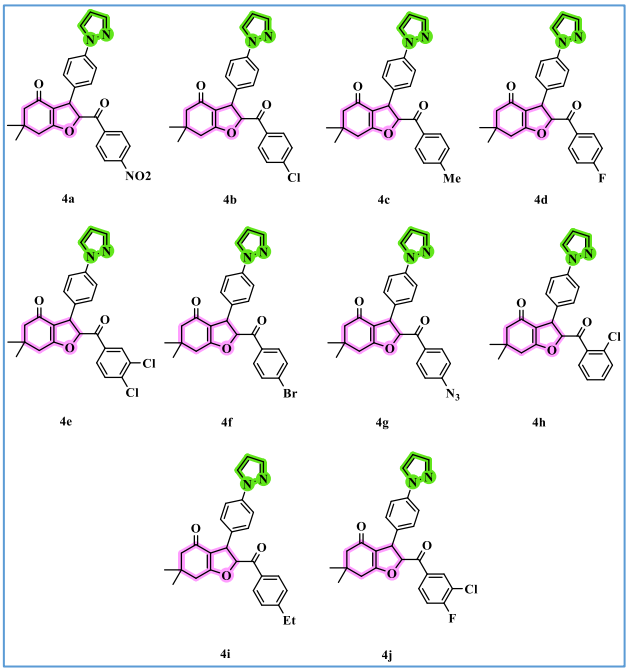


Fig. 2. MCRs approach to synthesize a library of tetrahydrobenzofuran-4(2*H*)-one (4a-4j).

Based on these observations, Et_3N (10 mol%) with pyridine in ACN at reflux conditions was identified as the optimal condition, yielding 81 % of the desired product in 12 h. The combination of Et_3N and pyridine likely promotes effective enolate formation and enhances the nucleophilicity of intermediates, thereby accelerating the reaction.

Table 1. Optimized reaction conditions for the substitutes of pyridine base for the synthesis of tetrahydrobenzofuran-4(2*H*)-one (4a)[a].

Entry	Catalyst (mol%)	Solvent	Yield[b]
1	Et_3N (10)	DMF	42
2	Et_3N (10)	ACN	60
3	Et_3N + Py (10)	ACN	81
4	K_2CO_3 (10)	DMF	30
5	K_2CO_3 (10)	ACN	36
6	K_2CO_3 + Py (10)	ACN	62
7	CS_2CO_3 + Py (10)	ACN	69
8	CS_2CO_3 (10)	DMF	50
9	CS_2CO_3 (05)	ACN	65
10	Py (10)	ACN	44

[a]Reaction conditions: dimedone 1 (1 mmol), 4-(1*H*-pyrazol-1-yl)benzaldehyde 3 (1 mmol) and phenacyl bromide 2a (1 mmol). [b]Isolated yield and kept uniform reaction time (as described in experimental) for better optimization. Abbreviations: ACN: Acetonitrile, DMF: Dimethyl formamide, Py: Pyridine.

The absence of three different molecules in the same series, despite using 4-methoxy, 3,4-dimethoxy, and 3,4,5-trimethoxy-substituted benzaldehydes, can be attributed to electronic effects, steric hindrance, and reaction selectivity. The methoxy (-OCH_3) group is an electron-donating substituent that increases electron density on the benzaldehyde ring through the mesomeric effect. However, the presence of multiple methoxy groups, especially in 3,4-dimethoxy and 3,4,5-trimethoxy derivatives, alters the reactivity of the aldehyde center [33]. The additional methoxy groups at positions 3 and 5 create steric hindrance around the reactive site, potentially interfering with the initial condensation step and leading to lower reactivity or side reactions. Moreover, the reaction likely proceeds via an intermediate enamine, where steric effects influence the ease of enamine formation and subsequent cyclization [34]. Surprisingly, 4-methoxybenzaldehyde, even though having the least steric hindrance and a well-balanced electronic environment, not facilitated product formation, whereas the 3,4-dimethoxy and 3,4,5-trimethoxy derivatives led to unstable intermediates and no product yields (Fig. 3).

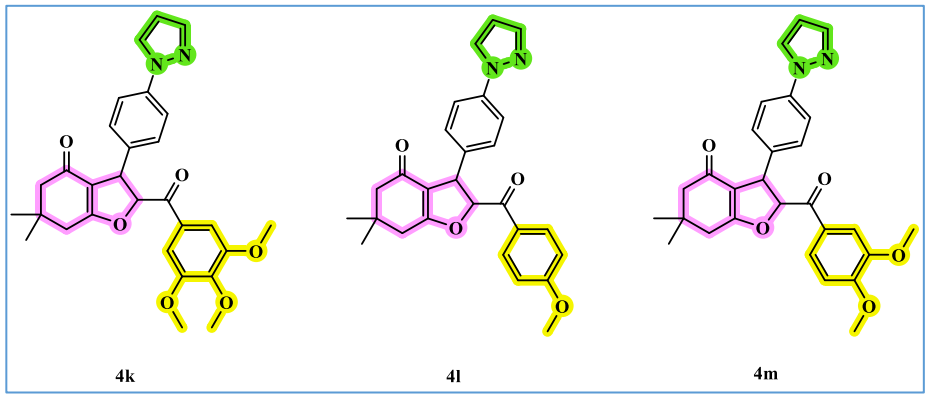


Fig. 3. Failure of MCRs with mono/multi methoxy derivatives.

During the reaction, an attempt was made to use 4-thiomethyl phenacyl bromide as a substrate under the optimized conditions. However, the reaction exhibited significant challenges due to the high instability of the resulting product, leading to decomposition. The thiomethyl (-SCH_3) group is known to be sensitive to oxidation and prone to degradation under prolonged heating or basic conditions. Additionally, the final product caused severe lacrimation, indicating its volatility or possible irritant properties. This instability hindered successful isolation and purification, making it unsuitable for further study under the given conditions (Fig. 4).

3.3. *Spectral analysis*

The IR spectrum showed a strong absorption at 1705 cm^{-1}, characteristic of the carbonyl (>C=O) group, along with peaks at 1627 and 1519 cm^{-1} corresponding to aromatic ring system. A band at 2954 cm^{-1} corresponded to aliphatic C–H stretching vibrations. The ^1H

NMR spectrum displayed aromatic proton signals around δ 8.5-6.5 ppm range, consistent with the presence of pyrazolyl and phenyl moieties. The signals at δ ~6.5 and δ ~4.5 corresponded to chiral methine protons of the tetrahydrobenzofuran system. Multiplet at δ ~2.5 and δ ~2.0 were due to the methylene protons, while two sharp singlets at δ ~1.2 and ~1.1 confirmed the presence of geminal dimethyl groups. The ^{13}C NMR spectrum supported the structure, showing characteristic carbonyl carbons around at δ 200 and 190 ppm. Resonances in the δ 180–105 ppm region corresponded to aromatic and heteroaryl carbons. The methine carbons were observed at δ ~90 and ~50, while the methylene carbons appeared at δ ~45 and ~35. Two signals at δ ~30 confirmed the two methyl substituents. The mass spectrum showed a molecular ion peak in agreement with the molecular formula. Elemental analysis also supported the proposed structures.

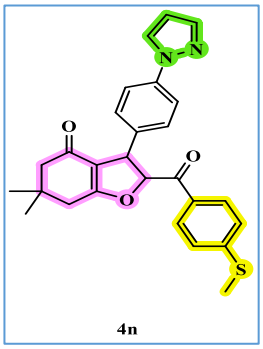


Fig. 4. Unstable and Lacrimation product (-SMe based phenacyl).

3.4. *In vitro antioxidant assay protocol (DPPH Assay)* [35]

To determine the anti-radical potential of all the produced compounds, we used the DPPH method to examine their radical scavenging capabilities. The synthesized compounds were mixed with 2 mm of the DPPH solution (12.5 mg/L) and left to stand at room temperature for 30 min. A UV/Vis Spectrophotometer (Shimadzu UV-1900) was used to measure the absorbance at 517 nm, with methanol serving as a baseline adjustment. The following formula was used to express the antioxidant activity of all synthesized substances as percentage inhibition, with ascorbic acid serving as the standard.

% Inhibition of DPPH = (A-B)/A*100

Where A = absorbance of blank and B = absorbance of the sample.

Table 2. Antioxidant assay (free radical scavenging effect by DPPH) of 4a-4j (expressed in IC_{50} values).

Comp ID	Substituents (R)	$IC_{50} \pm SD$ (μM)
4a	4-NO_2	12.90 ± 0.60
4b	4-Cl	26.21 ± 0.91
4c	4-Me	15.02 ± 0.86
4d	4-F	56.01 ± 0.55
4e	3,4-Cl_2	29.48 ± 0.64

4f	4-Br	26.54 ± 0.29
4g	4-N_3	44.18 ± 0.63
4h	2-Cl	29.21 ± 0.75
4i	4-Et	14.50 ± 0.59
4j	3-Cl,4-F	27.11 ± 0.60
Ascorbic acid	$C_6H_8O_6$	12.10 ± 0.09

The antioxidant potential of the synthesized compounds (4a–4j) was evaluated by determining their IC_{50} values (µM), with ascorbic acid used as the standard reference compound (IC_{50} = 12.10 ± 0.09 µM). The results, presented in Table 2, indicate a significant variation in activity based on the nature of the substituent (R) on the phenyl ring.

Among the tested compounds, 4a (4-NO_2, IC_{50} = 12.90 ± 0.60 µM) exhibited the highest antioxidant activity, closely approaching the potency of ascorbic acid. The presence of the strong electron-withdrawing nitro (-NO_2) group likely enhances radical-scavenging ability by stabilizing the electron transfer process. Similarly, compounds 4c (4-Me, IC_{50} = 15.02 ± 0.86 µM) and 4i (4-Et, IC_{50} = 14.50 ± 0.59 µM) showed notable activity, suggesting that moderate electron-donating alkyl groups contribute to antioxidant potential. Conversely, compounds containing halogen substituents, such as 4b (4-Cl, IC_{50} = 26.21 ± 0.91 µM), 4d (4-F, IC_{50} = 56.01 ± 0.55 µM), 4e (3,4-Cl_2, IC_{50} = 29.48 ± 0.64 µM), and 4f (4-Br, IC_{50} = 26.54 ± 0.29 µM), displayed moderate to lower antioxidant activity. The presence of halogens, which are mild electron-withdrawing groups, may reduce radical stabilization, thereby decreasing their efficacy. Notably, 4d (4-F) showed the weakest activity (IC_{50} = 56.01 ± 0.55 µM), possibly due to fluorine's strong electronegativity and poor radical stabilization ability.

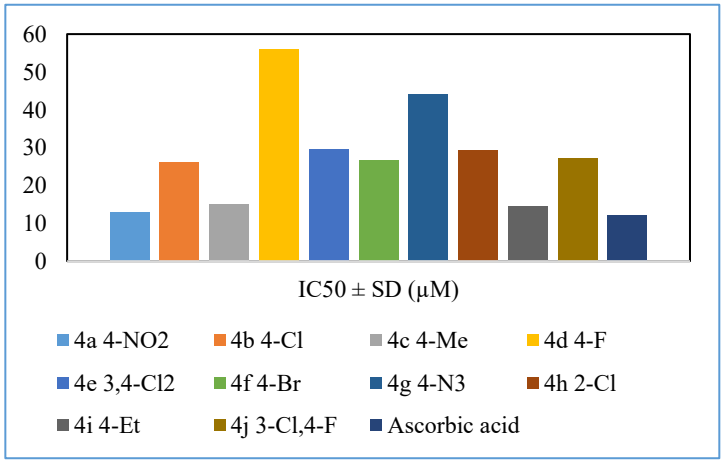


Fig. 5. Effect of 4a-4j towards DPPH. (Values are mean ± SD of three individual experiments).

Interestingly, 4g (4-N_3, IC_{50} = 44.18 ± 0.63 µM) showed lower activity than expected, despite being an electron-withdrawing group. This may be attributed to steric or resonance effects reducing its radical-scavenging efficiency. 4h (2-Cl, IC_{50} = 29.21 ± 0.75 µM) and 4j

(3-Cl,4-F, IC_{50} = 27.11 ± 0.60 µM) demonstrated moderate activity, further confirming that position and combination of halogen substituents influence antioxidant performance. Overall, compounds with electron-withdrawing groups at the para position (e.g., 4-NO_2, 4-Cl) and moderate electron-donating alkyl groups (e.g., 4-Me, 4-Et) exhibited relatively higher antioxidant activity, while those with fluorine or multiple halogens showed reduced efficiency (Fig. 5).

4. Conclusions

In this study, a one-pot, base-assisted MCR approach was successfully developed to synthesize tetrahydrobenzofuran-pyrazole derivatives (4a–4j). The optimal reaction conditions involved triethylamine and pyridine in acetonitrile under reflux, yielding high efficiency and product diversity. Substrate scope analysis showed that electronic and steric effects influenced product formation, while 4-thiomethyl phenacyl bromide exhibited instability under the reaction conditions. Antioxidant testing revealed that the 4-nitro (4a) and 4-ethyl (4i) derivatives displayed the highest radical-scavenging activity, comparable to ascorbic acid. These findings suggest that the functional groups' position and nature impact antioxidant potential. The results highlight MCRs as a powerful synthetic method for developing heterocyclic compounds with potential therapeutic applications.

Acknowledgements

We would like to express our heartfelt gratitude to DKV Science College (affiliated with Saurashtra University), Jamnagar (Gujarat-India) and BITS Pilani (Hyderabad-India) for their support and guidance throughout my research. We also extend our sincere thanks to Cambridge Software for providing the ChemDraw software, which has been instrumental in visualizing chemical structures and enhancing the quality of this work. The resources and encouragement from these institutions have significantly contributed to the success of the study.

References

1. G. Graziano, A. Stefanachi, M. Contino, R. Prieto-Díaz, A. Ligresti, P. Kumar, A. Scilimati, E. Sotelo, and F. Leonetti, Int. J. Mol. Sci. **24**, 6581 (2023). https://doi.org/10.3390/ijms24076581
2. R. I. Piludiya, D. Sriram, J. Kumari, and K. M. Kapadiya, Curr. Catal. **13**, 25 (2024). https://doi.org/10.2174/0122115447286547231208092915
3. H. Vaidya, K. Kapadiya, J. H. Kamdar, and G. Jani, Chemistry Select **10**, ID e202406112 (2025). https://doi.org/10.1002/slct.202406112
4. A. Dömling, W. Wang, and K. Wang, Chem. Rev. **112**, 3083 (2012). https://doi.org/10.1021/cr100233r
5. C. Zavarise, J. C. Cintrat, E. Romero, and A. Sallustrau, RSC Adv. **14**, 39253 (2024). https://doi.org/10.1039/D4RA04152F
6. B. L. Gondaliya and K. M. Kapadiya, Polycyclic Arom. Comp. **43**, 686 (2021). https://doi.org/10.1080/10406638.2021.2019804
7. K. M. Kapadiya, K. M. Kavadia, P. A. Manvar, and R. C. Khunt, Anti-Infective Agents **13**, 129 (2015). https://doi.org/10.2174/2211352513666150915235745

8. N. M. Panchani, K. M. Kapadiya, and H. S. Joshi, J. Heterocycl. Chem. **59**, 2084 (2022). https://doi.org/10.1002/jhet.4543
9. R. Piludiya, J. H. Kamdar, V. M. Khedkar, C. B. Sangani, W. S. Saeed, M. Christy, N. Teraiya, and K. Kapadiya, Chemistry Select **9**, ID e202304216 (2024). https://doi.org/10.1002/slct.202304216
10. A. A. Aziem, B. S. Baaiu, and A. O. Abdelhamid, J. Heterocycl. Chem. **54**, 3471 (2017). https://doi.org/10.1002/jhet.2970
11. M. Rupapara, N. Teraiya, C. Sangani, K. Sangani, K. Kapadiya, and N. Patel, Mol. Divers. (2025) https://doi.org/10.1007/s11030-025-11227-1
12. C. J. L. Sousa, T. H. M. Albuquerque, and A. M. Silva, Pharmaceuticals **16**, 1668 (2023). https://doi.org/10.3390/ph16121668
13. C. Pandit and K. M. Kapadiya, Folia Med. **61**, 551 (2019). https://doi.org/10.3897/folmed.61.e47955
14. M. Bhatt, K. Kapadiya, J. Kamdar, and J. Upadhyay, Results Chem. **18**, ID 102715 (2025). https://doi.org/10.1016/j.rechem.2025.102715
15. J. Jampilek, Molecules **24**, 3839 (2019). https://doi.org/10.3390/molecules24213839
16. K. Kapadiya, R. Kotadiya, K. Kavadia, R. Kothari, K. Mehariya, and R. Khunt, Lett. Drug. Des. Discov. **13**, 505 (2016). https://doi.org/10.2174/1570180812666150914220727
17. S. S. Bhalodiya, M. P. Parmar, D. B. Upadhyay, C. D. Patel, D. P. Vala, D. Rajani, and H. M. Patel, Results Chem. **7**, ID 101304 (2023). https://doi.org/10.1016/j.rechem.2023.101304
18. A. Abdel-Aziem, J. Heterocycl. Chem. **54**, 2985 (2017). https://doi.org/10.1002/jhet.2906
19. R. Naik, D. S. Harmalkar, X. Xu, K. Jang, and K. Lee, Eur. J. Med. Chem. **90**, 379 (2015). https://doi.org/10.1016/j.ejmech.2014.11.047
20. M. Ríos and J. Portilla, Chemistry **4**, 940 (2022). https://doi.org/10.3390/chemistry4030065
21. K. Sanghavi, B. Y. Patel, V. Khedkar, and K. M. Kapadiya, Imidazo-Pyridines: A Hybrid N-Heterocycles for Their Sustainable Synthetic Approaches and Significant Clinical Diversity, in Five Membered Bioactive N and O-Heterocycles: Models and Medical Applications, ed. S. Kulkarni et al. (IGI Global Scientific Publishing, 2025) pp. 435-494. https://doi.org/10.4018/979-8-3693-7267-8.ch011
22. M. J. Naim, O. Alam, F. Nawaz, M. J. Alam, and P. Alam, J. Pharm. Bioallied. Sci. **8**, 2 (2016). https://doi.org/10.4103/0975-7406.171694
23. K. N. Sanghavi, M. N. Kher, and K. M. Kapadiya, J. Heterocycl. Chem. **60**, 993 (2023). https://doi.org/10.1002/jhet.4644
24. M. Rupapara, M. Chauhan, C. B. Sangani, M. Afzal, A. Alarifi, M. Christy, and K. Kapadiya, J. Fluor. Chem. **270**, ID 110171 (2023). https://doi.org/10.1016/j.jfluchem.2023.110171
25. B. Mohite, B. K. Chabhadiya, K. M. Kapadiya, V. M. Khedkar, and S. Jauhari, Chemistry Select **9**, ID e202404601 (2024). https://doi.org/10.1002/slct.202404601
26. F. Azimi, H. Azizian, M. Najafi, G. Khodarahmi, L. Saghaei, M. Hassanzadeh, J. B. Ghasemi et al., Sci. Rep. **11**, 1 (2021). https://doi.org/10.1038/s41598-021-99899-1
27. A. Bendi, P. Devi, H. Sharma, G. Yadav, N. Raghav, R. Pundeer, and M. Afshari, Chem. Biodivers. **2**, ID e202402370 (2024). https://doi.org/10.1002/cbdv.202402370
28. G. Szabó, J. Fischer, A. Kis-Varga, and K. Gyires, J. Med. Chem. **51**, 142 (2008). https://doi.org/10.1021/jm070821f
29. R. Karinen, G. Høiseth, K. O. Svendsen, S. Rogde, and V. Vindenes, Forensic Sci. Int. **248**, e13 (2015). https://doi.org/10.1016/j.forsciint.2015.01.001
30. J. Gao, H. Yin, Y. Dong, X. Wang, Y. Liu, and K. Wang, Mol. Pharmacol. **103**, 241 (2023). https://doi.org/10.1124/molpharm.122.000638
31. G. K. Azad and R. S. Tomar, Mol. Biol. Rep. **41**, 4865 (2014). https://doi.org/10.1007/s11033-014-3417-x
32. R. L. Mohlala, T. J. Rashamuse, and E. M. Coyanis, Front. Chem. **12**, ID 1469677 (2024). https://doi.org/10.3389/fchem.2024.1469677
33. L. Wang, J. Wei, R. Wu, G. Cheng, X. Li, J. Hu, Y. Hu, and R. Sheng, Org. Chem. Front. **4**, 214 (2017). https://doi.org/10.1039/C6QO00674D

34. Y. Teffera, A. Colletti, J. C. Harmange, L. Hollis, B. Albrecht, A. Boezio, J. Liu, and Z. Zhao, Chem. Res. Toxicol. **21**, 2216 (2008). https://doi.org/10.1021/tx800307n
35. A. P. Shah, M. N. Kher, J. V. Beladiya, V. M. Khedkar, and K. M. Kapadiya, Results Chem. **7**, ID 101272 (2023). https://doi.org/10.1016/j.rechem.2023.101272