Synthesis of α-Sulfoximino Tetrazoles via Azido-Ugi 4-Component Reaction

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Abstract: The sulfoximine based tetrazoles have been synthesized via Azido-Ugi four component reactions of sulfoximines, isocyanides, aldehydes, and TMS-azide in MeOH at 70 °C in the presence of InCl₃. Replacement of sulfoximine with sulfonimidamide (SIA) have delivered corresponding SIA based tetrazole. Interestingly, SIA is also acting as a surrogate amine to accomplish corresponding aminotetrazole as by-product.

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Synthesis of α-Sulfoximino Tetrazoles via Azido-Ugi 4-Component Reaction

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Abstract The sulfoximine-based tetrazoles have been synthesized via azido-Ugi four-component reactions of sulfoximines, isocyanides, aldehydes, and TMS-azide in MeOH at 70 °C in the presence of InCl3. Replacement of sulfoximines with sulfonimidamides (SIA) has delivered the corresponding SIA-based tetrazole. Interestingly, SIA also acts as a surrogate amine to furnish the corresponding aminotetrazole as a by-product.

Key words Sulfoximine, sulfonimidamide, Ugi, tetrazole, isocyanide,

Tetrazoles are of great importance due to their distinctive chemical and biological properties. This moiety has found applications in fields, such as medicine, biochemistry, pharmacology, materials, coordination chemistry, organocatalysis (Figure 1) and synthetic chemistry. Most importantly, tetrazoles are well-established bioisosteres of carboxylic acids.

Sulfoximines have recently received attention in synthetic, medicinal and agrochemical areas. Sulfoximine-containing bioactive molecules include Atuveciclib, BAY 1251152 and AZD6738. Additionally, sulfoximines have been used as chiral auxiliaries and ligands in asymmetric synthesis, and as directing groups in ortho-C-H functionalization.

Considering the importance of tetrazoles, together with our recent interest in sulfoximines and related chemistry, we herein report that sulfoximine-based tetrazoles, i.e., α-sulfoximino tetrazoles, have been prepared via four-component reaction of sulfoximines, isocyanides, aldehydes and TMS-N3.

The classical four-component Ugi reaction utilizes carboxylic acids as one of the nucleophiles to synthesize the bis-amide. Replacement of the carboxylic acid with an azide delivers the corresponding tetrazole in the Azido-Ugi tetrazole reaction (UT-4CR). UT-4CRs have been widely employed to construct diverse tetrazole-based systems by altering the substituents in the substrate. However, most of the previous UT-4CRs reports employ sp3-hybridized primary or secondary amines as amine component. Hence, Despite being a very well-established field, the reaction behaviour with sp2 hybridized imine nucleophiles remains to be studied. In this context, we employed sulfoximines, which contain the sp2-hybridized imino group as nucleophile in the UT-4CR to synthesize α-sulfoximino tetrazoles.

Previously, Bolm et al. prepared N-(1H)-tetrazole sulfoximines via a ZnBr2-catalysed cycloaddition reaction (Scheme 2a). Recently, the same research group prepared 2-sulfoximidoyl acetic acids via Petasis reaction (Scheme 2b). Our α-sulfoximino tetrazoles can be considered as tetrazole isosteres of 2-sulfoximidoyl acetic acid (Scheme 2b).
The starting NH-sulfoximines were prepared following the reported protocol. We initiated investigations with a 4-component reaction of sulfoximine (1a), p-tolyaldehyde (2a), t-butyli isocyanide (3a) and TMS-N₃ (4) under conditions that are summarized in Table 1. Initially, the reaction mixture was stirred in methanol at room temperature for 24 h, but the desired tetrazole (5a) was obtained only in 10% yield along with unreacted sulfoximine and aldehyde (Table 1, entry 1). To try to improve matters, the Lewis acid ZnCl₂ was added as mediator and a 40% yield of (5a) was isolated (Table 1, entry 2). Increased temperature gave a better yield of (5a) (Table 1, entries 3 & 4) and replacement of ZnCl₂ with InCl₃ resulted in a further improved yield at 70 °C (Table 1, entry 6). Other Lewis acids such as Cu(OTf)₂, CuBr and Zn(OTf)₂ were not as effective as InCl₃ at 70 °C (Table 1, entries 6-9). Other solvents, including EtOH, CH₂CN, DCE, toluene, and DCM were investigated (Table 1, entries 10-14) but MeOH was found to be the best solvent for the transformation. When we replaced the TMS-N₃ in the reaction by NaN₃ we could isolate only 41% of (5a) (Table 1, entry 15). It should be noted that the Lewis acids were needed in 50 mol%. Use of lesser amounts (5/10/20/30/40 mol%) InCl₃ led to diminished product formation along with isolation of unreacted starting sulfoximine and aldehyde. A higher amount of InCl₃ (60%) did not give any better outcome.

Table 1 Optimization process for the synthesis of sulfoximine derived tetrazoles°

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Reaction condition</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>MeOH</td>
<td>RT/24 h</td>
<td>10%</td>
</tr>
<tr>
<td>2°</td>
<td>MeOH</td>
<td>ZnCl₂/RT/15 h</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>ZnCl₂/70 °C/12 h</td>
<td>46%</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>CuBr/70 °C/12 h</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>InCl₃/12 h</td>
<td>55%</td>
</tr>
<tr>
<td>6°</td>
<td>MeOH</td>
<td>Cu(OTf)₂/70 °C/12 h</td>
<td>61%</td>
</tr>
<tr>
<td>7°</td>
<td>MeOH</td>
<td>Cu(OTf)₂/70 °C/12 h</td>
<td>20%</td>
</tr>
<tr>
<td>8°</td>
<td>MeOH</td>
<td>CuBr/70 °C/12 h</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>Zn(OTf)₂/70 °C/12 h</td>
<td>54%</td>
</tr>
<tr>
<td>10</td>
<td>EtOH</td>
<td>InCl₃/70 °C/12 h</td>
<td>36%</td>
</tr>
<tr>
<td>11</td>
<td>CH₂CN</td>
<td>InCl₃/70 °C/12 h</td>
<td>21%</td>
</tr>
<tr>
<td>12</td>
<td>DCE</td>
<td>InCl₃/70 °C/12 h</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>InCl₃/70 °C/12 h</td>
<td>12%</td>
</tr>
<tr>
<td>14</td>
<td>DCM</td>
<td>InCl₃/70 °C/12 h</td>
<td>26%</td>
</tr>
<tr>
<td>15°</td>
<td>MeOH</td>
<td>InCl₃/12 h</td>
<td>41%</td>
</tr>
</tbody>
</table>

With the optimal reaction conditions in hand, next we explored the scope and limitations of the method for the synthesis of sulfoximine based tetrazoles (5). Differently substituted sulfoximines, aldehydes and isocyanides were utilized, and the results are shown in Scheme 3. Various aromatic aldehydes with electron-poor/electron-rich substitution patterns underwent successful reaction. It was noted that, electron-deficient aryl aldehydes provided better outcomes than their electron-rich counterparts. Bulky triphenylamine aldehyde and heteroaromatic benzothiophene aldehyde also delivered very (5n-5p) in good yields. Several cyclic and acyclic isocyanides such as cyclohexyl, adamantyl and t-butyli isocyanide furnished the desire products in moderate to good yields. Unfortunately, the primary alkyl isocyanate (p-toluenesulfonylmethyl isocyanide) and aromatic isocyanate (4-methylphenyl isocyanide) both failed to produce the desired products (5s-5t). The modifications of the S-aryl group (phenyl to substituted phenyl) and S-alkyl group (methyl to ethyl) of the NH-sulfoximines were well tolerated in the conversion. In addition to S-aryl-S-alkyl sulfoximines, diaryl/dialkyl symmetrical sulfoximines underwent reaction smoothly to produce the corresponding products (5u-5v). The electronic effects induced by S-aryl substituents appeared to have only a minor influence on product formation.
All the synthesized compounds were characterized by $^1$H and $^{13}$C spectroscopy, and HR-MS, and structures were unambiguously confirmed by single-crystal XRD analysis of two representative compounds (5c) and (5e) (see Supporting Information).

The successful utilization of NH-sulfoximines as nucleophiles in the UT-4CR, inspired us to apply sulfonimidamide (SIA) (6) (Scheme 4) to construct SIA derived tetrazoles via UT-4CR. SIAs, the mono-aza analogues of sulfonamides, with a stereogenic tetrahedral sulfur atom and sp$^2$ hybridized imino group (free -NH) are considered as an important emerging scaffold due to their applications in asymmetric synthesis, medicinal and the agrochemical industry.\textsuperscript{20}

Initially, SIA (6a) was treated with aldehyde (2a) isocyanide (3a) and TMS-N$_3$ (4) under the previously optimized reaction conditions (Table 1, entry 6), but the desired product (7a) was formed in only minor amounts; accompanied by the side-product, cyclic amine-based tetrazole (8a) as the major product. SIA (6) would appear to be acting as surrogate amine to yield (8). A previous report from our group had already described the surrogate nature of SIA under specific conditions.\textsuperscript{14a}

Considering that the elevated reaction temperatures may result in S-N bond cleavage, the reaction was performed at lower temperature (Table 2, entry 3) and (7a) was obtained as the major product (52 %) at 45°C, along with 18 % of by-product (8a). Screening of other Lewis acids, such as ZnCl$_2$ and Zn(OTf)$_2$ showed that they were not as effective as InCl$_3$ (Table 2, entries 4-5).

Hence, following the optimized condition (Table 2, entry 3), we scrutinized the scope and generality of the reaction with SIA (Scheme 5).

Reaction of SIAs with various S-aryl (-Ph, 4-MePh, 4-OMePh) and S-cyclic amines (pyrrolidine and piperidine) worked equally well to deliver the corresponding product (7).

Diverse substituted aromatic aldehydes, with electron-withdrawing and donating substituents were employed successfully. The bulky triphenylamine benzaldehyde readily took part in the reaction to furnish (7e). Different secondary and tertiary isocyanides were also well tolerated to deliver the desired products in moderate yield. However, our attempts to use a primary alyl isocyanide (p-toluenesulfonyl methyl isocyanide) and an aromatic isocyanide (4-methoxyphenyl isocyanide) were unsuccessful (7i-7j).

### Table 2 Optimization process for the synthesis of sulfonimidamide derived tetrazoles\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Yield (7/8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH/ InCl$_3$/ 70°C/ 10 h</td>
<td>7a 18%, 8a 65%</td>
</tr>
<tr>
<td>2</td>
<td>MeOH/ InCl$_3$/ RT/ 10 h</td>
<td>7a 0%, 8a 20%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH/ InCl$_3$/ 45°C/ 10 h</td>
<td>7a 52%, 8a 18%</td>
</tr>
<tr>
<td>4</td>
<td>MeOH/ ZnCl$_2$/ 45°C/ 10 h</td>
<td>7a 30%, 8a 40%</td>
</tr>
<tr>
<td>5</td>
<td>MeOH/ Zn(OTf)$_2$/ 45°C/ 10 h</td>
<td>7a 34%, 8a 38%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions for the one-pot 4-component reaction: (6a) (1.2 equiv.), (2a) (1.2 equiv.), (3a) (1.0 equiv.), (4) (1.0 equiv.), Lewis acid (0.5 equiv.), in 1 mL solvent. \textsuperscript{b} Isolated yields.
A probable mechanistic approach based on previous literature reports and current findings is portrayed in Scheme 6. In the presence of InCl₃, sulfoximine (1) reacts with aldehyde (2) to generate (5la), which on reaction with the isocyanide yields intermediate nitritium cation (5lb). Subsequent cycloaddition of (5lb) with azide delivers expected product (5) via (5ic). SIA (6) follows a similar route to furnish the corresponding tetrazole (7). However, the surrogate nature of the SIA, that leads to (8) can be explained as in Scheme 7. In the presence of InCl₃, the sp³ amine of SIA attacks the aldehyde to generate intermediate (8ia), which undergoes intramolecular rearrangement (transacylation) and C-O bond cleavage of (8ib) to produce iminium intermediate (8ic) via elimination. Successive reaction of isocyanide with (8ic) and further 3+2 cycloaddition of (8id) with azide leads to the formation of (8).

In conclusion, we have demonstrated the azido-Ugi-4-component reaction for the synthesis of α-sulfoximinoo tetrazoles. A wide range of sulfoximines, aldehydes and isocyanides has been assembled with TMS-azide in the presence of InCl₃ to form two new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process. Use of SIAs instead of sulfoximines has delivered the new C-N bonds, one C-C bond and one N-N bond in a single process.
\(\text{N}-(1-(\text{4-Butyl})-1H-tetrazol-5-yl)-(p-tolyl)methyl)-S-methyl S-4-chlorophenyl sulfoximine (Si)\)

Yellowish viscous liquid, 57 % yield. TLC (SiO2): R\(_c\) 0.21 (30 % ethyl acetate in hexane).

\(\text{N}-(1-(\text{4-Butyl})-1H-tetrazol-5-yl)-(4-chlorophenyl)methyl)-S-methyl S-4-bromophenyl sulfoximine (Si)\)

Colorless viscous liquid, 62 % yield. TLC (SiO2): R\(_c\) 0.25 (30 % ethyl acetate in hexane).

\(\text{N}-(1-(\text{4-Butyl})-1H-tetrazol-5-yl)-(4-chlorophenyl)methyl)-S-ethyl S-4-methoxyphenyl sulfoximine (Si)\)

White solid, mp 120-122 °C, 67 % yield. TLC (SiO2): R\(_c\) 0.2 (30 % ethyl acetate in hexane).

\(\text{N}-(1-(\text{4-Butyl})-1H-tetrazol-5-yl)-(4-chlorophenyl)methyl)-S-ethyl S-4-methoxyphenyl sulfoximine (Si)\)

Colorless viscous liquid, 68 % yield. TLC (SiO2): R\(_c\) 0.21 (30 % ethyl acetate in hexane).

\(\text{N}-(1-(\text{Adamantyl})-1H-tetrazol-5-yl)-(4-chlorophenyl)methyl)-S-methyl S-5-methoxyphenyl sulfoximine (Si)\)

Brownish viscous liquid, 67 % yield. TLC (SiO2): R\(_c\) 0.30 (30 % ethyl acetate in hexane).
7.66 (d, J = 7.0 Hz, 3H), 1.81-1.76 (m, 2H), 1.73-1.71 (m, 1H), 1.48-1.45 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H).

\(^1^C\)NMR (125 MHz, CDCl\(_3\)): \(\delta\) 155.2, 140.7, 138.9, 137.5, 135.3, 131.6, 128.5, 128.3, 121.8, 58.9, 53.3, 51.1, 33.2, 25.5, 24.9, 7.9.

HRMS (ESI-TOF) m/z: [M+H]* cdlc for C\(_{31}\)H\(_{35}\)N\(_2\)O\(_{2}\)S\(_2\): 494.0678; found 494.0671.

N-(1-(tert-Butyl)-1H-tetrazol-5-yl)(N,N-diphenylalanine)methyl)-S-methyl S-4-methoxyphenyl sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 72 %.

(Diastereomer-1): White solid, mp 170-172 °C. TLC (SiO\(_2\)): R\(_f\) 0.24 (40 % ethyl acetate in hexane).

IR (KBr): 3308, 3039, 2937, 2835. HRMS (ESI-TOF) m/z: [M+H]+ cdlc for C\(_{31}\)H\(_{33}\)N\(_2\)O\(_2\)S, 559.2251; found 559.2250.

N-(1-(tert-Butyl)-1H-tetrazol-5-yl)(N,N-diphenylalanine)methyl)-S-methyl S-4-methoxyphenyl sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 70 %.

(Diastereomer-1): White solid, mp 159-170 °C. TLC (SiO\(_2\)): R\(_f\) 0.26 (40 % ethyl acetate in hexane).

IR (KBr): 3343, 2997, 2879, 2136, 1907, 1673, 1586, 1511, 1484, 1463, 1314, 1297, 1261, 1127, 1147, 1024, 1009, 982, 853, 665 cm\(^{-1}\).

HRMS (ESI-TOF) m/z: [M+H]+ cdlc for C\(_{31}\)H\(_{33}\)N\(_2\)O\(_2\)S, 559.2251; found 559.2250.

N-(1-(tert-Butyl)-1H-tetrazol-5-yl)(N,N-diphenylalanine)methyl)-S-methyl S-4-methoxyphenyl sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 70 %.

(Diastereomer-2): White solid, mp 167-168 °C.

IR (KBr): 3308, 3039, 2937, 2835. HRMS (ESI-TOF) m/z: [M+H]+ cdlc for C\(_{31}\)H\(_{33}\)N\(_2\)O\(_2\)S, 559.2251; found 559.2250.

N-(1-(tert-Butyl)-1H-tetrazol-5-yl)(N,N-diphenylalanine)methyl)-S-methyl S-4-methoxyphenyl sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 70 %.

(Diastereomer-1): White solid, mp 167-172 °C. TLC (SiO\(_2\)): R\(_f\) 0.24 (40 % ethyl acetate in hexane).

IR (KBr): 3308, 3039, 2937, 2835. HRMS (ESI-TOF) m/z: [M+H]+ cdlc for C\(_{31}\)H\(_{33}\)N\(_2\)O\(_2\)S, 559.2251; found 559.2250.

N-(1-(tert-Butyl)-1H-tetrazol-5-yl)(N,N-diphenylalanine)methyl)-S-methyl S-4-methoxyphenyl sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 70 %.

(Diastereomer-2): White solid, mp 167-168 °C.
\( ^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \): \( \delta \) 7.80 (d, \( J = 8.0 \text{ Hz, 2H} \)), 7.45 (brs, 4H), 7.29 (d, \( J = 8.0 \text{ Hz, 2H} \)), 6.48 (s, 1H), 3.08-3.06 (m, 2H), 2.93-2.91 (m, 2H), 2.41 (s, 3H), 1.71 (brs, 4H), 1.58 (s, 9H).

\( ^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \): \( \delta \) 156.6, 1434, 140.2, 131.5, 131.5, 129.6, 129.1, 127.8, 121.5, 62.2, 51.8, 48.3, 30.2, 25.2, 21.5.

HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C_{29}H_{33}BrN_{10}O_{11}: 517.1380; found 517.1385.

\( ^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \): \( \delta \) 155.0, 139.5, 134.5, 132.7, 132.2, 131.3, 129.7, 129.2, 128.1, 127.7, 122.8, 57.8, 48.8, 48.0, 33.1, 32.8, 25.6, 25.4, 25.2, 23.5.

Yellowish viscous liquid, 45 % yield. TLC (SiO\(_2\)): R\(_c\) 0.44 (30 % ethyl acetate in hexane).

\( ^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \): \( \delta \) 155.0, 139.5, 134.5, 132.7, 132.2, 131.3, 129.7, 129.2, 128.1, 127.7, 122.8, 57.8, 48.8, 48.0, 33.1, 32.8, 25.6, 25.4, 25.2, 23.5.

HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C\(_{29}\)H\(_{33}\)BrN\(_{10}\)O\(_{11}\): 621.0641; found 621.0644.

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**Supporting Information**

YES (this text will be updated with links prior to publication)

**Primary Data**

NO.

**Conflict of Interest**

The authors declare no conflict of interest.

**References**


SUPPORTING INFORMATION

Synthesis of α-Sulfoximino Tetrazoles via Azido-Ugi 4-Component Reaction
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7) HRMS spectra of representative compounds (5e, 5l, 5n, 7e and 7g) S41-S43

1. General
The starting material sulfoximine/sulfonimidamides were synthesized in the laboratory following the reported methods.1 The aldehydes, isocyanides, TMSN 3, InCl3 and MeOH were purchased from various suppliers and used as received. 1H and 13C NMR spectra were recorded on BRUKER NMR spectrophotometer operating at 500 MHz and 125 MHz respectively. CDCl3 and CD6CO were used as solvent to record NMR spectra. Mass spectra were recorded with Agilent QTOF G6545 XT spectrometer at 50,000 resolutions using ESI mode. Melting points were uncorrected.

2. General procedure for the synthesis of Sulfoximines
To a stirred solution of diaryl(or alkylaryl)sulfide (1 mmol) in MeOH (5 ml), (NH4)2CO3 (1.5 equiv.) and PhI(OAc) 2 (2.3 equiv.) were added and the solution was stirred at room temperature for 3-4 h. After the disappearance of the sulfide (checked by TLC), the solvent
was removed under reduced pressure. The crude product was purified by flash column chromatography (25–40 % EtOAc/Hexane). (20 mmol sulfide and 100 ml MeOH were used for the gram-scale reaction).

3. General procedure for the one-pot tandem synthesis of tetrazole based sulfoximine/sulfonimidamide$^a$ (5/7)

A solution of sulfoximine (30 mg 1.2 equiv.) aldehyde (1.2 equiv.) isocyanide (1.0 equiv.) and InCl$_3$ (0.5 equiv.) in 1.0 mL of methanol in a 20 ml sealed tube was stirred at 70 °C under argon atmosphere. After 15 mins, TMS-azide (1.0 equiv.) was added to the reaction mixture and the reaction was stirred for stipulated period. Completion of reaction was confirmed by TLC and the reaction mixture was poured in water and extracted with ethyl acetate (2×10 mL). The organic layer was washed with NaHCO$_3$ solution, water, brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography with 20−30 % of EtOAc in hexane as the eluent.

$^a$For sulfonimidamides, the reaction was stirred at 45 °C.

All the synthesized compounds (except 5q/5r) have more than one (generally two) stereogenic centres. Hence, two diastereomers were expected to form. However, we isolated only single diastereomer for 5a-5m, 5p, 5q and 7. Another diastereomer was formed in trace amount (5a-5m, 5p, 5q and 7). For compound 5n-5o, two diastereomers were isolated almost in equal amount.

4. Data for single crystal X-ray structure of 5c and 5e

The needle like crystals were obtained for both 5c and 5e by slow evaporation (at room temp) of DCM/Hexane mixture in 24 h.

The 5c (CCDC deposition No. 2208432) and 5e (CCDC deposition No. 2208431) compound crystals were mounted on Hampton cryoloops. All geometric and intensity data of the crystal was collected using a Super-Nova (Mo) X-ray diffractometer equipped with a micro-focus sealed X-ray tube Mo-Kα (λ = 0.71073 Å) X-ray source and HyPix3000 detector with increasing ω (width of 0.3 per frame) at a scan speed of 10 s per frame. The CrysAlisPro software was used for data acquisition and data extraction. Using Olex2, the structure was solved with the SIR2004 structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic thermal
parameters. Sample Preparation: The needle like crystal was obtained for both 5c and 5e by slow evaporation (at room temp) of DCM/Hexane mixture. Figure S1 and figure S2 represent ORTEP diagrams of compound 5c and 5e with thermal ellipsoid set to 50 % probability level.

Figure S1: The ORTEP diagram of compound 5c with thermal ellipsoid set to 50 %

Figure S2: The ORTEP diagram of compound 5e with thermal ellipsoid set to 50 %

Table S1. Crystal data and structure refinement for 5c and 5e

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5. Characterisation data of the isolated compounds

**Compound 5a**

It was obtained as a colorless sticky liquid, 61 % yield. TLC (SiO2): Rf; 0.25 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl3): \(\delta\) 7.63 (d, \(J = 8.5\) Hz, 2H), 7.57 (d, \(J = 8.5\) Hz, 2H), 7.23 (d, \(J = 8.0\) Hz, 2H), 7.10 (d, \(J = 8.0\) Hz, 2H), 6.01 (s, 1H), 3.08 (s, 3H), 2.29 (s, 3H), 1.41 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl3): \(\delta\) 156.2, 139.9, 138.9, 137.7, 137.4, 130.2, 129.4, 127.5, 61.7, 52.3, 45.6, 29.9, 21.1. HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C\(_{20}\)H\(_{25}\)BrN\(_5\)OS, 462.0958; found 462.0960.

**Compound 5b**

It was obtained as a yellowish sticky liquid, 60 % yield. TLC (SiO2): Rf; 0.26 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl3): \(\delta\) 7.65 (d, \(J = 7.0\) Hz, 1H), 7.57 (d, \(J = 8.5\) Hz, 2H), 7.32 (d, \(J = 7.5\) Hz, 1H), 7.27-7.24 (m, 2H), 7.19 (d, \(J = 8.0\) Hz, 2H), 7.05 (t, \(J = 8.0\) Hz, 1H), 6.01 (s, 1H), 3.06 (s, 3H), 2.34 (s, 3H), 1.36 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl3): \(\delta\) 156.3, 144.5, 140.8, 137.5, 136.5, 130.1, 128.7, 127.5, 123.6, 61.7, 52.6, 45.6, 29.9, 21.6. HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C\(_{20}\)H\(_{26}\)N\(_5\)OS, 384.1853; found 384.1857.

**Compound 5c**
It was obtained as a white solid, mp 114-116 °C, 65 % yield. TLC (SiO₂): Rf; 0.35 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.58 (brs, 4H), 7.28-7.27 (m, 4H), 6.00 (s, 1H), 3.12 (s, 3H), 1.42 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 155.8, 139.9, 139.1, 138.5, 133.8, 132.8, 130.1, 128.9, 128.9, 61.9, 52.0, 45.6, 29.8. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₁₉H₂₂BrClN₅O₂S, 482.0411; found 482.0418.

**Compound 5d**

It was obtained as a yellowish sticky liquid, 57 % yield. TLC (SiO₂): Rf; 0.21 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.01 (s, 1H), 3.08 (s, 3H), 2.29 (s, 3H), 1.41 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 156.3, 139.9, 138.4, 137.7, 137.5, 130.1, 129.7, 129.5, 127.5, 61.7, 52.4, 45.7, 29.9, 21.1. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₀H₂₅ClN₅O₂S, 418.1463; found 418.1472.

**Compound 5e**

It was obtained as a white solid, mp 117-118 °C, 68 % yield. TLC (SiO₂): Rf; 0.45 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.67 (dd, J = 8.0, 1.0 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.29 – 7.26 (m, 4H), 6.06 (s, 1H), 3.34-3.19 (m, 2H), 4.46 (m, 1H), 3.18 (s, 3H), 2.25-2.24 (m, 2H), 1.96-1.93 (m, 2H), 1.81-1.76 (m, 2H), 1.49-1.46 (m, 2H), 1.32-1.30 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 155.2, 140.6, 140.6, 136.1, 137.2, 133.9, 133.1, 130.1, 128.8, 128.0, 58.3, 51.5, 45.5, 33.2, 25.5, 24.9. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₁H₂₄BrClN₅O₂S, 508.0568; found 508.0571.

**Compound 5f**

It was obtained as a white solid, mp 120-122 °C, 62 % yield. TLC (SiO₂): Rf; 0.25 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.67 (dd, J = 8.0, 1.0 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.29 – 7.26 (m, 4H), 6.06 (s, 1H), 3.34-3.19 (m, 2H), 1.41 (s, 9H), 1.26 (t, J = 8.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 156.1, 139.9, 139.7, 137.7, 133.5, 129.5, 129.4, 128.9, 128.7, 61.8, 51.8, 51.4, 30.0, 7.1. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₀H₂₅ClN₅O₂S, 418.1463; found 418.1473.
**Compound 5g**

It was obtained as a white solid, mp 129-130 °C, 67 % yield. TLC (SiO₂): Rf; 0.21 (30 % ethyl acetate in hexane). \(^1^H\) NMR (500 MHz, CDCl₃): \(\delta\) 7.56 (d, \(J = 9.0\) Hz, 2H), 7.31-7.25 (m, 4H), 6.90 (d, \(J = 9.0\) Hz, 2H), 6.09 (s, 1H), 3.84 (s, 3H), 3.29 – 3.17 (m, 2H), 1.45 (s, 9H), 1.25 (t, \(J = 7.5\) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 163.6, 156.1, 139.8, 133.3, 131.4, 128.7, 128.5, 128.3, 114.6, 61.8, 55.6, 51.7, 51.6, 29.9, 7.1. HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C₂₁H₂₇ClN₅O₂S, 448.1568; found 448.1578.

**Compound 5h**

It was obtained as a white solid, mp 132-134 °C, 66 % yield. TLC (SiO₂): Rf; 0.25 (30 % ethyl acetate in hexane). \(^1^H\) NMR (500 MHz, CDCl₃): \(\delta\) 7.66 (d, \(J = 8.5\) Hz, 2H), 7.55 (t, \(J = 7.5\) Hz, 1H), 7.44 (t, \(J = 7.5\) Hz, 2H), 7.31 – 7.26 (m, 4H), 6.08 (s, 1H), 3.33 – 3.21 (m, 2H), 2.07 – 2.01 (m, 6H), 1.94-1.92 (m, 3H), 1.67-1.64 (m, 3H), 1.60-1.57 (m, 3H), 1.27 (t, \(J = 7.5\) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 156.1, 140.0, 137.9, 133.5, 133.4, 129.4, 129.3, 128.9, 128.7, 62.9, 51.9, 51.4, 42.1, 35.6, 29.6, 7.1. HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C₂₆H₃₁ClN₅OS, 496.1932; found 496.1935.

**Compound 5i**

It was obtained as a white solid, mp 179-181 °C, 70 % yield. TLC (SiO₂): Rf; 0.24 (30 % ethyl acetate in hexane). \(^1^H\) NMR (500 MHz, CDCl₃): \(\delta\) 7.63 (d, \(J = 9.0\) Hz, 2H), 7.31-7.26 (m, 4H), 6.91 (d, \(J = 9.0\) Hz, 2H), 6.04 (s, 1H), 3.84 (s, 3H), 3.14 (s, 3H), 2.08-2.04 (m, 6H), 1.98-1.96 (m, 3H), 1.68-1.65 (m, 3H), 1.61-1.59 (m, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 163.7, 156.1, 139.8, 133.5, 130.5, 128.9, 128.7, 114.7, 63.0, 55.8, 52.2, 46.0, 42.0, 35.6, 29.6. HRMS (ESI-TOF) m/z: [M+Na]^+ calcd for C₂₆H₃₀ClN₅NaO₂S, 534.1701; found 534.1711.

**Compound 5j**

It was obtained as a white solid, mp 125-127 °C, 57 % yield. TLC (SiO₂): Rf; 0.25 (30 % ethyl acetate in hexane). \(^1^H\) NMR (500 MHz, CDCl₃): \(\delta\) 7.75 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.69 (d, \(J = 8.5\) Hz, 2H), 7.53 (d, \(J = 8.5\) Hz, 2H), 7.50 (dd, \(J = 8.0, 1.0\) Hz, 1H), 7.27 (td, \(J = 7.5, 1.0\) Hz, 1H), 7.10 (td, \(J = 7.5, 1.5\) Hz, 1H), 6.39 (s, 1H), 2.94 (s, 3H), 1.46 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl₃):
δ 155.6, 139.2, 133.3, 132.5, 131.1, 129.9, 128.6, 128.2, 125.2, 123.2, 61.7, 51.6, 46.0, 29.8. HRMS (ESI-TOF) m/z: [M+H]+ calcd for C_{19}H_{22}Br_{2}N_{5}OS, 525.9901; found 525.9912.

**Compound 5k**

It was obtained as a colorless sticky liquid, 62 % yield. TLC (SiO_{2}): R_{f} 0.25 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl_{3}): δ 7.67 (d, J = 2.0 Hz, 1H), 7.53 (brs, 4H), 7.34 – 7.32 (m, 1H), 7.17-7.16 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 5.96 (s, 1H), 3.07 (s, 3H), 1.38 (s, 9H).

\(^13\)C NMR (125 MHz, CDCl_{3}): δ 155.6, 142.8, 139.9, 138.5, 132.8, 131.1, 130.6, 130.2, 130.1, 126.1, 122.9, 62.0, 52.0, 45.7, 29.9. HRMS (ESI-TOF) m/z: [M+H]+ calcd for C_{19}H_{22}Br_{2}N_{5}OS, 525.9889.

**Compound 5l**

It was obtained as a colorless sticky liquid, 68 % yield. TLC (SiO_{2}): R_{f} 0.21 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl_{3}): δ 7.65 (s, 1H), 7.47 (d, J = 9.0 Hz, 2H), 7.30 (dt, J = 7.5, 1.5, 0.5 Hz, 1H), 7.23 (dt, J = 7.5, 1.5, 0.5 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 5.91 (s, 1H), 4.49-4.46 (m, 1H), 3.80 (s, 3H), 3.22-3.16 (m, 2H), 2.21-2.18 (m, 1H), 2.01-1.98 (m, 1H), 1.94-1.92 (m, 1H), 1.87-1.84 (m, 1H), 1.78 – 1.71 (m, 1H), 1.55-1.53 (m, 1H), 1.31 – 1.26 (m, 1H), 1.23 (t, J = 7.5 Hz, 1H), 1.18-1.14 (m, 1H), 1.01-0.98 (d, J = 13.1 Hz, 1H), 0.90-0.88 (d, J = 12.4 Hz, 1H). \(^13\)C NMR (125 MHz, CDCl_{3}): δ 164.0, 155.5, 142.6, 140.7, 131.6, 130.9, 130.0, 126.9, 125.4, 122.8, 115.0, 58.9, 58.2, 55.8, 51.3, 33.2, 25.6, 24.9, 7.7. HRMS (ESI-TOF) m/z: [M+H]+ calcd for C_{23}H_{29}BrN_{5}O_{2}S, 518.1220; found 518.1229.

**Compound 5m**

It was obtained as brownish sticky liquid, 67 % yield. TLC (SiO_{2}): R_{f} 0.30 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl_{3}): δ 7.69 (d, J = 6.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.12 – 7.10 (m, 1H), 6.11 (s, 1H), 4.50-4.47 (m, 1H), 3.38-3.36 (m, 2H), 2.26-2.23 (m, 2H), 1.95-1.92 (m, 3H), 1.81-1.76 (m, 2H), 1.73-1.71 (m, 1H), 1.48-1.45 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H). \(^13\)C NMR (125 MHz, CDCl_{3}): δ 155.2, 140.7, 138.9, 137.5, 135.3, 131.6, 128.5, 128.3, 121.8, 58.9, 53.3, 51.1, 33.2, 25.5, 24.9, 7.9. HRMS (ESI-TOF) m/z: [M+H]+ calcd for C_{20}H_{23}BrN_{5}OS_{2}, 494.0678; found 494.0671
**Compound 5n:** Total yields (Both the Diastereomers) 72%.

(Diastereomer-1): It was obtained as a white solid. Mp 170-172 °C. TLC (SiO₂): Rₚ, 0.24 (40 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, J = 9.0 Hz, 2H), 7.22 (t, J = 8.0 Hz, 6H), 7.04 (dd, J = 7.5 Hz, 4H), 7.00-6.98 (m, 4H), 6.89 (d, J = 9.0 Hz, 2H), 6.02 (s, 1H), 3.83 (s, 3H), 3.12 (s, 3H), 1.46 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 163.5, 156.5, 147.6, 147.1, 134.6, 130.7, 129.2, 128.4, 124.3, 123.5, 122.9, 114.5, 61.6, 55.7, 51.9, 45.9, 29.9.

IR(KBr): 3059, 3038, 2937, 2835, 1735, 1587, 1508, 1487, 1405, 1375, 1317, 1259, 1215, 1154, 1078, 1025, 981, 800, 697 cm⁻¹. HRMS (ESI-TOF) m/z: [M+Na]+ calcd for C₃₂H₃₄N₆NaO₂S, 589.2356; found 589.2356.

(Diastereomer-2): It was obtained as a white solid, mp 172-173 °C. TLC (SiO₂): Rₚ; 0.24 (40 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, J = 9.0 Hz, 2H), 7.23 – 7.17 (m, 6H), 7.01 - 6.99 (m, 2H), 6.97 – 6.95 (m, 4H), 6.92 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.02 (s, 1H), 3.87 (s, 3H), 3.10 (s, 3H), 1.68 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 163.1, 157.0, 147.5, 147.1, 133.2, 130.3, 129.2, 128.9, 125.4, 124.3, 123.1, 122.9, 114.3, 61.5, 55.6, 52.5, 46.3, 30.1. HRMS (ESI-TOF) m/z: [M+Na]+ calcd for C₃₂H₃₄N₆NaO₂S, 589.2356; found 589.2356.

**Compound 5o:** Total Yield (Both the Diastereomers) 70%.

(Diastereomer-1): It was obtained as a white solid. Mp 169-170 °C. TLC (SiO₂): Rₚ, 0.26 (40 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.76 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.24-7.20 (m, 6H), 7.04 (d, J = 7.5 Hz, 4H), 7.00-6.97 (m, 4H), 6.01 (s, 1H), 3.14 (s, 3H), 1.43 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 156.4, 147.7, 147.3, 139.9, 134.5, 133.4, 129.5, 129.3, 128.6, 128.5, 124.5, 123.6, 123.0, 61.6, 52.0, 45.6, 30.0. HRMS (ESI-TOF) m/z: [M+Na]+ calcd for C₃₁H₃₂N₆NaO₂S, 559.2251; found 559.2257.

(Diastereomer-2): It was obtained as a white solid, mp 167-168 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.79 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.23 – 7.19 (m, 4H), 7.17 (d, J = 8.5 Hz, 2H), 7.00 (t, J = 7.5 Hz, 2H), 6.95 (d, J = 7.5 Hz, 4H), 6.80 (d, J = 8.5 Hz, 2H), 6.04 (s, 1H), 3.13 (s, 3H), 1.68 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 157.0, 147.6, 140.2, 132.9, 129.7, 129.3, 129.2, 129.1, 128.3, 127.2, 124.4, 123.3, 123.0, 61.7, 52.7, 46.1, 30.3. HRMS (ESI-TOF) m/z: [M+Na]+ calcd for C₃₁H₃₂N₆NaO₂S, 559.2251; found 559.2259.
**Compound 5p**

It was obtained as a brown sticky liquid, 58% yield. TLC (SiO₂): Rf; 0.18 (30% ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 8.18 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 9.0 Hz, 2H), 7.43 – 7.34 (m, 2H), 7.20 (s, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.46 (s, 1H), 3.83 (s, 3H), 3.26 – 3.24 (m, 1H), 3.17 – 3.14 (m, 1H), 1.34 (s, 9H), 1.20 (t, J = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 163.4, 156.1, 140.9, 137.2, 134.9, 131.4, 129.0, 125.7, 124.5, 124.3, 122.7, 122.3, 114.3, 61.2, 55.6, 51.7, 46.4, 29.6, 6.8. HRMS (ESI-TOF) m/z: [M+H]+ calecd for C₂₃H₂₈N₅O₂S₂, 470.1679; found 470.1689.

**Compound 5q**

It was obtained as off-white solid, mp 87-88 °C, 44% yield. TLC (SiO₂): Rf; 0.20 (30% ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.42 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 6.32 (s, 1H), 3.35 – 3.31 (m, 2H), 1.62 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 156.9, 141.3, 131.5, 129.1, 121.4, 61.9, 52.7, 51.8, 51.0, 30.1, 16.1, 15.7, 15.5, 15.4. IR (KBr): 3343, 2997, 2981, 2879, 2136, 1907, 1673, 1586, 1511, 1484, 1460, 1393, 1314, 1297, 1261, 1251, 1147, 1127, 1042, 1009, 950, 829, 783, 665 cm⁻¹. HRMS (ESI-TOF) m/z: [M+Na]+ calecd for C₁₈H₂₈BrN₅NaOS, 442.1271; found 442.1273.

**Compound 5r**

It was obtained as a yellowish sticky liquid, 47% yield. TLC (SiO₂): Rf; 0.28 (30% ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 6.5 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.60 (s, 1H), 4.30 – 4.27 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 1.98-1.95 (m, 2H), 1.83-1.79 (m, 1H), 1.60-1.56 (m, 3H), 1.34-1.31 (m, 2H), 1.19 (brs, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 171.5, 163.3, 163.2, 133.0, 132.2, 130.6, 130.4, 128.7 128.4, 127.0, 114.9, 114.7, 114.6, 61.8, 58.9, 55.8, 48.0, 33.1, 25.7, 24.8. HRMS (ESI-TOF) m/z: [M+H]+ calecd for C₂₈H₃₁ClN₅O₃S, 552.1831; found 552.1840

**Compound 7a**
It was obtained as a yellowish solid, mp 110-112 °C, 52 % yield. TLC (SiO₂): Rf; 0.45 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.97 (d, J = 7.5 Hz, 2H), 7.57 - 7.54 (m, 1H), 7.51-7.48 (m, 2H), 7.45 (d, J = 7.5 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 6.53 (s, 1H), 3.09-3.07 (m, 2H), 2.96-2.94 (m, 2H), 2.33 (s, 3H), 1.72 (brs, 4H), 1.59 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 157.1, 137.9, 137.2, 136.7, 132.4, 129.1, 128.9, 127.8, 127.4, 61.9, 51.1, 48.4, 30.2, 25.2, 21.2. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₃H₃₁N₆O₅S, 439.2275; found 439.2281

**Compound 7b**

It was obtained as off-white solid, mp 107-108 °C, 56 % yield. TLC (SiO₂): Rf; 0.45 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, J = 8.0 Hz, 2H), 7.54 – 7.51 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 6.52 (s, 1H), 3.09 – 3.08 (m, 2H), 2.95 – 2.93 (m, 2H), 1.72 (brs, 4H), 1.59 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 156.6, 139.5, 136.5, 133.5, 132.6, 129.1, 128.9, 128.7, 127.8, 62.2, 50.9, 48.5, 30.2, 25.2. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₂H₂₈ClN₆O₅S, 459.1728; found 459.1733.

**Compound 7c**

It was obtained as a white solid, mp 89-91 °C, 59 % yield. TLC (SiO₂): Rf; 0.44 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.80 (d, J = 8.0 Hz, 2H), 7.45 (brs, 4H), 7.29 (d, J = 8.0 Hz, 2H), 6.48 (s, 1H), 3.08-3.06 (m, 2H), 2.93-2.91 (m, 2H), 2.41 (s, 3H), 1.71 (brs, 4H), 1.58 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 156.6, 143.4, 140.2, 133.5, 131.5, 129.6, 129.2, 127.8, 121.5, 62.2, 51.0, 48.4, 30.2, 25.2, 21.5. HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₂₃H₃₀BrN₆O₅S, 517.1380; found 517.1385.

**Compound 7d**

It was obtained as a white solid, mp 83-95 °C, 61 % yield. TLC (SiO₂): Rf; 0.42 (30 % ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.50 (s, 1H), 3.86 (s, 3H), 3.09-3.07 (m, 2H), 2.96-2.94 (m, 2H), 2.31-2.28 (m, 3H), 2.11-2.19 (m, 4H), 1.64 – 1.61 (m, 8H). ¹³C NMR (125 MHz, CDCl₃): δ 162.8, 156.6, 139.8, 133.2, 129.9, 128.8, 128.4, 128.3, 114.0, 63.0, 55.5, 51.2, 48.3, 41.9, 35.6, 29.6, 25.1. IR
(KBr): 3357, 3259, 3085, 2960, 2839, 2581, 2037, 1898, 1727, 1590, 1494, 1390, 1325, 1261, 1154, 1098, 1059, 1017, 892, 833, 753, 677 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M+H]\(^+\) calcd for C\(_{29}\)H\(_{36}\)ClN\(_6\)O\(_2\)S, 567.2303; found 567.2307.

**Compound 7e**

It was obtained as a yellow solid, mp 189-191 °C, 58 % yield. TLC (SiO\(_2\)): R\(_f\); 0.45 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.82 (d, \(J = 8.0\) Hz, 2H), 7.45 (d, \(J = 8.5\) Hz, 2H), 7.27 (d, \(J = 8.0\) Hz, 2H), 7.24 – 7.21 (m, 4H), 7.05-7.03 (m, 5H), 7.02 – 6.98 (m, 3H), 6.47 (s, 1H), 3.10-3.05 (m, 2H), 2.97-2.93 (m, 2H), 2.40 (s, 3H), 1.64 (s, 9H), 1.62-1.61 (m, 4H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 157.1, 147.8, 147.2, 143.1, 135.0, 133.8, 129.5, 129.3, 128.6, 127.9, 124.4, 123.6, 123.0, 61.9, 51.1, 48.4, 30.3, 25.2, 21.5. IR (KBr): 3033, 2972, 2849, 1588, 1504, 1485, 1402, 1317, 1272, 1254, 1194, 1006, 789, 754, 699 cm\(^{-1}\). HRMS (ESI-TOF) m/z: [M+Na]\(^+\) calcd for C\(_{35}\)H\(_{39}\)N\(_7\)NaOS, 628.2829; found 628.2825.

**Compound 7f**

It was obtained as a yellowish solid, mp 112-113 °C, 55 % yield. TLC (SiO\(_2\)): R\(_f\); 0.44 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.74 (d, \(J = 8.0\) Hz, 2H), 7.55 (d, \(J = 8.5\) Hz, 2H), 7.35 – 7.32 (m, 4H), 6.23 (s, 1H), 4.72-4.67 (m, 1H), 2.90-2.85 (m, 2H), 2.80-2.76 (m, 2H), 2.44 (s, 3H), 1.99-1.97 (m, 1H), 1.93-1.87 (m, 1H), 1.76-1.74 (m, 1H), 1.68-1.66 (m, 5H), 1.49-1.47 (m, 2H), 1.42-1.39 (m, 2H), 1.33-1.25 (m, 3H), 1.18-1.16 (m, 1H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 155.7, 143.4, 138.7, 133.7, 132.7, 129.7, 128.8, 128.4, 127.7, 58.0, 49.8, 47.7, 32.4, 25.5, 25.3, 25.0, 23.6, 21.6. HRMS (ESI-TOF) m/z: [M+H]\(^+\) calcd for C\(_{26}\)H\(_{34}\)ClN\(_6\)OS, 513.2198; found 513.2193.

**Compound 7g**

It was obtained as a yellowish sticky liquid, 57 % yield. TLC (SiO\(_2\)): R\(_f\); 0.42 (30 % ethyl acetate in hexane). \(^1\)H NMR (500 MHz, Acetone): \(\delta\) 7.84 (d, \(J = 9.0\) Hz, 2H), 7.69 (d, \(J = 8.5\) Hz, 2H), 7.39 (d, \(J = 8.5\) Hz, 2H), 7.09 (d, \(J = 9.0\) Hz, 2H), 6.45 (s, 1H), 3.87 (s, 3H), 2.78 – 2.77 (m, 4H), 1.67 (s, 9H), 1.43 – 1.39 (m, 4H), 1.33 – 1.31 (m, 2H). \(^1\)C NMR (125 MHz, Acetone): \(\delta\) 163.9, 157.6, 141.6, 133.6, 130.7, 130.2, 129.2, 128.1, 114.9,

**Compound 7h**

It was obtained as a yellowish sticky liquid, 45 % yield. TLC (SiO2): Rf; 0.44 (30 % ethyl acetate in hexane). $^1$H NMR (500 MHz, CDCl3): $\delta$ 8.11 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.74 (d, $J = 8.5$ Hz, 2H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.54 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.22 – 7.18 (m, 1H), 6.52 (s, 1H), 4.79-4.73 (m, 1H), 2.82 – 2.79 (m, 2H), 2.67-2.62 (m, 2H), 1.99-1.88 (m, 5H), 1.81-1.78 (m, 1H), 1.71-1.69 (m, 1H), 1.37-1.32 (m, 3H), 1.29-1.25 (m, 3H), 1.21-1.18 (m, 3H). $^{13}$C NMR (125 MHz, CDCl3): $\delta$ 155.0, 139.5, 134.5, 132.7, 132.2, 131.3, 129.7, 129.2, 128.1, 127.7, 122.8, 57.8, 48.8, 48.0, 33.1, 32.8, 25.6, 25.4, 25.2, 23.5. HRMS (ESI-TOF) m/z: [M+H]^+ calcd for C_{25}H_{31}Br_2N_6OS, 621.0641; found 621.0644.

**References**

6. Spectral Data

$^1$H NMR and $^{13}$C NMR of 5a in CDCl$_3$
$^{1}$H NMR and $^{13}$C NMR of 5b in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5c in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5d in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5e in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5f in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5g in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5h in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5i in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5j in CDCl₃
$^1$H NMR and $^{13}$C NMR of 5k in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5l in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5m in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5n (diastereomer-1) in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5n (diastereomer-2) in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5o (diastereomer-1) in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5o (diastereomer-2) in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5p in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5q in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 5r in CDCl$_3$
$^{1}$H NMR and $^{13}$C NMR of 7a in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 7b in CDCl₃
$^1$H NMR and $^{13}$C NMR of 7c in CDCl$_3$
1H NMR and 13C NMR of 7d in CDCl3

H2O
$^1$H NMR and $^{13}$C NMR of 7e in CDCl$_3$
$^{1}H$ NMR and $^{13}C$ NMR of 7f in CDCl$_3$
$^1$H NMR and $^{13}$C NMR of 7g in CD$_6$CO
$^1$H NMR and $^{13}$C NMR of 7h in CDCl$_3$
7. HRMS Data

HRMS spectrum of compound 5e

M+H Peak = 508.0571

M+Na Peak

HRMS spectrum of compound 5l

M+H = 518.1229

M+Na = 518.1229
HRMS spectrum of Compound 5n

HRMS spectrum of compound of 7e

M+Na Peak = 589.2356

M+Na Peak = 628.2825
HRMS spectrum of compound 7g

**M+H Peak** = 503.2001