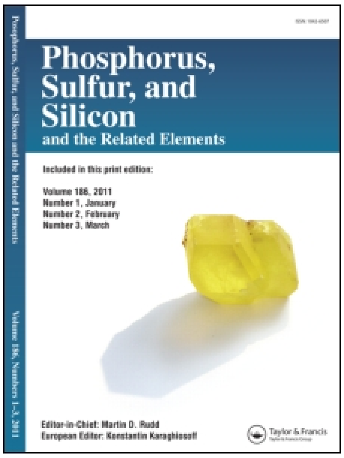

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Synthesis of Some Prospective Bioactive Azeto[2,1-d][1,5]benzothiazepinones

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SYNTHESIS OF SOME PROSPECTIVE BIOACTIVE AZETO[2,1-d][1,5]BENZOTHIAZEPINONES

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Ten azeto[2,1-d][1,5]benzothiazepinone derivatives 6a–j were synthesized starting from 4-acetyl-2-phenyl-1,2,3-triazole 1. First, condensation of 1 with various aldehydes 2a–e afforded α,β-unsaturated carbonyl compounds 3a–e, which subsequently underwent cyclization with o-aminothiophenol to yield the corresponding 2,4-disubstituted-1,5-benzothiazepines 4a–e. Treatment of 4a–e with chloroacetyl chloride 5a or phenoxyacetyl chloride 5b by [2+2] cycloaddition reaction gave the title compounds 6a–j. The assignment of the structures of 6a–j was made by ^{1}H NMR, MS, and elemental analyses.

Keywords 4-Acetyl-2-phenyl-1,2,3-triazole; benzothiazepine; [2+2] cycloaddition; β-lactam

INTRODUCTION

1,5-Benzothiazepine is an important seven-membered heterocyclic ring system. Intensively used clinically, the drug diltiazem contains this ring system.[1] It has been used as a calcium antagonist,[2] anticancer drug,[3,4] antibacterial,[5] anticonvulsant, tranquilizer,[6] nd antidepressant.[7] Due to its broad spectrum of biological activity, recent work has demonstrated the interest to affix an additional heterocycle on 1,5-benzothiazepines. Pharmaceutical properties of such compounds are magnified when the heterocycle is bound to the hepta-atomic nucleus.[8–10] The diverse pharmacological properties associated with 1,5-benzothiazepine moiety have been reviewed by Bariwal et al.[11]

In addition, the 1,2,3-triazole–containing compounds have displayed a wide range of biological activities. Many 1,2,3-triazole derivatives have been reported to exhibit anticancer,[12] insecticidal,[13] antibiotic,[14] antimycotic,[15] and anti-HIV activities.[16] Moreover, the introduction of a 1,2,3-triazole ring into a parent compound may improve its properties and biological activities, such as in tazobactam sodium.[17,18]

On the other hand, the β-lactam skeleton is the structural feature of the widely employed family of antimicrobial agents, which show biological activities that include inhibition of prostate specific antigen,[19] thrombin,[20] human cytomegalovirus protein,[21] human leukocyte elastase,[22] and cholesterol absorption.[23] Most important, antibiotics possess

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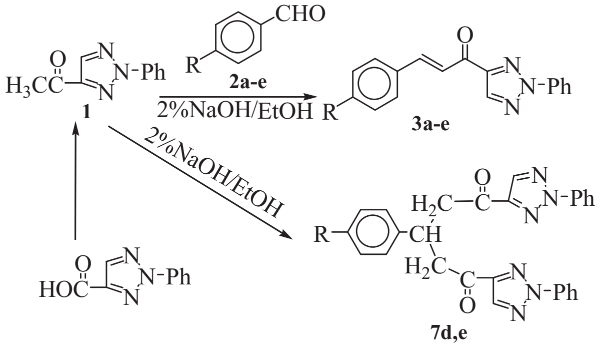
a representative structure of a β-lactam fused, five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms.[24–28]

However, to date there have been no reports on the syntheses of derivatives with a 1,2,3-triazole nucleus attached to a 1,5-benzothiazepine ring, which may show interesting biological activities. In view of these facts and in order to search for new 1,5-benzothiazepine compounds with higher bioactivity, this article deals with syntheses of compounds having a tricyclic ring system containing 1,5-benzothiazepine, 1,2,3-triazole, and β-lactam. This search is possibly correlated with the biological activity of 1,5-benzothiazepines and the fusion of the heterocyclic nucleus to the thiazepine system, which could induce an increase of the ring inversion barrier and consequently modify the activity profile.

RESULTS AND DISCUSSION

The α,β-unsaturated carbonyl compounds **3a–c** were prepared by a condensation reaction of 4-acetyl-2-phenyl-1,2,3-triazole **1** with substituted aldehydes **2a–c** according to the method described for benzalacetophenone,[29,30] but an attempt to prepare α,β-unsaturated carbonyl compounds **3d,e** by the same method failed and instead gave Michael-type addition products **7d**,**e** as major products. Therefore the procedure was altered by dropping the 4-acetyl-2-phenyl-1,2,3-triazole **1** into the solution of the aldehydes **2d**,**e** in ethanol slowly, so the expected α,β-unsaturated carbonyl compounds **3d**,**e** were obtained (Scheme 1).



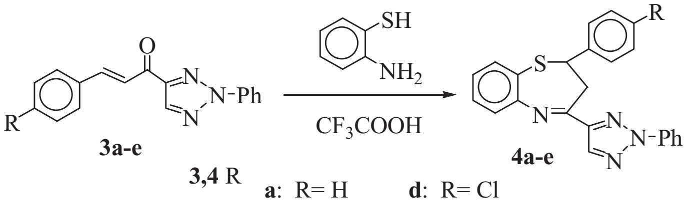
2,3,7 R
a: R= H **d**: R= Cl
b: R= CH_3 **e**: R= NO_2
c: R= OCH_3

Scheme 1

The α,β-unsaturated carbonyl compounds **3a–e** were treated with *o*-aminobenzenethiol in ethanol to afford the 1,5-benzothiazepines **4a–e**. The ^{1}H NMR spectra of the products are characteristic of the imino structure. The imino structure, formed instantaneously, would have given three distinct double doublets in the ABX pattern at δ 5.2∼3.0 ppm, which are the characteristic peaks of dihydrobenzothiazepine moiety.[31,32]

The generally applied routes for the construction of a β-lactam ring include the Staudinger cycloaddition of imines to ketenes, the enolate-imine condensations and subsequent ring-closure of β-amino esters, and the ketene-imine cycloaddition using metallo-carbene intermediates.[33,34] The Staudinger cycloaddition of imines to ketenes is probably the most important one. The 1,5-benzothiazepines **4a–e** were reacted with chloroacetyl chloride **5a** and phenoxyacetyl chloride **5b**, in the presence of triethylamine in anhydrous benzene, to give 2-chloro- or 2-phenoxy-2a-(2-phenyl-1,2,3-triazole-4-yl)-4-aryl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones **6a–j** through parallel solution-phase synthesis. Their structures were confirmed by ^{1}H NMR, IR, MS, and elemental analyses. The IR spectra of the compound **6a–j** exhibit characteristic C=O bands in the region of 1780–1760 cm^{-1}. It is noted that in the ^{1}H NMR spectra of β-lactam derivatives, a characteristic singlet of the azetidinone ring proton is recorded at δ 5.47–5.18 (s, 1H). Three distinct double doublets in the ABX pattern at δ 4.1~3.0 ppm were recorded in compounds **6a–j**, the S-C-2-H$_x$ proton singlet is recorded at δ 4.11–4.04 (dd, 1H) for its attachment with an electronegative sulfur atom and electronegative phenyl group and C-3-H$_a$, and C-3-H$_b$ proton singlets are recorded at δ 3.80–3.69 (dd, 1H) and δ 3.19–3.01 (dd, 1H). Absorption peaks as multiplets of compound **6a–j** aromatic protons were found at δ 8.08–6.94 (m, Ar—H), and the proton of the triazole-ring is also recorded at this region.

It is well-known that 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepine **1** adopts a boat-like conformation.[35] Based on literature results,[36–38] the nitrogen atom of the C=N bond in each benzothiazepine **1** attacks the carbonyl group of the ketene, generated from acyl chloride and triethylamine, to yield a zwitterionic intermediate **3** (Scheme 2), then undergoes a conrotatory ring closure in the downward direction, in which the whole azepine ring rotates downwards, to yield a boat-like product **4** through forming a β-lactam ring from the outside of the thiazepine ring. It then undergoes conformational transfer to produce finally the predominant chair-like product **2**. The structure of the products, however, shows that its dominant conformation favors an arrangement where the 2a-triazole group and the 2-halogen atom (or phenoxy) are on the same side.

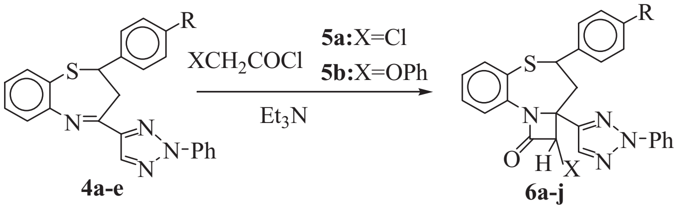


3,4 R **a**: R= H **d**: R= Cl
b: R= CH$_3$ **e**: R= NO$_2$
c: R= OCH$_3$

Scheme 2

The structures of all compounds are also confirmed by mass spectral analysis. The mass spectra show M$^+$ peaks at corresponding masses of respective moleculars.

In conclusion, we have described a convenient method for the synthesis of 2-chloro- or 2-phenoxy-2a-(2-phenyl-1,2,3-triazole-4-yl)-4-aryl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones **6a–j** from the corresponding aldehydes. Our search has been successful in synthesizing novel derivatives of 1,5-benzothiazepines **6a–j** with potential biological activity. Compounds **6a–j** reported are new and have been characterized by spectral and analytical data (Scheme 3).



6					
a:	R= H	X= Cl	**f**:	R= H	X= OPh
b:	R= CH_3	X= Cl	**g**:	R= CH_3	X= OPh
c:	R= OCH_3	X= Cl	**h**:	R= OCH_3	X= OPh
d:	R= Cl	X= Cl	**i**:	R= Cl	X= OPh
e:	R= NO_2	X= Cl	**j**:	R= NO_2	X= OPh

Scheme 3

EXPERIMENTAL

All purchased solvents and chemicals were of analytical grade and were used without further purification. Melting points were obtained on an X-5 micro melting point apparatus, and temperatures were uncorrected. ^1H NMR spectra were recorded with a Varian Mercury 400 MHz using $CDCl_3$ as the deuterated solvent and TMS as the internal standard at room temperature. The solid-state IR spectra were recorded from KBr on a Bruker Tensor 27 spectrophotometer. MS were recorded on an Agilent 5975 mass selective detector. Element analyses were performed on a Perkin-Elmer 240 CHN analyzer. The starting compound 2-phenyl-4-acetyl-1,2,3-triazole **1** was obtained from 4-carboxy-2-phenyl-1,2,3-triazole acid according to the literature.[39]

Preparation of 2-Phenyl-1,2,3-triazole-4-yl-α,β-unsaturated Ketones (3a–3c)

2-Phenyl-4-acetyl-1,2,3–triazole **1** (2.5 mmol) and aldehydes **2a–2c** (2.5 mmol) were dissolved in ethanol (20 mL), and a solution of aqueous (2%) sodium hydroxide (2.5 mL) was added dropwise slowly. The reaction mixture was kept under magnetic stirring at room temperature for 2–3 h. The precipitate was then separated by filtration, washed with water until the product was neutralized to pH = 7, washed with cold aq. Ethanol (2–3 mL), and then dried in air. The crude product was recrystallized from ethanol.

Compound (3a). Yield 80%, mp: 167–168°C. Pale yellow crystals. IR: 3126 (Ar—H), 1683 (C=O), 1594, 1493, 1454 (C=C). MS, m/z (%): 276 (M^++1), 172 (100%), 145, 117, 103, 91, 77. Anal.Calcd. (%) for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found (%): C, 74.06; H, 4.83; N, 15.29.

Compound (3b). Yield 83%, mp: 132–133°C. Pale yellow crystals. IR: 3125 (Ar—H), 2919 (CH_3), 1663 (C=O), 1595, 1491, 1451 (C=C). MS, m/z (%): 289 (M^+), 274 (100%), 145, 115, 91, 77. Anal.Calcd. (%) for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found (%): C, 74.64; H, 5.34; N, 14.58.

Compound (3c). Yield 86%, mp: 145–146°C. Yellow and green needle-like crystals. IR: 3130 (Ar—H), 2972 (CH_3), 1664 (C=O), 1594, 1513, 1449 (C=C), 1258 (C—O—C). MS, m/z (%): 305 (M^+), 290, 274, 172, 145, 134, 117, 102, 91, 77 (100%). Anal.Calcd. (%) for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found (%): C, 70.68; H, 5.10; N, 13.74.

2-Phenyl-1,2,3-triazole-4-yl-α,β-unsaturated Ketones (3d, 3e)

To an aldehyde **2d**,**2e** (5 mmol) and a solution of aqueous (2%), sodium hydroxide (2.5 mL) mixed in ethanol (15 mL) and 4-acetyl-2-phenyl-1,2,3–triazole **1** (2.5 mmol) in ethanol (30 mL) was added dropwise slowly. The reaction mixture was kept under magnetic stirring at room temperature for 2~3 h. The precipitate was then separated by filtration, washed with water until the product was neutralized to pH = 7, washed with cold aq. Ethanol (2–3 mL), and then dried naturally in air. The crude product was recrystallized from ethanol.

Compound (3d). Yield 82%, mp: 133–134°C. Pale yellow needle-like crystals. IR: 3103 (Ar—H), 1667 (C=O), 1606, 1491, 1462 (C=C). MS, m/z (%): 311 (M^++2), 309 (M^+), 274, 172, 165, 145, 137, 117, 102, 91, 77 (100%). Anal.Calcd. (%) for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found (%): C, 65.86; H, 3.86; N, 13.62.

Compound (3e). Yield 79%, mp: 171–173°C. Yellow needle-like crystals. IR: 3126 (Ar—H), 1673 (C=O), 1613 (—NO_2), 1596 1494, 1426 (C=C), 1516, 1299 (—NO_2). MS, m/z (%): 321 (M^++1), 176, 172 (100%), 145, 117, 102, 91, 77. Anal.Calcd. (%) for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found (%): C, 63.66; H, 3.91; N, 17.41.

2-Aryl-4-(2-phenyl-1,2,3-triazole-4-yl)-2,3-dihydro-[1,5] benzothiazepine (4a–4e)

To a solution of α,β-unsaturated ketone **3** (4.0mmol) in ethanol, 60 mL *o*-aminothiophenol (4.0 mmol) was added. The mixture was heated under reflux for 20–30 min, and then CF_3COOH (1.2 mL) was added. Refluxing was continued for 5–6 h. The solvent volume was reduced by half using a rotovap, and the resulting mixture was allowed to stand at room temperature. The crystalline solid product was filtered, washed with cold aq. ethanol (2–3 mL), and dried in air. The crude compound was recrystallized from ethanol.

Compound (4a). Yield 76%; Pale yellow crystals, mp: 159–161°C. IR: 3127 (Ar—H), 1647 (C=N), 1597, 1497, 1465 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17–6.80 (m, 15H, Ar—H and N=C—H), 5.17–5.11 (dd,1H, H_{2x}, J_{ax} = 4.72Hz, J_{bx} = 12.21 Hz), 3.14–3.08 (dd, 1H, H_{3a}, J_{ax} = 4.72Hz, J_{ab} = 12.42 Hz), 3.08–3.01 (dd, 1H, H_{3b}, J_{bx} = 12.21 Hz, J_{ab} = 12.42 Hz); 70ev MS, m/z (%): 382 (M^+), 349, 278, 210, 108, 104, 91, 77 (100%); Anal.Calcd. (%) for $C_{23}H_{18}N_4S$: C, 72.22; H, 4.74; N, 14.65. Found (%): C, 72.04; H, 4.81; N, 14.58.

Compound (4b). Yield 83%; Yellow and green crystals, mp: 170–171°C. IR: 3130 (Ar—H), 2960 (CH_3), 1635 (C=N), 1558, 1487, 1459 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14–6.81 (m, 14H, Ar—H and N=C—H), 5.16–5.11 (dd, 1H, H_{2x}, J_{ax} = 4.77 Hz, J_{bx} = 11.97 Hz), 3.66–3.47 (dd, 1H, H_{3a}, J_{ax} = 4.77 Hz, J_{ab} = 12.43 Hz), 3.09–3.01 (dd, 1H, H_{3b}, J_{bx} = 11.97 Hz, J_{ab} = 12.43 Hz), 2.48 (s, 3H, -CH_3); 70ev MS, m/z (%): 396 (M^+), 363, 278 (100%), 250, 118, 91, 77, 64; Anal.Calcd. (%) for $C_{24}H_{20}N_4S$: C, 72.70; H, 5.08; N, 14.13. Found (%): C, 72.52; H, 5.06; N, 14.19.

Compound (4c). Yield 81%; Yellow and green crystals, mp: 150–151°C. IR: 3131 (Ar—H), 2952 (CH_3), 1620 (C=N), 1598, 1509, 1454 (C=C), 1242 (C—O—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15–6.80 (m, 14H, Ar—H and N=C—H), 5.18–5.13 (dd, 1H, H_{2x}, J_{ax} = 4.80 Hz, J_{bx} = 12.01 Hz), 3.79 (s, 3H, -OCH_3), 3.70–3.65 (dd, 1H, H_{3a}, J_{ax} = 4.80 Hz, J_{ab} = 12.40 Hz), 3.08–3.01 (dd, 1H, H_{3b}, J_{bx} = 12.01 Hz, J_{ab} = 12.40 Hz); 70ev

MS, m/z (%): 412(M^+), 379, 278, 210, 134 (100%), 119, 108, 91, 77; Anal.Calcd. (%) for $C_{24}H_{20}N_4OS$: C, 69.88; H, 4.89; N, 13.58. Found (%): C, 69.60; H, 4.94; N, 13.52.

Compound (4d). Yield 80%; Pale yellow crystals, mp: 167–168°C. IR: 3124 (Ar—H), 1646 (C=N), 1596, 1491, 1467 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.18–6.80 (m, 14H, Ar—H and N=C—H), 5.18–5.10 (dd, 1H, H_{2x}, J_{ax} = 4.74 Hz, J_{bx} = 12.24 Hz), 3.74–3.71 (dd, 1H, H_{3a}, J_{ax} = 4.74 Hz, J_{ab} = 12.44 Hz), 3.10–3.06 (dd, 1H, H_{3b}, J_{bx} = 12.24 Hz, J_{ab} = 12.44 Hz); 70ev MS, m/z (%): 418(M^++2), 416 (M^+), 383, 278, 108, 102, 91 (100%), 77; Anal.Calcd. (%) for $C_{23}H_{17}ClN_4S$: C, 66.26; H, 4.11; N, 13.44. Found (%): C, 66.09; H, 4.17; N, 13.38.

Compound (4e). Yield 79%; Yellow crystals, mp: 193–194°C. IR: 3121 (Ar—H), 1642 (C=N), 1596, 1518, 1468 (C=C), 1516, 1299 ($-NO_2$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19–6.79 (m, 14H, Ar—H and N=C—H), 5.19–5.12 (dd, 1H, H_{2x}, J_{ax} = 4.73 Hz, J_{bx} = 12.23 Hz), 3.74–3.71 (dd, 1H, H_{3a}, J_{ax} = 4.73 Hz, J_{ab} = 12.46 Hz), 3.10–3.06 (dd, 1H, H_{3b}, J_{bx} = 12.23 Hz, J_{ab} = 12.46 Hz); 70ev MS, m/z (%): 427 (M^+), 278, 149, 119, 108, 103, 91 (100%), 77; Anal.Calcd. (%) for $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found (%): C, 64.32; H, 4.23; N, 16.43.

2-Chloro- or 2-Phenoxy-2a-(2-phenyl-1,2,3-triazole-4-yl)-4-aryl-2,2a,3,4-tetrahydro-1H-azeto[2,1-d][1,5]benzothiazepin-1-ones (6a–j)

1,5-Benzothiazepine **4** (1mmol) and acyl chloride **5** (2mmol) were dissolved in anhydrous benzene (15 mL), and dried triethylamine (0.28 mL, 2mmol) in anhydrous benzene (10 mL) was added dropwise into the solution over a period of 15 min. After having been stirred and refluxed for 5 h, the crystalline triethylamine hydrochloride that had formed was removed by filtration. After removal of the solvent, the residue was purified by silica gel column chromatography with light petroleum (60–90°C)/ethyl acetate (V:V = 8:1). A colorless crystal was cultured from light petroleum and ethyl acetate (V:V = 8:1).

Compound (6a). Yield 52%; White floccules, mp: 201–202°C. IR: 3097 (Ar—H), 1781 (C=O), 1612 (C=N, C=C), 1497 (C=C), 1367 (C—N), 762 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02–7.24 (m, 15H, Ar—H and N=C—H), 5.17 (s,1H, Cl—CH), 4.01–3.97 (dd, 1H, H_{2x}, J_{ax} = 1.12 Hz, J_{bx} = 10.84 Hz), 3.75–3.70 (dd, 1H, H_{3a}, J_{ax} = 1.12 Hz, J_{ab} = 14.56 Hz), 3.10–3.05 (dd, 1H, H_{3b}, J_{bx} = 10.84 Hz, J_{ab} = 14.56 Hz); 70ev MS, m/z (%): 460(M^++2), 458(M^+), 382, 349, 272, 211 (100%), 171, 108, 91, 77; Anal.Calcd. (%) for $C_{25}H_{19}ClN_4OS$: C, 65.42; H, 4.17; N, 12.21. Found (%): C, 65.34; H, 4.22; N, 12.16.

Compound (6b). Yield 56%; White floccules, mp: 192–193°C. IR: 3110 (Ar—H), 2920 (CH_3), 1767 (C=O), 1590 (C=N,C=C), 1479 (C=C), 1366 (C—N), 751 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01–7.24 (m, 14H, Ar—H and N=C—H), 5.18 (s, 1H, Cl—CH), 4.01–3.98 (dd, 1H, H_{2x}, J_{ax} = 1.09 Hz, J_{bx} = 10.31 Hz), 3.74–3.69 (dd, 1H, H_{3a}, J_{ax} = 1.09 Hz, J_{ab} = 14.56 Hz), 3.11–3.04 (dd, 1H, H_{3b}, J_{bx} = 10.31 Hz, J_{ab} = 14.56 Hz), 2.40 (s, 3H, CH_3); 70ev MS, m/z (%): 474 (M^++2), 472 (M^+), 437, 279, 226, 168, 117, 91 (100%), 77; Anal.Calcd. (%) for $C_{26}H_{21}ClN_4OS$: C, 66.02; H, 4.48; N, 11.85. Found (%): C, 66.11; H, 4.46; N, 11.91.

Compound (6c). Yield 59%; White floccules, mp: 193–194°C. IR: 3115 (Ar—H), 2916 (CH_3), 1777 (C=O), 1602 (C=N,C=C), 1479 (C=C), 1350 (C—N), 1245 (C—O—C), 755 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.05–6.94 (m, 14H, Ar—H and N=C—H), 5.18 (s, 1H, Cl—CH), 4.02–3.99 (dd, 1H, H_{2x}, J_{ax} = 1.12 Hz, J_{bx} = 10.38 Hz), 3.73–3.70

(dd, 1H, H_{3a}, $J_{ax} = 1.12$ Hz, $J_{ab} = 14.55$ Hz), 3.68 (s, 3H, OCH_3), 3.10–3.04 (dd, 1H, H_{3b}, $J_{bx} = 10.38$ Hz, $J_{ab} = 14.55$ Hz); 70ev MS, m/z (%): 490 (M^++2), 488 (M^+), 453, 412, 379, 241 (100%), 171,108, 91; Anal.Calcd. (%) for $C_{26}H_{21}ClN_4O_2S$: C, 63.86; H, 4.33; N, 11.46. Found (%): C, 63.79; H, 4.38; N, 11.51.

Compound (6d). Yield 45%; White floccules, mp: 231–232°C. IR: 3138 (Ar—H), 1770 (C=O), 1601 (C=N, C=C), 1483 (C=C), 1366 (C—N), 755 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.06–7.09 (m, 14H, Ar—H and N=C—H), 5.18 (s, 1H, Cl—CH), 4.01–3.98 (dd, 1H, H_{2x}, $J_{ax} = 1.07$Hz, $J_{bx} = 10.33$Hz), 3.74–3.70 (dd, 1H, H_{3a}, $J_{ax} =$ 1.07Hz, $J_{ab} = 14.54$Hz), 3.08–3.01 (dd, 1H, H_{3b}, $J_{bx} = 10.33$ Hz, $J_{ab} = 14.54$ Hz); 70ev MS, m/z (%): 496 (M^++4), 494 (M^++2), 492 (M^+), 457, 383, 279, 246, 138, 91 (100%), 71; Anal.Calcd. (%) for $C_{25}H_{18}Cl_2N_4OS$: C, 60.86; H, 3.68; N, 11.36. Found (%): C, 60.77; H, 3.75; N, 11.41.

Compound (6e). Yield 39%; White floccules, mp: 264–265°C. IR: 3130 (Ar—H), 1771 (C=O), 1600 (C=N, C=C), 1523 (C=C), 1345 (C—N), 1315 (—NO_2), 755 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.08–7.10 (m, 14H, Ar—H and N=C—H), 5.19 (s, 1H, Cl—CH), 4.11–4.08 (dd, 1H, H_{2x}, $J_{ax} = 1.10$ Hz, $J_{bx} = 10.36$ Hz), 3.79–3.75 (dd, 1H, H_{3a}, $J_{ax} = 1.10$ Hz, $J_{ab} = 14.56$ Hz), 3.11–3.04 (dd, 1H, H_{3b}, $J_{bx} = 10.36$ Hz, $J_{ab} = 14.56$ Hz); 70ev MS, m/z (%): 505 (M^++2), 503 (M^+), 468, 347, 279, 211, 146, 91 (100%), 77; Anal.Calcd. (%) for $C_{25}H_{18}ClN_5O_3S$: C, 59.58; H, 3.60; N, 13.90. Found (%): C, 59.50; H, 3.53; N, 13.98.

Compound (6f). Yield 51%; White floccules, mp: 198–199°C. IR: 3117 (Ar—H), 1769 (C=O), 1601 (C=N, C=C), 1482 (C=C), 1361 (C—N), 1240 (C—O—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98–7.11 (m, 20H, Ar—H and N=C—H), 5.47 (s, 1H, PhOCH), 4.07–4.04 (dd, 1H, H_{2x}, $J_{ax} = 1.15$ Hz, $J_{bx} = 10.74$ Hz), 3.77–3.74 (dd, 1H, H_{3a}, $J_{ax} =$ 1.15 Hz, $J_{ab} = 14.52$ Hz), 3.18–3.11 (dd, 1H, H_{3b}, $J_{bx} = 10.74$ Hz, $J_{ab} = 14.52$ Hz); 70ev MS, m/z (%): 516 (M^+), 423, 272, 211 (100%), 171, 108, 91, 77; Anal.Calcd. (%) for $C_{31}H_{24}N_4O_2S$: C, 72.07; H, 4.68; N, 10.85. Found (%): C, 72.12; H, 4.65; N 10.90.

Compound (6g). Yield 55%; White floccules, mp: 240–241°C. IR: 3121 (Ar—H), 2856 (CH_3), 1770 (C=O), 1601 (C=N, C=C), 1485 (C=C), 1372 (C—N), 1233 (C—O—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99–7.14 (m, 19H, Ar—H and N=C—H), 5.47 (s, 1H, PhOCH), 4.09–4.06 (dd, 1H, H_{2x}, $J_{ax} = 1.17$ Hz, $J_{bx} = 10.57$ Hz), 3.79–3.75 (dd, 1H, H_{3a}, $J_{ax} = 1.17$ Hz, $J_{ab} = 14.59$ Hz), 3.19–3.13 (dd, 1H, H_{3b}, $J_{bx} = 10.57$ Hz, $J_{ab} = 14.59$ Hz), 2.36 (s, 3H, CH_3); 70ev MS, m/z (%): 530 (M^+), 437, 319, 278 (100%), 118, 105, 91, 77; Anal.Calcd. (%) for $C_{32}H_{26}N_4O_2S$: C, 72.43; H, 4.94; N, 10.56. Found (%): C, 72.51; H, 4.89; N, 10.58.

Compound (6h). Yield 58%; White floccules, mp: 254–255°C. IR: 3122 (Ar—H), 2922 (CH_3), 1768 (C=O), 1601 (C=N, C=C), 1479 (C=C), 1376 (C—N), 1232 (C—O—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99–7.11 (m, 19H, Ar—H and N=C—H), 5.47 (s, 1H, PhOCH), 4.10–4.07 (dd, 1H, H_{2x}, $J_{ax} = 1.16$ Hz, $J_{bx} = 10.31$ Hz), 3.80–3.76 (dd, 1H, H_{3a}, $J_{ax} = 1.16$ Hz, $J_{ab} = 14.39$ Hz), 3.74 (s, 3H, OCH_3), 3.18–3.12 (dd, 1H, H_{3b}, $J_{bx} = 10.31$ Hz, $J_{ab} = 14.39$ Hz); 70ev MS, m/z (%): 546 (M^+), 453, 319, 302, 279, 134 (100%), 105, 77; Anal.Calcd. (%) for $C_{32}H_{26}N_4O_3S$: C, 70.31; H, 4.79; N, 10.25. Found (%): C, 70.23; H, 4.76; N, 10.29.

Compound (6i). Yield 43%; White floccules, mp: 264–265°C. IR: 3127 (Ar—H), 1773 (C=O), 1611 (C=N, C=C), 1483 (C=C), 1370 (C—N), 1235 (C—O—C), 754 (C—Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99–7.15 (m, 19H, Ar—H and N=C—H), 5.47 (s, 1H, PhOCH), 4.10–4.07 (dd, 1H, H_{2x}, $J_{ax} = 1.15$ Hz, $J_{bx} = 10.81$ Hz), 3.76–3.73 (dd, 1H, H_{3a}, $J_{ax} = 1.15$ Hz, $J_{ab} = 14.51$ Hz), 3.15–3.08 (dd, 1H, H_{3b}, $J_{bx} = 10. 81$ Hz, $J_{ab} = 14.51$

Hz); 70ev MS, m/z (%):552 (M^++2), 550 (M^+), 457, 319, 278 (100%), 138, 105, 91, 77; Anal.Calcd. (%) for $C_{31}H_{23}ClN_4O_2S$: C, 67.75; H, 4.21; N, 10.17. Found (%): C, 67.65; H, 4.17; N, 10.23.

Compound (6j). Yield 36%; White floccules, mp: 287–288°C. IR: 3126 (Ar—H), 1777 (C=O), 1608 (C=N, C=C), 1481 (C=C), 1370 (C—N), 1233 (C—O—C), 1297 (—NO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.00–7.17 (m, 19H, Ar—H and N=C—H), 5.47 (s, 1H, PhOCH), 4.09–4.06 (dd, 1H, H_{2x}, $J_{ax} = 1.13$ Hz, $J_{bx} = 10.83$ Hz), 3.77–3.73 (dd, 1H, H_{3a}, $J_{ax} = 1.13$ Hz, $J_{ab} = 14.50$ Hz), 3.15–3.09 (dd, 1H, H_{3b}, $J_{bx} = 10.83$ Hz, $J_{ab} = 14.50$ Hz); 70ev MS, m/z (%): 561 (M^+), 468, 278 (100%), 248, 105, 91, 77; Anal.Calcd. (%) for $C_{31}H_{23}N_5O_4S$: C, 66.30; H, 4.13; N, 12.47. Found (%): C, 66.23; H, 4.05; N, 12.53.

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