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# SYNTHESIS AND CHARACTERIZATION OF NOVEL SPIRO COMPOUNDS DERIVED FROM N-ETHYLMALEIMIDE INTEGRATED WITH 6-CHLOROBENZOTHIAZOLE MOIETY

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## ABSTRACT

Spiro compounds integrated with benzothiazole moiety have been widely explored because of their easy accessibility, varied chemical reactivity, and wide range of biological activities. Our interest was piqued by this, and we were encouraged to create better varieties of novel fused heterocyclic analogs. When 2 equivalents of N-ethylmaleimide and 1 equivalent of 6-chloro-*N*-(substituted benzylidene)benzothiazol-2-amine condensed in glacial acetic acid, to produce 2'-(6-chlorobenzothiazol-2-yl)-1,5'-diethyl-3' (substituted aryl)dihydro-2'H-spiro[pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole] -2,4',5,6' (5'H,6a'H)tetra one. All the compounds are well characterized by IR, $^{1}$H NMR, $^{13}$C NMR, and MS spectroscopy methods.

**KEYWORDS:** Benzothiazole, Schiff bases, Spiro, N-ethylmaleimide, and Synthesis.

## INTRODUCTION

The study of heterocyclic compounds and their numerous derivatives became a focus for organic chemists. As a result, numerous efforts are conducted each year to create new organic heterocyclic molecules. Maleimides are a new class of heterocyclic chemicals that have various biological uses.[1] Maleimide is moreover one of the potential heterocyclic compounds with a -CO-N(R)-CO chain. They can easily pass through biological membranes since they are hydrophobic and neutral.[2] Thus, they are frequently used for a variety of biological purposes, including cytotoxicity, DNA binding, apoptosis induction, antibacterial,[3] antimicrobial,[4] antiprotozoal,[5] analgesics,[6] antiangiogenic,[7] and antistress agents.[8] Maleimide, a thiol-reactive moiety, was utilized in lipoplex preparations of N-(4-(p-

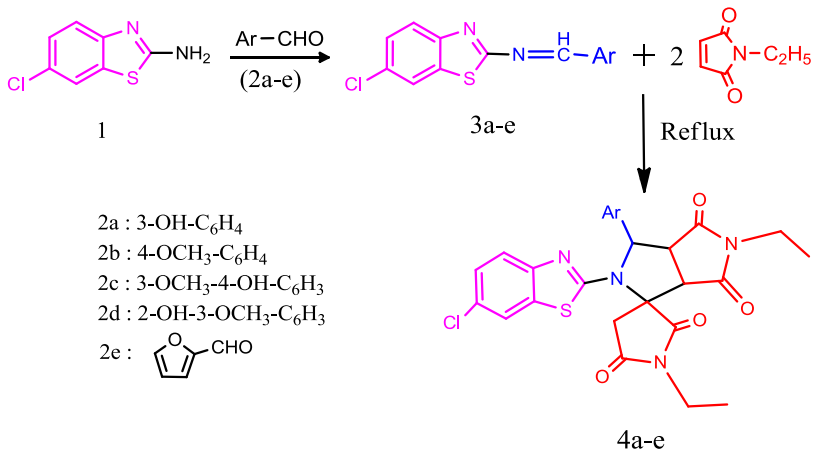
maleimidophenyl)butyryl) dipalmitoyl phosphatidylethanolamine(MPBDPPE)/lipospermine/ deoxyribonucleic acid/lipospermine/ deoxyribonucleic acid (DNA) to enriched gene delivery by Kichler et. al. in 1995.[9] Maleimide compounds can be employed as selective inhibitors, according to recent reports from numerous researchers.[10,11] N. S. Patil and colleagues created bundled derivatives of N-aryl maleimides and tested their antibacterial efficacy against various bacteria and fungi.[12] Li and Takeoka designed a maleimide-modified M-GGLG-liposome that takes advantage of thiol-conjugation to enhance cellular uptake.[13] Therefore many researchers are motivated to synthesize maleimide derivatives. Schiff bases are a general term for compounds having azomethine/imine (-CH=N-) groups. They are synthesized by losing a water molecule during the condensation of primary amines and active carbonyl compounds. Schiff bases having substituted benzothiazole are the most important heterocyclic compounds, which have attracted strong interest due to their biological and pharmacological properties. Since then, a range of methods for the synthesis of Schiff bases has been described. They have good, exceptional biological properties such as antibacterial,[14] antiproliferative activity,[15] antiviral,[16] antitumor,[17] antifungal,[18] anti-inflammatory,[19] antioxidative and radioprotective,[20] and antidiabetic.[21]

A system carrying a benzothiazole moiety combined with a spiro molecule was deemed to be interesting in the current investigation due to the amazing biological activities displayed by the benzothiazole nucleus. Additionally, it is presumable that it can be used as a strong contender for a range of biological applications. All synthesized compounds were characterized by IR spectroscopy, mass spectroscopy, $^{1}$H NMR, and $^{13}$C NMR spectroscopy.

## EXPERIMENTAL

### Materials

All reagents were commercially available and used without further purification. The melting points were taken with the help of an open capillary tube and were uncorrected. The purity of the synthesized compounds was checked by TLC on pre-coated silica gel aluminum plates (E-Merck) using EtOAc: n-hexane **(7:3)** and visualized in a UV chamber. The IR spectra of the compounds were recorded on Perkin Elmer FTIR Spectrum 2 with UATR accessory. $^{1}$H and $^{13}$C NMR spectra were recorded in DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Brucker spectrophotometer. The chemical shifts are reported as parts per million (ppm). Mass spectroscopy was recorded on Shimadzu GCMS QP 5000. The physical data and the yield of the synthesized compounds are compiled in **Table 1**.




Scheme 1: Synthesis of spiro compounds integrated with 6-Chlorobenzothiazole

## GENERAL PROCEDURE

The synthetic method for preparation of 2-amino-6-chlorobenzothiazole **(1)** and 6-chloro-*N*-(substituted benzylidene)benzo*[d]*thiazol-2-amine **(3a-e)** has been explained in the previous article.[22]

### Synthesis of Spiro analogues (4a-e)

In a dry, 50 ml round bottom flask, take 250 mg Schiff base (3a-e) and 500 mg N-ethylmaleimide. Add 10 ml of glacial acetic acid to dissolve the mixture, stir well at room temperature for about 5 min, and then refluxed for 2 hours. Cool the reaction mixture and poured into ice water, stir the precipitate well and stand by overnight. Filter the precipitate and re-crystallize it with acetone: water (1:1). This will give corresponding novel spiro-heterocyclic analogs (4a-e). The synthetic procedure is schematically represented in **Scheme 1**.

## RESULTS AND DISCUSSION

All the reactions were monitored through TLC observation till their completion using a suitable mobile phase. After the completion of the reaction, the products were purified by using appropriate solvents i.e. acetone: water (1:1). The structures of all the synthesized compounds were characterized based on their physical, and Spectral (NMR, IR, and MS) data. The $R_f$ was observed in the range of 0.61-0.81 by using EtOAc: n-Hexane (7:3) TLC solvent system. Overall the reactions proceeded smoothly with good yields. All final products gave satisfactory spectroscopic data in full concurrence with their assigned structures.

In accordance with **Scheme 1**, the condensation of 2-amino-6-chlorobenzothiazole **(1)** with various substituted aldehydes **(2a-e)** results in Schiff bases **(3a-e)** when glacial acetic acid is present as a catalytic amount. Utilizing glacial acetic acid as a solvent, these Schiff bases and N-ethylmaleimide are transformed into new Spiro analogs **(4a-e)**.

**Table 1: Physical constants of synthesized compounds.**

| Compd Code | Ar | M.F. | M.W. (g/mol) | M.P. $^0$C | Yield % | $^{\#}R_f$ |
|---|---|---|---|---|---|---|
| 4a | 3-OH-$C_6H_4$ | $C_{26}H_{23}ClN_4O_5S$ | 539.00 | 186-188 | 68.80 | 0.67 |
| 4b | 4-$OCH_3$-$C_6H_4$ | $C_{27}H_{25}ClN_4O_5S$ | 553.03 | 209-211 | 61.77 | 0.77 |
| 4c | 3-$OCH_3$-4-OH-$C_6H_3$ | $C_{27}H_{25}ClN_4O_6S$ | 569.03 | 153-155 | 56.49 | 0.79 |
| 4d | 2-OH-3-$OCH_3$-$C_6H_3$ | $C_{27}H_{25}ClN_4O_6S$ | 569.03 | 189-191 | 66.11 | 0.81 |
| 4e |  | $C_{24}H_{21}ClN_4O_5S$ | 512.97 | 204-205 | 69.70 | 0.61 |

IR spectrum of the synthesized compounds **(4a-e)** showed the stretching frequencies for the carbonyl group at 1725-1738 cm-1. The IR spectra show a sharp band at 1277 cm-1 which is attributed to the presence of C=N in the aromatic ring. The C-O stretching frequency is also observable in the IR spectrum at 1246-1281 cm-1 whereas 3360-3405 is the broad IR stretching frequency for the OH group. It also shows sharp stretching for the C-Cl group at 790-820. The aromatic C-C group has a stretching frequency at 890-916 in the IR spectra. The $^1$H NMR spectra of synthesized compound **4b** is shown in **Fig. 1**. The $^1$H NMR spectrum of the final compounds **4a-e** in DMSO exhibits signals at the range δ 1.12-1.20 ppm for six protons of –$CH_3$ from the N-ethylmaleimide group, broad singlet at the range δ 8.02-8.12 ppm for one proton of -OH group and a broad singlet at the range δ 2.21-3.75 ppm for three protons of -$OCH_3$ group of the aromatic substituted nucleus. The compounds **4a-e** showed doublet of a doublet at the range δ 2.70-3.47 ppm for two protons of the –CH- group and one doublet at δ 8.06-8.12 ppm for one proton of the –CH- group from the benzothiazole ring. The peaks in the range δ 6.61-7.86 ppm are attributed to the aromatic protons. The $^{13}$C NMR spectrum of synthesized compounds **4a-e** showed peaks in the range of 12.01-17.15 ppm for two carbon of the –$CH_3$ group from N-ethylmaleimide, 54.34-58.13 ppm for one carbon of the -$OCH_3$ group and 119.31-124.35 ppm for one carbon of –CH group from benzothiazole framework while for compounds **4a-e** showed characteristic peaks in the range 144.16-156.29 ppm for one carbon of -C-OH group. The $^{13}$C NMR spectrum showed peaks in the range 167.47-179.95 ppm for carbonyl (C=O) groups and 161.14-167.81 ppm for the – C=N-

group from thiazole. The peaks at the range 126.97-132.17 ppm are attributed to the presence of the –C-Cl group. In the mass spectra, the existence of daughter ions is assigned by suggested fragmentation patterns which are in agreement with the findings from relevant studies of compounds. All substances gave stable molecular ion peaks. The mass spectra of produced chemical compound 4b are shown in **Fig. 2**.

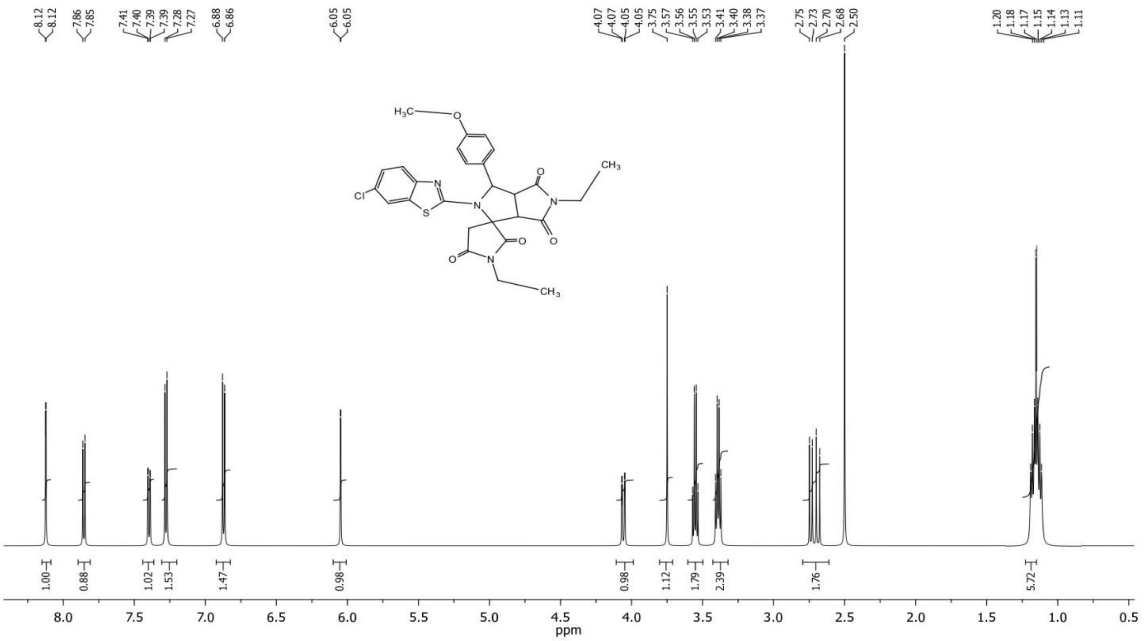



**Fig 1: The $^{1}$H NMR spectrum of compound 4b in DMSO-d6 solvent.**

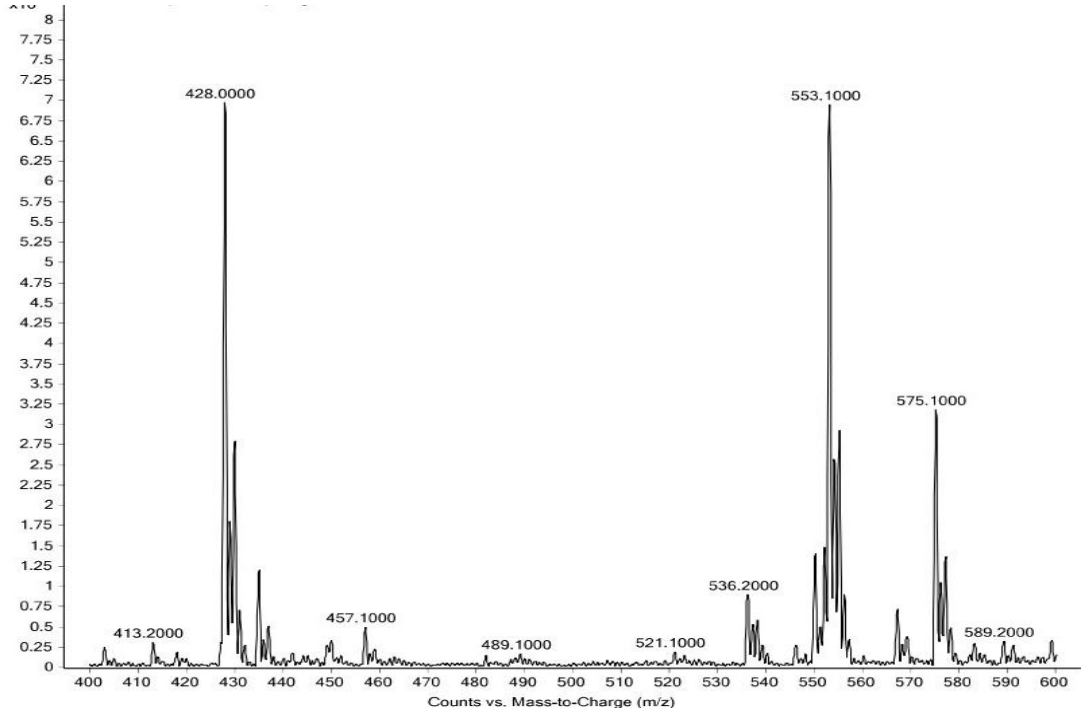



**Fig 2: The mass spectrum of compound 4b.**

**Spectroscopic Data**

2'-(6-chlorobenzo*[d]*thiazol-2-yl)-1,5'-diethyl-3'-(3-hydroxyphenyl)dihydro-2'H-spiro [pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6'(5'H,6a'H)-tetraone **(4a)**.

Color: Brown, IR($cm^{-1}$): 3391(O-H), 1738 (C=O), 1250(C-O), 916(C-C), 815 (C-Cl); $^{1}$H NMR(400 MHz, DMSO, δ in ppm): 8.39 (1 H, s), 8.06 (1 H, d, *J* 2.8), 7.80 (1 H, d, *J* 8.4), 7.33 (1 H, dd, *J* 9.1, 2.6), 7.04 (1 H, t, *J* 7.4), 6.83 (1 H, d, *J* 8.5), 6.76 (1 H, s), 6.66 – 6.55 (1 H, m), 6.09 (1 H, d, *J* 3.7), 4.00 (1 H, dd, *J* 10.0, 3.7), 3.49 (2 H, q, *J* 6.3), 3.31 (3 H, dd, *J* 12.6, 6.4), 2.88 (1 H, d, *J* 12.3), 2.66 (2 H, dd, *J* 35.8, 11.4), 1.12 (7 H, td, *J* 6.2, 2.0); $^{13}$C NMR (100MHz, DMSO, δ in ppm): 178.35, 178.02, 174.46, 170.91, 164.58, 156.28, 154.18, 140.03, 135.07, 133.04, 130.57, 127.71, 122.75, 121.92, 120.66, 117.72, 116.84, 70.78, 68.73, 55.88, 53.95, 46.78, 37.86, 36.82, 15.55; EI-MS (*m/z*): 539.00($M^{+1}$).

2'-(6-chlorobenzo*[d]*thiazol-2-yl)-1,5'-diethyl-3'-(4-methoxyphenyl)dihydro-2'H-spiro [pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6'(5'H,6a'H)-tetraone **(4b)**.

Color: Brown, IR($cm^{-1}$): 1733 (C=O), 1281(C-O), 1120, 1079, 980, 810(C-Cl); $^{1}$H NMR(400 MHz, DMSO, δ in ppm): 8.12 (1 H, d, *J* 1.9), 7.85 (1 H, d, *J* 8.1), 7.40 (1 H, dd, *J* 6.1, 2.1), 7.28 (2 H, d, *J* 6.9), 6.87 (1 H, d, *J* 8.1), 6.05 (1 H, d, *J* 3.3), 4.06 (1 H, dd, *J* 9.9, 2.4), 3.75 (1 H, s), 3.55 (2 H, q, *J* 7.5), 3.39 (2 H, dd, *J* 14.6, 7.2), 2.71 (2 H, dd, *J* 25.2, 11.1), 1.19 (6 H, td, *J* 6.2, 3.9); $^{13}$C NMR (100MHz, DMSO, δ in ppm): 178.47, 178.14, 174.57, 171.03, 164.69, 160.04, 154.30, 135.19, 130.69, 130.46, 130.26, 127.83, 122.87, 120.78, 115.22, 70.90, 68.68, 57.15, 56.00, 54.07, 46.89, 39.50, 37.98, 36.94, 15.67; EI-MS (*m/z*): 553.10($M^{+1}$).

2'-(6-chlorobenzo*[d]*thiazol-2-yl)-1,5'-diethyl-3'-(4-hydroxy-3-methoxyphenyl)dihydro-2'H-spiro[pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6'(5'H,6a'H)-tetraone **(4c)**.

Color: Brown, IR($cm^{-1}$): 3360(O-H), 1725 (C=O), 1246(C-O), 790 (C-Cl); $^{1}$H NMR(400 MHz, DMSO, δ in ppm): 8.11 (1 H, d, *J* 2.3), 8.02 (1 H, s), 7.78 (1 H, d, *J* 6.1), 7.70 (1 H, d, *J* 6.2), 7.45 (1 H, dd, *J* 9.6, 2.6), 7.30 (1 H, d, *J* 2.0), 7.21 (1 H, dd, *J* 10.3, 2.4), 5.94 (1 H, d, *J* 7.3), 3.76 (1 H, t, *J* 5.0), 3.57 (2 H, dd, *J* 14.2, 7.0), 3.47 (2 H, dd, *J* 12.7, 5.6), 3.22 (1 H, d, *J* 8.9), 2.36 (1 H, d, *J* 10.3), 2.21 (3 H, s), 2.08 (1 H, d, *J* 6.6), 1.27 – 1.14 (6 H, m, *J* 21.5, 14.4, 7.0); $^{13}$C NMR (100MHz, DMSO, δ in ppm): 174.11, 173.78, 170.22, 166.67, 160.34, 149.94, 144.78, 143.36, 130.84, 126.33, 126.17, 123.47, 118.54, 116.42, 111.39, 108.71, 66.54, 64.49, 53.54, 51.64, 49.71, 42.54, 33.63, 32.58, 11.31; EI-MS (*m/z*): 570.70($M^{+1}$).

2'-(6-chlorobenzo*[d]*thiazol-2-yl)-1,5'-diethyl-3'-(2-hydroxy-3-methoxyphenyl)dihydro-2'H-spiro [pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6'(5'H,6a'H)-tetraone **(4d)**.

Color: Brown, IR($cm^{-1}$): 3405(O-H), 1730 (C=O), 1277(C=N), 1100, 1063, 890, 815 (C-Cl); $^{1}$H NMR(400 MHz, DMSO, δ in ppm): 8.16 (1 H, d, *J* 2.9), 8.12 (1 H, s), 7.91 (1 H, d, *J* 7.5), 7.43 (1 H, d, *J* 7.1), 6.91 – 6.81 (2 H, m), 6.68 (1 H, dd, *J* 6.9, 1.7), 6.47 (1 H, d, *J* 1.3), 4.08 (1 H, dd, *J* 10.4, 1.1), 3.80 (1 H, s), 3.56 (2 H, dd, *J* 12.3, 6.3), 3.09 (2 H, dd, *J* 13.3, 6.9), 2.95 (1 H, d, *J* 12.3), 2.75 (1 H, d, *J* 10.1), 2.70 (1 H, d, *J* 12.1), 1.20 (6 H, td, *J* 6.2, 2.7); $^{13}$C NMR (100MHz, DMSO, δ in ppm): 178.70, 178.37, 174.81, 171.26, 164.93, 154.53, 151.48, 148.72, 135.42, 130.92, 128.06, 125.61, 123.58, 123.10, 121.01, 120.58, 114.12, 71.13, 63.34, 58.13, 56.23, 54.30, 46.72, 38.22, 37.17, 15.90; EI-MS (*m/z*): 569.10($M^{+1}$).

2'-(6-chlorobenzo*[d]*thiazol-2-yl)-1,5'-diethyl-3'-(furan-2-yl)dihydro-2'H-spiro[pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6'(5'H,6a'H)-tetraone **(4e)**.

Color: Brown, IR($cm^{-1}$): 1728 (C=O), 1255(C-O), 820 (C-Cl); $^{1}$H NMR(400 MHz, DMSO, δ in ppm): 8.10 (1 H, d, *J* 2.6), 7.84 (1 H, t), 7.75 (1 H, dd, *J* 8.9, 2.5), 7.58 (1 H, s), 7.44 (1 H, dd, *J* 8.6, 1.7), 7.29 (1 H, d, *J* 8.4), 7.21 (1 H, dd, *J* 6.5, 2.1), 3.56 (2 H, dd, *J* 14.4, 7.2), 3.47 (1 H, d, *J* 6.5), 3.04 (2 H, dd, *J* 17.1, 8.4), 2.91 (1 H, d, *J* 5.3), 2.82 (1 H, d, *J* 5.7), 2.78 (1 H, d, *J* 5.0), 1.26 – 1.05 (6 H, m, *J* 17.9, 12.3, 5.9); $^{13}$C NMR (100MHz, DMSO, δ in ppm): 179.95, 179.62, 177.97, 172.51, 167.81, 159.25, 155.78, 143.16, 136.68, 132.17, 129.31, 124.35, 122.26, 113.56, 103.31, 71.82, 61.56, 56.72, 55.55, 45.67, 39.47, 38.42, 17.15; EI-MS (*m/z*): 513.18($M^{+1}$).

## CONCLUSION

In this study, we completed the synthesis of the novel derivatives of 2'-(6-chlorobenzothiazol-2-yl)-1,5'-diethyl-3'-(substituted aryl)dihydro-2'H-spiro[pyrrolidine-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',5,6' (5'H,6a'H)-tetraone. The current method offers several benefits, including easy experimental setup, non-hazardous method, mild reaction settings, and basic workup procedure. We anticipate that several biological applications will be possible for the synthesized compounds.

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