**RESEARCH ARTICLE**

# Synthesis of Few New Carrier Polymers Derived from 2-hydrazinylbenzo[d]thiazole

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**ABSTRACT**

2-hydrazinylbenzo[d]thiazole compound [1] is produced from reaction of 2-mercapto-benzothiazole with hydrazine hydride in ethanol. Compound [1] reacted with maleic anhydride in DMF to produce (Z)-4-(2-(benzo[d] thiazol-2yl) hydrazinyl)-4-oxobut-2-enoic acid [compound (2)]. While the treatment of compound [2] with the ammonium persulfate $(NH_4)_2S_2O_8$ (as the initiator) in order to produce compound [3], then compound [3] reacted with thionyl chloride in benzene to produce compound [4], finally compound [4] reaction with various drugs: cephalexin, amoxicillin, sulfamethizole, elecoxib obtained polymers [5–8]. The structure of synthesized compounds identified by spectral data: fourier transform infrared (FTIR) and proton nuclear magnetic resonance ($^1$HNMR) spectroscopy. The polymers [5–8] have been screened for their antibacterial activities against *Staphylococcus aureus (G+), Escherichia coli (G-)* and compared with the drug (amoxicillin). The anticancer activity (Hep G2 (human liver cancer cell line) of some prepared polymers were also studied.

**Keywords:** 2-Hydrazinylbenzo[d]thiazole, Ammonium persulfate, Amoxicillin, Cephalexin, Hep G2.

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**Conflict of interest:** None

## INTRODUCTION

Nitrogen- and sulfur-containing heterocycles can be found in a wide range of the natural products, commercially available drugs, agrochemicals, and compounds with the potential of becoming active pharmaceutical materials.[1-14] Which is why, there have been continued interests in the development of new approaches for synthesizing the biologically active fused heterocycles, which incorporate the benzo-thiazole fragment.[15]

2- mercapto-benzothiazole presents great interests in pharmacology and chemistry due to its wide range of biological activities.[16,17] Benzothiazole must get the attention of the medicinal chemists due to their wide variety of biological activities, including anti-inflammatory, vasodilators, anti-tumor,[18-20] anti-tubercular, antifungal,[21] antimicrobial,[22] anticancer,[23] antidiabetic,[24] anti-convulsant,[25] antibacterial and antiviral activities.[26]

Maleimide is a chemical compound with the formula $H_2C_2(CO)_2NH$, maleimides can be defined as an important kind of heterocyclic compounds that exist in natural products[27] and find applications in organic as well as medicinal chemistry.[28] Maleimides have considerable significance in pharmaceutical products with biological particular, *e.g.,* antibacterial, anticancer, anti-tumor, tuberculostatic activity, antimicrobial, anti-viral and anti-genic activities.[29,30] The purpose of this work was to synthesize new series schiff base with maleic anhydride by using a simple method of binding it with drug compounds and preparing new polymers using ammonium persulfate as a starting polymerizer.

## EXPERIMENTAL

### Materials

All of the chemicals have been supplied by Merck and Aldrich.

### Methods

The fourier transform infrared (FTIR) spectra were recorded with the use of the KBr, discs on 8400 s Shimadzu spectrophotometer and FTIR spectrophotometer, Shimadzo (Ir prestige 21).

Proton nuclear magnetic resonance ($^1$H-NMR) spectra has been performed by: Bruker, ultra shield 400 MHz, University of Basra, Iraq, and have been reported in the ppm.

## SYNTHETIC PROCEDURES (SCHEME 1)

### 1- Synthesis of 2-hydrazinylbenzo[d]thiazole [1][31]

Solution of 2-hydrazinylbenzo[d]thiazole (1.67 g,0.01 mol) in 5 mL ethanol, hydrazine hydrate (0.01 mol) was added

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**Table 1:** FT-IR of polymers [5-8]

| *Compound no.* | *υ (N-H)* | *υ(C-H)aroma.* | *υ(C-H) aliph.* | *υ (C=O) amide* | *υ(C=O)COOH* | *υ (C=N)* |
|---|---|---|---|---|---|---|
| [5] | 3213 | 3070 | 2933–2872 | 1654 | 1720 | 1620 |
| [6] | 3209 | 3055 | 2924–2816 | 1654 | 1716 | 1637 |
| [7] | 3214 | 3086 | 2912–2800 | 1674 | - | 1639 |
| [8] | 3190 | 3070 | 2947–2877 | 1687 | - | 1620 |

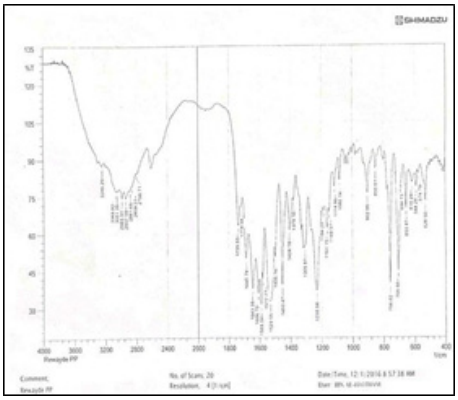


**Figure 1:** FT-IR of polymers [3]

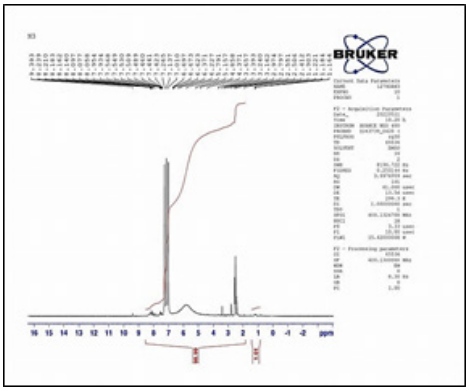


**Figure 2:** $^{1}$H-NMR of polymer [3]

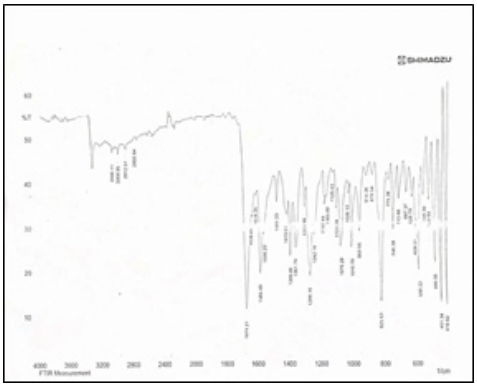


**Figure 3:** FT-IR of polymer [7]

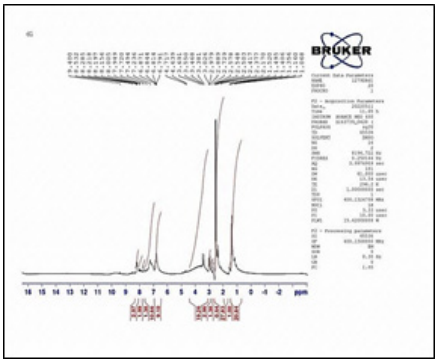


**Figure 4:** $^{1}$H-NMR of polymer [7]

**Table 2:** The inhibition zone of some synthesized polymers.

| *Compound no.* | *Escherichia coli* | *Staphylococcus aureus* |
|---|---|---|
| Amoxicillin | 17 | 23 |
| [3] | 16 | 16 |
| [6] | 19 | 21 |
| [7] | 20 | 22 |
| [8] | 24 | 25 |

**Table 3:** The inhibition of cells growth of some synthesized polymers µL/well

| *Compound no.* | *Inhibition of cells growth for Hep G2* |
|---|---|
| [6] | 44.7% |
| [7] | 50.2% |
| [8] | 59.6% |

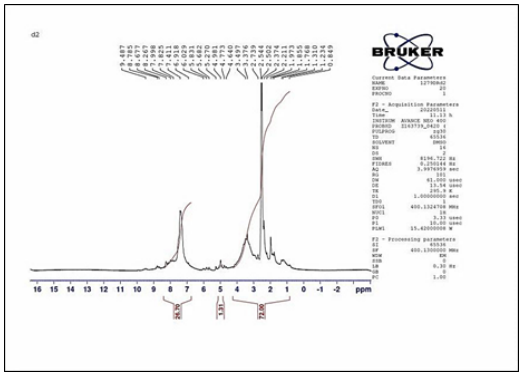


**Figure 5:** $^{1}$H-NMR of polymer [8]

drop-wise with stirring and the mixt has been then refluxed for a duration of 24 hours, after that, the excess of solvent has been evaporated and the solid has been re-crystallized from the chloroform for the purpose of giving the desired off white product. yield 95%, mp, 93–95°C.

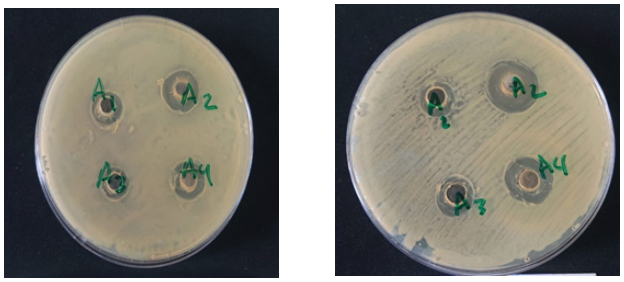
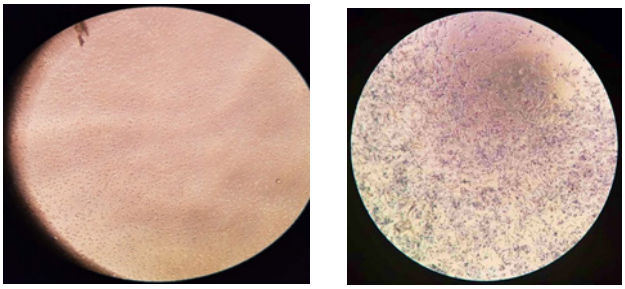
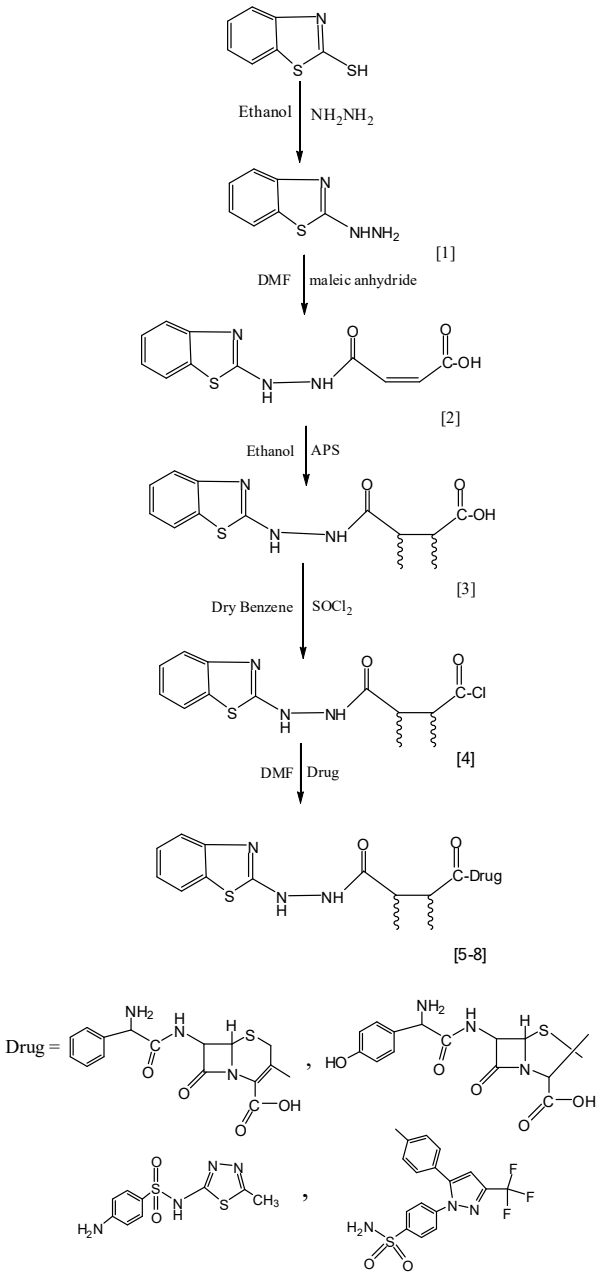


**Figure 6:** Antibacterial Activity of some polymers



(a) (b)

**Figure 7:** (a) Image of well Hep G2 before Staining (b) Image of well Hep G2 after Staining




**Scheme 1:** Synthetic procedures of polymers [1–8]

### 2-Synthesis of (Z)-4-(2-(benzo[d] thiazol-2-yl)hydrazinyl)-4-oxobut-2-enoicacid[2][32]

Mixing maleic anhydride (0.98 g., 0.01 mol) and (1.65 g., 0.01 mol) 2-hydrazinylbenzo [d]thiazole [1] in 25 mL of the DMF and after that, refluxed for approximately 4 hours, result has been washed by the diethyl ether and dried after that, at the temperature of the room (yield 75%).

### 3- Synthesis of Polymer [3][33]

(0.26 g, 0.001 mol) of the complex [2] has been mixed with (0.22 g) of the APS (*i.e.,* ammonium per sulfate) as a polymerization initiator in (15 mL) of the ethanol. This mix has been stirred for 2–3 hours at the temperature of the room, and after that, it was refluxed for approximately 12 hours after the filtering, it was washed by cold Et-OH absolute, dried and re-crystallized with the ethanol in order to give the required product [3].

### 3- Synthesis of Polymer [4][34]

0.01 mol of the compound [3] has been mixed with 0.010 mol of the thionyl chloride in 25 mL of the dry benzene then refluxed for (6 hours), $SOCl_2$ and benzene amount were separated after cooling under the vacuum.

### 4- Synthesis of Polymers [5-8][35]

A mix (0.010 mol) of compound [4] and (0.01 mol) of the drug (cephalexin or amoxicillin or sulfamethizole or celecoxib) in 20 mL. of the DMF. This mix has been refluxed for approximately 3 hours after that filtering, it has been washed by absolute ethanol, dried then re-crystallized from the Et-OH for producing the needed product [5-8].

## RESULT AND DISCUSSION

Compound [1] has been synthesized *via* reacting 2-mercapto-benzothiazol with hydrazine hydride in ethanol. FTIR of compound [1] display the appearance bands at (3396 $cm^{-1}$ and 3278 $cm^{-1}$) have been respectively a result of the asymmetrical and symmetrical stretching vibrations of the ($-NH_2$) group and disappearance (SH) group at 2357 $cm^{-1}$.

Compound [2] produce from reaction compound [1] with maleic anhydrides in DMF. Compound [2] was identified by FTIR spectroscopy. The FTIR absorption (υ,$cm^{-1}$):3180 (NH) group, 3039 (C-H arom.), 3400-2400 (OH), 1693 (C=O) of the carboxylic acid, 1630 (C=N), 1660 (C=O-NH), 1195 (C=S) and 1591(C=C) Aromatic.[36] Polymer [3] was synthesized by the

reaction compound [2] with ethanol by the use of the APS as the initiator. FTIR spectrum (υ, $cm^{-1}$) of polymer [3], Figure 1: show stretching band that refers to O-H of COOH moiety in a region (3400–2400) $cm^{-1}$, a stretching band of N-H group had appeared at 3246 $cm^{-1}$, 3051 (C-H aromatic), 2937,2881 (C-H aliph.) and a stretching band to C=O for the COOH had appeared at 1685 $cm^{-1}$. $^1$H NMR (δ ppm) of polymer [3], Figure 2 show: signals at 1.22 ppm due to six protons for two $CH_3$ groups, -CH=CH chemical shifting disappears and show chemical shifting at δ (2.79-3.39) because of -$[CH\text{-}CH]_n$-, (7.26-7.56) ppm that attributed to the four aromatic protons and 5.79 ppm, 8.23 ppm and 9.39 ppm for a sharp signals for a single proton could be a result of to CH=N, NH and one proton of (OH) carboxylic group. Polymer [4] through reaction polymer [3] with thionyl chloride in the dry benzene, FTIR for polymer [4], had shown band vanishing at (3400–2400) $cm^{-1}$ due to (OH) group of the carboxylic acid in addition to band appearance at (1770) $cm^{-1}$ that had been connected to acyl chloride. Polymers [5-8] were synthesized from reacted polymer [4] with drugs (cephalexin, amoxicillin, sulfamethizole, celecoxib). FTIR spectrum for polymer [7], Figure 3, the disappearance of absorption band to acyl chloride and absorption band appearance at (1674), (1639), (1076) $cm^{-1}$ due to C=O-NH, C=N and S=O, respectively.[37]

$^1$H NMR (δ ppm) of the polymers [7], Figure 4: singlet signal at δ 1.06 refer to ($CH_3$) group that is related to the ring of 1,3,4-thiadiazole, a sharp signals at 1.16 ppm due to six protons for two $CH_3$ groups, -CH=CH chemical shifting has disappeared and shown chemical shifting at δ (2.88–2.97) because of -$[CH\text{-}CH]_n$-, multiple signals at δ (6.79–8.21 that refer to aromatic protons, singlet signal at δ 4.71 as a result proton of NHNH-C=O, signal at δ (8.53) attributed to the one proton of NHNH-C=O and signal at δ (9.40 ) attributed to NH-S=O

$^1$H NMR (δ ppm) for polymer [8], Figure 5: signals at δ (0.84) and (1.13) ppm due to proton of ($CH_3$)-ph and $[(CH_3)]_2$ group respectively, -CH=CH chemical shifting is disappear and show chemical shifting at δ 3.37 ppm because of-$[CH\text{-}CH]_n$-, signal at δ 4.77 indicate proton of NH-NH C=O, signal at δ5.83 refer to the proton of a ring, multiple signals at (δ6.91- δ8.26) that attributed to aromatic protons, signals at δ (8.78) and (9.48) ppm attributed to the NH-C=O and NH-S=O, respectively. FTIR of all polymers is listed in Table 1.

### Biological Activity[38]

The polymers [3,6,7,8] have been tested for antibacterial activities towards *S. aureus (G+)* and *E. coli (G-) in-vitro* through agar well diffusion approach (Barry, 1977), a standard medication that has been utilized for the purpose of comparing with synthesized polymers is amoxicillin (50 µg/mL). Results have shown that all of the polymers had a higher diameter of the zone of growth inhibition, which has been given in Table 3. Compound [8] had shown good inhibition towards *E. coli;* this could be related to the presence of the drug because this drug is antibacterial that is obtained from a sulfonamide. It is effective as an antibiotic against broad range of the *G-* and *G+* bacteria. Also, polymer [8] contains maleimide group and schiff base materials which have good activities against bacteria. Some polymers and their antibacterial activities listed in the Figure 6.

### Anticancer Activity

The polymers [6-8] have been screened for anticancer activities, utilizing one cancer cell line type: Hep G2 (human liver cancer cell line). Freshney's protocol for the cell culture media, solutions and reagents have been followed.[39] HepG-2, viability after the addition of various concentrations of compounds [6-8] has been determined through the use of an enzyme-linked immunosorbent assay (ELISA) reader at 575 nm wavelength (Figure 6).

Cell growth-inhibiting rate has been calculated as follows[40]:

$$\text{Rate of Inhibition} = \frac{mean\ of\ control - mean\ of\ treatment}{mean\ of\ control} \times 100$$

Polymer [8] showed more than 50% inhibition for Hep G2 (human liver cancer cell line).

## REFERENCE


1. Ardón-Muñoz LG, Bolliger JL. Synthesis of Benzo [4, 5] thiazolo [2, 3-c][1, 2, 4] triazole Derivatives via CH Bond Functionalization of Disulfide Intermediates. Molecules. 2022 Feb 22;27(5):1464.
2. Hu DX, Withall DM, Challis GL, Thomson RJ. Structure, chemical synthesis, and biosynthesis of prodiginine natural products. Chemical reviews. 2016 Jul 27;116(14):7818-53.
3. Lamberth C. Heterocyclic chemistry in crop protection. Pest management science. 2013 Oct;69(10):1106-14.
4. Maienfisch P, Edmunds AJ. Thiazole and isothiazole ring–containing compounds in crop protection. Advances in Heterocyclic Chemistry. 2017 Jan 1;121:35-88.
5. Lamberth C, Walter H, Kessabi FM, Quaranta L, Beaudegnies R, Trah S, Jeanguenat A, Cederbaum F. The significance of organosulfur compounds in crop protection: Current examples from fungicide research. Phosphorus, Sulfur, and Silicon and the Related Elements. 2015 Aug 3;190(8):1225-35.
6. Heravi MM, Zadsirjan V. Prescribed drugs containing nitrogen heterocycles: an overview. RSC advances. 2020;10(72):44247-311.
7. Bhutani P, Joshi G, Raja N, Bachhav N, Rajanna PK, Bhutani H, Paul AT, Kumar R. US FDA approved drugs from 2015–June 2020: a perspective. Journal of Medicinal Chemistry. 2021 Feb 22;64(5):2339-81.
8. Pathania S, Narang RK, Rawal RK. Role of sulphur-heterocycles in medicinal chemistry: An update. European journal of medicinal chemistry. 2019 Oct 15;180:486-508.
9. Sharma V, Gupta M, Kumar P, Sharma A. A Comprehensive Review on Fused Heterocyclic as DNA intercalators: Promising Anticancer Agents. Current Pharmaceutical Design. 2020 Nov 17.
10. Sbenati RM, Semreen MH, Semreen AM, Shehata MK, Alsaghir FM, El-Gamal MI. Evaluation of imidazo [2, 1–b] thiazole-based anticancer agents in one decade (2011–2020): Current status and future prospects. Bioorganic & Medicinal Chemistry. 2021 Jan 1;29:115897.
11. Slivka MV, Korol NI, Fizer MM. Fused bicyclic 1, 2, 4-triazoles with one extra sulfur atom: Synthesis, properties, and

biological activity. Journal of Heterocyclic Chemistry. 2020 Sep;57(9):3236-54.
12. Sharma PC, Bansal KK, Sharma A, Sharma D, Deep A. Thiazole-containing compounds as therapeutic targets for cancer therapy. European journal of medicinal chemistry. 2020 Feb 15;188:112016.
13. Hussain H, Al-Harrasi A, Al-Rawahi A, Green IR, Gibbons S. Fruitful decade for antileishmanial compounds from 2002 to late 2011. Chemical reviews. 2014 Oct 22;114(20):10369-428.
14. Rana A, Siddiqui N, Khan SA. Benzothiazoles: a new profile of biological activities. Indian Journal of Pharmaceutical Sciences. 2007;69(1):10.
15. Aboelmagd A, Ali IA, Salem EM, Abdel-Razik M. Synthesis and antifungal activity of some s-mercaptotriazolobenzothiazolyl amino acid derivatives. European Journal of Medicinal Chemistry. 2013 Feb 1;60:503-11.
16. Ahmad MR, Ahmad AH. Synthesis and characterization of some New Derivatives from 2-Mercaptobenzothiazole. Iraqi Journal of Science. 2014;55(2A):319-33.
17. Rajeeva B, Srinivasulu N, Shantakumar SM. Synthesis and Antimicrobial Activity ofSome New 2-Substituted Benzothiazole Derivatives. E-Journal of Chemistry. 2009 Jul 1;6(3):775-9.
18. Kok SH, Gambari R, Chui CH, Yuen MC, Lin E, Wong RS, Lau FY, Cheng GY, Lam WS, Chan SH, Lam KH. Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. Bioorganic & medicinal chemistry. 2008 Apr 1;16(7):3626-31.
19. Pattan SR, Suresh CH, Pujar VD, Reddy VV, Rasal VP, Koti BC. Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidine)-2, 4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole.
20. Kaur H, Kumar S, Singh I, Saxena KK, Kumar A. Synthesis, characterization and biological activity of various substituted benzothiazole derivatives. Dig. J. Nanomater. Bios. 2010 Mar 1;5:67-76.
21. Blunt CE, Nawrat CC, LeBozec L, Liutkus M, Liu Y, Lewis W, Moody CJ. Oxidative routes to the heterocyclic cores of benzothiazole natural products. Synlett. 2016 Jan;27(01):37-40.
22. Kumar A, Mishra AK. Advancement in pharmacological activities of benzothiazole and its derivatives: An up to date review. Mini Reviews in Medicinal Chemistry. 2021 Feb 1;21(3):314-35.
23. Ballari MS, Cano NH, Wunderlin DA, Feresin GE, Santiago AN. One-pot sequential synthesis and antifungal activity of 2-(benzylsulfonyl) benzothiazole derivatives. RSC advances. 2019;9(50):29405-13.
24. Bhat M, Belagali SL. Structural activity relationship and importance of benzothiazole derivatives in medicinal chemistry: A comprehensive review. Mini-Reviews in Organic Chemistry. 2020 May 1;17(3):323-50.
25. Dhumal ST, Deshmukh AR, Kharat KR, Sathe BR, Chavan SS, Mane RA. Copper fluorapatite assisted synthesis of new 1, 2, 3-triazoles bearing a benzothiazolyl moiety and their antibacterial and anticancer activities. New Journal of Chemistry. 2019;43(20):7663-73.
26. Sun XT, Hu ZG, Huang Z, Zhou LL, Weng JQ. A Novel PIFA/KOH Promoted Approach to Synthesize C2-arylacylated Benzothiazoles as Potential Drug Scaffolds. Molecules. 2022 Jan 22;27(3):726.
27. Ali B, Kupa LD, Heluany CS, Drewes CC, Vasconcelos SN, Farsky SH, Stefani HA. Cytotoxic effects of a novel maleimide derivative on epithelial and tumor cells. Bioorganic Chemistry. 2017 Jun 1;72:199-207.
28. Chauhan P, Kaur J, Chimni SS. Asymmetric organocatalytic addition reactions of maleimides: A promising approach towards the synthesis of chiral succinimide derivatives. Chemistry–An Asian Journal. 2013 Feb;8(2):328-46.
29. Murali Krishna Kumar M, Devilal Naik J, Satyavathi K, Ramana H, Raghuveer Varma P, Purna Nagasree K, Smitha D, Venkata Rao D. Denigrins A–C: new antitubercular 3, 4-diarylpyrrole alkaloids from Dendrilla nigra. Natural Product Research. 2014 Jun 18;28(12):888-94.
30. Panov AA, Simonov AY, Lavrenov SN, Lakatosh SA, Trenin AS. 3, 4-Disubstituted maleimides: synthesis and biological activity. Chemistry of Heterocyclic Compounds. 2018 Feb;54(2):103-13.
31. Abed FA, Karam NH, Tomma JH. Synthesis, Characterization and Study of Liquid Crystalline Behavior of New Bent Core Mesogenes Derived From Isophthalic Acid. Ibn AL-Haitham Journal For Pure and Applied Science. 2017 Mar 8;29(1).
32. Chaudhary J, Purohit S, Jinger S, Chaudhary R. Radical Copolymerization of N-Substituted Maleimide and Acrylamide (AM)/Acrylic Acid/2-Hydroxy Ethyl Methacrylate: Determination of Monomer Reactivity Ratios.
33. Li X, Huang Y, Dan Y. Synthesis of sub-100 nm PMMA nanoparticles initiated by ammonium persulfate/ascorbic acid in acetone-water mixture. Colloid and Polymer Science. 2020 Mar;298(3):225-32.
34. Samir AH, Majeed IY, Hasan SM. Synthesis and Characterization of Some New Dioxoisoindolin Compounds Containing Thiazine, Azetidine, Thiazolidine and Amide Moities. Diyala Journal For Pure Science. 2018;14(03).
35. Ahamed LS. Synthesis of New Polyester-Amides from Polyvinyl Alcohol and Convert Some of Them to Polyester-Imide. Al-Nahrain Journal of Science. 2011 Jun 1;14(2):29-42.
36. Awad SH, Saeed RS, Hussein FA. Synthesis And Polymerization Of New Maleamic Linked To Schiff Base And Substituted With Different Drugs.
37. Saeed RS, Hussein FA, Awad SH, Al-rawi MS. Synthesis and Study Antibacterial Activity of Some New Polymers Containing Maleimide Group. InJournal of Physics: Conference Series 2021 May 1 (Vol. 1879, No. 2, p. 022070). IOP Publishing.
38. Barry AL. The antimicrobic susceptibility test: principles and practices. Lippincott Williams & Wilkins; 1976.
39. Freshney RI. Culture of animal cells: a manual of basic technique and specialized applications. John Wiley & Sons; 2015 Dec 23.
40. Gao S, Ya BP, Dong WG, Luo HS, World J. Gastroenterol., (2003), 9(10): 2362-2365.