REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

4,5,6,7-Tetrahydrobenzo[b]thiophene-Based Derivatives as Anticancer Agents: An overview

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Abstract

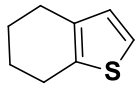
Heterocyclic compounds hold a pivotal place in medicinal chemistry due to their wide range of biological activities and thus, are exhaustively explored in the field of drug design and development. Continuous efforts are being carried out for the development of medicinal agents, especially for dreadful diseases like cancer. 4,5,6,7-Tetrahydrobenzo[b]thiophene has emerged as one of the relatively well-explored scaffold for the development of library of molecules having potential anticancer profile. 4,5,6,7-Tetrahydrobenzo[b]thiophene-based derivatives have been reported to bind with a wide range of cancer-specific protein targets, depending on the nature and position of substitutions. In the present review, authors have presented the information available on 4,5,6,7-tetrahydrobenzo[b]thiophene-based molecules as anticancer agents with special focus on biological profile.

Keywords: Heterocyclic**;** Tetrahydrobenzo[b]thiophene**;** anticancer agents

1. Introduction

Heterocyclic compounds play a paramount role in both medicinal chemistry and organic chemistry due to their immense biological action. Sulfur, nitrogen, and oxygen-containing heterocyclic compounds always seek the attention of medicinal chemists and researchers due to their diverse pharmacological profile (Pathania et al., 2019). One such heterocycle is 4,5,6,7-tetrahydrobenzo[b]thiophene. It has been established as a key scaffold due to its presence in many pharmacologically active compounds. It has earned the sobriquet of the wonder heterocycle owing to the wide range of biological activities, such as anticancer, antimicrobial, anti-inflammatory, anti-diabetic and antileishmanial (Xie et al., 2021, Kumari et al., 2017, Lahsasni et al., 2018, Félix et al., 2016). Out of all, considering the terrible nature of disease, anticancer profile of 4,5,6,7-tetrahydrobenzo[b]thiophene-based molecules have been extensively explored. Cancer

is the second cause of death over the world, about 13% of all deaths around the world is due to cancer and it is estimated that it will be responsible for the death of around 13 million persons by 2030 (Ismail et al., 2020, Elmetwally et al., 2019). To address the pressing need for the discovery and development of potent chemotherapeutic agents and to mitigate the problems associated with currently available anticancer drugs such as toxicity and drug-resistance, many researchers are continuously putting their sincere efforts by utilizing key heterocyclic motifs.

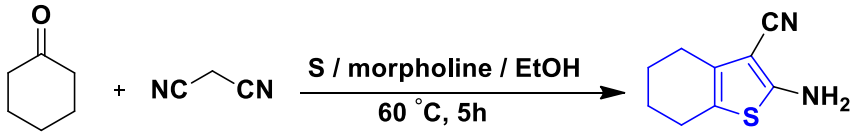


4,5,6,7-Tetrahydrobenzo[b]thiophene

4,5,6,7-Tetrahydrobenzo[b]thiophene, being one of the key scaffolds, is being continuously pursued to develop new anticancer agents by many researchers. In the present review, authors have presented the information available on 4,5,6,7-tetrahydrobenzo[b]thiophene-based molecules as anticancer agents with special focus on biological profile.

2. Synthesis of 4,5,6,7-tetrahdrobenzo [b] thiophene

4,5,6,7-Tetrahdrobenzo[b] thiophene is a fused system that consists of two different rings the first ring is the cyclohexane ring, and the second ring is thiophene. 4,5,6,7-Tetrahdrobenzo[b] thiophene can be prepared through Gewald reaction which is a reaction between cyclohexanone and malonitrile in the presence of morpholine and sulfur as illustrated in **Scheme 1**. The mechanism involves the activation of malonitrile using morpholine to produce methylene active nitrile that reacts with cyclohexanone by Knoevenagel condensation followed by thiolation of the result intermediate with sulfur. Then, the sulfureted compound cyclized to form thiophene followed by re-aromatization and proton transfer **(Gediya et *al.*, 2021)**.



Scheme 1. Gewald reaction

3. Biological activity of 4,5,6,7-tetrahdrobenzo[b]thiophene based structures

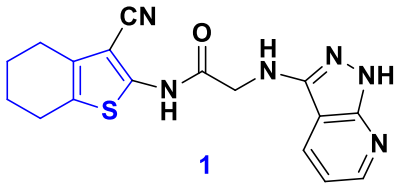
3.1. Receptor tyrosine kinases (RTKs).

Receptor tyrosine kinases (RTKs) are proteins that regulate cell pathways including cell proliferation, apoptosis, metabolism, differentiation, and growth through catalyzing gamma phosphate transfer from adenosine triphosphate (ATP) to tyrosine residues **(Fabbro, et *al.*, 2015)**.

3.1. 1. Epidermal growth factor receptor (EGFR)

One important class of RTKs is protein kinase (ErbB or HER) receptors that has four classes epidermal growth factor receptor EGFR (ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Due to the important role of EGFR and HER2 tyrosine kinases overexpression in the progression of several types of cancer their pathway inhibition is target for several anticancer drugs **(Barbosa, et *al.*, 2014)**.

In 2020, a series of novel thieno[2,3-d][1,2,3]triazine and acetamide motif were prepared and tested for their cytotoxic activity against non-small cell lung cancer cell line (H1299 cell line). Among the synthesized compounds, compound **(1)** has the highest activity against (H1299 cell line) with IC_{50} 12.5 nM that was superior to gefitinib IC_{50} 40 µm. *In vitro* evaluation of this compound for its EGFR and HER2 inhibition activity reveal that it has IC_{50} of 0.47 and 0.14 nM respectively that was superior to gefitinib IC_{50} 1.9 nM and comparable to imatinib that has IC_{50} of 0.11 nM against EGFR and 0.06 nM against HER2 **(Elrayess et *al.*, 2020)**.



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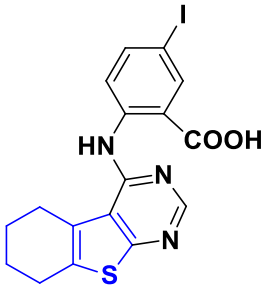
In 2019, Elmetwally *et al*. described the preparation of thieno[2,3d]pyrimidine analogues and evaluated them for their anticancer activity against HCT-116 (colon carcinoma), HePG2 (hepatocellular carcinoma), A431 (human epithelial carcinoma) and MCF-7 (human breast adenocarcinoma). From the tested analogues compound **(2)**, compound **(3)** and compound **(4)** showed the highest activity against the previous cell lines with IC_{50} between (7.0592 ± 0.032 and 16.006 ± 0.58 µm) that was comparable to that of the erlotinib (reference drug). Compound **(2)** and compound **(3)** have the lowest IC_{50} (16.006 ± 0.58 and 10.14 ± 1.10 µm) against HCT-116 while compound **(3)** and compound **(4)** were of the lowest IC_{50} (13.02 ± 1.00 and 7.975 ± 0.37 µm) against HePG2 cell line also compound **(4)** has the lowest IC_{50} (7.952 ± 0.32 and 9.64 ± 0.44 µm) against MCF-7 and A431 cell lines respectively. Also, compounds were tested for their EGFR kinase inhibitory activities using EGFR Kinase Assay Kit. Compound **(4)** was found to be the most active one against $EGFR^{T790M}$ comparable to erlotinib. Furthermore, the cell cycle progression and apoptosis of compound **(4)**, the highest active analogue, on MCF-7 cell line showed that has good apoptosis property and cause cell arrest at G2/M phase EGFR wild type **(Elmetwally et *al.*, 2019)**.



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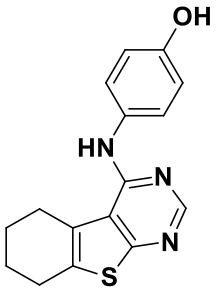

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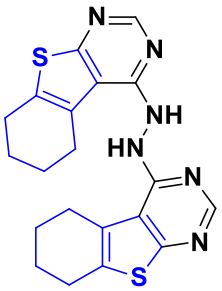

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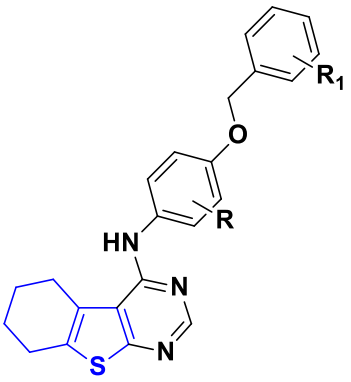
In 2016, Abdelhadi *et al.*, prepared series of 4-anilinothieno[2,3]pyrimidine and tested them as EGFR and HER-2 kinases inhibitors at concentration of 10 µm. Compounds **(5)**, **(6)**, **(7)**, **(8)**, and **(9)** have 93-100% inhibition of EGFR and 84-100% inhibition of HER-2 also measurement of enzyme inhibitory activity of these compounds illustrated that they have inhibited EGFR at IC_{50} value (1.2, 0.6, 0.3, 0.2 and 0.4 µm) and HER-2 kinases at IC_{50} value (8.2, 3.4, 1.3, 0.5 and 2.7 µm), respectively **(Abdelhadi et *al.*, 2016)**.

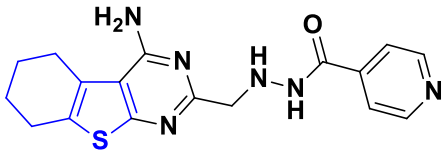


5, R=R_1=H
6, R= H, R_1=3-F
7, R= 3-Cl, R_1=H
8, R= 3-Cl, R_1= 3-F
9, R= 3-Cl, R_1= 2-F

3.1.2. Fibroblast growth factor receptors (FGFRs)

Another type of RTKs is fibroblast growth factor receptors (FGFRs). One of them is FGFR1 which is known by its over expression in a lot of cancer cells. To block the pathway of FGFR1 dependent cancer cell, ATP binding to FGFR1 should be prevented **(Liang, et *al*., 2013, Ye, et *al*., 2015)**.

In 2016, a series of tetrahydrobenzothino[2,3-d]pyrimidine analogues were synthesized and evaluated for their antitumor activity against H460, A549 and U251 cell lines. The results showed that compound **(10)** has the lowest IC_{50} value (7.7 ± 2.1, 18.9 ± 2.3 and 13.3 ± 2.4 µm) respectively against H460, A549 and U251 cell lines. Compounds **(12)** and **(11)** have IC_{50} value (19.1± 1.3, 23.1 ± 1.8, and 21.0 ± 1.6 µm) and (25.1 ± 0.8, 38.3 ± 2.5, and 27.6 ± 2.3 µm) against the previous cell lines. *In vitro* determination of FGFR1 kinase inhibition activity of the synthesized compounds showed that compound **(10)** has the best performance 78.8 percent at concentration of 10 µm **(Wang et *al.*, 2016)**.



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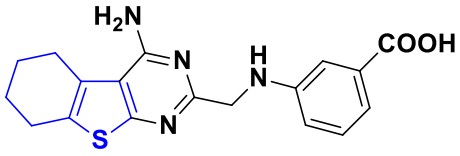

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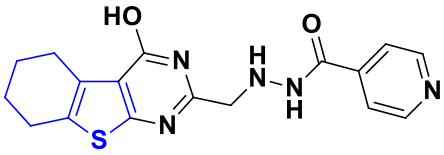

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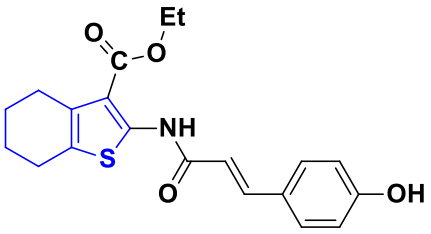
3.2. Transforming growth factors (TGFβ).

Transforming growth factors (TGFβ) regulate several physiological processes including cell apoptosis and proliferation. There is three TGFβ isoforms TGFβ 1, TGFβ 2, TGβF 3, but TGFβR1(transforming growth factor beta type I) is the target of several drug and the key player in cell apoptosis and proliferation. TGFβR1 inhibitors bind to adenosine triphosphate (ATP) binding site of the receptor and prevent autophosphorylation of the receptor **(Akhurst, et *al.*, 2012, Geldenhuys, et *al.*, 2010)**.

In 2020, Ismail *et al.*, synthesized new tranilast derivatives and evaluated them for their anticancer activity against HePG2 (hepatocellular carcinoma), PC-3 (prostate cancer cell) and MCF-7 (human breast adenocarcinoma). In addition to their safety on normal cell line WI-38, compounds **(13)**, **(14)** and **(15)** with thiophene core were found to have better activity against PC-3 cell line than other cell lines with IC_{50} value between (2.64 ± 0.21-6.29 ± 0.5 µm) against PC-3 cell lines which was better than IC_{50} of 5-FU (7.53 ± 0.57) (reference drug) against the same cell line. Regarding HePG2 cell line the IC_{50} value of compounds **(14)** and **(15)** (7.9 ± 0.67 and 2.85 ± 0.17 µm) which were better than that of 5-FU (IC_{50} 8.15 ± 0.61 µm) while compound **(13)** has IC_{50} (8.3± 0.75 µm) on HePG2 cell line. Anticancer activity against MCF-7 illustrate that IC_{50} value of compounds **(14)** and **(15)** (7.5 ± 0.8 and 3.5 ± 0.26 µm) which were better than that of 5-FU (IC_{50} 7.76± 0.46 µm) compound **(13)** has IC_{50} (8.27± 0.76 µm) on MCF-7 cell line. Due to their high activity on PC-3 cell line, the compound **(15)** was investigated for its inhibitory activity against TGFβR1 using reference drug galunisertib (IC_{50} 0.170 ± 0.057 µm) where IC_{50} of compound **(15)** is 1.379 ± 1.42 µm **(Ismail et *al.*, 2020)**.



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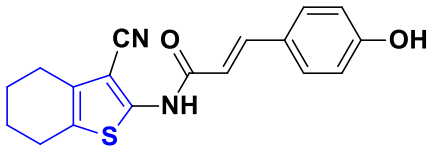

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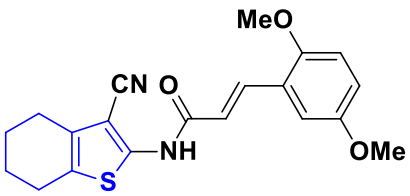

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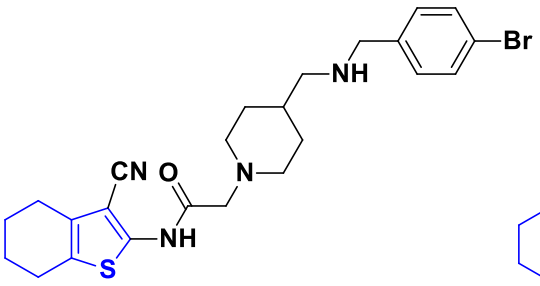
3.3. Histone deacetylase (HDACs).

Histone deacetylase (HDACs) play an important role in the expression of many proteins. Histone is the critical part of HDACs enzyme which play critical role in the regulation process through changes in chemical reactions (acetylation, methylation, and deacetylation) While acetylation of histone increase transcription, deacetylation of histone inhibits transcription. This inhibition of transcription affects cell cycle causing cancer. HDAC inhibitors lead to an increase in acetylated histone bringing about different cell processes including apoptosis and inhibition of proliferation. HDAC enzymes are classified into four different classes based on phylogenetic properties: class I (HDAC1, 2, 3 and 8), class II (class IIa: HDAC4, 5, 7, 9; and class IIb: HDAC6, 10), class III (sirtuins SIRT1-7), and class IV (HDAC11). HDAC classes I, II, and IV are zinc-dependent enzymes and class III HDACs are NAD+ dependent enzymes **(Whitehead, et *al*., 2011)**. In 2021, new tetrahydrobenzo[b]thiophene-3-carbonitriles were prepared and evaluated for their antiproliferative activity against MDA-MB-231(breast cancer cell line), A549 (lung cancer cell line) and Hela cells. Compound **(16)** has the potent activity against (MDA-MB-231) and (A549) with IC_{50} value 0.31 and 0.02 µm, respectively. The enzyme assay result showed that compound **(17)** has high selectivity for HDAC1 (IC_{50} 23.02 ± 2.47µm) which was 1.46 folds more selective than HDAC6 (IC_{50} 33.09 ± 0.80µm) while compound **(18)** has high selectivity for HDAC6 (IC_{50} 13.5 ± 0.45 µm) than HDAC1 (IC_{50} 45.3 ± 3.43 µm) both compounds **(17)** and **(18)** cause cell cycle arrest at sub-G **(Gediya et *al*., 2021)**.



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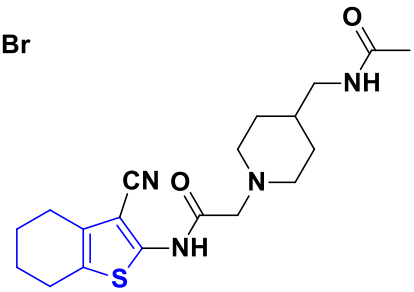

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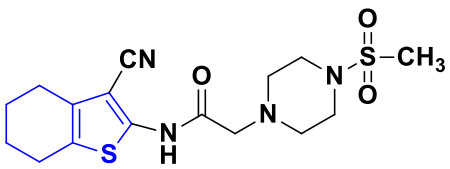

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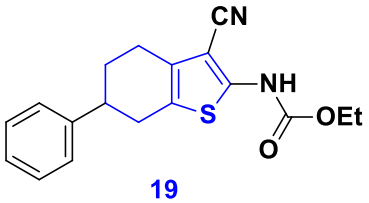
3.4. Tubulin Polymerization.

Compounds that inhibit tubulin polymerization leads to irreversible damage to vasculature of cells and so tumor damage **(Herbst, et *al*., 2003, Keri, et *al*., 2017)**. In 2021, Shimaa Kamal *et al.*, described the preparation of new 4,5,6,7-tetrahydrobenzo[b]thiophene derivatives. *In vitro* anticancer evaluation of the synthesized compounds showed that compound **(19)** has a significant activity against colorectal cancer (lovo and HCT-116) cell lines with IC_{50} 57.15 ± 2.48 and 71.00 ± 2.83 µg/ml, respectively. Although compound **(20)** has no anticancer activity, the nanoparticle modification on this compound with fe_3O_4 enhance the cytotoxic activity against lovo and HCT-116 with IC_{50} values 81.50 ± 3.54 and 60.35 ± 2.76 µg/ml, respectively **(Kamal et *al*., 2021)**.



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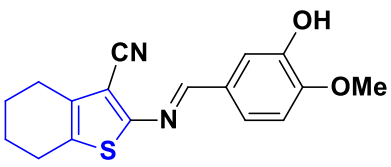

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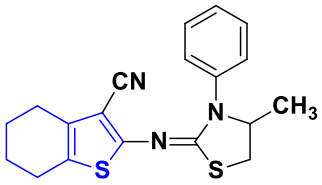
3.5. Others

In 2017, a group of scientists synthesized 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[d]thiophene derivatives and evaluated them for their cytotoxic activity against MCF-(breast adenocarcinoma), SF-268 (central nervous system cancer) and NCI-H460 (non-small lung cancer). From the synthesized derivatives, compounds **(21)**, **(22)**, **(23)**, **(24)**, **(25)** and **(26)** were found to have the highest cytotoxic activity against MCF, SF-268 and NCI-H60 cell line with IC_{50} ranging from (0.01 ± 0.001 – 0.08 ± 0.002 µm), (0.02 ± 0.003 – 0.08 ± 0.005 µm) and (0.02 ± 0.003 – 0.08 ± 0.003 µm), respectively that was lower than stander drug doxorubicin (IC_{50} 0.0428 ± 0.0082 µm), (0.0940 ± 0.0087 µm) and (0.0940 ± 0.0070 µm) **(Abdallah *et al.*, 2017)**.



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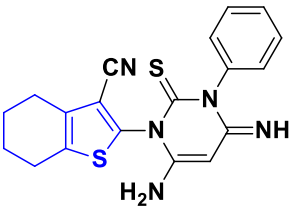

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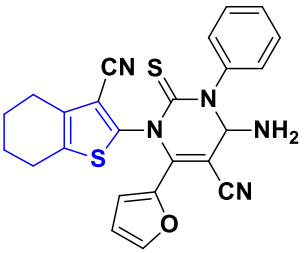

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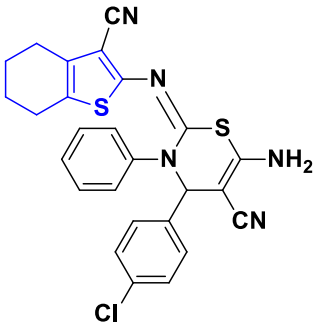

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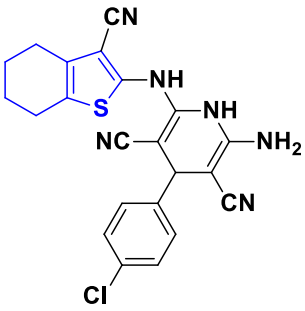

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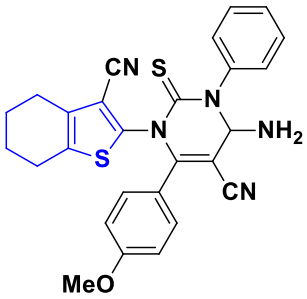

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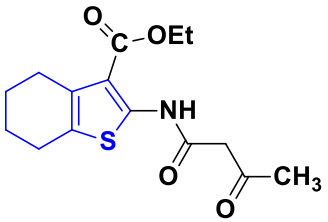
In 2023, Anwer *et al.*, prepared a series of thiophene derivatives and evaluated them for their antiproliferative activity against HEPG-2 (hepatocellular carcinoma), HCT-116 (colorectal carcinoma) and MCF-7 (mammary gland breast cancer) using doxorubicin as reference drug. Compound **(27)** showed the best activity with IC_{50} value 8.48 ±0.9, 14.52 ± 2.5 and 9.78± 1.2 µm toward HEPG-2, HCT-116 and MCF-7, respectively **(Anwer *et al.*, 2023)**.



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4. Conclusion

The review has uncovered 4,5,6,7-tetrahydrobenzo[b]thiophene as an incredible platform in the field of medicinal chemistry, particularly its anticancer profile, to offer detailed information to the researchers/scientists to plan and create novel, target-based and advanced thiophene analogs. A broad biological profile is shown by this scaffold that will prompt potential pharmaceutical agents. Thus, this review will help researchers to develop lead compounds in a different biological domain with a nidus on cancer chemotherapy.

5. References

Abd El Hadi, S.R., Lasheen, D.S., Hassan, M.A., Abouzid, K.A.M., 2016. Design and Synthesis of 4-Anilinothieno[2,3-d]pyrimidine-Based Compounds as Dual EGFR/HER-2 Inhibitors. Arch. Pharm. Chem. life Sci., 349, 827-847.

Abdallah, A.E.M., Mohareb, R.M., Khalil, E.M., Elshamy, M.A.M.A., 2017. Synthesis of Novel Heterocyclic Compounds Incorporate 4,5,6,7-Tetrahydrobenzo[b]thiophene Together with Their Cytotoxic Evaluations. Chem. Pharm. Bull., 65, 467-477.

Akhurst, R.J., Hata, A., 2012. Targeting the TGFβ signaling pathway in disease. Nat. Rev. Drug Discovery, 11, 790–811.

Anwer, K.E., Sayed, G.H., Kozakiewicz-Pikarz, A., Ramadan, R.M., 2023. Novel annulated thiophene derivatives: Synthesis, spectroscopic, X-ray, Hirshfeld surface analysis, DFT, biological, cytotoxic and molecular docking studies. J. mol. Struct., 1276, 134798.

Barbosa, M.L.D.C., Lima, L.M., Tesch, R., Sant'Anna, C.M.R., Totzke, F. , Kubbutat, M.H.G., Schachtele, C., Laufer, S.A., Barreiro, E.J., 2014. Novel 2-chloro-4-anilino- quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors. Eur. J. Med. Chem., 71, 1–14.

Elmetwally, S.A., Said, K.F., Eissa, I.H., Elkaeed, E.b., 2019. Design, synthesis and anticancer evaluation of thieno[2,3-d]pyrimidine derivatives as dual EGFR/HER2 inhibitors and apoptosis inducers. Bioorg. Chem., 88, 102944.

Elrayess, R., Abdel Aziz, Y.M., Elgawish, M.S., Elewa, M., Yassen, A.S.A., Elhady, S.S., Elshihawy, H.A., Said, M.M., 2021. Discovery of Potent Dual EGFR/HER2 Inhibitors Based on Thiophene Scaffold Targeting H1299 Lung Cancer Cell Line. pharmaceutical, 14, 1-21.

Fabbro, D., Cowan-Jacob, S.W., Moebitz, H., 2015. Ten things you should know about protein kinases: IUPHAR Review 14. Br. J. Pharmacol., 172, 2675–2700.

Félix M. B., Souza E., Lima M., Frade D., Rodrigues V., Néris P., Ribeiro F., Scotti L., Scotti M., Aquino T., Junior F., Oliveira M., 2016. Antileishmanial activity of new thiophene–indole hybrids: Design, synthesis, biological and cytotoxic evaluation, and chemometric studies. Bioorg. Med. Chem., 24, 3972–3977.

Gedya, P., Vays, V.K., Carafa, V., Sitwala, N., Torre, L.D., Poziello, A., KUrohara, T., Suzuki, T., Sanna, V., Raguraman, V., Suthindhiran, K., Ghosh, D., Bhatia, D., Altucci, L., Ghate, M.D., 2021. Discovery of novel tetrahydrobenzo[b]thiophene-3-carbonitriles as histone deacetylase inhibitors. Bioorg. Chem., 110, 104801.

Geldenhuys, W.J., Nakamura, H., 2010. 3D-QSAR and docking studies on transforming growth factor (TGF)-b receptor 1 antagonists. Bioorg. Med. Chem. Lett., 20, 1918–1923.

Herbst, R. S., Khuri, F. R., 2003. Mode of action of docetaxel-a basis for combination with novel anticancer agents. Cancer Treat. Rev, 29, 407-415.

Ismail, M.M.F., El-Zahabi, H.S.A., Ibrahim, R.S.,Mehany, A.B.M., 2020. Design and synthesis of novel tranilast analogs: Docking, antiproliferative evaluation and in-silico screening of TGFβR1 inhibitors. Bioorg. Chem., 105, 103468.

Kamal, S., Derbala, H.A., Alterary, S.S., Bacha, A.B., Alonazi, M., El-Ashrey, M.K., El-Sayed, N.N.E., 2021. Synthesis, Biological, and Molecular Docking Studies on 4,5,6,7-Tetrahydrobenzo[b]thiophene Derivatives and Their Nanoparticles Targeting Colorectal Cancer. ACS Omega, 6, 28992-29008.

Keri, R. S., Chand, K., Budagumpi, S., Balappa Somappa, S., Patil, S. A., Nagaraja, B. M., 2017. An overview of benzo [b] thiophenebased medicinal chemistry. Eur. J. Med. Chem., 138, 1002-1033.

Kumari M. A., Triloknadh S., Harikrishna N., Vijjulatha M., Venkata Rao C., 2017. Synthesis, Antibacterial Activity, and Docking Studies of 1,2,3-triazole-tagged Thieno[2,3-d]pyrimidinone Derivatives. J. Heterocyclic Chem., 54, 3672.

Lahsasni S., Al-Hemyari D., Ghabbour H. A., Mabkhoot Y. N., Aleanizy F. S., Alothman A.A., Almarhoon Z. M., 2018. Synthesis, Characterization, and Antibacterial and Anti-

Inflammatory Activities of New Pyrimidine and Thiophene Derivatives. J. Chem., 2018(11):1-11.

Liang, G., Chen, G., Wei, X., Zhao, Y., Li, X., 2013. Small molecule inhibition of fibroblast growth factor receptors in cancer. Cytokine Growth Factor Rev., 24:467–475.

Pathania S., Narang R. K., Rawal R. K., 2019. Role of sulphur-heterocycles in medicinal chemistry: An update. Eur. J. Med. Chem., 180, 486-508.

Wang., X., Chen, D., Yu S., Zhang, Z., Wang, Y., Qi X., Fu, W., Xie, Z., Ye, F., 2016. Synthesis and Evaluation of Biological and Antitumor Activities of Tetrahydrobenzothieno[2,3-d]Pyrimidine Derivatives as Novel Inhibitors of FGFR1. Chem. Biol. Drug Des., 87, 499-507.

Whitehead, L., Dobler, M.R., Radetich, B., Zhu, Y., Atadja, P.W., Claiborne, T., Grob, J. E., McRiner, A., Pancost, M.R., Patnaik, A., Shao, W., Shultz, M., R. Tichkule, Tommasi, R. A., Vash, B., Wang, P., Stams, T., 2011. Human HDAC isoform selectivity achieved via exploitation of the acetate release channel with structurally unique small molecule inhibitors. Bioorg. Med. Chem., 19 (15), 4626–4634.

Xie H. X., Zhang J., Li Y., Zhang J., Liu S., Zhang J., Zheng H., Hao G., Zhu K., Jiang C., 2021. Novel tetrahydrobenzo[*b*]thiophen-2-yl)urea derivatives as novel α-glucosidase inhibitors: Synthesis, kinetics study, molecular docking, and *in vivo* anti-hyperglycemic evaluation. Bioorg. Chem., 115,105236.

Ye, F., Chen, L., Hu, L., Xiao, T., Yu, S., Chen, D., Wang, S., 2015. Design, synthesis and preliminary biological evaluation of C-8 substituted guanine derivatives as small molecular inhibitors of FGFRs. Bioorg. Med. Chem. Lett., 25:1556–1560.