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Dependence of the anticancer activity of 1,3-oxazole derivatives on the donor/acceptor nature of his substitues

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Abstract

A series of new 1,3-oxazole derivatives, containing in position 5 both donor and acceptor substituents were synthesized. These substances were considered as potentially active anticancer pharmacophores in the human tumor cell line panel derived from nine cancer types, including lung, colon, melanoma, renal, ovarian, brain, leukemia, breast, and prostate. Primary in vitro one-dose anticancer screening was shown that compounds with acceptor substituents (such as –C(O)OMe, –CN) in the position 5 inhibit the growth of most cell lines, and compounds with donor substituents (such as –NHR, –SR) in the position 5 do not practically inhibit the growth of cancer cell lines. It can be assumed that the pharmacological activity of 1,3-oxazole derivatives depends on donor/acceptor nature of the substituents in position 5. It was proposed to evaluate the donor/acceptor ability of 1,3-oxazole derivatives using the special parameter φ_0, which takes into account the relative position of the boundary levels (HOMO end LUMO). The quantum-chemical modeling was performed; the special parameter φ_0 for 1,3-oxazole derivatives correlates with the experimental results. Quantum-chemical calculations of the special parameter φ_0 allow modeling the pharmacological activity of 1,3-oxazole derivatives by introducing donor or acceptor substituents at position 2 or 5. This work may be useful for chemists to develop a target synthesis of potential biologically active compounds.

1 | INTRODUCTION

The heterocyclic compounds with branched conjugated systems including oxazole, thiazole, or pyrazole moieties have shown themselfes as powerful scaffolds in drug design.[1–10] 1,3-Oxazoles play a vital role in the manufacture of various biologically active drugs as brain-derived neurotrophic factor inducers,[11] analgesic,[12] trypanocidal activity,[13] antimitotic agents with pro-apoptotic activity,[14] antibacterial and antituberculosis properties,[15] antifungal activity,[16] anti-inflammatory,[17] antidepressant,[18] antimicrobial,[3] antidiabetic and antiobesity,[19–22] antiviral, and analgesic effect.[5,6] Thus, 1,3-oxazole could be considered as perspective moiety in the design and further synthesis of novel biologically active agents that exert anticancer activity.[1–4,23–34]

So, the QSAR models were developed for wide site of 1,3-oxazole derivatives showing inhibitory effect on the NCI-60 cancer cell lines,[2,35] and the well correlation was established between many descriptors and biological activity. So, it was investigated the interaction of the azole derivatives with the tubulin inhibitors which significantly improve the clinical effectivity of novel

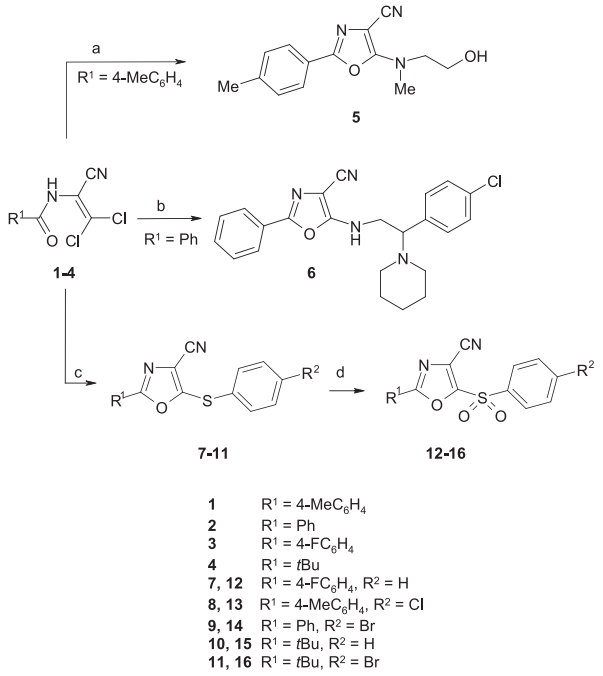
proposed biological active molecules as anticancer agents.[10]

Among the molecular characteristics to be used for structure-pharmacological activity relationship, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies have been shown to correlate particularly well with various biological activities.[36–42]

It is to be taken into account that biological activity or generation of the stable "rigid" structure with the receptors depends on the chemical constitution of target, including its possible electron structure.

In this case, the π-electron system of the 1,3-oxazole should effectively take part in the generation of the stable "rigid" complex with the receptors. Therefore, introducing of donor or/and acceptor substituents in the oxazole cycle can considerably influence on the positions of its frontier levels and hence on the donor or acceptor properties substitutiens of 1,3-oxazole core. We could propose that such intentional change of molecular level energies may influence on the biological activity.

This paper presents the results of the synthesis of the new promising biologically active agents and quantum-chemical modeling as well as the pharmacological testing of synthesized compounds.



SCHEME 1 Synthesis of 5-amino- (**5, 6**), 5-sulfanyl- (**7–11**), and 5-sulfonyl- (**12–16**) 1,3-oxazole-4-carbonitriles. Reagents and conditions: (a) 2-(methylamino)ethanol, Et_3N, THF, rt, 12 hours; (b) 2-(4-chlorophenyl)-2-piperidin-1-ylethanamine, Et_3N, THF, rt, 12 hours; (c) arenethiol, Et_3N, acetonitrile, rt, 8 hours; Ag_2CO_3, acetonitrile, reflux, 8 to 10 hours; (d) H_2O_2, AcOH, reflux, 1 hour

2 | RESULTS AND DISCUSSION

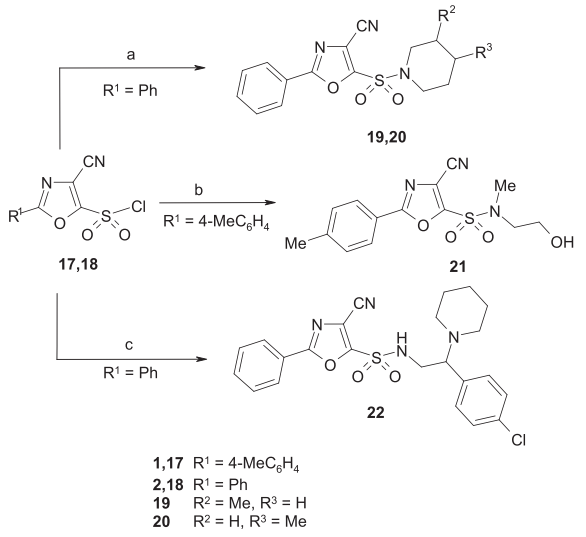
2.1 | Chemistry

The 2-acylamino-3,3-dichloroacrylonitriles **1-4** are known to be useful precursors for diverse 5-amino-, 5-sulfanyl-, and 5-sulfonyl derivatives of 1,3-oxazole (Scheme 1).[43] The convenient protocol of Drach et al[44] enabled efficient access to compounds **5** and **6** preparing from 2-acylamino-3,3-dichloroacrylonitriles **1** or **2**[43] with appropriate amine using excess of triethylamine.

The compounds **8** and **13** and its synthetic route were described previously.[45] The synthesis of similar 1,3-oxazoles **7**, **9**, **12**, and **14-16** was made by the same approach as for **8** and **13.**[45] The preparation of sulfanyl derivatives **7-11** involves treatment of 2-acylamino-3,3-dichloroacrylonitriles **1-4** with arenethiols in the presence of triethylamine to obtain 2-acylamino-3,3-bis (arylsulphanyl)acrylonitriles, which can be cyclized in the presence of silver carbonate to form 5-arylsulphanyl-1,3-oxazole-4-carbonitriles **7-11**. The latter were converted into the corresponding sulfonyl derivatives **12-16** by oxidation with hydrogen peroxide.[46]

4-Cyano-1,3-oxazole-5-sulfonyl amides **19-22** have been synthesized according to the procedure[35] from sulfonyl chlorides **17** or **18**[47] by refluxing with appropriate amine and excess of triethylamine (Scheme 2).

Methyl 5-((5-amino-3-1*H*-pyrazol-1-yl)sulfonyl)-1,3-oxazole-4-carboxylates **24, 25** were prepared by refluxing



SCHEME 2 Synthesis of 4-cyano-1,3-oxazole-5-sulfonyl amides **19-22**. Reagents and conditions: (a) 3- or 4-methylpiperidine, Et_3N, dioxane, reflux, 2 hours; (b) 2-methylaminoethanol, Et_3N, dioxane, reflux, 2 hours; (c) 2-(4-chlorophenyl)-2-piperidin-1-ylethanamine, Et_3N, dioxane, reflux, 2 hours

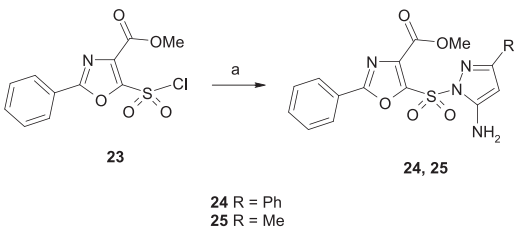
of methyl 5-chlorosulfonyl-2-phenyl-1,3-oxazole-4-carboxylate (**23**) with 3-methyl- or 3-phenyl-1*H*-pyrazol-5-amine and triethylamine in dioxane (Scheme 3).[48]

Data of synthesized novel 1,3-oxazole derivatives are presented in Section 4. NMR (^{1}H and ^{13}C NMR), chromato-mass, and elemental analysis confirm reliably the structure of the obtained compounds. The structure and composition of all obtained 1,3-oxazoles have been in good accordance with data of elemental analysis, ^{1}H, ^{13}C NMR, IR spectroscopy, and mass spectrometry. All CH-proton signals are visible in the ^{1}H NMR spectrum. The signal of the OH group (**5, 21**) is in the range from 4.79 to 4.93 ppm; NH_2 group (**24, 25**) is from 6.32 to 6.55 ppm. The intensive absorption bands of SO_2-group appeared at 1152 to 1192 cm^{-1} and 1353 to 1386 cm^{-1} in the IR spectra of compounds **12-16**, **19-22**, **24**, and **25**. Also, the broad intensive bands at 1731 to 1732 cm^{-1} corresponded to esters C═O bond of compounds **24**, **25**, and intensive bands at 2198 to 2251 cm^{-1} corresponded to CN group of **5-16, 19-22** were observed.

2.2 | In vitro evaluation of the anticancer activity

The synthesized compounds **5-16**, **19-22**, **24**, and **25** were screened for anticancer activity in the 60-cell panel in accordance with the protocol of the NCI, USA,[49–52] and the results of the single-dose (10μM) testing (**5-16**, **19-22**, **24**, and **25**) and five-dose (0.01, 0.1, 1, 10, and 100μM) (**12**, **14-16**, **19**, and **20**) experiments are presented in *Supplementary material*.

1,3-Oxazole derivatives exhibited distinctive pattern of anticancer activity. Compounds **5-9** and with amino or mercapto group in the position 5 of 1,3-oxazole ring have been shown to exhibit moderate anticancer activity ranging from 67.29 (for compound **7**, NCI-H522 of non-small cell lung cancer) to 131.64 (for compound **9**, OVCAR-3 of ovarian cancer).



SCHEME 3 Synthesis of methyl-5-((5-amino-3-1*H*-pyrazol-1-yl) sulfonyl)-1,3-oxazole-4-carboxylates **24, 25**. Reagents and conditions: (a) 3-phenyl- or 3-methyl-1*H*-pyrazol-5-amine, Et_3N, dioxane, reflux, 2 hours

5-Arylsulfonyl-1,3-oxazoles **12-16** and sulfonamides **19-22**, **24**, and **25** have been demonstrated potent anticancer activity against different cell lines unlike 5-amino- (**5, 6**) and 5-sulfanyl- (**7-9**) 1,3-oxazole-4-carbonitriles.

1,3-Oxazole-5-sulfonyl amides **21**, **22**, **24**, and **25** have demonstrated good antitumor activity against all lines of leukemia ranging from −18,14 (for compound **21**, HL-60(TB)) to 58,90 (for compound **24**, HL-60(TB)), non-small cell lung cancer from −25,83 (for compound **25**, NCI-H522) to 123,50 (for compound **21,** NCI-H226), almost all cell lines of colon cancer ranging from −63,88 (for compound **25**, COLO 205) to 115,34 (for compound **25**, HCC-2998), SF-539 of CNS cancer (43,01 for compound **21**), LOX IMVI of melanoma (from 21,91 for compound **22** to 76,84 for compound **25**) and MALME-3 M of melanoma (−37,06 for compound **25**, 2,22 for compound **24**), IGROV1 (44,16 for compound **22**), OVCAR-3 of ovarian cancer (42,30 for compound **21**; 20,43 for compound **25**), ACHN of renal cancer (−86,23 for compound **25**; 19,19 for compound **24**), T-47D of breast cancer (22,46 for compound **25**, 49,51 for compound **24**).

5-Arylsulphonyl-1,3-oxazoles **12-16** exhibited high-cytotoxic and cytostatic influence against different cell lines; sulfamides **19**, **20** demonstrated high-cytostatic activity against most of the cell lines.

Compound **12** was active against leukemia: CCRF-CEM (−21,44), HL-60(TB) (37,30), K-562 (3,28), MOLT-4 (−24,16), SR (0,73); non-small cell lung cancer: NCI-H522 (−81,24); colon cancer: HCT-116 (−49,12), SW-620 (−55,05); melanoma: LOX IMVI (30,03), MALME-3M (−54,48), M14 (41,75); renal cancer: ACHN (−0,84), TK-10 (−32,35); breast cancer: T-47D (−15,19).

Compound **13** was active against leukemia: CCRF-CEM (−10,68), K-562 (54,67), MOLT-4 (−6,82); colon cancer: SW-620 (54,03); melanoma: LOX IMVI (38,89).

Compound **14** was active against leukemia: CCRF-CEM (−13,84), HL-60(TB) (36,09), K-562 (1,85), MOLT-4 (−36,39), SR (−27,66); non-small cell lung cancer: NCI-H522 (−82,02); colon cancer: HCT-116 (0,21), SW-620 (−37,71); melanoma: LOX IMVI (7,99), MALME-3M (−47,84), M14 (38,39); renal cancer: ACHN (24,37), TK-10 (−25,29); breast cancer: T-47D (3,98).

Compound **15** was active against leukemia: CCRF-CEM (−14,67), HL-60(TB) (8,92), K-562 (2,06), MOLT-4 (−18,46), SR (5,77); non-small cell lung cancer: NCI-H23 (37,91), NCI-H522 (−68,79); colon cancer: HCT-116 (−91,06), SW-620 (−68,59); melanoma: LOX IMVI (39,82), MALME-3M (−56,67), M14 (27,28); ovarian cancer: OVCAR-4 (−16,60); renal cancer: ACHN (−84,39), TK-10 (−78,27); breast cancer: MCF7 (34,27), T-47D (−7,72), MDA-MB-468 (42,03).

Compound **16** was active against leukemia: CCRF-CEM (−33,31), HL-60(TB) (6,70), K-562 (0,29), MOLT-4 (−26,32), RPMI-8226 (49,16); non-small cell lung cancer: HOP-92 (−16,17), NCI-H226 (−7,94), NCI-H23 (53,46), NCI-H522 (−83,93); colon cancer: COLO 205 (−92,68), HCT-116 (−96,54), HCT-15 (−92,16), HT29 (−76,26), SW-620 (−91,05); melanoma: LOX IMVI (−88,95), MALME-3M (−61,25), M14 (−57,85), MDA-MB-435 (39,08), UACC-257 (−4,49); ovarian cancer: OVCAR-3 (−93,53), OVCAR-4 (36,18), OVCAR-8 (33,48); renal cancer: 786-0 (14,00), ACHN (−99,41), CAKI-1 (−94,50), RXF 393 (−89,62), SN12C (−22,92), TK-10 (−98,10), UO-31 (−73,68); breast cancer: MCF7 (11,21), BT-549 (−84,34), T-47D (−67,62), MDA-MB-468 (−80,16).

Compound **19** was active against leukemia: CCRF-CEM (−15,49), HL-60(TB) (−57,01), K-562 (−14,65), MOLT-4 (−41,86), RPMI-8226 (−42,02); non-small cell lung cancer: HOP-92 (−37,91), NCI-H226 (−36,24), NCI-H23 (−54,62), NCI-H522 (−75,15); colon cancer: COLO 205 (−92,62), HCT-116 (−100,00), HCT-15 (−53,74), HT29 (−38,65), SW-620 (−78,76); melanoma: LOX IMVI (−89,06), MALME-3M (−49,95), M14 (−70,71), MDA-MB-435 (−58,10), SK-MEL-2 (−39,82), SK-MEL-28 (−34,74), SK-MEL-5 (−30,05), UACC-257 (−41,20), UACC-62 (−60,96); ovarian cancer: IGROV1 (−22,11), OVCAR-3 (−94,30), OVCAR-5 (−2,97), OVCAR-8 (−59,58), NCI/ADR-RES (12,71); renal cancer: 786-0 (0,76), ACHN (−95,60), CAKI-1 (−87,89), RXF 393 (−95,60), SN12C (−52,21), UO-31 (−84,30); prostate cancer: DU-145 (−48,76); breast cancer: MCF7 (10,15), MDA-MB-231/ATCC (−2,03), BT-549 (−36,19), T-47D (−51,57), MDA-MB-468 (−67,54).

Compound **20** was active against leukemia: CCRF-CEM (−19,88), HL-60(TB) (−0,66), K-562 (−27,22), MOLT-4 (−45,41), RPMI-8226 (−34,62); non-small cell lung cancer: HOP-92 (−34,77), NCI-H226 (−63,05), NCI-H23 (−62,69), NCI-H522 (−78,38); colon cancer: COLO 205 (−86,32), HCT-116 (−100,00), HCT-15 (−47,42), HT29 (−20,13), SW-620 (−68,38); melanoma: LOX IMVI (−100,00), MALME-3M (−6,41), M14 (−54,13), MDA-MB-435 (−64,23), SK-MEL-2 (−35,32), SK-MEL-28 (−54,08), SK-MEL-5 (−74,73), UACC-257 (−13,34), UACC-62 (−4,37); ovarian cancer: IGROV1 (−18,64), OVCAR-3 (−72,09), OVCAR-5 (2,59), OVCAR-8 (−64,35), NCI/ADR-RES (−6,77); renal cancer: 786-0 (5,76), ACHN (−91,21), CAKI-1 (−89,51), RXF 393 (−98,82), SN12C (−57,79), UO-31 (−87,13); prostate cancer: DU-145 (−1,72); breast cancer: MCF7 (13,43), MDA-MB-231/ATCC (7,11), BT-549 (−30,17), T-47D (−32,93), MDA-MB-468 (−69,95).

Compounds **12**, **14-16**, **19**, and **20** satisfied the predetermined threshold inhibition criteria of the NCI-60 One-Dose Screening were tested against the panels of 60 cancer cell lines of NCI of the five-dose assay for anticancer activity against each cancer cell line.[46]

Compound **12** showed GI_{50} values ranging from 0.41μM (non-small cell lung cancer NCI-H522 cell line) to 37.3μM (CNS Cancer SNB-19 cell line), TGI—from 1.67μM (non-small cell lung cancer NCI-H522 cell line) to 75.9μM (CNS Cancer SF-395 cell line), and LC_{50}—from 6.0μM (renal cancer RXF-393 cell line) to 83.9μM (non-small cell lung cancer A549/ATCC cell line). LC_{50} for leukemia panel, EKVX, HOP-62, and NCI-H226 (lung cancer), SF-295 and SNB-19 (CNS cancer), NCI/ADR-RES and SK-OV-3 (ovarian cancer), HS-578T and T-47D (breast cancer) exceeded 100μM. TGI for SNB-19 (CNS cancer) was also more than 100μM.

Compound **14** showed GI_{50} values ranging from 0.63μM (leukemia CCRF-CEM cell line) to 25.6μM (CNS Cancer SNB-19 cell line), TGI—from 2.2μM (non-small cell lung cancer NCI-H522 cell line) to 85.3μM (CNS cancer SNB-19 cell line), and LC_{50}—from 6.1μM (non-small cell lung cancer NCI-H522) to 84.2μM (non-small cell lung cancer HOP-62 cell line). LC_{50} of compound NSC-762315 for leukemia panel, EKVX (lung cancer), SF-295 and SNB-19 (CNS cancer), NCI/ADR-RES (ovarian cancer) and HS-578T (breast cancer) cell lines exceeded 100μM.

Compound **15** showed GI_{50} values ranging from 0.27μM (non-small cell lung cancer NCI-H522 cell line) to 21.3μM (CNS Cancer SNB-19 cell line), TGI—from 1.7μM (non-small cell lung cancer NCI-H522 cell line) to 55.5μM (Breast Cancer HS 578 T cell line), and LC_{50}—from 5.8μM (colon cancer SW-620 cell line) to 98.0μM (ovarian cancer SK-OV-3 cell line). LC_{50} of compound NSC-762314 for leukemia panel with the exception of HL-60(TB), and cell lines NCI-H23 (lung cancer), SNB-19 (CNS cancer), NCI/ADR-RES (ovarian cancer), and HS 578T (breast cancer) exceeds 100μM.

Compound **16** showed GI_{50} values ranging from 0.43μM (leukemia SR cell line) to 22.4μM (breast cancer HS 578T cell line), TGI—from 2.5μM (colon cancer HCT-116 cell line) to 37.6μM (non-small cell lung cancer A549/ATCC cell line), and LC_{50}—from 5.0μM (colon cancer HCT-116) to 98.6μM (non-small cell lung cancer NCI-H460 cell line). LC_{50} for leukemia panel, NCI-H226 (lung cancer), HT29 (colon cancer), OVCAR-4 and NCI/ADR-RES (ovarian cancer), SF-295 and SNB-19 (CNS cancer), OVCAR-4 and NCI/ADR-RES (ovarian cancer), MCF-7, MDA-MB-231/ATCC, and T-47D (breast cancer) cell lines exceeded 100μM.

Both compounds **19** and **20** exhibited significant dose-dependent potent patterns of activity against most cancer cell lines.

The compound **19** had a broad action spectrum. The NCI-60 GI_{50} values ranged from 0.15μ*M* to 6.4μ*M*; the most sensitive cell lines were the leukemia SR, CCRF-CEM, MOLT-4, and K-562 (0.15μ*M*, 0.19μ*M*, 0.25μ*M*, 0.30μ*M*, respectively), colon cancer HCT-116, HCT-15, SW-620, and COLO 205 (0.21μ*M*, 0.25μ*M*, 0.35μ*M*, 0.50 μ*M*, respectively), melanoma MALME-3M, LOX IMVI, MDA-MB-435, and M14 (0.30μ*M*, 0.57μ*M*, 0.62μ*M*, 0.79μ*M*, respectively), ovarian cancer OVCAR-8 and breast cancer MCF-7 cell lines showing submicromolar GI_{50} values of 0.60μ*M* and 0.78μ*M*, respectively. The least growth inhibitory activity was for the non-small cell lung cancer NCI-H322M cell line ($GI_{50} = 6.4\mu M$).

For **20**, the NCI-60 GI_{50} values ranged from 0.21μ*M* to 16.9μ*M*. The leukemia cell lines showed a significant sensitivity to this compound; for out of five of the tested cell lines, namely, SR, CCRF-CEM, MOLT-4, and K-562 showed submicromolar GI_{50} values as small as 0.21μ*M*, 0.24μ*M*, 0.26μ*M*, and 0.35μ*M*, respectively, followed colon cancer HCT-15, HCT-116, and SW-620 cell lines showing submicromolar GI_{50} values of 0.38μ*M*, 0.43μ*M*, and 0.68μ*M*, respectively. The least growth inhibitory activity was for the CNS cancer SNB-75 cell line ($GI_{50} = 16.9\mu M$).

Thus, compounds **12**, **14-16**, **19**, and **20** displayed growth inhibitory (GI_{50}), and cytostatic activities (TGI) against the most sensitive cell lines at submicromolar (0.2μ*M*-0.6μ*M*) and micromolar concentrations (1μ*M*-3μ*M*), respectively. Cytotoxic activity (LC_{50}) of compounds **12**, **14-16**, **19**, and **20** against the most sensitive cell lines was also high (5μ*M*-6μ*M*).

Comparisons of active and inactive compounds provided preliminary structure-activity relationship information. The significant role of acceptor SO_2-group on antitumor activity of 1,3-oxazole derivatives should be highlighted. Further theoretical analyses are necessary for understanding the relationship between molecular properties and the biological effects.

2.3 | Quantum-chemical modeling of donor/acceptor property of substituted 1,3-oxazoles

To understand the connection between the chemical constitution of the 1,3-oxazole derivatives and their biological activity, particularly, as potential anticancer agents, the detailed study of the qualitative structure-activity relationship (QSAR) of the some substituted 2-phenyl-1,3-oxazoles were early performed.[2,35] It was a modeled formation of complex in the binding site of tubulin, and it showed the effective protein-ligand interaction. So, the results of molecular docking have indicated the formation of the π-σ interaction between the conjugated systems of the 1,3-oxazole ligand and peptide fragment (σ is lone electron pair at nitrogen atom), which stabilizes the protein-ligand complex; the predicted binding affinity ≈ −7.7 kcal/mol. Consequently, the whole π-electron system of 1,3-oxazole takes, supposedly, part in the forming of stable complex with receptor and hence influences on the first stage of bioactivity process.

On other hand, stability of the generated complex agent-biopolimer should undoubtedly depend on the donor/acceptor properties of the 1,3-oxazole derivatives, ie, on their electron structure. Therefore, we carried, additionally, out the quantum-chemical calculations of some molecules **I** in order to try to find out the possible connections between electron characteristic molecules studied and their biological activity or, more correctly, stability of the complex.

In our work, we could propose that the electron levels and charge distribution of the central conjugated part of molecules **I** are undoubtedly connected with the stability of the former complex and hence the relative position of the frontier level (connecting experimentally with electron affinity and first ionization potential) gives the substantial contribution in total biological activity.

In the quantum-chemical calculations, the nonconjugated fragments are modeled only by methyl groups. The optimization of molecular geometry and calculation of charge distribution as well as the change frontier level position were calculated by DFT/6-31 (*d*,*p*)/CAM-B_3LYP method (package GAUSSIAN 09).[53]

As a reference molecule, the unsubstituted 1,3-oxazole **26** was chosen; then the influence of the used donor and acceptor substituents was quantum-chemically investigated.

Firstly, the calculations show that the molecules **I** are planar; all conjugated substituents, Ph, CN, Me_2N, MeNH, C(O)OMe, lie in the plane of 1,3-oxazole cycle, while the acceptor groups SO_2Z (Z = Me (**33**), Ph (**34**), 4-ClC_6H_4 (**35**), 4-BrC_6H_4 (**14**)) are out from this plane. As regards to donor substitients MeS (molecule **31**) and PhS (molecule **32**), the residues Me and Ph at the sulphur atom are out from the 1,3-oxazole–S-fragment plane. Also, it is to be noticed that some substituents can rotate around single bond and hence can additionally increase the effective molecular space.

Introducing of the substituents influences not only on charge distribution in the 1,3-oxazole cycle but also on the positions of the frontier levels. Here, we have supposed that the positions of the highest occupied levels and the lowest vacant levels affect directly on the donor and acceptor ability of the compound studied and hence to a biological activity. So, it was stated above that the 1,3-oxazole derivatives exhibit the biological activity and

could generate the complex with the biological polymers by the non-covalent interaction between ligand and polimer molecule. Then, we could assume the non-covalent interaction should depend on donor-acceptor properties of the probe molecules.

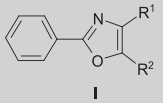
The calculated energies of the molecules **I** with different donors and acceptors are collected in Table 1.

It is to be primarily noticed that both frontier MOs are totally delocalized within the 1,3-oxazole cycle and phenyl substituent at position 5. Introducing of the donor or/and acceptor substituents influences weakly on the shape of both frontier MOs connected with donor/acceptor properties of conjugated molecules **I**. But the introduced substituents are seen from Table 1 to affect essentially on the positions of the molecular levels. So, going from the reference compound **26** with $R^1 = H$, $R^2 = H$ to compounds with the acceptor residues (CN (**27**), C(O)OMe (**28**) or SO_2Z (**33-35, 14**)) of 1,3-oxazole cycle is accompanied by the appreciable shift down of the highest occupied level, in the exact accordance with their electronic nature, while the shift of the lowest vacant levels is different, what is connected with the different change of the energy gap.

Earlier,[54] it was proposed to estimate the donor/acceptor ability of the conjugated systems by special parameter φ_0, which calculated as the relative position of the frontier levels by the following formulas:

$$\varphi_0 = \frac{\varepsilon_{LUMO} - \varepsilon_F}{\varepsilon_{LUMO} - \varepsilon_{HOMO}},$$

TABLE 1 Frontier level energies and index φ_0 calculated for some 1,3-oxazole molecules (in eV)



I

Compound I	R^1	R^2	ε_{HOMO}	ε_{LUMO}	φ_0
26	H	H	−7.45	0.22	0.49
27	CN	H	−8.03	0.33	0.46
28	C(O)OMe	H	−7.69	0.17	0.47
29	H	Me_2N	−6.08	0.64	0.62
30	CN	Me_2N	−6.72	0.12	0.53
31	CN	MeS	−8.33	2.24	0.54
32	CN	PhS	−8.56	2.13	0.53
33	CN	$MeSO_2$	−9.38	1.43	0.46
34	CN	$PhSO_2$	−9.23	1.34	0.46
35	CN	4-$ClC_6H_4SO_2$	−9.04	1.26	0.46
14	CN	4-$BrC_6H_4SO_2$	−9.26	1.19	0.45

Remark: donor substituents are marketed out by red color, acceptor substituents—by blue color.

where ε_{LUMO} and ε_{HOMO} are energies of the frontier levels while α is an energy of the so-called nonbonding MOs. For neutral conjugated molecules, α corresponds such dispositions of the frontier levels when the donor and acceptor properties are mutually balanced, for example, in long unsubstituted polyenes: then $\varphi_0 = 0.5$, ie, the energy gap is disposit symmetrically in respect to the imaginary level α. The calculation of the comparatively long polyene, $C_{12}H_{24}$, gives: $\varepsilon_{LUMO} = -1.296$ eV; $\varepsilon_{HOMO} = -5.747$ eV and $\alpha = -3.524$ eV; consequently, $\varphi_0 = 0.5$. Then, the shifting of the energy gap up and hence increasing of the parameter $\varphi_0 > 0.5$ indicates on the predominately donor properties of the conjugated molecules. Whereas, if the parameter $\varphi_0 < 0.5$ and the energy is shifted down, then the molecule is predominately acceptor.[55]

Table 1 gives the values φ_0 calculated for the compounds studied. One can see that introducing of the conjugated acceptor substituent (CN (molecule **26**) or C(O)OMe (molecule **28**)) in position 4 not only decreases the lowest occupied level, but also decreases the donor/acceptor parameter φ_0, relatively to the model molecule: compare data for compounds **26**, **27** and **28**.

On the contrast, introducing of the conjugated donor substituent, Me_2N, in position 5 (model molecule **29** causes shifting of the highest occupied and also the lowest vacant levels up; therefore, the donor/acceptor parameter naturally increases, so that $\varphi_0 > 0.5$.

Now, let us consider simultaneously introducing of donor and acceptor substituents in the adjacent positions 4 and 5; just that these cases are modeled the synthesized 1,3-oxazoles. So, the compound series contain the constant conjugated acceptor cyano group (CN) in the position 4, while the carbon in next position 8 of the oxazole cycle is bonded with such unambiguous donor substituent Me_2N or S-Y (Y = Me, Ph). It is followed from Table 1 the electron effect is predominant and hence the parameter is higher than the balanced value: $\varphi_0 > 0.5$ (compare **30–32** with $\varphi_0 = 0.40$ for the reference molecule **26**. We could suppose that the donor substituted do not stabilize the complex with the active biological center; then similar compounds do not influence on the inhibition process.

In other hand, it is logical that simultaneously introducing of two acceptor substituents in the positions 4 and 5 should induces the opposite substantial effect. In Table 1, the compounds **33–35** and **14** are presented; they contain the non-conjugated acceptor group SO_2Z, as well as the conjugated acceptor CN. Indeed, one can see that the calculated parameter φ_0 decreases appreciably: 0.46 for the molecule **33–35** or even to 0.45 for the compound **14**. Though, the effect of Cl or Br substituents in phenyl moiety is negligible

TABLE 2 Anticancer activity of 5-amino-4-cyano-1,3-oxazoles **5**, **6**, its sulphonamide analogs **21, 22**, 5-arylsulfanyl-(**7–9**), its 5-sulfonyl analogs (**12–16**), and sulfamides **19**, **20**, **24** and **25**

Compound	Anticancer activity, cell growth, %		
	Leukemia (CCRF-CEM)	Melanoma (LOX IMVI)	Colon Cancer (SW-620)
R3 – *Donor substitute*			
7	+92.23	+98.21	+112.93
9	+94.62	+92.56	+107.13
5	+81.93	+100.62	+100.72
6	+84.77	+97.22	+97.42
8	+88.91	+80.25	+107.65
R3 – *Balanced Donor-Acceptor substitute*			
25	+27.18	+72.29	+10.92
24	+9.20	+76.84	+6.13
13	−10.68	+38.89	+54.03
21	+2.67	+41.92	+35.14
22	+1.94	+21.91	+26.52
R3 – *Acceptor substitute*			
14	−13.84	+7.99	−37.71
15	−14.67	+39.82	−68.59
12	−21.44	+30.03	−55.05
19	−15.49	−89.06	−78.76
20	−19.88	−100.00	−68.38
16	−33.31	−88.95	−91.05

Remarck: Each value indicated percent growth of the treated cells when compared to the untreated control cells. The negative values represent percent of the dead cells compared with control before experiment.

($\Delta\varphi_0 \approx 0.01$). Parallelly, the calculations give the considerable shifting of the frontier levels.

Of course, the changes in the donor-acceptor parameter φ_0 upon introducing of the donor or acceptor substituents are appreciable, but they cannot be enough to intercommunicate between electronic influence of any substitutes and biological effects. Nevertheless, this simplest model enables to find the interrelation between the chemical constitution of the substrat and stability of its complex with biological polymer.

3 | CONCLUSIONS

The analysis of relationship between pharmacological activity and molecule structure shows unambiguously that compounds with the high acceptor substituents (**12, 14–16**, **19, 20**) at specific position 5 of 1,3-oxazole ring demonstrate the appreciable higher level of the effective inhibition of the cell growth comparing with the analogous 1,3-oxazole derivatives which contain the donor substituents (**5–9**) in position 5 do not practically affecting on the inhibition process (Table 2). Changing the substituent at position 2 of 1,3-oxazole ring from aryl to *tert*-butyl in the series of 5-arylsulphonyl-1,3-oxazole-4-carbonitriles **15, 16** also increases the activity significantly. 1,3-oxazole derivatives containing an acceptor group $-SO_2$ in position 5, balanced by a donor substituent -N-Me, -NH, -N-N- (**13, 21, 22, 24, 25**), do not show an unambiguous inhibition human cancer cell lines (such as leukemia (CCRF-CEM), melanoma (LOX IMVI), colon Cancer (SW-620)), unlike acceptor ($-SO_2$) substituents.

We have formed a mathematical relationship between donor-acceptor properties and anticancer activity of 1,3-oxazoles. We can correlate the anticancer activity with increasing of the relative position of the energy gap and hence increasing of the stability of the possible complex of 1,3-oxazole derivatives with protein. Different anticancer selectivity among sulfonyl derivatives can indicate the importance of steric factor on anticancer activity and/or possible complex forming with different targets.

4 | EXPERIMENTAL

4.1 | Chemistry

Melting points were determined on a Fisher-Johns apparatus. IR spectra were recorded on a Vertex-70 spectrometer from KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 400 (400 and 100 MHz, respectively) and Bruker Avance DRX 500 (500 and 125 MHz, respectively) spectrometers in DMSO-d_6 or $CDCl_3$ taking its residual protons signal as a standard. LC–MS analysis was performed on an Agilent 1200 Series system equipped with a diode array and a G6130A mass-spectrometer (atmospheric pressure electrospray ionization). Combustion elemental analysis was performed in the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry analytical laboratory. The carbon and hydrogen contents were determined using the Pregl gravimetric method, nitrogen- using the Duma's gasometrical micromethod, sulfur – by the Scheininger titrimetric method, chlorine – by the mercurometric method.

Chemicals and reagents were purchased from commercialy available sourses. 2-Methylaminoethanol, 3-phenyl- and 3-methyl-1*H*-pyrazol-5-amine were purchased from Aldrich. 2-(4-Chlorophenyl)-2-piperidin-1-ylethanamine was synthesized by the previously described method.[56] 2-Acylamino-3,3-dichloroacrylonitriles **1–4** and its synthetic procedure

were described in.[43,44] 4-Cyano-2-(4-methylphenyl)-1,3-oxazole-5-sulfonyl chloride (**17**) and 4-cyano-2-phenyl-1,3-oxazole-5-sulfonyl chloride (**18**) were synthesized previously[47] from appropriate enamide **1** or **2**. Methyl 5-chlorosulfonyl-2-phenyl-1,3-oxazole-4-carboxylate (**24**) have been synthesized by the method described in the literature.[48]

4.2 | General procedure for the synthesis of compounds 5 and 6

To a solution of 2-acylamino-3,3-dichloroacrylonitrile **1** or **2** (0.01 mol) in 40 ml of tetrahydrofurane, triethylamine (0.022 mol) and an appropriate amine (2-methylaminoethanol or 2-(4-chlorophenyl)-2-piperidin-1-ylethanamine (0.025 mol) were added. The mixture was stirred at room temperature during 12 h. The residue was triturated with water to give a crude product which was separated, recrystallized, and dried at 70–80°C.

4.2.1 | *5-(2-Hydroxyethylmethylamino)-2-(4-methylphenyl)-1,3-oxazole-4-carbonitrile* (5)

White solid; 70% yield (1.8 g); mp 104–106°C, (ethanol). IR: 3446 (OH), 2198 (CN). ^{1}H NMR (DMSO-d_6, 400 MHz) δ, ppm 7.72 (2H, d, J = 8.0 Hz, ArH), 7.30 (2H, d, J = 8.0 Hz, ArH), 4.92 (1H, t, J = 5.2 Hz, OH), 3.65–3.62 (2H, m, CH_2), 3.57–3.54 (2H, m, CH_2), 3.21 (3H, s, NMe), 2.34 (3H, s, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm 160.5, 150.9, 140.5, 129.5, 125.4, 123.1, 116.8, 84.8, 59.9, 54.0, 38.0, 21.5. MS (ESI) *m/z* 258 $[M + 1]^+$. Anal.calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.28; H, 5.86; N, 16.35.

4.2.2 | 5-(2-(4-Chlorophenyl)-2-piperidin-1-ylethylamino)-2-phenyl-1,3-oxazole-4-carbonitrile (6)

Yellow solid; 68% yield (2.76 g); mp 174–176°C, (ethanol). IR: 3340 (NH); 2206 (CN). ^{1}H NMR (DMSO-d_6, 500 MHz) δ, ppm 8.23 (1H, s, NH), 7.78 (2H, d, J = 8.0 Hz, ArH), 7.47–7.29 (7H, m, ArH), 3.98–3.95 (1H, m, 1/2CH_2), 3.72–3.69 (1H, m, CH), 3.54–3.51 (1H, m, 1/2CH_2), 2.41 (2H, bs, CH_2), 2.20 (2H, bs, CH_2), 1.36 (bs, 4H, 2CH_2), 1.21–1.20 (2H, m, CH_2). ^{13}C NMR (DMSO-d_6, 125 MHz) δ, ppm 162.0, 149.8, 136.1, 132.5, 131.0, 130.5, 129.5, 128.3, 126.3, 125.5, 116.3, 84.1, 68.6, 50.9, 44.6, 26.4, 24.6. MS (ESI) *m/z* 407 $[M + 1]^+$. Anal.calcd for $C_{23}H_{23}ClN_4O$: C, 67.89; H, 5.70; Cl, 8.71; N, 13.77. Found: C, 67.85; H, 5.69; Cl, 8.69; N, 13.69.

4.3 | General procedure for the synthesis of compounds 7–11

To a solution of appropriate 2-acylamino-3,3-dichloroacrylonitriles **1–4** (0.01 mol) in 30 ml of acetonitrile, triethylamine (0.02 mol) and an appropriate arenethiol (0.02 mol) were added, and the mixture was stirred at room temperature for 8 h. The residue was triturated with water to give a crude product which was separated, recrystallized, dried at 70–80°C, dissolved in 40 ml of acetonitrile and stirred at reflux for 8–10 h with three-fold excess of dry silver carbonate. The mixture was kept at room temperature for 8 h. The residue was triturated with water to give a crude product which was separated, recrystallized, and dried at 70–80°C.

4.3.1 | 2-(4-Fluorophenyl)-5-phenylsulfany)-1,3-oxazole-4-carbonitrile (7)

White solid; 70% yield (2.07 g); mp 106–108°C, (ethanol). IR: 2238 (CN). ^{1}H NMR (DMSO-d_6, 400 MHz) δ, ppm 8.14–8.07 (4H, m, ArH), 7.93–7.77 (3H, m, ArH), 7.45–7.43 (2H, m, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ, ppm 163.6, 152.9, 131.1, 130.6, 130.0, 129.9, 129.5, 122.1, 119.7, 117.3, 117.1, 112.4. MS (ESI) *m/z* 297 $[M + 1]^+$. Anal.calcd for $C_{16}H_9FN_2OS$: C, 64.85; H, 3.06; N, 9.45; S, 10.82. Found: C, 64.82; H, 3.04; N, 9.37; S, 10.71.

4.3.2 | 5-(4-Bromophenylsulfanyl)-2-phenyl-1,3-oxazole-4-carbonitrile (9)

Yellow solid; 67% yield (2.4 g); mp 83–84°C, (ethanol). IR: 2239 (CN). ^{1}H NMR (DMSO-d_6, 400 MHz) δ, ppm 7.98 (2H, d, J = 6.4 Hz, ArH), 7.65–7.51 (7H, m, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ, ppm 164.5, 152.1, 133.3, 132.9, 129.9, 127.2, 122.9, 120.0, 112.4. MS (ESI) *m/z* 359 $[M + 1]^+$. Anal.calcd for $C_{16}H_9BrN_2OS$: C, 53.80; H, 2.54; N, 7.84; S, 8.98. Found: C, 53.77; H, 2.52; N, 7.76; S, 8.87.

4.3.3 | 2-Tert-butyl-5-phenylsulfanyl-1,3-oxazole-4-carbonitrile (10)

The product was obtained as brown oil used in the next step without purification.

4.3.4 | 5-(4-Bromophenylsulfanyl)-2-tert-butyl-1,3-oxazole-4-carbonitrile (11)

White solid; 68% yield (2.3 g); mp 47–49°C, (acetonitrile). IR: 2242 (CN). ^{1}H NMR (DMSO-d_6, 400 MHz) δ, ppm 7.63 (2H, d, J = 8.4 Hz, ArH), 7.40 (2H, d, J = 8.4 Hz, ArH), 1.31 (9H, s, *t*Bu). ^{13}C NMR (DMSO-d_6, 100 MHz) δ, ppm 175.1, 151.4, 133.4, 132.6, 130.3, 122.8, 118.4, 112.5, 34.7, 28.1. MS (ESI) m/z 339 $[M + 1]^+$. Anal.calcd for C, 49.86%; H, 3.89%; N, 8.31%; S, 9.51%. Found: C, 49.84%; H, 3.87%; N, 8.39%; S, 9.45%.

4.4 | General procedure for the synthesis of compounds 12, 14–16[46]

Solution of appropriate 5-arylsulfanyl-1,3-oxazole-4-carbonitrile **7–11** (0.01 mol) in glacial acetic acid (20 ml) was heated to reflux. Three portions of 30% H_2O_2 of 2 ml each were added during 2 h. The mixture was kept at room temperature for 8 h. The residue was triturated with water to give a crude product which was separated, recrystallized, and dried at 70–80°C.

4.4.1 | 2-(4-Fluorophenyl)-5-phenylsulfonyl-1,3-oxazole-4-carbonitrile (12)

White solid; 73% yield (2.39 g); mp 155–160°C, (glacial acetic acid). IR: 2252 (CN); 1328, 1157 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 8.03–8.05 (2H, m, ArH), 7.40–7.58 (7H, m, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ, ppm 165.8, 163.8, 163.6, 152.9, 131.1, 130.6, 130.0, 129.9, 129.5, 122.1, 119.6, 117.3, 117.1, 112.4. MS (ESI) m/z 329 $[M + 1]^+$. Anal.calcd for $C_{16}H_9FN_2O_3S$: C, 58.53; H, 2.76; F, 5.79; N, 8.53; S, 9.77. Found: C, 58.50; H, 2.74; F, 5.70; N, 8.45; S, 9.69.

4.4.2 | 5-(4-Bromophenylsulfonyl)-2-phenyl-1,3-oxazole-4-carbonitrile (14)

White solid; 66% yield (2.56 g); mp 163–165°C, (glacial acetic acid). IR: 2246 (CN); 1332, 1154 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 7.97–8.06 (6H, m, ArH), 7.58–7.71 (3H, m, ArH). ^{13}C NMR (125 MHz, DMSO-d_6) δ, ppm 164.7, 152.5, 136.7, 134.0, 133.9, 131.0, 130.8, 130.0, 128.0, 124.5, 119.0, 110.9. MS (ESI) m/z 389 $[M + 1]^+$. Anal.calcd for $C_{16}H_9BrN_2O_3S$: C, 49.37; H, 2.33; N, 7.20; S, 8.24. Found: C, 49.35; H, 2.31; N, 7.12; S, 8.13.

4.4.3 | 5-Phenylsulfonyl-2-tert-butyl-1,3-oxazole-4-carbonitrile (15)

White solid; 68% yield (1.97 g); mp 118–120°C, (ethanol). IR: 2251 (CN); 1354, 1162 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 8.07 (2H, d, J = 7.6 Hz, ArH), 7.75–7.91 (3H, m, ArH), 1.29 (9H, s, *t*Bu). ^{13}C NMR (125 MHz, DMSO-d_6) δ, ppm 175.5, 153.0, 137.5, 136.5, 130.9, 128.6, 117.1, 110.8, 34.8, 28.0. MS (ESI) m/z 291 $[M + 1]^+$. Anal.calcd for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 57.90; H, 4.84; N, 9.55; S, 10.92.

4.4.4 | 5-(4-Bromophenylsulfonyl)-2-tert-butyl-1,3-oxazole-4-carbonitrile (16)

White solid; 73% yield (2.67 g); mp 93–95°C, (ethanol). IR: 2251 (CN); 1357, 1164 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 7.98 (4H, s, Ar), 1.30 (9H, s, *t*Bu). ^{13}C NMR (125 MHz, DMSO-d_6) δ, ppm 175.6, 152.4, 136.7, 134.0, 130.9, 130.6, 117.4, 110.7, 34.8, 27.9. MS (ESI) m/z 367 $[M + 1]^+$. Anal.calcd for $C_{14}H_{13}BrN_2O_3S$: C, 45.54; H, 3.55; N, 7.59; S, 8.68. Found: C, 45.51; H, 3.54; N, 7.50; S, 8.60.

4.5 | General procedure for the synthesis of compounds 19–22, 24 and 25

To a solution of 4-cyano-2-phenyl-1,3-oxazole-5-sulfonyl chloride (0.01 mol) in THF appropriate amine (0.011 mol) and Et_3N (0.011 mol) were added. The mixture was heated for 2 h and kept at 20–25°C for 12 h. The precipitate was filtered off, the solvent was removed in a vacuum. The residue was treated whis water, filtered off, dried and recrystallized.

4.5.1 | 5-((3-Methylpiperidin-1-yl)-sulfonyl)-2-phenyl-1,3-oxazole-4-carbonitrile (19)

White solid; 71% yield (2.35 g); mp 141–143°C, (ethanol). IR: 2248 (CN); 1378, 1152 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 8.06 (2H, d, J = 7.6 Hz, Ar), 7.62–7.73 (3H, m, CH_2CH_2), 3.58–3.68 (2H, m, CH_2), 2.91–2.96 (1H, m, 1/2CH_2), 2.63 (1H, t, J = 10.8 Hz, 1/2CH_2), 1.67–1.79 (3H, m, CH_2CH_2), 1.47–1.56 (1H, m, 1/2CH_2), 0.96–1.06 (1H, m, 1/2CH_2), 0.89 (3H, d, J = 6.4 Hz, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm 163.4, 151.1, 133.1, 129.5, 127.4, 124.4, 117.2, 110.8, 51.7, 45.7, 30.8, 30.2, 24.1, 18.5. MS (ESI) m/z: 332 $[M + 1]^+$. Anal.calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68. Found: C, 57.92; H, 5.14; N, 12.83; S, 9.89.

4.5.2 | 5-((4-Methylpiperidin-1-yl)-sulfonyl)-2-phenyl-1,3-oxazole-4-carbonitrile (20)

White solid; 75% yield (2.48 g); mp 146–148°C, (ethanol). IR: 2247 (CN); 1376, 1161 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 8.05 (2H, d, J = 7.2 Hz, Ar), 7.62–7.72 (3H, m, Ar), 3.72 (2H, d, J = 11.6 Hz, CH_2), 2.95 (2H, t, J = 11.6 Hz, CH_2), 1.75 (2H, d, J = 12.0 Hz, CH_2), 1.46 (1H, br s, 1/2CH_2), 1.13–1.22 (2H, m, CH_2), 0.89 (3H, d, J = 6.4 Hz, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm 163.4, 151.1, 133.1, 129.5, 127.4, 124.4, 117.3, 110.8, 45.6, 32.8, 28.8, 21.2. MS (ESI) m/z: 332 $[M + 1]^+$. Anal.calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68. Found: C, 57.94; H, 5.15; N, 12.78; S, 9.79.

4.5.3 | 4-Cyano-N-(2-hydroxyethyl)-N-methyl-2-(4-methylphenyl)-1,3-oxazole-5-sulfonamide (21)

White solid; 75% yield (2.48 g); mp 137–140°C, (ethanol). IR: 3552 (OH); 2252 (CN); 1371, 1155 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 7.93 (2H, d, J = 8.4 Hz, ArH), 7.43 (2H, d, J = 8.0 Hz, ArH), 4.79 (1H, s, OH), 3.56 (2H, s, CH_2), 3.35 (2H, s, CH_2), 3.02 (3H, s, NMe), 2.41 (3H, s, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm 163.1, 151.1, 143.2, 129.1, 126.5, 120.6, 116.5, 109.4, 58.7, 51.1, 34.4, 20.2. MS (ESI) m/z 322 $[M + 1]^+$. Anal.calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08; S, 9.98. Found: C, 52.29; H, 4.69; N, 13.13; S, 9.85.

4.5.4 | N-(2-(4-Chlorophenyl)-2-piperidin-1-ylethyl)-4-cyano-2-phenyl-1,3-oxazole-5-sulfonamide (22)

Yellow solid; 68% yield (2.3 g); mp 175–178°C, (ethanol). IR: 3251 (NH); 2250 (CN); 1364, 1164 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm 8.04 (1H, d, J = 7.2 Hz, ArH), 7.51–7.62 (3H, m, ArH), 7.23 (2H, d, J = 8.0 Hz, Ar), 7.05 (2H, d, J = 8.0 Hz, ArH), 5.01 (1H, bs, NH), 3.58–3.64 (2H, m, CH_2), 3.45–3.52 (1H, m, CH), 2.36 (2H, bs, CH_2), 2.20 (2H, bs, CH_2), 1.52 (bs, 4H, 2CH_2), 1.32 (2H, bs, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm 163.5, 153.0, 134.2, 133.5, 133.1, 129.7, 129.3, 128.6, 127.6, 124.3, 117.2, 110.3, 67.1, 43.3, 50.3, 26.1, 24.2. MS (ESI) m/z 471 $[M + 1]^+$. Anal.calcd for $C_{23}H_{23}ClN_4O_3S$: C, 58.66; H, 4.92; N, 11.90; S, 6.81. Found: C, 58.65; H, 4.91; N, 11.87; S, 6.68.

4.5.5 | Methyl-5-((5-amino-3-phenyl-1H-pyrazol-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (24)

White solid; 88% yield (3.73 g); mp 183–185°C, (acetonitrile). IR: 3481 (NH_2); 1731 (C=O); 1339, 1192 (SO_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ, ppm 7.72 (2H, d, J = 8 Hz, ArH), 7.72 (2H, d, J = 6 Hz, ArH), 7.57–7.68 (3H, m, ArH), 7.39 (3H, s, ArH), 6.55 (2H, s, NH_2), 5.90 (1H, s, CH), 3.93 (3H, s, OMe). ^{13}C NMR (125 MHz, DMSO-d_6) δ, ppm 162.5, 159.5, 157.4, 154.2, 146.5, 135.8, 133.5, 131.7, 130.0, 129.2, 127.6, 126.5, 124.7, 85.9, 53.8. MS (ESI) m/z 425 $[M + 1]^+$. Anal.calcd for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.80; N, 13.20; S, 7.55. Found: 56.58; H, 3.79; N, 13.18; S, 7.48.

4.5.6 | Methyl-5-((5-amino-3-methyl-1H-pyrazol-1-yl)sulfonyl)-2-phenyl-1,3-oxazole-4-carboxylate (25)

Yellow solid; 86% yield (3.11 g); mp 144–146°C, (acetonitrile). IR: 3481 (NH_2); 1732 (C=O); 1338, 1157 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm 7.96 (2H, d, J = 7.2 Hz, ArH), 7.59–7.69 (3H, m, ArH), 6.32 (2H, s, NH_2), 5.27 (1H, s, CH), 3.90 (3H, s, OMe), 1.98 (3H, s, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm 162.2, 158.9, 155.9, 150.5, 146.0, 134.7, 131.9, 128.1, 126.8, 126.7, 123.7, 89.1, 51.9, 12.7. MS (ESI) m/z 363 $[M + 1]^+$. Anal.calcd for $C_{15}H_{14}N_4O_5S$: C, 49.72; H, 3.89; N, 15.46; S, 8.85. Found: C, 49.69; H, 3.87; N, 15.38; S, 8.66.

4.6 | Pharmacology

4.6.1 | One doses full NCI 60 cell panel assay

The newly synthesized compounds were submitted to National Cancer Institute NCI, Bethesda, Maryland, U.S.A., under the Developmental Therapeutic Program DTP. The cell line panel engaged a total of 60 different human tumor cell lines derived from nine cancer types, including lung, colon, melanoma, renal, ovarian, brain, leukemia, breast, and prostate. Primary *in vitro* one dose anticancer screening was initiated, in which the full NCI 60 panel lines were inoculated onto a series of standard 96-well microtiter plates on day 0 at 5000–40000 cells/well in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine, and then preincubated in absence of drug at 37°C, and 5% CO_2 for 24 h. Test compounds were then added at one concentration of 10^{-5} M in all 60 cell lines, and incubated for a further 48 h at the same incubation conditions. Following

this, the media were removed, the cells were fixed *in situ*, washed, and dried. The sulforhodamine B assay is used for cell density determination, based on the measurement of cellular protein content. After an incubation period, cell monolayers were fixed with 10% (wt/vol) trichloroacetic acid and stained for 30 min, then the excess dye were removed by washing repeatedly with 1% (vol/vol) acetic acid. The bound stain was resolubilized in 10 mM Tris base solution and measured spectrophotometrically on automated microplate readers for OD determination at 510 nm.

4.6.2 | Five doses full NCI 60 cell panel assay

All the 60 cell lines, representing nine cancer subpanels, were incubated at five different concentrations (0.01, 0.1, 1, 10 and 100 μM) of the tested compounds. The outcomes were used to create $\log_{10}$ concentration versus percentage growth inhibition curves and three response parameters (GI_{50}, TGI and LC_{50}) were calculated for each cell line. The GI_{50} value (growth inhibitory activity) corresponds to the concentration of the compound causing 50% decrease in net cell growth. The TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition. The LC_{50} value (cytotoxic activity) is the concentration of the compound causing net 50% loss of initial cells at the end of the incubation period of 48 h.

Data calculations were made according to the method described by the NCI Development Therapeutics Program (https://dtp.cancer.gov/discovery_development/nci-60/default.htm).

The % growth curve is calculated as:

$$[(T - T_0)/(C - T_0)] \times 100,$$

where T_0 is the cell count at day 0,

C is the vehicle control (without drug) cell count (the absorbance of the SRB of the control growth).

T is the cell count at the test concentration at day 3.

The GI_{50} and TGI value are determined as the drug concentration that results in a 50% and 0% growth at 48 h drug exposure. Growth inhibition of 50% (GI_{50}) is calculated from:

$$[(T - T_0)/(C - T_0)] \times 100 = 50.$$

The TGI is the concentration of test drug where:

$$100 \times (T - T_0)/(C - T_0) = 0.$$

Thus, the TGI signifies a cytostatic effect.

The LC_{50}, which signifies a cytotoxic effect, is calculated as:

$$[(T - T_0)/T_0] \times 100 = -50, \text{ when } T < T_0.$$

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DISCLAIMER

This material should not be interpreted as representing the viewpoint of the National Institute of Allergy and Infectious Diseases (USA) and its Collaborative Antiviral Testing Group.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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REFERENCES AND NOTES

[1] D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, W. D. Craig, D. F. Smee, P. Grellier, O. Lesyk, *Eur. J. Med. Chem.* **2013**, *66*, 228. https://doi.org/10.1016/j.ejmech.2013.05.044

[2] V. Semenyuta, V. Kovalishyn, V. Tanchyk, S. Piyo, V. Zyabrev, V. Blagodatnyy, O. Trokhimenko, V. Brovarets, L. Meteytsia, *Comput. Biol. Chem.* **2016**, *65*, 8. https://doi.org/10.1016/j.compbiolchem.2016.09.012

[3] S. Carmeli, R. E. Moore, G. M. Patterson, T. H. Corbett, F. A. Valeriote, *J. Am. Chem. Soc.* **1990**, *112*(22), 8195. https://doi.org/10.1021/ja00178a070

[4] K. A. Fennell, M. J. Miller, *Org. Lett.* **2007**, *9*, 1683. https://doi.org/10.1021/ol070382e

[5] I. J. Turchi, *Id. Eng. Chem. prod. Res. Dav.* **1981**, *20*, 32. https://doi.org/10.1021/i300001a005

[6] V. Brovarets, V. Zyabrev, *Chemistry and biological activity of azoles* "Khimiya i biologicheskaya aktivnost' azolov", Lambert Academic Publishing, Saarbruken, Doutshland **2014**.

[7] C. J. Bailey, *Trends Pharmacol. Sci.* **2000**, *21*(7), 259. https://doi.org/10.1016/s0165-6147(00)01506-6

[8] G. Bruno, L. Costantino, C. Curinga, R. Maccari, F. Monforte, F. Nicolo, R. Ottana, M. G. Vigorita, *Bioorg. Med. Chem.* **2002**, *10*(4), 1077. https://doi.org/10.1016/S0968-0896(01)00366-2

[9] C. Charlier, C. Michaux, *Eur. J. Med. Chem.* **2003**, *38*(7–8), 645. https://doi.org/10.1016/S0223-5234(03)00115-6

[10] J. Chen, C.-M. Li, J. Wang, S. Ahn, Z. Wang, Y. Lu, J. T. Dalton, D. D. Miller, W. Li, *Bioorg. Med. Chem.* **2011**, *19*, 4782. https://doi.org/10.1016/j.bmc.2011.06.084

[11] T. Maekawa, N. Sakai, H. Tawada, K. Murase, M. Hazama, Y. Sugiyama, Y. Momose, *Chem. Pharm. Bull.* **2003**, *51*(5), 565. https://doi.org/10.1248/cpb.51.565

[12] M. I. Serrano, J. S. Serrano, A. Fernandez, J. M. Sanchez-carrasco, J. Fuentes, M. A. Pradera, M. C. Ortiz, J. M. Garcia Fernandez, *Arzneimittelforschung* **1995**, *45*(1), 22.

[13] V. Pinto, C. N. Pinto, M. C. Pinto, R. S. Rita, C. A. Pezzella, S. L. de Castro, *Arzneimittelforschung* **1997**, *47*(1), 74.

[14] F. M. Uckun, *Curr Pharm Des* **2001**, *7*(16), 1627. https://doi.org/10.2174/1381612013397177

[15] S. Eswaran, A. V. Adhikari, R. A. Kumar, *Eur. J. Med. Chem.* **2010**, *45*, 957. https://doi.org/10.1016/j.ejmech.2009.11.036

[16] J. Kunes, V. Balsanek, M. Pour, V. Buchta, *Collect. Czech. Chem. Commun.* **2001**, *66*(12), 1809. https://doi.org/10.1135/cccc20011809

[17] M. Kaspady, V. K. Narayanaswamy, M. Raju, G. K. Rao, *Lett. Drug Des. Disc.* **2009**, *6*, 21. https://doi.org/10.2174/157018009787158481

[18] G. A. Elmegeed, A. R. Baiuomy, M. M. Abdelhalim, H. Y. Hana, *Arch. Pharm.* **2010**, *343*, 261. https://doi.org/10.1002/ardp.200900244

[19] P. Gajdos, P. Magdolen, P. Zahradnik, P. Foltinova, *Molecules* **2009**, *14*(12), 5382. https://doi.org/10.3390/molecules14125382

[20] M. A. Mesaik, S. Rahat, M. K. Khan, Z. M. Choudhary, S. Murad, Z. Ismail, A. Rahman, *Bioorg. Med. Chem.* **2004**, *12*, 2049. https://doi.org/10.1016/j.bmc.2004.02.034

[21] K. M. Khan, U. R. Mughal, M. T. H. Khan, Z. Ullah, S. Perveen, M. I. Choudhary, *Bioorg. Med. Chem.* **2006**, *14*, 6027. https://doi.org/10.1016/j.bmc.2006.05.014

[22] K. R. Phatangare, B. N. Borse, V. S. Padalkar, V. S. Patil, V. D. Gupta, P. G. Umape, N. Sekar, *J. Chem. Sci.* **2013**, *125*(1), 141. https://doi.org/10.1007/s12039-012-0324-3

[23] X. Liu, L. Bai, C. Pan, B. Song, H. Zhu, *Chin. J. Chem.* **2009**, *27*, 1957. https://doi.org/10.1002/cjoc.200990329

[24] Z. Jin, *Nat. Prod. Rep.* **2003**, *20*, 584. https://doi.org/10.1039/B316104H

[25] Z. Jin, *Nat. Prod. Rep.* **2005**, *22*, 196. https://doi.org/10.1039/B316104H

[26] Z. Jin, *Nat. Prod. Rep.* **2006**, *23*, 464. https://doi.org/10.1039/b304142p

[27] Z. Jin, *Nat. Prod. Rep.* **2011**, *28*, 1143. https://doi.org/10.1039/C0NP00074D

[28] L. O. Haustedt, I. V. Hartung, H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **2003**, *42*, 2711. https://doi.org/10.1002/anie.200301643

[29] M. B. Nolt, M. A. Smiley, S. L. Varga, R. T. McClain, S. E. Wolkenberg, C. W. Lindsley, *Tetrahedron* **2006**, *62*, 4698. https://doi.org/10.1016/j.tet.2005.12.065

[30] J. A. Roesener, P. J. Scheuer, *J. Am. Chem. Soc.* **1986**, *108*, 846. https://doi.org/10.1021/ja00264a052

[31] K. A. Z. Siddiquee, P. T. Gunning, M. Glenn, W. P. Katt, S. Zhang, C. Schroeck, S. M. Sebti, R. Jove, A. D. Hamilton, J. Turkson, *ACS Chem. Biologia* **2007**, *2*(12), 787. https://doi.org/10.1021/cb7001973

[32] K. Takahashi, M. Kawabata, D. Uemura, *Tet. Let.* **1985**, *26*(8), 1077. https://doi.org/10.1016/s0040-4039(00)98516-2

[33] M. V. Kachaeva, S. G. Pilyo, B. A. Demydchuk, V. M. Prokopenko, V. V. Zhirnov, V. S. Brovarets, *Int. J. Curr. Res.* **2018**, *10*(5), 69410.

[34] V. S. Brovarets, V. A. Tsygankova, V. A. Ya, O. I. Shtompel, V. M. Kopich, S. G. Pilyo, V. M. Prokopenko, A. M. Kornienko, *RJLBPCS* **2017**, *3*(4), 102. https://doi.org/10.26479/2017.0304.09

[35] M. V. Kachaeva, D. M. Hodyna, I. V. Semenyuta, S. G. Pilyo, V. M. Prokopenko, V. V. Kovalishyn, L. O. Metelytsia, V. S. Brovarets, *Comput. Biol. Chem.* **2018**, *74*, 294. https://doi.org/10.1016/j.compbiolchem.2018.04.006

[36] Y. Zhang, J. X. Li, J. Zhao, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1629. https://doi.org/10.1016/j.bmcl.2005.01.061

[37] I. Azad, A. Jafri, T. Khan, Y. Akhter, M. Arshad, F. Hassan, N. Ahmad, A. R. Khan, M. Nasibullah, *J. Mol. Struct.* **2019**, *1176*, 314. https://doi.org/10.1016/j.molstruc.2018.08.049

[38] G. P. S. Mol, D. Aruldhas, I. H. Joe, S. Balachandran, A. R. Anuf, J. George, *J. Mol. Struct.* **2019**, *1176*, 226. https://doi.org/10.1016/j.molstruc.2018.08.092

[39] S. Murugavel, C. Ravikumar, G. Jaabil, A. Ponnusamy, *J. Mol. Struct.* **2019**, *1176*, 729. https://doi.org/10.1016/j.molstruc.2018.09.010

[40] R. M. Costa, J. K. Bastos, M. C. A. Costa, M. M. C. Ferreira, C. S. Mizuno, G. F. Caramori, G. R. Nagurniak, M. R. Simão, R. A. Santos, R. C. S. Veneziani, S. R. Ambrósio, R. L. T. Parreira, *Phytochemistry* **2018**, *156*, 214. https://doi.org/10.1016/j.phytochem.2018.10.005

[41] J. S. Al-Otaibi, *Rasayan J. Chem* **2018**, *11*(1), 88. https://doi.org/10.7324/RJC.2018.1111980

[42] M. S. Alia, M. A. Farah, H. A. Al-Lohedan, K. M. Al-Anazi, *J. Mol. Liq.* **2018**, *258*, 74. https://doi.org/10.1016/j.molliq.2018.02.090

[43] B. S. Drach, E. P. Sviridov, T. Y. Lavrenyk, *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 1278.

[44] B. S. Drach, E. P. Sviridov, A. A. Kisilenko, A. V. Kirsanov, *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 1842.

[45] S. G. Pil'o, V. S. Brovarets, T. K. Vinogradova, A. V. Golovchenko, B. S. Drach, *Rus. J. Gen. Chem.* **2002**, *72*(11), 1714. https://doi.org/10.1023/A:1023333011230

[46] M. V. Kachaeva, S. G. Pilyo, V. V. Zhirnov, V. S. Brovarets, *Med. Chem. Res.* **2019**, *28*(1), 71. https://doi.org/10.1007/s00044-018-2265-y

[47] A. N. Kornienko, S. G. Pil'o, V. M. Prokopenko, V. S. Brovarets, *Rus. J. Gen. Chem.* **2012**, *82*(11), 1855. https://doi.org/10.1134/s1070363212110229

[48] A. N. Kornienko, S. G. Pil'o, V. M. Prokopenko, V. S. Brovarets, *Rus. J. Gen. Chem.* **2014**, *84*(8), 1555. https://doi.org/10.1134/S1070363214080210

[49] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, *J. Nat. Cancer Inst.* **1991**, *83*(11), 757. https://doi.org/10.1093/jnci/83.11.757

[50] M. R. Boyd, K. D. Paull, *Drug Dev. Res.* **1995**, *34*, 91. https://doi.org/10.1002/ddr.430340203

[51] M. R. Boyd, in *Cancer Drug Discovery and Development*, (Ed: B. A. Teicher) Vol. 2, Humana Press, Dana–Farber Cancer Institute, Boston, MA **1997** 23 https://doi.org/10.1007/978-1-4615-8152-9.

[52] R. H. Shoemaker, *Nat. Rev. Cancer.* **2006**, *6*, 813. https://doi.org/10.1038/nrc1951

[53] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, *at all*, GAUSSIAN09; revision B.05, Gaussian, Inc., Pittsburgh PA, **2009**.

[54] N. Obernikhina, M. Kachaeva, V. Shchodryi, Y. Prostota, O. Kachkovsky, V. Brovarets, Z. Tkachuk, *Polycyclic Aromat. Compd.* **2019**, *39*(1), 1. https://doi.org/10.1080/10406638.2018.1538056

[55] O. Shablykin, D. Merzhyievskyi, N. Obernikhina, O. Kobzar, Y. Prostota, O. Kachkovsky, V. Brovarets, A. Vovk. Conference Proceedings IEEE 38-th International Conference on Electronic and Nanotechnology (ELNANO-2018). – Kyiv, **2018**, 449–453. https://doi.org/10.1109/ELNANO.2018.8477468

[56] K. Briner, I. Collado, M. J. Fisher, C. Garcfa-Paredes, S. Husain, S. L. Kuklish, A. I. Mateo, T. P. O'Brien, P. L. Ornstein, J. Zgombick, O. Frutos, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3449. https://doi.org/10.1016/j.bmcl.2006.04.002

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