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Abstract: Aim and Objective: It is known that rhodanine drug has various biocidal activities. The aim of this work was to improve the structure of rhodanine drug via alkylation at N, S, and O-centers in addition to the introduction of fluorine atoms. The new fluorinated modified rhodanines 2-16 were evaluated as enzymatic probes for cellobiase activity produced by fungi and as CDK2 inhibitors of tumor cells.

Materials and Methods: Novel fluorine substituted N-alkyl, S-alkyl and amino-rhodanines were obtained via hydroxy methylation, Mannich reactions, chlorination and amination of 5-(4'-fluorophenylene)-2-thioxothiazolidin-4-one, and the enzymatic effects of cellobiase produced by fungi and/or CDK2 inhibition of tumor cells were evaluated.

Results: Most of the targets were obtained in high yield and in the form of very pure crystals with characteristic colors. Only compounds 5, 8, 10, 13, and 14 exhibited a higher activity as cellobiase while compounds 2 and 5 showed a highly enzymatic effect on tumor cells. In addition, compounds 2 and 10 can be used as Olomoucine (standard reference).

Conclusion: Various N, S and O-alkyl derivatives of fluorine-substituted rhodanines were prepared via a simple method and used as enzymatic probes for cellobiase activity produced by fungi and CDK2 inhibitors for tumor cells. The more bioactive compounds had rich fluorine atoms as p-fluorophenyl and p-fluorobenzoyl bearing N, S, O-alkyl rhodanine. The highly active compounds may be used as enzymatic materials for various biological transformations in the future.

Keywords: Synthesis, fluorine substituted rhodanine, cellobiase activity of fungi, CDK2 inhibitors, bioactive probes, tumor cells.

1. INTRODUCTION

Most of the substituted-4-thiazolidinones exhibit a wide range of pharmacological, medicinal and biological properties as anti-bacterial [1, 2], antifungal [3], antitubercular [4], anticancer [5], antiinflammatory [6], antiinvasive [7], anticonvulsant [8], antidepressant [9], antiviral /anti HIV [10], antidiabetic [11], a muscarinic receptor1-agonist [12], an FSH receptor agonist [13], trypanocidal (anti-epimastigote) [14] and antiarrhythmic activity [15, 16].

Introduction of fluorine atoms to heterocyclic nitrogen systems often improves their physical with chemical advantages and enhances their biological activity [17-20]. Based on these observations, the present work describes the development of new fluorine compound substituted rhodane derivatives which may enhance the biological effects, as cellobiase produced by fungi as well as CDK2 inhibitors for tumor cell (DNA damage).

The structure-activity relationship has been discussed and their binding conformation is further clarified by molecular modification studies.

2. MATERIALS AND METHODS

All the melting points were determined on Stuart scientific SMP30 (Bibby, UK) melting point apparatus and reported as uncorrected. The FT-IR spectra were recorded on a Perkin-Elmer spectrum 100 spectrometer in ATR. $^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded on a Brucker advance DPX NMR spectrometer (400 and 100 MHz, respectively), by using DMSO-$d_6$ as a solvent (chemical shift in δ, ppm), and TMS as an internal standard. Elemental analysis was conducted by a 2400 Perkin Elmer series 2 analyzer. Mass spectra were determined by using quadruple MS (Electronic ionization mod E1 mode with source temperature: 200°C) at 70 eV. All the reactions were monitored by TLC, using silica gel coated Al plates with a fluorescent indicator F254 (Merck).

$^{19}$F NMR spectra of all the compounds 2-16 showed resonated signals as d,d at -119.75 and -123.16 ppm.

3. RESULTS AND DISCUSSION

3.1. Chemistry

A literature survey reported a new fluorine compound substituted for rhodanine at positions SH, NH, and active CH$_2$ positions [21] and is used for detecting Tau pathology in Alzheimer’s Brains [22] as well as inhibitors of JSP-1 [23].

In view of these results, the aim of this work was to search for new fluorine compounds derived from rhodanine drug with a hope to enhance their biological activity.

Thus, hydroxy methylation and/or Mannich bases of 5-(4'-fluorobenzylidene)-2-thioxothiazolidin-4-one (2) [24] via refluxing with HCHO-MeOH and/or HCHO-MeOH with secondary amines afforded N'-substituted rhodanine 3-5 (Scheme 1).
A simple nucleophilic attack of primary aliphatic/aromatic amines to SH group at position-2 of rhodanine by refluxing with ethanolamine, 4-fluoroaniline and sulfanilamide (1:1 by mol) in EtOH, furnished 2-substituted amino-5-(4'-fluorobenzylidene)-4-thiazolidinones (6-8) (Scheme 2).

Also, the treatment of compound 2 with POCl₃ under fusion condition yielded 4-chloro-5-(4-fluorobenzylidene)thiazol-2(5H)-thione (9). Chlorine atom at 4-position of rhodanine 9 was removed by treatment with primary amines. Thus, compound 9 upon attack by primary amines such as 4-fluoroaniline, hydrazinehydrate and/or 4-chlorophenyl-hydrazine under refluxing with DMF produced 5-(4-fluorobenzylidene)-4-(4-fluorophenyl) amino]thiazol-2(5H)-thione (10); 3-(4-fluorophenyl)-1,3-dihydro-pyrazolo[3,4-d]thiazol-5-thione (11), and/or 2-(4-chlorophenyl)-3-(4-fluorophenyl)-1,2-dihydropyrazolo[3,4-d]thiazol-5-thione (12) (Scheme 3).

Formation of 4 and 5 from 2 is shown in Fig. (1).
Synthesis of Novel Fluorine Compounds Substituted-4-thiazolidinones

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Scheme 3. Formation of compounds 9-12 from 2.

The formation of compound 11 is shown in Fig. (2).

Alkylation of compound 2 by refluxing with monochloroacetic acid in DMF yielded 2-[(5-(4-fluorobenzylidene)-4-oxo-4, 5-dihydrothiazol-2-yl)thio] acetic acid (13), which on decarboxylation via warming with aqueous K$_2$CO$_3$ gave 5-(4-fluorobenzylidene)-2-(methylthio) thiazol-4(5H)-one (14) (Scheme 4).

The structural formula of new systems was obtained from the correct elemental analysis and spectral data.

FT-IR absorption spectra of compounds 3-5 showed the absorption bands at 2980 & 2888 cm$^{-1}$, attributed to endo CH$_2$ and exo CH$_2$ with lack of NH group, and with the presence of NH at 1700, 1610, 1240 and 1180 cm$^{-1}$ due to C=O, C=C, C-F, and C=S respectively. Also, FT-IR spectra of compounds 6-8 recorded NH at 3180-3150 cm$^{-1}$ for bonded NH which lacks the SH groups. Moreover, FT-IR spectrum of compound 9 indicates a lack of C=O with the presence of NH at 700 cm$^{-1}$ for C-Cl. Also, FT-IR spectra of both the compounds 10 and 12 recorded NH at 3180, 1230 and 1188 cm$^{-1}$ which were attributed to the presence of NH, C-F, and C=S with lack of C=O, while 11 showed NH at 3200, 3180, 1590 and 1240 cm$^{-1}$ for NH, NH$_2$, C=N, C-F functional groups.

It is interesting to note that 1,4-disubstitutedthiazolo[5,4-d]pyrazole-piperazine (16) isolated from the interaction of compound 2 with piperazine (2:1 by mole) / in refluxing EtOH gave N$_1$, N$_2$-disubstituted piperazine 15 followed by hydrazinolysis in EtOH (Scheme 5).

FT-IR spectra of compounds 13 and 14 showed NH at 2980 and 2880 cm$^{-1}$ of alkyl groups, with the presence of two NH at 1720, and
**Fig. (2).** Formation of compound 11 from 2.

**Scheme 4.** Formation of compounds 13 and 14 from 2.

**Scheme 5.** Formation of compounds 15 and 16 from 2.
1690 cm\(^{-1}\) attributed to C=O of acid and C=O of thiazole nucleus. Its interesting to note that FT-IR spectrum of compound 15 showed lack of SH and / or NH groups, with the presence \(\text{\textbf{\textit{\textbullet}}}\) at 1700, 1610 and 1230 cm\(^{-1}\), for C=O, C=C, and C-F groups, respectively, while the spectrum of 16 showed lack of C=O, C=C, NH, and SH groups. Both the compounds 15 and 16 exhibited only \(\text{\textbf{\textit{\textbullet}}}\) at 2985, and 2880 cm\(^{-1}\) for stretching and \(\text{\textbf{\textit{\textbullet}}}\) at 1488, and 1440 cm\(^{-1}\) for bending of CH\(_2\), for piperazine, respectively.

\(^1\)H NMR spectra of the new compounds give more indications about their structures. Therefore, \(^1\)H NMR spectra of compounds 3-5 showed resonated signals \(\delta\) at 7.6 and 2.4 for the exo (C=CH-Ar) and endo N-CH\(_2\), while the spectra of compound 6-8 recorded \(\delta\) at 8.2 ppm for NH bonded with aromatic protons at 7-8 ppm.

Compound 6 showed \(\delta\) at 7.8 and 5.1 ppm attributed to NH, OH, and CH\(_2\) protons. Also, \(^1\)H NMR spectra of compounds 10-12 indicate the existence of NH protons with aryl protons at \(\delta\) 8.5-8.1 and 7.6-7.4 (m & m) ppm. Both the compounds 13 and 14 showed \(\delta\) at 2.5 ppm for aliphatic protons. Only \(^1\)H NMR spectra of compounds 15 and 16 exhibited resonated signals at \(\delta\) 2.90—2.51 ppm for N-CH\(_2\), and aryl-H with lack of both SH and NH protons. All the compounds recorded \(\delta\) at 7.5 and 7.4 (d,d) ppm being attributed to CH-F protons. The interaction can occur only in "Z" geometry. Thus, the exocyclic -CH=C- was deduced from recorded signals at higher chemical shift at 87.6 ppm [28].

Also, \(^13\)C NMR spectra of compounds 3-5 showed resonated signals at \(\delta\) 180, 170—165, 146 and 142 ppm for C=S, C=O, C-F, C=C respectively, while that of 6-8, there was lack of C=S carbons. \(^13\)C NMR spectra of both 10 and 12 exhibited signals at \(\delta\) 180, 146, 144, and 142-140 ppm which were attributed to C=S, C-F, C-Cl, C=N respectively, and aryl carbons at 133-128 ppm; while the spectra of compound 11 showed a resonated signal at 180 ppm for C=S. Mass fragmentation pattern of some compounds showed a molecular ion peak, which, under the fragmentation process pro-
duced the base peak m/e 95 attributed to 4-fluorophenyl ions shown in Figs. (3-5). The pathway fragment steps indicated the relationship between the common base peak which had a significant role in the biodynamic effects.

It is interesting that $^{13}$C NMR spectrum of compound 13, showed lack of C-OH proton, due to the H-bonding formed as shown in Fig. (6).

Finally, $^{19}$F NMR spectra of all the synthesized compounds 2-16 showed resonated signals as d,d at -119.75 and -123.16 ppm for the fluorine bonded to the aromatic nucleus.

### 3.2. Biological Evaluation

#### 3.2.1. Antifungal Activity

All the obtained compounds were evaluated as fungicidal probes against *Candida albicans* and *Aspergillus Fumigatus* fungi by using DMSO as the solvent (1mg/ml) and Ketoconazole as the standard drug. The inhibition was recorded by measuring the diameter inhibition zones at the end of 48 h according to the reported method (Table 1) [25].

| Compd. No. | *C. Albicans* ($\mu g/ml$) | *A. Fumigatus* ($\mu g/ml$) |
|------------|--------------------------|---------------------------|
| 3          | 16                       | 14                        |
| 4          | 15                       | 12                        |
| 5          | 16                       | 13                        |
| 6          | 14                       | 10                        |
| 7          | 15                       | 11                        |
| 8          | 20                       | 18                        |
| 9          | 12                       | 10                        |
| 10         | 19                       | 17                        |
| 11         | 12                       | 11                        |
| 12         | 15                       | 10                        |
| 13         | 18                       | 18                        |
| 14         | 19                       | 19                        |
| 15         | 10                       | 8                         |
| 16         | 8                        | 7                         |
| Ketoconazole | 18                     | 16                        |

Table 1. The biological activity as antifungal of the new fluorinated-substituted rhodanine.
From the results, we can conclude that all the fluorinated systems exhibited an antifungal activity. Higher effects of compounds were observed towards the two tested fungi as: 14 > 13, 8 > 7 > 6 and 10 > 12 > 11 > 3 > 5 > 4.

Also, the result obtained indicated a particular activity more than the standard drug used in the order 8 > 10 > 14 > 5 > 3, while compounds 1,4-disubstituted piperazine 15 and 16 exhibited a lethal activity.

3.2.2. The Enzymatic Effects on Cellobiase of Some Fungi

The efficiency of the synthesized fluorinated systems obtained towards the activity of cellobiase produced enzyme as thermophilic fungi namely, Thermomyces lanuginosus and Chaetomium Thermophillum was evaluated according to the reported method [26]. In DMF, which was used as a solvent, the enzyme solution and the substrate (cellobiase) was added and the solution was then dissolved in citrate-phosphate buffer at pH 5 and incubated at 40°C for 1 h. The freed reducing sugar was evaluated colorimetrically at 540 nm as an induction for the enzymatic activity [27].

Table 2. The efficiency of new compounds on cellobiase activity produced by thermophilic fungi.

| Compd. No. | Amount of Glucose (mg/ml) |
|------------|--------------------------|
|            | C. Thermophillum | T. lanuginous  |
| 5          | 4.6            | 5.2            |
| 8          | 8.0            | 8.8            |
| 10         | 7.8            | 8.0            |
| 13         | 6.2            | 7.0            |
| 14         | 7.0            | 7.7            |

*Blank: 9.78 and 0.80 mg/ml-without substance DMF. DMF: 0.7 and 0.72 mg/ml.

The data is recorded in Table 2. Only compounds 5, 8, 10, 13 and 14 showed higher activity against the tested fungi, which showed the activity of reducing sugar in the order 8 > 10 > 14 > 13 > 5. The relationship between the structure and activity showed that the presence of a sulfa drug, fluoroamine, and alkylithia of 5-(4-fluorobenzylidene) -2-thioxo-thiazol-5-one Skeleton enhanced the antifungal activity.

3.2.3. CDK2 Inhibition of Tumor Cells (DNA Damage)

Cyclin dependent-kinases is a family of serine/ threonine kinases, that strongly control the mammalian cell-cycle by binding to cyclins. Thus, CDK/ cyclin complexes are involved in the DNA repair when they are presented in the induction state in response to DNA damage [28-31].

Also, the presence of fluorine atom in various hetero-cyclic nitrogen/ sulfur and oxygen systems, has a significant effect on the modulation of electronic, lipophilic and steric parameters determining the pharmacodynamic and pharmacoKinetic properties [32].

Thus, the new fluorine substituted rhodanines (2-16) have been evaluated toward CDK2 in a biochemical assay. The inhibitory concentration (IC50) values were reported according to the methods described above [33]. Olomoucine has been used as a standard, and the results are reported in Table 3. From the data obtained, we can indicate that:

All the tested compounds showed a very significant CDK2 inhibitory activity. Only, compound 2 showed an Olomoucine effect, while the other tested compounds were observed to be more potent than the standard control. It is interesting to note that compound 10 had a higher enzymatic effect as the strong inhibitor for CDK2, which may be used as a new inhibitor in the future.

Table 3. CDK2 inhibiting activity of fluorinated rhodanine derivatives 2-16.

| Compd. No. | IC50 ± SD (μM)* |
|------------|-----------------|
| 2          | 5.0 ± 1.7       |
| 4          | 6.0 ± 1.8       |
| 8          | 3.7 ± 1.7       |
| 10         | 15.0 ± 2.7      |
| 14         | 12.0 ± 1.7      |
| 15         | 12.2 ± 1.5      |
| 16         | 4.1 ± 2.8       |
| Olomoucine | 5.0 ± 1.0       |

*IC50 in μM/dm3; SD: standard deviation.

4. EXPERIMENTAL

Compound 2 was obtained according to the reported method [24].

4.1. 5-(4-Fluorobenzylidene)-3-(hydroxymethyl)-2-thioxo-thiazolidin-4-one (3)

A solution of 2 (1.554 g, 6.5 mmol) and HCHO (0.195 g, 6.5 mmol) in MeOH (40 ml) was refluxed for 2 h. The mixture of was cooled down at room temperature. The precipitated product was filtered off and crystallized from dioxane to give compound 3. Orange crystals, Yield 75% (25.43 g), M.p: 128-130°C. FT-IR IR spectrum Ì (cm⁻¹): 3450-3420(broad, OH), 3060(ArH), 2944, 2880(aliph. CH), 1716(C=O), 1616(C=C), 1594(C=C), 1229(C=C), 1157(C=S), 889, 852, 793(subst. phenyl), 707(C=C). H NMR (400 MHz, DMSO-d6) δ (ppm): 7.76(s, 1H, Ar-CH=), 7.66, 7.64(d, 2H, CH=), 7.59-7.82(m, 2H, Ar), 4.59(s, OH), 2.51-2.50(s, CH2- OH). 13C NMR (100 MHz, DMSO-d6) δ (ppm): 180(C=O), 173(C=O) 167(C=O), 162(Ar CH=C), 142(C=F), 133.6-127.4(Ar carbons), 66.45(CH2-carbon). Calculated, C18H17N3O5S2: (269), %: C, 49.07; H, 2.97; N, 5.20; F, 7.06, S,23.79. Found, %: C, 48.77; H, 2.66; N, 5.01; F, 6.85, S, 23.69.

4.2. Mannich Bases 4 & 5

A mixture of compound 2 (1.554 g, 6.5 mmol), piperidine (0.55 g, 6.5 mmol) and/or morpholine (0.57 g, 6.5 mmol) and HCHO (0.195 g, 6.5 mmol) in MeOH (40 ml) was refluxed for 2h. The mixture was cooled down at room temperature. The obtained precipitate was filtered off and crystallized from dioxane to give 4 and/or 5.

4: Yellow crystals, Yield 75% (1.57 g), M.p: 165-167°C. FT-IR spectrum Ì (cm⁻¹): 3050(Ar CH), 2939, 2862, 2798 (aliph. CH), 1725(C=O), 1599(C=C), 1235(C-F), 880, 853(subst. phenyl), 723(C=F). 1H NMR (400 MHz, DMSO-d6) δ (ppm): 7.62(s, Ar-CH=), 7.60, 7.54(d, 2H , CH-F), 7.29-7.27(m, 2H, Ar), 2.4(N Me) 1.62 & 1.50(CH2 of piperidine), 13C NMR (100 MHz, DMSO-d6) δ (ppm): 180(C=S), 173(C=O), 164(C-S), 162(Ar=CH=), 146(C-F), 132.3-128.82( aromatic carbons), 50.55, 49.75(N-Me & CH2-CH2 of piperidine). Calculated, C18H17NH2F2O3 (336), %: C, 57.14; H, 5.05; N, 8.33; F, 5.65; S, 19.04. Found, %: C, 56.88; H, 4.91; N, 8.11; F, 5.55; S, 18.85.

5: Yellow crystals, Yield 78% (1.65 g), M.p: 163-165°C. FT-IR spectrum Ì (cm⁻¹): 2937, 2854(str. CH), 1676(C=O), 1600(C=C), 1448, 1412(bending CH), 1389(NCSN), 1266(C-F), 831, 803(arly ring). 1H NMR (400 MHz, DMSO-d6) δ (ppm): 7.6, 7.59(d, 2H, Ar), 7.52, 7.26(d, 2H , Ar), 3.79(s, 2H, CH2), 3.53, 2.46, 1.60, 1.54(CH2 protons). 13C NMR (100 MHz, DMSO-d6) δ (ppm):
180.19(C=S), 174.98(C=O), 163(C-S), 162.38(Ar-CH=C), 146(C-F), 132-116(Ar carbons), 66.27-65.42(2H, CH₂), 26.16-23.71(2H, CH₂). Calculated, C₁₉H₁₄N₂F₄S₄O₈ (338), %: C, 53.25; H, 4.43; N, 8.28; F, 5.62; S, 18.93. Found, %: C, 53.01; H, 4.13; N, 8.11; F, 5.50; S, 18.78.

4.3. 5-(4-Fluorobenzylidene)-2-[(2-hydroxyethyl)aminol thiazole-4(5H)-one (6)

An equimolar amounts of compound 2 and ethanolamine were mixed with in ethanol (40 ml) and refluxed for 6h. The mixture was then cooled down at room temperature. The precipitate obtained was filtered off and crystallized from dioxane to give compound 6. Yellow crystals, Yield 65% (1.125 g), M.p: 233-235°C. FT-IR spectrum 𝜖 (cm⁻¹): 3500 (OH), 3259(NH), 3050(ArH), 2900, 2869(aliph. CH), 1696(C=O), 1621(C-C), 1594(C=N), 1550(C=N), 1488, 444 (bending CH₂), 1228(C-F), 895, 895, 790(substit. phenyl), 751(C-F).¹ H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.86(s, 1H, NH), 7.47, 7.46(d, d, CH-F), 7.21-7.19(m, 2H, Ar), 5.1(s, 1H, OH), 3.45, 2.39(CH₂-CH₂).

¹C NMR (100 MHz, DMSO-d₆) δ (ppm): 163.54(C=O), 162.27(1Ar-CH=C), 146(C-F), 142(C=N), 132.5(C=O), 126.78(Ar carbons), 125.77(Ar carbons), 124.28(C-H & CH=CH-N), 115.96, 114.13(bending CH₂), 1228(C-F), 891, 856, 852(substituted phenyl), 735(C-F).¹ H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.2(s, 1H, NH), 7.67, 7.61(d, 2H, CH-F), 7.39-7.37(m, 4H, ArH).¹C NMR (100 MHz, DMSO-d₆) δ (ppm): 170(C=O), 169(1Ar-CH=C), 154(C=N), 147(C=O), 141.72(C=N), 137, 129.25(Ar carbons). Mass spectrum, m/z (mrel): 315 (M⁺, 3%), 181 (17, M⁺-2, 1.50 %), 110(23.8), 95(100), 84(15.15). Calculated, C₁₉H₁₄N₂F₄S₄O₈ (316), %: C, 60.75; H, 3.16; N, 8.86; F, 12.02; S, 10.12. Found, %: C, 60.55; H, 3.11; N, 8.59; F, 11.83; S, 10.01.

4.4. 5-(4-Fluorobenzylidene)-2-[(4-fluorophenyl)aminol thiazole-4(5H)-one (7)

Compound 2 (1.554 g, 6.5 mmol) and 4-fluorophenol (0.723 g, 6.5 mmol) were dissolved in EtOH (30 ml) and refluxed for 6h. The mixture was then cooled down at room temperature. The precipitated product was filtered off and crystallized from ethanol to give compound 7. Orange crystals, Yield 80% (1.64 g), M.p: 225-227°C. FT-IR spectrum 𝜖 (cm⁻¹): 3150(NH), 3050(ArH), 2854(aliph. CH), 1728(C=O), 1610(C=O), 1590(C=N), 1465, 1413(bending CH₂), 1228(C-F), 891, 856, 852(substituted phenyl), 735(C-F).¹ H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.2(s, 1H, NH), 7.67, 7.61(d, 2H, CH-F), 7.39-7.37(m, 4H, ArH).¹C NMR (100 MHz, DMSO-d₆) δ (ppm): 170(C=O), 169(1Ar-CH=C), 154(C=N), 147(C=O), 137, 129.25(Ar carbons). Mass spectrum, m/z (mrel): 315 (M⁺, 3%), 181 (17, M⁺-2, 1.50 %), 110(23.8), 95(100), 84(15.15). Calculated, C₁₉H₁₄N₂F₄S₂O₂ (316), %: C, 60.75; H, 3.16; N, 8.86; F, 12.02; S, 10.12. Found, %: C, 60.55; H, 3.11; N, 8.59; F, 11.83; S, 10.01.
The obtained product was filtered off and crystallized from MeOH. The reaction mixture was then cooled down at room temperature and then poured onto ice. The precipitated product was filtered off and crystallized from ethanol to give compound 13. Light-yellow crystals, Yield 65% (3.23 g), M.p: 238-240°C. FT-IR spectrum of  \( \bar{v} \) (cm\(^{-1}\)): 3500-3100(broad, OH), 3060(Arh), 2937, 2880(aliph. CH), 1693, 1675(2C=O), 1595(C=C), 1562(C=O), 1443, 1411(bend. CH), 1232(C-F), 1001(C-S-C), 827, 793(subst. phenyl), 749 (C-F). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \( \delta \) (ppm): 7.0(Ar CH=C), 7.69, 7.69(d, d, 2H, CH=), 7.63-7.64(m, 2H, ArH.), 2.50(2H, CH2).

5-(4-Fluorobenzylidene)-2-(methythio)thiazol-(4(SH)-one) (14)

Compound 13 (1.5 mmol) and ag. K₂CO\(_3\) (5%, 15 ml) were heated for 1h, and then cooled down followed by neutralization by AcOH to give 14. Light-yellow crystals, Yield 55% (0.70g), M.p: 173-175°C. FT-IR spectrum of \( \bar{v} \) (cm\(^{-1}\)): 3050(ArH), 2936(aliph. CH), 1674.9(C=O), 1620(C-C), 1599(C=N), 1467, 1411(bend. CH), 1224(C-F), 1050(C-S-C), 853, 832, 822(subst. phenyl), 723(C-F).

4.12. 2,2'-(Piperazine-1,4-diyldibis)[5-(4-fluorobenzylidene) thiazol-(4(SH)-one) (15)

Compound 2 (4 g, 16.73 mmol) and piperazine (0.721 g, 8.37 mmol) were dissolved in EtOH (70 ml), refluxed for 6-8h, and then cooled down. The precipitated product was filtered off and crystallized from ethanol to give compound 15. Yellow crystals, Yield 85% (3.53g), M.p: 273-275°C. FT-IR spectrum of \( \bar{v} \) (cm\(^{-1}\)): 3060(Arh), 2939, 2880(aliph. CH), 1690, 1666(2C=O), 1597(C=C), 1564(C=N), 1505, 1414(bend. CH), 1231(C-F), 847, 826, 810(subst. phenyl), 725(C-F). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) \( \delta \) (ppm): 7.70(Ar CH=C), 7.69, 7.68(d, d, 2H, CH=), 7.63-7.73(m, 7.37-7.16(2H , ArH), 2.51 (Me-S). \(^1\)C NMR (100 MHz, DMSO-d\(_6\)) \( \delta \) (ppm): 184, 179(C-S), 163.52 (Ar-CH=C), 162.70(C-F), 161.55(C=N), 136-121.51(3Ar CH), 26.21(Chl). Calculated, C\(_{16}\)H\(_{14}\)F\(_{2}\)S\(_{2}\), %: C, 52.17; H, 3.16; N, 5.53; F; 7.50; S, 25.29. Found, %: C, 52.01; H, 2.89; N, 5.28; F, 7.31; S, 25.11.

CONCLUSION

Due to the high resistance of fungi to antibacterial and drugs, the present work designed, synthesized and evaluated them as dual binding site modified fluorine compounds bearing rhodanine drug inhibitors.

Thus, in search for new rhodamine derivatives, the recent development of rhodamine via the introduction of both fluorine atoms followed by alkyl, amino and hydrazino substituents at C-2, N-3, C=O and CH corresponding to 2, 3, 4 and 5-position has been deduced with a hope to obtain highly biologically active probes for their enzymatic effects on the celiac biliary activity produced by some fungi and as CDK2 inhibitors of tumor cells.

The importance of novel fluorine substituted rhodanine as modified drugs has been highlighted in this study. The highly bioactive substitutes at positions 2 and 5 have gained more attention of the researchers. The study also concluded that both the compounds 2 and 10 can be used as Olomoicine (standard referees).

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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