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Synthesis of Eperezolid-Like Molecules and Evaluation of Their Antimicrobial Activities[1]

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Abstract—3-Fluoro-4-(4-phenylpiperazin-l-yl)aniline (**II**) prepared from 3,4-difluoro nitrobenzene was converted to the corresponding Schiff bases (**III**) and (**IV**) by treatment with 4-methoxybenzaldehyde and indol-3-carbaldehyde, respectively. Treatment of amine (**II**) with 4-fluorophenyl isothiocyanate afforded the corresponding thiourea derivative (**V**). Compound (**V**) was converted to thiazolidinone and thiazoline derivatives (**VI**) and (**VII**) by cyclocondensation with ethylbromoacetate or 4-chlorophenacylbromide, respectively. The synthesis of carbothioamide derivative (**X**) was performed starting from compound (**II**) by three steps. Treatment of compound (**X**) with sodium hydroxide, sulfuric acid, or chlorophenacyl bromide generated the corresponding 1,2,4-triazole (**XI**), 1,3,4-thiadiazole (**XII**), and 1,3-thiazolidinone (**XIII**) derivatives, respectively. The structural assignments of new compounds were based on their elemental analysis and spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and LC-MS) data. In the antimicrobial activity study all the compounds revealed high anti-*Mycobacterium smegmatis* activity.

Keywords: piperazin, 1,3-thiazolidinone, 1,2,4-triazole, 1,3,4-thiadiazole, antimicrobial activity

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INTRODUCTION

The treatment of infectious diseases remains an important and challenging problem due to a combination of factors including emerging infectious diseases and the increasing number of multidrug resistant microbial pathogens. In spite of the wide range of antimicrobial drugs with different mechanisms of action used to treat microbial infections, either alone or in combination, and the existence of many compounds undergoing different phases of clinical trials, microbial infections are becoming a worldwide problem. The problem with clinically used drugs is not only the increasing microbial resistance; also, administration of such drugs is accompanied by toxic side effects that are often dose limiting. Although a number of synthetic and semi-synthetic antimicrobial compounds have been developed for infectious disease treatment, the alarming rates of emerging microbial threats continuen to challenge public health. Among the infections leading to death, tuberculosis (TB) has retrieved its place. As per the survey reported by Global Alliances, there are 8–10 million new active cases of TB with approximately 3 million deaths each year [1–6].

Substituted piperazines are pharmacophores of a number of important drugs such as crixivan, an HIV protease inhibitor, piperazinyl-linked ciprofloxacin dimers, which are potent antibacterial agents, and an oxazolidinone antibiotic eperezolid [7, 8]. The drugs prazosin, lidoflazine, and urapidil, which contain a piperazine nucleus in their structures, are used as cardiovascular agents [9, 10].

Oxazolidinones are a new and promising class of synthetic antibiotics that exhibit activity against numerous multidrug-resistant Gram positive pathogens. Oxazolidinones have been believed to be not cross resistant with other types of antibiotics due to their different mode of action which includes interaction with the bacterial ribosome to inhibit bacterial growth [5, 11–14]. Eperezolid, that is an oxazolidinone antibiotic also containing a piperazine moiety, is currantly in the phase II clinical trial. Literature survey revealed that since phenyloxazolidin moiety is core of molecule, Eperezolid structure allows various modifications including the introduction of five-membered heterocyclic residues attached to the rest of the molecule by a methylene linker [15, 16].

There is a considerable interest in the chemistry of thiazolidinone ring which constitutes an important class of pharmaceuticals displaying a broad spectrum of biological activity such as anti-mycobacterial, antifungal, anticancer, antituberculosis, anticonvulsant, anti-inflammatory, and analgesic activities [17–24].

Here, we reportthe design and preparation of new heterocycles incorporating the known bioactive piperazi-

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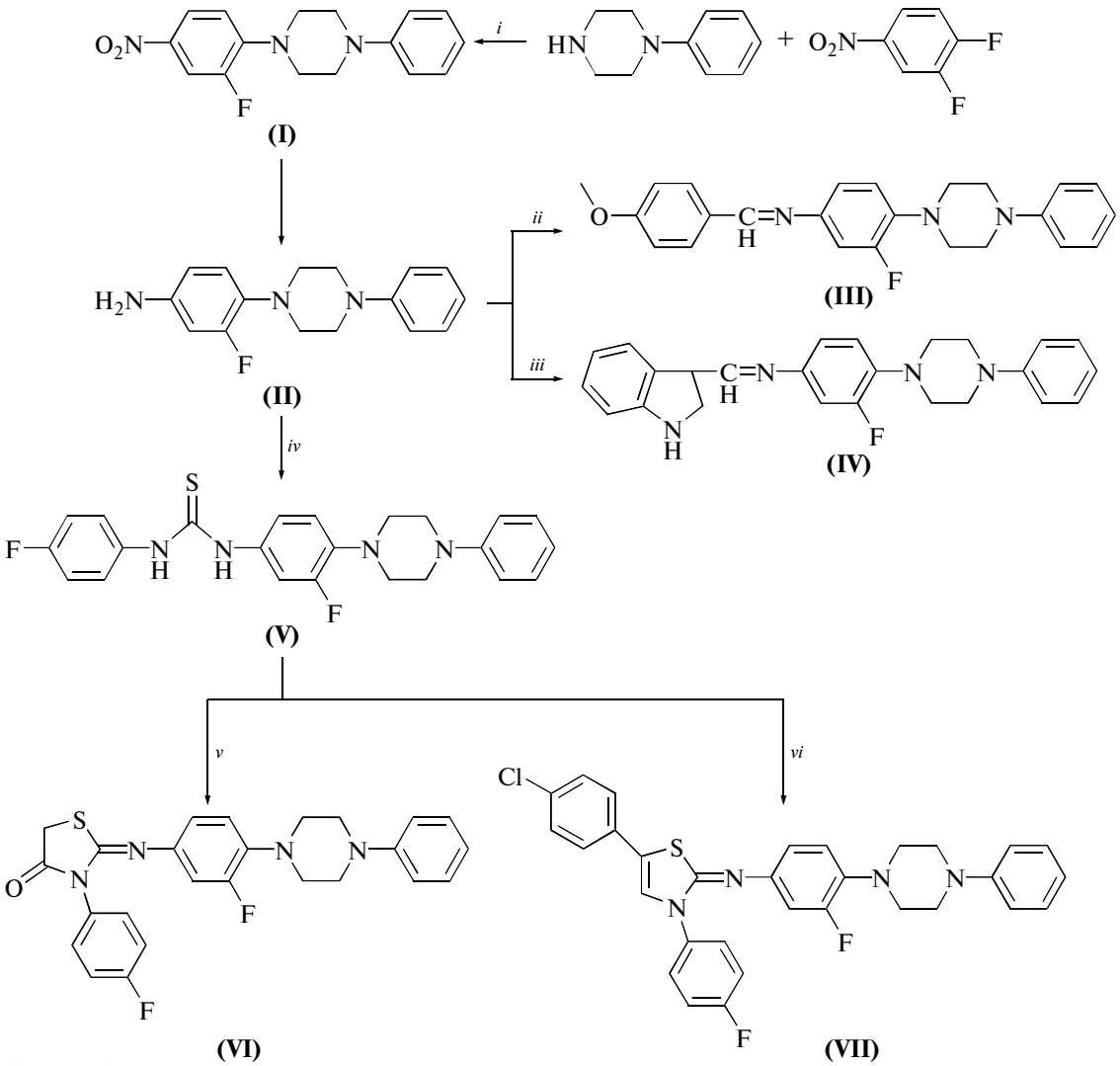
nyl-fluorophenyl-thiazolidinone core structure in order to obtain novel molecules with high therapeutic index.

RESULTS AND DISCUSSION

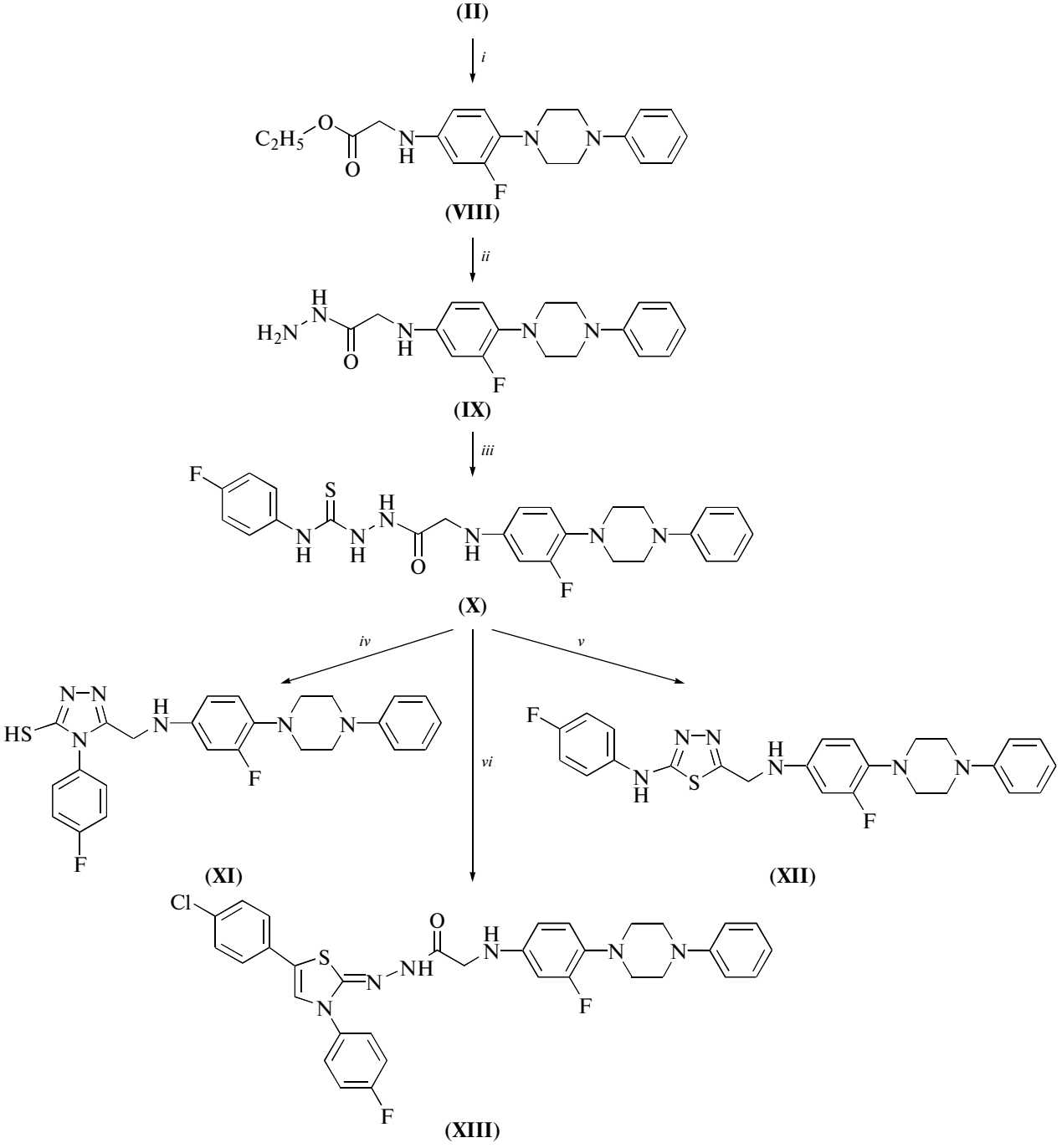
Synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2. Aromatic primary amines are widely-used building blocks in the synthesis of nitrogen-containing heterocycles, dyes, pigments, pharmaceuticals, and industrial products. In the present study, synthesis of compound (**I**) was performed by condensation of 3,4-difluoro nitrobenzene with phenylpiperazine. The compound was characterized by the presence of two strong bands at 1334 and 1495 cm^{-1} in the IR spectrum due to the nitro group. When compound (**I**) was converted to compound (**II**) by the reduction of the nitro group, these signals disappeared, while two strong absorption bands derived from $-NH_2$ functionality were observed at 3387 and 3487 cm^{-1}. In the ^{1}H-NMR spectrum the $-NH_2$ group resonated at 5.03 ppm (exch. with D_2O).



Scheme 1. Reactions and conditions for the syntheses of compounds (**I**)–(**VII**). *i*: Pd-C, H_2NNH_2, *ii*: 4-methoxybenzaldehyde, *iii*: indol 3-carbaldehyde, *iv*: 4-fluorophenylisothiocyanate, *v*: ethyl bromoacetate, *vi*: 4-chlorophenacyl bromide.

The treatment of compound (**II**) with anisaldehyde or indol-3-carbaldehyde has yielded 3-fluoro-*N*-[(4-methoxyphenyl)methylidene]-4-(4-phenylpiperazin-l-yl)aniline (**III**) and 3-fluoro-*N*-[(l*H*-indol-3-yl))methylidene]-4-(4-phenylpiperazin-l-yl)aniline (**IV**), respectively. The IR spectra of derivatives (**III**) and (**IV**) both contained an absorption band at 1501 (for **III**) or 1496 cm^{-1} (for **IV**) indicating the presence of C=N bond in the ring, while no signal derived from NH_2 group was present. Moreover, additional signals

derived from the aldehyde moiety were observed at the related chemical shift values in the ^{1}H- and ^{13}C NMR spectra of compounds (**III**) and (**IV**). In addition, a singlet characteristic for the N=CH group was observed at 8.32 (for **III**) and 8.38 (for **IV**) ppm in the ^{1}H NMR spectra of compounds (**III**) and (**IV**). This group was recorded at 165.42 (for **III**) or 166.68 ppm (for **IV**), in the ^{13}C NMR spectra.



Scheme 2. Reactions and conditions for the syntheses of compounds (**VIII**)–(**XIII**). *i*: $BrCH_2CO_2Et$, *ii*: H_2NNH_2, *iii*: (4-)FC_6H_4CNS, *iv*: H_2SO_4, *v*: NaOH, *vi*: $ClC_6H_4CH_2Br$.

The compounds having imine bonding can exist as *E*/*Z* isomers for C=N double bond [25–33]. According to the literature [27], in dimethyl-d_6 sulfoxide solution, imines are present preferably as *E* isomer. The *Z* isomer can be stabilized in less polar solvents by an intramolecular hydrogen bond. In the present study, the ^{1}H and ^{13}C NMR spectra of compounds (**III**) and (**IV**) have been obtained in dimethyl-d_6 sulfoxide solution and showed the presence of only one isomer. It can be concluded that compounds (**III**) and (**IV**) exist as their *E* geometrical isomers considering bulky arylidene substituent, which is in accordance with the literature data [28, 29, 34–38].

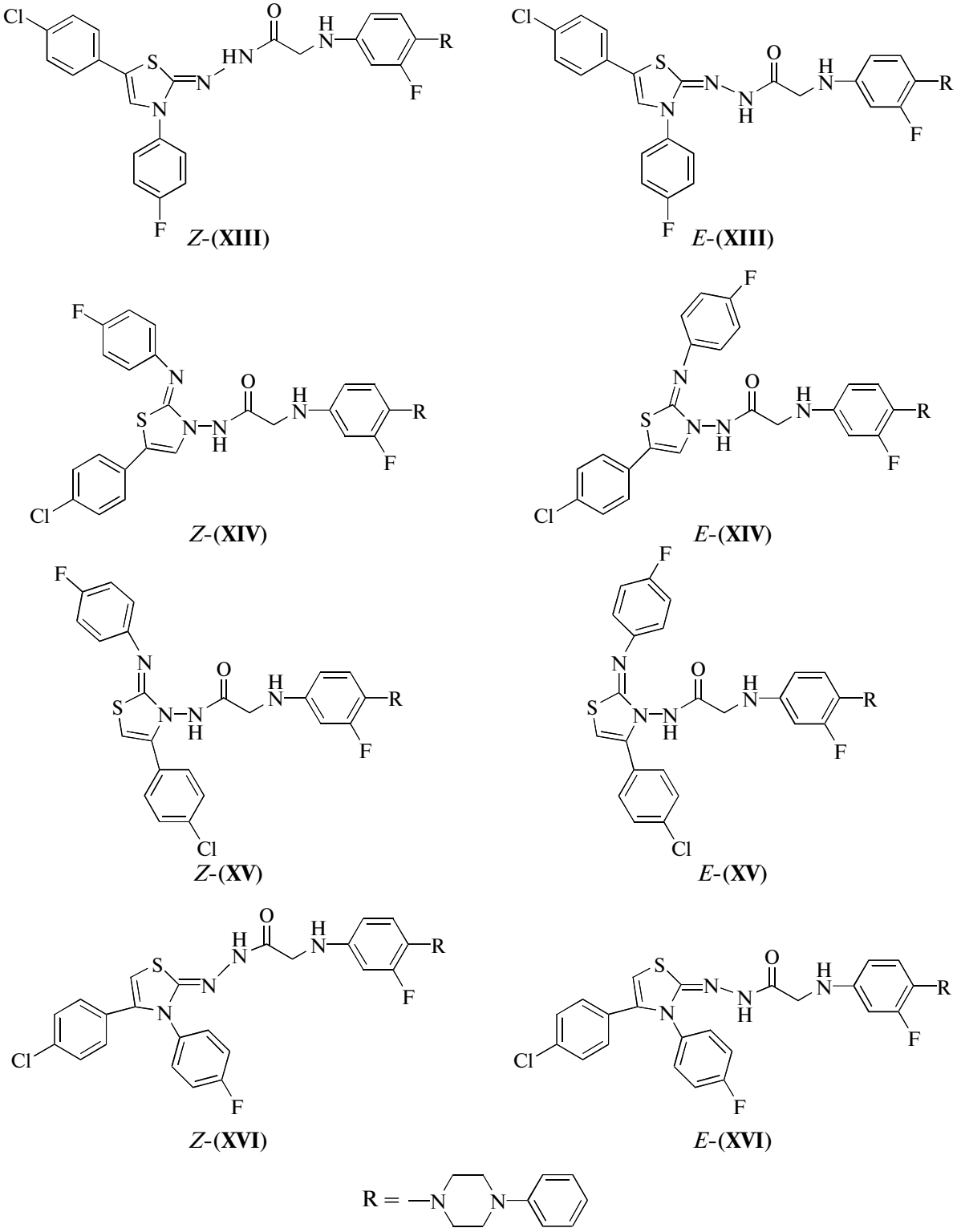
Isothiocyanates are other useful tools for synthesis of nitrogen, sulfur, or oxygen containing compounds. The intermediates (**V**) and (**X**), which have been synthesized by the reaction of compounds (**II**) and (**IX**) with 4-fluorophenylisothiocyanate, represent versatile building blocks for the synthesis of several heterocycles such as 1,2,4-triazoles, 1,3,4-thiadiazoles, and 1,3-thiazoles. The IR and ^{1}H-NMR spectra of compounds (**V**) and (**IX**) displayed signals derived from two NH (for **V**) or four NH (for **IX**) protons (exchangeable with D_2O). Moreover, the signals originated from 4-fluorophenyl moiety have been recorded at the aromatic region in the ^{1}H- and ^{13}C-NMR spectra. The synthesis of 2-{[3-fluoro-4-(4-phenylpiperazin-l-yl)phenyl]imino}-3-(4-fluorophenyl)-l,3-thiazolidin-4-one (**VI**) was carried out by refluxing of compound (**V**) in ethanol with 4-chlorophenacyl bromide in the presence of anhydrous sodium acetate. Compound (**VI**) was characterized by the presence of two strong bands, at 3245 cm^{-1}, representing NH group, and at 1726 cm^{-1}, revealing carbonyl function in the IR spectrum. This was considered as a confirmation of thiazolidinone nucleus formation. Another piece of evidence for cyclocondensation is the appearance of a singlet signal at 4.13 ppm in the ^{1}H NMR spectrum integrating for two protons, which apparently are the C5 protons of thiazolidinone nucleus. This carbon has resonated at 33.51 ppm in the ^{13}C-NMR spectrum. On the other hand, the condensation of compound (**V**) with 4-chlorophenacyl bromide afforded 5-(4-chlorophenyl)-2-[3-fluoro-4-(4-phenylpiperazin-l-yl)phenyl]imino-3-(4-fluorophenyl)-1,3-thiazolin (**VII**). ^{1}H-NMR spectrum of derivative (**VII**) displayed only one signal due to NH group integrating one proton as a result of condensation. Similarly, compound (**X**) produced compound (**XIII**) under the same reaction conditions, as expected. In the IR spectrum of compound (**XIII**), carbonyl absorption has been observed at 1646 cm^{-1}. The signals recorded at 4.39 and 10.47 ppm in the ^{1}H NMR spectrum were attributed to the two NH functions. These groups exchanged protons with D_2O. The absence of any –SH group signals from the IR and ^{1}H NMR spectra of compound (**XIII**) has constituted another evidence for cyclocondenzation between compound (**X**) and 4-chlorophenacyl bromide.

Although several methods for preparation of 1,3-thiazoles have been developed, Hantzsch synthesis of α-halocarbonyl compounds with thioamides is the method most often referred to [37, 38]. It has been agreed that a Hantzsch reaction begins with an attack of the sulfur atom of thioamide, which is present in its enethiole form, on the halogen atom of phenacyl bromide, and is followed by HBr and H_2O elimination, which leads to the 1,3-thiazole ring formation [37].

Due to the reason that the carbothioamide (**X**) has more than one nucleophilic center and henacyl bromide has two positions for nucleophilic attacks, there are at least four possibilities eading to the formation of four different structural isomers; each of them can exist as either *E* or *Z* geometrical isomer (Scheme 3). To identify the exact structure of compound (**XIII**), full geometric optimization of the possible products (**XIII**)–(**XVI**) was obtained by DFT/B3LYP (density functional theory with the Becke three-parameter hybrid functional combined with Lee–Yang–Parr exchange-correlation potential) [39, 40] method with the 6-31G (d, p) basis set and the structure of the molecules was also investigated in details. The solvent effect has been evaluated using the conducting polarized continuum model (CPCM) [41, 42]. By using the optimized geometries of molecules at the B3LYP/6-31G (d, p) level, their single-point energies have been computed using CPCM-B3LYP/6-31G (d, p) method. The calculated relative energies are given in Table 1. According to the obtained results, the most stable product is *Z*-(**XIII**) geometrical isomer. Therefore, thermodynamically, the formation of *Z*-(**XIII**) isomer is more favorable, whereas isomers of (**XVI**), which include the bulky substituents in the adjacent positions of 1,3-thiazole skeleton have been reported in the literature as reaction products between the compounds having thiourea nucleus and phenacyl bromides [4, 43]. According to the calculated energies of possible isomer molecules (**XIII**)–(**XVI**) represented in Table 1, it has been speculated that in the formula (**XVI**), the positions of the bulky groups is too close to each other and this leads to the less stable structure (**XVI**).

Although the stability of *Z*-(**XIV**) is close to the stability of *Z*-(**XIII**), the single spot on the TLC plate of compound (**XIII**) has strongly supported the formation of **XIII** geometrical isomer as the only reaction product. Moreover, melting point and NMR spectral data point to the formation of only one product. Contrary to the description in literature, [4, 39, 40, 43], the reaction between carbothiamide (**X**) and phenacyl bromide started with the attack of sulfur atom on the carbonyl carbon of phenacyl bromide instead of the attack on the halogen bearing carbon atom of the acyl component, because the latter attack would have led to the formation of derivative (**XVI**) which is a less favorable isomer (Scheme 4). The *Z* rearrangement of groups in these reactions is likely due to the steric hindrance of the bulky R group and fluorophenyl moiety in the isothio intermediate **A**. In the reaction media,

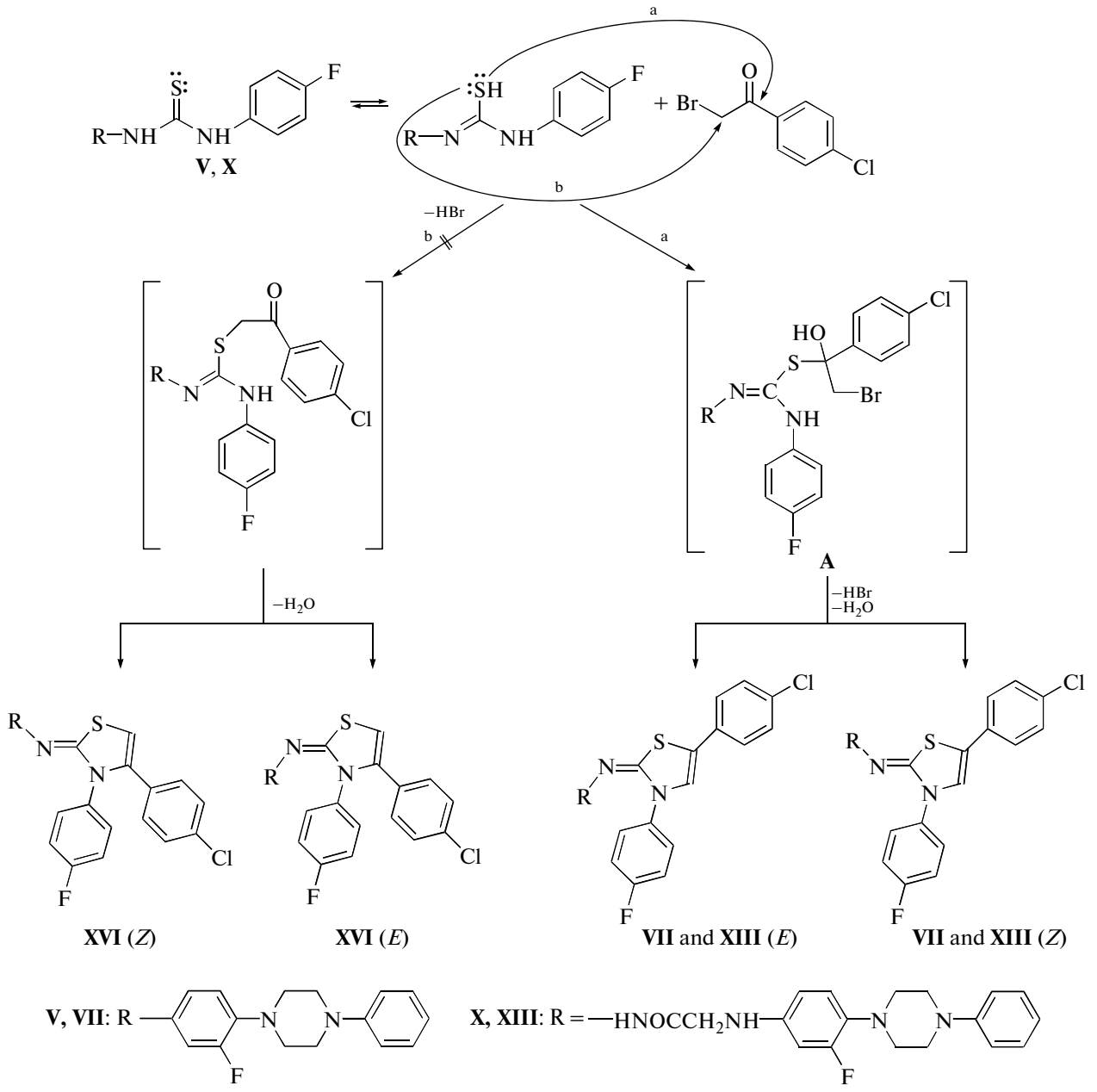
the presence of dried sodium acetate is necessary to accelerate the reaction by catching H_2O and HBr furnishing during the reaction. In the same manner, compound (**VII**) can be considered a *Z* isomer. Similarly, due to the hindrance between fluorophenyl rings and other bulky groups incorporating the piperazin-1-ylphenyl moiety, compounds (**VI**) and (**XII**) exist as their *Z* geometrical isomers.



Scheme 3. Possible structural and geometrical isomers of compound (**XIII**).

Table 1. The calculated relative energies of possible isomer molecules

Compound	Relative energy, kcal mol^{-1}	
	B3LYP/6-311G(d, p)	CPCM-B3LYP/6-311G(d, p) //B3LYP/6-31G(d, p)
Z-(**XIII**)	0.0	0.0
E-(**XIII**)	4.582	4.658
Z-(**XIV**)	0.869	1.812
E-(**XIV**)	3.865	7.303
Z-(**XV**)	3.258	5.130
E-(**XV**)	5.944	9.809
Z-(**XVI**)	4.796	3.827
E-(**XVI**)	9.700	10.225



Scheme 4. Mechanisms leading to formation of compounds (**VII**) and (**XIII**).

Table 2. Screening for antimicrobial activity of the synthesized compounds

Compound	Microorganisms and diameter of inhibition zone (mm)									
	Ec	Ea	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
(II)	–	–	–	–	–	–	–	20	15	20
(III)	–	–	–	–	–	–	–	10	10	15
(IV)	–	–	–	–	–	–	–	10	–	–
(V)	–	–	–	–	–	–	–	12	–	–
(VI)	–	–	–	–	–	–	–	10	–	–
(VII)	8	8	6	8	18	8	8	10	25	25
(VIII)	–	–	–	–	–	–	–	8	–	–
(IX)	–	–	–	–	–	–	–	8	–	–
(X)	–	–	–	–	–	–	–	10	–	–
(XI)	–	–	–	–	–	–	–	12	–	–
(XII)	–	–	–	–	–	–	–	10	–	–
(XIII)	10	–	–	–	–	–	–	8	–	–
Amp	10	10	10	18	35	10	15		–	–
Strep	–	–	–	–	–	–	–	35	–	–
Flu	–	–	–	–	–	–	–		25	<25

Note: Ec, *Escherichia coli* ATCC 25922, Ea, *Enterobacter aeruginosa* ATCC 13048, Yp, *Yersinia pseudotuberculosis* ATCC 911, Pa, *Pseudomonas aeruginosa* ATCC 43288, Sa, *Staphylococcus aureus* ATCC 25923, Ef, *Enterococcus faecalis* ATCC 29212, Bc, *Bacillus cereus* 702 Roma, Ms, *Mycobacterium smegmatis* ATCC607, Ca, *Candida albicans* ATCC 60193, Sa, *Saccharomyces cerevisiae* RSKK 251, Amp, Ampicillin, Strep, streptomycin, Flu, Flukonazol, (–), no activity.

All the newly synthesized compounds displayed elemental analysis results consistent with the proposed structures.

The additional support for the formation of the target compounds was obtained by the appearance of molecular ion peaks at corresponding m/z values confirming their molecular masses.

All the newly synthesized compounds were tested for their antimicrobial activities, the results obtained are presented in Table 2. The substitution of 1,3-oxazol-2-one scaffold in the structure of Eperezolid by 1,3-thiazole nucleus has caused loss of antimicrobial activity against ram positive bacterial strains, whereas Eperezolid is used as an antibiotic towards the infectious diseases caused by Gram positive pathogenic microorganisms. As seen in Table 2, only moderate activity against the tested microorganisms has been detected for compound (**VII**). In addition, moderate-to-high activity against yeast-like fungy, *Candida albicans* (Ca) and *Saccharomyces cerevisiae* (Sc) was observed for compounds (**II**), (**III**), and (**VII**). On the other hand, these structural modifications in Eperezolid molecule resulted in the emergence of anti-*Mycobacterium smegmatis* activity, a non-pigmented rapidly growing mycobacterium constituting one of the atypical tuberculosis factors leading to morbidity and mortality. The highest activities were observed for compound (**II**) with an amine functionality and compound (**XIII**) having 3-(4-fluorophenyl)thiazole moiety in the core structure of Eperezolid.

EXPERIMENTAL

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland) and used without further purification. Melting points of the synthesized compounds were determined in open capillaries on a Biichi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminium sheets with UV detection. The mobile phase was ethanol–ethyl acetate, 1 : 1. IR spectra (ν, cm^{-1}) were recorded using potassium bromide pelletson a PerkineElmer 1600 series FTIR spectrometer. ^1H NMR and ^{13}C NMR spectra were registered in DMSO-d_6 on a BRUKER AVENE II 400 MHz NMR spectrometer (400.13 MHz for ^1H and 100.62 MHz for ^{13}C). The chemical shifts are reported in ppm relative to Me_4Si as an internal reference, J values are given in Hz. The elemental analysis was performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. All the compounds demonstrated C, H and N analyses results within ±0.4% of the theoretical values. The mass spectra (except for compound (**V**)) were obtained on a Quattro LC-MS (70 eV) instrument.

1-(2-Fluoro-4-nitrophenyl)-4-phenylpiperazine (I). The solution of 3,4-difluoronitrobenzene (10 mmol) in excess amount of piperazine (20 mL) was allowed to reflux for 3 h (TLC controlled). Then, the mixture was poured into ice-water. The precipitated product was filtered off and recrystallized from ethyl acetate. Yield 2.80 g (93.16%), mp 155°C. IR: 1334 and 1495 (NO_2). MS m/z (%): 118.06 (17), 120.02 (100), 137.03 (35),

145.99 (12.5), 182.94 (27), 301.99 ([M]$^+$, 27). Found, %: C 63.68, H 5.27, N 13.85. $C_{16}H_{16}FN_3O_2$. Calculated, %: C 63.78, H 5.35, N 13.95. ^{1}H NMR: 3.27 (4 H, bs, $2CH_2$), 3.38 (4 H, bs, $2CH_2$), 6.79–6.94 (1 H, m, ArH), 6.94–7.18 (2 H, m, ARH), 7.18–7.25 (3 H, m, ArH), 7.98 (2 H, d, *J* 10.4, ArH). ^{13}C NMR: 48.80 ($2CH_2$), 49.69 (CH_2), 49.79 (CH_2), ArC [112.98 (d, CH, J_{C-F} 26.0), 116.36 (2CH), 118.76 (CH), 120.02 (CH), 122.04 (CH), 129.72 (2CH), 140.20 (d, C, J_{C-F} 9.6), 145.85 (C), 146.09 (C), 148.74 (d, C, J_{C-F} 265.5)].

3-Fluoro-4-(4-phenylpiperazin-1-yl)aniline (II). Pd-C (5 mmol) catalyst was added to the solution of compound (**I**) (10 mmol) in butanol, and the mixture was refluxed in the presence of hydrazine hydrate (50 mmol) for 6 h. The progress of the reaction was monitored by TLC. Then, the catalyst was separated by filtration and the reaction solvent was evaporated under reduced pressure. The white solid formed was recrystallized from ethanol. Yield 2.64 g (95%), mp 125°C. IR: 3387 and 3487 (NH_2), 3020 (ArCH). MS *m/z* (%): 104.01 (10), 118.08 (24), 120.11 (88), 125.01 (100), 133.13 (65), 153.08 (57), 272.23 ([M + 1]$^+$, 14). Found, %: C 70.78, H 6.64, N 15.40. $C_{16}H_{18}FN_3$. Calculated, %: C 70.83, H 6.69, N 15.49. ^{1}H NMR: 2.94 (4 H, bs, $2CH_2$), 3.20 (4 H, bs, $2CH_2$), 5.03 (2 H, s, NH_2, D_2O exch.), 6.29–6.41 (2 H, m, ArH), 6.75–6.84 (2 H, m, ArH); 6.88 (2 H, d, *J* 7.8, ArH), 7.21 (2 H, t, *J* 8.2, ArH). ^{13}C NMR: 48.48 ($2CH_2$); 51.08 ($2CH_2$); arC: [101.77 (d, CH, J_{C-F} 23.0), 109.40 (CH), 115.38 (2CH), 118.85 (CH), 120.49 (CH), 128.84 (2CH), 128.96 (C), 145.51 (C), 150.91 (C), 156.17 (d, C, J_{C-F} 240.8)].

General procedure for the synthesis of compounds (III) and (IV). The solution of compound (**II**) (10 mmol) in absolute ethanol was refluxed with indol-3-carbaldhyde or 4-methoxybenzaldehyde (10 mmol) for 6 h. Then, the reaction content was cooled to room temperature and a solid appeared. This crude product was filtered off and recrystallized from acetone.

3-Fluoro-*N*-[(4-methoxyphenyl)methylidene]-4-(4-phenylpiperazin-1-yl)aniline (III). Yield 1.37 g (81%), mp 195°C. IR: 3018 (arCH), 1603 (C=N). MS *m/z* (%): 104.27 (11), 117.99 (18), 120.02 (56), 131.92 (26), 136.12 (18), 160.96 (15), 162.99 (28), 242.99 (100), 256.98 (22), 270.91 (92), 390.17 ([M + 1]$^+$, 39). Found, %: C 74.24, H 6.13, N 10.75. $C_{24}H_{24}FN_3O$. Calculated, %: C 74.01, H 6.21, N 10.79. ^{1}H NMR: 2.82 (4 H, bs, $2CH_2$), 3.28 (4 H, bs, $2CH_2$), 3.42 (3 H, s, OCH_3), 6.12–6.46 (2 H, m, ArH), 6.65–6.74 (2 H, m, ArH), 6.82 (2 H, d, *J* 7.6, ArH), 6.92–7.11 (4 H, m, ar-H), 7.28 (2 H, t, *J* 8.0, ArH), 8.32 (1 H, s, N=CH). ^{13}C NMR: 47.68 ($2CH_2$), 50.12 ($2CH_2$), 55.22 (OCH_3), arC: [101.24 (d, CH, J_{C-F} 23.6), 104.56 (CH), 115.23 (CH), 116.28 (2CH), 117.56 (2CH), 122.64 (CH), 128.38 (2CH), 129.56 (C), 130.34 (2CH), 147.90 (C), 150.98 (C), 155.36 (d, C, J_{C-F} 260.4), 159.42 (C)], 142.28 (N=CH).

3-Fluoro-*N*-[(1*H*-indol-3-yl)methylidene]-4-(4-phenylpiperazin-1-yl)aniline (IV). Yield 1.12 g (72%), mp 187°C. IR: 3410 (NH), 3024 (ArCH), 1598 (C=N). MS *m/z* (%): 91.04 (16), 103.92 (38), 117.99 (90), 131.98 (100), 136.11 (59), 163.06 (63), 212.89 (15), 240.11 (77), 254.88 (44), 266.00 (21), 280.21 (19), 399.25 ([M + 1]$^+$, 12). Found, %: C 75.44, H 5.75, N 14.16. $C_{25}H_{23}FN_4$. Calculated, %: C 75.35, H 5.82, N 14.06. ^{1}H NMR: 2.94 (4 H, bs, $2CH_2$), 3.22 (4 H, bs, $2CH_2$), 6.22–6.52 (2 H, m, ArH), 6.62–6.68 (1 H, m, ArH), 6.86 (2 H, d, *J* 7.4, ArH), 6.90–7.22 (2 H, m, Ar-H), 7.30 (1 H, s, Ar-H), 7.36 (3 H, t, *J* 8.2, ArH), 7.46–7.66 (2 H, m, Ar-H), 8.38 (1 H, s, N=CH), 10.38 (1 H, s, NH). ^{13}C NMR: 49.27 ($2CH_2$), 51.87 ($2CH_2$), arC: [102.76 (d, CH, J_{C-F} 23.1), 110.47 (CH), 113.13 (CH), 116.21 (2CH), 116.31 (CH), 119.70 (CH), 121.23 (C), 121.31 (CH), 121.51 (CH), 122.89 (CH), 124.22 (CH), 126.02 (C), 129.67 (2CH), 130.02 (C), 137.88 (C), 145.38 (C), 151.70 (C), 156.45 (d, C, J_{C-F} 225.0)], 139.28 (N=CH).

1-[3-Fluoro-4-(4-phenylpiperazin-1-yl)phenyl]-3-(4-fluoro)phenyl thiourea (V). The solution of compound (**II**) (10 mmol) in absolute ethanol was refluxed with 4-fluorophenylisothiocyanate (10 mmol) for 7 h. On cooling the reaction mixture to room temperature, a solid was formed. This crude product was collected by filtration and recrystallized from ethanol. Yield 2.45 g (57%), mp 204°C. IR: 3192 and 3248 (NH), 1230 (C=S). MS *m/z* (%): 105.20 (43), 337.23 (15), 351.09 (100), 424.82 ([M]$^+$, 15). Found, %: C 65.28, H 5.14, N 13.58, S 7.34. $C_{23}H_{22}F_2N_4S$. Calculated, %: C 65.07, H, 5.22, N 13.20, S 7.55. ^{1}H NMR: 3.12 (4 H, bs, $2CH_2$), 3.25 (4 H, bs, $2CH_2$), 6.79–7.44 (13 H, m, ArH + NH), 9.76 (1 H, s, NH). ^{13}C NMR: 49.16 ($2CH_2$), 50.98 ($2CH_2$), ArC: [110.44 (CH), 112.89 (CH, d, J_{CF} 30.9), 115.45 (C), 116.31 (2CH), 119.57 (2CH), 120.82 (CH), 121.33 (CH), 129.02 (C), 129.70 (4CH), 134.88 (C), 137.27 (C), 151.63 (C), 154.82 (C, d, J_{CF} 241.6)], 180.12 (C=S).

2-{[3-Fluoro-4-(4-phenylpiperazin-1-yl)phenyl]imino}-3-(4-fluorophenyl)-1,3-thiazolidin-4-one (VI). The mixture of compound (**V**) (10 mmol) and ethyl bromoacetate in dry chloroform was refluxed in the presence of dried sodium acetate (50 mmol) for 5 h. Then, the reaction mixture was cooled to room temperature and the precipitated salt was separated by filtration. After removing the solvent under reduced pressure, a solid appeared. This crude product was recrystallized from ethyl acetate. Yield 2.85 g (61.8 %), mp 176°C. IR: 1726 (C=O), 1600 (C=N). MS *m/z* (%): 119.81 (100), 120.87 (65), 192.89 (87), 194.90 (46), 298.08 (18), 372,29 (18), 464.30 ([M]$^+$, 8). Found, %: C 64.42, H 4.75, N 11.95, S 6.97. $C_{25}H_{22}F_2N_4OS$. Calculated, %: C 64.64, H 4.77, N 12.06, S 6.90. ^{1}H NMR: 3.12 (4 H, bs, $2CH_2$), 3.25 (4 H, bs, $2CH_2$), 4.13 (2H, s, thiazolidinone-CH_2), 6.64–6.82 (3 H, m, ArH), 6.95–7.07 (4 H, m, ArH), 7.18–7.32 (5 H, m, ArH), 9.12 (1 H, s, NH). ^{13}C NMR: 33.51 (thiazolidinone-C5), 49.10 ($2CH_2$),

50.60 (CH_2), 51.00 (CH_2), ArC: [109.87 (CH, d, J_{C-F} 22.0), 116.26 (2CH), 116.89 (CH), 117.57 (2CH), 119.91 (2CH), 120.45 (CH), 125.76 (CH), 129.45 (C), 129.68 (2CH), 136.67 (C), 140.40 (C), 143.67 (C), 154.83 (C, d, J_{C-F} 241.3), 155.68 (C, d, J_{C-F} 244.2)], 151.61 (thiazolidinone-C2), 172.30 (thiazolidinone-C4).

5-(4-Chlorophenyl)-2-[3-fluoro-4-(4-phenylpiperazin-l-yl)phenyl]imino-3-(4-fluorophenyl)-1,3-thiazolin (VII). The mixture of compound (**V**) (10 mmol) and 4-chlorophenacylbromide (10 mmol) in dry chloroform was refluxed in the presence of dried sodium acetate (50 mmol) for 8 h. Then, the reaction mixture was allowed to reach room temperature and the precipitated salt was separated by filtration. After removing the solvent under reduced pressure, an oily product was recrystallized from ethyl acetate. Yield 3.58 g (63.3%), mp 195°C. IR: 3038 (ArCH), 1590 (C=N). MS *m/z* (%): 103.87(31), 131.81 (22), 147.00 (18), 212.87 (36), 242.97 (31), 249.83 (16), 397.05 (26), 411.89 (66), 425.96 (100), 440.10 (20), 511.30 (12), 559.18 ($[M]^+$, 10). Found, %: C 66.45, H 4.43, N 10.32, S 5.60. $C_{31}H_{25}ClF_2N_4S$. Calculated, %: C 66.06, H 4.51, N 10.02, S 5.74. ^{1}H NMR: 3.12 (4 H, bs, $2CH_2$), 3.26 (4 H, bs, $2CH_2$), 6.51 (1 H, s, thiazolidinone C_4-H), 6.69–6.83 (5 H, m, ArH), 6.98 (5 H, bs, ArH), 7.20 (5 H, d, *J* 7.8, ArH), 7.36 (1 H, d, *J* 8.0, ArH), 9.32 (1 H, s, NH). ^{13}C NMR: 48.32 ($2CH_2$), 50.32 ($2CH_2$), ArC: [108.97 (CH, d, J_{C-F} 21.0), 111.95 (CH, d, J_{C-F} 23.5), 115.48 (2CH), 116.72 (thiazole-CH), 118.67 (2CH), 118.75 (CH), 119.01 (CH), 119.88 (CH), 125.30 (CH), 128.29 (2CH), 128.85 (4CH), 129.68 (C), 133.09 (C), 137.76 (C), 146.20 (C), 150.73 (C), 150.81 (C), 154.34 (C, d, J_{CH} 235.3), 155.46 (C, d, J_{CH} 245.0)], 139.46 (thiazole C2), 159.60 (thiazole C5).

Ethyl {[3-fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino}acetate (VIII). To the mixture of compound (**II**) (10 mmol) and triethylamine (10 mmol) in dry tetrahydrofurane, ethylbromoacetate (10 mmol) was added drop by drop at 0–5°C. Then, the reaction mixture was allowed to reach room temperature and stirred for 12 h (the progress of the reaction was monitored by TLC). The precipitated triethylamonium salt was removed by filtration and the resulting solution was evaporated under reduced pressure to dryness. The obtained yellow solid was recrystallized from ethanol. Yield 2.27 g (75.9%), mp 135°C. IR: 3385 (NH), 3054 (ArCH), 1715 (C=O), 1214 (C–O). MS *m/z* (%): 120.18 (49), 137.12 (38), 151.82 (32), 163.02 (75), 165.26 (25), 210.96 (100), 238.89 (37), 271.30 (28), 358.31 ($[M + 1]^+$, 32). Found, %: C 67.15, H 6.82, N 11.68. $C_{20}H_{24}FN_3O_2$. Calculated, %: C 67.21, H 6.77, N 11.76. ^{1}H NMR: 1.15 (3 H, t, *J* 7.0, CH_3), 2.95 (4 H, bs, $2CH_2$), 3.20 (4 H, bs, $2CH_2$), 3.82 (2 H, s, CH_2), 4.07 (2 H, q, *J* 7.0, OCH_2), 5.93 (1 H, bs, NH, D_2O exch.), 6.26–6.43 (2 H, m, ArH), 6.72–6.95 (4 H, m, ArH), 7.19 (2 H, t, *J* 7.8, ArH). ^{13}C NMR: 14.81 (CH_3), 45.53 (CH_2), 49.24 ($2CH_2$), 51.77 ($2CH_2$), 60.97 (OCH_2). ArC: [101.2 (CH, d, J_{C-F} 24.0), 108.31 (CH), 116.19 (2CH), 119.66 (CH), 121.16 (CH), 129.62 (2CH), 130.33 (C), 145.59 (C), 151.69 (C), 156.98 (C, d, J_{C-F} 240.8)], 171.91 (C=O).

2-{[3-Fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino} acetohydrazide (IX). Hydrazine hydrate (25 mmol) was added to the solution of compound (**VIII**) (10 mmol) in ethanol and the mixture was heated under reflux for 8 h. On cooling the mixture in the cold overnight, white crystals appeared. The crude product was filtered off and recrystallized from ethyl acetate. Yield 8.88 g (87%), mp 185°C. IR: 3241, 3385 (NH + NH_2), 3027 (ArCH), 1725 (C=O). MS *m/z* (%): 119.98 (41), 131.88 (17), 151.06 (24), 164.85 (37), 196.84 (40), 270.9 (100), 284.07 (59), 344.13 ($[M + 1]^+$, 27). Found, %: C 62.72, H 6.38, N 20.28. $C_{18}H_{22}FN_5O$. Calculated, %: C 62.96, H 6.46, N 20.39. ^{1}H NMR: 2.95 (4 H, bs, $2CH_2$), 3.19 (4 H, bs, $2CH_2$), 3.55 (2 H, s, CH_2), 4.26 (2 H, bs, NH_2), 5.87 (1 H, bs, NH), 6.26–6.40 (2 H, m, ArH), 6.76–6.96 (4 H, m, ArH), 7.20 (2 H, bs, ArH), 9.08 (1 H, s, NH). ^{13}C NMR: 46.10 (CH_2), 49.51 ($2CH_2$), 52.05 ($2CH_2$), ArC: [101.30 (CH, d, J_{C-F} 24.2), 108.58 (CH), 116.22 (2CH), 119.72 (CH), 121.19 (CH), 130.35 (C), 145.79 (C), 151.70 (C), 157.00 (C, d, J_{C-F} 240.9)], 170.10 (C=O).

N-(4-Fluorophenyl)-2-({[3-fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino}acetyl) hydrazinecarbothioamide (X). The mixture of compound (**IX**) (10 mmol) and 4-fluorophenylisotiocyanate (10 mmol) in absolute ethanol was heated under reflux for 6 h. On cooling the reaction mixture to room temperature, a white solid appeared. This crude product was filtered off and recrystallized from ethyl acetate. Yield 4.55 g (91.2%), mp 194°C. IR: 3246, 3303 and 3337 (4NH), 1674 (C=O), 1227 (C=S). MS *m/z* (%): 119.99 (40), 148.94 (20), 284.17 (34), 318.28 (50), 344.27 (100), 497.37 ($[M + 1]^+$, 71), 519.34 ($[M + 1 + Na]^+$, 34), 535.32 ($[M + K]^+$, 21). Found, %: C 60.75, H 5.47, N 16.68, S 6.52. $C_{25}H_{26}F_2N_6OS$. Calculated, %: C 60.47, H 5.28, N 16.92, S 6.46. ^{1}H NMR: 2.99 (4 H, bs, $2CH_2$), 3.24 (4 H, bs, $2CH_2$), 3.78 (2 H, bs, CH_2), 6.42–6.50 (2 H, m, ArH), 6.83–6.99 (4 H, m, ArH), 7.22 (4 H, m, ArH), 7.38 (2 H, bs, ArH), 9.57 (1 H, bs, NH), 9.70 (2 H, bs, NH), 10.09 (1 H, bs, NH). ^{13}C NMR: 45.94 (CH_2), 49.30 ($2CH_2$), 51.86 ($2CH_2$), ArC: [101.42 (CH, d, J_{C-F} 21.6), 108.77 (CH), 115.51 (2CH, d, J_{C-F} 22.0), 116.34 (2CH), 119.94 (CH), 121.26 (CH), 128.71 (2CH), 129.71 (2CH), 129.71 (C), 130.50 (C), 136.05 (C), 145.92 (C), 151.54 (C, d, J_{C-F} 238.9), 157.00 (C, d, J_{C-F} 240.9)], 170.71 (C=O), 183.19 (C=S).

4-(4-Fluorophenyl)-5-({[3-fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino}methyl)-4*H*-1,2,4-triazole-3-thiol (XI). A solution of compound (**X**) (10 mmol) in ethanol water, 1 : 1, was refluxed in the presence of 2N NaOH for 3 h. Then, the resulting solution was cooled to room temperature and acidified to pH 4 with 37-%

HCl. The precipitate formed was filtered off, washed with water, and recrystallized from ethanol. Yield 4.23 g (88%), mp 245°C. IR: 3369 (NH), 2851 (SH), 1229 (C=S). MS *m/z* (%): 310.16 (59), 330.12 (31), 345.13 (37), 360.34 (25), 383.30 (65), 391.31 (50), 479.35 ($[M + 1]^+$, 100). Found, %: C 62.46, H 5.18, N 17.98, S 6.87. $C_{25}H_{24}F_2N_6S$. Calculated, %: C 62.74, H 5.05, N 17.56, S 6.70. ^{1}H NMR: 2.95 (4 H, bs, $2CH_2$), 3.22 (4 H, bs, $2CH_2$), 4.09 (2 H, bs, CH_2), 5.93 (1 H, bs, NH), 6.29–6.33 (2 H, m, ArH), 6.77–6.97 (4 H, ArH m), 7.20–7.46 (6 H, m, ArH), 13.80 (1 H, s, SH). ^{13}C NMR: 38.07–40.58 (DMSO-d_6 + CH_2), 48.42 ($2CH_2$), 50.91 ($2CH_2$), ArC: [100.47 (CH, d, J_{C-F} 24.2), 107.80 (CH), 115.39 (2CH), 116.15 (2CH, d, J_{C-F} 23.1), 118.86 (CH), 120.35 (CH), 128.81 (2CH), 130.25 (2CH), 144.17 (C), 144.38 (C), 150.21 (2C), 150.87 (2C), 155.99 (C, d, J_{C-F} 241.2), 162.06 (C, d, J_{C-F} 244.9)], 153.57 (triazole C-5), 168.15 (triazole C-3).

5-{[3-Fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino}methyl-2-(4-fluoroanilino)-1,3,4-thiadiazol (XII). Concentrated sulfuric acid (64 mmol) was added to compound (**X**) (10 mmol) dropwise while stirring and the reaction mixture was stirred in an ice bath for 15 min. Then, the mixture was allowed to reach room temperature and stirred for additional 3 h. The resulting solution was poured into ice-cold water and made alkaline (pH 8) with ammonia. The precipitated product was filtered, washed with water, and recrystallized from dimethysulfoxide-water, 1 : 1. Yield 4.11 g (86.1%), mp 229°C. IR: 3321 (2NH), 3060 (arCH), 1510, 1541 (C=N). MS *m/z* (%): 165.24 (10) 196.11 (14), 208.00 (36), 256.09 (10), 271.00 (100), 271.98 (72), 283.87 (31), 479.01 ($[M]^+$, 15). Found, %: C 62.44, H 5.32, N 17.48, S 6.58. $C_{25}H_{24}F_2N_6S$. Calculated, %: C 62.75, H 5.05 N 17.56, S 6.70. ^{1}H NMR: 2.98 (4 H, bs, $2CH_2$), 3.22 (4 H, bs, $2CH_2$), 4.48 (2 H, bs, CH_2), 6.44–6.55 (2 H, m, ArH + NH), 6.77–6.96 (5 H, m, ArH), 7.16–7.20 (5 H, m, ArH), 7.60 (1 H, bs, ArH), 10.25 (1 H, s, NH). ^{13}C NMR: 43.20 (CH_2), 49.27 ($2CH_2$), 51.71 ($2CH_2$), ArC: [101.69(CH, d, J_{C-F} 24.5 Hz), 116.06 (CH), 116.26 (2CH), 116.50 (CH), 119.54 (CH), 119.68 (2CH), 119.80 (CH), 121.39 (CH), 129.66 (2CH), 130.67 (C, d, J_{C-F} 9.5), 137.82 (C), 145.09 (C, d, J_{C-F} 10), 151.60 (C), 155.43 (C), 156.95 (C, d, J_{C-F} 246.5)], 160.17 (thiadiazole C-5), 161.80 (thiadiazole C-2).

2-[3-Fluoro-4-(4-phenylpiperazin-1-yl)phenyl]amino-2'-[5-(4-chlorophenyl)-3-(4-fluorophenyl)thiazolin-2-yliden)]acetohydrazide (XIII). The solution of compound (**II**) (10 mmol) in absolute ethanol was refluxed with indol-3-carbaldehyde or 4-methoxybenzaldehyde (10 mmol) for 6 h. Then, the reaction mixture was cooled to room temperature and a solid appeared. This crude product was filtered off and recrystallized from acetone. Yield 3.92 g (61.7 %), mp 180°C. IR: 3300 and 3403 (2NH), 3301 (2NH), 1646 (C=O), 1500 (C=N). MS *m/z* (%): 120.46 (14), 125.15 (23), 136.98 (17.5), 164.84 (32), 191.79 (29), 199.35 (12), 256.40 (29), 270.89 (45), 284.26 (100), 296.02 (19), 306.24 (12.5), 350.13 (19), 419.99 (12), 478.58 (14), 649.66 ($[M + H_2O]^+$, 36). Found: C 62.78, H 4.86, N 13.23, S 5.14. $C_{33}H_{29}ClF_2N_6OS$. Calculated, %: C 62.80, H 4.63, N 13.32, S 5.08. ^{1}H NMR: 2.96 (4 H, bs, $2CH_2$), 3.23 (4 H, bs, $2CH_2$), 3.60 (2 H, bs, CH_2), 4.39 (1 H, s, NH), 5.59–6.06 (3 H, m, ArH + thiazole H4), 6.22–6.29 (1 H, d, *J* 14.0, ArH), 6.42–8.01 (13 H, m, ArH), 10.47(1 H, s, NH).

Antimicrobial activity assessment. The following microorganisms obtained from the *Hifzissihha Institute of Refik Saydam* (Ankara, Turkey) were tested: *E. coli* ATCC35218, *E. aerogenes* ATCC13048, *Y. pseudotuberculosis* ATCC911, *P. aeruginosa* ATCC43288, *S. aureus* ATCC25923, *E. faecalis* ATCC29212, *B. cereus* 709 Roma, *M. smegmatis* ATCC607, *C. albicans* ATCC60193, *C. tropicalis* ATCC13803, *A. niger* RSKK 4017, and *S. cerevisiae* RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethylsulfoxide to prepare extract stock solutions of 5.000 mg/mL. Agar-well diffusion method screening [44] was used to test the newly synthesized compounds according to an adapted procedure [45]. Each microorganism was suspended in Mueller Hinton (MH) (Difco Detroit, MI) broth and diluted approximately to 106 colony forming units (CFU) per millilter. Cells were "flood-inoculated" onto the surface of MH agar, or Sabouraud dextrose agar (SDA) (Difco, Detriot, MI) in the case of *C. albicans* and *C. tropicalis*, and dried. Agar wells 5 mm in diameter were cut out with a sterile cork borer and 50 μL of the stock solutions was delivered to the wells. The plates were incubated for 18 h at 35°C. Antimicrobial activity was evaluated by measuring the zone of inhibition of the test organism growth. Ampicillin (10 mg), streptomycin (10 mg), and fluconazole (5 mg) were used as standard drugs. Dimethylsulfoxide and ethanol were used as solvent controls. The antimicrobial activity results are summarized in Table 2.

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