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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL IMIDAZO[2,1-*b*] THIAZOLYL ACETYL AMINO/HYDRAZONO 4-THIAZOLIDINONES

YENİ İMİDAZO[2,1-*b*] TİYAZOLİL ASETİL AMİNO/HİDRAZONO 4-TİYAZOLİDİNONLARIN SENTEZİ VE ANTİMİKROBİAL AKTİVİTELERİ

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Two series of new 2-aryl,3[[[6-(4-chlorophenyl) imidazo [2,1-b] thiazol - 3 - yl] acetyl] amino] - 4 - thiazolidinones (3) and 3-alky/aryl-2[[[6-(4-chlorophenyl) -imidazo [2,1-b]thiazol-3-yl]acetyl]hydrazono]-4-thiazolidinones (5) were synthesized from novel N-arylidene-[6-[4-chlorophenyl) imidazo [2,1-b]thiazol -3-yl]acetic acid hydrazides (2) and 4-alkyl/aryl-1-[[6 - (4 - chlorophenyl) imidazo [2,1 - b] thiazol - 3-yl]acetyl]-3-thiosemicarbazide (4), respectively. The acyclic precursors (2 and 4) as well as the 4-thiazolidinones (3 and 5) were evaluated for in vitro antibacterial and antifungal activity. None of the compounds showed significant antibacterial activity against the microorganisms used whereas 3a and 3b inhibited the growth of Trichophyton tonsurans (NCPF-245) and Trichophyton rubrum (MIC 25 μg/ml).

Bu çalışmada yeni N-ariliden-[6-(4-klorofenil)imidazo[2,1-b]tiyazol-3-il]asetik asid hidrazidleri (2) ve 4-alkil/aril-1-[[6-(4-klorofenil) imidazo [2,1-b] tiyazol - 3 - il] asetil] - 3-tiyosemikarbazidlerden (4) siklizasyonla 2-aril-3[[[6 - 4 - klorofenil) - imidazo [2,1-b] tiyazol - 3 - il]asetil]amino]-4-tiyazolidinon (3) ve 3-alkil\aril-2[[[6 -(4 - klorofenil) imidazo [2,1-b] tiyazol - 3 - il]asetil]hidrazono] - 4 - tiyazolidinon (5)yapısında bileşikler sentez edilmiştir. Sentezlenen tüm bileşiklerde in vitro antibakteryel ve antifungal etki araştırılmış, madde 3a ve 3b de Trichophyton tonsurans (NCPF-245) ve Trichophyton rubrum'a karşı antifungal etki saptanmıştır (MIC 25 μg/ml).

Keywords: *Imidazo[2,1-b]thiazoles; Arylidenehydrazides; Thiosemicarbazides; 4-Thiazolidinones; Antimicrobial activity*

Anahtar kelimeler: *İmidazo[2,1-b]tiyazoller; Arilidenhidrazidler; Tiyosemikarbazidler; 4-Tiyazolidinonlar; Antimikrobiyal aktivite*

Introduction

Over the years, 4-thiazolidinones have been synthesized for a wide range of pharmaceutical and biological purposes. Many 4-thiazolidinone derivatives have been shown to exhibit bactericidal (1), fungicidal(2), antitubercular(3), and pesticidal (4) properties. The imidazo [2,1-*b*] thiazole system contained in the well known antihelmintic and immunomodulatory agent levamisole is continuing to attract intense attention (5), due to the importance of modulation of human immune response in various diseases. These observations prompted the synthesis of two different structural types of 4-thiazolidinones incorporating the imidazo [2,1-*b*] thiazole moiety to investigate their antimicrobial potential.

Materials and Methods

Chemistry

Melting points were estimated with a Büchi 530 apparatus and are uncorrected. UV(EtOH), IR(KBr) and ^{1}H-NMR([d_6]DMSO-TMS) spectra were recorded on Shimadzu 2100 S, Perkin-Elmer 1600 FTIR and Bruker AC 200 (200 MHz)/Bruker DPx400 (400 MHz) instruments, respectively. EIMS were recorded on a VG Zab Spec (70 eV) instrument.In case of isotopic peaks, only the relative abundance of ^{35}Cl and ^{79}Br bearing fragments are given where appropriate. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

N-Arylidene-[6-(4-chlorophenyl)imidazo[2,1-b]thiazol -3-yl]acetic acid hydrazides ***2a-e***

A solution of **1** (0.005 mol) in EtOH (30 ml) and an appropriate aromatic aldehyde (0.005 mol) was heated under reflux for 4h. The precipitate obtained from the hot ethanolic solution was purified either by washing with hot EtOH (**2b-e**) or recrystallization from EtOH (**2a**).

2a : UV λ max nm (log ε) : 283.5(4.671), 220.5(4.548), 202.5(4.606). IR υ (cm^{-1}): 3078 (N-H), 1683 (C=O). ^{1}H-NMR (ppm): 11.67, 11.56 (2s, 1H, NH), 8.28(s, 1H, H-5), 8.21, 8.04 (2s, 1H, N=CH), 7.83 (d J=8.0Hz, 2H, ar), 7.62(d J=7.7Hz,2H,ar), 7.42(d J=7.7Hz,2H,ar), 7.25 (d J=8.0Hz,2H,ar), 7.09(s,1H,H-2), 4.33, 3.91 (2s,2H,CH_2), 2.34 (s, 3H,CH_3).

2c : UV λ max nm (log ε): 295.9(4.489), 220.0(4.323), 201.1(4.420). IR ν (cm^{-1}): 3449(O-H), 3062(N-H), 1665(C=O). ^{1}H-NMR δ (ppm): 11.77, 11.66(2s, 1H, NH), 8.26(s,1H,H-5), 8.23, 8.04 (2s, 1H,N=CH), 7.82(d J=8.7Hz,2H,ar), 7.69(d J=8.7Hz,2H,ar), 7.62(d J=8.7Hz,2H,ar), 7.42(d J=8.7Hz,2H,ar), 7.08(s, 1H,H-2), 4.33,3.91(2s, 2H, CH_2).

2-Aryl-3-[[[6-(4-chlorophenyl)imidazo[2,1-b]thiazol -3-yl]acetyl]amino]-4-thiazolidinones ***3a-e***

A mixture of **2** (0.005 mol) and merçaptoacetic acid (0.005 mol) was refluxed in drybenzene (30 ml) using a Dean-Stark water separator. Excess benzene was evaporated in vacua. The resulting residue was triturated with saturated $NaHCO_3$ solution until CO_2 evolution ceased and was allowed to stand overnight. The solid thus obtained was washed with water, dried, and recrystallized from EtOH-H_2O.

3a : UV λ max nm (log ε): 262.0(4.324), 202.0(4.663). IR ν (cm^{-1}): 3446(O-H), 3124(N-H), 1720(C=O ring), 1686(C=O). ^{1}H-NMR δ (ppm)10.60(s,1H,NH), 8.08(s,1H,H-5), 7.85(d J=8.4Hz,2H,ar), 7.47(d J=8.4Hz,2H,ar), 7.26(d J=8.4Hz,2H,ar), 7.08(d J=8.6Hz,2H,ar), 6.97(s,1H,H-2), 5.79(s,1H,NCHS), 3.92(d J=16.0Hz,1H,SCH_2), 3.82-3.69(m,3H,SCH_2 and CH_2), 2.27(s,3H,CH_3). EIMS m/z (rel.abun.%): 482,484 (M^+,$(M+2)^+$) (11), 440(20), 438(18), 408, 410(25), 292, 294(36), 291,293(18), 275, 277(40), 248,250(100), 241(35), 211(30), 214(35), 193(6), 161(8), 146(8), 137, 139(11), 135(14), 118(20), 102(11), 91 (18).

3c: UV λ max nm (log ε): 260.0 (4.550), 202.6(4.896). IR ν (cm^{-1}): 3446(O-H), 3109(N-H), 1719(C=O ring), 1685(C=O). ^{1}H-NMR δ (ppm): 10.59 (s,1H,NH), 8.06(s,1H,H-5), 7.78(d J=8.6Hz,2H,ar), 7.56(d J=8.5 Hz,2H,ar), 7.46(d J=8.5Hz,2H,ar), 7.39(d J=8.6Hz,2H,ar), 6.98(s,1H,H-2), 5.81(s,1H,NCHS), 3.94(d J=15.7Hz,1H,SCH_2), 3.79-3.69(m,3H,SCH_2 and CH_2). EIMS m/z (rel.abun.%): 546,548,550(M^+,$(M+2)^+$, $(M+4)^+$) (20), 473,475,477(12), 291, 293(35), 275, 277(38), 257,259(14), 248, 250(100), 211(39), 199,201(11), 182,184(16), 137, 139(15), 118(8), 102 (11).

4-Alkyl/aryl-1-[[6-(4-chlorophenyl)imidazo[2,1-b]thiazol -3-yl]acetyl]-3-thiosemicarbazides ***4a-e***

To a solution of **1** (0.005 mol) in EtOH (30 ml), an appropriate isothiocyanate (0.005 mol) was added. The resulting mixture was heated under reflux for 3h. After cooling, the precipitate was separated and purified either by washing with hot EtOH (**4a-d**) or recrystallization from EtOH (**4e**).

4a : UV λ max nm (log ε): 250.4(4.645), 204.0(4.734), IR ν (cm^{-1}): 3249(N-H), 1674(C=O). ^{1}H-NMR δ (ppm): 10.12(s,1H,NH), 9.27(s,1H,NH), 8.20(s,1H,H-5), 8.05(s,1H,NH), 7.83(d J=8.5Hz,2H,ar), 7.46(d J=8.5Hz,2H,ar), 7.09(s,1H,H-2), 3.81(s,2H,CH_2), 2.91(d J=4.4Hz, 3H,NCH_3).

4b: UV λ max nm (log ε): 251.4(4.255), 203.2(4.289). IR ν (cm^{-1}): 3207(N-H), 1673(C=O). ^{1}H-NMR δ (ppm): 10.12 (s,1H,NH), 9.22 (s,1H,NH), 8.20(s,1H,H-5), 8.07(s,1H,NH), 7.83(d J=7.8Hz,2H,ar), 7.46(d J=7.0Hz,2H,ar), 7.10(s,1H,H-2), 3.82(s,2H,CH_2), 3.50-3.48(m,2H,NCH_2),1.09(t J=6.4Hz,3H,CH_3).

3-Alkyl/aryl-2-[[[6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-4-thiazolidinones ***5a-e***

A mixture of **4** (0.005 mol), ethyl bromoacetate (0.005 mol) and fused sodium acetate (0.02 mol) in anhydrous ethanol (25 ml) was heated under reflux for 3h. The reaction mixture was cooled, diluted with water and allowed to stand overnight. The precipitate thus obtained was filtered, dried and recrystallized from EtOH.

5a : UV λ max nm (log ε): 259.0(4.405), 204.7(4.403). IR ν (cm^{-1}): 3149(N-H), 1728(C=O ring), 1679(C=O). ^{1}H-NMR δ (ppm): 10.55(s,1H,NH), 8.22(s,1H,H-5), 7.82(d J=8.4Hz,2H,ar), 7.44 (d J=8.4Hz,2H,ar),7.05(s,1H,H-2), 4.05, 3.87 (2s,4H, SCH_2 and CH_2),3.08 (s,3H,NCH_3). EIMS m/z (rel.abun.%): 419,421(M^+,$(M+2)^+$) (75), 291, 293(13), 275,277(80), 248, 250(100), 211(47), 203(14), 182(7), 172(31), 150(10), 137, 139(22), 116(9), 102(8).

5b : UV λ max nm (log ε):259.3(4.394),204.1(4.356). IR ν (cm^{-1}):3152(N-H), 1719(C=O ring), 1690(C=O). ^{1}H-NMR δ (ppm): 10.60(s,1H,NH), 8.25(s,1H,H-5), 7.83(d J=8.3Hz,2H,ar), 7.46(d J=8.3Hz,2H,ar), 7.06(s,1H,H-2), 4.05,3.87(2s,4H,SCH_2 andCH_2), 3.72(q J=7.0Hz,2H,NCH_2), 1.12(t J=6.9Hz,3H,CH_3). EIMS m/z (rel.abun.%): 433,435 (M^+,$(M+2)^+$) (51), 291, 293(12), 275,277(71), 248,250(100), 211(27), 203(7), 186(12), 137,139(9), 130(5) 121(27), 102(7).

Microbiology

Antibacterial activity

Disc diffusion method was used for antimicrobial activity. The cultures of bacteria and yeast strains were prepared in 4 ml of Mueller-Hinton broth at 37°C. After 24 h of incubation, the turbidity of culture suspension was adjusted with sterile Mueller-Hinton broth in order to obtain a turbidity comparable to a No.1 Mc Farland turbidity standard. One milliliter of this suspension was pipetted into the Mueller-Hinton Agar plate and distributed evenly over the surface of the medium by gently rocking the plate. Excess suspension was pipetted off. The surface of the medium

was allowed to dry for 15 min at room temperature. Compound (160 µg) impregnated discs were applied to the surface of inoculated plates. The petri plates were placed in an incubator at 37°C. After 18-24 h of incubation, the petri plates were examined and the diameter of the zone of inhibition was measured.

Antifungal activity

All the compounds to be tested were dissolved in DMSO at a concentration of 4000 µg/ml and the final concentration was reduced to 200 µg/ml with sterile distilled water. No effect of DMSO (5%) was observed upon growth of dermatophytes. The dermatophyte strains which were grown on slant medium of Sabouraud (Difco) were transferred to 3.5 ml nutrient broth (NB. Diagnostic Pasteur) and incubated for three to five days at 25°C. At the end of the incubation period these strains were transferred into screwcapped bottles containing sterilized beads and shaken for 4-5 min in a vortex (IKA-VF. Germany). The suspensions of the cultures were adjusted to have an absorbance degree of 0.6 at 450 nm. Eight different dilutions between 25-0.2 µg/ml were prepared in microplates by serial dilutions. All the wells except the 12th (positive control) were filled with 10 µl of the standardized strains. These plates were incubated at 25°C for five or six days. The minimum concentration at which no growth was observed was taken as the MIC value.

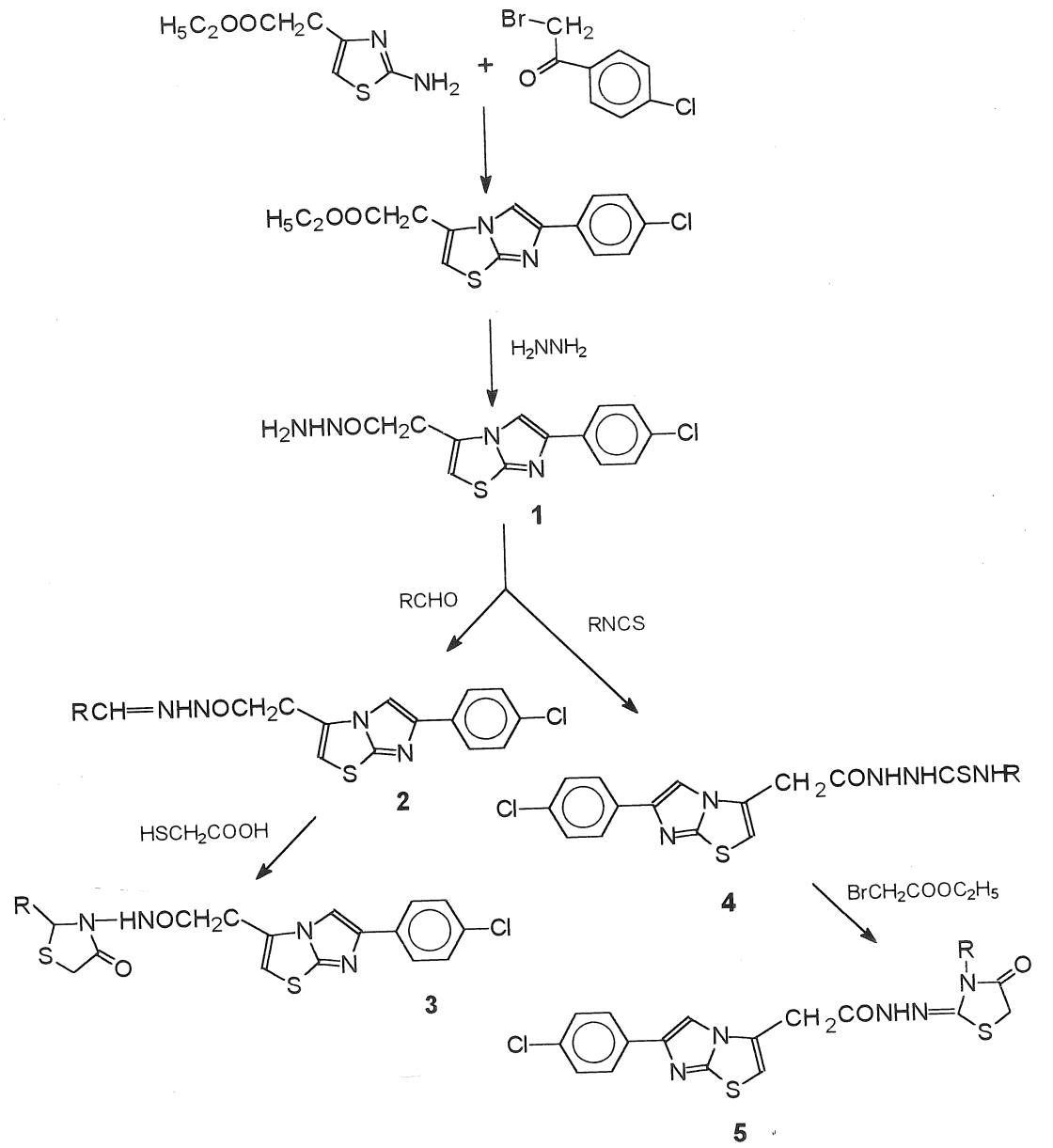
Results and Discussion

Chemistry

The target compounds were prepared from [6-(4-chlorophenyl) imidazo [2,1-b] thiazol-3-yl] acetic acid hydrazide **1** (5), by a two step synthesis as depicted in Scheme 1. Thus **1** reacted with aromatic aldehydes to afford N-arylidene derivatives **2** which furnished 4-thiazolidinones **3** on cyclodehydration with thioglycolic acid. 1-acyl-4-alkyl/arylthiosemicarbazides **4** were obtained from **1** and corresponding alkyl/arylisothiocyanates. On treatment with ethyl bromoacetate **4** yielded 4-thiazolidinones **5** (Table 1).

The structures of the acyclic adducts (**2** and **4**) as well as 4-thiazolidinones (**3** and **5**) were assigned by elemental analysis (CHN) and spectroscopic methods (UV,IR,^{1}H-NMR,EIMS). The IR spectra of **2** and **4** showed the N-H and C=O bands at about 3249-3062 and 1683-1672 cm^{-1}, respectively. The ^{1}H-NMR spectra of **2a** and **2c** revealed the presence of two isomers in the ratio of 2.5:1 in [d_6] DMSO as the NH, N=CH and CH_2 protons resonated as double singlets (6). It is assumed that the N=CH double bond restricts rotation and gives rise to the formation of *E* and *Z* isomers where the dominating isomer is the *E* isomer in **2**. The three resonances located in the δ 10.12-8.05 ppm region assigned to the NH resonances of the thiosemicarbazides supported the structures of **4a** and **4b** (3).

New C=O bands (1739-1719 cm^{-1}) displayed by the IR spectra of 4-thiazolidinones **3** and **5** provided confirmatory evidence for ring closure (7,8). Further support was obtained from the ^{1}H-NMR spectra of **3a** and **3c** which showed the C-H proton at the 2 position of the 4-thiazolidinone ring at δ 5.79 and 5.81 ppm, respectively. The upfield shift observed here was consistent with the change in the hybrid state of the involved carbon atom which was brought about by the addition of the SH function across the N=CH bond of **2** (8). The methylene ring protons absorbed as a doublet (δ 3.92 J=16.0Hz, **3a** and δ 3.94 J=15.7Hz, **3c**) and a multiplet (δ 3.82-3.69, **3a** and 3.79-3.69, **3c**) where the appearance of the latter was affected by the exocyclic methylene resonance located within the second doublet of the non-equivalent geminally interacting methylene protons (9). The exocyclic and ring methylene protons of **5a** and **5b** displayed two singlets at δ 4.05 and 3.87 ppm with unequal integrals (1.73:1 **5a**, 1.62:1 **5b**) indicating the presence of two isomers in unequal propotions in [d_6] DMSO. This may be explained on the basis of the difference in the relative stability of the *E* and *Z* isomers formed due to the rotational restriction about the exocyclic N=C bond at the 2-position of the 4-thiazolidinone ring. EIMS of **3a**,**3c**,**5a** and **5b** readily displayed molecular ions which confirmed their molecular weights. $(M+2)^+$ and $(M+4)^+$ ions resulting from the isotopic composition of the molecular as well as the fragment ions were observed at the expected mass values. The major fragmentation route both in **3** and **5** involved the cleavage of the exocyclic CH_2-CO bond which after protonation yielded the base peak $C_{12}H_9ClN_2S^+$ at mass 248(250). Rupture of the exocyclic CO-NH and NH-N bonds furnished common fragments $C_{13}H_8ClN_2OS^+$ (m/z 275(277) and



Scheme 1. Synthesis of compounds **2-5**

$C_{13}H_{10}ClN_3OS^+$ (m/z 291(293)), respectively. Fragment ions $C_{10}H_{11}NOS^+$ (m/z 193, **3a**), $C_9H_8BrNOS^+$ (m/z 257(259), **3c**), $C_5H_6N_3O_2S^+$ (m/z 172, **5a**), $C_6H_8N_3O_2S^+$ (m/z 116, **5b**), $C_4H_6NOS^+$ (m/z 116, **5a**) and $C_5H_8NOS^+$ (m/z 130, **5b**) were assigned to the intact 4-thiazolidinone fragments originating from the cleavage of the NH-N bond in **3** and exocyclic CH_2-CO and N=C bonds in **5**, respectively.

No fragment ions due to thiazolidinone ring fission were present in the EIMS of **5a** or **5b**, whereas peaks located at m/z 408(410) and 473(475,477) in the EIMS of **3a** and **3c** were suggestive of ring fission involving the 1,2 and 3,4 bonds of the 4-thiazolidinone system with subsequent protonation (10). Further spectral details are presented in the materials and methods.

Table 1. Physicochemical data of compounds **2-5**

Compound	R	Formula (MW)	Mp (°C)	Yield (%)	Analysis (calcd./found)		
					C	H	N
2a	$C_6H_4CH_3(4)$	$C_{21}H_{17}ClN_4OS$ (408.91)	242	84	61.68 4.19	13.70	
					62.15	4.19	13.70
2b	$C_6H_4Cl(4)$	$C_{20}H_{14}Cl_2N_4OS.2H_2O$ (465.35)	249-250	83	51.62	3.89	12.04
					50.85	3.14	11.45
2c	$C_6H_4Br(4)$	$C_{20}H_{14}BrClN_4OS.2H_2O$ (509.81)	239-240	69	47.11	3.55	10.99
					46.31	2.81	10.39
2d	$C_6H_4F(4)$	$C_{20}H_{14}ClFN_4OS$ (412.87)	257-258	88	58.18	3.41	13.57
					58.53	3.59	13.88
2e	$C_6H_4NO_2(2)$	$C_{20}H_{14}ClN_5O_3S$ (439.88)	244-245	69	54.61	3.20	15.92
					54.62	3.20	16.13
3a	$C_6H_4CH_3(4)$	$C_{23}H_{19}ClN_4O_2S_2.2H_2O$ (519.03)	135-137	96	53.22	4.46	10.79
					53.07	4.59	10.52
3b	$C_6H_4Cl(4)$	$C_{22}H_{16}Cl_2N_4O_2S_2.2H_2O$ (539.45)	140-141	98	48.98	3.73	10.38
					49.33	3.58	10.07
3c	$C_6H_4Br(4)$	$C_{22}H_{16}BrClN_4O_2S_2.2H_2O$ (583.91)	146-148	98	45.25	3.45	9.59
					45.00	3.37	9.21
3d	$C_6H_4F(4)$	$C_{22}H_{16}ClFN_4O_2S_2.H_2O$ (504.99)	154-155	91	52.32	3.59	11.09
					51.92	3.65	10.71
3e	$C_6H_4NO_2(2)$	$C_{22}H_{16}ClN_5O_4S_2.H_2O$ (532.00)	154-155	97	49.66	3.40	13.16
					49.52	3.55	13.17
4a	CH_3	$C_{15}H_{14}ClN_5OS_2$ (379.89)	>300	75	47.42	3.71	18.43
					48.20	3.79	19.23
4b	C_2H_5	$C_{16}H_{16}ClN_5OS_2$ (393.92)	231	77	48.78	4.09	17.78
					48.59	4.03	17.78
4c	CH_2-CH=CH_2	$C_{17}H_{16}ClN_5OS_2$ (405.93)	238-239	85	50.30	3.97	17.25
					50.34	4.11	17.61
4d	C_4H_9	$C_{18}H_{20}ClN_5OS_2$ (421.97)	250-251	82	51.23	4.77	16.59
					50.86	4.60	16.43
4e	C_6H_5	$C_{20}H_{16}ClN_5OS_2$ (441.96)	196-197	79	54.35	3.64	15.84
					53.81	3.64	15.78
5a	CH_3	$C_{17}H_{14}ClN_5O_2S_2$ (419.91)	235	78	48.62	3.36	16.67
					48.94	3.36	16.76
5b	C_2H_5	$C_{18}H_{16}ClN_5O_2S_2$ (433.94)	259-260	77	49.82	3.71	16.14
					50.14	3.93	15.91
5c	CH_2-CH=CH_2	$C_{19}H_{16}ClN_5O_2S_2$ (445.95)	222-223	97	51.17	3.61	15.70
					50.72	3.65	15.39
5d	C_4H_9	$C_{20}H_{20}ClN_5O_2S_2$ (461.99)	186	95	51.99	4.36	15.16
					51.84	4.36	15.35
5e	C_6H_5	$C_{22}H_{16}ClN_5O_2S_2$ (481.98)	270	86	54.82	3.34	14.53
					55.43	3.37	14.59

Microbiology

Compounds **2-5** were evaluated for in vitro antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 122228, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Salmonella typhi*, *Shigella flexneri*, *Proteus mirabilis* and *Escherichia coli* ATCC 8739 using the disc diffusion method (11) but none showed significant activity at the tested concentration. **2-5** Were also evaluated for antifungal activity against four dermatophyte strains *Trichophyton rubrum*, *Trichophyton tonsurans* (NCPF-245), *Microsporum gypseum* (NCPF-580) and *Microsporum canis* (12). **3a** and **3b** inhibited the growth of *T.rubrum* and *T.tonsurans* at 25 μg/ml.

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