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Synthesis and antimicrobial evaluation of novel derivatives of 1,3,4-thiadiazine incorporated with pyrazole-4-carboxylic acid moiety

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2-Amino-5-phenyl-6*H*-[1,3,4]-thiadiazine (**5a-c)** condense with pyrazole-4-carboxylate (**1a-e**) using alcohol as a solvent to give 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid-(5-phenyl-6*H*-[1,3,4]-thiadiazin-2-yl)-amide (**6a-i**) in 30% yield. The same product is obtained from pyrazole-4-acid (**2a-e)** in presence of HOBt (1-hydroxy-benzotriazole) and EDC (*N*-ethyl-*N'*-(3-dimethyl-aminopropyl)-carbodiimide hydrochloride) in triethyl amine using $CHCl_3$ as a solvent, in 75-85% yields. The structures of these compounds (**6a-i)** were characterized by FT-IR, ^{1}H NMR, mass spectroscopic techniques and elemental analysis. All synthesized pyrazole-1,3,4-thiadiazine (**6a-i)** derivatives were found to exhibit antimicrobial activities.

Key words: 2-amino-1,3,4-thiadiazine, pyrazole-4-carboxylic acid, antimicrobial.

INTRODUCTION

Heterocyclic compounds containing five- and six-membered ring systems are successfully used as drugs. Synthesis of such compounds containing condensed rings or more than one heterocyclic nucleus is gaining more and more popularity due to their specific use in medicine.

1,3,4-Thiadiazines may exist in three different tautomeric forms. Spectroscopic investigations suggest that the 6*H*-form is preferred. The 4*H*-form represents a potentially anti-aromatic 8π-system which can be transformed by valence isomerization to a thiahomopyrazole and by subsequent extrusion of sulfur to a pyrazole [1]. In addition, 1,3,4-thiadiazines exhibit a broad spectrum of biological activity, which includes matrix metalloproteinase inhibition, tuberculostatic activity against *Mycobacterium tuberculosis*, antiplatelet and antithrombotic properties, antiarrhythmic activity, cardiotonic and hypertensive activities, phosphodiesterase inhibition, and spasmolytic activity. In addition, compounds containing thiadiazine moieties are being used as anti-inflammatory, nonsteroidal contraception agents for females and also for the treatment of erectile dysfunction. Recent reports reveal that 1,3,4 thiadiazine derivatives are used as anesthetics, cardiovascular and hypometabolic agents, for prevention and/or treatment of anemia, for treating deficient bone growth, tumors and acquired immune deficiency syndrome (AIDS), heart failure, asthma, allergies. 1,3,4-Thiadiazine derivatives are also being used in agriculture as herbicides, fungicides, pesticides, insecticides and plant-growth regulators [2].

The 1,3,4-thiadiazine system was first reported by Bose [3], employing a reaction of α-bromoacetophenone with thiosemicarbazide. Bose isolated two reaction products, 2-amino-5-phenyl-l,3,4-thiadiazine and 2-hydrazino-4-phenylthiazole, by heating phenacyl bromide/chloride with TSC in methanol in yields of 70–80%. But 2-amino-l,3,4-thiadiazines are formed in higher yields (up to 96%) in acidic media (acetic acid and concentrated hydrochloric and hydrobromic acids). Also 2-amino-5-phenyl-6*H*-1,3,4-thiadiazines, 2-amino-5-(4-methylphenyl)-6*H*-1,3,4–thiadiazines and 2-amino-5-(4-bromophenyl)-6*H*-1,3,4-thiadiazines were prepared [4] from appropriate α-haloacetophenones and thiosemicarbazide.

Synthesis of *N*-haloacyl and *N*-hetarylthioacyl derivatives [5] of 2-amino-5-aryl-6*H*-1,3,4–thiadiazine were synthesized by *N*-acylation of 2-amino-5-aryl-6*H*-1,3,4-thiadiazines with trifluoroacetic anhydride and halogen-substituted carboxylic acid halides with retention of the initial hetero cyclic system 2-haloacylamino-5-aryl-6*H*–1,3,4-thiadiazines in preparative yields. The obtained 2-haloacylamino-5-aryl-6*H*-1,3,4-thiadiazines can alkylate heterocyclic thiols under mild conditions to give the corresponding 5-aryl-2-hetarylthioacetyl(butyryl)amino-6*H*-1,3,4-

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thiadiazine derivatives containing pharmacophore groups.

A new series [6] of novel bis[1,2,4]triazolo[3,4–*b*][1,3,4]-thiadiazines has been synthesized by the reaction of [5,5'-methylenebis(3-methylbenzofuran-7,5-diyl)]bis[(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methanone] with a variety of phenacyl bromides in ethanol under reflux for 6 h. All newly synthesized compounds were tested for *in vitro* activity against certain strains of bacteria and fungi.

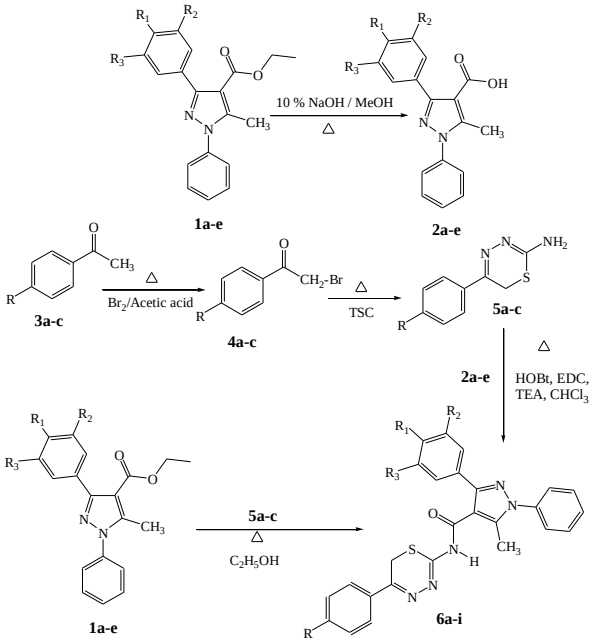
Synthesis of 3,6-diaryl-1,2,4-triazolo[3,4–b] –1,3,4-thiadiazines by condensation of appropriate 5– (3,4-dichlorophenyl)-2-(aroylmethyl)thio-1,3,4-oxadiazoles and hydrazine hydrate in acetic acid is described [7]. All compounds were evaluated for anti-inflammatory activity by determining their ability to provide protection against carrageenan-induced edema in rat paw. In addition, ulcerogenic activities of the compounds were determined. New route for the synthesis of pyrimido[4,5–*e*][1,3,4]thiadiazine derivatives [8] from 5-bromo-2-chloro-4-methyl-6-(1-methylhydrazino)pyrimidine with carbon disulfide was used and several alkyl halides gave an intermediate which was successfully converted to its corresponding derivatives in basic acetonitrile.

A series of heterocycle-substituted phthalimide derivatives [9] with various heterocyclic rings, such as furan, imidazo[1,2–a]pyridine, 1,3,4-thiadiazine, imidazo[2,1–b][1,3,4]thiadiazine, pyrazole, 1,2,4-triazolo[3,4–b][1,3,4]thiadiazine, thiazole and thiazoline can be rapidly synthesized from α-bromoketone intermediate. Their cytotoxic activity was also *in vitro* evaluated against five human cancer cell lines.

Pyrazole and its synthetic analogues have been found to exhibit antidepressant, anticonvulsant, antimicrobial, analgesic, and antitumor activity, as well as human acyl-Co A:cholesterol acyltransferase inhibitor activity. In fact, the pyrazole derivative celecoxib is now widely used in the market as anti-inflammatory drug [10, 11]. We have synthesized 1-(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)-ethanone [12] and ethyl 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate [13] *via* 1,3-dipolar cycloaddition of the enol form of acetyl acetone and ethyl acetoacetate with *in situ* generated nitrile imines by catalytic dehydrogenation of diphenyl hydrazone using chloramine-T. In view of these observations we report herein the synthesis of 1,3,4-thiadiazine with incorporated pyrazole-4-carboxylic acid moiety and the study of its antimicrobial activities.

RESULTS AND DISCUSSION

The synthesis of 5-methyl-1,3-diphenyl-1*H*–pyrazole-4-carboxylic acid (**2a-e**) obtained from 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate **1(a-e)** [13] refluxed with 10% NaOH solution in presence of methanol as a solvent for about 3-4 hours is described. On the other hand, 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazines (**5a-c)** [3,4] are synthesized from acetophenone with bromine in acetic acid to give phenacyl bromide (α-bromocarbonyl compounds) (**4a-c**). The obtained phenacyl bromide (**4a-c**) is treated with thiosemicarbazide (TSC) to produce a cyclocondensation product (**5a-c)**. The obtained pyrazole-4-acid (**2a-e**) is condensed with 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazine (**5a-c)** in presence of HOBt and EDC in triethyl amine using $CHCl_3$ as a solvent to produce the respective 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid-(5-phenyl-6*H*-[1,3,4]-thiadiazin-2-yl)-amide (6**a-i)** in good yield [**Scheme**].



2a = $R_1 = R_2 = R_3$ = H,
2b = R_1 = Cl, $R_2 = R_3$ = H,
2c = R_1 = -OCH_3, $R_2 = R_3$ = H,
2d = $R_1 = R_2$ = -OCH_3, R_3 = H,
2e = $R_1 = R_2 = R_3$ = -OCH_3,
5a = R = H,
5b = R = Cl,
5c = R = -OCH_3,

6a = R = $R_1 = R_2 = R_3$ = H,
6b = R = H, R_1 = Cl, $R_2 = R_3$ = H,
6c = R = H, $R_1 = R_2 = R_3$ = -OCH_3,
6d = R = Cl, $R_1 = R_2 = R_3$ = H,
6e = R = Cl, R_1 = Cl, $R_2 = R_3$ = H,
6f = R = -OCH_3, $R_1 = R_2 = R_3$ = H,
6g = R = -OCH_3, R_1 = Cl, $R_2 = R_3$ = H,
6h = R = H, R_1 = -OCH_3, $R_2 = R_3$ = H,
6i = R = H, $R_1 = R_2$ = -OCH_3, R_3 = H,

Scheme

Synthesis of 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid (**2a-e**) obtained from 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (**1a-e**) is performed by reflux with 10% NaOH solution in the presence of methanol for about 3-4 h. The structural proof for pyrazole-4-carboxylic acid is given by IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis. For instance, the ^{1}H

NMR spectra show the absence of a quartet in the region δ 4.12-4.31 ppm, (2H for $–OCH_2$- group), and a triplet in the region δ 1.18–1.30 ppm, (3H for $–OCH_2-CH_3$ group) and the presence of carboxylic acid peak at 9.10–9.86 ppm. In the ^{13}C NMR spectra the peaks δ 13.58–13.84 ppm (for $–OCH_2-\underline{C}H_3$) and δ 58.72– 58.96 ppm (for $–O\underline{C}H_2$-) were absent and the peak δ 169.36-173.40 ppm (for –<u>C</u>OOH) was seen. All pyrazole-4-carboxylic acids showed MH+ as a base peak in the mass spectra and significantly stable molecular ion peaks with a relative abundance of 20–90%, which strongly favors the formation of pyrazole-4-carboxylic acid.

The obtained pyrazole-4-carboxylic acid (**2a**–**e**) was condensed with 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazine (**5a**–**c**) in cold by slowly adding HOBt, then EDC and triethyl amine using chloroform as solvent. The resulting solution was stirred at room temperature in nitrogen atmosphere for about 5–6 h to give 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid-(5-phenyl-6*H*-[1,3,4]-thiadiazin-2-yl)-amide (**6a**–**i**). The obtained pyrazole-1,3,4-thiadiazines (**6a**–**i)** were confirmed by IR, ^1H NMR, MS studies and elemental analysis. The IR spectra showed amide –NH- frequency in the region 3328.88-3388 cm^{-1} and -C=O stretching frequency in the region 1670.20-1690.50 cm^{-1}. In the ^1H NMR spectra there was no carboxylic acid peak at 9.10-9.86 ppm, but the single peak due to -CO–NH- protons appeared in the region δ 7.90-8.34 ppm. All pyrazole-1,3,4-thiadiazines (**6a**–**i)** showed M+1 as a base peak in the mass spectra. Further, the elemental analysis supported the formation of the products.

Antimicrobial activity

The synthesized pyrazole-1,3,4-thiadiazines (**6a-i**) were tested (dose of 100 µg) for their *in vitro* antimicrobial activity against the human pathogenic bacterial strain *Bacillus cereus (B. cereus), Escherichia coli* (*E. coli*), *Klebsiella pneumonia* (*K. pneumonia*) and *Shigella flexneri* (*S. flexneri*) by the disc diffusion method [14, 15]. Plates were inoculated into 25 ml of N-broth (Nutrient Broth) and incubated for 24 h in an incubator at 37^0C and chloramphenicol was used as a standard drug. All compounds **6a** were also screened (dose of 100 µg) for their antifungal activity against *Candida albicans (C. albicans)* an-**i** d *Aspergillus flavus (A. flavus)* using Fluconazole as a standard drug. After the period of incubation the inhibition zones were measured in mm and the results obtained are shown in Table 1.

Table 1. Antibacterial activity of synthesized 1,3,4-thiadiazine derivatives (6a-i). (Zone of inhibition in mm).

Compound	Antibacterial activity				Antifungal activity	
	B. cereus	E. coli	K. pneu-monia	S. flexneri	C. albicans	A. flavus
6a	08	14	09	10	12	18
6b	08	12	12	14	14	14
6c	12	14	16	14	16	12
6d	08	12	10	08	14	10
6e	09	10	12	16	18	20
6f	09	12	14	10	12	14
6g	08	10	08	08	10	12
6h	10	14	10	10	10	12
6i	09	12	08	12	10	12
Chloramphenicol	14	18	20	24		
Fluconazole					28	30

The screening results revealed that the test compounds (**6a–i**) exhibited significant activity, but with a degree of variation. Among all synthesized compounds, the compound **6c** exhibited a pronounced activity against all four bacterial strains and **6e** showed higher antifungal activity. The compounds **6a**–**i** showed good activity against *E. coli*. The compounds **6a**–**i** showed moderate activity against both *C. albicans* and *A. flavus*.

EXPERIMENTAL SECTION

All melting points were measured in open capillaries and are uncorrected. IR spectra (nujol) were recorded on a Bruker Ft-IR spectrometer. ^1H NMR and ^{13}C NMR spectra ($CDCl_3$ as a solvent) were obtained on a Varian Gemini 400MHz spectrometer. TMS as internal standard, chemical shifts in (ppm); mass spectra: Agilent mass spectrometer operating at 70 eV; elemental analysis was performed on a Jusco microanalytical data unit at Mysore University, India.

General procedures for the synthesis of 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid (2a): The solution of ethyl 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylate (**1a**, 3.06g, 10.0 mmol) was treated with 10 ml of 10% NaOH solution in the presence of absolute methanol for about 3-4 h to give 5-methyl-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid (**2a,** 2.78g). The progress of the reaction was monitored by TLC (chloroform:acetone = 7 : 1 v/v). After the completion of the reaction the solvent was evaporated and the solution was acidified with dilute HCl to give a crude white precipitate. The obtained solid was filtered, dried and recrystallized from methanol to give a white solid (80% yield), m.p. 136ºC. The pyrazole-4-acid showed IR bands

(Nujol) ν: 1678 cm^{-1} (-COOH); ^1H NMR ($CDCl_3$) ∂: 2.7 (s, 3H, -CH_3), 7.45– 7.62 (m, 5H, Ar), 7.35–7.9 (m, 5H, Ar^1), 9.6 (s, 1H, -COOH); ^{13}C NMR (CDCl3) δ: 0.56 (q, 1C, H_3C), 108.32 (s, 1C), 118.08 (d, 2C), 126.42 (d, 1C), 128.66 (d, 2C), 128.22 (d, 2C), 128.74 (d, 2C), 130.28 (s, 1C), 131.08 (d, 1C), 132.42 (s, 1C), 148.6 (s, 1C, C-CH_3), 161.12 (s, 1C –C=N), 173.4* (s 1C, -COOH). MS (relative intensity) m/e for $C_{17}H_{14}N_2O_2$: 279 (M+1, 100), 260 (62), 233 (48). Anal. Calcd: C, 73.37; H, 5.07; N, 10.07%. Found: C, 73.78; H 5.19; N: 10.21%.

General procedures for the synthesis of 2-amino-5-phenyl-6H-[1,3,4]-thiadiazine (5a-c): 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazine (**5a)** was synthesized from acetophenone (2.0 g) with bromine in acetic acid (30 ml) to give phenacyl bromide (α-bromocarbonyl compound). The obtained phenacyl bromide was refluxed with thiosemicarbazide (TSC) in 20 ml of conc. HCl for about 30 min and the resulting solution was allowed to stand at room temperature to produce pale yellow solid. The obtained solid was filtered, washed with chloroform, dried and recrystallized from methanol to give pale yellow solid (85% yield), m.p. 126-128ºC. ^1H NMR spectra of **5a** ($CDCl_3$) ∂: 3.32 (s, 2H, -CH_2-), 7.26–7.42 (m, 5H, Ar-H), 8.1-8.8 (bs, 2H, -NH_2); ^{13}C NMR ($CDCl_3$) ∂: 25.8 (s, 1C, -CH_2-), 128.8 (d, 2C, C-2 and C-6 phenyl), 130.2 (d, 2C, C-3 and C-5 phenyl), 131.6 (s, 1C, C-4 phenyl), 132.4 (s, 1C, C-1 phenyl), 163.60* (s, 1C, C-NH_2), 164.4* (s, 1C, -C=N). MS (relative intensity) m/e for $C_9H_9N_3S$: 192 (M+1, 100), Anal. Calcd: C, 56.45; H, 4.68; N, 21.74; S, 16.70%. Found: C, 56.36; H, 4.52; N, 21.66; S, 16.64%.

Typical procedure for the synthesis of 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide (6a): 2-amino-5-phenyl-6H-[1,3,4]-thiadiazine (5a, 0.19 g, 10 mmol) was dissolved in 15 ml of $CHCl_3$ and stirred at 0ºC. Then 0.22 g of HOBt (15 mmol) was slowly added to the solution, after 15 min 0.20 g of EDC (15 mmol), 0.05ml of triethyl amine (15 mmol) and pyrazole-4-acid (2a 0.27g, 10 mmol) were added, the resulting solution was stirred at room temperature in nitrogen atmosphere for about 6–7 h. The progress of the reaction was monitored by TLC. After the completion of reaction the residue was extracted with $CHCl_3$ (30 ml), washed successively with 5% $NaHCO_3$ solution and 5% HCl solution. Finally, the solution was washed with water (2×30 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated to give yellow solid which was recrystallized from methanol to give pale yellow solid in 76% yield (0.33 g), m.p. 146-148 ºC. The obtained pyrazole-thiadiazine 6a showed IR bands (nujol) ν: 1670.20 cm^{-1} (-C=O), 1595.84 cm^{-1} (-C=N-), 3357.90 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.72 (s, 3H, CH_3), 3.56 (s, 2H, -CH_2-), 7.25–7.68 (m, 15H, Ar-H), 7.90 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{26}H_{21}N_5OS$: 452 (M+1, 100); Anal. Calcd: C, 69.16, H, 4.69, N, 15.51%. Found: C, 68.96, H, 4.60, N, 15.44%.

3-(4-Chloro-phenyl)-5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide (6b): Obtained from 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazine **(5a,** 0.19g, 10 mmol), 0.22g HOBt, 0.20g of EDC, 0.05ml triethyl amine and pyrazole-4-acid (**2b,** 0.30g, 10 mmol). Pale yellow solid, yield 78%, m.p. 158-160 ºC. IR bands (nujol) ν: 1676.04 cm^{-1} (-C=O), 1562.02 cm^{-1} (-C=N-), 3328.88 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.70 (s, 3H, CH_3), 3.60 (s, 2H, -CH_2-), 7.20–7.66 (m, 14H, Ar-H), 8.21 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{26}H_{20}ClN_5OS$: 486 (M+1, 100); Anal. Calcd: C, 64.26, H, 4.15, N, 14.40%. Found: C, 64.08, H, 4.04, N, 14.34%.

5-Methyl-1-phenyl-3-(3,4,5-trimethoxy-phenyl)-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide (6c): Obtained from 2-amino-5-phenyl-6H-[1,3,4]-thiadiazine (5a, 0.19 g, 10 mmol), 0.22 g HOBt, 0.20 g of EDC, 0.05ml triethyl amine and pyrazole-4-acid (2e, 0.37g, 10 mmol). Pale yellow solid, yield 82%, m.p. 152-154 ºC. IR bands (nujol) ν: 1684.04 cm^{-1} (-C=O), 1558.38 cm^{-1} (-C=N-), 3364.78 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.79 (s, 3H, CH_3), 4.06 (s, 2H, -CH_2-), 3.84 (s, 9H, -OCH_3), 7.22–7.96 (m, 12H, Ar-H), 8.34 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{29}H_{27}N_5O_4S$: 542 (M+1, 100); Anal. Calcd: C, 64.30, H, 5.00, N, 12.89%. Found: C, 64.24, H, 4.96, N, 12.80%.

5-Methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid-(5-(4-chloro-phenyl)-6H-[1,3,4]-thiadiazin-2-yl)-amide (6d): Obtained from 2-amino-5-(4-chloro-phenyl)-6*H*-[1,3,4]-thiadiazine (**5b,** 0.22 g, 10 mmol), 0.22 g HOBt, 0.20 g of EDC, 0.05 ml triethyl amine and pyrazole-4-acid (**2a,** 0.27 g, 10 mmol). Pale yellow solid, yield 84%, m.p. 160-162 ºC. IR bands (Nujol) ν: 1676 cm^{-1} (-C=O), 1560.32 cm^{-1} (-C=N-), 3360.64 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.68 (s, 3H, CH_3), 3.92 (s, 2H, -CH_2-), 7.28-7.82 (m, 14H, Ar-H), 8.26 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{26}H_{20}ClN_5OS$: 486 (M+1, 100); Anal. Calcd: C,

64.25, H, 4.08, N, 14.38%. Found: C, 64.22, H, 4.00, N, 14.34%.

3-(4-Chloro-phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid-(5-(4-chloro-phenyl)-6H-[1,3,4]-thiadiazin-2-yl)-amide (6e): Obtained from 2-amino-5-(4-chloro-phenyl)-6H-[1,3,4]-thiadiazine (**5b,** 0.22 g, 10 mmol), 0.22 g HOBt, 0.20 g of EDC, 0.05ml triethyl amine and pyrazole-4-acid (**2b,** 0.30 g, 10 mmol). Pale yellow solid, yield 80%, m.p. 144-146 ^{0}C. IR bands (nujol) ν: 1672 cm^{-1} (-C=O), 1566.24 cm^{-1} (-C=N-), 3380.52 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.72 (s, 3H, CH_3), 3.84 (s, 2H, -CH_2-), 7.28-7.82 (m, 13H, Ar-H), 8.08 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{26}H_{19}Cl_2N_5OS$: 520 (M+1, 100); Anal. Calcd: C, 60.00, H, 3.68, N, 13.62%. Found: C, 59.96, H, 3.64, N, 13.60%.

***5-Methyl-1,3-diphenyl-1H-pyrazole-4-carboxylic acid-(5-(4-methoxy-phenyl)-6H-[1,3,4]-thiadiazin-2-yl)-amide* (6f):** Obtained from 2-amino-5-(4-methoxy-phenyl)-6*H*-[1,3,4]-thiadiazine (**5c,** 0.22 g, 10 mmol), 0.22 g HOBt, 0.20 g of EDC, 0.05 ml triethyl amine and pyrazole-4-acid (**2a,** 0.26g, 10 mmol). Pale yellow solid, yield 85%, m.p. 132-134 ºC. IR bands (nujol) ν: 1684 cm^{-1} (-C=O), 1572 cm^{-1} (-C=N-), 3356.04 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.64 (s, 3H, CH_3), 4.14 (s, 2H, -CH_2-), 3.72 (s, 3H, -OCH_3), 7.32-7.92 (m, 14H, Ar-H), 8.12 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{27}H_{23}N_5O_2S$: 482 (M+1, 100); Anal. Calcd: C, 67.34, H, 4.81, N, 14.54%. Found: C, 67.30, H, 4.78, N, 14.50%.

***3-(4-Chloro-phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid-(5-(4-methoxy-phenyl)-6H-[1,3,4]-thiadiazin-2-yl)-amide* (6 g):** Obtained from 2-amino-5-(4-methoxy-phenyl)-6*H*-[1,3,4]-thiadiazine (5c, 0.22 g, 10 mmol), 0.22g HOBt, 0.20 g of EDC, 0.05 ml triethyl amine and pyrazole-4-acid (2b, 0.30 g, 10 mmol). Pale yellow solid, yield 78%, m.p. 172-174 ºC. IR bands (nujol) ν: 1672 cm^{-1} (-C=O), 1560 cm^{-1} (-C=N-), 3358 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.76 (s, 3H, CH_3), 4.22 (s, 2H, -CH_2-), 3.68 (s, 3H, -OCH_3), 7.20-8.06 (m, 13H, Ar-H), 8.22 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{27}H_{22}ClN_5O_2S$: 516 (M+1, 100); Anal. Calcd: C, 62.84, H, 4.30, N, 13.57%. Found: C, 62.78, H, 4.28, N, 13.52%.

***3-(4-Methoxy-phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide* (6h):** Obtained from 2-amino-5-phenyl-6*H*-[1,3,4]-thiadiazine (**5a,** 0.22 g, 10 mmol), 0.19 g HOBt, 0.20 g of EDC, 0.05 ml triethyl amine and pyrazole-4-acid (**2c,** 0.30 g, 10 mmol). Pale yellow solid, yield 80%, m.p. 154–156 ºC. IR bands (nujol) ν: 1682 cm^{-1} (–C=O), 1574 cm^{-1} (–C=N-), 3388 cm^{-1} (–NH–); H^1 NMR ($CDCl_3$): ∂ 2.80 (s, 3H, CH_3), 3.82 (s, 2H, –CH_2-), 3.58 (s, 3H, –OCH_3), 7.28–8.12 (m, 14H, Ar-H), 8.20 (d, 1H, –NH–CO–); MS (relative intensity) m/e for $C_{27}H_{23}N_5O_2S$: 482 (M+1, 100); Anal. Calcd: C, 67.34, H, 4.80, N, 14.54%. Found: C, 67.30, H, 4.78, N, 14.50%.

***3-(3,4-Dimethoxy-phenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid-(5-phenyl-6H-[1,3,4]-thiadiazin-2-yl)-amide* (6i):** Obtained from 5-(4-methoxy-phenyl)-6*H*-[1,3,4]-thidiazine-2-yl amine (**5a,** 0.19 g, 10 mmol), 0.22 g HOBt, 0.20 g of EDC, 0.05 ml triethyl amine and pyrazole-4-acid (**2d,** 0.33 g, 10 mmol). Pale yellow solid, yield 75%, m.p. 174-176 ºC. IR bands (nujol) ν: 1690 cm^{-1} (-C=O), 1564 cm^{-1} (-C=N-), 3366 cm^{-1} (-NH-); H^1 NMR ($CDCl_3$): ∂ 2.72 (s, 3H, CH_3), 4.16 (s, 2H, -CH_2-), 3.58 (s, 6H, -OCH_3), 7.28-8.08 (m, 13H, Ar-H), 8.16 (d, 1H, -NH-CO-); MS (relative intensity) m/e for $C_{28}H_{25}N_5O_3S$: 512 (M+1, 100); Anal. Calcd: C, 65.74, H, 4.93, N, 13.68%. Found: C, 65.70, H, 4.88, N, 13.60%.

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СИНТЕЗА И АНТИМИКРОБНИ СВОЙСТВА НА НОВИ ПРОИЗВОДНИ НА 1,3,4-ТИАДИАЗИН ВКЛЮЧЕНИ В СРЕДА ОТ ПИРАЗОЛ-4-КАРБОНОВА КИСЕЛИНА

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(Резюме)

2-амино-5-фенил-6*H*-[1,3,4]-тиадиазин (**5a-c)** се кондензира с пиразол-4-карбоксилат (**1a-e**) при алкохол като разтворител за получаването на 5-метил-1,3-дифенил-1*H*-пиразол-4-карбонова киселина-(5-фенил-6*H*-[1,3,4]-тиадиазин-2-ил)-амид (**6a-i**) с 30% добив. Същият продукт се получава от пиразол-4-киселина (**2a-e)** в присъствие на HOBt (1-хидрокси-бензотриазол) и EDC (*N*-етил-*N'*-(3-диметил-аминопропил)-карбодиимид хидрохлорид) в триетиламин използвайки $CHCl_3$ като разтворител с добиви 75-85%. Структурите на тези съединения (**6a-i)** са характеризирани чрез FT-IR, ^{1}H NMR, мас-спектрометрия и елементен анализ. За всички производни на пиразол-1,3,4-тиадиазина (**6a-i)** са установени антибактериални свойства.