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Synthesis and evaluation of a series of pyrimidine substituted 1,3,4-oxadiazole derivatives as antimicrobial and anti-inflammatory agents

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Abstract: Novel pyrimidine substituted 1,3,4-oxadiazole derivatives (**11a-k**) were synthesized from the condensation of different substituted aromatic carboxylic acids with substituted pyrimidine carboxy hydrazide using $POCl_3$ as condensing agent. Their structures were characterized by physical and spectral studies. The synthesized compounds were evaluated for their *in vitro* antimicrobial and anti-inflammatory activity. Some of the newly synthesized compounds showed good antimicrobial and anti-inflammatory activities.

Keywords: 1,3,4-oxadiazole; pyrimidine; antibacterial; antifungal; anti-inflammatory.

1. Introduction

Heterocyclic compounds containing the five-membered oxadiazole nucleus possess a diversity of useful biological effects. Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest, which was documented by a steadily increasing number of publications and patents. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants [1] and show antimitotic activity. Anti-inflammatory [2], antihepatitis B [3] and antidiarrheal activity [4] of some new 1,3,4-

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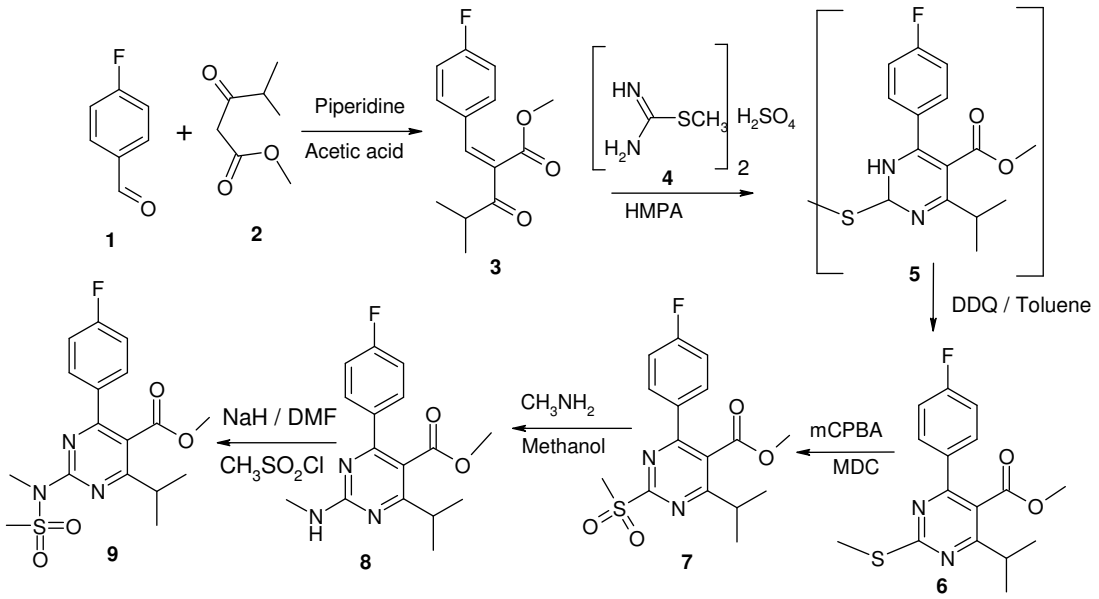
oxadiazole derivatives was also reported. Recently several 1,3,4-oxadiazole derivatives were identified as potentially active antimycobacterial[5,6], antitubercular[7], anticonvulsant[8], anticancer[9] activities and also reported as enzyme tyrosinase inhibitors. [10]

The objective of the present study was to synthesize new pyrimidine substituted 1,3,4-oxadiazole derivatives and evaluate them for antimicrobial and anti-inflammatory activities.

2. Results and discussion

2.1 Chemistry

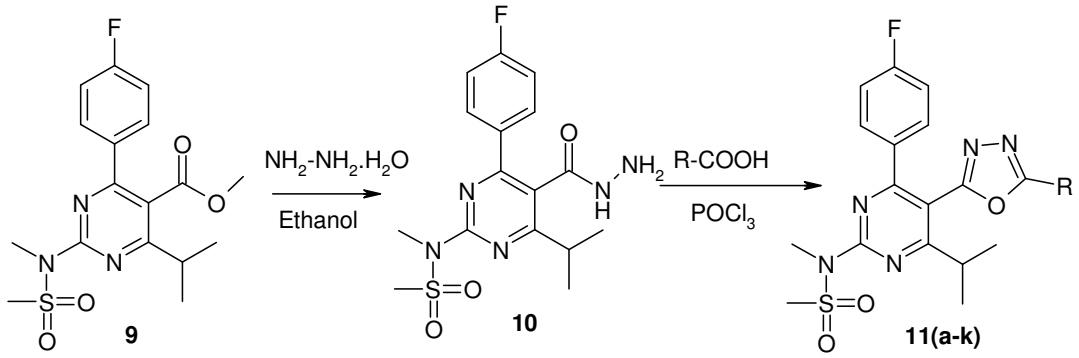
Novel pyrimidine substituted-1,3,4-oxadiazole derivatives were synthesized in a seven step process. The core intermediate for the synthesis of new pyrimidine-oxadiazole derivatives is compound **9** which was prepared by the known literature as shown in Scheme 1. [11-12]



Scheme 1. Synthetic method for the preparation of intermediate compound **9**

The compound **3** was synthesized from 4-flouro benzaldehyde (**1**) and methyl isobutyl acetate (**2**) by Knoevenagel condensation. The compound **3** was reacted with S-methyl thiourea hydrogen sulfate (**4**) in the presence of hexamethyl phosphoramide (HMPA) forms an intermediate **5,** which was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in toluene to furnish the compound **6**. The obtained S-methyl pyrimidine (**6**) compound was oxidized to sulfonyl methyl pyrimidine (**7**) using m-chloro perbenzoicacid. The N-methyl derivative (**8**) of the pyrimidine was synthesized by treating the compound **7** with methyl amine in methanolic medium. The compound **8** was further treated with methane sulfonyl chloride in the presence of NaH in anhydrous DMF to form compound **9.** The pyrimidine hydrazide (**10**) was synthesized from the compound **9** upon refluxing with hydrazine hydrate solution for 6 hours.

Cyclization of the hydrazide compound (**10**) with different aromatic acids in presence of phosphorous oxychloride gave the titled compounds **11a-k** (Scheme 2).



Scheme 2. Synthetic method for the preparation of pyrimidine oxadiazoles **11(a-k).**

The final compounds were obtained in good yields in the range of 64-85%. The completion of the reaction was monitored by TLC and the product was isolated by column chromatography in pure form.

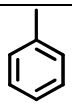
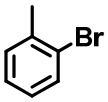
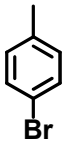
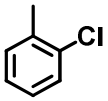
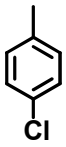
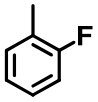
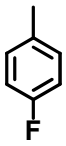
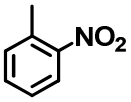
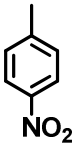
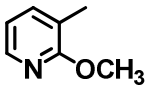
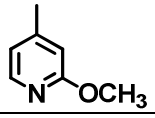
The structure of the newly synthesized compounds was elucidated by their Mass, IR, NMR and melting points. In the IR spectra, the band due to –C=C- and C=N group, which was present in all studies, the peaks were observed at about 1400 cm^{-1} and 1550 cm^{-1}, respectively. The bands at about 1300 cm^{-1} and 990 cm^{-1} were characteristic for the S=O (sulfonyl group) and C-F groups respectively. About 1100 cm^{-1} was characteristic for the C-O group. The molecular ion peaks in the mass spectra were in accordance with their molecular formulae. In ^{1}H NMR spectra, the pyrimidine attached isopropyl protons were appeared as, doublet at about δ 1.3 and septet at about δ 3.2 to 3.3, two singlets at about δ 3.7 and δ 3.5 in all derivatives. The other aromatic protons were observed as two double doublets at δ 7.65 – 7.45 and δ 6.95 – 7.05 with respective ortho and meta fluorine couplings, in all the synthesized compounds with four protons. Similarly in ^{13}C NMR spectra of all synthesized compounds, aromatic carbon peaks were observed at about δ 165 – 162, 133, 130, 115 with respective fluorine couplings and the aliphatic carbons corresponding to N-CH_3, SO_2CH_3, isopropyl peaks at about δ 42, 33, 32 and 21 respectively. The physical characteristic of the newly synthesized compounds were represented in Table 1.

2.2. Antimicrobial activity

The antimicrobial activity of newly synthesized compounds **11(a-k)** was determined by well plate method [13-14] in nutrient agar (antibacterial activity) and Sabouraud dextrose agar (antifungal activity). All the compounds were evaluated for their *in vitro* antimicrobial activity against *Bacillus subtilis* (MTCC-1789)*, Bacillus pumilus* (ATCC-7061)*, Escherichia coli* (ATTC-25922), and *Pseudomonas aeruginosa* (ATTC-27853), and antifungal activity against *Aspergillus niger* (MTCC-1781), *Colletotrichum arachidis* (BCRC-35277) and *Fusarium verticilloides* (FGSC-7600). Ciprofloxacin and Clotrimazole were used as standard drugs for bacteria and fungi respectively. Preliminary screening for the test compound and standard drugs were performed at fixed concentrations of 400 µg / mL. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 72 h for fungi. Each experiment was repeated twice. Based on the results of zone of inhibition, the minimum inhibitory concentration (MIC) of potent compounds **11(a-k)** against all bacterial and fungal strains was determined by two fold dilution method. Stock solutions of tested compounds with 400, 200, 100, 50, 25, 12.5 and 6.25 µg/mL concentrations were prepared with DMSO as solvent. Inoculums of the bacterial and fungal

culture were also prepared. To a series of tubes containing 1 mL each of test compound solution with different concentrations and 0.2 mL of the inoculums was added.

Table 1. Physical characterization data of compounds **11**(**a-k**)

Comp Code	R	Molecular formula	Mol. Wt.	M.P (^{0}C)	Yield (%)
11a		$C_{23}H_{22}FN_5O_3S$	467	194	73
11b		$C_{23}H_{21}FN_5O_3SBr$	546	155	70
11c		$C_{23}H_{21}FN_5O_3SBr$	546	177	75
11d		$C_{23}H_{21}FN_5O_3SCl$	501	182	80
11e		$C_{23}H_{21}FN_5O_3SCl$	501	165	72
11f		$C_{23}H_{21}F_2N_5O_3S$	485	265	65
11g		$C_{23}H_{21}F_2N_5O_3S$	485	186	72
11h		$C_{23}H_{21}FN_6O_5S$	512	155	70
11i		$C_{23}H_{21}FN_6O_5S$	512	205	85
11j		$C_{23}H_{23}FN_6O_4S$	498	199	64
11k		$C_{23}H_{23}FN_6O_4S$	498	242	85

Further 3.8 mL of the sterile water was added to each of the test tubes. These test tubes were incubated for 24 h at 37 °C and observed for the presence of turbidity. This method was repeated by changing test compounds with standard drugs Ciprofloxacin and Clotrimazole for comparison. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values. The comparison of the MICs (in μg/mL) of potent compounds and standard drugs against tested strains are presented in Table 2. Similarly the MIC for antifungal activity was determined using 72 h old broth culture. The results were compared with Clotrimazole and summarized in Table 2. Minimum inhibitory concentration (MIC) of all compounds was determined, which is defined as the lowest concentration of inhibitor at which bacterial growth was not visually apparent.

Investigation on antibacterial screening data (Table 2) showed some of the compounds were active against four human pathogenic bacteria. The results of antimicrobial activity of newly synthesized compounds **11(a-k)** reveals that out of eleven compounds, seven compounds were found to have good antibacterial activity and only five compounds showed good antifungal activity. Among these compounds the **11c, 11d, 11e, 11h, 11i, 11j** and **11k** were active against the bacterial strains and only the compound **11e** active against the all four bacterial strains where as the **11h** was found to be active against the *Bacillus subtilis, Bacillus pumilus* and *Pseudomonas aeruginosa.* The compound **11d** showed good activity against two organisms *Bacillus subtilis* and *Pseudomonas aeruginosa*. From the antifungal activity data it was clear that among the thirteen tested compounds only four compounds **11f, 11g, 11h** and **11j,** showed good antifungal activity, the compound **11f** was the only compound to show good activity against all three fungal strains**.**

Table 2. Minimum inhibitory concentration data for the compounds **11a-k**

Compounds	Minimum Inhibitory concentration (MIC) in μg / mL						
	Antibacterial activity				Antifungal activity		
	B.subtilis	***B.pumilus***	***E.coli***	***P.aeruginosa***	***A.niger***	***C.arachidis***	***F.verticilloides***
11a	200	100	100	400	200	12.5	12.5
11b	50	25	25	400	50	200	200
11c	12.5	50	25	25	50	100	100
11d	12.5	25	25	12.5	12.5	400	400
11e	12.5	12.5	12.5	12.5	50	100	50
11f	100	50	50	50	12.5	12.5	12.5
11g	400	400	200	200	12.5	50	25
11h	12.5	12.5	50	12.5	25	25	25
11i	25	12.5	25	12.5	200	200	100
11j	25	50	12.5	50	12.5	25	25
11k	25	50	12.5	50	50	25	25
Ciprofloxacin	6.25	6.25	6.25	6.25	-	-	-
Clotrimazole	-	-	-	-	6.25	6.25	6.25
DMSO	-	-	-	-	-	-	-

2.3. Anti-inflammatory activity

Anti-inflammatory activity was assessed by the method described by Winter *et al* [15]. Albino rats of either sex weighing 200-250 g were divided in 14 groups (N=6). Group-1 received 2% acacia gum suspension (control), Group-2 received 0.1 ml of 1% carrageenan suspension in normal saline (Toxicant control), Group-3 received Ibuprofen (reference standard 40 mg/kg, P.O) and group 4 to 14 were given the compounds **11(a-k)** (200 mg/kg p.o) in 2% acacia gum suspension. The standard Ibuprofen and synthesized compounds under study were administered orally to all rats. After 30 minutes 0.1 ml of 1% carrageenan suspension in normal saline was injected into the sub plantar region of the left hind paw of each rat to induce oedema. The oedema volumes of the injected paw were measured at 1st, 2nd, 3rd and 4th hour. The difference between the paw volumes of treated animals were compared with that of the control group and the mean edema volume was calculated. From the data obtained mean volume of oedema ± SEM and percentage reduction in oedema were calculated. Percentage reduction or inhibition in oedema volume was calculated by using the formula.

Percentage reduction in oedema volume was calculated by using the formula,

$$\text{Percentage reduction} = \frac{V_0 - Vt}{V_0} \times 100$$

Where

V_0 = Volume of the paw of control at time t

V_t = Volume of the paw of drug treated at time t

From the data obtained the mean edema volume and percentage reduction in oedema was calculated and the results were summarized in the Table 3.

2.4. Statistical analysis

Data analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. $P < 0.05$ was considered statistically significant.

The results of carrageenan induced rat paw oedema model indicated that all the synthesized compounds showed moderate to good anti-inflammatory activity. Out of all the synthesized compounds **11b, 11d, 11f** and **11h** showed highly significant good anti-inflammatory activity, whereas the compounds **11a, 11e** and **11j** showed moderate activity when compared with that of standard ibuprofen.

3. Conclusion

In conclusion, a series of novel pyrimidine substituted 1,3,4-oxadiazole derivatives.(**11a-k**) were synthesized and their antimicrobial and antiinflammatory activities were evaluated. The antimicrobial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested microorganisms. Among the newly synthesized compounds, **11c, 11d, 11e, 11h, 11i, 11j** and **11k** showed the most promising antibacterial activity and the compounds **11f, 11g, 11h** and **11j** showed promising antifungal activity. Whereas the anti inflammatory activity data suggest that the newly synthesized compounds showed moderate to equipotent anti inflammatory activity when compared to standard employed for the study. The compounds **11b, 11d, 11f** and **11h** showed good activity, whereas the compounds **11a, 11e** and **11j** showed moderate activity. Hence the fact that the compounds prepared in this study are chemically

unrelated to the current medication, suggests that further work with similar analogues is clearly warranted.

4. Experimental

4.1. General

All the reagents were purchased from Aldrich, Merck and SD fine (India), used as received, solvents were supplied by Qualligens fine chemicals, India. All the chemical reactions were performed under nitrogen atmosphere using standard techniques. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 spectrophotometer. ^{1}H NMR chemical shift values were reported on the scale in δ (ppm) relative to TMS (δ = 0.0) and ^{13}C NMR chemical shift values were reported relative to $CDCl_3$ (δ = 77.0). IR spectra were recorded on Perkin Elmer spectrum 100 FT-IR model. Column chromatography was performed with silica gel 60-120 mesh (Merck, Mumbai, India.). All the compounds were routinely checked for their reaction on silica gel 60 F254 TLC plates and their spots were visualized by exposing them to UV lamp or iodine vapor or $KMnO_4$ reagents. MS/MS part of the system contained API-2000 system (Sciex, Applied Bio-Systems, Canada). Yield reported was the isolated yield after purification of the compounds.

4.2 Synthesis

The compounds **3-9** were synthesized by following the reported procedure [11-12].

4.2.1. Procedure for the preparation of compound 10

The compound **9** (0.1 mol) and ethanol (50 ml) were placed in a round bottom flask fitted with reflux condenser and added hydrazine hydrate (99 %, 4.26 g, 0.3 mol) drop wise with stirring. The reaction mixture was heated under reflux for 18 h, cooled and poured onto the mixture of ice and water with stirring. The solid product thus separated was collected by filtration, washed with water and dried. Pale brown solid; yield: 85%; m.p: 132 °C; IR(KBr): 2952, 1552, 1512, 1437, 1351, 1278, 1121, 985, 773 cm^{-1}; Mass (ESI) m/z: 382.1 $(M+H)^{+}$; ^{1}H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.62 (brs, 1H, O=C-NH), 7.59 – 7.55 (dd, J_{H-F} = 4.82 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.33 – 7.28 (dd, J_{H-F} = 9.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 4.34 (brs, 2H, NH_2), 3.58 (s, 3H, -N-CH_3), 3.36 (s, 3H, -SO_2CH_3), 3.11 – 3.04 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.20 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 180.3, 166.8, 165.1, 164.8 & 158.3 (J_{C-F} = 250 Hz), 161.2, 135.12 & 135.09 (J_{C-F} = 3 Hz), 132.8 & 132.6 (J_{C-F} = 15 Hz), 114.0 & 113.5 (J_{C-F} = 25 Hz), 113.2, 38.9(CH_3-S), 33.1(CH, isopropyl), 30.1(CH_3-N), 21.7 (CH_3-isopropyl).

4.2.2. General procedure for the preparation of compound 11(a-k)

The compound **10** (0.1 mol) and appropriate benzoic acid (0.1 mol) in $POCl_3$ (25 ml) were placed in a round bottom flask fitted with reflux condenser. The reaction mixture was refluxed for 15-18 h, after completion of reaction, cooled and added to the mixture of ice and cold water with vigorous stirring. The obtained solid product was filtered and washed with water until the filtrate is neutral. The crude compound was purified by column chromatography using silica gel 60-120 and eluting with hexane: ethyl acetate mobile phase to get the pure compounds (yields 64-85 %).

Table 3. Anti-inflammatory activity of synthesized compounds **11(a-k)** in carrageenan induced (acute) paw oedema model in rats.
Animal: Albino rats Route: p.o.

Group	Treatment	Dose mg/kg	Oedema volume and percentage reduction in oedema volume at							
			1 h		2 h		3 h		4 h	
			Mean ±SEM	% ROV	Mean ±SEM	% ROV	Mean ±SEM	% ROV	Mean ± SEM	% ROV
1	Toxicant control	0.1 mL (1%w/v)	1.17±0.08**	-	1.23±0.05**	-	1.28 ±0.08**	-	1.35±0.05**	-
2	Standard Ibuprofen.	40	1.01±0.08ns	13.67	1.13±0.05ns	8.13	1.05 ±0.05**	17.96	1.01 ±0.05**	25.18
3	**11a**	200	1.12±0.10ns	4.27	1.15 ±0.10ns	6.50	1.12 ±0.11**	12.50	1.05 ±0.08**	**22.22**
4	**11b**	200	1.13±0.05**	3.41	1.23±0.05ns	0.00	1.13 ±0.10*	11.71	1.03 ±0.08**	**23.70**
5	**11c**	200	1.14±0.09**	2.56	1.14 ±0.08ns	7.31	1.22±0.08ns	4.68	1.12 ±0.08**	17.03
6	**11d**	200	1.12±0.05ns	4.27	1.15 ±0.05ns	6.50	1.10 ±0.06**	14.06	1.03 ±0.05**	**23.70**
7	**11e**	200	1.08±0.08ns	7.69	1.20 ±0.06ns	2.43	1.13 ±0.08*	11.71	1.05 ±0.05**	**22.22**
8	**11f**	200	1.03±0.05**	11.96	1.23 ±0.05ns	0.00	1.13 ±0.10*	11.71	1.03 ±0.08**	**23.70**
9	**11g**	200	1.14±0.08**	2.56	1.14 ±0.08ns	7.31	1.22±0.08ns	4.68	1.10 ±0.09**	18.51
10	**11h**	200	1.03 ±0.09*	11.96	1.20±0.06ns	2.43	1.10 ±0.06**	14.06	1.03 ±0.05**	**23.70**
11	**11i**	200	1.03 ±0.11*	11.96	1.23 ±0.10ns	0.00	1.15 ±0.05*	10.15	1.07 ±0.05**	20.74
12	**11j**	200	1.14±0.06**	2.56	1.17 ±0.10ns	4.87	1.17±0.08ns	8.59	1.05 ±0.05**	**22.22**
13	**11k**	200	1.10±0.05**	5.98	1.15±0.05ns	6.50	1.18±0.08ns	7.81	1.07 ±0.08**	20.74

n=6 ns (non significant) significant at P<0.05* and 0.01**. Toxicant control compared with normal control. Standard and synthesized compounds compared with toxicant control. ROV – Reduction in paw oedema volume.

2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-5-phenyl-1,3,4-oxadiazole (11a): White solid; yield: 73%; m.p: 194 °C; IR(KBr): 2970, 1597, 1543, 1445, 1386, 1239, 1156, 956, 711 cm^{-1}; Mass (ESI) m/z: 468.1$(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) ; 7.87 - 7.85 (m, 2H, Ar-H), 7.56 – 7.52 (m, 3H, Ar-H), 7.50 – 7.46 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.05 – 7.01 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.66 (s, 3H, -N-CH_3), 3.57 (s, 3H, -SO_2CH_3), 3.29 – 3.26 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.32 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.8, 165.7, 165.5, 165.2 & 162.7 (J_{C-F} = 250 Hz), 161.3, 159.6, 133.28 & 133.24 (J_{C-F} = 4 Hz), 132.1, 130.89 & 130.81 (J_{C-F} = 8 Hz), 129.1, 126.8, 123.1, 115.95 & 115.73 (J_{C-F} = 22 Hz), 109.1, 42.5(CH_3-S), 33.3(CH, isopropyl), 33.2(CH_3-N), 21.8 (CH_3-isopropyl).

2-(2-bromophenyl)-5-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11b): Pale brown solid; yield: 70%; m.p: 155 °C; IR(KBr): 2962, 1567, 1534, 1464, 1380, 1249, 1126, 972, 799 cm^{-1} Mass (ESI) m/z: 546.1: 548.1 (1:1 ratio Bromo pattern) $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.07 – 8.05 (m, 1H, Ar-H), 7.60 – 7.55 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.21 – 7.18 (m , 1H, Ar-H), 7.08 – 7.04 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 6.95 – 7.01 (m, 2H, Ar-H), 3.61 (s, 3H, -N-CH_3), 3.55 (s, 3H, -SO_2CH_3), 3.30 – 3.25 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.28 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.6, 165.4, 165.2 & 162.7 (J_{C-F} = 250 Hz), 164.6, 161.4, 159.7, 133.9, 132.87 & 132.84 (J_{C-F} = 3 Hz), 131.8, 130.89 & 130.81 (J_{C-F} = 8 Hz), 128.8, 128.6, 125.1, 122.6, 113.95 & 113.74 (J_{C-F} = 21 Hz), 108.5, 41.8(CH_3-S), 33.2(CH, isopropyl), 33.1(CH_3-N), 21.7(CH_3-isopropyl).

2-(4-bromophenyl)-5-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl sulphonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11c): Brown solid; yield: 75%; m.p: 177 °C; IR(KBr): 2974, 1576, 1543, 1446, 1382, 1247, 1156, 960, 792 cm^{-1}; Mass (ESI) m/z: 546.1: 548.1 (1:1 ratio Bromo pattern) $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 7.70 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.53 – 7.49 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.4 Hz, 2H, Ar-H), 7.05 – 7.01 (dd, J_{H-F} = 8.0 Hz, J_{H-H} = 8.4 Hz, 2H, Ar-H), 3.66 (s, 3H, -N-CH_3), 3.56 (s, 3H, -SO_2CH_3), 3.30 – 3.26 (sep, *J* = 6.8 Hz, 1H, isopropyl –CH), 1.31 (d, *J* = 6.8 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.8, 165.6, 165.2 & 162.7 (J_{C-F} = 250 Hz), 164.7, 161.5, 159.6, 133.28 & 133.24 (J_{C-F} = 4 Hz), 132.5, 130.84 & 130.75 (J_{C-F} = 9 Hz), 128.1, 126.8, 122.0, 115.95 & 115.74 (J_{C-F} = 21 Hz), 108.8, 42.4(CH_3-S), 33.2 (CH, isopropyl), 33.1(CH_3-N), 21.8(CH_3-isopropyl).

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2-(2-chlorophenyl)-5-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11d): Off white solid; yield: 80%; m.p: 182 °C; IR(KBr): 2970, 1523, 1472, 1328, 1274, 1163, 953, 815 cm^{-1}; Mass (ESI) m/z: 502.2 : 504.2 (3:1 ratio Chloro pattern) $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.16 – 8.14 (m, 1H, Ar-H), 7.80 - 7.78 (m, 1H, Ar-H), 7.55 – 7.50 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.27 – 7.24 (m, 2H, Ar-H), 7.04 – 6.99 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.61 (s, 3H, -N-CH_3), 3.52 (s, 3H, -SO_2CH_3), 3.28 – 3.21 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.30 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.1, 166.7, 165.22 & 162.71 (J_{C-F} = 250 Hz), 162.6, 157.6, 138.4, 134.4, 133.25 & 133.21 (J_{C-F} = 3 Hz), 131.4, 131.2, 130.76 & 130.68 (J_{C-F} = 8 Hz), 128.2, 127.9, 125.9, 115.76 & 115.55 (J_{C-F} = 21 Hz), 108.2, 42.3(CH_3-S), 33.5(CH, isopropyl), 33.4(CH_3-N), 21.6(CH_3-isopropyl).

2-(4-chloro phenyl)-5-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11e): Off white solid; yield: 72%; m.p: 165 °C; IR(KBr): 2975, 1543, 1446, 1382, 1247, 1157, 960, 805 cm^{-1}; Mass (ESI) m/z: 502.2 : 504.2 (3:1 ratio Chloro pattern) $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 7.77 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.53 – 7.50 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.05 – 7.01 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.66 (s, 3H, -N-CH_3), 3.56 (s, 3H, -SO_2CH_3), 3.31 – 3.25 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.32 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.8, 165.7, 165.22 & 162.71 (J_{C-F} = 250 Hz), 164.7, 161.5, 159.6, 138.4, 133.25 & 133.22 (J_{C-F} = 3 Hz), 130.86 & 130.78 (J_{C-F} = 8 Hz), 129.5, 128.0, 121.5, 115.96 & 115.75 (J_{C-F} = 21 Hz), 108.9, 42.4(CH_3-S), 33.2(CH, isopropyl), 33.0(CH_3-N), 21.8(CH_3-isopropyl).

2-(2-fluoro phenyl)-5-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11f): Pale cream solid; yield: 65%; m.p: 216 °C; IR(KBr): 2971, 1545, 1445, 1372, 1246, 1137, 942, 775 cm^{-1}; Mass (ESI) m/z: 486.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.24 – 8.21 (dd, J_{H-F} = 4.8 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 8.15 – 8.11 (m, 1H, Ar-H), 7.64 – 7.58 (m, 1H, Ar-H), 7.56 – 7.52 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.37 – 7.32 (m, 2H, Ar-H), 3.61 (s, 3H, -N-CH_3), 3.41 (s, 3H, -SO_2CH_3), 3.25 – 3.20 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.28 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 180.8, 178.0, 169.2, 164.65 & 162.13 (J_{C-F} = 252 Hz), 162.6, 161.64 & 159.14 (J_{C-F} = 250 Hz), 157.6, 143.36 & 143.32 (J_{C-F} = 4 Hz), 132.87 & 132.72 (J_{C-F} = 15 Hz), 132.24 & 132.06 (J_{C-F} = 18 Hz), 130.73 & 130.56 (J_{C-F} = 17 Hz), 128.0, 124.85 & 124.74 (J_{C-F} = 11 Hz), 117.02 & 116.81 (J_{C-F} = 21 Hz), 113.95 & 113.74 (J_{C-F} = 21 Hz), 110.28 & 110.01 (J_{C-F} = 27 Hz), 42.8(CH_3-S), 33.1(CH, isopropyl), 32.9(CH_3-N), 22.4(CH_3-isopropyl).

2-(4-flouro phenyl)-5-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11g): Cream solid; yield: 72%; m.p: 186 °C; IR(KBr): 2970, 1602, 1539, 1443, 1384, 1237, 1157, 956, 783 cm^{-1}; Mass (ESI) m/z: 486.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 7.84 – 7.80 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.51 – 7.48 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.16 – 7.12 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.03 – 6.98 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.63 (s, 3H, -N-CH_3), 3.54 (s, 3H, -SO_2CH_3), 3.27 – 3.23 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.29 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 179.0, 177.8, 166.18 & 163.66 (J_{C-F} = 252 Hz), 165.6, 165.18 & 162.68 (J_{C-F} = 250 Hz), 161.3, 159.6, 133.24 & 133.21 (J_{C-F} = 3.1 Hz), 130.85 & 130.76 (J_{C-F} = 9 Hz), 129.14 & 129.06 (J_{C-F} = 9 Hz), 119.46 & 119.42 (J_{C-F} = 3.1 Hz), 116.65 & 116.43 (J_{C-F} = 21.7 Hz), 115.93 & 115.71 (J_{C-F} = 21.7 Hz), 108.9, 42.4(CH_3-S), 33.2(CH, isopropyl), 33.1(CH_3-N), 21.8(CH_3-isopropyl).

2-(2- nitro phenyl)-5-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-1,3,4-oxadiazole (11h): Yellow solid; yield: 70%; m.p: 155 °C; IR(KBr): 2945, 1736, 1577, 1456, 1380, 1236, 1125, 975, 804 cm^{-1} Mass (ESI) m/z: 502.2 : 513.1 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.64 – 8.61 (m, 1H, Ar-H), 7.83 - 7.80 (m, 1H, Ar-H), 7.57 – 7.53 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.45 – 7.40 (m, 2H, Ar-H), 7.07 –7.01 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.69 (s, 3H, -N-CH_3), 3.55 (s, 3H, -SO_2CH_3), 3.29 – 3.22 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.31 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 176.7, 165.8, 165.26 & 162.74 (J_{C-F} = 250 Hz), 163.2, 162.7, 158.5, 149.7, 134.21 & 134.18 (J_{C-F} = 3 Hz), 134.3, 132.72 & 132.63 (J_{C-F} = 9 Hz), 131.5, 128.2, 125.5, 125.1, 116.05 & 115.83 (J_{C-F} = 21 Hz), 108.3, 41.9(CH_3-S), 32.1(CH, isopropyl), 32.0(CH_3-N), 21.4(CH_3-isopropyl).

2-(4-nitro phenyl)-5-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl) -1,3,4-oxadiazole (11i): Yellow solid; yield: 85%; m.p: 205 °C; IR(KBr): 2930, 1726, 1577, 1529, 1446, 1380, 1250, 1155, 959, 804 cm^{-1}; Mass (ESI) m/z: 513.1 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.34 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.02 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.53 – 7.50 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.06 – 7.02 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 3.67 (s, 3H, -N-CH_3), 3.57 (s, 3H, -SO_2CH_3), 3.32 – 3.28 (sep, *J* = 6.4 Hz, 1H, isopropyl –CH), 1.33 (d, *J* = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.9, 165.8, 165.25& 162.75 (J_{C-F} = 250 Hz), 163.7, 162.5, 159.7, 149.7, 133.22 & 133.19 (J_{C-F} = 3.1 Hz), 130.85 & 130.76 (J_{C-F} = 8.5 Hz), 128.5, 127.7, 124.4, 116.05 & 115.83 (J_{C-F} = 21.7 Hz), 108.4, 42.5(CH_3-S), 33.3(CH, isopropyl), 33.2(CH_3-N), 21.8(CH_3-isopropyl).

2-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-5-(2-methoxy pyridin-3-yl)-1,3,4-oxadiazole (11j): Pale yellow solid; yield: 64%; m.p: 199 °C; IR(KBr): 2969, 1542, 1501, 1425, 1371, 1263, 1146, 972, 825 cm^{-1}; Mass (ESI) m/z: 499.2 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.32 (dd, *J* = 5.6, 1.2 Hz, 1H, Ar-H), 8.04 (dd, *J* = 4.9, 1.2 Hz, 1H, Ar-H), 7.60 – 7.64 (dd, J_{H-F} = 5.2 Hz, J_{H-H} = 8.8 Hz, 2H, Ar-H), 7.05 – 7.01 (dd, J_{H-F} = 8.4 Hz, J_{H-H} = 8.8 Hz, 2H,

Ar-H), 6.90 (dd, J = 5.6, 4.9 Hz, 1H, Ar-H), 3.96 (s, 3H, -O-CH_3), 3.64 (s, 3H, -N-CH_3), 3.56 (s, 3H, -SO_2CH_3), 3.27 – 3.20 (sep, J = 6.4 Hz, 1H, isopropyl –CH), 1.28 (d, J = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 178.0, 171.3, 165.25& 162.75 ($J_{C\text{-}F}$ = 250 Hz), 162.6, 159.7, 157.6, 147.5, 143.36 & 143.33 ($J_{C\text{-}F}$ = 3.1 Hz), 132.1, 131.71 & 131.62 ($J_{C\text{-}F}$ = 9 Hz), 128.2, 122.9, 113.95 & 113.74 ($J_{C\text{-}F}$ = 21 Hz), 108.7, 54.5, 41.6(CH_3-S), 33.1(CH, isopropyl), 33.0(CH_3-N), 21.8(CH_3-isopropyl).

2-(4-(4-fluoro phenyl)-6-isopropyl-2-(*N*-methyl sulfonamide) pyrimidin-5-yl)-5-(2-methoxy pyridin-4-yl)-1,3,4-oxadiazole (11k): Pale yellow solid; yield: 85%; m.p: 242 °C; IR(KBr): 2973, 1569, 1541, 1450, 1384, 1240, 1157, 961, 853 cm^{-1}; Mass (ESI) m/z: 499.2 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$): (δ/ppm) 8.30 (d, J = 5.6 Hz, 1H, Ar-H), 7.48 – 7.51 (dd, $J_{H\text{-}F}$ = 5.2 Hz, $J_{H\text{-}H}$ = 8.8 Hz, 2H, Ar-H), 7.31 (d, J = 5.6 Hz, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 7.06 – 7.01 (dd, $J_{H\text{-}F}$ = 8.4 Hz, $J_{H\text{-}H}$ = 8.8 Hz, 2H, Ar-H), 3.97 (s, 3H, -O-CH_3), 3.66 (s, 3H, -N-CH_3), 3.57 (s, 3H, -SO_2CH_3), 3.28 – 3.21 (sep, J = 6.4 Hz, 1H, isopropyl –CH), 1.32 (d, J = 6.4 Hz, 6H, isopropyl 2XCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): (δ/ppm) 177.8, 165.8, 165.25& 162.75 ($J_{C\text{-}F}$ = 250 Hz), 164.7, 163.7, 162.3, 159.7, 148.4, 133.16 & 133.13 ($J_{C\text{-}F}$ = 3.1 Hz), 132.6, 130.81 & 130.72 ($J_{C\text{-}F}$ = 8.5 Hz), 116.04 & 115.82 ($J_{C\text{-}F}$ = 21.7 Hz), 113.2, 109.9, 108.6, 108.2, 53.9, 42.5(CH_3-S), 33.3(CH, isopropyl), 33.2(CH_3-N), 21.8(CH_3-isopropyl).

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References

[1] Yale, H. L.; Losee, K. 2-Amino-5-substituted 1,3,4-oxadiazoles and 5-imino-2-substituted Δ^2-1,3,4-oxadiazolines. A group of novel muscle relaxants, *J. Med. Chem.* **1966**, *9*, 478–483.

[2] Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. Design, synthesis and anti-inflammatory activity of some 1,3,4-oxadiazole derivatives, *Eur. J. Med. Chem.* **1996**, *31*, 819–825.

[3] Tan, T. M. C.; Chen, Y.; Kong, K. H.; Bai, J.; Li, Y.; Lim, S. G.; Ang, T. H.; Lam, Y. Synthesis and the Biological evaluation of 2-benzenesulfonyl alkyl-5-substituted-sulfanyl-(1,3,4)-oxadiazoles as potential anti-hepatitis B virus agents, *Antiviral Res.* **2006**, *71*, 7–14.

[4] Adelstein, G. W.; Yen, C. H.; Dajani, E. Z.; Bianchi, R. G. 3,3-Diphenyl-3-(2-alkyl-1,3,4-oxadiazol-5-yl)propylcycloalkylamines, a novel series of antidiarrheal agents, *J. Med. Chem*. **1976**, *19*, 1221-1225.

[5] Jha, K. K.; Samad, A.; Kumar, Y.; Shaharyar, M.; Khosa, R.; Jain, J.; Bansal, S. 3D QSAR Studies of 1,3,4-oxadiazole derivatives as antimycobacterial agents, *Iranian J. Pharm. Res.* **2009**, *8*, 163-167.

[6] Macaev, F.; Rusu, G.; Pogrebnoi, S.; Gudima, A.; Stingaci, E.; Vlad, L.; Shvets, N.; Kandemirli, F.; Dimoglo, A.; Reynolds, R.. Synthesis of novel 5-aryl-2-thio-1,3,4-oxadiazoles and the study of their structure-anti-mycobacterial activities, *Bioorg. Med. Chem.* **2005**, *13*, 4842-4850.

[7] Navarrete-Vazquez. G.; Molina-Salinas G. M.; Duarte-Fajardo, Z. V.; Vargas-Villarreal, J.; Estrada-Soto, S.; Gonzalez-Salazar, F.; Hernandez-Nunez, E.; Said-Fernandez, S. Synthesis and antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines, *Bioorg. Med. Chem.* **2007**, *15*, 5502-5508.

[8] Zarghi, A.; Tabatabai, S. A.; Faizi, M.; Ahadian, A.; Navabi, P.; Zanganeh, V.; Shafiee, A. Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1863-1865.

[9] Jin, L.; Chen, J.; Song, B.; Chen, Z.; Yang, S.; Li, Q.; Hu, D.; Xu, R. Synthesis, structure, and bioactivity of N′-substituted benzylidene-3,4,5-trimethoxybenzohydrazide and 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5036-5040.

[10] Sawant, R.; Lanke, P.; Jadhav, G.; Bhangale, L. QSAR analysis of structurally similar 1,3,4-oxadiazoles as enzyme tyrosinase inhibitors, *Drug Invention Today.* ***2010****, 2, 169-172.*

[11] Hirai, K.; Ishiba, T.; Koike, H.; Watanabe, M. Pyrimidine derivatives as HMG-CoA reductase inhibitors. *US Patent*, **1993,** 5260440**.** *Chem. Abstr.* **1993,** *118*, 254949.

[12] Ramesh, D.; Sambhu Prasad Sarma, M,; Narayan KASS, G.; Sukumar, N.; Sunil Kumar, B.; Gangadhar Bhima Shankar, N.; Sivakumaran,M.S. An improved process for preparing rosuvastatin calcium. *WO Patent* **2008**, 053334. *Chem. Abstr*. **2008**, *148*, 537968.

[13] Cruickshank, R.; Duguid, J. P.; Marmion, B. P.; Swain, R. H. A. Tests for sensitivity to antimicrobial agents, *Medical Microbiology* 12th Ed., Vol. *2*, **1975**, 196-197.

[14] Drago, L.; Mombelli, B.; Ciardo, G.; De Vecchi, E. Gismondo M. R. Effects of three different fish oil formulations on Helicobacter pylori growth and viability in in-vitro study, *J. Chemotherapy.* **1999**, *11*, 207-210.

[15] Winter, C. A; Risley, E. A, Nuss, G. W. Anti-inflammatory and antipyretic activities of indomethacin. l-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-indoie-3-acetic acid, *J. Pharmacol. Exp. Ther.* **1963,** *141*, 369-376.