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ENVIRONMENTALLY BENIGN PROTOCOL FOR THE SYNTHESIS OF SOME NOVEL OXADIAZINANE-4-THIONE DERIVATIVES AS PROMISING AGENT IN BILIARY TRACT DISORDERS TREATMENT

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ABSTRACT

Heterocycles containing nitrogen and oxygen have received significant attention because of the unique chemical as well as physical properties of different heterocyclic compounds. Six- membered heterocyclic rings with three hetero atoms are not found widely in the nature, but they have a superfine applications in the most important fields such as medical, as well as agriculture. Oxadiazine compounds are considered to be a supreme type of this family. The aim of the present study was to evaluate biological activity of the newly synthesized [1,3,5]-oxadiazine derivatives. Here we present a protocol for the synthesis of some novel oxadiazinane-4-thione derivatives where the 1,3-dibenzylthiourea [I] was reacted with different substituted aldehydes [II](a-j) by irradiation with microwaves (40% 280 watts) in scientific microwave oven to give different 3,5-disubstituted-2,6-diphenyl-[1,3,5] oxadiazinane-4-thione derivatives. The results clearly demonstrated a high efficiency of the microwave oven systems achieved in the chemical processes. The structures of all these compounds have been confirmed by IR, ^{1}HNMR, mass spectral data and elemental analysis. Library of such oxadiazinane-4-thione derivatives has been generated and the structures were subjected to PASS for their probabilities of being active biologically. Biliary tract disorders treatment, Aspulvinone dimethylallyl transferase inhibitor activities were predicted by PASS. QSAR study of the library was done to find out most active molecules.

KEYWORDS: Oxadiazinane-4-thione, Biological Prediction Study, Microwave Irradiation.

INTRODUCTION

Oxadiazines are interesting[1] and promising heterocyclic compounds. A diversity of biological effects is associated with oxadiazines bearing hetero atoms at 1, 2, 4 or 1,3,4 positions. 6H-1, 2, 4-oxadiazine-3, 5-(2H, 4H)-dione, the 6-oxa analogue of uracil, has been shown to significantly inhibit growth in several bacterial strains while not being highly inhibitory to mammalian cells.[2] 1, 3, 4-Oxadiazine derivatives exhibit cardiovascular, antibacterial, plant growth regulating, miticidal and nematocidal, acricidal, insecticidal and anticonvulsive activities.[3,4] In addition, oxadiazines are useful intermediates in the synthesis of tenidap prodrugs or β-lactam antibiotics, in particular into the synthesis of carbapenems and penems.[5,6] The invention relates to an optically active form of a pyridyl-4H-1, 2, 4-oxadiazine derivative[7], to the therapeutical use there of and to a pharmaceutical compositions containing the compound as active ingredient.

The nitrogen atom of thiourea derivatives reacts with various substituted aromatic aldehyde, where formation of oxadiazinane-thione[8] could occur by the nucleophilic attack of urea nitrogen on substituted aldehyde followed by dehydration.

PASS

Each biologically active compound reveals a wide variety of biological actions in biological systems (human organisms, animals, in vivo and in vitro assays). It is practically impossible to study each compound in all tests currently available. Therefore, the ability to select compounds with required types of biological activity and without unwanted adverse effects and toxicity is very desirable.

The software PASS (Prediction of Activity Spectra for Substances) by Pharma Expert was developed towards this purpose. PASS predicts biological activity spectra on the basis of structural formulae of chemical compounds. The biological activity of compounds is predicted on the basis of structure-activity relationships of known biological active substances presented in the training set. PASS 1.602 training set includes 45649 substances. PASS 1.602 can predict 1043 different types of biological activities including pharmacological effects, biochemical mechanisms, carcinogenicity, mutagenicity and teratogenicity. The mean prediction of accuracy in leave one out cross-validations of PASS is about 85%.

Pharma Expert determines the existing relationships between pharmacological effects and biochemical mechanisms. The current version of Pharma Expert covers 1587 mechanisms of action, 418 pharmaco-therapeutical effects and 2664 types of relationships between them.

PASS by Pharma Expert can give you an early indication, obtained cheap and fast if your compound might be a good or bad drug candidate.

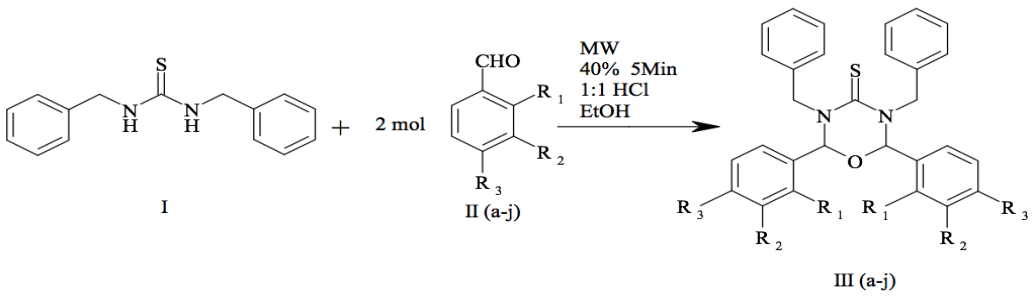
MATERIALS AND METHODS

Purity of the compounds were checked by TLC on silica- G plates. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO with TMS as internal standard on a Bruker spectrophotometer at 200 MHz. LC-MS of selected samples was taken on LC-MSD-Trap-SL_01046. QSAR studies have been carried out using computer programme PASS.

General Synthesis of 1, 3-Dibenzylthiourea

Benzyl amine 2.14 g (0.01 mole) was mixed with carbon disulphide0.76 g (0.01 mole)by careful adding with constant stirring to get white crystalline 1,3-dibenzylthiourea.[I] IR spectrum of 1,3-dibenzylthiourea shows significant characteristic absorption band in the region of ν_{max} 1107 (C=S), 3230 (>NH) cm^{-1}. ^{1}HNMR (DMSO): δ 4.70-4.72(s, 4H,N-CH_2-Ar),6.55(bs,2H-NH-), 7.28-7.36(m,10H, Ar-H) ppm. In mass spectrometry of 1,3-dibenzylthiourea (m/z): (M+) was observed at 256.1 which confirms the molar mass of the product with molecular formula $C_{15}H_{16}N_2S$. Elemental Analysis: found C, 70.70; H, 6.36; N, 11.03; S, 12.45; requires C,70.27; H, 6.29; N, 10.93; S, 12.51 %); m.p.146-148 ^oC .

General Synthesis of 3,5-Dibenzyl-2,6-bis-(4-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione III (a): 1,3-Dibenzylthiourea [I] 0.256 g, (0.001 mol) and 4-chlorobenzeldehyde II (a) 0.140 g (0.002 mol) were mixed in ethanol (15 mL) in 50 mL RBF, 1:1 HCl (1 ml) was added and the reaction mixture was irradiated with microwaves at 40% microwave power (140 W) for 5 mins. The reaction mixture was cooled and neutralized with NaOH to obtain the product. The separated product was filtered, washed with ethanol (5 mL) and recrystallized from ethanol. m.p. 230 ^oC, yield (78 %).



Scheme-I

Table-1: General characteristics and elemental analysis data of the compounds III (a-j)

Product	R_1	R_2	R_3	Time (in min.)	Yield	M.P. ^oC	Mol. Formula	Found/(Calculated) %		
								C	H	N
III-a	H	H	Cl	5	71	230	$C_{29}H_{24}N_2OSCl_2$	67.51 (67.55)	4.65 (4.66)	5.37 (5.39)
III-b	H	Cl	H	3	77	208	$C_{29}H_{24}N_2OSCl_2$	67.01 (67.05)	4.67 (4.66)	5.38 (5.39)
III-c	Cl	H	H	3	78	180	$C_{29}H_{24}N_2OSCl_2$	67.03 (67.05)	4.63 (4.66)	5.37 (5.39)
III-d	Cl	H	Cl	5	70	178	$C_{29}H_{22}N_2OSCl_4$	59.15 (59.20)	3.75 (3.77)	4.73 (4.76)
III-e	H	Br	H	4	62	190	$C_{29}H_{24}N_2OSBr_2$	57.24 (57.25)	3.96 (3.98)	4.58 (4.60)
III-f	H	NO2	H	3	63	168	$C_{29}H_{24}N_4O_5S$	64.41 (64.43)	4.45 (4.47)	10.33 (10.36)
III-g	H	H	OMe	4	69	220	$C_{31}H_{30}N_2O_3S$	72.89 (72.90)	5.91 (5.92)	5.47 (5.49)
III-h	H	H	OEt	4	71	202	$C_{33}H_{34}N_2O_3S$	73.55 (73.58)	6.35 (6.36)	5.18 (5.20)
III-i	H	H	OH	5	77	220	$C_{29}H_{26}N_2O_3S$	72.15 (72.17)	5.41 (5.43)	5.78 (5.80)
III-j	H	H	Me	3	73	202	$C_{31}H_{30}N_2OS$	77.81 (77.45)	6.32 (6.00)	5.88 (5.71)

Spectral Analysis

3, 5-dibenzyl-2,6-bis-(4-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione (III a)

IR ν_{max}: 1160 (C-O-C), 1200 (C=S),750 (C–Cl), 1040 (C-N), 3018 (Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.10-7.50(m,10H,Ar-H), 4.59(s,4H, >CH_2), 5.40(s, 2H, >CH), 8.24-8.41(m,8H,Ar-H), ppm.

^{13}CNMR ($CDCl_3$): δ 48.66(N-$\underline{CH_2}$-Ar), 90.08, 124.51, 122.55, 128.93, 130.40, 134.63, 136.75, 139.55, 141.34, 189.73 ($\underline{C}$=S).

MS (m/z): 518.0 (M+)

3, 5-dibenzyl-2,6-bis-(3-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione (III b)

IR ν_{max}: 1125 (C-O-C), 1232 (C=S), 850 (C–Cl), 1040 (C-N), 3018 (Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.18-7.34 (m, 10H, Ar-H), 4.58-4.67(s,4H, >CH_2), 5.19(s, 2H, >CH), 7.98-8.26(m,8H,Ar-H), ppm.

^{13}CNMR ($CDCl_3$): δ 48.52(N-$\underline{CH_2}$-Ar), 89.58, 126.10, 127.33, 127.53, 128.05, 128.18, 128.66, 128.77, 131.41, 136.10, 140.66, 175.10 ($\underline{C}$=S).

MS (m/z): 518.0 (M+)

3, 5-dibenzyl-2,6-bis-(2-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione (III c)

IR ν_{max}: 1120 (C-O-C), 1230 (C=S), 855 (C–Cl), 1040 (C-N), 3018 (Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.28-7.33 (m, 10H,Ar-H), 4.33-4.61(s,4H, >CH_2), 5.41(s, 2H, >CH), 7.13-7.41(m,8H,Ar-H), ppm.

^{13}CNMR ($CDCl_3$): δ 48.52(N-$\underline{CH_2}$-Ar), 89.58, 126.10, 127.33, 127.53, 128.05, 128.18, 128.66, 128.77, 131.41, 136.10, 140.66, 175.10 ($\underline{C}$=S).

MS (m/z): 518.0 (M+)

3, 5-dibenzyl-2,6-bis-(2,4-dichloro-phenyl)-[1,3,5] oxadiazinane-4-thione (III d)

IR ν_{max}: 1131 (C-O-C), 1298 (C=S), 871 (C–Cl), 1040 (C-N), 3382 (Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.18-7.35 (m,10H,Ar-H), 4.58-4.61 (s,4H, >CH_2), 5.50 (s, 2H, >CH), 8.25-8.38 (m,6H,Ar-H), ppm.

^{13}CNMR ($CDCl_3$): δ 48.61(N-$\underline{CH_2}$-Ar), 89.14, 121.55, 124.56, 126.61, 127.55, 128.94 , 131.11, 132.27, 134.53, 136.72, 182.16 ($\underline{C}$=S).

MS (m/z): 586.02 (M+)

3, 5-dibenzyl-2,6-bis-(3-bromo-phenyl)-[1,3,5] oxadiazinane-4-thione (III e)

IR ν_{max}: 1120 (C-O-C), 1220 (C=S),575 (C–Br), 1040 (C-N), 3018 (Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.18-7.33(m, 10H, Ar-H), 4.58-4.61(s,4H, >CH_2), 6.19((s, 2H, >CH), 7.71-7.81(m,8H,Ar-H) ppm.

^{13}CNMR ($CDCl_3$): δ 47.52(N-$\underline{CH_2}$-Ar), 87.28, 122.20, 125.35, 126.63, 127.05, 127.18, 127.65, 129.77, 135.41, 137.15, 142.76, 185.30 ($\underline{C}$=S).

MS (m/z): 605.0 (M+)

3,5-dibenzyl-2,6-bis-(3-nitro-phenyl)-[1,3,5] oxadiazinane-4-thione (III f)

IR ν_{max}: 1100 (C-O-C), 1350, 1550 (Ar- NO_2), 1203 (C=S), 3089(Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.03-7.23 (m,10H,Ar-H), 4.08(s,4H, >CH_2), 5.02((s, 2H, >CH), 8.03-8.25(m,8H,Ar-H) ppm.

^{13}CNMR ($CDCl_3$): δ 50.70(N-$\underline{CH_2}$-Ar), 90.17, 114.85, 126.05, 127.34, 129.82, 132.36, 133.59, 141.89, 158.51, 161.84, 169.20, 196.45 ($\underline{C}$=S).

MS (m/z): 540.0 (M+)

3, 5-dibenzyl-2, 6-bis-(4-methoxy-phenyl)-[1,3,5] oxadiazinane-4-thione (III g)

IR ν_{max}: 1130 (C-O-C), 1223 (C=S),3283(Ar-CH), cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 3.90 (s, 6H, >OCH_3), 7.24-7.31 (m,10H,Ar-H), 4.59(s,4H, >CH_2), 5.40(s, 2H, >CH), 8.00-8.20(m,8H,Ar-H) ppm .

^{13}CNMR ($CDCl_3$): δ 48.61(N-$\underline{CH_2}$-Ar), 55.94, 90.00, 123.44, 127.55, 128.44, 132.24, 136.72, 142.21, 148.11, 182.16 ($\underline{C}$=S).

MS (m/z): 510.0 (M+)

3, 5-dibenzyl-2,6-bis-(4- ethoxy -phenyl)-[1,3,5] oxadiazinane-4-thione (III h)

IR ν_{max}: 1125 (C-O-C), 1060 (-O-), 1225 (C=S) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 1.40 (t, 6H, >CH_3), 3.93-4.05(q,4H, >CH_2), 7.05-7.43(m,10H,Ar-H), 4.61(s,4H, >CH_2), 5.50(s, 2H, >CH), 8.20-8.33(m,8H,Ar-H) ppm.

^{13}CNMR ($CDCl_3$): δ 47.60(N-$\underline{CH_2}$-Ar), 18.69, 67.09, 88.67, 114.01, 125.35, 129.50, 135.33, 137.48, 139.40, 152.00, 163.09, 190.50 ($\underline{C}$=S).

MS (m/z): 538.0 (M+)

3, 5-dibenzyl-2,6-bis-(4-hydroxy-phenyl)-[1,3,5] oxadiazinane-4-thione (III i)

IR ν_{max}: 1122(C-O-C), 3310 (Ar-OH), 1223 (C=S) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 7.28-7.33(m,10H,Ar-H), 4.61(s,4H, >CH_2), 8.26(bs,2H, >OH),5.39(s, 2H, >CH), 6.68-7.01(m,8H,Ar-H) ppm.

^{13}CNMR ($CDCl_3$): δ δ 48.52(N-$\underline{CH_2}$-Ar), 89.67, 115.20, 127.54, 128.15, 128.50, 128.90, 135.10, 138.31, 157.80, 175.30($\underline{C}$=S).

MS (m/z): 482.16 (M+)

3, 5-dibenzyl-2,6-di-p-tolyl-[1,3,5] oxadiazinane-4-thione (III j)

IR ν_{max}: 1100 (C-O-C), 1228 (C=S), 3010 (Ar-CH) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ 2.50 (s, 6H, >CH_3), 7.05-7.43(m,10H, Ar-H), 4.61(s,4H, >CH_2), 5.50(s, 2H, >CH), 7.56-7.69(m,8H,Ar-H) ppm.

^{13}CNMR ($CDCl_3$): δ δ 47.60(N-$\underline{CH_2}$-Ar), 22.69, 88.67, 120.35, 124.50, 129.50, 135.09, 137.48, 139.40, 145.90, 149.00, 188.0 ($\underline{C}$=S).

MS (m/z): 478.2 (M+)

RESULTS AND DISCUSSION

The ten different 3,5-disubstituted-2,6-diphenyl-[1,3,5] oxadiazinane-4-thione derivatives were synthesized by reacting 1,3-dibenzylthiourea and various substituted benzeldehyde derivatives in ethanol in RBF, 1:1 HCl was added and the reaction mixture was irradiated with microwaves at 40% microwave power (140 W) for 3-5 mins. The reaction mixture was cooled and neutralized with NaOH to obtain the product. The obtained compound structures were characterized by its IR, ^{1}HNMR, ^{13}CNMR & Mass Spectrum. The obtained compound III-(a-j) shows three activities were predicted with top probability.

1 Biliary tract disorders treatment

2 Aspulvinone dimethylallyltransferase inhibitor

3 Chloride peroxidase inhibitor.

Table-II Biological Prediction Analysis of Activities with PASS of derivatives III-(a-j)

Activity Comp.	Biliary tract disorders treatment	Aspulvinone dimethylallyltransferase inhibitor	Chloride peroxidase inhibitor
	Pa	Pa	Pa
III-a	0.915	0.533	0.677
III-b	**0.918**	0.489	0.469
III-c	0.793	0.577	**0.706**
III-d	0.801	0.489	0.646
III-e	0.871	0.779	0.501
III-f	0.783	0.402	0.334
III-g	0.826	**0.821**	0.469
III-h	0.813	0.711	0.212
III-i	0.864	0.796	0.626
III-j	0.895	0.620	0.567

CONCLUSION

Biological prediction analysis revealed that the 3,5-dibenzyl-2,6-bis-(4-methoxy-phenyl)-[1,3,5] oxadiazinane-4-thione III-g is predicted to be significantly active as aspulvinone dimethylallyl transferase inhibitor. The 3,5-dibenzyl-2,6-bis-(2-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione III-c can be commendable as chloride peroxidase inhibitor. whereas, 3,5-dibenzyl-2,6-bis-(3-chloro-phenyl)-[1,3,5] oxadiazinane-4-thione III-b can exhibit promising activity in biliary tract disorders treatment hence it is recommended for the screening for the same activity.

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