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Environmental Benign Synthesis, Characterization and Prediction of Biological activity of some Novel Imidazole Derivatives by Computer System PASS

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Abstract: A series of imidazole derivatives are synthesized by condensation of, differently substituted 4-benzylidene-2-phenyloxazol-5(4H)-one and 2-aminothiazole, which on further reaction with Urea and Thiourea produces the final products. IR, H1 NMR and MASS spectral data confirmed the structure of the newly synthesized compounds. All the reactions were carried out by environmental benign Microwave synthesis. Further the biological activities of synthesized compounds were predicted by the software product - PASS (Prediction of Activity Spectra for Substances).

Keywords: Microwave assisted synthesis, imidazole, purine, PASS.

INTRODUCTION:

In last few years MORE chemistry has gained popularity as a non-conventional technique for rapid drug discovery and development[1]. Microwave irradiation produces efficient internal heat transfer (in situ heating), resulting in even heating throughout the sample as compared with the wall heat transfer that occurs when an water/ oil bath is applied as an energy source[2]. Microwave irradiation has been also applied to carry out synthesis in open vessel[3], using DMF, DCE, 1, 2 dichlorobenzene etc. as energy transfer media which absorb microwave energy efficiently through dipole rotation.

The application of Microwave irradiation to provide enhanced rate and improved product yield in chemical synthesis[4-8] has been extending to modern drug discovery in complex multiple step synthesis and it is proving quite successful in the formation of a variety of carbon – heteroatom bond.

Imidazole a five membered heterocycle having 3 carbon atom, 2 nitrogen atom and two double bond – appears in a no. of naturally occuring products like the amino acids, histidine and purines which comprises many of the most important bases in nucleic acids. Imidazole derivatives possess a broad spectrum of pharmacological activities[9-12] such as anti-parkinson, anticonvulsant and monoamineoxidase (MAO) inhibitory activity[13-15],

antirheumatoid arthritis[16], antiepileptic[17], anti-imflammatory[18-19], antibacterial activity[20-21], antifungal activity [22]antitubercular[23], antiviral[24] and anticancer activity[25-27] (i.e. possess significant cytotoxic activity against *Dalton's Lymphoma Ascites (DLA) and Ehrlich's Ascites Carcinoma (EAC) cell lines*.).

In the view of above mentioned biological activity of imidazole derivatives and in continuation of our interest in the development of environmentally benign protocols, we here in report a facile and rapid synthesis of substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one and substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione. The synthesized compounds were characterized by elemental analysis, IR, HNMR and MASS spectral data.

Further the synthesized compounds were analyzed for their pharmaceutical effect by the software product - PASS (Prediction of Activity Spectra for Substances).

The PASS (prediction of activity spectra for substances) is a software product, which predictsmore than 300 pharmacological effects and biochemical mechanism on the basis of structural formula of a substance.

EXPERIMENTAL SECTION:

Chemicals were purchased from commercial supplier and were used without any further purification. All the reactions were carried out in a Microwave oven.Melting point was determined by open capillary method and is uncorrected. The purity of the compound was ascertained by percolated TLC using silica gel G. The spots were visualized by using iodine vapors. The IR spectra were recorded on FT IR Spectrometer Shimadzu 8201. The HNMR spectra were obtained using a Bruker Advance spectrospin 400 (400 MHz) instrument using TMS as internal standard. Mass spectra were recorded on Accu TOF MS ES^+.

1(a-f):-General procedure for Synthesis of substituted 4-methylene-2-phenyloxazol-5(4H)-one.

Hippuric acid (0.01 mole), Sodium acetate (0.01 mole) and aldehyde (0.01 mole) are finely powdered and mixed in beaker. To the above mixture add Acetic anhydride (5ml for 1 gm).The reaction mixture was irradiated under microwave for 3 to 4 min. at 480W with intermitted irradiation of 30 sec. interval. Upon completion of reaction (monitored by TLC), alcohol was added to the reaction mixture for purification and kept overnight, which was then filtered. The filtered product was washed several times with water and dried.

2(a-f):-General procedure for Synthesis of substituted4-methylene-2-phenyl-1-(thiazol-2-yl)-1H-imidazol-5(4H)-one

The compound 1(a-f) (0.01 mole) is taken in Erlenmeyer flask in which alcohol and DMF (2:1) is added as solvent. To the above mixture 2-Amino Thiazole (0.01 mole) was added and 7 to 8 drops of pyridine was added as catalyst. The above reaction mixture was irradiated under microwave irradiation for 5 min. at 480W with intermitted irradiation of 30 followed by 15 sec. The progress of the reaction was monitored by TLC. After the reaction was completed the product was filtered, concentrated and precipitated in water – left overnight and filtered. The products (2a-f) was purified and recrystallized with alcohol.

3(a-f):-General procedure for Synthesis of substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

The compound 2 (0.01 mole) is taken in Erlenmeyer flask in which alcohol and DMF (4:1) is added as solvent. To the above solution Urea (0.01) and 1-2 drops of dil. HCl was added. The above reaction mixture was irradiated under microwave irradiation for 7.30 min. at 600W with intermitted irradiation of 30 followed by 15 sec. The progress of the reaction was monitored by TLC. After the reaction was completed the product was filtered, concentrated and precipitated in water – left overnight and filtered. The products (3a-f) were purified and recrystallized with alcohol.

3a :- 6,8-diphenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{20}H_{15}N_5OS$;mp150 C;IR (KBr): nmax1579 (C=N), 3214 (NH amide), 1542 (C=C conjugated), 1645 (C=O), 2910 (Ar-H), 690 (C-S);1H NMR (300 MHz, DMSO-d6): - 8.02-8.42 (m, Ar-H, 4H), 7.37-7.87 (m, Ar-H, 5H), 7.4 (s, NH, 1H), 7.188-7.197 (d, NH, 1H), 4.35-4.37 (m, CH=CH, 2H), 2.67 (s, Ar-C-H, 1H);MS: m/z 373.

3b:- 6-(4-fluorophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{20}H_{14}FN_5OS$;mp180 C;IR (KBr): nmax-- 1582 (C=N), 3218 (NH amide), 1550 (C=C conjugated), 1655 (C=O), 2914 (Ar-H), 692 (C-S), 758 (C-F);1H NMR (300 MHz, DMSO-d6): 7.87-8.27 (m, Ar-H, 4H), 7.22-7.72 (m, Ar-H, 5H), 7.25 (s, NH, 1H), 7.03-7.02 (d, NH, 1H), 4.2-4.22 (m, CH=CH, 2H), 2.51 (s, Ar-C-H, 1H);MS: m/z 180.

3c :- 6-(4-chlorophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{20}H_{14}ClN_5OS$;mp132 C;IR (KBr): nmax1588 (C=N), 3222 (NH amide), 1555 (C=C conjugated), 1660 (C=O), 2917 (Ar-H), 694 (C-S), 1160 (C-Cl);1H NMR (300 MHz, DMSO-d6): 7.9-8.3 (m, Ar-H, 4H), 7.25-7.75 (m, Ar-H, 5H), 7.28 (s, NH, 1H), 7.068-7.077 (d, NH, 1H), 4.23-4.25 (m, CH=CH, 2H), 2.55 (s, Ar-C-H, 1H);MS: m/z 407.

3d :- 6-(3-nitrophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{20}H_{14}N_6O_3S$;mp418 C;IR (KBr): nmax1594 (C=N), 3232 (NH amide), 1560 (C=C conjugated), 1668 (C=O), 2922 (Ar-H), 697 (C-S), 1486 (C-NO2);1H NMR (300 MHz, DMSO-d6): - 8.99 (s, Ar-H, 1H), 8.3-8.52 (m, Ar-H, 3H), 7.75-8.25 (m, Ar-H, 5H), 7.78 (s, NH, 1H), 7.57-7.58 (d, NH, 1H), 4.73-4.75 (m, CH=CH, 2H), 3.05 (s, Ar-C-H, 1H);MS: m/z 418.

3e :- 6-(4-hydroxyphenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{20}H_{15}N_5O_2S$;mp158 C;IR (KBr): nmax1596 (C=N), 3238 (NH amide), 1564 (C=C conjugated), 1672 (C=O), 2927 (Ar-H), 699 (C-S), 3502 (OH);1H NMR (300 MHz, DMSO-d6): - 7.68-8.08 (m, Ar-H, 4H), 7.03-7.53 (m, Ar-H, 5H), 7.06 (s, NH, 1H), 6.84-6.83 (d, NH, 1H), 4.01-4.03 (m, CH=CH, 2H), 2.37 (s, Ar-C-H, 1H);MS: m/z 389.

3f :- 6-(furan-2-yl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one

Elemental analysis:-Molecular Formula $C_{18}H_{13}N_5O_2S$;mp95 C;IR (KBr): nmax1596 (C=N), 3238 (NH amide), 1564 (C=C conjugated), 1672 (C=O), 2927 (Ar-H), 699 (C-S), 3502 (OH), 1085(C-O-C), 728 (CH Furan);1H NMR (300 MHz, DMSO-d6): 7.03-7.53 (m, Ar-H, 5H), 7.06 (s, NH, 1H), 6.84-6.83 (d, NH, 1H), 4.01-4.03 (m, CH=CH, 2H), 6.79 – 7.01 (m, furan, 3H); MS: m/z 363.

4(a-f):- General Synthesis of substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

The compound 2 (0.01 mole) is taken in Erlenmeyer flask in which alcohol and DMF (4:1) is added as solvent. To the above solution ThioUrea (0.01) and 2-3 drops of dil. HCl was added. The above reaction mixture was irradiated under microwave irradiation for 7.30 min. at 600W with intermitted irradiation of 30 followed by 15 sec. The progress of the reaction was monitored by TLC. After the reaction was completed the product was filtered, concentrated and precipitated in water – left overnight and filtered. The products (4a-f) was purified and recrystallized with alcohol.

4a :- 6,8-diphenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:-Molecular Formula $C_{20}H_{15}N_5S_2$; mp152 C;IR (KBr): nmax1626 [C=N (Thiazole)], 3215 [N-H (amide)], 1473 (C=S), 682 (C-S), 1524 [C=C(Conjugated)], 3068 and 2973 (Ar-H);1H NMR (300 MHz, DMSO-d6): 7.61-7.84 (m, Ar-H, 4H), 7.19-7.25 (m, Ar-H, 5H), 7.14 (s, NH, 1H), 6.76-6.77 (d, NH, 1H), 3.85-3.9 (m,CH=CH, 2H), 2.15 (s, Ar-C-H, 1H);MS: m/z $[M]^+$ 389.

4b :- 6-(4-fluorophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:-Molecular Formula $C_{20}H_{14}FN_5S_2$; mp182 C;IR (KBr): nmax-- 1630 [C=N (Thiazole)], 3217 [N-H (amide)], 1475 (C=S), 683 (C-S), 1526 [C=C(Conjugated)], 3070 and 2975 (Ar-H), 760 (C-F);1H NMR (300 MHz, DMSO-d6): 7.28-7.49 (m, Ar-H, 4H), 6.85-6.91 (m, Ar-H, 5H), 6.8 (s, NH, 1H), 6.43-6.45 (d, NH, 1H), 3.52-3.3 (m,CH=CH, 2H), 1.82 (s, Ar-C-H, 1H);MS: m/z $[M]^+$407.

4c :- 6-(4-chlorophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:- Molecular Formula $C_{20}H_{14}ClN_5S_2$;mp136 C;IR (KBr): nmax-- 1635 [C=N (Thiazole)], 3222 [N-H (amide)], 1478 (C=S), 688 (C-S), 1529 [C=C(Conjugated)], 3073 and 2977 (Ar-H), 1145 (C-Cl);1H NMR (300 MHz, DMSO-d6): 7.5-7.73 (m, Ar-H, 4H), 7.08-7.14 (m, Ar-H, 5H), 7.03 (s, NH, 1H), 6.65-6.66 (d, NH, 1H), 3.74-3.79 (m,CH=CH, 2H), 2.04 (s, Ar-C-H, 1H);MS: m/z 423.

4d :- 6-(3-nitrophenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:-Molecular Formula $C_{20}H_{14}N_6O_2S_2$; mp118 C;IR (KBr): nmax1646 [C=N (Thiazole)], 3225 [N-H (amide)], 1481 (C=S), 692 (C-S), 1531 [C=C(Conjugated)], 3075 and 2980 (Ar-H), 1481(NO_2);1H NMR (300 MHz, DMSO-d6): - 8.57 (s, Ar-H, 1H), 7.95-8.18 (m, Ar-H, 3H), 7.57-7.63 (m, Ar-H, 5H), 7.52 (s, NH, 1H), 7.14-7.15 (d, NH, 1H), 4.23-4.28 (m,CH=CH, 2H), 2.53 (s, Ar-C-H, 1H);MS: m/z 434.

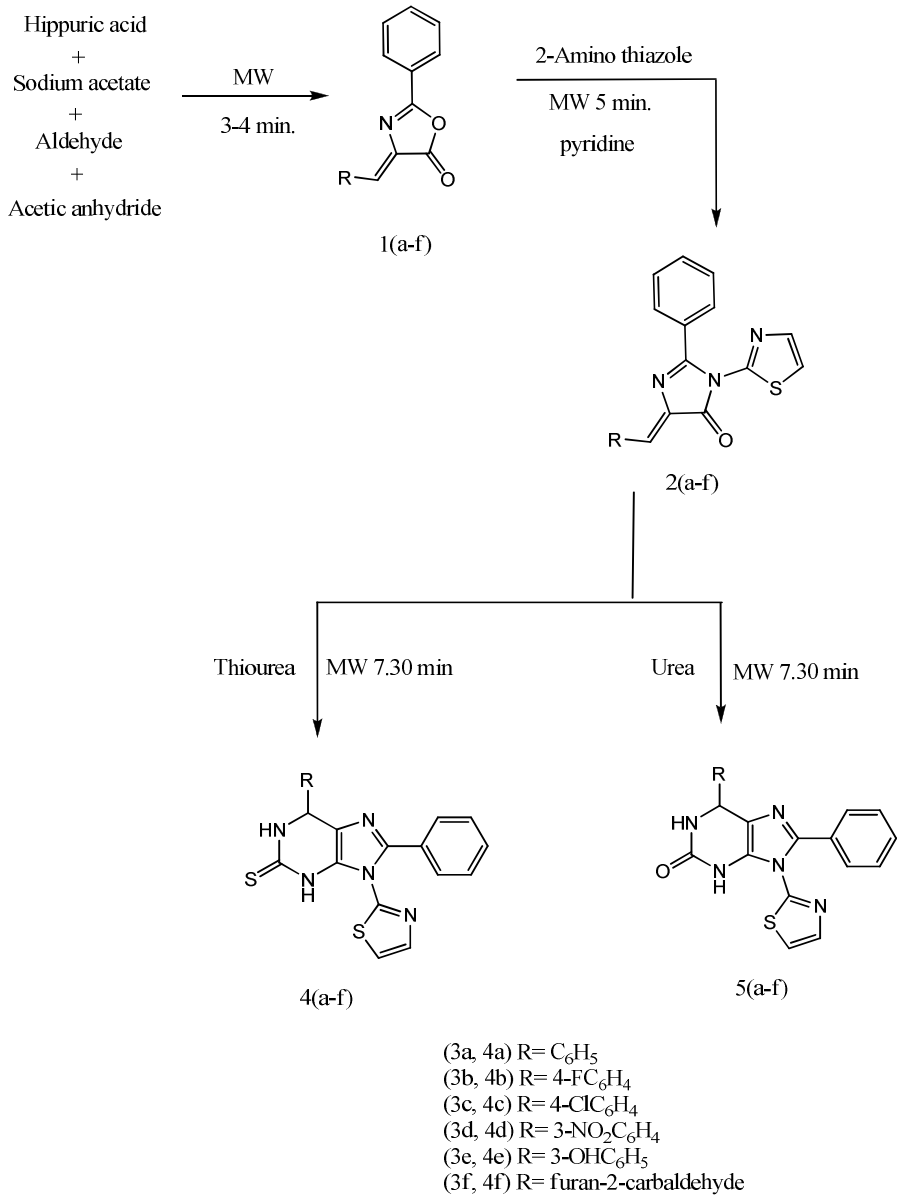
4e :- 6-(4-hydroxyphenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:-Molecular Formula $C_{20}H_{15}N_5OS_2$; mp105 C;IR (KBr): nmax1649 [C=N (Thiazole)], 3225 [N-H (amide)], 1484 (C=S), 696 (C-S), 1536 [C=C(Conjugated)], 3077 and 2982 (Ar-H), 3513(O-H);1H NMR (300 MHz, DMSO-d6): - 7.31-7.52 (m, Ar-H, 4H),), 6.88-6.94 (m, Ar-H, 5H), 6.84 (s, NH, 1H), 6.46-6.48 (d, NH, 1H), 3.55-3.6 (m,CH=CH, 2H), 1.85 (s, Ar-C-H, 1H);MS: m/z 405.

4f :- 6-(furan-2-yl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:-Molecular Formula $C_{18}H_{13}N_5OS_2$; mp98 C;IR (KBr): nmax-- 1647 [C=N (Thiazole)], 3225 [N-H (amide)], 1487 (C=S), 699 (C-S), 1539 [C=C(Conjugated)], 3078 and 2986 (Ar-H), 1081(C-O-C), 723 (CH Furan);1H NMR (300 MHz, DMSO-d6): 6.88-6.94 (m, Ar-H, 5H), 6.84 (s, NH, 1H), 6.46-6.48 (d, NH, 1H), 3.55-3.6 (m,CH=CH, 2H), 6.79 – 6.81 (m, furan, 3H); MS: m/z 379.

SCHEME:



(3a, 4a) R= C_6H_5
(3b, 4b) R= 4-FC_6H_4
(3c, 4c) R= 4-ClC_6H_4
(3d, 4d) R= 3-$NO_2C_6H_4$
(3e, 4e) R= 3-OHC_6H_5
(3f, 4f) R= furan-2-carbaldehyde

RESULT AND DISCUSSION:

The oxazolones derivatives were synthesized by condensation of various benzaldehydes, hippuric acid, acetic anhydride and sodium acetate under microwave irradiation method. The melting points of the synthesized compounds were checked by the given literature. The compounds 2(a-f) substituted4-methylene-2-phenyl-1-(thiazol-2-yl)-1H-imidazol-5(4H)-one were synthesized by the condensation reaction of 2- aminothiazole and oxazolones , under microwave irradiation of 480 W. The purity of compounds was analyzed by TLC using benzene: Ethyl acetate (7:3) as mobile base. The title compounds - substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purin-2(3H)-one 3(a-f) and substituted 8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione4(a-f) were synthesized by reaction of 2(a-f) with urea and thiourea respectively. The structures of the synthesized compound were confirmed on the basis of spectral and elemental analysis. The compound showed absorption band at around 3214 – 3238 (NH amide). Further in their H NMR (δ ppm DMSO d_6) spectrum the

appearance of signal at 6.84–7.4. Mass spectrum of the compounds showed molecular ion peak corresponding to their molecular formulas.

The biological activities of the synthesized compounds were predicted by the computer system PASS. All the compounds showed good activity.The predictions of PASS having Pa>0.45 are shown below.

3a

0,595	0,050	Phosphatase inhibitor
0,490	0,013	Immunomodulator
0,484	0,015	CYP2C19 inducer
0,492	0,033	Neurodegenerative diseases treatment
0,458	0,029	Chemosensitizer

3b

0,498	0,031	Neurodegenerative diseases treatment
0,467	0,015	Immunomodulator
0,529	0,089	Phosphatase inhibitor

3c

0,459	0,043	Neurodegenerative diseases treatment
0,611	0,042	Phosphatase inhibitor

3d

0,537	0,014	Chemosensitizer
0,500	0,110	Phosphatase inhibitor

3e

0,629	0,034	Phosphatase inhibitor
0,456	0,017	Transcription factor inhibitor
0,455	0,030	Chemosensitizer
0,477	0,093	Nicotinic alpha4beta4 receptor agonist

3f

0,634	0,004	Renal disease treatment
0,625	0,013	Neurodegenerative diseases treatment
0,598	0,049	Phosphatase inhibitor
0,474	0,017	CYP2C19 inducer

4a

0,592	0,052	Phosphatase inhibitor
0,511	0,049	Chloride peroxidase inhibitor
0,483	0,030	Analgesic, non-opioid
0,456	0,050	Analgesic

4b

0,534	0,021	Analgesic, non-opioid
0,498	0,038	Analgesic
0,523	0,093	Phosphatase inhibitor

4c

0,609	0,043	Phosphatase inhibitor
0,504	0,026	Analgesic, non-opioid
0,493	0,056	Chloride peroxidase inhibitor
0,477	0,044	Analgesic

4d

0,492	0,115	Phosphatase inhibitor

4e

0,628	0,034	Phosphatase inhibitor
0,495	0,083	Nicotinic alpha4beta4 receptor agonist

4f

0,607	0,004	Renal disease treatment
0,595	0,050	Phosphatase inhibitor
0,522	0,007	Mcl-1 antagonist
0,530	0,025	Neurodegenerative diseases treatment
0,463	0,014	Focal adhesion kinase 2 inhibitor

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