Environmental Benign Synthesis, Characterization and Antimicrobial Activity of Some Imidazole Derivatives

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Abstract

A series of imidazole derivatives 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(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)-thione 4(a-f)). IR, H^1 NMR and MASS spectral data confirmed the structure of the newly synthesized compounds. All the reactions were carried out by environmental benign, efficient and extremely fast procedure Microwave synthesis. The derivatives of these moieties were evaluated for antimicrobial activity.

Keywords: - Microwave assisted synthesis, imidazole, purine, Antibacterial activity, Antifungal activity.

الخلاصة

تم تحضير سلسلة مشتقات الايمدازول بواسطة التكثيف مع مختلف مشتقات 4–benzylidene–2–phenyloxazol–5(4H)–one and 2–aminothiazole يا والثايويوريا الناتج من تفاعل (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)–thione 4(a–f)) **نتائج اطياف** IR, H^1 NMR and MASS **تؤكد ان المركبات المحضرة من التفاعل اعلاه جديدة. وكل التفاعلات تم اجراؤها خارج تاثير الظروف الخارجية وتؤكد على ان التفاعلات بكفاءة عالية وسريعة باستخدام تحاليل المايكرويف ، وتم تطبيق هده المشتقات لغرض ايجاد فعاليتها البايلوجية.**

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 accuring 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.

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. Above reaction was

carried based on the methods descried in the literature[28].

2(a-f) :- General procedure for Synthesis of substituted 4-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. Above reaction was carried based on the methods descried in the literature[28] given for the synthesis of similar compound.

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 $C_{20}H_{15}N_5OS$; mp 150 °C; IR (KBr): nmax 1579 (C=N), 3214 (NH amide), 1542 (C=C conjugated), 1645 (C=O), 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 $C_{20}H_{14}FN_5OS$; mp 180 °C; IR (KBr): nmax -- 1582 (C=N), 3218 (NH amide), 1550 (C=C conjugated), 1655 (C=O), 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 $C_{20}H_{14}ClN_5OS$; mp 132 °C; IR (KBr): nmax 1588 (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 $C_{20}H_{14}N_6O_3S$; mp 418 °C; IR (KBr): nmax 1594 (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 $C_{20}H_{15}N_5O_2S$; mp 158 °C; IR (KBr): nmax 1596 (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 $C_{18}H_{13}N_5O_2S$; mp 95 °C; IR (KBr): nmax 1596 (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 $C_{20}H_{15}N_5S_2$; mp 152 °C; IR (KBr): nmax 1626 [C=N (Thiazole)], 3215 [N-H (amide)], 1473 (C=S), 682 (C-S), 1524 [C=C(Conjugated)], 3068 (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 $C_{20}H_{14}FN_5S_2$; mp 182 °C; IR (KBr): nmax -- 1630 [C=N (Thiazole)], 3217 [N-H (amide)], 1475 (C=S), 683 (C-S), 1526 [C=C(Conjugated)], 3070 (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 $C_{20}H_{14}ClN_5S_2$; mp 136 °C; IR (KBr): nmax -- 1635 [C=N (Thiazole)], 3222 [N-H (amide)], 1478 (C=S), 688 (C-S), 1529 [C=C(Conjugated)], 3073, 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 $C_{20}H_{14}N_6O_2S_2$; mp 118 °C; IR (KBr): nmax 1646 [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.

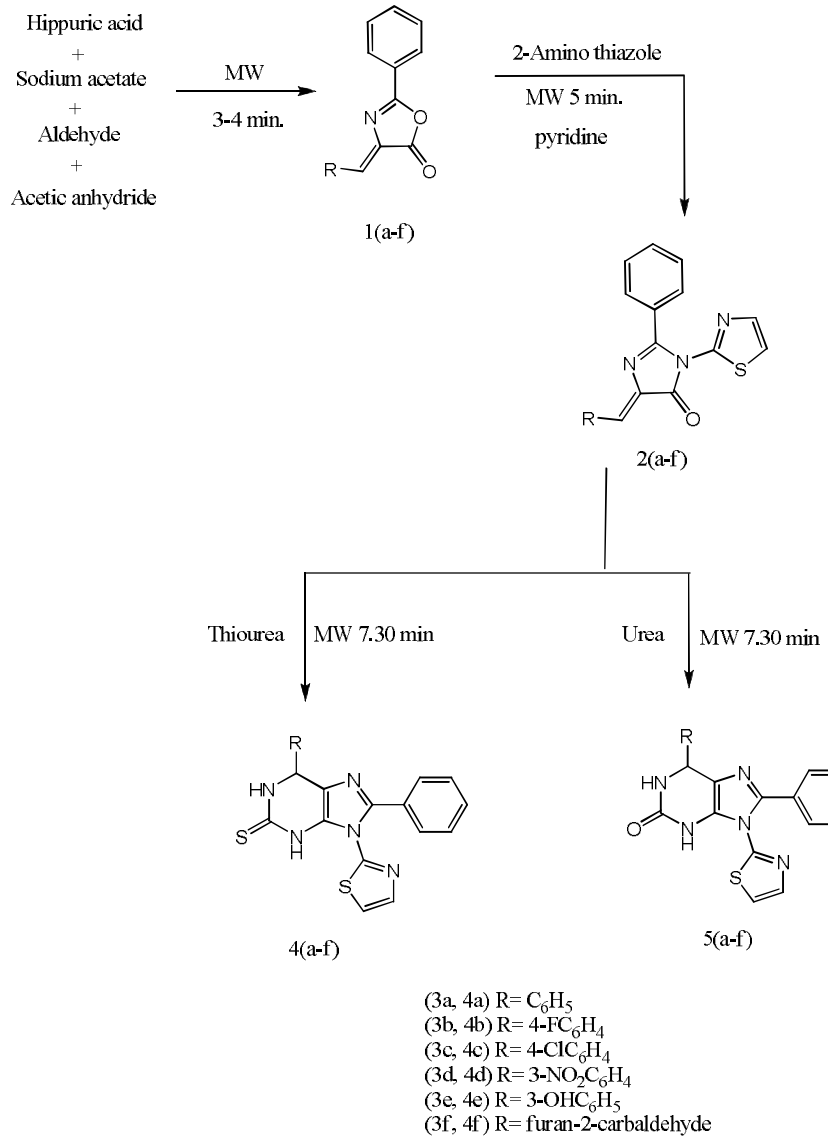
4e :- 6-(4-hydroxyphenyl)-8-phenyl-9-(thiazol-2-yl)-6,9-dihydro-1H-purine-2(3H)-thione

Elemental analysis:- Molecular Formula $C_{20}H_{15}N_5OS_2$; mp 105 °C; IR (KBr): nmax 1649 [C=N (Thiazole)], 3225 [N-H (amide)], 1484 (C=S), 696 (C-S), 1536 [C=C(Conjugated)], 3077 (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 $C_{18}H_{13}N_5OS_2$; mp 98 °C; IR (KBr): nmax-- 1647 [C=N (Thiazole)], 3225 [N-H (amide)], 1487 (C=S), 699 (C-S), 1539 [C=C(Conjugated)], 3078 (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 1,3-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) substituted 4-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 fase. 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)-thione 4(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 compounds were tested in vitro for antibacterial activity against the test *organisms E.coli (MTCC 443), P.aeruginosa (MTCC 1688), S.aureus (MTCC 96) and S.pyogenus (MTCC 442)* and antifungal activity against the organisms *C.albicans (MTCC 227), A.niger (MTCC 282)* and *A.clavatus (MTCC 1323)*. 'Broth Dilution Method' was used for MIC determination. The data were compared to the standard Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin for bacteria and Nystatin and Greseofulvin for fungi.

The tested compounds exhibited mild to moderate antibacterial activity against all four strains of bacteria. The compounds 4b and 4d showed 100 µg/mL MBC against *S. pyogenus*. The compounds 3b, 3c, 3f, 4b and 4c showed 125 µg/mL MBC. Other compounds showed MBC 200 and 250 µg/mL MBC. On comparing the compounds it was observed that the compounds are more active against gram negative ones.
The tested compounds exhibited mild antifungal activity against all the strains of fungus. The compounds 3d and 4f showed 250 µg/mL MFC against *A. niger*. Other compounds showed MBC ranging from 500 and above.

Table 1:- In vitro antibacterial avtivity of synthesized compounds

Compound	Minimal Inhibition Concentration (µg/ml)			
	E. coli MTCC 442	*P. aeruginosa* MTCC 441	*S. aureus* MTCC 96	*S. pyogenus* MTCC 443
3a	250	250	200	250
3b	200	200	125	200
3c	200	200	125	200
3d	250	250	200	200
3e	250	200	200	250
3f	200	200	200	125
4a	250	250	200	200
4b	200	200	125	100
4c	200	125	200	125
4d	200	200	200	100
4e	250	200	200	200
4f	250	250	200	200
Ampicillin	100	--	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table 2:- In vitro antifungal avtivity of synthesized compounds

Compound	Minimal Inhibition Concentration (µg/ml)		
	C. albicans MTCC 227	*A. Niger* MTCC 282	*A. clavatus* MTCC 1323
3a	500	500	500
3b	500	1000	1000
3c	1000	>1000	1000
3d	1000	250	500
3e	1000	>1000	1000
3f	>1000	500	500
4a	500	1000	1000
4b	>1000	1000	1000
4c	500	1000	1000
4d	1000	>1000	1000
4e	500	500	500
4f	1000	250	500
Nystatin	100	100	100
Greseofulvin	500	100	100

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