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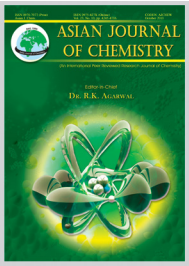

Microwave-Assisted Synthesis and Antifungal Activity of Novel Substituted Azetidinone Derivatives of Edaravone

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This paper describes development of new chemical entities of edaravone. The chemical name of edaravone is 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one. The starting material 3-methyl-1-substituted-1*H*-pyrazol-5(4H)-ones (**1**) were synthesized in high yields by the treatment of ethyl aetoacetate with appropriate 1-phenylhydrazine. Ethyl-2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*- pyrazol-4-yl)acetate (**2**) was synthesized by reaction of ethyl chloroacetate with compound (**1**). 2-(4,5-Dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide (**3**) prepared by reaction of hydrazine hydrate with compound (**2**) in presence of ethanol. The microwave assisted reaction of compound (**3**) with different substituted aldehydes in presence of ethanol gives *N*-(substituted benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (**4a-4e**). The microwave assisted reaction of (**4a-4e**) with chloroacetyl chloride and triethylamine in presence of DMF gives formation of 2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-substituted phenylazetidin-2-one) (**DTa-DTe**). The products, characterized on the basis of spectral data, have shown moderate to good antifungal activity against bacteria and fungi.

Key Words: Edaravone, 2-Azatidinone, Antifungal, Pyrazolone.

INTRODUCTION

Recently, a new pyrazolone compound, edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, also known as MCI-186), has been developed as a medical drug for brain ischemia and has also been reported to be effective for myocardial ischemia[1]. In this study, we focused on and explored the pyrazolone compounds derived from edaravone, as antipyrine agents and found new and highly active antipyrine compounds. Our initial goal was to prepare a small focused library of edaravone derivatives. The preparation of pyrazolone compounds was achieved by refluxing the corresponding β-ketoester and hydrazine compound in ethanol or acetic acid[2,3].

Pyrazolone moiety, possess anticancer[4], antiviral[5], antitubercular[6], antihyperlipedaemic[7], antidepressant[8], anticonvulsant[8], antioxidant[9], antibacterial[9], anti-HIV[10], antiinflammatory[11], analgesic[11] and antipyretic[11] activities.

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including various emerging diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance, created in the last decades, a substantial medical need for new class of antibacterial agents.

A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross resistance with the present therapeutically can occur[12].

The microwave-assisted synthesis is one of the areas where substantial progress has been made. One of its noteworthy application has been demonstrated in the area of neat reaction, which has become an emerging technology in green chemistry recently[13-15].

EXPERIMENTAL

All melting points were determined in micro-controller melting point apparatus Chemi line CL-725 and are uncorrected. TLC was performed on silica gel plates TLC plates and visualized under UV light (UV chamber: Rolex UV cabinet Model No. R/340/OC) or iodine chamber. All FT-IR spectra were recorded on Shimadzu 8400-S FT-IR spectrophotometer using KBr. Microwave reactions were carried out using microwave oven (LG Model No. MG-396 WA, 1000 W, microwave frequency 2450 MHz). The ^{1}H NMR spectra were recorded in a Bruker spectrophotometer AMX-400 (400 MHz), Bruker Optik (Germany) in $CDCl_3$ using TMS as an internal standard. All Mass spectra were recorded using a Jeol-D-300 mass spectrophotometer (70 ev), SHIMADZU (Japan) by LCMS-2010A.

Procedure for the preparation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one[3,16]: Mix together 50 g (49 mL, 0.384 mol) of ethyl acetoacetate and 40 g (36.5 mL, 0.37 mol) of phenyl hydrazine in a round bottomed flask. Heat the mixture on a boiling water bath in the fume cupboard for *ca.* 2 h. Allow heavy reddish syrup to cool somewhat and add *ca.* 100 mL of ether and stirred mixture vigorously. The syrup, which is insoluble in ether will solidify within 15 min. Filter the solid at the pump and remove coloured impurities by washing with ether several times and recrystallized from ethanol.

3-Methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1): IR (KBr, ν_{max}, cm^{-1}): 3345 (NH), 2883 (CH_3 stretch), 1724 (C=O ketone), 1373 (CH_3 bend), 1297 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 2.20 (s, 3H, CH_3), 7.12 (t, 1H, ArH), 7.32 (t, 2H, ArH), 7.40 (d, 2H, ArH), 7.90 (s, 1H, NH); mass: m/z 174 (M^+), 175 (M+1, 11.4 %).

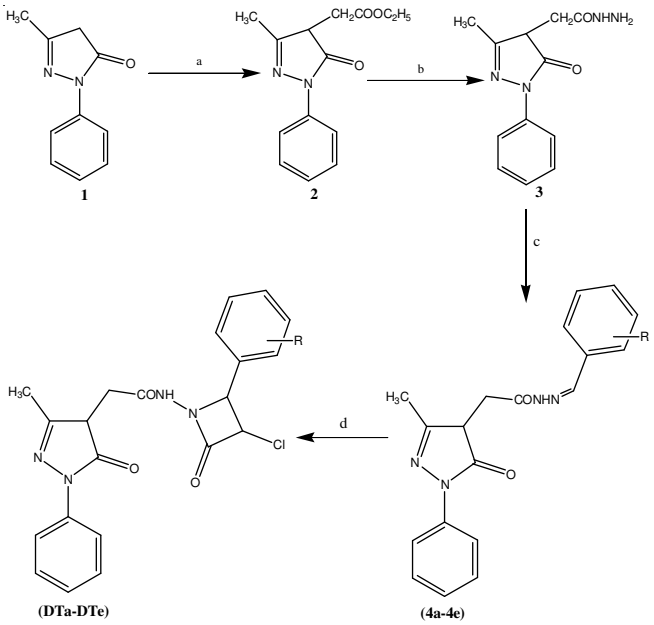
Procedure for the preparation of ethyl 2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetate: Mix compound **1** (0.01) and chloroethyl acetate (0.01 mol) in 1,4-dioxane (15 mL) was refluxed for 8 h. The reaction mixture further stirred for 1 h and poured in water. The resulting mixture was filtered and recrystallized from ethanol.

Ethyl-2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetate (2): IR (KBr, ν_{max}, cm^{-1}): 3348 (NH), 2881 (CH_3 stretch), 1740 (C=O ester), 1724 (C=O ketone), 1372 (CH_3 bend), 1293 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.30 (s, 2H, CH_2), 1.70 (q, 2H, CH_2), 1.50 (t, 3H, CH_3), 2.22 (s, 3H, CH_3), 7.10 (t, 1H, ArH), 7.35 (t, 2H, ArH), 7.40 (d, 2H, ArH), 7.97 (s, 1H, NH); mass: m/z 260 (M^+), 261 (M+1, 15.4 %).

Preparation of 2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide (3): Compound **2** (0.01 mol) and hydrazine hydrate (0.02 mol) were refluxed in absolute methanol (15 mL) for 20 h. The mixture was concentrated, cooled and poured in ice cold water. The solid thus separated out was filtered, dried and recrystallized from ethanol. IR (KBr, ν_{max}, cm^{-1}): 3378, 3365 (NH_2), 3340 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1372 (CH_3 bend), 1293 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.50 (s, 2H, CH_2), 2.22 (s, 3H, CH_3), 3.35 (s, 3H, NH and NH_2), 7.15 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.45 (d, 2H, ArH), 8.05 (s, 1H, NH); mass: m/z 247 (M+1, 10.4 %).

General procedure for the preparation of *N*-(substituted benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4a-4e) (Scheme-I): Substituted aldehydes (0.01 mol) in ethanol were added to solution of 0.01 mol of compound **3** in 15 mL of ethanol. Then mixture was irradiated in a microwave oven (320 W) for appropriate time (Table-1). After cooling the mixture, the solid was filtered, dried and recrystallized from ethanol.

***N*-(*p*-(*N,N*-dimethylamino)benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4a):** IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1650 (C=N), 1372 (CH_3 bend), 1293 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.50 (s, 2H, CH_2), 2.50 [s, 6H, $(CH_3)_2$], 2.22 (s, 3H, CH_3), 3.40 (s, 1H, NH), 7.15 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.50 (m, 6H, ArH), 8.00 (s, 1H, NH); mass: m/z 377 (M^+), 378 (M+1, 23.10 %).



a = Chloroethyl acetate, 1,4-dioxane
b = NH_2NH_2. H_2O, MeOH, Reflux 20 h
c = Substituted Aldehydes, EtOH, MW, 320 W
d = Chloroacetyl chloride, triethylamine, DMF, 320 W

DTa = R = -4-[N,N-$(CH_3)_2$]; DTb = R = -4-OH; DTc = R = -4-NO_2; DTd = R = -Cl; DTe = R = -CH_3

(Scheme-I)

TABLE-1
PHYSICAL DATA OF COMPOUNDS (**4a-4e**) AND (**DTa-DTe**)

Compound code	-R	m.f.	Microwave irradiation time (min)	Yield (%)	m.p. (ºC)
4a	4-N-$(CH_3)_2$	$C_{21}H_{23}N_5O_2$	6.0	88.96	100
4b	-4-OH	$C_{19}H_{18}N_4O_3$	6.0	90.10	110
4c	4-NO_2	$C_{19}H_{17}N_5O_4$	6.3	89.10	105
4d	-4-Cl	$C_{19}H_{17}N_4O_2Cl$	6.4	88.96	116
4e	-4-CH_3	$C_{20}H_{20}N_4O_2$	6.5	92.10	128
DTa	4-N-$(CH_3)_2$	$C_{23}H_{24}N_5O_3Cl$	7.0	92.00	200
DTb	-4-OH	$C_{21}H_{19}N_4O_4Cl$	7.5	89.00	160
DTc	4-NO_2	$C_{21}H_{18}N_5O_5Cl$	7.1	88.60	250
DTd	-4-Cl	$C_{21}H_{18}N_4O_3Cl_2$	7.0	90.80	163
DTe	-4-CH_3	$C_{22}H_{21}N_4O_3Cl$	8.0	91.10	195

***N*-(*p*-hydroxy benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4b):** IR (KBr, ν_{max}, cm^{-1}): 3450 (OH), 3350 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1650 (C=N), 1372 (CH_3 bend), 1293 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.50 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.45 (s, 1H, NH), 4.10 (s, 1H, OH), 7.15 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 350 (M^+), 351 (M+1, 20.10 %).

***N*-(*p*-nitro benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4c):** IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1650 (C=N), 1540 and 1330 (NO_2), 1372 (CH_3 bend), 1293 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.95 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 3.40 (s, 1H, NH), 7.10 (t, 1H, ArH), 7.30 (t, 2H, ArH), 7.50 (m, 6H, ArH), 8.00 (s, 1H, NH); mass: m/z 379 (M^+), 380 (M+1, 22.15 %).

***N*-(*p*-chloro benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4d):** IR

(KBr, ν_{max}, cm_{-1}): 3355 (NH), 2880 (CH_3 stretch), 1728 (C=O ketone), 1655 (C=N), 610 (Cl), 1370 (CH_3 bend), 1290 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.90 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 3.45 (s, 1H, NH), 7.00 (t, 1H, ArH), 7.35 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 368 (M^+), 370 (M+2, 32.25%).

***N*-(*p*-methyl benzylidenyl)-[2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)acetohydrazide] (4e):** IR (KBr, ν_{max}, cm^{-1}): 3355 (NH), 2885 (CH_3 stretch), 1728 (C=O ketone), 1655 (C=N), 1375 (CH_3 bend), 1290 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.95 (s, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.40 (s, 1H, NH), 7.00 (t, 1H, ArH), 7.35 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 368 (M^+), 370 (M+2, 32.25 %).

General procedure for the preparation of 2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-substituted phenylazetidin-2-one) (DTa-DTe): The compounds (**4a-4e**) (0.0017 mol) in DMF were taken in a round bottom flask. To it chloroacetyl chloride (0.2 mL) and triethylamine (0.2 mL) were added slowly. Then it was irradiated in a microwave oven (320 W) for appropriate time (Table-1). Reaction mixture diluted with ice-cold water. The solid product formed was filtered, dried and recrystallized from ethanol.

2-(4,5-Dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-(p-*N,N*,dimethylamino) phenylazetidin-2-one) (DTa): IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1690 (C=O), 1372 (CH_3 bend), 1293 (C-N), 610 (Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.50 (s, 2H, CH_2), 2.50 (s, 6H, $(CH_3)_2$), 2.22 (s, 3H, CH_3), 3.40 (s, 1H, NH), 5.10 (d, 1H, CH), 5.40 (d, 1H, CH), 7.15 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.50 (m, 6H, ArH), 8.00 (s, 1H, NH); mass: m/z 453 (M^+), 454 (M+1, 25.10 %).

2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-(*p*-hydroxy)phenylazetidin-2-one) (DTb): IR (KBr, ν_{max}, cm^{-1}): 3450 (OH), 3350 (NH), 2881 (CH_3 stretch), 1728 (C=O ketone), 1685 (C=O), 1372 (CH_3 bend), 1293 (C-N), 610 (Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.50 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.45 (s, 1H, NH), 4.10 (s, 1H, OH), 5.15 (d, 1H, CH), 5.35 (d, 1H, CH), 7.15 (t, 1H, ArH), 7.40 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 426 (M^+), 428 (M+2, 34.30 %).

2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1H-pyrazol-4-yl)-acetamide-(3-chloro-4-(p-nitro)phenylazetidin-2-one) (DTc): IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 2881 (CH_3 stretch), 1724 (C=O ketone), 1685 (C=O), 1540 and 1330 (NO_2), 1372 (CH_3 bend), 1293 (C-N), 610 (Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.95 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 3.40 (s, 1H, NH), 5.15 (d, 1H, CH), 5.40 (d, 1H, CH), 7.10 (t, 1H, ArH), 7.30 (t, 2H, ArH), 7.50 (m, 6H, ArH), 8.00 (s, 1H, NH); mass: m/z 455 (M^+), 456 (M+1, 24.05 %).

2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-(p-chloro)phenylazetidin-2-one) (DTd): IR (KBr, ν_{max}, cm^{-1}): 3355 (NH), 2880 (CH_3 stretch), 1728 (C=O ketone), 1685 (C=O), 1370 (CH_3 bend), 1290 (C-N), 610 (Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.90 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 3.45 (s, 1H, NH), 5.20 (d, 1H, CH), 5.45 (d, 1H, CH), 7.00 (t, 1H, ArH), 7.35 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 444 (M^+), 446 (M+2, 63.38 %).

2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-(*p*-methyl)phenylazetidin-2-one) (DTe): IR (KBr, ν_{max}, cm^{-1}): 3355 (NH), 2885 (CH_3 stretch), 1728 (C=O ketone), 1685 (C=O), 1375 (CH_3 bend), 1290 (C-N), 610 (Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm), 1.95 (s, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.40 (s, 1H, NH), 5.25 (d, 1H, CH), 5.40 (d, 1H, CH), 7.00 (t, 1H, ArH), 7.35 (t, 2H, ArH), 7.55 (m, 6H, ArH), 8.10 (s, 1H, NH); mass: m/z 424 (M^+), 425 (M+1, 25.15 %).

RESULTS AND DISCUSSION

The antifungal activity of compounds (**4a-4e**) and (**DTa-DTe**) are reported in (Table-2) respectively. Compounds with para *N,N*-dimethyl amino, *para* hydroxy, *para* methyl substitution on phenyl ring attached to 4th position of azetidin-2-one ring such as **DTa, DTb, DTe** revealed good antifungal activity as compared to compounds **DTc, DTd**, which contain *para* nitro and *para* chloro substitution on same ring.

Under identical conditions the standard fluconazole (30 µg/mL) exhibit zone of inhibition of 20 and 19 mm against *Penicillium notatum* and *Aspergillus niger* respectively. The antifungal activity of compound **DTb** is almost more than that of fluconazole against *Penicillium notatum*.

TABLE-2
ANTIFUNGAL ACTIVITY OF COMPOUNDS[#] (**4a-4e**) AND (**DTa-DTe**)

Compound code	*Penicillium notatum*			*Aspergillus niger*		
	10 (µg/mL)	20 (µg/mL)	30 (µg/mL)	10 (µg/mL)	20 (µg/mL)	30 (µg/mL)
Fluconazole	14	16	20	13	16	19
Control	-	-	-	-	-	-
4a	13	15	17	12	15	16
4b	14	16	18	13	15	17
4c	09	10	11	07	08	10
4d	07	08	08	07	07	09
4e	14	15	19	13	16	16
DTa	11	13	17	12	14	18
DTb	15	17	21	11	16	18
DTc	11	11	11	09	09	11
DTd	09	09	09	10	11	11
DTe	14	15	18	16	16	18

= zone of inhibition in mm

Conclusion

Various 2-(4,5-dihydro-3-methyl-5-oxo-1-phenyl-1*H*-pyrazol-4-yl)-acetamide-(3-chloro-4-substituted phenylazetidin-2-one) (**DTa-DTe**) derivatives were synthesized and screened for antifungal activity. Compounds (**4a-4e**) reacted with chloroacetyl chloride and triethylamine in microwave oven to give corresponding phenylazetidin-2-one (**DTa-DTe**) in very good yields. It was interesting to note that out of five compounds **DTa, DTb, DTe** were found to have antifungal activity near to standard. In view of these observations, we conclude that (**DTa-DTe**) could be developed as a novel class of antifungal agents. However, further in detailed antifungal screening with QSAR studies is required to identify the potent molecule without severe side effects.

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