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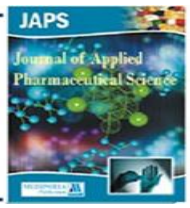

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Synthesis and antimicrobial study of N-[4-(2-piperidine-1-yl-ethoxy) phenyl] acetamide analogues

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ABSTRACT

In the present study, a novel series of N-[4-(2-piperidine-1-yl-ethoxy) phenyl]-acetamides were synthesized from 4-aminophenol and characterised by IR, ^{1}H-NMR, Mass spectral studies and elemental analysis. The antimicrobial potency of compounds is tested against variety of fungal and bacterial strains by disc agar diffusion technique. in comparison to to fluconazole and chloramphenicol respectively. Some of the synthesized compounds exhibit the potency comparable to that of standard drugs.

Keywords: N-[4-(2-piperidine-1-yl-ethoxy)phenyl]-acetamide; Synthetic sequence; Antimicrobial study; Disc agar diffusion technique

INTRODUCTION

Today the design of new molecules and study of their biological potency is very important target. The synthesis new antimicrobial agents with reduced toxicity and lower side effect is a continuous process to combat antimicrobial resistance (Lewis 1985; Vanessa et al., 2011). As the microorganisms are becoming resistant more quickly than new drugs are being made available, the feature research in antimicrobial therapy is to overcome resistance to antimicrobials or how to treat infections with alternate means such as species specific phages (Molecular mechanisms, 1994; Neu, 1996). The acetamide moiety is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including antimicrobial, antioxidant, anti-inflammatory, tranquilizer and antagonist properties (Jian Jeffrey Chen, 2008; Olgen and Bakar, 2011; Cappelli, 2011; Huma Jawed, 2010; Kanagarajan, 2010). Introduction of acetamide moiety on certain drugs found to enhance their pharmacological property on respiratory tract Pathogens(Nomura, 2006). Recently mechanism of inhibition of the enzyme HIV-1 reverse transcriptas by certain thienyl acetamide derivatis were performed(Herschhorn, 2008). The potency of piperidine analogues as chemotherapeutic agents, in particular antibacterial and antifungal agents are well documented. The analogous were found to exhibit efficient antimalarial, anticancer and anti HIV activities (Harper, 2005; Sahoo, 2010; Venkatachalam, 2000). Scientists studied relationship between structure and biological activity of derivatives of piperidine (Komoto, 2000). Piperidino-acetamides posses excellent anxiolytic, analgesic, sedative, antiepileptic and antagonist properties (Naya, 2001; Kenda, 2004; Palin, 2007; Rezvani, 2007). Based on this information it was considered valuable to synthesize a new class of piperidino acetamides and to study their antimicrobial proficiency.

MATERIAL AND METHODS

Synthetic sequence

Chemicals used were of analar grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus using digital thermometer. ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million down field from tetramethyl silane. Mass spectra were recorded on a VG70-70H mass spectrometer.

I. Synthesis of N-(4-hydroxyphenyl)acetamides

The synthetic sequence is out lined in scheme-1. A mixture of 4-aminophenol (**1.**10 mmol) and corresponding carboxylic acid (**2a-e**. 10 mmol) in few ml of water and few drops of pyridine catalyst was stirred for 24 hours at room temperature. The product was extracted with ice cold ether (3x40 ml). The ether layer was washed with 2% sodium carbonate solution (3x20 ml), 2% hydrochloric acid solution (3x30 ml) and distilled water. Then the organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was recrystallized using alcohol to afford N-(4-hydroxyphenyl)acetamides (**3a-e**).

Charecterisation of compounds (3a-e)

Compound 3a. N-(4-hydroxyphenyl)acetamide

mp 168-170^{0}C; IR(Nujol) 1670cm^{-1} (amide, C=O), 3395cm^{-1} (amide, N-H), 3515-3630cm^{-1} (O-H); ^{1}H NMR($CDCl_3$); δ 2.47(s, 3H, CH_3), 3.1(s distd , 1H, N-H), 6.9-7.4(m, 4H, Ar-H), 9.0(br s, 1H, OH); EI-MS; m/z 152 (M^+, 82), 153 (M^+, 72), 151 (100), 137 (65), 92 (35). Anal. Calcd for $C_8H_9NO_2$ (151); C, 63.57; H, 6.00; N, 9.27. Found; C, 63.61; H, 6.05; N, 9.31.

Compound 3b. N-(4-hydroxyphenyl)-2-phenyl acetamide

mp 185-187^{0}C; IR(Nujol) 1685cm^{-1} (amide, C=O), 3420cm^{-1} (amide, N-H), 3520-3620cm^{-1} (O-H); ^{1}H NMR($CDCl_3$); δ3.09(s distd, 1H, N-H), 6.8-7.6(m, 9H, Ar-H), 9.0(br s, 1H, OH); EI-MS; m/z 227 (M^+, 100), 226 (M^+, 85), 228 (M^+,59), 137 (62), 92 (42), 90(71). Ana. Calcd for $C_{14}H_{13}NO_2$ (227); C, 73.95; H, 5.78; N, 6.17. Found; C, 74.02; H, 5.72; N, 6.12.

Compound 3c. N-(4-hydroxyphenyl)-2-(4- chlorophenyl)acetamide

mp 192-194^{0}C; IR(Nujol) 1680cm^{-1} (amide, C=O), 3375cm^{-1} (amide, N-H), 3515-3630cm^{-1} (O-H); ^{1}H NMR($CDCl_3$); δ 3.08(s distd , 1H, N-H), 6.9-7.5(m, 8H, Ar-H), 9.0(br s, 1H, OH); EI-MS; m/z 262.5 (M^+, 73), 261.5 (M^+, 95), 260 (M^+,45), 136 (63), 92 (35), 124.5(78). Anal. Calcd for $C_{14}H_{12}ClNO_2$ (261.5); C, 64.22; H, 4.61; Cl, 13.54; N, 5.35. Found; C, 64.24; H, 4.57; Cl, 13.51; N, 5.38.

Compound 3d. N-(4-hydroxyphenyl)-2-phenoxy acetamide

mp 178- 180^{0}C; IR (Nujol) 1640 cm^{-1} (amide, C=O), 3370cm^{-1} (amide, N-H), 3510-3625cm^{-1} (O-H); ^{1}H NMR($CDCl_3$); δ 2.6(s, 2H, CH_2), 3.0(s distd , 1H, N-H), 6.8-7.5(m, 9H, Ar-H), 9.0(br s, 1H, OH); EI-MS; m/z 243 (M^+, 89), 244 (M^+, 55), 242 (M^+,78), 151 (92), 137(73). Anal. Calcd for $C_{14}H_{13}NO_3$ (243); C, 69.11; H, 5.39; N, 5.75. Found; C, 69.05; H, 5.41; N, 5.79.

Compound 3e. N- (4- hydroxyphenyl)- 2- (2, 4-dimethoxyphenyl) acetamide

mp 182-184^{0}C; IR(Nujol) 1660cm^{-1} (amide, C=O), 3380cm^{-1} (amide, N-H), 3510-3630cm^{-1} (O-H); ^{1}H NMR($CDCl_3$); δ 2.5(s, 2H, Ar-CH2), 3.0(s distd , 1H, N-H), 3.8(s, 6H, OCH_3), 7.0-7.6(m, 7H, Ar-H), 9.0(br s, 1H, OH); EI-MS; m/z 288.4 (M^+, 72), 287.4 (M^+, 83), 285.5 (M^+,92), 137 (89), 151(35). Anal. Calcd for $C_{16}H_{17}NO_4$ (287); C, 66.85; H, 5.94; N, 4.86. Found; C, 66.77; H, 5.97; N, 4.85.

II. Synthesis of N-[4-(2-piperidine-1-yl-ethoxy)phenyl]acetamides

A mixture of 3a-e (2 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (2 mmol) in presence of anhydrous potassium carbonate (5 mmol) and dimethyl sulfoxide (15 ml) was refluxed for 10 hours and then cooled. The residual mass was triturated with ice water to remove potassium carbonate and dimethyl sulfoxide. Then the product was extrated with chloroform (3x20 ml). The organic layer was washed with saturated sodium chloride solution (3x20 ml) and 2% sodium hydroxide solution (3x20 ml) followed by distilled water and dried over anhydrous sodium sulfate. The crude product obtained by the evaporation of organic layer on recrystallizaton using ethanol affords pasty mass of title compounds N-[4-(2-piperidine-1-yl-ethoxy)phenyl]acetamides (**4a-e**). The compounds 3a-e and 4a-e were characterized by IR, ^{1}H-NMR, Mass spectral studies and elemental analysis.

Compound 4a. N-[4-(2-piperidine-1-yl-ethoxy)phenyl]acetamide

Pasty mass mp 182-184^{0}C; IR(Nujol) 1678cm^{-1} (amide, C=O), 3390cm^{-1} (amide, N-H); ^{1}H NMR($CDCl_3$); δ 1.043(m, 6H, ring 3CH_2), 1.203(t, 4H, ring 2N-CH_2), 2.0(t, 2H, N-CH_2), 2.474(s, 3H, CH_3), 3.0(s distd , 1H, N-H), 3.8(t, 2H, O-CH_2), 7.0-7.6(m, 4H, Ar-H); EI-MS; m/z 264 (M^+, 65), 263 (M^+, 78), 112 (M^+, 95), Anal. Calcd for $C_{15}H_{22}N_2O_2$ (262); C, 68.67; H, 8.44; N, 10.65. Found; C, 68.70; H, 8,42; N, 10.71.

Compound 4b. N-[4-(2-piperidine-1-yl-ethoxy)phenyl]-2-phenyl acetamide

Pasty mass mp 190-192^{0}C; IR(Nujol) 1682cm^{-1} (amide, C=O), 3425cm^{-1} (amide, N-H); ^{1}H NMR($CDCl_3$); δ 1.040(m, 6H, ring 3CH_2),1.20(t, 4H, ring 2N-CH_2), 2.02(t, 2H, N-CH_2), 3.0(s distd , 1H, N-H), 3.8(t, 2H, O-CH_2), 6,8-7.8(m, 9H, Ar-H); EI-MS; m/z 339 (M^+, 91), 338 (M^+, 85), 113 (93), Anal. Calcd for $C_{21}H_{26}N_2O_2$ (338); C, 74.5; H, 7,73; N, 8.26. Found; C, 73.8; H, 7.72; N, 8.23.

Compound 4c. . N-[4-(2-piperidine-1-yl-ethoxy)phenyl]-2-(4-chlorophenyl)acetamide

Pasty mass mp 188-190^{0}C; IR(Nujol) 1685cm^{-1} (amide, C=O), 3490cm^{-1} (amide, N-H); ^{1}H NMR($CDCl_3$); δ 1.05(m, 6H,

ring $3CH_2$),1.22(t, 4H, ring $2N\text{-}CH_2$), 2.02(t, 2H, $N\text{-}CH_2$), 3.0(s distd , 1H, N-H), 3.8(t, 2H, $O\text{-}CH_2$), 6,9-7.8(m, 8H, Ar-H); EI-MS; m/z 373 (M^+, 93), 372 (M^+, 84), 374 (M^+, 82), 112 (89), Anal. Calcd for $C_{21}H_{25}ClN_2O_2$ (372.5); C, 67.58; H, 6.74; Cl, 9.48; N, 7.48. Found; C, 67.55; H, 6.75; Cl, 9.5; N, 7.47.

Compound 4d. N-[4-(2-piperidine-1-yl-ethoxy)phenyl]-2-phenoxy acetamide

Pasty mass mp 184-186^{0}C; IR(Nujol) 1620cm^{-1} (amide, C=O), 3440cm^{-1} (amide, N-H); ^{1}H NMR($CDCl_3$); δ 1.03(m, 6H, ring $3CH_2$), 1.2(t, 4H, ring $2N\text{-}CH_2$), 2.0(t, 2H, $N\text{-}CH_2$), 2.6(s, 2H, CH_2), 3.05(s distd , 1H, N-H), 3.8(t, 2H, $O\text{-}CH_2$), 6.9- 7.8(m, 9H, Ar-H); EI-MS; m/z 356.5 (M^+, 85), 357.5 (M^+, 69), 355 (M^+, 72), 113 (72), Anal. Calcd for $C_{21}H_{26}N_2O_3$ (354); C, 70.9; H, 7.35; N, 7.88. Found; C, 71.14; H, 7.33; N, 7.85.

Compound 4e. N-[4-(2-piperidine-1-yl-ethoxy)phenyl]-2-(2,4-dimethoxyphenyl)acetamide

Pasty mass mp 176-178^{0}C; IR(Nujol) 1665cm^{-1} (amide, C=O), 3400cm^{-1} (amide, N-H); ^{1}H NMR($CDCl_3$); δ 1.1(m, 6H, ring $3CH_2$), 1.24(t, 4H, ring $2N\text{-}CH_2$), 2.02(t, 2H, $N\text{-}CH_2$), 2.5(s, 2H, Ar-CH2), 3.08(s distd , 1H, N-H), 3.2(t, 2H, $O\text{-}CH_2$), 3.8(s, 6H, OCH_3), 6.9- 7.8(m, 7H, Ar-H); EI-MS; m/z 400 (M^+, 76), 401 (M^+, 62), 399 (M^+, 90), 112.3 (68), Anal. Calcd for $C_{23}H_{30}N_2O_4$ (398); C, 69.21; H, 7.54; N, 6.95. Found; C, 69.3; H, 7.55; N, 6.98.

Antimicrobial study

The compounds 1, 3a-e, 4a-e and piperidine were screened for antifungal and antibacterial activity by disc agar diffusion technique at different concentrations ranging from 25 to 250 micro g/mL in ethylacetate (Bauer. A. W 1966). The specific bacterial culture was spread uniformly over nutrient agar in Petri plates. Then the test solution, standard and control of known similar concentration were spotted in sample wells at specific distance. The zones of inhibition were measured after 24 hour incubation at 37^{0}c for antibacterial activity and 48 hour incubation at 25^{0}c for antifungal activity (Barry; 1979). The inhibitory concentration of 50 micro g/mL, was selected and the experiments were carried out induplicate repeatedly to get reproducible results.

RESULT AND DISCUSSION

Antifungal activity

The in vitro antifungal activity of compounds were evaluated against the fungi F.oxysporum, A.flavus, C.capsici and C.krusei ausing fluconazole as the reference standard and the results are summarized in table-1. The synthesized acetamides 3a-e possess enhanced activity when compared piperidine and the compound 4-aminophenol which is the core structure in the series. The efficacy of title compounds 4a-e is comparable with that of standard drug fluconazole. The screening results reveal that the activity of compound 4a, a simple acetamide is nearly same as that of standard to all the four fungi. The compound 4b with benzyl group attached to acetamide linkage is more potent to F.oxysporum but less potent to the other three fungi. It is worth to notice that compound 4c with chlorine on C_4 of aromatic ring is more potent than the standard fluconazole against A.flavus, equipotent against C.copsici and slightly less potent against F.oxysporum and C.krusei. The compounds 4d and 4e with phenoxy methyl group and 2,4-dimethxy benzyl group are more potent than the standard against A.flavus and C.capsici where as less potent against F.oxysporum and C.krusei.

Table. 1: Antifungal screening results of compounds 3a-e and 4a-e at concentration 50 µg/ml Zone of inhibition in mm.

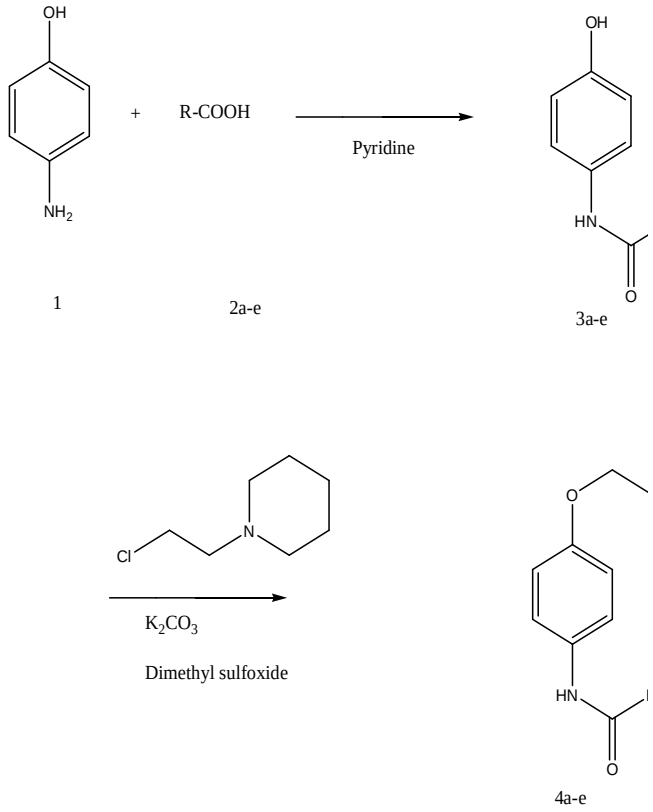
Compound	F.oxysporum	A.flavus	C.capsici	C.krusei
3a	2.0	2.0	2.5	2.0
3b	3.5	3.0	2.0	2.5
3c	2.5	3.5	2.5	2.0
3d	2.0	3.0	3.0	2.5
3e	2.0	3.5	3.0	2.5
4a	7.5	6.5	6.0	4.0
4b	9.5	6.0	4.5	4.0
4c	6.0	8.5	6.5	3.5
4d	6.5	8.0	7.5	4.0
4e	6.5	8.5	7.0	3.5
Control	-	-	-	-
1	1.0	1.0	0.5	0.5
Piperidine	1.5	1.5	1.0	1.0
Fluconazole	8.5	7.5	6.5	5.0

Antibacterial activity

The results of in vitro antibacterial activity against the bacteria E.coli, R.solanacearum C.botulinum and B.subtilis using chloramphenicol as reference standard are summarized in table-2. Once again the synthesized acetamides 3a-e showed increased potency when compared to piperidine and 4-aminophenol and the efficacy of title compounds 4a-e is comparable with that of standard drug chloramphenicol. The compound 4a is marginally less potent to chloramphenicol for all the bacteria. The compounds 4b and 4c are more potent than the standard against E.coli and R.solanacearum. The enhanced activity may be due to the benzyl group and 4-chloro benzyl group bonded to amide carbon. The compounds 4d and 4e shows lesser efficacy.

Table. 2: Antibacteerial screening results of compounds 3a-e and 4a-e at concentration 50 µg/ml Zone of inhibition in mm.

Compound	E.coli	R.solanacearum	C. botulinum	B.subtilis
3a	3.5	4.5	3.0	3.0
3b	4.5	5.0	3.5	3.0
3c	4.5	5.5	3.5	3.5
3d	3.5	4.5	2.5	3.5
3e	3.0	4.0	2.0	3.0
4a	7.5	8.5	5.0	6.0
4b	9.0	9.5	5.5	6.5
4c	9.5	9.5	6.0	7.5
4d	8.0	7.0	5.5	7.5
4e	8.5	6.5	5.5	7.0
Control	-	-	-	-
1	1.0	1.5	0.5	1.0
Piperidine	2.0	1.5	1.0	1.5
Chloramphenicol	8.0	9.0	6.0	7.5



a: R = CH_3 b: R = CH_2-C6H_5 c:R = CH_2-C6H_5Cl(4) d:R =

e: R = CH_2-$C_6H_3(OCH_3)_2$(2,4)

Scheme 1.

CONCLUSION

In conclusion the synthesized compounds were found to posses more antibacterial activity than antifungal activity compared to respective reference standards. . The antimicrobial potency of the compounds is more against gram negative bacteria compared to gram positive bacteria. The excellent potency of compound 4c with chlorine on aromatic ring indicates the importance of functional groups in enhancing the biological activity. Weaker efficacy was exhibited by all synthesized compounds against the bacteria C. botulinum and the fungus C.krusei with few exceptional cases. It is important to notice that the compounds 4d and 4e possessing phenoxy group and dimethoxy benzyl group were lesser active against all the bacteria and fungi with the exception of F.oxysporum, C.krusei and E.coli. In view the significant activity of compounds can be exploited in the formulation of bactericides and fungicides.

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